ORIGINAL ARTICLE

# Therapeutic Protection against COVID-19 Infection While Waiting for Herd Immunity

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## ABSTRACT

**Background:** The COVID-19 pandemic has threatening features: High infectivity, divergent presentations – 5–10% severe; 10–15% moderate; and 70–80% mild; but low mortality. The main challenge so far has been the extremely high risks experienced by the medical carers and close contacts. While the absolute effectiveness of vaccines is yet uncertain, other means to boost up the immunological defense could be explored. **Materials and Methods:** A close look at the pulmonary responses to invading pathogens and how the related innate immunity system reacts would be the first step towards the planning. Various means of immune boosting agents have been studied and practically used. Vitamin D could be a good example which has been studied in detail of how a natural product could offer immune boosting effects. While herbal products have been popular in Chinese Medicine as preventive agents against different forms of infection their real value could be explored through the modern approach of drug development. **Results:** Classical records could help with the selection of herbs. Clinical records collected in the past epidemics could also help. The proper engagement starts with the organization of *in vitro* and *in vivo* platform studies to verify the immunological influences of selected items, followed by clinical trials with human volunteers. A research protocol emphasizing on macrophage activities is presented. **Conclusion:** It is proposed that appropriate medicinal herbs together with Vitamin D could be a good combination in the search for therapeutic protection to reach synergistic prevention.

**Key words:** Chinese medicine, COVID-19, herd immunity, therapeutic protection

## INTRODUCTION

The mysterious nature of the COVID-19 pandemic has been unveiled gradually. The nasty aspects being: It infects rapidly, especially among close circles like family members and living centers; it affects the elderly and chronically ill people much more than the young and healthy and the highest mortality rate is related to elderly home dwellers and various types of socially deprived groups. The soothing facts are that at least 80% of infected people had mild symptoms and they recovered well.[1,2] Therapeutic measures specific to the virus are actively going on trials with some promising, early results.[3] Vaccination has been an outcry ever since the start of the pandemic, and currently numerous groups and pharmaceuticals have produced vaccine candidates for emergency use.[4]

Effective therapy specific for the virus and the vaccine is considered so imminent because there is a general expectation that even when the current wave is eventually cleared, recurrent waves are expected. Moreover, wider spreads in Africa and South America still looks rather obscure.

The pandemic has certainly initiated different degrees of panic among different regions of the world so that socio-political activities in response to the spread of infection have concentrated mainly on quarantine isolations, border closures,

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socio-distancing, home-binding etc. Not much discussion has been put on personal protections apart from the use of face-masks and testing's related to the viral infection. Nutritional supplements like the use of Vitamin D might have convincing evidence of protection against influenza,[5] but people might consider it a belated message and only vaccines aiming at specific prevention with immediate responses is worth consideration.

We all agree that an effective vaccine is the common goal. Is it really true once, we get the effective vaccine, nothing needs be done? In any epidemic outbreak, apart from the chronically ill and aged people being more vulnerable, many others are apparently more resistant. In leprosy and tuberculosis, one or two members of the family might be infected while the other close members remain healthy. In this pandemic, only about 15–20% of infected people develop severe symptoms, while the rest recover rather smoothly.[1] A lot of them did not receive specific treatment.[2] There must be a defense system within the individual capable of resisting the infection effectively. We realize this is related to the innate immunodefensive system which could be effective or defective.

Hence, in this COVID-19 pandemic, while distributing and receiving the new vaccines, there could be explorations on the ways to effectively boost up the innate immunodefense of individuals, particularly those at high risk like medical personnel's and affected family members, before they have vaccination and even after.[6,7]

The innate immunodefense system protects mainly through activities of T cells which produce suitable environments of defense through the production of complicated enzymatic materials: The chemokines, cytokines, and interferons (IFN). Boosting of the defense ability refers to a quantitative increase in the cellular components and a qualitative enhancement of their related activities.[8] Since inflammation is always involved, control of inflammation forms an important part.

## METHODS AND RESULTS

### Pulmonary innate immunity

Pathogens entering the respiratory tract need to go through defense barriers before gaining access to the human body. Epithelial cells produce seroussecretions (commonly known as sputum) which contain lysozymes, lactoferrins, and defensins[5,8,9] which have direct lytic effects on the peptidoglycans of organisms.

After breaking through this defense, pathogens have to face the complements, a major component of innate immunity generating cytolytic activities. Then they need to face immunoglobulins created by the B lymphocytes after being introduced by the T cells. The successful entry of pathogens then faces a complicated environment of interplay between cytokines and IFNs. They could possibly be eliminated through this non-specific, antigen-independent immune network.

