Review

A Survey of the Studies on Compatible Law of Ingredients in Chinese Herbal Prescriptions

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To prescribe a Chinese herbal prescription for the patient is the main thing done by the doctor in TCM clinic, and also an important link in TCM differential treatment. The key point in the study of TCM prescriptions is the compatibility of herbal ingredients in a prescription. To reveal the compatible law of TCM prescriptions is an important component part for TCM modernization. The following is a brief account on this kind of studies.

The Study on Literary Theory

Making a prescription with compatible ingredients is the characteristic for TCM application of herbs. The compatibility theory involves not only the compatibility of different roles of ‘monarch, minister, assistant, and guide’ played by the different ingredients of a prescription in their actions, but also the compatibility of effects of the ingredients corresponding to the ‘seven emotions’. The compatible ingredients in a prescription not only have mutual reinforcement and mutual-assistance relationships in giving cooperative or antagonistic effects, but also play the different role of monarch, minister, assistant, or guide in giving the therapeutic effects. The compatibility of mutual reinforcement and mutual-assistance can help increasing the medicinal effects; mutual restraint and mutual-detoxication can help restraining the herb’s toxic property; but mutual inhibition and antagonism may increase the herb’s toxic property. At present, among the studies on compatible law of ingredients in a prescription, those on the relationships of mutual reinforcement and mutual-assistance between herbs are mostly seen. 1

Under the theoretical guidance and based on the prescription with a single symptomatologic drug and special patent-drug formula for special disease, Jiang Yongguang, et al. 2 proposed the idea of ‘compatibility of patent formulae’, i.e. by imitating the pattern of Chinese herbal decoction prescription and taking patent formula as a compatible unit, to compatibly use more than two patent drugs in the treatment, so as to realize the differential application of herbs with patent drugs as the carrier. From the angle of systemic science, Song Yongmei studied the compound compatibility, holding that a prescription is a typical system composed of several drugs, the function of which is not simply the combination of these drugs, but their interacting result. 3 Therefore, making of a prescription with compatible drugs should lay stress on the integration of a compound formula to embody the unification of prescription with syndrome, i.e. making the treating principle based on syndrome, applying the treating method based on the principle, taking syndrome as the fundamental, and making prescription according to the syndrome.

The Study on Chemical Compositions

The chemical compositions of a prescription are very complicated. After combining with other herbs to form a prescription, the action of each of the original herbs will be changed. The essential change is in the chemical compositions, i.e. the formation of new substances, 4 which are the material bases for therapeutic effects. Qualitative and quantitative researches on the changes in chemical compositions before and after the compatible application are very
important for ascertaining the material bases of pharmacodynamics. Chen Xin, et al. 5 adopted enzyme immunoassay (EIA) to determine the concentration of glycyrrhetinic acid in Gan Cao (甘草 Radix Glycyrrhizae). They found that the concentration of glycyrrhetinic acid obviously raised when it was used compatibly with Bai Shao (白芍 Radix Paeoniae Alba). Then, they adopted high-performance liquid chromatography combined with mass spectrogram to make qualitative and quantitative analyses on changes in the blood composition of rat after receiving stomach lavage with Gan Cao Fu Zi Tang (甘草附子汤 Decoction of Radix Glycyrrhizae and Radix Aconiti Lateralis Preparata). They found two new chemical compounds, which were probably the active compositions of the prescription, and may be the essential parts for the pharmacodynamic action after compatibility. In the study of Liu Wei Di Huang Tang (六味地黄汤 Decoction of Six Drugs Including Rehmanniae), Xie Yuesheng, et al. 6 found that different compatibility of herbs could affect the decocted quantity of loganin. When Mu Da Pi (牡丹皮 Cortex Moutan) and Shan Zhu Yu (山茱萸 Fructus Corni) were decocted together, the decocted quantity of loganin would increase. When all the herbs in the prescription were decocted together, the quantity would decrease. And when Shan Zhu Yu (山茱萸 Fructus Corni), Shan Yao (山药 Rhizoma Dioscoreae) and Shu Di Huang (熟地黄 Radix Rehmanniae Preparata) were decocted together, the decocted quantity of loganin was similar to the quantity decocted with single Shan Zhu Yu (山茱萸 Fructus Corni).

