Review

The Significance of Natural Product Derivatives and Traditional Medicine for COVID-19

Dongdong Wang [1,2,*] **, Jiansheng Huang** [3] **, Andy Wai Kan Yeung** [4] **, Nikolay T. Tzvetkov** [5] **, Jarosław O. Horbańczuk** [6] **, Harald Willschke** [7,8] **, Zhibo Gai** [9,10] **and Atanas G. Atanasov** [6,7,11,12,*]

1   The Second Clinical Medical College, Guizhou University of Traditional Chinese Medicine, Fei Shan Jie 32, Guiyang 550003, China
2   Centre for Metabolism, Obesity and Diabetes Research, McMaster University, 1280 Main St. W., Hamilton, ON L8N 3Z5, Canada
3   Department of Medicine, Vanderbilt University Medical Center, 318 Preston Research Building, 2200 Pierce Avenue, Nashville, TN 37232, USA; jiansheng.huang@vumc.org
4   Oral and Maxillofacial Radiology, Applied Oral Sciences and Community Dental Care, Faculty of Dentistry, The University of Hong Kong, Hong Kong, China; ndyeung@hku.hk
5   Department of Biochemical Pharmacology and Drug Design, Institute of Molecular Biology "Roumen Tsanev", Bulgarian Academy of Sciences, 21 Acad. G. Bonchev Str., 1113 Sofia, Bulgaria; ntzvetkov@gmx.de
6   Department of Biotechnology and Nutrigenomics, Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, 05-552 Jastrzębiec, Poland; olav@rocketmail.com
7   Ludwig Boltzmann Institute for Digital Health and Patient Safety, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria; harald.willschke@meduniwien.ac.at
8   Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria
9   Experimental Center, Shandong University of Traditional Chinese Medicine, Jinan 250355, China; zhibo.gai@usz.ch
10 Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, University of Zurich, 8006 Zurich, Switzerland
11 Department of Pharmacognosy, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria
12 Institute of Neurobiology, Bulgarian Academy of Sciences, 23 Acad. G. Bonchev Str., 1113 Sofia, Bulgaria
*   Correspondence: wangd123@mcmaster.ca (D.W.); atanas.atanasov@univie.ac.at (A.G.A.)

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Abstract: Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, there have been more than 10 million reported cases, more than 517,000 deaths in 215 countries, areas or territories. There is no effective antiviral medicine to prevent or treat COVID-19. Natural products and traditional medicine products with known safety profiles are a promising source for the discovery of new drug leads. There is increasing number of publications reporting the effect of natural products and traditional medicine products on COVID-19. In our review, we provide an overview of natural products and their derivatives or mimics, as well as traditional medicine products, which were reported to exhibit potential to inhibit SARS-CoV-2 infection in vitro, and to manage COVID-19 in vivo, or in clinical reports or trials. These natural products and traditional medicine products are categorized in several classes: (1) anti-malaria drugs including chloroquine and hydroxychloroquine, (2) antivirals including nucleoside analogs (remdesivir, favipiravir, β-D-N4-hydroxycytidine, ribavirin and among others), lopinavir/ritonavir and arbidol, (3) antibiotics including azithromycin, ivermectin and teicoplanin, (4) anti-protozoal drug, emetine, anti-cancer drug, homoharringtonine, and others, as well as (5) traditional medicine (Lian Hua Qing Wen Capsule, Shuang Huang Lian Oral Liquid, Qingfei Paidu Decoction and Scutellariae Radix). Randomized, double-blind and placebo-controlled large clinical trials are needed to provide solid evidence for the potential effective treatment. Currently, drug repurposing is a promising strategy to quickly find an effective treatment for COVID-19. In addition, carefully

combined cocktails need to be examined for preventing a COVID-19 pandemic and the resulting global health concerns.

Keywords: SARS-CoV; coronavirus; traditional Chinese medicine; COVID-19; natural products

