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A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19)

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ABSTRACT

Coronavirus disease 2019 (COVID-19) as a life-threatening disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is accounted as global public health concern. Treatment of COVID-19 is primarily supportive and the role of antiviral agents is yet to be established. However, there are no specific anti-COVID-19 drugs and vaccine until now. This review focuses on traditional medicine such as medicinal plant extracts as promising approaches against COVID-19. Chinese, Indian and Iranian traditional medicine, suggests some herbs for prevention, treatment and rehabilitation of the diseases including COVID-19. Although, inhibition of viral replication is considered as general mechanism of herbal extracts, however some studies demonstrated that traditional herbal extracts can interact with key viral proteins which are associated with virus virulence. Chinese, Indian and Iranian traditional medicine, suggests some herbs for prevention, treatment and rehabilitation of the diseases including COVID-19. However the beneficial effects of these traditional medicines and their clinical trials remained to be known. Herein, we reviewed the latest updates on traditional medicines proposed for treatment of COVID-19.

1. Introduction

Coronaviruses are enveloped single-stranded RNA positive sense viruses with an average size between 60 nm and 140 nm in diameter with a crown-like shape under electron microscopy [1]. The novel coronavirus (nCoV-2019), coronavirus disease 2019 [2] or Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is being first reported from Wuhan of Hubei Province of China before being detected in other countries [3]. The first case was reported in December 2019, then, five patients were hospitalized with acute respiratory signs that one of these patients died [4]. On 30 January 2020, the World Health Organization [5] declared a public health emergency of international concern for COVID-19 [6]. Although the WHO said: "There is no specific medicine recommended to prevent or treat the novel coronavirus till now. The WHO, European Medicines Agency [7], US Food and Drug Administration (FDA) and the Chinese government and drug manufacturers are coordinating with researchers and industrials to accelerate the development of new drugs for COVID-19 [8].

Natural products and their derivatives have potential activities in the treatment of viral infections [9,10]. Until now, several herbal extracts or their derivatives have shown potential antiviral efficacy. However, there are no adequate studies on the development of anti-COVID-19 agents from herbal extracts [2]. Such herbal extracts are important to prevent and combat COVID-19. Generally, Chinese Medicine (CM) has suggested great clinical experiences, effective and applicable herbal formulas on the inhibition and treatment of respiratory diseases [11]. Chinese Traditional Medicine (CTM) suggests the Chinese medicinal herbs based on patients symptoms according to the Chinese diagnostic patterns. CTM could be an alternative strategy for the prevention of COVID-19 in high-risk populations [12]. However, some studies showed that Chinese herbal formula may be associated with viral replication and blocking of the viral proliferation [13]. Chinese herbal medicine with western medicine have suggested the regimen which decrease viral complications. On 24 January 2020, the first patient with symptoms of COVID-19 pneumonia, was recovered from hospital after treatment with traditional Chinese herbal medicine [14]. On 27 January 2020, the Chinses

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national health office issued diagnosis and treatment of COVID-19 pneumoniae. Although, traditional Chinese herbal medicine in being applied for COVID-19 pneumonia, its effectiveness remains uncertainly [15].

Indian medicinal plants are a promising field for treatment of several diseases [16]. Ayurveda and Siddha practices originated in India and are still widely used among the Indian population. In addition, identification of phyto-components of medicinal plants may be helpful for alleviate the infection. Hence, Indian medicinal plants can be considered as new option for their role to overcome viral transmission [17]. At this time, all of countries have to join hands together to fight COVID-19 by practicing hand-hygiene and social distancing. In the current study, we reviewed and summarized the published data about traditional herbal medicine for possible treatment of COVID-19.

2. General virology and epidemiological characteristics of COVID-19

Coronaviruses cause a lot of disorders, including respiratory, enteric, hepatic and neurologic disease [4]. The SARS-CoV-2 genome has approximately 29 kb size which encodes a large four structural proteins and five accessory proteins including ORF3a, ORF6, ORF7, OR8 and ORF9 [3]. The SARS-CoV-2 can enter to respiratory cells via the angiotensin-converting enzyme 2 (ACE-2) receptor [18]. After binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE-2), the viruses firstly infects lower airways and induced the inflammatory cytokines [19]. The primary cell disruption mechanism is the extreme activation of cytokine [20]. The activated immune cells via virus have led to cytokine and chemokine secretion into pulmonary vascular endothelial cells. Among inflammatory cytokines, IL-12, IL-7, IL-10, GCSF, MCP1 and TNF-α produced more in comparison to other cytokines [21]. Several studies showed that some of the patients who were admitted to the intensive care unit revealed a high level of pro-inflammatory cytokines such as IL-12, IL-17, IL-10, GCSF and TNF-α in their blood samples [22].

