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Potential Targets for Treatment of Coronavirus Disease 2019 (COVID-19): A Review of Qing-Fei-Pai-Du-Tang and Its Major Herbs

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Abstract: COVID-19 has been declared a pandemic by WHO on March 11, 2020. No specific treatment and vaccine with documented safety and efficacy for the disease have been established. Hence it is of utmost importance to identify more therapeutics such as Chinese medicine formulae to meet the urgent need. Qing Fei Pai Du Tang (QFPDT), a Chinese medicine formula consisting of 21 herbs from five classical formulae has been reported to be efficacious on COVID-19 in 10 provinces in mainland China. QFPDT could prevent the progression from mild cases and shorten the average duration of symptoms and hospital stay. It has been recommended in the 6th and 7th versions of Clinical Practice Guideline on

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COVID-19 in China. The basic scientific studies, supported by network pharmacology, on the possible therapeutic targets of QFPDT and its constituent herbs including *Ephedra sinica*, *Bupleurum chinense*, *Pogostemon cablin*, *Cinnamomum cassia*, *Scutellaria baicalensis* were reviewed. The anti-oxidation, immuno-modulation and antiviral mechanisms through different pathways were collated. Two clusters of actions identified were cytokine storm prevention and angiotensin converting enzyme 2 (ACE2) receptor binding regulation. The multi-target mechanisms of QFPDT for treating viral infection in general and COVID-19 in particular were validated. While large scale clinical studies on QFPDT are being conducted in China, one should use real world data for exploration of integrative treatment with inclusion of pharmacokinetic, pharmacodynamic and herb-drug interaction studies.

Keywords: Coronavirus; QFPDT; Therapeutic Targets; *Ephedra sinica*; *Bupleurum chinense*; *Pogostemon cablin*; *Cinnamomum cassia*; *Scutellaria baicalensis*; *Glycyrrhiza uralensis*.

Introduction

COVID-19, caused by SARS-Cov-2, has spread globally. If containment and mitigation measures are not done, it will infect 25–70% of the population with a mortality rate of 1–5%. The key clinical presentations include fever, fatigue, dry cough, upper airway congestion, sputum production, and shortness of breath, while a minority of patients presented with myalgia, arthralgia, and gastrointestinal symptoms (Chan *et al.*, 2020; Guan *et al.*, 2020). At present, there is no established pharmacological intervention nor vaccine for COVID-19 (Chan *et al.*, 2020; Lipsitch *et al.*, 2020).

Early studies on CM indicated that some CM formulations have the potential in symptomatic relief, shortening fever duration, reversing radiological changes, and shortening hospital stay (Chan *et al.*, 2020; Lu *et al.*, 2020; Xia *et al.*, 2020; Yao *et al.*, 2020; Wang *et al.*, 2020a). In the latest clinical guideline for COVID-19, QFPDT is recommended for all stages of the disease (Wang *et al.*, 2020b; National Health Comission and National Administration of Traditional Chinese Medicine, 2020).

QFPDT composes of 21 herbs. The herbs and dosages are as follows: Ephedrae Herba 9g, Glycyrrhizae Radix et Rhizoma 6g, Armeniacae Semen Amarum 9g, Gypsum Fibrosum 15–30g, Cinnamomi Ramulus 9g, Alismatis Rhizoma 9g, Polyporus 9g, Atractylodis Macrocephalae Rhizoma 9g, Poria 15g, Bupleuri Radix 16g, Scutellariae Radix 6g, Pinelliae Rhizoma 9g, Zingiberis Rhizoma Recens 9g, Asteris Radix et Rhizoma 9g, Farfarae Flos 9g, Belamcandae Rhizoma 9g, Asari Radix et Rhizoma 6g, Dioscoreae Rhizoma 12g, Aurantii Fructus Immaturus 6g, Citri Reticulatae Pericarpium 6g, Pogostemonis Herba 9g.

In silico studies identified over 210 possible targets of QFPDT and 50 common targets with COVID-19. These targets are associated with several key immunological pathways including T helper (Th) 17 cell differentiation, T cell, B cell, tumor necrosis factor (TNF), mitogen-activated protein kinase (MAPK), vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 (HIF-1), and toll-like receptor (TLR) signaling with good affinity to ACE2 receptor (Wu *et al.*, 2020; Xue *et al.*, 2020; Zhao *et al.*, 2020).