1. Introduction

Coronavirus disease 2019 (COVID-19) has, as a causative agent, a new betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/2019-nCoV/CoV-2) [1]. SARS-CoV-2 is a single-stranded, positive-sense, RNA-enveloped virus. It makes use of a densely glycosylated viral structural spike (S) protein to gain entry into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor of host cells [2,3]. Host transmembrane protease serine 2 (TMPRSS2) activates the S protein, and facilitates SARS CoV-2 cell entry [4]. Similar to other coronaviruses, SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, following receptor binding, the virus particles use the non-/endosomal pathway to enter the host cells [5]. Once inside the cell, SARS-CoV-2 then dissemble intracellularly to release their RNA into the cytoplasm for the synthesis of the large replicase polyproteins (such as RNA-dependent RNA polymerase (RdRp) and helicase) and for the replication of viral genomic RNA [5]. The virus structural and accessory proteins are synthesized from subgenomic mRNAs. The helical nucleocapsid, genomic RNA and the other structural proteins form the assembled virions, which are then released from cells [5]. These viral lifecycle steps (virus entry, synthesis of the large replicase polyproteins, replication of genomic RNA, and assembly of virus) provide potential targets for inhibition of SARS-CoV-2 replication [2], as shown in Figure 1.
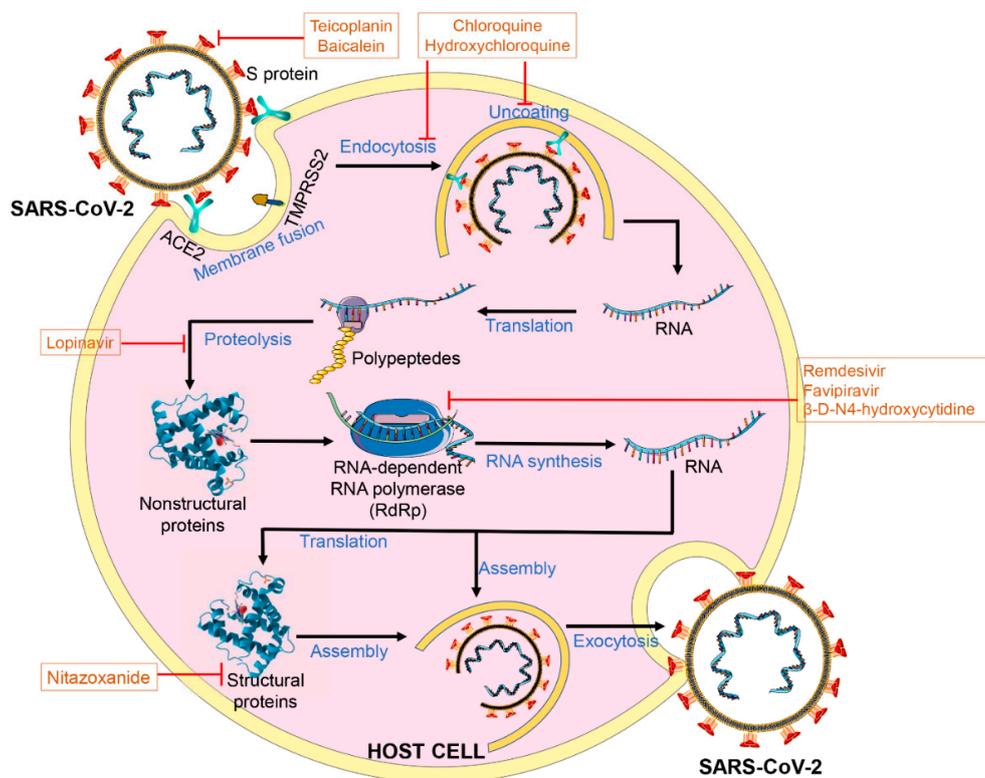

Figure 1. Schematic representation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication cycle within host cells. Proposed targets of the examined natural products, their derivatives and mimics are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; TMPRSS2, type 2 transmembrane serine protease, RdRp, RNA-dependent RNA polymerase.

As of July 26th, 2020, there have been more than 15 million reported cases resulting in more than 640 thousand deaths in 216 countries, areas or territories (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). People infected by SARS-CoV-2 have ranged from exhibiting no symptoms, mild, or moderate symptoms to severe illness and death. A recent study has shown that there is a large number of undocumented infections, which boosts the community dissemination of SARS-CoV2 [6]. The most common symptoms of COVID-19 are fever, a cough and tiredness [7]. Recent studies suggest that loss of smell and taste might be a frequent and early symptom of COVID-19 [8,9]. Some patients may have pains, nasal congestion, runny nose, sore throat and/or diarrhea [10]. Around 16.67% patients with COVID-19 become seriously ill, develop pneumonia and develop difficulty breathing. Older people and those with underlying medical problems like hypertension, heart problems or diabetes, are more likely to exhibit cytokine release syndrome (CRS) and develop serious illness [11]. In the early stage, the symptoms of COVID-19 include fever and a cough [12]. The following stage of COVID-19 is the acute pneumonia phase, in which the immune system is affected [12]. The severe stage includes organ dysfunction (e.g., acute respiratory distress syndrome (ARDS), shock, acute kidney injury, and acute cardiac injury) [13]. In total, a 3.4% mortality rate was estimated by the World Health Organization (WHO) as of March 3. There are some available materials published that could be used to treat COVID-19, such as the 7th version of "Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment" (http://kjfy.meetingchina.org/msite/news/show/cn/3337.html) published by the Chinese National Health Commission, and the Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/introduction/) from US National Institutes of Health (NIH) [14]. These guides include a deeper contemporary understanding of the clinical manifestations and pathological features of the disease and "the accumulation of experience in diagnosis and treatment" from clinical experts.

