

# Therapeutic Effects and Molecular Network Mechanism of Chinese herbs for Coronavirus Disease-19

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## Research

**Keywords:** The coronavirus disease-19, integrated traditional Chinese and Western medicine, network pharmacology analysis, Quercetin, Prostaglandin G/H synthase 2

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# Abstract

**Background:** The coronavirus disease-19 (COVID-19) outbreak on December 2019. The present study was aimed to explore the therapeutic effects and the network pharmacology mechanism of Chinese herbs in COVID-19 patients.

**Methods:** In this retrospective study, demographic, clinical signs, radiography, and laboratory of 78 patients were analysis from patients' medical records. Network pharmacology was applied to characterize the action mechanism of herbs decoction.

**Results:** Of all patients were imported cases with familial aggregation. Survival analysis showed that the proportion of cough ( $\chi^2 = 3.864$ ,  $P=0.049$ ) and fever ( $\chi^2 = 5.549$ ,  $P=0.018$ ) in TCM group declined faster than control group. There was a significant radiographic lesions remission difference between groups ( $\chi^2 = 7.666$ ,  $P=0.006$ ). After adjusted by baseline data, the changes of Lymphocytes, ALT and LDH were greater in TCM group ( $P=0.023$ ,  $0.005$ ,  $0.015$ , respectively). A total of 1852 ingredients in 13 herbs were obtained, among which, the ingredients-target network included 168 compounds and 189 targets, 38 GO terms and 63 pathways were found in enrichment analysis.

**Conclusion:** The therapeutic effect of Chinese herbs was amelioration of cough and fever, facilitated the absorption of inflammatory infiltrates seen in the lungs, and increased the number of lymphocytes, protection of liver function via the mechanism of inhibition of coronavirus attack organs and immune cells directly. Molecular mechanisms need to be further validate in vitro and vivo.

## 1. Background

The use of Chinese herbs, traditional Chinese medicine (TCM), emphasizing individuality based on body balance and mind-body interaction, plays an holistic role in the treatment of chronic disease (Liao, Li, Lin, Lin, Chiang, & Li, 2017). Furthermore, many researches has been shown that TCM can also be successfully used for acute and severe diseases treatment, especially when Western medicine is not very working (Luo, Wang, Hesse-Fong, Lin, & Yuan, 2019). A retrospective study from the Chinese University of Hong Kong found that an approach of integrated Chinese herbs, which contained kaempferol and quercetin for severe acute respiratory syndrome (SARS) had led to satisfactory clinical outcomes (Lin et al., 2003; Schwarz et al., 2014; Zhang, & Chen, 2008).

The coronavirus disease-19 (COVID-19) caused by a novel type of beta-coronavirus (2019-nCoV), is an acute infectious disease to which the population is generally susceptible (Zhou et al., 2020; Zhu et al., 2020). A global health emergency has been declared by WHO on January 30, 2020 (Li et al., 2020). To date, more than 1 million new cases of COVID-19 have been confirmed in 205 countries, with a total of 51688 deaths. The epidemiological and clinical characteristics of COVID-19 patients have been described in many articles (Zhu et al., 2020; Li et al., 2020). The current outbreak of COVID-19 is both similar and different from previous outbreaks of SARS and Middle East respiratory syndrome (MERS) (Peeri et al., 2020; Al-Tawfiq, J.A., 2020). However, no effective antiviral drug has been found. The limited available

knowledge underscores the need for supportive treatment and adjunctive drug therapy that is specific for patients with COVID-19 (Arabi, Fowler, & Hayden, 2020).

COVID-19 is classed as plague in TCM, of which the pathogenesis is dampness, toxin, stasis and heat obstructing the lung. TCM believes that "healthy Qi is stored in, evil cannot be dried", our team emphasized the treatment principle of "nourishing healthy Qi, dispelling dampness evil". On the basis of the previous research on the effect of Shenqi Bufe Decoction on chronic obstructive pulmonary disease (Zhang, Wu, Zhang, Yang, & Yang, 2017), we formulated a prescription of "Bufei Quwen Decoction" (BFQW) that benefits for strengthening the lung resistance to eliminate 2019-nCoV, and involved 13 commonly Chinese herbs, *Codonopsis Pilosula*, *Adenophrae Ae Radix*, *Hedysarum Multijugum Maxim*, *Pogostemon Cablin (Blanco) Benth*, *Mori Cortex*, *Trichosanthes Kirilowii Maxim*, *Alpinia Katsumadai Hayat*, *Atractylodes Macrocephala Koidz*, *Cinnamomi Ramulus*, *Poria Cocos (Schw.) Wolf*, *Radix Salviae*, *Forsythiae Fructus*, *Lonicerae Japonicae Flos*.

Therefore, the purpose of this study was to demonstrate the superior ability of those Chinese herbs in exerting therapeutic benefit properties for COVID-19. To this aim, in the present research the clinical characteristics and therapeutic effects of integrated herbs and Western medicine for 78 patients diagnosed with COVID-19 in Guizhou Province have been displayed and the network pharmacology analysis of the herbs prescription was used to explore the molecular mechanism of BFQW in COVID-19 which provide a theoretical basis for clinical practice.

