

## Review Article

# Clinical Use of Chinese Medicine in the Current COVID-19 Crisis and Related Research Planning

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**Abstract**

During the current COVID-19 pandemic, since the crisis started in China, extensive reports regularly came out from China National Health Authorities and individual epidemiological and viral experts of different origins, giving the up-date data of the spread and treatment regularly. Reports concerning the use of Traditional Chinese Medicine were plenty. Collection and analysis of the rich data provide good understanding how Tradition Chinese Medicine was utilized in the combat against the COVID-19 infection. Early reports obviously emphasized the treatment aspects. Later reports had more information on the preventive side since the overall clinical presentation of COVID-19 involved many mild cases, treatment of which, using herbal medicine, should resemble situations of prevention before the actual contraction of the infection.

Later, the National Bureau of Traditional Chinese Medicine and the Committee on Public Health and Hygiene gave proper recommendations on the prevention side and advocated the joint utilization of one common herbal formula.

Apart from critically looking at the clinical value of the selected common herbal formula, the basic mechanisms leading to prevention: how is personal protection achieved need to be explored. Could it be related to the boosting of the innate immunological system? This could be the direction of current research planning.

The plan of research involves a systematic investigation on how the innate immunological system respond to the herbal treatment. The research procedures under planning concentrate on the in-vitro and in-vivo investigations in laboratory platforms on the responses to herbal treatment. A small pilot study will further strengthen the evidences when 30-40 healthy volunteers will get their blood checked before and after consumption of the innovative formula.

The herbal formula recommended by the Chinese Authorities will not be used as the target of investigation since it contains 21 herbs one of which (Asarum) is well known for renal toxicity. Instead, an innovative formula of simpler composition that has won good clinical trust in the SARS crisis of Hong Kong in 2003 will be the subject of study, to be investigated together with Vitamin D as a coupling supplement for infection prevention of the respiratory tract.

**INTRODUCTION**

Seventeen years ago, right after the SARS epidemic in Hong Kong and China. We prepared a manuscript entitled "The Efficacy of Chinese Medicine for SARS: A Review of Publications after the Crisis [1]." Today within the present COVID-19 pandemic, we would continue our work through objective observations on how Chinese Medicine is being used in China to counteract the COVID-19 crisis, thence get prepared to start a timely research project planning.

During the SARS crisis in China, 40-60% infected patients, at some stages of their treatment, received Chinese medicine on top of the standard modern medicine treatment. This practice was endorsed and encouraged by the Chinese Center for Disease Control and Prevention, and some details of the herbal treatment were provided. A review of the publications during and after the SARS crisis enabled us to get an objective view of the true value of the adjuvant therapy using Chinese medicinal herbs. Of the 130 articles searched, 90 were of reasonable quality and contained

sufficient information for the enlightenment of the situation. The review revealed positive but inconclusive indications about the efficacy of the combined treatments using Chinese medicine as an adjuvant. Positive effects using adjuvant herbal therapy included better control of fever, quicker clearance of chest infection, lesser consumption of steroids and other symptom relieves. In a few reports, some evidences of immunological boosterings were also found [1].

One important publication after the SARS crisis summarized the total drug expenditure in the Beijing Xiao Tang Shan Hospital, which was built as an emergency set-up to accommodate over 680 SARS patients. The statistics given by the dispensary indicated that the majority of drugs used fell into the modern medicine categories, whereas only a small proportion was of Chinese medicine nature. The varieties of the latter included items for the control of symptoms like cough, high fever and diarrhea, i.e. for supplementary uses [2].

An outbreak of pneumonia caused by Novel Coronavirus

(CoVID-19) in Wuhan, Hubei province in China, started in December 2019, and spread to other countries worldwide. This outbreak brought back memories of the severe acute respiratory syndrome (SARS) in China and Hong Kong in 2003, caused by a SARS-CoV2-coronavirus [3-5]. SARS-CoV-2 rapidly spread from southern China in 2003 and infected more than 3000 people, killing 774 by 2004.

