

Academic Exploration

Discussion on Relevance and Studies of Prescription Compatibility in Chinese Medicine

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ABSTRACT With Chinese medicine (CM) gaining popularity in recent years, researchers and clinicians have put in much interest and effort into the makings and effects of it, especially after the recent announcement of World Health Organisation's incorporation of CM into mainstream medical compendium. Individual herb has complex properties, coming from its pharmacological properties and the Chinese medical principles of organ-directed, taste and dynamic orientational behaviours. The use of individual herb in CM is rare, where various herbs/ingredients are mostly found in a prescribed formula. To fully reveal the effects of CM is a great challenge. The complexity of various herbs in combined effect, the absorption and utility rate by the body, uniqueness of individual physique, sub-types of pathological behaviors and time-line progression of the healing process add on to the complication of understanding the full effect of CM. Various theories such as pathophysiology guidance, pharmacokinetic-pharmacodynamic compatibility method, and Global Systems Biology for Integrative Genomics, Proteomics and Metabolomics, which interactively provide a wider scope, more details, with the consideration of development time-line, may shed more light to revealing the full picture of the effects of compatibility prescription.

KEYWORDS Chinese medicine, integrative effects, methodologies, prescription compatibility

With thousands of years of application and experiences, Chinese medicine (CM) has been widely used in the modern society on disease prevention, treatment and health care. There are increasing interest and investments on the scientific research of CM among medical and healthcare communities worldwide. From the recognition of Nobel Laureate Tu You-you's discovery on artemisinin treating malaria in 2015,⁽¹⁾ to the most recent World Health Organization's recognition of traditional medicine in its influential global medical compendium,⁽²⁾ interest in CM has reached a new height. It is to be noted, however, that artemisinin is an extract from the plant *Artemisia apiacea*, which can at most be considered an herbal medicine (or herbal extract) but falls short of being classified as CM. By definition, a CM prescription is (usually) a combination of various herbs with different properties that are grouped together to provide treatment for a certain condition based on the basic foundation theory of CM.⁽³⁾ Compatibility of herbs is a special feature of syndrome differentiation, which is a unique methodology of CM diagnosis. The characteristic of compatibility herbs is the ability to adapt to the environment and changes.⁽⁴⁾ Herbs compatibility can reduce the side effects, enhance efficacy of drugs, and is more suitable for the treatment of complex diseases.

has been put into studying the biological properties of various herbs that are commonly used. Though exhaustive as it can possibly be, Chinese herbal medicine has not been able to reveal the full effect of its properties in the clinical application and that there may be more to find out at prescription level *in vivo*.^(5,6) Further justification of the clinical efficacy of CM prescriptions may have to come from understanding the compatibility of herbs in a prescription and the mechanism of drug absorption in human body. Therefore, the study of the compatibility of herbs within a prescription should not only focus on the drug quality and quantity changes (apparent compatibility), but instead pay more attention to the absorption of drug components, effects of the direct action of the substances in the body, and the intrinsic compatibility. Based on the overall metabolic changes due to the intrinsic compatibility of prescriptions and the study of ingredients (ingredients-*in vitro*-and-*in vivo*), this could reflect the compatibility and efficacy of CM.

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Initiated by China at the 50's last century, much effort

Li, et al⁽⁷⁾ reported that the CM prescription interactive research includes: (1) the ranking of the compositions in four groups—Monarch, Minister, Assistant, Guide (also known as "Jun, Chen, Zuo, Shi"); (2) the compatibility from the seven emotions; (3) the four properties and five flavours of the herbs; (4) the dosage and ratio of interactive ingredients, which are important factors that will affect the efficacy and nature of the prescription; and (5) the environment, which will affect the efficacy of the prescription.⁽⁸⁾

Based on pharmacodynamics (PD), the study of the compatibility of the CM prescription shows that amalgamation results in the formation of new substances change in chemical compositions and active ingredients. For example, common inorganic compounds, small molecules (such as volatile oils, alkaloids, flavonoids, saponins, etc.) and bio-macromolecules (peptides, proteins, glycopeptides, polysaccharides, etc.) are the basic ingredients of pharmacodynamic substances. Modern research can be carried out from different angles: one is the change of the composition of the drug *in vitro* after herbs compatibility; the other is that after the drug reaches the body, it undergoes biotransformation such as absorption, distribution, metabolism, excretion (ADME), and changes in the basis of pharmacodynamic substances.^(9,10) The expression of genes in the molecular level can also be used in the study of the compatibility of herbs in the prescription. For example, study on the pattern characteristics of gene expression profiles of cells, cardiomyocytes, and endothelial cells after intervention could be done, and it should focus on the effects of drugs on gene expression and regulation.⁽¹¹⁾