Liang Qiande, et al. 7 made analysis and comparison on the sites of C1, C2, C3 of Siwu Tang (四物汤 Decoction of Four Ingredients) and on the corresponding sites of the four single herbs, and found that C1 contained ferulic acid, paeoniflorin, ligustilide, but very little carbohydrate substance; the compositions of C2 were mainly paeoniflorin, monosaccharide, and disaccharide; and the compositions of C3 were mainly monosaccharide and disaccharide. Thus, rich informations about the extracted sites of Siwu Tang (四物汤 Decoction of Four Ingredients) were obtained. Ning LiLi, et al. 8 separated the prescription of Wu Zhu Yu Tang (吴茱萸汤 Decoction of Fructus Evodiae) to form 9 different compatible prescriptions to make HPLC analysis and conduct the analgesic and antemetic pharmacological experiments. The regression analysis on the obtained chemical and pharmacological data showed that the material bases for the pharmacodynamic action of this prescription were the chemical compositions producing the chromatographic peak X4, X9, X10 and X12. It has been confirmed that X9 is rutaecarpine.

The Study on Pharmacology
This study is mainly focused on the changes in drug effect and the mechanism of the actions of the compatible ingredients in a prescription. The two kinds of methods adopted are the complete prescription study and the prescription-separating study. And the prescription-separating study includes drug-withdrawal, factorial analysis, orthogonal research, and cluster analysis. 9

1. Drug-withdrawal study: This study is to compare the drug effect of the prescription after withdrawal of each of the ingredients with that of the complete prescription and with that of each single ingredient, so as to observe the influence of each single drug on the complete prescription. For instance, when Fu Zi (附子 Radix Aconiti Lateralis Preparata), Gan Jiang (干姜 Rhizoma Zingiberis) and Gan Cao (甘草 Radix Glycyrrhizae) were left out one by one from Sini Tang (四逆汤 Decoction for Resuscitation), it was found that the Monarch herb Fu Zi (附子 Radix Aconiti Lateralis Preparata) could obviously increase the cardiac output and played the leading role in the prescription; whereas, the effects of Gan Jiang (干姜 Rhizoma Zingiberis) and Gan Cao (甘草 Radix Glycyrrhizae) were not so obvious. And the effect of anti-cardiac failure given by the complete prescription was obviously superior to that of the single herb. This reflects the scientific nature of making the TCM prescriptions. 10

2. Factorial analysis:
a) Drug-pair analysis: Drug-pair is the basic form in
compatible use of herbs, and sometimes is the simplest prescription, such as *Zuo Jin Wan* (左金丸) and *Liang Fu Wan* (良附丸). Galangal and Cyperus Pill). Although the prescription is very simple, it is never a simple use of the two herbs, but a compatible use based on the key link of pathogenesis, and according to the herb’s property and the law of compatibility. For the pain in mice induced by hot plate and body-torsion, and in rabbits with K+-induced pain and bulbar pain, *Chuan Wu* (川芎 Radix Aconiti) in a combined use with *Bai Shao* (白芍 Radix Paeoniae Alba) can give better analgesic effect than only one of them used alone, and with a prolonged analgesic time. 11,12 Ren Shen (人参 Radix Ginseng) combined with *Fu Zi* (附子 Radix Aconiti Lateralis Preparata) can make guinea pigs with acute cardiac failure induced by pentobarbital have a mean rise of 90% in MAP, and with a 11.7% rise of LVP; and can make the rat with anoxia cardiac failure have the amplitude of myocardial contraction increased by 44.4%. However, when Ren Shen (人参 Radix Ginseng) or *Fu Zi* (附子 Radix Aconiti Lateralis Preparata) was used alone, the effects were reduced.13

