Overview report of studies on
Shufeng Jiedu
against
viral respiratory tract infections
and COPD

Hamburg, 21.12.2020
Dr. Thomas Friedemann and PD Dr. Sven Schröder
Index

1. SHUFENG JIEDU AND COVID 19 ................................................................. 4
   BACKGROUND ........................................................................................... 4
   COVID-19 AND TCM ................................................................................ 5
   SFJD AND COVID-19 ................................................................................ 6
   CONCLUSION ............................................................................................. 11
2. SHUFENG JIEDU AND INFLUENZA ......................................................... 13
   BACKGROUND ........................................................................................... 13
   INFLUENZA IN TCM .................................................................................. 14
   SFJD AND INFLUENZA .............................................................................. 15
   CONCLUSION ............................................................................................. 20
3. SHUFENG JIEDU AND COMMON COLD .................................................. 22
   BACKGROUND ........................................................................................... 22
   CLINICAL TRIALS ON SFJD FOR COMMON COLD ................................. 22
   CONCLUSION ............................................................................................. 23
4. SHUFENG JIEDU AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) ................................................................. 25
   BACKGROUND ........................................................................................... 25
   COPD AND TCM ....................................................................................... 27
   EXPERIMENTAL AND CLINICAL STUDIES ON SFJD AGAINST COPD ................................................................. 27
   CONCLUSION ............................................................................................. 33
   REFERENCES................................................................................................. 34
Shufeng Jiedu

and

COVID-19
1. Shufeng Jiedu and COVID-19

Key points

- The WHO has announced that the new coronavirus pneumonia (COVID-19) epidemic originated from Wuhan, China, as a public health emergency of international concern.
- To date, more than 77 million cases have been confirmed positive and around 1.7 million deaths were reported globally.
- After 5-6 days of incubation period, main symptoms appear such as fever, fatigue and dry cough, accompanied by body aches, nasal congestion, diarrhea, conjunctivitis, sore throat etc.
- No specific treatment is available but supplemental oxygen, antiviral drugs, broad-spectrum antibiotics, fluid replacement, fever management and getting rest are main part of the supportive care.
- Since the beginning of pandemic, Chinese government included the herbal medicine of TCM in the treatment strategy along with western medicine to regulate the body's inflammatory response and strengthen the immune system of the body.

Background

On January 30, 2020, the World Health Organization (WHO) has announced that the new coronavirus pneumonia (COVID-19) epidemic originated from Wuhan, China, would be listed as a public health emergency of international concern. Since then, this acute respiratory infectious disease has been managed as a Class A infectious disease based on the law of the People's republic of China on the prevention and control of infectious diseases. To date, more than 77 million cases have been confirmed positive and around 1.7 million deaths were reported but no specific cure is available. The first vaccinations were approved in various countries such as the UK and the USA. However, the effectiveness of the vaccines in protecting against COVID-19 is still unclear, especially in light of recently discovered mutations in virus.
Clinical manifestations vary, but after 5-6 days of incubation period, fever, fatigue and dry cough most frequently appear [1]. Patients also can less commonly present body aches, nasal congestion, diarrhea, conjunctivitis, sore throat etc. COVID-19 symptoms are usually mild and gradually exacerbates. 4 out of 5 people with COVID-19 are able to recover without being hospitalized but 1 out of 5 people will require hospitalization owing to rapid aggravation of the symptoms, especially difficulty in breathing. In these severe cases, it can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, or multiple organ failure [1].

To date, there is no specific treatment or prevention against COVID-19 available. The available treatment strategy varies between countries and also between the severity of illness of patients from asymptomatic infection to critical illness [2]. As matters stand now, supplemental oxygen, antiviral drugs, broad-spectrum antibiotics, fluid replacement, fever management and getting rest are the main part of the supportive care to manage the disease.

**COVID-19 and TCM**

Considering its flu-like symptoms and due to the still limited options against COVID-19, Traditional Chinese medicine is an optimal alternative option since it already showed clinical effectiveness in former epidemic outbreaks such as SARS or MERS [3]. ZHANG et al. asserts that TCM can be a better option for COVID-19, because the herbal medicine takes effect by regulating the body's inflammatory response, strengthening the immune system of the body and thereby expelling the cause of the disease on its own [4]. Unlike the case of SARS in 2002-2003, traditional Chinese medicine was included in the official treatment guideline from the beginning stage of 2019-nCoV pandemic. In the "New Coronavirus Pneumonia Diagnosis and Treatment Program ", it is recommended to use herbal medicine for treating COVID-19, but only based on the condition of the disease, differences in local climate characteristics and physical condition of the patient. When the patient presents fatigue with fever in the initial phase of COVID-19, Huoxiang zhengqi capsules, Jinhua Qinggan granules , Lianhua Qingwen capsules (granules) and Shufeng Jiedu capsules (granules) are recommended by the National Sanitation and Health Commission of the People's Republic of China [5].
SFJD and COVID-19

Previous studies already showed that SFJDC is clinically effective against viruses such as influenza A virus H1N1 (FM1 strain, PR8 strain, B10 strain, B59 strain), herpes simplex virus type 1 and 2, respiratory syncytial virus etc [6]. Moreover, scientific basis of SFJDC being included in the treatment plan was mainly because of its antiviral, anti-inflammatory, antipyretic and immune regulating pharmacological effect (Pharmacological Effect and Clinical Application of Chinese Patent Medicine in Novel Coronavirus Pneumonia 2019). In this study, 3 clinical studies were included to evaluate the synergistic effect of SFJDC combined with western medicine against COVID-19.

At the very early stage of the pandemic, in January 2020, 2 mild patients and 2 severe patients diagnosed with 2019-nCoV pneumonia at Shanghai public health clinical center have been prescribed with lopinavir/ritonavir, Arbidol and SFJDC as an antiviral treatment scheme [7]. Blood analysis and chest CT was conducted to understand the patients’ status and improvement of the 6-15 days of treatment. 3 among 4 patients showed significant improvement in pneumonia associated symptoms during the data collection period. Especially, the pneumonia and multiple nodules were visibly improved after the treatment (see Figure 1.1). To further verify the clinical effect of SFJDC, bigger scale of clinical study was conducted as the pandemic expanded the reach globally.

Qu et al. conducted a retrospective clinical study to analyze the synergistic effect of SFJDC combined with Arbidol for treating COVID-19 [8]. Among 70 patients with COVID-19, control group (n=30) received conventional treatment including Arbidol and experiment group (n=40) received an additional SFJDC for 10 days. Arbidol is an antiviral against influenza A and B and other respiratory viral infections [9], which was also included in COVID-19 treatment guideline for its symptom improvement effect. Previous studies reported that applying Arbidol in the early stage of COVID-19 can shorten the course and abate the symptoms as well as reducing the incidence of complications [10]. All cases in this study
were relatively young patients (39.82±6.40 years) with mild COVID-19 and showed flu-like symptoms. Clinical efficacy parameter included body temperature, cough, nasal congestion, runny nose, sore throat, fatigue and diarrhea as well as the virus negative time. The results are as follows (see Table 1.1).

