FEATURE ARTICLE

What Has Been Overlooked on Study of Chinese Materia Medica in the West?

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ABSTRACT Chinese materia medica (CMM), including Chinese herbal, animal, and mineral medicine, has been widely researched in the past century for their biological and pharmacological activities. However, their mechanism and clinical efficacy studies did not always give expected results. For example, the most commonly used Chinese herb for menstrual disorders, *Radix Angelicae sinensis*, showed neither estrogenic nor progesteronic activity in laboratory and clinical studies. Its efficacy should not be denied simply based on such results, because it is mostly used together with other herbs in formulae. Moreover, its regulation on menstruation may take effect through other mechanisms, such as regulation of blood circulation. The key difference of Chinese medicine (CM) from conventional medicine is its unique holistic view on human body and diseases. CMM is mostly applied in clinic in the form of formulae. Study on individual CMM, simply using methods for development of conventional drugs, is unable to thoroughly reveal the power of CMM formulae. The reason may partly result from improper design due to the lack understanding about application principle of CMMs in CM, and/or to current lack of knowledge about the causes of some symptoms and diseases. This paper will introduce the importance of qi and blood in CM etiology and pathology, Zheng differentiation, formulation of CMMs, and explain why one formula can treat different diseases and one disease can be treated with different formulae. Examples in the paper will demonstrate that proper studies on Zheng and its corresponding clinically proven formulae could help scientists find new direction to explain and treat symptoms and diseases that so far modern medicine has been unable to, provided that the designer properly understands CM theories, etiology and pathology of CM, as well as modern medicine. Strategy suggestions about research methods for CMM and its formulae will be given at the end.

KEYWORDS Chinese medicine, etiology and pathology, Zheng differentiation, Chinese materia medica, formulation

In the 1970's, with the discovery of drugs originating from plants, such as digoxin, vincristine, and taxol, etc., big pharmaceutical companies in Western countries began to set up natural medicine departments or centers in succession in attempts to screen for potent bioactive compounds from plants collected over the world, including Chinese herbs. Unfortunately, most of the departments or centers were shut down one after another around the end of the 20th century because the screening results were not as expected.

Today, Chinese materia medica (CMM) is becoming increasingly welcomed worldwide due to their efficacy and less side effects, attracting more scientists to perform research. Please notice that CMM is used here because it is composed of not only herbs, but also animals and minerals. Discoveries of artemisinin for malaria[1] and arsenic trioxide for leukemia[2] have inspired many scientists to revisit the utility of CMM.

To meet the growing need and consumption of herbal medicine, a Food and Drug Administration (FDA) Guidance for Industry—Botanical Drug Products and a Traditional Herbal Registration Processing Instructions were introduced, respectively, in the United States (US) and European Union (EU) in

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2004. In March 2012, Di'ao Xinxuekang (地奥心血康), an extract of rhizomes of *Dioscorea nipponica*, was granted marketing authorization as the first Chinese herbal medicine to the EU. Several other Chinese herbal products are under clinical trial as part of the FDA application process for registration as botanical drugs in the West.

Chinese medicine (CM) is the most popularized choice of traditional medicine. CMM plays the most vital role in the treatment of diseases in CM. Most CMMs have been widely used for over thousands of years, and countless people have proved their preventative and therapeutic efficacies. Preclinical research performed by scientists throughout the world using modern chemical, *in vitro* biological and *in vivo* pharmacological methods in the past century have mostly provided evidences to support the application of CMM.[3] However, most of the biological activities of individual compounds isolated from CMMs are much less than that of current available drugs. In addition, mechanism study on CMMs could not always give expected positive results to explain their claimed efficacy through the assays or animal testing methods used for modern drug development. Clinical trials on single CMM sometimes also gave negative results.

For example, *Radix Angelicae sinensis* (angelica) is one of the most commonly used CMMs for menstrual disorder. CM believes that angelica regulates menstruation through its function of tonifying and invigorating blood. Laboratory study showed that it has neither estrogenic nor progestronic activities when screened with assays of estrogen receptor-binding and mRNA expressions induction of progestrone receptor (PR) and estrogen receptor (ER).[4] Moreover, clinical trial did not provide evidence for angelica in the treatment of menopausal symptoms.[5] This example tells that preclinical or clinical studies on single CMMs that simply copied methods for screening drug candidates could help evaluate their biological and pharmacological activities, but results from such studies are sometimes insufficient to comprehensively explain the clinical application of CMMs.