## 2. Methods

### 2.1 Herb Preparation and Treatment

BFQW was designed by our Chinese-herb consulting physician team according to the theory of Chinese medicine and our clinical experience. A total of 13 different kinds of herbs with 5-20g of each made up the formula, including 3 monarch herbs, 8 ministerial herbs, and 2 adjuvant herbs were shown in Table 1. Five to 7 packets of BFQW were submerged in cold water 3cm-5cm above the surface for 30 minutes, and then put the soaked herbs into the decoction machine (YJD30-GL, DONGHUAYUAN MEDICAL, China) with the water at 110°C for 20 min. Decoction was separated 100ml per sachet after cooling, and stored in refrigerator at 4°C. The decoction amount of each packet was 300 ml, and water loss during processing was 2500ml. So the water amount of decocting herbs was calculated as number of packets×300ml+2500ml. The decoction was administered 100ml each time, three times a day throughout the hospital stay.

### 2.2 Patients

For this retrospective, of the 78 coronavirus disease 2019 (COVID-19) patients diagnosed according to WHO interim guidance were recruited from Jan 20, 2020 to Mar 8, 2020. Eighteen of those patients took BFQW combined with Western medicine as the TCM group versus 60 cases by treatment protocol (trail

version 7) in the control group (Jin et al., 2020). We obtained demographic, epidemiological, clinical signs and symptoms, laboratory, and outcome data from patients' medical records.

## 2.3 Exposure history and clinical classification

According to WHO Interim Guidance, the case in this study was defined as any one with exposure history and consistent with any two clinical manifestations and the pathogenic evidence (Wu et al.,2020).

Exposure history: (1) Input, within 14 days before the onset of the disease, there were tourism or residence histories of Wuhan or its surrounding areas, or other communities with confirmed cases; (2) Close contacts, within 14 days before the onset of the disease, there were contacts with confirmed cases of COVID-19 or aggregation in an enclosed environment (such as a family house, a construction site, an office, etc.).

Clinical classification: (1) Mild, the clinical symptoms were mild, with no radiographic findings; (2) Moderate, with fever, cough and other respiratory symptoms, imaging findings of pneumonia; (3) Severe, with dyspnea, respiratory frequency $\geq 30$ /min, blood oxygen saturation $\leq 93\%$ , partial pressure of arterial oxygen to fraction of inspired oxygen ratio  $< 300$ , and/or lung infiltrates  $> 50\%$  within 24 to 48 hours.

## 2.4 Chest CT Image Analysis

Two radiologists with 12 and 10 years of experience in interpreting chest CT imaging, respectively, reviewed all chest CT images at admission and discharge and classified the cumulative lesion distribution range as  $< 10\%$ ,  $10\% - 25\%$ ,  $26\% - 50\%$ ,  $51\% - 75\%$ ,  $> 75\%$  for COVID-19 patients. The degree of radiographic lesions remission was expressed by the difference of imaging changes between discharge and admission.

## 2.5 Disease-drug-target network construction

In absorption, distribution, metabolism, and excretion processes, the ingredients that conformed the Lipinski rules with oral bioavailability (OB)  $\geq 30\%$  and drug likeness (DL) index  $\geq 0.18$  were selected as active substances in the current study. Bioactive ingredients of BFQW and those potential targets were retrieved from the traditional Chinese medicine systems pharmacology database (<http://tcmospw.com/>) (Ru et al., 2014). To associate a therapeutic target with COVID-19, we retrieved coronavirus infected disease and acute respiratory distress syndrome(ARDS)-associated therapeutic targets from GeneCards and OMIM database. A drug-targets-disease network was mapped and visualized using Cytoscape 3.6.1 (Shannon et al., 2003).

## 2.6 Network analysis

In these graphical networks, the compounds, proteins, or pathways were expressed as nodes, whereas the compound-target or target-pathway interactions were expressed as edges. Using CentiScaPe 2.2 plug-in of Cytoscape, the critical nodes in the network were filtered by twice the median of degree, closeness and betweenness. ClueGO plug-in of Cytoscape was used to analyze the pathway enrichment of the critical targets of BuFeiQuWen decoction in the treatment of COVID-19.

## 2.7 Statistical analysis

SPSS software (IBM, Chicago, IL) were used for statistical analyses. Means(SDs) were used for normally and non-normally descriptive statistics of continuous variables. The classification variable is presented as a count (%). Skewed data among the groups were analyzed using *Kruskal - Wallis* test. Categorical variables were estimated for clinical characteristics by the *Linexlist data chi-square* test. Survival analysis of cough and fever was performed by the Kaplan-Meier method with Log-rank test. The changes of laboratory indicators were calculated by the difference of these at admission and discharge. In changes analysis, the difference of baseline lymphocytes, alanine aminotransferase (ALT), and lactic dehydrogenase (LDH) were statistically significant between control group and TCM group, therefore the changes adjusted by linear regression analysis using baseline data. Throughout the study,  $P < 0.05$  was taken as the minimum level of statistical significance. The relevant datasets were directly uploaded to Mendeley Data (Zha, & Da, 2020).

