

The rationale behind the four major anti-COVID-19 principles of Chinese herbal medicine based on systems medicine

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Abstract

As the novel coronavirus disease 2019 (COVID-19) and its variants continue to rage into the second year of a global pandemic, many success stories of applying Chinese herbal medicine (CHM) to treat COVID-19 patients continue to emerge from China and other part of the world. Herewith, from a systems medicine perspective, the authors analyze those experiences and categorize them into four major treatment principles: (1) focusing on eliminating toxins in the early stage of the disease, (2) tonifying deficiency of the body throughout the entire disease course, (3) treating the affected lung and intestine simultaneously based on visceral interactions, (4) cooling blood and removing blood stasis at the later stage, as well as interpret the rationale of these principles. This is helpful not only in reducing the complexity of promoting the CHM applications to enhance anti-COVID-19 efficacy, but also in ramping out the process of integrating traditional Chinese medicine with modern medical practices.

Keywords: Anti-COVID-19, Chinese herbal medicine, Systems medicine, Treatment principles, Rationale

1 Introduction

As coronavirus disease 2019 (COVID-19) and its multi variants continue to spread globally, numerous success stories regarding the application of Chinese herbal medicine (CHM) for managing COVID-19 symptoms continue to emerge from China and other countries. However, significant doubt remains regarding its efficacy and significance, as the effects of CHM are often difficult to interpret scientifically, seriously hampering proper evaluation, promotion, and development of the approach in a global anti-pandemic effort.

In the spring of 2020, China began to standardize a popular CHM treatment protocol called “three medicines and three traditional Chinese medicine (TCM) prescriptions”^[1-2] Specifically, the “three medicines” refer to Jinhua Qinggan granules, Lianhua Qingwen capsules, and Xuebijing injections, while the “three TCM prescriptions” refer to Qingfei Paidu decoction, Huashi Baidu decoction, and Xuanfei Baidu decoction. However, many provinces or regions in China often prefer to use their custom CHM derived from their local TCM experts, albeit with much success. Here comes another question to ponder: why do many of those region-specific custom CHM have comparable effectiveness to “three medicines and three TCM prescriptions” ?

In present-day China, the majority of trained TCM professionals practice classical styles of TCM diagnostics and treatment, whereas “specific CHM for a specific person” is prescribed via pattern differentiation because each person or case may exhibit specific constitutions or patterns based on their individual circumstances. However, during the pandemic, especially in the early period when the COVID-19 virus was spreading quickly, that approach was mostly abandoned in favor of an approach called “one or several CHMs” for “thousands of urgent cases”, including other patent herbal remedies that have been widely applied in China for COVID-19. By clarifying and summarizing the applications of such principles, we hope to help remove significant hurdles in the modernization process of TCM and promote effective CHM applications that could enhance their anti-pandemic efficacy.

This article describes and analyzes four major anti-coronavirus principles derived from successful CHM prevention and treatment strategies for COVID-19 and elucidates their rationale based on systems medicine.

2 Successful experiences of applying CHM for COVID-19

According to a recent study, all confirmed COVID-19 cases in China were treated with standard care under the guidelines issued by the National Health Commission (NHC) and the State Administration of TCM of China^[1]. Multiple CHMs were recommended by China’s NHC in a series of guidelines for the treatment of COVID-19 (Diagnosis and Treatment Protocol), and 91.5% (or 74,187 individuals) of COVID-19 patients were treated with some form of CHM^[3]. In some of the mild or ordinary cases – in the United States, they are called “moderate” cases – CHM was exclusively used for symptom management. From a larger perspective, compared with the COVID-19 treatments used in developed countries, the use of CHM on COVID-19 is undoubtedly a unique experience and may have played a

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significant role in countering the spread of this deadly virus. For example, it was reported that the use of Qingfei Paidu decoction (sometimes with modification) plus standard care, across 30 COVID-19 specific hospitals in 14 provinces of China and across a total of 1,476 adult patients, resulted in a total symptom relief rate of 90.0%–94.8% over a treatment course of 3–9d^[4]. Based on these experiences with a large number of patients, China's NHC designated this herbal formula as an effective preventive CHM for COVID-19; the Qingfei Paidu decoction was subsequently widely distributed, either in its original CHM formulation or by customizing it to each patient's individual condition.

Indeed, as it stands today, China's standard TCM treatment protocol has been “three medicines and three TCM prescriptions”. All are prescribed according to the various stages or phases (early, middle, and late) of a patient's viral infection. However, it is known that there are many other region-specific CHMs that have positive effects comparable with “three medicines and three TCM prescriptions”. For example, the “Dayuan drink” or “Maxing Shigan decoction” were the preferred CHMs in the city of Guangzhou. CHMs such as “Pneumonia No.1 Formula” (*Lonicerae Japonicae Flos*, *Forsythiae Fructus*, and other 16 cold-natured herbs) and the classical Yupingfeng powder (*Astragali Radix* 30g, *Atractylodis Macrocephalae Rhizoma* 15g, and *Saposhnikovia Radix* 10g) were also shown to be effective in managing COVID-19 symptoms. Preventive CHMs from the Hubei and Shanxi provinces were also deemed effective, including “Modified Pneumonia No.1 Formula”, in which *Atractylodis Rhizoma* 3g, *Lonicerae Japonicae Flos* 5g, *Citri Reticulatae Pericarpium* 3g, *Rhizoma Phragmitis* 2g, *Mori Folium* 2g, and *Astragali Radix* 10g are boiled with hot water and taken for 7–10 d. The ingredients of the Shanxi province's empirical CHM were primarily based on the above Yupingfeng powder mixture.

As mentioned above, numerous CHMs are reported to be effective for COVID-19; some were applied based on TCM pattern differentiation, while others were dispensed via a single modifiable empirical CHM.

