中藥不良反應

朱顯中

醫學科學

哲學碩士論文

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二零零二年七月

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Abstract of thesis entitled: Adverse Reaction of Chinese Herbal Medicines

Submitted by CHU Hin Chung Henry

For the degree of Master of Philosophy

At the Chinese University of Hong Kong in July 2002

Traditional Chinese medicine (TCM) plays an important role in health care systems in many parts of the world. Most people in the Asiatic countries are firm believers in traditional herbal medicines for cure and for body-strengthening purposes. A general perception that TCM lacks systematic pharmacological, toxicological, and clinical studies. The deficiency in efficacy and safety has been a major hindrance to the progress of TCM, despite the success of herbal medicine in treatment of diseases for which the orthodox drugs in western medicine are ineffective. Although there is a huge amount of data available documenting the pharmacologically active ingredients of many herbal medicine, cases of severe toxicity resulting from use of herbal medicine were documented occasionally. This brief review aims to serve as an introduction and a reference guide to TCM toxicology. The reason of herbal toxicity occurs not only because of a lack of pharmaceutics quality control in harvesting and because the increased awareness among physicians and allied professionals of the toxic potential of some of these substances. In order to clarify the adverse reaction caused by
herbal medicine, a systematic research is necessary. With the information from my studies show that problems may arise when toxic herbs are used in excessive doses, with improper preparation, or when they are substituted erroneously. Future TCM research, new drug development, and safety evaluation require adequate toxicity testing and mechanistic toxicology studies. Considering the extent of use of Chinese herbal medicine, a large scaled continued surveillance program is necessary to detect, evaluate, and develop mechanisms to prevent the adverse effects of Chinese herbal medicine. (299 words)
傳統的中藥在全球各地醫療領域中均佔一重要席位，尤其亞洲地區的居民更深信傳統的中藥除可治病外更有強身保健的效果，但一般民眾對傳統中藥的理解所知不多，普遍認為傳統中藥雖然對某類西藥未能治療的頑疾有效，但其真正的療效及安全性等均缺乏科學化理據的支持，而且更缺乏公認的臨床藥理及毒理方面的試驗引證，所以亦造成發展傳統中醫藥的一大障礙。雖然近年科學界公佈大量有關各種草藥之有效藥理成份數據結果，但同時亦有不少的中藥不良反應個案公開，這種情況不但是由於草藥製品於生產過程中存在質量控制的問題，更由於醫療人員及民眾對此提高警覺及加深認識所致。為對中藥的不良反應加深了解，是有必要對此作出深入的研究；而從今次的研究中發現大多數中毒個案是由於過量使用有毒中藥及其配製方面出錯或錯誤運用其他有毒中藥所致。爲日後能全面發展中醫藥，對中藥的安全性是需要有足夠之毒理分析及研究，而大規模的普查系統對防治中藥引致的不良反應則更為重要。
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<tr>
<td>Acetyl CoA</td>
<td>Acetyl coenzyme A</td>
</tr>
<tr>
<td>AHMAC</td>
<td>Australian Health Ministers Advisory Council</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>AMA</td>
<td>American Medical Association</td>
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<tr>
<td>APL</td>
<td>Acute promyelocytic leukemia</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute renal failure</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>As,O,</td>
<td>Arsenic trioxide</td>
</tr>
<tr>
<td>BEN</td>
<td>Balkan endemic nephropathy</td>
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<tr>
<td>CAM</td>
<td>Complementary and alternative medicine</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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<tr>
<td>CHN</td>
<td>Chinese herbs nephropathy</td>
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<tr>
<td>CML</td>
<td>Chronic myeloid leukemia</td>
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<tr>
<td>CMMRC</td>
<td>Chinese Medicinal Material Research Center</td>
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<tr>
<td>CMPs</td>
<td>Chinese Medicine Practitioners</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CPA</td>
<td>Consumer Protection Association</td>
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<td>CPM</td>
<td>Chinese proprietary medicine</td>
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<tr>
<td>DHS</td>
<td>Department of Human Services</td>
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<tr>
<td>DIC</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethylarsinic acid</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DPIB</td>
<td>Drug and Poisons Information Bureau</td>
</tr>
<tr>
<td>DSHEA</td>
<td>Dietary Supplement Health and Education Act</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>EC</td>
<td>European Community</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal symptoms</td>
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<tr>
<td>FDA</td>
<td>The Food and Drug Administration</td>
</tr>
<tr>
<td>FDB</td>
<td>Food and Drug laboratory Bureau</td>
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<tr>
<td>GAS</td>
<td>Ginseng Abuse Syndrome</td>
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<tr>
<td>GBE</td>
<td>Ginkgo biloba extract</td>
</tr>
<tr>
<td>G6PD</td>
<td>Glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>G.I.</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>GPMSP</td>
<td>Good Post-Marketing Surveillance Practice</td>
</tr>
<tr>
<td>HAR</td>
<td>Herbal Adverse Reaction</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>IDDM</td>
<td>Insulin dependent diabetes mellitus</td>
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<tr>
<td>L-THP</td>
<td>Levo-tetrahydropalmatine</td>
</tr>
<tr>
<td>MHW</td>
<td>Ministry of Health and Welfare</td>
</tr>
<tr>
<td>MMA</td>
<td>Monomethylarsonic acid</td>
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Publication in press

   Tomlinson B, Thomas GN, Chu HHC, Lan W and But PPH.

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Chapter 1 - Introduction

Modern medicine developed very quickly and made major contributions to disease control in the past century. Interestingly, despite a rapid growth in knowledge and techniques in modern medicine, the later decade of the last century also saw a dramatically increased interest in traditional medicine. The increasing public demand for its use has led to considerable interest among policy-makers, health administrators, and medical doctors on the possibilities of bringing traditional and modern medicine together. This increasing use of traditional medicine is also raising the interest of governments. Several countries and areas in the region are seriously considering integrating traditional medicine into their conventional health care system. However, such government involvement needs government policy on traditional medicine, which clearly states the level and the direction of its involvement.

Based on the accumulation of experience over many thousands years, traditional Chinese medicine (TCM) draws on materials that are widely available in nature, including plants, animals and minerals.\cite{Tai YT, But PH et al, 1993} The great majority of Chinese herbal preparations are safe, and some useful Western drugs have been derived from these herbs. This system of medicine presupposes an elaborate mechanism of homeostasis within the body, disturbance of which results in disease. Treatment depends on not only correction or repletion of the disrupted elements but strengthening of “related parts”. The use of traditional Chinese medicine (TCM) is universal in Chinese populations throughout the world and is becoming increasingly frequent in the West. It is used as first line treatment for many minor ailments and some chronic diseases in Chinese populations. A major attraction of this type of therapy is the apparent lack of
side effects compared with the drug therapies used in allopathic medicine. However the increased use of herbal medicines has resulted in mounting concern about both the efficacy and safety of these products.

Chinese herbal medicines (CHM) and Chinese proprietary medicines (CPM) are widely used by people of Chinese origin throughout the world. Generally speaking, uncontaminated herbal medicines in recommended doses are safe. Although the use of these medicinal materials rarely causes significant toxic effects, cases of severe and even fatal poisoning have occurred after medication with herbs containing aconitine, podophyllin, and anticholinergic substances. Furthermore, CHM and CPM are often adulterated with substituted herbs, heavy metals, and western medicines; such contamination can have important clinical consequences. However, standards for evaluating the safety and quality of herbal medicine and herbal medicine products have not been well established.

In TCM, ingredients are commonly used in combinations, allowing the use of smaller doses of herbs with synergistic beneficial effects, and it is thought that some materials may counteract the potential toxicity of others. Most popular herbal medicines are relatively harmless at usual doses, with adverse effects consisting primarily of mild and infrequent gastrointestinal or dermatological reactions. However, such kind of poisonings by Chinese herbal medicines is difficult to assess. It was because the existing knowledge of the pharmacological effects of Chinese herbal medicines is limited and each prescription typically consists of 10-15 herbs, which in turn contain many ingredients. The diagnosis can be easily missed if patients are not questioned about the use these preparations. Furthermore the herbalists are often reluctant to disclose the contents of their prescriptions.
In order to evaluate the extent of herbal poisoning worldwide, an extensive research
and systemic review is necessary. This review focuses on examples from experience of
adverse effects of Chinese herbal medicine and some other herbal medicines used
worldwide. The information generated through this review may be expected to facilitate
future management of such cases, to offer concrete data for policy-making in the control
of herbal medicines, and to upgrade the scientific contents of Chinese and other herbal
medicines by defining their safety limits.
Chapter 2 - Chinese herbal medicines used in Hong Kong

2.1 Overview

TCM has been practiced in China for over 2000 years. Both Western medicine and TCM are widely available in Hong Kong. Despite the dominance of Western medicine in Hong Kong, a result of the favored position enjoyed by Western medicine during the British rule, both Western people and the local population have used Chinese medicines concurrently. Before 1997, the British Hong Kong Government adopted a non-interventionist approach towards the practice of Chinese medicine in Hong Kong. Any adults of Chinese descent were allowed to practice any form of use of Chinese medicines but its development otherwise received very little government attention, and certainly no support. On the other hand, Western medicine was the only form of medicine receiving formal government recognition and support. Hong Kong Medical College, which subsequently amalgamated with the University of Hong Kong, was established to provide Western medical training in Hong Kong over 100 years ago. Throughout the past century, the Western medical health care system developed and flourished in Hong Kong. However, the majority of the population probably explains and understands their illnesses in Chinese medical concepts rather than Western medical principles. These two types of professional services are coexisting in the pluralistic health context of Hong Kong. By 1999, there were over 9000 doctors registered in Hong Kong serving a population of almost 7 million. Most of the hospital care is provided in the public hospital system. On the other hand, 3000 private general practitioners provide over 80% of the primary care. The Government's general outpatient
clinics and other registered practitioners, including practitioners of TCM, provide the other 20% of primary care in Hong Kong. TCM practitioners are widely available in Hong Kong, but they only need to acquire a business registration without any assessment of their qualifications or standard of training and, hence, their standard varies. Some of them are often attached to an herbal medicinal shop and their charges are often no more than HK$20–30. Depending on the herbs prescribed, the total costs are often less than HK$50–60 per consultation. (Lam TP, 2001)

2.2 The Policy In Hong Kong – Past And Present

The lack of legal control over herbal practice in Hong Kong dated back to the Nanking Treaty of 1842, in which Chinese medicine was protected from control as part of "Chinese customs and usages". In the past, all the Chinese patent medicine sold in Hong Kong was only under the regulation of Undesirable Medical Advertisements Ordinance, which provided that it was illegal to advertise in respect of diseases specified in the Ordinance. The Hong Kong Government used to adopt a policy of nonintervention in the use of traditional Chinese Medicine. The Pharmacy and Poisons Ordinance (Chapter 138), which stipulates the need of registration of pharmacists and related matters, also provides that “nothing in this Ordinance shall apply to the sale, manufacturing, dispensing or compounding of traditional Chinese medicines as listed in the Chinese Herbal Materia Medica (Bencao Gangmu) or which are made from herbs customarily used by the Chinese people” (But PPH and Kan WK, 1995) This laissez-faire practice left much room for erroneous identification, careless dispensing, improper processing, unscrupulous substitution, or even intentional adulteration of herbs and herbal products, and also for quacks and unqualified or ill-trained practitioners. (But PPH, Tai YT et al, 1995) The local herbal industry, relying only on experience and
organoleptic inspection, was allowed to handle its trade. Proprietary Chinese medicines are further subject to import licensing control and post-marketing surveillance for adulteration with western medicine and contamination by heavy metals.

The policy for the future development of Chinese medicine was enshrined in the Basic Law of the Hong Kong Special Administrative Region. Article 138 of the Basic Law provides that "the Government of the Hong Kong Special Administrative Region shall, on its own, formulate policies to develop western and traditional Chinese medicine and to improve medical and health services. Community organizations and individuals may provide various medical and health services in accordance with law." The Chief Executive, in his 1998 Policy Address, declared the vision to establish Hong Kong as a world center for the development of health foods and pharmaceuticals based on Chinese medicines. Hong Kong is aiming to establish itself as the global center for the scientific study and commercial exploitation of traditional Chinese medicines. (Cyranoski D, 2001)

Before 2002, The Hong Kong's Innovation and Technology Commission, the main applied research funding body in the territory, has already spent more than HK$100 million over the past few years on research into traditional medicine, involving many of Hong Kong's leading biomedical researchers. Given its historical and business connections to the West and its close cultural connections to China, Hong Kong could very well become the center for internationalization of Chinese medicine. The Government has also recently launched a new initiative on the development of regulatory standards for Chinese medicinal herbs. Alongside the regulatory and infrastructural development, the Government, with the pledged donation of HK$500 million (or US$64 million) from the Hong Kong Jockey Club Charities Trust Limited, has set up the Hong Kong Jockey Club Institute of Chinese Medicine Limited
(HKJCICM) to steer, co-ordinate and strengthen the modernisation and further development of Chinese medicines in Hong Kong.

Although adverse reactions caused by traditional Chinese medicine are infrequent and low, it is important for the government to be aware of these. In a prospective study of hospital admissions during an 8-month period in Hong Kong, adverse events due to CHM accounted for 0.2% of admissions (3 patients in 1701 admissions), and those due to Western pharmaceuticals accounted for 4.4%. (Chan TY, Chan JC et al, 1993) This study only measured severe adverse event, and the lack of data on the relative use of CHM and Western medicine makes this comparison difficult to interpret.

2.3 The Preparatory Committee on Chinese Medicine (PCCM)

In August 1989, the Secretary for Health and Welfare of the Hong Kong Government set up the Working Party on Chinese medicine to review the use and practice of Chinese medicine in Hong Kong and to advise on measures that should be taken to promote the proper use and good practice of Chinese medicine. The working party has made recommendations on: (I) Registration of Chinese medicine practitioners; (II) Restricted use of proprietary Chinese medicines; (III) Processing, manufacturing and trading of Chinese medicine; (IV) Training and research in traditional Chinese Medicine; (V) Training of dispensers and public education. Following the Working Party's recommendation, the Preparatory Committee on Chinese Medicine (PCCM) was appointed in 1995. The Preparatory Committee on Chinese medicine and its two sub-committees, consisting mainly of members of the traditional Chinese medicine profession and supported by health officials and academics, were formed in April 1995 to manage the implementation of these recommendations. During its four years of appointment, the Preparatory Committee conducted a census on Chinese medicine
practitioners in Hong Kong. Based on the submission of PCCM’s first report in 1997, which recommended the creation of a regulatory framework and a statutory body for regulation and control, and based on second report in 1999 recommending further regulation and development, the Chinese Medicine Ordinance was passed by the Legislative Council in 14 July 1999. The government policy included the following main topics: development of a statutory framework, development of education, and scientific research in TCM. (WHO, 1999)

2.4 The Chinese Medicine Council of Hong Kong

The Chinese Medicine Ordinance provides for the setting up of the Chinese Medicine Council of Hong Kong ("The Council"). This statutory regulatory body comprises practicing Chinese medicine practitioners, members of the trade of Chinese medicines, academics, laypersons and government officials. The contents of the Chinese Medicine Ordinance include the composition and functions of the Chinese Medicine Council, Chinese Medicine Practitioners Board, Chinese Medicines Board and the six committees established under the Chinese Medicine Council; the regulatory system for Chinese medicine practitioners, which includes registration, examination and discipline of Chinese medicine practitioners; and the regulatory system for Chinese medicines, which includes licensing and regulation of Chinese medicines traders and registration of proprietary Chinese medicines. In addition, the Ordinance contains Schedule 1 of 31 types of potent/toxic Chinese herbal medicines and Schedule 2 of 574 types of Chinese herbal medicines. Proprietary preparations containing a combination of herbal ingredients and conventional drugs are regulated in the same manner as other conventional drugs.
The Council was established in September 1999 and is responsible for implementing the regulatory measures for Chinese medicine. A licensing system and a registration system to regulate manufacture and trade were established in the year 2000. Under the new licensing system for Chinese medicine practitioners, Chinese medicine doctors in Hong Kong must prove they have practiced continuously for at least 15 years, as of January 3, 2000, to avoid taking licensing examination and registration assessment. (Chak M, 2001) Totally 8,000 applications were collected by the Chinese Medicine Council of Hong Kong but twenty-eight Chinese medicine practitioners were investigated by the police because of allegedly faking documentation. (Chak M, 2001) Totally 7,707 eligible applicants were placed on the List of Listed Chinese Medicine Practitioners and were listed in the Government of the Hong Kong Special Administrative Region Gazette, which was published on 21 December 2001. Only these Listed Chinese Medicine Practitioners (CMPs) will be allowed to practice Chinese medicine in the Hong Kong Special Administrative Region on March 1, 2002 when the relevant legislation comes into effect. Their practice could continue when the Listed CMPs become Registered CMPs or until the end of the transitional period on such date as specified by the Secretary for Health and Welfare.

For Chinese medicines, upon completion of relevant subsidiary legislations, the Council will implement the licensing system of Chinese medicine traders and the registration system of proprietary Chinese medicines by phases. Products already in the market on 1 March 1999 when a new legislation was set into force are “grand fathered” and will be reviewed particularly on quality aspects. New products require assessment of safety, quality and efficacy by the Chinese Medicine Board. The dispensation, storage and labeling of Chinese herbal medicines will also be regulated. A government survey
of patent Chinese medicines on the market revealed over 3,000 patent Chinese medicines. The majority of these patent Chinese medicines are imported from Mainland China.

In order to safeguard public health, besides regulating the practice of Chinese medicine, the Chinese Medicine Council regulates the manufacture, sale and use of Chinese medicines. The regulatory measures for Chinese medicines include a licensing system for Chinese medicine traders and a registration system for proprietary Chinese medicines. For the former, retailers and wholesale dealers of Chinese herbal medicines and wholesale dealers and manufacturers of proprietary Chinese medicines are required to obtain the appropriate licenses from the Chinese Medicines Board of the Chinese Medicine Council for their businesses. In addition, all proprietary Chinese medicines will be assessed and registered by the Chinese Medicines Board before they are allowed to be sold or manufactured. As with conventional synthetic drugs, safety and toxicity data that are collected on herbal medicines should be distributed to health professionals, both in Hong Kong and abroad. Moreover, the Chinese Medicine Council also set up a toxic herbs name list for herbalists to use as in China and Taiwan. (See Table 2a and 2b)

2.5 Development of Standards

The establishment of a statutory framework laid the solid foundation for the future development of Chinese medicine in Hong Kong. (Leung TH and Fung YK, 2001) Other strategies include the development of health-related and industry-related standards. Locally, the Chinese medicine Council of Hong Kong sets standards for the regulation and registration of Chinese medicine. To facilitate the development of international standards relevant to Chinese medicine concerted efforts from the World Health Organization (WHO) and experts worldwide are required. A WHO meeting on Methodologies for
Research and Evaluation of Traditional Medicine was held in April 2000 in Hong Kong. An internationally accepted guideline was published and disseminated to member states for reference in early 2001.

2.6 Development of Centers of Good Clinical Practice

It is proposed in the “Consultation Document on Health Care Reform” (Health and Welfare Bureau, Government Secretariat, Government of the Hong Kong Special Administrative Region. The People's Republic of C., 2000) released at the end of 2000 that the provision of Chinese medicine in the public health care system would be introduced. As the first step, the mode of delivery of outpatient Chinese medicine services will be examined. Primary care is one of the strengths of Chinese medicine. This proposal will enable this strength to be maximized for the benefits of the patients. It is also proposed to pilot the practice of Chinese medicine in selected public hospitals supporting clinical research for the evaluation of health benefits derived from Chinese medicine-based products and facilitating the development of standards and models of interface between western and Chinese medicine. In the long term, Chinese medicine will be integrated into the public health care system providing treatments to patients in collaboration with western medicine.

2.7 Establishment of a Good System of Education and Training

Before 1998, there were no full time training courses in Chinese medicine. (Leung TH and Fung YK, 2001) At present, full-time degree courses on Chinese medicine are provided by three universities. In the long run, an adequate pool of high calibre professionals can be produced locally to support Hong Kong's development to become an international center for Chinese medicine. Furthermore, it is important to create a network of research institutions of high standing to support new
drug development and enhance competitiveness of industry. Locally an institute of Chinese medicine has been set up with donations from the Hong Kong Jockey Club to support research on Chinese medicine. Moreover, it is planned to introduce Chinese medicine into the public healthcare system. This includes providing out-patient Chinese medicine services in the public sector, piloting the practice of Chinese medicine in selected public hospitals, supporting clinical research, and facilitating the development of standards and models of interface between western and Chinese medicines.

### 2.8 Investigation of Suspected Herbal Toxicity Cases

In order to investigate the particular situation of Chinese medicine in Hong Kong, several surveys were performed. A survey done in 1980 showed that (I) the majority (over one half) of respondents resorted to western doctors and 10% consulted traditional Chinese medicine practitioners, mostly herbalists. (II) In addition, Chinese medicine was generally perceived to be better than or as good as Western, scientific medicine in some ways, such as for tonic care, for fewer side effects, for curing the cause (not symptoms) of diseases, and for treating certain diseases. Therefore, to ordinary Chinese people, Chinese and Western medicine may perform either equivalent or complementary functions. (III) As regards the process of seeking medical care, most people seem to follow the pattern of moving from self-medication, using Chinese and/or western home remedies, to western-style doctors, to Chinese-style practitioners, and finally to a western medical hospital. Another two surveys done in 1993 and 1995 regarding the role of traditional Chinese medicine in health care produced similar results. (Wai WT, Lan WS et al, 1995; Lau J and Yu A, 2000)

In contrast to the situation for conventional drugs, there was no government scheme for monitoring or reporting adverse reactions to herbal medicines before 1999. The
Chinese Medicinal Material Research Center (CMMRC) (Now changed into The Institute of Chinese Medicine) of the Chinese University of Hong Kong and Drug and Poisons Information Bureau (DPIB) within the Clinical Pharmacology Department (Now changed into Department of Medicine & Therapeutics) at the Prince of Wales Hospital were established in 1979 and 1988 respectively to collect adverse reaction data on herbal medicine and perform multidisciplinary research on various aspects of Chinese medicine. These two units also provide consultation and assistance in response to both local and overseas requests.

2.8.1 Herbal Safety Surveillance

This two-year project is partially supported by the University and Polytechnic Grants Committee (UPGC). The principal investigators in this project are Professor Paul But from the Chinese Medicinal Material Research Center (now changed to the Institute of Chinese Medicine) at the Chinese University of Hong Kong and Professor Brian Tomlinson from Department of Clinical Pharmacology, Prince of Wales Hospital, the Chinese University of Hong Kong.

The aim of the project is to actively collect cases of suspected herbal poisoning and try to determine the actual or potential causes of the adverse reactions. The information generated through this project is expected to facilitate future management of such cases, to offer concrete data for policy-making in the control of herbal medicines, and to upgrade the scientific contents of Chinese and other herbal medicines by defining their safety limits. Both prospective and retrospective cases are the concerns in this project.

Totally 96 cases of suspected herbal poisoning were collected within 2 year. Several case were reported and published by the pharmaceutical journal. However, most of the cases are lack of enough information or evidences to follow. When a case of adverse
reaction to Chinese herbal medicine is suspected, the difficulty in establishing the diagnosis is well recognized. Each preparation (herbs or compound medicines) typically is made up of a number of ingredients that in turn consist of many different chemicals. Very often, the chemical nature and pharmacological actions of these ingredients and their constituents are largely unknown. If the actual prescription cannot be traced, chemical analysis of each ingredient is not possible. On the other hand, the success in making the diagnosis to some extent will also depend on the clinician’s suspicion and an awareness of particular patterns of clinical features which may suggest CHM toxicity rather than being features of the underlying disease or being related to toxic effects of pharmaceutical drugs.

In the absence of the residues of the preparations taken on, comments can only be made based on the remaining sample of preparations and the prescriptions given by the patient's familiyer and the TCM practitioner are reluctant to cooperate to disclose the prescription because of economic consideration. Furthermore, they would like to use an alias or secret signal to replace the common name of some herbal medicine and make confusion. So investigation is very difficult. Methods for grading herb toxicity (in therapeutic use or overdose) were developed based on a combination of the quality of reports, severity of adverse reaction, supporting animal studies, extrapolation from pharmacology and empirical evidence.

2.9 Conclusion

In the 21st Century, there remain other issues that need to be addressed to realize the full role and function of Chinese medicine in the health care system. These, among others, include the use of modern scientific knowledge to explain Chinese medicine so that Chinese medicine can be understood and accepted by the international community and
the determination of the strategic positioning Chinese medicine in the health care system. The development of models of interface of Chinese medicine practitioners and practitioners of western medicine and the promotion of the integration Chinese and western medicine.
Chapter 3 - Herbal medicines used in other countries

3.1 Overview

It is difficult to use traditional medicine effectively to support primary health care without the commitment of governments. In turn the government’s involvement needs a national policy that provides a clear statement on the role of traditional medicine and the government’s position with regard to the relationship between traditional medicine and the official health service system. The adoption of such a policy will be particularly helpful in establishing appropriate standards for traditional medicine.

The WHO is supporting Member States to improve the quality of herbal medicines. Since 1992, several workshops and training courses on the quality of herbal medicines and control of heavy metals in herbal medicine have been conducted in China. A collaborative research project on pesticide residue in medicinal plants was also conducted in China. The WHO has worked with interested countries to apply good manufacturing practices (GMP) to the manufacture of herbal medicine products.

3.2 China

China has a vast amount of land, with a population of 1.2 billion people. Over thousands of years, traditional Chinese medicine has developed a theoretical and practical approach to the treatment and prevention of disease. The first documented source of Chinese medical theory, the Huangdi Nei Jing ("Inner Classic of the Yellow Emperor") was written between 300 BC and 100 BC. It describes the diagnosis and treatment of a huge range of disorders and gives advice about healthy lifestyles, exercise, and diet which conforms remarkably well to current recommendations for the prevention of chronic disease.(Hesketh T and Zhu WX, 1997)
China is the only country in the world where Western medicine and the traditional medicine work alongside each other at every level of the healthcare system. Every city has a hospital practicing traditional Chinese medicine, and there is a plan for every county to have one. Based on State Administration of Traditional Chinese Medicine (SATCM) information, in 1998, there were 2,629 hospitals for TCM in China, including hospitals for TCM integrated with Western medicine (WM) and hospitals of national minority medicine with 260,000 beds in these hospitals. In addition, there were 288 clinics for TCM. TCM has made great contributions to the medical care. According to statistics, in 1998, 150 million outpatients and 2.87 million inpatients had treatment in hospitals for TCM. All the general or special hospitals of Western medicine (WM) in China have departments of TCM with outpatients amounting to 22% of the total in hospitals of WM and beds at the departments of TCM accounting for 5-10% of the total beds in hospitals of WM. TCM serves one third of outpatients and a quarter of inpatients in rural areas of China. (see Table 3a) More than 170,000 TCM workers are employed in over 50,000 clinics. The majority of the 970,000 rural physicians use both TCM and WM in treatment and prevention of diseases. At present, TCM has greatly expanded its coverage and it is playing an important and irreplaceable role in the medical and healthcare systems in China.

In general, although hospitals of TCM are generally smaller than those of WM in scale, each physician in hospitals of TCM treats more outpatients than those in hospitals of WM at the same level. If the two systems are to be truly complementary, more research in this area is essential to facilitate a more rational approach.

Traditional Chinese medicine has become a source of great interest to the international research community. It is acknowledged that many of the treatments have
enormous potential and could be utilized more widely. In China, the licensing and official regulation of traditional Chinese medicine and the Chinese Proprietary medicine was by the State Administration of Traditional Chinese Medicine (SATCM). It has its own medical schools, hospitals, and research institutes. The licensing of drugs and official regulation of their sale is equally stringent for Western and Chinese medicines. At each different level of administration particular administrative institutions were formed. Thus, an administrative system exists from top to bottom. (WHO, 1999) There are five different levels of legislation on traditional TCM from the state constitution (where the legal status of TCM is stipulated) to local laws in provinces and municipalities. New drugs have to be examined and approved according to the Drug Administration Law. New drug approvals require documentation of identification, cultivation, physical and chemical characteristics, pharmacology, standards of clinical use, stability, and preparation methods along with three reference samples. After approval, a New Drug certificate is granted an approval number. The factory is then permitted to put the product on the market. To date over 1000 new drug applications have been approved. (WHO, 2000) Further development of TCM in the future would include creation of new laws and revision of the existing ones, and enlargement of international exchange and cooperation programmes.

In China, the use of TCM is supported by central government, and it is practiced alongside ‘Western’ medicine at every level of healthcare, so that treatments with western and herbal medicine are often prescribed simultaneously. However, the largest expansion of traditional and herbal medicines is occurring in the industrialized cities, as patients look for alternative and less invasive approaches to healthcare. Furthermore,
patients often use herbal and traditional medicines without informing their 'Western' medicine healthcare practitioner.

Training in traditional Chinese medicine varies from family apprenticeships to three to five year university training at a college of traditional Chinese medicine, though the educational standard of these undergraduates is generally lower than their counterparts at the Western medical schools. All Western medical schools devote around 10-15% of curriculum time to traditional Chinese medicine, so all doctors have some traditional training. (Hesketh T and Zhu WX, 1997)

The introduction of a market based economy into the health care system in China since the early 1980s have meant that health professionals and hospitals have to generate most of their income, including the salaries of staff in many cases. Drugs can be charged at a mark up of 15%. Furthermore, staff in pharmacies is often untrained and unregulated medicines are widely sold and many products are available over the counter. It is estimated that only 20% of China's hospitals buy medicines from licensed state wholesalers, because the black market products are much cheaper. This complicated situation contributes to the numbers of adverse reaction to TCM reported in the Chinese literature every year. In China alone, there were over 600 reported cases in the past 30 years. (Wu YB, 1988)
Table 3a: Numbers of Hospitals of TCM, Beds and Physicians in China.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Hospitals of TCM</th>
<th>Hospitals of TCM above county level</th>
<th>Hospitals affiliated to colleges of TCM</th>
<th>Hospitals of TCM integrated with WM</th>
<th>Other hospitals of TCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>678</td>
<td>647</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>1986</td>
<td>2050</td>
<td>1576</td>
<td>31</td>
<td>12</td>
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</tr>
<tr>
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<td>2371</td>
<td>41</td>
<td>40</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>2629</td>
<td>2444</td>
<td>43</td>
<td>53</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Beds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>49977</td>
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<td>-</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td>1986</td>
<td>128784</td>
<td>113008</td>
<td>10931</td>
<td>3627</td>
<td>1218</td>
<td></td>
</tr>
<tr>
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<td>17603</td>
<td>8875</td>
<td>2770</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>260386</td>
<td>229000</td>
<td>17695</td>
<td>10863</td>
<td>2828</td>
<td></td>
</tr>
<tr>
<td>Physicians</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>73458</td>
<td>72097</td>
<td>-</td>
<td>-</td>
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</tr>
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<td>198158</td>
<td>169591</td>
<td>21263</td>
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<td>309401</td>
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<td></td>
</tr>
<tr>
<td>1998</td>
<td>397235</td>
<td>349261</td>
<td>27908</td>
<td>17054</td>
<td>3012</td>
<td></td>
</tr>
</tbody>
</table>

(Information from State Administration of Traditional Chinese Medicine, People's Republic of China)

Note:

1. According to statistics issued by the Health Ministry in 1996 (every 5 years), there were 71838 beds at the departments of TCM in hospital of WM (general, special and affiliated hospitals) in China in 1996.

2. "-" in the table indicates no available data.
Table 3b. Toxic Herbs Controlled in China and Taiwan. (Richard KJ, 1999)

<table>
<thead>
<tr>
<th>Toxic Herbs Controlled in China.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unprocessed main root of Aconitum carmichaeli</td>
</tr>
<tr>
<td>2. Unprocessed tuber of Aconitum kusnezoffii</td>
</tr>
<tr>
<td>3. Unprocessed lateral root of Aconitum carmichaeli</td>
</tr>
<tr>
<td>4. Unprocessed tuber of Typhonium giganteum</td>
</tr>
<tr>
<td>5. Unprocessed tuber of Pinellia ternata</td>
</tr>
<tr>
<td>6. Unprocessed root of Euphorbia ebracteolata and E. fischeriana</td>
</tr>
<tr>
<td>7. Unprocessed tuber of Euphorbia kansui</td>
</tr>
<tr>
<td>8. Tuber of Arisaema erubescens, A. heterophyllum and A. amurense</td>
</tr>
<tr>
<td>9. Root-tuber of Aconitum brachypodum</td>
</tr>
<tr>
<td>10. Unprocessed resin of Garcinia morella</td>
</tr>
<tr>
<td>11. Flower of Datura metel</td>
</tr>
<tr>
<td>12. Flower of Rhododendron molle</td>
</tr>
<tr>
<td>13. Unprocessed seed of Strychnos pierriana and S. nux-vomica</td>
</tr>
<tr>
<td>14. Unprocessed seed of Euphorbia lathyris</td>
</tr>
<tr>
<td>15. Unprocessed seed of Hyoscyamus niger</td>
</tr>
<tr>
<td>16. Unprocessed fruit of Croton tiglium</td>
</tr>
<tr>
<td>17. Body of Lytta caraganae</td>
</tr>
<tr>
<td>18. Body of Huechys sanguinea and H. philaeumata</td>
</tr>
<tr>
<td>19. Body of Mylabris phalerata and M. cichorii</td>
</tr>
<tr>
<td>20. Secretion of Bufo bufo gargarizans and B. melano-stictus</td>
</tr>
<tr>
<td>21. Arsenic</td>
</tr>
<tr>
<td>22. Mercury</td>
</tr>
<tr>
<td>23. Calomel</td>
</tr>
<tr>
<td>24. Mercuric oxide Realgar</td>
</tr>
<tr>
<td>25. Processed mixture of mercury, niter, and alunite</td>
</tr>
<tr>
<td>26. Crystals formed with mercurous chloride and mercuric chloride</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxic Herbs Controlled in Taiwan.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Root of Euphorbia fischeriana and E. ebracteolata</td>
</tr>
<tr>
<td>2. Root of Knoxia valerianoides</td>
</tr>
<tr>
<td>3. Seed of Hyoscyamus niger</td>
</tr>
<tr>
<td>4. Seed of Strychnos nux-vomica</td>
</tr>
<tr>
<td>5. Body of Mylabris phalerata and M. cichorii</td>
</tr>
<tr>
<td>6. Body of Buthus martensii</td>
</tr>
<tr>
<td>7. Calomel</td>
</tr>
<tr>
<td>8. Chalcanthite</td>
</tr>
<tr>
<td>9. Realgar</td>
</tr>
<tr>
<td>10. Arsenolite</td>
</tr>
<tr>
<td>11. Root of Aconitum carmichaeli</td>
</tr>
<tr>
<td>12. Tuber of Arisaema erubescens, A. heterophyllum and A. amurense</td>
</tr>
<tr>
<td>13. Root of Euphorbia kansui</td>
</tr>
<tr>
<td>14. Root of Aconitum coreanum</td>
</tr>
</tbody>
</table>

21
15. Tuber of Aconitum kusnezoffii
16. Root of Phhtolacca acinosa and P. americana
17. Stem bark and root bark of Melia azedarach and M. tooendan
18. Resin of Rhus verniciflua
19. Flower bud of Daphne genkwa
20. Flower of Datura metel
21. Seeds of Pharbitis nil and P. purpurea
22. Seed of Impatiens balsamina
23. Seed of Ricinus communis
24. Fruit of Croton tiglium
25. Seed of Euphorbia lathyris
27. Body of Tabanus bivittatus
28. Skin slough of Elaphe carinata, E. taeniura, and Zaocys dhumnades
29. Secretion of Bufo bufoargarizans and B. melano- stictus
30. Body of Scolopendra subspinipes mutilans
31. Sal-ammoniac

3.3 Macau

Traditional Chinese medicine (TCM) is a popular form of health care in Macau. Many of the people still consult doctors and practitioners of TCM. In addition, a very high percentage of the population regularly uses TCM in preparing soups, herbal teas or herbal tonics as supplementary food. In view of this situation, the Health Authority realized several years ago that it was crucial to establish laws and other regulations to improve the quality, efficacy and safety of these medicines, and to define the professional backgrounds and technical skills for trading in and dispensing pharmaceutical products, the most important aspects.

The first Chinese traditional pharmacy was registered in the Health Department in 1936, and by 1990, there were already 102 licensed traditional Chinese pharmacies. Since the law regulating licensing was very old, it could not deal with updated technological requirements developed in the last two decades. The new law, Decreta-Lei n 53/94/M, was enacted in November 1994 and aimed at better public health through adequate licensing of
medicines, import, export and wholesalers companies, dispensing pharmacies, and pharmacists and other technicians of traditional pharmacies. Based on this law, a list that includes 456 types of traditional medicinal material, which may only be sold in Chinese pharmacies of Macau, was prepared. The list consists of two sub-lists: Part 1. - toxic traditional Chinese materials; and Part 2. - common therapeutic traditional Chinese materials. Under this law, a simple but effective registration system for imported traditional medicines, the so-called "alternative registration system" started to be implemented. Only traditional medicines that have been registered in a country can be imported into the Macau market; but for those from Hong Kong, Singapore and other countries without a registration system at the moment, the importer must provide analytical certificates issued by the manufacturer or recognized laboratories. Throughout Macau, there are two hospitals but the government hospital is not providing TCM therapy but one of the health centers provides outpatient TCM clinic services.

### 3.4 Taiwan

Healthcare delivery in Taiwan has inherited the culture of TCM practices since early immigration in the late seventeenth century. (Huang WF, Wen KC et al, 1997) Taiwan's health care system has also been much affected by Japanese colonization (1895-1947) before the Nationalist Government fled to Taiwan from China in 1949. Contrary to western medical professionals who are educated through established medical school programs, TCM practitioners in Taiwan are produced from diversified backgrounds, mainly through apprenticeship, and a small percentage through an institutional education process. The two medical practice systems have been in coexistence for more than half a century. In Taiwan, 60% of the public uses multiple healing systems, including modern Western medicine, Chinese medicine, and religious
The medicines used in each type of medical practice generally remain within individual domains of modern medicines and TCM, respectively.

In Taiwan, the government has put great efforts into promoting the modernization of Chinese medicine. As a result, there are now people trained in both traditional Chinese and modern Western medicine who have made commendable contributions to the treatment of hepatitis, high blood pressure, cancer, and other diseases that are so far difficult to treat. In the area of pharmacology, researchers have evaluated effectiveness, analyzed, tested, and formulated concentrated dosages of Chinese pharmaceutical products for commercial sale. The prescriptions for these drugs are easier to fill, and are much more convenient for the patient than the old boiling method. In the area of basic science, modern research is being conducted in the field of pulse diagnosis. The three fingers used in the past to determine illness through the feeling of the pulse are now being replaced by pressure reactors. The pressure reactor converts variances in pulse pressure into electromagnetic waves, and registers them on a screen. These data are then analyzed by a computer. Many important new discoveries have been made through unique combinations of traditional and modern science.

Contrary to western medical professionals who are educated through established medical school programs, traditional Chinese medicine practitioners in Taiwan are produced from diversified backgrounds, mainly through apprentice-ship, and a small percentage through an institutional education process. The two medical practice systems have been in coexistence for more than half a century. The medicines used in each type of medical practice generally remain within individual domains of modern medicines and traditional Chinese medicines, respectively. The current practice of traditional
Pharmaceutical products, both in western and in traditional Chinese medicine dose forms are required to have premarketing approvals by the Department of Health in accordance with Taiwan's Pharmaceutical Affairs Law. Addition of unlabeled therapeutic substances other than the approved formula is strictly prohibited by law. The National Laboratories of Foods and Drugs (NLFD) functions as the technical gatekeeper for the Department of Health in food and drug analysis in Taiwan. It has been regularly monitoring the commercial packages of traditional Chinese medicines since the 1970s, as such prohibited adulterations of traditional medicines from Asian sources were reported occasionally in other countries. Samples are collected from Chinese medicine practitioners and drugstores periodically for inspection and to establish systematic analytical methods. Since 1975, the Food and Drug laboratory Bureau (FDB) of the Department of Health, Executive Yuan, has had an ongoing program of Traditional Medicine Analysis Survey. The purpose of this program is to identify unlicensed traditional medicine and the possible mixtures with western medicine. Between 1975 and 1981, among the 249 cases of unlicensed traditional medicine tested, 214 (86%) were found to contain "western medicines"(Deng JF, 1994).

Traditional Chinese medicines produced in China, however, usually receive no premarket approval by the Department of Health according to current regulatory practices in Taiwan, and the commercial distribution of these products is not legal. The existing channels to pursue drug safety control of traditional medicine in Taiwan include: (1) Consumer Protection Service Center at County Health Departments; (2) Consumer
Protection Association (CPA); (3) Medical Centers; (4) Department of Justice; (5) the Food and Drug Laboratory Bureau (FDB). (Deng JF, 1994)

The distribution of prescribed medicines or bulk materials has not been effectively controlled in accordance with the existing medical and pharmaceutical laws, mainly because the dispensing practices of physicians, inherited from the Japanese colonization, continue to prevail and because of a lack of commitment by the health authorities to a policy to change such practices. Therefore, the National Laboratories of Foods and Drugs initiated the program to monitor traditional Chinese medicines in 1992. This was the first time an island-wide approach was adopted to monitor, through hospital pharmacies, the prohibited adulteration of traditional Chinese medicines. The objective of this program was to screen samples of traditional Chinese medicines, suspected of adulteration that were used by the patients in several major hospitals. It was purported to serve as a basic model of incorporating hospitals into a safety-monitoring system for traditional Chinese medicines.

In Taiwan, herbs can be obtained from temples, night markets, street vendors, herb stores, traditional medicine doctors, and neighborhoods or relatives. People like to recommend the medicine they used to their relatives and friends without safety considerations. The general public and many of the traditional medicine practitioners also believe that the herbs are non-toxic and can be used in managing many health problems.

Younger people appeared to consider the value of TCM and were more likely to favor its use. Those with higher education levels were more likely to be familiar with TCM, but were also more likely to present a negative attitude towards its effectiveness.
3.5 Japan

Traditional medicines have been used effectively in Japanese society for more than a thousand years. Japanese traditional medicine may be divided into folk medicine and Chinese medicine from ancient China, the so-called Kampo medicine. Kampo Medicine is extremely popular in Japan, where the per capita consumption of herbal medicine seems to be the highest in the world. The drugs used are known as Kampo drugs. Each Kampo drug is a formula usually consisting of 5-10 different herbs. New features have been introduced into the practice of Kampo. Most of the modern ready-to-use forms of the original formulae are produced in industrialized granular, powdered or other forms based on the classical decoction. Introduced in 1957, it is now estimated that more than 95% of Kampo drugs used in Japan are taken in such a ready-to-use form as ethical drugs. Since 1961, the National Health Insurance (NHI) has covered almost 100% of the Japanese population. 43 Kampo drugs for ethical use were included in the NHI Drug Price Tariff in 1976, joining a few predecessors. More Kampo drugs were included later, and now 147 Kampo drugs (as formulae) are available as ethical drugs. As the Ministry of Health and Welfare (MHW) already registered these as drugs, their inclusion might be assumed to have been a matter of course. Their acceptance took place without clinical validation studies. In Japan, 80% of practicing physicians have experience using herbal formulas. Japan now produces 210 Kampo herbal formulas according to strict quality controls, 147 of which are covered by health insurance. (Yamada Y, 1991)

Along with the expanding consumption of the Kampo medicines in the clinical treatments, several side effects of the Kampo medicines has recently been reported by the collection of adverse reaction data of MHW, these side effects are important signals for believing the safety of natural drugs. (Satake M, 1998) Safety and efficacy have been
estimated based on general methods employed by modern medical science. In 1972, the MHW designated 210 formulas as over-the-counter drugs. This selection was based mainly on the experience of doctors actually practicing Chinese galenical medicine. In 1976, the Ministry specified 146 prescriptions as NHI applicable prescription drugs. In the case of an application for approval of a prescription other than those mentioned, specified data on safety, stability, comparison with other drugs, clinical test results, etc. are required to be submitted.

Plant materials have been characterized and classified into five categories, by the Ministry of Health and Welfare (MHW), Japanese Government, in 1971, which include three medicine divisions and two food divisions. (Satake M, 1998) New Kampo drugs are regulated in essentially the same way as Western drugs in Japan. They are regarded as a form of combined drug, and the same data required for new Western drugs are required for new Kampo drugs in the NDA. The time-consuming and expensive chronic toxicity tests and special toxicity tests such as for mutagenicity, carcinogenicity and teratogenicity depend on the possible length of treatment and indications that apply to them. Data for three-phase clinical trials are also required. For generic Kampo drugs, bioequivalence data are required, which may discourage development, because pharmacokinetic studies of Kampo drugs are difficult to conduct and bioassay methods are quite limited.

There was an improvement in the quality control of Kampo drugs in the mid-1980s. (Yamada Y, 1991) After a report on the situation of quality control, the Advisory Committee for Kampo Drugs was established in 1982 in close association with the Pharmaceutical Affairs Bureau of the MHW. The Pharmaceutical Affairs Bureau setting standards for the manufacture of Kampo drugs and quality control of Kampo drugs established a Working Group on the Quality of Kampo Drugs. This ensures that the
quality of herbs used in each original formula meets precise standards. The regulations also call for quality monitoring of specific ingredients, using at least two different chemical or physical methods to test them. Since October 1986, Good Manufacturing Practice (GMP), a standard required of pharmaceutical drugs issued by MHW in 1976, applies also to Kampo drugs. In addition, in 1988, the Japan Kampo Medicine Manufacturers' Association drew up self-imposed guidelines that take into consideration the unique nature of Kampo drugs. (Yamada Y, 1991) In 1985, guidelines for ethical extract products in oriental medicine formulations were developed, according to which the data from a comparative study of the extract and a standard decoction have to be provided by the manufacturer of an ethical extract product. Besides data on the crude drug and on the standard decoction prepared in accordance with the Chinese traditional medicine prescription, a comparative study has to describe the content of an indicator ingredient in the finished product, which is required to be more than 70% of the content of the indicator ingredient in the standard decoction.

The Ministry of Health and Welfare (MHW) has three major systems for the collection of domestic adverse reaction data. The first is the Adverse Drug Reaction Monitoring System under which 2,915 monitoring hospitals have been designated and requested to report cases of adverse reactions to the MHW. (Yamada Y, 1991) This is a "voluntary" monitoring system, and 1,158 cases of adverse reaction were reported in 1990, of which 15 cases pertained to Kampo drugs.

The second data collection system is the Pharmacy Monitoring System formed by 2,733 pharmacies. This system mainly collects data on cases of adverse reactions to over-the-counter drugs. In recent years, about 400 cases have been reported annually. Among these, reactions caused by Kampo drugs are the most common, though most of these
adverse reactions are minor, involving symptoms such as gastric discomfort and skin problems. Fifty cases were reported in 1989. (Yamada Y, 1991)

The third system is Adverse Reaction Reporting from Manufacturers. Several severe cases caused by "Shosikoto", including drug-induced hepatitis and pneumonitis, were documented at medical conferences and in journals and were reported to the MHW by the responsible company in 1990. In addition, since 1988, the newly drafted Good Post-Marketing Surveillance Practice (GPMSP) has been used on a pilot scale for Western drugs dispensed in Japan. When new Kampo drugs are approved and appear on the market, this guideline will also apply to them.

3.6 Singapore

Singapore's healthcare services are based on Western medical science. There is a role for TCM to play as a complementary form of medical care in Singapore. In Singapore about 45% of the population has consulted traditional Chinese medical practitioners. (Singapore MOH, 1995) Only those properly trained in TCM should be allowed to practice TCM. The local TCM training schools have made valuable contributions to the training of TCM practitioners in the past. However, the training they provide and the quality of trainees are not up to the standard of the TCM colleges in some other countries. Government and community efforts to upgrade the training of TCM practitioners and the standard of TCM practice in Singapore should be supported.

Apart from the control of poisons, the Ministry of Health has in the past not been actively involved in TCM practices in Singapore. This is largely due to the lack of expertise in this area and the relatively low usage of TCM by the population. However, with the development of TCM particularly in China over the past 2 to 3 decades, and increasing interest in complementary medicine the world over, public interest in TCM
has also risen. It is therefore timely to review the standards of training and practice of TCM in Singapore. In July 1994, the Minister of Health appointed a Committee to review the practice of TCM and recommend measures to safeguard patient interest and safety, and to enhance the standard of training of TCM practitioners. The Committee recommends that the two main local schools upgrade their part-time courses to a 3-year full-time diploma course or a 6-year part-time equivalent. Moreover, as the dispensers play an important role in the delivery of traditional Chinese medicines to customers and patients, the local TCM organizations are planning to provide refresher-training courses for existing dispensers. In future, dispensers may also be required to receive formal training and be registered. (Singapore MOH, 1995)

At present, the Government imposes minimal control on Chinese Proprietary Medicine. The enforcement activities currently carried out are targeted more towards safeguarding the public from toxic substances, prevention of adulteration and exaggerated claims. As most raw herbs have low toxicity and herbs containing toxic substances are already controlled under the Poisons Act, the control of raw CMM (in terms of the import, export, sale and distribution) can be maintained at the present level. The Singapore Trade Development Board has reported that Singapore imported US$ 79 million worth of herbs and ginseng in 1993 and re-exported $ 13 million worth of these products during the same year. (WHO, 2000)

3.7 Australia

Traditional Chinese medicine, best known for the practices of acupuncture and Chinese herbal medicine (CHM), has been practiced in Australia for many years and is being used now more than ever before. (Bensoussan A, Myers SP et al, 2000) In order to elevate the usage of TCM in Australia, the Victorian Department of Human Services
(DHS) (formerly known as Health & Community Services) sought tenders for research into the practice of Traditional Chinese Medicine (TCM) in that State at 1995. The first stage involved a major research project to collect information on the risks and benefits of TCM and the nature of the TCM work force; and to consider the need, if any, for registration of TCM practitioners and regulation of Chinese herbal medicines. The outcome was that the researchers recommended to the Australian Health Ministers Advisory Council (AHMAC) and to all State governments that occupational regulation of the profession of TCM proceed as a matter of urgency.

In Australia in 1996-97, the Commonwealth Health Insurance Commission paid over $17.7 million in Medicare rebates for 960,000 acupuncture treatments by registered medical practitioners. There has been a similar increase in the practice of other aspects of Traditional Chinese medicine, including herbal medicine, therapeutic massage, manipulation, dietary therapy and exercise therapy. (Bensoussan A, Myers SP et al, 2000) Moreover, complementary medicine services in Australia have grown to the extent that consumers now spend approximately twice as much on complementary medicines as their out-of-pocket contributions to pharmaceuticals. The resulting research report, Towards a Safer Choice: The Practice of Traditional Chinese Medicine in Australia, was launched in November 1996. The researchers found that the risks in the practice of TCM relate primarily to the practice of acupuncture and Chinese herbal medicine, which have resulted in at least five documented deaths in Australia.

With the growing use of TCM, regulatory authorities, health professionals, and the public need to understand the risks involved in TCM. Consumer complaints are dealt with by the Department's Therapeutic Goods Unit concerning herbal preparations, some of which had been adulterated with potent western medicines, along with the difficulties
experienced by the Commonwealth Therapeutic Goods Administration in controlling this area.

In Australia, products for human medicinal use must be placed on the Register of Therapeutic Goods [Therapeutic Goods Act 1989 (Cwlth)] in one of two categories -- "listed" or registered. Formulations can be listed for a small fee if they contain substances regarded by the Therapeutic Goods Administration (TGA) as being of low public health concern and comply with the Therapeutic Goods Advertising Code. (Drew AK and Myers SP, 1997) This restricts wording of claims to "assist" rather than "treat" and limits indications to minor self-limiting conditions. The products have to be manufactured by a TGA-licensed manufacturer following a recognized code of Good Manufacturing Practice. Labeling requirements are the same as those for registered products. Efficacy data have to be held by the manufacturer/distributor of such products and can be called on at any time by the TGA or the Australian.

Competition and Consumer (formerly, the Trade Practices) Commission. About 4500 plant-based products are listed; these are given an "AUST L" number, indicating their listing on the register and that they can be sold legally in Australia.

Registered products, which bear an "AUST R" number, contain herbs that are either restricted by the federal Standards for the Uniform Scheduling of Drugs and Poisons, those for which efficacy claims are more substantial, or those which are specified by the TGA as being of some health concern. For registration, which is more costly, appropriate documentation outlining clinical trial work must be submitted to the Traditional Medicines Evaluation Committee (established in 1991 -- soon to be replaced by the Complementary Medicines Evaluation Committee) which advises the TGA. Fewer than five CAM products have been evaluated in this way. Although Australia has
more regulatory controls than many other countries for CAM preparations, including herbals, most of these preparations are not exposed to the premarketing evaluation process that prescription and scheduled proprietary medicines undergo. Few CAM preparations can be patented, so they are not subject to the financial incentive that drives the pharmaceutical market. (Drew AK and Myers SP, 1997)

There is significant black market activity in the importation of unlisted and/or unregistered patent medicines. Deficiencies exist in the ability of the Federal Therapeutic Goods Administration to address both this problem and that of the importation of raw herbs. In order to control such a situation, a tighter regulation of importation of raw herbs and patent medicines are needed to protect the public adequately.

In Australia, reporting of adverse effects of any medication, whether alternative or conventional, is usually undertaken by a medical practitioner, pharmacist or dentist, who completes and forwards a "blue card" to ADRAC. Although the person reporting needs not assess the association between the medication and the adverse effect, this process enables trends to be spotted. ADRAC has received 154 reports relating to complementary and alternative medicine (CAM) in 25 years. (Drew AK and Myers SP, 1997)

A study performed in Australia in 1996 collected data on adverse events that occurred in clinical practice and have been self-reported by practitioners of TCM, including those who practiced only TCM and those whose primary specialty was not TCM. Totally four hundred fifty-eight (30%) of 1517 medical practitioners responded and the adverse reaction rate caused by TCM was 0.16%. (Bensoussan A, Myers SP et al, 2000)
3.8 Others Asian countries

In the Philippines, eight public hospitals provide acupuncture clinics and treatment. Several doctors at these hospitals have been trained in acupuncture with WHO support. (WHO, 2000) In Vietnam, 45 traditional medicine hospitals at national and provincial levels and 265 general hospitals provide traditional medicine services. In the Republic of Korea, a national medical law was passed in 1952 and traditional medicine was introduced into the health service as a parallel system alongside modern medical science. In the Republic of Korea, there are 11 colleges providing formal education on traditional medicine and there are about 9210 licensed traditional medicine doctors.

In Malaysia the market for traditional medicine is estimated at about RM 1 billion annually and more than 16,000 traditional medicine products have been submitted to the National Pharmaceutical Control Bureau, Ministry of Health, for registration. (WHO, 1998)

3.9 USA

The commercialized herbal industry is now blossoming in the United States. More than 500 different herbs are currently marketed in the United States, and Americans spent more than US$12 billion on natural supplements in 1997, nearly double the amount spent in 1994, while sales still continue to grow by more than 10% a year.

Increasingly, alternative therapies such as herbal products are being used in the United States. Approximately 25% of Americans who consult their physician about a serious health problem are employing unconventional therapy, but only 70% of these patients inform their physician of such use. (Eisenberg DM, Kessler RC et al, 1993)

Another national survey of alternative medicine performed in 1997 demonstrated that 42% of Americans used alternative medicine in the past year. (Eisenberg DM, Davis RB
et al, 1998) The result of the studies showed that female gender, age 35–49 years, college education, annual income greater than $50,000 and residence in the western quarter of the United States best characterizes users of alternative medicine. More than this, an investigative survey in 1997 showed that nearly 30% of Americans aged 65 and older were using alternative medicine.(Forster PJG, Calverley M et al, 1979) Almost three million people aged 65 and older took herbal therapies, with two million taking both herbal therapies and prescription medications. Those who use both prescription medications and herbal therapies are at potential risk for unintended adverse interactions.

