

Behavior in Chinese Medicine and Prescription Compatibility: A Concise Overview

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Abstract: In recent years, Chinese medicine (CM) has been more popular, which has piqued the interest of both researchers and clinicians in its origins and effects. This is particularly true in light of the news that the World Health Organization has included CM in its mainstream medical compendium and the encouraging results that came from using CM during the most recent pandemic. Chinese medicine is based on the concepts of organ-directedness, taste, and dynamic orientational behaviors, and each plant has its own unique set of pharmacological effects. It is unusual for a CM prescription to include a single herb. The majority of prescription formulas include at least two components. The impacts of CM need to be clearly revealed. Complicating matters further, one must consider the compound reactions of different herbs, the body's absorption and utilization rates, the individuality of the body, the subtypes of abnormal behaviors, and the time-line advancement of the healing process in order to comprehend the whole impact of CM. When taking the development timeline into account, theories like Global Systems Biology for Integrative Genomics, Proteomics, and Metabolomics; Pathophysiology Guidance; and the Pharmacokinetic-Pharmacodynamic Compatibility Method all work together to give a fuller picture of the effects of compatibility prescription.

Background of Compatibility of Herbs in a Formular

Traditional Chinese medicine (TCM) has a long history of success in preventing, treating, and managing illness, and its practices are being integrated into contemporary healthcare systems. The medical and healthcare communities throughout the globe are showing a growing interest in and funding for the scientific study of Chinese medicine (CM).

Interest in traditional Chinese medicine (TCM) has skyrocketed for a number of reasons, including the 2015 Nobel Prize in medicine for Tu Youyou's discovery of artemisinin as a treatment for malaria and the most recent acknowledgment of traditional medicine in the World Health Organization's influential global medical compendium. Be advised

that artemisinin does not meet the criteria for CM; rather, it is a herbal medication (or herbal extract) derived from the plant *Artemisia apiacea*. Following the guidelines laid forth in the Basic Foundation Theory of Traditional Chinese Medicine (TCM), a traditional Chinese medicine (TCM) prescription would often include a synergistic blend of herbs with complementary medicinal effects. A distinctive aspect of syndrome differentiation, a technique of TCM diagnosis, is the use of herbs that are compatible with the patient's condition. The capacity to adjust to new circumstances is a hallmark of compatibility herbs. When it comes to treating complicated conditions, herb compatibility is preferable since it lessens the likelihood of adverse effects while increasing the effectiveness of medications.

Research into the medicinal and physiological effects of common herbs began in China in the 1950s and has continued to this day. It is possible that more has to be discovered at the prescription level *in vivo*^{5,6} before the entire impact of Chinese herbal medicine's qualities can be shown in clinical application. Understanding the human body's medication absorption process and the compatibility of herbs in a prescription may be necessary for further clinical substantiation of TCM prescriptions' effectiveness.

The absorption of drug components, effects of the direct action of the substances in the body, and intrinsic compatibility should thus take precedence over changes in drug quality and quantity (apparent compatibility) when studying the compatibility of herbs within a prescription. This may represent the compatibility and effectiveness of conventional CM based on the total metabolic alterations caused by the inherent compatibility of prescriptions and the investigation of components (institutions-*in vitro*-and-*in vivo*).

Here are some key points from the TCM prescription interactive research, according to Li⁷: (1) the composition ranking in four groups (Jun, Chen, Zuo, Shi); (2) compatibility based on seven emotions; (3) herb properties and flavors; (4) dosage and ratio of interactive ingredients, which impact the prescription's efficacy and nature; and (5) environmental factors, which impact the prescription's efficacy. ⁸. A pharmacodynamic analysis of the TCM prescription's compatibility reveals that amalgamation creates novel compounds with altered chemical compositions and active components. The building blocks of pharmacodynamic substances include, for instance, inorganic chemicals, small molecules (such as volatile oils, alkaloids, flavonoids, saponins, etc.), and bio-macromolecules (such as peptides, proteins, glycopeptides, polysaccharides, etc.). One way that modern research can be approached is by looking at how the drug's composition changes *in vitro* after herbs are considered compatible. Another way is by considering the biotransformation that occurs after the drug reaches the body, including changes in the basis of pharmacodynamic substances, absorption, distribution, metabolism, and excretion (ADME)^{9,10}. Herbal prescription compatibility studies may also make use of molecular gene expression data. As an example, research on the post-intervention pattern features of cell, cardiomyocyte, and endothelial cell gene expression patterns

is possible, and it need to center on how medications influence the regulation and expression of genes.

