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Application regularity of medicinal and dietary substances for patients during COVID-19 rehabilitation

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A R T I C L E I N F O A B S T R A C T

Article history Received 15 August 2022 Accepted 03 September 2022 Available online 25 September 2022

Keywords

Corona Virus Disease 2019 (COVID-19) Rehabilitation Data mining Traditional Chinese medicine diet therapy Medicinal and dietary substances Both reinforcing and reducing treatment **Objective** This study focused on the application regularity of medicinal and dietary substances (MDS) of traditional Chinese medicine (TCM) diet therapy during rehabilitation, in order to help patients with Corona Virus Disease 2019 (COVID-19) reduce sequelae and improve their life quality.

Methods The official websites of the national and provincial health committees, the website of the National Administration of Traditional Chinese Medicine, the China BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang Database were used to search the keywords, such as "coronavirus" "novel coronavirus pneumonia" "COVID-19" "protocol" "guideline" "consensus" and "rehabilitation period". The search time was from the establishment of databases to July 31, 2022. The prevention and control protocols of various provinces and cities were manually supplemented and screened out. The information on the frequency, property, flavor, meridian tropism, and efficacy of MDS was collected for association rule analysis through the Apriori algorithm. Hierarchical cluster analysis was performed using the Euclidean distance and longest distance.

Results A total of 18 protocols were screened out, including 56 lists of TCM diet therapy, and 47 kinds of MDS with a frequency of 132 times during the rehabilitation of COVID-19. Among them, six lists of diet therapy were collected from national websites, 26 from local government websites, and 24 from social and academic institution websites. The intended population can be divided into seven categories including normal recovery, lung-spleen Qi deficiency, deficiency of both Qi and Yin, spleen-stomach weakness, deficiency of Yang Qi, kidney Qi deficiency, and blood deficiency. Shanyao (Dioscoreae Rhizoma) and Lianzi (Nelumbinis Semen), followed by Dazao (Jujubae Fructus) were used most commonly in MDS, with mainly flat property, sweet flavor, and spleen and lung meridians in meridian tropism. Besides, deficiency-tonifying drugs were commonly used in MDS. Through association rule

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Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: 10.1016/j.dcmed.2022.10.001

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Citation: LUO BF, HE QY, YI XQ, et al. Application regularity of medicinal and dietary substances for patients during COVID-19 rehabilitation. Digital Chinese Medicine, 2022, 5(3): 242–252.

analysis, 12 groups of association MDS pairs were obtained. The pair of Yiyiren (Coicis Semen) and Chenpi (Citri Reticulatae Pericarpium) had the highest Lift value, and Yiyiren (Coicis Semen) was used most frequently in the MDS category for eliminating pathogenic factors. The results of complex network analysis showed that the core MDS were Yiyiren (Coicis Semen), Shanyao (Dioscoreae Rhizoma), Huangqi (Astragali Radix), Fuling (Poria), and Dazao (Jujubae Fructus). Three core categories were classified by cluster analysis, including the category of strengthening spleen, nourishing kidney, and grasping Qi, the category of removing phlegm, abating panting, and regulating Qi, and the category of strengthening the middle-energizer and reinforcing Qi.

Conclusion Based on the TCM theory, most patients during the rehabilitation of COVID-19 are in a state of lingering pathogens due to deficient vital Qi. TCM diet therapy is based on the principle of "giving both reinforcing and reducing treatment", and the MDS combinations focus on both reinforcing the health Qi and eliminating pathogenic factors. The diet therapy mainly uses the MDS with flat property and sweet flavor, which belongs to deficiency-tonifying drugs, adding suitable MDS of pathogen-eliminating drugs according to different situations. The ultimate goal is to promote lung inflammation absorption, improve pulmonary fibrosis, increase immunity, reduce the occurrence of sequelae, and improve life quality.

1 Introduction

In 2020, the Corona Virus Disease 2019 (COVID-19) swept the world. On March 11, 2020, WHO declared the novel coronavirus outbreak a worldwide pandemic^[1]. As of 24:00 on August 31, 2022, China reported that there were 6 298 confirmed cases (34 severe cases) in China, with 231 925 discharged cases and 5 226 deaths [2]. A total of 243 449 confirmed cases have been reported ^[2]. At present, the Omicron variant has replaced other strains as the main circulating strain, which is characterized by high infectivity but low pathogenicity ^[3, 4]. Most of the patients infected with Omicron are asymptomatic or have mild symptoms. The focus of domestic epidemic prevention and control has shifted from the treatment of critical illness to the recovery and prognosis of patients ^[5]. Many studies have shown that the sequelae of COVID-19 seriously endanger the physical and mental health and life quality of patients, such as respiratory dysfunction [6], psychological dysfunction ^[7], gastrointestinal symptoms ^[8], and renal dysfunction [9]. Among them, exertional dyspnea (71.7%) and fatigue (54.6%) were the most common sequelae during the rehabilitation ^[10]. Therefore, how to help convalescent patients reduce the occurrence of sequelae and improve their life quality is an urgent problem that remains to be solved now.