In 1962, thalidomide was found teratogenic and Congress passed an amendment to the Food and Drug Act to increase assurance of drug safety and efficacy. While successful in general, the amendment initiated a regulatory dilemma regarding herbal therapies in the United States.(O'Hara M, Kiefer D et al, 1998) Before 1994, dietary supplements were regulated under the Food, Drug, and Cosmetic Act as either foods or drugs, depending on the intended application.(Rotblatt MD, 1999) For new foods or food additives, safety had to be demonstrated before marketing. A product was considered a drug if the manufacturer, including structure or function claims, made any therapeutic claims or if other evidence existed that the intended use was as a drug.

In 1994 the Dietary Supplement Health and Education Act (DSHEA) was passed by Congress and created a new category for dietary supplements. Under the act, supplements can claim to affect structure and function, but they cannot be intended to treat, prevent, mitigate, cure, or diagnose disease. Under DSHEA, herbs can be labeled and advertised as having certain healthful or nutritional properties as long as no therapeutic claims are made. Labeling can include suggested doses, despite the fact that few dose-response studies of herbal medicines have been conducted. Nonspecific
labeling statements such as these both confuse consumers and promote skepticism among healthcare professionals. Basically, manufacturers can allude to a therapeutic use of an herb, whether it is effective or not. Herbal medicines and other dietary supplements were not subject to approval by the FDA before marketing. (U.S. Public Law S, 1994) Theoretically, manufacturers should be able to substantiate their "structure and function" claims, but they are not required to share this information with the FDA or make it publicly available. In fact, manufacturers are not required to notify the FDA of label claims until 30 days after their products are marketed. The FDA can take action only once a supplement is on the market and found to be a significant or unreasonable risk to consumers. New dietary supplement labeling regulations, implemented in March 1999, ensure that labels should include complete ingredient listings in a format that is easy to understand, but manufacturers are not required to furnish information such as side effects, contraindications, or warnings. According to DSHEA, dietary supplements must include the following statements in the product labeling: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease." (Klepser TB and Klepser ME, 1999)

Quality control and manufacturing standardization are not required of herbal medicines in the United States. (Rotblatt MD, 1999) With guidance from the Commission on Dietary Supplement Labels (appointed by President Clinton and established by the Congress in the DSHEA), the FDA is considering other regulations, such as working to improve post market surveillance of dietary supplements, requiring pertinent warning statements in product information, and taking action to protect consumers and withdraw unsafe products from the market or take other protective
Partly due to the lack of GMPs, some dietary supplements contain impurities and adulterants. Unlike pharmaceutical companies, supplement manufacturers often lack personnel to obtain information on overdoses or adverse events.

Although the FDA regulates labeling, advertising of dietary supplements fall under the purview of the Federal Trade Commission. The FDA has suggested that manufacturers not make any claims with respect to their products and use in pregnancy. (O'Neil C and Fetrow C, 2001)

Numerous big pharmaceutical companies in United States and Europe were doing research on Chinese medicine. (Cyranoski D, 2001) The Center for Food Safety and Applied Nutrition of the FDA recently published a document entitled, "Dietary Supplement Strategy: Ten Year Plan." (FDA US, 2000) It outlines the strategy to reach its goal to have a "science-based regulatory program" that provides consumers with a "high level of confidence in the safety, composition, and labeling" of the products. The FDA developed six strategy teams that are organized into categories of safety, labeling, boundaries, enforcement, research, and outreach. The plan is to fully implement the DSHEA. The FDA's 10-year plan is an ambitious undertaking and will help solve many of the unresolved issues.

Furthermore, western medical professionals have also changed their perspective. The American Medical Association (AMA) resolved in 1995 that alternative / complimentary / herbal medicine should be included in the medical curriculum. Now, over 50% of the medical schools in the U.S. have a course on this subject.

Base on the fact that herbal remedies are considered food products under the DSHEA and hence they are not subject to rigorous clinical testing, as are pharmaceutical products. No manufacturing standards regulate the quality and production of herbal
remedies. All these factors have led to increase adverse reactions in patients choosing alternative therapies.

Adverse reactions associated with dietary supplements in USA, especially herbal remedies, can be caused by inherently toxic herbs, by herb overdoses, or by drug-herb interactions, especially with pharmaceuticals that have a narrow therapeutic index. They can also represent idiosyncratic reactions to herbs, such as allergic responses or anaphylaxis. Other adverse reactions can be due to adulteration caused by manufacturing and quality problems, misidentification, substitution of one herb for another, variability in the amount of active ingredients, inaccurate or incomplete label identification, improper processing and preparation, or contamination. Physicians who are treating patients suspected of herb-related adverse reactions are encouraged to contact the US Food and Drug Administration’s MEDWATCH program or the local poison control center, so that data can be collected and analyzed.

3.10 United Kingdom

The use of Chinese herbal medicines is increasing rapidly in Britain, and relatively few patients are now Chinese. (David AJ, 1994) This has led to problems, as most of those who now seek treatment are unable to distinguish between adequately and inadequately trained practitioners. Practitioners fall into three broad categories: those who have had a full training in the discipline (available only in China), those who have received limited training in Britain or China, and those who have no training. No data exist on how many practitioners now offer Chinese herbal treatment in Britain, and only some of them belong to a professional body. The main body is the Register of Chinese Herbal Medicine, which maintains minimum standards of training and practice. This body's main shortcoming is that virtually none of the fully qualified Chinese
practitioners currently belong to it.

In Great Britain and the Republic of Ireland there is no direct regulation of non-medically qualified practitioners: they can practice freely, subject to minor limitations imposed by various laws. (Fisher P and Ward A, 1994) For instance, they may not treat venereal disease or claim to be members of state registered health professions. A survey in the United Kingdom in 1980-1 suggested that there were 12.1 non-medically qualified practitioners per 100000 population—27% of the number of general practitioners. The number of non-medically qualified practitioners was estimated to be growing by about 10% a year. More recent evidence suggests growing interest in complementary therapies among general practitioners - surveys have shown 31-38% of general practitioners had received training in complementary therapies, with 15-42% wanting further training. (Fisher P and Ward A, 1994)

The herbs prescribed by practitioners of traditional Chinese medicine in Britain are generally purchased from wholesale companies that specialize in this trade. These companies import herbs from the People’s Republic of China either directly or through dealers in Hong Kong. The quality of imported herbs varies considerably, and great skill is needed to ensure that the correct herbs are provided to the practitioner. Some substitution of herbs is acceptable in China but can lead to problems if the wholesaler or practitioner is unaware of the substitution. Confusion may arise over the precise identity of the herb being ordered: no standardized nomenclature exists for herbs. Fortunately, the best wholesalers and properly trained practitioners are able to make fairly reliable checks, at least visually.

The acceptance and regulation of complementary medicine, including herbal medicines, varies considerably between Western countries. (De Smet PAGM, Hansel R
et al, 1993) Since 1991, the UK National Poisons Unit, based at Guy's Hospital, London, has taken a special interest in toxicological problems resulting from exposure to herbal medicine. They have recently published summary statistics from their database of adverse effects (Chan TY, 1997) The data were collected retrospectively from enquiries to the National Poisons Information Service from January 1983 to March 1989, and prospectively in 1991. It is unclear what degree of follow-up was undertaken to identify the products involved. There were 5,536 enquiries relating to vitamins, minerals, amino acids, fish oils, evening primrose oil, kelp, yeast, herbal preparations, royal jelly and slimming preparations. Of these, 656 (12%) were symptomatic at the time of the call. A total of 1,070 enquiries related to herb extracts, royal jelly, pollen, enzyme preparations and hormonal and glandular products, of which 270 (25%) were symptomatic, suggesting that this body of products is more likely to generate symptomatic adverse effects than the overall family of traditional medicines. The paper reports one adverse effect with a Chinese herbal product used for eczema that resulted in acute fatal liver failure.

3.11 Europe

Complementary or unconventional treatments are used by many doctors and other therapists throughout Europe. The major forms are acupuncture, homeopathy, manual therapy or manipulation, and phytotherapy or herbal medicine. The relative popularity of therapies differs between countries, but public demand is strong and growing. Over the last 10 years, Europe has witnessed a rapid growth in Traditional Chinese Herbal Medicine (TCM). Practitioners number around 11,400, while the annual market is estimated to total S$60 million. The European market for phytopharmaceuticals in 1995 was reported to be US $ 1,098 million and it was estimated that this would increase to
US $ 1,375 million by the year 2001. (Fisher P and Ward A, 1994) The European Community has developed a comprehensive legislative network to facilitate the free movement of goods, capital, services and persons in the Community. According to Directives 65/65/EEC and 75/318/EEC, pharmaceutical products require pre-marketing approval before gaining access to the market. Requirements for the documentation of quality, safety, and efficacy, the dossier and expert reports are laid down in Directive 91/507/EEC.

Direct comparisons of numbers and types of practitioners between countries, even within the European Union, are impossible because of varying legal situations. In most member states of the European Union, including Belgium, France, Spain, Italy, and Greece, the practice of medicine, except by statutorily recognised health professionals, is illegal. This is also technically the situation in the Netherlands, but the Dutch government has stated that it will not prosecute non-medically qualified practitioners unless there has been malpractice. In Denmark non-medically qualified practitioners may practice but the scope of their activities is restricted by law.

On 1 January 1994 two European Council directives—on homeopathic medicinal products and on homeopathic veterinary medicinal products—came into force. (Fisher P and Ward A, 1994) The directives are intended to ensure a single European market for these products. The provisions cover manufacture and inspection, marketing, and labeling. The most important provision is the establishment of a simplified registration procedure applying to medicines containing less than one part per 10,000 of the undiluted tincture or less than "1/100th of the smallest dose used in allopathy."

EC directive 65/65 on proprietary medicinal products has considerably constrained product licenses for herbal medicines. Concern at the possible carcinogenic effects of
pyrrolizidine alkaloids, which occur in a number of medicinal herbs, most importantly comfrey (Symphytum officinale), has recently prompted both the German and British governments to restrict the availability of these herbs. The case of comfrey highlights a regulatory problem—the plant is common in many European countries and is sometimes taken as a tea or vegetable. This problem remains unresolved; the European Court of Justice has had to adjudicate on whether vitamins and herbal medicines are foods or medicines. (Fisher P and Ward A, 1994)

3.12 Germany

In Germany, the Ministry of Health established the Commission E, a committee of doctors, pharmacists, scientists and herbalists to evaluate the safety, quality and efficacy of herbs. (Valli G and Giardina EGV, 2002) Commission E approves new remedies and publishes monographs with recommendations on dose, indications, contraindications, interactions and mechanisms. Physician prescriptions for herbs account for more than one-half of sales in Germany and nearly one-quarter are for cardiovascular conditions. (Fleming T and Montvale NJ, 2000) The German equivalent of the FDA requires absolute safety and has high standards for quality control. Because good clinical studies were generally not available until recently, however, approvals for herbal drugs were based on “reasonable certainty” of efficacy. (Rotblatt MD, 1999)

Germany has the unique Heilpraktiker (health practitioner) system. Originally introduced in 1939, it licenses practitioners who are not members of recognised health professions to practice provided they have passed an examination in basic medical knowledge and are registered. (Fisher P and Ward A, 1994) The system is administered by the Lander (provincial governments), and standards vary considerably between
regions. Heilpraktikers are specifically prohibited from practicing obstetrics, dentistry, and venereology. Nonmedical psychotherapists are regulated by the same system.

German has allowed some 600–700 herbal products to be marketed in that country. Approximately 70% of German physicians now prescribe phytopharmaceuticals to their patients, which serves to maintain one of the worlds' largest markets for herbal drugs. In 1978, the German government established an expert committee, the Commission E, to evaluate the safety and efficacy of over 300 herbs and herb combinations sold in Germany. For the past 3 decades, the German Health Authority has systematically reviewed the evidence on about 300 herbs and formulated clinical guidelines. An English translation of the resulting German Commission E Monographs was due for release in 1998. (O'Hara M, Kiefer D et al, 1998)

A positive trend towards the use of natural medicines in Germany could be shown in a study conducted by the Institute for Demoscopic Research Allensbach in 1997. According to this study, the group of users of natural medicines comprised two thirds of the German population (65%). In 1970, only 52% of the population were included in this group. The users estimated the risk attached to natural medicines was lower than the ones attached to chemical pharmaceutical products. 80% of the population believed that the risk of natural medicines is low, whereas 47% and 37%, respectively, of the population estimated the risk of chemical medicines as intermediate and great, respectively. (WHO, 1999) Although acceptance of traditional medicine has grown during the last few years, traditional medicine is not officially recognized in most countries. Even when a government has formally announced its support for the proper use of traditional medicine, this is not always accompanied by strong political, legal or material support. Doubts about the appropriate role for traditional medicine may remain,
and scientifically-based evidence on traditional medicine is being produced only slowly. There is also slow progress in developing quality standards and regulations on herbal medicines, in part because few resources are devoted to assessing traditional herbal remedies.
Chapter 4 - Herbal Adverse reaction – General Aspect

4.1 Overview

In many developing countries, traditional medicines are still the only available health services that can be afforded by the majority of the population. Traditional therapies are applied in public hospitals in China, Japan, the Lao People’s Republic, Mongolia, Papua New Guinea, the Philippines, the Republic of Korea, Singapore and Viet Nam. About 25% of modern pharmaceutical drugs have botanical origins, such as digoxin from foxglove, morphine from poppies, aspirin from willow bark, and tamoxifen from the Pacific yew tree. (Tyler VE, 1994)

Examination of today’s allopathic medications reveals that approximately 25–33% of currently available modern medicines in the United States have their origin in plants, animal, or mineral systems. Traditional medicine provided a first line and basic health service for people living in these areas. In industrialized countries, this picture is quite different because the services provided by modern medicine are readily available. For many people, conventional therapies may not be available or ineffective or may carry significant risk that the user may not be willing to accept. People begin to appreciate the application of natural products in preventing disease and improving quality of life. The use of traditional medicine has increased in popularity in recent years and is becoming a significant healthcare option for many people. In addition to herbal and homeopathic products, traditional therapy includes acupuncture, chiropractic therapy, yoga, meditation, and nutritional therapy. People nowadays are more health conscious than before as their standard of living has improved.
4.2 Traditional Chinese medicine

Traditional Chinese medicine (TCM) has a history of several thousand years and is one of a few forms of ‘alternative’ (as opposed to conventional) medicine that are endorsed by the World Health Organization. (Tang JL and Wong TW, 1998) TCM is a highly developed system, well documented and with its own body of theory.

Traditional Chinese medicine was exported to neighboring countries such as Japan, Taiwan, Republic of Korea and Viet Nam, which then developed their own variants. TCM makes a significant contribution to the health of the peoples of the Region. Its influence is growing as more people are prepared to look for alternative approaches to maintain their health. Western medicine is often regarded as more effective in acute situations or where the etiology is known, traditional Chinese medicine is more effective for immune conditions, chronic illness, or where the etiology is unknown.

Chinese herbal medicines (CHM) and Chinese proprietary medicines (CPM) continue to be widely used by people of Chinese origin throughout the world. The main reasons for their popularity appear to be: (1) a belief that CHM and CPM are more effective than Western medicines for common ailments such as excessive 'endogenous beat' (a concept in traditional Chinese medicine), cough, phlegm and indigestion; (2) a belief that most CHM, having been used for centuries in China and being of natural origin, are fairly harmless; or (3) an intention to save money and the bother of visiting a medical practitioner.

Recently, there has been a reported increase in adverse reactions due to herbs. The higher incidence is probably due to increase physician awareness and a better surveillance system. From 1915 to 1990, there were 2788 cases of adverse reactions associated with 460 different herbs reported in 408 Chinese medical journals. Prior to
1950, there were only 26 cases of adverse reactions reported, from 1950–1969, 147 cases, 398 cases in 1970–1979, and in the 1980s, 2217 cases.(Du S, Cao F et al., 1992) Of the total adverse reaction reports in the Chinese literature, herbs constituted approximately 40% of all products (herbs and pharmaceuticals). The most common herb-related adverse reactions were with aconite roots (576 cases), followed by *Tripterygium wilfordii Hook f.* (90 cases), and *Isatis tinctoria L.* (38 cases). In 1990, there were 46 cases due to aconite root related adverse reactions and 16 cases due to *Isatis tinctoria L.*

The recognition of toxic potentials of medicinal materials could be traced to the very early phase of the development of TCM. A prevailing view in the ancient times simply regarded all medicines as poisons or poisonous, for their ability to influence or modify the functions of the body. The Book of Rites (1100-50 B.C.) recorded that "physicians handled medical matters, and stocked poisons (poisonous herbs) for therapeutic uses." Another much quoted statement concerning the legendary Divine Plowman or Heavenly Husbandman is that he "tasted hundreds of herbs and found 70 poisons (poisonous herbs) in a day". A more explicit comment was presented in Ban Cao Hui Bian (15% A.D.) by Wang Ji who wrote that "medicines, in form of such kinds as plants, fishes, insects, fowls and beasts, with the ability to combat diseases, are all regarded as poisons".(But PPH. and Kan WK, 1995)

Information on the toxic potentials and other properties of Chinese medicines has been systematically recorded in some 330 editions of bencaos (Chinese herbals) issued in the last two thousand years. In the oldest herbal, the Divine Plowman's Herbal (Shen Nong Ben Cao Jing) which was compiled between 200 B.C.-200 A.D., herbs were classified into three categories:(But PPH, Hu SY et al., 1980)
(a) Superior category -- herbs of the superior category are non-toxic and are used for longevity and maintenance of health; they can be consumed regularly;

(b) Medium category-- herbs of the medium category are toxic or non-toxic and are to be used with discretion in convalescence and debility; and

(c) Inferior category -- herbs of the inferior category are toxic and should be used only when necessary in the treatment of diseases, but never for prolonged consumption.

Information on toxic potentials of Chinese medicines continues to appear in modern publications. Even the P.R.C. Pharmacopoeia (1990 edition) includes such information under each entry of herbs. For example, in the entry on the aconite Chuanwu (Aconitum cannichaeli rootstock), the herb is noted to be "very toxic", and cautioned that "normally the cured (processed) form is used and care must be taken if used for oral consumption."

The potent toxic herbs were using for thousands of years. The Yellow Emperor's Classic of Internal Medicine (Huangdi Neifmg, 1000-200 B.C.) noted that "in the use of very poisonous herbs for treating diseases, discontinue when the disease is cleared by six-tenths. In the use of poisonous herbs for treating diseases, discontinue when the disease is cleared by seven-tenths. In the use of slightly poisonous herbs for treating diseases, discontinue when the disease is cleared by eight-tenths. In the use of poisonless herbs for treating diseases, discontinue when the disease is cleared by nine-tenths. Then use foods such as the five grains, five fruits, and five vegetables for nourishment, to allow gradual recovery of the positive essence and elimination of evil factors."
4.2.1 Compound Prescriptions to Reduce Toxicity

In order to use such kind of toxic herbs to treat disease, some processing procedure was invented to control toxicity. Another approach of TCM to control toxicity is to apply herbs in compound prescriptions. Guiding principles have been established for strategic combination of several herbs in a compound prescription, for the simultaneous actions on various target organs or systems, and for the restoration of the whole body to the normal or “balanced” state. Toxicity of potent herbs may be eliminated or reduced by other herbs included in a prescription. For example, in many classical prescriptions using aconites issued by masters in Chinese medicine, honey or licorice are often included and considered helpful in reducing adverse reactions. Experience also led to the notion that certain herbs should not be used simultaneously, such as licorice in the presence of euphorbia (*Euphorbia pekinensis* root) as it has been noted that the two herbs together would induce adverse reactions.\(^{(Hsu HY, Chen YP et al, 1986)}\)

Properties of individual herbs, including their reputed functions, nature, and effects on organs and channels, are to be taken into consideration. Such combinations of herbs, each in small amounts, aim to maximize the beneficial actions of each herb and to minimize the adverse effects of the potent items.

4.2.2 Processing Of Chinese Herbs

Accepting that some herbs can be toxic or can cause adverse reactions, TCM deals with toxicity by curing (processing) the potent herbs. Various curing methods have been developed, including boiling, steaming, frying, soaking in water, defatting, fermenting, and denaturing with wine, vinegar, licorice, bile or urine. One of the important objectives in curing herbs is to reduce the toxicity of herbs.\(^{(Hsu HY, Chen YP et al, 1986)}\)
Traditional Chinese medicine is a science founded on the accumulated experiences of the ancestral Chinese. Chinese herbal drugs come from natural products. As they instructed, most medicinal herbs should be processed before use. Traditional Chinese medicine places great importance on the processing of herbal drugs. The term for the processing in Chinese is "Pao Zhi (Pao Chih, 炮製)".

As early as the book Huang Di Nei Jin (Huang Ti Nei Ching, 黃帝內經, The Yellow Emperor's Classic of Internal Medicine, 6274 B.C.), a processing method for Pinellia was recorded. Later, other books such as Shang Han Lun (傷寒論, Treatise on Febrile Diseases) and Ben Cao Gang Mu (Pen Ts'ao Kang Mu, 本草綱目, General Catalog of Herbs) followed suit. For example, Shang Han Lun records processing methods for various herbal components of 113 formulas. Today, different methods of herbal processing are still used in accordance with the therapeutic, dispensing and pharmaceutical requirements of the herbal drugs. In China, the pharmacopoeia has standardized the processing methods for different Chinese herbs. In Taiwan, traditional herbal pharmacies generally follow methods of processing mentioned in Lei Gong Pao Zhi Lun (Lei Kung Pao Chin Lun, 雷公炮炙論). In fact, despite the lack of scientific verification, today is processing methods for Chinese herbal drugs are mainly based on the ancestral experiences.

4.2.2.1 The Aims of Herbal Drug Processing

(1) Cleaning and increasing in purity is necessary to remove impurities and unwanted parts. For example, the skin of apricot kernel and peach kernel is removed before the kernels are used medically. (2) Reduction of toxicity and adverse effects is important for the toxic herbs such as aconite (烏頭). The raw pinellia causes throat
irritation, processing reduces or eliminates this adverse effect. (3) Promotion of therapeutic effects of some particular herbs. Processing with liquid adjuvants such as wine, vinegar and ginger juice can obtain designed quality and action of herbal drugs. For example, after wine processing, Dang Guei (當歸) can be easily extracted. The alkaloids of corydalis are hardly soluble in water, but after vinegar processing they become readily soluble, thus enhancing the therapeutic effect. (4) Alteration of drug properties also needed for some herbs and it often augments or alters drug properties after processing. For example, raw He Shou Wu (何首鳥) is cathartic, but after steaming it nourishes yin and invigorates liver. Moreover, processing could (5) improve flavor and have odor removing. Crude drugs are inevitably subject to contaminants and some have unpleasant odor. Processing cleans the drugs; prevents mould growth, rotting, and degeneration; removes the unpleasant odor and renders them palatable.

4.2.2.2 The Methods of Herbal Drug Processing

Certain herbal preparations require specific methods of preparation to reduce their toxicity. Herbal drugs usually undergo screening, cutting, and one or more of the following five basic types of processing. These techniques facilitate the storage of drugs, rendering drugs more suitable for therapeutic use. Processing methods have developed over a period of several thousand years.

4.2.2.3 External processing (simple treatment by trimming)

By this method the parts to be used are retained while the non-usable parts, contaminants, or impurities are removed by hand, by cutting, or by simple implements. This method entails various activities:
a) picking or selecting (杉選) to separates usable from non-usable parts; i.e. separating
    lonicera leaves from the flowers.

b) sifting or sieving (篩) to remove soil, sand, gravel and contaminants from the herbal
drugs.

c) winnowing or joggling (颠簸), because of the difference in density between the drugs
    and the contaminants. Thus they can be separated with a fan or winnower.

d) scraping (刮) off unwanted parts; i.e. removing the coarse outer cork layer of
    magnolia bark or cinnamon bark.

e) brushing (刷) off the attached hairs or contaminants; i.e. the hair on loquat leaves or
    the hairy roots of cyperus.

f) mashing or pounding (搗) and cutting (切) larger herb into smaller pieces.

4.2.2.4 Water processing

This method removes impurities from drugs by means of water, or renders drugs
soft and easy to cut, or reduces the toxicity of drugs.

a) washing (洗), soil and impurities are washed away from drugs with water. Close
    attention must be paid to the length of washing time to prevent loss of the active
    ingredients of the herbs.

b) immersing (浸) or moistening (潤) herb in water, softens them and facilitates cutting.

Sometimes adjuvants are added to water to remove the toxicity; i.e. alum is added
in water for processing pinellia.
c) soaking (泡), this process requires less time than immersion. Herbal drugs that can be readily cut by being subjected to brief water soaking, or the active ingredients in herb are not stable by immersion are processed in this way.

d) leaching (漂), herb may be stirred and leached in large amounts of water, water should be changed from time to time to leach toxic constituents or salt. This process applies especially to seaweeds and kelp.

4.2.2.5 Fire processing

According to the heating temperature, heating time, and methods of heating, this process has the following methods:

a) Frying (炒), drugs are stir-fried until the desired extent of heating is reached, i.e. frying till the herb cracks, to a yellow colour, charred or carbonized.

b) Frying with solid adjuvants (加輔料炒) to reduce toxicity, remove oil, moderates drug potency and improves taste; i.e. processing with bran, rice, shell powder, talcum powder and sand. The heating temperature is higher than that of stir-frying and more evenly heated with sand, and sand-heating is usually used for processing the drugs which are difficult to be heated, such as caparax (Gui Ban 龜板, Bie Jia 鰂甲).

c) Calcining (鍛), drugs are calcined with fire. This method involves open and anaerobic calcining; i.e. pyritum.

d) Wrap-up roasting (包烤), drugs are wrapped up in moist paper or wheat flour and roasted in a bed of red-hot ashes or in powdered talc that has been heated. Paper wrap-up roasting removes the oil content of the drugs; i.e. myristica is processed in this way.
e) Baking with liquid adjuvants (炙) in order to impregnate the drugs with adjuvants, such as honey, ginger juice, wine, vinegar, and salt. Processing with honey imparts a sweet taste, a mollifying action, and an aridity-moistening effect; with ginger imparts a warming and dispersive character for expectorants; with wine causes ascending and counteract chills; with salt leads drugs downward and entering kidney.

4.2.2.6 Water-fire processing

a) Steaming (蒸), drugs are steamed above boiling water; i.e. steaming raw rehmannia cures it; steaming aconite roots (Chuan Wu 川烏, Chao Wu 草烏, Fu Zi 附子) reduces their toxicity.

b) Boiling (煮), drugs are cooked by boiling alone or together with adjuvants; i.e. scute is boiled with wine to reduce the degradation of active components.

c) Boil-scalding (煬), drugs are dropped into boiling water, stirred a while, then taken out and their out skin removed; i.e. apricot.

4.2.2.7 Other methods

a) Defatting or ashing, drugs (often seeds) are compressed and strained to remove their oil content. The remaining portion is used medically; i.e. croton seeds.

b) Fermenting, some drugs, such as Liu Shen Qu (Liu Shen Chu 六神麴), are fermented.

c) Blending, drugs are blended with another drug or adjuvants; i.e. polygala is blended with liquorice, and He Shou Wu (何首烏) with black beans.

4.3 Practical Problem in Traditional Chinese Medicine

Extensive work of varying quality, clinical relevance and accessibility have suggested that, in vitro at least, individual chemicals derived from a variety of plants
may have antibacterial, antioxidant, anticytokine, antispasmodic, cytotoxic and neuromodulatory actions. Chemistry and bioavailability of herbal medicines remedies derived from herbs contain a huge range of compounds, some common to many plants (for example pyrrolizidine alkaloids) and others specific to individual plants. It is clearly difficult to extrapolate from a knowledge of the chemical composition of a given plant extract to its possible efficacy (or safety) in vivo. This will depend on a variety of factors including amounts of individual constituents in the extract (which may vary with the plant origin and method of preparation of the extract), interactions between individual constituents, and their pharmacokinetics, itself largely unstudied.

Conventionally TCM decoctions are prepared at home by the patient or the family. Therefore quantitative and qualitative control become a problem. Decoction is prepared in an unscientific way, e.g. various amounts of water used, different temperatures and duration of boiling, the “age of the plant,” (for plants and herbs, there is no expiry date). The patients invariably end up receiving different dosages of medicine each time, seriously affecting the therapeutic effect.

In TCM, herbal medicines are prepared by boiling, and re-boiling to produce a decoction. Through boiling for many hours, some of the active ingredients might have dissolved in the water to produce a therapeutic effect. Some preparations require mixing with alcohol; presumably some ingredients dissolve better in alcohol. It was found that many standardized herb extracts failed to deliver full potential. The therapeutic effect might have been different had the whole plant been used. Therefore it was postulated that in TCM many active ingredients work together, rather than one single ingredient. It is not known whether the ingredients have complementary, synergistic, antagonistic effect.
If a drug containing a single chemical extracted from herb is produced for use, it can no longer be considered as TCM practice. In TCM, it is the whole herb that is prescribed as formulation. Would the product still be considered as “herbal”? It is more akin to a novel and unlicensed drug! It is in fact a modern formulation with a pharmaceutical approach. The drug might have an unknown direct toxic effect! Another difficulty encountered in the study of herbal medicines is that the actions of herbs are multiple. One single herb has anti-microbial, hypotensive, choleric, diuretic, and sedative actions. Some effects are beneficial but others are undesirable, or even harmful. Some herbs have an opposing effect when given in different dosages. For example, Da-huang (rhubarb or Rheum officinale), when prescribed in a larger dose (1-5 gm of sennoside A) causes catharsis; but in a smaller dose (0.05 to 0.3 gm) causes constipation.

In TCM, one plant product is considered a single item in the prescription. But one plant product contains multiple pharmacological agents or chemical compounds. These chemical compounds may act on non-target organs the therapeutic effects of which may be considered undesirable. Furthermore, pharmacokinetic study of various components is extremely difficult.

4.4 Evaluation of herbal adverse reactions

To have a better understanding of the types of adverse effects and hence preventive measures associated with taking herbal medicines, a classification system has been proposed.

4.4.1 Type A reactions

Some agents in the Chinese materia medica have direct toxicity and predictable adverse effects, with a number considered sufficiently toxic to be included.
4.4.2 Type B reactions

These reactions are not related to the principal pharmacological properties of a drug and they do not improve when the dose is reduced — the drug has to be withdrawn completely. They are idiosyncratic reactions that occur in only a minority of patients. Although type B reactions occur in only a minority of the users, they can be so severe that withdrawal of the responsible agent from general drug use is warranted. An example of a herbal medicine, which has been repeatedly associated with type B reactions, is the Japanese Kampo medicine Sho-saiko-to. (De Smet PAGM and D'Arcy PF, 1996)

4.4.3 Type C reactions

When reactions develop during chronic therapy in a pharmacologically predictable way, they are called type C reactions. A herbal example is the occurrence of muscular weakness due to hypokalemia in long-term users of herbal anthranoid laxatives. (De Smet PAGM and D'Arcy PF, 1996)

4.4.4 Type D reactions

This category consists of certain delayed effects, such as teratogenic and carcinogenicity. (Ellenhorn MJ, Schonwald S et al, 1997; O'Hara M, Kiefer D et al, 1998)

4.5 Chinese Proprietary medicine

Many traditional Chinese medicinal prescriptions are now being formulated into tablets, pills, and liquids. (Richard KJ, 1999) These new formulations are known as Chinese patent medicines (CPM), herbal pills or liquids, or other terms to distinguish them from unprocessed medicinal plants, minerals, and dried animal parts. CPMs have gained wide acceptance by the Asian community in the past 20 years and have increased in popularity among non-Asian consumers who seek alternative therapy. They are sold
as over-the-counter medicines labeled with indications and instructions, and patients no
longer rely on the technical knowledge of a traditional Chinese medical doctor. Unfortu-
nately, many patent medicines manufactured in foreign countries contain toxic
ingredients such as mercury, lead, arsenic, or prescription and unapproved active
ingredients that may or may not be declared on the label.

4.6 Potential Risks for Herbal Adverse Reaction

When a case of herbal adverse reaction was suspected, the difficulty in establishing
the diagnosis was well recognized. Each preparation (herbs or compound medicines)
typically is made up of a number of ingredients that in turn consist of many different
chemicals. Very often, the nature and actions of these ingredients and their constituents
is large unknown. If the actual prescription cannot be traced, chemical analysis of each
ingredient is not possible. On the other hand, the success in making the diagnosis to
some extent will also depend on the clinician’s suspicion.(Chan TY, Chan AY et al,
1992)

The follow mainpoint were the potential risks for herbal adverse reaction:

4.6.1 Misidentification

Misidentification can result in erroneous associations being made, with potential
clinical implications. It is difficult to track and identify adverse effects of herbal
ingredients, as the plants can be named in four different ways -- the common English
name, the transliterated name, the latinised pharmaceutical name, and the scientific
name. It is essential that plants are referred to by their binomial Latin names for genus
and species; misidentification can occur when other names are used. Furthermore, plant
material can be misidentified at the time of the manufacturer's bulk purchase or when
wild plants are picked. The most notorious trouble is the toxic herb Guijiu (鬼臼) which
is derived from the root and rhizome of *Podophylium hexandrum* (P. emodi).

### 4.6.2 Lack of standardisation

Poor quality of herbs that require proper curing and of proprietary medicines is also found to be a major cause of herbal poisoning. The therapeutic/toxic components of plants vary depending on the part of the plant used, stage of ripeness, geographic area where the plant is grown, and storage conditions. Therefore, batch-to-batch reproducibility of plant material should be assessed in the production of marketed products, but, in practice, product variation in herbal medicines can be significant.

### 4.6.3 Contamination

During growth and storage, pesticide residues, microorganisms, aflatoxins, radioactive substances, western medicine and heavy metals can contaminate crude plant material.

### 4.6.4 Incorrect preparation / dosage

The processing of crude plant material carried out by a manufacturer, TCM practitioner or the patient is a major determinant of the pharmacological activity of the finished product. Certain herbal preparations require specific methods of preparation to reduce their toxicity such as *Aconitum carmichaelia*. Failure to specify these requirements clearly can result in severe toxic reactions including cardiovascular collapse and cardiac arrhythmias.

Another point to consider is that the activity of crude plant material may differ from that of the purified constituents, as some constituents may modify the toxicity of others.

### 4.6.5 Excessive dosage

Some of the cases of herbal poisoning are due to excessive doses. The beetles *Mylabis phaletata* and *M. cichoni* are known as Banmao (斑蝥) in Chinese medicine.
The recommended dose of this herb in the PRC Pharmacopoeia is 0.03-0.06 g. (But PP, 1994) A young unmarried pregnant woman tried to induce abortion by consuming a decoction prepared by boiling in water over 200 pieces of Banmao. The dose amounted to over 50 g. The woman went into shock and later died with acute renal failure, hematuria and bleeding. (Cheng KC, Lee HM et al, 1990)

4.6.6 Individual errors

Errors committed by individual patients can lead to herbal poisoning. A patient made a mistake to drink a spoonful of the orthopedic tincture Tonbigy (痛必治). This preparation contains extracts of aconites and other potentially arrhythmogenic glycosides and is intended for only topical application. The patient thus suffered serious arrhythmia.

4.6.7 Individual response

Each individual may have idiosyncratic responses to Chinese medicines that are generally regarded as safe to the average patients. A girl without any history of allergy presented with urticaria, puffy eyelids and difficulty in breathing, two hours after taking a soup made from Dazao, the fruit of Ziziphus jujuba. (Chan TY, Chan AY et al, 1992)

4.6.8 Unqualified herbal practitioner with wrong prescriptions.

Adverse events associated with TCM are usually associated with poor training and/or unethical conduct. Potential harm is likely to be minimized if the patient's response to treatment is adequately monitored by an appropriately trained practitioner, who will make appropriate referrals when necessary. Practitioners should have sufficient knowledge of western medicine to know when to refer a patient to a medical practitioner. In a fatal case of aconite poisoning, aconites were prescribed together with Chuanbeimu
from the bulb of *Fritillaria cirrhosa*.(But PPH, 1994) This two herbs should not be used in the same prescription, according to principles and experience of traditional Chinese medicine, as they would have adverse interaction resulting in higher toxicity.(Hsu HY, Chen YP et al, 1986)

4.6.9 Interaction with Western medicine

Also very little knowledge is available concerning the potential adverse reactions due to interaction of Chinese and Western medicines. We analyzed the herbs used by a patient suffering from multiple organ failure and coagulopathy in Australia,(Gorey JD, Wahlqvist ML et al, 1992) and found that the patient took both Western medication containing aspirin and herbs including Danshen (*Salvia miltiorrhiza*) and Tianqi (*Futus Panax potoginseng*) which have anticoagulatory effects.

4.6.10 Prolonged usage

Very little knowledge is known about the chronic toxicity of most Chinese herbs. In Belgium, a health clinic prescribed capsules containing a combination of herbs and pharmaceuticals as a slimming regimen. After enrolling in the program and taking the capsules for 6 months to three years, 70 women suffered progressive renal fibrosis; 30 of them had terminal renal failure. The case was identified to the presence of the herb Cuangfangji (廣防己) derived from the root of *Aristolochia fangchi*, which Lontains the nephrotoxic aristolochic acid.(But PPH, 1993; Vanherweghem JL, Depierreux M et al, 1993)

4.6.11. Coexisting disease

Coexisting disease is another important problem since diseases can alter the metabolism of the herbs and affect their pharmacology. Many herbs are found to have
special reaction when coexist with other disease. *Coptis chinensis/japonicum* and *Artemisia scoparia* are highly effective in displacing bilirubin from its serum protein binding site and should not be used for patients with hyperbilirubinemia or in infants who are deficient in glucose-6-phosphate dehydrogenase. As in previous chapter mention, Kernicterus in preterm infants with neonatal jaundice caused by huang–lian (*Coptis chinensis*) is probably due at least in part, if not all, to its major and active ingredient, berberine, which acts as both a potent bilirubin displacer and an inhibitor of bilirubin metabolism. Immunoallergic reactions can occur that may not be apparent. Germander has been associated with hepatitis and it has been suggested that the mechanism of the adverse reaction is consistent with an allergic reaction. Vasculitis has been associated with an herbal preparation containing Passiflora extract reflecting an idiosyncratic hypersensitivity reaction to Passion flower extract. Other allergic reactions associated with herbs ranged from rash to anaphylaxis. Individuals with genetic diseases may be at higher risk for toxic effects. Glucose-6-phosphate dehydrogenase deficient patients who ingest herbs containing *Acalypha indica* or *Salix caprea* have an increased risk of acute intravascular hemolysis.

4.7 Conclusion

Although some pharmacy publications included articles that encourage the sale of herbal medicines, editorials and commentaries in a number of journals and consumer publications preached caution, physicians and pharmacists have begun to recognize the relative safety and efficacy of at least some of the more well researched herbs on the market, many have concerns about contraindications, potential adverse reactions, and possible herb-drug interactions.
Chapter 5 - Substitution, Adulteration or Misusing with Toxic Herbs.

5.1 Overview

The term "adulteration" refers to traditional Chinese medicines that are tested and found to contain chemical substances not prescribed or labeled as part of the intended use. In traditional Chinese medicines (TCM), herbal raw materials are commonly used in combinations, which may allow the use of smaller doses of herbs with synergistic beneficial effects, and some materials may counteract the potential toxicity of others. Some herbal combinations that may potentiate toxicity have been recognized and can usually be avoided but interactions between herbal materials and standard drug treatments have not been widely studied and represent a potential area of concern.

Herbal poisoning has occurred in self-styled and weekend botanists who unwittingly picked the wrong herb. Besides this, it also conceivable that the careless gathering, storage, or distribution of medicinal plant material results in accidental substitution or contamination with another botanical. Inexpert or negligent herbal drug dealers may fail to recognize such a problem in time. (De Smet PAGM, Hansel R et al, 1997) Serious poisoning by herbal medicine can occur when an importer or retailer mistakes one herb for another, owing to similarity in appearance or confusion about the nomenclature.

The use of common names to label or to order plant materials often with devastating consequences. Croom pointed out in 1983 that Cimicifuga racemosa had 22 different common names offering ample scope for confusion and that it is important to record common names of plants because the scientific name is itself easily subject to
error particularly when recording traditional plant usage. He also pointed out that just as
a single species may have a number of common names so one common name may refer
to several different plants and he gave the example of Black Snake Root which could
apply not only to Cimicifuga racemosa, family Ranunculaceae but also to Asarum
canadense family Aristolochiaceae and to two Sanicula species of the family Apiaceae. It
is similarities in common names that are most likely to result in confusion e.g the name
Jia-pi for Periploca and as part of the Chinese name for Eleutherococcus.

The most tragic example of this confusion is the Fang Ji case. In the early 1990's, a
weight loss clinic in Belgium was dispensing a weight loss regimen that contained
numerous drugs and two Chinese herbs. The herbs used were Stephania tetrandra (han
fang ji) and Magnolia officinalis (hou po). However, instead of using Stephania
tetrandra (han fang ji), the incorrect herb Aristolochia westlandi (guang fang ji) was
used. After ingesting this combination of drugs and herbs over a long period of time,
several illnesses were reported. (for detail please see Chapter 12)

5.2 Adulteration by Guijiu

Adulteration of traditional Chinese medicine by a cheaper, and often more toxic,
substitute is also common. Herbal drug dealers may deviate from pharmacopoeia or
other authoritative specifications of botanical identity for various reasons:

Inadvertent dispensing of this type has led to two patients being given Guijiu (the
roots of Podophyllum emodi wall), which contains podophyllin, instead of the intended
longdancao (Gentiana species).(Ng TH, Chan YW et al, 1991) Both patients developed
podophyllin intoxication with severe gastrointestinal, renal, hepatic, and haematological
signs and permanent neurological damage. In China, there have been many warnings
about the use of Guijiu as an adulterant of longdancao. (Lin HR and Chen SJ, 1988; Chan TY, Chan JC et al, 1993)

In Hong Kong, in 1995 and 1996 respectively, three and nine cases of neuropathy have been reported after consumption of the adulterant mixed with Wai-Ling-Sin in 55 importers. (But PPH, Kwok I et al, 1996) Health searched for Wai-Ling-Sin in 55 importers and 867 retail outlets and found podophyllum in 22 of the 234 samples analyzed. The adulterated samples were imported by five importers and distributed to the retailers by 14 distributors. The poisoning is caused by ingestion of the herb known in Cantonese as Gwai-Kou, which is derived from the roots and rhizomes of *Podophyllum hexandrum* (also known as *P. emodi*; podophyllum). The herb Guijiu, called ‘Taoerqi’ in northwestern China, is derived from the roots of *Podophyllum emodi Wall.*, also known under the synonyms *P. emodi Wall* var. *chinensis Sprague* and *Sinopodophyllum emodi* (Wall).

The patients with podophyllum poisoning first developed serious vomiting and diarrhea. Patients complained of numbness of the arms and legs and difficulty in walking, and clinical findings included an absence of jerks, reduced plantar responses, lack of coordination of the fingers, ataxic and unsteady gait, poor standing balance, and impaired proprioception and vibration sense. Sensory responses and motor coordination returned partially over months. In the two cases that occurred in 1989, after ingestion of a high dose of podophyllum (probably greater than 20 g), encephelopathy was still present five months after the incident.

The Chinese Medicinal Material Research Center (the former of Institute of Chinese Medicine) in The Chinese University of Hong Kong developed two instant methods for spot-checking the contamination of the toxic herb *Podophyllum hexandrum*
in herb samples of *Clematis chinensis* (威靈仙) and this method was published in the journal Veterinary and Human Toxicology. (But PPH, Cheng L et al., 1997; Kwok IMY, Cheng L et al, 1998)

Two young persons developed gastrointestinal symptoms with vomiting and diarrhoea after taking a decoction supposedly prepared from the rootstock of *Gentiana rigescens* Longdancao (Gentianaceae). (Ng TH, Chan YW et al, 1991) On admission, they were lethargic and mute and became comatose 12 h later. They were treated in the intensive care unit with ventilatory assistance and haemoperfusion, but the condition was remained unchanged for the next 10 days. Both patients developed severe encephalopathy with extensive and permanent neurological damage - cognitive dysfunction, cortical atrophy, optic neuropathy, axonal peripheral and autonomic neuropathy. One was left with severe disability, and the other recovered with mild to moderate impairment of higher mental functions.

The decoction consumed by the 2 patients was intended to have been prepared from the herb longdancao. (Ng TH, Chan YW et al, 1991) According to the Pharmacopoeia of the People's Republic of China, the officially accepted plant origin of this herb is the root of *Gentiana manschurica* Kitag., *G. scabra* Bunge, *G. triflora* Pall. and *G. rigescens* Franchet. Commodities from the last species, generally regarded as a lower grade, are more specifically called "guizhou longdancao" (桂洲龍膽草) in the local herbal industry. Because of the apparent similarity in morphology, both the importer and retailer mistook guizhou for longdancao.

The herb Guijiu, called 'Taoerqi' in northwestern China, is derived from the roots of *Podophyllum emodi* Wall., also known under the synonyms *P. emodi* Wall var.
cinensis Sprague and Sinopodophyllum emodi (Wall). Podophyllotoxin, demethylpodophyllotoxin, sikkirinotoxin, diphyllin, demethyldeoxypodophyllotoxin, deoxypodophyllotoxin, kaempferol and quercetin can be found in this herb.

Longdancao has been in use through the centuries without report of major side effects, apart from mild diarrhea when given in excess. Pharmacognostic evaluation of the herb samples revealed that the samples were adulterated by the root of Podophyllum emodi Guijiu (Berberidaceae), which contain the neurotoxin podophyllotoxin. Chromatographic analysis of the herb samples, decoctions and corresponding gastric lavage contents confirmed the presence of podophyllin toxin in high concentrations.

Neurotoxicity of podophyllin manifests in a variety of ways. Cerebral involvement results in acute alteration of sensorium ranging from mild confusion to frank coma, as well as permanent impairment of higher mental functions.(Filley CM, Graff-Radford NR et al, 1982) In this 2 cases, the patients were suffered severe encephelopathy in the acute stage, followed by irreversible cognitive dysfunction. Pathological sequela could found in the first case, probably due to greater absorption of the toxin because gastric lavage was not performed. Cerebral atrophy could see in CT and MRI as a result of the toxic insult. Moreover, symmetrical sensorimotor polyneuropathy, autonomic neuropathy, dorsal radiculopathy and optic atrophy could found also. Electrodiagnostic studies in these 2 patients indicated axonal degeneration.

Subsequent investigation revealed that the supplier in China was responsible for the substitution and the herbal trade missed the error. Guijiu was reported to have been exported also as an adulterant or substitute of Weilingxin from China to Malaysia and Taiwan. Furthermore, the presence of podophyllum in some herbal preparations for use as laxatives or slimming preparations can lead to accidental poisoning.(Cullis JE, 1962)
5.3 Anticholinergic reactions Caused by Yangjinhua

"Yangjinhua" refers to the flower of *Datura metel* and *D. innoxia* (Solanaceae). In the herbal industry in Hong Kong, it is called "Naoyanghua". (Chan JC, Chan TY et al, 1994) It is noted for its antasthmatic, antirheumatic, anesthetic, and analgesic effects. It is employed in asthma, convulsion or epilepsy, and in rheumatism. It is also used as an anesthetic in surgery. The bioactive components in "Yangjinhua" are scopolamine, hyoscyamine and atropine. The typical features include confusion or coma, fever, tachycardia, flushed dry skin, dilated pupils, dry mouth and urinary retention. The herbs contain scopolamine, hyoscyamine and atropine. They are often used for upper respiratory problems such as chronic bronchitis or asthma or various painful conditions.

Four women in Hong Kong suffered drowsiness or confusion after the consumption of herbal decoctions. These cases improved after conservative management and were discharged after a few days. The four patients consulted the same TCM practitioner and had their prescriptions dispensed at the same herbshop. Examination of the herb samples revealed that the problem arose from “Lingxiaohua”, a herbal ingredient in the compound prescription. According to the Pharmacopoeia of the People's Republic of China, “Lingxiaohua” should be the flower of *Campsis grandiflora* and *C. radicans* (Bignoniaceae). In Hong Kong and other parts of southern China, this herb is frequently substituted by 'paotunghua' (the flower of *Paulownia fortunei* and *P. tomentosa*). It is indicated for upper respiratory tract infections, mumps, enteritis, dysentery and conjunctivitis. However, in these four cases, the actual flower found in the herb samples was “Yangjinhua”. The amounts of “Yangjinhua” range from 6 g in the drowsiness cases to 11 g in those of confusion. Thin-layer-chromatographic analysis confirmed the presence of atropine and scopolamine. A subsequent search by the police concluded that
the retailer at the herbshop made the mistake.

But et al. described a pediatric case of anticholinergic poisoning after the ingestion of 'naoyanghua'. (But BWM, Chan WH et al., 1999) Like her mother, this 7-year-old girl was found confused. Initial physical examination showed that the child was delirious. Her blood pressure was 160/110 mmHg and pulse was 90 beats/minute. Her body temperature was 35.2°C. She had facial flushing and both pupils were dilated. The urinary bladder was palpable. Gastric lavage was performed. Activated charcoal was given and supportive care was provided. It was subsequently noted that the child had drunk a decoction intended to be 'Lingxiaohua' on the night of admission. The child became fully conscious 12 hours after admission and blurred vision initially present subsided a day later.

The great majority of patients with (herb-induced) anticholinergic poisoning made a complete recovery. However, heat stroke, which carries a high morbidity and mortality, may occur in high environment temperatures and during intensive physical activity. With severe poisoning, intravenous physostigmine can be used to reverse the anticholinergic features. (Ramirez M, Rivera E et al., 1999)

*Datura metel* L. is widely distributed in south Asia and south China. Its flowers, leaves and seeds all contain atropine and other anticholinergic substances and are therefore poisonous. Ingestion of its flowers and/or seeds, either accidentally or as herbal remedies for some common ailments, can cause severe poisoning. (Yuan H and Tan D, 1991; Zhu T and Jiang PC, 1992) The clinical presentations may include dry mouth, dilated pupils, agitation, tachycardia, tachypnea, unsteady gait, hallucination, coma and even deaths. Moreover, four other Datura species, *D. innoxia* Mill., *D. stramonium* L., *D. tabula* L. and *D. fastuosa*, are known to contain anticholinergic
substances and have been used as Chinese herbal medicines. (He LY, 1982; Kang TG, Ji JY et al, 1987) In Chinese materia medica, 'yangjinhua' (the dried flowers of *D. metel L.*) is used for treating bronchial asthma and chronic bronchitis. Other indications include epigastric pain, rheumatic pain, pain from injury, toothache, surgical anesthesia, convulsion and psychosis. It has been given by the oral or intravenous routes or as cigarette smoke. The recommended oral dose is 0.3-0.6 g. 'Yangjinhua' contains 0.3-0.43% alkaloids, mainly scopolamine (85%) and hyoscyamine/atropine (15%). The alkaloid components and amounts vary greatly with the place of origin and season of harvest. The dried seeds of *H. Niger L.* contain 0.2% alkaloids, mainly hyoscyamine, scopolamine and atropine. The seeds of *H. bohemicus F.W.* contain hyoscyamine 0.04% and scopolamine 0.01%.

In addition, an outbreak of cholinergic poisoning were occurred in New York City in 1994. (Carl HK, Paul L et al, 1995) Seven individuals from three families of South American origin were affected. Signs and symptoms of illness included dry skin, hyperthermia, tachycardia, dilated pupils, agitation, and hallucinations within 3 days. Onset of illness in all cases was temporally associated with consumption of a tea that was labeled "Paraguay Tea" and was purchased from a grocery store specializing in South American foods. Paraguay tea, made from the leaves of the holly, *Ilex paraguariensis*, contains caffeine and theophylline and is a popular beverage in South America. Samples of the tea analyzed with gas chromatography contained belladonna alkaloids but neither caffeine nor theophylline. The tea is nontoxic with normal use, and the leaves do not contain belladonna alkaloids. The only reported toxic effects of Paraguay tea is a single case of hepatic veno-occlusive disease in Great Britain in a
patient who consumed large amounts of Paraguay tea over a period of years. (McGee JD, Patrick RS et al, 1976)

After analysis, the suspected herbal Paraguay tea has some unusual brown stems and branchlike appearance rather than the familiar leafy reddish mixture, and those who drank it stated that it did not have the taste of Paraguay tea. A number of plants are known to contain belladonna alkaloids. These plants are toxic to humans by ingestion and inhalation if smoked. Jimsonweed (*Datura stramonium*) may be the cause of such poisoning and this herb has a worldwide distribution. Ingestion of the leaves produces rapid onset of anticholinergic symptoms, with tachycardia, hypotension, hyperthermia, confusion, hallucinations, mydriasis, dry mucous membranes and skin, diminished bowel sounds, and urinary retention. In severe poisonings, seizures and coma can occur. Cases of human poisoning with plants containing belladonna alkaloids are reported with regularity.

For instance, it has become difficult to obtain real golden rod (*Solidago virgaurea*), but this species can be justifiably substituted with the related *S. gigan* tea or *S. canadensis*. It is obvious that such changes are only acceptable when the replacing herb is properly labeled with its correct identity.

A less honorable practice is the deliberate, undeclared substitution of medicinal herbs by inferior and/or cheaper species. Some years ago, a Belgian consumer organization reported that the majority of locally purchased peppermint herbs and capsules did not contain *Mentha piperita* at all, but the much cheaper species *M. crispa*. Likewise, most samples of lime-tree flower did not originate from *Tilia cordata* or *T. platyphyllos*, but from the inferior species *T. argentea*. Another eloquent example is the recent widespread availability of roots marketed as *Echinacea* but in reality coming from
the less expensive composite *Parthenium inlegrifolium*.

In many cases of botanical adulteration, direct toxicological implications for the user are unlikely or remain unknown. As the following examples show, however, every now and then a report appears in the literature about increased health hazards of a herbal medicine due to substitution or contamination with a toxic botanical.(De Smet PAGM, Hansel R et al, 1997)

Cases of suspected anticholinergic poisoning after ingestion of a broth of ginseng (*Panax ginseng*) bought in China were reported. The chemical content of ginseng varies greatly in different brands of the preparation. Ginseng preparations on the US market were reported to be adulterated with *Mandragora officinarum* (scopolamine), *Rauwolfia serpentina* (reserpine), and *Cola species*. (Siegel RK, 1977) These contaminants yield the well-known toxic compounds reserpine and belladonna alkaloids, respectively.

Seeds of the poison hemlock (*Conium maculatum*) have occasionally been found in anise seed, and roots of *Veratrurn album* are sometimes mislabeled as Primula roots. (De Smet PAGM, Hansel R et al, 1997) Conium seeds have well-known nicotine-like toxicity due to the presence of conime and related-alkaloids, and Veratrurn alkaloids can produce severe toxic symptoms, such as bradycardia and hypotension. (Lampe KF and McCann MA, 1985)

Fruits of the star anise tree (*Illicium verum*) may be adulterated with those of the related shikimi tree (*I. anisatum*). The latter are more dangerous than the former due to the presence of the toxic sesquiterpene dilactones anisatin and neoanisatin. (Zanglein A, Schultze W et al, 1989)

Belladonna root (*Atropa belladonna*) has been identified as a substitute for marshmallow root, an admixture to elfdock root, and as an adulterant of burdock
root. (De Smet PAGM, Hansel R et al, 1997) Burdock root tea preparations and other commercial herbal products that normally do not contain atropine-like substances have been regularly associated over the past years with delirium and the vegetative symptoms of anticholinergic poisoning.

5.4 Overdosage

The problem has often been related to use of excessive doses of these herbs. Herbs used commonly as food flavorings and apparently innocuous in small amounts can be toxic in large amounts.