Currently, there is no effective vaccine or drug for preventing or managing COVID-19 [15]. Natural products and traditional medicine products are an excellent source for discovery of new drug leads, since they display a great diversity of chemical structural and a various range of biological activities [16–18]. Natural products include compounds from animals, plants, fungi and prokaryote [19,20]. Traditional medicine (or folk medicine) is the sum of the traditional knowledge, skills, and practices based on indigenous theories and experiences, used in the prevention and treatment of diseases, such as traditional Chinese medicine (TCM), ancient Iranian medicine, traditional African medicine, or Islamic medicine [16,21]. There is an increasing number of publications reporting the effect of natural products and traditional medicine products on COVID-19. In our review, we provide an overview of natural products and their derivatives or mimics, as well as traditional medicine products, which were reported to exhibit potential to treat COVID-19 in vitro, in vivo, or in clinical reports or trials.

2. Natural Products and Their Derivatives or Mimics

Currently, clinical management for COVID-19 includes prevention of infection, control measures and supportive health care including oxygen supplement and mechanical ventilation [22]. Effective vaccines against SARS-CoV-2 will also be an important strategy to prevent the second wave of COVID-19, which, however, will require quite a long time (at least 12–18 months) to be developed [23]. A comparative analysis of genome sequences of SARS-Cov-2 with SARS-CoV sequence reveals that the catalytic domains of essential enzymes for viral replication such as RdRp and proteinase are highly conserved between these coronaviruses [23–25]. More importantly, it is plausible that the protein sequence of the drug binding pocket of the enzymes is highly homogeneous [26,27]. Thus, the S protein and enzymes could be very promising drug targets for developing an effective approach for the treatment of COVID-19. Moreover, repurposing approved drugs would be a quick and efficient strategy to manage a COVID-19 pandemic. At present, many antivirals and immunomodulating agents, which belong to natural products, their derivatives or mimics, are already shown to exhibit anti-CoV-2 activity, or are used in treatment of COVID-19 clinically or tested in different clinical trials to evaluate their effects

(Table 1). These nature-related medicines from published data and/or recommendations are categorized in several classes: (1) anti-malaria drugs including chloroquine and hydroxychloroquine, (2) antivirals including nucleoside analogs (remdesivir, favipiravir, β-D-N4-hydroxycytidine, ribavirin and among others), lopinavir/ritonavir (LPV/RTV) and arbidol, (3) antibiotics including azithromycin, ivermectin and teicoplanin, as well as (4) anti-protozoal drugs, emetine, anti-cancer drugs, homoharringtonine, and others.

