

PERSPECTIVE

Understanding Interactions Between Chinese Medicines and Pharmaceutical Drugs in Integrative Healthcare

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ABSTRACT In the 21st century, the public are more informed, mainly via the Internet, about health and medical products and have 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 and over-the-counter (OTC) medicines apart from prescribed pharmaceutical drugs (PD). Some of those non-prescribed products may have doubtful quality control and contain harmful additives or unchecked ingredients; thus their usefulness is in doubt. The increasing popularity world-wide of using Chinese medicines (CM) and related OTC functional products has raised concerns over their concomitant use with PD and the consequential adverse effects. In most cases the alleged causes of adverse effects are linked with herbal sources, although the

authorised information on the interactions between CM-PD is not plentiful in the literature. There is an urgent need for such a data base. The future professionals in health and medical care should be knowledgeable or aware of what their patients have been taking or given. In actual practice the patients may receive both treatments intentionally or unintentionally, with or without the awareness of the practitioner. In these situations a reliable database for interactions between CM-PD will be extremely useful for consultation when treatment problems appear or during emergency situations. Their combining of medications may be involved with possible outcomes of adverse reactions or beneficial effects. Such a database will be welcomed by both practitioners of herbal medicines and orthodox medicine practitioners in the emerging trend of integrative medicine. The author has been involved in various research projects of basic and clinical aspects in mainly CM among other herbal and PD. Examples will be given largely on those related to these disciplines as illustrations in this overview.

KEYWORDS Chinese medicines and pharmaceutical drugs interactions, adverse effects, beneficial co-treatment, herb-drug interaction, possible mechanisms, future directions

Introduction

Background Information

Nowadays traditional Chinese medicine (TCM), recognized as experience-based practice, has played a key role in maintaining the peoples' health in China and several Asian regions over centuries, is now becoming popular world-wide because some chronic diseases respond better to TCM treatment when conventional medications fail to give satisfactory treatment;⁽¹⁾ its contribution to healthcare however remains not entirely accepted in conventional medical circles.⁽²⁾ On the other hand, people are generally more informed about medical products and knowledgeable about matters relating to their health and in curing and preventing illnesses. They demand good quality treatment from both orthodox as well as other complementary medicine. The future professionals in medical and health care should be knowledgeable on their patients'

medications and be aware of possible treatment interactions as they may be given both treatments intentionally or unintentionally, with or without the awareness of the practitioner.

Worldwide Development of Integrative Medicine

Historical record indicates that, as reported in the review written by Dobos and Tao,⁽³⁾ the post 1911 Chinese government banned TCM and took measures to impede its further development. From 1911 to 1949, acupuncture was not included in the curriculum

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of medical degree similar to the contemporary orthodox medical degree. During that period cities in China were cut off from pharmaceutical medicines supply and had to depend on rural TCM medicines. The concept of integrating the practice of TCM into orthodox medicine (OM) in China, preceded the Western model of integrative medicine (IM) by almost 50 years,⁽³⁾ has given the opportunity to look at the advantages and disadvantages of each practice and considered the benefit from each discipline in order to encourage improvement of healthcare.

In a comprehensive review of the current situation and progress in IM in China,⁽⁴⁾ the authors point out that China is the only country that has developed a healthcare system, which has incorporated TCM into the healthcare policy for the nation while most of the Western models have not included complementary medicine into their national health plan. Evidently such integrative treatment progress has been practised in China since the 1950s.⁽⁴⁾ Within the system the two forms of medical treatment work alongside with each other at every level of the healthcare structure. In particular, patients can benefit from preventive medicine, reducing side effects from OM or TCM medications and improved quality of life in terminal cases and other chronic diseases, which experience difficulties using orthodox medical treatment alone. During the 50 years of development and progress of IM, various aspects of policy, scientific research, clinical practice and research and curriculum development of Chinese model of IM have taken place mainly in a hospital environment. Such progressing examples in the Chinese IM model indicate that to achieve these goals it will take a lot of understanding from professionals of both disciplines. No longer should practitioners from TCM 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.