Efficacy and Toxicity

Herb Temperature, the Four Qi, the Five Tastes, the Channel Tropism, and other individual properties form the basis of traditional Chinese herb study. These properties include heat, neutrality, coolness, and saltiness, as well as the following: sourness, bitterness, sweetness, acidity, and saltiness, with the additional qualities of blandness and astringency. The foundation of compatibility formulae is the interaction between herbs. This can take the form of synergistic interactions like Xiang Xu and Xiang Shi, or antagonistic interactions like Xiang Wu, Incompatibility, Suppression, and Mutual Counteraction. ¹². According to the Traditional Chinese Medicine (TCM) book "Shen Nong's Herbal Classic" (Shen Nong Ben Cao Jing)^{12,13}, the Chinese herbal medicine formulas are categorized into seven compatible relationships: "Single effect, Mutual Reinforcement, Mutual Assistance, Mutual Restraint, Mutual Detoxification, Mutual Inhibition, Antagonism," which represents the transformation of drug effectiveness and toxicity following TCM compatibility. The four main modifications that have resulted from herbal medicine's compatibility are as follows: increased effectiveness, decreased toxicity, decreased efficacy, and increased toxicity. The metabolites of Paeonia lactiflora (Baishao) and Toosendan Fuctus (Chuanlianzi) were studied by Wang¹⁴ using Nuclear Magnetic Resonance (NMR). Comparing the groups that have both Toosendan Fuctus and Paeonia lactiflora shows that the changes in urinal metabolites (such as succinic acid, formic acid, glucose, creatine/creatinine, lactic acid, glutamine, trimethylamine N-oxide, and 2-ketoglutaric acid) are not as pronounced in the latter group. The results demonstrate that Paeonia lactiflor mitigates the harmful effects of Toosendan Fuctus.

As part of their investigation of Zuojin Pill's pharmacokinetics in rats, Ni et al.¹⁵ intragastrically gave SD rats a decoction of the herb together with berberine (Huanglian) and tetradium ruticarpum (Wuzhuyu). The amounts of berberine and rutaecarpine were determined and calculated using the high performance liquid chromatography (HPLC) technique. An increase in berberine and ruticarpum concentrations occurred approximately half an hour after Zuojin Pill administration; at this point, ruticarpum was able to better inhibit gastrointestinal motility, which protected the gastric mucosa, and maintain its anti-inflammatory and antibacterial effects.

Zhong¹⁶ and other research reports on the effects of Chinese materia medica (CMM) compound in recent years, with the compatibility of two TCMs, compatibility

of traditional Chinese prescriptions, and compatibility of monomer components, concluded that the compatibility of CM mainly achieve its effect of reducing toxicity and increasing efficiency.