5.4.1 Overdose of Aconitine

Aconite poisoning is one of the most serious adverse effects of CHM. The common species used in Chinese medicine are the rootstocks of *Aconitum carmichaeli* Chuanwu, *A. kusnezofii* Caowu, and *A. brachypodum* Xueshang Yizhihao, and the lateral root of *A. carmichaeli* Fuzi. (But PPH and Kan WK, 1995) They contain the C19-diterpenoid ester alkaloids (including aconitine, mesaconitine, and hypaconitine) and other biologically active substances. 'Chuanwu' and 'caowu' are regarded as 'interior-warming, chill-repelling herbs', which may increase general or local blood flow, improve energy metabolism and increase the digestive and absorptive activities of the gastrointestinal tract. For these reasons, they have been used to treat conditions such as rheumatism, arthritis, bruises, post-traumatic pain, fractures, hemiplegia, diarrhoea and acute abdominal pain due to 'pathogenic cold' (a concept in traditional Chinese medicine). In China, aconitine poisoning may be due to 'Fuzi' (the lateral root of *A. carmichaeli*) or five other less commonly used aconite roots as well as the more common 'Caowu' and 'Chuanwu'. (Ng YB, 1988) In Japan, 'Bushi' prepared from Aconitine species of Chinese and Japanese origin is the most important cause of aconitine
poisoning. Asians living in Australia and other Western countries may have surprisingly easy access to CHM containing aconite roots. (Kelly SP, 1990) In western countries, aconitine poisoning usually occurs after ingesting aconite roots as medicines or the wild Aconitum plant.

Raw aconite tubers are extremely toxic. For this reason, they are always 'processed' or 'cured' before use, with the aim of reducing the content of toxic ingredients. Aconites are processed by prolonged steaming or boiling in water, which leads to hydrolysis of the aconitone alkaloids into the less toxic derivatives benzoylaconitines and aconites. (Kosuge T and Yokota M, 1976) Soaking and boiling in water with or without the addition of chemicals may reduce the original alkaloid content by as much as 90%. Recommended dosages for processed aconites in the Pharmacopoeia of the People's Republic (1990 edition) are as follows; Fuzi 3-15 g, Caowu 1.5-3 g, and Chuanwu 1.5-3 g.

Several factors may be of importance in deciding whether poisoning will occur following the ingestion of 'chuanwu' and 'caowu'. The alkaloid contents and amounts in these herbs, which vary with the factors described above, will determine the severity and clinical presentations. The use of inadequately processed samples will increase the likelihood of poisoning. Some patient with tetraplegia could have taken a preparation with hypaconitine as the predominant constituent. Poisoning may occur if patients do not prepare the decoction as instructed. These different factors may explain why some of our patients were apparently well with their first dose. Perhaps, they hurried the preparation procedures for later doses or obtained the preparations from another shop. Severe poisoning has been reported after the consumption of a decoction made from 6 g of "processed" aconite root. A dose of 7-11 g each had been prescribed for our patients,
although the recommended dose has been lowered progressively to 1.5-3 g after reports of toxicity.

In the past five years, more than 35 cases of accidental herb-induced aconite poisoning have been managed in six public hospitals in Hong Kong. (But PPH and Kan WK, 1995) The decoctions or tinctures were used mainly for the treatment of musculoskeletal disorders including rheumatism, arthritis and post-trauma pain. Based on the analytical result performed by Chan TY(Chan JC, Chan TY et al, 1994) stated that all patients became unwell after taking the first dose of aconite roots (mostly 'chuanwu' and 'caowu') together with approximately 10 other herbs. Among patients in whom the prescription could be traced, a dose of 7-11 g each of 'chuanwu' and 'caowu' had been prescribed. The latent period between ingestion of decoction and the occurrence of symptoms ranged from 0.3 to 1.5 hours (mean 0.9 hour).

The great majority of patients presented with neurological features starting with burning sensation and paraesthesia in the mouth and tongue and progressing to paraesthesia in the extremities and generalised muscle weakness, cardiovascular features (hypotension, bradycardia or ventricular ectopics) and gastrointestinal features (nausea and vomiting). Moreover, the clinical presentation of poisoning due to “Chuanwu” and “Caowu” can be explained by the actions of aconitine and related alkaloids in various parts of the body. Aconitine is a known neurotoxin and cardiotoxin and acts on the voltage-sensitive sodium channels of the excitable membranes. It produces a state of persistent activation of sodium channels resulting in increased permeability to sodium and prolonged depolarization preventing repolarisation of the excitable membranes. Through its action on the sodium channels in the axons, aconitine can produce conduction block and muscle paralysis. Hypaconitine activates the sodium channels in
the axons more selectively and is more potent in producing the neuromuscular block than aconitine and mesaconitine. Through its action on the fast sodium channels in the heart, aconitine has digitalis-like cardiotoxic effects. It has a positive inotropic effect on the heart by prolonging the sodium influx during the action potential. The associated increase in intracellular calcium concentration via Na+/Ca2+ exchange induces and enhances automaticity, which, together with the increased vagal activity and slowed atrioventricular conduction, leads to arrhythmias. The slowed atrio-ventricular conduction may progress to complete heart block. The negative inotropic and cardiodepressant effects appear to be vagal as they can be blocked with atropine, and this is appropriate treatment when these features are present.

Aconitine also acts on the central nervous system. The stimulation of the medullary centre results in slowing of heart rate and reduction in blood pressure. A central action may be the explanation for the presence of hyperventilation in some patients. The numbness or paresthesia first starts in the mouth and tongue and then progresses to the extremities. Generalised convulsions have been reported. Other features include hypokalemia, metabolic acidosis, respiratory acidosis, respiratory alkalosis, renal impairment, hepatic impairment, and aspiration pneumonia. (Tai YT, But PH et al, 1993) The diagnosis of herb-induced aconitine poisoning is based on the history and clinical features. The management of aconitine is essentially supportive, as there is no specific antidote other than atropine for the features of cholinergic excess. All patients should be observed in the hospital because of the risk of ventricular arrhythmias, which are most likely to occur in the first 24 hours. Toxic symptoms occur after an average of 0.9 hour, suggesting of rapid absorption of the alkaloids by the upper gastrointestinal tract. Hence, measures to reduce absorption, e.g. the use of activated charcoal, might only be of use if
patients are seen soon after ingestion. Hypokalaemia and dehydration as a result of vomiting and diarrhoea should be corrected. Patients should be closely monitored for blood pressure and cardiac rhythm disturbances for at least 24 hours. It is not clear which of the anti arrhythmic drugs would be most effective.

After analyzes, the following problems have been identified in the 30-35 cases of aconite poisoning: (1) prescription of excess amounts of the aconites, (2) inconsistent quality control with suboptimal curing of the aconites, (3) inappropriate combination of herbs in the prescriptions, (4) nonadherence to recommended methods for preparation of the herbal decoction on the part of the patient, resulting in inadequate detoxication, and (5) individual differences in the ability to tolerate the potent components (Tai YT, But PPH et al, 1993)

5.4.2 Overdose of Liquorice ('gancao')

Liquorice (*Glycyrrhiza glabra*) and its extracts are commonly used in traditional Chinese medicine and in confectionery. Licorice root, widely used to flavor confections, has caused sodium and water retention, severe hypokalemia, hypertension, heart failure, and cardiac arrest. They contain glycyrrhizic and glycyrrhetinic acids, which may cause the syndrome of mineralocorticoid excess by inhibiting 11-β-hydroxysteroid dehydrogenase and hence conversion of cortisol to cortisone (Stewart PM et al, 1987). Licorice is present in clinically significant amounts in Lydia Pinkham's Compound, an over-the-counter preparation used to treat "women's problems", and at least one case of hypokalemic myopathy related to long-term ingestion of this compound has been reported (Lai F, Venna N et al, 1980). Patients have presented with symptoms of hyperaldosteronism after regularly consuming licorice in the form of candy.

Glycyrrhetic acid, a metabolite of glycyrrhizin produced by human microbial flora,
has a chemical structure closely resembling that of aldosterone. Most reports of adverse reactions have been associated mainly with its excessive use, and clinical presentations include hypertension, edema due to sodium and water retention, and hypokalemia. This herb may precipitate hypokalemic periodic paralysis attacks in patients with thyrotoxicosis. (Chan TY, Chan AY et al, 1992)

In traditional Chinese medicine, 'gancao' is used to treat pharyngolaryngitis, cough, palpitations, stomachache, peptic ulceration, pyogenic infections and skin ulcers. Liquorice intoxication is a well-known exogenous cause of hypokalemia. Liquorice abuse can thus lead to enhance cortisol action on the mineralocorticoid receptor in the distal tubuli of the kidneys. This will promote potassium excretion and sodium and water retention, leading to hypokalemia and hypertension, respectively. (Walker B and Edwards CRW, 1994) Peripheral edema in this patient may occur and the hypokalemia may lead to muscle pain and weakness, tetany, parasthesias, headaches and cardiac dysrhythmias. An example of a 44-year-old woman, attended the hospital because of irregular heart rhythm and she displayed repeated episodes of life-threatening torsades de pointes ventricular tachycardia after ingested moderately large amounts of liquorices every day for 4 months. (Eriksson JW, Carlberg B et al, 1999) The patient recovers after cessation of liquorice and receives symptomatic treatment. Another case is a young woman who had an acute embolic episode that affected her right upper limb after long time consumption of liquorice. (Lozano P, Flores D et al, 2000) The patient had a long lasting history, longer than ten years, of continuous licorice ingestion. Blood samples showed severe hypokalemia that caused EKG changes. Transesophagel echocardiogram discovered mild mitral valve prolapse. An axillo-brachial thromboembolectomy was performed after which distal pulses were recovered. The
combination of surgery and potassium supplements was successful in treating this rare and potentially life-threatening disease.

5.4.3 Overdose of Chansu

Chansu refers to toad venum from *Bufo bufo gargarizan* and *B. melanostictus* (Bufonidae). It contains the cardiotonic bufotoxins and used its anti-inflammatory analgesic and anaesthetic properties. (Tomlinson B and But PPH, 8-11 November 1994) The recommended dosage is 0.015-0.03 g. In Hong Kong, a herbal practitioner reported a fetal case due to over-prescription of 5 g of this herb, and the patient was finally died. It is also found in the proprietary Chinese medicine ‘Lushenwan’, which is a famous and popular remedy for upper respiratory symptoms or used as a topical preparation for skin infections. Overdosage of these tiny pills can cause cardiac glycoside toxicity in children and topical applications may cause local skin inflammation.

5.5 Misusing — Personal abuse

5.5.1 Banmao

The risk that a poisonous plant is used instead of the required medicinal herb might become particularly high when people without botanical expertise start to collect their own plant material. Every now and then, a case report in the literature makes it abundantly clear that the erroneous identification of self-selected plant material can result in serious or even lethal poisoning. In Hong Kong, a 23-year-old unmarried pregnant woman tried to induce abortion by consuming a decoction prepared by boiling in water over 200 pieces of Banmao. (But PPH and Kan WK, 1995) The dose of the herb amounted to over 50 g. A few hours after consuming the decoction, she presented to hospital with pain in the mouth and throat, nausea, vomiting, diarrhea, and abdominal pain. Physical examination showed swelling and multiple erosions of the mucous
membranes of the mouth, the tongue and the pharynx. Blisters were found in the lower limbs. Gastric lavage and intensive treatment were not useful, and her conditions continued to deteriorate. Sixteen hours after admission, the fetal heart sounds became undetectable and spontaneous abortion occurred nine hours later. She later went into shock with acute renal failure, hematuria and bleeding. She remained in deep coma and died two days after admission. Autopsy of the body found congested and bleeding patches in visceral organs. The amounts of cantharidin found in ante-mortem blood, ante-mortem urine, postmortem blood, and liver were 0.27 µg/ml, 4.45 µg/ml, 0.11 µg/ml, and 1.24 µg/g, respectively.

Banmao refers to the beetles *Mylabris phalerata* and *M. cichoni* (Meloidae). It has antivirulent, antulcerative, anticoagulant, and discutient actions. It is mainly used to treat malignant sores, abdominal mass, lymph node tuberculosis, thyroid tumor and rabies. It has also been used to induce abortion. The Pharmacopoeia of the People's Republic of China (1990 edition) (Pharmacopoeia C, 1990) noted that Banmao is very toxic and should be used with care for oral consumption and avoided during pregnancy. The recommended dosage of this herb is 0.03-0.06 g and the major bioactive component is cantharidin. Cantharidin was formerly used as a counter irritant and vesicant, in hair lotions for their rubefacient action, and in flexible collodion for the removal of warts. The lethal dose of cantharidin has been reported to be in the range of 10-60 mg, which is equivalent to about 4-24 pieces of the dried beetles.

5.6 Discussion

A botanist of appropriate training and experience should examine herbs. A qualified botanist to identify herbs may be difficult to find and other professionals
should be consulted. Schools for pharmacognosists, acupuncturists, naturopathic practitioners, and herbalists can serve as invaluable sources. Other experts in herbs include trade professionals like importers and herbal product manufacturers. Traditional identification methods may include organoleptic as well as visual. Two independent qualified experts should be utilized to confirm the identity of the herbs. Consistent terminology (Latin or scientific names) should be used in the identification process since familiar toxic agents may be hidden behind unfamiliar names.

After the suspected herbs have been visually identified, it is essential to confirm the identity of the herbs by laboratory analysis since misidentification, substitution, improper preparation, and contamination are all possible causes of adverse reactions. Confirmation can be done by pharmacognostical study of the morphology and anatomy of the herbs, chemical analysis, or bioassay. If an adverse reaction does not correspond to the known pharmacological actions of the identified herb, improper preparation and contamination should be considered and detailed chemical analysis should be pursued to determine possible adulterant(s).

Chemically defined constituents of medicinal plants can play an important role in the quality control of herbal products. Some constituents may serve a qualitative purpose; their presence in a herbal product assures that the product has been prepared from the correct botanical ingredient. If possible, one should monitor the constituents which are held responsible for the pharmacological activity of a herbal drug. When the active constituents are uncertain or unknown, however, quality control may be based on so-called chemical markers, i.e., constituents which are considered characteristic for the herbal ingredient. The Committee for Proprietary Medicinal Products of the EC has explicitly recognized the usefulness of markers in the quality assurance of herbal
remedies. This Committee specifies in its recent "Note for Guidance on the Quality of Herbal Remedies" that a marker may serve to calculate the quantity of vegetable drug or preparation in a finished product if that marker has been quantitatively determined in the vegetable drug or preparation when the starting materials were tested. (De Smet PAGM, Hansel R et al, 1997)

Traditional methods for analyzing natural products include thin-layer chromatography (TLC) and gas and liquid chromatography (GC and LC) linked to mass spectrometry. For example, a TLC check on the presence of menthofurane in a peppermint drug may verify that it comes from Mentha piperita and not from M. arvensis var. piperascens. Other constituents are used in a more quantitative way, that is to say, a certain level in a herbal remedy is taken as a measure of the amount of the herbal ingredient in that product. All three methods offer the advantage of screening for a wide range of polar and nonpolar compounds especially when the ingredients are unknown. However, the extraction process can be complicated and time consuming. In recent years, researchers have shown that supercritical fluid extraction is an alternative for many of these matrices and analyte.

For instance, in an evaluation of commercial ginseng products on the US market, ginsenosides (panaxosides) were determined to assess the amount of Panax root in each product. Capsules containing powdered root or slurries of ground root showed a total ginsenoside level comparable to dried root samples, but teas for infusion yielded only low concentrations, and tablets did not contain detectable ginsenosides. (De Smet PAGM, Hansel R et al, 1997)

Beside this, restrictive using and import of poisoning herbal medicine is important. Such kind of procedure can decrease the morbidity caused by toxic herbs. In China,
Taiwan and Hong Kong already setup laws and some toxic herbal name list for regulates the manufacture, sale and use of Chinese herbal medicines. In Hong Kong, the regulatory measures for Chinese herbal medicines include a licensing system for Chinese medicines traders and a registration system for proprietary Chinese medicines. For the former, retailers and wholesale dealers of Chinese herbal medicines and wholesale dealers and manufacturers of proprietary Chinese medicines are required to obtain the appropriate licenses from the Chinese Medicines Board of the Chinese Medicine Council for their businesses.

5.7 Conclusion

In the long term, the government should provide screening services to the public for traditional medicine. This monitoring program provides a mechanism to identify adulterated traditional medicines. As for the countries that have not established adequate regulations covering the distribution of traditional Chinese medicines, the appropriate health authorities should be made aware of the potential hazards in such illegal adulterations to the health of their public. Public education on health hazards of such adulteration should be advocated. In addition, legislative requirements on adequate labeling of dispensed medicines, showing particularly the name of the product or its ingredients, is essential in enforcing prohibition of such hazardous practices.
Chapter 6 - Chinese proprietary medicines—General

Aspects

6.1 Chinese proprietary medicines

6.1.1 Introduction

In recent years, as more extensive studies have been carried out on herbal medicines, the knowledge of the chemistry and pharmacology of their active principals has increased remarkably. (Ko RJ, 1999) With freeze-drying technology and advances in extraction methods, many traditional Chinese medicinal prescriptions are now being formulated into tablets, pills, and liquids. These new formulations are known as Chinese proprietary medicines (CPM).

Owing to the extensive modifications of drug formulations and chemical extraction from an expanding range of natural products, more cases of adverse reactions have been reported in recent years. (Li X and Yu QH, 2000) Misuse, mislabeled and inappropriate preparations may lead to serious health consequences.

CPMs have gained wide acceptance by the Asian community in the past 20 years and have increased in popularity among non-Asian consumers who seek alternative therapy. They are sold as over-the-counter medicines labeled with indications and instructions, and patients no longer rely on the technical knowledge of a traditional Chinese medical doctor. More than this, the main or unapproved active ingredients that may or may not be declared on the label. (Li X and Yu QH, 2000) The true incidence of side effects to herbal products is not known because the systems for reporting adverse reactions are limited.
CPM-related adverse reactions can be caused by natural toxins, heavy metal poisoning, drug interaction, and drug overdoses. (Horowitz S, 2000) In traditional Chinese theories, CPMs often contain cinnabar (mercuric sulfide), realgar (arsenic sulfide), or litharge (lead oxide) as part of the traditional formula. Other common toxic herbal ingredients found in the imported patent medicines include borneol (similar to camphor), aconite, Bufo secreta (toad secretion), mylabris, scorpion, borax, acorus, and Strychnos nux vomica (strychnine). Since certain herbs are highly potent, both Taiwan and China have required control of their sales. In Hong Kong, nearly 3,300 kinds of Chinese proprietary medicines were available on the market with about 500 being locally manufactured. (Medicine WPOC, 1991)

Although western medicine has already become the mainstream of Chinese modern medicine, it would stride forward significantly as the renovation of modern science and technology as well as the further development of life science, but it still is confined by the unconquerable limitation of ideological mechanical materialism. (Zhou JH, 1999) Chinese proprietary medicines are quite popular now in worldwide because of its convenient and therapeutic effect. There is a widespread belief in the therapeutic values of Chinese proprietary medicines, even among highly educated elite groups. A proportionate stratified random sample of 109 full-time faculty members of Chinese origin in The Chinese University of Hong Kong revealed that, in terms of over-the-counter proprietary medicines kept at home for self-medication, 13% reported that they had more Chinese than Western medicines, 52% kept as many Chinese as Western medicines, and 35% had more Western than Chinese medicines. (Lee RP, 1980)

The Pharmacy and Poisons Ordinance (Cap. 135), which specifies the regulations for pharmacists, pharmacies and pharmaceuticals, simply waived such requirements for
Chinese medicines. The last paragraph in that Ordinance states that “Nothing in this Ordinance shall apply to the sale, manufacturing, dispensing or compounding of traditional Chinese medicines as listed in the Chinese Herbal Materia Medica (本草綱目), or which are made from herbs customarily used by the Chinese people”. In this context, the Government did very little on Chinese medicines except occasionally taking random samples to check if they contain Western pharmaceutical and excessive heavy metals. This laisser-faire practice has sometimes left rooms for discrepancies or even abuse.

Because physician’s dispensing of western and traditional Chinese medicines has been in existence for nearly half a century, policy makers in the Department of Health have been quite passive in pursuing the release of prescriptions from medical practitioners to community pharmacies. The missing requirement of adequate labeling on packages of dispensed medicine is an intentional omission: It represents a denial of the public’s right to safe and effective medications. Without an affirmed policy on the right to adequate product information and labeling, all governmental efforts in monitoring and persecuting such misconduct as adulteration of medicines by practitioners of traditional Chinese medicine will meet with only limited success. (Huang WF, Wen KC et al, 1997)

6.1.2 Herbal Injection and Infusion

In western pharmaceutical medicine, drugs are given in a 'pure' form with a single active ingredient and have different kind of administrations. In China, herbal medicine is well developed and is marketed as pills, capsules, or tinctures and injection form also and was a kind of popular treating method in the hospital. The transformation of herbal
medicine from crude material to a modern injection form illustrates principles of modern pharmacology that have helped make herbal medicine safer and more effective. However the percentage of herbal adverse reaction from the injection form were still greater than form of medicines. In China, a retrospective analysis was reported in 2000 stated that nearly 42 % of herbal adverse reaction in 1096 cases was caused by injection.(Di SL, 2000) (Table 6a) It may relate to the following reason.

6.1.2.1 Variety & Processing

Controlled, high quality, manufacturing conditions, including authentication of ingredients, are essential to the production of safe, high quality herbal medicines. Improper processing and manufacturing can influence the pharmaceutical effects. Nonspecific labeling statements such as these both confuse consumers and promote skepticism among healthcare professionals. Basically, manufacturers can allude to a therapeutic use of an herb, whether it is effective or not. Theoretically, manufacturers should be able to substantiate their “structure and function” claims, but they are not required to share this information with the government’s pharmaceutical laboratory or make it publicly available. Poor quality-control personnel or lack of standard procedures to evaluate their products for its purity and reliability. Therefore, batch-to-batch variability is a serious problem with herbal preparations.(Gazella JG, Pinto JT et al, 1987) Factors predisposing to pharmacological adverse reactions may related to the impurities and unknown chemical substance. It was because herbal preparations are usually not evaluated for purity and consistency of active components, they often contain accidental contaminants.

6.1.2.2 Stabilization

Clearly, plants have ingredients with therapeutic activity, but their preparations
must be standardized to yield consistent products, which therefore can be given in doses that are maximally safe and effective. The uncertain composition of many herbal materials raises questions about their safety and stability. More than this, with the limitation of technical support, it was difficult to maintain the pH value and the stability for the mixed herbal solution, especially when mixing with glucose or normal saline solution for dilution. In addition, some unvisible or unknown chemical reaction may occur and caused adverse reaction after mixing the injection material for clinical usage.

6.1.2.3 The Molecular Size

The molecular size of the herbal material was large and insoluble in in water, especially when mixed with other chemical molecule or disturbed by acid-base inequilibrium. Insoluble molecule was form with different solubility and the molecule will obstructed the capillaries. In addition, the molecule may irritate the autoimmune system to start defence mechanism and cause anaphylactic reaction.

Table 6a. Adverse Reactions Caused by Herbal Injection in Tientsin, China during 1997-2000. (Di SL, 2000)

<table>
<thead>
<tr>
<th>Name of Herbal Injection</th>
<th>No. of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xie Sai Tong ZhusheYe (血塞通注射液)</td>
<td>7</td>
<td>18.92</td>
</tr>
<tr>
<td>Sheng Mai ZhusheYe (生脈注射液)</td>
<td>6</td>
<td>16.22</td>
</tr>
<tr>
<td>Fufang Danshen ZhusheYe (複方丹參注射液)</td>
<td>5</td>
<td>13.51</td>
</tr>
<tr>
<td>Shuang Huanglian ZhusheYe (雙黃連注射液、粉針)</td>
<td>5</td>
<td>13.51</td>
</tr>
<tr>
<td>Qing Kai Ling ZhusheYe (清開靈注射液)</td>
<td>4</td>
<td>10.81</td>
</tr>
<tr>
<td>Huang Ji ZhusheYe (黃耆注射液)</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Deng Zhan Hua ZhusheYe (燈盏花注射液)</td>
<td>3</td>
<td>8.1</td>
</tr>
<tr>
<td>Can Mai ZhusheYe (參脈注射液)</td>
<td>2</td>
<td>5.40</td>
</tr>
<tr>
<td>Ge Gen Su ZhusheYe (葛根素注射液)</td>
<td>2</td>
<td>5.40</td>
</tr>
<tr>
<td><strong>Total 37 cases</strong></td>
<td></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
The allergic reaction always happened in venous injection and the patient may have fever, allergic rash and even shock after injection. The duration of episode between several minutes to several days and not related to the dosage. In order to decrease the episode of adverse reaction, some standard protocol and instructions were recommended to all hospitals in China to assess herbal injection. (Di SL, 2000) For instance, the period of using herbal injection therapy was suggested within the period of treatment and should under the guideline to practice. More than this, pharmaceutical manufacturer should keep quality control in the major position and the production should under GMP standard to decrease the possibilities of accidental contamination. In China, all proprietary Chinese medicines will be assessed and registered by State Administration of Traditional Chinese Medicine (SATCM).

6.1.3 Adverse Reactions Caused by Chinese Proprietary medicines

6.1.3.1 Aconitine poisoning

In China, poisoning may occur after taking CPM containing aconite roots. (Chan TY and Critchley JA, 1996) So far, there have not been any reports of CPM-induced aconitine poisoning from outside China but it is conceivable that Western-trained physicians would miss such aetiology.

6.1.3.2 'Nan Lien Chui Fong Toukuwan'

The great majority of reports of poisoning by CPM in Western countries were due to 'Nan Lien Chui Fong Toukuwan', which was sold as tablets/capsules for the treatment of various musculoskeletal disorders. (Anonymous, 1975; Ries CA and Sahud MA, 1975; Brooks PM and Lowenthal RM, 1977; Forster PJG, Calverley M et al, 1979; Offerhaus L, Dukes MN et al, 1979; Yuen S and Lau-Cam CA, 1985)

It has now been withdrawn in most countries. Depending on the manufacturer and
the country of export, adulterants of this preparation included aminopyrine, phenacetin, phenylbutazone, indomethacin, mafenamic acid, diazepam, hydrochlorothiazide, dexamethasone, mercuric sulphide and heavy metals such as lead and cadmium. Consequently, there have been cases of agranulocytosis following ingestion of some of these preparations. (Chin J and Fleming DS, 1974)

6.1.3.3 'Jin Bu Huan'

'Jin Eu Huan' is manufactured in China and is used as a sedative and analgesic. There were two reports in 1993 of severe toxicity following the use of this CPM in the U.S.A. (Horowitz RS, 1993; Woolf WGM, 1993) Life-threatening bradycardia of rapid onset and central nervous system and respiratory depression were seen in three children while in three adults, liver damage developed. (For detail please see Chapter 11. -- Review of Herbal Hepatotoxicity)

6.1.3.4 'Baoyingdan'

Two babies developed extrapyramidal symptoms including retrocollis, stiffening of the body, weak cry and marked tremor, a few hours after taking a bottle of Baoyingdan (Po Ying Pills). (But PPH and Kan WK, 1995) One of the babies had also been prescribed maxolon 0.25 mg by a general practitioner 12 hours earlier. (Chan TY, Chan JC et al, 1993) There is a possibility that the extrapyramidal symptoms were caused by herbal ingredients in the Baoyingdan. The presence of western drugs that could cause such symptoms was not excluded.

6.1.4 Heavy metals in CPM

Details please see Chapter 15. -- Adverse Effects of Heavy Metal contamination.

6.1.5 The Necessarily to Develop Randomize Herbal Clinical Trial

The effectiveness of a modern drug is ultimately judged by the results of clinical
trials. Ordinarily, such trials are designed to test the assumption that a drug's pharmacologic activity will favorably affect a disease process, which in turn is viewed in terms of a physiologic model. Clinical trials yield convincing results, however, only if they are conducted in accordance with principles that, for example, ensure elimination of bias and reduce the possibility that results occurred merely by chance. Trials must also use drug preparations with consistent pharmacologic properties. These principles apply to all drugs, whether they originate as traditional remedies or in precepts of molecular biology. Randomized clinical trials have become the gold standard for evaluating the efficacy of a drug and have assumed a similar status for evaluating an herbal remedy.

Although the methodology of herbal trials is improving, some studies cited in herbal compendia have shortcomings. One problem is that results of herbal trials often do not reach statistical significance because they enroll fewer participants than trials of a conventional drug, and the role of chance may be overlooked in interpreting such trials.

Yet, when the active principle of an herb is not known and there is no accepted method of standardization, a clinical trial offers an attractive approach to evaluating the activity of an herbal preparation. In other words, instead of standardizing a medicinal herb before it is tested in a clinical trial, the results of a clinical trial might be used to identify an effective herbal formulation. This strategy, however, requires both a consistent formulation and a large study sample.

6.1.6 Recommendation

Understandable warnings in the package insert can certainly help to reduce the risk of inappropriate uses and adverse reactions.(De Smet PAGM, Hansel R et al, 1997) Besides improved their products quality, herbal pharmaceutical company should actively by banning unsafe remedies and by discouraging unsafe practices. Unfortunately, the
introduction of herbal medicine-like products into the market is not adequately monitored in various countries. This unsatisfactory situation could be greatly improved by the creation of a special licensing system for herbal medicines. Such a system would not only help to keep out preparations from herbs with known unsafety but it would also provide a valuable tool to improve herbal product quality. (De Smet PAGM, 1995)

Moreover, limited the indication of herbal medicine is useful and the governmental health department was not necessary to take risks by always require a full ban of some specific herbal ingredients.

In order to improve the quality of herbal medicine, develop analytical technique to rapidly screen for undeclared toxic and therapeutic substances in CPM is necessary. Such as using high performance liquid chromatography-diode-array detection method was developed and used to screen for undeclared therapeutic substances in CPM. In addition, solute identification by comparing the analytical data (UV spectra, retention time and relative retention time) and Gas chromatography-mass spectrometry was always used as a confirmation method. (Liu SY, Woo SO et al, 2001) In recent years, researchers have shown that supercritical fluid extraction is an alternative for many of these matrices and analytes also.

Herbal companies should be legally bound to report suspected adverse reactions to their products to the competent authorities, just as is now required from synthetic drug manufacturers. (De Smet PAGM, 1995)

6.1.7 Conclusion

Systematic efforts to collect, evaluate and disseminate scientific data about the safety or unsafety of herbal medicines should be continued and expanded. In addition to collecting data about real herbal medicines, it would also be useful to produce and
circulate exhaustive lists of those herbal products, which have been shown to contain
dangerous amounts of heavy metals or pharmaceuticals. Update herbal OTC drugs data
collections must also include non-Western herbs, not only because Western doctors are
increasingly confronted with non-Western patients who seek refuge in traditional
remedies of their homeland but even more so because herbal therapy plays a vital role in
the health care of developing countries.
Chapter 6.2 - Adulteration by synthetic therapeutic substances

Throughout the world, Chinese proprietary medicines (CPM) are widely used in Chinese communities for the treatment of many common conditions such as colds and musculoskeletal pain. Partly because of this wide availability, CPM is commonly used for self-poisoning in many Chinese communities. (Chan JC, Chan TY et al, 1994) There is reason to believe that such medicines with adulterations of synthetic therapeutic substances also exist in many other countries. (Huang WF, Wen KC et al, 1997) Numerous case reports originating from countries such as Australia, Belgium, China, The Netherlands, New Zealand, UK and USA demonstrate the adulteration of TCMs with synthetic drugs and associate the use of adultered remedies with health problems of the user. (Ernst E, 2002) It is generally known that traditional Chinese medicines have been distributed without being adequately regulated in many countries.

The term "adulteration" refers to traditional Chinese medicines that are tested and found to contain chemical substances not prescribed or labeled as part of the intended use. (Huang WF, Wen KC et al, 1997) Depending on the manufacturer, adulterants of this preparation included variable amounts of aminopyrine, phenacetin, phenylbutazone, indomethacin, mefenamic acid, diazepam, hydrochlorothiazide, dexamethasone, mercuric sulphide, and even heavy metals such as lead and cadmium. (see Table 6b & 6c) The resulting clinical consequences are often serious and sometimes life threatening: agranulocytosis, Cushing's syndrome, coma, the excessive increase of the international normalized ratio (INR) has all been reported. Some of the medicines have been identified as coming from Oriental commercial sources while some were not identifiable because of unknown supplying sources. Although several reports stated that the
possibilities of certain adverse effect were high, people still reassured that Chinese medicines are natural and can cause no harm.

The adulteration of traditional Chinese medicines with unlabeled synthetic therapeutic substances is hazardous to the public health at least in two respects. (Huang WF, Wen KC et al, 1997) First, it is not in the interest of the public for any medicine to be inadequately labeled. Many believers in traditional Chinese medicines tend to trust the "moderate nature" of herbal preparations; they are generally more reluctant to be treated by western medicines, which are misconceived as producing more adverse reactions than traditional Chinese medicines. Such adulterated preparations mislead consumers to expect effective treatment from traditional medicines. Second, adulterated traditional Chinese medicines sometimes contain certain poisonous synthetic therapeutic substances, for example, corticosteroids or phenylbutazone, that even medical doctors take cautions in prescribing. The adulterant is usually added without carefully assaying of its dose quantity; thus severe adverse effects are very likely to develop within a short period of treatment.

People worry more about the safety of traditional medicines they procured. Consumers are far from cooperative in providing information to the health authorities on identities of distributors or in revealing the source(s) of supply. Adulterated samples are very rarely found in commercial packages of traditional Chinese medicines, because they require premarketing regulatory approvals and complete labeling of the contents; but such samples are often found in traditional Chinese medicines dispensed by practitioners, peddlers, or quacks. Because physicians' dispensing of western and traditional Chinese medicines has been in existence for nearly half a century, policy makers in the Department of Health have been quite passive in pursuing the release of
prescriptions from medical practitioners to community pharmacies. The missing requirement of adequate labeling on packages of dispensed medicine is an intentional omission. It represents a denial of the public's right to safe and effective medications. Without an affirmed policy on the right to adequate product information and labeling, all governmental efforts in monitoring and persecuting such misconduct as adulteration of medicines by practitioners of traditional Chinese medicine will meet with only limited success.

6.2.1 The Experiences in China

In China, the population widely accepts herbal products such as Chinese proprietary medicines (CPM) was an effective treatment for diseases and would like to purchase by themselves without any medical consultation. Chinese proprietary medicines are considered OTC drugs and must comply with the product standard and formulations specified in the People's Republic of China Pharmacopoeia. However, there are inconsistent quality controls at the manufacturing level and the central government has limited authority and resources to regulate the industry. (Koo J and Arain S, 1999) After several cases of intoxication caused by CPM, people worry more about the safety of CPM they procured. Consumers are far from cooperative in providing information to the health authorities on identities of distributors or in revealing the source(s) of supply.

In China, the licensing and official regulation of traditional Chinese medicine and the Chinese proprietary medicine was by State Administration of Traditional Chinese Medicine (SATCM). The licensing of drugs and official regulation of their sale is equally stringent for Western and Chinese medicines. New drugs have to be examined and approved according to the Drug Administration Law. After approval, a New Drug
The certificate is granted an approval number. The factory is then permitted to put the product on the market. Adulterated samples could be found in commercial packages of traditional Chinese medicines, because they require premarketing regulatory approvals and complete labeling of the comments.

Randomised controlled trials (RCTs) have already been conducted in TCM. There are, however, a few methodological issues that need to be resolved so that the quality of trials can be further improved. The first RCTs in TCM in China were conducted in the early 1980s; the number of trials has doubled every 2 to 3 years over the past 15 years. (Tang JL and Wong TW, 1998) A preliminary systematic review of the evidence for the effectiveness of TCM has identified some 2800 RCTs that were published in medical journals in China. Further work is needed to identify and to register all clinical trials ever published in the medical literature. The misunderstanding and scepticism about TCM therapies will likely continue until their clinical effectiveness is demonstrated by RCTs. Demonstration of the clinical effectiveness of TCM is thus an immediate and urgent task for researchers of TCM.

Most of the Chinese proprietary medicines (CPM) that sold in Southeast Asia were produced in China, however, usually receive no premarket approval by the State Administration of Traditional Chinese Medicine (SATCM). Some of the Chinese proprietary medicines that sold in the pharmacy were from the black market and its commercial distribution was not legal. More than this, even batches of CPM from the same manufacturer may contain variable amounts of active or potential toxic ingredients. (Li AM, Chan MHM et al, 2000)

The unadulterated and adulterated samples of traditional Chinese medicines are further classified according to their supplying sources: traditional Chinese medicine...
hospitals, clinics, and drugstores; chiropractors; herbalists; peddlers; quacks; and other sources. Herbalists are crude herbal retailers; peddlers are unauthorized retailers of various commodities along roadsides or in marketplaces; quacks are medical practitioners without professional licenses; and "others" are such sources as friends, relatives, mail order, etc.

On the other hand, combination of western medicine and traditional Chinese medicine into proprietary form is the characteristic form in China. TCM and WM each have its own ideologic and philosophic basis. To pursue the "two combine into one" blindly is undesirable to the development of TCM and the people's health care. The practice over scores of years has proved that the combination way is correct, which bears the characteristics of Chinese culture and medicine. The controversies regarding the combination of synthetic therapeutic substances and traditional Chinese medicines without adequate labeling should be resolved through regulatory actions for better safety of drug use. (Huang WF, Wen KC et al, 1997)

6.2.2 The Experiences in Hong Kong

Because of their easy availability, CPM is commonly used for self-poisoning in Hong Kong. In Hong Kong, CPM is readily available without prescription as 'over-the-counter' drugs. CHM are also freely available from most drug stores. The choice of a particular combination of herbs and other ingredients may be based on that individual's own experience or beliefs. More often, particularly for minor complaints, the employees at the drug store may decide what combination of ingredients is best for a specific patient. Alternatively, a patient may request to be seen by one of the herbalists associated with the drug store and be given an individualized prescription. (Chan TY and Critchley JA, 1996)
As increasingly frequent warnings of Chinese health products containing prescription drugs highlight the dangers of using unregulated herbal products and should alert patients and their doctors to the risks associated with mixing Chinese and western medicines. For example, the Hong Kong Department of Health (DH) has recently issued a public warning regarding two Chinese health products that have been adulterated with a potentially harmful drug ingredient. Two oral tonics that imported from the mainland were found to have contained sildenafil, which is used to treat erectile dysfunction. Sildenafil is currently available in Hong Kong on a prescription only basis. It can cause headache, flushing, dyspepsia and visual disturbances, and in some cases was associated with severe cardiovascular adverse effects. In Hong Kong, products containing western medicine are considered as pharmaceuticals and therefore must be registered with the Pharmacy and Poisons Board. The two TCM products have not been registered and importers have been instructed to recall them immediately from the market. The possession and sale of unregistered pharmaceuticals is a legal offence liable to heavy penalties. However, some importers and distributors are willing to take the risk while others may be unaware that the herbal preparations contain western prescription drugs. The same situation could be seen in Macau where the Macau health department banned one oral tonic that contained sildenafil, which was imported from mainland China.

Chan TY et al performed a retrospectively studied from a general medical wards at the Prince of Wales Hospital between January 1988 and December 1993 and suggested that topical medicaments (72%), which may contain methylsalicylates as wintergreen oil, and CPM tablets/capsules (24%), which may contain paracetamol, were the most important CPM used for self-poisoning in Hong Kong. (Chan TY, Lee KK et al, 1995)
Since there was a predominance of Vietnamese subjects in this study, the proportion of patients using topical medicaments might have been exaggerated.

6.2.3 The Experience in Taiwan

The adulteration by synthetic therapeutic substances of traditional Chinese medicines has been reported on various occasions and has been a public health concern in Taiwan over the past several years. Over the years, traditional Chinese medicines referred to the National Laboratories of Foods and Drugs from various sources have contained adulterants. It is obvious that the "unlabeled" addition of synthetic therapeutic substances to traditional Chinese medicines has been a quite alarming phenomenon, regardless of the illegal nature of such a practice. Whether western medicines could be combined with traditional Chinese medicines has been long debated in Taiwan and deserves more serious consideration by the regulatory authorities. However, fundamental differences in the disciplines underlying these two alternative approaches to disease treatments remain to be explored.

Recent statistics indicate that consistently high percentages of 27.7%, 25.3%, and 22.3% of adulterated medicines were detected among samples referred to local health authorities through consumers' complaints during 1991, 1992, and 1993 respectively. The large-scale survey was performed in 1992 and totally screened 2,609 samples which were collected by eight major general hospitals in Taiwan. (Huang WF, Wen KC et al, 1997) After analyzed, nearly 23.7% (n = 618) of the samples collected from the eight hospitals were adulterated unlabeled, synthetic therapeutic substances. The result showed that the traditional Chinese medicine samples that have premarketing approvals contained less adulterants may be related to the government attitude and regulatory enforcement. Pharmaceutical products, both in western and in traditional Chinese
medicine dose forms are required to have premarketing approvals by the Department of Health in accordance with Taiwan's Pharmaceutical Affairs Law. Law strictly prohibits addition of unlabeled therapeutic substances other than approved formula. (Huang WF, Wen KC et al, 1997) Not only because Taiwan's pharmaceutical regulations do not permit the combination of western pharmaceuticals with traditional Chinese medicine preparations, with violating manufacturers subject to severe penalty, but also because health authorities at various levels regularly perform inspections of manufacturing facilities and take inspection samples from the market for laboratory analysis. (Huang WF, Wen KC et al, 1997) Such kinds of commercial packages were produced in China and indicate that the prohibition of registering traditional medicines from China is not an effective mechanism for controlling such product distribution to Taiwan.

6.2.4 Discussion

The undeclared occurrence of thyroid hormones induced by botanical remedy was recently discovered when several United States residents developed thyrotoxicosis following the use of purportedly herbal slimming capsule adulterated with thyroid, diethylpropion, and hydrochlorothiazide. The product had been imported into the United States from Peru. Herbal products are claimed to cure numerous disorders ranging from diabetes to obesity, but these claims are often not supported by well-controlled clinical trials. In addition, herbal products are rarely packaged in childproof containers. (Anderson LA, 1996)

In England, a 44 years old woman was admitted to the hospital because of taking some herbal remedies for weight lost and got new onset hypertension, palpitation, anxiety, with a body mass index of 19 kg/m². (Metcalfe K, Corns C et al, 2002) Initially, researchers suspected Ephedra or Ma Huang, herbs that widely used in the United States
and elsewhere in the world for weight loss but also linked to adverse side effects. However, after chemical analysis revealed there was a high concentration of fenfluramine in two of the products (sold as ‘Qian Er’ and ‘Ma zin dol’) and also in the patients’ urine. The Food and Drug Administration (FDA) pulled Fenfluramine and dexfenfluramine from the market in 1997 after numerous reports the off-label cocktail combo increased the risk of heart valve damage in the United States and in the United Kingdom. This finding was published as a letter in the March 15 issue of British Medical Journal.

Another preparations that found to contain western drugs include “Tong Shap Yee’s Shuenchih Wan” (pill for easy breathing) (theophylline) and “Leung Pui Kee cough pills” (bromhexine). (Tay SAB and Johnston MA, 1989) This old brand name of Chinese proprietary medicine was sold in Hong Kong and South East Asia for more than 30 years. This drug has anti-asthmatic effects and contains powdered licorice 50 mg, aminophylline 20 mg, ephedrine HCl 1.3 mg, and starch 68.7 mg. The label instructs the user to take 10 pills 3 times a day when “short of breath” or five pills 3 times a day when asymptomatic. (Wong HCG, 2001) Nowaday it is readily available in Chinese herbal shops across Canada and probably elsewhere as well. The prescription drug aminophylline is clearly identified as one of the ingredients in the preparation, and not as an contaminant. The dosage of ephedrine used during the symptomatic period exceeds the maximal daily dose (24 mg) recommended by the US Food and Drug Administration’s 1997 proposal, which was raised because of its adverse reactions. (Wong HCG, 2001)

In addition, awareness of herbal medicine has also been facilitated by the proliferation of home computers and the explosive growth of the Internet, which have
provided ready access to information about herbs. Ordering supplies of botanical products from around the world is usually an easy process but such kind of botanical products are without any quality assurance. Health authorities have enforced inspections, and screening services have been made available through different channels to the general public with minimal cost. Although the health authorities usually have a list of CPM containing western drugs, such information may not be readily available. CPM may be adulterated with undeclared and, often more toxic, drugs.(Chan TY, Lee KK et al, 1995)


<table>
<thead>
<tr>
<th>Preparation(s)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chuifong Toukuwan Nan Lien</td>
<td>(Ries CA and Sahud MA, 1975)</td>
</tr>
<tr>
<td>2. Long Life Brand Ginseng Hui Sheng Tsaiwaowan</td>
<td></td>
</tr>
<tr>
<td>3. Sanlungpai Ginseng Hui Sheng Tsaiwaowan</td>
<td></td>
</tr>
<tr>
<td>4. Fonsuning Tongwan</td>
<td></td>
</tr>
<tr>
<td>5. Lilongpai Fonsuning</td>
<td></td>
</tr>
<tr>
<td>6. Hippo Brand secret</td>
<td></td>
</tr>
<tr>
<td>(Formula Chui Fung Eng (Nan Lien Pharm. Co., Taiwan and Hong Kong)</td>
<td></td>
</tr>
</tbody>
</table>

* All 6 brands contained amino phenazone and phenylbutazone.

* Three of the brands (with 23-43 mg and 17-34 mg, respectively) produced life-threatening agranulocytosis in 4 patients, when taken in doses of 8-12 pills/day. One patient died.
<table>
<thead>
<tr>
<th>Preparation(s)</th>
<th>Chemical and clinical Details*</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chuifong Toukuwan (Hong Kong)</td>
<td>One patient developed agranulocytosis after starting treat.</td>
<td>(Brooks PM and Lowenthal RM, 1977)</td>
</tr>
<tr>
<td></td>
<td>Analysis of different batches showed varying amounts of amino phenazone, phenylbutazone, and phenacetin.</td>
<td></td>
</tr>
<tr>
<td>- Chuifong-Toukuwan (Hong Kong)</td>
<td>One patient developed Cushing's syndrome from 12 pills/day.</td>
<td>(Uitdehaag CMJ, Hekster Y A et al, 1979)</td>
</tr>
<tr>
<td></td>
<td>The pills contained dexamethasone (0.112 mg), indomethacin (7.5 mg), Hydrochlorothiazide, and diazepam (see next entry).</td>
<td></td>
</tr>
<tr>
<td>- Chuifong Toukuwan (Nan Lien Pharm.Co., Hong Kong)</td>
<td>Dexamethasone 0.112 mg</td>
<td>(Anoniem, 1979)</td>
</tr>
<tr>
<td></td>
<td>Indomethacin 7.3-8.3 mg</td>
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<td></td>
<td>Hydrochlorothiazide 4.1 mg</td>
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<td></td>
<td>Diazepam 0.45 mg</td>
<td>(Dose: 12 pills/day)</td>
</tr>
<tr>
<td>- Chuifong-Tou-Geu-wan</td>
<td>One patient developed a low plasma cortisol concentration and a cushingoid look.</td>
<td>(Forster P J G, Calverley M et al, 1979)</td>
</tr>
<tr>
<td>- Chuifong Toukuwan (Nan Lien Pharm.Co., Singapore)</td>
<td>Prednisolone 0.4 mg</td>
<td>(Anoniem, 1979)</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide 4.0 mg</td>
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<tr>
<td></td>
<td>Chlordiazepoxide 0.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpheniramine 1.3 mg</td>
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<tr>
<td></td>
<td>Thiaminedisulfide 5.0 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Dose: 12 pills/day)</td>
<td></td>
</tr>
<tr>
<td>- Chuifong Toukuwan (Shou Sing Pharm. Co., Taiwan)</td>
<td>Aminophenazone 8 mg</td>
<td>(Anoniem, 1979)</td>
</tr>
<tr>
<td></td>
<td>Phenylbutazone 0.6-6.0 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thiamine (Dose: 12 pills/day)</td>
<td></td>
</tr>
<tr>
<td>- Dumeap capsules (Duzcap Pharmacy, Pakistan)</td>
<td>Prednisolone 4mg</td>
<td>(Moric A., 1986)</td>
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<tr>
<td></td>
<td>Betamethasone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Dose: 3 capsules/day)</td>
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</tr>
<tr>
<td>- Chihsiton (Yi Chung Tai Med. Manuf. Co., Taiwan)</td>
<td>Paracetamol 8.1 mg</td>
<td></td>
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<tr>
<td></td>
<td>Ethaverine 0.26 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorzoxazone 2.0 mg</td>
<td></td>
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<tr>
<td></td>
<td>Diazepam 0.55 mg</td>
<td></td>
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<tr>
<td></td>
<td>Caffeine 1.9 mg</td>
<td></td>
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<tr>
<td></td>
<td>Thiamine (Dose: 18 pills/day)</td>
<td>(Morice A., 1987)</td>
</tr>
<tr>
<td>- Deecap capsules (Shaham Romeo Pharmacy, Pakistan)</td>
<td>Prednisolone</td>
<td></td>
</tr>
<tr>
<td>- Amborum special-F syrup (Sri Lal, United States)</td>
<td>Dexamethasone 0.02-0.2 mg/ml</td>
<td>(Steinigem M, 1987)</td>
</tr>
<tr>
<td>Preparation(s)</td>
<td>Chemical and clinical Details</td>
<td>Ref</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Cow's Head Brand Tung Shueh (Ta Ang Pharm. Co., Taiwan)</td>
<td>One patient developed a low plasma cortisol concentration. Each pill contained 0.09 mg dexamethasone (dose: 12 pills/day).</td>
<td>(De Smet et al., 1990)</td>
</tr>
<tr>
<td>Chuiifong Toukuwan (Nan Lien)</td>
<td>Dexamethasone, Indomethacin, Mefenamic acid, Hydrochloorthiazide &amp; Diazepam ¹</td>
<td>(De Smet PAGM, Elferink F, 1988)</td>
</tr>
<tr>
<td>Unmarked green capsules (Chinese herbalist, Kuala Lumpur)</td>
<td>Phenylnbutazone, One patient gained weight and became moonfaced, Powder #3 contained prednisolone (0.5 mg/g) and paracetamol (63 mg/g), Powder #6 contained similar amounts of both drugs as well as phenylbutazone (42 mg/g).</td>
<td>(Bury RW, Fullinfaw RO et al., 1987)</td>
</tr>
<tr>
<td>Dr Tong Shap Yee's asthma pills</td>
<td>Theophylline 12 mg per pill, Bromhexine 0.7 mg per pill</td>
<td>(Tay SAB and Johnston MA, 1989)</td>
</tr>
<tr>
<td>Nan Lien Chui Fong Toukuwan</td>
<td>Diazepam 0.6mg, Theophylline 12 mg, Bromhexine 0.7 mg</td>
<td>(Tay SAB and Johnston MA, 1989)</td>
</tr>
<tr>
<td>Dr. Tong Shap Yec's asthma pills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leung Pui Kee Cough (Hong Kong)</td>
<td></td>
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<tr>
<td>ASFO Natural Herbs Tea (Sri Lal, Sri Lanka)</td>
<td>Betamethasone 0.1-0.5 mg/ml</td>
<td>(Anonymous, 1988)</td>
</tr>
<tr>
<td>Thong Yen Obat China (Lim Yik Kong)</td>
<td>Prednisolone</td>
<td>(Anonymous, 1988)</td>
</tr>
<tr>
<td>Unspecified Chinese herbal preparations</td>
<td>Phenazone, propyphenazone, and methyltestosterone have also been identified as adulterants of Chinese herbal products.</td>
<td>(Yuen S. and Lau-Cam CA, 1985)</td>
</tr>
<tr>
<td></td>
<td>Undeclared pharmaceuticals that have been found in traditional Chinese remedies.</td>
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<td>---</td>
<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>1.</td>
<td>Acetaminophen (paracetamol)</td>
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<td>2.</td>
<td>Aminopyrine</td>
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<td>3.</td>
<td>Caffeine</td>
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<td>4.</td>
<td>Carbamazepine</td>
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</tr>
<tr>
<td>5.</td>
<td>Chlorzoxazone</td>
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<tr>
<td>6.</td>
<td>Clobetasol propionate</td>
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<tr>
<td>7.</td>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Diazepam</td>
<td></td>
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<tr>
<td>9.</td>
<td>Diclofenac</td>
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<tr>
<td>10.</td>
<td>Ethoxybenzamide</td>
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<tr>
<td>11.</td>
<td>Fluocinolone acetonide</td>
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<tr>
<td>12.</td>
<td>Glibenclamide</td>
<td></td>
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<tr>
<td>13.</td>
<td>Hydrochlorothiazide</td>
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<tr>
<td>14.</td>
<td>Hydrocortisone</td>
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<tr>
<td>15.</td>
<td>Indomethacin</td>
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<tr>
<td>16.</td>
<td>Mefenamic acid</td>
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<tr>
<td>17.</td>
<td>Methylsalicylate</td>
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</tr>
<tr>
<td>18.</td>
<td>Phenacetin</td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Phenylbutazone</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Valproate</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 6.3 - Oil of Wintergreen (methyl salicylate)

6.3.1 Overview

In Hong Kong, there are at present more than 160 adult and pediatric preparations containing salicylates registered with the Government. This figure does not include the wide range of medicated oils containing methyl salicylate (wintergreen oil) that are commonly used in the self-treatment of conditions such as musculoskeletal pains and common cold. In Hong Kong, medicated oils containing methyl salicylate account for 48% of acute salicylate poisoning cases treated in the general medical ward of the Prince of Wales Hospital. (Chan TY and Critchley JA, 1996)

Oil of Wintergreen (methyl salicylate) is a common ingredient for liniments, ointments and essential oils used in self-treatment of musculoskeletal pain. Its pleasant smell also encourages its use to flavor confectionery. (Botma M, Colquhoun-Flannery W et al, 2001) The toxic potential of this preparation is not always fully appreciated by the general public and physicians. To appreciate the danger of this oil it can be compared to aspirin tablets (325 mg dose): one teaspoon (5 ml) of Oil of Wintergreen is equivalent to approximately 7000 mg of salicylate or 21.7 adult aspirin tablets. Ingestion of as little as 4 ml in a child can be fatal.

Methyl salicylate in topical analgesic preparations may cause irritant or allergic contact dermatitis. (Chan TY and Critchley JA, 1996) Excessive usage of these preparations in patients receiving warfarin may result in adverse interaction and bleeding complications. (Joss JD and LeBlond RF, 2000) A 22-year-old white woman presented with an INR of 12.2 after applying a topical pain-relieving gel to her knees daily for eight days. The potentiation of the warfarin anticoagulation was attributed to the low-
dose methyl salicylate contained in the product. Methyl salicylate may increase warfarin action by affecting vitamin K metabolism or by displacing warfarin from protein-binding sites.

In view of the toxic potential of medicated oils containing methyl salicylate, Chan performed studies to the existing packaging of 7 commonly used preparations from Hong Kong and Singapore. (Chan TY, Lee KK et al, 1995; Chan TY, 1996) (See Table 6 d) The medicated oils were all packed in translucent bottles without child-resistant closures. The result showed that the methyl salicylate content ranged from 15 to 67%. Many preparations also contained other potentially toxic ingredients in significant amounts, such as turpentine oil and camphor. Koong Yick Hung Far Oil had the highest methyl salicylate content (67%) and was available only in 60-ml bottles. If the entire bottle of this product were ingested, the equivalent of 184 adult 300-mg aspirin tablets would have been swallowed. Accidental ingestions of as little as 6 ml of Koong Yick Hung Far Oil by a child can be fatal. The other six products contained 15-40% methyl salicylate and their biggest bottle sizes were range from 28-57 ml. (Chan TY, 1996) Furthermore, the contents of the larger bottles could generally be emptied more easily because of the greater size of their openings. The product with the highest methyl salicylate content also had the biggest opening of all.

"Koong Yick Hung FA Oil" (KYHFO) (67% wintergreen oil {>70% methyl salicylate}, 22% turpentine oil, 5% cinnamic aldehyde, 4% cinnamon leaf oil, 2% citronella oil), made in Singapore, is readily available in any Asian grocery store. (Maryann H, Jose ED et al, 1998) "KYHFO" claims to be useful in the self-treatment of respiratory obstruction, cardiac pain, hemiplegia, paresthesia, sciatica, rheumatism, beriberi, abdominal pain, headaches, fatigue, burns, scalds, and bruises. As
per its product label, it is primarily indicated for external use, but can be taken orally for enhanced efficacy.