**Table 1.** Natural products, their derivatives or mimics fighting COVID-19.

| Natural Products	Structure	In Vitro and In Vivo Studies	Clinical Studies	Registered Trials
Chloroquine		Inhibits SARS-CoV-2 replication in Vero E6 cells with an half maximal effective concentration (EC50) of 1.13 µM at an MOI of 0.05 [28]	Shortened hospital stay time, improved patient outcome [29], novel coronavirus pneumonia and promoted quick recovery (Dose: 500 mg, orally, twice/day for 10 days) [30]. no clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19 (https://www.recoverytrial.net/).	ChiCTR: >25 USCTR: >52
Hydroxychloroquine		Inhibits SARS-CoV-2 replication in Vero E6 with an EC50 of 4.51-12.96 µM cells at MOI of 0.01-0.8 [31]	Hydroxychloroquine (~0.46 µg/mL in serum) reduced of the viral carriage in 3-6 days-post inclusion [32]	ChiCTR: >11 USCTR: >148
Remdesivir (GS-5734)		Inhibits CoV-2 replication in Vero E6 cells with an EC50 of 0.77 µM at MOI of 0.05 [28]; Inhibited virus infection in Huh-7 cells [33]; Reduced signs of respiratory disease, pulmonary infiltrates on radiographs and virus titers in bronchoalveolar lavages as early as 12 h after first treatment in a rhesus macaque model [34].	Remdesivir (Day 1: 200 mg daily, Days 2-9: 100 mg daily, administered intravenously) shorten the time of clinical improvement [35], and improved 36 of 53 patients (68%) clinical symptoms [36].	ChiCTR: 0 USCTR: >18
Favipiravir		Inhibits CoV-2 activity with an EC50 of 61.88 µM [28]	Favipiravir (Day 1: 1600 mg twice daily, Days 2-14: 600 mg twice daily) decreased viral clearance time, improved chest imaging [37]; Favipiravir (Day 1: 1600 mg twice daily, Days 2-10: 600 mg twice daily) shortened latencies to relief for both pyrexia and cough [38]	ChiCTR: >8 USCTR: >8
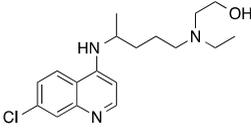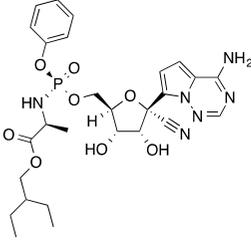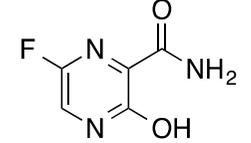
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Natural Products	Structure	In Vitro and In Vivo Studies	Clinical Studies	Registered Trials
β-D-N4-hydroxycytidine		Inhibits CoV-2 replication with an EC50 of 0.3 μM in Vero cells, with half maximal inhibitory concentration (IC50) of 0.08 μM in Calu-3 cells, and in HAE cells at 0.01-10 μM [39].	NA	ChiCTR: 0 USCTR: 0
Ribavirin		Does not inhibit viral replication under 100 μM in vitro [33].	NA	ChiCTR: >2 USCTR: >4
Lopinavir/ritonavir (LPV/RTV)		Lopinavir but not ritonavir displayed anti-CoV-2 activity with an IC50 of 26.63 μM in Vero cells [33].	A clinical trial reported no significant benefit of LPV/RTV in hospitalized SARS-CoV-2 patients than standard care [40]; Co-treatment of arbidol and LPV/RTV (arbidol: 200 mg thrice per day orally, and LPV/RTV: 400/100 mg twice per day orally) decreased the percentage of infected patients compared to only LPV/RTV treatment and improved the pneumonia [41].	ChiCTR: >13 USCTR: >33
Arbidol (Umifenovir)		NA	Arbidol (200 mg thrice per day orally) decreased the percentage of infected patients compared to LPV/RTV treatment (400/100 mg twice per day) [42].	ChiCTR: >3 USCTR: >8
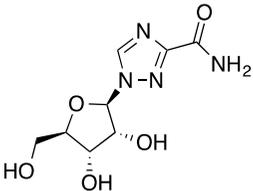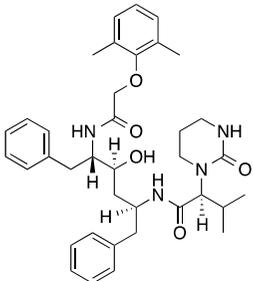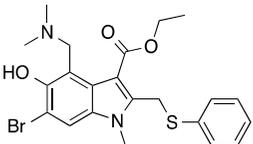
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Natural Products	Structure	In Vitro and In Vivo Studies	Clinical Studies	Registered Trials
Galidesivir (BCX4430, Immucillin-A)		Does not inhibit CoV-2 replication under 100 μM in Vero E6 cells [33].	NA	ChiCTR: 0 USCTR: >1
Oseltamivir		Does not inhibit CoV-2 replication under 100 μM in Vero E6 cells [33].	NA	ChiCTR: 0 USCTR: >10
Darunavir		NA	NA	ChiCTR: 0 USCTR: >2
Nitazoxanide		NA	NA	ChiCTR: 0 USCTR: >5
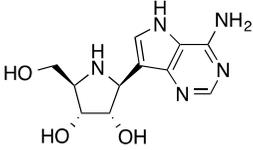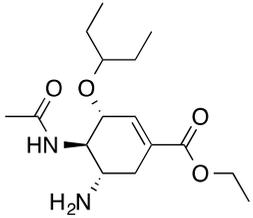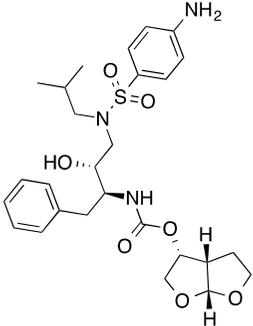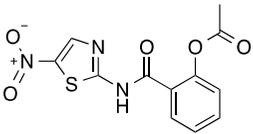
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| Natural Products	Structure	In Vitro and In Vivo Studies	Clinical Studies	Registered Trials
Azithromycin		Inhibits CoV-2 replication in Vero E6 cells with EC50 of 2.12 μM at an MOI of 0.002 [43].	A combination of hydroxychloroquine (200 mg, orally, thrice/day for 10 days) and azithromycin (Day 1: 500 mg, Days 2-4: 250 mg daily) decreased nasopharyngeal viral loading in patients with relatively mild COVID-19 [44].	ChiCTR: 0 USCTR: >45
Ivermectin		Inhibits CoV-2 replication with IC50 of 2.5 μM in Vero/hSLAM cells at an MOI of 0.1 [45]	NA	ChiCTR: 0 USCTR: >3
Teicoplanin		Prevents the entrance of 2019-nCoV-Spike-pseudoviruses into the cytoplasm in A549 cells, with an IC50 of 1.66 μM, as well as repressed CoV-2 entrance into HEK293T cells and Huh7 cells [46].	NA	ChiCTR: 0 USCTR: 0
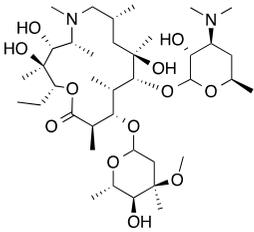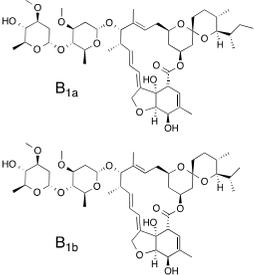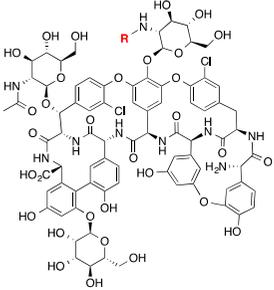
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Natural Products	Structure	In Vitro and In Vivo Studies	Clinical Studies	Registered Trials
Emetine		Inhibits CoV-2 replication with EC50 of 0.5 μM in Vero E6 cells [33].	NA	ChiCTR: 0 USCTR: 0
Homoharringtonine/Omacetaxine mepesuccinate (Synribo)		Inhibits CoV-2 with EC50 of 2.10 μM in Vero E6 cells [33].	NA	ChiCTR: 0 USCTR: 0
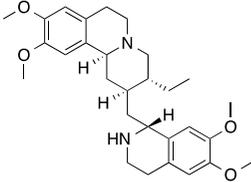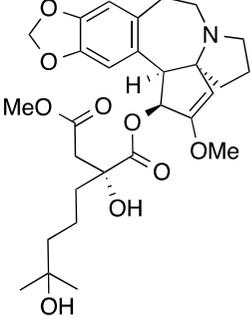
ChiCTR: Chinese Clinical Trial Register, USCTR: US Clinical Trial Register, NA: not applicable.

