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The Potential Effectiveness of an Ancient Chinese Herbal Formula Yupingfengsan for the Prevention of COVID-19: A Systematic Review

Xin Yang[1], Rong Tian[1], Catherine Shi[2] and Alan Wang[3,4,5,6,*]

[1]School of Basic Medical Sciences, Chengdu University of Traditional Chinese Medicine, China

[2]Auckland Institute of Intelligent Medicine, New Zealand

[3]Auckland Bioengineering Institute, University of Auckland, New Zealand

[4]Faculty of Medical and Health Sciences, University of Auckland, New Zealand

[5]Centre for Co-Created Ageing Research, University of Auckland, New Zealand

[6]Centre for Brain Research, University of Auckland, New Zealand

Abstract: The COVID-19 has been spreading all over the world, and human health is at stake. Conventional medicine played an important role in the treatment and syndrome relief, while there is limited research evidence to support any prevention or antiviral treatment for COVID-19. Yupingfengsan is a classic formula with the effect of replenishing qi, consolidating exterior, and arresting sweating. Yupingfengsan has been widely used to treat various diseases in China and Southeast Asia for hundreds of years. Accumulating evidence suggests that YPFS has both immune-regulatory and anti-virus effects clinically, but leaving the mechanism elusive. In this paper, we reviewed the recent progress of Yupingfengsan in immune-regulatory and anti-virus activities, including the effect on mucosal immunity, biological antagonism, macrophages, adaptive immunity, and natural killer cells. From this systematic review, we speculate that YPFS can play an effective role in the prevention of SARS-CoV-2, but further experimental studies are expected to investigate the specific mechanisms. This review suggests an alternative direction for the prevention of COVID-19.

Keywords: Yupingfengsan, Traditional Chinese Medicine, COVID-19, immune-regulatory, review

1. Introduction

In December 2019, 27 cases of pneumonia of unknown origin were found in Wuhan, China. In January 2020, these cases were reported to be caused by a new coronavirus. In February 2020, the virus was then named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the disease was defined as Coronavirus Disease 2019 (COVID-19) [1]. The World Health Organization announced the COVID-19 a pandemic on March 11, 2020. COVID-19 represents a series of clinical manifestations, mainly including fever, cough, and fatigue, accompanied by lung infection [2]. SARS-CoV-2 is highly contagious, and humans are generally susceptible [3]. The virus continues to spread during 2020, with more than 50 million confirmed cases worldwide, but the end of the pandemic of COVID-19 is still unknown. To date, asymptomatic infection is a hidden factor threatening public health, but there is no effective and harmless vaccine or antiviral treatment for COVID-19. Therefore, it is very important to determine a prevention program as soon as possible.

Traditional Chinese Medicine (TCM) has a long history in preventing the spread of a pandemic. Since the 2nd century BC, it has been proposed that "abundant healthy qi inside can protect the body from external pathogens" in The Huang Di Nei Jing [4]. In recent years, it has played an effective role in preventing SASR and H1N1 [5, 6]. To prevent the spread of COVID-19, 23 provinces of China issued TCM prevention and control programs [6]. The results show that *Astragalus membranaceus* (Huangqi), *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Radix Et Rhizoma* (Gancao), and *Radix saposhnikoviae* (Fangfeng), are the most frequently used Chinese herbs [6] (Table 1). Coincidentally, except *Radix Et Rhizoma* (Gancao), the most commonly used assistant herb, the other three drugs can form a classic prescription called Yupingfengsan (YPFS).

YPFS was originally created by Liu Wansu (1110~1200 AD) with the formula of Baizhu Fangfengtang and Huangqitang in *Suwen Bingji Qiyi Baoming Ji*. The ingredients are the same in these two prescriptions, contain *Astragalus membranaceus* (Huangqi), *Rhizoma Atractylodis Macrocephalae* (Baizhu), and *Radix saposhnikoviae* (Fangfeng) but the proportion are 1:1:2 and 1:1:1. Later, after years of inheritance and improvement, it became

*__Corresponding author:__ Alan Wang, Auckland Bioengineering Institute, Faculty of Medical and Health Sciences, Centre for Co-Created Ageing Research and Centre for Brain Research, University of Auckland, New Zealand. Email: Alan.wang@auckland.ac.nz