Generally, there are three routes for transmission of COVID-19: 1) aerosol transmission, 2) droplets transmission, and 3) contact transmission [23]. Study of a large number infected patients found out that the main transmission route of SARS-CoV-2 is person-person contact [24]. Moreover, it appears that the fomites can be as second suspected source of infection [5]. Recently, Chinese researchers reported that COVID-19 can be detected in the patient's feces, showing a possible fecal-oral transmission [25].

For patients with suspected infection, some molecular tests such as Real-Time Polymerase Chain Reaction (RT-PCR) and next-generation sequencing was suggested for viral detection and characterization. The most common clinical samples is used for detection of SARS-CoV-2 are throat swab, secretion of lower respiratory tract and sputum. In addition, CT imaging can be useful for detection of SARS-CoV-2 and several studies revealed that CT is often positive in patients with SARS-CoV-2 which have cough, fever and fatigue. In patients with severe disease, bilateral pulmonary parenchymal grounded-glass shadow and nodules is observed [26].

3. Prevention and treatment options

3.1. Conventional treatment candidates for COVID-19

To date, there are no specific antiviral agents or vaccines against COVID-19 infection and only the treatment method is supportive and symptomatic. The common principles are maintaining hydration, nutrition condition and controlling the fever [4]. In patients who suffering from hypoxia, supply oxygen via mechanical ventilation, high flow nasal cannula and face mask in an essential procedures. There are some anti-viral drugs that can be used as anti- SARS-CoV-2 agents including interferon-alpha (IFNα), Lopinavir/ritonavir (Kaletra), Ribavirin, Chloroquine, Arbidol (umifenovir) and Remdesivir [27,28]. IFNα belongs to type 1 IFNs which plays an important role in host resistance to viral infection. Inducing of innate and adaptive immune responses by IFNα can inhibit the viral infection via interfering with the replication process. Experimental data and in-vivo analysis showed that IFNα inhibits the replication of SARS-CoV in vitro and cynomolgus monkeys. So, IFNα can be considered as a drug candidate for COVID-19 therapy [29].

Kaletra was used as a protease inhibitor for human immunodeficiency virus [16] which interferes with viral replication. Several molecular studies indicated that Kaletra can bind to endopeptidase C30 of SARS-CoV-2 protease. In addition, some researchers showed that the use of Kaletra alone or in combination with other antiviral drugs can improve the treatment efficacy in patients with SARS or MERS. As a result, Kaletra may have an anti- SARS-CoV-2 effect but further studies are needed to confirm this possibility [30]. Ribavirin as a nucleoside analogue can interfere with guanosine triphosphate (GTP) synthesis in both DNA and RNA viruses. In Hong Kong, ribavirin was extensively used to treat SARS cases. Thus, ribavirin could be considered as anti-SARS-CoV-2 drug candidate. Chloroquine is one of another drug used for malaria and autoimmune diseases. Recently, chloroquine has been used as an antiviral agent and it can effectively inhibit SARS-CoV-2 virus in in vitro [31].

Arbidol is an anti-influenza drug that is used in Russia and China and some studies showed that Arbidol and Arbidol mesylate had potential anti- SARS-CoV-2 in in-vitro. In addition, many randomized clinical trials are being performed about Arbidol efficiency on COVID-19 infection in China [19]. Remdesivir (GS-5734) as a nucleoside analogue was shown to inhibit SARS-CoV and MERS-CoV in in-vitro [32]. Remdesivir in cells and tissues convert to an active form that inhibits viral RNA dependent RNA polymerase in the early phase of infection. Remdesivir was developed for the treatment of Ebola hemorrhagic fever for the first time. In the USA, the first case of SARS-CoV-2 infection was treated via remdesivir injection. However, randomized controlled trials are needed for the safety and efficacy of remdesivir.

In conclusion, the mentioned anti-viral drugs may be promising treatment choices for treatment of COVID-19 infection. However, the side effects of drugs, including diarrhea, nausea, vomiting and interaction with other therapeutic drugs should be considered [33]. Remdesivir is an anti-viral drug undergoing phase 3 clinical trials for treatment of patients with COVID-19 infection. Clinical trials are studying remdesivir with a loading dose of 200 mg intravenously followed by 100 mg intravenously daily for 5–10 days in adult patients. However, it showed side effects in some patients including nausea, vomiting, gastroparesis, or rectal bleeding. Moreover, these patients had more ratio of aminotransferase levels occurring 1–5 days after initiating remdesivir [34]. Favipiravir is an RNA-dependent RNA polymerase inhibitor similar to remdesivir which is developed by Toyama Chemical (Division of Fujifilm, Japan). After the administration of favipiravir, viral replication can be reduced and its specific drug for Influenza and there is less clinical study support for treatment of COVID-19. In March 2020, favipiravir was approved in China as the first choice for COVID-19 therapy. However, the clinical trial showed some side effects [35]. Chloroquine derivatives including chloroquine phosphate and hydroxychloroquine, have been used for the treatment of malaria in the 1900s for the first time. In addition, chloroquine analogues have immunomodulatory effects which can be used for autoimmune diseases such as lupus erythematosus and rheumatoid arthritis. Recently, hydroxychloroquine has also been studied against SARS-CoV-2 in in-vitro. The anti-viral and anti-inflammatory activities of chloroquine are practical choice in preventing COVID-19-related pneumonia [36]. Boosting the immune system is an alternative way for treating the COVID-19 patients. Interferons can inhibit the replication of the virus via inducing the innate and adaptive immune response. Many clinical trial studies indicated that interferon alpha can be efficient for treatment of SARS and MERS-CoV infected patients. Based on studies findings, interferon suggests for treatment of COVID-19 infection. In addition, thymosin alpha-1 (Ta1) is one immune booster for infected patients with SARS and it can prevent