Research Approach

Reports by Deng⁵ and Zhang¹¹ stressed the need to compare the direct combination form grounded in prescription theories with the combination form grounded in effectiveness. On the one hand, the latter's mechanism may support existing theories of conventional combinations; on the other, it might inspire the creation of novel combinations with more targeted effects and more study potential. But while we're looking for scientific proof of Chinese medicine's efficacies, we mustn't lose sight of Chinese medicine theory; otherwise, the results of these studies could be theoretical and not applicable to real-world clinical practice. Discovering biomarkers^{18,19}, early illness diagnosis²⁰, pathogenesis^{21,22}, and pharmaceutical impact evaluation²³ are all areas where metabolomics is now making a big splash. Studies on cancer, cardiovascular disease, diabetes, and other serious illnesses have made use of all of these. Huanglian Jiedu Decoction was shown to have a favorable intervention effect in two heaty syndromes by Liu et al.²⁸ using metabolomics technology. Through urinary metabolomics research, Zhao et al.²⁹ examined the effects of the Erzhi Pill on endogenous metabolites in naturally aging mice. They discovered 36 alterations in these metabolites, which may enhance the body's immunity. It aids in metabolism, controls endocrine function, eliminates free radicals, and controls nerve activity. Additionally, it slows down the aging process by acting on several levels, routes, and targets. For their study, Qu et al. (30) utilized the "Banxia Xiexin Decoction" formula as an example. They synthesized four components—saponins baicalin, berberine, ginsenoside, and glycyrrhizic acid—from the decoction and used them to create immunized animals, clones, and models to investigate the biological pathway and interaction of the formula's components. To examine the *in vivo* mechanisms and compatibility of the primary ingredients in "Banxia Xiexin Decoction," we first created monoclonal hybridoma cell lines by cell fusion, then produced monoclonal antibodies, and finally developed appropriate immunoassay procedures. The immunoassay technique (IAT) is said to be more specific than conventional methods like gas chromatography (GC), high-performance liquid chromatography (HPLC), or liquid chromatography-mass spectrometry (HPLC-MS). IAT incorporates a number of technical modalities, including radioimmunoassay (RIA), enzyme immunoassay (EIA), and fluorescence immunoassay, and it is quick, easy, and very sensitive.

(FIA), solid phase immunosensor, chemiluminescence immunoassay, etc.

Current Research Methods

Wang, et al³¹ used principles from the pharmaco

metabolomics 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". Using UPLC/MS technology, 45 compounds were identified from *in vitro* samples of "Yinchenhao Decoction" concoctions *in vivo* to reveal the pharmacological properties and compatibility of ADME/T.

Xu³² suggested that many experimental studies had neglected the theoretical connotation of TCM 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 of depression: Central nervous system and endocrine system, the combination of the thalamus-pituitary-adrenal (HPA) axis.

Wang, et al³³ reports 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 TCM theory. Five steps were proposed to use the pharmacodynamics(PD) and pharmacokinetics(PK) biomarkers parameters for analysis, that is, to explain the compatibility of CM herbs from the intrinsic requirements of the whole TCM theory.

