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Especial sobre Interacción de Productos Naturales y Fármacos / Special Issue on Natural Products and Drug Interactions

An overview on safety issues of interactions between traditional herbal medicines and pharmaceutical medicines

[Una apreciación global sobre la seguridad de las interacciones entre las medicinas herbarias tradicionales y los fármacos]

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Abstract

The increasing popularity world-wide of using herbal medicinal materials (HMM) from ethnic traditional medicine such as the widely used Chinese materia medica (CMM) or other ethnic herbal medicines and related proprietary health products (PHP), functional food and prescription herbal medicines has raised concerns over their concomitant use with pharmaceutical medicines (PHARMED) and the consequential adverse effects. In most cases the alleged causes of adverse effects are linked with herbal substances, although the authoritive information on the interactions between HMM/PHP and PHARMED is not plentiful in the literature. There is an urgent need for such a data base. In the 21st century, the public are more informed, from the Internet, about health and medical products and become more knowledgeable about matters relating to their health conditions and well-being in curing and preventing illnesses. They often self-medicate themselves with various health products as well as those over-the-counter (OTC) PHARMED. Some of theses products may have doubtful quality control and contain harmful additives or unchecked ingredients. The future professionals in health and medical care should be knowledgeable or aware of what their patients have been taking or given. Their combining medications may be involved with possible outcomes of adverse reactions or beneficial effects. In actual practice the patients may receive both treatments intentionally or unintentionally, with or without the awareness of the practitioner. In these situations an available authoritive database for interactions between HMM/PHP or prescribed PHARMED will be extremely useful for consultation when treatment problems appear or during emergency situations. Such a database will be welcomed by both practitioners of herbal medicines and orthodox medicine (OM) practitioners. The author has been involved in various research projects of basic and clinical aspects in mainly Chinese medicines among other herbal and pharmaceutical medicines hence examples will be given largely on those related to these disciplines as illustrations in this overview. It is envisaged that some of the safety issues and all other aspects discussed in the following texts are also relevant to other traditional or ethnic medicines.

***Keywords**: Principles of interactions, Safety issues, Pharmaceutical medicines, Chinese medicinal materials, Traditional herbal medicines, Adverse reactions, Beneficial effects.*

Resumen

El incremento de la popularidad mundial del uso de los materiales medicinales herbarios (HMM), de la medicina étnica tradicional, tales como la ampliamente usada materia médica china (CMM) u otras medicinas étnicas herbarias y productos propios de salud (PHP) relacionados, alimento funcional y la prescripción de las medicinas herbarias, han aumentado las preocupaciones sobre sus usos concomitantes con los fármacos (PHARMED) y los efectos adversos consiguientes. En la mayoría de los casos, las causas alegadas de efectos adversos están vinculadas con sustancias herbarias, aunque la información autorizada sobre las interacciones entre HMM/PHP y PHARMED no es abundante en la literatura. Existe una necesidad urgente por semejante base de datos. En el siglo XXI, el público está más informado, del Internet, sobre la salud y los productos medicinales y se ha vuelto más conocedor sobre las materias que relacionan a sus condiciones de salud y bienestar, curando y previniendo enfermedades. Frecuentemente, ellos se auto-administran con varios productos de salud como también con productos PHARMED *over-the-counter* (OTC). Algunos de estos productos pueden tener dudoso control de la calidad y contener aditivos dañinos o ingredientes no chequeados. Los futuros profesionales en salud y el cuidado médico deben conocer o estar conscientes de lo que han estado tomando o han dado a sus pacientes. La combinación de sus medicamentos puede estar involucrada con posibles reacciones adversas o efectos beneficiosos. En la práctica real los pacientes pueden recibir ambos tratamientos intencionalmente o involuntariamente, con o sin el conocimiento del practicante. En estas situaciones será sumamente útil para la consulta una base de datos disponible autorizada para analizar las interacciones entre HMM/PHP o PHARMED prescritos cuando aparecen las reacciones al tratamiento o durante las situaciones de emergencia. Semejante base de datos será bienvenida tanto por practicantes de medicinas herbarias como de la medicina ortodoxa. El autor de esta revisión ha estado involucrado en varios proyectos de investigación de aspectos básicos y clínicos en medicinas chinas principalmente, entre otras medicinas herbarias y farmacéuticas. En esta apreciación global se darán amplios ejemplos en aquéllos casos relacionados a estas disciplinas. Se enfatiza que algunos de los problemas de seguridad y todos los otros aspectos discutidos en los textos siguientes también son pertinentes a otras medicinas tradicionales o étnicas.

***Palabras clave:** Principios de interacciones, Seguridad, Medicamentos, Materiales medicinales chinos, medicinas herbales tradicionales, Reacciones adversas, Efectos beneficiosos.*

Abbreviation list:
ADRAC- Adverse Drug Reactions Advisory Committee
ADROIT- Adverse Drug Reactions On-line Information Tracking
ADRs- Adverse Drug Reactions
CM- Chinese medicine
CMM- Chinese materia medica
Dis- Drug interactions
HMM- Herbal medicinal materials
MFC- Methotrexate, fluorouracil combinations
MFV- Methotrexate, fluorouracil, vinblastin
MHRA- Medicine and Healthcare products Registration Agency
OM- Orthodox medicine
OTC- Over-the-counter
PCM- Proprietary Chinese medicines
PHARMED- pharmaceutical medicines
PHP- Proprietary health products
QSE- Quality, safety and efficacy
SMZ- Sulfamethoxazole
SXT- Sheng Xue Tang
TMP- Trimethoprim

INTRODUCTION

Herbs and herbal products, known as botanicals in some regions of the world such as North America, play an important role in the healthcare of nearly 80% of the world population particularly in developing countries (Akerele, 1993). For example, Chinese medicinal materials (CMM) and their manufactured products as well as Ayurvedic medicines have been used for thousands of years (Table 1) for prevention and treatment of diseases in China and in India, respectively, apart from relatively recent introduced synthetic pharmaceuticals in orthodox medical (OM) practice in the late 1800s. Without any doubts, all medicinal products used in human and animals should have proven quality, safety and efficacy (QSE). Problems and difficulties arise in the quality assurance of herbal medicinal products because there are so many unidentified chemical entities in the finished products, and the actual bioactive components are seldom known. The physico-chemical properties and mechanisms of actions of herbal products are quite different from pharmaceutical medicines (Table 2). Most of the herbal products from practice of traditional medicine are prescribed using a number of herbal mixtures. Recent advances in analytical chemistry and bimolecular techniques and related disciplines have helped elucidating the complex chemical compositions and bioactivities of these in natural products research. Thus the safety issues of interactions between traditional herbal medicines, or the newer botanicals, and pharmaceutical medicines can be addressed on according to the following sections in this overview.

1.1. Observation on the simultaneous consummation of Chinese Materia Medica (Chinese medicinal materials, CMM) and Pharmaceutical Medicines (PHARMED)

Chinese medicine (CM), one of the world's oldest continuous surviving traditions (Zhen, 1995), has been practiced to maintain good health and treat diseases in the Chinese communities and recently by other ethnic groups worldwide (Chan, 2004). CMM and other natural substances and products, acupuncture and related physical therapies and special life style are often used together in the practice, co-existing with orthodox medicine (OM) in China and some regions in the Far East (Chan, 2005). However in the west increasing uses of CM have created both scepticism and support of CM practice that have been the major debate since the successful randomized clinical trial on the use of 10 CMM prescription on atopic eczema was published in 1992 (Atherton et al., 1992). However available in the market are CMM products adulterated with pharmaceutical drugs and wrongly supplied crude CMM with liver and kidney toxicity. These unprofessional practices from commercial organizations do not give CM the right reputation and recognition. It is emphasized that government regulatory agencies should set up harmonized regulatory control over the import and export of natural or herbal products to ensure safety of the public who consume them.

Table 1. Medicinal products from natural sources in various ethnic cultures.