The COVID-19 virus bears similarities with SARS CoV in molecular structures, but the infectivity and clinical presentations of the infected have been quite different. The incubation period is more variable, and the respiratory symptomatology is somewhat unpredictable [6]. The outbreak in Wuhan and subsequent spread in China have already shown the scale of involvement is much much larger than the SARS epidemic and the 80,000 more infected have demonstrated a hundred times more difficulties in the clinical managements. A joint international inspection on the COVID-19 epidemic in China was organized by the WHO in February 2020. Following that, a joint report gives detailed data: the responsible virus, the outbreak, the infectivity, clinical pictures and the managements [7].

One unique feature given in the report is that infected people could be categorized as Very Severe (5%), Severe (10-15%), Moderate and Mild (80%). In China where Traditional Medicine is so popular with standard infrastructures like Traditional Chinese Medicine hospitals and clinics, those infected and present with moderate to mild symptoms would naturally seek remedy from Chinese Medicine. In addition, those undiagnosed or worrying about infection, would also look for Chinese Medicine rescue. Such vast areas of epidemic infection in China has created excellent venues for research related to the use of Traditional Chinese Medicine [8].

## REPORTS FROM CHINA

[From the very early stage of the epidemic in January 2020, different Chinese Medicine Universities and Institutes in different provinces started to give open advice to the public on the use of classical herbal formulae for COVID-19 sufferers. In general, 20-30 classical herbal formulae were recommended as anti-viral agents under different clinical situations personally felt by the user. As usual, Traditional Chinese Medicine experts would insist on herbal consumption only after expert's diagnosis and recommendation. The high-level recommendations indeed, have made serious precautionary warnings that "consulting the experts is mandatory" and "refrain from personal use [9]". Brief press releases on results of treatment for those diagnosed and hospitalized are also appearing. How the use of the ancient formulae correlate with the use of modern hospital treatment are unclear.

So, reports on the use of Chinese Medicine in this early part of the COVID epidemic appear quite similar to the SARS crisis in 2003. Searching through the WHO Joint Report of February 2020, one realizes that Traditional Chinese Medicine is mentioned in three areas, all related to treatment. One would have wished that the role of Chinese Medicine as a preventive agent could be included.

Living through the present Pandemic, we are getting up-date information from the internet day by day. Solitary reports could

be conveniently synthesized to give more information towards the later stages of the epidemic in China.

Thus it has been reported that all over China 630 hospitals serving COVID-19 patients have been using Traditional Chinese Medicine inclusively with other treatment. Nearly 600 top Chinese Medicine experts over the country have been involved in the planning and treatment. 10 classical formulae are most frequently used and the choice has dampened the need for easing pulmonary problem (heat and dampness). In the mild cases Chinese Medicine treatment overwhelms (only 10% patients use modern pharmaceuticals together.) In the more severe cases being treated in the hospitals, around 5% are also using Chinese Medicine. The overall observation is that over 90% of all recorded treatment programs have involved Traditional Chinese Medicine [10].

Academician Zhang Bo-li carefully analysed the results of different herbal formulae used for treatment of COVID-19 patients and concluded that one effective formula could be constituted from the present experiences and he is preparing a proper drug trial protocol to get proper endorsement from the China FDA (China Press April 2020).

On the other hand, the highly reputed Academician Dr. Zhong Nan Shan advocated the use of one popular herbal proprietary product "Lianhua Qingwen capsule" as a good treatment option for very mild symptoms as well as for the prevention of getting infected. The capsule has been popular in China, well known as an anti-influenza proprietary drug and has undergone many clinical trials for influenza patients. One meta-analysis of the reports indicated that: when compared with the anti-virus drug oseltamivir, it showed superiority in the relief of fever, headache, throat discomfort and cough [11].

The extensive geographic involvement of the COVID-19 epidemic, the large number of infected people with mild symptoms, and the clinical evidences of herbal medicine's efficacy in viral respiratory infections in the last decades, are all driving forces behind an enthusiastic interest and commitment on the research on Traditional Chinese Medicine, not only for treatment but also for prevention.

In March 2020, a group of Traditional Chinese Medicine experts from Hunan collected all available information from across China and analysed the different treatment programs under varying clinical circumstances (i.e. From very mild, mild, moderate, severe to very severe).