Maryann H, et al reported that a 70-year-old Asian woman with a history of hypertension and arthritis ingested 60 mL of topical “KYHFO” (~1.2 g/kg salicylate equivalents) for relieve chronic knee pain. (Maryann H, Jose ED et al, 1998) One hour after ingestion abdominal pain, restlessness, and diaphoresis developed. On arrival in the emergency department, she was afebrile, euglycemic, and the ECG monitor showed a narrow complex tachycardia. Abdomen was soft, nondistended, and without active bowel sounds. However, a voluminous brown liquid bowel movement was noted. The neurologic exam revealed a confused and agitated patient with impaired attention and limited awareness to the surroundings. After analysis, the “KYHFO” bottle (60 mL) contains 56.2 g salicylic acid and equivalent to 186 regular-strength adult aspirin tablets. Ingestions of as little as 4 to 6 mL of wintergreen oil can result in fatalities; a lethal adult dose is usually estimated as 30 mL.

A significant central nervous system (CNS) deterioration (without seizures) developed after three hours of ingestion and required orotracheal intubation; marked metabolic acidosis with some respiratory compensation and a salicylate (SA) level of 108.6 mg/dL also were noted. After treating with lavage and activated charcoal, the patient received three times of hemodialysis. Rhabdomyolysis (creatine phosphokinase 19,570 U/L {20-149 U/L}), hepatitis (aspartate aminotransferase 4,190 U/L; alanine aminotransferase 2,808 U/L), coagulopathy (prothrombin time 17.1; partial thromboplastin time 89), and nephrotoxicity (blood urea nitrogen 29 mg/dL; creatine 2.7 mg/dL) were found after 48 hours. The hemoglobin level steadily decreased (14.8 to 7.9 g/dL) requiring transfusion. No site of active bleeding was identified. By the sixth
hospital day, all laboratory values had returned to normal. Unluckily, she was died on the 13th hospital day because of anoxic encephelopathy. (Maryann H, Jose ED et al, 1998)

6.3.2 Prevention

It was much more difficult to collect toxicity information on CPM than on therapeutic drugs, for several reasons. (Chan TY, Lee KK et al, 1995) Many patients knew the nature but not the brand name of the product they had taken. Even if patients knew the group name of the CPM, for example, Medicated Oil, there is a multitude of products collectively known as Medicated Oil which are locally manufactured or imported. Different manufacturers may use almost identical brand names for their products, which differ in their contents, and few patients or physicians will be able to note the subtle differences in the nomenclature. Futhermore, for the older people who lived in Chinese population, they always have a misunderstanding for the usage of such kind of old-brand-named proprietary medicine and take it by mouth habitually when they felt “sickness”. In Hong Kong, a fatal case was reported several years ago that an old lady was die after taken the medicated oil.

According to the fact that oil of wintergreen was available in an inappropriately labeled container may bear fatal consequences, so several points can probably 'reduced' the accidental ingestion of medicated oils. (i) Child-resistant containers should be implemented as required by the Poison Prevention Packing Act (1972) for all liquid products containing more than 5% methyl salicylate by weight; (ii) restricting the size of both the openings and the bottles; and (iii) reducing the methyl salicylate content (Lee K, Chan TY et al, 1997); (iv) public education.

Prevention of accidental ingestion of methyl salicylate containing products can be
achieved by keeping the products out of reach of children, using child resistant bottles, restricting the size of the openings of the bottles, appropriate labeling on products and reducing the salicylate content. (Botma M, Colquhoun-Flannery W et al, 2001)

Treatment is aimed at gastric decontamination with multiple doses of activated charcoal, replacement of fluid and electrolytes, and correction of acid-base abnormalities and hypoglycemia. (Maryann H, Jose ED et al, 1998) Alkalinization of urine is effective in increasing salicylate clearance. Early hemodialysis is indicated for acute SA levels in excess of 100 mg/dL, severe acid-base disturbance, hepatic or renal failure, pulmonary edema, deteriorating vital signs, or persistent CNS toxicity. Hemoperfusion has a higher rate of drug clearance than hemodialysis; however, it is not effective in correcting pH, fluid, and electrolyte abnormalities. (Flomenbaum BE and Goldfrank LR, 1994)

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical medicaments</td>
<td></td>
</tr>
<tr>
<td>1. Pak Far Oil (White Flower Oil)</td>
<td>• Menthol crystal 30%, wintergreen oil 40%, eucalyptus oil 18%, camphor 6%, lavender oil 6%</td>
</tr>
<tr>
<td>2. Hung Far Oil (Red Flower Oil)</td>
<td>• Cinnamon leaf oil 4%, cinnamic aldehyde 5%, citronella oil 2%, turpentine oil 22%, wintergreen oil 67%</td>
</tr>
<tr>
<td>3. Jaminton Healing Oil or Lion Medicated Oil</td>
<td>• Camphor 3%, spirit turpentine 9%, eucalyptus oil 0.5%, liquid paraffin 87.5%</td>
</tr>
<tr>
<td>4. Tiger Balm</td>
<td>• Menthol 10%, camphor 25%, clove oil 5%, cassia oil 5%, peppermint oil 6%, cages oil 7%, NH₃ solution 0.1%, wax and petrolatum 41.9%</td>
</tr>
</tbody>
</table>

Table 6 d. Ingredients of some commonly used Chinese proprietary medicines in Hong Kong. (Chan TY, Lee KK et al, 1995)
Chapter 7 - Adverse reactions to Ginseng

7.1 Overview

Ginseng is a highly valued herb in the Far East and has gained popularity in the West during the last decade (Attele AS, Wu JA et al, 1999). The ginseng root has been used for over 2000 years, in the belief that it is a panacea and promotes longevity. Ginseng is regarded as the king of herbs and throughout the world it is treasured as a supreme health-tonic for its purported anti-stress, anti-fatigue and anti-aging properties. (But PPH, Lee TYS et al, 1995) In the US, ginseng is considered a nutraceutical. The root is sold directly as a herbal remedy, or it may be extracted or powdered for use in dietary supplements. In Europe, ginseng is more closely regulated. Currently, the German government’s Commission E allows Panax ginseng products containing at least 1.5 percent ginsenosides, calculated as ginsenoside Rg1, to be labeled for use as a tonic for invigoration and fortification during times of fatigue and debility. In traditional Chinese medicine, the pharmacological effects of ginseng have been demonstrated in the CNS and in cardiovascular, endocrine, and immune systems. However, ginseng has been variously incriminated in herbal poisoning. A review of the reported cases suggests that adverse reactions to ginseng may occur because of the following problems.

7.2 Botany

There is extensive literature on the beneficial effects of ginseng and its constituents. Seven major species of ginseng are distributed in East Asia, Central Asia, and North America. Most studies of ginseng, including those cited in this commentary, have utilized constituents from three common species: Panax ginseng (Asian ginseng), Panax
**quinquefolius** (American ginseng), and *Panax japonicus* (Japanese ginseng). (Attele AS, Wu JA et al, 1999) The major active components of ginseng are ginsenosides, polysaccharides, peptides, polyacetylenic alcohol, and fatty acids. (Chang H and But P, 1987) There is a wide variation (2-20%) in the ginsenoside content of different species of ginseng. However, many mechanisms of ginsenoside activity still remain unknown. Since ginsenosides and other constituents of ginseng produce effects that are different from one another, and a single ginsenoside initiates multiple actions in the same tissue, the overall pharmacology of ginseng is complex.

### 7.3 Pharmacological Effects

The efficacy of ginseng was known in the West by the 18th century, and the study of ginseng has a long history. (Huang KC, 1999) Recently there has been a renewed interest in investigating ginseng pharmacology using biochemical and molecular biological techniques. Pharmacological effects of ginseng have been demonstrated in the CNS and in cardiovascular, endocrine, and immune systems. In addition, ginseng and its constituents have been ascribed antineoplastic, anti-stress, and antioxidant activity. Most pharmacological actions of ginseng are attributed to ginsenosides. (Huang KC, 1999) More than twenty ginsenosides have been isolated, and novel structures continue to be reported, particularly from *Panax quinquefolius* and *Panax japonicus*. (Yoshikawa M, Murakami T et al, 1998) The chemical composition of ginseng products may vary with the plant extract derivative, the age of the root, the location where grown, the season when harvested, and the method of drying. (Klepser TB and Klepser ME, 1999) Cultivating the plant during autumn and allowing at least five to six years of growth yields more ginsenosides. The drying technique influences...
the concentration of various ginsenosides in the final product; air-drying produces white ginseng, and steam produces red ginseng. (Bahrke MS and Morgan WP, 1994)

Early studies revealed its modulatory effects on the higher center of the central nervous system (CNS), facilitating both the physical and mental activities. Since ginsenosides and other constituents of ginseng produce effects that are different from one another, and a single ginsenoside initiates multiple actions in the same tissue, the overall pharmacology of ginseng is complex. The ability of ginsenosides to independently target multi-receptor systems at the plasma membrane, as well as to activate intracellular steroid receptors, may explain some pharmacological effects. (Attele AS, Wu JA et al, 1999) Scientific investigations have shown that these agents can release histamine; block calcium mobilization in smooth muscle, producing hypotension; stimulate \( \alpha \)-adrenergic receptors; stimulate erythropoiesis; increase adrenocorticotropic hormone, antidiuretic hormone, and cortisol secretion; raise sperm count; increase glucose utilization; increase levels of circulating immunoglobulins; and inhibit the cells of tumor cells cultivated in vitro. (Huang KC, 1999)

7.4 Adverse reaction of Ginseng

7.4.1 Overdosage:

A report of the much-publicized Ginseng Abuse Syndrome (GAS) concluded that patients developed hypertension, nervousness, sleeplessness, skin eruptions, edema and morning diarrhoea after long-term intake of ginseng products. (Siegel RK, 1979) Depression was also reported in those cases with ginseng doses higher than 15 g. The effects are similar to organic brain syndromes associated with corticosteroids and corticotrophin and may be related to ginseng’s interference with cortisone and corticotrophin levels. (Kim C, Kim CC et al, 1970) Furthermore, elevation of mood was
also very common in GAS. The study, which was undertaken at the University of California, followed 133 ginseng users for a period of two years and suggested that GAS was a result of long-term abuse with ginseng. Such effects might be due to ginseng dammarenetriol glycosides, which have strong central nervous system excitatory actions. Treatment of patients with GAS should include withdrawal from ginseng and other stimulants. Larger doses of ginseng (15 g daily) have resulted in feelings of depersonalization, which can mimic psychosis. These adverse effects are thought to result from the central nervous system accumulation of ginseng alkaloids. Treatment is to discontinue use of the herb. Other potential adverse effects of ginseng include premature uterine contractions in pregnant women and possible interaction with monoamine oxidase inhibitor antidepressants, producing headache and tremulousness. (Michael S, 1999)

Another report from China described two cases of visual defect, which appeared to be related to ginseng poisoning. (Lou BY, Li CF et al, 1989) After taking ginseng, the patients developed bilateral mydriasis and disturbance in accommodation, with systemic symptoms which included dizziness and impaired consciousness, which might be associated with hyper-excitability of the sympathetic nervous system due to overdose of ginseng.

7.4.2 Substitution with cheaper and more toxic herbs

In the United States, where roughly 60% of the population take herbal supplements, some manufacturers label the level of active compound voluntarily, but they are not legally required to do so or to guarantee a certain level. Nor do the products need government approval for safety and efficacy. (Harkey MR, Henderson GL et al, 2001) Some ginseng preparations available in the USA were found to be adulterated with
*Mandragora officinarum, Rauwolfia serpentina* and Cola species. (Siegel RK, 1977) A few fatal/serious cases were reported in the Chinese literature, but the herb used was actually *Physochlaina infundibularis*, which contains atropine and related alkaloids. Also, Siberian ginseng (*Eleutherococcus senticosus*) has been confused with ginseng (*Panax ginseng*), (Awang DV, 1991) and the former has been found adulterated with *Periploca sepium*, which contains cardiotonic glycosides.

Anticholinergic poisoning was reported after consumption of ginseng products. Analysis of the incriminated samples led to the conclusion that they were actually derived from or contaminated with other herbs (e.g. ephedrine).

Additionally, some reports have incriminated ginseng to be the causative agent for various adverse reactions, but the actual identity of the products could not be properly established. This lack of substantiated information made it difficult to truly assess the problems, since it is quite common to find adulteration, contamination and poor quality control in ginseng products. For example, a 44 year-old lady had post-menopausal bleeding after using a ginseng face cream. (Hopkins MP, Androff L et al, 1988) After examined the level of follicle-stimulating hormone, they found that the hormone level was affected after using this ginseng face cream but the ingredients of this face cream were not known. The symptoms of this patient were disappeared after stopped using this cosmetic.

Another 70 year-old lady developed swollen and tender breasts after taking ginseng powder regularly for three weeks. (Palmer BV, Montgomery AC et al, 1978) Her breast symptoms was settled after cessation of the ginseng powder. The patient had two further trials with this preparation and on each occasion the same symptoms
reappeared again. However, the serum prolactin levels were normal even the patient had taken ginseng or not.

A 39-year-old Czech man was found to have hypertension (Blood pressure 154/106 mm Hg) after taken about 3 years of different ginseng preparations orally. (Hammond TG and Whitworth JA, 1981) On examination his retinal arteries showed definite hypertensive changes. The patient was normotensive (140/85 mm Hg) 5 days later without anti-hypertensive medication. He remained normotensive without treatment after three months and his symptoms resolves.

A 33 year-old Chinese man with past good health suddenly convulsed and vomited of gastric content after taken 200cc of Red ginseng extract after several hours. (Zheng JY, 1984) He had high grade fever (38.8°C) and high blood pressure (140/100 mmHg) accompany with incontinence. After resuscitation, the patient finally died with acute left heart failure and upper gastrointestinal bleeding. Based on this patient clinical manifestation, the author stated that this patient may died of misusing of the ginseng medication because ginseng has pharmaceutical effect of vessel dilation and not suitable for the patient with congenital cerebral vessel malformation. However, the author hasn't provided the follow up information about the case.

All these cases have no further information about the ginseng product, so the relation cannot be substantiated. Another report from Australia (Hammond TG and Whitworth JA, 1981) also stated that a 39 year-old man had hypertension, dizziness and inability to concentrate after having taken a variety of different unknown ginseng preparations for about 3 years and the symptoms settled after discontinuing further intake of ginseng preparations. Ryu (Ryu SJ and Chien YY, 1995) also report a 28 year-old woman who had a severe headache after taking a large quantity of ethanol-extracted
ginseng to overcome physical fatigue. She ingested a bowel of extract (approximately 200 ml) from 60 slices of ginseng root (approximately 25 grams dry weight) that was stewed with 400 ml rice wine (22% alcohol). The patient developed an explosive headache, nausea and vomiting with chest tightness after eight hours later. This was the first episode and the headache was severe and was temporarily relieved by acetaminophen. She was referred to the hospital 6 days later. There was no special finding after general and laboratory examination. Cerebral angiograms showed “beading” appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis. The hospital course was uneventful, and her headache gradually disappeared over the next 10 days. Based on the result of the angiography of this patient, the appearance of cerebral arteritis may be associated with use of sympathomimetics or cocaine, various CNS inflammatory processes, or aneurysmal subarachnoid hemorrhage. However, detailed medical history excluded use of cocaine or any sympathomimetic drugs, and there was no CNS infection or aneurysm. The close temporal association between the intake of ginseng and cerebral arteritis may indicate a possible causal relationship but the nature and mechanism of this is uncertain.

Some reports state that 200 ml of the ginseng tincture or large doses of ginseng powder could result in intoxication giving rise to rose spots, pruritus, headache, vertigo, hyperpyrexia and bleeding, the last symptom was the characteristic manifestation of acute intoxication induced by ginseng. (Chang H and But PPH, 1987) Overdaseage of ginseng may also result in breathlessness, chest discomfort and abdominal distension. Radish has been used as a folk remedy for ginseng intoxication but the mechanism was not clear.
Misuse and abuse of ginseng could lead to adverse reactions. Herbal remedies are often touted in magazines and other popular media as being natural and safe, and many people take herbal preparations in addition to conventional medications prescribed or recommended by medical practitioners. Patients taking herbal medicines do not always volunteer this information to their physician. (McRae S, 1996) Many mislabeled and contaminated ginseng products further aggravate the problem. Thus, consumers should exercise appropriate caution in using ginseng products and proper controls should be levied on manufacturers of these preparations. Given widespread mislabeling, ingredients not listed in ginseng products may be responsible for therapeutic or adverse effects. Individuals with hypertension, diabetes, psychologic disorders, or insomnia should avoid or cautiously use ginseng.

A 28-year-old woman was admitted because of severe headache. (Ryu SJ and Chien YY, 1995) Six days before admission, she had a sore throat and took some western medication by herself. Two hours later, to overcome physical fatigue, she ingested a bowl of extract (approximately 200 ml) from 60 slices of ginseng root (approximately 25 grams dry weight) that was stewed with 400 ml rice wine (22% alcohol). Eight hours after drinking the ginseng extract, she developed an explosive headache, nausea and vomiting, and chest tightness. The headache was severe and was temporarily relieved by acetaminophen. The patient has no history of hypertension or use of drugs such as oral contraceptives or anorexiants. Laboratory tests that included complete blood count, sedimentation rate, and biochemistry were also normal. CT of the brain showed slightly increased density over the falx, and subarachnoid hemorrhage was suspected. Cerebral angiograms demonstrated multiple areas of alternating focal constriction and dilatation ("beading" appearance) in the anterior and posterior cerebral
arteries and the superior cerebellar artery, which is consistent with arteritis. The hospital course was uneventful, and her headache gradually disappeared over the next 10 days.

The temporal association between the ingestion of ethanolic ginseng extract and the onset of severe headache in this case strongly suggests a causal relationship. The angiographic appearance of cerebral arteritis may be associated with use of sympathomimetics or cocaine, various CNS inflammatory processes, or aneurysmal subarachnoid hemorrhage. However, detailed medical history excluded use of cocaine or any sympathomimetic drugs, and there was no CNS infection or aneurysm. The syndrome seen in our patient was most likely related to ingestion of a large amount of ginseng extract. Although the acute oral toxicity \((LD_{50})\) for ethanolic extract of ginseng has been determined in mice, its toxic dose in humans is not known.

Patients who take ginseng risk paying a high price without proven benefit. In Asian cultures, ginseng is commonly consumed by pregnant women and is given to newborns in hopes of bolstering energy. (O'Hara M, Kiefer D et al, 1998) A case-control study of 88 pairs of women (matched only for age and parity) found a significantly lower rate of pregnancy-induced hypertension, but a 3-fold higher incidence of gestational diabetes among ginseng consumers. (Chin RK, 1991) Ginseng was not recommending for pregnant or lactating women or for children until safety and efficacy are proven in randomized controlled trials.

7.5 Drug – herb Interaction

Both Asian and American ginseng have been shown to reduce blood glucose levels and hemoglobin A1c levels in people with type 2 Diabetes mellitus. (Sotaniemi E, Haapakoski E et al, 1995; Vuksan V, Sievenpiper JL et al, 2000; Vuksan V, Sievenpiper JL et al, 2001) Given concurrently with insulin or oral antidiabetic agents, ginseng may,
without careful blood glucose monitoring, result in hypoglycemia. There has been one case report of ginseng decreasing the effect of warfarin in a previously stable patient with a mechanical heart valve. Within two weeks of adding ginseng, the INR dropped to 1.5 from the targeted 3.0-4.0 and returned to 3.3 after ginseng was discontinued. (Janetzky K and Morreale AP, 1997) However, some current animal experimental showed no significant impact of ginseng on the pharmacokinetics / pharmacodynamics of warfarin when they are concomitantly administered. (Zhu M, Chan KW et al, 1999)

A 74-year-old asymptomatic man taking a constant dose of digoxin for many years to control atrial fibrillation and was found to have an elevated serum digoxin level. (McRae S, 1996) No signs of digoxin poisoning such as mental disturbance, nausea, vomiting or abnormal vision. The patient then revealed that he was taking Siberian ginseng, a popular herbal remedy. After stopping ginseng intake, the serum digoxin level soon returned to an acceptable level. However, the patient resumed taking ginseng several months later and the serum digoxin level again rose. After regional forensic laboratory analyzed the samples of the Siberian ginseng capsules; no digoxin or digitoxin contamination was found.

Siberian ginseng contains eleutherosides, which are chemically related to cardiac glycosides such as digoxin. In this patient, some component of the Siberian ginseng capsules may have been converted in vivo to digoxin. The case reported here should remind physicians to ask patients about nonprescribed medications, "natural" or otherwise, and to consider those remedies as possible factors when unexpected symptoms or complications arise.
7.6 Conclusion

Based on the accumulation of experience over many thousands of years, some principles have been developed to guide the use of Chinese medicines. According to the lack of standardization of ginseng products and the common practice of adulteration with cheaper substitutes, it is often difficult to be certain of the extent to which true ginseng was involved in some previous reports of its alleged adverse effects. (D'Arcy PF, 1991) Both medical professionals and the general public should be alerted to the potential toxicity of herbal remedies. Furthermore, in order to gain better understanding of the toxicity of ginseng and its individual allergic reactions, research should be encouraged.
Chapter 8 – Herbal Medicines With Cardiovascular Adverse Reactions

8.1 Overview

The use of alternative therapies, herbs, and supplements occurs at a very high rate among patients attending a variety of health care settings. Such therapy may cause significant interactions or effects on hypertension and other cardiovascular disorders and needs to be considered by clinicians. Plants that contain cardiac glycosides are used throughout the world for the treatment of heart failure and some arrhythmias. Current conventional pharmacological treatment includes at least five classes of drugs: Antiadrenergic, vasodilators, Calcium channel blockers, diuretics, and ACE inhibitors. It is rare to use single drug therapy. Non-drug conventional therapy limits itself to diet counseling, exercises, and the cessation of smoking and drinking. Herbals including ma huang, St. John’s wort, yohimbine, garlic, and licorice all may cause important consequences in the hypertensive patient. Added care is needed in monitoring the use and effects of herbal and alternative therapies in the hypertensive population.

8.2 Hypertension

Hypertension is very prevalent with some 50 million Americans diagnosed with hypertension and the majority taking antihypertensive drugs. Based on the fact that tighter goal for the treatment of hypertension, hyperlipidemia, and hyperglycemia has been recommended, multidrug therapy is routine for these disorders.

8.3 Atherosclerosis

Atherosclerosis is a multifactorial disease, and other factors besides lipid peroxidation can accelerate atherogenesis independently or in association with lipid
peroxidation. Increased retention and aggregation of LDL in the arterial wall and LDL oxidation are key events in the acceleration of atherogenesis. Because LDL and macrophages are retained in the atherosclerotic lesion on the arterial wall and macrophages release proteoglycans to their surroundings under atherogenic conditions, the macrophage-mediated aggregation of LDL may play a physiologic role in LDL modification in vivo.

8.4 Arrhythmias

There is increasing awareness of the problem of drug-induced cardiac arrhythmias.(Lean MF and Lee A, 1999) A cardiac arrhythmia is defined as any abnormal cardiac rhythm, whether the abnormality is one of rate, regularity or origin of the impulse initiating each heart beat. Drug-induced arrhythmias may be an adverse effect of a non-cardiac drug, a pro-arrhythmic complication of an anti-arrhythmic drug, or may arise from a drug overdose. Predisposing factors include underlying rhythm disturbances (especially ventricular tachycardia or fibrillation), impaired left ventricular function, pre-existing heart disease, high plasma levels of antiarrhythmic drugs and electrolyte abnormalities, especially hypokalemia and hypomagnesemia. Effects on the QT interval The QT interval on the electrocardiogram (ECG) are an indirect measure of the duration of the ventricular action potential and ventricular repolarisation. Prolongation of ventricular repolarisation can cause arrhythmias, the most characteristic of which is torsades de pointes (twisting of the points), a specific form of ventricular tachycardia which causes dizziness or syncope, it may lead to ventricular fibrillation and sudden death. Causes include bradycardia, certain inherited disorders, biochemical disturbances such as hypokalaemia, and acquired heart disease. Some patients with
torsade de pointes may be asymptomatic while others experience dizziness, light-heartedness, syncope, collapse, irregular heartbeat and palpitations.

8.5 Cardiac Failure

A number of herbs contain potent cardioactive glycosides, which have positive inotropic actions on the heart. (Nick HM, George IL et al, 1998) The drugs digitoxin, derived from either *D. purpurea* (foxglove) or *Digitalis lanata*, and digoxin, derived from *D. lanata* alone, have been used in the treatment of congestive heart failure for many decades. The only way to control dosage is to use standardized powdered digitalis, digitoxin, or digoxin. As is evident, treating congestive heart failure with nonstandardized herbal drugs would be dangerous and foolhardy.

8.6 Angina Pectoris

*Crataegus* of hawthorn is an important tonic for the cardiovascular system that is particularly useful for angina in TCM. *Crataegus* leaves, flowers, and fruits contain a number of biologically active substances, such as oligomeric procyanins, flavonoids, and catechins. *Crataegus* extract antagonizes the increases in cholesterol, triglyceride, and phospholipid levels in low-density lipoprotein (LDL) and very low-density lipoprotein in rats fed a hyperlipidemic diet; thus, it may inhibit the progression of atherosclerosis. (Shanthi S, Parasakthy K et al, 1994) *Crataegus* also prevents cholesterol accumulation in the liver by enhancing cholesterol degradation to bile acids, as well as suppressing cholesterol biosynthesis. (Rajendran S, Deepalakshmi PD et al, 1996)

8.7 Thromboembolic Disorders

Thromboembolic disorders result from the sudden occlusion of a blood vessel by a blood clot (thrombus) in the arterial or venous circulation. (Lean MF and Lee A, 1999)
Venous thromboembolism is common and is associated with a mortality of 1-2 per cent. Deep vein thrombosis (DVT) usually arises in the veins of the lower limbs or pelvis. Clinical features include pain involving the calf or thigh associated with swelling, redness and warmth. Management involves restoring normal circulation and anticoagulation. If part of a venous thrombus breaks off it can lodge in the pulmonary circulation, causing pulmonary embolism (PE). This can present with breathlessness, chest pain and collapse. In the arterial circulation, a thrombus may result in peripheral arterial occlusion, either in the lower limbs or in the cerebral circulation, where it may result in stroke.

8.8 Discussion

Several herbs offer potential for treating cardiovascular conditions including venous insufficiency, intermittent claudication, hyperlipidemia, hypertension and congestive heart failure (CHF). (Valli G and Giardina EGV, 2002) (See Table 8 a & b) Varied mechanisms, including antioxidant, antiplatelet, fibrinolytic, antiatherosclerotic, antihyperlipidemic, antiarrhythmic and vasodilatory actions, are ascribed to herbs. In addition, the growing demand for soft drinks and foods with herbal additives greatly expands public exposure. More than this, Chinese herbs were also reported to have the possibilities to cause heart disease in Belgium. (Vanherweghem JL, 1997) Vanherweghem J.L. stated that nearly 30% patients with drug induced renal failure (they were taken as appetite suppressants: fenfluramine, dexfenfluramine, or phentermine, alone or in combination) were found to have aortic insufficiency. The valvular heart disease in Chinese-herb nephropathy seen in Belgium seems most likely to be due to the combined use of (dex)fenfluramine and Chinese herbs. It is also obvious that the nephropathy recorded both in Belgium and in Japan is not caused by (dex)fenfluramine,
and that tubulointerstitial disorders are induced by the prolonged use of Chinese herbs that contain aristolochic acid.

The adverse effects, efficacy and interactions for herbal therapies that impact on the cardiovascular system are as follow.

Table 8a. Herbs With Adverse Cardiovascular Effects. (Valli G. and Giardina EGV, 2002)

<table>
<thead>
<tr>
<th>Herb</th>
<th>Adverse Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belladonna</td>
<td>Tachycardia</td>
<td>Herbal source of atropine (Blumenthal M, Busse WR et al, 1998)</td>
</tr>
<tr>
<td>Danshen</td>
<td>Platelet dysfunction</td>
<td>In vitro evidence of platelet antagonism (Wang Z, Roberts JM et al, 1982)</td>
</tr>
<tr>
<td>Dong quai</td>
<td>Increased bleeding</td>
<td>Presence of natural coumarins and in vitro evidence of platelet antagonism (Zhu DP, 1987; Page RL, 2nd and Lawrence JD, 1999)</td>
</tr>
<tr>
<td></td>
<td>tendency</td>
<td></td>
</tr>
<tr>
<td>Feverfew</td>
<td>Platelet dysfunction</td>
<td>In vitro evidence of platelet antagonism (Heptinstall S, White A et al, 1985) not supported in clinical trials (Groenewegen WA, Knight DW et al, 1992; Vogler BK and Ernst E, 1999)</td>
</tr>
<tr>
<td>Garlic</td>
<td>Increased bleeding</td>
<td>Case reports of hemorrhage. (Rose KD, Croissant PD et al, 1990; Burnham BE, 1995)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Animal studies of specific purified ginger compounds demonstrate pressor effects (Suekawa M, Aburada M et al, 1986; Kobayashi M, Ishida Y et al, 1988)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Herb</th>
<th>Adverse Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo</td>
<td>Increased bleeding tendency, platelet dysfunction</td>
<td>Case reports of central nervous system hemorrhage. Pharmacologic evidence of platelet antagonism; however, active compounds not present in sufficient amounts in most extracts (Braquet P, 1993; Skogh M, 1998)</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Hypertension</td>
<td>An abuse syndrome involving hypertension is described in chronic users. (Siegel RK, 1979) However, evidence from clinical trials also supports hypotensive effects (Han KH, Choe SC et al, 1998)</td>
</tr>
<tr>
<td>Hellebore</td>
<td>Hypotension, bradycardia</td>
<td>Accidental ingestion occurs when plant is mistaken for another, especially gentian (Jaffe AM, Gephardt D et al, 1990; Quatrehomme G, Bertrand F et al, 1993)</td>
</tr>
<tr>
<td>Kava</td>
<td>Platelet dysfunction</td>
<td>Limited in vitro evidence (Gleitz J, Beile A. et al, 1997)</td>
</tr>
<tr>
<td>Licorice</td>
<td>Hypertension, pulmonary edema, cardiomyopathy (rarely)</td>
<td>Occur as a result of decreased inactivation of cortisol causing symptoms of mineralocorticoid excess (Walker B and Edwards CRW, 1994)</td>
</tr>
<tr>
<td>Ma huang</td>
<td>Stroke, myocardial infarction, arrhythmia, hypertension</td>
<td>Numerous case reports of serious adverse events in healthy young people. (Haller CA and Benowitz NL, 2000) Myocarditis Rare case report (Zaacks SM, Klein L et al, 1999)</td>
</tr>
<tr>
<td>Oleander</td>
<td>Arrhythmia</td>
<td>Cardiac glycosides cause symptoms similar to digoxin toxicity. Responds to digoxin antibody treatment (Safadi R, Levy I et al, 1995)</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Hypertension, arrhythmia</td>
<td>Increases norepinephrine levels and central sympathetic outflow via $\alpha_2$ antagonism (Grossman E, Rosenthal T et al, 1993; Hoffman BB, Lefkowitz RJ et al, 1996)</td>
</tr>
</tbody>
</table>
Table 8b. Important Cardiovascular Drug Interactions.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Herb</th>
<th>Evidence for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Dong quai</td>
<td>Case reports of elevation of PT and INR in patient stable on warfarin. (Page RL, 2nd and Lawrence JD, 1999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Demonstration of pharmacological interaction in rabbits. (Lo ACT, Chan K et al, 1995)</td>
</tr>
<tr>
<td>Danshen</td>
<td></td>
<td>Decreases warfarin clearance and increases bioavailability. Case reports of hemorrhage in subjects on warfarin. (Yu CM, Chan JCN et al, 1997; Chan TY, 1998)</td>
</tr>
<tr>
<td>Garlic</td>
<td></td>
<td>Rare reports of elevation in INR in subjects previously stable on warfarin. (Sunter W, 1991)</td>
</tr>
<tr>
<td>Ginkgo</td>
<td></td>
<td>Case report of CNS hemorrhage in patient previously stable ofwarfarin. (Matthews MK, Jr, 1998)</td>
</tr>
<tr>
<td>Ginseng</td>
<td></td>
<td>Case report of decreased INR in patient stable on warfarin. (Janetzky K and Morreale AP, 1997)</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>Dong quai</td>
<td>In vitro evidence of platelet antagonism. (Page RL, 2nd and Lawrence JD, 1999)</td>
</tr>
<tr>
<td>(NSAIDs, ticlopidine, others)</td>
<td>Feverfew</td>
<td>Potential antiplatelet effects. (Heptinstall S, White A et al, 1985) No case reports of hemorrhage.</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>Case reports of platelet dysfunction with increased bleeding time (Rose KD, Croissant PD et al, 1990; Burnham BE, 1995)</td>
</tr>
<tr>
<td></td>
<td>Ginger</td>
<td>In vitro evidence of antiplatelet activity, but no effects seen in clinical trials and no case reports of adverse events.</td>
</tr>
<tr>
<td>(NSAIDs, ticlopidine, others)</td>
<td>Kava</td>
<td>In vitro evidence of platelet antagonism. (Gleitz J, Beile A et al, 1997)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Yohimbine</td>
<td>Competitive $\alpha_2$-antagonist. (Hoffman BB, Lefkowitz RJ et al, 1996)</td>
</tr>
<tr>
<td>Drug</td>
<td>Herb</td>
<td>Evidence for Interaction</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Hawthorn</td>
<td>Claims of interaction but no case reports and no pharmacologic data. (Miller LG and Murray WJ, 1998)</td>
</tr>
<tr>
<td></td>
<td>Herbal laxatives</td>
<td>Herbal laxatives such as buckthorn, cascara sagrada and senna can cause loss of potassium leading to digitalis toxicity. (Tyler VE, 1994)</td>
</tr>
<tr>
<td></td>
<td>Oleander</td>
<td>Contains active cardiac glycosides. (Eddleston M, Rajapakse S et al, 2000)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>St. John’s wort</td>
<td>Reduces serum digoxin levels. (Johne A, Brockmoller J et al, 1999)</td>
</tr>
<tr>
<td></td>
<td>Siberian ginseng</td>
<td>May interfere with assay, does not cause elevated digoxin levels (Awang DVC, 1996; McRae S, 1996)</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Yohimbine</td>
<td>Antidepressants potentiate pressor effects. (De Smet P. and Smeets O, 1994)</td>
</tr>
<tr>
<td>Methysergide, pizotifen, other serotonin antagonists</td>
<td>Feverfew</td>
<td>Antagonizes serotonin release, may potentiate the effect of other serotonin antagonists. (Wong HCG, 1999)</td>
</tr>
</tbody>
</table>

CNS _ central nervous system       NSAID _ nonsteroidal anti-inflammatory drug       INR _ international normalized ratio       PT _ prothrombin time.

8.8.1 Herbal Medicine Used in Cardiovascular System

8.8.1.1 Ginseng

Ginseng is regarded as the king of herbs and throughout the world it is treasured as a supreme health-thon for its purported anti-stress, anti-fatigue and anti-aging properties. (Chong SK and Oberholzer VG, 1988) In China it is utilized for angina pectoris, MI and CHF. It has been evaluated for many other indications, most notably for use as an antihyperglycemic. The active compounds are heterogeneous triterpene saponin glycosides, collectively termed ginsenosides. The exact ginsenosides vary by Panax species, (Attele AS, Wu JA et al, 1999) root age (Gillis CN, 1997) and preparation.
method (i.e., red or white). The Commission E monograph recommends a dosage of 1 to 2 g of root daily. (Blumenthal M, Busse WR et al, 1998)

Clinical trials in China and Korea have investigated ginseng for cardiac function, although there is no known mechanism and little data from placebo-controlled or blinded studies. An open trial evaluating CHF contrasted, 1) red ginseng, 2) digoxin, and 3) digoxin plus red ginseng, and found that hemodynamic improvement was most marked with combined therapy. (Ding DZ, Shen TK et al, 1995) In a double blind, placebo-controlled trial of coronary heart disease, a mixture of Chinese herbs, including ginseng, found that stroke volume index and cardiac index improved. (Fang J, Jian J et al, 1987)

Ginseng has been shown to have both hypertensive and hypotensive effects in animal studies trials. (Gillis CN, 1997) Hypotensive effects are attributed to enhanced synthesis of nitric oxide. An open trial of 4.5 g red ginseng daily found systolic blood pressure decreased after eight weeks. (Han KH, Choe SC et al, 1998) In contrast, a ginseng-abuse syndrome has been described wherein hypertension, behavioral changes and diarrhea occur. (Siegel RK, 1979; Siegel RK, 1980) In an observational study of 133 chronic ginseng users, 22 developed elevated blood pressure. (Siegel RK, 1979) Such effects might be due to ginseng dammarenetriol glycosides, which have strong central nervous system excitatory actions.

Animal studies suggest that ginseng scavenges free radicals. (Gillis CN, 1997) In a placebo-controlled trial of 30 patients undergoing mitral valve surgery, ginseng and ginsenoside Rb were evaluated for protective effects in ischemia and reperfusion injury. (Zhan Y, Xu XH et al, 1994) Both improved postoperative cardiac function; however, ginseng provided greater benefit than the isolate ginsenoside Rb. An
interaction of ginseng with warfarin, in which the INR was reduced to subtherapeutic levels, has been reported. (Janetzky K and Morreale AP, 1997) However, no mechanistic evidence for the interaction has been provided. (Vaes LP and Chyka PA, 2000) Interaction with digoxin, or with the digoxin assay and Siberian ginseng, has been observed, though this may have been due to a contaminant. (Awang DVC, 1996) Of note, many products that claim ginseng content have no ginsenosides. (Liberti LE and Der Marderosian A, 1978; Cui J, Garle Metal, 1994) Some ginseng preparations have been contaminated with germanium, which has led to an account of ginseng related diuretic resistance and renal failure. (Becker BN, Greene J et al, 1996)

8.8.1.2 Ma huang (Ephedra sinica)

Ma huang is a natural source of ephedrine and has potent sympathomimetic activity. Herbal remedies and soft drinks used for energy or weight loss often contain ma huang. Its pharmacokinetics and bioavailability are similar to standard doses of ephedrine. (White LM, Gardner SF et al, 1997) but the effects are delayed in onset. This is one of the most commonly taken supplements and is called by a variety of names including ma huang, ephedra extract, *ephedra sinica*, *ephedra equisetina*, *ephedra intermedia*, *ephedra geradiana*, ephedra herb powder, epitonin, or ephedrine. (Mansoor GA, 2001) Between 1997 and 1999, a total of 140 reports of adverse events were related to ma huang; (Haller CA and Benowitz NL, 2000) 13 caused permanent impairment and 10 resulted in death. Ephedrine and related alkaloids have been associated with adverse cardiovascular events, including acute myocardial infarction, severe hypertension, myocarditis, and lethal cardiac arrhythmias. (To LB, Sangster JF et al, 1980; Wiener I, Tilkian AG et al, 1990) Constriction of coronary arteries and, in some cases, vasospasm is believed to be the mechanisms of myocarditis and myocardial
infarction. The adrenergic effects of ephedrine shorten cardiac refractory periods, permitting the development of reentrant cardiac arrhythmias. Ephedrine can predispose patients to both hemorrhagic and ischemic stroke. (Bruno A, Nolte KB et al, 1993) Many reports concern healthy young people without known cardiac disease. The majority had new-onset hypertension, and other findings included cerebrovascular accidents, arrhythmias and MI. Several reports link the adverse response of ma huang to concurrent use of caffeine, guarana (a source of caffeine and theophylline) (Carlson M. and Thompson RD, 1998) or exercise. In a 2-year period in Texas, some 5000 reports of adverse effects of dietary supplements containing ephedra were reported. (CDC, 1996) It makes good sense to specifically instruct patients with hypertension, diabetes mellitus, thyroid disease, cardiac rhythm disorders, and seizures not to take herbals with ephedra.

Subarachnoid hemorrhage is thought to be a result of the hypertensive action of ephedrine, which can be short lived, or of cerebral vasculitis, which has been described in association with a variety of sympathomimetic drugs. (Wooten MR, Khangure MS et l, 1983; Fallis RJ and Fisher M, 1985) Thrombotic stroke is presumably related to vasoconstriction of large cerebral arteries, which leads to local thrombosis as a result of stasis and sympathomimetic-induced platelet activation.

An additional cause of concern for clinicians treating hypertension is the reported association of kidney stones with ephedra ingestion. (Powell T, Hsu FF et al, 1998) Chemical analysis has revealed these concretions to contain ephedrine and its metabolites. Renal calculi containing ephedrine have also been found in patients consuming large amounts of guaifenesin and ephedrine in over-the-counter preparations. (Assimos DG, Leinbach RF et al, 1999) It should be noted that ephedra has
also been linked to cases of psychoses, (Jacobs KM and Hirsch KA, 2000) mood disorders, and myocarditis. (Zaacks SM, Klein L et al, 1999)

Many of the cases we reviewed involved side effects such as anxiety, tremulousness, insomnia, palpitations, and personality changes that are well known to occur with the use of stimulant drugs. When ephedrine is used for medical purposes, these types of reactions are considered side effects and must be included in the assessment of risks and benefits. (Haller CA and Benowitz NL, 2000) In fact, ephedrine is rarely prescribed today for medical purposes, because newer drugs have more specific actions and fewer side effects. The risks of taking ephedra alkaloids as a dietary supplement, however, are difficult to justify because the alkaloids have no demonstrated benefit.

**Caffeine** is present in many products that contain ephedra alkaloids, and those who take these products might also be consuming considerable quantities of caffeine in coffee, tea, and soft drinks. Caffeine is likely to enhance the cardiovascular and central nervous system effects of ephedrine. Caffeine acts by competitively antagonizing the receptors for adenosine, a hormone released by endothelial cells that dilates blood vessels. (Benowitz NL, 1990) By inhibiting adenosine-mediated dilatation of blood vessels, caffeine constricts blood vessels and may increase blood pressure in persons prone to hypertension. Caffeine also augments the release of catecholamines, an effect that, when combined with that of ephedrine, could lead to increased stimulation of the central nervous system and cardiovascular system. (Robertson D, Frolich JC et al, 1978)

**Phenylpropanolamine**, another ephedrine alkaloid, was marketed with caffeine in various weight-reducing aids until 1983, when the combination was banned by the FDA after numerous reports of adverse effects. Several studies have shown that caffeine and phenylpropanolamine have an additive effect on blood pressure. (Brown NJ, Ryder D et
al, 1991) These interactions between phenylpropanolamine and caffeine support the idea that the combination of ephedrine and caffeine in a dietary supplement could increase the risk of adverse effects.

8.8.1.3 Yellow oleander (*Thevetia neriifolia*)

Yellow oleander (*Thevetia neriifolia*) is a commonly grown tree found widely in Eastern India. (Bose TK, Basu RK et al, 1999) The seeds of yellow oleander are highly poisonous and contain three glycosides—thevetin, thevetoxin and peruvoside. Yellow oleander seed ingestion is usually with suicidal intent in Eastern India.

In the case of oleander, all plant tissues, including the seeds, roots, stems, leaves, berries, and blossoms, are considered extremely toxic. (Safadi R, Levy I, et al, 1995) In fact, death in humans has been reported following ingestion of as little as 1 oleander leaf. (Szabuniewicz M, McGrady JD et al, 1971) The clinical manifestations of oleander intoxication, as well as other natural glycosides, are virtually identical to digoxin overdose. Morbidity and mortality are mainly related to cardiotoxic adverse effects that usually include life-threatening ventricular tachyarrhythmias, bradycardia, and heart block. The diagnosis should rely on the clinical presentation of unexplained hyperkalemia, and cardiac, neurologic, and gastrointestinal symptoms. (Safadi R, Levy I et al, 1995)

Poisoning symptoms indicated serious cardiac, neuromotor and mental malfunctioning, and manifested as tachycardia, arrhythmia, paralysis, ataxia and disorientation. (Oji O and Okafor QE, 2000) Serious yellow oleander induced arrhythmias were associated with higher serum cardiac glycoside concentrations and hypokalemia but not with disturbances of magnesium. (Eddleston M, Ariaratnam CA et al, 2000) Anti-digoxin Fab fragments are a safe and effective treatment for serious
cardiac arrhythmias induced by yellow oleander. The diagnosis can be further supported by the detection of the substance digoxin in a radioimmunoassay for digoxin.

8.8.1.4 Stephania tetrandra

*Stephania tetrandra* is an herb sometimes used in traditional Chinese medicine to treat hypertension. Tetrandrine, an alkaloid extract of *S. tetrandra*, has been shown to be a calcium ion channel antagonist, paralleling the effects of verapamil. Tetrandrine blocks T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-channel binding sites, and suppresses aldosterone production. *(Rossier MF, Python CP et al, 1993; Sutter MC and Wang YX, 1993)* A parenteral dose (15 mg/kg) of tetrandrine in conscious rats decreases mean, systolic, and diastolic blood pressures for more than 30 minutes; however, an intravenous 40-mg/kg dose killed the rats by myocardial depression. In stroke-prone hypertensive rats, an oral dose of 25 or 50 mg/kg produced a gradual and sustained hypotensive effect after 48 hours without affecting plasma renin activity. *(Kawashima K, Hayakawa T et al, 1990)*

In addition to its cardiovascular actions, tetrandrine has reported antineoplastic, immunosuppressive, and mutagenic effects. *(Sutter MC and Wang YX, 1993)*

Tetrandrine is 90% protein-bound with an elimination half-life of 88 minutes, according to dog studies; however, rat studies have shown a sustained hypotensive effect for more than 48 hours after a 25- or 50-mg oral dose. Tetrandrine causes liver necrosis in dogs orally administered 40 mg/kg of tetrandrine 3 times weekly for 2 months, reversible swelling of liver cells with a 20-mg/kg dose, and no observable changes with a 10-mg/kg dose. *(Sutter MC and Wang YX, 1993)* Given the evidence of hepatotoxicity, many more studies are necessary to establish a safe dosage of tetrandrine in humans.

More recently, tetrandrine has been implicated in an outbreak of rapidly progressive
renal failure, termed Chinese herb nephropathy. Numerous individuals developed the condition after using a combination of several Chinese herbs as part of a dieting regimen. It has been hypothesized that the cause may be attributed to misidentification of S tetrandra; nonetheless, questions still remain as to the role of tetrandra in the development of this serious toxic effect. (Vanherweghem JL, 1994; Schmeiser HH, Bieler CA et al, 1996; Violin C, 1997)

8.8.1.5 Danshen (*Salvia miltiorrhiza*)

*Salvia miltiorrhiza* (Danshen), a relative of the Western sage *Salvia officinalis*, is native to China. (Mashour NH, Lin GI et al, 1998) Danshen is used in TCM to promote blood flow and treat cardiovascular diseases. Besides function of circulatory stimulant, sedative, and cooling are also available. It is sold in over-the-counter herbal preparations, prescribed by TCM doctors and administered in Chinese hospitals for angina pectoris, acute myocardial infarction (MI) and ischemic and thrombotic disorders.

*Salvia miltiorrhiza* may be useful as an antianginal drug because it has been shown to dilate coronary arteries in all concentrations, similar to *P. notoginseng*. Furthermore, *S. miltiorrhiza* also shown to have protecting function of myocardial mitochondrial membranes from ischemia-reperfusion injury and lipid peroxidation because of its free radical-scavenging effects. (Zhao BL, Jiang W et al, 1996) In vitro and animal studies suggest it may be vasoactive, scavenge free radicals and inhibit platelet aggregation. (Wang Z, Roberts JM et al, 1982) The active compounds in danshen are tanshinones and phenolic compounds. (Lei XL and Chiou G.C, 1986)

8.8.1.6 Ginkgo biloba

*Ginkgo biloba*, is derived from the leaves of the maidenhair tree. (Valli G and Giardina EGV, 2002) Although the root and kernels of *G. biloba* have long been used in
traditional Chinese medicine, the tree gained attention in the West during the 20th century for its medicinal value after a concentrated extract of *G. biloba* leaves was developed in the 1960s. (Mashour NH, Lin GI et al, 1998) It is used for cognition and memory as well as cerebrovascular disease, peripheral vascular disease, sexual dysfunction, affective disorders, multiple sclerosis, retinal disorders and hearing loss.

The mechanisms by which ginkgo and its constituent compounds improve vascular health include free radical scavenging, antiplatelet actions, anti-inflammatory actions, vasodilation and decreased blood viscosity. Gamma-aminobutyric acid receptor agonism and inhibition of monoamine oxidase-B have also been investigated. Active isolates of ginkgo fall into two classes: flavonoids and terpenoids.

At least two groups of substances within *G. biloba* extract (GBE) demonstrate beneficial pharmacological actions. The flavonoids reduce capillary permeability as well as fragility and serve as free radical scavengers. The terpenes (ie, ginkgolides) inhibit platelet-activating factor, decrease vascular resistance, and improve circulatory flow without appreciably affecting blood pressure. Continuing research appears to support the primary use of GBE for treating cerebral insufficiency and its secondary effects on vertigo, tinnitus, memory, and mood; also, GBE appears to be useful for treating peripheral vascular disease, including diabetic retinopathy and intermittent claudication. Ginkgo may improve intermittent claudication via vasoregulation, platelet antagonism and protection against postischemic oxidative damage. (Kleijnin J and Knipschild P, 1992; Matthews MK, Jr, 1998)

Ginkgo may inhibit platelets and platelet-induced postischemic inflammatory response by antagonism of platelet activating factor (PAF), which has been implicated in reperfusion injury and cardiac dysfunction in shock. (Montrucchio G, Alloatti G. et al,
Ginkgolide B is a potent inhibitor of PAF in humans. (Chung KF, Dent G et al, 1987; Braquet P, 1993) Other components of ginkgo extract have been identified as inhibitors of phospholipase A2, and thus the production of PAF as well as eicosanoids.

Although approved as a drug in Europe, Ginkgo is not approved in the United States and is instead marketed as a food supplement, usually supplied as 40-mg tablets of extract. The recommended dosage in Europe is one 40-mg tablet taken 3 times daily with meals (120 mg/d). (Z'Brun A, 1995) Commission E recommends 120 to 240 mg extract two to three times daily for cerebral insufficiency. (Blumenthal M, Busse WR et al, 1998)

Two cases of CNS hemorrhage occurred with ginkgo, 120 to 160 mg/day. (Rowin J and Lewis SL, 1996; Vale S, 1998) Common side effects are nausea, dyspepsia, headache and allergic skin reactions. (Kleijnin J and Knipschild P, 1992; Pittler MH and Ernst E, 2000) More serious adverse effects, including spontaneous subdural hematomas, (Rowin J and Lewis SL, 1996) intracerebral hemorrhage (Vale S, 1998) and hyphema, (Rosenblatt M and Mindel J, 1997) as well as warfarin and trazodone interactions, have been described.

8.8.1.7 Dong Quai (Angelicae Sinensis)

Dong quai is a popular Chinese herbal medicine. (Page RL, 2nd and Lawrence JD, 1999) In China, it is prepared as a soup, with half-dollar-sized pieces of thinly cut, dried root of Angelica sinensis added to chicken stock. In the United States, dong quai is sold as a powder contained in capsules. It is among the 20 top selling herbal medicines.

In humans, dong quai has been evaluated for estrogenic effects. (Hirata JD, Swiersz LM et al, 1997) It is taken by women as palliation for dysmenorrhea, irregular menstruation, anemia, postpartum weakness, and uterine hypotonia. Quinidine-like
effects have been reported in animals, (Zhu DP, 1987) but not evaluated in clinical trials. Antithrombotic effects are attributed to coumarin derivatives and ferulic acid contained in the oil of the root. (Zhu DP, 1987; Page RL, 2nd and Lawrence JD, 1999)  Ferulic acid may cause platelet dysfunction by inhibiting production of thromboxane A2. (Page RL, 2nd and Lawrence JD, 1999) Case reports of warfarin potentiation have been reported, and an interaction is supported by animal studies, which demonstrate alteration of warfarin pharmacodynamics after dong quai.

More than this, dong quai was reported to have relation to cause hypertension. (Namibar S, Schwartz RH et al, 1999) A previously health 32 year old woman of Chinese-Malaysian origin. Three weeks postpartum, was admitted to an emergency ward due to an acute onset of headaches, weakness, lightheadedness, and vomiting. The patient stated that she had ingested a special ethnic soup prepared by her mother, who had recently arrived from Malaysia to help with postpartum chores. The soup had been made with pieces of the Dong quai root (Angelica sinensis) purchased in Malaysia. She improved rapidly and was normotensive within 12 hours. However, her 3-week old son was taken to the pediatrician for evaluation and was confirmed to have hypertension on the next day. The baby was not treated with antihypertensive medication, and luckily his pressure normalized within 48 hours.

8.8.1.8 Licorice (Glycyrrhiza Glabra)

Licorice, an extract of the root of Glycyrrhiza glabra, is used as a sweetening and flavoring agent in Western countries. But in China, it has its pharmacutical function and used in pharyngolaryngitis, cough, palpitation, stomachache due to asthenia, peptic ulcer, pyogenic infection and ulceration of the skin. (Walker B and Edwards CRW, 1994;
The active constituent of licorice is glycyrrhizic acid. A metabolite, glycyrrhetinic acid, inhibits renal 11β-hydroxysteroid dehydrogenase and causes a state of mineralocorticoid excess by impeding the inactivation of cortisol. The extract, powder, glycyrrhizin, and glycyrrhetinic acid of the herb exhibited deoxycorticosterone-like action, reducing the urinary volume and sodium excretion and increasing potassium excretion in various animal species. (Chang H and But P, 1987) However, the herb could not maintain the electrolyte balance in bilaterally adrenalectomized rats, nor could it prolong their lives. A so-called pseudo-aldosteronism with manifestations of edema and hypertension could develop in association with its clinical use. When used in high dosages for long periods, licorice may cause pseudoaldosteronism, which can be manifested as headache, lethargy, sodium and water retention, hypokalemia, hypertension, heart failure, and cardiac arrest. To minimize the risk of adverse effects, German Commission E recommends that licorice be used for no longer than four to six weeks.

Case reports link licorice to hypertension, hypertensive encephalopathy, pulmonary edema, edema, hypokalemia, arrhythmias, CHF, muscle weakness and acute renal failure. Dilated cardiomyopathy resulting from excessive use of licorice and glycyrrhizin for gastritis has been reported. Moreover, a patient with hypokalemia and severe ventricular tachycardia of torsades de pointes type, which turned out to be caused by an apparent mineralocorticoid excess syndrome, associated with liquorices consumption. Base on the information stated that 50 to 100 g of confectionary licorice, or 50 to 300 mg glycyrrhetinic acid, over weeks may cause adverse effects. (Heikens J, Fliers E et al,
1995) Adverse effects may take weeks to reverse because of suppression of the reninangiotensin - aldosterone axis and because glycyrrhetinic acid has a large volume of distribution. The use of licorice is contraindicated in patients with liver cirrhosis, cholestatic liver disorders, hypertonia, kidney diseases, hypokalemia, pregnancy, and cardiovascular diseases. (Walker B and Edwards CRW, 1994)

8.8.1.9 Berberine

Berberine, is an alkaloid from Hydrastis canadensis L., Chinese herb Huanglian. (Lau BH, 2001) It is widely used in traditional Chinese medicine as an antimicrobial in the treatment of dysentery and infectious diarrhea. Berberine has positive inotropic, negative chronotropic, antiarrhythmic, and vasodilator properties. Both derivatives of berberine have antiarrhythmic activity. Some cardiovascular effects of berberine and its derivatives are attributed to the blockade of K^+ channels (delayed rectifier and K(ATP)) and stimulation of Na^+-Ca^{2+} exchanger. Berberine has been shown to prolong the duration of ventricular action potential.