Plain Questions of the Yellow Emperor's Inner Classics (Huang Di Nei Jing · Su Wen, 《黄帝内经·素问》) advocates that "The cereal, meat, fruit, and vegetable are ingested as diet therapy to regulate health, avoiding over-treatment and damaging the healthy Qi"^[11]. SUN Simiao, the master of Chinese medicine, even wrote a chapter on diet therapy in his book, the Important Prescriptions Worth a Thousand Gold (Qian Jin Yao Fang, 《千金要方》), suggesting that "Food is the root of human beings", and advocating that "Doctor should know the cause of the disease and the damaged organ. Besides, they should first treat it with food, and only consider using the medicine if the food does not work" ^[12]. These statements reflect the principle that "diet therapy is better than medicine". Therefore, diet therapy has been an important method in maintaining our health since ancient times, which plays an important role in the defense against diseases and keeping harmony. In addition, the latest *Diagnosis and Treatment Protocol for COVID-19* (trial version 9) proposed to attach importance to early rehabilitation intervention for patients, promoting rehabilitation training, and strengthening the application of traditional Chinese medicine (TCM) non-drug therapy ^[13, 14]. Therefore, this study systematically sorts out the diet therapy information, and summarizes the regularity and mechanism of diet therapy, with the aim to provide dietary references for the recovered patients.

2 Data and methods

2.1 Data sources

The official websites of the national and provincial health committees, the National Administration of Traditional Chinese Medicine, the China BioMedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wanfang Database were searched up until July 31, 2022, to obtain the protocols of epidemic prevention and control. The "coronavirus" "novel coronavirus pneumonia" "COVID-19" "protocol" "guideline" "consensus" and "rehabilitation" were selected as the keywords.

2.2 Inclusion criteria

(i) TCM prevention and treatment protocols for COVID-19 published by national, provincial, and municipal health committees, and various academic organizations.
(ii) A protocol containing information on the prevention and treatment of COVID-19 during the rehabilitation.
(iii) The prevention and treatment protocols including TCM diet therapies.

2.3 Exclusion criteria

(i) Protocols containing Chinese herbs, non-medicinal and dietary substances (MDS) or medicated diet. (ii) Information released by non-official organizations such as journals and personal accounts. (iii) Protocols or information that are repeated. (iv) Protocols that have been revoked by the issuing agency at the time of retrieval, and the relevant content cannot be obtained.

2.4 Literature screening and data extraction

Two researchers read and screened the retrieved protocols independently and carefully in strict accordance with the inclusion and exclusion criteria. Then, by reading the full text, the items that were not relevant to TCM diet therapy were screened out. If there is any disagreement, it will be resolved through consultation with the third researcher.

Two researchers were responsible for extracting information from protocols that met the inclusion criteria, and then checked the extracted information one by one. If there are any differences, the researchers will resolve them through discussion and re-reading. The extracted content mainly includes the basic information of the protocols (title, posting department, posting date, etc.), and the information on TCM diet therapy (applicable population, diet therapy prescription, composition, preparation method, etc.).

2.5 Data standardization

The extracted information is classified according to the publishing department. If the information on diet therapy in the different versions of protocols that were published by the same department has not been updated, only the latest version will be retained. The names of MDS were standardized following the List of Items that are both Food and Medicine ^[15]. For example, the "Gouqi (Lycii Fructus)" was standardized to "Gougizi (Lycii Fructus)", "Xian Shanyao (Fresh Dioscoreae Rhizoma)" was standardized to "Shanyao (Dioscoreae Rhizoma)". In addition, the property, flavor, meridian tropism, and efficacy of MDS were standardized following the Chinese Pharmacopoeia (2020 edition) [16], and the "the 13th Fiveyear Plan" textbook of Chinese Medicine for national universities of TCM [17]. For example, the "Weiwen (light warm)" was standardized to "Wen (warm)", and "Weihan (light cold)" was standardized to "Han (cold)".