3 The concept of balance in TCM and the basic formula of systems medicine

TCM uses the terms “*yin* and *yang* harmony” and “relative equilibrium of *yin* and *yang*” to describe one's overall state of health and well-being. It also regards “taking balance as the expectation and harmony as the priority” as the ultimate goal of treatments such as CHM and acupuncture. It is commonly said in TCM that one should “treat coldness with hot, treat hotness with cold, treat warmth with cool, treat coolness with warm, treat exhaustion by collection, treat stagnation with dispersion, treat dryness with moistness, treat pressing with easing, treat nodules with dissipation, treat brittleness with stabilization, tonify the weak, purge the excess”^[5]. These classical treatment principles of TCM are not only suitable approaches for managing chronic diseases, but also useful for the treatment of COVID-19 and other acute diseases. In Western and systems medicine, clinicians tend to refer to the concept of “homeostasis”, which is very similar to the TCM concept of “balance”^[6]. In this article, we will attempt to express the rationale behind the CHM treatment principles from the perspective of practitioners involved primarily in systems medicine.

Principles of Systems Medicine^[7] proposed two basic axioms for systems medicine: axiom 1 – any fundamental internal steady state (homeostasis) of the life system (such as body temperature, blood pressure, and cardiac output) corresponds to a unique function. The internal steady state is an attractor of the function manifested as a self-coupling system, where its output becomes its input at the next moment. Axiom 2 – life is a system with self-healing abilities.

Based on Axiom 1, a mathematical expression of the degree of homeostatic deviation named “the basic formula of systems medicine” was derived (Fig. 1). This is a fraction in which the quotient *S* equals homeostatic deviation; numerator *b* equals the disturbance factor; and the denominator is the difference between the system's homeostatic mechanism (*k + a*) and 1, in which *k* is a homeostatic parameter. If the quotient *S* is regarded as a pathological state, the numerator *b* is a pathogenic factor; (*k + a*) in the denominator represents the decline of a person's self-healing ability or homeostatic mechanism. The increase or decrease of *b* (as the numerator) and (*k + a*) (as the part of the denominator) can affect the value of quotient *S*. The relationship between *b* and *S* is proportional. That is, the decrease in *b* can reduce the degree of homeostatic deviation. Indicating that the disease is subsiding. The closer the (*k + a*) is to 0 (between 0 and 1), the closer the denominator is to 1; that is, the smaller the homeostatic deviation, the milder or more stable the diseased state, and vice versa. This formula can easily be applied for the purposes of defining a disease, the factors affecting the occurrence of a disease (internal or external), and the overall complexity of a disease. In this article, those experiences of applying for “three medicines and three TCM prescriptions” for COVID-19 are analyzed using this formula. It is not only qualitative but also semi-quantitative to express the relationship between various influencing factors.

It is important to understand that systems medicine not only regards life as a steady-state (homeostasis) but that it can also be considered as a collection of countless steady states, namely, the “complete sets of homeostatic states”. If the homeostasis of the system is used to interpret the state of health, under the interaction of internal and external pathogenic factors, the homeostasis of a certain subsystem in the body system will temporarily deviate, leading to what we call “sub-health”. Under the effect of the homeostatic mechanism (ie, the self-healing abilities described later), the system usually auto-corrects any deviations to restore health. If it cannot do this, for example when the homeostatic mechanism is destroyed, then the homeostatic deviation of the subsystem will resume, and the diseased states will continue to degrade.

$$S = \frac{b}{1-(k+a)}$$

- S:** Homeostatic deviation (diseased state)
b: Disturbance or pathogenic factor
k: Homeostatic parameter
(k+a): Homeostatic mechanism
 (self-healing capability)

Figure 1. The basic formula of systems medicine.

Once the homeostasis of multiple subsystems deviates for a prolonged time one after another, then the complete sets of homeostatic states will be destroyed; this often leads to the death of the patient^[7].

Axiom 2 has long been recognized in both modern medicine and TCM. Hippocrates said, everyone has a doctor in their body, and all we have to do is help it work. The self-healing ability within each of us is the greatest healing power^[8]. Que Bian (pseudonym) said, it's not that I can resurrect the dead, it's that he didn't die before, but I just got him up^[9]. Of course, the self-healing abilities of the body include many aspects, such as immunity, anti-inflammatory, analgesics, hemostasis, anticoagulation, detoxification, and emergency or stress response, as well as tissue repair and regeneration. We are perhaps most familiar with the spontaneous hemostasis that occurs when bleeding, or the self-healing that arises a few days after catching a cold, as well as the elimination of free radicals from the body^[10].

For COVID-19, why might CHM be effective? For those with moderate medical or scientific training, the most easily understood concept relating to the efficacy of CHM is the proven antiviral effect of certain single Chinese herbs. For example, a recently published study in *Cell Discovery* demonstrated that the ingredients in the Jinyinhua decoction could be effectively absorbed by the body after consumption and could effectively inhibit the replication of the COVID-19 virus in the body while also accelerating the positive-to-negative conversion rate of COVID-19 patients^[11]. Starting from the basic formula of systems medicine, we can sort various regional anti-COVID-19 experiences using CHM into the following four major treatment principles.

4 Four major treatment principles of CHM and their rationales

Let us first analyze the mild cases of COVID-19. There are generally two situations: (1) although there is a viral infection, the immune function of the patient has not been significantly damaged; therefore, the virus is quickly eliminated without obvious symptoms or (2) although there are initial symptoms, the disease condition is quickly mitigated without complications. In the latter situation, although an individual's innate immunity may have been reduced due to age and other reasons, few viruses have replicated, or the disease's toxicity has not yet reached a dangerous level; therefore, the disease condition is also mild. For these two types of mild cases, regardless of whether the intervention utilized is of modern medicine or TCM, the homeostatic deviation can be corrected as long as the numerator or denominator of the formula of systems medicine is altered by the chosen interventions.