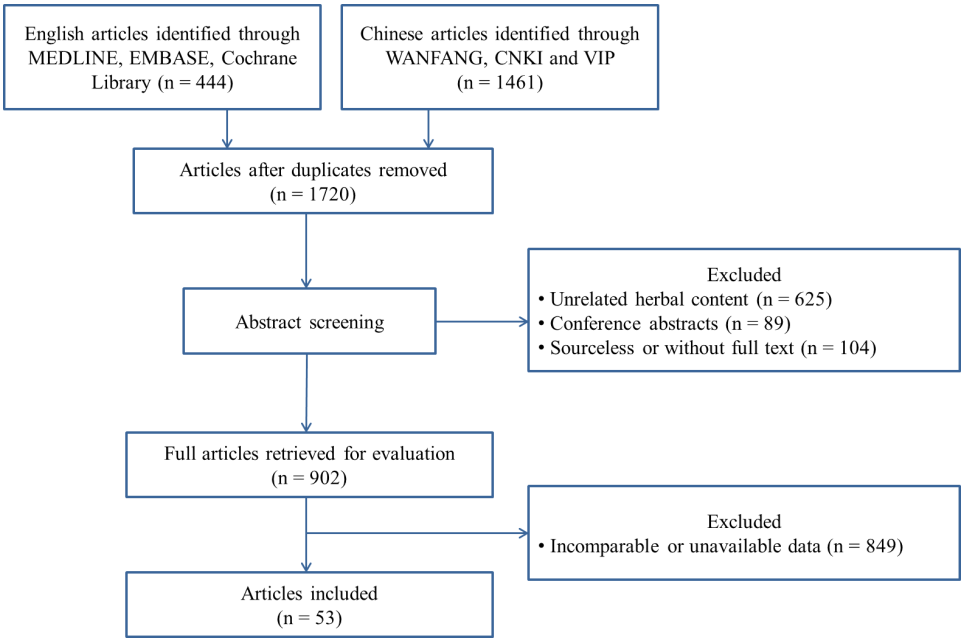

Figure 1. Flowchart of search strategy.

Search Strategy and Selection of Studies

The systematic search was conducted by an independent reviewer (WCL) on Medline, Embase, Cochrane Library, Wanfang, CNKI (China National Knowledge Infrastructure), and VIP up to April 2020. The inclusion criteria were: (i) the 21 herbs in QFPDT; (ii) their therapeutic targets based on: (a) antiviral effects; (b) immune modulation; (c) cytokine storm prevention; (d) anti-oxidative activities; and (e) ACE2 receptor binding effects, with no language restriction. The exclusion criteria were: (i) conference abstracts; (ii) studies that did not report individual therapeutic targets. Names of the herbs were collected and searched according to the Pharmacopoeia of the People's Republic of China, 2015 Edition. The search results were screened first by title and abstract and then by full text. Disagreement was resolved by a second author (WY). The workflow of study selection is shown in Fig. 1.

Results

The 21 Chinese herbs in QFPDT are listed in Table 1. It shows the parts of the plant used for preparation of CM, the components with potential therapeutic use, the mode of action according to CM theory, and the pharmacological activities.

The majority had anti-inflammatory, anti-oxidant, or immuno-modulating functions with effects on bacteria, viruses, protozoa, or fungi. Some could relief signs and symptoms of fever, cough, edema via diuresis and indigestion by regulating gastric acid secretion.

Table 1. The Composition and Actions of Each Herb in QFPDT

English Name	Chinese Name Pinyin System (Latin Pharmaceutical Name[1])	Sources[a]	Major Ingredients	CM[a]	Pharmacological Activities[1]
Ephedra sinica	Ma-huang (Ephedrae Herba)	Herbaceous stem of *Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk et C.A.Mey., and *Ephedra equisetina* Bge.	Ephedrine; Pseudo-ephedrine	Promote sweating to dissipate cold, diffuse the lung to calm panting, induce diuresis to alleviate edema	Stimulate sympathetic nervous system with cardiac stimulation
Glycyrrhiza uralensis	Gan-cao (Glycyrrhizae Radix et Rhizoma)	Root and tuber of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat., and *Glycyrrhiza glabra* L.	Glycyrrhizin; Glycyrrhetic acid; Glycuronic acid	Tonify the spleen and harmonize the stomach, replenish qi and improve circulation	Antivirus, enhance liver detoxification
Apricot kernel	Ku-xing-ren (Armeniacae Semen Amarum)	Mature seed of *Prunus armeniaca* L.var.ansu Maxim., *Prunus sibirica* L., *Prunus mandshurica* (Maxim.) Koehne, and *Prunus armeniaca* L.	Amygdalin; Emulsin; Amygdalase	Direct qi downward to suppress cough, moisten the intestines to relax the bowels	Anti-atherogenic, prevent pulmonary fibrosis, anti-inflammatory and immuno-modulation
Gypsum	Sheng-shi-gao (Gypsum Fibrosum)	Mineral containing hydrated calcium sulphate	Calcium sulphate	Clear heat and purge fire, relieve irritability and thirst	Relieve fever and pruritus
Cinnamomum cassia	Gui-zhi (Cinnamomi Ramulus)	Twig of *Cinnamomum cassia* Presl	Cinnamaldehyde; Sodium cinnamate	Promote sweating, warm interior of body, assist yang transform into qi	Relieve fever, anti- bacteria and virus
Alisma plantago-aquatica	Ze-xie (Alismatis Rhizoma)	Tuber of *Alisma orientale* (Sam.) Juzep.	Alisol A, B, C; Alismol; Alismoxide	Induce diuresis, discharge heat, relieve abnormal discharge	Stimulate uterine muscles, regulate blood cholesterol level
Polyporus umbellatus	Zhu-ling (Polyporus)	Sclerotium of *Polyporus umbellatus* (Pers.) Fries	Ergosterol; Ergone	Induce diuresis	Stimulate uterine smooth muscles, immuno-modulation

Table 1. (*Continued*)