Table 1.1 Comparison of symptom improvement between two groups after 10 days of treatment *p<0.05: compared to the control group

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Fever clearance time/d</th>
<th>Symptom recovery time/d</th>
<th>SARS-CoV-2 negative time/d</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dry cough</td>
<td>Nasal congestion</td>
<td>Runny nose</td>
</tr>
<tr>
<td>Control group</td>
<td>30</td>
<td>5.10±1.40</td>
<td>5.89±1.56</td>
<td>5.08±1.78</td>
<td>4.02±0.56</td>
</tr>
<tr>
<td>Experiment group</td>
<td>40</td>
<td>3.24±0.89*</td>
<td>4.06±1.21</td>
<td>3.26±0.75*</td>
<td>2.35±0.75*</td>
</tr>
</tbody>
</table>

The result showed that improvement time of flu-like symptoms was shorter when the Arbidol was co-administered with SFJDC (p<0.05). In terms of safety, 2 cases from the control group and 1 case from the experiment group showed symptoms of nausea during the course of treatment, which is known as a typical adverse reaction of Arbidol. In conclusion, SFJDC in the treatment of COVID-19 promotes the improvement of clinical symptoms and therefore it is worthy of further investigation and clinical research with bigger samples to analyze the exact mechanism behind.

Similar format of study was conducted by Xiao [11] and Chen, [12] to observe the effect of SFJDC in the treatment of mild COVID-19 with randomly selected 200 patients in Wuhan central hospital, China. Control group was given with Arbidol and experiment group received an additional SFJDC. The course of treatment lasted 2 weeks. Clinical effectiveness, white

---

1 Effective: the body temperature gradually decreases after admission for treatment, and the body temperature is normal within 5-7 days and other flu-like symptoms gradually improve after admission and treatment, and the symptoms disappear within 5-7 days; SARS-CoV 2 swab was tested once every other day after the 12th day, and it was both negative;  
Ineffective: the body temperature does not drop or continues to rise after admission, and cannot return to normal within 5-7 days. Other flu-like symptoms cannot be improved and further aggravated, and the symptoms will not disappear within 5-7 days; SARS-CoV 2 Swab test is performed every other day after the 12th day, and any test was positive;  
Cured: body temperature returned to normal for more than 3 days, respiratory symptoms improved significantly, lung imaging showed obvious absorption of inflammation, two consecutive SARS-CoV 2 Swab tests were negative (the sampling interval was at least 1 day), and isolation and discharge can be lifted.

2 Symptom reduction rate = (Before treatment-after treatment) / Before treatment  
The treatment is regarded as effective when symptom reduction rate is > 30%, the treatment is regarded as ineffective when Symptom reduction rate is ≤ 30%  
Total effective rate of treatment = (No. of effective cases / total no. of cases)
blood cell (WBC) count, lymphocyte percentage, chest CT and adverse reactions were observed before and after the treatment. The most remarkable aspect of the observation was the significant increase of WBC count and lymphocyte percentage compared to before the treatment and also compared to the control group (see Table 1.2).

Table 1.2 Compared to this group before treatment, *p<0.05; compared with the control group after treatment, △p<0.05

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>WBC count (×10⁹/L)</th>
<th>Lymphocyte percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>2.53±1.24</td>
<td>13.49±2.65</td>
</tr>
<tr>
<td>(n=100)</td>
<td>After treatment</td>
<td>5.65±2.17*△</td>
<td>20.26±5.61*△</td>
</tr>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>2.42±1.37</td>
<td>13.22±2.83</td>
</tr>
<tr>
<td>(n=100)</td>
<td>After treatment</td>
<td>4.50±1.47*</td>
<td>17.84±3.88*</td>
</tr>
<tr>
<td>Normal range</td>
<td></td>
<td>4.50 to 10.00</td>
<td>20 to 40</td>
</tr>
</tbody>
</table>

Low WBC count and lymphocyte percentage can indicate a possible infection in the body. Considering the fact that COVID-19 patient presented significant decrease in WBC count and lymphocyte percentage, the increase in these indices might indicate the effect of immune regulation in the treatment for COVID-19 [14].

In the observation of CT absorptions, when the infected lesions were absorbed more than 50% after the treatment, it was considered as significantly improved. More patients (87 cases) in the experiment group showed significantly improved chest CT compared to the control group (72 cases). A few cases in each group showed insignificant adverse reactions such as drug allergy and abdominal pain. To sum up, the clinical feedback revealed that SFJDC has certain level of additive therapeutic effect on the treatment of COVID-19.

Since COVID-19 is a new type of virus, neither plenty of clinical studies nor animal studies are available until now. However, previous animal studies to analyze the mechanism of SFJDC on other diseases may be able to provide the theoretical basis. In Ji et al.’s animal study to analyze the mechanism of SFJDC on influenza A virus, it is indicated that the SFJDC and oseltamivir phosphate (antiviral) have a similar mechanism of clinical effect in the inflammation pathways by down-regulating the level of proinflammatory cytokines (IL-1β and IL-18) [15].

Coherent result was also seen in an animal study conducted by Mei et al., to investigate the effect of SFJDC on lung injury in rats with allergic rhinitis [16]. Rat models were divided into
a model group, SFJDC low-dose group, SFJDC medium-dose group, SFJDC high-dose group, a cetirizine (antihistamine drug) group and a control group. All groups except for the control group were administered with nasal dripping of olfactory rhinitis and control group received same volume of saline instead for 7 days. Afterwards, rat models in the cetirizine group and SFJDC groups received respective treatments for 14 days.

As a result, TNF-α and IL-1β level in serum from ELISA test and in lung tissue from western blotting test both showed that there was a significant increase in model group compared to control group (see Figure 1.2). However, groups treated with SFJDC or Cetirizine had decreased levels of TNF-α and IL-1β both in serum and lung tissue. This result indicates that SFJDC can downregulate the inflammatory factors such as TNF-α and IL-1β levels in the inflammation process. This might explain why SFJDC can be effective in the treatment of COVID-19, as the prognosis of the disease can be worsened by increased level of proinflammatory cytokines, such as TNF-α, IL-1, IL-6 etc. which usually target lung tissue [17].

Xia et al further investigated the mechanism behind this regulating effect of SFJDC through network analysis [18]. Network analysis showed that 11 inflammation and immunomodulation-related pathways were influenced by bioactive compounds of SFJDC. This might explain the mechanism behind the clinical effectiveness of SFJDC, as seen from the study of Costela-Ruiz et al., that downregulated proinflammatory factors (TNF-α, IL-1, IL-6 etc.) may be the result of the activity of these verified pathways. The antiviral and anti-inflammatory
properties of SFJDC were confirmed by the mouse model. The decreased inflammatory factors in the lung tissue of coronavirus-infected mice can be explained by attenuation of pro-inflammatory pathways by bioactive compounds of SFJDC. The main ingredients of SFJDC: quercetin, wogonin, and polydatin bind directly to the main protease (Mpro) of SARS-CoV-2 (see Figure 1.3).