Concern over CM-PD Interactions

However, the use of herbal products, including Chinese medicines (CM), in conjunction with pharmaceutical drugs (PD) still poses a problem in clinical management and has attracted considerable attention in the West.^(5,6) Patients with chronic, serious

or recurrent medical conditions, such as those with cancer and diabetes, are more likely to use herbal medicine and also more likely to be prescribed with conventional medications, therefore are at a greater risk for potential herb-drug interactions.^(7,8) As of to date very few documentations describe comprehensive guidelines for safe co-prescribing CM and PD. Incidents of reported CM-PD interactions often are single case-related episodes. A collection of these reported incidents of CM-PD interactions, published as a text-book, indicates that apart from adverse side-effects the co-administration CM-PD, case-studies on beneficial prescribing of the two groups of medications were also reported.⁽⁹⁾ Mechanism, explanation and guidelines for reporting of CM-PD interactions were also included in the text book. It was pointed out that the future professional should be knowledgeable on their patients' medications and be aware of possible OM and CM treatment interactions as they may be given both treatments intentionally or unintentionally and possibly taken both medications with or without informing the practitioner.⁽²⁾ The consequence of ignorance will lead to adverse reactions in most cases. Beneficial outcomes of intentional combined use will ascertain the advantages of proper integrative treatment.

The present overview focuses on suggestions to update this text on CM-PM interactions on reliable data collections with clinical significance, possible mechanism, current beneficial outcomes or adverse reactions as a consequence of co-administration.

Current View on Pharmaceutical Drug-drug Interactions

In OM practice, the incidence of drug-drug (DD) interactions has been the concern for practitioners treating patients on multiple drug regimens. The greater the number of drugs the patient takes the greater likelihood that adverse reactions may result. DD interactions 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 the patients' conditions. The relevance of DD interactions depends on how clinically significant is the therapeutic outcomes. Adverse interactions can be defined as a situation in

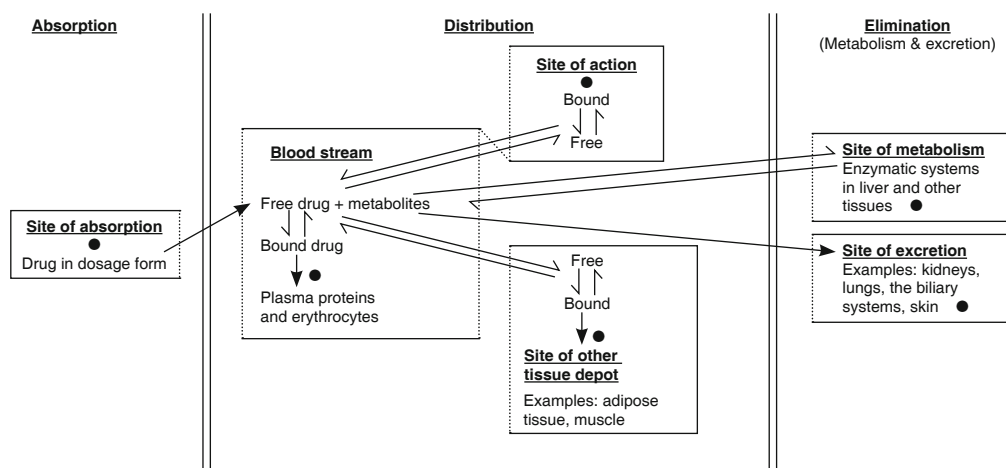


Figure 1. The Fate of A Reversely Acting Drug in the Body

Notes: ● denotes possible site of drug interactions. Broken lines indicate presence of biological membranes

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 the other interacting drug. 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, DD interactions may produce enhanced drug effect that is synergistic; the outcomes of interactions may be beneficial or harmful. DD interaction can be classified 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 Ref. 9) summarise possible sites of DD or CM-PD interactions, which involve both pharmacokinetic and pharmacodynamic characteristics of the interacting drugs at various stages after gaining entry to the body.