In TCM, the disturbance of the *yin-yang* balance must meet two conditions: the lack of righteous *qi* and the invasion of evil *qi*^[5]. As a classical TCM quote states, "if *zheng qi* remains strong, *xie qi* cannot invade the body". The righteous(-ness) *qi* in TCM may also refer to the body's self-healing capability, which can be represented as the power of self-maintaining homeostasis (a homeostatic mechanism) in systems medicine. As a type of righteous *qi*, defensive *qi* in TCM may refer to the body's immunity to disease, which is responsible for protecting the body from the attacks or invasion of the evil *qi* of COVID-19. The so-called evil *qi* is a factor that directly interferes with the normal physiological functions of the

human body, including but not limited to six external factors, seven emotions, epidemic toxins, and other illnesses caused by improper diet, work and rest, phlegm, and blood stasis^[5].

The majority of TCM practitioners consider COVID-19 to be a "cold and damp disease", a "damp toxin disease", or a "pestilence"^[12], in which the evil *qi* is primarily the dampness of the six evils (wind, cold, heat, dampness, dryness, and fire) and "pestilential *qi*". From this, we can rewrite the basic formula of systems medicine with the above TCM terminology as shown in Figure 2(1) and obtain two relevant CHM treatment principles for managing COVID-19, particularly when dealing with its mild symptoms; these principles are detoxification and tonification, as shown in Figure 2(2). The interpretation of Figure 2(3) is detailed later.

Pneumonia is often a turning point for COVID-19 cases; in that, pneumonia often changes a patient's disease state from mild to severe. Approximately 15% of severe cases of COVID-19 turn severe or critical as soon as pneumonia occurs, and these patients become critically ill within 3-5d, which is namely the "*zhe zhong*" (direct attack) in TCM. Most of these patients have low innate immunity, such as older adults or those undergoing chemotherapy, while some patients with severe COVID-19 may suffer from underlying chronic diseases; most of these cases change from mild to severe in 7-10 d^[13]. To prevent the diseased state from worsening, TCM also has two other treatment principles: (1) treating the affected lung and intestine simultaneously, (2) cooling and removing blood stasis.

4.1 Treatment principle 1: focusing on eliminating toxins in the early stage of the disease

Eliminating toxins can also be called toxin removal, which includes antitoxin and detoxification. Some CHM approaches have been shown to inhibit the reproduction of the COVID-19 virus or to reduce its toxicity, but most CHM principles have at least some effects of promoting excretion.

Notably, some of the most common symptoms of COVID-19, such as coughing with sticky or clear sputum, sneezing, diarrhea, and sweating, are also components of the body's natural self-protective mechanism. It has been found that the viral load observed in the sputum samples of critically ill patients with COVID-19 is higher than that of uninfected patients. The amount of viral load in feces is about 100 times that of samples taken from patients' nasal swabs. Although there is no scientific evidence to prove that sweat can spread the COVID-19 virus, some experts believe that sweating can help prevent COVID-19. As for urination: the urine viral load is low, but it has been proven pathogenic. Therefore, consciously using CHM to dredge any blockage of these pathways (eg, promoting sweating when no sweating is present; lubricating the intestines when constipation occurs; and resolving phlegm when thick phlegm exists) is advised to fight the disease and improve overall health, but prompt attention and proper medical care remain necessary for treating severe symptoms.

Certain effective CHMs for the treatment of COVID-19 often include terms such as *pai du*, *bai du*, and *jie du*, such as the Qingfei Paidu decoction, Huashi Baidu decoction, and Xuanfei Baidu decoction. The following