the spread of infection. So, the administration of Ta1 can be used as drug candidate for COVID-19 treatment [37,38].

There are some reports regarding immunotherapy of viral infection using antiviral antibodies (IgG, IgA, IgM, IgE and IgD) which recovered from plasma of patients. Earlier, plasma therapy has been used for poliomyelitis, influenza A (H5N1) and Ebola. For COVID-19 treatment, immune therapy can be achieved by plasma from COVID-19 patients [39]. Some reports showed that plasma therapy of SARS patients can decrease viral load from 10^5 copies/mL to near zero after 24 h plasma therapy. So, plasma therapy can be considered a promising achievement for COVID-19 treatment. In addition, monoclonal antibodies are another drug candidate for viral therapy. Monoclonal antibodies against inflammatory cytokines or innate immunity responses is another immunotherapy achievement. Prior research revealed that monoclonal antibody can bind to SARS-CoV spike protein which can inhibit the virus cell entry. One of the promising monoclonal antibodies can be CR3022 due to its binding affinity to virus for the treatment of COVID-19 [40]. Monoclonal antibodies against IL-6 can be useful to decrease the cytokine storm. Tocilizumab is a monoclonal antibody against IL-6 receptor which is approved by the FDA. A report of 21 COVID-19 infected patients who received 400 mg showed a decrease in clinical manifestation in 91% of patients. Sarilumab is another IL-6 receptor antagonist which is approved RA and is being studied in phase 2/3 clinical trial. There are monoclonal antibodies such as bevacizumab, fingolimod and eculizumab which is in a clinical trial in China [41] (see Table 1).

In Italy, a great study done by the Istituto Nazionale Tumori, Fondazione Pascale di Napoli is focused on the use of tolicizumab. It is a humanized IgG1 monoclonal antibody, directed against the IL-6 receptor and commonly used in the treatment of rheumatoid arthritis. In some countries, there are no options for treatment and prevention such as vaccine or specific coronavirus drugs, so, convalescent plasma therapy is an alternative strategy to decrease the course of infection in hospitalized patients [42]. The studies showed that convalescent plasma therapy has more efficacy in patients with SARS infection. In 2009, Hung et al., showed that in infected patients with Influenza H1N1 which received the convalescent plasma had low rate of mortality [43]. In addition, the persons who recovered from COVID-19, their plasma include specific antibodies against COVID-19 and it could be useful to disease prevention. Moreover, the antibodies can reduce the viral replication in the acute phase of infection and help to clear the virus and recovery [44]. Overall, in the first week of most viral infection, viremia occur and it should be more useful to a collection of convalescent plasma. Finally, plasma globulin could be collected from COVID-19 patients and it used to recovery patients [45]. However, randomized double-blinded clinical trials with large sample sizes should be used as the standard to determine whether antiviral drugs could be used in clinical practice [46,47]. Recently, many drugs formulates are in clinical trials and they can be considered as new drug candidates for SARS-COV-2 (Table 2). After search the terms of COVID-19 or SARS-COV-2 on clinical-trials.gov resulted in 291 trials related to COVID-19 as of April 2, 2020. Among 291 clinical trials, around 109 trials included pharmacological therapy for treatment of COVID-19 in adult persons. Researcher used previously antiviral agents against SARS and MERS as drug candidates for COVID-19 [48].

Table 1
Ongoing clinical trial drugs listed for treatment COVID-19.