## 3. Results

### 3.1 Identification of bioactive ingredients in BFQW and targets in COVID-19

A total of 1852 ingredients in BFQW were obtained from TCMSP database, 236 of which belong to *Lonicerae Japonicae Flos*, had the most ingredients and a minimum of 34 ingredients to *Poria Cocos(Schw) Wolf*. Among these ingredients in BFQW, 212 (11.50%) met the requirements of Lipinski rules, OB 30% and DL index 0.18 (Table 1). After eliminating the overlaps, 188 ingredients were chosen as candidate active ingredients for further analyses.

Table 1  
Composition of Bu Fei Qu Wen Decoction

Pharmaceutical Name	Chinese Name	Principles of System Theory	Dose (g)	Weight	Number of Ingredients	Number of Active Ingredients
Codonopsis pilosula	Dang Shen	Monarch	20	10.26%	134	18
Adenophrae Ae Radix	Nan Sha Shen	Monarch	20	10.26%	82	5
Hedysarum Multijugum Maxim	Huang Qi	Monarch	20	10.26%	87	14
Pogostemon Cablin (Blanco) Benth	Huo Xiang	Ministerial	10	5.13%	94	9
Mori Cortex	Sang Bai Pi	Ministerial	20	10.26%	194	27
Trichosanthes Kirilowii Maxim	Gua Lou	Ministerial	10	5.13%	80	10
Alpinia Katsumadai Hayat	Dou Kou	Ministerial	10	5.13%	71	12
Atractylodes Macrocephala Koidz	Bai Zhu	Ministerial	15	7.69%	55	7
Cinnamomi Ramulus	Gui Zhi	Ministerial	5	2.56%	220	7
Poria Cocos(Schw.) Wolf	Fu Lin	Ministerial	15	7.69%	34	13
Radix Salviae	Dan Shen	Ministerial	20	10.26%	202	59
Forsythiae Fructus	Lian Qiao	Adjuvant	15	7.69%	150	17
Lonicerae Japonicae Flos	Jin Yin Hua	Adjuvant	15	7.69%	236	15
codonopsis pilosula, adenophrae ae radix, hedysarum multijugum maxim, pogostemon cablin (blanco) benth, mori cortex, trichosanthes kirilowii maxim, alpinia katsumadai hayat, atractylodes macrocephala koidz, cinnamomi ramulus, poria cocos(schw.) wolf, radix salviae, forsythiae fructus, loniceriae japonicae flos,						

1703 protein targets were retrieved from TCMSP database among the 188 candidate bioactive components. 3767 coronavirus infected disease and acute respiratory distress syndrome (ARDS) related human genes were collected from GeneCards and OMIM database. Then, these protein targets of BFQW

were mapped with COVID-19 using Venny analysis. As a result, 189 targets of 168 components in BFQW were associated with COVID-19. These detailed information were shown in Supplement 1-4.

## **3.2 Demographics and clinical characteristics of patients infected with COVID-19**

Of all the 78 patients without medical staff in Guizhou Province were investigated in this study. 29 cases (37.18%) had a history of chronic diseases, including 11 cases cardiovascular and cerebrovascular diseases, 4 cases respiratory system diseases, 2 cases diabetes and 12 other malignant tumors or surgery history. Comparison of demographics and clinical characteristics between control group (n=60) and TCM group (n=18) were shown in Table 2. There were no statistically significant differences in age, gender, exposure history, virus duration and chronic diseases (data was not shown) between two groups. Groups were also similar in antiviral treatment and immune protection therapy. In TCM group, the severity of diseases they were suffered from and the number of oxygen therapy and antibiotic medications they took were greater than those of control group.

**Table 2**  
**Clinical characteristics of Patients with COVID-19**

	Control group (n=60)	TCM group (n=18)	Statistics	P
<b>Age, years</b>				
Mean(SD)	32.21(16.53)	39.28(18.17)	t=0.757	0.124
Range	55 days -78	4 - 67	-	-
<b>Sex</b>				
Female	32(53.3)	9(50.0)	$\chi^2 = 0.062$	0.804
Male	28(46.7)	9(50.0)		
<b>Exposure</b>				
Input	33(55.0)	10(55.6)	$\chi^2 = 0.002$	0.967
Close contacts	27(45.0)	8(44.4)		
<b>Diagnosis</b>				
Mild	12(20.0)	1(5.6)	$\chi^2 = 12.073$	0.002
Moderate	34(56.7)	12(66.7)		
Severe	14(23.3)	5(27.8)		
<b>Treatment</b>				
Oxygen therapy	34(56.7)	17(94.4)	$\chi^2 = 8.731$	0.003
Antiviral treatment*	57(95.0)	18(100.0)	$\chi^2 = 0.963$	0.333
Antibiotic treatment	6(10.0)	11(61.1)	$\chi^2 = 21.22$	<0.001
Immune protection therapy <sup>§</sup>	13(21.7)	4(22.2)	$\chi^2 = 0.003$	0.960
<b>Clinical outcome</b>				
Radiographic lesions remission	23(38.3)	14(77.8)	$\chi^2 = 7.666$	0.006
<b>Clinical characteristics of Patients with COVID-19</b>				