![Figure 1.3 Molecular docking of SFJDC active compounds with COVID-19 virus Mpro; A) Docking Poses of COVID-19 virus Mpro- Polydatin complex binding mode.](image)

In parallel a real-world study comparing conventional antiviral drug therapy AVD (n ==33) with AVD plus SFJD (n =43) showed, that the addition of SFJDC shortened the symptomatic course of COVID-19 in patients with mild and moderate symptoms, reduced cough and fatigue. The results furthermore indicated, that it is beneficial to administer SFJD immediately from the onset of the first symptoms (see Figure 1.4) [18].
Conclusion
In conclusion, there are already enough previous studies to approve that the clinical application of SFJDC for COVID-19 in combination with western medicine is appropriate in the prevention, control and intervention of the epidemic. Integrating TCM into COVID-19 strategy has advantages in symptom improvement, reducing the course of disease, delaying the process of the disease and reducing the mortality [4]. However, as COVID-19 virus is relatively new and much of this disease is yet unknown, theoretical basis has to be established through animal and cell studies to understand the mechanism behind the therapeutical effect of SFJDC on COVID-19. Furthermore, since a lot of researches and development regarding the treatment medicine and vaccination for COVID-19 will be completed in the near feature, we should be prepared for further clinical researches to see the potential synergistic effect of TCM and new drugs.
Shufeng Jiedu

and

Influenza
2. Shufeng Jiedu and Influenza

Key points

- Influenza is an acute respiratory infection caused by influenza viruses which results in the annual breakout of epidemics
- Worldwide, it is estimated to result in about 3 to 5 million cases of deaths and about 290 000 to 650 000 only due to respiratory diseases
- Fever and body aches in the initial stage, accompanied by cough, sore throat, headaches, fatigue and runny nose are the most frequent symptoms of influenza
- Flu treatment focuses on symptomatic treatment and reducing the chances of infection and antiviral medication is recommended for high-risk groups to abate the symptoms and shorten the duration of the disease
- As of now, vaccination is the most effective way to prevent and control Influenza
- In China, it is recommended to prescribe herbal medicine in parallel with the western medicine treatment in the influenza treatment guideline.

Background

Influenza is an acute respiratory infection caused by influenza viruses and primarily influenza type A and B travel and result in the annual breakout of epidemics [19]. Seasonal influenza result in 290 000 - 650 000 deaths annually, due to respiratory diseases alone, not taking influenza-related cardiovascular disease-induced death into consideration [20]. Hence, Influenza virus infection is a serious threat to public health and substantial burden to the healthcare system. It is characterized by symptoms such as fever and body aches usually in the initial stage, accompanied by cough, sore throat, headaches, fatigue and runny nose [21]. Children are known to additionally show diarrhea and vomiting which are not so common among the adult population with flu.

In general, it is advised to manage influenza by focusing on symptomatic treatment and avoiding contact with other people to minimize the risk of infection. In the case of high-risk
group or patients with severe symptoms, it is recommended to take antivirals such as neuraminidase inhibitors (i.e. oseltamivir) [19]. To effectively control the symptoms, to shorten the course of disease and to reduce the severe complications are the key factors in the treatment of influenza, hence antiviral medication becomes an important part of flu treatment [22]. However, Jefferson et al. showed that antiviral drugs such as oseltamivir and zanamivir have only small effects on reducing symptom duration in adults, and it even increases the risk of adverse effects such as nausea, vomiting and psychiatric effects [23]. Moreover, the development of resistance against antiviral drugs started to question the sustainability of the current influenza treatment guidelines [24].

As of now, influenza vaccination is considered to be the most effective means for the prevention and control of influenza [25]. WHO recommends annual vaccination for people in the high-risk group such as pregnant women, elderly individuals, children up to 5 years old, individuals with underlying disease and health-care workers [19]. In the recent meta-analyses, licensed seasonal vaccines such as live attenuated influenza vaccine or trivalent inactivated vaccine showed mean efficacy of 60% in healthy adults and 83% in children [26,27]. But when these vaccines don’t match the circulating influenza strain, or when new kinds of virus emerge, it fails to bring the ideal effect [28]. Moreover, current vaccination is known to leave out the most vulnerable population with higher risk of influenza such as the elderly [29]. Given the current situation, where neither prevention nor treatment options for influenza are sufficient, alternative options such as herbal medicine are worth of consideration to provide the patients with treatment that is with lower risk of side effects and higher therapeutical effectiveness.

**Influenza in TCM**

In Traditional Chinese Medicine, Influenza falls into the category of exogenous warm disease or *wen-bing* (溫病), which is a disease caused by warm-heat pathogenic qi, that penetrates the body via nose and mouth and into the lungs [30]. *Wen-bing* is a disease that can develop into an epidemic under certain circumstances and its onset and progress can be relatively rapid, but it depends on the status of the individual and the virulence and mutability of the disease. In TCM, *Shang-Han Lun* (Treatise on cold damage diseases) and *Wen-Bing-Tiao-Bian* (Detailed analysis of epidemic warm diseases) have been regarded as guidelines of treating influenza since centuries and therefore TCM have accumulated empirical therapeutic data regarding influenza [31]. Influenza is usually differentiated into two types: wind-cold syndrome and wind-heat syndrome. Wind-cold syndrome patients show chills, mild fever, headache, body
pain, stuffy nose with nasal discharge, and cough with sputum. Wind-heat syndrome patients show rather a high fever, slight aversion to cold, headache, sore throat with congestion, and expectoration of yellowish sputum [32].

Chinese Guidelines for Diagnosis and Treatment of Influenza [33] from the ministry of health of China suggests several treatment options based on the TCM diagnosis and recommends herbal medicine, including herbal decoction, patent medicine and herbal extract products [34]. SFJDC is one of the recommended patent medicines for non-severe, early-stage cases which are identified as wind-heat type of influenza. A number of studies on the therapeutic effect and safety in the clinical use of SFJDC for the treatment of influenza have been already conducted and presented positive results.

**SFJD and Influenza**

Wu et al. conducted a study to compare the therapeutic effectiveness for influenza between SFJDC and oseltamivir [35]. Oseltamivir is an antiviral medication, widely used to treat and prevent influenza under the brand name Tamiflu. It is known to reduce the duration of the symptoms when administered promptly [36]. A total of 220 patients with seasonal influenza were randomly divided into two groups; Experiment group to be treated with SFJDC and control group to be treated with oseltamivir for 5 days. Even though both groups showed an improvement in the symptoms such as onset of fever, chills, headache and body ache, there was no statistically significant difference in the effectiveness and adverse reactions between the two groups (p>0.05), except for the improvement in sore throat, in which SFJDC was more effective (p=0.04). It implies that SFJDC can be a safe and effective alternative for antiviral medicine in treating seasonal influenza.

In a similar format of study, 150 patients with influenza-like illnesses were treated for 3 days for the cost-effectiveness analysis [37]. Influenza-like symptoms refer to the clinical symptoms similar to influenza, mainly manifested as fever, chills, body aches and so on. Clinical studies have found that most patients with influenza are accompanied by flu-like symptoms in the early stage of Influenza [38]. Experiment group was given with SFJDC and control group was given with oseltamivir, to be followed up for a clinical and cost data collection. Even though there were no significant differences in remission rate, response rate or antipyretic effectiveness rate after the treatment between two groups, the total outpatient medical cost and drug expenses of SFJDC were lower than oseltamivir treatment, 28% and 39.6% respectively, suggesting the
cost-effectiveness of SFJDC over oseltamivir phosphate (p<0.01). Despite some limitations such as the limited number of patients, short duration of the treatment and exclusion of the indirect medical costs, the finding is valuable because it provides a basis for the health-economic advantage of SFJDC in the treatment of Influenza.