Clinical trial phase	Drug formulation	Number of Clinical samples	Ref.
III, IV	CD24Fc	230 participants with COVID-19	[85]
III, IV	ASC-09 + ritonavir	160 participants with COVID-19	[86]
III, IV	Dapagliflozin	900 participants with COVID-19	[87]
III, IV	Lopinavir/ritonavir without or with Rebif	3100 participants with COVID-19	[88]
III, IV	Tocilizumab	400 participants with COVID-19	[89]
III, IV	Sarilumab	400 participants with COVID-19	[90]
II	Azithromycin	600 participants with COVID-19	[91]
III	Lenzilumab	238 participants with COVID-19	[92]
III, IV	favipiravir	40 participants with COVID-19	[93]
N/A	Chloroquine	10000 patients with COVID-19	[94]
N/A	CTM + lopinavirritonavir, IFN-alpha	150 samples positive with COVID-19	[53]
I	Recombinant human IFN- a2b	328 samples positive with COVID-19	[94]
II	Thalidomide	100 Pneumonia cases caused by COVID-19	[95]
II	Vitamin C	140 severe participants caused by COVID-19	[96]
II	Methylprednisolone	80 SARS-CoV-2 infected individuals	[8]
II	Thalidomide	100 Pneumonia cases caused by COVID-19	[95]
II	Fingolimod	30 samples positive for 2019-nCoV	[94]
II/III	Bevacizumab	20 infected participants with severe 2019-nCoV	[97]
III	Oseltamivir, favipiravir, and chloroquine	80 SARS-CoV-2 positive samples	[98]
III	Pirfenidone	294 severe COVID-19 participants	[94]
III	Remdesivir	308 patients with Moderate COVID-19	[94]
III	Darunavir + cobicistat	30 Pneumonia cases caused by COVID-19	[98]
III	Remdesivir	452 severe infected persons	[99]
III	Hydroxychloroquine	30 COVID-19 infected patients	[84]
IV	Arbidol	380 individuals caused by COVID-19	[94]
IV	Arbidol/lopinavir-ritonavir	125 COVID-19 patients	[100]
IV	Carrimycin/lopinavir-ritonavir/ Arbidol/chloroquine phosphate	520 COVID-19 infected patients	[29]

3.2. Traditional herbal medicine

3.2.1. Botanical claims

A series of herbal and fruit extract was reported as claims to remedy virus infections. Sri Lankan herbal drink is used for inhibition of viral infections such as SARS-CoV-2 which reduces the fever symptoms. Some studies demonstrated that Andrographis paniculata boost the immune system and it can decrease the symptoms of coronavirus. Also, Tinospora crispa (makabuhay) was used as an antiviral drug candidate for coronavirus where used as an eye drop. Drinking lemon juice in warm water has been claimed to prevent COVID-19 disease by elevating the vitamin C levels. However, WHO reported that there is no evidence for this claim but recommended consuming fresh fruits. In addition, there are some claims about banana, garlic, Juice of bittergourd, turmeric and Azadirachta indica to prevent COVID-19 but there is no supporting data [49].

3.2.2. Traditional herbs

Traditional herbs from different habitats and geographical locations can be considered as new candidate combination for treatment of viral infections such as SARS-CoV. Preliminary studies have shown that concanavalin A, a phytoagglutinin in jack beans (*Canavalia ensiformis*) can binds to glycosylated membrane proteins and prevent the target cell

Table 2
Herbal formula used for the treatment of SARS-CoV infection.

Name of herbal formula	List of compound	Ref.
Ma Xing Shi Gan Decoction	*Semen armeniacae amarum* (ku xing ren), *Glycyrrhizae radix preparata* (gan cao), *Gypsum fibrosum* (shi gao), *Ephedrae herba* (ma huang)	[94]
Da Yuan Yin decoction	Houpo (*Magnoliae officinalis cortex*), Binlang (*Arecae semen*), Caoguo (*Tsaoko fructus*), Huangqin (*Scutellariae radix*), Gancao (*Glycyrrhizae raadix et rhizoma*), Zhimu (*Anemarrhenae rhizoma*), Shaoyao (*Dioscoreae rhizoma*)	[101]
Qing Fei Pai Du decoction	Shigao (*Gypsum fibrosum*), Mahuang (*Ephedrae herba*), Banxia (*Pinelliae rhizoma*), Shengjiang (*Zingiberis rhizoma recens*), Zhishi (*Aurantii fructus immaturus*)	[11]
Sang Ju Yin	Sang Ju Yin [made with chrysanthemum, mulberry leaf, and 6 other herbs]	[103]
Yu Ping Feng San	*Astragali radix, Astragalus membranaceus, Atractylodes macrocephala, and Saposhnikoviae Radix*	[102]

recognition and virus entry. However, subsequent studies showed that its intense hepatotoxicity restrict the therapeutic utility [50]. More studies showed that some medicinal plants extract including *Lycoris radiata, Artemisia annua, Pyrrosia lingua, and Lindera aggregata* exerted anti-SARS-CoV at 2.4–88.2 μg/mL [51]. Some reports showed that lycorine, an active phyto-compound from *Lycoris radiate* inhibited SARS-CoV with effective concentration of 15.7 nM [52]. Moreover, high toxicity of lycorine against VERO E6 and HepG2 cell lines makes it as good drug candidate for anti-cancer activity. Lau et al. demonstrated that the aqueous extract of *Houttuynia cordata* can inhibit two efficient protein namely chymotrypsin-like protease (3CLpro) and RdRp in SARS-CoV [53]. In addition, the *H. cordata* extract can enhanced the $CD4^+$ and $CD8^+$ cell count in in vitro tests in animals showing its immune-stimulatory effect that can considered as important feature for inhibition of viral replication [54]. Similarly, some medicinal plant extracts including *Rheum officinale, Polygonum multiflorum*, emodin and some other active components of these herbs were found to inhibit the bindings of SARS-CoV (S) spike protein to ACE2 with IC50 values between 1 and 10 μg/mL, and 200 μM for emodin [55].