Efficacy and Toxicity

The fundamental study of Chinese medicinal herbs is based on their individual properties such as: Herb Temperature (hot, warm, neutral, cool, cold); the Four Qi (ascending, descending, floating, sinking); the Five Tastes (sour, bitter, sweet, acrid, and salty with extra tastes/properties of bland and astringent) and the Channel Tropism [Fei (Lungs), large intestine, Wei (Stomach), Pi (Spleen), Xinbao (pericardium), Sanjiao (Triple Engeizer), etc.). Herb-to-herb interactions constitute the basic principle of Compatibility Formulae, which include synergistic interactions such as mutual accentuation (Xiang Xu) and mutual enhancement (Xiang Shi); as well as antagonistic interactions such as mutual counteraction (Xiang Wei), suppression (Xiang Sha), antagonism (Xiang Wu), incompatibility (Xiang Fan).⁽¹²⁾

CM classic "*Shen Nong's Herbal Classic*" (Shen

Nong Ben Cao Jing)^(8,12) summarizes the Chinese herbal medicine formulae into 7 compatible relationships: "single effect, mutual reinforcement, mutual assistance, mutual restraint, mutual detoxification, mutual inhibition, and antagonism", indicating the change in drug efficacy and toxicity after the compatibility of CM. The changes from the compatibility of herbal medicine can be summarized as four aspects: enhancing efficacy, reducing toxicity, reducing efficacy, and enhancing toxicity. Wang⁽¹³⁾ used nuclear magnetic resonance in the study of the metabolites of the *Paeonia lactiflora* (Baishao) and *Toosendan Fuctus* (Chuanlianzi). The group with both *Paeonia lactiflora* and *Toosendan Fuctus* as compared to the group with only *Toosendan Fuctus* has a relatively milder change in urinal metabolites (formic acid, glucose, and lemon acid, succinic acid, 2-ketoglutaric acid, creatine/creatinine, lactic acid, glutamine, trimethylamine N-oxide). This shows that *Paeonia lactiflor* has a certain neutralizing effect against the toxicity of *Toosendan Fuctus*.

Ni, et al⁽¹⁴⁾ in the study of the pharmacokinetics (PK) of Zuojin Pill (左金丸) in rats, intragastrically administered the decoction of Zuojin Pill, berberine (*Rhizoma Coptidis*, Huanglian) and tetradium ruticarpume (*Fructus Evodiae*, Wuzhuyu) into SD rats. High performance liquid chromatography (HPLC) method was used to determine and calculate berberine and tetradium ruticarpum. It was found that after the administration of Zuojin Pill, berberine and rutaecarpine reached a higher concentration at about 0.5 h, in which tetradium ruticarpum can sustain at higher concentration to have anti-inflammatory, antibacterial functions and tetradium ruticarpum can better inhibit gastrointestinal motility to protect gastric mucosa. Zhong, et al⁽¹⁵⁾ reported the effects of Chinese materia medica compound in recent years, with the compatibility of two CMs, compatibility of traditional Chinese prescriptions, and compatibility of monomer components, and concluded that the compatibility of CM mainly achieves its effect of reducing toxicity and increasing efficiency.

Research Approach

Deng, et al⁽⁵⁾ and Zhang, et al⁽¹¹⁾ both in their reports highlighted the importance of comparing both the direct combination form based on prescription theories versus the combination form based on efficacy. The mechanism of the latter may on one hand lead to further strengthening of conventional combination theories, and on the other hand lead to development of new combinations that are relatively effect-specific and research viable. However, in the midst of seeking scientific evidence to prove efficacies of CM, it is

imperative that CM theory should not be lost in the process, otherwise any results derived from these studies may be detached from reality and found themselves useless in the field of actual clinical application.⁽¹⁷⁾

At present, metabolomics plays an important role in the discovery of biomarkers,^(17,18) early diagnosis of diseases,⁽¹⁹⁾ pathogenesis,^(20,21) and evaluation of pharmacological effects.⁽²²⁾ All these have been used in the study on malignant tumors,^(23,24) heart disease,⁽²⁵⁾ diabetes⁽²⁶⁾ and other major diseases research. Using metabolomics technology, Liu, et al⁽²⁷⁾ discovered that Huanglian Jiedu Decoction (黄连解毒汤) has a good intervention effect on two heaty syndromes. Zhao, et al⁽²⁸⁾ studied the effects of Erzhi Pill (二至丸) on endogenous metabolites in natural aging mice through urinary metabolomics analysis, and found that there are 36 changes in mouse urine metabolites, which can improve immunity from the body. It regulates nerve function, regulates endocrine, promotes metabolism, anti-oxidation, and removes free radicals. It also delays aging through multiple levels, multiple pathways and multiple targets.