SFJDC can also be administered simultaneously with antiviral drugs to enhance the therapeutic effect and reduce the adverse reactions. To analyze the synergistic therapeutic effect of oseltamivir phosphate combined with SFJDC on H1N1 influenza A, a total of 86 patient diagnosed with influenza A H1N1 at Civil aviation general hospital in Beijing were recruited for the study [22]. Inclusion criteria was to present fever, accompanied by cough, sputum, nasal congestion, sore throat; severe influenza A patients with pneumonia were ruled out. All patients received conventional treatment, such as taking a rest, drinking more water, intake of balanced nutrition and antipyretic medicine if necessary. Additionally, control group of 42 cases was treated with oseltamivir phosphate alone and experiment group of 44 cases was treated with oseltamivir phosphate combined with SFJDC for 5 days. The duration of fever, clinical symptom (cough and sore throat) improvement time, influenza A virus negative time were compared as well as the incidence of adverse reactions.

The therapeutic effect of oseltamivir phosphate combined with SFJDC showed better result than oseltamivir phosphate alone, by reducing the duration of fever, cough recovery time and duration of sore throat (p<0.05). The number of adverse reactions reported in the experiment group were not higher than the control group and these adverse reactions, such as nausea and vomiting, were relatively mild and alleviated within a short period of time after the symptomatic treatment. The result showed that SFJDC is capable of improving the therapeutic effectiveness of the antiviral medication without causing more side effects, which provides noteworthy clinical evidence for the application of SFJDC in the management of influenza.
A few clinical studies evaluated the potential synergistic effect of SFJDC with other antivirals on treating influenza. Yuan et al. conducted a study with 86 children between age 2-14 years diagnosed with influenza and divided into two groups. Control group was treated with ribavirin granules alone and experiment group was treated with SFJDC in parallel with ribavirin granules for 7 days. If necessary, both groups received symptomatic treatment, against cough, phlegm and etc. Ribavirin is an antiviral medication recommended for indications such as respiratory syncytial virus (RSV), parainfluenza virus and influenza virus [39] and is approved for the treatment against Hepatitis C and RSV [40]. The clinical effect was marked ‘significantly effective’, ‘effective’ and ‘ineffective’, based on ‘Criteria for diagnosis and curative effect of cold and influenza [41]’ to observe the improvement of clinical symptoms and signs within 24 hours to 48 hours after the medication. The total effective rate of experiment group and control group was 95.35% and 81.39% respectively, which implies that SFJDC was able to enhance the antiviral effect of ribavirin (p<0.05). Unfortunately, this study does not provide an analysis on the specific effect and mechanism of the SFJDC. However, the study showed that the overall effect of the antiviral treatment was improved from the administration of SFJDC for children patients that belong to the group with high risk for Influenza, without obvious adverse reactions.

Analysis on the Clinical Effect of Shufeng Jiedu Capsule on Influenza [42] randomly divided 754 patients with influenza into three groups to clarify the clinical effectiveness, side effects and synergetic effect of SFJDC and acyclovir. Acyclovir is an antiviral medication used against herpes simplex virus and varicella zoster virus infections [43] and considered not to have ant-influenza properties [44]. Control group was treated only with acyclovir, experiment group 1 was given with SFJDC and experiment group 2 was treated with SFJDC combined with acyclovir for 7 days. The symptom improvement time, degree of symptoms such as fever (body temperature>38.0 °C), accompanied by cough or/and sore throat, headache, nasal congestion, runny nose, fatigue, etc. was observed throughout the study and therapeutic effect was measured.

3 Significantly effective: the main symptoms of the whole body and local areas such as fever and runny nose disappeared or reduced within 24 hours after taking the medicine.
Effective: the symptom relief appeared within 24 hours to 48 hours after taking the medicine.
Ineffective: the patient does not fall into any of those categories above.
Total effective rate = (significant effect + effective) / total number of cases × 100%.

4 Cured: clinical symptoms completely disappeared, the body temperature was normal, and curative effect index was ≥95%;
Effective: clinical symptoms are significantly improved, the body temperature is normal, curative effect index ≥70%, <95%;
Improved: Partially improved clinical symptoms, lower body temperature than before, curative effect index ≥30%, <70%.
Invalid: no change of clinical symptoms, or even aggravation, the efficacy index is <30%

Effective rate (%) = (pre-treatment score-post-treatment score)/pre-treatment score × 100%.
Table 2.4 Comparison of clinical symptom relief rate of each group after 7 days of treatment n (%) Compared with the control group, $\Delta P < 0.05$

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Normal body temperature</th>
<th>Cough disappeared</th>
<th>Sore throat disappeared</th>
<th>Headache disappeared</th>
<th>Runny nose disappeared</th>
<th>Body aches disappeared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>251</td>
<td>146 (57.77)</td>
<td>131 (52.19)</td>
<td>148 (58.96)</td>
<td>139 (55.38)</td>
<td>133 (53.00)</td>
<td>166 (66.14)</td>
</tr>
<tr>
<td>Experiment group 1</td>
<td>252</td>
<td>159 (63.10) $\Delta$</td>
<td>149 (59.13) $\Delta$</td>
<td>152 (60.32) $\Delta$</td>
<td>169 (67.06) $\Delta$</td>
<td>168 (66.66) $\Delta$</td>
<td>187 (73.21) $\Delta$</td>
</tr>
<tr>
<td>Experiment group 2</td>
<td>251</td>
<td>189 (75.30) $\Delta$</td>
<td>189 (75.30) $\Delta$</td>
<td>185(73.71) $\Delta$</td>
<td>171 (68.13) $\Delta$</td>
<td>197 (78.493) $\Delta$</td>
<td>209(83.27) $\Delta$</td>
</tr>
</tbody>
</table>

Experiment group 2, treated with SFJDC and acyclovir simultaneously, showed significantly reduced clinical symptoms such as fever, cough or/and sore throat and headache compared to experiment group 1 treated with SFJDC only or control group treated with acyclovir only. No obvious adverse reactions occurred in each group.

Neither ribavirin nor acyclovir is a prioritized antiviral medication for the treatment of influenza, but these two studies show the improvement through the concomitant administration of antivirals and SFJDC in the antiviral treatment. In conclusion, the treatment of influenza with SFJDC and antiviral medicine combined can accelerate the disappearance of symptoms and improve the therapeutic effect without costly expenses and adverse reaction. The findings of these studies necessitate the health-professionals to reconsider the cost-effective, easily accessible yet effective anti-influenza strategy other than solely depending on the antiviral medicine [45].

The aforementioned researches showed that the clinical effectiveness of simultaneous treatment of SFJDC and antiviral medication and the safety of SFJDC application on influenza. However, the mechanism of the action of SFJDC has to be further investigated and evaluated. For the analysis of underlying mechanism of SFJDC, it is ideal to conduct biochemical, cell and animal studies that can provide the theoretical support to pharmacological understanding on SFJDC.