Methanolic extract of *Cibotium barometz* and *Dioscorea batatas* showed inhibitory activity against SARS-CoV 3CLpro with IC50 values of 39 and 44 μg/mL, respectively [56]. In addition, *Anthemis hyalina, Nigella sativa*, and *Citrus sinensis* extracts exhibited the inhibitory effects on MHV-A59 (mouse hepatitis virus–A59) with priority of *A. hyaline* extract. Its mechanisms depends on down-regulation of TRP gene expression and increase the level of intracellular calcium level [57].

Recent published data showed that plant alkaloids namely tetrandrine, fangchinoline, and cepharanthine can significantly reduce the cell death due to viral infection in MRC-5 human lung cells. In addition, some active phyto-constituents including ten diterpenes, two sesquiterpenes, two triterpenes, five lignans, and curcumin can inhibit the SARS-CoV. The isolated Kazinol A, kazinol B, kazinol F, and kazinol J from *Broussonetia papyrifera* inhibit SARS-CoV 3CLpro. Sivestrol, an active phyto-component of *Aglaia foveolata* has potent in vitro cytotoxicity against human cancer cell lines. Moreover, this constituent inhibit the HCoV-229E mRNA translation with IC50 value of 40 nM [58]. On the other hand, ferruginol, a phenolic compound extracted from the redwood Sequoia sempervirens, betulinic acid, hinokinin, savinin, and curcumin showed anti-SARS-CoV replication activity. In addition, ouabain decreased significantly the viral RNA copies number. There are some reports in regarding to Tylophorine extracted from *Tylophora indica* as inhibitor of viral replication in from CoV-infected swine testicular cells [59].

Chinese traditional herbal medicine (CTM) played a key role and has long background in the treatment and control of several epidemic diseases from plague to SARS. CTM was used for the treatment of SARS-CoV outbreak in 2002. During this epidemic, CTM was reported to have favored effects to control SARS disease. Lau and co-workers used CTM herbal extract namely Sang Ju Yin plus Yu Ping Feng San for 1063 volunteers including 926 hospital workers and 37 laboratory technicians working in high-risk virus laboratories. The results of this study showed that none of CTM users were infected by the virus. It was suggested that *Sang Ju Yin* plus *Yu Ping Feng San* could regulate T cells for boosting the immune system [60]. In addition, some studies demonstrated that supplementary treatment with CTM could be useful for the improvement of symptoms. Leung et al. studied 90 peer-reviewed articles and concluded that combination of CTM used combination with conventional treatment had some positive effects, including diminished fever, faster clearance of chest infection and other symptoms. However, such positive effect of CTM is not conclusive and more clinical studies are needed [11].

Moreover, some flavonoids such as herbacetin, isobavaschalcone, quercetin 3-β-D-glucoside, and helichrysetin have inhibitory activity against MERS-CoV 3CL protease. Findings of many studies indicated that after administration of some herb-derived constituents such as sinigrin, indigo, aloe-emodin, hesperetin, quercetin, epigallocatechin gallate, gallocatechin gallate, herbacetin, rhoifolin and pectolinarin, the activity of the SARS 3CLpro could be blocked. It was reported that the extracts of *Kang Du Bu Fei Tang, Sinomenium acutum*, *Coriolus versicolor* and *Ganoderma lucidum* inhibited SARS-CoV RNA-dependent RNA polymerase. Emodin extracted from genus *Rheum* and *Polygonum*, baicalin from in *Scutellaria baicalensis*, nicotianamine from foodstuff (especially "soybean ACE2 inhibitor (ACE2iSB), scutellarin, tetra-*O*-galloyl-β-D-glucose (TGG) from *Galla chinensis* and luteolin from *Veronicalina riifolia* significantly inhibited the interaction of SARS-CoV S-protein and ACE2 [61]. As well as, inhibition of the 3a ion channel by emodin or kaempferol derivatives-juglanin could significantly block the viral release from the infected cells. Saikosaponins, glycyrrhizin, quercetin and TSL-1 originated from *Toona sinensis* Roem had potent anti-SARS-CoV effects by inhibition of viral cellular entry, adsorption, and penetration [62,63].