Table 1. Frequency and dose of commonly used herbs in preventive formulae for COVID-19

Latin name	Pinyin	Frequency	Proportion	Dmean	Dmin	Dmax
Astragalus Membranaceus	Huangqi	16	16/24(66.67%)	13.3 g	9 g	20 g
Radix Glycyrrhizae	Gancao	16	16/24(66.67%)	6.67 g	3 g	15 g
Saposhnikovia Divaricata	Fangfeng	13	13/24(54.17%)	8.83 g	6 g	10 g
Atractylodes Macrocephala	Baizhu	12	12/24(50%)	11.73 g	9 g	15 g
Flos Lonicerae	Jinyinhua	12	12/24(50%)	13.36 g	9 g	30 g
Fructus Forsythiae	Lianqiao	9	9/24(37.5%)	13.56 g	9 g	30 g
Rhizoma Atractylodis	Cangzhu	8	8/24(33.3%)	9.63 g	8 g	12 g
Radix Platycodonis	Jiegeng	8	8/24(33.3%)	10.63 g	9 g	15 g
Pogostemonis Herba	Huoxiang	7	7/24(29.17%)	10.43 g	6 g	15 g
Osmundae Rhizoma	Guanzhong	7	7/24(29.17%)	9.07 g	5 g	20 g
Perillae Folium	Suye	6	6/24(25%)	8 g	6 g	10 g

YPFS is composed of *Astragalus membranaceus* (Huangqi), *Atractylodes Macrocephala* (Baizhu), and *Saposhnikovia Divaricata* (Fangfeng) in a ratio of 1:2:1 and three slices of ginger.

famous as "Yu Pingfeng San". Regarding the interpretation of its name, scholars in the Ming and Qing Dynasties have two opinions. One opinion is because it is used for patients who are exterior deficient with the effect of replenishing qi and consolidating exterior and can help resist external evils like a screen. Another opinion is because the sovereign medicinal of YPFS is *Astragalus membranaceus* (Huangqi) called "pingfeng" as alias, and "yu" means that its property is pure and does not hurt the healthy qi, so it is called *Yupingfengsan* [7].

The earliest surviving record of YPFS is in *Danxi's Experiential Therapy*, compiled by Zhu Zhenheng (1281~1358 AD), composed of *Astragalus membranaceus* (Huangqi), *Atractylodes Macrocephala* (Baizhu), *Saposhnikovia Divaricata* (Fangfeng) (1:2:1), and three slices of ginger. The safety of YPFS has been investigated by many articles and confirmed by clinical practice for hundreds of years [8, 9]. As for clinical practice, it can be used to treat a variety of diseases, including respiratory system diseases, digestive system diseases, autoimmune system diseases, urinary system diseases, endocrine system diseases, geriatric diseases, skin diseases, otolaryngology diseases, gynecological diseases, pediatrics diseases, etc. [10].

Due to the sustainability of the pandemic and the uncertainty of effectual vaccine, we aim to explore YPFS's potential function for prevention of COVID-19. After systematic investigation and summary, we found that YPFS has potential effectiveness in the prevention of viral pneumonia, which leads to the systematic review in this paper.

2. Materials and Methods

Five databases were searched, including China Network Knowledge Infrastructure, Wanfang Database and Chinese Scientific Journals Database, PubMed, and Google Scholar, with the keywords of "Yu Ping Feng" (or "Yu Ping Feng San" or "Yu Ping Feng Powder" or "Yupingfeng" or "Yu-ping-feng" or "Gyokuheifu-san"), "Pneumonia" (or "respiratory tract infection"), "COVID-19"(or "severe acute respiratory syndrome coronavirus 2" or "ncov" or "2019 ncov" or "sars cov 2" or "SARS-CoV-2"), "immunity" (or "immune" or "immuned" or "immunes" or "immunization" or "immunization") Select all relevant studies published before November 1, 2020.