Complementary Medicine	Natural Sources	Origins	Recent Turnover Trade
Ayurvedic	P,A,M	India	No figure
Chinese	P,A,M	China	> 1.3 billion US$
Indusyunic	P,A,M	Pakistan	No figure
Islamic	P,A,M	Middle East	No figure
Kampo	P,A,M	Japan	Getting competitive
Korean	P,A,M	Korea	No figure
Other oriental	P,A,M	Other Asian countries	No figure
Aromatherapy	P	European	£14 m in 1996 (UK figure)
Herbalism	P	European	£38 m in 1996 (UK figure)
Homoeopathy	P	European	£20 m in 1996 (UK figure)
Botanicals	P	American	10% annual increase

P- Medicinal plants, A- Animal sources, M- Mineral sources (modified from Chan, 2003)

Table 2: Comparisons between properties of Chinese medicinal materials (CMM) and pharmaceutical drugs.

Properties	Remarks	
	CMM Products	**Pharmaceutical Drugs**
Physico-chemical Properties		
Active ingredients	Often unknown	Known
Availability of pure compound	Rare	Yes
Availability of raw material	Limited	Yes
Quality of raw material	Variable	Good
Stability of preparation	Uncertain	Good
Biomedical Properties		
Mechanism of action	Often unknown	Usually known
Toxicological tests	Usually not available in animals	Mandatory
Empirical data	Very important	Often meaningless
Specific adverse effects	Rare through experience	Frequent
Tolerance of therapy	Usually good	Limited
Therapeutic window	Wide	Usually narrow
Suitability for chronic use	Often well tested	Not yet tested for new drugs
Placebo controls	Difficult to achievable	Achievable
Controlled clinical trial	Usually not available	Mandatory

(Adopted from ref: Chan, 1995)

Patients in the Far East intentionally or un-intentionally may be prescribed CMM and other OTC tonic products containing CMM and OTC-PHARMED for alleviating their illnesses. In the past there were practices of incorporating PHARMED into CMM preparations. The rationale may be that it is hoped to reduce side effects of PHARMED, or to produce synergistic effects for better treatment outcome. In most cases the pharmacological mechanisms of the combinations are not well studied and exaggerated adverse effects or therapeutic failures have been observed, although beneficial effects were noted. Patients may also self-medicate with CMM tonic preparations, consumed as dietary soup during convalescence period, while being treated with PHARMED. It is well documented that when several PHARMED are taken together, drug-drug interactions with detrimental effects occur (Li & Jurima-Romert, 1997) and the situation becomes more complicated when CMM products are taken simultaneously. Outside the Far East, apart from the Chinese communities, non-Chinese ethnic patients will probably be exposed to CMM medications through increasing popularity. The problems of PHARMED-CMM interactions will exist. Therefore adverse reactions consequential to CMM products may not be as simple as those due allegedly to toxicity of the herbs only (Chan, 2000).

1.2. The Integrative Practice of Traditional Chinese Medicine and Orthodox Medicine in China

The integrative practice of traditional Chinese medicine (CM) into orthodox medicine (OM) in China since the early 1950s has given the opportunity to look at the advantages and disadvantages of each practice and to investigate the benefit from each discipline in order to encourage improvement of healthcare and possibly save treatment costs. China probably is the only country in the world that has developed a healthcare system that incorporates traditional CM into the healthcare policy for the nation. Within the healthcare system the two forms of medical treatment work along side with each other at every level of the healthcare structure. In particular, patients can benefit from preventive medicine, reducing side effects from OM or CM medications and improved quality of life in terminal cases. To achieve these goals it will take a lot of understanding from professionals of both disciplines. No longer should practitioners from traditional CM and OM be working in isolation. Professionals who are supportive of this concept of integration should also work to find out if there is any benefit at all in combination treatments. Augmenting OM with acupuncture has been recognized in several areas of pain relief, drug dependence, etc. in the West. However this overview only concerns with CMM-PHARMED interactions relating to beneficial outcomes or adverse reactions as a consequence of co-administration.

In China, increasing attention has turned towards organized scientific research on this aspect of interactions with beneficial outcomes. From the diet and nutrition aspects many Chinese patients in the community often self medicate with tonic CMM products after serious illnesses or surgical operations while they are still on OM medications. They believe that the herbs will help them to recover rapidly. It is normal procedure to carry out diagnosis of the same patient using traditional CM procedures and OM modern instruments and techniques in hospital practice in China. Experienced CM and or OM practitioners who are knowledgeable of using both types of medications have prescribed both types for certain diseases in order to get effective treatments. The improvement or deterioration of patients' disease conditions is the measurement of success or failure of treatment. Some of the observations have been published, mainly in Chinese, in medical journals available in China.

2. Mechanisms of interactions between herbal medicines and pharmaceutical medicines

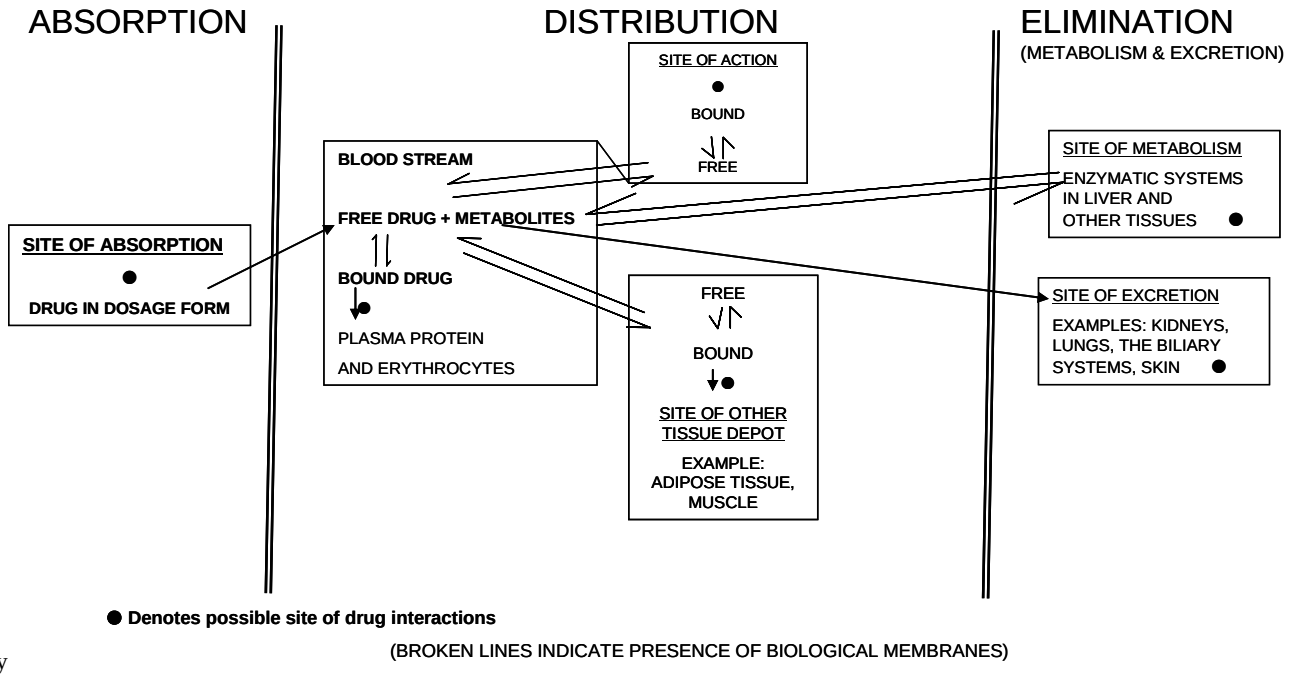
In general drug interactions (DIs) refer to clinical phenomena during drug therapy when the pharmacological or therapeutic actions of a drug are altered by the co-administration of other drugs or substances. The consequence can be advantageous if used properly. But the clinical outcomes can either be an exaggeration of pharmacological or toxic effects or a diminished efficacy of drug treatment; leading to therapeutic failure and endanger patients' conditions. The relevance of drug interactions depends on how clinically significant is the therapeutic outcomes. Thus we can consider different categories of drug interactions. Adverse drug interactions can be defined as a situation in which one drug interferes with the pharmacokinetics (at processes involving absorption, distribution,

metabolism and excretion) or pharmacodynamics (at receptors, enzyme systems or other sites of actions) of another. The initial drug can modify the effect of the second drug, and lead to an enhanced effect, particularly drug toxicity; or a reduced effect, particularly lack of efficacy. Thus, drug interactions may produce enhanced drug effect that is synergistic; the outcomes of interactions may be beneficial or harmful. Interactions can be classified on basis of their significance as: major when life-threatening or permanent damage is involved; moderate if additional treatment is required; or minor when the therapeutic outcome is unnoticeable or not sufficient to affect the desired therapy goals. Figure 1 (Adopted from Chan & Cheung, 2000) illustrates the possible sites of drug-drug or drug-herb interactions.