The above example explains why when CMMs have been increasingly imported to the West as dietary supplements, most Western doctors are still unwilling to let their patients take CMM with the argument of "poor evidence", in addition to concerns about safety and drug-herb interaction. Leaving discussion aside on whether empirical trials on countless people over thousands of years are scientific, and whether preclinical and clinical studies on CMMs carried out in the West might have resulted from improper design by researchers without enough knowledge about CMM clinical application,[6] one should admit that there are still many "unknowns" of diseases in modern medicine. Some knowledge learned from medical school decades ago has turned out to be inaccurate or incomplete. Therefore, it is risky to simply use a negative result from a laboratory experiment to deny the functions of CMMs summarized through accumulated clinical practice.

Recently, *Nature* and *Science* published special issues with titles respectively on "Outlook: traditional Asian medicine" and "The art and science of traditional medicine". In these issues, topics are discussed from CM introduction and modernization, the integration of Western and Eastern medicine, to CMM genomics, quality control, regulation, patent protection, clinical trail, safety, treatment of influenza and cancer, as well as preclinical and clinical study of formulae, and its inspire to novel drug discovery.[7-21]

The author wants to call attention to researchers here that, first, CM views diseases differently from modern medicine; second, formulae, rather than individuals, make up the typical clinical applications of CMM. Many scientists who performed research on CMMs were unaware of or ignore that CMMs are used in the form of formulae, and that formulation of CMMs is guided by CM theories and based on CM diagnosis and differentiation. Researchers must understand the CM theories especially CM etiology and pathology, learn CM diagnosis and differentiation as well as the principle of formulation.

Understanding CM Etiology and Pathology

Medicine is an empirical science. Both CM and modern medicine are constantly updated from clinical observation and new discovery, as well as lessons from mistakes. The rule of nature is "survival of the fittest." CM has survived and extended worldwide because it has met the needs of human beings.

Both acupuncture and CMM treatment are performed under the guidance of CM theories and based on CM diagnosis and differentiation. To study

mechanism and efficacy of CMM, CM etiology and pathology must be known first.

The ancient Chinese created special terms such as qi, meridians, and others to describe functions of organs and tissues of the human body and substances essential to maintain life, when there were no modern medical terminologies available. These terms are still used in CM today.[22] This fact makes CM difficult to understand for the modern Chinese population, not to mention people in the Western countries.

CM believes that qi and blood are the two most vital materials to life. Qi is yang, and blood is yin. Qi and blood are co-dependent and interrelated and circulate in meridians that connect all organs and tissues to carry out physiological activities in human body. Qi generates blood, and blood transports qi.[22]

Diseases can be caused by the six exogenous pathogens (called evil qi), seven excessive emotions, improper diet and sleeping habits, excessive work or rest, insect bites or cuts, and, most uniquely, phlegm liquid and stagnant blood.[22] All of these factors can impact the formation and transportation of qi and blood, lead to qi or/and blood disorders, either deficiency or blocked circulation, and further result in yin-yang imbalance thereby causing disease. Although qi and meridians are quite mysterious and complex, scientists must understand their foundation in order to truly understand CM and explore the principle of treatment with acupuncture and herbal formulae.

In fact, discoveries in modern medicine have provided fundamental supports to explain the meaning of qi. Briefly, according to definitions in CM, qi could be generally explained as the substances necessary to maintain the health and survival of human being, as well as the functioning of all systems, including "energy" as many people believe.[6] It may also cover substances and functions that are yet unknown. These substances include neurotransmitters, hormones, enzymes, genes, and cytokines that regulate body function, while blood provides nutrients to all cells including nerve cells and endocrine glands, also carrying hormones to target tissues.

It is said that people become sick when their internal righteousness qi is too weak to fight the external evil qi. The righteousness qi is easily to be connected with immune function, while the evil qi reminds us exogenous pathogens such as bacteria, virus and other pathogenic microorganisms, which are covered in the six evils (wind, cold, heat, dampness, dryness, and fire). Besides, excessive emotional outbursts, chronic stress, improper diet or sleeping habits, excessive work or rest can also cause illness by impacting the righteousness qi, or formation and circulation of qi and blood.