2.1. Chloroquine and Hydroxychloroquine

Chloroquine is an analog of quinine, which could be extracted from the bark of the Cinchona tree (Cinchona officinalis L.). Chloroquine has been reported to exhibit a curative effect on malaria since the 1600s [47]. Hydroxychloroquine is a derivative synthesized from chloroquine [47], and has a better clinical safety profile compared to chloroquine (during long-term use) and permits a higher daily dose [48]. Chloroquine and hydroxychloroquine have been successfully used to treat malaria, human immunodeficiency virus (HIV), and immune-mediated diseases, among others [47]. Chloroquine is usually dispensed as phosphate, sulfate, and hydrochloride salts.

In vitro studies showed that chloroquine is effective against SARS-CoV [49]. A study, using African green monkey kidney Vero E6 cells infected by SARS-CoV-2, showed that at a multiplicity of infection (MOI) of 0.05, chloroquine was highly effective in reducing SARS-CoV-2 replication with a half-maximal effective concentration (EC50) of 1.13 μM and an 90% effective concentration (EC90) of 6.90 μM [28], which is substantially lower than the plasma concentrations that are reached in human malaria treatment at a dose of 25 mg/kg over 3 days [49]. Chloroquine functioned at both the entry and post-entry stages of the SARS-CoV-2 infection in Vero E6 cells (Figure 1) [28]. The anti-SARS-CoV-2 effect of chloroquine might be caused by increasing endosomal pH and interfering with the glycosylation of cellular receptor of SARS-CoV-2, which is similar with its anti-SARS-CoV activity [28]. Similarly, hydroxychloroquine at different MOIs (0.01, 0.02, 0.2, and 0.8) reduced SARS-CoV-2 replication in Vero E6 cells with EC50 of 4.51, 4.06, 17.31, and 12.96 μM, respectively, higher than that of chloroquine [31]. On the contrary, another study shows that treatment with hydroxychloroquine for 48 h (EC50 = 0.72 μM) was more potent than chloroquine (EC50=5.47 μM) in SARS-CoV-2-infected Vero cells [50]. Further studies suggest that both hydroxychloroquine and chloroquine impaired SARS-CoV-2 transport from early endosomes (EEs) to endolysosomes (ELs), which participate in the release of viral RNA into the cytoplasm [31]. The established physiologically-based pharmacokinetic models (PBPK) suggest that 400 mg (twice/day) of hydroxychloroquine sulfate orally for the first day and 200 mg (twice/day) for the following 4 days could be used to treat COVID-19 [50]. It is also predicted that the potency of chloroquine phosphate increases by three times when 500 mg (twice/day) for 5 days is administered in advance [50].