2.6 Data analysis

All of the information about MDS were sorted out from protocols. The frequency, property, flavor, and efficacy of the MDS were recorded and counted, and a database was established. Apriori algorithm in SPSS Modeler 18.0 was used to perform association rule analysis on the MDS, with Support value $\geq 10\%$, Confidence value $\geq 30\%$, and Lift value ≥ 1.0 as the standard. A number of links obtained by association rule analysis were adopted as the edge weight, and Gephi 9.3 was adopted to perform complex network analysis of MDS. SPSS statistics 25.0, Euclidean distance, and longest distance were used to conduct cluster analysis on high-frequency MDS.

3 Results

3.1 Proposal selection and data extraction

A total of 79 protocols were selected from official agencies, such as the National Health Community of the People's Republic of China, and 728 lists of diet therapy about COVID prevention were collected through four Chinese databases, such as CNKI. After excluding duplicates and non-related literature, 18 protocols were included in the analysis (Figure 1).

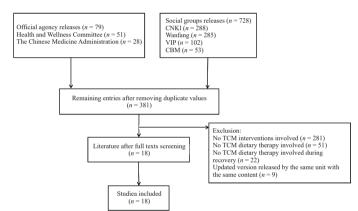


Figure 1 The literature screening process

3.2 Basic information of the included protocols

A total of 18 protocols were included, of which one was released by the National Health Commission of the People's Republic of China [18], eight were officially released by local governments ^[19-26], and nine were released by academic institutions ^[27-35]. The date of publishing was from January 2020 to March 2022 (Supplementary Table S1). In those protocols, 56 lists of diet therapy during the rehabilitation were recorded, of which six were published by the National Health Committee of the People's Republic of China, 26 by local governments, and 24 by academic institutions (Table 1). The applicable groups are divided into the normal recovery group (12), lungspleen Qi deficiency group (15), deficiency of both Qi and Yin group (13), spleen-stomach weakness group (6), deficiency of Yang-Qi group (5), kidney Qi deficiency group (4), and blood deficiency group (1) (Figure 2).

Table 1 Publishing agencies of diet therapy information during COVID-19 rehabilitation

Publishing organization	Publishing agency	n
National organization	National Health Committee of the People's Republic of China, National Administration of Traditional Chinese Medicine	6
Local government organization	Hunan Provincial Administration of Traditional Chinese Medicine, Health Commission of Shandong Province, Health Commission of Gansu Province, Health Commission of Hainan Province, Health Commission of Jiangxi Province, Beijing Administration of Traditional Chinese Medicine, Tianjin Municipal Health Commission, Qingdao Municipal Health Commission	26
Academic organization	Chinese Association of Integrative Medicine, China Association of Chinese Medicine/Chinese Association of Rehabilitation Medicine, Specialty Committee of Pulmonary Rehabilitation of World Federation of Chinese Medicine Societies/Specialty Committee of Pulmonary Diseases of China Medical Association of Minorities, Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University, Specialty Committee of Pulmonary Diseases of Beijing Association of Chinese Medicine, Specialty Committee of Pulmonary Diseases of Beijing Association of Chinese Medicine, Specialty Committee of Pulmonary Diseases of Beijing Association of Chinese Medicine, Guandong Association of Chinese Integrative Medicine, Hunan Medicinal Cuisine & Dietotherapy Research Association, Specialty Committee of Pulmonary Diseases of Shandong Association of Chinese Medicine/Chinese Medicine Pulmonary Disease Physician Branch of Medical Doctor Association of Shandong Province	24

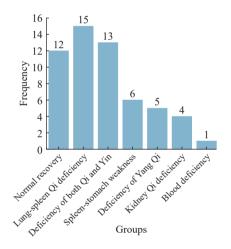


Figure 2 Diet therapy for different applicable groups during COVID-19 rehabilitation

3.3 Frequency analysis of diet therapy

A total of 47 MDS were recorded in the protocols with a frequency of 132 times, and the top five MDS in terms of frequency were Shanyao (Dioscoreae Rhizoma) (12 times, 9.09%), Lianzi (Nelumbinis Semen) (12 times, 9.09%), Dazao (Jujubae Fructus) (9 times, 6.81%), Yiyiren (Coicis Semen) (8 times, 6.06%), and Huangqi (Astragali Radix) (7 times, 5.30%) (Table 2).