Qu, et al⁽²⁹⁾ used the formulae Banxia Xiexin Decoction (半夏泻心汤) as an example and artificially synthesized 4 components (saponins baicalin, berberine, ginsenoside and glycyrrhizic acid) from the decoction to make immunized animals, clones and other immunized models to study the interaction and biological pathway of the formula components in the body. Monoclonal hybridoma cell lines were established by cell fusion, monoclonal antibodies were prepared, and corresponding immunoassay methods were established to analyze the *in vivo* processes and compatibility of the main components of Banxia Xiexin Decoction. It is also proposed that the immunoassay technique has high specificity compared with traditional gas chromatography, HPLC or liquid chromatography-mass spectrometry (HPLC-MS). Indirect antiglobulin test has high sensitivity, is convenient and fast, and includes various technical modes such as radioimmunoassay, enzyme immunoassay, fluorescent immunoassay, chemiluminescence immunoassay and solid phase immunosensor, etc.

Current Research Methods

Wang, et al⁽³⁰⁾ used principles from the pharmacometabolomics of chinmedformulae, and PK-PD binding theory on the direct effect of prescription compatibility on the overall effect in the body, to analyse the compatibility of the composition of Yinchenhao Decoction (茵陈蒿

汤). Using HPLC/MS technology, 45 compounds were identified from *in vitro* samples of Yinchenhao Decoction formula *in vivo* to reveal the pharmacological properties and compatibility of ADME/T. Xu⁽³¹⁾ suggested that many experimental studies had neglected the theoretical connotation of CM in combination with prescriptions. In order to study the compatibility mechanism of prescriptions, a research method of "targeted drug combination of disease pathophysiology guidance" was proposed. This theory uses the specific disease-syndrome-target prescription combination approach to understand the multi-targeted effect of Chinese herbal compound in the body. This theory suggests that the "functional unit" should be highlighted when studying the drug target, such as (1) cell function unit: pathway signal/metabolic pathway; (2) tissue and organ function unit: vascular smooth muscle-nerve-humoral regulation; (3) whole body function unit: the central nervous system and endocrine system of depression, the combination of the thalamus-pituitary-adrenal axis.

Wang, et al⁽³²⁾ reported the focus of research on the prescription theory in the prescription itself and its dynamic process (pharmacokinetics). It is proposed that the research method can together focus on the pharmacokinetic-pharmacodynamic compatibility of the "chemical composition of CM" and "intestinal micro-ecological balance" in the syndrome-prescription CM theory. Five steps were proposed to use the PD and PK-biomarkers parameters for analysis, that is, to explain the compatibility of CM herbs from the intrinsic requirements of the whole CM theory.

Case Study for Prescription Compatibility Studies Acquiredimmuno Deficiency Syndrome

In July 2006, the US Food and Drug Administration (FDA) approved the launch of Atripla, a new anti-AIDS drug, which is a combination of three FDA-approved drugs, Viread, Emtriva and Sustiva, for a "cocktail therapy" combination. This fully shows that the mainstream international society also recognizes the limitations of the Western single drug model, and begins to learn from the CM mode of compound drug use.⁽³³⁾ American professor Leory Hood first integrated genomics, proteomics and computation into what is known as the integrative systems biology,⁽³⁴⁾ the significance of which is to study the inter-relationship between various elements in the biological systems.⁽³⁵⁾ Based on the established metabolomics approach, Prof. Nicholson⁽³⁷⁾ proposed global systems biology for integrative genomics, proteomics and metabolomics,⁽³⁶⁾ as shown in Figures 1–3.

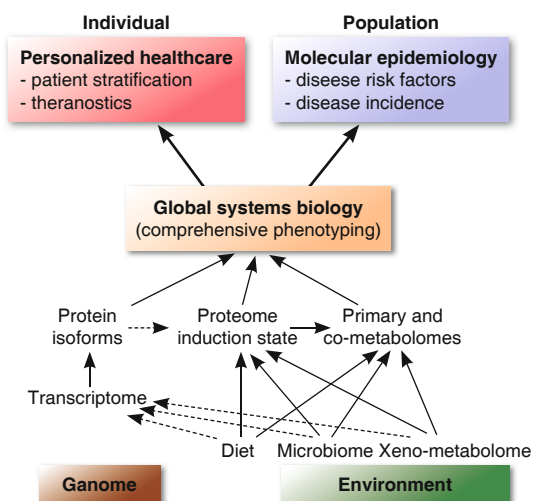


Figure 1. Relationships between Systems Biology, Personalized Healthcare and Molecular Epidemiology
Notes: dotted lines indicate indirect connections or influences