A published narrative letter showed that chloroquine phosphate promoted a virus negative conversion, inhibited the exacerbation of pneumonia, and shortened the disease course [51]. However, this is an announcement without detailed data to support it. Based on clinical experiences of the experts in this field, it was announced that chloroquine might improve the success rate of treatment, shorten hospital stay time and improve patient outcome [29]. They also suggest that using the chloroquine phosphate tablet, 500 mg twice per day for 10 days could be used to treat COVID-19 patients with mild, moderate and severe pneumonia [29]. Moreover, patients with COVID-19, who received 600 mg of hydroxychloroquine sulfate (~0.46 μg/mL in serum) daily, showed a significant reduction of the viral carriage in 3–6 days-post inclusion compared to control [32]. Co-treatment with hydroxychloroquine and azithromycin was more efficient for virus reduction compared to hydroxychloroquine, suggesting a synergistic effect of the combination of hydroxychloroquine and azithromycin [32]. Another small clinical report showed that the percentages of patients who became SARS-CoV-2 negative in chloroquine (500 mg, orally, twice/day for 10 days) group (n=10) were slightly higher at Day 7, Day 10, and Day 14, compared to LPV/RTV (400/100 mg, orally, twice/day for 10 days) group (n = 12) [30]. Chloroquine also improved novel coronavirus pneumonia and promoted quick recovery compared to the LPV/RTV group [30]. There is no significant difference in T-cell (CD3+, CD4+, CD8+) counts between chloroquine and LPV/RTV groups [30]. These reports are small size (10-20 patients/group) studies without long-term outcome follow-up.

A mechanistic pharmacokinetics/virologic/corrected QT Interval (QTc) model for hydroxychloroquine was created to predict the SARS-CoV-2 decline rate and QTc prolongation [52]. Doses of hydroxychloroquine > 400 mg (twice a day) for ≥5 days were predicted to be effective to decrease viral loading, the number of patients infected with SARS-CoV-2 and treatment term, compared

to lower dose (≤400 mg daily). However, doses >600 mg (twice per day) probably prolongs QTc in the model [52]. At present, data about the effect of chloroquine and hydroxychloroquine on COVID-19 are quite limited and inconclusive. High-quality, coordinated, randomized, clinical trials are urgently needed. At least 25 different trials for SARS-CoV-2 were already registered in the Chinese Clinical Trial Register (http://www.chictr.org.cn/searchprojen.aspx) and more than 40 different trials in the US Clinical Trial Register (https://clinicaltrials.gov/) to test chloroquine or hydroxychloroquine for the treatment of COVID-19.

The low cost of chloroquine and hydroxychloroquine would be a major advantage and benefit for all countries, especially middle- and low-income counties in the context of the COVID-19 pandemic. Although side-effects of chloroquine and hydroxychloroquine are generally mild and transitory, chloroquine side effects have been associated with cardiovascular disorders, such as arrhythmias, QT prolongation, and other cardiac toxicity effects [53], which can be life-threatening, especially for critically ill patients and with cardiovascular diseases. The side effects of chloroquine should be considered in clinical trials. Unfortunately, On June 17th, 2020, WHO stopped the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective COVID-19 treatment, since the UK's Recovery trial indicted that there is no clinical benefit from use of hydroxychloroquine in hospitalized patients with COVID-19 (https://www.recoverytrial.net/).

2.2. Remdesivir

Remdesivir is a nucleotide analog, specifically an adenosine derivative, acting as a mimic of naturally occurring nucleosides. It exhibits antiviral activity by being metabolized to an analog of adenosine triphosphate to further inhibit viral RdRp [35]. Remdesivir has broad-spectrum antiviral activity, including against Ebola virus, SARS-CoV, and MERS-CoV [54]. Remdesivir appears very safe for patients, because doses of between 3 mg and 225 mg were well-tolerated without any side effects on liver or kidney in phase 1 clinical trials [55].

A study, using Vero E6 cells infected by SARS-CoV-2, showed that remdesivir was highly effective in reducing SARS-CoV-2 replication with the EC50 of 0.77 µM and the EC90 of 1.76 µM at a MOI of 0.05 [28]. Another study showed that remdesivir exhibited anti-CoV-2 with the EC50 of 23.15 µM and 26.90 µM, respectively, when fitting viral load in logarithm scale (log10TCID50 (50% tissue culture infective dose)/mL and log10 viral RNA copies/mL) [33]. Remdesivir also inhibited virus infection in human liver cell line Huh-7 cells. Remdesivir was initially effective in the early stage of post-entry virus entry (Figure 1) [28]. The molecular mechanism of remdesivir to inhibit SARS-Cov-2 might be by pre-mature termination of viral RNA replication via competing with ATP incorporation into nascent viral RNA chains [28]. This mechanism is consistent with its putative antiviral mechanism as a nucleotide analog. Further study indicated that remdesivir inhibited RdRp from CoV-2 with high potency because RdRp efficiently incorporated the active triphosphate form of remdesivir, and further terminated RNA synthesis [55]. A comparative analysis has shown how remdesivir binds to the binding pocket of RdRp of SARS-CoV-2 [24,56]. Furthermore, in a rhesus macaque model infected by SARS-CoV-2, remdesivir ameliorated the symptoms of respiratory disease, pulmonary infiltrates on radiographs and virus titers in bronchoalveolar lavages as early as 12 h after first treatment [34]. The necropsy results showed that remdesivir decreased lung viral loading and the damage in the lung tissue, which demonstrates the efficacy of remdesivir to potentially manage the COVID-19 pandemic [34].