2.1. Beneficial interactions between CMM-PHARMED

The integral treatment of illnesses using traditional CM and OM medications aims to bring together the general concepts of syndrome differentiation of CM with the OM principles of disease differentiation. It is obvious that the two systems vary greatly in approaches of diagnosis and treatment. For instance, OM concerns with microcosmic differentiation of disease state, quantitative analysis of regional lesions or tissues damages, distinction between different disease based on characteristics of pathogenic factors and pathology of lesions. The CM practice on the other hand, deals with macrocosmic differentiation of syndrome, comprehensive qualitative analysis of whole body, distinction between different syndromes based on complex responses to external and internal pathogenic factors. It is logical to combine observations from disease differentiation (OM) and syndrome differentiation (CM) of the patient in order to draw accurate diagnostic conclusion. Treatment can be derived to target regional lesion or malfunction of particular receptor or organ (OM) and imbalance holistic conditions (CM) of the patient. This is one of the principles for integral treatment based on CM and OM. Modern medical technology and sophistication will help to make OM differential diagnosis while experience and personal approaches is needed for accurate CM diagnosis. It is necessary to relate the relationship of CM principles of *Yin* and *Yang* balance of the body to the OM understanding of the inter-play between the body's nervous-endocrine-immune regulations.

Figure 1. The fate of a reversely acting drug in the body



Experience of integrative medical practice in China has observed, through experience of practice and recorded case studies, beneficial treatment observation and outcomes with probable explanation or possible mechanisms of interactions although more experimental research and clinical evidences are needed to confirm such observations. This is partly because the OM gold standard of randomized clinical trials is not entirely applicable in the individualized approaches for treatment in CM practice. The following tentative categories of case studies illustrate synergy effects of treatment consequential to co-administration of OM drugs and CMM medications. These case studies were abstracted from medical journals published in China and have been translated into English and edited by the authors for presentation in the text (Chan & Cheung, 2000). The information is reproduced here with permission from the author for illustration. Yet most of these examples did not show any of the 'gold standard of RCT indicated in the practice of orthodox medicine. The debating issues will be that these are reported cases as practiced of integrative medical approaches shown in China that illustrate the beneficial treatment effects when CMM and PHARMED are co-administered together.

Category 1: Combining antibiotics with CMM products producing added beneficial effects

Example 1. Trimethoprim (TMP) and Shui Yang Mei (*Adinarubella*) in treating typhoid. (Luo, 1982):

A group of 33 patients took part in the studies and they were given 30ml of CMM decoction Shui Yang Mei (orally 3 times a day) plus TMP (0.1g, twice daily) for treating the typhoid. In the control group, 21 patients were given sulfamethoxazole (SMZ; 1G) and TMP (0.1g), twice daily for the same infection. Both groups of patients were all fully recovered with no recurrence. The curative effects of the two groups were mostly identical (P>0.05). But the CMM-TMP group had no noticeable side effects. From laboratory experimental evidence, 10% Shui Yang Mei aqueous solution showed bacteriostasis to *Shigella dysenteriae*. This combined CMM-PHARMED showed synergic effect on *Salmonella typhia*.

Example 2: Treatment of acute bacillary dysentery with traditional Chinese medicine and western medicine combined on analysis of 117 cases (Wu, 1984):

The 117 patients with acute bacillary dysentery were divided into 3 different treatment groups, orthodox medication, PHARMED only, sulfamethoxazole (SMZ 40 patients), Chinese Materia Medica (CMM) prescription 1 (CMM 1, 36 patients), and PHARMED plus CMM prescription 2 (SMZ plus CMM2, 41 patients). CMM prescription 1 consisted of 10 CMM herbs: Bai Shao (*Radix Paeoniae Alba*), Bai Tou Weng *(Radix Pulsatillae*), Chi Shao (*Radix Paeoniae Rubra*), Da Fu Pi (*Pericarpium Arecae*), Da Huang (*Radix et Rhizoma Rhei*), Dang *Gui (Radix Angelica Sinenis*), Huang Lian (*Rhizoma Coptidis*), Huang Qin (*Radix Scutellariae*), Mu Xiang (*Radix Aucklandiae*) and Qin Pi (*Cortex Fraxini*). CMM prescription 2 consisted of 10 CMM herbs: Bai Zhu (*Rhizoma Atractylodis Macrocephalae*), Bai Shao (*Radix Paeoniae Alba),* Bing Ling *(Semen Arecae),* Chi Shao (*Radix Paeoniae Rubra),* Dang Gui (*Radix Angelica Sinenis),* Fu Ling (*Poria*), Huang Qin (Radix Scutellariae), Mu Xiang (*Radix Aucklandiae),*Shan Yao (Rhizoma Dioscoreae) and Sheng Jun (Radix et Rhizoma Rhei). Four herbs were common in both CMM prescriptions.

Treatment outcomes indicated that the combination medication gave the best results than either of the two groups with single medication treatment (P< 0.005). Comments from the publication are: the SMZ had strong bacteriostatic action that often leads to disproportionate population of intestinal bacteria and dysfunction of the stomach and intestine. The CMM medication is not only free of side effects, it can also increase the body defense mechanism by enhancing the release of immunological factors, phagocytosis of reticulo-endothelial system, and by activating the kinase system it increases the amount of bateriophages in acute bacillary dysentery.

Example 3: Reduction of side effects of Streptomycin by Gan Cao (Radix Glycyrrhiza). (Xu, 1987):

It is well known that streptomycin can cause damage to the VIIIth cranial nerve and lead to sensorineural deafness. This toxicity of streptomycin was reduced when it was co-administered with Gan Cao (liquorices root) extract. About 80% of the patients who previously were not able to tolerate the side effects persisted in streptomycin treatment. Gan Cao is a well-known and widely used CMM, often

incorporated in composite herbal mixture in CMM prescriptions.

Category 2: Combating infection with antibiotics and immune-strengthening CMM products

In the Chinese integrative medicine approach, bacterial infection in the body can be eliminated by using PHARMED antibiotics (i.e. the OM region treatment approach) while reinforcing the body immuno-function using CMM herbs to strengthen the body defense system (i.e. traditional CM holistic approach). The body's immune system recognizes and destroys substances foreign to the body, including bacterial cells, other microbes, and foreign toxic compounds. The principles of these combinational approaches can be interpreted as follows. Cells in the circulatory and the lymphatic systems that recognize and destroy these cells are generated in the bone marrow and the lymphatic tissue (thymus, lymph nodes, spleen and tonsils), respectively. These 'stem cells' when initially produced are featureless and cannot be distinguished as what type of blood cells (erythrocytes or different kinds of white blood cells) they will become. After their release into the blood stream they are delivered to all parts of the body. Some become 'memory cells' that as the name implies, recognize specific foreign cells or chemicals to which they have been exposed, and react immediately on the next encountering of those compounds. Substances, such as vaccines, that effect the 'memory cells' stimulate only to one disease or antigen. In general, most herbs that contain so many different chemical compounds, for the immune system do not affect 'memory cells', but are general immune system stimulators or immunostimulants. They induce the activities of the immune system but are not specific to a particular disease or antigen (i.e. the protein against which immune cells act). They increase resistance by mobilising 'effector cells' that act against all foreign particles, rather than one specific type. Thus the combination of OM antibiotics with CMM products for treating infectious diseases is a logical approach. This may help to reduce bacterial resistance to antibiotics.