Because of the similarity between in SARS-CoV-2 and SARS-CoV in the context of virology, genomics and pathogenesis and successes of CTM for controlling of SARA in 2002–2003, CTM could be an alternative choice instance of chemical drugs for prevention of SARS-CoV-2 outbreak. After outbreak the COVID-19, Chinese herbal medicine treatment program, allocates expert Scientifics in the field of CTM to discover and formulate a traditional prescription for controlling COVID-19. The first case of COVID -19 cured and discharged from hospital by prescription of CTM was reported on 24 January 2020 in Beijing [64].

According to the evaluation of the cases infected with COVID-19 who treated by CTM, the results showed that the time of disappearing of clinical symptoms, staying of patient in hospital decreased by 2, 1.7, 2.2 days, respectively. CTM alone or in combination of western medicine like antibiotic or antiviral drugs regimen could be effective for treatment or prevention of COVID-19. China reported traditional medicine to treatment of patients with COVID-19 and Chinese researchers showed that 91.6% of patients in Hubei province and 92.4% of patients nationwide have been treated with traditional medicine. The studies showed that some formulas can be effective in treating the disease. Jimhua Qinggan granule is one of herbal formula which consists 12 herbal components including honeysuckle, mint and licorice. It can decrease the body temperature and remove toxic substances from lungs. This formula has significant effects in treating the patients with moderate influenza H1N1 and can increase the recovery rate of lymphocytes and white blood cells. Similar experiments indicated that the patients who received the Jimhua Qinggan granule, two days earlier recovered compared to those didn't receive it. As, the recovery time in these patients (patients who took Jimhua Qinggan granule) was eigth days compared to other groups (10.3 days) [64]. Another herbal formula is Lianhua Qingwen capsule/granule which is very common herbal extract for treatment of cold and flu [65].

In another study was shown that Sang Ju Yin plus Yu Ping Feng San extract was used for treatment of 1063 patients of SARS in 2003 that

showed a significant effect. Also, these herbs could increase host defense through modulation of T cells. Glycyrrhizin in Chinese medicine is used as an inhibition factor for SARS-CoV in vitro and its high dose has been used in clinical trials. Some reports showed that glycyrrhizin could have the ability to bind ACE2 as anti- SARS-CoV-2 drug candidate. In traditional Chinese medicine, Hesperetin, a well-known flavonoid in citrus fruits is used as 3C-like protease suppressor for SARS-CoV in cell culture experiments. In addition, Hesperetin can bind to ACE2 and inhibit it [66]. In Chinese medicine, Baicalin, flavone extract from Scutellaria baicalensis, was used as anti-viral agent against SARS-CoV. In a recent study, a new drug known as EIDD-2801 discovered to treat COVID-19 infection. The result shows that EIDD-2801 significantly reduces virus replication in mouse model. EIDD-2801 is a ribonucleoside analog with antiviral activity against influenza, Ebola and CoV, can be taken as pill reverse of remdesivir. Recently, many drugs formulates are in clinical trials and they can be considered as new drug candidates for COVID-19 (Table 2) [67]. According to Chinese traditional science, food is categorized ying (cool) or yang (hot). It was believed that SARS infected yang (hot) body system because of that it was recommended people to consume liang (cool) foods. Kim et al. revealed that Phellodendron cortex, Sophora subprostrata Radix, Cimicifuga Rhizome, Coptidis rhizometreated could inhibit expression S and N protein and RNA synthesis in coronavirus. It is also virus reported that the virus assembly and release might be affected by Coptidis Rhizome and Meliae cortex [68].

Traditional medicine especially CTM has shown significant and effective therapies for influenza A H1N1, H7N9, Ebola and SARS-CoV. Based on the beliefs of ancient Chinese traditional medicine man is a part of nature and environment is pivotal factor in pathogenesis of diseases like the plaque. In the case of SARS-CoV-2 they think that this virus characteristic depends on the climatic condition of Wuhan. According to CTM reference "Standard Therapy of COVID-19" Ma Xin Gan Shi decoction with Da Yuan Yin extract could be effective to decrease the symptoms in COVID-19 patients. The Ma Xin Gan Shi and Da Yun Yin decoction were evaluated for the treatment of SARS-CoV [61]. In Table 3 the detailed compound of these extracts are listed. According to related study the five compounds: 7-methoxy-2-methyl isoflavone, formononetin, quercetin, baicalein and kaempferol could be interfering with SARS-CoV 3CL protease. Another study indicated that Qing Fei Pai Du decoction [69] (Table 3), that is a modification of Ma Xing Gan Shi, She Gan Ma Huang, Xiao Chai Hu, and Wu Ling San decoctions, is not effective in effective in treating COVID-19. Huo Xiang Zheng Qi capsule (derived from Tai Ping Hui Min He Ji Ju Fang) which has patent medicine can be effective for treatment of the gastrointestinal symptoms of COVID-19 [61]. Also Lian Hua Qing Wen capsules and Fang Feng Tong Sheng pills can decrease the severity of symptoms (fever, fatigue and Cough) related to COVID-19, also Lian Hua Qing Wen capsule can be effective for SARS, MERS and influenza. Numerous studies showed promising results for prevention and treatment of COVID-19 by CTM. Yao et al. and Lu et al. demonstrated that the most of confirmed COVID-19 infected patients had relieved in their symptoms such as fever and cough [70]. Qing Fei Pai Du Tang is another herbal formulate which is used in China for treatment of 214 COVID-19 patients. After administration of this formula, the symptoms of the most patients (≥60%) were significantly improved and 130 patients were completely cured [44].