One clinical report showed that delayed treatment with remdesivir may be effective in treating SARS-CoV-2, unlike other antiviral drugs, which exhibit more effectiveness when applied earlier [57]. In a recent cohort, patients hospitalized for severe COVID-19 received a 10-day course of remdesivir (Day 1: 200 mg daily, Days 2-9: 100 mg daily, administered intravenously) [35]. In total, 36 of 53 patients (68%) had an improvement in the oxygen-support group, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated during a median follow-up of 18 days. A total of 25 patients (47%) were discharged [35]. However, this study had a lack of placebo-control to

show remdesivir's effect, and did not test viral load to confirm the antiviral effects of remdesivir. More than 10 different trials were registered in the US Clinical Trial Register to evaluate its safety and efficacy. The Gilead company has initiated two Phase 3 randomized, open-label, multicenter clinical studies. One randomized, double-blind, placebo-controlled, multicentre trial indicated that remdesivir (n = 158, Day 1: 1200 mg, Day 2-10: 100 mg/day, infusions) was not associated with statistically significant clinical benefits for the severe COVID-19 cases compared to placebo (n = 79) [58]. Remdesivir could shorten the time of clinical improvement, but without statistical significance [58]. It was suggested that the numerical reduction in time to clinical improvement in those treated earlier required confirmation in larger studies [58]. In another cohort of patients with severe Covid-19, treatment with compassionate-use remdesivir improved 36 of 53 patients' (68%) clinical symptoms [36]. It is still early to conclude whether remdesivir is effective in patients with serious COVID-19. On May 1, 2020, The US FDA issued emergency use authorization of remdesivir for potential COVID-19 treatment (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment).

2.3. Favipiravir

Similar to remdesivir, favipiravir, a nucleoside guanine analog, is pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazinecarboxamide). It is well-known as a broad-spectrum antiviral drug by inhibiting the RdRp [59]. Favipiravir displayed anti-SARS-CoV-2 activity with a half maximal inhibitory concentration (IC50) of 61.88 μM in Vero cells and 50% cytotoxic concentration (CC50) >400 μM [28]. However, another study showed that favipiravir did not exhibit anti-SARS-CoV-2 activity in Vero E6 cells under 100 μM [33]. The contradictory results may be caused by using different MOI.

An open-label before-after controlled clinical trial examined the effects of favipiravir plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily) versus LPV/RTV plus IFN-α on COVID-19 [37]. The results showed that favipiravir (n = 35, Day 1: 1600 mg twice daily, Days 2-14: 600 mg twice daily) significantly decreased viral clearance time as compared with the group (n = 45) treated with LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) (median 4 days versus 11 days) [37]. Favipiravir also improved chest imaging compared with LPV/RTV group (91.43% versus 62%) [37]. After adjustment for potential confounders, favipiravir still significantly promoted viral clearance and improved chest imaging [37]. Another prospective, controlled, randomized, open-label multicenter trial was conducted to compare the effect between favipiravir (n = 116, Day 1: 1600 mg twice daily, Days 2-10: 600 mg twice daily) and arbidol (umifenovir) (n = 120, Days 1-10: 600 mg thrice daily) on COVID-19 [38]. This study indicated that favipiravir significantly shortened latencies to relief for both pyrexia and cough compared to arbidol, but did not influence clinical recovery rate on Day 7, as well as the rate of auxiliary oxygen therapy (AOT) or noninvasive mechanical ventilation (NMV) [38]. FUJIFILM Toyama Chemical Co. Ltd. has initiated a Phase 3 clinical trial in Japan to evaluate the safety and efficacy of favipiravir on COVID-19. At least 8 different trials for SARS-CoV-2 were already registered in the Chinese Clinical Trial Register and more than 8 different trials in the US Clinical Trial Register to test the effect of favipiravir on COVID-19.