English Name	Chinese Name Pinyin System (Latin Pharmaceutical Name[1])	Sources[a]	Major Ingredients	CM[a]	Pharmacological Activities[1]
Atractylodes macrocephala	Bai-zhu (Atractylodis Macrocephalae Rhizoma)	Tuber of *Atractylodes macrocephala* Koidz.	Atractylol; Atractylon	Fortify the spleen and replenish qi, induce diuresis, decrease sweating, prevent abortion	Stimulate uterine smooth muscles, immunomodulation, inhibit platelet aggregation
Poria	Fu-ling (Poria)	Sclerotium of *Poria cocos* (Schw.) Wolf	Pachymic acid; Tumulosic acid; Pachymic acid methyl ester	Induce diuresis, fortify the spleen, pacify the mind	Antioxidant, immunomodulation, stimulate uterine smooth muscles
Bupleurum chinense	Chai-hu (Bupleuri Radix)	Root of *Bupleurum chinense* DC. and *Bupleurum scorzonerifolium* Willd.	Saikosapoins a, b, c, d; 2-methyl cyclopentaone	Disperse heat, soothe the liver to release stagnation, raise the yang qi	Relief fever, antiviral and antibacterial effects
Scutellaria baicalensis	Huang-qin (Scutellariae Radix)	Root of *Scutellaria baicalensis* Georgi	Baicalein; Baicalin; Wogonin	Clear heat and dry dampness, purge fire to detoxify, stop bleeding, prevent abortion	Antiprotozoa, relieve fever
Pinellia ternata	Ban-xia (Pinelliae Rhizoma)	Tuber of *Pinellia ternate* (Thunb.) Breit.	3-acetoamino-5-methylisooxazole; Butyl-ethyleneether; 3-methyleicosane	Warm the middle to resolve phlegm, antiemesis	Relieve cough, regulate blood clotting
Zingiber officinale	Sheng-jiang (Zingiberis Rhizoma Recens)	Tuber of *Zingiber officinale* Rosc.	Zingiberol; Zingiberene	dissipate coldness, resolve phlegm to suppress cough, antiemesis, detoxify	Regulate gastric acid secretion, antibacteria and protozoan

Table 1. (*Continued*)

English Name	Chinese Name Pinyin System (Latin Pharmaceutical Name[1])	Sources[a]	Major Ingredients	CM[a]	Pharmacological Activities[1]
Aster tataricus	Zi-wan (Asteris Radix et Rhizoma)	Root and tuber of *Aster tataricus* L.f.	Freidelin; Shionone; Shionoside A, B, C	Moisten the lung and direct qi downward, eliminate phlegm and suppress cough	Relieve cough, antibacteria
Tussilago farfara	Kuan-dong-hua (Farfarae Flos)	Bud of *Tussilago farfara* L.	Faradiol; Butin; Hyperin	Moisten the lung and direct qi downward, suppress cough and resolve phlegm	Relieve cough and asthma, regulate blood pressure
Belamcanda chinensis	She-gan (Belamcandae Rhizoma)	Tuber of *Belamcanda chinensis* (L.) DC.	Irigenin; Tectorigenin; Belamcanidin	Clear heat and detoxify, resolve phlegm, soothe the throat	Relieve fever, antivirus
Asarum sieboldii	Xi-xin (Asari Radix et Rhizoma)	Root and tuber of *Asarum heterotropoides* Fr. Schmidt var.*mandshuricum* (Maxim.) Kitag., *Asarum sieboldii* Miq.var. *seoulense* Nakai, and *Asarum sieboldii* Miq.	A-pinene; Camphene; Asaricin	dissipate coldness, relieve pain, relieve the stuffy nose, warm the lung and resolve phlegm	Relieve fever, antibacteria
Dioscorea polystachya	Shan-yao (Dioscoreae Rhizoma)	Tuber of *Dioscotea opposita* Thunb.	Diosgenin; Dopamine; Batatasine hydrochloride	Tonify the spleen and boost qi, moisturize and replenish lung function, tonify the kidney and secure essence	Regulate blood glucose level, immuno-modulation, stimulate smooth muscles in the gastro-intestinal tract

Table 1. (*Continued*)

English Name	Chinese Name Pinyin System (Latin Pharmaceutical Name[1])	Sources[a]	Major Ingredients	CM[a]	Pharmacological Activities[1]
Citrus trifoliata	Zhi-shi (Aurantii Fructus Immaturus)	Young fruit of *Citrus aurantium* L. and *Citrus sinensis* Osbeck	Hesperidin; Neohesperidin; Naringin	Break qi and eliminate accumulation, resolve phlegm and dissipate stuffiness	Regulate blood clot, stimulation smooth muscles in the gastrointestinal tract
Dried Tangerine Peel	Chen-pi (Citri Reticulatae Pericarpium)	Ripe peel of *Citrus reticulata* Blanco	Hesperidin; Narirutin	Regulate qi and fortify the spleen, resolve phlegm	Anti-inflammation, antioxidant and immunomodulation, regulate blood viscosity
Cablin Patchouli Herb	Guang-huo-xiang (Pogostemonis Herba)	Aerial part of *Pogostemon cablin* (Blanco) Benth.	Patchouli alcohol; Methylchavicol; Anethole	Resolve turbidity with aroma, antiemesis, relieve summer heat	Immuno-modulation, relieve indigestion by regulating gastric acid secretion

[a]According to the Pharmacopoeia of the People's Republic of China (2015 Edition).