Huang Qi (*Radix Astragalus*), a widely used CMM often prescribed as an important herbal component in composite prescription formulae, alone is used as a tonic herb and as medicinal herb in combination with others for strengthening the *Lung* for frequent colds or shortness of breath. It has no demonstrable anti-bacterial effects but it increases the immune system by increasing the number of 'stem cell' in bone marrow and lymph tissues, promoting immune cells from the 'resting' state into heightened activity and reducing the negative side effects of co-administered steroids on the immune system. Quite a few of the CMM products in the form of established proprietary medications or well-tried prescriptions have been shown to possess immuno-strenghtening or modulating properties. In a review on the role of CMM in chemotherapy of cancer the principles of such integrative approaches was illustrated by Wan in 2002.

Category 3: Augmenting cardiovascular PHARMED treatment with CMM products

Propranolol, a well used PHARMED belonging to the beta-adrenergic blocker group of therapeutics, has been co-administered with aqueous extract of Dan Shen (*Radix Salviae Miltiorrhzae*) as intravenous injection for treating patients suffering acute myocardial-infarction in Intensive Care Coronary Unit in some hospitals in China since the mid 1980s. The combination treatment gives significantly better outcomes than propranolol alone. Dan Shen aqueous extracts, among many other pharmacological properties, increase microcirculation, inhibit platelet aggregation and have centrally acting anti-anxiety actions. These may explain the beneficial effects with co-administration of propranolol. Extensive research works have been carried out over the past 20 years on Dan Shen in Shanghai and Hong Kong academic research institutes. It is interesting to note that isolated single chemical entities from Dan Shen roots have not produced any useful and marketable conventional PHARMED. Apart from injectables other oral preparations of single herb or composite formulae of Dan Shen are available to the public as preventive remedies against cardiovascular diseases. If these products are not used properly, however, adverse reactions may result if taken with other PHARMED to produce harmful interactions (See subsequent sections below for details).

Category 4: Augmenting anti-inflammatory action of PHARMED with CMM Products

Example 1: Lupus nephritis treated with impact therapy of cyclophosphamide and traditional Chinese medicine (Ruan & Ye, 1994).

The seventy-six patients suffering from lupus nephritis were divided into two treatment groups, PHARMED with cyclophosphamide and steroid (35 patients) and combined PHARMED with CMM decoction of 14 herbs (41 patients). The 14 herbs were, Bai Hua She She Cao (*Herba Heyotis Diffusae*), Ban Zhi Lian (*Herba Scutellariae Barbatae*), Dan Pi (*Cortex Moutan Radicis*), Fu Ling (*Poria*), Han Lian Cao (*Herba Eclipitae*), Ju Hua (*Flos Chrysanthemi*), Nui Zhen Zi (*Fructus Ligustri Lucidi*), Qi Zi (*Fructus Lycii*), Shan Yao (*Rhizoma Dioscororeae*), Shan Zhu Yu (*Fructus Corni*), Shu Di (*Radix Rehmanniae Preparata*), Wu Gong (*Scolopendr*a), Wu Shao She (*Zaocy*s) and *Ze Xie (Rpizoma Alismatis).*

After a six-month treatment course, the therapeutic efficacy was significantly higher in the combination group than the PHARMED medication only group ($P<0.05$). The PHARMED cyclophosphamide is itself inactive; after oral administration it is metabolized to active metabolites. In OM practice, prednisone (corticosteroid) is often used together in order to increase the rate of metabolism of cyclophosphamide; although single doses of the steroid will inhibit activation of this potent immunosuppressant. Cycolphosphamide causes liver toxicity and long term steroid treatment also causes systemic side effects. The use of CMM may help to build up beneficial effects by rectifying the imbalance of the body functions according to traditional CM concepts. Lupus nephritis usually manifests itself as *Liver-Kidney Yin Xu* (deficiency) with symptoms such as, lassitude of the loin and legs, dizziness, tinnitus, dry mouth and throat, deep and small pulse, red tongue with a little coating etc. The 14 CMM in the decoction nourish the *Liver and Kidney*, *Yin* and clear away *Heat*, according to the CM practice principles.

Example 2: Observation on 134 patients with adult primary nephrotic syndrome with combined traditional Chinese medicine and Western medicine treatment. (Ye et al., 1993).

The 134 patients suffering adult primary nephrotic syndrome were separated randomly into two groups and treated with corticosteroid (66 patients) and steroid with a decoction consisting of 10 CMM. These were: Dan Shen (*Radix Salviae Miltiorrhzae*), Di Gu Pi (*Cortex Lycii Radicis*) Gui *Ban (Plastrum Testudinis*), Han Lian Cao (*Herba Ecliptae*) Hong Hua (*Flos Carthami*), Nu Zhen *Zi (Fructus Ligustri Lucidi*),Qi Zi (*Fructus Lycii*), Sheng Di (*Radix Rehmanneae*) and Yi Mu Cao (*Herba Leonuri*).

The percentage of success from the corticosteroids treatment and the combined therapy was 56.1% and 85.3% respectively and the corresponding percentages for incidence of side effects were 48% and 14.8%. These observations indicate that corticosteroid plus CMM decoction of the 10 components mixture could enhance curative success of adult nephritic syndromes with fewer side effects.

Category 5: Reducing adverse effects due to PHARMED chemotherapy during treatment of cancers by CMM products

Treatment of cancers (malignant neoplasm or new growth) using chemotherapeutic agents is often started after not so successful of surgical removal, or in conjunction with, radiation therapy. At this late stage patients become physically weak with quite a few signs of adverse effects as the treatment used often affects normal cells. The most severe toxic effects include bone marrow suppression, and nausea and vomiting apart from impairment of healing, depression of growth, causing sterility and hair loss. Some patients become in tolerable to chemotherapy and their quality of life is much reduced. Their immune system is highly compromised. The cytotoxic groups for cancer treatment using PHARMED of cytotoxic agents, depending on which cancer types and the policy for chemotherapy, often consists of at least three and more different groups of anti-neoplasmic agents. They are anti-metabolites (cytarabine, fluorouracil, methotrexate, and mercaptopurine), cytotoxic antibiotics (bleomycin, dactinomycin, doxurubicin, epirubicin, and mitomycin), plant derivatives (etoposide, vincristine), hormones and their antagonists (glucocorticoid, oetrogens such as fosfestrol, anti-oestrogen such as tamoxifen, progestrogens such as megestrol, anti-androgen antagonists such as cyproterone and flutamide, and gonadotrophin-releasing hormone such as goserelin, radio-isotopes such as ^{131}I for thyroid tumours and inhibitors of DNA and RNA (procarbazine).

Chemotherapy treatment of cancers using integral approach of PHARMED and CMM has been practiced in some hospitals in China. The concept is to utilize PHARMED cytotoxic agents to target the cancerous cells and CMM medications for restoring imbalances, as diagnosed from clinical picture, due either to the neoplasm or chemotherapy. The following examples illustrate some of the observations.

Example: Clinical and experimental studies on chemotherapy combined with Sheng Xue Tang (SXT) recipe for the treatment of late stage gastric cancer (Rao et al., 1990).

Eighty-one patients with late-stage gastric cancer were treated with chemotherapy (MFV, methotrexate, fluorouracil, vinblastin; or MFC, methotrexate, fluorouracil combinations). Among them, 63 patients also took the CMM composite formula, SXT, while other 18 patients were treated with chemotherapy only as control group. The prescription formula included following eight herbs: *Radix Astragalus*; *Radix Pseudostellariae*; *Caulis Spatholobi*; *Rhizoma Atyractylodis Macrocephalae*; *Poria*; *Fructus Lycii*; *Fructus Ligustri Lucidi* and *Semen Cuscutae*. Clinical observations showed that the CMM prescription could reduce the side effects caused by chemotherapy with improved body weight (see following summaries on Tables 3 and 4).

The clinical observation was complemented with laboratory experimental studies that indicated the SXT decoction could prolong the life of the S-180 tumour bearing mice undergone chemotherapy.

2.2. Harmful effects of interactions between CMM-PHARMED

Information on harmful interactions between CMM and PHARMED medications can be obtained from the literature mainly available in Chinese language. These information were edited and compiled into Tables reported previously (Chan & Cheung, 2000). Some clinical observations have been confirmed with experimental investigation. In general the mechanisms described for drug-drug interactions in for PHARMED are also applicable for the CMM-PHARMED interactions as understood from conventional science and medical aspects. Complications arise because of the presence of so many chemical entities in the single herb or in the decoction of the composite formulae, and many of which have not yet be identified. Such observations are also applied to other traditional herbal medicines. The following categories summarize the likely mechanisms of involved.