3.4 Frequency analysis of property, flavor, and meridian tropism

The analysis of property, flavor, and meridian tropism of 47 MDS showed that the frequency of property was 132 times, and the top three properties were flat (55 times, 41.67%), warm (52 times, 39.39%), and cool (16 times, 12.12%). The frequency of the flavors was 174 times, with the most flavor being sweet (102 times, 58.62%). The

Table 2Top 20 MDS in terms of frequency during COVID-19 rehabilitation

Name	Freq- uency	Perce- ntage (%)
Shanyao (Dioscoreae Rhizoma)	12	9.09
Lianzi (Nelumbinis Semen)	12	9.09
Dazao (Jujubae Fructus)	9	6.81
Yiyiren (Coicis Semen)	8	6.06
Huangqi (Astragali Radix)	7	5.30
Baihe (Lilii Bulbus)	7	5.30
Shengjiang (Zingiberis Rhizoma Recens)	6	4.55
Chenpi (Citri Reticulatae Pericarpium)	5	3.79
Qianshi (Euryales Semen)	4	3.03
Hetaoren (Juglandis Semen)	4	3.03
Fuling (Poria)	4	3.03
Suanzaoren (Ziziphi Spinosae Semen)	3	2.27
Gouqi (Lycii Fructus)	3	2.27
Gegen (Puerariae Lobatae Radix)	3	2.27
Danggui (Angelicae Sinensis Radix)	3	2.27
Zisuzi (Perillae Fructus)	2	1.52
Xingren (Armeniacae Semen Amarum)	2	1.52
Xiyangshen (Panacis Quinquefolii Radix)	2	1.52
Shanzha (Crataegi Fructus)	2	1.52
Xiaomai (Tritici Semen)	2	1.52

frequency of meridian tropism was 349 times, and the top three meridians were spleen meridians (90 times, 25.79%), lung meridians (84 times, 24.07%), and kidney meridians (49 times, 14.04%) (Figure 3 - 5).

3.5 Frequency analysis of efficacies

The top 20 MDS in terms of frequency were classified according to their efficacies and could be divided into eight categories with a frequency of 100 times. Among them, deficiency-tonifying drugs (47 times, 47%), astringent

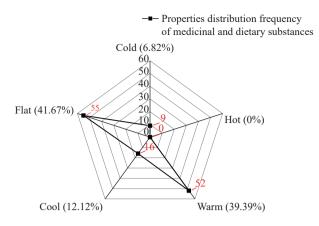


Figure 3 Property of MDS during COVID-19 rehabilitation

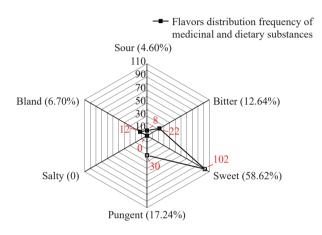


Figure 4 Flavor of MDS during COVID-19 rehabilitation

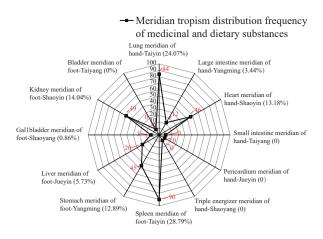


Figure 5 Meridian tropism of MDS during COVID-19 rehabilitation

drugs (26 times, 26%), and water-drainage drugs (12 times, 12%) were predominant (Table 3).

3.6 Association rule analysis of MDS

A network graph of MDS was obtained through association rule analysis (Figure 6). The study fixed Support value at $\geq 10\%$, Confidence value at $\geq 30\%$, and Lift value at ≥ 1.0 ^[36]. The results showed that 12 groups of association MDS pairs were obtained (Table 4). The Lift value can be used to judge the strength of rules. The Lift values of the MDS pair over 1 indicate that the MDS pair has a positive correlation. The pair of Yiyiren (Coicis Semen) and Chenpi (Citri Reticulatae Pericarpium) showed the highest Lift value, and the Yiyiren (Coicis Semen) was

Category	Efficacy	Name	Frequency	Percentage (%)
	Deficiency-tonifying	Shanyao (Dioscoreae Rhizoma)	12	12.00
		Dazao (Jujubae Fructus)	9	9.00
		Huangqi (Astragali Radix)	7	7.00
		Baihe (Lilii Bulbus)	7	7.00
		Hetaoren (Juglandis Semen)	4	4.00
		Gouqi (Lycii Fructus)	3	3.00
Body-strengthening category		Danggui (Angelicae Sinensis Radix)	3	3.00
Body-strengthening category		Xiyangshen (Panacis Quinquefolii Radix)	2	2.00
	Astringent	Lianzi (Nelumbinis Semen)	12	12.00
		Qianshi (Euryales Semen)	4	4.00
		Xiaomai (Tritici Semen)	2	2.00
	Qi-regulating	Chenpi (Citri Reticulatae Pericarpium)	5	5.00
	Tranquilizing	Suanzaoren (Ziziphi Spinosae Semen)	3	3.00
	Water-drainage	Yiyiren (Coicis Semen)	8	8.00
	water-urainage	Fuling (Poria)	4	4.00
	Cough-relieving	Zisuzi (Perillae Fructus)	2	2.00
Pathogen-eliminating category		Xingren (Armeniacae Semen Amarum)	2	2.00
	Exterior-releasing	Shengjiang (Zingiberis Rhizoma Recens)	6	6.00
	Laterior-releasing	Gegen (Puerariae Lobatae Radix)	3	3.00
	Digestion-promoting	Shanzha (Crataegi Fructus)	2	2.00