This report, however, fails to give confirmation about the real treatment value for severe cases. It has chosen to put some emphasis on the mild cases and prevention of deterioration [12].

Some details of this report will be given in the following paragraphs.

Concerning Treatment: the choice of herbal application followed the general staging of the disease and the complications after hospital admissions, to be advised by Chinese Medicine experts. Since different provinces and cities have their own groups of experts, the herbal formulae advocated were widely divergent although "Lung Toxicity" remained the common target. Descriptions on treatment details and results are obviously

simple and brief.

Concerning Prevention: the report emphasized a lot after giving a leading commentary, stating that historically the classical formulae stressed a lot about the value of prevention: advocating an intelligent intake of medication well ahead of the expected epidemic [12].

14 herbs were listed as the common choices in different formulae and varying circumstances of prevention. Moreover, other classical formulae and their minor modifications were presented from different provinces and cities. Sophisticated considerations were recommended for fine tunings of the formulae basing on different symptoms and judgments of "Balanced Health"; "Heat Tendency", "Cold Tendency"; "Flail Tendency" etc. Special groups of people like children, elderlies, pregnant women and chronically ill were also addressed.

The Hunan Review is a perfect collection of facts related to the use of Traditional Chinese Medicine within the COVID-19 epidemic, for treatment and particularly for prevention. Modern biological and pharmacological evidences are not the main concern.

In February 2020, the National Bureau of Traditional Chinese Medicine and the Committee on Public Health and Hygiene made a general recommendation that during the COVID-19 crisis one carefully selected herbal formula deserved to be used as a priority choice for the patients. The formula is compiled from four very well known classical formulae used extensively for influenza-like symptoms affecting the respiratory tract. The formula consists of 21 herbs and is advocated to be used under all circumstances and at all stages of the disease [9,13,14].

This directive must have been well-taken and followed. If there is a joint effort using this one formula in large number of treatment centres, the clinical results would be of great values.

Indeed among many clinical applications, one report just came out from Sichuan which has completed one clinical trial on a group of 98 admitted patients with proven COVID-19 infection screened and diagnosed strictly according to National Criteria [15-17]. The patients were admitted into 4 hospitals. There was no significant gender discrepancy and the age ranged from 40 to 70. The severities of pneumonic symptoms were classified as: Mild 55.1%, Moderate 33.7%, and Severe 11.2%.

The Clinical assessments: mainly fever, cough and weakness, were taken every 3 days. During the treatment period using the priority formula there were clear observations of progressive improvement. All patients survived and adverse effects had been minor. Laboratory investigations included standard liver and renal function tests, basic blood pictures and some inflammation related data like C reactive protein. There was no specific exploration on any change in the immunological defense system before and after taking the medicine.

The following conclusions were made: the overall clinical improvements in the first 3 days reached 84.2% (21% of which totally recovered and 30% improved greatly). In the following 3 days, 31% totally recovered and 30% improved a lot. At the end of 9 day's treatment, all recovered.

In this report, no reference was given whether the herbal medicine was given as the sole treatment agent or whether other pharmaceuticals were given together. Since only 11 cases belonged to the severe group, the value of the herbal medicine could possibly be related to the prevention of deterioration through a boosting up the natural defense of the diseased.

As the authors admitted: the trial involved only a small number of patients and understandably, there was no time to take into account other concomitant measures; yet the quick recovery of the mild group should have well supported the preventive use of the herbal medicine.

In spite of the convincing reports of good results, when the 21 herbal combination is studied carefully one discovers that there is one herb of great controversy: Asarum. The problem herb contains aristolochic acid, which is renal toxic and carcinogenic, hence not suitable for long term consumption [18-20]. Although there are many classical writings supporting its special and careful uses [20], in the present era, medicine containing Asarum should not qualify as a safe preventive agent.