Recent discoveries in psychoendoneuroimmunology have revealed that stress and bad emotions will impact the functional adjustment of neural, endocrine and immune systems.[23] It is also well known that improper diet will not only affect functioning of the digestive system, but also cause deficiency and imbalance of chemical composition in the blood, consequently alter the regulation of nervous, hormone and immune functions, resulting in qi and blood deficiency or disorder, consequently cause sickness. Therefore, CM puts great emphasis on management of proper diet and emotion while treating illness.

The most commonly used qi-tonifying herbs, such as *Radix ginseng* and *Astragalus membrana* have been proven to enhance immune functions and regulate endocrine systems including activity of hypothalamus-pituitary-adrenal (HPA) axis and hypothalamus-pituitary-gonadal (HPG) axis. This further confirms that qi relates to neuro-endo-immune (NEI) function. In addition, most qi-regulating CMMs are able to regulate contraction or movement of smooth muscle of the digestive system to relieve spasm or pain, or fullness that are caused by dysfunctional regulation of digestive or endocrine system.[24]

Phlegm fluid and blood stasis are the most characteristic etiologies of disease in CM. Phlegm fluid refers to abnormal substances accumulated out of the blood vessels. The phlegm in CM not only refers to phlegm spit out from the mouth, but also the abnormal turbid and thick substances within the body. The fluid refers to abnormal, excess, clear liquid accumulated within the body. Phlegm fluid could be resulted from infections of exogenous pathogens, poor emotions or improper diets, injury or other factors, but they also result in many diseases.[22] Lipoma, fibroid, or other accumulated metabolites from cells, internal pus caused by infection, edema resulting from

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abnormal water balance (transudate), or exudate due to inflammatory can all be considered phlegm fluid.

The author believes that phlegm and fluid are at least partly resulted from accumulated metabolites, pathological products, inflammatory exudate, and abnormal water metabolism. It has been known that inflammation can be caused by infection and injury, psychological stress, and food allergy. Many patients come to CM clinic after administration of antibiotics or antiviral drugs for infection prescribed by their physicians, with complains such as constant cough after flu, neuralgia from zoster, facial paralysis or ear pain due to Bell's palsy, etc. This tells us that although drugs can kill the pathogenic microorganisms, the inflammation incurred may remain there and cause chronic, low-grade inflammation and impact local blood circulation. This consequently affects neural and endocrine functions, leading to qi and blood disorders. Such inflammation can also occultly happen within organs or tissues and endothelial cells in vessels, causing symptoms that cannot be diagnosed with blood test and or instrument examination. Dr. Appleton listed many diseases in her book of Stopping Inflammation: Relieving the Cause of Degenerative Diseases.[25] But there are many more diseases relating to inflammation.

CM believes that stagnant blood not only cause many diseases, but also aging.[26] Stagnant blood as the cause of diseases has been confirmed in modern medicine. Well-known examples include strokes and coronary heart diseases (CAD). Angiology studies have found many other diseases related to blocked blood circulation.[27] Moreover, it is also known that more than 50% of people at age 40 have vessel blockage of different degrees.[28] The blockage of vessels is a slowly aggregated process. The atherogenic cascade has been identified as not merely a degenerative process but also a multifactorial inflammatory disorder. Lesions of vessels not only happen to coronary, cerebral, and peripheral arteries, but also in the abdominal tract such as the mesenteric arteries, the common iliac arteries and in other parts of the body.[27]

Modern pharmacological studies have revealed that blood-invigorating CMMs can regulate circulation by improving hematologic and hemodynamic properties and microcirculation as well as inhibiting thrombotic formation, tissue damage or abnormal proliferation. Many of them also have anti-inflammatory activities. These findings will help scientists understand why CMMs having blood-invigorating function are prescribed most frequently in formulae for prevention and treatment of many diseases by experienced CM doctors. A good example is that angelica has neither estrogenic nor progestronic effects, but it plays importance role in formulae for menstrual disorders by regulating blood circulation and smooth muscle in the uterus.[24]

The author likes to use the three sayings to summarize the cause of disease in CM: (1) if the righteousness qi is strong enough, the evil qi could not invade; (2) if the Spleen (Pi) and Stomach (Wei) are injured, a hundred types of diseases will be generated; (3) blocked circulation of qi and blood can contribute to the development of hundred types of diseases.