### 3.3 Clinical signs and CT findings of patients with COVID-19

The most common signs were cough, fever, phlegm, digestive symptom, and hypodynamia, which accounted for 46 cases (58.97%), 36 cases (46.15%), 25 cases (32.05%), 23 cases (29.49%) and 15

cases (19.23%) in all patients respectively. Except for 6 patients (7.69%) with liver and digestive injury, there was no other organ damage. The proportion of clinical signs at admission, the fifth day and at discharge, and the scale of pulmonary imaging lesions between control group and TCM group were shown in table 3. Survival analysis showed that the proportion of cough ( $\chi^2 = 3.864$ ,  $P = 0.049$ ) and fever ( $\chi^2 = 5.549$ ,  $P = 0.018$ ) in TCM group declined faster than that of the control group (Figure 1). Of note, hypodynamia in control group increased at day 5 and continued to the end of the hospital stay (Supplement 5). The scale of pulmonary imaging lesions at admission and at discharge were also shown in Supplement 5. There was a significant radiographic lesions remission difference between control group and TCM group ( $\chi^2 = 7.666$ ,  $P = 0.006$ , table 2).

**Table 4**  
**Changes of laboratory results in patients with COVID-19**

	Control group (n=60)	TCM group (n=18)	<i>P value</i>
<b>Leucocytes (×10<sup>9</sup>/L; normal range 3.5-9.5)</b>			
Baseline Mean(SD)	6.17(1.96)	6.12(2.76)	0.796
Changes(SD)	-0.45(1.75)	-0.18(3.02)	0.240
<b>Neutrophils percentage (%; normal range 40-70)</b>			
Baseline Mean(SD)	57.81(12.80)	65.23(17.57)	0.092
Changes(SD)	-1.04(10.82)	-9.56(16.71)	0.110
<b>Lymphocytes (×10<sup>9</sup>/L; normal range 1.1-3.2)</b>			
Baseline Mean(SD)	2.01(0.92)	1.44(0.86)	0.019
Adjusted Changes(SD)&	0.002(0.127)	0.081(0.119)	0.023
<b>C-reactive protein (mg/L; normal range 0-5)</b>			
Baseline Mean(SD)	7.32(9.89)	23.60(37.18)	0.131
Changes(SD)	-0.45(10.67)	-13.29(41.53)	0.976
<b>Glucose (mmol/L; normal range 3.9-6.1)</b>			
Baseline Mean(SD)	5.41(1.40)	6.81(4.05)	0.439
Changes(SD)	0.10(1.29)	-0.69(1.52)	0.374
<b>Alanine aminotransferase (U/L; normal range 9-50)</b>			
Baseline Mean(SD)	21.75(19.46)	35.35(22.12)	0.008
Adjusted Changes(SD)&	5.86(12.09)	-4.12(15.04)	0.005
<b>Aspartate aminotransferase (U/L; normal range 15-40)</b>			
Baseline Mean(SD)	27.44(20.02)	27.00(13.27)	0.389
Changes(SD)	-1.92(23.96)	-5.45(5.09)	0.182
<b>Lactic dehydrogenase (U/L; normal range 120-250)</b>			
Baseline Mean(SD)	191.95(83.80)	238.53(94.27)	0.020
Adjusted Changes(SD)&	-26.72(72.54)	-69.44(82.58)	0.015
<b>&amp;: Adjusted by Baseline laboratory index.</b>			

## 3.4 Changes of laboratory results in patients with COVID-19

There were no statistically significant differences of baseline data and changes in leucocytes, percentage of neutrophils, C-reactive protein, glucose, aspartate aminotransferase, but the decreasing trend of these indicators in TCM group was higher than that of control group in table 3. After adjusted by baseline data, the changes of Lymphocytes, ALT and LDH were greater than those of control group ( $P=0.023$ ,  $0.005$ ,  $0.015$ , respectively).

## 3.6 Ingredients-targets network and analysis

In our study, the ingredients-target network of BFQW on COVID-19 was constructed (Figure 2A). Six active ingredients and 13 targets were selected with indirect degree greater than 26 in network may explain the important therapeutic effect of BFQW on COVID-19 (Figure 2B). Six active ingredients involved quercetin (MOL000098, degree =133, PubChem CID: 5280459),  $\beta$ -sitosterol (MOL000358, degree = 91, PubChem CID: 222284), kaempferol (MOL000422, degree = 73, PubChem CID:5280863 ), luteolin (MOL000006, degree =71, PubChem CID: 5280445), stigmasterol (MOL000449, degree = 27, PubChem CID: 5280794), and 7-O-methylisomucronulatol (MOL000378, degree = 26, PubChem CID: 15689652). Thirteen targets namely, PTGS2 (degree = 57), PTGS1 (degree = 52), NCOA2 (degree = 44), SCN5A (degree= 41), PPARG (degree= 41), ADRB2 (degree =39), AR (degree = 39),SCN5A (degree= 41), PRSS1 (degree =35), CHRM1 (degree =35), CHRM3 (degree =27), CHRM2 (degree =26), and ACHE (degree =26). The high-degree protein targets in network may explain the important therapeutic effect of BFQW on COVID-19.