Some targeted pulmonary fibrosis (Armeniacae Semen Amarum) and asthma (Farfarae Flos). Effects on metabolic syndrome included regulation of blood cholesterol and glucose (Alismatis Rhizoma). Ephedrae Herba acted on the sympathetic nervous system with cardiac stimulation; Glycyrrhizae Radix et Rhizoma enhanced liver detoxification; while others stimulated smooth muscles in the gastro-intestinal tract and the uterus. A number of herbs regulated blood viscosity (Citri Reticulatae Pericarpium), blood clotting (Pinelliae Rhizoma, Aurantii Immaturus) and inhibited atheroma formation (Armeniacae Semen Amarum) and platelet aggregation (Atractylidis Macrocephalae Rhizoma).

Antiviral Effects

Table 2 displays seven herbs with antiviral effects, showing the pharmacologically active fractions, the target viruses, the experimental models, and the mechanisms.

The virus targets included influenza A, H1N1, H3N2, HIV, hepatitis B & C, and herpes simplex. The models used were Madin-Derby canine kidney (MDCK) cells, T cell lymphoma virus 1 (HTLV1), human hepatoma, Hep G, HEp 2, A549 cells, and 294 T cells. There were studies on inhibition of viral DNA replications, by suppression of viral matrix protein (M) gene, neuraminidase (NA) protein, chemokine "Regulated on Activation, Normal T cells Expressed and Secreted" (RANTES); inactivation of TLR 3, 4, 7 signal pathways, and modulation of Phosphatidyl Inositol-3-Kinase/Protein Kinase B (PI3K/AKT) or Extracellular Regulated Kinase 1/2/Mitogen-Activated Protein Kinase (ERK/MAPK) signal pathways. There were stimulation of interferon (IFN)-beta, upregulation of IFN-induced antiviral signaling and activation of AMP-activated protein kinase (AMPK) or RIG-1-like helicases (RLH) pathways.

Baicalein from Scutellariae Radix could inhibit autophagy in A549 and Ana-1 cells induced by influenza virus H3N2 (Zhu *et al.*, 2015). Baicalein improved the effect of Ribavirin on Influenza A cell culture and infected mice. Drug combination had greater suppression of the viral M gene expression than ribavirin alone on MDCK cells. It improved survival and reduced weight loss in mice (Chen *et al.*, 2011).

Immune-Modulating Effects

Table 3 shows the immune-modulating effects of 9 herbs showing the pharmacologically active fractions, the experimental models, and the mechanisms.

Ephedra alkaloids, major bioactive compounds in Ephedrae Herba, especially L-ephedrine (LEP) and D-pesudo-ephedrine (DPEP) markedly inhibited Toll-like receptors (TLR2, TLR4 and TLR7) signaling pathways. In the influenza virus-infected mice, LEP and DPEP markedly alleviated lung injury, inhibited TLRs, Myeloid differentiation primary response 88 (MyD88), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) p65 mRNA and protein expression with significant increase of thymus index. They promoted the immunologic function and adjusted the TLRs and respiratory growth induced protein 1 (RGI-1) pathways of the host to inhibit the virus (Wei *et al.*, 2019).

Table 2. Antiviral Effects of the Major Herbs in QFPDT

Chinese Name Pinyin System (Latin Pharmaceutical Name[a])	Fraction	Virus	Model	Mechanism
Ma-huang (Ephedrae Herba)	Ephedra Alkaloids-L-methylephedrin (LMEP), LEP and DPEP	Influenza A/PR/8/34 (H1N1) (PR8)	MDCK cells and ICR mice	Inhibit viral replication and TLR3, TLR4 and TLR7 signaling pathways
	Water extraction-tanin	Influenza A/PR/8/34 (H1N1) (PR8)	MDCK cells	Inhibit acidification on endosomes and lysosomes
Chai-hu (Bupleuri Radix)	Acetone extract	Pandemic 2009 H1N1 Influenza virus	MDCK cells and A549 cells	Suppress on RANTES secretion
Guang-huo-xiang (Pogostemonis Herba)	Patchouli alcohol-methanol extracted from Pogostemonis Herba	Influenza A virus H1N1 (A/Puerto Rico/8/34), H1N1 (A/NWS/33) and H1N1 (A/Virginia/ATCC1/2009)	MDCK cells	Inhibit IAV strain multiplication, inactivate virus particles, cellular PI3K/AKT and EMR/MAPK signaling pathways
		Influenza A/PR/8/34 (H1N1) (PR8)	MDCK cells and mice	Inhibit viral replication
Gui-zhi (Cinnamomi Ramulus)	Volatile oil especially Cinnamaldehyde	Herpes simplex virus type 1, respiratory syncytial virus	MDCK and Vero cells	Inhibit viral replication
	Cinnamaldehyde, Supercritical fluid extraction, ethanol extract	Hepatitis B virus	Human	Inhibit Hepatitis B replication
Zhu-ling (Polyporus)	Polysaccharide	Human respiratory syncytial virus- (HRSV Long strain: ATCC VR-26)	HEp-2 and A549 cell lines	Inhibit viral replication and stimulation on IFN-β
Gan-cao (Glycyrrhizae Radix et Rhizoma)	Water extract	HIV-1IIIB	Human T-cell leukemia virus I (HTLV-I)-bearing CD4-positive human T-cell line MT-4	Inhibit of viral replication
		Hepatitis C virus	Huh7.5 cells	Inhibit viral replication