Table 3
Recently TCM herbal medicine research for treatment of SARS-CoV-2 infection.

Clinical trial phases	TCM herbal medicine	Number of tested samples	Form/Rout of administration	Ref.
N/A	Gu Biao Jie Du Ling	200 COVID-19 samples	–	[67]
N/A	Tan Re Qing	72 COVID-19 samples	Capsules	[67]
IV	Tan Re Qing	72 COVID-19 samples	Injection	[84]
IV	Lian Hua Qing Wen	400 COVID-19 samples	Capsule/Granule	[67]
N/A	Jin Yin Hua Tang	110 COVID-19 samples	–	[14]
IV	Shuang Huang Lian	400 COVID-19 samples	Oral Liquid	[67]
IV	Xi Yan Ping	348 COVID-19 samples	Injection	[81]
IV	Shen Fu	300 COVID-19 samples	Injection	[67]
IV	Jing Yin Granule	300 COVID-19 samples	Granules	[67]
IV	Shen Qi Fu Zheng	160 COVID-19 samples	Injection	[104]
IV	Kang Bing Du	160 COVID-19 samples	Granules	[60]
IV	Ke Su Ting Syrup /Ke Qing	72 COVID-19 samples	Capsule	[67]

Recently it has been reported that about 60107 cases were treated by CTM. According to treatment results reported from China qingfei paidu decoction (QPD), gancaoganjiang decoction, sheganmahuang decoction and qingfei touxie fuzheng recipe could be effective for diagnosis and treatment of SARS-CoV-2 (93). The reported have shown that 701 patients cured by QPD which 130 persons were treated and sent back to the home, in 51 and 268 cases clinical signs were lost and improved respectively, and in 212 patients the symptoms were stable. The rate of COVID-19 treatment by QPD is more than 90%. According to molecular interaction analysis it has been shown that patchouli alcohol, ergosterol and shionone provided new drug choice for treatment of SARS-CoV-2. SHL (Shuang huang lian oral liquid) consists of three Chinese plants including honeysuckle, forsythia, and *Scutellaria baicalensis* and because of cost and no serious side effect used for treatment of sore throat, cough with fever and cold. In a study conducted by Ni et al., SHL combined with other treatment (Intravenous immunoglobulin, dexamethasone, antibiotics, and antivirus drugs) were used for treatment of COVID-19. The results showed that this regimen prescription could resolve the symptoms and improvement without side effects [47].

Wang et al. suggested that Shen Fu Injection could decrease the level of IL-1β, TNF-α, IL-8, IL-10 and some related inflammatory cytokines. The results of this study showed that Shen Fu Injection could inhibit the lung inflammation [71]. An in vitro study indicated that Shuang Huang Lian Oral Liquid had the inhibitory effect on COVID-19. However, its clinical efficacy and safety for the treatment of COVID-19 patients has not been studied. Respiratory Detox Shot (RDS), is a kind of CTM which contain nine CTM substances including Schizonepetae Herba (Jingjie), Lonicerae Japonicae Flos (Jinyinhua), Forsythiae Fructus (Lianqiao), Scrophulariae Radix (Xuanshen), Gleditsiae Spina (Zaojiaoci), Armeniacae Semen Amarum (Kuxingren), Nidus Vespae (Fengfang), Glycyrrhizae Radix et Rhizoma (Gancao) and Ginseng Radix et Rhizoma (Renshen). These herbal ingredients has therapeutic benefits for respiratory tract infections especially COVID-19 [62,63].

Behind, previous studies have revealed that these herbal products effectively prevented release of inflammatory cytokines (TNF-α, IL-1β, a nd I L-6) in lipopolysaccharide-stimulated murine alveolar macrophages. Consequently, CTM may be effective in the treatment of severe patients with the ability to prevent cytokine storm and its disturbing consequences [67].