8.8.2 Potential Problem Caused by Chinese Proprietary Medicine.

Base on the fact that many products that contain ephedra also contain multiple stimulants such as caffeine and are marketed for weight loss, energy and performance enhancement, body building, and as substitutes for street drugs. Such kind of 'cocktails' containing multiple pharmacological compounds appears to have produced an undesirable and potentially dangerous interaction. Furthermore, the amount of the active substance stated may not be accurate. (Gurley BJ, Gardner SF et al, 2000; Mansoor GA, 2001) In addition, these kinds of products may contain multiple ephedra alkaloids that may cause summation adverse effects by acting through similar mechanisms of action. The Food and Drug administration has not approved any product with multiple ephedra-
like alkaloids because of fear of synergistic side effects. Consumers should consider buying from manufacturers that have obtained Pharmacopoeia standards for product purity and content reliability, thus at least ensuring some standards are used in manufacture.

8.9 Other Herbal Adverse Effects and Drug Interactions

Interactions of herbals and supplements with the cardiovascular medications will affect the pharmacokinetic or pharmacodynamic properties of antihypertensive drugs. In the case of hypertension, the achievement of goal blood pressure (BP) especially in high-risk patients with diabetes or renal disease routinely requires multiple drugs. Therefore, not only is it likely that drug–drug interactions will occur as the number of drugs increases in an individual patient but also the likelihood that drug–supplement or drug–herb interactions will occur. Any herb with cardioactive, hypertensive or hypotensive action may interfere with nitrate drugs (e.g. isosorbide dinitrate) which are potent coronary dilators or with calcium channel blocking drugs (e.g. nifedipidine) used to treat angina, hypertension and arrhythmias. A number of herbs, including adonis, black Indian hemp (apocynum), black hellebore, lily-of-the valley (convallaria), squill and strophanthus, contain cardiac glycosides that can potentiate digoxin. (Tyler VE, 1994) St. John’s wort (Hypericum perforatum) decreases serum levels of digoxin through induction of a p-glycoprotein drug transporter. (Johne A, Brockmoller J et al, 1999) In a single-blind, placebo-controlled study, after 10 days of St. John’s wort, digoxin levels were reduced more than 25%. (Johne A, Brockmoller J et al, 1999) Several herbs used for a laxative effect, such as senna, cascara sagrada and buckthorn, (Tyler VE, 1994) may augment potassium loss and lead to toxicity in digoxin users. Belladonna, an herb used for gastrointestinal symptoms, is a source of atropine and may cause
tachycardia. (Blumenthal M, Busse WR et al, 1998) A number of herbs contain sympathomimetic amines, e.g. parsley, and there is the risk of developing hypertension when used with pharmaceutical medicines which also have sympathomimetic action (e.g. isoprenaline, ephedrine). *Gypsum Fibrosum, Concha Ostreae, Os Draconis* and *Os sepiæ* are contain calcium ion and are not suitable in using with digoxin.

8.10 Conclusion

Continuing research is necessary to elucidate the pharmacological activities of the many cardiopotent herbal medicines and to stimulate future pharmaceutical development of therapeutically beneficial herbal drugs. Legal surveillance of herbal medicine use with low safety margins should be instituted for the sake of public health; this is especially imperative for those herbs with adverse cardiovascular reactions and drug interactions. Adverse effect data is almost exclusively available as case reports and, as a result, may be vastly underreported. (Valli G and Giardina EGV, 2002) Lack of regulation of quality control and of product standardization makes it difficult to establish safe doses of herbal products. Considering that the growing appeal of herbal remedies is likely to continue, physicians, particularly cardiologists, must become familiar with the available cardiovascular information on herbs. As more information becomes available regarding the safety and efficacy of herbal medicines through new clinical trials, research-supported claims may one day become available to consumers and physicians in a manner similar to the allopathic medicines.
Chapter 9 - Review of the Adverse Reactions to Herbal Treatments of Obesity

9.1 Overview

Overweight and obesity are the most common nutritional disorders in modern society. Successful weight loss and healthy weight management depend on long-term lifestyle changes such as reducing calorie consumption and increasing physical activity. However, because patients find these changes difficult, easily obtained nonprescription weight loss products and prescription diet pills are an appealing alternative to the increasingly overweight worldwide population. In 1999, $321 million was spent in the United States on prescription medications to treat obesity. (Wilhelm C, 2000) Between 1996 and 1998, 2.5% of the adults in the United States — or about 4.6 million persons — reported having used such medications. (Khan LK, Serdula MK et al, 2001) Approximately 10% of women and 3% of men with a body-mass index of 30 or higher have reported using weight-loss medications for obesity. Health care professionals should be concerned about overweight and obesity because of the well-established relations between excess body weight and such medical conditions as type 2 diabetes, hypertension, and osteoarthritis. (Anonymous, 2000) Medications for the treatment of obesity are currently approved for use in adults who have a body-mass index of 27 or higher plus obesity-related medical conditions or a body-mass index of 30 or higher in the absence of such conditions. (Montvale NJ, 2001)

9.2 Combination With Unknown Medication

The adulteration of Chinese patent medicines with synthetic therapeutic substances has been reported in several industrialized countries over the past two decades. The
Department of Health in Hong Kong advised members of the public not to buy and use the "slimming health food -- Slim Smile" which contained a western drug ingredient -- mazindol last year. This patent medicine "Slim Smile" was sold in the form of capsules and is imported from the United States and the adverse effects of mazindol include nervousness, fatigue, irregular heart beat, insomnia, dizziness, headache and abdominal cramps. As a result, a surveillance programme held by government to regularly sample and analyze "health food" and proprietary Chinese medicine was necessary to detect the presence of western medicine ingredients. Even batches of the herbal medicine from the same manufacturer may contain variable amounts of active or potential toxic ingredients.

9.3 Dietary Supplements and Herbal Preparations

According to the fact that many patients do not inform their physicians about their use of these products. Dietary supplements and alternative therapies are a particular challenge for physicians. In the past few years, the FDA has investigated more than 800 reports of adverse reactions associated with more than 100 different products that contained or were thought to contain Ephedra alkaloids. Many herbal supplements used to treat obesity also have caffeine and ephedrine-containing herbs in them. Commercially available products are not well standardized, varying greatly in content of active ingredients.

Allison and colleagues critically reviewed the published literature on herbal and dietary supplements for which claims have been made about the promotion of weight loss: chitosan, chromium picolinate, conjugated linoleic acid, ephedra alkaloids (ma huang), and garcinia cambogia. (Allison DB, Fontaine KR et al, 2001) They found that most such reports were based on poorly designed trials that lacked randomization, blinding, or control groups. Although some dietary supplements have mechanisms of
action that could plausibly lead to weight loss or have shown promising results in small-scale studies in humans or animals. Allison et al. found that there were insufficient data to provide evidence of either the safety or the efficacy of any of these compounds as agents promoting weight loss. Herbal compounds containing ephedra alkaloids and caffeine are the only types for which there are data from randomized, double blind, placebo-controlled trials indicating efficacy in promoting weight loss. (Boozer CN, Nasser JA et al, 2001)

Ephedrine is an adrenergic agent with thermogenic and appetite-suppressant properties. Ephedra contains alkaloids, including ephedrine, pseudoephedrine, norephedrine, methylephedrine, and norpseudoephedrine. (Gurley BJ, Gardner SF et al, 1998) Ephedra causes dose-dependent increases in blood pressure and heart rate. Dietary supplements that contain ephedra alkaloids are widely promoted and used in the United States as a means of losing weight and increasing energy. (Haller CA and Benowitz NL, 2000) Ephedrine in combination with caffeine, aspirin, or both, has been found in controlled trials to produce greater weight losses than placebo for periods of up to one year, although most studies have been short-term. (Astrup A, Breum L, Toubro S, Hein P, Quaade F, 1992; Breum L, Pedersen JK, Ahlstrom F, Frimodt-Moller J, 1994)

Ephedra (ma huang) is commonly found in herbal weight-loss products referred to as "herbal fen-phen." Marketed uses of ephedrine-containing products such as "herbal ecstasy" include induction of a euphoric state and heightening of awareness and sexual sensations. Dietary supplements containing ephedra alkaloids frequently contain a dosage that differs substantially from that indicated on the product label. Case reports concerning ephedra alkaloids (often in combination with caffeine) have noted serious cardiovascular and central nervous system events, including hypertension, cardiac
arhythmia, stroke, seizure, myocardial infarction, and sudden death. Concomitant use of ephedra and monoamine oxidase inhibitors can result in life-threatening hyperpyrexia, hypertension, and coma. Finally, heavy use of ephedra has been documented as a very rare cause of radiolucent kidney stones. (Powell T, Hsu FF et al, 1998) Subarachnoid hemorrhage is thought to be a result of the hypertensive action of ephedrine, which can be short lived, or of cerebral vasculitis, which has been described in association with a variety of sympathomimetic drugs. (Wooten MR, Khangure MS et al, 1983; Fallis RJ and Fisher M, 1985) Because of potential adverse health effects among persons with diabetes, hypertension, heart disease, and other conditions, the FDA has recommended a labeling statement that instructs ephedra users to seek the advice of a health care provider before use.

Since obesity is a chronic disease, it is possible that individuals may use nonprescription products to maintain weight loss; however, use of these products by normal-weight individuals could expose them to risks for which there are no counterbalancing benefits.

9.4 Conclusion

Losing weight is difficult for most obese persons, yet long-term maintenance of a reduced weight is even more challenging. Even several kinds of prescription were currently approved for control body weight, and can help carefully selected obese patients lose weight and can reduce the rate of regain, behavioral interventions to improve diet and increase physical activity are considered the primary means to promote and maintain weight loss. Weight-loss medications should be considered as an adjunct only for patients who are at substantial medical risk because of their obesity and in whom nonpharmacologic treatments have not resulted in sufficient weight loss to
improve health or to prevent regain. Providing appropriate science-based advice will be a challenge for health care professionals because of the increasing variety of nonprescription products on the market and the lack of methodologically sound efficacy studies. With such understanding, we can hope not only to develop safe and effective ways to help obese persons to achieve and maintain a healthy weight but also to understand how to prevent the development of obesity in those who are at risk.
Chapter 10 - Adverse effects of CHM used for Diabetes.

10.1 Introduction

Type 2 diabetes is a global health problem of enormous magnitude, especially in newly industrialized nations. (Paul Z, 1999) Projections recently published by the World Health Organization (WHO) suggest that there will be well over 150 million people with diabetes in the year 2000 and expect the number to reach 300 million by the year 2025. (Gojka R et al, 1999) The majority of the new cases will be those with Type 2 diabetes and the majority of these will be in China, the Indian subcontinent and Africa. Although insulin is a life-saving drug it is not a “cure-all”. A growing public interest in herbal medications for this metabolic disorder has developed around the world. Insulin-resistance and the poor response of neuropathic complications in diabetic patients receiving insulin treatment have encouraged the development of alternative medication. (Cheng JTYRS, 1983) The known use of plant treatments for diabetes dates from the Ebers papyrus of about 1550 BC. (John C et al, 1998) Many traditional plant treatments for diabetes are used throughout the world.

10.2 Traditional Chinese medicine used in Diabetes

Traditional Chinese herbs are used for protecting from and treating diseases under the guidance of therapy of TCM and they have properties of natural herb, but it has the special connotation and unique theory system and application method. Many herbs used in Chinese traditional medicine and natural products have been attributed with hypoglycemic effects. (see Table 10 a)
Table 10 a. Herbs used in Chinese traditional medicine that may be attributed with hypoglycemic effects.

<table>
<thead>
<tr>
<th>Chinese Name</th>
<th>Herb</th>
<th>Botanical Name</th>
<th>Active Part</th>
<th>Main Chemical Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baizhu</td>
<td>Atractylodes macrocephala</td>
<td>Rhizome</td>
<td>Volatile oils - mainly atractylol and atractylone</td>
<td></td>
</tr>
<tr>
<td>Cangzhi</td>
<td>Xanthium sibiricum</td>
<td>Fruit</td>
<td>Glycosides etc</td>
<td></td>
</tr>
<tr>
<td>Cangzhu</td>
<td>Atractylodes lancea</td>
<td>Rhizome</td>
<td>Volatile oils mainly β-eudesmol and hinesol</td>
<td></td>
</tr>
<tr>
<td>Changchunhua</td>
<td>Catharanthus roseus</td>
<td>Plant</td>
<td>Alkaloids including vinblastine and vincristine</td>
<td></td>
</tr>
<tr>
<td>Danshen</td>
<td>Salvia miltiorrhiza</td>
<td>Root</td>
<td>Tanshinones and derivatives</td>
<td></td>
</tr>
<tr>
<td>Digupi</td>
<td>Lycium chinense</td>
<td>Root bark</td>
<td>Betaine, β-sitosterol etc</td>
<td></td>
</tr>
<tr>
<td>Dihuang</td>
<td>Rehmannia glutinosa</td>
<td>Rhizome</td>
<td>β-sitosterol, mannitol etc</td>
<td></td>
</tr>
<tr>
<td>Gouqizi</td>
<td>Lycium barbarum</td>
<td>Fruit</td>
<td>Betaine etc</td>
<td></td>
</tr>
<tr>
<td>Huangjing</td>
<td>Polygonatum spp.</td>
<td>Rhizome</td>
<td>Mucilage etc</td>
<td></td>
</tr>
<tr>
<td>Jiegeng</td>
<td>Platycodon grandiflorum</td>
<td>Root</td>
<td>Platycodin etc</td>
<td></td>
</tr>
<tr>
<td>Maiya</td>
<td>Hordeum vulgare L. germinating</td>
<td>Sprouts</td>
<td>α-amylase, β-amylase, maltose etc</td>
<td></td>
</tr>
<tr>
<td>Sangye</td>
<td>Morus alba L.</td>
<td>Leaf</td>
<td>Ecdysterone etc</td>
<td></td>
</tr>
<tr>
<td>Xianhecao</td>
<td>Agrimonia pilosa</td>
<td>Plant</td>
<td>Agrimonin etc</td>
<td></td>
</tr>
<tr>
<td>Xuanshen</td>
<td>Scrophularia ningpoensis</td>
<td>Root</td>
<td>Scrophularin etc</td>
<td></td>
</tr>
<tr>
<td>Yinyanghuo</td>
<td>Epimedium spp.</td>
<td>Plant</td>
<td>Icariin, flavones etc</td>
<td></td>
</tr>
<tr>
<td>Yumixu</td>
<td>Zea mays</td>
<td>Style and Potassium nitrate, vitamin K etc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuzhu</td>
<td>Polygonatum odoratum</td>
<td>Rhizome</td>
<td>Convallamarin and various glycosides</td>
<td></td>
</tr>
<tr>
<td>Zexie</td>
<td>Alisma orientalis</td>
<td>Tuber</td>
<td>Triterpenes etc</td>
<td></td>
</tr>
<tr>
<td>Zhimu</td>
<td>Anemarrhena asphodeloides</td>
<td>Rhizome</td>
<td>Saponins etc</td>
<td></td>
</tr>
</tbody>
</table>

10.3 Adverse Reactions to Alternative Diabetic Treatments

Many natural products are promoted to improve the health status of patients with diabetes by people making a profit on these products. (Gori M and Campbell RK, 1998)

Few of these claims have any scientific basis. Certain natural products are potentially
damaging to patients with chronic diseases, especially if the products are used instead of proven scientific treatment regimens.

Diabetic patients who are treated with insulin and/or hypoglycemic drugs are at a greater risk of suffering hypoglycemic episodes than diabetic patients treated by diet only, a fact that has been supported by the widespread systemic monitoring of blood glucose during the last decade. (Unger RH, 1982; Bolli G, De Feo P et al, 1983) Several mechanisms for the development of hypoglycemia during renal insufficiency have been found, including reduced renal gluconeogenesis and decreased energy intake. 45% of new glucose supply from renal gluconeogenesis in normal patients could be found during prolonged starvation. (Rutsky E, McDaniel HG et al, 1978) Therefore, elderly diabetic patient with impaired renal function should be aware from episode of drug-induced hypoglycemia. (see Table 10 b)

An investigative survey in 1997 showed that nearly thirty percent of Americans aged 65 and older using alternative medicine. (Foster DF, Phillips RS et al, 2000) Almost three million people aged 65 and older took herbal therapies, with two million taking both herbal therapies and prescription medications. Those who use both prescription medications and herbal therapies are at potential risk for unintended adverse interactions. Especially for some Chinese proprietary medicines contain western drugs either legitimately, with a declaration on the package or package insert, or as a hidden adulterant which may increase the short-term efficacy of the preparation. Hypoglycemia due to the consumption of “Xiao Kee Wan” has been described in the Chinese literature. Hue reported a case of a 67 year old diabetic male who died from severe hypoglycemia after taking “Xiao Kee Wan” 8 pills tad for 1 month. (Hui X, Li J et al, 1992) Due also reported 2 cases of hypoglycemia with the use of “Xiao Ke Wan”. (Xue D and Xue LX,
Both patients were female diabetics, aged 73 and 67 years, with normal renal function and they had taken 5 pills bid for 5 days and 4 pills bid for 14 days respectively. Both recovered after intravenous glucose. Tomlinson B. reported another case of severe hypoglycemia caused by “Xiao Ke Wan” and “Liu Wei Di Huang Wan”. A 53-year-old Chinese male was brought to Emergency department due to loss of conscious. He was found to be hypoglycemic with plasma glucose of 2.0 mmol/L. Physical examination revealed a mild left hemiparesis, bilateral symmetrical glove-and-stock sensory neuropathy, bilateral retinopathy with previous laser scars and bilateral ankle edema. Investigations revealed that the patient had severe renal impairment with plasma urea 24.9 mmol/L, creatinine 549 μmol/L and 24-hour urine protein 4.8 g/d. There was a normochromic normocytic anaemia and phosphate retention as well as metabolic acidosis. The patient was suffered 4 years of diabetes mellitus with bilateral proliferative retinopathy. He had a cerebrovascular accident whilst in China three months later and he was treated with Chinese herbal medicines. When he come back to Hong Kong, he started to treat his diabetes by himself with three over-the-counter Chinese patent medicines “Xiao Ke Wan”, “Xin Nao Shu Tong” and “Liu Wei Di Huang Wan” which were purchased from a pharmacy in China. The patient adjusted the dosage by himself without any consultation with herbal practitioner. Two weeks before this admission, he had increased the dosage of “Xiao Ke Wan” from 5 pills to 10 pills daily because of bilateral ankle swelling, polyuria and nocturia over the previous month. After analyzed, the dosage that the patient took was approximately 1.25 mg glibenclamide daily that may have produced adequate diabetic control, but after doubling the dose to increase the diuretic effect he developed toxicity. The action of glibenclamide may be enhanced by various other drugs such as “Liu Wei Di Huang
Vautier report a case of
fulminant hepatic failure happened after taken a locally dispensed Chinese herbal remedy called "eternal life," as treatment for simple lipomas for 4 weeks. (Vautier G and Spiller RC, 1995) One week later he was deeply jaundiced and became encephelopathic. Despite urgent liver transplantation he died and no viral, immunological, or metabolic cause for his liver failure was identified. Analysis of the herbal remedy that this man had taken confirmed the presence of Dictamnus dasycarpus; this herb was found to have hepatotoxicity. Another similar adverse reaction was a 27-year-old insulin-dependent diabetic man presented with a two-week history of progressive jaundice after consuming "eternal life." (Sanders D, Kennedy N et al, 1995) After analyzed, there was a high possibility of relation between the herbal tea and this patient's hepatitis. Liver biopsy showed inflammation around the portal tract and piecemeal necrosis. The patient's clinical condition improved over the next four weeks.

A 72-year-old Portuguese woman experienced sudden onset of nausea, vomiting, and diaphoresis after she drank a glass of extract made from lupine beans. (Tsiodras S, Shin RK et al, 1998) She also complained of blurred vision and generalized weakness. She took the preparation with the belief it represented a cure for her recently diagnosed diabetes. Analysis of the patient's lupine bean extract identified a significant amount of the preponderant compound as oxo-sparteine by gas chromatography / mass spectrometry. Lupine beans are commonly eaten as an appetizer in Southern Europe and the Middle East. People in Portugal and Southern Europe believe that the extract from boiled lupines has hypoglycemic effects even no scientific supports such a belief that lupine extract could lower blood sugar levels. It should be noted that nearly 100 different species are found in the United States but not all species are poisonous. Toxicity actually depends on the amount of toxic alkaloids contained. Sparteine like
other quinolizidine alkaloids (such as anagyrine and lupanine, as well as piperidine) have been implicated in producing dyspnea, restlessness, spasms, coma, and even death as a result of respiratory paralysis in cases of acute intoxication in animals, as well as classic anticholinergic effects. Lupine beans in a natural state are very bitter and toxic and need debittering process continues for several days. In this case, the patient drank a glassful of the bitter water in which the beans had been initially boiled in the belief that it could lower her blood sugar level. The patient was discharged home less than 24 hours after her initial admission.

Another herb need to pay caution was ephedra (Ma Huang). It is an herbal stimulant that acts similarly to amphetamine. Approved by the U.S. Food and Drug Administration (FDA) in some asthma medications, but it was also widely used in combination with caffeine in unregulated supplements for losing weight, building muscle, or giving energy. These alkaloids were implicated in over 800 reports of adverse effects including nervousness, insomnia, irritability, psychosis, headache, dizziness, seizures, stroke, premature ventricular contraction, hypertension, myocardial infarction, and death. (Boullata J and Nace AM, 2000) As a result the FDA proposed limits on the use of ephedrine-containing products: a maximum of 8 mg/dose and 24 mg/day for no more than a week, and combined with no products that contain caffeine. Studies show the actual doses of ephedra found in supplements vary dramatically from much less to much more than the stated content on the label. For people with diabetes, the risks are even greater because ephedra can raise blood sugars dramatically and make control extremely difficult.

Gill GV (Gill G, Redmond S et al, 1994) reported that four patients with insulin-dependent diabetes reduced or stopped their insulin in favor of therapeutic approaches
including prayer, faith healing, unusual diets, and supplements of vitamins and trace elements. This resulted in ketoacidosis in three, in one case life threatening; and weight loss and hyperglycemia in the other. One patient developed serious retinopathy.

A case of acute hepatic and renal toxicity associated with drinking sheep bile for diabetic treatment was report in Saudi Arabia. (Anonymous, 1996) A traditional healer in Al-Wadein village had advised patients with diabetes to drink raw sheep bile as a treatment for their diabetes. After drinking sheep bile, the patient was found to have gastrointestinal, hepatic, and renal toxicity.

Table 10 b. Herbs Affecting Blood Glucose and Associated Adverse Effects.

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Associated Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aconitum carmichaelie</em></td>
<td>Subject to poison control in some Australian states</td>
</tr>
<tr>
<td><em>Arctium lappa</em> (burdock root)</td>
<td>Commission E state the root is not permitted for therapeutic use; usefulness not documented adequately; no risks was known</td>
</tr>
<tr>
<td><em>Artemisia abbyssinica</em></td>
<td>Essential oil should not be used; listed as unsafe in FDA (1975)</td>
</tr>
<tr>
<td><em>Catharanthus roseus</em></td>
<td>Subject to poison control in some Australian states</td>
</tr>
<tr>
<td><em>Echinacea spp.</em> (coneflower)</td>
<td>Contraindicated in progressive systemic diseases (eg. Tuberculosis, MS) according to Commission E; associated with metabolic worsening in some diabetic patients; should not be used more than three weeks.</td>
</tr>
<tr>
<td><em>Eleutherococcus senticosus</em></td>
<td>Should not be given to patients whose blood pressure exceed 180/90 mmHg; palpitations, pressure headaches, and arrhythmias have been reported in the Russian literature.</td>
</tr>
<tr>
<td><em>Lupinus termis</em></td>
<td>Lupinus extracts cause &quot;crooked calf disease&quot;, a congenital abnormality in bovine stock</td>
</tr>
<tr>
<td><em>Momordica charantia</em> (karela, bitter melon)</td>
<td>Hepatic necrosis has been associated with excessive intake; testicular lesions have occurred in dogs.</td>
</tr>
<tr>
<td><em>Taraxacum officinalis</em> (dandelion root)</td>
<td>Contraindicated in biliary obstruction empyema of gallbladder and ileus; can produce poisoning especially in children (nausea, vomiting, diarrhea and arrhythmias)</td>
</tr>
<tr>
<td><em>Vaccinium myrtillus</em> (huckleberry)</td>
<td>Doses &gt; 1g may result in nausea, vomiting, diarrhea, fibrillation, dyspnea, cyanosis, delirium and collapse; hemolytic anemia, cachexia, hepatic steatosis, and hair depigmentation have been reported; fetal doses range from 2 to 12 g.</td>
</tr>
</tbody>
</table>
10.4 Conclusion

Diabetes is a chronic incurable disease, for which modern treatments remain somewhat unsatisfactory. It is therefore perhaps not surprising that some patients seek alternative treatments with more attractive claims. However, the lack of such trials has been characterized as a major deficiency in the assessment of alternative therapies. It is important to remember that these adverse events are extremely unusual. Chinese herbal medicine is generally both safe and effective, and there are many patients who have experienced dramatic benefits to their health from treatment. All medicines are assessed in terms of their risk-benefit ratio and it should not be surprising that Chinese herbal medicines may also have occasion rare but significant adverse events. Patients should be taught the importance of using proven effective treatment regimens. Diabetes health professionals need to be aware of the potential dangers associated with some of these treatments. Patients should not stop using drug treatments abruptly as there is a risk of hyperglycemia or diabetic ketoacidosis. Any patient who decides to use a natural product should be followed closely to make sure that no toxic effects occur and that treatment objectives are achieved. According to the risk that concurrent use of drugs and herbal treatment may have synergistic effects on lowering the blood glucose levels. During the transition period when the patients take both drugs and herbs, they should under the instruction of family doctor and their blood glucose levels should be monitored at least twice daily to assess the effectiveness of the treatment and to avoid hypoglycemia. Dosage must be adjusted as needed to keep blood glucose within the normal range. Herbal treatment may reduce the dosage and frequency of insulin injections needed; however, it can never replace insulin, especially in insulin dependent diabetes mellitus (IDDM) patients.
Chapter 11 – Herbal Hepatotoxicity

11.1 Introduction

Treatment options for common liver diseases such as cirrhosis, fatty liver, and chronic hepatitis are problematic. (Luper S, 1998) The effectiveness of treatments such as interferon, colchicine, penicillamine, and corticosteroids are inconsistent at best and the incidence of side effects profound. All too often the treatment is worse than the disease. Conservative physicians often counsel watchful waiting for many of their patients, waiting in fact for the time when the disease has progressed to the point that warrants the use of heroic measures. Physicians and patients are in need of effective therapeutic agents with a low incidence of side effects.

Herbs have been used traditionally by herbalists and indigenous healers worldwide for the prevention and treatment of liver disease. Clinical research in the past had already confirmed the efficacy of the herbal medicine in the treatment of liver disease. Basic scientific research has uncovered the mechanisms by which some plants afford their therapeutic effects. The effectiveness of treatments such as interferon, colchicine, penicillamine, and corticosteroids are inconsistent at best and the incidence of side effects profound. In most cases, research has confirmed traditional experience and wisdom by discovering the mechanisms and modes of action of these plants as well as reaffirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies.

Hepatotoxicity of Chinese herbs has been recognized, e.g. during treatment of patients with atopic eczema. However, the mechanism of herbal-induced liver injury is unknown, and the pathologic findings are nonspecific, with steatosis, acute and chronic...
hepatitis, hepatic fibrosis, zonal or diffuse hepatic necrosis, bile duct injury, veno-occlusive disease, acute liver failure requiring liver transplantation and carcinogenesis.

Recently, reports have mounted about hepatotoxicity of herbal remedies, which ranges from mild liver enzyme alterations to chronic liver disease and liver failure. Unfortunately, there are no formal data on the incidence even of acute severe side effects, such as liver failure after certain herbal medications, and knowledge of longer-term sequelae such as mutagenicity and carcinogenicity is even more scanty.

11.2 Drug-induced hepatic injury

Drugs and other chemical toxins account for less than 5% of cases of jaundice or acute hepatitis and fewer cases of chronic liver disease, but they are an important cause of more severe types of hepatic injury. (Farrell GC, 1997) Drug reactions produce an array of hepatic lesions that mimic all known hepatobiliary diseases; this poses a diagnostic challenge for physicians and pathologists. Diagnosis of drug-induced hepatic injury is circumstantial, with positive rechallenge being the only factor that unequivocally implicates a particular agent. Nonetheless, other aspects of the temporal relationship between drug ingestion and adverse reaction, exclusion of other diseases, the presence of extrahepatic features of drug hypersensitivity and some findings on liver biopsy can lend support to the diagnosis.

In western medicine, factors that predispose to dose-dependent hepatic injury will be considered in relation to acetaminophen, an example of acute hepatotoxicity, and methotrexate, an agent that can produce hepatic fibrosis. Flucloxacillin will be discussed as an example of drug-induced cholestatic hepatitis often associated with prolonged cholestasis and the vanishing bile duct syndrome. Minocycline and diclofenac will be mentioned as two drugs for which drug hepatitis is an exceedingly rare complication.
Many drugs and chemicals are idiosyncratic hepatotoxins: isoniazid, amiodarone, tetracycline, methyldopa, bromobenzene, valproic acid, and halothane. (Haller CA, Dyer JE et al, 2002) Hepatotoxins may have intrinsic, idiosyncratic, or immune-mediated mechanisms of liver injury. Intrinsic hepatotoxins, such as acetaminophen, amanitin (found in Amanita phalloides mushrooms), or carbon tetrachloride, produce liver damage in a predictable, dose-dependent manner. Toxic hepatitis may also occur sporadically due to differences in individual susceptibility related to factors such as age, sex, underlying disease, concomitant medications, and genetic influences. (Haller CA, Dyer JE et al, 2002) Hypersensitivity or immune-mediated hepatitis may develop after repeated exposure to a causative agent. Immune-mediated hepatitis may manifest with systemic findings such as fever, rash, eosinophilia, or atypical lymphocytosis and recur with reexposure. Liver injury due to drugs such as sulfonamides, chlorpromazine, erythromycin, and phenytoin is thought to be immune-mediated.

Treatment includes removing exposure to the toxic agent and supportive patient care. (Haller CA, Dyer JE et al, 2002) Often, herbal-related acute hepatitis will resolve spontaneously once ingestion of the offending product is discontinued. Rarely, acute liver injury progresses to fulminant failure, necessitating transfer to a tertiary care facility with a liver transplantation service. Clinical deterioration may develop rapidly in toxin-induced hepatic failure, so the decision to transfer the patient should be made quickly. Some hepatotoxic herbs cause chronic pathologic liver changes. Herbs such as coltsfoot (Roulet M, Laurini R et al, 1988), comfrey (Ridker PM and McDermott WV, 1989), bush tea, and senecio contain pyrrolizidine alkaloids, (Smith LW and Culvenor CCJ, 1981) direct hepatotoxins that can cause centrilobular necrosis, veno-occlusive disease, portal hypertension, and an increased risk of hepatocellular carcinoma. (Stillman...
11.3 Types of Liver Injury

In the cases of herbal hepatotoxicity, several kinds of pathological changes could be seen in the liver during liver biopsy. These include zonal necrosis, necrotic lesions with steatosis or bile duct injury and vascular injury, especially veno-occlusive disease, which is commonly caused by pyrrolizidine alkaloids. (Chittiiri S and Farrell GC, 2000)

Some herbs are thought to be intrinsic hepatotoxins and show dose-related liver toxicity, either through direct hepatocellular damage, such as with *Atractylis gummifera*, or through the generation of a reactive metabolite, as is the case with pennyroyal oil (*Mentha pulegium*). (Anderson IB, Mullen WH et al, 1996) Recently, greater celandine, which is widely used for biliary disorders and dyspepsia, was identified as a cause of cholestatic hepatitis. Hepatotoxic reactions have also been observed after the ingestion of *Atractylis gummifera, Callilepsis laureola, Senna, Kavapyrone* and *Pulegium*.

11.4 Hepatotoxicity Herbs

In Chinese literature, the following herbs are taken orally and have been associated with incidents of hepatitis: *Dioscorea bulbifera* (bulb), *Livistona chinensis* (fruit), *Lycoris radiata* (blub), *Melia toosendan* (fruit), *Pinellia ternata* (tuber), *Ricinus communis* (seed), *Taxillus chinensis* (leafy twig), *Tripterygium wilfordii* (root), *Typha species* (pollen), *Viscum coloratum* (leafy twig), and *Xanthium sibiricum* (fruit). (But PPH, Tomlinson B et al, 1996) (see Table 11 d)

11.4.1 *Tripterygium wilfordii*

*Tripterygium wilfordii* *Hook f.* (TWH) is a plant of the genus *Tripterygium* of the family *celastraceae*. (Ming J, 1996) Many preparations, mainly from its root, have been used in the clinic, among which the polyglycoside (TP) has shown better effects with
relatively mild side effects. Its pharmacological effect is mainly inhibitory on all stages of cell cycle TP and acts much like cytotoxic drugs. Traditionally it is used as an antirheumatic and to clear out channels and collaterals for the treatment of rheumatic arthritis. Although much of the clinical experience with this herb comes from uncontrolled studies and anecdotal reports, recent clinical trials have confirmed the efficacy of TWH in the treatment of rheumatoid arthritis and other autoimmune diseases. In patient with lupus nephritis unresponsive to prednisone and other immunosuppressive drugs, combined administration of prednisone and TP resulted in reduction or even complete disappearance of protein in urine in 40% to 50% of cases.

Many side effects, however, have been reported. About 45% of patients who received polyglycoside complained of such adverse effects as skin rashes, skin pigmentation, stomatitis and softening of finger nails. Intoxication of _Tripterygium wilfordii_ showed gastrointestinal symptoms such as nausea and vomiting, abdominal pain with diarrhea, hepatomegaly with tenderness, etc. Fatty infiltration and necrosis of the liver with appearance of liver direct intoxication. Intrahepatic cholestasis with inflammation was seen in pathologic appearance. Besides this, leukopenia and irregular menstruation in women also. In male patients, the number and motility of sperms were reduced and the sperms disappeared completely after one month of this herb intake. In general, the longer the duration of administration and the older the patients, the smaller the probability of their menses or sperms returning to normal.

11.4.2 _Rhizoma Discordae Bulbiferae_

This drug consists of the dried rhizome of _Discordae bulbiferae L._ (family Discordaceae). It is used as hemostatic and to eliminate evil heat from blood and as a detoxicant for the treatment of various kinds of bleeding, boils and carbuncles, but
nowadays mainly used for the treatment of tumors and goiters. The main toxic ingredient was Dioscorein and Dioscoretoxin. Fatty infiltration and lobar necrosis could see in animal models. In China, several cases of intoxication of *rhizoma Discordae bulbiferae* were reported and patient had jaundice, lethargy, poor appetite and hepatomegaly with mal liver function.

### 11.5 Consumption of Insect Herbs

A 67-year-old man was admitted to hospital because of jaundice and general weakness after taking herbal medicine for few days. This patient consulted a traditional Chinese practitioner because of lumbago for one month and the practitioner prescribed several dosage of anticonvulsive medication which include fresh centipede (*Scolopendra subspinipes mutilans* L. Koch) 12 g and fresh scorpion (*Buthus martensii Karsch*) 15g. The patient felt weakness and jaundice could see in the sclera and whole body after taken the medication for few days. No itching sensation but has tea colour urine. Laboratory examination and liver echography confirmed diagnosis of acute hepatitis, which was caused by consumption of toxic herbs (insect). After symptomatic treatment, the jaundice disappear and the liver function return to normal. (Yeung PH, 2000)

Toxic insects were always used in subduing the hyperactivity of the liver and the endogenous wind. It used for anti-convulsion as for the treatment of various kinds of tic, convulsions and tetanus. Only a minor dosage was recommend because of its renal and liver toxicity. If prolong usage or mixed with other toxic herbs, accumulation with toxicity will result. So, regular checking for the liver function is necessary.

### 11.6 Hepatotoxicity Cause by Chinese Proprietary Medicine
Hepatic impairment resulting from the use of conventional drugs is widely acknowledged, but there is less awareness of the potential hepatotoxicity of herbal preparations and Chinese proprietary medicine, many of which are believed to be harmless and are commonly used for self-medication without supervision. Injections prepared from *Crotalaria sessiliflora* (whole plant), *Trichosanthes kirilowii* (root), and several combinations of herbs have also led to hepatotoxicity. (Zhou OH, 1988; Zhao JY, 1991; But PPH, Tomlinson B et al. 1996)

11.6.1 Jin Bu Huan

“Jin Bu Huan Anodyne Tablets” (*Lycopodium serratum*), a traditional Chinese herbal remedy, has been used for more than 1000 years as a sedative and analgesic but has only been available in the United States for 10 years. (Dharmananda S, 1993) The name “Jin Bu Huan” literally means 'not to exchange (even) for gold', implying that the herb is invaluable in certain treatments. In the Encyclopedia of Chinese Materia Medica, (Anonymous, 1977) the name “Jin Bu Huan” applies to eleven herbs: *Anectochilus taizwanensis* (Orchidaceae), *Aristolochia yunnanensis* (Aristolochiaceae), *Asystasiella neesiana* (Acanthaceae), *Lycopodium serratum* (Lycopodiaceae), *Panax pseudoginseng var. notoginseng* (Araliaceae), *Polygala chinensis* (Polygalaceae), *Rumex madaio* (Polygonaceae), *R. patientia* (Polygonaceae), *Selaginella involvens* (Selaginellaceae), *Stephania delavayi* (Menispermaceae) and *S. sinica* (Menispermaceae). Many of these herbs are used as an analgesic. The alkaloid levotetrahydropalmatine is responsible for the morphine-like properties of “Jin Bu Huan” but the hepatotoxic mechanism was unknown.

A recent study described three children who had taken unintentional overdoses of Jin Bu Huan tablets and who developed central nervous system and respiratory...
depression with bradycardia. (Horowitz RS, 1993) Seven cases of hepatitis have been reported in adults who used Jin Bu Huan and had no history of hepatic disease, obesity, diabetes mellitus, or atopy. (Woolf WGM, 1993) All denied a history of excessive alcohol or hepatotoxic drug intake. Liver disease occurred after a mean duration of use of 20 weeks (range, 7-52 weeks). Six of the 7 patients showed complete resolution of symptoms within 8 weeks. Two patients had a recrudescence of symptoms with re-exposure to the herb. The duration of use before manifestations of clinical hepatitis was the same for “Jin Bu Huan” as for another hepatotoxic herb, germander.

The package insert for “Jin Bu Huan” recommended a dosage of 2 to 4 tablets 1 to 3 times a day for pain relief or 1 to 3 tablets at night for insomnia. Thus, all patients were taking appropriate doses. The insert also indicated that tablets contained 70% starch and 30% levo-alkaloid from the plant Polygala chinensis. Although the insert of “Jin Bu Huan Anodyne Tablets” indicates in the English description that the ingredient is 'Polygala Chinensis L. Alkaloid', results of the analysis show that the alkaloid is L-THP which is not found in P. chinensis. (Jinniucao GSL, 1988) Among the other ten herbs also known as “Jin Bu Huan”, only those derived from species of the genus Stephania are known to contain L-THF. Therefore, the description on the insert that the ingredient is 'Polygala Chinensis L. Alkaloid' is definitely an error and a mislabeling. (But PPH, 1994) Although L-THP can be obtained from plant sources, it is used as a fine pharmaceutical in mainland China and is registered as such under Rotundinum (rotundine) in Part 2 of the Pharmacopeia of the People's Republic of China; the recommended single and daily oral doses of rotundine are 60 to 120 and 60 to 480 mg respectively. (Pharmacopoeia C, 1990)

“Jin Bu Huan Anodyne Tablets” presents an excellent case example for review on
what actually constitutes a herbal preparation. For pure and potent components presented in sufficient quantities, even though derived from natural sources, reclassification would deem necessary to ensure proper supervision by health authorities for the protection of consumers in the territory.

11.6.2 Chi R Yun (Breynia officinalis)

*Breynia officinalis* has the Chinese proprietary name, “Chi R Yun”, which means dizziness or vertigo for 7 d. (Lin TJ, Tsai MS et al, 2002) In daily practice, it has been used to treat venereal diseases, contusion, heart failure, growth retardation and conjunctivitis in combination with other traditional Chinese medicines. Two hospital-based cases of *Breynia officinalis* poisoning have been reported to the Poison Control Center. The first case was a 43-y-old female who consumed a mixture of 1,500 g lower stem and root of Ji Mu Ju in boiled water in a suicide attempt. Her AST reached 264 and ALT reached 2443. Another case was a 51-y-old female who consumed 20 pieces of lower stem and root of Ji Mu Ju stewed with meat and 100 ml of wine to treat chronic contact dermatitis. Her AST reached 3815 and ALT reached 6625. In both cases *Breynia officinalis* was identified as the cause of poisoning. Poisoning in humans involves the neurologic, gastrointestinal, hepatic, urinary and respiratory systems. Hepatotoxic effects have been reported for some Chinese herbal medicines, but not *Breynia officinalis*: *Breynia officinalis* poisoning causes hepatocellular liver injury rather than cholestatic liver injury.

11.6.3 Sho-saiko-to

Another famous example of herbal hepatotoxic, which has been repeatedly happened in Japan, was a Kampo medicine, which called “Sho-saiko-to”. This traditional herbal complex consisting of *Bupleuri radix*, *Ginseng radix*, *Glycyrrhizae*
radix, Pinelliae tuber, Scutellariae radix, Zingiberis rhizoma, and Zizyphi fructus. This formula has been used in treating hepatitis in China since the Han Dynasty (i.e. about 100 AD), and it was generally considered to be devoid of serious side effects. There is now a respectable series of case reports from Japan, however, which associate its use with allergic pneumonitis and/or hepatitis.\( \text{(Kubo K, Watanabe F et al, 1986; Tsukiyama K, Tasaka Y et al, 1989; Daibo A, Yoshida Y et al, 1992; Imokawa S, Sato A et al, 1992; Takada N, Arai S et al, 1993; Kawasaki A, Mizushima Y et al., 1994; Itoh S, Marutani K et al, 1995)}\) “Sho-saiko-to” is by no means the only Oriental herbal medicine which is associated with rare but serious cases of hepatitis.\( \text{(Perharic L, Shaw D et al, 1995)}\)

Itoh reported four patients treated with the herbal medicine “Sho-saiko-to” exhibited acute drug-induced liver injury.\( \text{(Itoh S, Marutani K et al, 1995)}\) All of the patients showed a rise in amino-transferases after re-administration or challenge test. The liver histology revealed centrilobular confluent necrosis, acute hepatitis with centrilobular necrosis or spotty necrosis, microvesicular fatty change, acidophilic degeneration, and a granuloma.

11.6.4 Shou-Wu-Pian

Hepatitis developed in a 31-y-old pregnant Chinese woman after consumption of “Shou-Wu-Pian”, a proprietary Chinese medicine prepared from \textit{Polygonum multiflorum}.\( \text{(But PPH, Tomlinson B et al, 1996)}\) Laboratory examination showed malfunction of the liver. On detailed questioning the patient admitted that for several weeks prior to this illness she had been taking tablets of the proprietary Chinese herbal medicine, “Shou-Wu-Pian”, at the recommended dosage to treat hair loss. She used to have a previous episode of acute hepatitis about 2 y ago after taking a liquid extract,
“Shou-Wu-Zhi”, prepared from the same herb. Her liver function tests returned to normal after stopping that preparation.

The proprietary Chinese medicine incriminated was “Shou-Wu-Pian”, manufactured in Shanghai, China. (But PPH, Tomlinson B et al, 1996) The package was a bottle of 100-coated tablets. The ingredient, according to the label description on the product was 100% Radix Polygoni Multiflori (root tuber of Polygonum multiflorum or the Chinese corobind). The recommended dosage was 5 tablets 3 times/day. It is often taken to prevent graying of hair. Thin-layer chromatographic analysis of the tablets confirmed the presence of 2 anthraquinones, emodin and phycsin.

After analysis of “Shou-Wu-Pian”, anthraquinones were found to be present and it is known that anthranoid derivatives can form highly reactive anthrones in the colon, which are then able to induce liver damage after absorption and transportation to the liver. A case of toxic hepatitis in a young female patient was reported after the excessive use of senna which contains similar kinds of anthraquinones. (Beuers U, Spengler U et al, 1991; Kestendorf JI, 1993) Another case of hepatotoxicity was associated with excessive use of the laxative DOXIDAN, which contains the anthraquinone danthron (1,8-hydroxyanthraquinone) and dioctyl calcium sulfosuccinate. (Tolman KG, Hammar S et al, 1976) Anthraquinones present in “Shou-Wu-Pian” was highly suspected for either an idiosyncratic response or a toxic effect from prolonged or excessive usage.

Polygonum multiflorum is a member of Polygonaceae and is used either raw or processed. The raw herb is a laxative, but is rarely used because excessive dosage or prolonged use of the raw herb causes diarrhea, abdominal pain, nausea, vomiting, tonic spasm, convulsion, restlessness and even respiratory paralysis. The processed herb is
the common form and is prepared by cooking the raw herb with Chinese yellow wine and the juice of the black soybean. It is used as a tonic for dizziness with tinnitus, premature graying of hair, lumbago, spermatorrhea and leucorrhoea.

Several cases of adverse reactions caused by Polygonum multiflorum were reported. Erythema appeared in one case after taking “Shou-Wu-Pian” for 5 d [Zhang Q.R., 1987]; and the other was taken the decoctions made by several kind of herbs which including the vine or the root tuber of P. multiflorum. (Du XZ, 1984; Zhang QR, 1987; Li SH, 1992; Zhu T and Jiang PC, 1992) Besides this, rashes and pruritus appeared after taking “Yi-Ning-Jing”, (Liu F, 1990) and “Sham-Hai-Dan”, (Zhao CR, 1994) and both of them contained several herbs which included the root tuber of P. multiflorum. Dyspnea, palpitation, upper abdominal pain, restlessness, tachypnea, itching rashes, dizziness, and blurred vision would appeared after taking a decoction containing the root tuber of P. multiflorum. (Li Y and Cheng Y, 1998)

11.7 Importance of Drug-Herb and Herb-Herb Interactions

Possible drug-herb interactions are of concern to primary care physicians, but published clinical studies are scarce. (Adriane F and Ernst E, 2001) (see Table 11c) Recent studies show that Saint-John's-wort has pharmacokinetic interactions with drugs that are substrates for cytochrome P-450 enzymes and P-glycoprotein transport mechanisms, such as cyclosporine, ethinyl estradiol, and digoxin. (Barone GW, Gurley BJ et al, 2000) Herbs that induce hepatic cytochrome P-450 enzymes could potentiate the toxicity of intrinsic hepatotoxins such as acetaminophen. Other herbs may have clinically relevant drug interactions or synergistic actions with other botanicals. For example, herbs with anticoagulant effects such as ginkgo biloba, ginseng, and garlic could increase the risk of bleeding in patients taking warfarin or platelet inhibitors.
There are few published data in the English-language literature to support the practice of combining numerous active herbal ingredients in a single product, and yet, such products are widely available in nutrition and health food stores, retail pharmacies, and supermarkets, potentially increasing the risk of serious herb-herb interactions. For instance, there is growing concern about combination products that contain several cardiovascular stimulant herbs such as ephedra, guarana, and Citrus aurantium that could increase the risk of adverse effects, including hypertension, cardiac arrhythmia, and stroke. (Gurley BJ, Gardner SF et al, 1998; Haller CA and Benowitz NL, 2000)

11.8 Diagnosis of Herbal Hepatotoxicity

Toxic hepatitis shows no specific pattern of symptoms and is difficult to diagnose. When considering herbs as a cause for toxic hepatitis, physicians will frequently rely on the elimination of other causes and a temporal relationship between ingestion of herbs and onset of hepatitis and between withdrawal of herbs and recovery. (Ko RJ, 1999)

The important considerations for establishing an accurate diagnosis of herbal hepatotoxicity include a thorough history, pattern recognition, awareness of the spectrum of herbal liver injury and botanic identification where at all possible. (Chitturi S and Farrell GC, 2000) Unlike the pharmaceutical industry, makers of herbal remedies are not required to provide premarketing evidence of efficacy and safety, as herbs are considered dietary supplements. Manufacturers also do not need to guarantee herbal ingredients, and the ingredients of identically named supplements from different companies vary. Furthermore, patients do not always mention herbal medicines when questioned about the use of medications. For instance, at least one-third of patients attending an academic liver clinic failed to disclose concurrent herb use. This underscores the importance of encouraging patients to check the ingredient of the herbal
medicine intake and provide information about all concurrent drug intakes, including natural products. Because no specific diagnostic tests exist, it is particularly important to consider the temporal relationships between drug ingestion, the onset of illness, the response to drug omission (dechallenge) and any history of deliberate or inadvertent drug rechallenge.

11.9 Recommendation

Establishing a diagnosis of herbal-related toxic hepatitis is difficult because the effects of herbs are often chronic and nonspecific and may not become clinically apparent for some time. (Haller CA, Dyer JE et al, 2002) Proper documentation of adverse effects of herbal medicines is hindered by several factors. Physicians may not ask patients about their use of herbal medicines, or patients may be reluctant to discuss their use of alternative remedies. More than this the manufacturers of herbal supplements are not required to guarantee the ingredients of their products. As a result, many cases of herbal-related toxic hepatitis may go unrecognized and unreported. Inadequate product labeling, multiple-ingredient herbal products, batch-to-batch variation, and adulterants or contaminants may complicate attempts to accurately identify the toxic component. Because the English-language literature consists mostly of case reports of herbal toxicity rather than scientific studies, there is often little sound evidence to support a clinical diagnosis of herbal-related hepatitis.

A retrospective study for suspected cases of herb-induce hepatotoxicity was reported in China 2 years ago. (Peng XL, Li CS et al, 1999) (see Table 11 a) This study collected those cases within recent 13 years (from 1986~1998) and showed that nearly 80% intoxication were under the instruction from the practitioner!! Misusing or wrong
prescription became the major problem for herbal intoxication. This means even the herbal practitioner didn’t have enough experience or knowledge about herbal hepatotoxicity. Therefore, a registration of medical practitioners is necessary on their achievement of qualifications considered to indicate competence to practice. Ensuring that practitioners maintain annually certified levels of competence is left up other mechanisms such as the activities of the professional colleges. Maintaining theoretical and practical standards are thus the task of continuing medical education, peer review and quality assurance activities.