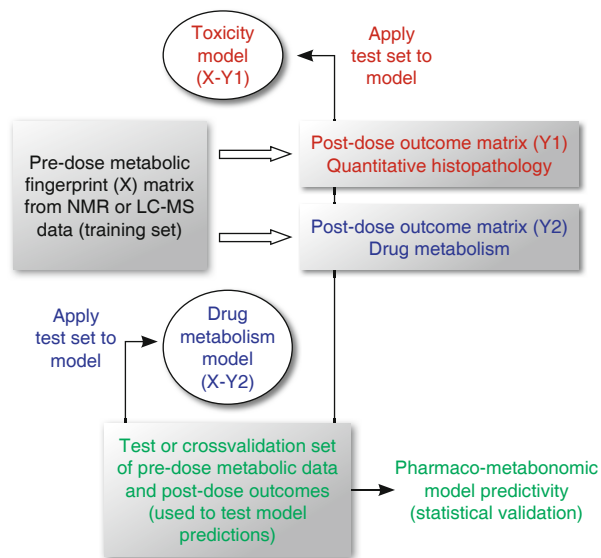


Figure 2. Pharmaco-Metabonomic Modeling Procedure

Notes: spectroscopic data on pre-dose metabolic fingerprints (X matrix) from biofluids such as urine and plasma are statistically linked to outcome [quantitative toxicity (Y1) drug metabolism (Y2) matrixes] of a drug intervention via multivariate statistics such as partial least squares methods. Typically, 20%–50% of all data is used in the training set construction. The predictive power of the models is then tested using a test set or a cross-validation set to assess model robustness. It is also possible as an additional test to avoid overfitting of data, to deliberately permute the training set matrixes to induce a false model that should have a very low predictive capability.

Li, et al⁽³⁸⁾ pointed out that the usage of a combinatory of the effective components is different from the "cocktail therapy" adopted by highly active antiretroviral therapy (HAART) in the research and methodology for treating AIDS. The latter is made up of several antiviral chemical monomers, whose main

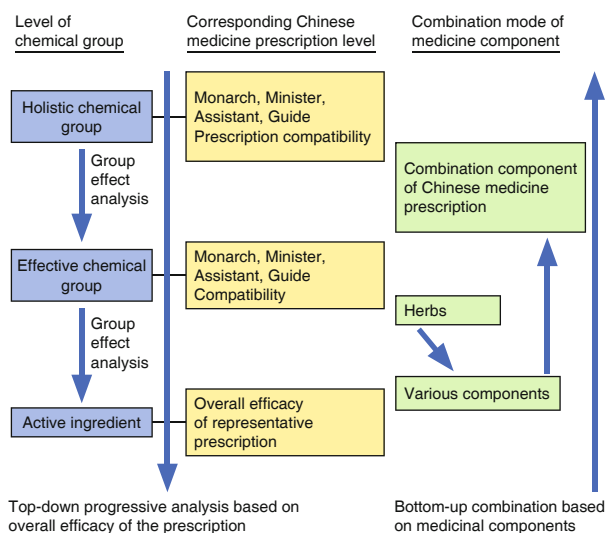


Figure 3. Comparison of Chemical Components and Herbal Composition

target is the human immunodeficiency virus, and the "combinatory of effective components group" belongs to the CM treatment system, which complies with the compatibility rules of "Jun, Chen, Zuo, Shi" and "Seven Emotions" for targeted treatment. The molecular basis and targeted treatment from this system could be multiple. Using the Kang'ai Baosheng Pills (康爱保生浓缩丸) for treatment of AIDS as an example, this formula consists of *Astragalus membranacens* (Huang qi) that can regulate immunity, and *Viola philippica* (Zihua Diding) which inhibits the virus. The compounded effect produced by the complimentary use of these two herbs in the formula is obviously higher than that of the single-flavoured medicine or from the disassembled prescription.