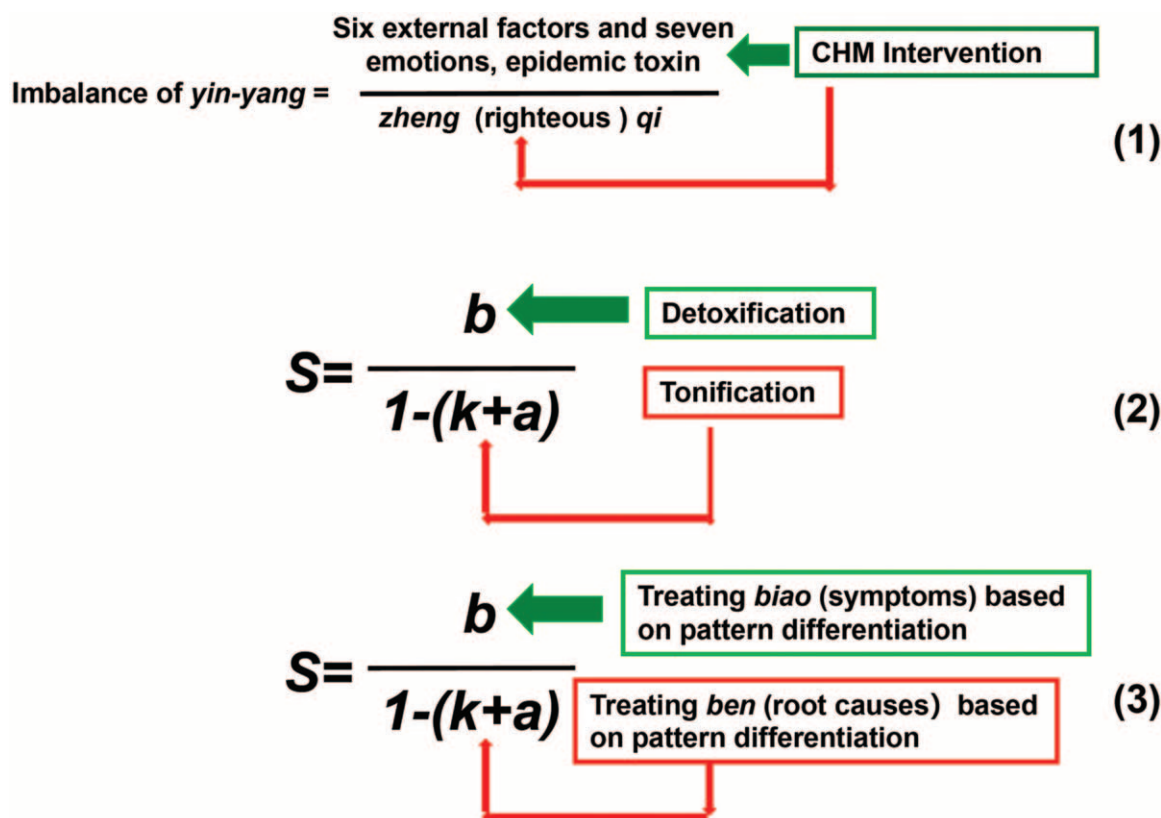


Figure 2. TCM interpretation of the basic formula of systems medicine. TCM: traditional Chinese medicine; CHM: Chinese herbal medicine.

are some examples of “three medicines and three TCM prescriptions” that deal with toxins via CHM.

Qingfei Paidu decoction. Among the “three CHMs”, this is often used for mild cases. It is composed of four classical TCM decoctions (Maxing Ganshi decoction, Shegan Mahuang decoction, Xiaochaihu decoction, and Wulingsan decoction). Their main functions are to disperse the lung *qi* and to dispel dampness among which, the Maxing Ganshi decoction and Shegan Mahuang decoction are the main choices for dispersing the lung *qi*, and the Wulingsan decoction is stronger for dispelling dampness. Judging from the modern pharmacological effects of some of the CHMs being used, the main objectives are to resolve phlegm, expectorate phlegm, and induce diuresis, respectively. From the basic formula of systems medicine, the goal is to mainly reduce numerator *b* (viruses, toxins, and other pathogenic factors) by promoting detoxification. Of course, directly fighting the virus is also the effect of certain CHMs, such as *Bupleuri Radix* and *Scutellariae Radix* in the Xiaochaihu decoction, but such cold-natured herbs in the decoction are rarely used at a high dosage. *Ephedrae Herba*, the emperor drug in the Maxing Ganshi decoction and Shegan Mahuang decoction, has a sympathomimetic effect, which not only can help improve ventilation and sputum reduction by expanding the trachea, thus reducing the molecule *b* but can also have a significant effect on the denominator $1 - (k + a)$. It is now known that sympathetic nerve excitement is closely related to immunity. The *Gypsum Fibrosum* in the Maxing Ganshi decoction, *Bupleuri Radix* in the Xiaochaihu decoction, and *Ginnamomi Ramulus* in the Wulingsan decoction primarily have antipyretic and

analgesic effects. The *Ginseng Radix et Rhizoma* and *Fructus Jujubae* in the Xiaochaihu decoction are used as tonics, which also achieve their effects by influencing the denominator.

Jinhua Qinggan granules. Among the “three medicines”, Jinhua Qinggan granules are often used for mild disease cases. These granules were first deemed as an effective CHM strategy in the fight against H1N1 influenza that arose in 2009, and they have recently shown effectiveness in treating mild and moderate cases of COVID-19. In addition to the four ingredients of the Maxing Ganshi decoction, it also contains *Lonicerae Japonicae Flos*, *Scutellariae Radix*, *Forsythiae Fructus*, *Fritillariae Bulbus*, *Anemarrhenae Rhizoma*, *Arctii Fructus*, *Artemisiae Annuae Herba*, and *Menthae Haplocalycis Herba* to strengthen the body’s heat-clearing and detoxification functions (with several herbs that can induce anti-viral, anti-bacteria, and antipyretic effects). Modern pharmacological studies have shown that these CHMs can shorten the duration, increase the recovery rate of lymphocytes and white blood cells, and improve related immunological indicators. From the basic formula of systems medicine, their effective mechanism seems to primarily reduce numerator *b* (viruses, toxins, and other pathogenic factors) by promoting detoxification and purging toxins.

Specific single Chinese herbs that have strong anti-viral properties. Modern studies have confirmed that many Chinese herbs show a strong effect in inhibiting viruses; these include *Scutellariae Radix*, *Coptidis Rhizoma*, *Lonicerae Japonicae Flos*, *Forsythiae Fructus*, *Rosae Laevigatae Fructus*, *Propolis*, *Linderae Radix*, *Green Aucklandiae Radix*, *Polygoni Cuspidati Rhizoma* et

Radix, *Sargassum*, *Luffae Fructus*, *Retinervis*, and *Granati Pericarpium*. The use of proprietary CHMs in the clinical treatment of viral infections is also extremely common: Huoxiang Zhengqi liquids treat colds and enterovirus-induced diarrhea; Fangfeng Tongsheng pills treat colds and herpes simplex; Banlangen granules treat wind-heat type colds, mumps, hepatitis, measles, and other viral infections; Xiaochaihu granules or Chaihu oral liquids treat influenza; Yuxingcao injection treats influenza, herpes simplex, and viral myocarditis; and compounded Daqingye mixture treats influenza and Japanese encephalitis. Some hospitals in China have even used simple Gancao Ganjiang decoctions to prevent COVID-19. In addition to being able to act as an antitussive and expectorant, *Glycyrrhizae Radix et Rhizoma* has adrenal cortex hormone-like effects, which can resist inflammation and provide detoxification^[14].