## 3.7 GO and pathway enrichment analysis

To identify the biological characteristics of putative targets of BFQW on COVID-19 in detail, figure 3 shown the GO and pathway network for characterization the molecular mechanism conducted by ClueGO (Number of gene=15, Min percentage=6.0% and Kappa score $\geq$ 0.4), included 38 GO terms and 63 pathways (Supplement 6). The significantly enriched GO terms indicated that regulation of integrin binding, signaling receptor activity, circulatory system process in membrane region, and neurotransmitter levels in presynaptic membrane to exert therapeutic effects of BFQW on COVID-19. The pathway in AGE-RAGE signaling (39.02%) and IL-17 signaling (31.00%) exhibited the largest percentage of associated genes among the targets. Immunocell damage and immune inflammation related pathways ( such as T cell receptor signaling, IL-17 signaling, NF- $\kappa$ B signaling, Th17 cell differentiation) were mainly found in the network.

## 4. Discussion

The virulence of 2019-nCoV spreads rapidly, mainly through close contact and respiratory droplets, which are easy to cause outbreaks and epidemics in the population (Al-Tawfiq, 2020). The medical team in Guizhou province insists on adopting the "Four Early" measurements, namely "early detection, early

isolation, early diagnosis and early treatment", to achieve treatment and contain the outbreak. In our opinion, integrated Chinese and Western medicine can obtain satisfactory therapeutic effect, not to mention the specific treatment for COVID-19 has not yet been developed and more frequent side effects or adverse events induced by antiviral therapy.

In our study, most patients are imported cases, with familial aggregation as the main transmission dynamics. The proportion of gender was equal and the younger average age that contradicted the findings of studies in Wuhan cases (Chen et al., 2020; Huang et al., 2020). The latter concluded that elderly male were more prone to the 2019-nCoV infection than female. It may be influenced by the transmission dynamics and small sample size. Almost all patients were treated with interferon atomization combined with 1 to 2 antiviral drugs. Compared with control group, TCM group needed more nasal catheter and mask oxygen therapy and moxifloxacin for antibiotic medications was associated with the severity of the disease.

The proportion of clinical signs, cough and fever at admission were lower than those of in Wuhan (Chen et al., 2020), in addition to phlegm, diarrhea and poor appetite (digestive signs), and hypodynamia. Survival analysis showed that BFQW shortening the duration of cough and fever. Moreover, there was no increase of fatigue in the TCM group on the fifth day of hospital stay, indicating that the effect of BFQW was initiated significantly and better at amelioration of disease symptoms via enhancement of muscle strength and facilitated the absorption of inflammatory infiltrates seen in the lungs from radiographic image.

Based on limited knowledge of 2019-nCoV, the invasion of respiratory mucosa and down-regulation of angiotensin converting enzyme 2 (ACE2) expression synchronously initiated the self-injury pattern of lung, liver, kidney, and heart in human body (Hoffmann et al., 2020), then triggers a series of immune responses, inducing cytokine storms and causing changes in immune components such as peripheral blood leukocytes and lymphocytes, especially T cells (Channappanavar et al., 2017; Yao et al., 2020). Our laboratory tests found that patients mainly suffered from lung and liver injuries, no kidney damage according to serum creatinine. In order to eliminate the interference and improve agreements of baseline variation, linear regression were applied to correct the data of indicators changes (Tu, Baelum, & Gilthorpe, 2005), and found that the lymphocytes were significantly increased and ALT, LDH were decreased by BFQW treatment. In addition, it has been reported that patients with COVID-19 infection elevated glucose and CRP level (Wu et al., 2020), were also observed in our study and only had a downward trend without statistical significance for the therapy of BFQW.

In recent research, it has been reported that TCM enhanced antibody production, maintain the balance between Th1 and Th2/Th17 cells for the prevention of viral pneumonia (Fu et al., 2018). This study has proved that BFQW had a better therapeutic effect in patients with COVID-19. Network pharmacology analysis of BFQW bioactive ingredients-targets-disease was constructed to illustrate the key targets and potential mechanism (Molgora et al., 2018). Six active ingredients and 13 targets were predicted to explain the possible mechanism of BFQW on COVID-19. Cyclooxygenase-2 (COX-2), namely Prostaglandin G/H

synthase 2 (PTGS2) was the most important targets, and the basic researches had found that activating PTGS2 expression and signal cascades by SARS-CoV nucleocapsid and spike protein resulting in inflammation of the lungs (Zhao, & Iyengar, 2012; Yan et al., 2006). Quercetin, the most powerful ingredients was found to protect T cells via restoring Th17/Treg balance through NF- $\kappa$ B and Toll-like receptor signaling pathway (Liu et al., 2007). Ligands for peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) had emerged as potent insulin sensitizers used in the treatment of type 2 diabetes (Wei, Tao, Jiang, Zhou, Zhang, & Yuan, 2017). According to the analysis results, the main mechanism of BFQW was the inhibition of coronavirus attack organs and immune cells directly, and elimination of the cytokine storm.