Table 3. A summary of adverse effects during chemotherapy treatment with and without SXT recipe.

Groups	**Chemotherapy plus SXT recipe 33 cases (100%)**	**Chemotherapy only (control) 12 cases (100%)**
Loss of appetite	12 (19%)	6 (50%)
Nausea and Vomiting	12 (19%)	6 (50%)
Diarrhoea	0	6 (50%)
Tiredness	20 (31%)	8 (67%)
Limp numbness	0	4 (33%)

Table 4. A summary of changes in patients' body weight (kg) during chemotherapy treatment with and without SXT recipe.

Groups	Chemotherapy plus SXT recipe	Chemotherapy only (control)
Number of cases	29	12
Before treatment (X ± SD)	58.51 ± 1.85	58.73 ± 5.53
After treatment (X ± SD)	60.66 ± 3.08	57.16 ± 5.66
T value	18.22	0.688
P value	<0.001	>0.05

Category 1: Formation of insoluble complexes during absorption phase leading to therapeutic failure

Some CMM medications whether single herbs or composite prescription decoction or proprietary herbal products contain metal ions that may form insoluble chelates or complexes with PHARMED Tannic acid in some CMM medications can form insoluble complexes with PHARMED antibiotics and drugs containing tertiary amine-alkaloids and metal ions. Alkaloids in CMM medications form precipitates with metal ions in PHARMED. CMM medications containing quercetin (phenols with 5-OH and 4-keto functional groups) can precipitate CMM drugs containing aluminium, bismuth, calcium, ferrous, and magnesium ions. Gan Cao (Liquorice root, Radix Glycyrrhizae) interacts with tetracycline group of antibiotics by reduction of their oral absorption. Yin Chen (Herba Artemisiae Capillaris) forms precipitates with quinidine and antagonizes chloramphenicol actions.

Category 2: Affecting transport of drug molecules in the body by CMM leading to reduced effects

Some CMM medications have high contents of acids that will alter the physiological pH and thus affect the transport mechanisms of PHARMED drug molecules leading to reduced actions or physiological precipitation. Similarly some CMM medications contain alkali that affect the physiological solubility of the PHARMED drugs thus influencing their excretion and transport. For examples, the presence of acids in Nu Zhen zi (*Fructus Ligustri Lucidi*), Shan Zha (*Fructus Cartaegi*), Shan Zhu Yu (*Fructus Corni*), Wu Mei (*Fructus Mume*), Zhi Qiao (*Fructus Aurantii*), etc. will decrease the antimicrobial activities of the aminoglycoside group of antibiotics. (Gong, 1989a;b).

Category 3: Affecting function of PHARMED diuretics and body electrolyte balance by CMM medications

Some PHARMED diuretics such as the potassium-sparing group (amiloride, spironolactone, etc.; Stockley, 1996) should not be co-administered with some CMM medications. These products (Gong, 1989b; Zhu, 1994) contain potassium ions in various forms. Hyperkalaemia may result due to accumulation of the ion from the herbal products and retention from the diuretics. A large group of CMM containing potassium was given as examples in the reference (Chan & Cheung, 2000).

Category 4: Destroying amylase in some CMM medications by PHARMED anti-biotics

Amylase contents in some CMM products are active principles that can be destroyed by PHARMED such as the antibiotics tertracylines and sulphonamides. Key CMM includes Dan dou Chi (*Semen Soyae Preparatum*), Gu Ya (*Fructus Oryzae Sativae Germinatus*), Mai Ya (*Fructus Hordei Germinatus*), Shan Yao (Rhizoma Dioscoreae) etc. (Gong, 1989a; Editorial, 1987; Lin, 1990)

Category 5: Destroying glycosides in some CMM products by acidic PHARMED

Glycosides in some CMM products may be the active ingredients that can be destroyed if acidic PHARMED (Ascorbic acid, nicotinic acid, glutamic acid and drugs containing mineral acid components as salts) are administered concurrently. (Gong, 1989a;b).

Category 6: Releasing toxic cyanide from CMM medications by PHARMED

Some CMM herbs, in particular, seeds when co-administered with PHARMED release hydrocyanic acid that inhibits the respiratory centre. PHARMED such as codeine, morphine, should not be co-administered with CMM such as Bai Guo (Semen Ginkgo), Ku Xing Ren (Semen Armeniacae) and Tao Ren (Semen Persicae) (Ou 1989; Leng, 1988; 1991).

Category 7: Affecting liver metabolizing enzymes that eliminate PHARMED by CMM

CMM single herb or complex mixture products may modify the metabolic elimination of PHARMED leading to reducing activity (enzyme induction) or increasing activity (enzyme inhibition) of PHARMED. The pharmacokinetics of warfarin is compromised during co-administration with Dan Shen (Radix Salvia Miltiorrhiza) leading to uncontrollable steady state of plasma concentration. (Chan et al., 1992; 1995) Warfarin is mainly eliminated by the liver and has a narrow therapeutic window during clinical treatment when chronic anticoagulation administration is needed. If the steady state is affected haemorrhagic or clotting episodes will occur. (Lo et al., 1995). The active ingredient of Gan Cao (*Radix Glycyrrhizae*), glycyrrhizin, is an inhibitor of 11 beta-hydroxysteroid dehydrogenase, a major metabolic enzyme of glucocorticoids in the liver. Co-administration of Gan Cao potentates the action of prednisolone due to enzyme inhibition.

3. Approaches on Research into Interactions between herbal medicines and pharmaceutical medicines

From the observations listed in the above sections the complexity of interactions between herbal ingredients and pharmaceutical drugs is indeed enormous. It is crucial to review steps that can be planned to investigate such interactions. One appreciates that only the clinically significant interactions are relevant to clinical practice. As a result of the focus on adverse drug interactions over the past decades many of the interactions between drugs of the PHARMED are now predictable and unwanted reactions using drug combinations can be avoided by dosage adjustment of one or more of the interacting drugs. Unfortunately investigations on interactions between herbal medicines such as CMM with PHARMED become more difficult and documentations in literature are not plentiful.

Moreover many drug interactions that have been listed in the literature are at times not meaningful nor helpful for clinical practice if they are not relevant. This is because some reported interactions are theoretically possible on the basis of in vitro investigations or animal experimentation that may not have been studied in patient situation. Some studies are based on healthy volunteer investigations or at non-therapeutic doses. The following headings describe possible steps one can initiate studies on drug-drug interactions

3.1. Criteria for choosing interaction studies of clinical relevance

Initially, the project leaders should ascertain how valid the reported interaction is, and whether it is worthwhile to design a study to verify the importance of the reported or suspected interactions. Investigational studies of drug-drug interactions can be of predictive value if they mimic the clinical situation and they can be related to drug combinations and regimen that are practiced in the clinic.

PHARMED with problematic disposition and pharmacokinetic characteristics and those required for long-term treatment carry the higher risk of occurrence of possible clinically relevant interactions. Situations when patients self-medicate or are put on multiple drugs regimen also warrant investigations. The criteria summarized in Table 5 will be helpful to make a decision.

Specific studies, based on the relevant criteria listed in Table 6, can be carried out during the development of new drugs (or CMM products refer to later headings). These may be designed to measure certain biochemical or physiological processes or functions being affected by drug treatment with narrow therapeutic ratios. These functions or biomarkers consequential to drug or herbal treatment, or a combination of the CMM or PHARMED are useful measurements of adverse, beneficial or synergic effects. Table 6 gives examples of the pharmacological classes of drugs and respective processes involved for monitoring.

Table 5. Criteria considered as potential risks f or occurrence of drug-drug interactions

▪ Drug-drug interactions of 2 or more drugs observed in clinical practice for confirmations
▪ Drugs with steep dose-response curve (a small change in concentration will lead to exaggerated effects)
▪ Drugs with small therapeutic range especially in combination dosage forms
▪ Drugs with problematic disposition or pharmacokinetics
▪ Drugs used for long term treatment having effects on drug accumulation, enzyme induction etc.
▪ Drugs prescribed simultaneously by several physicians intentionally or unintentionally
▪ Drugs self-medicated by patients
▪ Drugs showing genetic polymorphism in metabolic elimination (cytochrome P450 CYP2D6, CYP2C19, etc.)