Ying et al. aimed to explore the effect of SFJDC on the lung index$^5$, lung viral load and preventive effect in the mortality rate of the model mice with H1N1 influenza virus [46]. A total of 70 mice were randomly divided into 7 groups: normal control group, model control

---

$^5$ Lung index = lung wet weight (g) / body weight (g).
Lung index inhibition rate = (lung weight of virus control group-lung weight of experimental group) / (lung weight of virus control group-lung weight of normal control group) x 100%
Compared with the normal control group, $a P<0.01$; compared with the model control group, $b P<0.05$, $c P<0.01$
group, cyclophosphamide control group, Tamiflu® control group, SFJDC in large, medium and small dose groups. All the models were infected with Influenza virus fluids (FM1 and PR8 strain) and were immunocompromised but normal control group was not immunocompromised.

Table 2.5 Compared with the normal control group, a P<0.01; compared with the model control group, b P<0.05, c P<0.01

<table>
<thead>
<tr>
<th>Groups</th>
<th>Weight (kg)</th>
<th>No.</th>
<th>FM1 strain Lung index</th>
<th>Inhibition rate (%)</th>
<th>PR8 strain Lung index</th>
<th>Inhibition rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control group</td>
<td>-</td>
<td>10</td>
<td>0.66 ±0.08</td>
<td>-</td>
<td>0.66 ±0.08</td>
<td>-</td>
</tr>
<tr>
<td>Model control group</td>
<td>-</td>
<td>10</td>
<td>1.23±0.12a</td>
<td>-</td>
<td>1.20±0.15a</td>
<td>-</td>
</tr>
<tr>
<td>Cyclophosphamide control group 0.1</td>
<td>0.81 ±0.06°</td>
<td>10</td>
<td>0.81 ±0.06°</td>
<td>-</td>
<td>0.81 ±0.09°</td>
<td>-</td>
</tr>
<tr>
<td>Tamiflu control group</td>
<td>0.03</td>
<td>10</td>
<td>1.04 ±0.14c</td>
<td>47.03</td>
<td>1.00 ±0.08°</td>
<td>50.70</td>
</tr>
<tr>
<td>SFJDC large dose group</td>
<td>2.2</td>
<td>10</td>
<td>1.06±0.12c</td>
<td>41.35</td>
<td>0.94±0.07c</td>
<td>65.58</td>
</tr>
<tr>
<td>SFJDC middle dose group</td>
<td>1.1</td>
<td>10</td>
<td>0.98 ±0.18°</td>
<td>60.50</td>
<td>1.00 ±0.17b</td>
<td>49.69</td>
</tr>
<tr>
<td>SFJDC small dose group</td>
<td>0.55</td>
<td>10</td>
<td>1.06±0.16b</td>
<td>40.09</td>
<td>1.03±0.08c</td>
<td>43.89</td>
</tr>
</tbody>
</table>

After the infection of influenza A H1N1 virus FM1 strain and PR8 strain, the lung index increased significantly, which was statistically different from the normal control group (P<0.01); but in three SFJDC groups where SFJDC was given prophylactically for 4 days before infection, none of the those groups showed significant reduction in lung index. It implies that SFJDC has a preventive effect on the pneumonia model of immunocompromised mice with influenza virus infection.

Table 2.6 The protective effect of drugs on the death of pneumonia in immunocompromised mice with FM1 strain of influenza virus, Compared with the model control group, a: P <0.05, b: P <0.01

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Number of Deaths</th>
<th>Death rate (%)</th>
<th>Protection rate (%)</th>
<th>Average survival (d)</th>
<th>Life extension rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model control group</td>
<td>20</td>
<td>14</td>
<td>70</td>
<td>-</td>
<td>6.55 ±1.10</td>
<td>-</td>
</tr>
<tr>
<td>Tamiflu control group</td>
<td>20</td>
<td>1</td>
<td>5</td>
<td>92.86b</td>
<td>7.95±0.22b</td>
<td>21.37</td>
</tr>
<tr>
<td>SFJDC large dose group</td>
<td>20</td>
<td>5</td>
<td>25</td>
<td>64.29a</td>
<td>7.60±0.82b</td>
<td>16.03</td>
</tr>
<tr>
<td>SFJDC middle dose group</td>
<td>20</td>
<td>5</td>
<td>25</td>
<td>64.29a</td>
<td>7.50±0.95b</td>
<td>14.50</td>
</tr>
<tr>
<td>SFJDC small dose group</td>
<td>20</td>
<td>1</td>
<td>5</td>
<td>92.86b</td>
<td>7.95±0.22b</td>
<td>21.37</td>
</tr>
</tbody>
</table>

In SFJDC small dose group, the mortality of the infected mice was significantly reduced and the average survival days was prolonged compared to the model control group and the effect was comparable to Tamiflu control group. However, the small dosage of SFJDC showed higher protective effect compared to when a middle or large dosage of SFJDC was given. From this result, it can be inferred that unlike the general bias that herbal medicine is always safe and
effective, herbal medicine should be handled with accurate instructions from the health professionals and patients should abide by the prescribed dosage.

Even though China Food and Drug Administration (CFDA) has already recommended SFJDC for its antiviral effect in the treatment for H1N1- and H5N9-induced influenza, the theoretical basis regarding the component identification of SFJDC is still lacking [47]. Hence, Tao et al. identified which substances are responsible for the anti-inflammatory effect of SFJDC to explain the antiviral mechanisms of SJFDC. The study characterized that certain components of SFJDC such as forsythoside E, verbenalin, and emodin, are involved in the reduction of cytokines, which eventually leads to suppressing the spread of the influenza virus.

**Conclusion**

Basic and clinical research showed that SFJDC can be used to treat Influenza and that the treatment has only mild side effects.

However, although there have been numerous clinical studies conducted to analyze the therapeutic effectiveness of SFJDC and large quantity of SFJDC is prescribed successfully on a daily basis in clinics, there is still a lack of solid theoretical support to some extent to explain the underlying mechanism of action in detail. Thus, further researches to investigate the pharmacological mechanism and biochemical analysis will be beneficial for sustainable clinical application of SFJDC.
Shufeng Jiedu

and

common cold
3. Shufeng Jiedu and common cold

Key points

- The common cold is a viral infectious disease of the upper respiratory tract and the most frequent infectious disease in humans.
- Adults get 2-3 common colds per year, children up to 6-8.
- Common cold affects the nose, throat, sinuses, and larynx.
- Symptoms include coughing, sore throat, runny nose, sneezing, headache, fever.
- There are 200 virus strains that can cause common cold, with rhinoviruses being the most common.
- Usually, the symptoms disappear within 10 days
- There is no vaccine for the common cold.
- Main infectious period is winter
- There is no effective treatment in western medicine beside antiphlogistic/antipyretic drugs.

Background
SFJD is recommended in the Chinese Guidelines for Diagnosis and Treatment of Influenza from the ministry of health of China for non-severe, early stage cases [33]. While clinical symptoms of early-stage influenza are similar to common cold, SFJD is widely used for common cold as well. SFJD has been tested in multiple studies for symptoms of common cold in adults and children.

