Review Article

A narrative review of the scientific natures of the prevention and treatment of COVID-19 with traditional Chinese medicine

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Abstract: Corona virus disease 2019 (COVID-19) has shown a pandemic around the world and it has caused more than a million cases in more than 130 countries or regions. While it has taken thousands of lives, there are no vaccines, antibodies nor anti-viral drugs at present. Confronted by massive difficulties, researchers have still gained great success in the prevention and treatment of COVID-19 via vigorously using the integrated therapy of traditional Chinese medicine (TCM) and western-style medicine. To describe and discuss the cognitions of SARS-CoV-2, pathogenesis of COVID-19, mainly around ACE2, and application TCM in the prevention and treatment of COVID-19 to provide clinical references of this disease. An overview of pathogenesis of SARS and COVID-19 and TCM may be used in the treatment of SARS and COVID-19 is presented. Narrative overview of the literature synthesizing the findings of literature retrieved from searches of computerized databases. Characteristics of TCM are the organic conception of the human body and discriminate and dialectical demonstration. It is worth noting the application of TCM in the prevention and treatment of COVID-19 to provide clinical references of this disease. Through block of key links of the disease and the combined treatment, we would finally heal SARS and COVID-19 patients.

Keywords: SARS-COV-2; corona virus disease 2019 (COVID-19); SARS CoV; traditional Chinese medicine (TCM)

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Introduction

Corona virus disease 2019 (COVID-19) has been worldwide detected in more than 216 countries (1). Chinese scientists identified structure of this virus at first time. The novel coronavirus was finally named as SARS-CoV-2 by Coronavirus Study Group (CSG) of International Committee on Taxonomy of Viruses (ICTV) because the virus is thought as a sister species of severe acute respiratory syndrome associated coronavirus (SARS-CoVs) (2). This paper intends to summarize the previous researches in PubMed of SARS-CoV and COVID-19 by combining with the current comprehending treatment with therapy of TCM.

We present the following article in accordance with the Narrative Review checklist (available at http://dx.doi.org/10.21037/lcm-20-58).

Methods

Narrative overview of the literature synthesizing the findings of literature retrieved from searches of computerized databases of PubMed.

Structural and biological characteristics of SARS-CoV and SARS-CoV-2

SARS CoV spike virus is isolated from Himalayan palm civet gained from Guangdong wild animal market. Compared with human SARS CoV, animal SARS CoV has 29 additional nucleotide sequences. In the additional 29 nucleotide sequences of animal SARS CoV 10 and 11 open reading frame (ORF) combine as a novel ORF, encoding 122 putative proteins which biological significance is unknown (3). It is not clear how the precursor virus adapts itself in human to achieve effective transmission in populations. But it showed that replication of SARS CoV is attenuated by a 29-nucleotide deletion in SARS-coronavirus acquired during the early stages of human-to-human transmission. Without this mutation, the SARS epidemic in 2003 would have gone through a more serious result (4). It is known that SARS-CoV is a virus with positive-sense, non-segmented, single-stranded RNA genomes and belongs to the genus Betacoronavirus of Coronaviridae (5). Its first two thirds of RNA sequences encode the replicase genes, which are translated into two large polyproteins that are processed into 15 or 16 non-structural proteins (nsp) via proteolytic cleavage (5). The other one third of the RNA sequences are ORFs for the structural proteins, namely the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins and accessory proteins of SARS-CoV , namely ORFs 3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b (6). SARS-CoV-2 also belongs to the genus Betacoronavirus and has a 30-kb genome which 80% are homologous genome compared with SARS-CoV (7), The protein structures of SARS-CoV-2 and SARS CoV are very similar, mainly are spike (S), membrane (M), and nucleocapsid (N) proteins (7), and also contains SARS-CoV-2 accessory proteins namely orf1a, orf1b, S, ORF3a, ORF6, ORF7a, ORF7b, ORF8,ORF10 (8).