Table 6. Pharmacological classes of drugs with clinical relevant interactions.

Pharmacological Class	Functions to be monitored	Indices/Biomarkers
Antacids drug	Formation of non-absorbable complexes	Plasma levels
Anti-arrhythmics	Cardiac rhythm	ECG monitoring
Anti-asthmatics	Respiratory stress	Respiratory test
Anti-coagulants	Blood clotting or hemorrhagic crisis	Prothrombin time
Anti-convulsants	Uncontrolled epilepsy or over sedation	Seizure frequency
Anti-diabetics	Glucose homeostasis	Blood glucose levels
Anti-hypertensives (beta-blockers)	Irregular blood pressure (BP)	Monitor BP
Cardiac glycosides	Heart failure or over-digitalization	Monitor arrhythmia
Cytotoxic agents	Over-suppression of immune functions	Immune biomarkers
H_2 receptor blockers	Inhibition of drug metabolic elimination	Plasma levels
Psychotropic agents (particularly lithium, MAOIs)	Hypertensive crisis	Monitor BP

3.1. Difficulty and barriers towards research in herbal medicine in developed regions

In countries where the healthcare system is run by practice of orthodox medicine, clinical and scientific research into the efficacy of herbal medicines in general using conventional methods has met difficulties (Mills, 1996). Practical obstacles in pursuing good research for herbal medicines under can be considered as follows:

1. To obtain results with sufficient statistical weighting is expensive and laborious. Herbal medicine presently receives little or no funding from teaching hospitals, universities or industries in most organizations in the West. Recently through the Office of Alternative Medicines set up by the National Institute of Health in the USA some efforts have be made to fill the gap of information on the quality, efficacy and safety of complementary or herbal medicine. In the UK the Medical Research Council has become more inclined towards funding well designed studies on complementary therapies.
2. Herbal medicinal products are complex mixtures with a vast amount of chemicals that may be pharmacologically active or inert. The composite formulae or prescriptions may have different properties from that of the single constituent acting alone. Acceptable models for investigation of herbal medicines from the orthodox medicine camp are not readily available. Herbal practitioners do not generally consider some orthodox models as relevant

to assess herbal products that have been shown effective through time.

3. The principles and approaches of using herbal ingredients and their effects on the body is not the same as usually understood for conventional medications. For example, CMM medications are used to holistically evoke healing responses in the body to rebalance body functions rather than to attack symptoms as orthodox medications do. Research of these types on CMM medications in the West is not plentiful. Clinical observations in the Chinese language are plentiful. This gap could be reduced in the near future through more international collaboration and understanding of methodology.

In his overview on research strategies of herbal medicines Mills (1996) gave some positive approaches that could help research on herbal medicines in the West. However the progress of 'official' contribution from herbal medicine to the mainstream healthcare in developed regions has been slow over the past decade.

4. Proposed designs for study of interactions between CMM and PHARMED

Most of the interactions between CMM and PHARMED described in the literature are observations reported from clinical practice. They come from the integral approach of medical practices obtain the beneficial effects of combination treatment and some are adverse effects due to intentional or unintentional combination of the two groups of medications. These observations are published mainly in Chinese language. Information gap exists on herbal medicines and their potential for interaction with PHARMED medications. Evidently research in these areas is urgently needed regions where orthodox medical practice is the main stream of healthcare provider when their patients consume herbal medications. The most important step is to obtain reliable sources of case studies. It may be necessary to accept initially the observed effects as suspected interactions and design studies to ascertain the finding by careful follow-up investigations within the patient group who needs the combination herb-drug treatment. All information on the interacting PHARMED stated in Tables3 and 4 should be taken into account and considered the interaction study design. Consideration should include the traditional CM information on the CMM medications and their reported conventional pharmacological group functions. Using this approach it is possible to adopt study design from the drug-drug interaction protocol only for those needed for patients. It is considered unethical to test on healthy volunteers for such study.

4.1. Design for interaction study between CMM and PHARMED

Using example of Category 5 under Section 2.1, 'Reducing adverse effects due to PHARMED chemotherapy during treatment of cancers by CMM products', it is possible to design a reasonable study. In the study reported by Rao et al. (1990), the indications given for significant successful reduction of side effects were the general well being of the patients with stomach cancer on combination of chemotherapy and Sheng Xue Tang, SXT (literally means decoction or recipe producing new blood components). The results as reported could be more significant and convincing if other measure outcomes were explored and included in the trial. This might be due to the limited design and certain facilities that were not available during that study. It was obvious that the chemotherapy with MFV (methotrexate, fluorouracil and vinblastine) should not be stopped throughout treatment as decided by the oncologist; the co-administration of SXT would help to alleviate syndromes, due to adverse effects of the MFV treatment, as diagnosed by the traditional CM methodology.

If this trial were to be repeated according the present suggested design here, it will include several entry requirements and other outcome measures with better statistical assessment. The 81 late stage gastric cancer patients could be divided into 3 groups of 21 each for 3 different treatments of MFV chemotherapy, MFV chemotherapy plus SXT decoction and MFV chemotherapy plus placebo decoction respectively. Details of design consideration are summarized below:

4.1.1. Trial conditions and procedure

1. Inclusion of a placebo preparation or decoction should give a better outcome of a controlled trial. A decoction similar in color, smell but without the traditional CM effects could be prepared. The successful controlled trial in the atopic eczema

study (Atherton et al., 1992) also included a placebo to increase the trial's confidence level of significance.

2. Entry by randomization of number of patients into the three treatment groups was a better design. Thus the 'Chemotherapy plus Sheng Xue Tang' group and the 'Chemotherapy plus Placebo Tang' could be compared with the Chemotherapy group only.
3. Pre-chemotherapy profiles of all patients for clinical biochemistry and hematology and kidney and liver function should be available and recorded accordingly together with other parameters for assessment of well being using Quality of Life instruments specifically for cancer group patients. The well being measurements should be administered by trained persons based on properly designed questionnaires. The person making the assessment should be blinded of both treatment groups.
4. Measurement of adverse effects should also be performed with thoroughly designed protocol and recorded without biased remarks or comments. Same procedures should be administered for every patient.
5. Run-in steady state of basic chemotherapy treatment should be achieved by measuring the pharmacokinetic parameters of the chemotherapy drugs during the first week before giving the SXT decoction or Placebo Decoction. Evaluation of pharmacokinetics of the chemotherapy drugs should commence simultaneously.
6. Determination of pharmacodynamics and pharmacokinetics after steady state has attained should be carried out. Observation of adverse side effects and improvement or deterioration of blood picture and other related. Indices or other related biomarkers for cancer progression should be recorded.