## RESEARCH PLANNING

Now that good experience has been gathered from two coronal virus epidemics (SARS and COVID-19), and the creation of specific vaccine, is to be waited, we need to consider some other possibility of building up one's self-defense against infections. Traditional Chinese Medicine in the current combat against COVID-19 has gained so much attention and has made great contributions, particularly for the mild cases. Additional efforts could be put on the development of a simple, safe herbal formula that would boost up the immunological defense system against viral infection. The formula should not raise toxicity concerns and should have sufficient historical support, feasible for quality assurance and immunological platform studies.

At the peak of the SARS epidemic in Hong Kong, hospital workers were under high risks of the infection. During the SARS outbreak, herbal preparations had been used jointly with standard modern treatment in China. As a means to protect the at-risk hospital workers, an innovative herbal formula was created and consumed by 3160 of them for two weeks. During the two weeks, symptoms and adverse effects were close monitored. 37 of them had their serum checked for immunological responses.

The results showed that none of the herb consumers contracted the infection, compared to 0.4% among the non-consumers. Adverse effects had been infrequent and mild. There were hardly any influenza-like symptoms and the quality of life improved. In the group who volunteered to have their immunological state checked, significant boosting effects were found [21-23].

A total of 37 laboratory technicians completed the blood tests. There were no derangements in total white cells and lymphocytes, but the CD4/CD8 (helper/suppressor), ratio of T-lymphocytes increased significantly from  $13.1 \pm 0.5$  on days 0 to  $14.1 \pm 0.6$  on day 15 ( $p = 0.015$ ), and returned to the initial level on day 29. The B-lymphocyte count (cell/ $\mu$ l), however, decreased from  $282 \pm 142$  on day 0 to  $263 \pm 99$  on day 15 and  $247 \pm 94$  on day 29, both  $p < 0.05$ . There was no gender difference in these

changes. Both the transient increase in CD4/CD8 ratio and the persistent decrease in B-lymphocytes occurred when taking the herbal preparation. It is suggested that the herbal preparation might be producing beneficial immunomodulatory effects during its consumption [24].

The pleasant experience using an innovative anti-influenza Chinese Medicine formula in the SARS crisis of 2007 has prompted us to engage in a repetition of the same protocol with modifications to acquire personal protection against the COVID-19 infection. The emphasis is put on in-depth laboratory studies related to macrophage activities in their support to the innate immunological system in preparation to viral attack. On the other hand, a pilot study also target at the innate immunological changes of volunteers instead of their infection rate, (since Hong Kong had a low infection rate throughout the crisis) [24].

Coronavirus is an enveloped positive-sense RNA virus, which is characterized by club-like spikes projecting from its surface [25]. Macrophages, the major effector cells in the innate immune system, recognizes viral infection through Pattern Recognition Receptors (PRRs), PRRs such as Toll like receptors (TLRs), and RIG-I-like receptor (RLRs), which detect the conserved microbial components called pathogen-associated molecular patterns (PAMPs). During infection, TLR and RLR are essential for the recognition of microbial pathogens to activate intracellular signaling pathways for distinct pattern of gene expression that result in innate immune response against microbial infections and the development of antigen-specific acquired immunity. Among various know PRRs, TLR3 responses to double stranded RNA, a replication intermediate for many viruses [26]. TLR3 is therefore involved in antiviral responses by triggering the production of antiviral cytokines such as interferon (IFN), and other Th1 cytokines. RIG-1-like receptors (RLRs), constitute a family of cytoplasmic RNA helicases which are important to initiate the host antiviral responses. For example, RIG-1/retinoic-acid-inducible gene 1 has been shown to sense viral RNA, leading to production of type I interferons/IFNs [27]. In our previous studies on by studying adults hospitalized with viral infection, we confirmed that TLRs played play an important role for innate viral inhibition in naturally occurring influenza [28].

The innovative formula adopted from the SARS crisis consists of 12 herbs which are taken from two popular ancient anti-flu formulae: one from the Southern part of China and one from the North. Mixing the idea and tradition between the Northern and Southern of the country carries the assumption that since the formula is meant for the preventive boosting of all Chinese in different regions, it is more desirable to take reference to both Northern and Southern districts (Table 1).