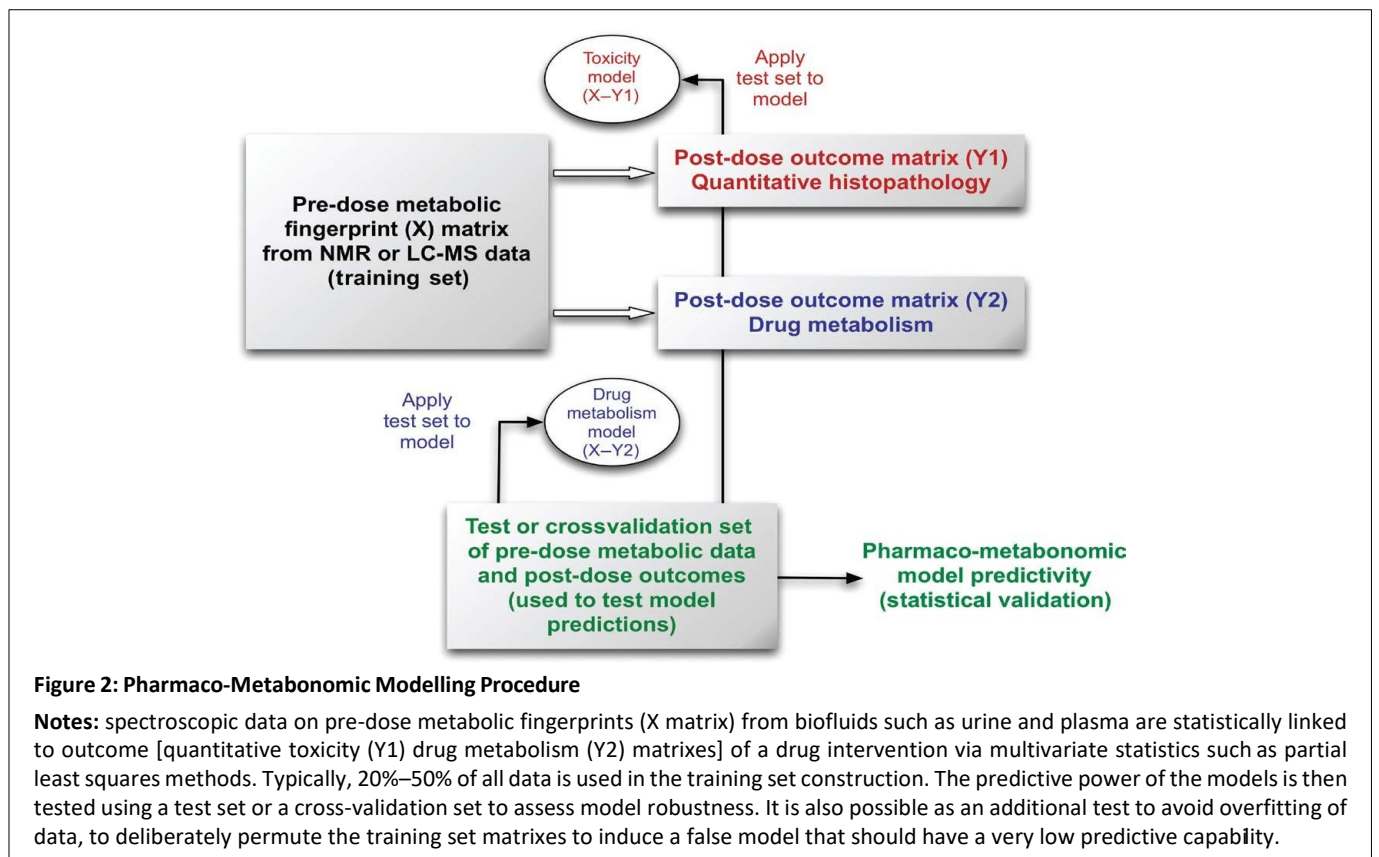
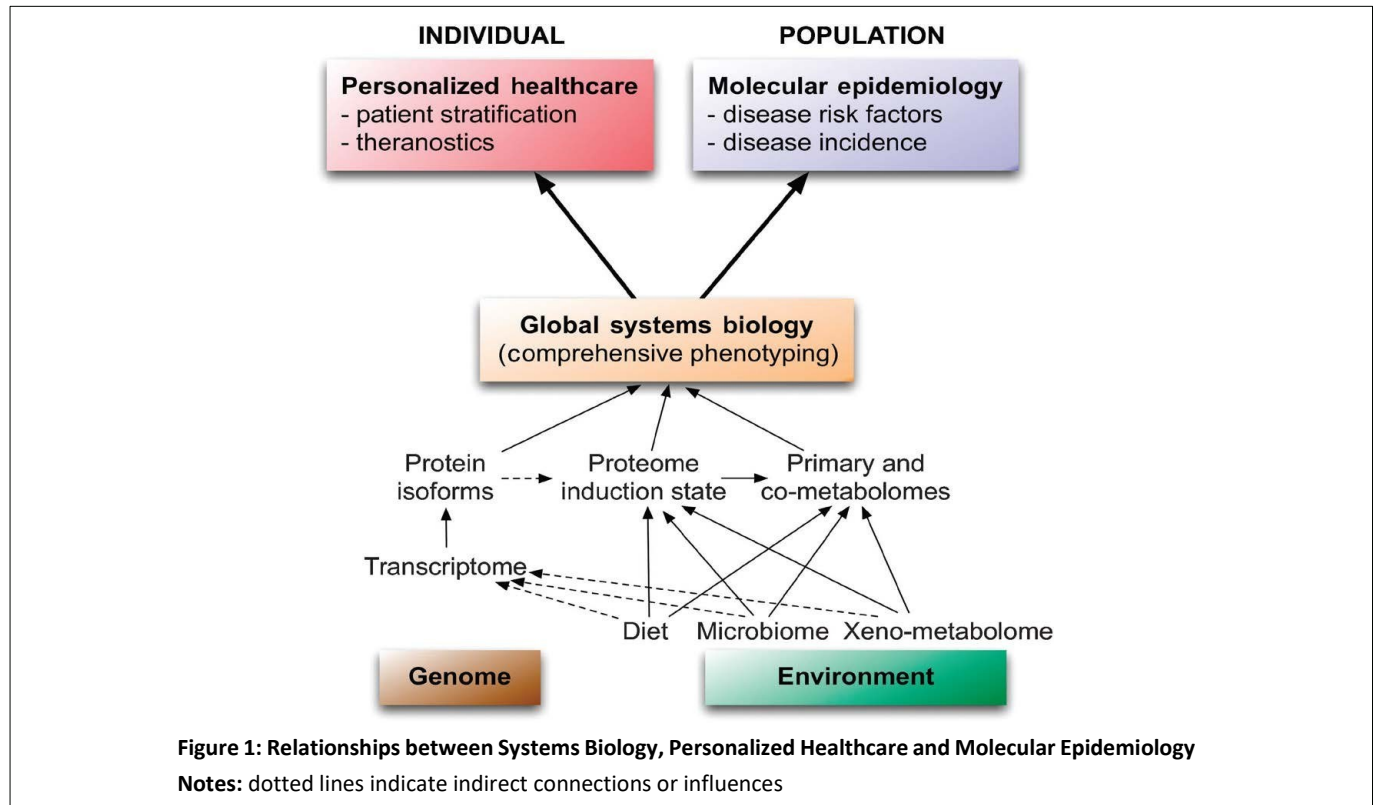
Prescription Compatibility in Molecular, Genomic and Systemic Studies for Various Illnesses