4.1.2. Assessment of Outcomes

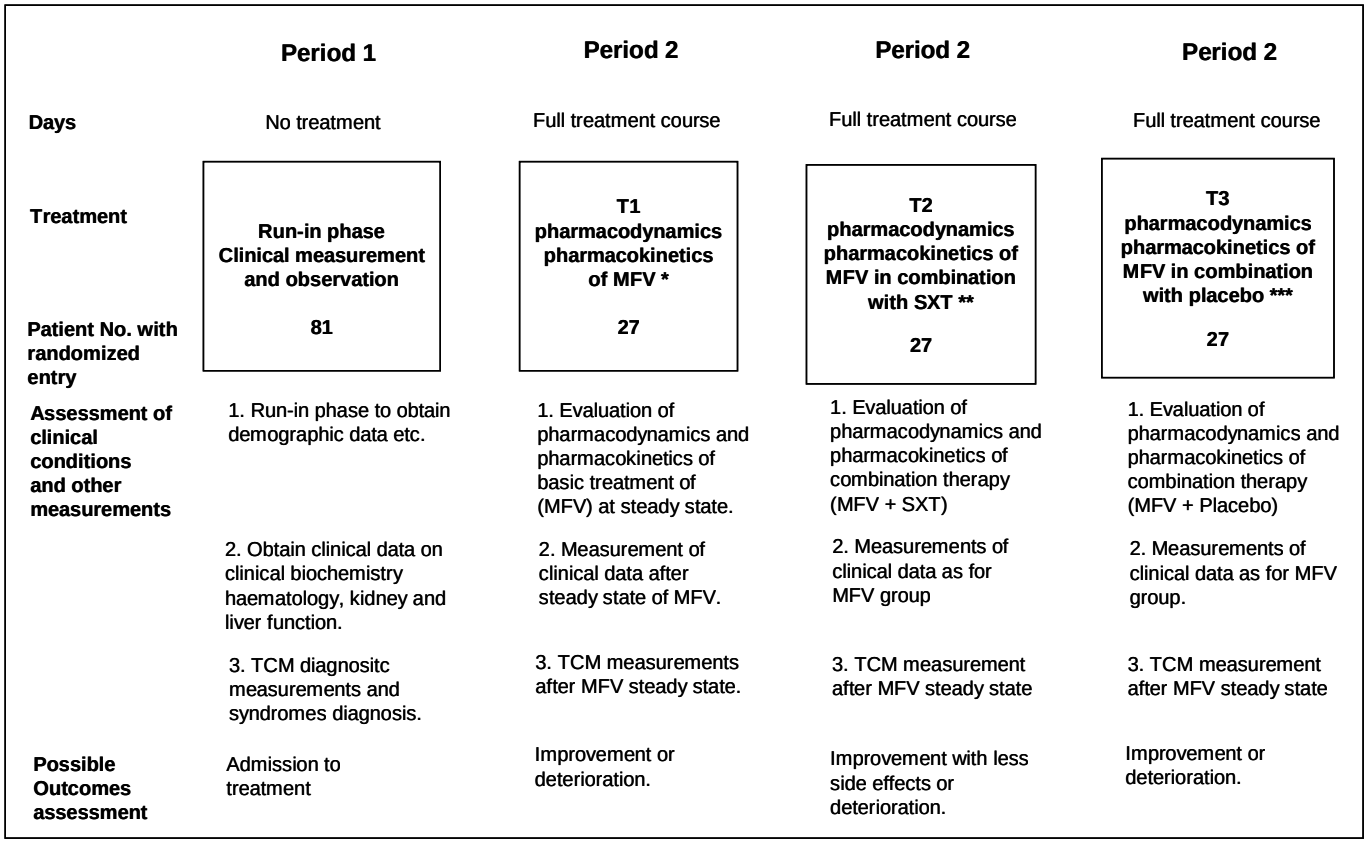
The possible outcomes may be as follows:

1. If the SXT decoction is effective to reduce adverse effects of the MFV chemotherapy such as prevention of hair loss due to PHARMED, improving overall well being due to the immuno-protective or -stimulant actions of the CMM preparation, the confidence level of the significance will be higher due to the randomization and inclusion of a placebo. The clinical biochemistry and hematology reports and kidney and liver function tests and related biomarkers would be favorable. These data are essential indications how the body reacts to the combination treatment.
2. The pharmacokinetics of the three PHARMED cytotoxic drugs could be altered due to the complexity of the unknown chemicals in the SXT and placebo preparations. This alternation could only be detected if the disposition of these PHARMED were followed during the trial.

4.2. A co-ordinated effort for reporting of Adverse Drug Reactions (ADRs) involving herbal medicines

Medical practitioners in main stream healthcare practice in developed countries or regions have expressed the concern and fear of herbal medicines and related products causing toxicity and adverse effects. Yet reported cases of toxicity often do not provide with comprehensive information such as those of the prescribed herbal materials or related products, pre-treatment clinical profiles of patients' bio-chemistry, hematology, liver and kidney functions and PHARMED that were co-administered. This can only lead to difficulty in drawing clear conclusions of the significance and relevance of the interactions described. Data as mentioned in the Section 4 of the present overview on proposed design for study of interactions will be needed for consideration. Some other reported cases of toxic reactions due to herbal medications or related products those including CMM

Figure 2. Study design for drug interaction studies in cancer patients



* MFV = Methotrexate, Fluouracil, Vinblastin; ** SXT= Sheng Xue Tang (a CHM decoction of 8 herbs) *** Placebo = a decoction of similar colour and taste but no SXT activity

have involved unqualified practitioners or the products that were adulterated with PHARMED. These can be related to poor documentation of reporting incidents of adverse reactions. Moreover rarely are reported of the beneficial effects resulting from the intentional co-administration of both CMM and PHARMED in integrative medical practice. Proper evidence-base investigations are essential for further development. Contributions from these practices are urgently needed to enlighten the benefit of complementary medicine towards healthcare world-wide.

In handling adverse reactions of PHARMED, well-established reporting schemes have been in operation in some developed regions. The author is familiar with schemes operating in the UK and Australia. The intention is to describe briefly here such that by modifying and adopting these two schemes it is possible to use the principles behind for recording and reporting adverse reactions involving CMM or other herbal medicines with PHARMED interactions. A centralized co-ordinating effort will be needed for quality information to make decision on all medications regarding restriction in use, reduction in dose, or special warnings and precautions.

4.2.1. The Yellow Card Scheme

Working with the Medicine and Healthcare products Registration Agency (MHRA) the UK Committee on Safety of Medicines has established the Yellow Card Scheme (Rawlins, 1988, 1988a) for reporting adverse reactions of medications since 1964. The system receives reports of suspected ADRs directly from doctors, dentists, coroners, pharmacists and other health professionals and indirectly through pharmaceutical companies. It is the UK Adverse Drug Reactions Reporting Scheme that these received reports are placed on a specialized computer system, Adverse Drug Reactions On-line Information Tracking (ADROIT), to facilitate rapid processing and analysis. The scheme has been critically important in monitoring drug safety for all PHARMED in normal clinical practice, increasing knowledge about known

adverse reactions, and acting as an early warning system for the identification of previously un-recognized adverse reactions. The organization and operation of the Scheme includes collection of reports of suspected adverse reactions, data processing, verification and confirmation of information, and dispatching of advice etc. The data received from reports of suspected ADRs will be analyzed and presented and dispatched via the 'Current Problems in Pharmacovigilence' which is distributed to all doctors, dentists, coroners and pharmacists periodically throughout the year.

Obviously the accuracy of initial source of information of the suspected adverse reactions is extremely important. Guidelines on reporting are given. Table 7 shows a general format of reporting suspected adverse reactions arisen due to CHM medication-OM drug interaction proposed for action by the authors (Chan & Cheung, 2000). It is also a suggestion for traditional CM practitioners and OM practitioners' Good Clinical Practice to self-regulate until a similar scheme is accepted by appropriate health organizations in regions that such a scheme is considered for monitoring. It is adopted from the UK Yellow Card Scheme reporting card issued by the Scheme operators. It is understood that the present UK Scheme also welcomes inclusion of suspected adverse reactions due to herbal medications. Table 7 listed categories of 'Adverse Reactions' considered serious for reporting as specified in the UK Yellow Card Scheme. In general, serious reactions include those that are fatal, life-threatening, disabling, incapacitating or that result in or prolong hospitalization.

The Blue Card System

Chan and Cheung (2000) also suggested, depending on convenience and circumstantial situations, to adopt the Blue Card System initiated originally by the Adverse Drug Reactions Advisory Committee (ADRAC), a subcommittee of the Australian Drug Evaluation Committee, who encourages the reporting of all Suspected Adverse Reactions to drugs or other medical substances, including herbal, traditional or alternative remedies. Regular Australian Adverse drug Reactions Bulletin is distributed to appropriate healthcare professionals for their information free of charge. A modified 'Blue Card' is proposed to deal with reporting or recording interactions between CMM products and PHARMED for practitioners' self-regulatory practice (Table 8). Other countries in developed regions may also have similar establishments who would deal with ADRs reporting. Whatever systems are available, it is possible to modify them for reporting and recording ADRs due to interactions between CMM medications and PHARMED.