Mc Greevey from Harvard, during the early pandemic, called for the attention on Vitamin D as a preventive agent against cold and influenza. He quoted two most informative publications concerned with the use of Vitamin D to protect against Cold and Flu. (29) Scientific evaluations are concentrated on immunological defence while clinical reports are concerned with epidemiological efficacy data. The authors gave good evidences of Vitamin D providing anti-inflammatory effects via innate and adaptive immune responses [30]. On the clinical side, controversial reports did not allow definite conclusions on the

**Table 1:** Innovative Formula.

|                                     |         |
|-------------------------------------|---------|
| <i>Folium Mori</i> (桑葉)             | 3.75 gm |
| <i>Flos Chrysanthemi</i> (菊花)       | 1.5 gm  |
| <i>Semen Armeniacae Amarum</i> (杏仁) | 3 gm    |
| <i>Fructus Forsythiae</i> (連翹)      | 2.5 gm  |
| <i>Herba Menthae</i> (薄荷)           | 1.25 gm |
| <i>Radix Platycodonis</i> (桔梗)      | 3 gm    |
| <i>Radix Glycyrrhizae</i> (甘草)      | 1.25 gm |
| <i>Rhizoma Phragmitis</i> (蘆根)      | 3 gm    |
| <i>Radix Scutellariae</i> (黃芩)      | 6 gm    |
| <i>Folium Isatidis</i> (大青葉)        | 8 gm    |
| <i>Radix Astragali</i> (黃芪)         | 7.5 gm  |
| <i>Radix Saposhnikovia</i> (防風)     | 5 gm    |

preventive efficacy [31]. In view of the lack of effective preventive agent, he advised that Vitamin D should be considered together with other essential nutritives as favorable supplements in the overall support and fight against viral infections [32].

The extended plan of research therefore, would include Vit. D as an additional supplement to the innovative herbal formula to explore for additional or synergistic immunological boosting effects.

## DISCUSSION & CONCLUSION

Cold and Flu affections most probably have been common for all human beings ever since the pre-historical era. Traditional Chinese Medicine which served the Chinese people since over 3,000 years ago, has valuable records on the use of herbs for the treatment and prevention of febrile illnesses. In the past decades, many of these herbs and herbal formulae have been studied on bioactivity platforms and shown to be anti-inflammatory and immunologically boosting [33,34]. Clinical trials with different levels of reliability have also been done, resulting in observations of plausible but unconfirmed efficacy. The complex immunological responses favouring prevention in situations of viral attacks appear similar to those observed in Vitamin D research related to prevention of cold and flu.

COVID-19 appears to be hitting the health system harder than infected individual patients, since recovery, though unpredictable, could be quick, and mortality tends to be low. The large numbers infected lead to the overloading of health-care facilities and unsurmountable risks and stress for the careers. An agent that possibly improves the general self-defense of the people within the epidemic zone would be of additional value to the future target orientated vaccine: both of them would lead to a smaller number of infected patients. Chinese Medicine has been working on a symptom relief basis. The mild cases apparently are protected from developing into the severe stages. This observation might be similar to a situation of Prevention for the individual when the viral agent is on its way to attack. The attack would not succeed because of the boosted immunological defense

of the individual after taking the immuno-supportive medicine.

The research protocol being planned has a major emphasis on the herbal medication's immunological effects in the laboratory. A pilot clinical trial would be organized to serve as a preliminary investigation on its real preventive effects. The changes in the immunological state of the volunteers would be helpful as further evidence on the preventive value.

None of the constituents of the innovative formula is phytochemically toxic and reported adverse effects have all been mild. Once the complex events which affect the immunological responses during the consumption of the herbal formula could be clearly worked out, its endorsement of application as a personal protection agent, like Vitamin D alone is expected. The platform studies will give evidence-based support to the said formula's immunological boosting effects, thus giving it solid support for subsequent development into a Preventive Agent against viral respiratory infection at large.

Using Chinese Medicine as self protective supplement during an outbreak of infectious disease apparently has been a well-accepted public practice in Chinese communities with taken for granted effects. Academics and experts might not consider that in-depth explorations to justify this practice is worthwhile [35]. After the SARS and COVID-19 pandemic, there should be.

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