Study indicated that both SARS-CoV and SARS-CoV-2 entire human cells through binding with receptors which is a metallopeptidase, namely angiotensin-converting enzyme 2, or ACE2 receptor (9). And it is clearly that SARS-CoV infects target cells mainly via bindings spike proteins with ACE2. ACE2 has already been proved to be a functional receptor of SARS CoV (10) and its binding domain of SARS CoV to ACE2 is known as the 270-510 amino acid sequence of S protein (11). S protein is also thought as specific to bind to ACE2 with strong affinity via biochemistry and crystal structure analysis (12,13). The N-terminal of S protein (S1) of SARS CoV is receptor binding region, while the C-terminal (S2) is a membrane anchored membrane fusion subunit, which contains two heptapeptide repeat regions (HR1 and HR2) (14). S1 subunit contains receptor binding domain, which can bind to the peptidase domain of ACE2, and S2 is responsible for membrane fusion function (14). When S1 region binds to the receptor of ACE2, the cleavage site on S2 is exposed and cleaved by the protease of host, which is crucial for virus infection (15).

After binding to ACE2 of the target cell, the transmembrane protein changes its conformation through the binding to HR1 and HR2, forming a six helix-oligomer complex, which leads to the fusion of the virus and the target cell membrane (16). While cells expressing ACE2 mediate SARS CoV infection, its role in initiating virus replication is not clear.

After binding with ACE2, S protein was destroyed by a way of acid dependent hydrolysis trough protease (17). SARS CoV can infect cells from lung, intestine, liver, distal convoluted renal tubule, sweat gland, parathyroid gland, pituitary gland, pancreas, adrenal gland and brain, defecate, lymph node, spleen, heart and skeletal muscle (18,19).

Clinical characteristics of SARS andCOVID-19 (Table 1)

The main clinical manifestations SARS and COVID-19 are shown in *Table 1*.

Pathogenesis of SARS and COVID-19

The damage effect of SARS CoV and SARS CoV-2 induced by combination with ACE2

Extensive lung injury in SARS patients seems to be related to a high initial virus load (29), which may relate with two damage direct effects: the first is to combine with ACE2, the other is to cause a series of immune reactions SARS-CoV.

The binding of S protein of SARS CoV with ACE2 on target cells can cause the down-regulation of ACE2 and the increasing of local of Ang II (30) and finally leads to acute lung injury (31), which can be improved by blocking the renin-angiotensin pathway. Low ACE2 can transform Ang II into Ang 1-7 that has effects of vasodilation and can increased pulmonary vascular permeability, by activating AT1R and leads to further lung tissue damage (30). SARS-COV-2 mainly infects the lower respiratory tract and infect alveolar epithelial cells via binding to ACE2 (32). But studies have shown that ACE2 gene polymorphism is not related to the susceptibility and prognosis of SARS, suggesting that the reduction of ACE2 caused by SARS

Table 1 Clinical characteristics of SARS andCOVID-19

Clinical characteristics	SARS	COVID-19
Fever	Fever was the main clinical feature of SARS (19)	99% caes had syptom of fever, in some cases, there was no sign of fever before the onset (20)
Gastrointestinal symptoms	Watery diarrhea was the most common extrapulmonary symptom, 40–70% of SARS patients will have diarrhea symptoms within first week (19)	10.1% cases had symptoms of diarrhea or nausea (20)
Liver function	Most cases have liver dysfunction and the liver enzyme level is obviously increased (21)	Some show a high liver enzyme level (22)
Renal function	Acute renal dysfunction is not common in SARS, but lead a high mortality (23)	29% cases have acute renal injury (24)
Respiratory symptoms	ARDS mainly infected airway and alveolar epithelial cells (19)	Dry cough, dyspnea and acute respiratory distress syndrome (20)
Cardiovascular symptoms	Tachycardia was the most common cardiovascular complication. Other complications include hypotension shock, atypical chest pain, bradycardia, cardiac hypertrophy, and atrial fibrillation in very few patients (25,26)	Increased troponin, palpitation, and cardiac failure often occurs in patients with potential cardiovascular disease (27,28)

Overview of the main clinical manifestations SARS and COVID-19. COVID-19, corona virus disease 2019; SARS, severe acute respiratory syndrome.

CoV has a relatively limited role in the occurrence and development of the disease (33).

Damages of SARS-CoV, SARS-CoV-2 caused through immune mechanism

SARS and COVID-19 patients present with various underlying medical conditions, so far, no specific cytokine markers have been found, which also indicates that the immune response caused by SARS-CoV and SARS-CoV-2 may involve in multiple ways. Lymphopenia with rapid decrease of CD4 and CD8 T cells is common in acute phase of SARS (34), which mechanism is unknown and may be related with lymphocyte apoptosis induced by virus without the involvement of ACE2. There is no ACE2 expression in T, B lymphocytes or macrophages in all hemolymph organs (35).