The righteousness qi covers the immune functions. Therefore, the first saying emphasizes the importance of self-immune function. The second and third sayings emphasize the importance of formation and transportation of qi and blood. The meaning of Spleen and Stomach in CM covers the functions of the entire digestive system. Improper diet and damage of Spleen and Stomach functions can easily cause qi and blood deficiency because they can impact the digestion and absorption of nutrients, the source of qi and blood. Meanwhile, circulation of qi and blood can be easily blocked by negative emotions and stress. Therefore, CM puts great emphasis on prevention and treatment of digestive function and circulation when treating diseases.

The above explains why qi and blood tonifying or regulating herbs are most frequently used in formulae together with herbs treating symptoms in CM clinic. It tells us that CM does not simply look at and aims to treat symptoms of a disease, but also its causation. Researchers who study the formulae must be aware of this.

CM Treatment Is Based on Zheng Differentiation

One of the unique characteristics of CM is that, in addition to diagnosis, doctors need to differentiate Zheng (证) before making a treatment plan. Zheng differentiation refers to a comprehensive analysis of overall information obtained through the four CM diagnostic methods (inspection, listening and

smelling, inquiry, and pulse taking and palpation) using the basic CM theories of organs, meridians, etiology, and pathogenesis so as to identify the location and pathogenesis of the diseases as well as the symptom characteristics.

Zheng differentiation is translated into syndrome pattern in most English books and literature.[29] However, although syndrome (征) and symptom (症) are pronounced identically to Zheng (证) in Chinese, their meanings are different, and Zheng is distinct from either of these other terms.

There are several types of Zheng differentiation methods: eight principle differentiation (exterior and interior; cold and heat; excessive and deficient; yin and yang), Zang-fu organ differentiation, six meridian differentiation, San-jiao differentiation, qi and blood differentiation, and etiological differentiation.[22] CM doctors usually combine different differentiations together.

For examples, Kidney (Shen) yang deficient means yang deficiency in Kidney. The symptoms include male impotence; female infertility and uterine cold; chronic diarrhea at early morning; edema at legs; cold on limbs; fatigue and difficult to cheer up; pale or dark on face; tongue pale in color with white coating; pulse weak and deep, etc.[30] Symptoms can vary between patients. The causes include heredity, aging, kidney dysfunction, excessive sexual intercourse, etc. Kidney failure patients mostly have some of these symptoms.[31]

Dr. SHEN Zi-yin, a famous integrative medicine expert in China, started his study on Zheng in the 1960's. His group has combined modern diagnostic technologies to analyze Kidney yang deficiency, and also compared the difference before and after treatment with different formulae. They discovered that Kidney yang deficiency involves dysfunction of hypothalamic-pituitary gland, consequently HPA axis, hypothalamic-pituitary-thyroid (HPT) axis, and HPG axis. Therefore, they deduced that the main problem onset of Kidney yang deficiency links with the dysfunction of the hypothalamus. With further comparison studies on a formula for Kidney tonifying with formulae for invigorating Spleen and blood, they believe that Kidney yang deficiency is actually the disorder of NEI network, centrally regulated by the hypothalamus.[32]

Effective CM treatment is mainly based on correct Zheng differentiation. One disease or syndrome diagnosed in modern medicine can be differentiated into several different types of Zheng and thus be treated by different formulae. Meanwhile, different diseases or symptoms can be attributed into the same Zheng and thus be treated by one formula. For example, arteriosclerosis, cerebral infarction, ovarian cysts, endometriosis, uterine fibroid, dysmenorrheal, amenorrhea, persistent lochia after delivery all can be attributed to blood stasis, thus be treated by one formula. Examples are given in the last two sections.

It has been just recently realized that a number of unsatisfactory randomized controlled trial on acupuncture and CMM formulae were the result of improper designs, partly due to the lack of CM Zheng differentiation.[29] This was mainly due to improper study designs by scientists in the West who lacked sufficient knowledge on CM theories and Zheng differentiation.