4.2 Treatment principle 2: tonifying deficiency of the body throughout the entire disease course

The innate immune function of the elderly is significantly lower than that of younger people. For example, the innate immunity of a 40-year-old is typically half that of an 18-year-old, and that of a 70-year-old is typically one-tenth that of an 18-year-old. The majority of elderly people have a myriad of pre-existing conditions or chronic diseases, and most young people who die of COVID-19 are those with either extremely weak immune function or those who are already suffering from underlying or preexisting conditions.

To improve the body's innate immunity, TCM generally implies a principle of "tonifying deficiency". Four of the ten types of the physique of the human body are named after "deficiency", specifically: *qi* deficiency, blood deficiency, *yin* deficiency, and *yang* deficiency. If these deficiencies correspond to the body's self-healing mechanism or immunity, the corresponding CHMs that promote the body's self-healing mechanism shall mostly be as follows: Sijunzi decoction or Buzhong Yiqi decoction for deficiency of *qi*; Siwu decoction for deficiency of blood; Zhibai Dihuang pills for deficiency of *yin*; Jinkui Shenqi pills or Fugui Bawei pills for deficiency of *yang*; Bazhen decoction for deficiency of both *qi* and blood; and Shiquan Dabu pills (Bazhen decoction plus *Astragali Radix*, *Cinnamomi Cortex*) for deficiency of *qi*, blood, *yin*, and *yang*.

The relationship between long-term chronic diseases and deficiency syndrome is relatively easy to understand, but the relationship between acute diseases such as COVID-19 and deficiency syndrome (so-called acute deficiency syndrome) still cannot be overlooked^[15]. As tonifying deficiency of the body is essential for the prevention or treatment of COVID-19, many TCM experts have already proposed "tonifying deficiency of the body throughout the entire disease course" as a treatment approach. When choosing the appropriate method of tonification, the primary focus should be reinforcing *qi* and warming *yang*, although nourishing *yin* and enriching blood may be required for severe cases or during the recovery stage. For the deficiency of both *qi* and *yin*, the Shenmai drink (*Panax Ginseng* or *Eleutherococcus Senticosus*, *Ophiopogonis Radix*, *Schisandrae Chinensis Fructus*) can be selected. A recent study showed that a 2-week treatment with the Shenmai drink improved chest-tightness symptoms more than the placebo, as well

as effectively improved lung and heart function and the quality of life of patients recovering from COVID-19^[16].

According to the basic formula of systems medicine, the approaches of reinforcing any deficiency, herewith, achieve their effects by increasing the denominator; hence, the homeostatic deviation of the body would be less.

4.3 Treatment principle 3: treating the affected lung and intestine simultaneously based on visceral interactions

There are two common ways for COVID-19 to induce the homeostatic deviation to spread or expand throughout the body: (1) through the functional connection of the lung-intestine, (2) *via* the connection between the blood supply of various systems (ie, inflammatory factors and microthrombosis in the blood vessel wall). There is evidence that under pathological conditions, the lungs and intestines interact with one another, and lung diseases can modify the structure of intestinal flora. For example, viral infections in the lungs can cause disturbances in the homeostasis of the intestinal flora, induce intestinal inflammation, and cause tissue damage and diarrhea^[17]. Intestinal inflammation can also increase the permeability of the capillaries in the intestinal wall, causing inflammatory factors, bacteria, or viruses in the intestine to easily enter the circulatory system and the lungs through the portal vein, liver, and heart; this can all exacerbate lung inflammation or change the body's pulmonary flora, resulting in secondary fatal bacterial infections.

It has been often observed in clinics that the first inflammatory response of COVID-19 occurs in the intestine. Diarrhea, nausea, and other gastrointestinal symptoms are often the earliest symptoms in patients with COVID-19 pneumonia, although fever and cough are the most common symptoms in general. COVID-19 viral can be detected in specimens of feces besides nasopharyngeal swabs, sputum, lower respiratory tract secretions, and blood^[1]. The latest research also shows that the microflora in the respiratory tract and intestine influence one another and are able to synchronize their immune response as well as cell factors^[18]. Therefore, it is evident that inflammation of the lung and the intestine is reciprocally causal. The vicious circle (Fig. 3) further amplifies the inflammatory response, leading to the failure of organ function.

This interrelationship between the lung and intestinal inflammations is modern evidence of the classic expression that "the lung and large intestine are exterior-interiorly related" based on TCM theories. The large intestine in TCM is not the same as the large intestine in modern anatomy, and it may refer to the entire digestive system from the perspective of its functions. Hence, the authors have proposed the treatment principle of "treating the affected lung and intestine simultaneously", in which the intestine also represents all abnormalities of the digestive system.

Numerous clinical studies have shown that CHMs not only can relieve lung inflammation but also regulate intestinal flora, improve the barrier function of the intestinal mucosa, and help restore the balance of the lung-intestinal system.

The clinical manifestations of COVID-19 are quite different from those of other respiratory infectious diseases. In patients with severe COVID-19 infections, the early symptoms are mostly imperceptible, but the virus spreads rapidly, often directly attacks the lungs; additional symptoms appear, and patients may quickly take a turn