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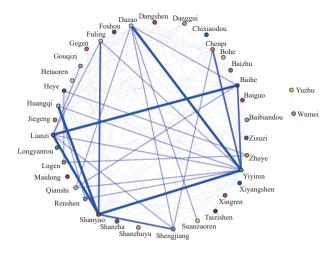


Figure 6 Complex network diagram of MDS based on association rule during COVID-19 rehabilitation

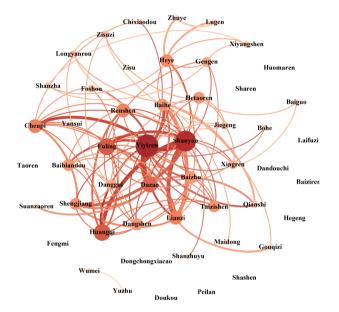


Figure 7 Complex network diagram of MDS during COVID-19 rehabilitation

the most frequently used MDS in the category for eliminating pathogenic factors (Table 3).

3.7 The complex network analysis of MDS

Complex network analysis of 47 MDS resulted in the core drugs mainly including Yiyiren (Coicis Semen), Shanyao (Dioscoreae Rhizoma), Huangqi (Astragali Radix), Fuling (Poria), and Dazao (Jujubae Fructus) (Figure 7).

3.8 Cluster analysis of MDS

The Euclidean distance and longest distance methods were used for cluster analysis of 15 MDS with a frequency $\ge 3^{[37]}$ (Figure 7), and three cluster combinations were obtained: the category of strengthening spleen, nourishing kidney, and grasping Qi, the category of removing phlegm, abating panting, and regulating Qi, and the category of strengthening the middle-energizer and reinforcing Qi (Figure 8 and Table 5).

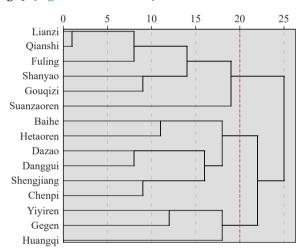


Figure 8 Cluster analysis of high-frequency MDS during COVID-19 rehabilitation (frequency \ge 3 times)

MDS pair	Support (%)	Confidence (%)	Lift
Yiyiren (Coicis Semen)-Chenpi (Citri Reticulatae Pericarpium)	10	60.00	3.00
Shanyao (Dioscoreae Rhizoma)-Fuling (Poria)	10	60.00	2.50
Lianzi (Nelumbinis Semen)-Baihe (Lilii Bulbus)	14	57.14	2.38
Shanyao (Dioscoreae Rhizoma)-Huangqi (Astragali Radix)	14	57.14	2.38
Shanyao (Dioscoreae Rhizoma)-Shengjiang (Zingiberis Rhizoma Recens)	14	42.86	1.79
Yiyiren (Coicis Semen)-Baihe (Lilii Bulbus)	14	42.86	2.14
Shengjiang (Zingiberis Rhizoma Recens)-Chenpi (Citri Reticulatae Pericarpium)	10	40.00	2.86
Lianzi (Nelumbinis Semen)-Fuling (Poria)	10	40.00	1.67
Yiyiren (Coicis Semen)-Fuling (Poria)	10	40.00	2.00
Yiyiren (Coicis Semen)-Dazao (Jujubae Fructus)	20	40.00	2.00
Shanyao (Dioscoreae Rhizoma)-Yiyiren (Coicis Semen)	20	40.00	1.67
Shanyao (Dioscoreae Rhizoma)-Lianzi (Nelumbinis Semen)	24	33.33	1.39