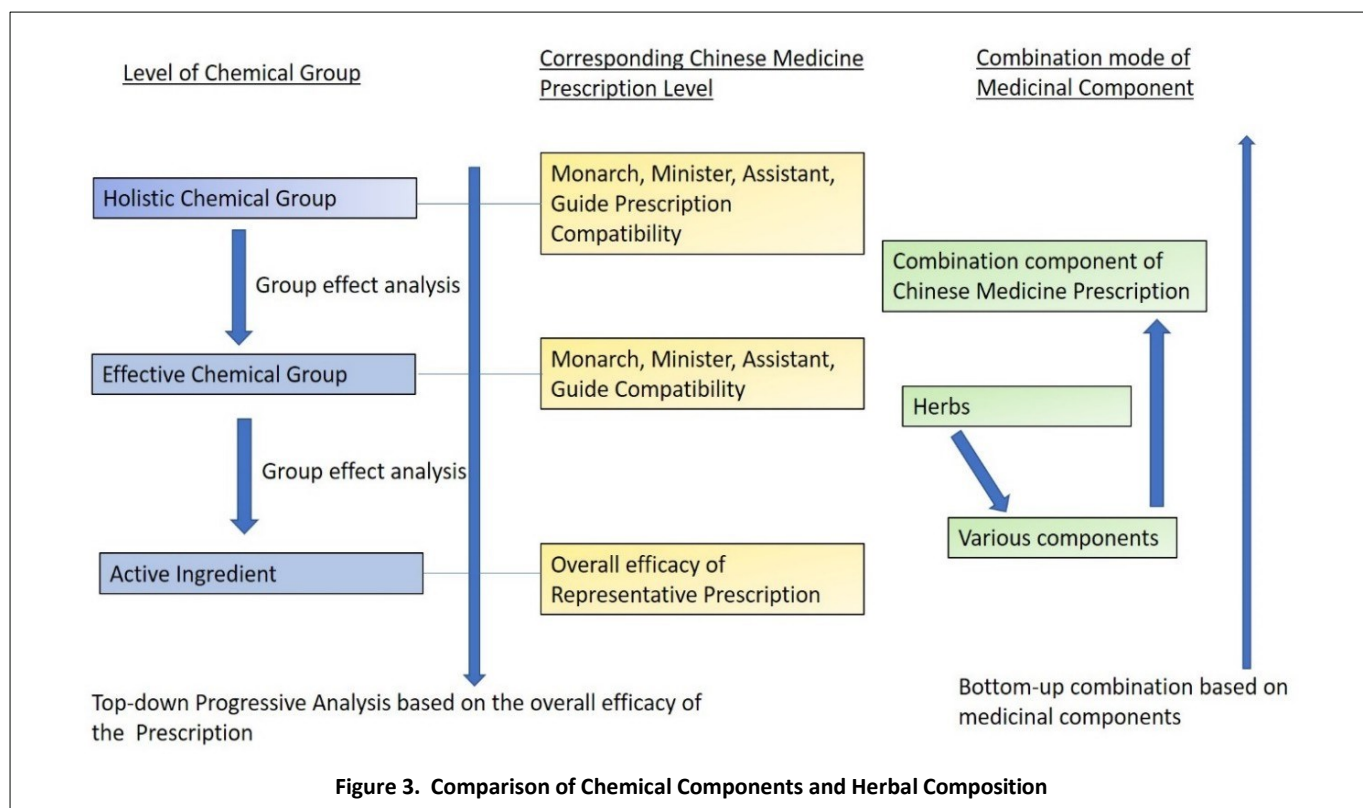
AIDS

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 use³⁴. American professor Leory Hood first integrated genomics, proteomics and computation into what is known

as the Integrative Systems Biology³⁵, the significance of which is to study the inter-relationship between various elements in the biological systems³⁶. Based on the

established metabolomics approach, Professor Nicholson proposed Global Systems Biology for Integrative Genomics, Proteomics and Metabolomics³⁷. Attachment: Figures 1-3³⁸.





Li, et al³⁹ 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 target is the human immunodeficiency virus (HIV), 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 “Kangai Baosheng Pills” for treatment of AIDS as an example, this concoction consists of *Astragalus* (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 2 herbs in the concoction is obviously higher than that of the single-flavoured medicine or from the disassembled prescription.

Cancer

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. Progressive development of anti-cancer drugs such as kinase inhibitors Sorafenib and Lenvatinib, or monoclonal antibody Ramucirumab, tend to exhibit low response and high toxicity.

In the competing endogenous RNA (ceRNA) regulation

mechanism, MicroRNA (miRNA) response element (MRE) is the binding site of mRNA and miRNA,

serving as a natural molecular sponge for miRNA, miRNA in turn inhibits its target by binding with MRE, causing translational inhibition or mRNA degradation. During such regulation process, each miRNA can regulate multiple RNA targets. Large numbers of miRNA binding sites exist in different types of RNA transcripts, indicating that multiple RNA transcripts containing miRNA binding sites can be mutually regulated via shared competition. This further illustrate that the synergistic effect of miRNA and RNA transcripts is the main source of ceRNA regulation⁴⁰.

LI Lu⁴¹ explore the anti-tumor mechanism of traditional Chinese medicine based on ceRNA regulation. In the occurrence and development of HCC, the mechanism of competitive endogenous RNA (ceRNA) plays an important role, in which miRNA is the core of its regulatory functions. Li reported that under the action of miRNA response element (MRE), mRNA, pseudogene transcripts, Long non-coding RNAs (lncRNA), Circular RNA (circRNA) and others competitively combine with miRNA to form a ceRNA regulatory network. Although researches on this mechanism at present it is still at the exploratory stage, it may well be an important anti-tumor mechanism for the diagnosis, treatment and research of tumor in traditional Chinese medicine.