Some weaknesses and limitations in the present research should be noted. First of all, retrospective nature limited sample size and severity of illness, the conclusions may be influenced by baseline variability although they have been corrected by linear regression. Secondly, the differentially expressed genes of 2019-nCoV infected human have not been obtained. "Coronavirus infected disease and ARDS" was used as the key words to retrieve the existed target molecules of diseases, which may lack of 2019-nCoV specific targets that different from SARS or MERS. Thirdly, since biological characteristics of the new virus have not been fully understood, and the virus nucleic acid tested positive again during follow-up period in some patients, this study did not include the clinical outcome of the first virus duration.

## 5. Conclusion

In this study, we have found that the therapeutic effect of BFQW was amelioration of cough and fever, facilitated the absorption of inflammatory infiltrates seen in the lungs, and increased the number of lymphocytes, protection of liver function via the mechanism of modulating the body's physiological state, inhibition of coronavirus attack organs and immune cells directly, and elimination of the cytokine storm by six active ingredients, quercetin,  $\beta$ -sitosterol, kaempferol, luteolin, stigmasterol, and 7-O-methylisomucronulatol. Those molecular mechanisms predicted by network pharmacology analysis need to be further explore and validate in vitro and vivo. It is the first study to display the effect of BFQW in the integrated Chinese and Western medicine on COVID-19 and to clarify the network mechanism of its active compounds in those 13 herbs. The current study is valuable and noteworthy in clinical practice.

## Abbreviations

ACE2, angiotensin converting enzyme 2

ARDS, acute respiratory distress syndrome

ALT, alanine aminotransferase

BFQW, Bufe Quwen Decoction

COVID-19, coronavirus disease-19

COX-2, cyclooxygenase-2

LDH, lactic dehydrogenase

MERS, Middle East respiratory syndrome

PPAR $\gamma$ , peroxisome proliferator activated receptor gamma

PTGS2, prostaglandin G/H synthase 2

SARS, severe acute respiratory syndrome

TCM, traditional Chinese medicine

## Declarations

## Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of Guizhou Provincial People's Hospital. Informed consent was obtained from all the enrolled patients before data were collected retrospectively.

## Consent for publication

All authors have read and approved the submission of the manuscript.

## Availability of data and materials

The relevant datasets were directly uploaded to Mendeley Data, "Zha, Yan; Da, Jingjing (2020), "Therapeutic Effects of Traditional Chinese Medicine in Coronavirus Disease-19", Mendeley Data, V1, doi: 10.17632/94mddr7xkf.1".

## Competing interests

All authors declare that they have no conflict of interest.

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# Authors' contribution

Jingjing Da: Conceptualization, Visualization, Writing- Original draft preparation. Xiangyan Zhang: Methodology, Writing – Review & Editing, Supervision. Fa Sun: Methodology, Investigation. Kui Zhang: Methodology, Investigation. Hourong Zhou: Data curation, Formal Analysis. Weidong Wu: Visualization, Investigation. Xianchun Zeng and Rongpin Wang: Interpreting Chest CT images. Yan Zha: Project Administration.