Table 11 a. The Relation Between the Medicine Intake Behavior and Liver Damage.(Peng XL, Li CS et al, 1999)

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Case</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under instruction</td>
<td>54</td>
<td>78.26</td>
</tr>
<tr>
<td>Presume taking</td>
<td>13</td>
<td>18.84</td>
</tr>
<tr>
<td>Mistaking</td>
<td>2</td>
<td>2.89</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>100</td>
</tr>
</tbody>
</table>

When a physician suspects a toxic reaction from an herbal medicine, the patient should be urged to provide the product in its original packaging, along with the date and place of purchase. Because herbal products are sometimes poorly labeled or contain misinformation, a definitive diagnosis can be established only with laboratory confirmation of hepatotoxins. Unfortunately, access and availability of such assays are limited. State and county health departments may provide such analytic testing free of charge. Specimens of the patient's urine and blood should also be obtained and frozen for possible future testing to confirm the presence of the hepatotoxins.
11.10 Conclusion

TCM is of a long history and has accumulated a rich store of clinical experience. The dominant Western medical culture has largely ignored this knowledge until recently. Research into plants traditionally used in the treatment of liver disease has significantly advanced in the recent years, and much of what has been discovered supports traditional knowledge. However, people still need to pay attention to the usage of TCM due to herbs can be hazardous in many ways. They may be directly toxic or toxic when taken in combination with other preparations. In order to aware the toxic effect from herbal medicine, there is necessary to undergone long-term, large-scale, randomized, double-blinded trials to get more information about TCM in the future. Furthermore, herbalists prescribing and dispensing herbal preparations, and medical practitioners whose patients may be reluctant to admit that they are taking them, should be aware of their potential for occasional serious hepatotoxicity.
Table 11 b. Adverse effects of herbal remedies on the liver. (Langmead L and Rampton DS, 2001)

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Botanical name</th>
<th>Main use</th>
<th>Liver injury</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal tea</td>
<td>Senecio and Crotalaria</td>
<td>tonic</td>
<td>veno-occlusive disease</td>
<td>(McDermott WV and Ridker PM, 1990)</td>
</tr>
<tr>
<td>Pennyroyal</td>
<td>Hedeoma puleioides</td>
<td>abortifacient</td>
<td>hepatitis</td>
<td>(Sullivan J, Jr, Rumack BH et al, 1979)</td>
</tr>
<tr>
<td>Germander</td>
<td>Teucrium chamaedrys</td>
<td>obesity</td>
<td>fulminant hepatitis</td>
<td>(Larrey D, Vial T et al, 1992)</td>
</tr>
<tr>
<td>Greater celandine</td>
<td>Chelidonium majus</td>
<td>diuretic</td>
<td>hepatitis</td>
<td>(Benninger J, Schneider HT et al, 1999)</td>
</tr>
<tr>
<td>Chapparal</td>
<td>Larrea tridentata</td>
<td>anti-inflammatory</td>
<td>cholestatic hepatitis</td>
<td>(Sheikh NM, Philen RM et al, 1997)</td>
</tr>
<tr>
<td>Kava</td>
<td>Piper methysticum</td>
<td>anxiety</td>
<td>fulminant hepatic failure</td>
<td>(Escher M and Dsemeules J, 2001)</td>
</tr>
<tr>
<td>Skullcap</td>
<td>Scutellaria spp.</td>
<td>stress</td>
<td>hepatitis</td>
<td>(MacGregor FB, Abernethy VE et al, 1989)</td>
</tr>
<tr>
<td>Vallerian</td>
<td>Valeriana officialis</td>
<td>stress</td>
<td>hepatitis</td>
<td>(MacGregor FB, Abernethy VE et al, 1989)</td>
</tr>
<tr>
<td>Comfrey</td>
<td>Symphytum spp.</td>
<td>arthritis</td>
<td>veno-occlusive disease</td>
<td>(Ridker PM and McDermott WV, 1989)</td>
</tr>
<tr>
<td>Sassafras</td>
<td>Sassafras albidum</td>
<td>tonic</td>
<td>carcinoma</td>
<td>(Segelman AB, Segelman FP et al, 1976)</td>
</tr>
<tr>
<td>Chinese Herbal</td>
<td>Paeonia spp.</td>
<td>psoriasis</td>
<td>hepatitis</td>
<td>(Walton P and Murray V, 1992; Kane JA, Kane SP et al, 1995)</td>
</tr>
</tbody>
</table>
Table 11 c. Interactions between herbal remedies and conventional drugs of relevance to gastroenterology.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Conventional drug</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interactions causing gastrointestinal side-effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feverfew, ginseng, garlic, warfarin</td>
<td></td>
<td>Potentiation leading to GI bleeding</td>
</tr>
<tr>
<td>Gingko, ginger, iron</td>
<td></td>
<td>Reduced absorption</td>
</tr>
<tr>
<td>St. John’s wort, cyclosporin</td>
<td></td>
<td>Reduced blood levels</td>
</tr>
<tr>
<td>Echinacea, anabolic steroids, methotrexate, amiodarone, ketoconazole</td>
<td></td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Tamarind, aspirin</td>
<td></td>
<td>Potentiation leading to GI bleeding</td>
</tr>
<tr>
<td>Inkcap, alcohol</td>
<td></td>
<td>Disulfiram effect</td>
</tr>
<tr>
<td><strong>Interactions with herbs used in gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chilli/capsaicin</td>
<td>ACE inhibitors</td>
<td>Cough</td>
</tr>
<tr>
<td>Psyllium, lithium</td>
<td></td>
<td>Reduced blood levels</td>
</tr>
<tr>
<td>Shosaiko-to, prednisolone</td>
<td></td>
<td>Reduced bioavailability and effectiveness</td>
</tr>
<tr>
<td>Liquorice, spironolactone, prednisolone</td>
<td></td>
<td>Antagonism of effect increased salt/water retention, hypokalaemia</td>
</tr>
</tbody>
</table>

Table 11 d. Traditional Chinese Medicine with Hepatotoxicity. (Huang KC, 1999)

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Toxic ingredient</th>
<th>Pathological Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bulbus Lycoris</em> 石蒜</td>
<td>Lycorine &amp; Sekisenine</td>
<td>Diffuse fatty infiltration of the liver and increase the liver transaminase enzymes and bilirubin. Intrahepatic cholestasis with inflammation.</td>
</tr>
<tr>
<td><em>Radiatae</em> 石蒜</td>
<td>Hederagenin</td>
<td>Damage of liver cells.</td>
</tr>
<tr>
<td><em>Caulis Akebiae</em> 木通</td>
<td>Safrole</td>
<td>Diffuse fatty infiltration of the liver with necrosis.</td>
</tr>
<tr>
<td><em>Chloranthus Serratus</em> 及已</td>
<td>Albizzin</td>
<td>Necrosis of the liver cell could see in animal study.</td>
</tr>
<tr>
<td>Herbs</td>
<td>Toxic ingredient</td>
<td>Pathological Appearance</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cortex Meliae</td>
<td>Toosendonin</td>
<td>Degenerative swelling of the hepatocyte. Toosendonin can increase the capillary permeability and affect coagulation, so cause internal massive bleeding of the organ.</td>
</tr>
<tr>
<td>Croton Tiglium</td>
<td>Crotin &amp; Crotonoside</td>
<td>Toxic hepatitis appearance with hepatocyte necrosis.</td>
</tr>
<tr>
<td>Eucalyptus Globulus</td>
<td>Oleum Eucalypti</td>
<td>In vivo study showed damage of liver cells.</td>
</tr>
<tr>
<td>Foliium Illicis Purpureae</td>
<td>Protocatechuic acid</td>
<td>Toxic hepatitis</td>
</tr>
<tr>
<td>Fructus Bruceae</td>
<td>Bracamine, Yatanine &amp; Brucealin</td>
<td>Bracamine are severe cytotoxin and could cause the animal organs have diffuse hemorrhage and congestion.</td>
</tr>
<tr>
<td>Fructus seu Radix Campto-thecae Acuminatae</td>
<td>Camptothecine</td>
<td>The appearance of liver intoxication could see in the liver, focal necrosis of hepatocytes and necrotic cholecystitis.</td>
</tr>
<tr>
<td>Fructus Xanthii</td>
<td>Xanthostrunarin</td>
<td>Fatty infiltration of the animal liver with hemorrhage and necrosis.</td>
</tr>
<tr>
<td>Fufang Qing Dai Wan (CPM)</td>
<td>Include Indigo Naturalis.</td>
<td>Can increase the liver transaminase enzymes and bilirubin level with jaundice.</td>
</tr>
<tr>
<td>Herba Chenopodii</td>
<td>Ascaridole</td>
<td>Toxin can accumulate in the intestine and caused hepatomegaly, jaundice and renal damage.</td>
</tr>
<tr>
<td>Herba Senecionis Oryzotori</td>
<td>Senecio Alkaloids</td>
<td>The main toxicity can cause liver damage and necrosis in acute phase. In Chronic phase, the toxin can make degeneration of liver, cirrhosis and ascites and even coma.</td>
</tr>
<tr>
<td>Hydno-carpus Anthelminatica</td>
<td>Chaulmoogric acid &amp; Hydrocarpic acid</td>
<td>Fatty infiltration of the liver could see in animal studies.</td>
</tr>
<tr>
<td>Hyristicafragrans Hoult</td>
<td>Myristicin</td>
<td>Fatty infiltration of the liver and kidney.</td>
</tr>
<tr>
<td>Indigo Naturalis</td>
<td>Indigo, Indircan, &amp; Indirubin</td>
<td>Focal necrosis of the liver cell. Indirubin can decrease the RNA of liver cell and decrease protein synthesis and cause atrophy of liver cell.</td>
</tr>
<tr>
<td>Herbs</td>
<td>Toxic ingredient</td>
<td>Pathological Appearance</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><em>Milabris Phanalerata</em></td>
<td>Cantharidin, (C₁₀H₁₂O₄)</td>
<td>Degeneration of the liver cell and necrosis of the liver cell may happened.</td>
</tr>
<tr>
<td><em>Mistletoe</em></td>
<td>Cantharidin, (C₁₀H₁₂O₄)</td>
<td>Necrosis of hepatocytes could see and later change into Mistletoe Hepatitis. (Harvey Jand Colin-Jones DG, 1981)</td>
</tr>
<tr>
<td><em>Punica Granatum</em></td>
<td>Iso-pelletienine &amp; Methionine</td>
<td>Fatty infiltration and necrosis of the liver with appearance of liver intoxication.</td>
</tr>
<tr>
<td><em>Radix Aconiti</em></td>
<td>Hypaconitine, Aconitine, Mesaconitine</td>
<td>Pathological appearance of liver intoxication could see in animal studies.</td>
</tr>
<tr>
<td><em>Radix et Rhizoma Rhei</em></td>
<td>Rhein, Chrysophanol &amp; Emodin</td>
<td>Degeneration of the liver cell with venous congestion could see in animal studies.</td>
</tr>
<tr>
<td><em>Radix Stephaniae</em></td>
<td>Magnoflorine, Allantoin &amp; Aristochic acid B,C</td>
<td>Necrosis of the liver cell could see in animal studies.</td>
</tr>
<tr>
<td><em>Radix Tripterygii</em></td>
<td>Wilforine, Wilfotrine, Wilfotrine &amp; Wolfertine</td>
<td>Congestion of the liver and swelling of the liver cells could see in animal studies.</td>
</tr>
<tr>
<td><em>Ricinus Communis</em></td>
<td>Ricinice &amp; Ricin</td>
<td>Toxin can change the liver cell into turbid form and have necrosis. Result of necrosis of liver cell could see in animal liver.</td>
</tr>
<tr>
<td><em>Rhizoma Discoreae</em></td>
<td>Dioscorein &amp; Dioscoretoxin</td>
<td>Dilatation and congestion of the central venous system &amp; portal sinus. Vacuole like degeneration of liver cell with focal necrosis.</td>
</tr>
<tr>
<td><em>Rhizoma et Radix Veratri</em></td>
<td>Jervine, Germerine &amp; Rubijervine</td>
<td>Diffuse hemorrhage and congestion could see in liver and spleen tissue.</td>
</tr>
<tr>
<td><em>Rhizoma Pinelliae</em></td>
<td>Homogentisic acid &amp; Photo-chatechuic aldehyde</td>
<td>The non-processing form of the herb can make the liver transfermice enzyme increase.</td>
</tr>
<tr>
<td><em>Rhizoma Polygoni</em></td>
<td>Polygonin &amp; Polydatin</td>
<td>Necrosis of hepatocytes could see in animal studies.</td>
</tr>
<tr>
<td>Herbs</td>
<td>Toxic ingredient</td>
<td>Pathological Appearance</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td><em>Senecio Scandens</em></td>
<td>Isatidine, Lasiocarpin, Retrorsine, Momno-crotaline, Senciphyllin &amp; Senecionine.</td>
<td>Fatty infiltration of the liver could see in animal studies.</td>
</tr>
<tr>
<td>千里光</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Terminalia Chebula</em></td>
<td>Chebulibn</td>
<td>Appearance of liver intoxication and necrosis of liver cell.</td>
</tr>
<tr>
<td>荸子</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Trichosanthes Kirilowii</em></td>
<td>Trichosanthin</td>
<td>Mild degeneration could see in animal liver and renal cell.</td>
</tr>
<tr>
<td>天花粉</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 12 – Herbal Nephropathy

12.1. Introduction

Members of the genus of Aristolochia have been used as medicines in the Orient and the West. However, the nephrotoxic response to several Aristolochia species has surfaced in recent decades. Two renal diseases, Balkan endemic nephropathy (BEN) and Chinese herbs nephropathy (CHN), have been traced to Aristolochia species. BEN is widespread in the Balkan region where poor peasants consumed wheat contaminated with the seeds of Aristolochia clematitis. CHN, on the other hand, was reported in Belgium where more than 100 cases suffered interstitial fibrosis in the kidney after taking a slimming regimen containing the herb, Aristolochia fangchi.

12.2. Aristolochia acids (AA)

Recently, rapidly progressive renal failure resulting in end-stage renal disease has been reported to occur in women who have taken weight-reducing pills containing the Chinese herbs Stephania tetrandra and Magnolia officinalis which containing nephrotoxic and carcinogenic aristolochic acids (AA). Aristolochic acid, the component implicated in the present case, has been used in Germany for more than 25 years as an immunomodulatory drug.(De Broe ME, 1999) Vanherweghem J.L. first described the new entity of CHN.(Vanherweghem JL, Depierreux M et al, 1993) He reported 2 patients with rapidly progressive renal failure with similar renal biopsy specimens showing extensive interstitial fibrosis and severe tubular loss most prominent in the outer cortex. These patients were the index cases in a cluster of cases of rapidly progressive renal failure occurring in young women in 1992 to 1993. All the women received a slimming regimen containing Chinese herbs prescribed by the same physician.
Besides this, a nonexclusive list of agents that have been firmly implicated in causing allergic interstitial nephritis include the penicillins, cephalosporins, sulfonamides, rifampin, ciprofloxacin, NSAIDs, thiazide diuretics, furosemide, cimetidine, phenytoin, and allopurinol.

It is estimated that 1,741 patients in Belgium took the slimming medication, more than 100 cases have been described in Belgium related to the ingestion of a potentially nephrotoxic ingredient that had been mistakenly substituted for a nontoxic substance. (Vanherweghem LJ, 1998) Vanherweghem's investigation revealed that in 1990, *Stephenia tetrandra* and *Magnolia officinalis* had replaced pancreas powder, laminaria powder, and fucus extract in the traditional slimming regimen. Initially the medication, in use for 15 years contains the herb Han Fang Ji (*Radix Stephania tetrandra*) and had no reported side effects. Subsequently it was discovered that there was mistaken identity of the herb. After the outbreak, thin-layer chromatography was performed on the preparation, and *Aristolochia manshuriensis* rich in aristolochic acid (*Radix Aristolochiae fangchi, Guang fangji*) was found instead of *Stephenia tetrandra* (*Radix Stephaniae tetrandrae, Fangji*). Aristolochic acid was identified independently by groups from Hong Kong and Belgium from a sample of "pure" Stephenia powder distributed in Belgium. (Vanhaelen M, Vanhaelen-Fastre R et al, 1994) In the cases reported by Vanherweghem and colleagues, the herbs were not used according to established principles and cannot be accepted as Chinese medicine. As pointed out by Professor Atherton and colleagues, the cases reported in Belgium raise the additional issue of the risk of adverse interactions between herbs and modern medicine. In China, there is much research into the possibility of integration of traditional Chinese and modern medicine involving careful experimental and clinical design, and systematic
observation and monitoring of efficacies, interactions, and side-effects. The Belgian cocktail is not an integration of traditional and modern medicine, but a confusion of the two. (Tai YT, But PPH et al, 1993)

12.2.1 Intoxication of Aristolochic acids in Worldwide

Cases of severe interstitial nephritis associated with rapidly progressive renal failure have been reported in other countries other than Belgium. In 1996, Spanish investigators reported a case of rapidly progressive renal failure in a man who self-treated right upper quadrant pain for 4 years with a homemade infusion containing mint and *Aristolochia pistolochia* (used to treat jaundice in farm animals). (Pena JM, Borras M et al, 1996) Renal toxicity due to Aristolochia was already reported in China in 1964, (Zhu YP and Woerdenbag HJ, 1995) i.e. almost thirty years before the Belgian outbreak of renal Aristolochia toxicity was described. In 1998 in United Kingdom, two illnesses were reported following years of ingestion of herbs. Upon examination, it was found that there was a dispensing error. Graham Lord and colleagues report these two cases of nephropathy from ingesting Chinese herbal remedies that were traceable to a derivative of the herb MuTong.

In Japan, Tanaka reported 2 cases of CHN from a slimming regimen that contained aristolochic acid but differed from the Belgian formula in that appetite suppressants (fenfluramine, dexfenfluramine, phentermine, and diethylpropion) were not present. (Tanaka A, Nishida R et al, 1997) Moreover, ten more similar cases of nephropathy were reported in Japan in 1995, of which five could be attributed to a herbal medicine imported from China by a company in Osaka. (Tanaka A, Nishida R et al, 1997) After a warning was published, the suspected product was recalled. (Hashimoto K, Higuchi M et al, 1999) Toxicity occurred in this case because *Aristolochia*
manshuriensis had been substituted in the Chinese product for *Akebia quinata Decaisne*, a herb with diuretic properties that is included in the Japanese Pharmacopoeia. The presence of aristolochic acid was confirmed in *Aristolochia manshuriensis* and other plants of the genus Aristolochia (Aristolochiaceae), and Asarum (Aristolochiaceae), but not in authentic samples of *Akebia quinata Decaisne*. *Aristolochia manshuriensis* and other plants of the genus Aristolochia are not contained in the Japanese Pharmacopoeia and the Japanese Herbal Medicine Codex, the basic compendia used by the manufacturers of traditional Japanese herbal medicines (Kampo) in Japan.

The interaction between the components in *<Cuangfangji>* and western synthetic drugs deserves further investigation, especially when unscrupulously mixed together with such synthetic pharmaceuticals as acetazolamide and prescribed for prolonged consumption as a weight control regimen.(Cosyns JP, Jadoul M et al, 1994; Cosyns JP, Jadoul M et al, 1994)

### 12.2.2 Morphological findings

Depierreux et al described the pathological findings from the renal biopsies of 33 cases of CHN.(Depierreux M, Van Damme B et al, 1994) There was a gradient of intensity from most severe in the outer cortex to less involvement in the inner cortex and medulla. The extent of interstitial fibrosis, tubular atrophy, and complete tubular disappearance was striking. The interstitium was remarkably hypocellular. There were few lymphocytes infiltrating between tubular epithelial cells. Granulocytes were absent. There was thickening of the walls of interlobular and afferent arterioles. Morphological changes consisted of intimal thickening with fibroblast proliferation and peripheral sclerotic thickening. Glomeruli were relatively spared compared with the severity of tubulointerstitial fibrosis. Immunofluorescent staining was essentially negative.(Cosyns
Mild low-molecular-weight proteinuria, hypertension, severe anemia, and development of uroepithelial atypia are characteristic of CHN. CHN developed as early as 2 months after exposure to the slimming regimen and as late as 3 years after discontinuation of the drug. Generally, the course to end-stage renal disease was subacute and faster than in other tubulointerstitial nephropathies. Rate of progression was inversely related to the duration of treatment with the Chinese herbs and seemed to be dose related. Those patients who ingested a low dose over many years experienced delayed onset of renal failure.

12.2.3 Carcinogenicity

Base on the fact that Aristolochic acids is a mixture of nitrophenanthrene derivatives known for their potent carcinogenic action in rats (Mengs U, Lang W et al, 1982) and their mutagenic properties in bacterial (Schmeiser HH, Pool BL et al, 1986) and mammalian models. (Pezzuto JM, Swanson SM et al, 1988) Register postulated that there were both a direct cytotoxicity and a more chronic change involving modification of DNA. The presence of aristolochic acid DNA adducts in renal tissue and the association with late development of uroepithelial tumors in patients with CHN support this view. Moreover, Schmeiser et al. were able to detect DNA adducts formed by metabolites of aristolochic acid (aristolactams) in samples of kidneys removed from five patients with Chinese-herb nephropathy. [Schmeiser H.H., Bieler C.A. et al., 1996] These adducts are specific markers of exposure to aristolochic acids and are directly involved in tumorigenesis. (Bieler CA, Stiborova M et al, 1997) For these reasons, patients with Chinese-herb nephropathy, or aristolochia nephropathy, appear to be at risk for the development of cancer. Unfortunately, two of three patients
that got Chinese-herb nephropathy were found to have urothelial carcinoma. (Cosyns JP, Jadoul M et al, 1994) A follow up survey was performed for 43 other patients with Chinese-herb nephropathy and found that 39 of them confirm to have high prevalence of urothelial carcinoma.

The role of Chinese herbs (specifically, aristolochia species) as a cause of renal failure and urothelial carcinoma is still a matter of debate, for several reasons. First, promoters of Chinese herbs have claimed that the renal disease originated from the injection of a "hidden substance" (serotonin) at the time of mesotherapy; this claim has not been confirmed. (Malak J, 1998; McIntyre M, 1998) Second, analgesic nephropathy is a frequent type of renal disease in Belgium (De Broe ME and Elseviers MM, 1998) and could thus be misdiagnosed as Chinese-herb nephropathy, since urothelial cancer develops in up to 10 percent of patients with analgesic nephropathy. (Kliem V., Thon W. et al., 1996) Third, similarities between Chinese-herb nephropathy and Balkan endemic nephropathy have been described, including the association of both with urothelial carcinoma. Some evidence suggests that Balkan endemic nephropathy is an environmentally induced disease, perhaps related to exposure to fungal or plant nephrotoxins such as ochratoxin A and aristolochic acids. (Stefanovic V and Polenakovic MH, 1991) Both compounds are nephrotoxic and carcinogenic. Studies performed by Nortier JL indicated that regular intake of powdered Chinese herbs of the aristolochia species dramatically increases the risk of urothelial carcinoma. (Nortier JL, Martinez M.-CM et al, 2000)

Furthermore Vanherweghem JL also suggested that there may be a high possibilities that Chinese-herb nephropathy may corelated to the vascular disease because he discovered that a symptomless diastolic murmur could detected by routine examination
in about a third of patients with Chinese-herb nephropathy. (Vanherweghem JL, 1997) 45 cases of the original Belgian group was received ultrasound studies and 14 patients were found aortic insufficiency even all patients with nephropathy had been given appetite suppressants: fenfluramine, dexfenfluramine, or phentermine, alone or in combination.

12.3 MuTong (Aristolochia manshuriensis)

MuTong is the name of the Chinese plant derived either from Aristolochia manshuriensis or various species of akebia or clematis. (Goshi T, 1992) Mutong is the stem of Akebia quinata (Thunb.) Decne (Lardizabalaceae). (Chang H. and But PPH, 1987) There is, however, much confusion regarding the products which are used as the Chinese herb Mutong. This lack of verification can result in the inadvertent use of Aristolochia manshuriensis and subsequent adverse health effects. Pharmacognostic study, however, revealed that most of the so-called "Mutong products" being sold in the market are actually <Guanmutong> derived from the dried vines of Aristolochia manshuriensis Kom. (Aristolochiaceae), which have a bitter taste and "cold" property. The herb is credited with latent-heat-clearing antipyretic, sthenic "heat"-purging, diuretic and lactagogue actions.

The acute toxicity of excessive doses of MuTong has been previously reported in Chinese publications. One woman wanting to promote milk production ate soup containing 70 g MuTong and red beans; she and her father-in-law who also ate the beans developed acute renal failure. (Wu SH, 1964) Another woman who took a decoction made with 175 g of MuTong also had acute renal failure and none of them died. Less fortunate were the other two men and two women who took decoctions prepared with 50 g, 70 g, 60 g, and 120 g MuTong respectively and they died of renal failure. (Wu SH,
There is no report on the long-term adverse effects of MuTong, except a case of renal-function impairment in a man who took ten doses of a decoction containing 25 g of MuTong. (Liu JY and Ceng HJ, 1994) All these cases were probably caused by GuanMuTong, which is derived from Aristolochia manshuriensis.

12.4 Ma-dou-ling (*Fructus Aristolochiae*)

Members of the genus of Aristolochia have been used as medicines in the Orient and the West. A Chinese herb, Ma-dou-ling (*Fructus Aristolochiae*), is derived from the fruits of *A. contorta* Bunge. or *A. debilis* Sieb. et Zucc. In traditional Chinese medicine, the pharmaceutical function of Ma-dou-ling is to remove heat from the lung and relieve cough and asthma, and to remove heat from the large intestine (rectum) for the treatment of hemorrhoid. Short-term prescription of Ma-dou-ling was used for treatment of cough and asthma at doses ranging from 3-9 g without any side effects. However, two cases of adverse reaction were reported due to overdose. In one case, a woman vomited severely after having taking a decoction prepared with 15 g of Ma-dou-ling. (Xiao P, 1989) Another case showed symptoms of nausea, dizziness and severe vomiting resulted from the intake of a decoction prepared with 30 g of Ma-dou-ling. Overdose and long-term usage of Ma-dou-ling should be avoided. (Yin R, 1983)

12.5 Tripterygium wilfordii

*Tripterygium wilfordii* Hook f. (TWH) is a plant of the genus Tripterygium of the family celastraceae. (Ming J, 1996) In China *Tripterygium wilfordii* was used to treated renal disease because the polyglycoside (TP) have pharmacological effect in autoimmune system. However, a case of herb-induce renal failure was reported in China. (Chai SR and Qu J, 1987) A patient suffer with Psoriasis consulted a practitioner
and was prescribed 8 g of *Tripterygium wilfordii* for one time daily and boiled with water for a month. However, the patient presumes using 12 g of *Tripterygium wilfordii* for the first time and only boiled for 20 minutes. Nausea and vomiting happened 2 hours later but he didn’t seek medical help. He took 8 g of *Tripterygium wilfordii* on the next day and started to have frequent vomiting and only have 100 ml of urine for that day. He was taken to hospital and found electrolyte imbalance with acidosis and symptoms of acute renal failure. The cause of ARF may relate to overdosage of *Tripterygium wilfordii* and the patient recover 2 months later. The mechanism of the intoxication may be related to the damage caused by direct toxin and ischaemia. (Bi KB, 2000) This was because the circulation of the renal system will decrease due to hypovolumic condition caused by diarrhea and vomiting after intoxication. Damage of the renal tubular cell from toxin directly may happen and changed into degenerating necrosis. 2 cases of biopsies confirmed the main cause of ARF from *Tripterygium wilfordii* intoxication was came from the toxin by the herb directly. (Bi KB, 2000)

### 12.6 *Gastrodia Elata*

The drug consisted of the dried tuber of *Gastrodia elata* Bl. In traditional Chinese theory, it used as antihypertensive and anticonvulsive agent for the treatment of headache, vertigo and numbness of limbs, induced by hypertension and the premonitory symptoms of apoplexy. An anaphylactic reaction for *Gastrodia elata* was reported in China that a 50 years old lady was found vertigo, nausea and vomiting after taken 10 g of for 6 hours. (Liu ZB, 1991) Purpura and skin itching was found for the whole body. Persistent abdominal pain and oliguria happened on the 2-day and she was diagnosed to have herb-induced ARF. She was recovering after one week of symptomatic treatment but the mechanism of the anaphylactic reaction was still unknown.
12.7 Licorice (*Glycyrrhiza glabra*)

An early report documented acute renal failure due to rhabdomyolysis, which was a consequence of chronic licorice ingestion and, possibly, due to the administration of furosemide for the two days prior to presenting. Withdrawal of the licorice and renal dialysis brought about complete recovery. (Mourad G, Gallay P et al, 1979)

In a subsequent case, myoglobinemia led to glomerulopathy and tubulopathy, but there was no clinical evidence of acute renal failure (ARF). (Heidemann HT and Kreuzfelder B, 1983) It was proposed that the mineralocorticoid-like actions of glycyrrhizin cause sodium retention and volume expansion, and thereby prevent the decrease in the glomerular filtration rate and the development of ARF, in spite of evidence of tubular dysfunction. (Mourad G, Gallay P et al, 1979; Heidemann HT and Kreuzfelder B, 1983) Moreover, another case reported the development of reversible tubulopathy. (Delcroix C, Poncin E et al, 1985)

Besides this, a 72-year-old man that developed acute renal failure following severe hypokalemic rhabdomyolysis, subsequent to chronic use of a glycyrrhizin-containing antacid. (Chubachi A, Wakui H et al, 1992) This patient presented with several predisposing factors, complicating the implication of glycyrrhizin, but was stabilized via plasma exchange, hemodialysis, potassium supplementation, and modest use of a glycyrrhizin-containing preparation. These authors conclude that the mineralocorticoid-like actions explained above may be inadequate to protect all persons, especially elderly people with decreased renal function and severely dehydrated patients. (Chubachi A, Wakui H et al, 1992)

More than this licorice root containing glycyrrhizin has been reported in association with Fanconi syndrome. (Izumotani T, Ishimura E et al, 1993) The authors hypothesized
that glycyrrhizin inhibits the Na K-ATPase activity of proximal tubular cells, possibly leading to irreversible Fanconi syndrome.

12.8 Hippocampus (Sea Horse)

Hippocampus is the dried body of Hippocampus kellogi Jordan et Snyder. It is used to replenish the vital function of the kidney especially that of sexual organs for the treatment of impotence, swelling in the abdomen and is also used externally for the treatment of carbuncles and furuncles. In traditional Chinese theory, Hippocampus were given to the newborn babies for strengthen the body within 3 days after delivery. 6 cases of newborn babies were found to have oliguria, fever, cyanosis, alert and abdominal distention after taken 1-2 pieces of Hippocampus and one of the babies was dead. (Yuan HN, 1992) Another cases of renal intoxication was reported that a patient who took a herbal decoction including Hippocampus due to mal-renal function.

12.9 Milabris Phanalerata

The dried body of Milabris Phanalerata Pall. or Milabris cichorii L. is used externally as a rubefacient, irritant and caustic to promote local blood circulation, remove dead tissue and accelerate the healing of wounds for the treatment of psoriasis, neurodermatitis, chronic ulcers and scrofula. If used internally, it was used for treating of the swelling of the lymph nodes and rabies. Cantharidin included was a severe toxin and caused adverse reaction in China occasionally. 2 cases of a 10 years old girl and a 46 years old man was taken herbal decoction that included 0.15g and 0.25 g of Milabris Phanalerata respectively due to prevention of rabies. (Liao LJ, 1987) Both of them started to have symptoms of ARF (oliguria, purpura and BUN increased rapidly) and were treated in the hospital. According to the severe toxin from Milabris Phanalerata, it betters to have caution for this when using in the elderly and children.
The clinical manifestations of intoxication are: Skin: Dehydration and vesicle formation, erosion of the buccal cavity with patchy hemorrhage. Gastrointestinal: nausea and vomiting, abdominal tenderness with diarrhea. In severe case, hemoptysis and melena will occur; Urologic: lumbar pain, frequent urination, dysuria, proteinuria, hematuria, anuria or oliguria; Neurologic: blurred vision, headache and dizziness with paralysis of extremities; Circulation: increase blood pressure first and change to hypovolumic with circulation failure with arrhythmia.

No special antidote and symptomatical and supportive treatment are suitable.

12.10 Chinese Proprietary Medicine

A case of reversible acute renal failure associated with the ingestion of a Chinese herbal medicine adulterated with a nonsteroidal anti-inflammatory agent and diazepam was reported.(Arthur AB, John OY et al, 1995) Such kind of adulteration with synthetic therapeutic substances is a main problem of herbal adverse reaction. A 51-year-old woman prepare to receive cholecystectomy in the hospital but needed to delay because she was found creatinine level around 300 micromol/L and rapidly progressive glomerulonephritis was rendered. The patient had taken eight herbal pills daily for 4 weeks and her medications included estrogen, a herbal tea, and a Chinese herbal medicine (Tung Shueh pills). Chemical analysis of the Tung Shueh pills confirmed the presence of mefenamic acid (not quantitated) and diazepam (0.43 mg per pill) accompanied with the herbal tea contained caffeine.

Excessive dosage or contamination of heavy metal in some Chinese proprietary medicine is sometimes present. Cinnabar (mercuric sulfide), realgar (arsenic sulfide), or litharge (lead oxide) may be present as part of the traditional formula and used in China for thousand of years. Other common renal-toxic herbal ingredients found in these
imported patent medicines include borneol (similar to camphor), aconite, bufo secreta (toad secretion or bufotoxin), mylabris, scorpion, borax, and Strychnos nux vomica (strychnine).

In the case of aristolochic poisoning, But PPH (But PPH and Ma SC, 1999) suggested that in the People's Republic of China Pharmacopoeia, there are seven kinds of Chinese proprietary medicines that contain GuanMuTong. For example, are registered, “Anyang Jingzhi plaster”, “Dahuang Qingwei Pills”, “Daochi pills”, “Fenqing Wulin pills”, “Fuke Fenqing pills”, “Longdan Xiegan pills”, and “Xiao'er Jindan tablets”. According to the toxicity of aristolochic acid, priority should be given to review of the long-term safety of these products, and GuanMuTong should be excluded from further use. Other sources of MuTong, for example ChuanMuTong from Clematis armata and C. montana, which do not contain aristolochic acids, could be used instead.

12.11 Conclusion

Many cases of CHN developed because of failure to verify the identity of the prescribed herbs. Some of the confusion arose from name similarity (Fangchi vs Fangji) and from lack of precision about the type of MuTong Chinese plant used. MuTong can be derived either from Aristolochia manshuriensis or from various species of Akebia or Clematis. Some patented Chinese medicines contain GuanMuTong, which is derived from Aristolochia manshuriensis. Others contain ChuanMuTong from Clematis armata and Clematis montana and do not contain aristolochic acids. Patients and practitioners should try to avoid using Mu-Tong containing aristolochic acid and pay attention to monitoring the renal function if the medication has to be given. Incidents of this kind highlight the importance of developing and enforcing appropriate quality assurance
procedures for herbal medicines.

Table 12 a. The Renal-toxicity of Traditional Chinese Medicine & Chinese Proprietary Medicine.

<table>
<thead>
<tr>
<th>Traditional Chinese Medicine (TCM)</th>
<th>Chinese Proprietary Medicine (CPM)</th>
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<tbody>
<tr>
<td>1. Aloe (蘆薈)</td>
<td>1. Angong Niuhuang Wan (安宮牛黃丸)</td>
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<tr>
<td>2. Caulis Aristolochiae Manshuriensis (關木通)</td>
<td>2. NiuHuang Jiedu Wan/Pian (牛黃解毒片)</td>
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<td>3. Cinnabar (朱砂)</td>
<td>3. San Xiandan (三仙丹)</td>
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<td>4. Cortex Magnoliae Officinalis (厚朴)</td>
<td>4. Suxiao Sangfeng Jiaonang (速效傷風膠囊)</td>
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<tr>
<td>5. Flos Rhododendri Mollis (鬱羊花)</td>
<td>5. TianWang Buxin Dan (天王補心丹)</td>
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<td>6. Folium Sennae (番瀉葉)</td>
<td>6. Yunnan Baiyao (雲南白藥)</td>
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<td>7. Fructus Aristolochiae (馬兜鈴)</td>
<td>7. Zhusha Anshen Wan (朱砂安神丸)</td>
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<td>8. Fructus Bruceae (蟾蜍子)</td>
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<td>9. Fructus Crotonis (巴豆)</td>
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<td>10. Fructus Quisqualis (使君子)</td>
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<td>11. Fructus Xanthii (蒼耳子)</td>
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<td>12. Gastrodia Elata (天麻)</td>
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<td>13. Herba Leonuri (益母草)</td>
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<td>14. Hippocampus (海馬)</td>
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<td>15. Mel (蜂蜜)</td>
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<td>16. Mylabris (斑蝥)</td>
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<td>17. Radix Trichosanthis (天花粉)</td>
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<td>18. Radix Tripterygii Wilfordii (雷公藤)</td>
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<td>19. Realgar (雄黃)</td>
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<td>20. Radix Angelicae Pubescensis (獨活)</td>
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<td>21. Rhizoma Alismatis (澤瀉)</td>
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<td>22. Ricinus Communis (蓖麻子)</td>
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<td>23. Semen Arecae (檳榔)</td>
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<td>24. Semen Strychni (馬錢子)</td>
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<td>25. Scolopendra (蜈蚣)</td>
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<td>26. Scorpio(全蝸)</td>
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<td>27. Trichosanthes Kirilowii (天花粉)</td>
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<td>28. Tripterygium hypoglaucum (昆明山海棠)</td>
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Chapter 13 - Adverse Reaction of Herbal Medicine in Dermatology.

13.1 Overview

Herbal therapy is becoming increasingly popular among patients and physicians. Many herbal preparations are marketed to the public for various ailments including those of the skin. It emphasizes the importance of using many herbs that are combined in different formulations for each individual patient. Among some segments of the patient population it has become increasingly popular as a mode for treating dermatologic diseases. As a result, it is now worthwhile for dermatologists throughout the West to gain some familiarity with this method. Yet, dermatologists are largely unfamiliar with TCM and may possess some misconceptions.

Herbal treatments are increasingly popular. A recent survey implied that, between 1990 and 1997, the general population usage of unconventional treatments had risen from 33% to 42%. It also suggested that 8.6% of people who use unconventional drugs did so to treat dermatological problems, and showed that the usage of herbal remedies has increased by 380% in this time span. This level of popularity clearly begs the question as to how safe herbal treatments are.

Thus dermatologists should know about their potential to cause adverse events. Some agents, particularly Chinese herbal creams, have been shown repeatedly to be adulterated with corticosteroids. Virtually all herbal remedies can cause allergic reactions and several can be responsible for photosensitization. Some herbal medicines, in particular Ayurvedic remedies, contain arsenic or mercury that can produce typical skin lesions. Other popular remedies that can cause dermatological side effects include
St Johns Wort, kava, aloe vera, eucalyptus, camphor, henna and yohimbine. Finally, there are some herbal treatments used specifically for dermatological conditions, e.g. Chinese oral herbal remedies for atopic eczema, which have the potential to cause systemic adverse effects.

13.2 Chinese Herbal Medicine Used in Psoriasis

According to TCM, psoriasis is subtyped into 3 main categories: "blood-heat" type, "blood deficiency-dryness" type, and "blood stasis" type. (Koo J and Arain S, 1999) According to the subtype of psoriasis the patient has, a different mixture of herbs is suggested. For example, when inflicted with blood stasis psoriasis the lesions are indurated and have little tendency to resolve spontaneously. There is also a purplish or dark red coloring of the tongue with occasional petechia. The pulse is often small and loose.

The principle of treatment of this type of psoriasis is to activate the blood and eliminate the stasis. The most often used prescriptions include Herba Hedyotis diffusae, Flos carthami, Semen persicae, Ramulus euonymi, Rhizoma sparganii, Rhizoma curoumae, Pericarpium Citri reticulatae, and Caulis spatholob. (Koo J and Arain S, 1999) These are only the core ingredients that are recommended. They are ingested as decoctions. According to the needs of each patient, this list would be altered.

To treat blood deficiency-dryness a different set of herbs is considered more suitable. Among the physical manifestations of this type is the appearance of the tongue characterized by pinkish color with a thin coating. (Koo J and Arain S, 1999) Western dermatologists do not routinely inspect the tongues or pulses of their patients with psoriasis. Thus, it is difficult to make a comparison between this two treatment.
13.2.1 Tripterygium wilfordii

Tripterygium wilfordii Hook and Triptergium hypoglaucum Hutch are 2 popular TCMs. (Koo J and Arain S, 1999) Tripterygium wilfordii Hook has yielded positive therapeutic effects when used to treat various types of psoriasis. Although Tripterygium wilfordii Hook's possible mechanism of action has been investigated to be both anti-inflammatory and immunosuppressive, there have been several negative consequences. The clinical efficacy is similar for Triptergium hypoglaucum Hutch and Tripterygium wilfordii Hook. Chinese medical literature concludes that with the current results Tripterygium wilfordii Hook and Triptergium hypoglaucum Hutch have shown modest efficacy with an acceptable adverse effects profile. (Long YI, Zhou GP et al, 1983; Zheng FZ, 1984; Gao JC, 1990) Some toxic effects have been observed in both animals and human subjects. Among these are gastrointestinal reaction, cutaneous/mucotaneous reactions, and abnormal menstruation. Some abnormalities in the hematopoietic system were also noted. In addition, exacerbation of latent chronic hepatitis and abnormal liver function was observed in several cases.

13.2.2 Radix Angelicae pubescentis and Radix Angelicae dahuricae

Although TCM has been used to treat a variety of skin diseases, of particular interest to us is psoriasis. Both topical and systemic use of herbs has been administered to treat psoriasis, as well as a combination of herbal medications with UV-A. This method is similar to psoralen-UV-A phototherapy. Radix Angelicae pubescentis and Radix Angelicae dahuricae were the Chinese herbal medicine that were administered in combination with UV-A irradiation. Radix Angelicae dahuricae UV-A therapy was reported to have an obvious result with 46.8% in 204 psoriasis patients and inducing
marked improvement in 121 patients (42.6%) in whom psoriasis was not completely cleared. (Koo J and Arain S, 1999)

13.2.3 Radix macrotomiae seu Lithospermi Injection

Although TCMs are commonly found in topical, oral, and photochemotherapeutic modalities, some of them are also injectable. (Koo J and Arain S, 1999) Sometimes the injectable agent yields better results than when used in the other forms. For instance, *Radix macrotomiae seu Lithospermi* when injected resulted in a more significant therapeutic effect in treating psoriasis than in an oral formulation.

13.3 Chinese Herbal Decoction For Atopic Dermatitis

Traditional Chinese medicine (TCM) for the treatment of atopic dermatitis and psoriasis has recently received much attention. In traditional Chinese theory, the body is treated as a whole and the aim of therapy is to restore harmony to the functions of the body. (Atherton DJ, Sheehan MP et al, 1992) This requires a mixture of various herbs individually formulated for the patient, making randomized controlled trials difficult to undertake. (Sheehan MP, Rustin MH et al, 1992) Recently, 2 randomized placebo-controlled crossover trials were performed in England to study the effects of orally administered CHM in the treatment of atopic dermatitis in which traditional Western therapy had failed. (Sheehan MP and Atherton DJ, 1992; Sheehan MP, Rustin MH et al, 1992; Armstrong N and Ernst E, 1999) The investigators were aided by a Chinese physician who was able to create a standardized mixture of 10 herbs useful in treating atopic dermatitis characterized by erythema, lichenification, and plaques of dermatitis in the absence of active exudation or clinical infection. The standard TCM practice emphasizes the importance of using many herbs combined in different compositions for each individual patient. The formulation is based on the diagnosis and individual
condition of the patient. Whereas Western medicine emphasizes monotherapy, standard TCM promotes herbal mixtures sometimes involving more than 10 different herbs and other agents. The 10 herbs used were Potentilla chinensis, Tribulus terrestris, Rehmannia glutinosa, Lophatherum gracile, Clematis armandii, Ledebouriella saseloides, Dictamnus dasycarpus, Paeonia lactiflora, Schizonepeta tenuifolia, and G glabra. (Sheehan MP and Atherton DJ, 1992) These herbs were placed in sachets and boiled to make a decoction that was orally administered daily as a tea. The placebo arm consisted of a decoction made from several herbs with similar smells and tastes that have no known efficacy in the treatment of atopic dermatitis. The first study focused on 37 children and showed a median decrease in erythema score of 51.0% in the treatment group compared with only a 6.1% improvement in the placebo group. The percentage surface involvement also decreased by 63.1% and 6.2% for the treatment and placebo groups, respectively. In this initial study, no serious adverse effects were found. These 37 children were offered continued treatment with the CHM and then followed up for 1 year. (Sheehan MP, Rustin MH et al, 1992) Eighteen children completed the year of treatment and showed 90% reduction in eczema activity scores. The children who withdrew from the study did so because of lack of further response to treatment, unpalatability of the tea, or difficulty in preparation of the treatment. By the end of 1 year, 7 patients were able to discontinue therapy without relapse. Asymptomatic elevation of aspartate aminotransferase level was noted in 2 patients, which returned to normal with discontinuing treatment. No other serious sequelae were observed. In the other study, the design was similar; however, the investigators studied 31 adult patients with atopic dermatitis. (Sheehan MP, Rustin MH et al, 1992) Again, the decrease in erythema and surface damage was statistically superior in the treatment group compared
with the placebo group. There was also subjective improvement in itching and sleep. These patients were also followed up for a year, with continued improvement and no serious adverse effects, whereas the patients who discontinued treatment noted a decline in their condition. (Sheehan MP, Rustin MH et al, 1992) Although the sample sizes were limited during the course of the study, initial results were promising for patients in whom standard therapy failed. The main limitation appeared to be the taste and the preparation of the decoction. It should be emphasized, however, that, although no serious adverse effects were noted in this study, careful monitoring of complete blood cell count and liver function is recommended, as reports of liver failure and even death have been reported when baseline laboratory values were not followed up. (Brown G, 1992; Kara M, Pauwels A et al, 1992; Koo J and Arain S, 1998)

13.3.1 Tea Extracts

Ultraviolet solar radiation may induce a variety of adverse effects in humans, including melanoma, (Koh H, Kligler B et al, 1990) photoaging of the skin (Wenk J, Brenneisen P et al, 2001); (Krutmann J, 2000), sunburn (Biesalski H and Obermueller-Jevic U, 2001), and immunosuppression. (Gil E and Kim T, 2000; Hart P, Grimaldeston M et al, 2001) Protection against UV-induced skin damage includes avoidance of sun exposure, application of sunscreens, low-fat diets, (Black H, 1998; Hakim I, Harris R et al, 2000) and pharmacologic intervention with retinoids. (DiGiovanna J, 2001) More recently, green tea extracts have been reported to be beneficial in treating UV-induced photodamage. (Levin CBA and Maibach HMD, 2002) The (-)-epigallocatechin-3-gallate and (-)-epicatechin-3-gallate polphenolic fractions were most effective in a dose-dependent reduction of UV-induced erythema as measured by chromatometry and visual evaluation. Histological examination showed a decrease in sunburn cells in green tea
polyphenolic (GTP)-treated skin. Epidermal Langerhans cells, the antigen-presenting cells involved in the skin immune response, were significantly protected against UV damage. Furthermore, oral and topical standardized black tea extracts also decreased photochemical damage to the skin.

13.4 Potential Adverse Effect with Herbal Medicine

Many patients have the misconception that, because herbs are "natural," there are no adverse effects. Physicians often do not question patients about herbal supplements, and patients are often reluctant to divulge the use of these agents for fear of criticism from their physician. It is important that dermatologists become aware of the most common, as well as the more serious, effects.(see Table 13 a & 13 b) This will aid in better education of patients, as well as better diagnosis of possible fatal sequelae.

13.4.1 Allergic skin reactions

Many cutaneous reactions to herbal preparations have been reported. The most common cutaneous adverse effect of herbal preparations is allergic contact dermatitis. However, more serious cutaneous reactions have been reported. Allergies are a potential adverse effect with virtually any herbal (or indeed synthetic) medication.(Mantyranta T and Haahtela T, 1993) The risk obviously increases with topical administration and long-term usage. A notable case describes an aromatherapist with allergic eczema and positive patch tests to 18 different essential oils.(Selvaag E, Holm J et al, 1995)

The number of cases related to allergic reactions to herbal remedies reported in the medical literature is too large to be comprehensively reviewed here. Table 13 a provides examples only. Emphasis is put on more recent case reports with clinical relevance. Two patients developed erythroderma after using topical herbal treatments for psoriasis and atopic dermatitis, and 1 patient developed Stevens-Johnson syndrome after taking...
"Golden Health Blood Purifying Tablets," which contained multiple herbs, including red clover, burdock, queen's delight, poke root, prickly ash, sassafras bark, and Passiflora. (Monk B, 1986) There have been reports of bullous and nodular lichen planus induced by ingestion of native African medicines. (Soyinka F, 1973) A young woman has also been described with leukemia-related Sweet syndrome elicited by pathergy to topical arnica cream. (Delmonte S, Brusati C et al, 1998)

13.4.2 Stevens-Johnson syndrome

Following the consumption of a health drink containing ophiopogonis tuber, a 66-year-old woman noted erythema and swelling of her face, neck and chest (Table 13 a). (Mochitomi Y, Inoue A et al, 1998) Subsequently, she developed bullous and eroded lesions on the skin of her entire body as well as of the mucous membranes of her mouth, conjunctiva and cornea. She also had a fever and liver dysfunction. Diffuse necrosis of the epidermis was confirmed by biopsy. She tested positive in drug lymphocyte stimulation and patch tests as well as on a rechallenge with 1/1000 of the original dose. The patient made a full recovery on steroid therapy.

13.4.3 Photosensitization

Essential oils used topically for aromatherapy and herbal creams have repeatedly been implicated as the cause for photosensitization. A particularly dramatic case was reported recently; a 33-year-old woman was admitted to a U.K. burns unit with 70% superficial partial thickness burns. (Cocks H and Wilson D, 1998) She had self-administered an aromatherapy bath 3 days previously using six drops of bergamot and six drops of geranium oil. After the bath she had spent about half an hour on a sunbed. During the ensuing 48 h she noted increasing erythema and blistering on the exposed areas. The authors conclude that bergamot oil (which contains 5-methoxypsoralen and is
a known photosensitizer) was the cause of this event. Numerous other herbal remedies contain psoralens (Rutaceae, Umbelliferae, Moraceae, Leguminosae) and can therefore cause photosensitivity. (Koo J and Arain S, 1999)

Based on animal data, photosensitivity has always been considered a possible adverse effect of St Johns Wort, a best-selling herbal antidepressant. (Stevinson C and Ernst E, 1999) German dermatologists reported a case of a 61-year-old patient who presented with an itching erythema of the light-exposed areas. She was on St Johns Wort extract for depression. Using a systemic oral photoprovocation test, these authors were able to demonstrate a decreased minimal erythema dose for ultraviolet radiation B that was reversible after withdrawal of the herbal remedy. (Golsch S, Vocks E et al, 1997)

Recently a further case report of photosensitivity after oral administration of St Johns Wort was published. (Bove GM, 1998) A 35-year-old women took 500 mg/day of ground whole St Johns Wort leaf for about 1 month when she began to feel a stinging pain on the skin of her face and dorsum of her hand. The pain was exacerbated through exposure to the sun. The problem spread to all areas of the skin exposed to the sun. When she discontinued self-medicating with St Johns Wort the pain ceased promptly.

A further case of acute photosensitivity following treatment with an herbal remedy relates to Psorolea corylifolia (Babchi). The patient had taken the herbal treatment in the form of a cream that he had used to treat his long-standing vitiligo and subsequently experienced erythema in exposed areas. (Maurice PDL and Cream JJ, 1989) By excluding other causes, a diagnosis of photosensitivity due to P. corylifolia was made. This diagnosis was subsequently confirmed through inadvertent rechallenge. The herb, which is frequently used for vitiligo in Indian populations, contains psoralen, isopsoralen
and psoralidin. Its extracts have been demonstrated to have potent sensitizing activity on guinea-pig skin. (Pathak MA, Daniels F et al, 1962)

13.4.4 Pellagra

A 25-year-old woman presented with a 6-week history of photosensitive dermatitis with painful erythema of the feet and progressive involvement of sun-exposed areas. (Wood B and Wishart J, 1997) Dermatological examination revealed erythematous plaques with well-demarcated, peeling hyperpigmented borders, which were distributed symmetrically over the dorsal aspect of the limbs. She also showed the classic Casals necklace. A clinical diagnosis of pellagra was made and she recovered quickly on oral nicotinamide. Even though no satisfactory mechanism of action could be identified, the authors considered the patients self-medication with Kombucha tea the most likely cause for the pellagra.

13.4.5 Hepatotoxic Effects

Serious systemic adverse effects have been reported with the use of TCM for the treatment of dermatologic disorders. (Monica BK and Philip SD, 2002) The most common are hepatotoxic effects. Although most patients recover without serious consequences as long as the medication is stopped, there have been reports of patients with acute liver failure and death.

In Great Britain, a 29-year-old woman was prescribed Chinese herbal treatment for eczema. (Walton P and Murray V, 1992) She consequently developed 2 episodes of hepatitis that led to hospitalization. She had acute liver failure after the second hospitalization. This later led to her death, despite an emergency liver transplantation. The British governmental agency has recorded 11 cases of liver damage following the use of TCM for skin conditions from January 1991 to December 1993. In many of the
cases, recovery occurred after discontinuation of the herbal medicines. Later when rechallenged with the same herbal medicine, there was a recurrence of hepatitis. Although it is difficult to establish absolute etiologic association for all 11 cases, there is an obvious circumstantial link between TCM and the consequent liver damage.

13.4.6 Others Adverse Reaction

There are also reports of renal failure and agranulocytosis. (Brown G, 1992; Kara M, Pauwels A et al, 1992; Koo J and Arain S, 1998) One patient has been described with adult respiratory distress syndrome after administration of a CHM, Kamisyoyo-san, for seborrheic dermatitis. (Shota Y, Wilson JG et al, 1961) Another patient was described with reversible dilated cardiomyopathy after treatment for her atopic dermatitis with a Chinese herbal tea. (Ferguson JE, Chalmers R et al, 1997)

13.4.7 Potential Adverse Reaction Caused by Interactions

There are many possible drug interactions with herbs and prescription medications. The most important in the dermatologic setting are discussed. (Ferguson JE, Chalmers R et al, 1997) The immune-modulating effects of Echinacea, Astragalus, licorice, alfalfa sprouts, vitamin E, and zinc may decrease the efficacy of corticosteroids and immunosuppressants. (Miller LG, 1998) There are herbs that have been shown to cause hepatitis and therefore should not be used in combination with such medications as methotrexate. These include many of the ingredients in the CHM preparations, as well as Echinacea, chaparral, germander, ragwort, and life root. (Ferguson JE, Chalmers R et al, 1997; Borins M, 1998) Herbs containing gamolenic acid, such as evening primrose oil, which has been used for dermatitis, psoriasis, and xerosis, lower the seizure threshold, and therefore dosages of anticonvulsants may need to be increased.
13.5 Adverse Reaction Caused by Contaminants of Chinese Herbal Product

Various authors have previously published analyses of Chinese herbal medications. (Koo J and Arain S, 1999) These findings have revealed many types of contaminants. Methyltestosterone, dexamethasone, indomethacin, chlordiazepoxide, prednisolone, betamethasone, lead, diazepam, mefenamic acid, prednisone, or hydrocortisone is some of many substances that have been found in these medications. Other possible contaminants of Chinese herbal medications include Hydrochlorothiazide, chlorpheniramine, phenylbutazone, aminopyrine, paracetamol, thiamin, caffeine, and ethaverine.

13.5.1 Herbal creams adulterated with corticosteroids

The most important and perhaps most prevalent adulterants in herbal creams are corticosteroids. This seems to be a particular problem with Chinese herbal creams. A 53-year-old woman with psoriasis saw a Chinese herbalist and purchased a herbal cream from a Chinese health center. (Wood B and Wishart J, 1997) She experienced excellent improvement of her skin condition but discontinued the medication because she could not afford it any longer. Subsequently, liquid chromatographic analysis showed that the cream contained significant amounts of clobetasol propionate. Similar cases have been reported repeatedly. (Shaw D, Leon C et al, 1997) In a large-scale investigation from Taiwan, 2,609 samples of traditional Chinese remedies were analyzed. Thin-layer chromatography demonstrated that 24% of them were adulterated. (Huang WF, Wen KC et al, 1997) More recently a team of dermatologists from London asked 10 patients to bring in their Chinese herbal creams for analysis and submitted these to chromatographic analysis. (Keane FM, Munn SE et al, 1999) Eight of 11 samples contained dexamethasone at a mean concentration of 456 mg/g (range 64-1500 mg/g). It
is obvious that the risk of adverse effects of such potent topically applied steroids is considerable and is increased through inappropriate use.

13.5.2 Arsenic dermatoses

Traditional Indian (Ayurvedic) and Chinese medicines worryingly often contain arsenic. (Ernst E and De Smet PAGM, 1996) This can lead to serious intoxication, and several cases with dermatological side effects have been reported. A 35-year-old Indian man had consulted his hakim for his atopic eczema and was given an Ayurvedic herbal remedy. Six weeks later he was seen by a dermatologist who noted hyperkeratosis of the soles of the feet and impaired cutaneous sensation following a glove and stocking distribution. In addition, there were signs of symmetrical muscle wasting on the limbs. The patient’s urinary concentration of inorganic arsenic was more than 30 times the normal value. (Kew J, Morris C et al, 1993) The remedy was analyzed and the patient’s daily dose was shown to be equivalent to 210 mg of inorganic arsenic trioxide. In spite of adequate treatment, the patient was unable to work 2 years after these events.

The National Skin Center of Singapore reviewed all records of patients with cutaneous lesions related to chronic intake of arsenic seen between 1990 and 1996. (Wong SS, Tan KC et al, 1998) The sample consisted of 17 Chinese patients, 14 of who had taken Chinese herbal remedies contaminated with inorganic arsenic. The most frequent dermatological manifestations were Bowen’s disease, arsenical keratosis and squamous cell carcinoma. Such complications have been repeatedly related to the administration of Asian herbal remedies. Between 1972 and 1973 no less than 74 cases were reported in Singapore. (Tay CH, 1974)

13.5.3 Mercury poisoning

Asian (e.g. Ayurvedic and traditional Chinese) herbal preparations are often
contaminated with mercury. (Kew J, Morris C et al, 1993) This can lead to dermatological signs like tylotic eczema, dryness of the skin, skin ulceration and erythroderma. (De Groot AC, 1996)

Table 13 a. Allergic skin reactions to herbal remedies and aromatherapy oils.

(Ernst E, 2000)

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Indications</th>
<th>Application</th>
<th>Type of adverse effect</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
<td>various effects</td>
<td>topical</td>
<td>severe and prolonged allergic dermatitis</td>
<td>(Hunter D and Frumkin A, 1991)</td>
</tr>
<tr>
<td>Aristochol</td>
<td>cholagogue</td>
<td>oral</td>
<td>allergic contact dermatitis</td>
<td>(Bayerl C and Jung EG, 1996)</td>
</tr>
<tr>
<td>Balsam of Peru</td>
<td>cosmetic wound healing</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Hausen BM, Simatupang T et al, 1995)</td>
</tr>
<tr>
<td>Black cumin oil</td>
<td>acne, eczema and others</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Steinmann A, Schatzle M et al, 1997)</td>
</tr>
<tr>
<td>Camomile</td>
<td>anti-inflammatory</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Van Ketel W, 1987)</td>
</tr>
<tr>
<td>Camphor</td>
<td>various</td>
<td>topical</td>
<td>erythematous, papuluous oedematous, pruriginous eruptions</td>
<td>(Marguery MC, Rakotondrazafy J et al, 1995)</td>
</tr>
<tr>
<td>Cedarwood oil</td>
<td>aromatherapy</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Franz H, Frank R et al, 1998)</td>
</tr>
<tr>
<td>Chinese herbal mixture</td>
<td>Various unknown herbal</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Leow YH, 1997)</td>
</tr>
<tr>
<td>Citrus hystrix</td>
<td>insect bite</td>
<td>topical</td>
<td>delayed erythema</td>
<td>(Koh D and Ong C.N, 1999)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>various</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Hata M, Sasaki E et al, 1997)</td>
</tr>
<tr>
<td>Echinacea</td>
<td>immune stimulant</td>
<td>oral</td>
<td>generalized urticaria anaphylaxis</td>
<td>(Koh D and Ong CN, 1999; Mullins RJ, 1998)</td>
</tr>
<tr>
<td>Herbs</td>
<td>Indications</td>
<td>Application</td>
<td>Type of adverse effect</td>
<td>Ref</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>French marigold</td>
<td>aromatherapy</td>
<td>topical</td>
<td>allergic dermatitis</td>
<td>(Bilsland D &amp; Strong A, 1990)</td>
</tr>
<tr>
<td>Garlic</td>
<td>lipid-lowering</td>
<td>oral</td>
<td>urticaria, angioedema</td>
<td>(Asero R, Mistrello et al, 1998)</td>
</tr>
<tr>
<td>Jasmine</td>
<td>aromatherapy oil</td>
<td>topical</td>
<td>contact allergy (oedematous, exudative, erosive erythema)</td>
<td>(Suss R &amp; Lehmann P, 1996)</td>
</tr>
<tr>
<td>Kava</td>
<td>anxiolytic</td>
<td>oral</td>
<td>contact-type dermatitis</td>
<td>(Schaller M &amp; Korting HC, 1995)</td>
</tr>
<tr>
<td>Lavender</td>
<td>aromatherapy oil</td>
<td>topical</td>
<td>allergic contact dermatitis (oedematous, exudative, erosive erythema)</td>
<td>(Isaksson M &amp; Bruze M, 1999)</td>
</tr>
<tr>
<td>Olive oil</td>
<td>used as a massage oil</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Pazzaglia M, Venturo N et al, 1995)</td>
</tr>
<tr>
<td>Paprika/capsaicin</td>
<td>musculoskeletal pain</td>
<td>topical</td>
<td>dermatitis anaphylaxis</td>
<td>(Foti C, Carino M et al, 1997; Williams SR, Clark RF et al, 1994)</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>aromatherapy</td>
<td>topical</td>
<td>allergic contact dermatitis (erythematous eruption)</td>
<td>(Weiss RR and James WD, 1997)</td>
</tr>
<tr>
<td>Rosewood</td>
<td>aromatherapy oil</td>
<td>topical</td>
<td>contact allergy (oedematous, exudative, erosive erythema)</td>
<td>(Suss R &amp; Lehmann P, 1996)</td>
</tr>
<tr>
<td>Tea tree oil</td>
<td>aromatherapy, cosmetics</td>
<td>topical</td>
<td>allergic contact dermatitis</td>
<td>(Weiss RR &amp; James WD, 1997)</td>
</tr>
<tr>
<td>Herbs</td>
<td>Indications</td>
<td>Application</td>
<td>Type of adverse effect</td>
<td>Ref</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>----------------------</td>
<td>-----------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Various aromatherapy oil mixes</td>
<td>aromatherapy</td>
<td>topical or airborne</td>
<td>allergic contact dermatitis</td>
<td>(Knight TE &amp; Hausen BM, 1994; Selvaag E, Holm J et al, 1995; Suss R &amp; Lehmann P, 1996)</td>
</tr>
<tr>
<td>Ylang-ylang</td>
<td>aromatherapy</td>
<td>topical</td>
<td>allergic contact dermatitis (erythematous eruption)</td>
<td>(Weiss RR &amp; James WD, 1997)</td>
</tr>
</tbody>
</table>

Table 13 b. Herbal Medicine that could cause Skin Allergy Reaction.