Some DD interactions that have been listed in the literature are neither meaningful nor helpful for clinical practice if they are not relevant, because some interactions are theoretically possible based on *in vitro* investigations or animal experimentation that may not have been studied during patient-treatment situation.

Criteria for Careful Attention of Detecting DD or CM-PD Interactions in Clinical Practice

Based on the pharmacokinetics and disposition

characteristics of the PD, it is possible to identify a potential list of PD that will produce DD interactions of significant adverse effects: PD 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 Box 1 adopted from Ref. 9 will be helpful to make a decision.

Box 1. Some Criteria Considered as Potential Risks for Occurrence of DD Interactions

- DD interactions of 2 or more drugs observed in clinical practice for confirmations
- Drugs with steep dose-response curve (a small concentration changes 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 cumulation, enzyme induction, etc.
- Drugs prescribed simultaneously by several physicians intentionally or unintentionally
- Drugs self-medicated by patients
- Drugs showing genetic polymorphism in metabolic elimination (CYP2D6, CYP2C19, etc.)

Specific attention, based on the relevant criteria listed in Table 1, can be focused during the development of new drugs (or CM products). These may be designed to measure certain biochemical markers or physiological processes or functions being affected by drug treatment with narrow therapeutic ratios. These functions or biomarkers consequential to DD or CM-PD treatment are useful measurements of adverse, beneficial or synergic effects. Table 1 gives

examples of the pharmacological classes of drugs and respective processes involved for monitoring.

To equip practitioners' ability to spot the likely CM-PD interactions, both CM and OM professionals need to acquire the background knowledge on using these two types of highly unrelated concepts of medical treatments. Some introductory information on CM principles of using Chinese material medica (CMM) and their prescriptions are described below for readers who are not familiar. Proper training and accumulating experience of both OM and CM practice in the use of two different types of medications will undoubtedly be necessary for patient care in an integrative approach.⁽⁴⁾

Possible Approaches of Integrative Diagnosis and Treatment Applying OM and CM

The integrative treatment of illnesses using TCM 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 is concerned 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 the whole body, distinction between different syndromes based on complex responses to external and internal pathogenic factors.

As an integrative approach 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 holistic balance of the body to the OM understanding of the inter-play between the body's nervous-endocrine-immune regulations using biomarkers available as monitoring parameters.⁽¹⁰⁾ Further integral steps should relate these biomarkers with patients reported outcomes to monitor the progressing conditions/ improvement of the treatment.⁽¹¹⁾ There is an urgent need of these specialty medical and health professionals for the future development of IM both in education and research directions. They are required to lead, for the assessment of reported adverse or beneficial effects of CM-PD interactions and the cost effectiveness of IM involving TCM in conventional healthcare and medical practice.

Proposed Mechanisms to Understand CM-PD Interactions

Adverse Effects of CM and PD Interactions

Clinically there is a lack of good documentation of interactions between CM-PD. When adverse reactions are reported in the literature, CM products have been referred to as the cause of the incidents as

Table 1. Pharmacological Classes of Drugs with Clinical Relevant Interactions

Pharmacological class	Functions to be monitored	Parametres monitored
Antacids	Formation of unabsorbable complexes	Plasma levels of drug
Anti-arrhythmics	Cardiac rhythm	ECG monitoring
Anti-asthmatics	Respiratory stress	Respiratory functions
Anti-coagulants	Blood clotting or haemorrhagic crisis	Prothrombin time
Anti-convulsants	Uncontrolled epilepsy or over-sedation	Check seizure frequency
Anti-diabetics	Glucose homeostasis	Blood glucose levels
Anti-hypertensives (β -blockers)	Irregular BP	Monitoring BP
Cardiac glycosides	Heart failure or over-digitalisation	Monitoring arrhythmia
Cytotoxic agents	Over-suppression of immune functions	Check immune indices
H ₂ receptor blockers	Inhibition of drug elimination	Check plasma levels
Psychotropic agents (MAOIs)	Hypertensive crisis	Check blood pressure