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## Figures

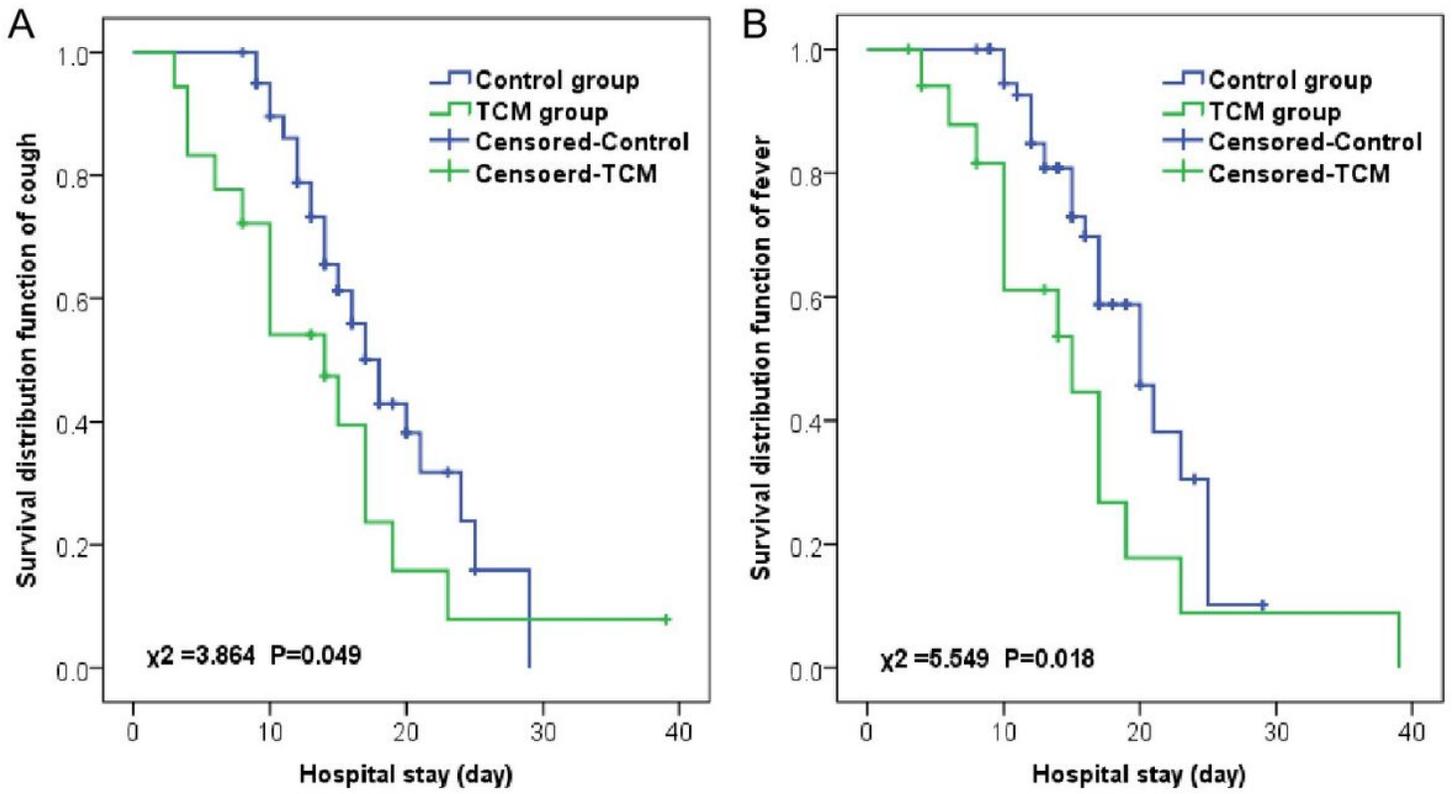


Figure 1

Survival analysis of cough and fever . (A) for cough  $\chi^2 = 3.864$ ,  $P = 0.049$ ; (B) for fever  $\chi^2 = 5.549$ ,  $P = 0.018$