After literature accumulation and analysis, we concluded that YPFS has an excellent performance in treating recurrent respiratory infections and improving immunity. We screened and excluded non-drug treatment research, research on other respiratory diseases (such as chronic obstructive pulmonary disease, asthma, chronic bronchitis, and allergic rhinitis), review research, and theoretical research. The immune function has been summarized multiple ways, multiple targets, and multiple components (Figure 1).

3. Results

In total, 2829 records (2,497 in Chinese and 332 in English) were obtained through database searches with the keyword "Yupingfeng". After adding other keywords and screening titles and abstracts, 44 articles relevant to recurrent respiratory infections and 59 articles about immune function remain. Studies about recurrent respiratory infections are all clinical research, while animal experiments and clinical research are demonstrated by the studies about immune function.

3.1. Effect on the human immune system

In many years of clinical practice, YPFS has effectively treated recurrent respiratory infections, influenza, and SARS. Meanwhile, after collecting and sorting out prevention formulae for COVID-19, it was found that *Astragalus Membranaceus* (Huangqi), *Atractylodes Macrocephala* (Baizhu), and *Saposhnikovia Divaricata* (Fangfeng) are the most frequently used Chinese herbs and couplet medicinals [6, 11, 12] (Table 1). In clinical trials of recurrent respiratory infections, after one year of observation, the YPFS treatment group (73.13%) was superior to the pidotimod group (67.15%), and the proportion of recurrent respiratory tract infection returning to normal standard level was higher than the rate in the placebo group [13]. Additionally, after applying YPFS, serum IgG and IgM levels were significantly increased, and the total number of lymphocytes and CD+3, CD+4, and CD+8 returned to normal levels [14]. For antiviral treatment, YPFS has also played an important role. YPFS inhibits the neuraminidase activity of influenza virus (IFV) A in epithelial cells because YPFS has the function of preventing virus release and spreading [15]. In 2013, medical staff in Hong Kong used YPFS for the prevention of SARS. None of the 1063 participants treated with Chinese medicine was infected with SARS, while the control group's infection rate (15,374) was 0.4% [5]. By protecting the cell membrane, Jiawei-YPFS prevents the IFV and the human respiratory syncytial virus (HRSV) from entering, and it reduces the lethality of the virus to mice, prolongs survival time, and reduces lung tissue damage [16]. The critical preventive functions of YPFS are summarized in the following seven aspects (Figure 1).