Cancer

In the treatment of cancer, through the usage of suitable compatible herbs can not only significantly inhibit the development of cancer, but can also reduce the dosage of the original drug while sustaining the original efficacy or even enhancing efficacy, thereby reducing the side effects of the drug and prolonging or preventing the body's resistance to the drug. At the same time, it can improve the immune function of cancer patients, and quality of life of patients. The usage of compatibility Chinese herbs can also effectively inhibit targeted toxic side effects, and provides very positive synergistic effect. Xiong, et al⁽³⁹⁾ verified that Prof. ZHOU Zhong-qi's self-prepared treatment of tumor combined with cisplatin can effectively enhance cisplatin-induced A549 cells apoptosis and attenuate the toxic effects caused by cisplatin. Ren, et al⁽⁴⁰⁾ observed the effects of myelosuppression after chemotherapy with 54 cases

of postoperative breast cancer patients using Chinese herbal compound Guipi Decoction (归脾汤) and Guilu Erxian Decoction (龟鹿二仙汤). The findings indicated leukopenia occurrence rate (LOR) for observation group (OG) at 74.1% compared to control group (CG) of 87.0%. And recovery time for leukocyte to reach normal range was shorter for OG than CG, with the application of recombinant human granulocyte colony-stimulating factor significantly lower for OG than CG ($P < 0.05$).

Diabetes

Ma, et al⁽⁴¹⁾ used the software Microsoft Office Excel 2003 to build a database for the prescriptions in the book "450 Treatment methods of Diabetes". Xiaoke Pill (消渴丸) used in the study, which is targeted for mellitus diabetes type 2 with qi-yin deficiency syndrome, was proven an effective CM prescription for the prevention and treatment of diabetes according to the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China".⁽⁴²⁾ Compared with a variety of CMs that have the effect of lowering blood sugar, the herbs used in Xiaoke Pill is at the forefront of the statistical analysis list. Comparing with the other top 20 Chinese herbs in the formula, it shows that Xiaoke Pill has properties of tonifying, removing heat, dissipating cold and astringency effect.⁽⁴³⁾

Coronary Heart disease

Liu, et al⁽⁴⁴⁾ studied the Shexiang Baoxin pills (麝香保心丸), which is used in the treatment of coronary heart disease and angina pectoris. From the chemical basis, pharmacological action and system biology, it suggests that the effect of complimentary herbs in the formulae is better than 7 individual effects of the components in the formulae.

Discussion

One intrinsic difference between Western and CM is the approach towards perception and treatment of sicknesses. Western drug is highly standardized and able to pin-point pathogens and zoom in to precise causative location to as far as genomic level. Whereas CM adopts a more broad-based and holistic approach, which in the midst of treating the ailment, also includes maintaining the patient's quality of life and improving overall wellbeing. One of the very reasons in prescription compatibility is to reduce side-effects while enhancing treatment efficacy. This nourishment and preventive maintenance effect is similar to enhancing immunity in the western science perspective.

This report has not covered prescription compatibility in the genomic aspect as studies in this area

are still quite limited. While it is imminent to investigate the genomic impact, it may be premature to do so at this juncture for prescription compatibility on proteomic studies are not completely covered and genetic science itself is yet to be fully chartered. In many a case, studies investigated one or few aspects of the full spectrum, and many of the outcome measures that may be considered important were absent. There was a shortage of clinically relevant event outcomes and especially with little or no measurement of patients' quality of life.

Due to the nature of Chinese herbal medicine, and its use in combination with various components (ranking of the compositions), knowing its main efficacy for a particular condition is attainable, but to fully understand all relationships and cause-and-effects it has on the body remains a great challenge. Bearing in mind that each herb is multi-targeted, multi-level and multi-link in effect; various herbs in amalgamation will produce a more complex second tier effect; *in-vivo* absorption will produce a third-tier effect. Notwithstanding the fact that individual difference in age and physique plays an equally important part in the reaction and efficacy of the medicine. Another characteristic in the application of CM is the dynamic adjustment of prescription during the process of treatment, allowing it to capture the finest change in the body system and target those changes accordingly. In order to avoid missing the forest for the trees, a bird's eye view and evaluation for the entire time line of treatment would be crucial.

Studies and methodologies proposed by various experts such as: (1) "targeted drug combination of disease pathophysiology guidance"; (2) the pharmacokinetic-pharmacodynamic compatibility method; (3) the Global Systems Biology for Integrative Genomics, Proteomics and Metabolomics, synergistically integrated to provide a wider scope, fuller details, and development time-line, may perhaps come close to revealing the full picture of the effects of compatibility prescription. Establishing a framework that is unanimously accepted by the research community on the study of prescription compatibility in CM (or any medicine for the matter), may help to bridge differences between Chinese and Western medicine, synergize philosophies of east and west on drug applications and shed more light to a current predominantly random and scattered research environment.

Conflict of Interests

All authors declare that they have no conflict of interests.

Author Contributions

Loh CT: writing-original draft, review. Goh XY: writing-review, editing. All authors have read and approved the final manuscript.

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