By Oral administration

1. *Bombyx Batryticatus* (僵蠶)
2. *Borneolum Syntheticum* (冰片,梅片)
3. *Bulbus Fritillariae Cirrhosae* (川貝母)
4. *Cinnabaris* (朱砂)
5. *Cornu Saigae Tataricae* (鈴羊角)
6. *Cortex Phellodendri* (黃柏)
7. *Folium Mori* (桑葉)
8. *Fructus Amomi* (砂仁)
9. *Fructus Evodiae* (吳茱萸)
10. *Herba Andrographitis* (穿心蓮)
11. *Herba Desmodii Styracifolii* (廣金錢草)
12. *Herba Houttuyniae* (魚腥草)
13. *Herba Taraxaci* (蒲公英)
14. *Pericarpium Trichosanthis* (瓜蒌皮)
15. *Radix Bupleuri* (柴胡)
16. *Radix et Rhizoma Rhei* (大黃)
17. *Radix Isatidis* (板藍根)
18. *Radix Notoginseng* (三七)
19. *Radix Rehmanniae Preparata* (熟地黃)
20. *Radix Scutellariae* (黃芩)
22. *Rhizoma Pinelliae* (生半夏)
23. *Scolopendra* (蜈蚣)
24. *Scorpio* (全蝎)
25. *Venenum Bufonis* (蟾酥)

By External Used

1. *Calomelas* (輕粉)
2. *Eupolyphaga Seu Steleophaga* (土鶏)
3. *Fructus Bruceae* (鴉膽子)
4. *Fructus Xanthii* (黃耳子)
5. *Radix Aconiti Lateralis Preparata* (附子)
6. *Radix Clematidis* (威靈仙)
7. *Radix Rehmanniae Preparata* (熟地黃)
8. *Radix Trichosanthis* (天花粉)
9. *Radix Tripterygii Wilfordii* (雷公藤)
10. *Rhizoma Alismatis* (澤瀉)
11. *Rhizoma Zingiberis Recens* (生姜)
12. *Semen Ricini* (蓖麻子)

13.6 Dermatological Adverse Reaction Caused by Herbs

13.7 Contact Dermatitis Caused by CPM

Topical application of Chinese medicines is a popular treatment in Chinese medicines, particularly for rheumatic pain, traumatic injury, and skin diseases. It is not uncommon to find allergic or irritant responses to such topical treatments.

13.7.1 ‘Liushenwan’

“Liushenwan” (Lushenwan) is a common over-the-counter proprietary Chinese medicine, manufactured with six items: toad venom (*Chansu*), ox gall-stone (*Niuhuang*), musk (*Shexiang*), borneol (*Bingpian*), pearl (*Zhenzhu*), and realgar (*Xionghuang*). It is often used for the treatment of upper respiratory infections, especially tonsillitis and other causes of sore throat; by oral ingestion. It is sometimes also applied topically to treat boils, carbuncles, cellulitis and other skin infections. A woman applied “Lushenwan” to her neck to relieve neck pain. Within two days, she
developed an itchy erythematous rash on her neck. The erythematous patches bear well-defined margins, lichenification and excoriation. A few microvesicles were present in some lesions. Another woman applied “Liushenwan” to her eyelids to treat itchiness there. By the next morning, her eyelids had become red, swollen and very itchy. On examination, both eyelids were red, swollen and edematous. The borders of the lesions were well-defined and excoriations were seen. Patch tests confirmed that “Liushenwan” caused an irritant rather than an allergic type of reactions. Patch tests of each of the six herbs in “Liushenwan” revealed that only toad venom Chansu was the cause of the irritant reaction. (Lee TY & Lam TH, 1988)

13.7.2 ‘Heiguiyou’

“Heiguiyou” or “Black Man Oil” is an over-the-counter medicament retailed in Hong Kong. Its Malay name is “Minyak Orang Hitam Obat Gosok”. Its ingredients include thymol crystal, citronella oil, wintergreen oil and turpentine oil. A male patient applied the oil for itchiness on his neck but developed erythematous patches with well-defined margins, edema, vesicles and excoriation, over the anterior neck. Another male patient applied the oil to his genitals for itchiness of the scrotum. But on the next day, there was marked redness, swelling and exudation of the scrotum. Patch tests confirmed that the oil was the cause of the irritant reactions. Turpentine oil was regarded as the most likely putative irritant. (Lee TY & Lam TH, 1989)

13.7.3 ‘101 Hair Regrowth Liniment’

“101 Hair Regrowth Liniment” is manufactured with 19 herbs for restoring hair on the head. A woman applied the liniment for two weeks and developed redness and itching over the scalp. She stopped applying it and the symptoms subsided in a week. She applied it again and the symptoms reappeared two days later. Another patient used
the liniment for gradual diffuse alopecias. A week later, his scalp showed multiple erythematous lichenified patches with well-defined margins and mild excoriation. Patch tests on these two patients confirmed the allergic reactions were due to the liniment. However, a control study of another 20 eczematous control patients, with no history of using the liniment, showed no allergic response at 48 and 96 hours after application of the liniment. (Lee TY & Lam TH, 1989)

13.7.4 ‘Zhenggushui’

“Zhenggushui” is a Chinese herbal orthopedic tincture. According to the product description, it is prepared with Croton tiglium <Wuma qincheng>, Cinnamomum cainphora <Jig uxiang>, Angelica dahurica <Baizhi>, Moghania macrophylla <Qianjinba>, Inula cappa <Daliwang>, Panax notoginseng <Tianqi>, menthol <Bohenao> and camphor <Zhangnao>. Four patients developed blisters, redness, swelling, edema, excoriation and lichenification over the areas topically applied the tincture. A control study on 20 patients showed that four patients developed erythema and another four developed erythema with overlying microvescicles but no infiltration. (Lee TY & Lam TH, 1991)

13.7.5 ‘Tiedayaojing’

<Tiedayaojing> or Tieh Ta Yao Gin is another Chinese herbal orthopedic tincture. Its ingredients are: mastic <Ruxiang>, myrrh <Moyao>, flower of Carthamus tinctorius <Honghua>, extract of twig of Acacia catechu <Ercha>, root of Panax notoginseng <Tianqi>, gel of Aloe vera <Luhui>, root of Angelica sinensis <Danggui>, and resin from Daemonorops draco <Xuejie>. After topical application of the tincture, three patients developed rashes with edema and microvesicles. Patch tests confirmed that the allergic contact dermatitis was due to the tincture. The putative allergens were identified
as mastic and myrrh in the tincture. (Lee TY & Lam TH, 1992)

Table 13  c. Dermatological signs caused by adverse effects of herbal remedies. (Ernst E, 2000)

<table>
<thead>
<tr>
<th>Dermatological signs (location)</th>
<th>Responsible herbal remedy (mode of application)</th>
<th>Type of reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>paprika (topical)</td>
<td>allergy</td>
</tr>
<tr>
<td>Angioedema (exposed areas)</td>
<td>Garlic (oral)</td>
<td>allergy</td>
</tr>
<tr>
<td>Bowen’s disease</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>arsenic poisoning</td>
</tr>
<tr>
<td>Burning skin (exposed area)</td>
<td>Aloe vera (topical)</td>
<td>not known</td>
</tr>
<tr>
<td>Burns, partial thickness</td>
<td>Bergamot aromatherapy oil (topical)</td>
<td>photosensitivity</td>
</tr>
<tr>
<td>Contact dermatitis (usually exposed area)</td>
<td>Numerous herbal remedies (usually topical)</td>
<td>allergy</td>
</tr>
<tr>
<td>Dry skin with scaly yellow pigmentations (palms, soles, forearms, back, shins)</td>
<td>Kava (oral)</td>
<td>chronic abuse (mechanism unknown)</td>
</tr>
<tr>
<td>Dryness of skin</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>mercury poisoning</td>
</tr>
<tr>
<td>Eczema (exposed areas)</td>
<td>Krameria triandra (oral)</td>
<td>allergy</td>
</tr>
<tr>
<td>Erythema (exposed areas)</td>
<td>Psorolea corylifolia (oral)</td>
<td>photosensitivity</td>
</tr>
<tr>
<td>Erythematous plaques (symmetrical over dorsum of limbs)</td>
<td>Kombucha tea (oral)</td>
<td>pellagra</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>mercury poisoning</td>
</tr>
<tr>
<td>Exudative erythema (exposed areas)</td>
<td>Jasmine (oral)</td>
<td>allergy</td>
</tr>
<tr>
<td>Exudative erythema</td>
<td>Rosewood (topical)</td>
<td>allergy</td>
</tr>
<tr>
<td>Generalized urticaria (exposed areas)</td>
<td>Echinacea (oral)</td>
<td>allergy</td>
</tr>
<tr>
<td>Hyperkeratosis (soles of feet)</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>arsenic poisoning</td>
</tr>
<tr>
<td>Itching erythema (light-exposed areas)</td>
<td>St John’s Wort (oral)</td>
<td>photosensitivity</td>
</tr>
<tr>
<td>Itching skin (exposed area)</td>
<td>Aloe vera (topical)</td>
<td>not known</td>
</tr>
<tr>
<td>Lupus-like syndrome</td>
<td>Yohimbine (oral)</td>
<td>not known</td>
</tr>
<tr>
<td>Necrotic skin lesions (face and leg)</td>
<td>Arnica (topical)</td>
<td>Sweet’s syndrome</td>
</tr>
<tr>
<td>Dermatological signs (location)</td>
<td>Responsible herbal remedy (mode of application)</td>
<td>Type of reaction</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Painful skin (light-exposed areas)</td>
<td>St John Wort (oral)</td>
<td>photosensitivity</td>
</tr>
<tr>
<td>Papulous itching eruptions (exposed areas)</td>
<td>Camphor (topical)</td>
<td>allergy</td>
</tr>
<tr>
<td>Skin ulceration</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>mercury poisoning</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>arsenic poisoning</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Ophiopogonis tuber (oral)</td>
<td>allergy</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Mai-Men-Dong-Tang (Chinese herbal remedy) (oral)</td>
<td>allergy</td>
</tr>
<tr>
<td>Tylotic eczema</td>
<td>Contamination of (Asian) herbal preparation (oral)</td>
<td>mercury poisoning</td>
</tr>
</tbody>
</table>

13.8 Non-dermatological adverse effects of systemic herbal treatments used for dermatological conditions.

A Chinese mixture of numerous herbs has been promoted as a symptomatic treatment of atopic eczema. (Armstrong N & Ernst E, 1999) Since it has been in popular use in the U.K. numerous cases have been reported of liver damage and one case of cardiomyopathy associated with this mixture. (Davies EG, Pollock I et al, 1990; Ferguson JE, Chalmers RJG et al, 1997) One poison unit in London recorded 21 cases of hepatotoxicity following the use of Chinese herbal treatments for dermatological conditions; 47 in 14 of these there was sufficient evidence to suggest a causal relationship. Two cases of eczema patients treated with Chinese herbal mixtures have been recently reported. Both developed end-stage renal failure that required renal transplants. The herbal mixtures were demonstrated to contain aristolochic acid, possibly due to the inadvertent use of *Aristolochia manshuriensis* as one plant in the mixture.
The topic of traditional Chinese medicine for dermatological conditions has recently been reviewed elsewhere in some detail. (Koo J & Arain S, 1999)

13.9 Conclusion

Many practicing dermatologists in the industrial cities are only familiar with orthodox Western procedures for the treatment of skin disorders. However, an increasing number of patients have begun to seek TCM as an alternative mode of therapy. It has been demonstrated in published studies that there is a real possibility that TCM has a substantial efficacy beyond a simple placebo effect. However, TCM has also been associated with notable adverse effects, some fatal. It is concluded that adverse effects of herbal medicines are an important albeit neglected subject in dermatology, which deserves further systematic investigation. The current clinical studies in the Chinese medical literature are not a complete source of information about TCM.

Many of the studies have been conducted without a placebo arm and it is difficult to interpret the results in comparison studies. This is so because the standard Western medications used for comparison in China are often not those agents currently used in Western medicine. Further research should target this complex area more systematically with a view to establishing reliable incidence figures and increasing patient’s safety. The above data suggest that adverse effects of herbal treatments are an important issue in dermatology. Dermatologists should be aware that these remedies can cause adverse effects which, at times, may be serious. It thus seems important for clinicians to ask patients about their use of such therapies, particularly as a large proportion would not normally volunteer such information.

In the hopes of determining any future adverse effects, we recommend that Chinese herbal medications be subjected to drug licensing, monitoring, and surveillance.
procedures. This should be done in a manner similar to what any new drug is subjected
to for approval in the United States or United Kingdom. The individualized
drug Polypharmacy approach of TCM is intuitively sensible. This is especially in countering a
complex, chronic, and often recalcitrant inflammatory process such as psoriasis or
eczema in which it would be most beneficial to attack the process through many facets
simultaneously. However, this approach would lead to extremely difficult scientific
analysis of these medications. A more rigorous, systematic analysis and testing of
therapeutic agents used in TCM may eventually lead to the development of a standard
set of therapeutic agents that may be administered with reliable efficacy and good
quality control.
Chapter 14 - Chinese Herbal Medicine in Pregnancy, Infants & Children.

14.1 Overview

Despite widespread popularity, the use of many Chinese herbal medicine and dietary supplements during pregnancy remains poorly documented and inadequately studied in controlled clinical trials. (Beatrice T, Cathi DE et al, 2001) Certain traditional Chinese medicine (TCM) is commonly consumed by Chinese women during pregnancy with the belief that these herbs will have beneficial effects on the mother and/or the baby. Herbal medicines are often used by the general public in the self-treatment of many common diseases. A survey of 1,004 Chinese pregnant women living in Hong Kong in 1983-84 revealed that 54% used TCM. There is very important to take serious consideration for the pregnant woman and its baby because in pregnancy, there are two parties involved, the mother, who willingly incurs any benefits or risks associated with the product, and the fetus, who is an unwilling participant. (Beatrice T, Cathi DE et al, 2001) It is clear that pregnant women who choose to use dietary supplements need to be adequately informed about which products have undergone sufficient clinical study to warrant a recommendation for use during pregnancy (eg, folic acid) and which rely more on historical precedence for their efficacy and safety data.

When a herb has oxytocic properties (the capacity to cause contraction of the uterus), the risks of its unrestricted use during pregnancy will be readily discovered. However, when a sick baby is born, who will attribute the disease to maternal consumption of a herbal preparation many months before the baby's delivery? Herbal drugs containing pyrrolizidine alkaloids may have been used since prehistoric
times, (Lietava J, 1992) but the first case report about neonatal hepatotoxicity following the use of such a remedy during pregnancy did not appear until a few years ago. (Roulet M, Laurini R et al, 1988; Spang R, 1989) There is a great need for more and better information about the embryotoxic and fetotoxic risks of herbal drugs, not in the least because herbal drug use during pregnancy is sometimes encouraged by uncritical publications. (Bunce KL, 1987) This need for better information is illustrated by an Australian study, in which calls to a drug information center about drug use in pregnancy and lactation were analyzed.

14.2 Asian Cultures for Pregnancy

The traditional practice of selecting food to maintain the body in balance between 'Yin' and 'Yang' in the Chinese usually means the avoidance of a large number of items which are highly nutritive. (Please see Table 14 a & b) Certain foods are also believed to provoke undesirable body reactions, making the choice of foods for the growing child fairly limited. This is particularly significant during weaning, which most Asians regard as the period of 'cessation of milk-feeds'. (Yeung CY, 1988)

**TABLE 14 a. Traditional Chinese belief of foods provoking undesirable body reactions.** (From C.Y. YEUNG. Traditional Asian Practices and their Influences on Child Health. 1988)

<table>
<thead>
<tr>
<th>Hot</th>
<th>Cool</th>
<th>Toxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>All fried foods</td>
<td>Fruits - banana, peach, melon etc.</td>
<td>Shell fish - crab, crab</td>
</tr>
<tr>
<td>especially deep fried</td>
<td>Vegetables - cabbage, mustard green</td>
<td>shoots</td>
</tr>
<tr>
<td>Game meats</td>
<td>Roots - ginger</td>
<td>Carp</td>
</tr>
<tr>
<td>Roastings</td>
<td>Beans - green bean</td>
<td>Bamboo</td>
</tr>
<tr>
<td>Milk powder</td>
<td>Ice cream</td>
<td>Eggs</td>
</tr>
<tr>
<td>Beef, mutton</td>
<td>Soft drinks</td>
<td></td>
</tr>
<tr>
<td>Pigeon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In Asian cultures, ginseng is commonly consumed by pregnant women and is given to newborns in hopes of bolstering energy. A case-control study of 88 pairs of women (matched only for age and parity) found a significantly lower rate of pregnancy-induced hypertension, but a 3-fold higher incidence of gestational diabetes among ginseng consumers. (Chin RK, 1991) Ginseng was not recommended for pregnant or lactating women or for children until safety and efficacy are proven in randomized controlled trials.

**TABLE 14 b. Chinese Herbal Medicine Not Suitable For Pregnancy.**

<table>
<thead>
<tr>
<th>Herbs for invigorating blood circulation</th>
<th>Herbs for diuretic</th>
<th>Herbs with Fragrant Odour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen Persicae 桃仁</td>
<td>Talcum 滑石</td>
<td>Moschus 劫香</td>
</tr>
<tr>
<td>Flos Carthami 紅花</td>
<td>Semen Abutili 冬葵子</td>
<td>Fructus Tsaoko 草果</td>
</tr>
<tr>
<td>Rhizoma Sparganii 三棱</td>
<td>Radix Euphorbiae Kansui 甘遂</td>
<td>Flos Caryophylli 丁香</td>
</tr>
<tr>
<td>Rhizoma Zedoarvae 菖朮</td>
<td>Radix Euphorbiae Pekinensis 大戟</td>
<td>Lignum Dalber giae Odoriferae 降香</td>
</tr>
<tr>
<td>Herba Lycopi 澤蘭</td>
<td>Flos Genkwa 花荒</td>
<td></td>
</tr>
<tr>
<td>Tabanus 虻蟲</td>
<td>Croton tigilium 巴豆</td>
<td></td>
</tr>
<tr>
<td>Olibanum 乳香</td>
<td>Semen Pharbitidis 牽牛子</td>
<td></td>
</tr>
<tr>
<td>Myrrha 没藥</td>
<td>Caulis Aristolochiae Manshouriensis 關木通</td>
<td></td>
</tr>
<tr>
<td><strong>Toxic Herbs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radix Aconiti Lateralis Preparata 附子</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radix Aconiti 川烏</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radix Aconiti Kusnezoffii 草烏</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chinese mothers living in Hong Kong are used to giving their babies special medicinal food to strengthen the infant's internal defences and to restore the body's harmonious state. (Sung RY, Lui S et al, 1988) However since the majority of registered doctors are trained in the Western pharmacological tradition it is difficult for them to comprehend the concepts and idioms of this practice. Their common use and the continued availability of toxic preparations may explain the frequent occurrence of serious and even fatal poisonings. (Chan TYK & Critchley JA, 1996) The main causes
of death in patients were taken aconites and have cardiovascular collapse and ventricular arrhythmias. Moreover, children may also be accidentally poisoned by herbal medicines given by their parents for the treatment of minor ailments in childhood.

Infants and children may be even more susceptible to some of the adverse effects and toxicity of these products because of differences in physiology, inadequate hepatic drug biotransformation and detoxification enzymes systems, and dose per body weight. As neonatal jaundice is a highly prevalent pediatric condition in the South East Asians, especially in Chinese, it is not surprising that herbal therapy may have a role for managing this problem. Even in a modern and westernized city like Hong Kong, nearly 42% of the pregnant mothers among the Chinese community in 1982 were still taking herbs themselves and another 40% had given their children in the neonatal period herbal tea for various reasons. (Yeung CY, 1994)

Yeung and colleagues reported in 1990 nearly 28-51% of Chinese infants in Hong Kong were given "Chuen-lin" by their mothers to "clear the toxin of pregnancy". (Yeung C, Lee FT et al, 1990) However, several herbs (Chuen-lin, Ngau-Huang and Yin-Chen) which are popularly consumed in the neonatal period are found to be highly effective in displacing bilirubin from its protein-binding and generate an increased amount of unbound bilirubin. "Yin-Chen", which is normally given as a herbal tea, has been processed and prepared as an intravenous extract in China. In recent years, based on anecdotal stories of success, the intravenous preparation of the herbal extract "Yin-Chen" (Artemisia scoparia) was used by many hospital pediatric units in China to treat neonatal jaundice. However, its displacing bilirubin function could generate increase the amount of unbound or 'free' bilirubin, which could potentially damage various tissues, especially the brain.
Although kernicterus or bilirubin-induced brain damage has become much less prevalent in Hong Kong, its continued occurrence is seen in many other South East Asian countries. Clinical statistics of a hospital in Hong Kong showed that herbal consumption was an outstanding factor in jaundiced infants with kernicterus. (see Table 14 c) Increased frequency of herb-taking was associated with increasing severity of the jaundice in the group of jaundiced infants admitted for treatment. (Yeung C, Lee FT et al, 1990) Laboratory studies showed that berberine could displace bilirubin from its serum binding proteins, which can result in a rise in the free bilirubin concentration. Since there is a high prevalence of glucose-6-phosphate dehydrogenase deficiency and neonatal hyperbilirubinaemia among southern Chinese, kernicterus is common in Chinese infants. It was suggested that feeding the jaundiced infants with “Huanglian” might increase the risk of brain damage, by further increasing the concentrations of free bilirubin. Ox gallstone “Niuhuang” and “Yin-Chen” are also shown to be bilirubin-displacement agents. It is not clear which source herb of “Yin-Chen” was incriminated. As neonatal hyperbilirubinemia is highly prevalent among Southern Chinese, the use of “Chuen-lin” and “Yin-Chen” in the perinatal period should be strongly discouraged.

Table 14 c. Herb exposure and neonatal jaundice. (Yeung CY, 1988)

(From C.Y. YEUNG. Traditional Asian Practices and their Influences on Child Health. 1988 )

<table>
<thead>
<tr>
<th>Infants</th>
<th>Moderate jaundice &lt; 10 mg/dl</th>
<th>Severe jaundice &gt; 20 mg/dl</th>
<th>With brain damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>1811</td>
<td>581</td>
<td>156</td>
</tr>
<tr>
<td>No. of given herbs</td>
<td>364</td>
<td>211</td>
<td>90</td>
</tr>
<tr>
<td>Rate with herbs</td>
<td>20.1%</td>
<td>36.3%</td>
<td>57.7%</td>
</tr>
</tbody>
</table>

a bilirubin > 10 mg/dl.  
b bilirubin > 20 mg/dl.  
c All infants were referred for admission for jaundice.
Besides generating increased amount of free bilirubin in the jaundiced serum predisposing the infants to brain damage, many herbs are also known to precipitate acute haemolytic crisis in G6PD deficient children. (Wong HI, 1980; Hotham NJ, 1990) Sudden severe haemolytic jaundice occurred repeatedly following casual administration of herbal tea. Although the child or the newborn may appear healthy and asymptomatic, a significant morbidity occurs with acute haemolytic anaemia, jaundice, haemoglobinuria and renal failure.

Babies and children are particularly at risk because both traditional Chinese medicine (TCM) and Chinese proprietary medicine (CPM) are used for the treatment of minor ailments in childhood. Moreover, babies and children may be given higher doses of these preparations / kg body weight than adults would normally consume. They may lack the hepatic enzymes responsible for drug biotransformation and detoxication. It should also be remembered that TCM and CPM taken during pregnancy and just prior to delivery might affect the fetus and baby, respectively.

Sung et al studied 166 Chinese mothers and their babies in 1984 with regards the use of Chinese herbs during the first 30 mo after birth. (Sung RY, Lui S et al, 1988) About 89% of the babies in that study were given CHM or medicinal foods at some stage, with the frequency of their administration varying from weekly to once or twice monthly. The most popular compound herb preparations and their indications (in brackets) were: "milk preparation solution" (49%) (to make up milk formula in place of water); "flower teas" (31%) (to eliminate endogenous heat); and various "cool teas" (17%) (to eliminate endogenous heat). In this study, these herb preparations did not appear to have a harmful effect on the baby.
Table 14 d. Herbs or Herbal Combinations Commonly Taken by Pregnant Women in Hong Kong. (Chan TYK, Chan JCN et al, 1998)

<table>
<thead>
<tr>
<th>Herb/herb combination</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-flower tea</td>
<td>Urinary frequency, indigestion, constipation</td>
</tr>
<tr>
<td>“Lianzi” (Nelumbo nucifera)</td>
<td>To facilitate delivery</td>
</tr>
<tr>
<td>“Danggui” (Angelica sinesis)</td>
<td>To improve the general wellbeing and vitality</td>
</tr>
<tr>
<td>“Zicao” (Lithospermum officinale)</td>
<td>Soothing effect, for the treatment of urinary frequency and constipation</td>
</tr>
<tr>
<td>“Renshen” (Panax Ginseng)</td>
<td>To improve the general wellbeing and vitality, to provide the extra energy required for labour</td>
</tr>
<tr>
<td>13B herbs</td>
<td>To ensure firm implantation of the foetus in the uterus and for the treatment of threatened abortion</td>
</tr>
<tr>
<td>“Xiakucao” (Prunella vulgaris)</td>
<td>For the treatment of indigestion and flu</td>
</tr>
<tr>
<td>12B herbs</td>
<td>Same as for 13B herbs</td>
</tr>
<tr>
<td>“Jinyinhua” (Lonicera japonica)</td>
<td>Same as for 5-flower tea</td>
</tr>
</tbody>
</table>

14.3 Teratogenic Herbs

Teratogenic herbs are known to have the tendency or likelihood of causing danger or harm to the fetus during pregnancy and thus leading to birth-defects or spontaneous abortion. (Chen J, 1998) Teratogenic herbs are classified into two categories: prohibited and use with caution.

Prohibited herbs are very potent and very toxic. The use of these herbs during pregnancy is prohibited to avoid possible harm to the fetus. Prohibited herbs include Semen Crotonis (Ba Dou), Semen Pharbitidis (Qian Niu Zi), Radix Euphorbiae (Da Ji), Mylabris (Ban Mao), Radix Phytolaccae (Shang Lu), Moschus (She Xiang), Rhizoma Sparganii (San Leng), Rhizoma Zedoariae (E Zhu), Hirudo seu Whitmania (Shui Zhi) and Tabanus (Meng Chong).

Herbs that should be used with caution are herbs that are pungent and warm in nature and have the functions to activate Qi, activate Blood circulation, and remove blood stasis. They are also very potent in nature and should be avoided during pregnancy.
whenever possible. The use of these herbs should be limited only to later stages of pregnancy and only when the benefits of using the herbs outweigh the risks. Herbs that should be used with caution include *Semen Persicae* (Tao Ren), *Flos Carthami* (Hong Hua), *Radix et Rhizoma Rhei* (Da Huang), *Fructus Aurantii* (Zi Shi), *Radix Aconiti* (Fu Zhi), *Rhizoma Zingiberis* (Gan Jiang), and *Cortex Cinnamomi* (Rou Gui).

### 14.4 Chinese proprietary medicines

Apart from herbal extracts, CPM may contain western drugs, including paracetamol, aspirin and antihistamines, which may or may not be listed in the manufacturer's information leaflet. (Chan TY & Critchley JA, 1994) A survey performed in 1993 by the National Poison Center in Taiwan reported that 103 cases of poisoning were found in relation to the use of herbal medicine. Surprisingly, 33% of the cases recorded were in children below 15 years old. This implies that many of the pediatric poisonings are actually directly related to the inappropriate safety concepts and attitudes preexisting in the parents. Through the data collection system of National Poison Center, nine cases of poisoning in children were related to the use of “Pa-Bow Fen”, “Chi-Yin Wan” and “Gin-Fong-Fen”. According to the severity of the poisoning, the cases can be classified as mild (22%): nausea, vomiting, abdominal fullness, diarrhea; moderate (33%): organ dysfunction such as liver, kidney, and metabolic acidosis; severe (29%): unconsciousness, cardiopulmonary distress, death. (Deng JF, 1994)

#### 14.4.1 "Tse Koo Choy"

Kang-Yum and Oransky recently described a case of mercury poisoning in a 4-y-old Chinese boy living in the US. (Chan H, Billmeier GJ et al, 1977) He had been given "Tse Koo Choy", which contains calomel (mercurous chloride), by his mother for his respiratory symptoms. Moreover, Yu and Yeung described in 1987 the second of lead
babies were brought back for follow-up the next day.

14.4.4 “Jin Bu Huan” Toxicity in Children

Consumption of traditional ethnic remedies can have adverse health effects, especially among children. Life-threatening bradycardia with rapid onset and central nervous system (CNS) and respiratory depression developed in three unrelated children in Colorado during 1993 following ingestion of “Jin Bu Huan” tablets, a Chinese herbal medicine used for relieving pain. (Horowitz RS, 1993; Woolf WGM, 1993) After analyzed the tablets retrieved from the patient’s parents. It included 36% concentrated weight-by-weight levo-tetrahydropalmatine (L-THP), a substance present in the plant genus Stephania but not in the genus Polygala - - the plant of origin indicated on the product package insert. However, the investigation has not detected any evidence of pharmaceutical contamination of this product. The potential toxicity may result from a combination of factors, including the extreme potency of L-THP, the misidentification of the plant from which the product was derived, the false and potentially misleading medical claims, the availability of the product, and lack of childproof packaging.

14.5 Topical Preparations

As in adults, babies and children may develop contact dermatitis due to topical application of "Yunnan Paiyao" and "Lu Shen Wan". Some of the Chinese topical herbal medicaments have been shown by patch testing to cause mild to moderate irritation in patients with a history of endogenous eczema or contact dermatitis due to other substance. (Lee TY & Lam TH, 1990) These include "Red Flower Oil" or "Hung Far Oil", "White Flower Medicine Oil", "Jaminton Healing Oil" or "Lion Medicated Oil" and "Tiger Balm". (Ingredient of the medicated oil in pages 119) Excessive topical application of these and other preparations may result in significant absorption of the
active ingredients and systemic toxicity. (Lee TY & Lam TH, 1988)

Many brands of ointments are frequently used to rub over various sites for the
treatment of a number of ulcers and disease. The use of an oil such as “Pak Fa Oil”
rubbed onto the abdomen of the crying infant to treat colic is very common
practice. (Yeung CY, 1988) Ointments are also applied to bruised areas and sore points.
Oils of many kinds are frequently smeared around the temporal region for dizziness,
vomiting or motion sickness. Those nauseating smells in the cabins of aircraft full of
Oriental passengers on long distance fights are only too familiar to frequent travellers.
Besides being socially unacceptable, many of these ointments or liniments frequently
produce local reactions such as skin rashes and exfoliation and accidental ingestion with
poisoning in young children has also been observed.

14.6 Dietary supplement

A survey performed between November 1999 and March 2000 in University of
California showed that nearly 13% of 150 was using dietary supplements during
pregnancy. (Beatrice T, Cathi DE et al, 2001) The most common products were
echinacea (4/45, 8.9%), pregnancy tea (4/45, 8.9%), and ginger (3/45, 6.7%). The most
common reasons for beginning or discontinuing use of dietary supplements were to
relieve nausea and vomiting (25%) and to avoid potential harm to the fetus (25%). Even
most of the side effects were mild and included gastrointestinal discomfort, late-onset
thrombocytopenia was reported in a mother who used St John’s wort for depression
during pregnancy. (Grush LR, Nierenberg A et al, 1998) In another case, hypoxia, renal
failure, and seizures occurred in an infant whose mother had used a combination of
black and blue cohosh during pregnancy. (Gunn TR & Wright IMR, 1996) Physicians
and pharmacists should be more diligent in asking questions about the use of dietary
supplements, particularly in those patients who are of childbearing age.

14.7 Conclusion

It is anticipated that the use of herbal medicine will also increase in children, as parents incorporate alternative therapies into their family health care. Pregnant patients and babies may use these products instead of prescription medications. However the effects of such kind of supplements on a developing fetus are largely unknown; the teratogenicity of dietary supplements in humans and their mutagenicity are often speculated on the basis of in vitro and animal data. Therefore mothers should keep in mind and discouraged from treating their children with herbal or proprietary medicines.

In order to prevent cases of unintentional poisoning associated with herbal and other botanical products, such products should be sold in childproof packaging and kept in childproof containers, and parents should be informed about the potential toxicity of herbal products. Health care providers can play an important role in educating patients and their parents about the potential risks of herbal therapies and the need to closely monitor any use in children.
Chapter 15 - Heavy metals poisoning in traditional Chinese medicines.

15.1 Introduction

Traditional Chinese medicine (TCM) is gaining popularity as a form of complementary and alternative medicine. (Koh HL & Woo S, 2000) Despite the belief that TCM and herbal remedies are of natural origin, unlike Western medicine, and are hence safe and without many adverse effects, there have been numerous reports of adverse effects associated with herbal remedies. Numerous case reports and case series of heavy metal poisoning associated with the use of TCM have been published. (Ernst E, 2002) Mercury, lead and arsenic are the three heavy elemental toxins pathology laboratories are most often requested to measure. Lead has relatively often been implicated as the cause of such poisoning but mercury, cadmium, arsenic, copper, and thallium have also been found in TCM. In many cases, TCM intake had been prolonged until a diagnosis of intoxication was made. Intoxications are not confined to Southeast Asia but have also been documented in the West.

Several possibilities exist to explain the presence of heavy metals in TCM. (Peter AGMDS, 1992) The first reason was the usage of heavy metal as a part of the herbal formulation and those prescriptions are still widely accepted by ordinary people, especially in China. Some senior herbal practitioner still prefer using complex mineral drugs as did their ancestors thousands of years ago. Second, the presence of heavy metals may be the result of accidental contamination during manufacture, for instance, from grinding weights or lead-releasing containers or other manufacturing utensils. Third, medicinal herbs may contain heavy metals when grown in seriously polluted soil.
Contamination of the general environment with toxic metals has increased. The sources of the environmental pollution are quite varied, ranging from industrial and traffic emissions to the use of purification mud and agricultural expedients, such as cadmium-containing dung, organic mercury fungicides, and the insecticide lead arsenate. Beside environmental pollution, contamination may also occur in those “homemade” herbal medicines such as the case of “Boa Ning Dan”.

Californian officials have screened for undeclared pharmaceuticals and heavy metals in imported Chinese remedies on sale in Californian herbal retail stores (Ko RJ, 1998). Seven percent of the 251 products tested contained undeclared pharmaceuticals (e.g. ephedrine, chlorpheniramine, methyl-testosterone and phenacetin). Twenty-four products contained at least 10 ppm lead, 36 contained an average of 14.6 ppm arsenic, 35 contained an average of 1046 ppm mercury, and 23 had more than one contaminant and/or adulterant. Koh and Woo reported the detection of toxic heavy metals that exceeded Singapore’s legal limits in 42 Chinese proprietary medicines (Koh HL & Woo S, 2000). They collected 2080 samples of such medicines in Singapore and tested them for heavy metal content. Forty-two different medicines were found to contain metals in amounts exceeding the legal limits. Mercury was found in 28 products, lead in eight, arsenic in six and copper in one. One product contained both mercury and lead and another product contained both mercury and arsenic.

Beside traditional Chinese medicine, Indian medical systems also have the same problem. Indian medical systems (e.g. Ayurveda and Unani) have a long and rich history of herbal medicine, and heavy metals have been a regular and deliberate constituent of traditional Indian remedies. A London-based toxicology unit published a case series of adverse events associated with traditional medicines that were reported to
them between 1991 and 1995. (Shaw D, Leon C et al. 1997) Of 12 cases of poisoning with lead, arsenic or mercury, nine cases were associated with herbal remedies from India and the remainder was due to traditional Indian cosmetics (e.g. “Surma”).

15.2 LEAD

15.2.1 Overview

While lead is a very old poison whose toxicity was known to the ancient Greeks, new information about mechanisms and effects of lead toxicity is continually being discovered. The sources of lead intoxication in adults without occupational exposure are often insidious and the diagnosis can be missed in the absence of a typical history. Exposure to lead-based paint is the leading cause of high-dose lead exposure among children. However, previous reports have documented childhood lead poisoning related to the use of traditional ethnic remedies. (Colgrove ML, Zinion M et al. 1984; Flattery J, Gambatese R et al. 1993) In recent years, mistaken herbal medicine that contaminated with heavy metal was found in Asian population occasionally and made people pay attention to those herbal medicines. Several well-documented cases of lead intoxication associated with Chinese patent medicine which indicate that the use may significantly contribute to the overall incidence of lead toxicity in the Asian population. However, the relative risk in this ethnic problem has not been clearly established. (Bayly GR, Braithwaite RA et al. 1995)

Exposure to traditional remedies and cosmetics containing lead has also been identified as a potential cause of childhood toxicity in the Asian community in the United Kingdom. (Ali AR, Smales ORC et al. 1978) Several of these products obtained in the Indian subcontinent and in Britain were found to contain high concentrations of heavy metals. Surma samples have been found to contain up to 86% lead.
15.2.2 Poisoning Cases of “Boa Ning Dan”

Totally 19 citizens in Hong Kong was found suffering from lead poisoning after taking pills prepared by a TCM practitioner a year ago. Based on the published information state that a 23-year-old lady was first found to have non-specific musculoskeletal pain by herself and she seek medical help thereafter.(Auyeung TW, Chang KK et al, 2002) Physical examination was unremarkable but the laboratory studies of the parameters of heme biosynthesis revealed an enzymatic inhibition. The diagnosis of lead poisoning was confirmed by detection of an elevated blood lead level. (The first blood lead level was 3.03 µmol/L (<1.5 µmol/L)). The patient took some herbal pills recently form a traditional Chinese practitioner and the drug was called “Boa Ning Dan”. This herbal pills was made by this practitioner and she have to take four to six pills daily. She totally took this herbal pill for two months in order to treat acne. Chelating therapy was not given because of the deranged liver function. Her liver function normalised in 3 weeks after stopped taking the herbal pills.

Another victim was a 35-year-old housewife, who had been suffering from anxiety neurosis for eight years, was receiving follow up treatment in Psychiatry Clinic regularly. She consulted the same TCM practitioner as in the first patient and was taking “Boa Ning Dan” in the belief that it could “help excrete the toxin of the psychiatric medication from the body and stop the left groin pain”. She had been taking four pills daily for 6 months. She received screening for blood lead level after learning that “Boa Ning Dan” contained excess lead and her first blood lead level was 5.6 µmol/L (< 1.5 µmol/L). Furthermore, a 48-year-old housewife who had suffered from common cold symptoms consulted the same TCM practitioner. She took four “Boa Ning Dan” pills
daily for three days. Her blood lead level was 6.7 μmol/L (< 1.5 μmol/L). She was referred to received further management. The highest blood lead level in the third patient could be caused by acute lead intake and the lead needs time to distribute to the body tissues. At this stage, the body tissues could still be free from lead deposition. This explains why she had no clinical features of poisoning despite having the highest blood lead level.

The second and third patient, although relatively asymptomatic, were treated with chelating therapy. In doubtful clinical situations, a Calcium Disodium EDTA mobilization test can be done to decide whether chelating therapy should be given.

The Department of Health has already banned the distribution of the pills and confiscated the patient list from this practitioner for further investigation. The department appealed to people who have taken the pills to come forward for free lead screening and appropriate treatment. Nearly eighty people have to take blood lead screening test by the Department of Health after learning that the pills contained excess lead.

The herbal pill was analyzed chemically by the laboratory of the Department of Health and showed that each pills contained 200 times more lead than the daily allowable intake. Based on the practitioner statement showed that no heavy metal was used in this formula and the presence of heavy metals might be the result of contamination during manufacture.

According to the fact that in China there was no formal regulation for traditional medical practice and qualified medical pactitioners in the past. Some TCM practitioners are trained specifically as Chinese herbal medicine practitioners and have little or no knowledge of medicine. They only get training from the senior practitioner and lack of
western medical concept also. Some of them even made the herbal drug by themselves at home and the constituents of the herbal pills cannot be standardized or regulated.

15.2.3 Lead Poisoning Worldwide

Beside “Bao Ning Dan”, several cases of lead poisoning reported in recent years. Lead poisoning cases may happen in different countries. (Fisher A & Couteur D, 2000) A 4-month-old boy presented at a Hong Kong hospital with a history of fever, cough, anorexia, vomiting, and a grand mal seizure. (Chan TY, 1997) On physical examination he was comatose with repeated tonic-clonic convulsions. His whole blood lead level was 137 \( \mu \text{g}/\text{100g} \) and the 24-h urinary lead excretion was 52 \( \mu \text{g} \). Since birth the boy had been treated with several Chinese herbal medicines (16 unit dose packages of “Po Ying Tan”, 5 packages of “Chun Chu Mu”, and one package each of “Po Lung Yuen” and “Siu Fun San”).

In Chinese communities, these medicines are used very frequently, without prescription, for many minor ailments. All these medicines were found to contain lead. The analyses of 11 brands of Chinese herbal medicines by flameless atomic absorption spectrophotometry revealed that one of the medicines, “Po Ying Tan” had a mean lead content of 7.5 mg per unit dose; the other 10 brands had lower but still significant lead contents. Samples of six other “Po Ying Tan” brands showed lead levels from 0.012 to 0.07 mg/dose. (Chan TY, 1997) A survey done by the Hong Kong Medical and Health Department showed that 2 of 44 patent herbal medications contained > 30 \( \mu \text{g}/\text{pill} \) of lead and would provide > 3 mg/week when taken in recommended doses (i.e. more than the provisional weekly tolerable intake for lead established by FAO/WHO). (Yu ECL & Yeung CY, 1987)
A semiconscious 2-month-old boy was admitted with repeated convulsions to a Hong Kong hospital. (Yu ECL & Yeung CY, 1987) Subsequent investigations showed a blood lead level of 195 μg/dl and a 24-h urinary lead excretion of 20.7 mg. Since the 4th day of his life he had been treated with a herbal powder mixture with a total and leachable lead content of 23.3% and 15.6%, respectively. At least 0.2 g of this powder had been painted onto his buccal mucosa twice a week, resulting in a lead intake of 62.4 mg/week.

Heavy metal intoxication of newborn infants fed with "Ba-Pao-Neu-Hwang-San" has been reported every year by many hospitals in Taiwan. Nearly ten years ago, the National Laboratories of Foods and Drugs of the Department of Health, Executive Yuan, have a case report for a five-month-old female infant who died as a result of long term feeding with "Ba-Pao-Neu-Hwang-San". The drug was found to have contained lead 44,000 ppm. (Chi YW, Chen SL et al, 1993)

A 59-year-old woman in the United States developed anemia, diffuse pain, insomnia, irritability, and paranoia as well as difficulty using her hands. (Lightfoote J, Blair HJ et al, 1977) Her 24-h urinary lead excretion was 1044 μg. Four months before, she had been instructed by a herbalist, acupuncturist to take 30 Chinese herbal pills per day. Since the pills showed a lead content of 0.5 mg per pill, this advice amounted to a lead intake of 15 mg/day. (Lightfoote J, Blair HJ et al, 1977)

"Chuifong tokuwan pills" (Nan Ling Pharmaceutical Company, Hong Kong) illegally sold in Texas contained not only synthetic Western drugs (diazepam, indomethacin, Hydrochlorothiazide, mefenamic acid, dexamethasone) but also lead and cadmium. (Anonymous, 1989) When 93 persons who had ingested these pills were
tested for exposure to these heavy metals, none showed elevated levels of lead, but 22 (24%) had abnormally high urinary cadmium levels over 2.5 μg/l ml and 39 (42%) showed elevated urine values for retinol-binding protein, a low molecular weight protein indicative of renal tubular dysfunction. (Anonymous, 1989)

A series of five cases of lead poisoning due to traditional remedies in the West Midlands. (Bayly GR, Braithwaite RA et al, 1995) All developed typical clinical features. Blood lead and zinc protoporphyrin (ZPP) concentrations were elevated 2-10 times the upper limit of normal. The remedies contained up to 60% lead by weight. Confirmation of the medicines as the cause of the poisoning was made in one patient by measurement of lead isotopic ratios. (see Table 15 a) Moreover, two cases of lead poisoning from the Chinese herbal medicine Cordyceps were reported by the Department of Health in a laboratory-based blood lead surveillance program in Taiwan. (Wu TN, Yang KC et al, 1996) This was caused by. These two patients took Cordyceps herbal medicine for treatment of underlying diseases. Loss of appetite and anemic signs of lead poisoning were manifested in one patient with a blood lead level of 130 microg/dl, while the other patient was asymptomatic with a blood lead level of 46 microg/dl. After cessation of intake in the asymptomatic patient, and cessation of intake and treatment with chelating agents in the symptomatic patient, the blood lead levels returned to normal range.

A 33-year-old Korean woman was diagnosed to have combination of chronic lead and arsenic poisoning following consumption of a Korean herbal medicine prescribed for haemorrhoids. (Heggs M, Conway M et al, 1990) The patient had malaise, severe difficulty walking, arthralgia, oedema and abdominal pain with diarrhoea. Investigation showed anaemia with basophilic stippling, fragmentation and a raised reticulocyte count. Laboratory examination showed that the blood and urine lead levels and urine arsenic
levels were raised. Analysis of the herbal medicine revealed a high lead and arsenic content. Treatment with the newer chelating agent 2,3-dimercaptosuccinic acid was successful, with no detectable side-effects. Another South Korean case report describes lead poisoning (abdominal pain, anemia, and a urinary lead level of 739.4 µg/l) due to a herbal medicine containing a high concentration of lead. (Chung JG, Yoon YB et al, 1980)

In western Europe, a patient was suffered from severe anaemia after ingestion of several kinds of ayurvedic drugs during travel to India. (Spriewald BM, Rascu A et al, 1999) This 37 year old man was admitted to the hospital because of weakness, dizziness, nausea, and diffuse muscle pain that had developed over the past few weeks. The patient stated that two months before he had travelled to India and took some herbal medicine when he made visited a traditional ayurvedic medical centre. He took nearly all the medication before admission. The metallic appearance of the paste and the detection of basophilic stippling in the red blood cells raised the suspicion of heavy metal poisoning. The diagnosis of lead intoxication was confirmed by high blood lead concentrations, an increased urinary lead concentration, and an increased urinary excretion of delta-aminolaevulinic acid. Also, slightly increased urinary concentrations of arsenic and silver were found. After chelation treatment with D-penicillamine treatment, the patient recovered.

15.3 MERCURY

15.3.1 Overview

Mercury has been used in medicine and industry for over 2000 years, e.g.; by medieval alchemists in gold extraction. (Campbell BG, 1999) A large variety of inorganic and organic compounds containing mercury have been used as cathartics.
antiseptics, vermicides and diuretics. Mercury is a ubiquitous substance in our environment. Mercury vapor in the atmosphere makes its way into fresh and salt water by falling in precipitation. Methyl mercury compounds are created by bacterial conversion of inorganic mercury in water and soil, which subsequently concentrates in seafood and fish. Beside this, mercury is also used as medicinal purpose and spiritual practice in some other countries such as Caribbean islands. (Luis ZH & Philip OO, 1996)

15.3.2 Cinnabar

Mercury compounds were also used in traditional Chinese medicine (TCM) for thousand years. Cinnabar, a crude form of mercury sulphide (HgS), has been widely used in the traditional Chinese medicines. (Tseng HH) It consisted of a mineral composed of red mercuric sulphide. It is used as sedative and tranquilizer for the treatment of palpitation, insomnia, infantile convulsion due to fever, epilepsy. In traditional Chinese medicine, mercury is part of some preparations under the terminology of “cinnabaris” (mercury sulfide), “calomel”(mercury chloride) or “hydrargyri oxydum rubrum: (mercury oxide). Such products are used for a variety of indications including, for example, as a tranquiliser, an anti-epileptic, for ulcers or to treat insomnia. (Koh HL & Woo S, 2000) In traditional Chinese theory, the usage may depend on its pharmaceutical function and the dosage of the heavy metal used may larger than the safety level. However, in western attitude, this kind of heavy metal contamination was unacceptable and dangerous. The approximate minimum lethal dosage for a 150-lb man is 500 mg (mercuric chloride); other inorganic and organic mercury compounds vary widely in toxicity.

Cinnabar is insoluble in water but the free partial of mercury compounds and some compounds are soluble in water. Different kind of processing may affect the percentage
of the soluble and free mercury compounds. Based on the result from the research of the soluble mercury and free mercury compounds, it showed that only the traditional grinding method can remove those impurities. Adding water to elutriate could allow the turbid fluid to settle in tanks and then collecting the deposit. After elutriate, the percentage of soluble part of mercury and the free particle of mercury compounds will decrease and have low toxicities. In the animal experiment of Cinnabar showed that there was a clear dose-response effects could see in the clinical and pathological situation with the appearance of nodulation and edema of liver, kidney and spleen with serious gastrointestinal and necrosis. (Tseng HH)

15.3.3 Presentation

The manifestations of mercury toxicity vary, depending on the chemical form of the mercury compound and patient sensitivity. (Li AM, Chan MHM et al, 2000) In the acute phase, symptoms are produced within minutes of exposure. These include a burning sensation in the mouth and throat, abdominal pain, vomiting, eschars on the lips, loss of fluids and electrolytes, tachycardia followed by shock and peripheral vascular collapse. Delayed actions are evident after about 12 hr to several days. These include ulcerative colitis, excessive salivation, foul breath, and metallic taste. Initially the urine volume increases, later there is oliguria, anuria, uremia, acidosis and renal tubular necrosis. Exposure may be by all portals of entry.

In chronic exposure to mercury compounds, the kidney is a major target organ. In chronic intoxication, inflammation of the mouth, swollen salivary glands, soft spongy gums, loose teeth, blue-black gum line, excessive salivation, metallic taste, foul breath, muscular tremors and behavioral changes are symptoms which should be confirmed by mercury determinations in the urine. In organic mercury intoxication, gastrointestinal
symptoms are rare, mental and nervous symptoms, such as ataxia, visual disturbances, paresis and delerium, predominate.

15.3.4 Poisoning Cases

A 5 year old Chinese boy presented with recurrent oral ulceration followed by motor and vocal tics. (Li AM, Chan MHM et al, 2000) The oral ulceration, which mainly affected the left lateral aspect of his tongue, appeared approximately five weeks prior to the onset of tics. Herpetic ulceration was diagnosed and confirmed by the isolation of herpes simplex virus (HSV) type 1 from his tongue swab. Symptom was improved after medication but relapse several days later. His family then consulted a local pharmacist and then started to used a Chinese patent medicine named “Watermelon Frost”. It is an oral spray for healing mucosal ulcer. After using this medication for several weeks, the symptom improved. However, the patient family found that the patient developed a sudden onset of motor tics that consisted of eye blinking, head turning, and shoulder shrugging. There was no preceding history of flu like symptoms, head injury, or consumption of other drugs or herbs. There was no family history of any psychiatric or neurological problems. He was taken to hospital to received follow up investigation and no abnormalities were revealed after examination. The patient admitted that he had been using the this herbal oral spray up to 20 times a day for the preceding four weeks, when the recommended dose was only one spray twice a day. As the use of herbal medication always arouses the suspicion of heavy metal exposure in the locality, screening for heavy metals was performed. After analyzed, the mercury content of the spray was 878 ppm (2% methylmercury and 98% inorganic mercury) and the patient’s blood mercury level was 83 nmol/l (normal for adults <50 nmol/l). His tics completely resolved at
follow up four weeks later and the blood mercury level also returned to normal after stopped taking the herbal spray.

"Watermelon Frost" is an old famous patent medicine in Southeast China. This patent medicine was widely used and easily obtainable over the counter in China and Asian population also because of its low price and pharmecutical value. The medicine that the patient took was contained 878 ppm of mercury and mainly in the inorganic form. Although methylmercury constituted only 2% of total mercury in this preparation, the content was 18 times the action level of mercury in food as proposed by the Food and Drug Administration. (FDA, 1998) This high mercury intake, together with the temporal association between symptom onset and increased blood mercury level, and the subsequent resolution of symptoms with normalisation of mercury concentration, make chronic mercury poisoning the most likely culprit.

Recently, a lawsuit in New York City netted two million dollars for a child who suffered from permanent neurological symptoms related to the use of the product "Tse Koo Choy", which contains calomel (mercurous chloride). (Elaine KY, 1994) A Chinese store and two hospitals were cited in the case for the sale of the product and the failure to diagnose the symptoms of toxicity.

15.4 ARSENIC

15.4.1 Overview

Arsenic intoxication is known for centuries as a result of suicidal and homicidal intentions. Arsenic has been in use as a therapeutic agent and as a poison for more than 2,400 years. Its use as a general remedy and tonic was common in Europe last century (eg; in Fowler’s solution which contained 1% potassium arsenite) In the early 1970s, it was introduced to treat acute promyelocytic leukemia (APL) and chronic myeloid
leukemia (CML) in China and showed surprising clinical efficacy. (Ni JH, Chen GQ et al. 1998)

15.4.2 Arsenic Toxicity

The clinical picture of acute arsenic poisoning due to ingestion starts with abdominal pain, vomiting and diarrhoea followed by hypovolemic and hemodynamic alterations, renal failure secondary to acute tubular necrosis from ischemia or direct cortical necrosis. (see Table 15 c) Gastrointestinal absorption of inorganic arsenic depends on the solubility of the arsenical compound. For most trivalent and pentavalent arsenical compounds dissolved in water, the gastrointestinal absorptive rate exceeds 90% in human and animal studies with greatest absorption occurring predominantly in the small intestine, follow by the colon. Nervous symptoms (peripheral neuritis, encephalopathy) could found in advanced poisoning. Amenic crosses the placental barrier, and acute maternal arsenic poisoning has been incriminated in neonatal death. Arsenic also produces hepatic cytolysis, myocarditis (with AV block, prolonged QT, flat or inverted T waves and ventricular tachycardia) and encephalopathy (coma and convulsions). With a massive intoxication, death supervenes with cardiogenic and hypovolemic shock, profound metabolic acidosis and DIC.

Inorganic arsenic compounds are established carcinogens in man. Occupational and medicinal exposures to arsenical products have been associated with lung cancer (due to chronic inhalation), skin cancer and visceral cancers.