Table 2. (*Continued*)

Chinese Name Pinyin System (Latin Pharmaceutical Name[a])	Fraction	Virus	Model	Mechanism
	Methanol extract of G. uralensis roots and its chloroform fraction	influenza virus strain A/WSN/33 (H1N1) and VSV-G pseudo-typed HIV-1 virus	MDCK cells and 293T cells	Inhibit viral replication
	Triterpenoid saponins	Hepatitis B	HepG 2.2.15 cell	Inhibit viral DNA replication
	Glycyrrhetinic acid and its derivatives	HIV-1IIIB	Human T-cell leukemia virus I (HTLV-I)-bearing CD4-positive human T-cell line MT-4	Inhibit viral replication
	Alkaline Extraction	H1N1 strain (PR/8/34), oseltamivir-resistant seasonal H1N1 strain (B/55/08), pandemic H1N1 lineage that emerged in 2009 (J/8178/09), and a H3N2 virus (HK/68)	MDCK cells	Inhibit NA
	Methanol extract, the aglycone-enriched fraction and compounds purified	HIV-1IIIB and HSV-1 (strain F)	Human T-cell leukemia virus I (HTLV-I)-bearing CD4-positive human T-cell line MT-4 and Vero cells	Inhibit viral replication
	Water and alkaline extracts; Flavonoid and chalcone derivatives	Influenza viral strains, H1N1, Hemagglutinin 9 Neuromidase 2 novel H1N1 (WT), and oseltamivir-resistant novel H1N1 (H274Y)	293T cells	Inhibit NA
	Chalcones	Hepatitis B virus	Human hepatoma cells	Suppress HBV core promoter activity

Table 2. (*Continued*)

Chinese Name Pinyin System (Latin Pharmaceutical Name[a])	Fraction	Virus	Model	Mechanism
Huang-qin (Scutellariae Radix)	Water extract	Influenza virus H1N1 (A/FM/1/47)	MDCK cells and mice	Inhibit H1N1 activity
	Flavonoids-enriched extract	Influenza A/FM1/1/47 (H1N1)	MDCK cells and mice	Suppress the viral matrix protein (M) gene expression
	Baicalein	Influenza A/FM1/1/47 (H1N1) and influenza A/Beijing/32/92 (H3N2) virus	MDCK cells and mice	Inhibit NA
		Influenza virus A3/Beijing/30/95 (H3N2)	A549 and Ana-1 cells	Attenuate cells autophagy
	Wogonin	Human influenza virus A/Puerto-Rico/8/34 (H1N1) PR8; H1N1, H3N2 and B (yamagata lineage)	MDCK cells and A549 cells	Upregulate IFN-induced antiviral signaling and activate AMPK pathway

[a]According to the Pharmacopoeia of the People's Republic of China (2015 Edition).

Table 3. Immunomodulatory and Prevention of Cytokine Storm by the Major Herbs in QFPDT

Chinese Name Pinyin System (Latin Pharmaceutical Name[a])	Fraction	Model	Mechanism
Ma-huang (Ephedrae Herba)	Ephedrae alkaloids	MDCK cells and ICR mice	Inhibit TLR2, TLR4 and TLR 7 signaling pathways *in vitro* and adjust TLRs and RGI-1 pathway *in vivo*
Guang-huo-xiang (Pogostemonis Herba)	Patchouli alcohol	16 HBE and immune cells	Suppress IL-4, IFN-γ and regulation of RLH signal pathway
	Patchouli alcohol	LPS-stimulated RAW264.7 cells	Decrease the production of TNF-α, IL-1β, IL-6, nitric oxide, prostaglandin E2 and mRNA expression of TNF-α, IL-1β, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2
Ku-xing-ren (Armeniacae Semen Amarum)	Water extract	Female BALB/c mice	Suppress type 2 helper T cells to lower IL-4
Bai-zhu (Atractylodis Macrocephalae Rhizoma)	Water extract	Female ICR mice	Response to ConA and LPS, produce IL-5 and IFN-γ
	RAMPtp	Bovine supranmammary lymph node	(1) Increase [Ca2+]i and cell numbers in S and G2/M phases (2) IFN-γ and IL-17A upregulation and IL-4 downregulation
Fu-ling (Poria)	A purified immunomodulatory protein	Primary lymphocytes from murine spleens and female BALB/c mice	Active Th1 response and regulate T-bet and STAT4 and IFN-γ and IL-2 section
	Polysaccharides and their derivatives	Female Balb/c mice	(1) Increase antigen-specific antibody and induce anti-HBSAg (2) Improve splenocytes proliferation and stimulate IL-12p70 and TNF-α production
Gan-cao (Glycyrrhizae Radix et Rhizoma)	Water extract	Human peripheral blood mononuclear cells	Inhibit pytohaemag glutinin-induced proliferation
		Raw 264.7 cells	Inhibit TNF-α, IFN-γ and IL-10

Table 3. (*Continued*)