Indian traditional medicine in one of the oldest treatments in human history and Ayurveda, Siddha, Unani and Yoga, Naturopathy and Homeopathy plays an important role for treating the various diseases [72]. Approximately, 2500 medicinal plant based formulation have been used in Indian traditional medicine. Since a lot of Indian medicinal plants showed antiviral, anti-oxidant and anti-cancer activities that it may be important to consider their precise activities [72]. However, several clinical trials must be done to confirm its activity [72]. There are many studies about anti-coronavirus activity using medicinal plants in India. In one study, it was shown the medicinal plants including *Indigofera tinctoria* (*AO*), *Vitex trifolia*, *Gymnema sylvestre*, *Abutilon indicum*, *Leucas*

aspera, *Cassia alata*, *Sphaeranthus indicus*, *Clitoriaternatea*, *Clerodendruminerme Gaertn*, *Pergulariadaemi* and *Evolvulus alsinoides* in Tamil Nadu has anti-mouse coronavirus activity [73]. Among them, *Vitex trifolia* and *Sphaeranthus indicus* have been shown to decrease the inflammatory cytokine level using the NF-kB pathway, an important pathway in respiratory distress in SARS-CoV [74]. In addition, *Clitoria ternatea* has been found as ADAM17 metalloproteinase inhibitor which is involved in ACR shredding. Some studies have shown that the *Glycyrrhiza glabra* and *Allium sativum* have inhibitory effect on SARS-CoV replication and then they can be considered as a promising drug candidate for COVID-19 [75]. *Clerodendrum inerme Gaertn* is another medicinal herb which has been found to have viral ribosome inhibitory effect and this can be further studied for its ability as drug candidate for COVID-19 protein translation. Moreover, *Coriandrum sativum, Boerhaavia diffusa, Cynara scolymus, Coscinium fenestratum, Punicagranatum Cassia occidentalis* and *Embeliaribes* have inhibitory effects on ACE and can be used as potential anti-COVID-19 drug candidate [76]. These medicinal plants need to be investigated more for their potential effect on SARS-CoV-2 entry to target cells. Some medicinal plants such as *Acacia nilotica, Eugenia jambolana* and *Euphorbia granulate* have also shown inhibitory effect on HIV protease and these plants can be considered as drug candidate for COVID-19 [77]. Some plants such as *Ocimum sanctum, Ocimumkilim* and *scharicum, Solanum nigrum* and *Vitex negundo* have inhibitory effect on reverse transcriptase of HIV and can be investigated for SARS-CoV-2 [78]. Ganjhu et al. reported that the *Sambucus ebulus* has inhibitory effect on virus envelope [79]. In conclusion, more studies are needed to perform for Indian medicinal plants in order to the design and development of drug specific to COVID-19 [79].

As mentioned earlier, COVID-19 binds to ACE2 receptor to enter the host lung cells. Ziai and Heidari studied the 20 herbal extracts and found that the *Cerasus avium (L.) Moench, Alcea digitata (Boiss.) Alef, and Rubia tinctorum L, Citrus aurantium L.; Berberis integerrima Bge; Peganum harmala L.*and *Allium sativum L* had ACE inhibitory effects. Therefore, these herbals extracts or other plant extracts with similar mechanisms may be suggested as new strategies for the treatment of COVID-19 [80]. It should be mentioned that ACE inhibitors can increase the expression of ACE receptor and may increase the susceptibility of COVID-19 infection. However, the persons who are treated with ACE inhibitors must be excluded from these herbal medicines [79,81]. In addition, WHO recognizes that medicinal plants such as *Aretmisia annua* are being considered as possible treatment for COVID-19 and the efficacy and side effects must be examined [2,82]. Thus, it can be suggested the Iranian type of *A. annua* can be used as drug candidate for treatment of COVID-19. In addition, four Iranian companies have launched studies to make herbal medicine for the treatment of COVID-19. However, the clinical tests have begun since March 5, 2020 and after success in the clinical tests, the products should be confirmed by the food and drug organization [14,83,84].

4. Conclusion

With the appearance of COVID-19 outbreak many scientific researchers and clinicians tried to propose effective drugs for eradication of this pandemic disease. Chinese, Indian and Iranian herbal medicine with 1000 years' experience in the prevention of pandemic and endemic infectious diseases are worth learning and providing alternative candidate for controlling of patients with COVID-19 infection. Nowadays, there are not effective treatment for COVID-19, as a result it provides a biggest opportunity to test different plants and decoction for management of this disease. Hopefully, positive results from clinical trial experiments elucidate the positive effects of Chinese, Indian and Iranian herbal medicine alone and in combination with western medicine to recovery of SARS-CoV-2. Our review suggests the further studies on the Chinese, Indian and Iranian herbal medicine would be needed to discover the novel anti-COVID-19 substances useful for eradication of SARS-CoV-2. It highlight the ways that the herbal-based medicines may efficient to overcome COVID-19 fatal infections.

Data availability

Data will be made available upon request.

Declaration of competing interestCOI

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ctcp.2020.101214.

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