Most SARS-CoV-2 patients (82.1%) were found to have peripheral lymphocytopenia, indicating that lymphocytes may infiltrate in the lung and/or cell damage pathway through apoptosis or heat shock which leads to the release of a large number of proinflammatory factors, which can lead to the release of a large number of proinflammatory factor (17). The imbalance of inflammatory pathway of endothelial cells is a key factor that leads to coagulation disorder and the increased vascular permeability, which also can promote sepsis and cause organ failures. Endothelial cells also participate in many physiological processes, such as regulation of vascular tension, selective permeability of blood vessels, and provision of coagulant and anticoagulant surfaces (36,37). Strong pro-inflammatory cascade may be induced by LPS which eventually leads to acute injury of capillaries and alveolar epithelial cells (38-40) and stimulates the production of proinflammatory mediators which indirectly activate endothelial cells and causes endothelial dysfunction. LPS promotes the combination of eNOS and NADPH oxidase 2 (NOX2) and the superoxide produced by NOX2 leads to the uncoupling of eNOS and the dysfunction of endothelial barrier and influences adhesion of leukocytes to the vascular wall (41,42). LPS can also down regulate the expression of protein and mRNA of eNOS (43).

Possible mechanism of prevention and treatment of COVID-19 by TCM

TCM is used for treatment of COVID-19 and is effective in prevention of process which moderate stage trans to severe stage. And progress of COVID-19 or mortality of COVID-19 are greatly reduced by TCM using.

Protecting the function of respiratory barrier is helpful to the prevention and treatment of early sage COVID-19

Shegan Mahuang Decoction is known as an expectorant, which can warm the lung and disperse the cold and is used to purify phlegm. Study indicated that Shegan Mahuang Decoction can reduce the lung infiltration of CD3+ and CD4+ T cells in mice (44). Maxingshigan decoction (Decoction of Ephedra, Apricot Kernel, Gypsum and Licorice) is a compound Chinese medicine preparation composed of ephedra, almond, gypsum and licorice. It is reported that Maxingshigan decoction can significantly improve the lung injury in rats and protect the alveolar capillary barrier by regulating HMGB1/TLR4/NF-κB pathway and inflammatory response (45).

Mucous of respiratory tract is not only the main site of virus attack, but also is the defense system against virus infection. The innate immune system first senses virus invasion and the starts nonspecific clearance of virus. But if the virus escapes the early defense, it will be cleared by adaptive immunity. The main adaptive immune mechanisms include: (I) the participation of specific SIgA antibody and CD8+ CLTS in the recovery period of the initial virus infection; (II) when the virus-ig complex cleans up the virus, the pre-formation of specific SIgA antibody and IgG play an important role. And in fact, many single traditional Chinese medicine (TCM) or compound prescription, such as Astragalus, Sanqi, Siwu Decoction and some jiebiao prescriptions, regulate mucosal immunity by increasing the secretion of S-IgA (46). Studies showed that Astragalus, Yupingfeng powder and other TCM have certain regulatory effect on respiratory symbiotic bacteria in the treatment of influenza (46). The anti-influenza effect of volatile oil and cinnamaldehyde in cassia twig was also promoted by activating TLR7 pathway in mucosal immunity, inducing the expression of i-rak-4 protein and promoting the high expression of IFN-β (46), which suggested that TCM can prevent or reduce the invasion of SARS-CoV-2 and the direct damage of it by improving the resistance of respiratory mucosa to virus.

Inhibition or elimination of coinfected virus and reduction of further invasion of SARS-CoV-2

Many TCMs have the antiviral effect via direct or indirect ways, which is the material base for the clinical application of one or two TCMs to treat cold. For example, Emodin is one of the main effective components of rhubarb, Polygonum cuspidatum and other TCMs (47). Emodin can also inhibit the interaction between S-protein and ACE2 protein and inhibit the infection of S-protein retrovirus in a dose-dependent manner (48).