No.	Composition	Efficacy category
C1	Lianzi (Nelumbinis Semen), Qianshi (Euryales Semen), Shanyao (Dioscoreae Rhizoma), Gouqizi (Fructus Lycii), Suanzaoren (Ziziphi Spinosae Semen)	Strengthening spleen, nourishing kidney, and grasping Qi
C2	Baihe (Lilii Bulbus), Hetaoren (Juglandis Semen), Dazao (Jujubae Fructus), Danggui (Angelicae Sinensis Radix), Shengjiang (Zingiberis Rhizoma Recens) , Chenpi (Citri Reticulatae Pericarpium)	Removing phlegm, abating panting, and regulating Qi
C3	Yiyiren (Coicis Semen), Gegen (Puerariae Lobatae Radix), Huangqi (Astragali Radix)	Strengthening the middle-energizer and reinforcing Qi

Table 5 Cluster analysis of MDS during COVID-19 rehabilitatiom

4 Discussion

TCM diet therapy is convenient, palatable, inexpensive, safe, and effective [38], which plays an important role in the healing and recovery of COVID-19^[35]. The results of this study showed that the treatment principle of TCM diet therapy during rehabilitation is reinforcing the healthy Qi and removing the pathogenic factor. Most of the MDS used during rehabilitation belongs to the deficiency-tonifying drug, with a flat property and a sweet flavor, and are mainly attributed to the spleen and lung meridian. The core MDS pairs derived from the association rule analysis also belong to the deficiency-tonifying drug. Renshen (Ginseng Radix et Rhizomo), Huangqi (Astragali Radix), and Dazao (Jujubae Fructus) were the most frequent drugs for reinforcing Qi, while the Yiviren (Coicis Semen) was the most frequent drug for eliminating pathogenic factors. The core drugs derived from the complex network analysis are: Yiviren (Coicis Semen), Shanyao (Dioscoreae Rhizoma), Huangqi (Astragali Radix), Fuling (Poria), and Dazao (Jujubae Fructus), and their effects are classified as (i) strengthening spleen, nourishing kidney, and grasping Qi, (ii) removing phlegm, abating panting, and regulating Qi, (iii) strengthening the middle-energizer and reinforcing Qi. In the category of strengthening spleen, nourishing kidney, and grasping Qi, Lianzi (Nelumbinis Semen) and Shanyao (Dioscoreae Rhizoma) strengthen the spleen and benefit the Qi, together with Gouqi (Lycii Fructus) and Suanzaoren (Ziziphi Spinosae Semen) nourishing the Yin and tranquilizing the mind, which is suitable for patients with Yin deficiency or deficiency of the spleen and kidney in the rehabilitation. In the category of removing phlegm, abating panting, and regulating Qi, Hetaoren (Juglandis Semen) relieves cough and resolve phlegm, together with Baihe (Lilii Bulbus) and Dazao (Jujubae Fructus) moistening the lung and reinforcing Qi, adding Shengjiang (Zingiberis Rhizoma Recens) to warm the middle energizer and resolve retained morbid fluid, which is suitable for patients suffering from cough and asthma due to phlegm-dampness in the lungs and lung Qi deficiency. In the category of strengthening the middle-energizer and reinforcing Qi, Huangqi (Astragali Radix) could tonify the

middle energizer and reinforce Qi, and Gegen (Puerariae Lobatae Radix) could promote Yang Qi. When they combine with Yiyiren (Coicis Semen), the spleen will be strengthened and dampness will be removed, which is suitable for patients with deficient health Qi and unresolved residual pathogens.

Studies have shown that more than half of the patients who recovered from COVID-19 had varying degrees of pulmonary impairment, exhibiting deficiency symptoms such as fatigue, shortness of breath, and spontaneous sweating, and in severe cases, they were even at the risk of pulmonary fibrosis [39]. Therefore, the recovery and life quality of patients who have been discharged from hospitals need close attention. Nowadays, the Omicron variant is the main prevalent strain, which causes less severe symptoms in infected individuals compared to other strains and tends to infect the upper respiratory tract ^[40]. Some patients might suffer from weakness, poor appetite, and other deficiency symptoms after infection^[41]. According to TCM theory, regardless of the time, pneumonia caused by COVID-19 is the result of the pandemic and poisonous pathogens offending the lungs. When the disease progresses to the rehabilitation, the pathogenic factors decline and the health Qi is depleted after the fight, and the patient is in a state of health Qi deficiency^[42, 43]. The Yellow Emperor's Inner Classics says: "If there is enough healthy Qi in the body, the pathogenic factor will be kept out". Therefore, "reinforcing the healthy Qi" is the basic principle of TCM throughout the COVID-19 recovery. The Essential Recipes for Emergent Use Worth A Thousand Gold (Bei Ji Qian Jin Yao Fang, 《备急千金要 方》) says: "When patients are recovering from a serious illness and their Qi and blood have not yet recovered, you should have more time to rest. If there is a need for medicine, herbs that are flat in property should be considered at first"^[44]. It indicates that the human body is healthy when it is in a calm state, and if medication is needed during rehabilitation, it should be chosen from calm drugs with flat property to prevent the cold, hot, warm, and cool property of the drugs from being too biased and affecting the recovery of the body and the healthy Qi. In this study, we found that most of the MDS used to help