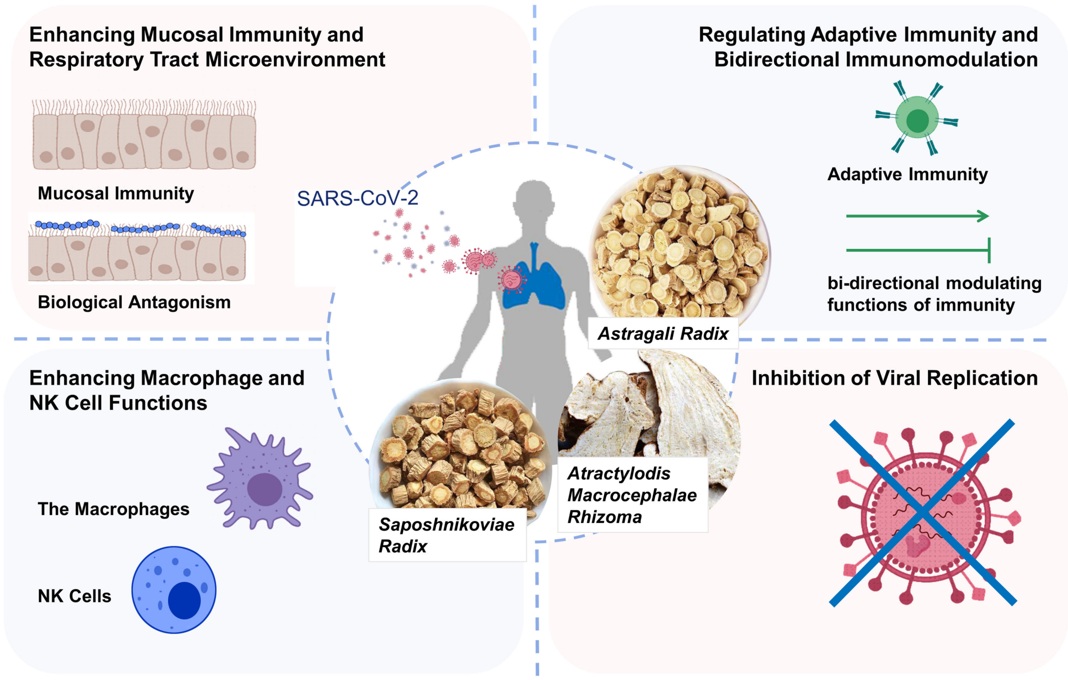

Figure 1. Multiple ways for the prevention of COVID-19

3.2. Mucosal immune defense mechanism

The respiratory tract, oral mucosa, and conjunctival epithelium are the first tissues SARS-CoV-2 invades [17]. These issues have both physical and secretory defense protection. The tightly connected cilia in the respiratory tract swing directionally, which can expel the inhaled pathogens and act as a physical barrier. At the same time, secretory immunoglobulin A (sIgA) secreted in the mucosa prevents pathogens from multiplying in the mucosal epithelial layer and prohibits them from entering the human body. Presenting the first defense line, mucosal can protect the body from viruses by secreting sIgA through mucosa-associated lymphoid tissue [18, 19]. When the viral load on the mucosa is low and does not enter the body to multiply, the effect of blocking virus invasion is considerable [20].

Therefore, Jiawei-YPFS reduced the susceptibility of cells to the invasion of the human respiratory syncytial virus, preventing the virus from entering the respiratory system, and achieving the effect of defending against the IFV [16]. An experiment on Yupingfengsan total polysaccharide (YTP) found that the prophylactic administration group can antagonize the decline in mucosal immunity caused by cyclophosphamide, and the level of IgA in the respiratory mucosa is higher than the treatment group [21]. At the same time, they found that YTP not only has a positive effect on the immunity of the respiratory mucosa but also has an immune-enhancing effect on the intestinal mucosa [21]. The theory of Chinese medicine can be explained by the interior-exterior relationship of lung and large intestine. In an experiment of YPFS prophylactic administration on H1N1 influenza A virus-infected mice, it was found that the inhibitory effect of YPFS was significant, and the level of slgA on the alveolar mucosa was higher than other control groups [22].

3.3. Improvement of the respiratory tract microenvironment

Recently, studies have shown that bacteria have diverse immune defense systems against viruses, such as restriction-modification, CRISPR–Cas system, and abortive infection systems [23]. Normal florae and conditional pathogens are present in the respiratory tract, but conditional pathogens will reduce human immunity to cause infection. Strengthening the normal flora and weakening the conditional pathogenic bacteria will help us prevent COVID-19, which is called biological antagonism [24]. Yanqin et al. found that *Astragalus Membranaceus* (Huangqi) and *Atractylodes Macrocephala* (Baizhu) can promote the growth of Streptococcus A, which play a role of spacing occupation or biological antagonism to prevent infection [25]. Giving modified YPFS to COPD model rats with low immunity can significantly reduce the number of Haemophilus influenzae, Klebsiella pneumonia, and Pseudomonas aeruginosa in the airways [26]. In the immunosuppressed state, the recovery of normal respiratory tract flora is suppressed, but the respiratory tract microenvironment is improved after being treated with YPFS [27]. Treatment with fermented Yupingfeng polysaccharides resulted in predominant flora and differences in gut microbiota [28].

3.4. Effect on mononuclear macrophages

As the second line of defense, dendritic cells, macrophages, and neutrophils start the immune reaction [20]. Monocytes from macrophages pass through blood vessels, swallowing pathogens and possessing host defense functions. Therefore, if innate immunity can detect the virus early and eliminate it effectively, the disease could be controlled at an early stage [29]. YPFS also has experimental records in enhancing the function of proliferation, activation, and nitric oxide synthesis of macrophages. It is performed that the unfermented Yupingfeng dreg polysaccharides (UYDP) and fermented Yupingfeng dreg polysaccharides (FYDP) markedly stimulate macrophage proliferation and enhance the immune activity of macrophages [30]. YPFS has a positive regulatory effect on peritoneal macrophages' immune activity in tumor-bearing mice [31]. The percentage of phagocytic cells and phagocytic index in the peritoneal cavity of immunosuppressed mice caused by hydrocortisone were significantly reduced, and the administration of YPFS can raise the above indicators to normal levels [32]. After using YPFS, the phagocytic function of peritoneal macrophages in immunosuppressed mice caused by cyclophosphamide was significantly improved [33].