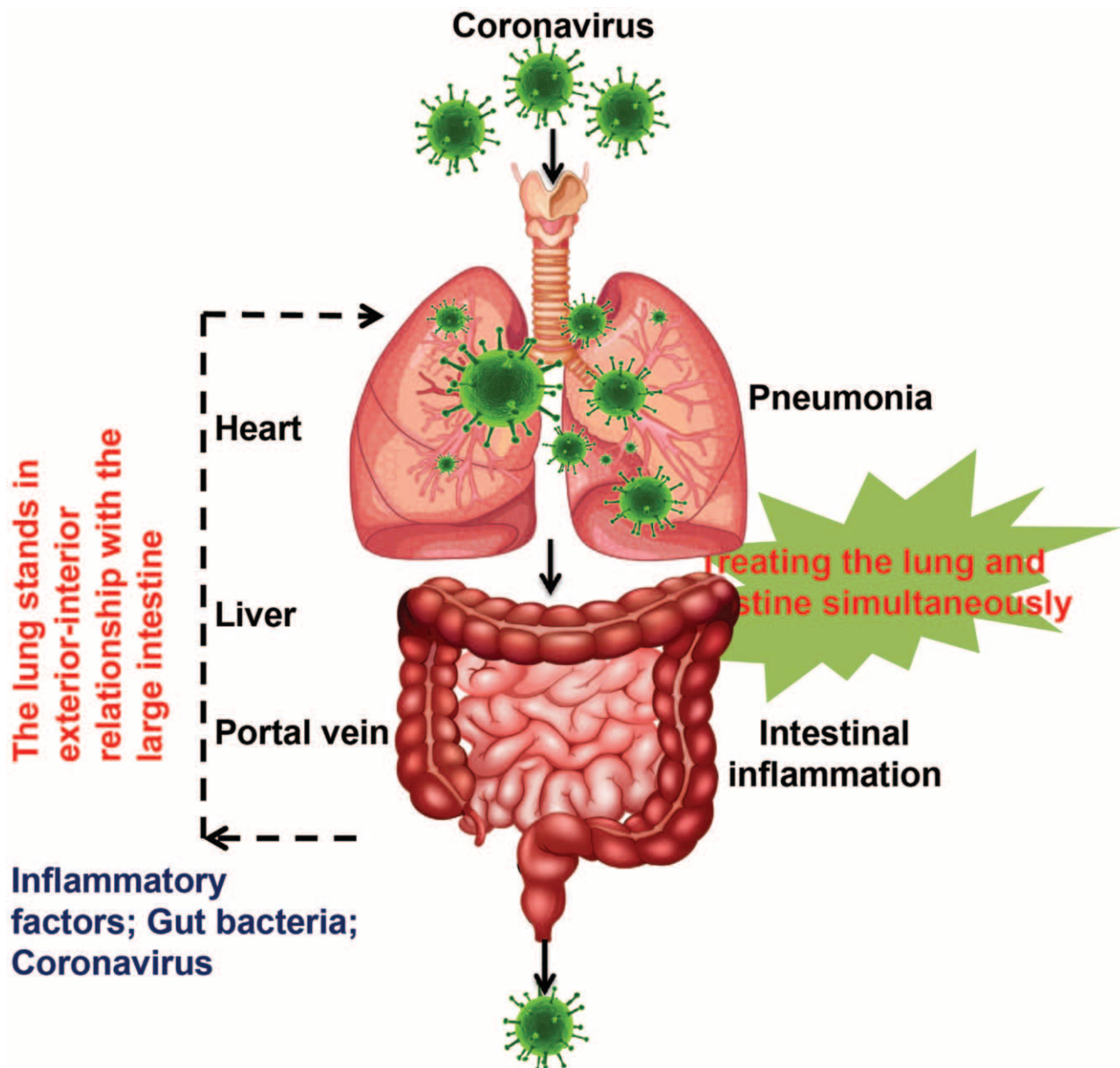


Figure 3. The vicious cycle of lung-intestinal inflammation and simultaneous treatment of the lung and intestine.

for the worse, with their condition going from fair to severe, with symptoms such as high fever, shortness of breath, abdominal distension, diarrhea, or constipation. For these types of severely ill cases, TCM experts in Shanghai, China, first proposed the principle of “treating the affected lung and intestine simultaneously” in their specific region of care, with which the authors agree wholeheartedly^[19]. For this, there are at least two CHMs applicable: Lianhua Qingwen capsules and Dachengqi decoction. For lung treatment, all four herbal ingredients of the “Maxing Ganshi decoction” are needed to prevent the disease from worsening, and additional heat-clearing and detoxifying herbs such as *Forsythiae Fructus*, *Lonicerae Japonicae Flos*, *Isatidis Radix*, *Houttuynia Cordata*, and *Menthae Haplocalycis Herba* should be added. This classical CHM was used as a primary reference in the creation of Jinhua Qinggan granules. Of course, other effective CHMs could also be used for intestinal problems. For example, for fatigue with gastrointestinal discomfort,

vomiting, and diarrhea in cases with mild symptoms and under medical observation, Huoxiang Zhengqi liquids or tablets should be the first choice; for those with fever and constipation, Fangfeng Tongsheng pills^[20] can be used.

Any pre-existing intestinal disorders may aggravate intestinal inflammation in patients with COVID-19. Different herbs and their combination may be selected, but the principle remains the same. Either acupuncture or moxibustion can be selected to treat pre-existing intestinal symptoms, despite the presence of diarrhea or constipation because they have the same bi-directional regulatory roles.

Simultaneous treatment of the affected lung and intestine is a form of multi-target therapy, such as the “cocktail therapy” used for AIDS treatment, which benefits from having compound formulations (ie, multiple ingredients with synergistic properties). The Qingfei Paidu decoction for COVID-19 also belongs to such compound formulations and may generate more benefits over single herbs. These multi-target therapies include requiring only

small effective doses for each ingredient (ie, the synergy of several different herbs with similar effects), and being able to mutually offset side effects (ie, when a cold-natured herb is used in combination with a hot-natured herb). This is particularly suitable when the TCM pattern differentiation is unknown or when the patient's condition is extremely dire, with little time to differentiate the syndrome before administering treatment. It must be noted that this principle does not mean treating the symptoms of the lung and intestine equally. When the pulmonary syndrome is shown as the primary issue, it is still necessary to first clear the lungs. When gastrointestinal symptoms are the primary concern, the spleen and stomach organs may first need to be regulated according to TCM theories. During the treatment, it is especially important to pay attention to problems associated with the connective mechanisms of the two organs (such as improving the permeability of the intestinal wall) to break the vicious circle, which represents how those functions of these two subsystems deviate mutually from their steady states. Breaking the circle by treating these problems simultaneously is critical to controlling the severity of the disease.