patients recover from COVID-19 were found to have a flat nature, because the flat property can not only harmonize Yin and Yang and promote the body to maintain the balance of Yin and Yang, but also have the characteristics of "slowly restoring deficiency and preventing overtreatment" [45]. This is in line with the concept of "The healthy Qi is stored within human bodies" as stated in the Yellow Emperor's Inner Classics. Besides, the Spiritual Pivot (Ling Shu, 灵枢) also pointed out that "If people are affected by pathogenic factors ... with weak pulse, the Qi of Yin and Yang is deficient, and the patients should be treated with drugs in sweet flavor instead of needling". It indicates that drugs with sweet flavor can treat the deficiency of Yin, Yang, physique, and Qi in the human body by "harmonizing, soothing and tonifying". The high-frequency MDS in the protocols contain Shanyao (Dioscoreae Rhizoma), Dazao (Jujubae Fructus), Huangqi (Astragali Radix), Renshen (Ginseng Radix et Rhizoma), etc. Modern pharmacological studies have proven that Shanyao (Dioscoreae Rhizoma) polysaccharides can enhance human immunity^[46]. Dazao (Jujubae Fructus) polysaccharides can achieve effective improvement of body immunity by promoting lymphocyte proliferation ^[47]. Extraction of Lianzixin (Nelumbinis Plumula) has an inhibitory effect on lung fibroblasts [48, 49]. Various active compenents of Huangqi (Astragali Radix) have immune-enhancing and anti-pulmonary fibrosis effects [50-52]. Ginsenosides have anti-pulmonary fibrosis effects ^[53]. In summary, the drugs of reinforcing healthy Qi can enhance the immune and improve pulmonary fibrosis to enrich the body's healthy Qi. Hence, during rehabilitation, eating sweet and flat MDS can restore the healthy Qi and improve the immunity of the patients.

SUN Simiao, a famous physician in ancient times, also suggested that the principle of "giving both reinforcing and reducing treatment" should be followed during rehabilitation. Although the pathogen is almost gone during the rehabilitation, there might be some pathogens left in the body. Besides, most of the patients during rehabilitation may lack healthy Qi and the Qi-transformation function, which can easily lead to Qi stagnation, blood stasis, and dampness [54]. In addition, recent studies have shown that some patients recovering from COVID-19 still have inflammation in their lungs after discharge, and inflammatory factors have not returned to normal for months after discharge [55], which may cause poor prognosis [56]. The MDS can reduce the damage of inflammation to organs by regulating inflammatory factors, which in turn can have a pathogen-eliminating effect. Yiyiren (Coicis Semen) could act as an anti-inflammatory agent by reducing vascular permeability and inflammatory exudation and lowering the level of inflammatory factors ^[57]. Kuxingren (Armeniacae Semen Amarum) could inhibit the expression of inflammatory factors IL-1 β , IL-6, and TNF- α ^[58]. Ethanolic extract of Fuling (Poria) could reduce the secretion of inflammatory mediators, such as TNF- α and IL-1 β ^[59]. Shengjiang (Zingiberis Rhizoma Recens) is able to reduce neutrophil infiltration and the release of pro-inflammatory cytokines [60]. In summary, the treatment of patients during COVID-19 rehabilitation should based on reinforcing healthy Qi and eliminating pathogenic factors to suppress the inflammatory response. The results of this study showed that nine out of 12 core MDS pairs belonged to the combination of both the body-strengthening drug and pathogen-eliminating drug, which was in line with the treatment principle of "giving both reinforcing and reducing treatment" (Figure 9).