Chinese Name Pinyin System (Latin Pharmaceutical Name[a])	Fraction	Model	Mechanism
	Water extract, isoliquiritigenin and naringenin	C57BL/6 mice; Foxp3-IRES-GFP mice; Primary CD4 T-cell purification	Promote Regulatory T cells
	Ethanol extract	Female C57BL/6 mice and primary mouse splenocytes	Modulate on IFN-γ-related autoimmune response
	Glycyrrhizic acid	Specific pathogen-free female BALB/c mice	(1) Inhibit Raw and eosinophil count induced by OVA (2) Decrease IL-4, IL-5 and IL13 and increase IFN-γ (3) Enhance Tregs
Gui-zhi (Cinnamomi Ramulus)	3-phenyl-propenal	Raw 264.7 cells	Block TLR2 and TLR4 over-expression and downregulate MyD88 and TRAF-6
Chai-hu (Bupleuri Radix)	Saikosaponin a and saikosaponin d	Raw 264.7 cells	Inhibit TNF-α, IL-6 and translocation of NF-κB
	Saikosaponin a	HUVEC cell line	Decrease proinflammatory cytokines, iNOS and COX-2
	Saikosaponin a	Mouse embryo fibroblast 3T3-L1 preadipocytes, the mouse embryo fibroblast 3T3-L1 cells	Decrease the expression of TNF-α, IL-1β, IL-6 and reduce iNOS and COX-2 and suppress NO production
Huang-qin ⟨Scutellariae Radix⟩	Flavonoids-enriched extract	Specific pathogen-free BALB/c mice	Decrease nitric oxide production and the levels of TNF-α, IL-6 a
	Heat-Processed Scutellariae Radix extract	(LPS-) induced acute lung injury in mice Mice with acute lung injury induced by lipopolysaccharide (LPS)	Decrease MCP-1 and IL-6
	Scutellariae Radix water extract	LPS-induced RAW 264.7 macrophages	Inhibit NO production, IL-3, IL-6, IL-10, IL-12p40, IL-17, interferon-inducible protein (IP)-10, keratinocyte-derived chemokine (KC), and vascular endothelial growth factor (VEGF)

[a]According to the Pharmacopoeia of the People's Republic of China (2015 Edition).

In Pogostemonis Herba, Patchouli alcohol inhibited H1N1 on 16 human respiratory epithelial cell model (HRE) co-cultured with immune cells by suppressing the expression of cytokines interleukin (IL)-4 and interferon (IFN)-γ and regulated the innate immune RLH signal pathway (Wu *et al.*, 2013). Patchouli alcohol also had anti-inflammatory effect on lipopolysaccharide (LPS)-stimulated RAW264.7 cells. It could reduce tumor necrosis factor-α (TNF-α), IL-1β, IL-6, nitric oxide, prostaglandin E2, and downregulate the mRNA expression of TNF-α, IL-1β, IL-6, inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX)-2 (Xian *et al.*, 2011).

In Armeniacae Semen Amarum, water extract considerably lowered the level of IL-4 in the broncho-alveolar lavage fluid (BALF) on a mice model of allergic asthma via suppressing type 2 helper T cell (Th2) (Do *et al.*, 2006).

Atractylodis Macrocephalae Rhizoma, water extract (RAM) enhanced splenocyte proliferation via responses to Concanavalin A (Con A) and lipopolysaccharides (LPS) and production of IL-5 and IFN-γ by splenocytes in immunized mice. It modulated immune responses to vaccination against food and mouth disease in mice (Li *et al.*, 2009). When added into bovine supra-mammary lymph node (SMLN), the homogeneous polysaccharide extracted from RAM, increased $[Ca^{2+}]_i$, and cell numbers in S and G2/M phases. It also upregulated mRNA expression of IFN-γ and IL-17 A and downregulated IL-4. It could bind to SMLN lymphocytes (Xu *et al.*, 2017).

A purified immunomodulatory protein isolated from Poria could regulate mammalian immune cells, activate Th1 response *in vitro* and *in vivo*. It regulated the expression of T-box protein expressed in T cells (T-bet), signal transducer, activator of transcription 4 (STAT4), and the secretions of IFN-γ and IL-2 (Lu *et al.*, 2014). A new polysaccharide isolated from sclerotium of Poria, increased antigen-specific antibody levels in mice immunized with influenza vaccine at significantly higher titers. It improved splenocytes proliferation and stimulated IL-12p70 and TNF-α production in dendritic cells and macrophages respectively (Wu *et al.*, 2016).

Water extraction of Glycyrrhizae Radix et Rhizoma inhibited phytohaemagglutinin-induced proliferation in human peripheral blood mononuclear cells and production of TNF-α, IFN-γ, and IL-10. Extracts of Herba Schizonepetae and Glycyrrhizae Radix significantly inhibited LPS-induced nitric oxide production in mouse macrophages, which meant both had anti-inflammatory activities (Yue *et al.*, 2012). Glycyrrhizinic Acid (GA), main bioactive ingredient of Licorice, ameliorated the progress of asthma induced by ovalbumin (OVA) on mice, via its inhibition of increase of airway resistance (Raw) and eosinophil count induced by OVA. GA decreased IL-4, IL-5, and IL-13 and increased IFN-γ levels in bronchoalveolar lavage fluid; inhibited OVA-induced eosinophilia and enhanced regulatory T cells (Tregs) in lung and airway tissues (Ma *et al.*, 2013). Water extract of Licorice and its two constituents isoliquiritigenin and naringenin improved Treg cell induction and function by promoting differentiation with therapeutic effects on autoimmune and inflammatory diseases (Guo *et al.*, 2015).