5. Establishing a data base for safety issues on interactions between CMM and PHARMED

Most of the CMM used for prevention or treatment of diseases according to traditional CM practice are considered safe, even when potent/poisonous herbs are included. This is because, according to Chinese Medicine Theories, when administered as mixtures of CMM, composite formulae (Fu-Fang, in Chinese), through proper combinations of CMM may interact to enhance the therapeutic efficacy and to eliminate or minimize adverse reactions. It is considered that toxic CMM could be rendered non-toxic or less toxic through such combinations. Fu-Fang is the basic practice in Chinese Medicine prescribing. Yet there is little published scientific data in the west to substantiate such observations that have sustained through test of time. Nevertheless, poisoning cases do occur due, probably, to one of the many reasons such as: lack of understanding on how to use CMM; improperly processed items; over-dosing; use of fake or substituted CMM; contamination especially by heavy metals and/or insecticides; poor quality control during manufacturing and adulteration with pharmaceutical drugs; and interactions between CMM and co-administered pharmaceuticals. Hence it is important to identify where the toxicity comes from and what aspects of toxicity are measured.

***Table 7.** Form for reporting suspected adverse reactions due to interactions of Chinese herbal medicines and pharmaceutical medicines

information is kept as confidential records

Do not be put off reporting because some details are not known

REPORTER: HEALTH CARE PROFESSIONALS

Name _____

Professional _____

Address _____

_____

_____

Telephone _____

Speciality _____

Signature: Date:

OM PRACTITIONERS/TCM PRACTITIONERS

Name _____

Professional _____

Address _____

_____

_____

Telephone _____

Speciality _____

Has this case been discussed with the consultant / GP Yes ☐ No ☐

PATIENT'S DETAILS Sex **M** ☐ **F** ☐ Weight Kg

SURNAME _____ Hospital if relevant _____

Other names _____ Hospital Number _____ Date of birth (or age)_____

00

SUSPECTED CHINESE HERBAL MEDICINAL PRODUCTS

Give brand name of formulae or herbs	Route	Daily dose	Date started	Date stopped	Therapeutic indication
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/___/___	__/___/____	_____

ORTHODOX DRUGS TAKEN IN THE LAST 3 MONTHS INCLUDING SELF-MEDICATION

Give brand if known. Write None if no other drugs has been taken	Route	Daily dose	Date started	Date stopped	Therapeutic indication
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____

SUSPECTED REACTIONS

Is the patient hospitalised because of the reaction? Yes ☐ No ☐			**Date reaction started**	**Date reaction ended**	**Outcome** eg. fatal recovered, continuing
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____
_____	_____	_____	___/____/__	___/___/___	_____

Relevant additional information including medical history, investigations, known allergies, suspected drug interactions. For congenital abnormalities state all other drugs taken during pregnancy and the LMP. Please attach additional pages if necessary

_____

_____

_____

If you would like information about other reports associated with the suspected drug , tick here ☐

* Adopted form the Yellow Card Scheme for Reporting ADRs, UK

4.2.2.

***Table 8.** Form for reporting suspected adverse drug reaction involving interactions of Chinese herbal medicines and pharmaceutical medicine drugs

(Note: Identities of Reporter, Patient and Institution will remain **Confidential**)

Patient (Initials or Record No. Only)

Age: Height:

Sex: Weight:

Adverse Reaction Description: Date of Onset of Reaction: / /

All Chinese Herbal Medicinal Products and OM Drugs Prior to Reaction Asterisk Suspected Drug(s) (Please use trade names)	**Daily Dosage and Route**	**Date Begun**	**Date Stopped**	**Reason for Use**

Treatment (of reaction):

Outcome: Recovered ☐ Date of Recovery / /

Not Yet Recovered ☐ Unknown ☐ Fatal ☐ Date of Death / /

Sequelae: No ☐ Yes ☐ (describe)

Comments (eg. relevant history, allergies, previous exposure to this drug):

Reporting Doctor ☐ or Pharmacist ☐ Others ☐ (Please tick)

Name:

Address:

Signature_____ Date: / /

Return Forms(s) To University Department on Professional Association of Traditional Chinese Medicine

Address: Fax:

* Adopted from the Blue Card System of the ADRAC, Australia

5.1. Assessment of Intrinsic Toxicity of CMM

Intrinsic toxicity of properly processed (i.e. Quality Control-checked) potent/poisonous CMM can be assessed using various models available. Specific potent/poisonous CMM included in well-known composite formulae have survived the test of time, but such potent CMM and Fu-Fang containing them, although included in the Chinese Pharmacopoeia, can only be prescribed by qualified traditional CM practitioners. Individual CMM, which are highly potent or poisonous are seldom used singly, and when used in clinical settings where the principles of CM are not understood or not followed, their use can be highly dangerous. Experience and incidents of occurrence can be shared via networking. Existing toxicology models can be used to ascertain the toxicity of the Fu-Fang. For examples, cardiac, liver and neurological toxicity can be assessed, using cell culture and *in vivo* animal models if toxicity is suspected.

Toxicity of components of individual potent/poisonous or non toxic CMM, if needed for assessment, is far more difficult and may not be relevant to the composite use of CMM. Most of the authenticated CMM, when used properly in the form of decoction, have stood the test of time for their safety issues as Pharmacopoeia composite formulae. Nevertheless, if toxicity assessment is needed in vivo animal models can be used. But other forms of extraction in proprietary Chinese medicines (PCM) of these CMM may show toxicity that has not been tested in human use. The toxicity of these PCM should be assessed according to those animal toxicity tests used for pharmaceuticals. The opportunity of networking to exchange experience in these issues will be beneficial to acquire the present understanding and allow future drafting of guidelines for what toxicological tests are needed.

5.2. *In vitro* and *in vivo* methods to assess CMM-PHARMED interactions and clinical safety

As mentioned above, one of the major causes of toxicity of CMM may come from interactions between them and pharmaceutical medicines. Such information in the English text is not abundant; the situation of integrative practice of traditional CM with orthodox medicine has shown both beneficial and adverse effects of CMM when co-administered with pharmaceutical medicines. Data collections from practices within and outside China will be essential to identify such observations. The database will collate all published reports of experimental, theoretical data and clinical reports of toxicity and CMM-PHARMED interactions. This is important as laboratory 'predictions' do not always correlate with significant clinical adverse events, and it is important to validate experimental methods. The lack of reliable data has led to a situation where theoretical and unproven potential interactions are presented as contraindications, despite a lack of clinical reports confirming them. This practice is immensely damaging to the perception of traditional CM by the orthodox medical and pharmacy professions, and is often misplaced or misleading.

To ascertain the validity and relevance of CMM-PHARMED interactions a series of cell culture and *in vivo* models can be devised using expertise in China and other regions as appropriate, to test the effect of CMM on the inhibition or induction of a range of cytochrome P450 isozymes; interaction with P-glycoprotein and other efflux mechanisms, plasma protein binding and clinical pharmacokinetic interaction trials may be performed. Experimental results can produce an indication of inhibition or induction of various isoforms by CMMs, which can alter the metabolic properties of drugs, thus resulting in changes in the pharmacological and/or toxicological effects of other drugs administered concurrently. To establish a battery of such tests and validate their contribution to the clinical assessment of the potential problems of individual interactions will be an important contribution to healthcare when the two groups of medications are co-administered.

5.3. New methodologies and techniques for quality, safety & efficacy evaluation of CMM

The evaluation of CMM safety is complicated by multiple factors, such as the geographical origin of plant material, different processing techniques, dosage, route of administration and compatibility with other medicines. This variation in chemical constitution can make it difficult to elucidate the toxic component(s) and to explain all the pharmacological mechanisms of CMM. The advent of system biology including metabonomics, which provides a new platform for the study of CMM in the post-genomic era, and has been successfully applied in many other fields such as drug discovery, phytochemistry, and clinical research. Due to the diversity in polarity, molecular weight, and concentrations of active molecules, it is generally accepted that a single analytical technique cannot provide sufficient visualization of the metabolome, and multiple technologies are needed for a comprehensive view. NMR, chromatographic and their hyphenated techniques are the most popular analytical methods used. As with the treatment concept of CMM, the key point of metabonomics is to emphasize holistic effects, especially regarding clinical efficacy and potential toxicity. Metabonomics can identify the principle changes in the chemical components and pharmacological activities of CMM under different conditions. Combined with in vivo and molecular biology protocols, metabonomics can help to explain mechanisms and evaluate the safety and efficacy of CMM.

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