4.4 Treatment principle 4: cooling blood and removing blood stasis in later stages

The cause of blood stasis in TCM can be generally classified as either cold coagulation or heat toxicity. When blood stasis is caused by cold coagulation, there is usually pain associated; in that case, a key treatment principle with CHM is promoting blood circulation. When blood stasis is caused by heat toxicity due to acute inflammation,

in addition to promoting blood circulation, specific anti-inflammatory CHMs (cooling blood herbs) must be added.

It has been observed in clinical settings that heat toxicity and blood stasis are common manifestations of critically ill patients with pestilence or damp toxicity. For example, patients with COVID-19 in later stages (II–III) (Fig. 4) may develop numerous coagulation dysfunctions and may be harmed by the formation of microthrombi, mostly caused by acute inflammation and the destruction of blood vessel walls. Although the incidence of thrombosis in patients with COVID-19 has not been determined, approximately 50% of cases are accompanied by hypercoagulability during disease progression, and this proportion is as high as 100% in COVID-19-related deaths^[21]. Therefore, the method of cooling blood and removing blood stasis must be adopted as early as possible.

Many Chinese herbs could cool blood and remove blood stasis. Notably, all the herbs could be divided into two main types (anti-thrombotic or hemostatic functions), respectively. Those with the anti-thrombotic function are *Paeoniae Radix Rubra*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Angelicae Sinensis Radix*, *Chuan-xiong Rhizome*, *Carthami Flos*, and *Ginseng Radix et Rhizoma* etc. Those with the hemostatic function are *Carthami Flos*, *Rubiae Radix et Rhizoma*, *Sophorae Flos*, *Imperatae Rhizoma*, *Cirsii Japonici Herba*, *Cirsii Herba*, and *Agrimoniae Herba* etc. For patients with COVID-19 who are prone to microthrombosis, anti-thrombotic Chinese herbs should be used instead of promoting hemostasis. Certain Chinese herbs that can cool blood, such as *Anemarrhenae Rhizoma*, *Rhei Radix et Rhizoma*,

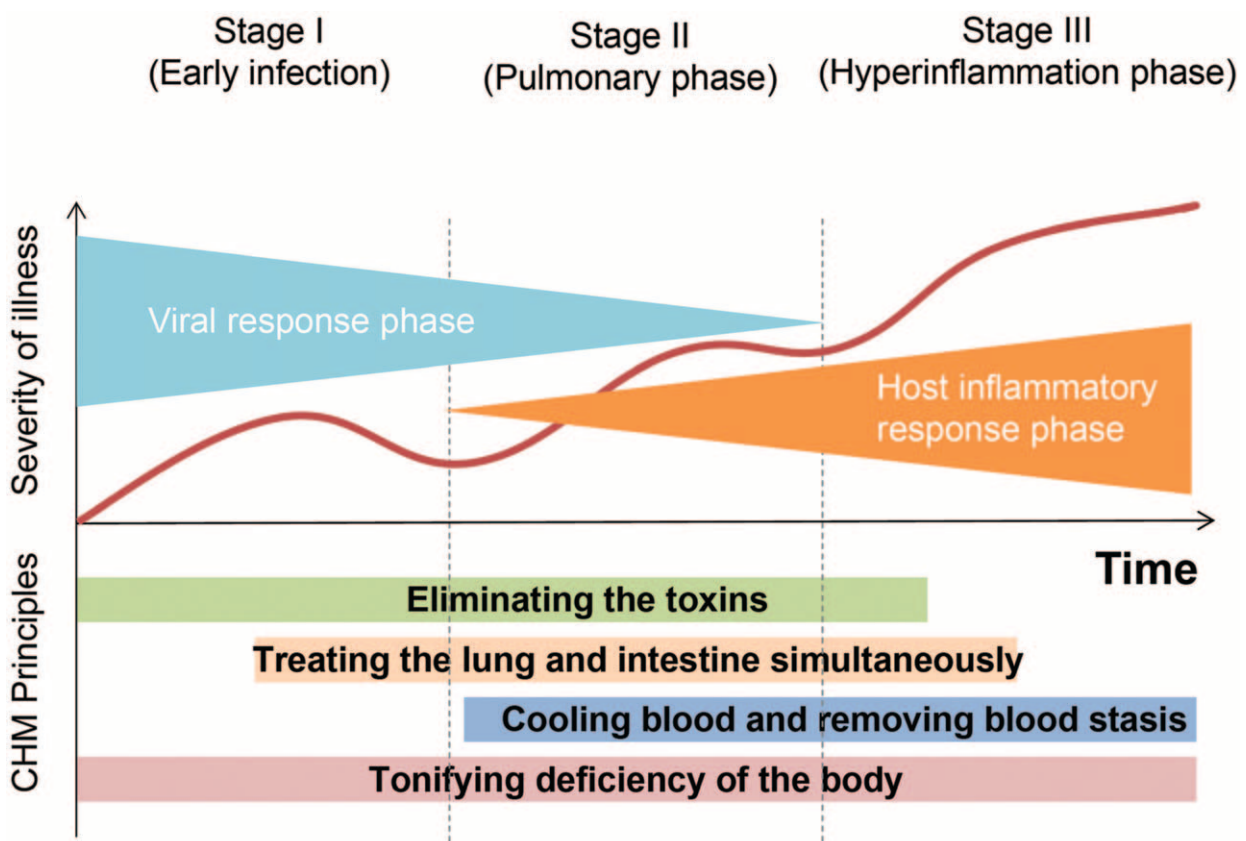


Figure 4. Chinese herbal medicine treatment principles for different stages of COVID-19. COVID-19: coronavirus disease 2019.