Combining studies on Zheng differentiation with modern diagnostic, pharmacological and clinical studies will innovatively impact the direction of medical research, not only leading to new etiological and pathological findings, but also a revolution of new drug and novel medical equipment development.[32,33]

Formulae Rather Than Individual CMMs Are Mostly Used in CM Clinic

In the past century, most commonly used CMMs have been individually well investigated and many biological or pharmacologically active compounds in them have been reported.[3,24] Biological or pharmacological studies on chemical components isolated from most herbs have greatly helped the elucidation of their functions and standardization of the materials and products. However, only a few compounds from CMMs have been developed into new drugs. I was once disappointed when my own screening results showed that linoleic acid, one of the most common fatty acids in plants, was the most active anti-inflammatory component in *Radix Angelicae Pubescentis*[34] and estrogenic compound in chaste berry.[35] This made me doubt the efficacies of the CMM that I learned about. I did not realize, until switching to clinical practice and being convinced by the clinical efficacies of formulae, that to truly reveal the secret of CMM, studies must be carried out on

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formulae based on CM theories and clinic efficacy.

Formulae are usually composed of 2–15 individual CMMs; some formulae are composed of greater than 20 CMMs. Treatment with CMM formulae was first recorded in books by ZHANG Zhong-jing about 2,000 years ago. Since then, more and more formulae have been collected in CM books.[36] Some of the famous formulae have been used over thousands of years. The superior CM doctors of each generation not only use or reference old famous formulae from their ancestors, but also create their own.

CM emphasizes treatment from the root (cause). For many dysfunctional symptoms or diseases, such as gynecological, digestive, autonomic disorders that modern drugs fail to treat or can only temporally relieve symptoms, CMM formulae can effectively reduce or eliminate the symptoms effectively through cooperated regulation of qi and blood, i.e. adjusting nerve, endocrine, and immune functions and circulation, thereby reducing or eliminating many symptoms. To get such efficacy, formulation of herbal ingredients must base on correct Zheng differentiation and under the guidance of CM theories.[33]

Principle of Formulation

To perform research on formulae, traditional functions of CMMs and principles of formulation (also called prescription compatibility) must be known.

Formulation of CMMs is based on diagnosis and Zheng differentiation, also the holistic view of CM and treatment principle. The purpose of formulation is not simply to add herbs with similar effects, but rather to have herbs with different functions work synergistically—each plays different roles. Chief, depute, assistant, and envoy (Jun, Chen, Zuo, and Shi) are used to figuratively describe the roles of ingredients in a formula.[37] In modern terminology, herbs in a formula can exhibit different biological and pharmacological effects and simultaneously work on different systems or targets.

Take Wuzhuyu Decoction (吴茱萸汤) as an example. This is a formula composed of four herbs, *Fructus Evodiae*, *Rhizoma Zingiberis recens*, *Radix Ginseng*, and *Fructus Jujubae*. It is often used to stop vomiting and reduce nausea. The chief herb *Fructus Evodiae* can effectively stop vomiting, but is slightly toxic. *Rhizoma Zingiberis recens* has similar but weaker effects than the chief herb, thereby enhancing the efficacy of *Fructus Evodiae*. *Radix Ginseng* is used to help regain the qi that being easily lost through vomit. *Radix Ginseng* is used to coordinate the effects of the other three. In a pharmacological study on its compatibility, the conclusion was that the whole formula exhibited the highest anti-emetic effect and the least toxicity than *Fructus Evodiae* and any another herb in this formula.[38]

One formula can be used for different diseases or syndromes in clinic. Meanwhile, many formulae can be used to treat one disease or syndrome. To most scientists and clinical physicians, this sounds impossible to accept. But they would be convinced once they have understood CM etiology and pathology, Zheng differentiation, and modern pharmacology of CMMs.