3.5. The adaptive immunity

The adaptive immunity of COVID-19 is still under further study. However, like most viruses, SARS-CoV-2 has a strong immunosuppressive ability against adaptive immune responses [20]. However, in the severe stage of COVID-19, the immune system overreacts, forming a cytokine storm and worsening the patient's condition. We believe that enhancing adaptive immunity early may be beneficial. Under YPFS condition, the number of T-cell subsets in the spleen and thymus of mice immunosuppressed by traumatic stress was significantly higher than that of the control group [34]. Besides, the expression of NF-KB mRNA and IL-10 mRNA in the spleen and thymus was increased, serum INF level was decreased, and TGF level was increased [34]. YPFS improved the proportion of CD4+/CD8+ to the normal value in the dexamethasone-induced mice, elucidating that YPFS could regulate the T-cell subset of cellular immunity [35]. In in vitro and in vivo tests, polysaccharides isolated from YPFS obviously increased lymphocyte proliferation, and the ratio of CD4+/CD8+ T cells was significantly higher than the control groups and groups treated with PHA [36]. In vitro experiment showed that YPFS increased the percentage of mature DCs and stimulated IL-12 secretion in DCs, decreased the proportion of CD4+ T cells, and increased levels of Th1 cytokines [37].

In children with simple nephrotic syndrome using immunosuppressants, the serum IgG and IgA levels of the YPFS group returned to normal and were significantly higher than those of the control group [38]. Its recurrence and infection were lower than the control group, and the ratio of CD4+ cells and the ratio of CD4+/CD8+ were higher than the control group [38]. Xue Z et al. experimented on the lung injury mice induced by smoked soot; with preventive treatment, the levels of CD4+, CD8+, IgE, and IgG were greatly improved, elucidating YPFS can enhance cellular and humoral immunity [39].

3.6. Bi-directional modulating functions of immunity

We need the immune system to develop a balanced way to out of control and cause a cytokine storm with severe consequences. Studies have demonstrated that YPFS can both induce and suppress cytokines' expressions (IL-1β, IL-6, and TNF-α) in cultured macrophages [40]. YPFS not only enhances the immune suppression but also slows immune hyperactivity in murine T-lymphocytes and macrophages [41]. Carry out the Bi-directional immunomodulating activity of UYDP and FYDP in murine lymphocytes and macrophages [30].

3.7. Effect on Natural killer cells

Natural killer cell (NK cell) is involved in anti-virus, immune regulation, and anti-tumor. It is an all-round immune cell that contains three functions: immune surveillance, immune response, and immune memory. It plays a role in innate immunity against viruses without the need for prior sensitization. [42]. While NK cells' mechanism in eliminating SARS-CoV-2 has not yet been elucidated, the levels and functions of NK cells in mild and severe COVID-19 patients are significantly lower than ordinary people. Furthermore, the reduced NK cell levels and functions are associated with the disease's severity [43]. The study of the effect of YPFS on NK cells is of great significance for the prevention of COVID-19. When referring to killing activity, NK cells are independent of antibody, have no MHC limit, and play an outstanding role in anti-virus, and immune regulation. YPFS could strengthen NK cells' killing activity in an immunosuppressive model induced by dexamethasone [35].

It is elucidated that YPFS does have an immunomodulatory effect, and the enhancement effect on NK cells reaches its peak at 1 hour, and its efficacy gradually decreases after 3 hours [44]. An experimental study has shown that the immune function of amputation mice is affected, and NK cells' activity decreases significantly. However, the decrease in mice's NK cell activity taking modified YPFS is reduced, especially the high concentration of modified YPFS [45]. After using YPFS in S180-tumor-bearing mouse model, the growth of sarcoma is inhibited and NK cells' activity is increased [31]. For immunosuppressed mice caused by cyclophosphamide, NK cell activity can also be improved after taking YPFS [46].