One of the principle compounds from Cinnamomi Ramulus, 3-phenyl-propenal, may have an antagonistic effect on TLR3 and TLR4 by blocking the over-expression of TLR3 and TLR4 and downregulating their downstream signaling components (Zhao *et al.*, 2008).

In Scutellariae Radix (SR), besides its antiviral effects, flavonoids-enriched extract from S. Baicalensis root (FESR) significantly decreased nitric oxide production and the levels of TNF-α, IL-6, and Monocyte Chemoattractant Protein-1(MCP-1) (Zhi *et al.*, 2019). Heat-Processed SR had high concentration of its representative flavonoid contents baicalin, baicalein and wogonin. It could effectively decrease monocyte chemo-tactic protein-1 (MCP-1) and IL-6 levels in LPS-stimulated cells (Xian *et al.*, 2011). On LPS-induced RAW 264.7 macrophages, SR water extract had significant, dose dependent, inhibition on NO production, IL-3, IL-6, IL-10, IL-12p40, IL-17, interferon-inducible protein (IP)-10, keratinocyte-derived chemokine (KC), and vascular VEGF (Yoon *et al.*, 2009).

Saikosaponin a (SSa) and its epimer saikosaponin d (SSd), two major triterpenoid saponin derivatives from Bupleuri Radix, could suppress TNF-α and IL-6 in a dose-dependent manner and inhibit the translocation of NF-κB. Study on murine model showed that SSa and SSd have conspicuous acute anti-inflammatory activity (Lu *et al.*, 2012; Ma *et al.*, 2016). Besides reducing inflammatory factors like NO synthase (iNOS) and cyclooxygenase-2(COX-2), it also suppressed NO production on cell model. It inhibited phosphorylation of inhibitor of nuclear factor kappa B (I κBa). Furthermore, SSa suppressed NF-κB translocation through mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway, inhibited inflammatory-associated genes on cell models and inhibited NF-κB activation (Fu *et al.*, 2015; Li *et al.*, 2018). On mouse embryo fibroblast 3T3-L1 preadipocytes and mouse embryo fibroblast 3T3-L1 cells, SSa significantly reduced pro-inflammatory cytokine TNF-α, IL-1β and IL-6 expression. SSa could decrease inflammatory factors iNOS and COX-2 and suppress NO production (Kim *et al.*, 2015).

Anti-Oxidative Activities

"Reactive oxygen species (ROS)" such as superoxide (O−), hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and singlet oxygen are oxygenated byproducts inevitably generated from cells' utilization of oxygen as a final electron acceptor in the mitochondrial energy metabolism (Hayyan *et al.*, 2016). Most ROS have a cell-damaging effect. The oxidative stress means an imbalance between prooxidant and anti-oxidant systems (Sohn *et al.*, 2018; Liu, 2019). Oxidative stress may damage the cellular function because of the oxidation of some essential host micro-molecules (Lin *et al.*, 2018; Park *et al.*, 2018). Some viruses facilitated their replication in the cells by inducing oxidative stress (Lee *et al.*, 2013; Lee *et al.*, 2018).

In vitro, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay, used to assess anti-oxidant activity, showed scavenging capacities of Ephedra herb extracts (Kallassy *et al.*, 2017). Polysaccharides from Poria and their derivatives were identified to enhance serum anti-oxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) activities in rats (Ke *et al.*, 2010). Water, alkaline extracts, and 50% ethanol-soluble fraction of Licorice root showed effective scavenging by O_2^- than OH (Ohno *et al.*, 2014). Flavanoids are natural anti-oxidant and free radical scavenging components. Baicalin, a flavone from Scutellariae Radix and gallocatechin flavanols from

Ephedrae Herba tested with DPPH, showed that the scavenging ability was associated with the number and position of hydroxyl group (Okawa *et al.*, 2001).

ACE2 Receptor Binding Effects

Coronaviruses that cause severe acute respiratory syndrome such as SARS-CoV and SARS-CoV-2, infect their target cells via their Spike (S) proteins associated with cellular receptors. Angiotensin converting enzyme 2 (ACE 2), a metallopeptidase isolated from SARS coronavirus (SARA-CoV)-permissive Vero E6 cells, was shown to be a functional receptor for SARS-CoV and SARS-CoV-2 (Li *et al.*, 2003; Zhang *et al.*, 2020). SARS-CoV infection via S protein of the SARS-CoV suppressed the expression of ACE 2 (Kuba *et al.*, 2005).

A soluble form of ACE2 could block the association of the S1 domain with Vero E6 cells which means that excessive ACE2 may neutralize the virus and rescue cellular ACE2 activity. Thus, it could negatively regulate the renin-angiotensin system (RAS) and protect the lung from the injury induced by the virus infection (Li *et al.*, 2003). ACE2 is the key for viral entry into cells and hence viral spread. On the other hand, it could protect the lung from injury (Zhang *et al.*, 2020). Thus, blocking ACE2 receptor with antibodies or delivering excessive soluble form of ACE2 may be effective methods to treat COVID-19.