Clinical trials on SFJD for common cold
In a randomized controlled study with 200 participants, SFJD was compared with Paracetamol, with 100 cases in each group. SFJD was significantly superior in recovery of fever, and clinical symptoms. Adverse events were lower in the SFJD group [52]. Similar, SFJD treatment (n = 80) was compared with a group, who were treated with a combination of paracetamol and amantadine hydrochlorid (n = 80) for 3 days. SFJDC had a superior curative effect on “wind-
heat” syndrome symptoms fever, stuffy nose, sneezing, coughing, runny nose, throat symptoms, headache and body aches, each [53].

The mechanism of the symptom reduction in bronchial symptoms might be due to reduction of airway inflammation. In a randomized controlled trial patient with a common cold and cough received only routine treatment in the control group (n = 129), and routine treatment plus SFJD in the experiment group (n = 129) for 5 days. SFJD significantly reduced exhaled nitric oxide (FeNO) levels and changed inflammatory factors (TNF-a, IL-6, IL-12, CRRP) in parallel to faster recovery of symptoms [53].

In as similar study design, patients with rhinitis as the major symptom of common cold received either routine treatment (n = 60) or routine treatment plus SFJDC for 7 days. The SFJDC group received a significantly faster improvement with a high patient’s satisfactory rate [54].

A multicenter, open-label phase IV clinical trial with 2031 participants on SFJDC found that they were efficacious in treating acute upper respiratory track infections ("wind-heat syndrome"). After 3 days of treatment, the cure rate was 41.31% and the total efficacy was 90.40%. The median time for onset and duration of defervescence were 4.50 hours and 20.00 hours, respectively. In this large population, no relevant adverse drug reaction was observed. However, no control group was introduced in this study.

Furthermore, SFJDC have been compared with another TCM patent medicine for common cold (Shuanghuanglian [55] and Kuaike Capsule [56]) and was found to be more effective.

SFJDC efficiently reduced cough also in children in two clinical studies [57], [58]. In a latter larger random controlled trial 64 patients were treated with western medicine (Dextromethorphan Hydrobromide, Chlorpheniramine Maleate and Pseudoephedrine hydrochloride Solution’) and in 64 cases SFJD was added to the western medicine. The combination of SFJD with western medicine was significantly clinically effective in the treatment of cough and the regulation of high levels of cytokines in serum samples.

**Conclusion**

In summary, SFJD showed efficacy in common cold in multiple studies in adults and children, in some studies with a large scale of patients. It has been shown efficacy in studies in comparison with basic care alone, paracetamol, paracetamol plus amantadine. In children it had been added to antitussive western medication and showed higher efficacy than western medicine alone. However, the available studies are published in Chinese only and large-scale randomized placebo-controlled studies are so far missing.
Shufeng Jiedu

and

chronic obstructive pulmonary disease (COPD)
4. Shufeng Jiedu and chronic obstructive pulmonary disease (COPD)

**Key points**

- Chronic Obstructive Pulmonary Disease (COPD) is a lung disease characterized by chronic breathing problems and limited airflow that causes breathlessness, chronic cough, and sputum production
- In 2015, COPD caused 5% of all deaths globally and the most of those deaths occurred in low and middle-income countries
- It potentially leads to exacerbations and serious illnesses such as pulmonary hypertension, respiratory infections and heart problems
- Inhaled bronchodilators, inhaled corticosteroids and antibiotics are the main medications for the symptom management in western medicine
- In TCM, COPD is caused mainly by the deficiency of qi of the lung and stagnation of the phlegm and blood
- Guidelines for COPD in TCM recommends applying herbal medicine on the basis of western medicine according to the syndrome differentiation and stage of the disease, to improve the therapeutic effect

**Background**

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease characterized by chronic breathing problems and limited airflow that causes breathlessness, chronic cough, and sputum production. It progressively leads to exacerbations and serious illnesses such as pulmonary hypertension, respiratory infections and heart problems [62]. People who are exposed to tobacco smoke, air pollution, industrial dusts and chemicals in the long term have higher possibility of developing COPD but many cases are preventable through avoiding the risk factors [62].

Globally, COPD was the most prevalent chronic respiratory disease in 2017, also the most prevalent in the central and eastern Europe regions [63]. In 2015, COPD accounted for 5% of all deaths globally and most of those deaths occurred in low and middle-income nations. COPD
not only imposes economic and social burden on the national/international level, but also effects on the individual level with physical, emotional and social satisfaction with life.

Any patient who presents the typical symptoms of COPD is open to possibility of COPD, but the confirmation of the diagnosis should be made based on the spirometry. Spirometry is the standard respiratory function test to measure the volume and flow of the inhaled and exhaled air, used to measure the airflow limitation and lung function and to diagnose respiratory diseases such as asthma and COPD. At present, spirometry is the most reproducible and objective method for the diagnosis of COPD [64].

Moreover, COPD patients are prone to Acute exacerbation(s) of chronic obstructive pulmonary disease, known as AECOPD, which is a sudden aggravation of the symptoms of COPD such as dyspnea, cough and sputum production [65]. Since AECOPD is often triggered by bacteria, people who are at high risk of exacerbations are recommended to take antibiotics, to reduce the frequency of exacerbations and improve the quality of life [66]. However, Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy remarks that the evidences to support this antibiotic therapy is “somewhat inconsistent” and therefore its effect is yet uncertain [67]. Therefore, in the UK, doctors are recommended to follow an updated treatment guideline, preferably not to prescribe antibiotics to COPD patients except for the very severe cases [68].

As of now, COPD is not curable, so the treatment aims to relieve the symptoms, improve the quality of life and reduce the risk of exacerbations. In the case of smokers, the first step of intervention should be the smoking cessation. The primary medications used are inhaled bronchodilators, inhaled corticosteroids and antibiotics, to reduce the respiratory symptoms, prevent infections and improve the quality of life [69]. Even though pharmacological management of COPD has relatively good safety profiles, recent studies reported overwhelming number of evidences that long-term application of inhaled corticosteroids fail to deliver significant clinical benefit due to the steroid resistance [70]. In a cohort study with COPD patients (n=175,906), the rate of inhaled corticosteroid usage and dosage was positively associated with the risk of hospitalization for pneumonia [71]. Moreover, dosage-dependent association between the use of inhaled corticosteroid and cataracts was confirmed in case control study [72]. Considering the reliability of the present COPD treatment, it leaves a question if the benefits of the current therapy indeed outweigh the potential risk from the adverse reactions.
**COPD and TCM**

In modern TCM, etiology of COPD lies in the deficiency of the lung qi combined with phlegm and blood stasis [73]. The onset of COPD is mainly due to the deficiency in the lung possibly accompanied by penetration of external pathogens, hampering the inhalation of the clean air and causing the stagnation of the turbid qi in the lungs. Eventually it causes the pathological damage of the lungs. When the accumulation of the phlegm and blood worsens, it causes the obstruction which clinically appears as an acute exacerbation of COPD [74]. Therefore, the treatment for COPD in TCM concentrates on invigorating the qi of the lung and eliminating the pathogen and stasis. Due to the complexity and variability of the disease itself and the etiology, guidelines for TCM diagnosis and treatment of COPD [74] suggests to manage COPD mainly with herbal medicine, considering the excess and deficiency to treat the root causes of the disease. In previous studies, the clinical effectiveness of TCM treatment, especially herbal medicine in treating COPD has already been addressed and proved. In this article, the clinical effectiveness of Shufeng Jiedu Capsule (SFJDC, 疏风解毒胶囊) accompanied by western medicine medication in treating COPD and AECOPD is investigated based on the recently published clinical studies and animal studies.