b) Drug-group analysis: A compound prescription is a therapeutic system with the compatible combination of the monarch, minister, assistant and guide herbs. According to their actions, the herbs can be divided into different drug groups. Han Dong, et al.14 studied the influence on the fibrinolytic system exerted by the complete prescription of *Buyang Huanwu Tang* (补阳还五汤 Decoction for Invigorating Yang and Recuperation), by the *qi*-reinforcing herb *Huang Qi* (黄芪 Radix Astragali), and by the blood-invigorating drugs *Dang Gui Wei* (当归尾 tassel of Radix Angelicae Sinensis), *Chi Shao* (赤芍 Radix Paeoniae Rubra), *Di Long* (地龙 Pereritima Aspergillum), *Chuan Xiong* (川芎 Rhizoma Chuanxiong), *Tao Ren* (桃仁 Semen Persicae), and *Hong Hua* (红花 Flos Carthami). Zhou Jianyin, et al. 15 observed the influence of *Buyang Huanwu Tang* (补阳还五汤 Decoction for Invigorating Yang and Recuperation) and the separated use of the prescription on rat’s body weight, serum lipid, and TC and TG of the aorta. They found that single herb *Huang Qi* (黄芪 Radix Astragali) and the blood-invigorating and channel-dredging drugs in the prescription all have the actions in increasing the body weight, decreasing the content of TC and TG, and raising the content of HDL-C, but the action in lowering down blood lipids is weaker than the complete prescription.

c) Drug-property analysis: The property and taste of Chinese herbs are the very important factors for determining their actions, and are also the important bases for making prescriptions and separating the prescriptions. Fang Zhaqin, et al. 16 applied *Er Xian Tang* (二仙汤 Decoction of Two Elixirs) and its two separated prescriptions, one in warm nature containing Xian Mao (仙茅 Rhizoma Curculiginis), *Yin Yang Huo* (淫羊藿 Herba Epimedii), Ba Ji Tian (巴戟天 Radix Morindae Officinalis) and *Dang Gui* (当归 Radix Angelicae Sinensis), and the other one in cold nature containing Zhi Mu (知母 Rhizoma Anemarrhenae) and *Huang Bai* (黄柏 Cortex Phellodendri), to test their regulatory actions on rat’s hypophysis GnRH and GTH, and serum GTH and SH (T, E2). The results showed that *Er Xian Tang* (二仙汤 Decoction of Two Elixirs) and its two separated prescriptions can in varying degrees increase the contents of GnRH and GTH of the hypophysis, decrease the content of serum GTH, raise the contents of serum E2 in female rats and serum T in male rats. However, the complete prescription showed the strongest action. Dai Erqing, et al. 17 found that the pungent group of the herbs in *Xuanfu Daizhe Tang* (旋复代赭汤 Decoction of Inula and Hematitum) tend to inhibit the muscular contraction of the esophagus with an obvious decrease in frequency of the contraction; the sweet-tonifying group, and the adverse-*qi*-lowering and sweet-tonifying group of the herbs obviously decrease the amplitude of contraction; the pungent and adverse-*qi*-lowering group, the pungent and sweet-tonifying group and the complete prescription group of the herbs obviously accelerate the frequency of contraction; and the adverse-*qi*-lowering group, the pungent and adverse-*qi*-lowering group, and the complete prescription group of the herbs obviously increase the amplitude of contraction. This indicates
that these drug groups may show either cooperative action or inhibiting action, and only the pungent and adverse-qi-lowering group, and the complete prescription group can obviously increase both the amplitude and the frequency of muscular contraction of the esophagus.