3.8. Effect of antiviral

YPFS exerts antibacterial and antiviral effects in innate immunity [15]. After the mice were infected with human metapneumovirus, the virus titer in the lung tissue of the YPFS group was significantly lower than the model group; besides, its pathological changes of the lung tissue were close to normal [47]. In animal experiments, YPFS has the highest IFV inhibition rate than other groups, reaching 95%, indicating that its antiviral effect is evident [48]. Also, YPFS has an inhibitory effect on viruses outside the respiratory tract, such as herpes simplex virus (HSV) that causes HSV keratitis and varicella-zoster virus that causes herpes zoster [49, 50]. In addition, YPFS directly inhibits SARS-CoV-2 by the combination of SARS-CoV-2 protein and angiotensin-converting enzyme II (ACE2), which plays a role in the prevention of COVID-19 [51, 52].

3.9. Anti-coronaviral effect

Researches have suggested that SARS-CoV-2 infects human cells because of the combination of spike proteins and ACE2 [53–55]. This combination is essential for coronavirus infection. However, it is essential for countermeasure, as well. Coronaviruses employ the RNA-dependent RNA polymerase (RdRp) for coronaviral replication and transcription after entering cells, which shows potential for the treatment of COVID-19 viral infections [56]. In addition, the 3CL hydrolase (Mpro) of SARS-CoV-2 has a pivotal role in mediating coronaviral replication and transcription [57]. During the SARS-CoV-2 genome expression, a viral cysteine protease, papain-like protease, processes the encoded polyprotein precursor to release most of the proteins required virus replication [58]. These proteins would significantly impact the infection, replication, and proliferation of the virus in the host and provide a therapeutic target for developing antivirals to treat COVID-19 [59].

YPFS, a well-known TCM formula, is commonly used to cure respiratory systems and immune system diseases. The active constituents may be related to the effect of YPFS in diseases of the respiratory and immune systems [60, 61]. 11 flavonoid-related and 2 saponin-related components were detected in rat plasma by ultra-performance liquid chromatography coupled with electrospray ionization/quadrupole time-of-flight mass spectrometry [62]. Moreover, bioactive components of *Astragalus Membranaceus* possess the bioactivity of Antiviral Potential and Anti-inflammatory [63]. The bioactive compounds of *Astragalus Membranaceus* are flavonoids, triterpene saponins, and polysaccharides [64]. Numerous pharmacological studies have shown anti-inflammatory, antiviral, and antioxidant activities for the constituents of *Astragalus Membranaceus* [63, 65, 66]. Pharmacochemical analysis of *Atractylodes Macrocephala* showed that the main compositions were volatile oil, lactones, polysaccharides. Furthermore, *Atractylodes Macrocephala* possessed anti-tumor activities, neuroprotective effect, anti-hepatotoxicity, immune, anti-oxidation, and anti-inflammatory activity [67].

The therapies acting on the coronavirus themselves include inhibiting the virus binding to host cell receptors, blocking coronavirus replication by acting on the coronaviral critical enzymes, and inhibiting the coronaviral self-assembly process acting on crucial proteins [68]. Jia Yuan et al. analyze therapeutic targets for SARS-CoV-2 and discover YPFS is the potential formula by molecular docking [51]. Twenty-six active constituents showed acceptable binding interactions with ACE2, and nineteen active constituents showed good binding affinities with Spike protein, which could inhibit coronavirus infection. Moreover, 24 active constituents interact with the binding domains of RdRp, Mpro, and PLpro to inhibit coronavirus replication and transcription [51].

3.10. Potential material basis of YPFS

Astragalus Membranaceus, Huangqi, is renowned for its tonifying effects on the body's defenses and its ability to strengthen the immune system. It contains a variety of active components, including astragalus polysaccharides, astragalosides, and flavonoids, which contribute to its immune-boosting, anti-fatigue, hepatoprotective, diuretic, and anti-inflammatory properties. In the context of COVID-19, Astragalus has shown relative activity against SARS-CoV-2, potentially modulating the host's immune response and inhibiting viral replication. The targets of Astragalus include signaling pathways related to immune modulation, such as T-cell activation, cytokine production, and inflammatory responses [11, 69, 70].