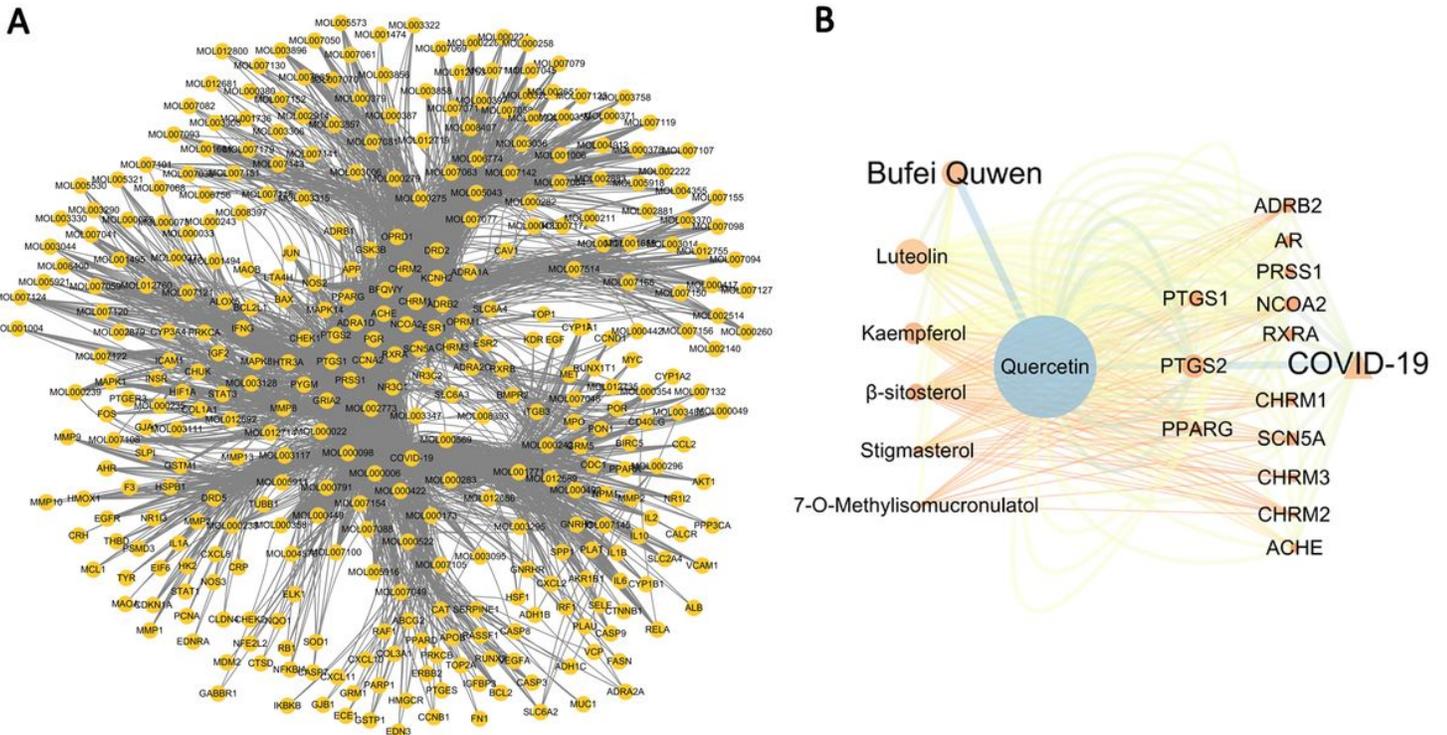


Figure 2

Ingredients-target network of Bufei Quwen Decoction. (A) 189 targets of 168 ingredients were constructed for the network. The orange nodes represent candidate active compounds and potential protein targets. The edges represent the interactions between them and node size is proportional to their degree. (B) Six active ingredients and 13 targets were selected with undirected degree greater than 26 in network

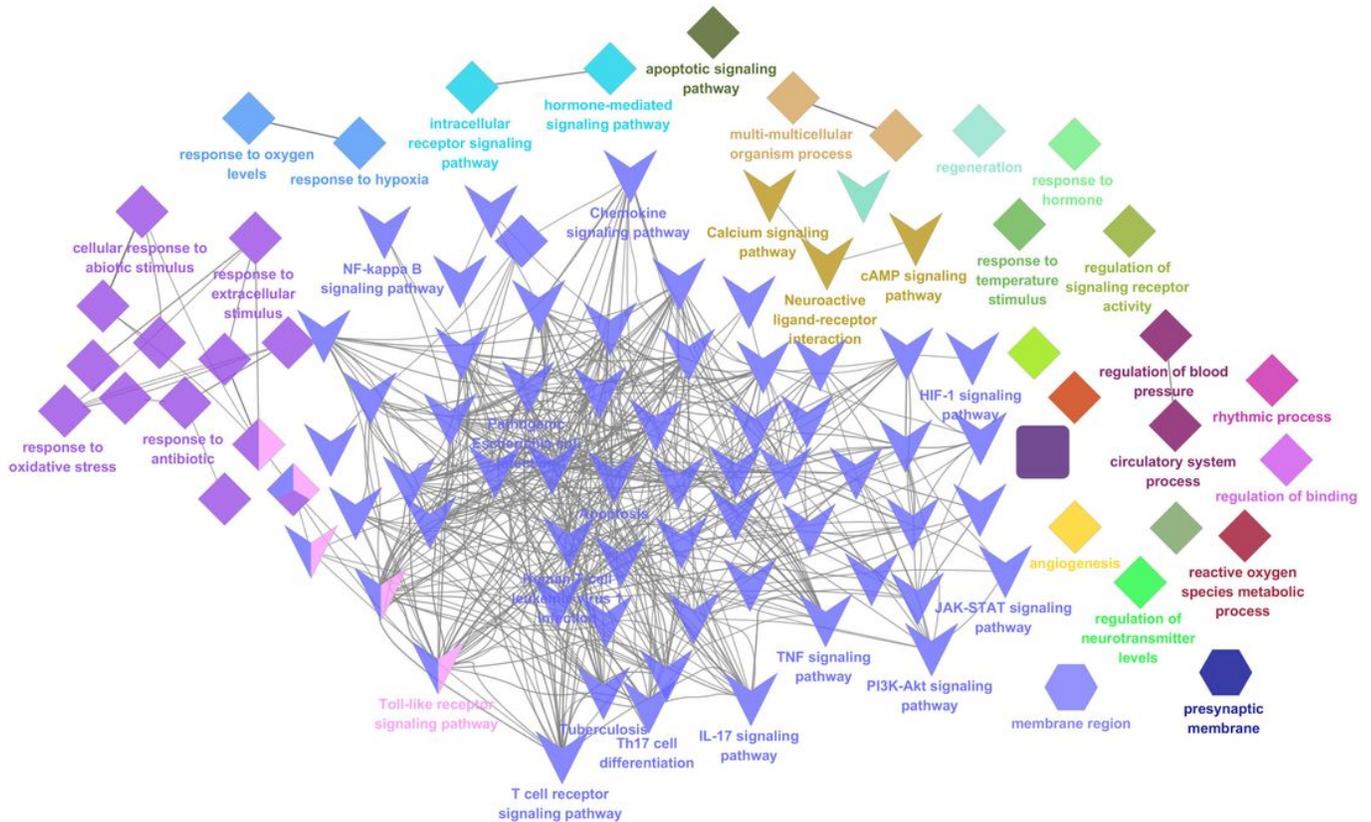


Figure 3

Results of signal pathway analysis of Bufei Quwen Decoction in treatment of COVID-19. The diamond nodes represent biological process, the hexagon nodes represent cellular component targets and the rectangle nodes represent molecular function from GO analysis. The triangle nodes represent pathways from KEGG analysis. The edges represent the interactions between them

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