Seafood may contain large amounts of arsenic in a non-toxic form and this is very important in interpretation of urinary arsenic measurements. However, the arsenic in most seafood is predominantly in the form of organoarsenicals, mainly arsenobetaine and arsenocholine, and these compounds are non-toxic. (Bruce G, 1999)
absorbed, they do not metabolised and then excreted unchanged. The majority of this “seafood” arsenic is excreted within three days.

15.4.3 The Toxicologic Mechanisms of Inorganic Arsenic

The acute toxicity of arsenic has been shown to vary according to the chemical species involved. The 50% lethal doses for oral administration to mice are as follows: 3 mg/kg for arsine; 14 mg/kg for arsenite [As \(^{3+}\)]; 20 mg/kg for arsenate [As \(^{5+}\)]; 700-1800 mg/kg for monomethylarsonic acid (MMA); 700-2600 mg/kg for dimethylarsinic acid (DMA); and >10 000 mg/kg for arsenobetaine and arseneocholine. Therefore, the inorganic species of As\(^{3+}\) and As\(^{5+}\) are more toxic than their methylated forms MMA and DMA. Arsenobetaine and arseneocholine are nontoxic and are eliminated rapidly in the urine after absorption. The lethal dose of inorganic arsenic is 100-200 mg of arsenic trioxide for an adult individual, although people have survived larger doses. (Hindmarsh JT and McCurdy RR, 1986) After acute intoxication, the inorganic arsenic was partly methylated into MMA (monomethylarsonic acid) and DMA (dimethylarsinic acid), which are excreted largely in the urine. (see Table 15 d)

A Chinese study of excretion of arsenic sulphide in 4 healthy volunteers stated that realgar was first absorbed in the body and excreted by the renal system. (Chung QW & al e, 1991) The period of excretion was regularly and last for 7-10 days. The peak of excretion of arsenic in urine was in the second day after ingestion. However the total volume of arsenic excretion prominently less than the intake volume (One patient had already taken 132930.0\(\mu\)g, the total volume of excretion after 11 days was 1387.6\(\mu\)g, so the ratio was 96:1). This means large amount of arsenic may excreted by another route or accumulated inside the body.
Tasteless and odorless, arsenic is well-absorbed via the gastrointestinal, respiratory, and parental routes. (Savory J. et al. 1977) The principal biochemical lesion in acute arsenic intoxication is the reversible combination of arsenite with susceptible sulfhydryl-containing enzymes. The resultant blockade of cellular oxidative processes results in capillary and relative tissue injury and relative tissue hypoxia leading to vasodilatation and transudation of fluid. (Schoolmeester WL & White DR, 1980) The toxicity of arsenite (As \(^3\)) is primarily due to its high reactivity with sulfhydryl groups of dihydrolipoamide, preventing regeneration of lipoamide, which is a necessary cofactor in the conversion of pyruvate to acetyl coenzyme A (acetyl CoA). Diminished acetyl CoA levels, in turn, reduce citric acid cycle activity with resulting decreased production of adenosine triphosphate (ATP). Arsenate toxicity may result from its substitution for phosphate in enzyme-catalyzed reactions. (Vahter M, 1983) Arsenic also interferes with glucose production and uptake. The drop in acetyl CoA levels, also inhibits the activity of pyruvate carboxylase, which catalyzes the conversion of pyruvate to oxaloacetate, the initial step in gluconeogenesis. Animal study showed that impaired gluconeogenesis combined with carbohydrate depletion due to the stress of poisoning can result in hypoglycaemia. Arsenic also affects other sulfhydryl-containing enzymes, including membrane transport enzymes involved with insulin-independent cellular glucose uptake. Thus cellular lack of glucose may be a consequential problem in As \(^3\) poisoning although it remains unproven in human. Trivalent arsenic also inhibits glutathione synthetase, glucose-6-phosphate dehydrogenase, and glutathione reductase. This result in decreased levels of reduced glutathione, which facilitates arsenic metabolism, protects red blood cells (RBCs) from oxidate damage, and maintains hemoglobin in the ferrous
form $[\text{Fe}^2]$). In human, the highest concentration of arsenic are found in tissue rich in sulfhydryl groups such as the skin, hair, and nails.

15.4.4 Poisoning Cases

A 13-year-old patient who had previously been well was admitted to Macau Government Hospital because of mild fever 4 days. (Cunha J, Pereira L et al. 1998) She had few productive cough with some sputum, and severe dyspnea with frequency vomiting. The patient’s mother remembered that the patient had a complain of gingivitis ten days before admission, so her mother told her to take two patent medicines "Niu Huang Chieh Tu Pien" [牛黃解毒片] and "Yin Chiao Jiedu Pian" [銀翹解毒片] by herself. Based on the information given by the patient's mother stated that her daughter's fever seems better but her dyspnea and vomiting were deteriorated. She could not lay flatly in bed in recent two days associated with oliguria and thirst. However the urine colour remained the same as usual. According to the patient's condition was getting worse, she was taken to the hospital and was transferred to the Intensive Care Unit for rescurition. After examination, the patient was diagnosed as cerebral edema, multisystem organ failure, acute renal and liver failure, metabolic acidosis, pulmonary edema, and pericarditis and died after ten days. Based on the clinical course and post-mortem examination the authors proposed that arsenic in the traditional Chinese medicines was the cause of her death, causing acute arsenic intoxication. After this case happened, Macau government had led to a complete ban on all brands of “Niu Huang Chieh Tu Pien” from October 1996 for one year. Currently all imported “Niu Huang Chieh Tu Pien” products are subject to analytical test of Arsenic contents of which must be within the acceptable range of Arsenic level.
15.4.5 Discussion

Dr. Espinoza EO et al have reported that after they examined samples of some Chinese patent medicines, they found that most of the patent medicine preparations had a potentially serious health risk to consumers because of arsenic contamination. As in the case mention above, an interesting question was pointed out — why Arsenic trioxide (As₂O₃) could be found in those patent medicine contain realgar? Based on the information from P.R.C. Pharmacopoeia (1995 Edition) showed that the main component of realgar is As₂S₂, (nearly 90%) and the rest of the component were other mixed metal (including the impurity arsenic trioxide As₂O₃). Those impurities are the main cause of its toxicity and needed to be clear by curing before used.

In China, the high quality of realgar is so expensive because the processing procedure was complicated. If the procedure is not enough, impurities such as arsenic trioxide As₂O₃ would be retained. Furthermore, improper heating process could lead to the conversion of arsenic disulphide to arsenic trioxide also and was toxic. (Yuan ST, 1987) Therefore, a qualified processing procedure is very important in the making of realgar. However, many unauthorized manufacturers prefer using the unqualified realgar compound in stead of it in order to decrease the production price. That’s the reason why the level of As₂O₃ in the sample of the suspected medicine was very high. A similar research also showed similar result. (Koi KI & et al, 1998) The result stated that the ranges of arsenic level from these testing sample were between 4 -12000 p.p.m.

Another report of chronic arsenic sulfide poisoning from the consumption of traditional Asian medicinal agents in Singapore were also stated that the patients was ingested approximately 10 mg per day. (Tay CH & Seah CS, 1975) Arsenic poisoning was observed in 74 patients who had been using Chinese herbal medicines providing a
high inorganic arsenic intake. Among the various symptoms noted were sensorimotor polyneuropathy, psychosis, acute toxic hepatitis, anemia, transient albuminuria, skin cancers, and internal malignancies. Three patients died from spreading arsenic-induced carcinomas and one from ventricular arrhythmia. Of those remaining alive, 12% were moderately disabled.

Forty-seven patients (64%) had taken an antiasthmatic herbal pill called “Sin Lak”, which contained 12 mg/g arsenic sulfide. This pill provided an arsenic intake of about 10.3 mg/day when used as recommended. Another 28 brands of Chinese herbal preparations with high concentrations (ranging from 45 μg/g to 107 mg/) of arsenic sulfide or trioxide were identified. These preparations resulted in daily exposures to 0.5-3.3 mg arsenic.(Tay CH & Seah CS, 1975)

15.5 Conclusion

Unexpected or accidental intoxication by medication containing heavy metal, in any formula, should call attention for quality control on manufacture, trading and medical prescription. In the long term, the governmental department should setup a standard regulation system for herbal medicine that operate under the basis of Chinese Pharmacopoeia, in reference of international regulations, to work out the standard of microbe, residual pesticide and heavy metal content in Chinese herbal medicine. The government should lay down rules regarding production, importation, wholesaling, retailing, testing and licensing also. Only if the government does so will citizens regain confidence in TCM. Though still relatively rare, heavy metal poisoning with herbal medicine should always be suspected if a previously healthy child develops unusual symptoms, especially those involving the central nervous system.
### Table 15a: Symptoms of Lead Poisoning in Different Blood Lead Concentrations

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>&lt;25 µg/dL</th>
<th>25-50 µg/dL</th>
<th>50-80 µg/dL</th>
<th>&gt;80 Mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>None</td>
<td>None</td>
<td>Mild, nonspecific complaints</td>
<td>Colic, irritability, drowsiness, nausea and vomiting, seizures, coma</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Unknown</td>
<td>Urinary ALA may increase</td>
<td>Increase in urinary ALA and coproporphyrins, increased EP</td>
<td>Same as 50-80 µg/dL</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Decreased RBC survival, increased RBC production (reticulocytes, basophilic stippling)</td>
<td>Same as 50-80 µg/dL</td>
</tr>
<tr>
<td>Renal</td>
<td>Unknown</td>
<td>No acute effects; possible chronic nephritis</td>
<td>Minimal acute dysfunction; chronic irreversible nephritis</td>
<td>Fanconi-like syndrome (reversible)</td>
</tr>
<tr>
<td>CNS</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Cognitive deficits</td>
<td>Minimal to severe brain damage (permanent)</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Unknown</td>
<td>Possible decreased nerve conduction</td>
<td>Decreased nerve conduction</td>
<td>Child: weakness or paralysis; neuropathy rare</td>
</tr>
<tr>
<td>Endocrinologic</td>
<td>Unknown</td>
<td>Impaired spermatogenesis and oogenesis</td>
<td>Unstudied Same as 25-50 µg/dL</td>
<td>Unstudied Same as 25-50 µg/dL</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Impaired cognitive development</td>
<td>Presumably increasing impairment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

249
### Table 15b. Characteristics of Acute and Chronic Lead Intoxication.

<table>
<thead>
<tr>
<th>Symptom and Signs</th>
<th>Chronic</th>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms and signs</td>
<td>Nonspecific: vague aches and pains, already, nephritis, peripheral neuropathy</td>
<td>Anorexia, constipation, abdominal pain, behavioral changes, vomiting, lethargy, fatigue, hyperactivity, clumsiness, ataxia, convulsions, coma</td>
</tr>
<tr>
<td>Presumptive evidence</td>
<td>Lab: anemia (Hb &lt; 10 g/dL), basophilic stippling, increased urinary ALA.</td>
<td>Lab: same as in chronic increased urinary coproporphyrins, hemolysis</td>
</tr>
<tr>
<td>Radiographic:</td>
<td>opacities on abdominal radiographs: lead lines (children).</td>
<td>Radiographic: same as in chronic</td>
</tr>
<tr>
<td>History:</td>
<td>environmental lead source, family history</td>
<td>History: same as in chronic</td>
</tr>
<tr>
<td>Diagnostic evidence</td>
<td>Blood lead concentration 30-60 μg/dL and EP less than 7 times normal</td>
<td>Blood lead concentration &gt; 60 μg/dL and EP &gt; 190 μg/dL or 7-10 times normal</td>
</tr>
</tbody>
</table>

### Table 15c. Characteristics of Mercury Poisoning.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elemental</th>
<th>Inorganic</th>
<th>Organomercurial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of exposure</td>
<td>Inhalation</td>
<td>Oral</td>
<td>Oral, food chain</td>
</tr>
<tr>
<td>Target organ</td>
<td>CNS, kidney</td>
<td>Kidney</td>
<td>CNS, liver</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Bronchial irritation, Pneumonitis</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>GI tract</td>
<td>Metallic taste, Stomatitis, Gingivitis, Excessive salivation</td>
<td>Metallic taste, Stomatitis, Gastroenteritis</td>
<td>Nil</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Elemental</td>
<td>Inorganic</td>
<td>Organomercurial</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Kidney</td>
<td>Tubular necrosis</td>
<td>Tubular necrosis</td>
<td>Nil</td>
</tr>
<tr>
<td>CNS</td>
<td>Erethism</td>
<td>Nil</td>
<td>Ataxia, chorea, athetosis, tremor</td>
</tr>
<tr>
<td></td>
<td>Tremors</td>
<td>Nil</td>
<td>Convulsions, paresthesia, erethism</td>
</tr>
<tr>
<td>Toxic level</td>
<td>Blood 50 nmol/L</td>
<td>50 nmol/L</td>
<td>50 nmol/L</td>
</tr>
<tr>
<td></td>
<td>Urine 50 nmol/24H</td>
<td>50 nmol/24H</td>
<td>50 nmol/24H</td>
</tr>
<tr>
<td></td>
<td>Treatment CaNa₂-EDTA</td>
<td>BAL</td>
<td>DMSA</td>
</tr>
<tr>
<td></td>
<td>Biologic half-life 10-15 days</td>
<td>65-70 days</td>
<td>70-90 days</td>
</tr>
</tbody>
</table>

### Table 15 d. Presenting symptoms in Acute and Chronic Arsenic Poisoning.

<table>
<thead>
<tr>
<th>Dermatologic</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair: delayed loss, Skin eruptions</td>
<td>Nail: Mees’ lines (2-3 weeks’ postigestion)</td>
<td>Melanosis - mottled brown spots</td>
</tr>
<tr>
<td></td>
<td>Hyperkeratosis - palmer and plantar surfaces</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Hypoxic convulsions, coma</td>
<td>Peripheral neuritis, tremors</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain, severe nausea, profound diarrhoea, rice-water stools, projectile vomiting</td>
<td>Ulceration of gastrointestinal tract</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Fatty infiltration</td>
<td>Chronic hepatitis, liver cirrhosis</td>
</tr>
<tr>
<td>Renal</td>
<td>Oliguria uremia</td>
<td>Proteinuria, haematuria</td>
</tr>
<tr>
<td>Haematologic</td>
<td>-----</td>
<td>Bone marrow suppression, pancytopenia, anemia, impaired folate absorption</td>
</tr>
<tr>
<td>Cardiac</td>
<td>ST segment and T-wave abnormality, cardiac arrhythmia</td>
<td>-----</td>
</tr>
</tbody>
</table>
Chapter 16 - Review of Herb – drug Interaction

16.1 Overview

Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Many herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. This means herbs can potentiate or modify the action of a drug or another herb, leading to a situation where interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either one. (Berman AF, 2000) Clinically important interactions appear to involve effects on drug metabolism via cytochrome P-450 isoenzymes, impairment of hepatic or renal function, and other possible mechanisms. (Scott GN, 2002)

Experimental data in the field of herb-drug interactions are limited, case reports scarce, and case series rare. This lack of data is also true of drug-drug interactions: published clinical studies are mainly case reports (controlled trials are scarce, since the random assignment of patients to trials that examine unintended effects is not ethical). The true prevalence of drug interactions is substantial but unknown. (Berman AF, 2000) (See Table 16 b)

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Many reports of herb-induced interactions lack crucial documentation on temporal relations and concomitant drug use. Perhaps the most serious problem encountered in analysing such reports is the consistent absence of any effort (beyond that of reading the label) to establish a positive identification of the herb involved, and to exclude the effect of contaminants or adulterants. (Berman AF, 2000) Therefore, practitioners should inquire
about all the herbal supplements, prescriptions, and over-the-counter (OTC) medicines that patients are taking (as well as asking about diet and other life style factors), and patients should be counseled about potential crossreactions. As a general rule, concomitant use of herbs and drugs that produce like effects is best avoided to avert “synergistic overload.” (Horowitz S, 2000) Approximately 25–30 percent of all conventional drugs are derived from plants, and cautions that such double-dosing becomes more likely. It was because herbs, as they move incrementally further from their plant origins in becoming more standardized, are transformed into herbal drugs that are capable of producing similar side effects to potent biomedicine.

Natural products that have been reported to interact with drugs in humans include coenzyme Q10, dong quai, ephedra, Ginko biloba, ginseng, glucosamine sulfate, ipriflavone, melatonin, and St. John’s wort. (Scott GN, 2002) In many cases, more research is needed to confirm these interactions and to determine whether other natural products may also interact with drugs. To effectively counsel patients about interactions involving natural products, pharmacists should be familiar with the most commonly used products and have access to information on more obscure products. Interactions between natural products and drugs are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Natural products may affect the absorption of drugs and other natural products.

Two studies reported in the February 12, 2000, issue of The Lancet journal implicated the use of St. John’s wort (Hypericum perforatum), one of the most popular herbals used primarily to treat depression, as potentially detrimental in two very specific medical circumstances. St. John’s wort was found to compromise the efficacy of both the HIV protease inhibitor indinavir. (Piscitelli SC. Burstein AH et al, 2000) and the anti-
rejection transplant drug cyclosporin (Chitzka RF & et al. 2000) that is used to suppress the immune system of heart transplant patients. While such situations may represent atypical cases, given that phytochemicals tend to be in less potent form than pharmaceuticals and that most have been used safely throughout history, these cases do focus attention on the fact that botanicals are medicines that deserve as much respect and professional supervision as synthetically produced allopathic prescription drugs.

Another example is using laxative or bulk-forming agents. Both agents will speed intestinal transit, and thus may interfere with the absorption of almost any intestinally absorbed drug. The most popular stimulant laxative herbs are the anthranoid-containing senna (Cassia senna and C angustifolia) and cascara sagrada (Rhamnus purshiana). Dried exudate from the aloe vera (Aloe barbadensis) leaf (not gel) also contains anthranoids and is used as a laxative. Aloe vera gel, found within the leaves, is used topically for burns and cuts, and is sometimes recommended by herbalists for internal ingestion to treat ulcers and other disorders. The gel (or juice made from the gel) does not contain anthranoids, but some oral preparations are contaminated by the laxative leaf. Less commonly used anthranoid-containing plants are frangula (Rhamnus frangula), yellow dock (Rumex crispus), and Chinese rhubarb (Rheum officinale).

While many drug interactions can be serious, the consequences of some involving such as St. John's wort are potentially life-threatening. (Berman F & Ernst E, 2001) Significant decreases in antiretroviral drug concentrations can lead to treatment failure and viral rebound in HIV-seropositive patients; drops in cyclosporine levels have been shown to cause organ rejection in kidney and heart transplant patients. Pharmacists in these two areas of practice must be especially vigilant to protect their patients from such interactions.
16.2 Effects of Herb–drug interactions

16.2.1 Gastro-intestinal system

The majority of all absorption occurs in the intestines, where herbs or drugs must pass through the intestinal wall to enter the blood. Several mechanisms may interfere with the absorption of drugs through the intestines. The efficacy of antacids or antiulcer drugs used in therapy may be affected in individuals taking herbs such as horse chestnut which is irritant to the gastro-intestinal tract. (Newall CA & Phillipson D) Drugs such as Questran (cholestyramine), Colestid (colestipol) and Carafate (sucralfate) may bind to certain herbs, forming an insoluble complex, and decrease absorption of both substances because the size of the insoluble complex is too big to pass through the intestinal wall. It is possible that the activity of a laxative may be potentiated or its side effects increased by concomitant use of a herbal laxative such as senna.

The absorption of herbs may be adversely affected when the herbs are given together with some drugs that change the pH of the stomach. Drugs such as antacids, Tagamet (cimetidine), Pepcid (famotidine), Axid (nizatidine), Zantac (ranitidine) and Prilosec (omeprazole) may neutralize, decrease or inhibit the secretion of the stomach acid. With the subsequent decrease of stomach acid, herbs may not be broken down properly, leading to poor absorption in the intestines. To minimize the risk of interaction, it is best if the drugs and the herbs are taken separately by approximately two hours.

Lastly, drugs that affect the G.I. motility may affect the absorption of herbs. G.I. motility is the rate at which the intestines contract to push the content from the stomach to the rectum. Slower G.I. Motility means the herbs stay in the intestines for a longer period of time and there will be an increase in absorption. Conversely, faster G.I. Motility means the herbs stay in the intestines for a shorter period of time and there may
be an decrease in absorption. Drugs such as Reglan (metoclopramide) and Propulsid (cisapride) increase G.I. Motility and possibly decrease absorption of herbs; and drugs such as Haldol (haloperidol) decrease G.I. Motility and may increase absorption of herbs. Therefore, it may be necessary to decrease the dosage of herbs when the patient takes a drug that decreases the G.I. Motility and increases overall absorption; and increase the dosage of herbs when the patient takes a drug that increases the G.I. Motility and decreases overall absorption.

16.2.2 Cardiovascular system

A number of pharmaceutical drugs with different modes of action may be prescribed for cardiovascular abnormalities. (Newall CA & Phillipson D) Diuretics are commonly prescribed for the management of hypertension and their activity may be potentiated by co-administration of herbal diuretics such as dandelion. Elderly patients, in particular, are susceptible to the side effects of diuretics. Herbs which either lower blood pressure (e.g. ginseng) or raise it (e.g. broom), or have mineralocorticoid activity (e.g. liquorice) or are diuretic (e.g. dandelion) may adversely affect the beneficial clinical effects of antihypertensive therapy. Blood lipid levels, already lowered by treatment with lipid-lowering drugs, may be further reduced by the use of hypolipidaemic herbs such as alfalfa.

Herbs, such as angelica, which contain coumarins have anticoagulant activity whereas other herbs, such as agrimony, are reported to have coagulant activity. Aspirin increases the risk of bleeding in warfarin therapy and it is possible that herbs such as willow, which contains salicylates may have similar effects. Therapeutic doses of garlic should not be given to patients with slow blood clotting time and caution is recommended for those on anticoagulant therapy.
16.2.3 Central nervous system

Hypnotics and anxiolytics may react with sedative herbs, e.g. passiflora, valerian, or with stimulant herbs, e.g. ginseng. (Newall CA & Phillipson D) Evening primrose oil may have the potential to manifest undiagnosed temporal lobe epilepsy and caution should be exercised in patients taking epileptogenic drugs such as phenothiazines. Herbal sedatives, e.g. hypericum, may affect the activity of antidepressant drugs and it is possible that any sedative herb may interfere with the activity of analgesic and antiepileptic drugs.

16.2.4 Endocrine system

Drugs acting on the endocrine system including antidiabetics, corticosteroids and oral contraceptives may interact with herbal remedies. (Newall CA & Phillipson D) Alfalfa has hypoglycaemic activity whereas devil’s claw is reportedly hyperglycaemic and therefore it is possible that co-administration of these herbs with conventional diabetic therapy may result in adverse effects.

16.3 Reasons contributing to herb–drug interactions.

16.3.1 Lack of Knowledge About Herbs

In USA, nearly 300,000 higher plant species and only approximately 10 percent have been carefully assessed for their medicinal and toxic properties. In China, nearly 12,807 species of herbal medicine could use, 11,146 are plant species and 1,581 are animal species and 50 kinds of mineral herbs. Nearly 200 species are always used in medical treatment. Even an experienced herbalist might not be familiar with more than 1000–2000 of these species. Doctors who rely on standard Western medicine are apt to be even less knowledgeable in this area.
16.3.2 Mislabelling or Adulteration

Such mislabelling or adulteration may account for some of the problems noted with in the reactions with prescription medicines, thus complicating the scientific assessment of herbal–drug interactions. (Horowitz S, 2000)

16.3.3 Lack of Patient Communication About Use of Botanicals

Despite the steadily increasing popularity of medicinal herbs, surveys indicate that only a small percentage of patients disclose such usage to their mainstream physicians and pharmacists. Patients may neither report or be asked about their diets and use of nutritional supplements. Furthermore, such surveys reveal that a majority of patients do not inform their allopathic physicians of herbal use because of fear of the practitioners’ disapproval of alternative medical treatments and the conventional top-down information flow from physician to patient.

16.3.4 Lack of Practitioner Knowledge About Potential Interactions

While the trend toward more integrative or complementary medical practice and education continues, information regarding potential harmful interactions between herbal and pharmaceutical drugs is still largely lacking in mainstream medical school curricula and professional literature. (Horowitz S, 2000)

16.4 Metabolism and Herb-Drug Interactions

Many herbs and drugs are metabolized by the liver into inactive derivatives. The rate at which the liver metabolizes these herbs and drugs determines the length of time these herbs or drugs stay active in the body. If the liver were induced to speed up its metabolism, herbs and drugs would be inactivated at a faster pace and the overall effectiveness of ingested substances would be lower. On the other hand, if the liver
were induced to slow down its metabolism, herbs and drugs would be inactivated at a slower pace and the overall effectiveness of the substances would be higher.

In general, drugs that induce liver metabolism do not exert an immediate effect. The rate of liver metabolism changes slowly over several weeks. Therefore, the effect of increased liver metabolism is not seen until weeks after the initiation of drug therapy. Some examples include Dilantin (phenytoin), Tegretol (carbamazepine), phenobarbital and rifampin. These drugs speed up liver metabolism. Therefore, the herbs may be inactivated faster and their overall effectiveness may be lower. Under such circumstances, the patient may need a higher dose of herbs to achieve the desired effectiveness.

On the other hand, drugs that inhibit liver metabolism have an immediate onset of action. The rate of liver metabolism may be greatly impaired within a few days. Therefore, there is a higher risk of herbs accumulating inside the body as the function of the liver to inactivate them is compromised. Examples of drugs that slow down or inhibit liver metabolism include, but are not limited to, Tagamet (cimetidine), erythromycin, ethanol, Diflucan (fluconazole), Sporonox (itraconazole) and Nizoral (ketoconazole). Therefore, the herbs may be inactivated more slowly and the overall effectiveness may be prolonged. In this case, one may need to lower the dosage of herbs to avoid unwanted side-effects.

16.5 Pharmacologic Interactions

It should be noted that there is more theorizing to date about herbal–drug interactions than experimental data; patients tend to underreport such crossreactions to allopathic physicians and pharmacists. (Horowitz S, 2000) In addition, much clinical experience of such metabolic interaction problems is typically based on a small number
of patients and a re specific product-related and dose-related.

In clinical practice, polypharmacy is common, and to the mixture physicians prescribe, patients add various over-the-counter medications, vitamins, herbs, and foods. All ingested substances have the potential to interact. (Berman AF, 2000)

16.5.1 Interaction with Antibiotics

Tetracycline hydrochloride and St. John’s wort act synergistically to increase the photosensitivity side-effect of each medicine. (Horowitz S, 2000) Besides herbs, mineral supplements, such as calcium, iron, magnesium, and zinc, can prevent the absorption of tetracycline, ciprofloxacin (Cipro) and other antibiotics, if taken together with such pharmaceuticals. Even grapefruit juice was recently found to inactivate medications used to treat allergies, cancer, heart failure, and high blood pressure, as well as for immunosuppression in patients who receive organ transplants. The juice also was found to increase the potency of some antihistamines and calcium-channel blockers. (Herbst D, 1999)

16.5.2 Interaction with Nonsteroidal Anti-inflammatory Drugs

The NSAIDS should not be used with herbal medicinals that are known to cause gastrointestinal damage. (Miller LGPB, 1999) Gossypol has been associated with tissue congestion, mucosal sloughing, mucosal necrosis, and ileus and intestinal wall hemorrhage. (Wailer OP, Zaveveld UD et al, 1985) Other gastric irritants include Arctostaphylos uva-ursi, Ruta graveolens, Cetraria islandica, Sanguinaria canadensis, Chamaelirium luteum, Schinus terebinthifolia, Coffea arabica, Schinus molle, Cola acuminata, Symplocarpus foetidus, Cola nitida, Trillium erectum, and Quillaja saponaria. (Smet PAAD, Hansel R et al, 1993; Smet PAAD, Hansel R et al, 1996) Hence, a patient complaining of unexpected gastrointestinal upset should be questioned.
regarding herbal medicinal use and concomitant use with known gastrointestinal irritants, such as NSAIDs, should be avoided.

16.5.3 Interaction with Sedatives

In general, concomitant use of herbs and drugs that produce similar effects is best avoided. (Horowitz S. 2000) This rule applies to herbs utilized as anti-anxiety drugs and sleep aids such as kava and valerian (Valeriana officinalis), which are liable to enhance the sedating or tranquilizing effects of psychopharmacologic drugs such as Valium (diazepam), other benzodiazepines, and night time pain formulas containing diphenhydramine.

Kava is used as a sedative to enhance sleep. (Miller LGPB, 1999) Long-term use is not advised because tolerance has been shown to develop rapidly in animals. (Duffield PH & Jamieson D, 1991) Additionally, long-term use has led to kawaism, which is characterized by dry, flaking, discolored skin and reddened eyes. (Ruzo P, 1990; Norton SA & Ruze P, 1994) The toxicity of kava is increased if taken with alcohol.

α-Pyrone, the active component of kava, has been found to have weak effects on γ-aminobutyric acid and benzodiazepine receptors in vitro, although this has been disputed. (Davies LP, Drew CA et al, 1992; Davies LP, Drew CA et al, 1992; Jussofie A, Schmiz A et al, 1994) Synergism between α-pyrones and other active sedatives with γ-aminobutyric acid was verified in 1994 by a German study group. (Almeida JC & Grimsley EW, 1996) However, concomitant use with benzodiazepene is ill advised based on a case of coma following concomitant use.

A 54-year-old man was hospitalized in a lethargic and disoriented state. (Stimpel M, Proksch A et al, 1984) His medications included alprazolam, cimetidine, and terazosin.
hydrochloride; his alcohol levels were negative and his drug screen was positive for benzodiazepene. He became more alert after several hours and stated that he had been taking kava for 3 days; he denied overdosing on kava or alprazolam. (Stimpel M, Proksch A et al, 1984) The kava-alprazolam drug interaction was identified as the cause.

Mixing kava and valerian may also produce excess sedation or worse. Patients have been hospitalized for being disoriented and extremely lethargic after ingesting such combinations even on a short-term basis.

16.5.4 Interaction with Anticoagulants

Several herbs are popular because of their clot-protective benefits, such as garlic (Allium sativum) and ginger (Zingiber officinale). (Horowitz S, 2000) Herbs with anticoagulant effects include herbs that have blood-activating and blood-stasis-removing functions. In general, concomitant use of herbs and drugs that produce similar effects is best avoided. Several case reports have documented increased bleeding problems with ginkgo (Ginkgo biloba), with or without concomitant anticoagulant drug therapy, and interactions between warfarin and Panax ginseng (ginseng) or Angelica sinensis (dong quai). Herbs that interfere with Coumadin (warfarin) include Salviae Miltiorrhizae (Dan Shen), Ligustici Chuanxiong (Chuan Xiong), Persicaceae (Tao Ren), Carthami Tinctorii (Hong Hua) and Hirudo seu Whitmania (Shui Zhi). The synergistic interaction between herbs and Coumadin (warfarin) may be advantageous for the patient as the dosage of both the herbs and the drugs can be reduced without compromising clinical effectiveness. The reduction in dosage will also decrease the frequency and severity of side effects of the drugs. Any anticoagulant drug, such as aspirin, may cross react with blood-thinning herbs such as ginkgo and feverfew (Tanacetum parthenium), and may seriously reduce the platelet aggregation needed for postsurgery clotting. (Miller LGPB, 1999) Based on
the potential interaction of herbal medicines with anesthetics, the American Society of Anesthesiologists advises physicians to ask their patients about what herbal supplements are being used and to tell patients to discontinue use of the se herbs 2–3 weeks prior to surgery. (see Table 16 c)

16.5.5 Interaction with Antihypertensives and Diuretics

Use of herbs to excess or in combination with thiazide-type diuretics that are used to treat high blood pressure and edema, however, can lead to hypokalemia, a serious condition resulting from potassium loss. (Horowitz S, 2000) Licorice (Glycyrrhiza glabra) taken with diuretics, or with stimulant laxative herbs such as cascara sagrada (Rhamnus purshiana) or senna (Cassia senna), can also deplete potassium and even trigger a life-threatening arrhythmia. Herbal and other medicines that are used to treat the same condition should probably not be used together such as in the case of using garlic with other hypertensives. Such “doubling dosing” may lower blood pressure too drastically. (Miller LGPB, 1999)

Goldenseal is an aquateric, but is referred to by most herbalists as a diuretic. Other herbal diuretics include agrimony, artichoke, boldus, broom, buchu, burdock, celery seed, zea, coughgrass, dandelion, elder, guaiacum, juniper, pokercot, shepherd’s purse, squill, uva-ursi, and yarrow. (Newall CA, Anderson LA et al. 1997) The differentiation between a diuretic and an aquateric is of clinical significance because with diuretics, sodium is excreted with the water whereas with aqueteric, sodium is not excreted. Therefore, aquaterics are not well suited for the treatment of edema and hypertension and may in fact worsen it. If taken with a diuretic (eg, hydrochloorthiazide) or any allopathic antihypertensive drug, it is conceivable that the antihypertensive effects will be diminished or offset as sodium is retained. (Miller LGPB, 1999)
16.5.6 Interaction with Spironolactone

Licorice may offset spironolactone's effects. (Miller LGPB, 1999) Licorice is advocated as an antispasmodic and anti-inflammatory herb for use in gastritis and peptic ulcer disease. The hemisuccinate derivative of glycyrrhetinic acid, a component of licorice, is carbenoxolone, which is used allopathically for duodenal and gastric ulcers. (Reynolds JEF, 1989) Licorice renders the patient unable to convert 11-deoxycortisol or deoxycorticosterone into the active glucocorticoids, cortisol, and corticosterone, respectively. (Gomez-Sanchez CE & Yamakita N, 1995) This acquired 11-β-hydroxylase deficiency results in sodium retention, hypertension, and hypokalemia. (Gomez-Sanchez CE & Yamakita N, 1995) Within 10 days to 3 weeks of the discontinuation of the licorice regimen, the blood pressure will return to baseline. (Biachley JD & Knochel JP, 1980; Piccoli BC, Salvade S et al, 1985) Given the underlying mechanism of licorice's effect on hypertension, spironolactone's antihypertensive effects may be diminished by licorice. Conversely, hypertension caused by licorice may be effectively treated with spironolactone.

16.5.7 Interaction with Corticosteroids and Cyclosporine

The theoretical concern underlying this drug-herb interaction is that immunostimulating herbs will offset or minimize the immunosuppressive effects of corticosteroids and cyclosporine. Echinacea is classified as an immunotonic agent because of its ability to augment basophils, mast cells, and white blood cell counts. (Stimpel M, Proksch A et al, 1984) Astragalus stimulates T-cell activity and ginseng is thought to nourish major immune system glands but in an unspecified manner. (Jin R, Wan LL et al, 1995) Licorice root supposedly stimulates interferon production and pau d'arco with its antioxidant and anti-inflammatory activity has been
recommended for use by herbalists for immunodeficiencies. (Dinnen RD & Ibibuzaki K, 1997; Utsunomiya T, Kobayashi M et al. 1997) Alfalfa sprouts and some vitamin E products contain toxic amino acid L-canavanine that has been implicated in cases of systemic lupus erythematosus and other autoimmune diseases. (Herbert V & Kasdan TS, 1994)

16.5.8 Interaction with Estrogen Replacement Therapy

Theoretically, concomitant use of phytoestrogens with estrogen replacement may result in symptoms of estrogen excess such as nausea, bloating, hypotension, breast fullness or tenderness, migraine headache, and edema. (Miller LGPB, 1999) Phytoestrogens are naturally occurring plant or food substances that are functionally similar to estradiol. (Kincheloe L, Miller LG et al. 1998) While more than 500 plant species contain phytoestrogens, the more common herbs include dong quai, red clover, alfalfa, licorice, black cohosh, and soybeans. (Costello C, 1950; Holt S, 1997) To date, no incidents of estrogen excess have been reported following concomitant use, but prudence would dictate avoiding simultaneous use if at all possible.

16.5.9 Interactions between Natural Product and Drugs

Evidence for natural product - drug interactions in which effects on drug metabolism occur is growing. Interactions between natural products and drugs are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Natural products, like drugs, can affect cytochrome P-450 (CYP) isozymes. The best-investigated metabolic interactions are those involving St. John's wort. For example, herbs such as Zinc lozenges taken for the common cold can chelate fluoroquinolones and tetracyclines, resulting in lower serum antimicrobial levels. St. John's wort (Hypericum perforatum) induces intestinal P-glycoprotein, which may decrease the
absorption of common P-glycoprotein substrates, such as digoxin, etc. (Durr D, Stieger B et al. 2000)

Of interactions involving natural products, those that occur because of changes in volume of distribution are probably the least clinically important. Theoretically, a drug with high plasma protein binding that has a small volume of distribution can be displaced by a natural product competing for the same binding sites. Because an increase in metabolism or excretion usually offsets higher serum drug levels, the clinical effect may be transient or may be meaningful only when drugs are added or discontinued. Theoretically, aescin, a constituent of horse chestnut seed (Aesculus hippocastanum), might interfere with highly plasma protein bound drugs, such as warfarin. (Rothkopf M, Vogel G et al. 1977) Natural product-drug interactions that involve distribution mechanisms have not been reported.

16.6 Herb-to-Herb Interactions

Cases of pharmacodynamic interactions have also been documented in Oriental Medicine. (Chen J, 1998) The additive effect is generally referred to as mutual accentuation (Xiang Xu) or mutual enhancement (Xiang Shi), such as the combination of Gypsum (Shi Gao) and Rhizoma Anemarrhenae (Zhi Mu) to “clear heat and purge” fire. The antagonistic effect is generally referred to as mutual counteraction (Xiang Wei), mutual suppression (Xiang Sha) or mutual antagonism (Xiang Wu), such as the combination of Semen Raphani (Lai Fu Zi) and Radix Ginseng (Ren Shen), in which the effect of the latter herb is decreased.

In addition, classic Chinese texts state numbers herb-to-herb interactions, such as the Eighteen Incompatibles (Shi Ba Fan) and Nineteen Counteractions (Shi Jiu Wei). Eighteen Incompatibles (Shi Ba Fan) is a classic list of eighteen herb-to-herb
interactions. **Nineteen Counteractions** (Shi Jiu Wei) is a classic list of nineteen herbal combinations in which the herbs counteract each other. Combinations of such herbs will likely lead to adverse side effects and/or toxic reactions.

Table 16 a. The list of Eighteen Incompatibles (Shi Ba Fan) & Nineteen Counteractions (Shi Jiu Wei) (Chen J, 1998)

<table>
<thead>
<tr>
<th>Eighteen Incompatibles (Shi Ba Fan)</th>
<th>Incompatible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radix Glycyrrhizae (Gan Cao)</td>
<td>- Radix Euphorbiae Kansui (Gan Sui), - Radix Euphorbiae seu Knoxiae (Da Ji), - Flos Genkwa (Yuan Hua), - Herba Sargassum (Hai Zao)</td>
</tr>
<tr>
<td>Rhizoma Aconiti (Wu Tou)</td>
<td>- Bulbus Fritillariae Cirrhosae (Chuan Bei Mu), - Bulbus Fritillariae Thunbergii (Zhe Bei Mu), - Fructus Trichosanthis (Gua Lou), - Rhizoma Pinelliae (Ban Xia), - Radix Ampelopsis (Bai Lian), - Rhizoma Bletillae (Bai Ji)</td>
</tr>
<tr>
<td>Rhizoma et Radix Veratri (Li Lu)</td>
<td>- Radix Ginseng (Ren Shen), - Radix Glehniae (Bei Sha Shen), - Radix Adenophorae (Nan Sha Shen), - Radix Sophorae Flavescentis (Ku Shen), - Radix Salviae Miltiorrhizae (Dan Shen), - Radix Scrophulariae (Xuan Shen), - Radix Paeoniae Alba (Bai Shao), - Radix Paeoniae Rubra (Chi Shao), - Herba Asari (Xi Xin)</td>
</tr>
</tbody>
</table>
### Nineteen Counteractions (Shi Jiu Wei)

<table>
<thead>
<tr>
<th>Ingredient 1</th>
<th>Ingredient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfur (Liu Huang)</td>
<td>Mirabilites (Mang Xiao)</td>
</tr>
<tr>
<td>Mercury (Shui Yin)</td>
<td>Arsenolite (Pi Shuang)</td>
</tr>
<tr>
<td>Rhizoma Euphorbiac E.</td>
<td>Lithargyrum (Mi Tuo Seng)</td>
</tr>
<tr>
<td>Semen Crotonis (Ba Dou)</td>
<td>Semen Pharbitidis (Qian Niu Zi)</td>
</tr>
<tr>
<td>Flos Caryphyli (Ding Xiang)</td>
<td>Radix Curcuma (Yu Jin)</td>
</tr>
<tr>
<td>Nitrum (Ya Xiao)</td>
<td>Rhizoma Sparganii (Shan Ling)</td>
</tr>
<tr>
<td>Cornu Rhinoceri (Xi Jiao)</td>
<td>Rz. Aconiti Kusnezoffii (Cao Wu)</td>
</tr>
<tr>
<td>Cortex Cinnamomi (Rou Gui)</td>
<td>Hallostrium Rubrum (Chi Shi Zhi)</td>
</tr>
</tbody>
</table>

#### 16.7 Conclusion

Natural products can interact with drugs and with other natural products by the same pharmacokinetic and pharmacodynamic mechanisms as drugs. Herb–drug interactions occur but are under-researched. In many cases there is no plausible mechanism to explain the observed phenomena and causality is uncertain. Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another, however, little is known about the incidence and consequences of drug interactions. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications. Pharmacists must also be aware that natural products may have variable potencies, unidentified components, unproven efficacy, and unknown adverse effects and interactions. To reduce the risk, pharmacists should recommend only those products that are manufactured to high quality-control standards. Natural product information resources should provide objective, complete, referenced information, including data on interactions and adverse effects, to help health care practitioners provide accurate information to consumers. A reference that is regularly updated will provide the most useful information. Some online
References offer more frequent updates than printed references, but these may not be easily accessible in all settings. Pharmacists should consult reliable, independent sources of information on natural products rather than rely on literature provided by manufactured to high quality-control standards.
Chapter 17 - Recommendation

17.1 Overview

Medicinal plants and herbal medicines have been used for thousands of years and in many cases there is already a strong body of knowledge on their use. Patients who use herbal remedies often self-diagnose and may delay seeking medical attention.

17.2 The need to evaluate the clinical effectiveness of traditional Chinese medicine

Some scientists believe that a regulation drive will bring necessary legitimacy to the traditional remedies. But others fear that it could confer false legitimacy on compounds that have no proven medical value. (Cyranoski D, 2001) As herbs are increasingly packaged and advertised to compete with pharmaceutical drugs, consumers and healthcare providers expect botanical products to meet comparable quality standards. However, quality control and manufacturing standardization are not required of herbal medicines in many countries such as the United States. (Because botanical medicinals are classified as dietary supplements, they must comply only with the Good Manufacturing Practice (GMP) regulations for foods.) (Rotblatt MD, 1999) Even the FDA is considering more extensive GMP regulations for dietary supplements, but has not yet finalized those standards. (Rotblatt MD, 1999) Furthermore, herbal medicines products are not, in general, subject to patent protection. This reduces the motivation for drug companies to invest in trials. (Linde K, Gerben ter R et al, 2001) Many of the existing herbal medicine manufacturers are comparably small companies, often with limited research resources and expertise. May be partly for these reasons, the quality of many older herbal medicine trials is low. Moreover, negative trials which could threaten the company's survival might not become published.
Standardization of specific active constituents within herbal medicines is also proving to be difficult and complex, unlike that of drug products with a single chemical entity. Standardization often implies that the preparation contains a designated percentage of a certain chemical component thought to be therapeutically active. Traditional Chinese medicine and those botanicals may contain hundreds of bioactive chemicals, however, and the compounds responsible for therapeutic activity are usually not known. Moreover, additive or synergistic activity of several constituents may be required for effectiveness. In the case of herbals, therefore, standardization is not a reliable control for pharmacologic activity; instead, it is best thought of as a control for accurate plant identification or for batch-to-batch replicability. (Rotblatt MD, 1999)

Although many ethical herbal medicine manufacturers are thought to be producing high-quality products with careful identification procedures, batch-to-batch standardization, and assays for impurities, it is difficult to identify which brands and products meet even basic quality standards. In the absence of generic equivalents and regulatory standards of quality, health care professionals and patients considering to prescribe or take a particular herbal product should check carefully whether the respective product or extract has been tested in the trials included in a review. (Linde K, Gerben ter R et al, 2001)

17.3 For the Pharmaceutical Industries

1. To facilitate control and minimize poisoning incidents, various administrative measures have been levied to ensure the authenticity and quality of Chinese medicines and also the qualifications of practitioners and dispensers. The circulation of many potent toxic herbs are restricted by laws. For example, in Mainland China and Taiwan, respectively, 27 and 31 potent herbs are controlled. Only qualified
practitioners and dispensers are allowed to prescribe or handle these potent herbs. (But PPH. Tai YT et al. 1995)

2. Pharmacists must stay informed and keep up with new developments of herbal medicine and have a responsibility to educate themselves about herbal therapies in order to help patients discern the facts from the fiction, avoid harm, and gain what benefits may be available. (Klepser TB & Klepser ME. 1999)

3. The products should be reviewed as any other drug, evaluating for drug-related problems such as allergies, drug-drug, drug-disease, or drug-food interactions, and possible therapeutic duplication.

4. Government should increase effort in research and development for the standardization of the active ingredient in the herbs such as DNA fingerprinting analyzes herbs by using polymerase chain reaction to identify the active ingredients by their DNA characteristics. (Briggs K, 2000)

5. Supplements with known harmful effects or questionable efficacy should not be recommended.

6. Pharmacists should inform consumers about the lack of GMPs and thus the risks of contamination, adulteration, and inadequate or excessive concentration of the active ingredient.

7. As more research with dietary supplements is conducted and better controls and regulations are implemented, there will likely be increasing use of complementary medicine, both as sole therapy and in conjunction with allopathic medicine.

17.4 For the physicians & patient

1. It is important for physicians and other healthcare providers to establish open communication with their patients regarding the use of herbal medicine and dietary
supplements. Many patients are unwilling to inform their physicians, fearing disapproval and perceiving a lack of knowledge and understanding in their physicians. A British survey reported that more than 40% of patient would not consult their family doctor or seek medical advise even they got a serious adverse reaction from herbal medicine. (Tang JL & Leung PC, 2001) Inquiring about the use of herbs, vitamins, and other remedies should be part of normal history taking, along with other questions about social habits and background. Physicians often talk with patients about controversial subjects, so discussing the merits and drawbacks of herbs does not require new skills. (Eisenberg DM, 1997; Zink T & Chaffin J, 1998)

2. When communicating with the patient, the physician should pose questions that are direct, neutral, and nonjudgmental. Patients often consider herbal remedies as natural products or food and not as medicine. They assume, therefore, that herbal remedies are free from side effects.

3. Physicians need to emphasize that many pharmaceuticals were originally derived from plant products and that herbal remedies can be as potent as pharmaceuticals.

4. Physicians need to ask specific questions regarding the use of vitamins, minerals, herbs or other botanicals, amino acids, concentrates, metabolites, extracts, and any other dietary substances being used by their patients and they should also obtain information about directions for use, methods of preparation, and dosage formulations. It is especially important for physicians to inquire about method of preparation when raw botanicals are being used.

5. Patients should be asked whether they have consulted with other healthcare providers, e.g., acupuncturists, herbalists, naturopathic practitioners, or natural
healers. Asking this question directly will often reveal other complaints, other symptoms, or the choice of alternative treatments, including herbal medicine.

6. Knowing the method by which an herbal remedy has been prepared is important, because many toxic herbs can become relatively safe for use if they have been processed properly.

7. In suspected adverse reactions, the physician should secure the prescriptions, packaging, residue of the herbs used, samples of unused herbs still possessed by the patient, and samples of the herbs dispensed by the same herb shop using the prescription, and physicians should also obtain an estimate of the amount of herbs (or decoction) consumed. (Ko RJ, 1999)

8. Patients should be advised to avoid using a wide variety of herbs concomitantly because herb-herb interactions are poorly understood. The starting dosage should be the lowest at which the desired effects occur.

9. Long-term use of herbal products should be discouraged because long-term effects are unknown.

17.5 Conclusion

For the advancement of traditional medicine as well as conventional medicine, there should be a balance (or more appropriately an imbalance) between benefits and harm—useful treatments should be able to bring about more good than harm. The best way to demonstrate this balance is through a clinical trial, though trials may not always be feasible or provide information within a desired time-frame, particularly when the harmful effect is with long-term use and rare.
Chapter 18 - Conclusion

Chinese medicine has a documented history of over two thousand years. It is still serving as a major source of primary healthcare with satisfactory results in China and the Orient. Until recently, the safety of herbal preparations was considered in medical journals only when toxicity was detected from a contaminated herbal product, usually because of careless or unscrupulous manufacturing practices. Unlike other medications, the risk of unexpected effects may be influenced by a user's age, gender, genetics, nutrition status, and concurrent disease states and treatments. A toxic herb might replace the traditional one, a conventional drug might be added covertly, or a harmful contaminant might appear without the manufacturer's knowledge. As a result of limited oversight, consumers and clinicians alike should have concerns for safety, efficacy, contents, bioavailability, and dosing of the variety of products available on the market.

True herbal toxicity, on the other hand, is almost certainly underreported. Users of herbal remedies are generally convinced of their safety and are therefore biased against reporting an adverse clinical event of possible herbal origin. Furthermore, physicians are often unaware of the herbs their patients are taking, either because they do not ask about them or the patient does not tell them. Indeed, half of the herbs taken by patients are not reported to their physicians.

To help maximize the benefits of Chinese medicine, the subject of safety of Chinese medicines deserves proper attention. Although excessive emphasis on adverse effects could stifle the development of TCM and lead to the rejection of efficacious therapies. In fact, as obvious in the cases mentioned above, many cases of adverse reactions were the result of human negligence or mistakes.
All medicinal agents have potentially unexpected effects including toxicity, and herbals are no different. If the raw herbs or herb powders are ingested without any processing or treatment, adverse reactions are likely caused by the naturally occurring medicinal compounds in the herbs or less often by heavy metal. However, toxicity from herb decoctions can be due to complicated chemical reactions of different herbs, heat stable medicinal compounds, and organic or inorganic contaminants in the containers used to boil the herbs. Due to the different methods of preparation, the physical and chemical characteristics of many medicinal compounds can aid in identification. On the other hand, herbal tea generally has a lower concentration of active ingredients and any adverse reactions are often from chronic consumption rather than acute poisoning.

Based on the fact that our knowledge of the constituents of herbal medicines and their pharmacological and possible toxic effects is extremely limited. In this research thesis, I present a wide-ranging, though not exhaustive, review of reports in the English or Chinese language literature of adverse events involving Chinese herbs.

Misidentification or substitution of the herbal components can result in outbreaks of severe poisoning. Plant misidentification may be due to similarities in appearance during bulk purchase or when harvested. In addition, confusing nomenclature or several terms with common, transliterated, Latin, and scientific names lead to misidentification. Inadvertent substitution of raw materials may cause adverse effects and contamination is a repeated problem due to lack of quality control.

Besides renal and liver toxicity, many herbs (include heavy metal and insect) have their own pharmaceutical value and unique side effects. This is to say that TCM has her own special evaluating standards, special disposal measures, as well as special observation index and cognitive methods, for instance, seeking the cause form patterns.
identified, etc. Such experience should be developed with the help of modern scientific mode.

For the Chinese proprietary medicines, it was much more difficult to collect toxicity information on this than on therapeutic drugs for several reasons. Many patients only knew the nature but not the brand name for the product they had taken. Different manufacturers may use almost identical brand names for their products, which differ in the contents. Unfortunately, only few patients or physicians will be able to note the subtle differences in the nomenclature. Contamination of herbal products consumed by both adults and children with prescription and nonprescription drugs may lead to adverse clinical outcome and even death. Although the health authorities usually have a list of Chinese proprietary medicines containing western drugs, such information may not be readily available. This means a better quality control of imported Chinese proprietary medicines is very important. There should be regular monitoring of imported herbs for adulterants. Any outbreaks of poisonings should be fully investigated. Any use of fake herbs should always be prohibited.

In Hong Kong or other cities, the exact incidence of poisonings by Chinese herbal medicines is difficult to assess. First of all the diagnosis can be easily missed if patients are not questioned with regard to the use these preparations. The second point is the existing knowledge of the pharmacological effects of Chinese herbal medicines is limited and each prescription typically consists of 10-15 herbs, which in turn contain many ingredients. Accompany with scratchy character mixed with secret signals always found in the prescription, especially for some old practitioner who worked within the herbal shop. The aim for this secret pothook was to compel the customers to buy the herbal material in their own shop every time. In addition, the herbalists are often
reluctant to disclose the contents of their prescriptions. All this may increase the difficulties for investigation. As for western medicines, there was no government scheme to monitor the safety of these compounds also. That is why patients may not report milder adverse effects.

In TCM, however, the need to demonstrate clinical efficacy has not been widely recognized. For the past 50 years in China, resources have been focused on the search for the scientific basis of TCM, for the active substances used in therapies, and for the mechanisms of action. Experience shows that this mechanism-centered approach has been costly and largely unsuccessful. The advancement of TCM now requires that the demonstration of clinical efficacy is placed high on the research agenda, with basic research taking place only after efficacy has been clearly demonstrated in clinical trials. More than this, attention was also called to those possible interactions between herbs and prescription drugs recently.

At present, only a small proportion of herbal remedies has been subjected to in-depth pharmacological, analytical and clinical studies. The most basic requirement for quality assurance for herbal products is that the correct botanical ingredients should be used. This essential rule may be broken by adulteration, by erroneous substitution of herbal products. Toxicological data in animals do not necessarily reveal all human hazards. Clinical trials in human volunteers are often small. Moreover, the lack of stringent quality assurance for herbal medicines also necessitates monitoring the safety of these products. In fact, even lack of knowledge about the mechanisms and active substances involved does not have to prevent the use of clinically efficacious therapies. Many powerful medical interventions, such as penicillin and smallpox vaccinations, were accepted and widely used before their mechanisms were understood.
With the increasing complexity of medications available today, a comprehensive Herbal Adverse Reaction (HAR) surveillance program is necessary to detect, evaluate, and develop mechanisms to prevent HARs and their associated morbidity, mortality, and increased costs. For the long run, development of TCM may be best to conduct research in the reverse order, commencing with demonstration of the clinical efficacy in humans using randomised controlled clinical trials. Clinical efficacy refers to the capacity of a drug to bring about more good than harm in treated patients and is what matters most for any medical intervention. In the efficacy-driven approach, investigation into the mechanisms and the search for active substances is also important, but should be undertaken after clinical efficacy is firmly demonstrated.

In this era of regular review, it may also be appropriate to stress audits to ensure efficacy, safety and maximum cost-effectiveness. For clinical evaluation of herb-induced poisoning, there should be a high index of suspicion and awareness of the problem. Close clinical-scientific collaboration should be available and mechanisms established for prompt notification of suspected cases. This should lead to coordinated efforts to seek out possible offending agents and exclude alternative causes. Such assessments should include evaluation of the herbal prescription, pharmacognostic as well as chemical analysis of herb samples, herb residue and authentic herb decoctions. It’s worth to put more coordinated efforts to evaluate the potential hazards, to establish protocols for authentication and quality control, and to standardize the procedures in handling potent and strong herbs. At a scientific level, international, interinstitutional and multi-disciplinary collaboration should be facilitated. Critical scientific reappraisal of the use of Chinese medicines should be undertaken to provide scientific support of their anticipated efficacy. If an herbal therapy does not work clinically, then it should be
discarded and not subjected to further investigation. Demonstration of clinical efficacy first will thus save resources by avoiding unnecessary basic research into ineffective therapies.

Finally, it should emphasis that Chinese herbs should only ever be prescribed by fully trained practitioners of Chinese herbal medicine, in accordance with a traditional individualized diagnosis. Chinese herbs should be prescribed in the traditional manner, according to an individualized diagnosis based on the theory and practice of Oriental medicine. Moreover the herbs should be used according to their traditional indications and in established combinations.
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