One Formula for Different Diseases

Each CMM usually has several different functions because it contains several types of compounds, each type has its specific biological efficacy due to its particular chemical composition, thus can be used for different diseases. For example, *Radix Ginsen* contains glycosides of saponin and triterpene (called ginsenosides), flavonoids, polysaccharides, etc. Each possesses different biological activities. Ginsenoside Rb1 and Rg1 can effectively improve memory and prevent brain cells from injury by cerebral ischemia; Rd has excitatory effects on the HPA axis; Rg3 and Rh2 exhibit significant anti-tumor activities. Ginseng polysaccharides are known to enhance the immune function and inhibit gastric ulcer.[39] A formula is composed of several herbs. Therefore, it is not surprising that one formula has several functions and is used to treat different diseases.

Besides, CM views diseases differently from modern medicine. As mentioned in the first section, it believes that stagnant qi and blood can cause hundreds of diseases; thus, a formula with blood- or qi-regulating function can be used to treat many disorders.

Take Guizhi Fuling Pill (桂枝茯苓丸, GZFLP) as an example. GZFLP is a famous formula from the book *Synosis of the Goldern Chanber* (Jin Gui Yao Lue), written by ZHANG Zhong-Jing 2000 years ago. This formula is composed of five herbs, *Ramulus Cinnamom*, *Poria*, *Radix Paeoniae Alba*, *Cortex Moutan*,

and *Semen Persicae*. It was originally formulated for fetal irritability with constant dark blood spotting from the uterus caused by blood stasis; it can invigorate blood circulation and remove blood stasis and mass. Now, its application has been extended to treat many gynecological disorders caused by blood stasis, including ovarian cysts, endometriosis, uterine fibroids, menorrhagia, dysmenorrhea, amenorrhea, infertility, recurrent miscarriage, persistent lochia after delivery, and ectopic pregnancy, etc. In addition, it has also been used for other diseases that are differentiated into blood stasis, including hyperlipidemia, arteriosclerosis, cerebral infarction, complications of diabetes, chronic nephritis, prostatic hypertrophy, and chronic prostatitis.[40] GZFLP is currently under phase Ⅲ clinical trial for a new drug treating dysmenorrhea in the US.

Pharmacological and clinical studies on GZFLP have been performed widely with many significant results. In addition to those carried out by Chinese scholars, Japanese scientists also performed a series of studies on GZFLP (called Keishibukuryogan in Japanese, KBG). Their results not only confirmed the efficacy of this formula, but also helped understand the mechanism of its treatment. It has been found that KBG could improve symptoms of hypermenorrhea and dysmenorrhea and make uterine myomas shrink,[41] significantly lower incidence of adenomyosis in the uteri,[42] decrease plasma calcitonin gene-related peptide level in subjects with hot flash,[43] and elevate skin temperature not through conferring estrogen activity on plasma.[44] Only one pharmacological study suggested that KBG may act as a luteinizing hormone-releasing antagonist and/or as a weak anti-estrogen.[45] But the author believes that KBG works on menstrual regulation mainly through its effect on blood circulation, based on the pharmacological studies of each ingredient in the formula of regulating vascular muscle and improving circulation.

It must be known that GZFLP is mainly used for symptoms that are differentiated into Zheng of blood stasis, such as cramping followed by clots in blood or dark brown spots. If blood deficiency is ensured, such as intractable bleeding with fresh-colored blood and no clotting, formulae containing qi- and blood-tonifying and hemostatic herbs should be prescribed. Study on GZFLP and other formulae may help find further scientific evidence to reveal the relationships between hematology and angiology with menstrual disorders, or recurrent miscarriage and infertility.

GZFLP is not only applied for gynecological disorders, but also for other diseases that are differentiated into Zheng of blood stasis. Results from the group of Dr. Yutaka Shimada at University of Toyama revealed that KBG could significantly prevent the red blood cell deformability which is often seen in cerebro-vascular disorders,[46] improve vascular function and hematological factors related to diabetes,[47] slow the progression of diabetic nephropathy due to its ability to improve metabolic abnormalities[48] and atherosclerosis by limiting oxidative density lipoprotein modification,[49] inhibit the early stage of atherosclerosis through protecting the vascular endothelial function,[50] exhibit significant effect on the liver injury of non-alcoholic fatty liver disease,[51] and improve endothelial function in patients with metabolic syndrome-related factors[52] and rheumatoid arthritis.[53]

Efficacy studies of GZFLP strongly support that many diseases are caused by blood stasis. In addition to the above mechanisms revealed for GZFLP, improvement of peripheral circulation and anti-inflammatory activities of all these five herbs also make great contribution to the effective treatment.[25]

Different Formulae for One Disease

It was reported that, based on literature searching for ancient CM books and recent CM related journals, 283 formulae were found for the treatment of coronary heart disease (CHD). Among them, 19 of them are currently frequently used in clinic.[54] How could this be explained?