Atractylodes Macrocephala, or Baizhu in TCM, is primarily used for strengthening the spleen, eliminating dampness, and stabilizing fetal development. Its chemical constituents comprise volatile oils, polysaccharides, and flavonoids. The mechanisms of action of atractylodes may involve regulating the digestive system, enhancing spleen function, and improving intestinal motility. In terms of immune regulation, atractylodes may influence the production of cytokines and the activity of immune cells [11, 69, 70].

Saposhnikovia Divaricata, or Fangfeng, is a TCM herb known for its ability to relieve exterior symptoms and alleviate pain associated with dampness. It contains coumarins and other active compounds. The antiviral mechanisms of saposhnikovia may involve disrupting virus-host interactions or inhibiting viral replication. Its anti-inflammatory, analgesic, and antiallergic effects suggest a role in modulating the body's immune response to pathogens [11, 69, 70].

Radix Glycyrrhizae, or Gancao, is a versatile TCM ingredient with demulcent, anti-inflammatory, and antiviral properties. Its main components are glycyrrhizic acid and glycyrrhizin. Glycyrrhiza's mechanisms of action may include anti-inflammatory, antiviral, immunomodulatory, and hepatoprotective effects. In COVID-19 treatment, Glycyrrhiza may modulate the host's immune response and directly inhibit viral replication, with its targets encompassing a range of immune and inflammatory pathways [69, 70].

In summary, Huangqi, Baizhu, Fangfeng, and Gancao are traditional medicinal herbs with multiple bioactive constituents that exert their therapeutic effects through various mechanisms, including immune modulation, anti-inflammation, and direct antiviral activity. These herbs have shown potential in the treatment of COVID-19, with their targets and mechanisms providing a scientific rationale for their use in TCM. However, further clinical trials and research are necessary to confirm and elaborate on their specific mechanisms of action.

4. Discussion

The identification of cold chain food contamination as a primary transmission route underscores the need for comprehensive preventive measures. Globally, the pandemic has reaffirmed that no country can navigate this crisis in isolation [3, 71]. The relatively low infection and death rates among children suggest a potential protective role of stronger immune responses [72]. Early interventions to bolster individual immune systems could be a valuable strategy in preventing COVID-19 spread [20]. Targeting the coronavirus itself is another effective preventive approach. The emergence of new COVID-19 variants, such as those with the N501Y mutation in the spike protein, has been noted by Covid-19 Genomics UK [73]. This mutation enhances the virus's ability to bind to the ACE2 receptor, increasing its infectivity [74]. Strategies that inhibit virus binding to host cell receptors could be crucial in preventing infection and disease progression [75].

Chinese herbal medicine has been widely used in the antiviral treatment and has the characteristics of multiple ways, multiple targets, and multiple components [76, 77]. The combination of medicinals in TCM is very delicate. Different preventive formulas have been proposed in 23 provinces because of regional and seasonal features and factors. However, preventive formulas issued by 12 provinces (Heilongjiang, Shanxi, Hubei, Hainan, Jiangxi, Shandong, Zhejiang, Shaanxi, Ningxia, Chongqing, Yunnan, Ningxia) are all based on YPFS. Though the formula variations exist, such as Hubei plus *Cyrtomium fortunei J. Sm.* (guan zhong) and *Lonicerae Japonicae Flos* (jin yin hua), Shandong plus *Radix Pseudostellariae* (tai zi shen) and *Radix Ophiopogonis* (mai dong), Shaanxi plus *Herba Agastaches* (huo xiang) and *Radix Glehniae* (bei sha shen), their core formula is always YPFS. Moreover, the formulas have different variations for people in each province according to different body constitutions and underlying diseases. For example, in the Shandong preventive program, pregnant women, children, the senior, and medical staff are provided with different modified YPFS. The differences in individual, regional, and seasonal factors determine the principle of medication. It is suggested that the application of YPFS in clinics needs formula variation by considering the signs and symptoms individually or regionally. It is consistent with the theory of "act according to time, place, and person" in ancient Chinese medicine.