and *Moutan Cortex*, can be combined. Additionally, Xuebijing injection is another great alternative compound, with its main ingredients being *Carthami Flos*, *Paoniae Radix Alba*, *Chuanxiong Rhizome*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Angelicae Sinensis Radix*, and other extracts. Here, the ingredient of Safflor Yellow A can help antagonize endotoxin *in vitro*, which helps prevent inflammation and subsequent cytokine storms. The second benefit of applying Xuebijing injection is its anti-thrombotic function, as it has been used in conjunction with acupuncture to treat severe COVID-19 cases^[22].

From the perspective of systems medicine, at later stages (II–III) of COVID-19, applying the method of cooling blood and removing blood stasis is critical to avoid a domino effect that may eventually result in the destruction of the complete sets of homeostatic states.

5 Discussion and conclusions

The useful insights that have come out of successful experiences of using CHM for COVID-19 are as follows.

First, ancient TCM physicians and experts have accumulated a solid experience in applying CHM to fight various epidemics throughout the history of China. For example, the Qingfei Paidu decoction in the “three medicines and three TCM prescriptions” is a combination of several classic CHMs in the book titled *Treatise on Cold Pathogenic and Miscellaneous Diseases (Shǒng Hán Zǎ Bing Lùn)*^[23].

Second, the advantage of applying CHM is found not only in the treatment of chronic diseases but also in the treatment of many acute diseases. In our opinion, the positive experience of applying CHM in preventing and treating acute diseases absolutely deserves a proper evaluation, promotion, and development from the greater scientific and medical community.

Third, effective CHMs for COVID-19 are not limited to just “three medicines and three TCM prescriptions”. Many other CHMs using different recipes can generate equally effective results as long as they are prescribed according to TCM theories. In the above, the authors categorized them into four major treatment principles: (1) focusing on eliminating toxins in the early stage, (2) tonifying deficiency of the body throughout the entire disease course, (3) treating the affected lung and intestine simultaneously based on visceral interactions, (4) cooling blood and removing blood stasis in later stages. The rationale of the application of these four CHM treatment principles is derived from analyzing different stages of the disease’s progression or outcome^[24] (Fig. 4): eliminating toxins is of the utmost importance at the early-mid onset stages (I–II). Tonifying deficiency of the body should be conducted throughout the entire disease process. Simultaneous treatment of the lung and the intestine is mainly suitable for cases that have initial gastrointestinal symptoms or coexisting respiratory and digestive symptoms; cooling blood and removing blood stasis is particularly important for severe or critical patients at later stages (II–III).

Here a question may arise, that is whether TCM pattern differentiation is absolutely required during the treatment of COVID-19, especially when a single CHM formula was effectively used for thousands of cases in China. If a custom CHM formula is administered for each COVID-19 patient, will that produce a better

curative effect than the aforementioned single CHM formula for thousands of cases? According to TCM theories, pestilence is a type of acute disease. For such acute diseases, the treatment targeting individual symptoms is particularly critical. *Inner Canon of Huangdi (Huáng Dì Nèi Jīng)* is also in line with the notion of “the disease may be mild or severe, and treatment may be urgent or conservative”^[5]. Therefore, in a pinch, using a single CHM to treat “thousands of urgent cases” remains viable. Besides, even if applying only a single CHM, there is usually a myriad of Chinese herbs composed in that formulation, covering all the symptoms or pathogenesis that need to be controlled and suitable for patients of different constitutions. Nevertheless, for cases that are in the recovery period, the treatment based on TCM pattern differentiation may have better results. From the basic formula of systems medicine, it is easier to grasp the relationship between disease (symptoms) differentiation and pattern differentiation: the intervention of its numerator b can be regarded as “treating *biao* (symptoms)”. Currently, symptom differentiation or disease differentiation is more important than pattern differentiation. As for the intervention of its denominator $1 - (k + a)$, it can be regarded as “treating *ben* (root causes)”, and the treatment based on pattern differentiation should have the optimal effect as shown in Figure 2(3).

From the above reviews and analyses, it is obvious that the holistic and systemic views of TCM have always sowed the seeds of development of systems medicine^[25] and this anti-pandemic role of CHM can provide another niche for applying the principles of systems medicine to develop TCM and quicken its integration with modern medicine. On the other hand, the goals of TCM interventions, specifically CHM, are adjusting the balance (achieving the balance of *yin-yang*) of the body, and systems medicine has the most assertive, modern, and scientific expression on how to approach such balance point (steady-state), not only *via* qualitative descriptions, but also *via* quantitative calculation. Applying systems medicine can not only help interpret the rationale and advantages of using CHM as a primary anti-pandemic intervention, but also help derive patterns or principles from the numerous effective experiences of CHM applications in the anti-pandemic fight. In addition, the basic formula of systems medicine can also guide the flexible applications of TCM principles of pattern differentiation or disease differentiation.

To summarize, in this article, four CHM treatment principles are analyzed to guide the clinical treatment for different stages of COVID-19, and the rationale behind these principles is clarified from the view of systems medicine. This is helpful not only in reducing the complexity of promoting the extensive applications of CHM to further improve the anti-coronavirus efficacy, but also in ramping out the process of integrating TCM with modern medicine.

Conflicts of interest statement

The authors have no conflicts of interest to disclose or declare.

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Author contributions

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Ethical approval of studies and informed consent

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