**Experimental and Clinical studies on SFJD against COPD**

Since symptoms such as cough, dyspnea and sputum production are directly associated with the quality of life of COPD patient, several studies were conducted, using symptom score as a parameter, to measure the clinical effectiveness of SFJDC or synergistic effect of SFJDC combined with conventional treatment on COPD. *Li* conducted a study with 100 AECOPD patients with pulmonary infection to observe the symptom improvement when SFJDC was applied in addition to the western medicine therapy [75]. Control group was given with antibiotics (ceftriaxone) and experiment group received an additional SFJDC for 10 days.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Cough</th>
<th>Sputum</th>
<th>Pulmonary rales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>5.9±1.4</td>
<td>6.9±1.3</td>
<td>7.5±1.7</td>
</tr>
<tr>
<td>Experiment group</td>
<td>50</td>
<td>4.7±1.1*</td>
<td>5.1±1.7*</td>
<td>6.7±1.5*</td>
</tr>
</tbody>
</table>

*Table 4.7 Comparison of recovery time of main clinical symptoms and signs between the two groups of patients (x±s, d) Note: Compared with the control group, *P<0.05*
The result (see Table 4.1) showed that combined use of SFJDC and conventional treatment can speed up the relief of symptoms such as cough and sputum, and accelerate the subsidence of pulmonary inflammations without causing side effect in both groups. Studies that quantified the clinical effect of SFJDC combined with western medicine based on the formula\(^6\) from "Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2013 Revised Edition)" also showed promising results with statistical significance. All of these studies have prescribed conventional western medicine medication (antibiotics, inhaled bronchodilator, oxygen therapy, inhaled corticosteroids etc.) to AECOPD patients and experiment group received an additional SFJDC.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (western medicine)</th>
<th>Experiment group (western medicine +SFJDC)</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58.5%</td>
<td>75.4%*</td>
<td>10 days</td>
</tr>
<tr>
<td></td>
<td>66.67%</td>
<td>85.37%*</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>70%*</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td>70.59%</td>
<td>91.84%*</td>
<td>10 days</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>70%*</td>
<td>7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group (western medicine)</th>
<th>Experiment group (western medicine +SFJDC)</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[76] (n=130)</td>
<td>[77] (n=80)</td>
<td>[78] (n=80)</td>
</tr>
<tr>
<td></td>
<td>58.5%</td>
<td>66.67%</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>[79] (n=100)</td>
<td>[80] (n=60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70.59%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.2 Comparison of clinical effectiveness between control group and experimental group. Note: Clinical effectiveness was calculated using formula\(^1\). Compared with the control group, \(*P<0.05\)

These clinical studies show sufficient coherence that SFJDC combined with conventional western medicine treatment for AECOPD can deliver enhanced effects compared to conventional therapy alone (see Table 4.2). It enables the overall clinical symptoms of patient to be alleviated faster and eventually enables the patient to lead a life with better quality. During or after the treatment, no case of adverse reaction was reported in all of 5 studies. Not only the clinical symptoms but also the value from spirometry helps to quantify and understand the presence and severity of COPD. Among the parameters measured from spirometry, FEV\(_1\) (forced expiratory volume in one second) divided by FVC (forced vital capacity) ratio indicates the percentage of the one’s lung capacity that can be exhaled in one

---

\(^6\) Effective rate (%) = (number of \(\oplus\)clinically controlled cases + number of \(\oplus\)significantly effective cases)/ \(\oplus\) + \(\oplus\) + \(\oplus\) + \(\oplus\) total number of cases \(\times\) 100%. 

\(\oplus\) Clinically controlled: the patient returns to daily life, chest X-ray and blood test return to normal or almost normal. Stable medication can effectively control the condition. There is no fluctuation in the condition within 24 hours and can be discharged; 

\(\oplus\) Significantly effective: the patient can be treated with daily stable medications and the chest X-ray and blood test return to normal or almost normal. After the activity, there are obvious symptoms such as asthma, and the patient still needs to be observed; 

\(\oplus\) Improved: the patient’s main symptoms and signs have improved, but patient still needs high dose of daily medication; 

\(\oplus\) Invalid: the patient’s symptoms and signs have not been significantly relieved.
second [81]. FEV$_1$ is an amount of air that one can forcefully exhale in one second. Normal value of FEV$_1$ varies depending on age, gender, height and race. FEV$_1$/FVC ratio less than 70% and FEV$_1$ value less than 80% of the predicted value confirms the airflow obstruction and diagnosis of COPD [67].

<table>
<thead>
<tr>
<th>Group</th>
<th>边巍, 2016 (n=77)</th>
<th>ZHAO Yong1, 2020 (n=120)</th>
<th>[84] (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before the</td>
<td>After the</td>
<td>Before the</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td>treatment</td>
<td>treatment</td>
</tr>
<tr>
<td>Control group (western medicine)</td>
<td>62.79±7.52</td>
<td>65.60±8.69</td>
<td>46.08±12.95</td>
</tr>
<tr>
<td>Experiment group (western medicine +SFJDC)</td>
<td>61.36±8.31</td>
<td>68.18±6.23*</td>
<td>47.57±13.62</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7 days</td>
<td>60 days</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Table 4.3. Comparison of FEV$_1$/FVC ratio before and after treatment between the two groups (% , x±s)
Compared with this group before the treatment, *P <0.05. Compared with the control group after the treatment , Δ<0.05

边巍 (2016), ZHAO Yong (2020) and 张俊雅 (2019) compared the improvement of lung function between two groups of AECOPD patients, prescribing conventional western medicine for COPD to control group and additional SFJDC to experiment group. FEV$_1$/FVC ratio was measured from spirometry test before and after the treatment.

FEV$_1$/FVC ratios of the experiment group significantly increased after treatment with SFJDC and the degree of increase was significantly bigger in the experiment group than the control group. Since the FEV$_1$/FVC ratio smaller than 70% confirms the airway obstruction, the result (see Table 4.3) implies that the combination treatment of SFJDC and western medicine enhances the therapeutic effect on respiratory disturbance.

The test result from spirometry is not always coherent with the symptoms that patients clinically present and therefore, these result cannot assure the improvement of the disease itself [85]. Consequently, the diagnosis of COPD or the clinical effectiveness has to take various parameters into account, not to mention the symptom screening of the patient. Nevertheless, result of the spirometry tests visualizes the functioning of the lung with numerical values and helps to understand the clinical effectiveness of the treatment to a certain degree.

Functioning of the lung can also be reflected in the blood gas analysis parameters such as arterial oxygen partial pressure (PO$_2$) and partial pressure of carbon dioxide (PCO$_2$). PO$_2$ is a
parameter for the blood oxygen concentration, which indicates the oxygen intake in the lungs and can be decreased through various pathological status such as decrease in the amount of inhaled oxygen [86]. PCO₂ reflects sufficient ventilation within the lungs and increased PCO₂ can lead to respiratory acidosis, which can result in respiratory failure [87]. Therefore, PO₂ and PCO₂ are both important markers for COPD patients and blood gas analysis can help to analyze the clinical effectiveness of the treatment for COPD and other respiratory diseases.