TCM diet therapy should not only follow the principle of "giving both reinforcing and reducing treatment", but also retain the TCM characteristics of "treatment based on syndrome differentiation". Hence, the selection of the MDS pairs is based on the patient's different syndrome. In addition to the three categories derived from the cluster analysis, the protocols also recommend MDS that have the effect of eliminating pathogens. For example, if the rehabilitation is during a hot summer, Heye (Nelumbinis Folium) and Hegeng (Lotus Petiole) should be used as a supplement to clear the summer heat and benefit the Qi to prevent patients from the summer-heat pathogen. If the patient is suffering from superficies syndrome, Zisu (Perillae Folium) and Dandouchi (Sojae

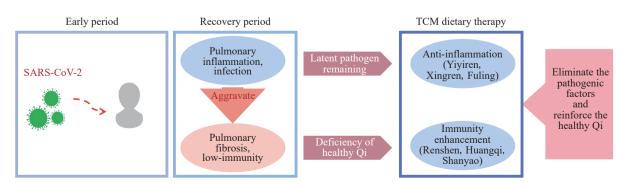


Figure 9 Mechanism diagram of the "giving both reinforcing and reducing treatment" principle

Semen Praeparatum) should be used as a supplement to eliminate superficial pathogens. If patients have lung and spleen deficiency, Qianshi (Euryales Semen) and Dangshen (Codonopsis Radix) can be used as a supplement to strengthen the spleen, reinforce Qi, and enhance the ability of the spleen and stomach to transport and transform. If the residual evil has been detained for a long time in the body and turned into heat, which may result in endogenous heat due to Yin deficiency and mind disturbance, Baiziren (Platycladi Semen) should be used as a supplement to nourish Yin and heart for tranquillization, and clear endogenous heat in the body.

5 Conclusion

The study found that the MDS pairs containing both body-strengthening and pathogen-eliminating drugs are in line with the TCM theory of "giving both reinforcing and reducing treatment", and it is a good choice for patients recovering from COVID-19. The MDS with flat property, sweet flavor, and effect of eliminating pathogens should be chosen for treatment according to the patient's physical conditions, season, and geographical environment, which can help to reduce the sequelae and improve life quality. The therapeutic effect of MDS can be achieved by suppressing lung inflammation, improving pulmonary fibrosis, and enhancing immunity. However, there is a lack of clinical studies and efficacy evaluations of TCM diet therapy in patients during the rehabilitation of COVID-19. Therefore, follow-up studies should be devoted to promoting the clinical application of TCM diet therapy to help improve the life quality of patients during COVID-19 rehabilitation.

Fundings

Jiangxi Traditional Chinese Medicine Young and Middleaged Backbone Talent Preject Second Batch (1242001415).

Competing interests

The authors declare no conflict of interest.

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药食两用物质在新型冠状病毒肺炎康复期的应用规律

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【摘要】目的 探析中医食疗药食两用物质在新型冠状病毒肺炎康复期的应用规律,帮助患者减少后遗症的发 生,提高生活质量。方法 计算机检索国家及各省市卫生健康委员会官网、中医药管理局官网、中国生物医学文 献数据库、中国知网、维普和万方数据库,以"冠状病毒""新冠肺炎""COVID-19""方案""指南""共识""康复期"等 关键词为检索词,检索时间自建库至2022年7月31日,手工补充检索各省市防控方案,筛选出包含康复期食 疗方的信息。对所有药食两用物质的推荐频次、性味归经、功效进行统计,运用 Apriori 算法对药食两用物质进 行关联规则分析,采用欧氏距离和最长距离法对高频药食两用物质进行系统聚类分析。结果 筛选出 18 个方 案, 共推荐56条新型冠状病毒肺炎康复期食疗信息, 47种药食两用物质, 累计推荐频次132次。其中食疗信息 包括国家级 6 条,地方政府级 26 条,社会学术机构级 24 条;适用人群分为 7 类;正常恢复人群、肺脾气虚人群、 气阴两虚人群、脾胃虚弱人群、阳虚人群、肾气亏虚人群、血虚失养人群;推荐频次前3的物质分别为山药、莲 子、大枣;性味以平、甘为主;归经以脾、肺经为主;功效分类以补虚药为主;物质关联分析显示药物组合共 12 对,薏苡仁-陈皮为提升度最高的组合,薏苡仁是药对中出现频次最多的祛邪类物质。复杂网络可视化分析 显示核心药物为:薏苡仁、山药、黄芪、茯苓、大枣:聚类分析筛选出高频药食两用物质组合3类,依次为健脾益 肾纳气类、化痰平喘理气类和补中益气类。结论 中医认为新型冠状病毒肺炎康复期患者出院后多处于正虚邪 恋状态,中医食疗以"补泻兼施"为基本原则,食疗配伍主张扶正祛邪并用,使用性平味甘为主的补虚类药食两 用物质,根据不同情况配伍适宜的祛邪类物质,最终达到促进肺部炎症吸收、改善肺纤维化、提高免疫力、减少 后遗症发生及提高生活质量的目的。

【关键词】新型冠状病毒肺炎;康复期;数据挖掘;中医食疗;药食两用物质;补泻兼施