Uterine Fibroids

Zheng⁴² explored the molecular mechanism of

concoction formula Modified Guizhi Fuling Wan in 72 specific pathogen free (SPF grade) SD rats with uterine fibroids. The experiment uses HE staining to observe the morphological changes at the uterus, miRNA gene chip to detect the expression profile of uterine miRNA gene; bioinformatics methods screening of miRNA for Differential expressions. Gene function enrichment was then used to predict the possible signaling pathways in rats with uterine fibroids under the influence of Guizhi Fuling Wan.

Gene function enrichment analysis indicated that four signaling pathways were closely related to uterine fibroids. They were MAPK signaling pathway, Wnt

signaling pathway, mTOR signaling pathway and VEGF signaling pathway. The result indicated Chinese medicine Modified Guizhi Fuling Wan affected the expression profile of miRNA in rat model of uterine fibroids induced by estrogen and progesterone, suggesting its involvement in a variety of biological processes such as signal transduction and gene regulation in the treatment of uterine fibroids.

Coronary heart disease

Factors in the environment and several genes contribute to the complicated nature of coronary heart disease. One of the differential syndromes in TCM is blood stasis syndrome. Because of its prominence in cardiovascular research, epigenetics provides a framework for understanding how genes and their environments interact. Abnormal DNA methylation may have a role in the onset and progression of coronary heart disease, even though DNA alterations can be undone. According to the study conducted by Li et al.⁴³, the development of atherosclerosis may be accelerated by an increase or high expression of MMP-9. The study conducted by Ghaznavi et al.⁴⁴ revealed that the frequency of ATP-binding cassette transporter A1 (ABCA1) gene methylation was much greater in the CHD patient group compared to the control group. This finding implies that ABCA1 gene methylation plays a substantial role in the development of coronary artery disease. Through the regulation of both aberrant hypermethylation and hypomethylation genes, Zhou et al.⁴⁵ shown that the Chinese medicine formula Zhizi Chuanxiong Capsules may cure atherosclerosis. The inflammatory pathway, vascular endothelial growth factor signal transduction route, MAPK signal transduction pathway, and protein kinase C activation are all impacted by the changed methylation genes.

Discussion

The view of illness and its treatment is fundamentally different in Western medicine and traditional Chinese medicine. Western pharmaceuticals are able to pinpoint

microbes and root causes down to the genetic level with

pinpoint accuracy. Whereas CM takes a more all-encompassing and comprehensive approach, addressing the patient's condition while simultaneously focusing on their quality of life and general wellness. Reducing adverse effects while increasing therapeutic effectiveness is one of the main reasons for prescription compatibility. This nourishing and preventative maintenance impact is analogous, from a western scientific point of view, to boosting immunity. Prescription compatibility from a genetic perspective has not been addressed in this study because of the paucity of research in this area. The genomic effect has to be investigated soon, but it could be too soon given the gaps in our understanding of prescription compatibility in proteomic research and the state of genetic knowledge. Study after study only looked at a small subset of the broad spectrum, and crucial outcome metrics were often missing. Few clinically meaningful event outcomes were available, and measuring patients' quality of life was severely lacking.

Conclusion

It is possible to determine the primary effectiveness of Chinese herbal medicine for a given condition by studying its compositions and their interrelationships, but it is far more difficult to comprehend the whole scope of its effects on the body. The effects of several herbs combined create a more nuanced second-tier impact, while the effects of herbs absorbed into the body create a third-tier effect, all while keeping in mind that each herb has many targets, levels, and links. Regardless of the fact that an individual's response and the medicine's effectiveness are both affected by their age and body type. An additional feature of CM is its ability to adapt prescription dynamically as therapy progresses, which enables it to detect and target even the smallest changes in the body's systems. Having a high-level overview and assessment of the whole treatment timetable is vital to make sure that nothing is overlooked. Proposed studies and methodologies by different experts, such as: (1) "targeted drug combination of disease pathophysiology guidance"; (2) the pharmacokinetic-pharmacodynamic compatibility method; and (3) the Global Systems Biology for Integrative Genomics, Proteomics, and Metabolomics, which work together to offer a broader perspective, more comprehensive details, and a development timeline, could potentially shed light on the complete picture of compatibility prescription's effects.

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.

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