Protective immune therapeutics may act by neutralizing or inducing the direct lysis of pathogens, by interfering with microbial gene expression and growth, by enhancing and activating immune cells or a combination thereof.[10,11] When there is an urgent need, compounds of endogenous origin like cytokines could be used as nonspecific activating agents. Other non-specific immune modulators include attenuated or dead microbial products, natural compounds, plant fractions, glucans, synthetic compounds, antibiotics, and probiotics.[12]

### Immunoboosting agents for clinical use

For wide coverage to be offered to large circles of need, that is, the at risk, close or near contacts, artificially prepared agents need to be used instead of endogenous mediators like convalescent serum. The best known substances with immunotherapeutic effects are related to plants which own long histories of preventive applications, long before the full knowledge of infections, their causative agents and the course of events. Many of them have attracted bioscientists' attention and gained early evidences of therapeutic value.

Some examples of herbal origin are given as follows:

1. Extracts from tea leaves to control protease release from the severe acute respiratory syndrome (SARS) virus
2. The natural polyphenols in tea-leaves have been found to contain a compound 3-isotheaflavin-3-gallate capable of inhibiting the activities of 3C protease which is required for the viral replication.[13,14]
3. Herbal extracts promoted T cell activities and increase CD4/CD8 ratio
4. Peripheral blood samples taken before and after consumption showed increased total lymphocyte counts and helper/suppressor (CD4/CD8) ratio, indicating immune-boosting effects.[15,16]
5. Herbal material had been used as adjuvant component to enhance the immunogenicity of vaccines
6. One approach was to coadminister cytokines, sterile constituents of bacteria, or polysaccharides to influence the antigen-presenting cells, especially the dendritic cells.[17,18]
7. Potential gene-related targets like Mannose-Binding-Lectin (MBL)
8. MBL could be an important constituent of the human innate immune system. Studies have shown the association between MBL mutations and increased susceptibility to infections and autoimmune diseases. MBL may therefore be used as a target in the innate immunity when immunotherapy is being planned.[19,20]

9. Clinical studies using herbal extracts as a preventive agent against getting infected among the high-risk medical workers during an epidemic. One good example was provided n Hong Kong during the SARS crisis in 2003.[21] When medical workers were found resistant to SARS infection.[15]

### Vitamin D as another example

Historically Vitamin D deficiency has been linked with respiratory ailments such as common cold and influenza because of their seasonal variations. The prevalence is related to the cold cloudy months of the year with the least amount of sunlight which seriously affect the normal production of Vitamin D under the skin. Clinical studies have confirmed the correlation.[5]

Subsequently, laboratory studies have worked out the molecular mechanisms behind Vitamin D's preventive effects against respiratory viral infections.

Activities of Vitamin D rely totally on the presence of the Vitamin D receptors (VDR) which are found in most tissues throughout the body. Through the VDR Vitamin D modulates the innate and adaptive immune systems.[21] On the cellular level, it activates T and B cells, regulates anti-microbial peptides (AMP), upregulates toll like receptors (TLRs), and induces destruction of pathogens through autophagy.[22] Vitamin D facilitates adaptive responses through the T cells and B cells. Among the different types of cytokines produced, it particularly regulates the inflammation related groups such as Tumor necrosis factor α and IFN. The immunomodulatory effects of Vitamin D are related both to the early as well as the late phases of pathogen invasion.[23,24]

Vitamin D does not have the vaccine effect. It is nonspecific to the invading organism, and there is yet no recommended time frame with which it could claim the best efficacies. It acts like an endogenous antibiotic, stimulating the production of AMP's and at the same time putting inflammation under control.[25]

Before the very early days of the COVID-19 pandemic Mc Greevey in Harvard University called to the World's attention about the potential use of Vitamin D as a personal protective agent against respiratory epidemic.[26,27]

### Developing an evidence based immunobooster

The encouraging result of our 2003 SARS experience: Using a modified classical "anti-flu" formula for the personal protection of at risk medical workers against the infections is currently giving us much encouragement to get engaged in further research to get more evidence on its efficacy, with the aim of producing an herbal booster for immunological defense.[28-30]