YPFS is being researched for its potential in viral infection management, particularly COVID-19. It is known for its historical use in respiratory health and immune support. Current studies are focused on understanding its complex components and their effects on immune cells, which could lead to more effective, personalized treatments. YPFS also shows promise in public health, potentially strengthening community immunity against viruses. Despite the need for further research and standardization, YPFS represents a significant bridge between traditional practices and modern healthcare solutions.

Infection with SARS-CoV-2 is an internal cause of COVID-19 and develops into COVID-19 as a result. There is an external condition between the cause and the result that links them together. Therefore, the breakthrough in disease prevention is not only to change the internal causes but also to change the external conditions. When our physical condition is good enough to reach a situation where evil-qi cannot intervene, the virus is no longer scary. In short, the entry point of Chinese medicine to prevent diseases is to harmonize physical condition and support right qi. It is also consistent with the thought of "treating predisease" in ancient Chinese medicine.

There are some limitations to this study. Firstly, although pharmacological studies have identified the underlying mechanisms, biological pathways, and targets for YPFS to prevent COVID-19, direct evidence from experimental studies is still missing from the literature, pointing out the research direction for the potential clinical trials of YPFS in the application of COVID-19 prevention. Secondly, the compounds in YPFS are numerous, and concrete preventive COVID-19 component validation still could be challenging and need further investigation in depth. Finally, the regulation function of YPFS to adjust the immune system was studied on subjects without COVID-19 conditions.

YPFS has a simple combination of herbs with a very complex compound system and thus has multiple ways to prevent COVID-19, which also makes it difficult to clearly and completely clarify its mechanism in a short time. For future studies, further in vivo and in vitro experimental validations are expected to demonstrate the specific effects of YPFS. Additionally, we recommend large-scale randomized, double-blind clinical trials to objectively evaluate the effectiveness of YPFS in the prevention of COVID-19.

Although YPFS has shown potential in preventing COVID-19, understanding of its specific mechanisms of action is still limited. Future research should further explore the immunomodulatory effects of key components in YPFS and how they influence the host's immune response to SARS-CoV-2. Moreover, large-scale randomized controlled trials are essential for verifying the preventive effects of YPFS in different populations. Additionally, considering the virus's mutability, studying the potential effects of YPFS on emerging viral variants is also of great significance. These studies will provide more scientific evidence for the role of TCM in global health crises and promote the integration of traditional and modern medicine.

5. Conclusion

Although governments worldwide want to reduce the impact of the epidemic and have developed various vaccines, the global epidemic has not yet resolved its crisis. At present, the immune system plays a vital role in the occurrence and development of COVID-19. The virus infects the respiratory tract and causes a local immune response, the most primitive disease stage. Intervention against the immune system and viruses to prevent COVID-19 is a valuable prevention strategy. YPFS has been widely used in treating viral infections and has the characteristics of multiple ways, multiple targets, and multiple components to resist viral infections. First, it can interfere with the immune system in different ways, such as the mucosal immune system, macrophage system, and acquired immunity. Secondly, it can also regulate the immune system in both directions to maintain the immune system's stability. Maintaining immune homeostasis is a distinctive feature of Chinese medicine in treating diseases called yin-yang balance. Finally, it can also inhibit viruses. Therefore, we recommend adopting the TCM prevention program and expanding the epidemic prevention program.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contribution Statement

Xin Yang: Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Visualization. **Rong Tian:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Catherine Shi:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Alan Wang:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision.

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Abbreviations

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	Coronavirus Disease 2019
TCM	Traditional Chinese Medicine
YPFS	Yupingfengsan
HRSV	Human respiratory syncytial virus
IFV	Influenza virus
SIgA	Secretory immunoglobulin A
YTP	Yupingfengsan Total Polysaccharide
UYDP	Unfermented Yupingfeng dreg polysaccharides
FYDP	Fermented Yupingfeng dreg polysaccharides
NK cell	Natural killer cell
HSV	Herpes simplex virus
ACE2	Angiotensin-converting enzyme II
RdRp	RNA-dependent RNA polymerase
Mpro	3CL hydrolase
PLpro	Papain-like protease
RBD	Receptor-binding domain