3. Orthogonal study: A TCM prescription is composed of various herbs in different doses, therefore, it has multi-factors and multi-levels of properties. The various herbs can be properly arranged based on the 'even comparable' character of the orthogonal list. The overall information can be obtained by means of analysis on the results to find out the influence of each factor on the various indexes, the primary or secondary role they play, and the interrelationship between them, so as to determine the best combination of each level of the various factors.\(^{18}\) By taking the rising rate of heart rate as the index and according to the orthogonal experimental list L\(_9\) (3\(^4\)), Meng Jie, et al.\(^{19}\) compared the actions of 3 dose-level prescriptions of Shen Xian Sheng Mai Yin (参仙升脉饮) in mice with slow arrhythmia, and found that compound prescription could raise the heart rate of the model mice, in which Yin Yang Huo (淫羊霍 Herba Epimedii) had the biggest range and was the main factor that influenced the drug effect, therefore called the monarch herb in the prescription. Besides, they found the best combination was A\(_1\) B\(_2\) C\(_1\) D\(_1\), namely Ren Shen (人参 Radix Ginseng)10g, Yin Yang Huo (淫羊霍 Herba Epimedii)20g, Dan Shen (丹参 Radix Salviae Miltiorrhizae)25g, and Ma Huang (麻黄 Herba Ephedrae)5g.

4. Even design: The even design method is an experimental method with combination of the number theory and multiple statistics, making 'even distribution' of each experimental point in the experimental scope, thus greatly decreasing the number of times of the experiment and saving the working hours as compared with the orthogonal design. And the experimental results can undergo multiple statistics and regressive analysis by the computer, hence a good means for detecting and bettering the experimental conditions, and seeking the best compatibility. At present, it is used as a means of screening in the studies on compatible law of ingredients in Chinese herbal prescriptions, beneficial to learning of the connotation of a prescription.

5. Cluster study: This study is to make analysis on the compatibility of herbal ingredients in classical prescriptions. The herbs are usually classified according to their nature, taste and channel tropism by means of fuzzy mathematics, so as to explore the law of making the prescriptions.\(^{20}\) According to the requirements for pre-processing of the primary data, Jiang Yongguang, et al.\(^{21}\) dealt with more than one thousand spleen-stomach prescriptions in their standardization, structuralization and digitization. By applying cluster analysis, correspondence analysis, and frequent collection in line way or non-line way, they made multi-level and multi-angle quantitative analyses on the fuzzy non-quantitative data of the core herbs in the spleen-stomach prescriptions, on the prescription structure, and on the corresponding connection of the drug-pair and drug-group with 'prescription-herb-syndrome'. They have discovered some special phenomena and patterns of the compatibility and established corresponding technical rules and processing procedures.

6. The basic-line, geometric-ratio and add-subtract design: To select the best ratio of the ingredients in a herbal prescription, the orthogonal design and even design may have varying degrees of shortcomings for having more times of the experiment, and lack of reliability for the optimized prescription. The basic-line, geometric-ratio and add-subtract design can just do the make-ups. In a comparison test of drug-effect with different ratio of Dan Shen (丹参 Radix Salviae Miltiorrhizae) and San Qi (三七 Radix Notoginseng), Shang Hongcai, et al.\(^{22,23}\) took the pharmacopoeial ratio of the compound Dan Shen (丹参 Radix Salviae Miltiorrhizae) and San Qi (三七 Radix Notoginseng) as the basic line, and lined evenly on both sides with several experimental points according to a certain add-subtract ratio to gradually reach the maximum of the two herbs. Through dynamic observation with multiple statistical analyses on various effect-indexes,
they have got the best ratio of the herbs in the prescription.

Summary
The law of compatibility of ingredients in Chinese herbal prescriptions is the essence of TCM theory, and it is also a major problem that needs to be solved in the TCM modernization. Generally, the studies should be given on the effective site, the chemical compositions of a single herb, the integral drug effect, tissues and organs, serum pharmacology, and on the levels of cells and molecules, so as to expound the biological effects, material bases, and the mechanism for the actions of the prescription. And the studies should follow the principles of ‘combination of the disease with syndrome, prescription-syndrome correspondence, and unification of the treating principle with prescription. Attention should be paid to the qualitative judgment and quantitative calculation, the compatibility of potion-pill and the compatibility of composition, the combination of micro and macro analysis, and the combination of theories of reduction and entirety. And the clinical indications should be clarified on the basis of explanation of the mechanism and the effective substances of the prescription. This is the appropriate thinking for modern researches on the law of compatibility of ingredients in Chinese herbal prescriptions, and it is very important for carrying on and developing the TCM theory of compatibility, guiding the clinical treatment, and for screening out new effective drugs.

References