Corona virus is an enveloped positive-sense RNA virus, which is characterized by club-like spikes projecting from its surface.[31] Macrophages, the major effector cells in the innate immune system, recognize viral attacks through Pattern Recognition Receptors such as TLRs and RIG-I-like receptor (RLRs) which identify the conserved microbial components called pathogen-associated molecular patterns. During the infection, TLR and RLR are essential for the recognition of microbial pathogens, followed by the activation of intracellular signaling pathways with distinct pattern of gene expression. The innate immune response against microbial infections is thus developed.[32] TLR3 is therefore involved in antiviral responses by triggering the production of antiviral cytokines such as 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-I/retinoic-acid-inducible gene 1 has been shown to detect viral RNA, leading to production of type I IFNs.[33] In our previous studies on adults hospitalized with viral infection, we confirmed that TLRs played an important role for innate viral inhibition in naturally occurring influenza.[34]

The research protocol under planning includes Macrophage Studies,' cytokines and chemokines studies; cell adhesion studies; luciferase reporter assay for NF-kβ activities; and special animal studies.[16,35-38] Since Vitamin D has gone through thorough platform studies of its immune-boosting effects[21] and although the clinical results of prevention have not been conclusive, the development of an evidence based preventive agent could include Vitamin D to form a combined Herbal-Vitamin D twin supplement.

Once the preclinical tests are completed, the immunoboosting agent could be put under clinical trials following the strict rules of drug development.

## DISCUSSION

In the 100 years following the "Spanish Pandemic" of Influenza, variants of the influenza virus had been responsible for three other serious epidemics in China and Hong Kong; and at least 8 more regional epidemics in the world.[39] Every time when China experienced the epidemic, herbal medicine in different formulations would be used for treatment. Zhang in 2006 reported 117 published articles discussing about the value of Chinese Medicine in influenza treatment.[29]

In spite of the popular use of herbal formulae specific for the prevention of seasonal influenza attacks throughout China, yet in the past 10 years only four very brief published reports on clinical trials for treatment and prevention are available. The target populations were medical staff; people in close

contact; and students. The sample size varied from a few cases to over 20,000. The low quality of the trials is very obvious. Only general impressions were given about the preventive effects.[40-44]

During the SARS outbreak, Traditional Chinese Medicine was included into many of the treatment programs. After the epidemic WHO held a special meeting with international participations to evaluate the effects of Chinese Medicine in the combat against SARS. Many reports gave convincing observations about the value of symptom controls such as improving dyspnea and fatigue; improving oxygenation, lessening steroid dependence, and hastening rehabilitation.[45] No report on prevention was available.

During the SARS epidemic, Lau and Leung reported a clinical trial at the peak of the crisis in Hong Kong aiming at the prevention of getting infected among the at risk medical workers serving SARS patients. An innovative formula combining two popular patent Chinese Medicines: one from Northern China, the other from the South, with the aim of achieving better harmony was used. 3160 workers were given 2 weeks' consumption after which infection rate and adverse effects were studied. Other hospital workers not consuming the formula were used as controls. The results showed that none of the herbal group contracted the infection, compared to 0.4% infection rate among the control group. Adverse effects were minimal.[46]

In the current COVID-19 Crisis the Commission of Health of the People's Republic of China issued "Guidelines on the Diagnosis and treatment of coronavirus disease 2019." In the sections related to the use of Chinese Medicine: 14 types of Chinese Patent Medicine were officially recommended for the treatment of the disease. 11 on-going clinical trials with divergent inclusions: From mild, moderate, to critically ill patients had been arranged in different cities in China, registered under the Chinese Clinical Trial Registry.[46] These trials were organized for confirmed cases receiving conventional treatment in hospital settings, while herbal medicine was also used.

The overwhelming enthusiasm on vaccine production is challenged by other known facts: The effectiveness of antiviral vaccines might not match expectations because of the frequent dynamic changes of the RNA sequencing of the corona virus leading to variants. In addition, elderly people and chronically ill patients might not be suitable for vaccine administration.[47,48]

## CONCLUSION

While we are waiting for reliable detail reports about the efficacy of the emergency vaccinations to stop the pandemic we could take a more open view on additional ways to protect people exposed to the viral threat: They are the medical attendants taking care of the infected patients, their family members and other close contacts. At the height of an epidemic large numbers of people would be at risk. Specific supplements might serve the purpose of protecting these high-risk groups through the boostering of their innate immunological defense. Vitamin D research enthusiasts have worked out the laboratory evidences of this vitamin in the boosting of innate and adaptive immunological responses of the individual against external biological invasions.[31] Reports on Vitamin D's clinical effects against cold and influenza-like infections are also plentiful.[32,33] As we witness good results with herbal treatment in China, the formulae used in mild cases for the control of deterioration, could be considered also suitable for prevention against the viral attack.[49-51] Development of an evidence-based immunoboosting agent from selected, simplified classical herbal formulae for the prevention of viral infections would be very much desired, possibly together with Vitamin D to achieve synergistic effects.

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