TCM with bacteriostatic that treat the deterioration of COVID-19 disease

Many TCMs for clearing away heat and detoxifying have antibacterial and virus killing properties, among which Coptis, phellodendron, Houttuynia cordata, Ligusticum chuanxiong and prickly ash are the most famous.

Pudilan Xiaoyan oral liquid, which is composed of dandelion, isatis root, kuditin and scutellaria, has the special effects of bacteriostasis and antiviral and clear away heat and detoxification via improving pharynx symptoms, detumescence, effectively blocking the replication and reproduction of the virus *in vivo* (49).

Houttuynia cordata is also a traditional herbal medicine used to clear away heat and detoxify. Its polysaccharide (CHCP) can significantly reduce the acute lung injury caused by hemorrhagic shock and LPS infusion in rats and inhibit the fever, the deposition of complement activation products in the lungs and increase of leukocyte (50). It can also restore the level of serum complement, reduce the pulmonary edema and protein exudation in BALF. The total flavonoids extracted from the leaves of crotalaria mucronat also showed bacteriostatic effect on Escherichia coli, Bacillus subtilis, Proteus vulgaris, Staphylococcus aureus and Pseudomonas aeruginosa (51).

Berberine is an alkaloid of broad-spectrum antibacterial drug, which can inhibit and eliminate a variety of G+ bacteria, G-bacteria, fungi and molds. It has a good inhibitory effect on Staphylococcus aureus and methicillin-resistant Staphylococcus aureus (51). Cinnamon oil also has obvious antibacterial activity against Escherichia coli, Staphylococcus aureus and resistant Staphylococcus aureus (51).

Tea polyphenols can destroy the cell membrane structure of Staphylococcus aureus and Pseudomonas aeruginosa, especially a higher concentration of tea polyphenols would destroy the cell membrane structure in a short period of time, resulting in the leakage of electrolyte inside the cell, and the gradual leakage of carbohydrate outside the cell, thus affecting the stability of cell structure, and finally making the cell gradually aureus (51).

Regulation of the endothelial function and reversion of the process of COVID-19

Statistical analysis showed that there were significant gender differences in incidence rate and mortality rate of SARS and

COVID-19, that is, male patients and mortality rates were significantly more than females, suggesting that estrogen plays an important role in the occurrence and development of SARS and COVID-19.

It was reported that estrogen receptors, including ER α, ER β and G protein coupled estrogen receptors (GPERs), also expressed in endothelial cells (52).

Many TCM and its effective components have the function of activating estrogen receptor, and play a protective role on the structure and function of vascular endothelial cells. Flavonoids is thought to be the main active components that have estrogen like effect (53).

Salvia miltiorrhiza (Danshen) can significantly increase the expression of ERα and ER β protein and their mRNA, upregulates serum estradiol (E2) but decrease follicle stimulating hormone and luteinizing hormone and luteinizing hormone, which is very similar to the effect of estrogen (54). But compared with estrogen, Salvia miltiorrhiza can play the role of estrogen without adverse reactions, and improve the expression of ER in target tissues (54). Both Daidzein and Genistein can produce estrogen like effects via activation of the transcription of estrogen response primitives reporter gene through ER α and ER β, two subtypes of ER, which can be blocked by ER antagonist ICI 182780 (54).

Discussion

An overview of pathogenesis of SARS and COVID-19 and TCM may be used in the treatment of SARS and COVID-19 is presented. LPS is a key factor of moderate and severe COVID-19. ACE2 is also involving in the dysfunction of vascular endothelial cells, the exploration of pathogenesis of COVID-19 may involving the interaction between LPS and ACE2.

TCM is a cultural and medical treasure left by the Chinese ancestors which is even a treasure to the world. In history, it has been made great contributions in the Chinese people's victory over disease and plagues. In modern times, it also showed a strong ability to cure and save patients presented with SARS and COVID-19. From the previous TCM we talked, it can be seen that TCM can block the progress of SARS and COVID-19 and make it good in a good prognosis.

But Studies included in article are non-RCTs, which leads to lack of reliability in the conclusions should be considered in the treatment of TCMs. It is worth noting that th TCM may be inspiration of future research in SARS and COVID-19.

Conclusions

It is worth noting that the characteristics of TCM are the organic conception of the human body and discriminate and dialectical demonstration. Through block of key links of the disease and the combined treatment, we would finally heal SARS and COVID-19 patients.

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Footnote

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