Baicalein, a natural flavone existing in Scutellariae Radix, can protect endothelial cells by ACE2 mRNA and protein expression. Baicalin significantly transformed Ang II into angiotensin-1-7 [Ang-(1-7)]. It activated ACE2/Ang-(1-7)/Mas axis to modulate apoptosis-associated protein bax, bcl-2, and cleaved caspase-3 expression with protection of endothelial cells from Angiotensin II (Ang II)-induced endothelial dysfunction and oxidative stress (Wei *et al.*, 2015). Besides, Baicalein inhibited angiotensin-I converting enzyme (ACE) not ACE2 with an IC_{50} value of 2.24 mM *in vitro* (Deng *et al.*, 2012). Hence, further study is needed to test whether Baicalein inhibits ACE2.

Network pharmacology studies on Baicalein demonstrated that beta-sitosterol, kaempferol, and stigmasterol, when compared with compounds from other herbs, had stronger affinity with SARS-CoV-2 and ACE2, which was better than some of the Western medicine compounds being tested for treatment of COVID-19 (Yang *et al.*, 2019). Meanwhile, patchouli alcohol (Pogostemonis Herba), tussilagone (Farfarae Flos), ergosterol (Polyporus), asarinin (Asari Radix et Rhizoma), ephedrina hydrochloridum (Ephedra Herba), and Shionone (Asteris Radix et Rhizoma) were found to have high affinity with ACE2 by network pharmacology studies and molecular docking (Wu *et al.*, 2020).

Discussion

The main herbs of QFPDT have antiviral effects via different mechanisms: (1) Direct effect on virus replication and autophagy. (2) Modulation of host pathways like TLRs, RGI, RLH, AMPK, P/13K/AKT, MAPK/ERK signal pathways. (3) Promotion of the human defense system via T and B cell functions. (4) Free radical scavenging activities by enhancing SOD, CAT and GPX.

Binding to the ACE2 receptor is the key pathway for coronavirus to get into host cells. In view of the strong affinity to ACE2 receptor by Scutellariae Radix and six other herbs, we hypothesize that the mechanism of action by multiple components of herbs to be the blockage of ACE2 receptors and prevention of binding of SAR-CoV-2 via spike protein S1 subunit. The role of the soluble form of ACE2 in this balance of power awaits elucidation.

When the immune system overreacts to the viral infection, excessive inflammation may damage the host, involving multiple organs. Inhibition on the endogenous cytokines may prevent cytokine storm (Gerlach, 2016). The utilization of Chinese herbs like Pogostemonis Herba, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma and Scutellariae Radix and four others in this study could modulate the inflammatory conditions by inhibition of inflammation associated genes, reduction of inflammatory factors, regulation of signal pathways and balance of cytokines. The multiple targets modulated by these compounds could suppress the cytokine storm induced thrombotic cascade, affecting vital organs.

Recent publications on COVID-19 have shown pulmonary interstitial edema with pulmonary vasculopathy, which could be produced by microvascular thrombosis, triggered by endothelial damage and cytokine storm. Patients with hypertension are associated with increased mortality which could be due to confounding variables and co-morbidities rather than their treatment with ACE1 inhibitors (ACEI). Indeed, ACEI may be beneficial due to their effect on coagulation. There is also debate regarding the use of non-steroidal anti-inflammatory drugs (NSAID) which may worsen endothelial dysfunction (Garret, 2020; Madjid *et al.*, 2020; Sanchis-G *et al.*, 2020; Tignanelli *et al.*, 2020; Vaduganathan *et al.*, 2020). Facing this controversy, this study documented Armeniacae Semen Amarum, Scutellariae Radix and four other herbs which have regulatory effects on the endothelium and coagulation mechanisms. The former has effect on pulmonary fibrosis too. This may explain the effectiveness of QFPDT in preventing deterioration of the disease and in the management of severe cases under close co-operation with physicians and intensivists (Jiang and Chen, 2020; Jiang *et al.*, 2020).

Based on network pharmacology analysis and molecular docking technology, the preliminary results showed that QFPDT compound-pneumonia target network contained 292 compounds and 214 corresponding targets, and the core targets involved serine/threonine kinase AKT1, IL6, MAPK 8, MAPK1, and jun proto-oncogene (JUN). Since QFPDT is recommended for use in all stages of COVID19, the multi-target therapeutic effects should be studied.

Conclusion

The available scientific evidence for each compound and herb in QFPDT were collected, collated, and reviewed with development of the hypotheses on the ACE2 receptor and the cytokine storm induced micro-vascular thrombosis. Thus, the multi-target therapeutic effects of this combination formula should be studied along those lines. Besides standard *in silico*, *in vitro*, *ex vivo*, *in vivo* studies, one should include the use of Chinese medicine

diagnosis-specific animal models for explanation of the Chinese medicine diagnostic classification.

For justification of dosage, and utilization by different age groups with different co-morbidities, pharmacodynamics, and pharmacokinetics studies including the effects of herb–drug interaction should be given top priority. It is necessary to carry out preclinical testing and randomized clinical trials to evaluate the efficacy and safety of QFPDT specific to COVID-19. Meanwhile, real world big data should be collected in support of the above. With evolution of the pandemic, the clinical picture, the infectivity, the public health measures, and the results arising from them should be monitored closely via information banks, in order to meet urgent therapeutic needs for integrative therapy with optimized dosages as alternative treatment options.

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