Notes: ECG: electrocardiograph; BP: blood pressure; MAOI: mono-amine oxidase inhibitors

most of the ingredients are often unknown, although some of the well-tried via past recorded experience CM products or composite formulae (Fufang) have not been involved in reported literature if used alone. In a recent review from the literature to compare the frequency and safety use of CMM and species used in Europe and China for TCM practice; it was observed that the main cause for concern is likely to be interaction with prescribed medication, especially in central nervous system and cardiovascular conditions where drug interactions have previously been reported most frequently and which would currently be more applicable in China than Europe.⁽¹²⁾ It is necessary to have a joint effort between professionals of OM and CM to set up research and documentation schemes in this area. Observed adverse reactions that have been reported in clinical situations can be studied and confirmed using properly designed experiments. It is feasible to set up laboratory protocol to screen commonly prescribed CMM products against those groups of OM drugs with potential adverse effects when combined with other substances.

Many *in vivo* animal models can be used to screen drug interactions between herbs and drugs. Pharmacokinetic and pharmacodynamic correlation may be achieved using these *in vivo* models. Pharmacokinetic clearance of OM drugs in presence of CMM products can be studied using *in vivo* models. The data obtained are useful qualitative guidelines for clinical studies. The following tentative categories of case studies, which illustrate adverse effects of treatment consequential to co-administration of PD and CM medications are summarised in Box 2 adopted from Ref. 9. These case studies were abstracted from medical journals published in China and have been translated into English and edited by the author and co-worker for presentation in the text.⁽⁹⁾ Due to copy-right restriction these data can not be reproduced in the present text. It is possible to design laboratory experiments to verify or substantiate the clinical significance.

Beneficial Effects of CM and PD Interactions

Experience of integrative medical practice in China has observed, over the past 50 years, through experience of practice and recorded case studies, beneficial treatment observations and outcomes with probable explanation or possible mechanisms of interactions although more experimental research and clinical evidences are needed to confirm such observations.

Box 2. Mechanism of Adverse CM-PD Interactions

- Category 1: Form insoluble complexes during absorption phase leading to therapeutic failure
- Category 2: Affect transport of drug molecules in the body by CMM leading to reduced effects
- Category 3: Affect function of PD diuretics and body electrolyte balance by CM medications
- Category 4: Destroy amylase in some CM medications by PD antibiotics
- Category 5: Destroy glycosides in some CM products by acidic PD
- Category 6: Release toxic cyanide from CM medications by some PD
- Category 7: Affect liver metabolising enzymes that eliminate PD by CM products

This is partly because the OM gold standard of randomised clinical trials (RCT) is not entirely applicable in the individualised approaches for treatment in CM practice. The tentative categories of case studies, which illustrate synergy effects of treatment consequential to co-administration of PD and CM medications are summarised in Box 3 adopted from Ref. 9. These case studies were abstracted from medical journals published in China and have been translated into English and edited by the author and co-worker for presentation in the text.⁽⁹⁾ Due to copy-right restriction these data can not be reproduced in the present text. Yet most of these examples did not show any of the 'gold standards' of RCT as required by OM practice, they are reported cases as practised of integrative medical approaches shown in China that illustrate the beneficial treatment effects when CM and PD are co-administered together.

Box 3. Mechanism of Beneficial CM-PD Interactions

- Category 1: Combining antibiotics with CM products producing added beneficial effects
- Category 2: Combating infection with antibiotics and immune-strengthening CM products
- Category 3: Augmenting cardiovascular PD treatment with CM products
- Category 4: Augmenting anti-inflammatory action of PD with CM Products
- Category 5: Reducing adverse effects due to PD chemotherapy of cancers by CM products

Future Directions in CM-PD Interactions Within the Context of Integrative Healthcare

Difficulty in Research and Development of Complementary and Alternative Medicines Including CM

In as early as 1996 Mills indicated that in regions where the healthcare system is run by practice of OM, clinical and scientific research into the efficacy of herbal medicines in general using conventional

methods has met difficulties.⁽¹³⁾ The author has been working in various regions over the past 30 years in understanding and experiencing how TCM has been developed and observed the various difficulties. The following key points summarized in Box 4 illustrates the obstacles and difficulties, to date, in pursuing good research for herbal medicines and complementary and alternative medicine (CAM) including TCM in developed regions or countries.