Clinical effectiveness of SFJDC combined with western medicine against mild to moderate AECOPD was analyzed based on the changes in PO₂ and PCO₂ levels [88]. Control group with 45 patients was treated with conservative treatment such as anti-infection (cefoperazone sulbactam), airway dilation and anti-inflammation treatment (prednisone tablets). Experiment group was treated additionally with SFJDC. After 10 days of treatment, PO₂ values in the arterial blood of the both groups were higher and PCO₂ values were lower than prior to the treatment. However, the rate of increase in PO₂ and decrease in PCO₂ in the experiment group (SFJDC group) was bigger than that in the control group. After or during the course of treatment, no significant side-effects were reported.

A similar study [89] with 120 patient diagnosed with AECOPD showed coherent result as aforementioned study [88]. For 7 days, both groups received a routine treatment bronchodilator (ipratropium bromide solution) and anti-inflammatory corticosteroid (prednisone tablets) and experiment group received an additional SFJDC. PO₂ and PCO₂ levels were measured before and after the treatment and the use of antibiotics and the occurrence of adverse reactions were recorded. Both groups showed increase in PO₂ level and decrease in PCO₂ level compared to before the treatment, but the experiment group (SFJDC group) showed bigger degree of change with significance (p<0.05). During the treatment, both groups did not show any case of adverse reactions. What’s also worthy of notice is that the antibiotic usage rate of the treatment group (18.3%) was lower than that of the control group (38.3%) during the treatment and the
difference was statistically significant (p=0.015). These results are particularly relevant in view of the increasing antibiotic resistance worldwide and suggest that treatment with SFJDC could significantly minimize the use of antibiotics in the treatment of AECOPD patients.

The shortcomings of the clinical studies in this article are that the observation time was not long enough and the sample size was not big enough to effectively judge the long-term efficacy and drug side effects of SFJDC in patients with COPD. Also, these clinical studies have a tendency to ignore the COPD grade or the severity of COPD of the individual patients which is also an important factor in the application of COPD treatment. However, these studies gave the overview of how SFJDC can enhance the clinical effectiveness when combined with the existing therapy on COPD without causing any significant adverse reaction such as liver or kidney abnormalities, skin irritations. Further research with precise study design is needed to understand the pharmacological effect and safety profile of SFJDC and to provide strong evidence of the effectiveness of SFJDC on COPD.

To further investigate the mechanism of clinical effect of SFJDC and interactive mechanism of SFJDC and antiviral western medicine (Oseltamivir phosphate) on influenza A-induced COPD, Ji et al. conducted a human cell culture study and subsequent rat model study [15]. Through the comparison of cell viability, concentration of 20 μg/ml of SFJDC and 1.0 μM of oseltamivir was chosen to be used in the experiments for the optimal inhibitory effect and to avoid cytotoxicity (see Figure 4.1).

![Figure 4.1 Cellular viability assessment via MTT with different concentrations of SFJDC and Oseltamivir (*P < 0.05, ** P < 0.01, ***P < 0.001 versus the control group; # P < 0.05, ## P < 0.01, ### P < 0.001 versus the SFJDC 20 μg/ml groups; &P < 0.05, && P < 0.01 versus the SFJDC 40 μg/ml groups)
Rat models were randomly divided into mock group, phosphate-buffered saline (PBS) group, SFJDC group, oseltamivir group, SFJDC plus Oseltamivir group. All the models except for the mock group received influenza A virus and the mock group, the non-virus infected control group, received saline instead of influenza A virus. PBS group, the virus infected control group, didn’t receive any anti-viral treatment. After SFJDC and/or oseltamivir was applied to each experiment group (SFJDC group, oseltamivir group, SFJDC plus Oseltamivir group), concentrations of interleukin (IL-1β and IL-18) in serum were examined. Both IL-1β and IL-18 are pro-inflammatory cytokines, which means that it plays an important role in the inflammation process as a part of the immune system. Therefore, increased level of IL-1β and IL-18 may imply an ongoing inflammation and successful intervention against the inflammation may down-regulate the level of IL-1β and IL-18 [15].

Analysis showed that SFJDC monotherapy group and oseltamivir monotherapy group had lower interleukin level compared to the PBS group (p<0.001) (see Figure 2). Furthermore, SFJDC plus Oseltamivir group showed even lower IL-1β and IL-18 level compared to monotherapy groups (p<0.01). These findings indicate that elevated interleukin levels can be optimally attenuated by SFJDC plus oseltamivir combination therapy but also SFJDC or oseltamivir alone can modulate the inflammatory factors.

From this study, it is indicated that SFJDC can interfere inflammation pathways to reduce pro-inflammatory cytokines (IL-1β, and IL-18) in the inflammation process of the lung tissue. Moreover, oseltamivir phosphate and SFJDC has similar mechanism in treating respiratory
inflammation and lung injury, which leads to the additive effect of SFJDC/Oseltamivir combination therapy.

A recent review compared thirteen RCTs (1036 patients, with 936 inpatients) which compared SFJD in combination with usual care (including antibiotics) to usual care alone. SFJD was associated with a significant reduction in treatment failure, from 20.1 to 8.3% and duration of hospital stay. No significant difference in adverse events was found between SFJD and control groups. However, there was a lack of blinding in all studies [61].

**Conclusion**

The presented evidence suggests that SFJD brings additional benefit for the treatment of COPD by reducing treatment failure, shorten hospital stay, and improving symptoms. Further large, high quality RCTs are needed to confirm its benefit and safety.

In conclusion, the recent studies confirm that the clinical application of SFJDC for COPD as monotherapy or in combination with western medicine has a potential as an alternative treatment strategy that can enhance the clinical effect compared to existing COPD treatment strategy. However, further clinical trials in a larger scale with longer treatment duration will be needed to verify the result shown by the previous studies. In addition, theoretical basis has to be strengthened through animal and cell studies for understanding the mechanism behind the activity of SFJDC and its safety profile.
References


5. General Office of the National Health Commission Office of the State Administration of Traditional Chinese medicine. New Coronavirus Infection Pneumonia Diagnosis and Treatment Plan. 2020;.


35. Wu. 疏风解毒胶囊治疗北京地区季节性流行性感冒100例临床观察. 2019; .
42. 李有跃. 疏风解毒胶囊治疗流行性感冒的临床研究. JETCM. 2018; 27(10):1689–1699.
48. 磷酸奥司他韦联合疏风解毒胶囊治疗甲型H1N1流感. 6–8.
57. He R, Jiang Y, Qiang D. Clinical study on Shufeng Jiedu Capsules combined with Pseudoephedrine Hydrochloride Chlorphenamine Maleate and Dextromethorphan Hydrobromide Solution in treatment of...


59. 蒋瑞家, 家飞, 陈长山. 疏风解毒胶囊治疗 129 例感冒后咳嗽患者的临床疗效分析及其对相关炎症状因子的表达研究. 临床肺科杂志. 2018; 23(7):2015.


88. Huang Juan L jia chang. Clinical curative Effect Observation of SFJDC in treating acute exacerbations of COPD.