Selection of herbs in a formula mainly depends on their functions and Zheng differentiation of the diseases based on diagnosis, but preference of CM doctors and availability of herbs are also factors to composition of a formula.

First, different formulae are used because CHD is differentiated into several Zhengs. Based on the differentiation, qi tonifying, blood invigorating, yin tonifying, qi regulating, and phlegm-resolving herbs are mostly used in these formulae. Although herbs are divided into different categories, many of them have blood invigorating activities and have been pharmacologically proven either to improve hematological/hemodynamic functioning, improve

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microcirculation, or to possess antithrombotic activity. For example, *Rhizoma chuanxiong*, *Radix Salviae Miltiorrhizae*, *Flos Carthami*, *Fructus Crataegi* and *Semen Persicae* all have blood invigorating and stasis resolving functions, and are thus frequently applied in formulae treating diseases differentiated into blood stasis. Because each also has other functions, doctors can select them based on all symptoms a patient has. For example, *Rhizoma chuanxiong* is customarily the first choice for patients with headache, *Flos Cartham* is given to patients with menstrual problems, *Fructus Crataegi* is prescribed for patients with poor appetite, while *Semen Persicae* is given patients with constipation. But all of these herbs can be used for CHD, gynecological disorders, and other blood stasis related diseases or symptoms.[25]

Functions or biological activities of an herb depend on its chemical composition. In general, different herbs having the same or similar function are mainly because they either contain the same or structurally-similar components or different type of compounds having the same or similar pharmacological activities. Knowledge about the chemicals in an herb and their pharmacological activities as well as traditional applications will greatly facilitate the development of a new effective formula.

Strategy Suggestions for Study on CMM and Its Formula

CM is a great treasure house for researchers and clinicians. The role of CMM should not be merely a "dietary supplement" for healthy maintenance; rather, it can be the primary medicine in treatment of many diseases. It is not only a source for drug development, but an old resource that can give us new inspiration for the direction of "polypharmacy." Josephine Briggs, head of the National Center for Complementary and Integrative Health in National Institute of Health, commented about the formula PHY906 (Huangqin Decoction, 黄芩汤) being an adjuvant to chemotherapy in patients with colon cancer.[55] Information given in this paper emphasizes that CMM formula is not a simple "polypharmacy." Like any formulation, CMM has its advantages and disadvantages. The integration of CMM with modern medicine will help many patients who are suffering from different types of illness.

Research on CMM should adopt methods for drug development, but study strategy should be different from it. Common mistakes in herbal medicine study has been pointed out in the book Traditional Herbal Medicine Research Methods: Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies.[6] As a concluding remark, some suggestions are emphasized again for researchers who are interested in study on CMM and its formula.

• Unlike drug development starting from lab, efficacy studies on CMM, particularly formula, should begin from clinic. Once clinical efficacy is confirmed, *in vitro* and *in vivo* study should be followed for mechanism study.

• Efficacy study on CMM formula should begin from the whole formula. Once the efficacy is confirmed, individual ingredients are then screened to find out their bioactive or pharmacological activities and the corresponding compounds for mechanism evaluation. Selection of screening targets should be multiple, based on functions of each CMM.

• Efficacy study on CMM formula should accompany with corresponding Zheng study. Zheng study should include not only the common medical clinical exams, but also the CM diagnosis. In addition, chemical analysis for hormones, neural transmitters or immune factors in blood, biochemical and biological analysis for enzyme activities, gene expression or cell function, as well as imaging exams can all be applied to compare the changes before and after the treatment with formula.

• Either evidence based clinical efficacy or mechanism study on CMM or its formula should be designed and performed by a team with clinicians, CM doctors, pharmacologists, chemists, and statisticians. The quality of the preparation of formula must be controlled and consistent through the whole study.

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