Box 4. Difficulty and Obstacle in Obtaining Research Funding for CM or CAM in Developed Regions

- Difficulty to obtain sufficient fund for RCT research in herbal medicine and CAM: Expensive and laborious. Research in herbal medicine or CAM receives little or no funding from academic agencies in the West. The Office of National Centre for Complementary and Alternative Medicine set up by the NIH in the USA have provided fund to fill the gap of information on the quality, efficacy and safety of CAM.⁽¹⁴⁾ EU Commission provided seed fund as information finding for Good Practice in TCM Research.⁽¹⁵⁾ Australia National Medical Research Council provided 0.5% of their total annual research funding for CAM research.⁽¹⁶⁾
- CM/herbal products are complex mixtures with a vast amount of chemicals possessing bioactivity/toxicity; Composite formulae or prescriptions with different properties from single constituents; Laboratory models for investigation of CM using OM method are not available or appropriate for assessment or shown effective in TCM practice.
- Differences in diagnostic and treatment principles in TCM, not understood in the OM circles to produce guidelines for assessment of applications for funding support in TCM research. This gap could be reduced in the near future through more international collaboration and understanding of methodology.

Positive Attitude to Document CM-PD Interactions as Key Direction for IM

In a recent review article Tsang and co-worker indicated that there have been no guidelines developed as to when and for what medical problems should CM and WM integration applied. However, these need to await the outcome of research studies demonstrating treatment benefit and studies to evaluate how integration would maximally benefit the patient.⁽¹⁷⁾ Although this may be a valid view, there needs to be a positive approach to give the patient community, advices of what they should or should not take to tackle their desperate illnesses. Cancer patients, in particular, are more prone to this situation as they often take herbal medicines and dietary supplements simultaneously with chemotherapy PD. Alsanand and co-workers carried out a systematic review of 818 published articles where they found interactions identified were mainly theoretical and not

supported by clinical data. No studies reported any adverse events associated with these combinations; most did not record the actual drug combinations taken, and the risk potential of some supplements appears to have been over-estimated. More effort should be made to investigate supplement use in this vulnerable patient group, based on sound evidence of plausible interaction, not only to avoid harm but also to provide reassurance where appropriate if the patient wishes to take a particular supplement.⁽¹⁸⁾

Some leadership is required to head positive development in the future of TCM integration into conventional healthcare to sort out observations detected in studies done Alsanand, et al.⁽¹⁶⁾ The experience in some institutes in China where IM has been practised will provide the platform and leadership with enormous database for future research. Future directions and tasks on CM-PD interactions can focus on categories of adverse and beneficial effects listed in Boxes 3 and 4 respectively in the present text. We have recently submitted for publication our finding on a systematic analysis on the interactions between Xiaoke Pills (消渴丸) and anti-diabetic drugs from a panel of TCM and OM professionals to assess incidents of CM-PD interactions (observations to be published). We can follow similar approaches to collect data from published literature and present practice experience.

The areas of importance and interest in integrative approaches can be proposed according to the high burden chronic diseases where most national health systems in developed regions experience high and escalating cost in the high burden diseases as indicated in Box 5 where both TCM and OM practices can contribute with great successes if proper collaborations can be arranged.

Box 5. Possible High Burden Diseases Can Be Benefited with IM

- Cardiovascular system: hypertensive complications, metabolic syndrome related diseases, which include cardiovascular complications after stroke attacks, diabetes related CVS complications,⁽¹⁹⁾ vascular dementia.
- Central nervous system (CNS): Alzheimer diseases, non-vascular dementia, Parkinsonism diseases or related central nervous complications induced by inflammation.
- Endocrine system: hormone related cancers (breast, cervical, prostatic).
- Immunological system: inflammatory process induced complications including rheumatoid arthritis, areas of immune-suppressant medications after surgery, centrally affected inflammation-induced CNS diseases.

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