2.4. β-D-N4-Hydroxycytidine

β-D-N4-hydroxycytidine (NHC, EIDD-1931) is a ribonucleoside analog, specifically a cytidine analog. NHC exhibited broad-spectrum antiviral activity against various RNA viruses, such as Ebola and SARS-CoV [39]. NHC displayed anti-CoV-2 activity with an IC50 of 0.3 μM and CC50 >10 μM in Vero cells, with IC50 of 0.08 μM in human lung epithelial cell line Calu-3 2B4 (Calu-3 cells). It also inhibited CoV-2 proliferation concentration-dependently (0.01-10 μM) in primary human airway epithelial (HAE) cells [39]. Both prophylactic and therapeutic administration of EIDD-2801, an orally bioavailable NHC-prodrug (β-D-N4-hydroxycytidine-5′-isopropyl ester), reduced virus titer, improved pulmonary function, and body weight loss in mice infected with SARS-CoV or MERS-CoV [39]. Unlike

remdesivir, this compound is orally active, so it can be administered as a pill. The efficacy of EIDD-2801 needs to be examined in animal and clinical studies.

2.5. Ribavirin

Ribavirin (Tribavirin), a nucleoside ribosyl purine analog, is an antiviral drug. Ribavirin (500 mg twice/thrice per day for less than 10 days) combined with IFN-α was recommended to treat COVID-19 in the Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (the 7th Edition) (http://kjfy.meetingchina.org/msite/news/show/cn/3337.html) edited by the China National Health Commission. However, one study showed that ribavirin did not inhibit viral replication under 100 μM in vitro [33]. There are no in vivo and clinical studies to test the effect of ribavirin on COVID-19. At least two different trials for SARS-CoV-2 were already registered in the Chinese Clinical Trial Register and more than four different trials in the US Clinical Trial Register to test the effect of favipiravir on COVID-19.

2.6. Lopinavir/Ritonavir and Arbidol

Lopinavir (a dicarboxylic acid amide) and ritonavir (an L-valine derivative) are antiretrovirals of the protease inhibitor class. Arbidol, features an indole core, and is an antiviral for influenza infection. An in vitro study indicated that lopinavir but not ritonavir displayed anti-CoV-2 activity with an IC50 of 26.63 μM in Vero cells [33]. A clinical trial reported no significant benefit of LPV/RTV in hospitalized SARS-CoV-2 patients than standard care [40]. A retrospective cohort study showed that the combination treatment of arbidol and LPV/RTV (arbidol: 200 mg thrice per day orally, and LPV/RTV: 400/100 mg twice per day orally; n = 16) significantly decreased the percentage of infected patients compared to only LPV/RTV treatment (400/100 mg twice per day; n = 17) (Day 7: by 75% versus 35%, Day 14: by 94% versus 52.9%) [41]. The combination treatment also improved the pneumonia [41]. These data suggest that the combination treatment of arbidol and LPV/RTV may be better than monotherapy of LPV/RTV. Another clinical report showed that arbidol (arbidol: 200 mg thrice per day orally, n = 16) significantly decreased the percentage of infected patients compared to LPV/RTV treatment (400/100 mg twice per day; n = 34) (Day 14: by 100% versus 55.9%) [42]. The results indicated that arbidol monotherapy may be superior to LPV/RTV in treating COVID-19. However, the sample size in these studies is the major limitation and their results are controversial. High-quality, coordinated, randomized, large clinical trials are urgently needed. At least 13 and 3 different trials were already registered in the Chinese Clinical Trial Register to test LPV/RTV and arbidol in the treatment of COVID-19, respectively. More than 33 and 8 different trials were registered in the US Clinical Trial Register to test LPV/RTV and arbidol in the treatment of COVID-19, respectively. Recently, on July 4th 2020, the WHO discontinued hydroxychloroquine and LPV/RTV treatment arms for COVID-19, since the interim trial results show that hydroxychloroquine and LPV/RTV produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care (https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19).

2.7. Other Antiviral Agents

BioCryst Pharmaceuticals have started a clinical trial (NCT03891420) to examine the efficacy of an adenosine analogue galidesivir in patients with COVID-19, although it did not inhibit SARS-CoV-2 replication under 100 μM in Vero E6 cells [33]. In addition, at least 10 different trials for SARS-CoV-2 were already registered on the US Clinical Trial Register to test the influence of a neuraminidase inhibitors oseltamivir on COVID-19, although it showed no apparent antiviral effect against the SARS-CoV-2 in Vero E6 cells at concentrations under 100 μM [33]. The clinical studies (NCT04252274, NCT04303299) about an antiretroviral medication darunavir were initiated for the treatment of COVID-19 recently, although there are no publications reporting its effect on SARS-CoV-2 activity in vitro or in vivo. Nitazoxanide is a broad-spectrum antiviral agent, which exhibited in vitro activity against coronaviruses by inhibiting the expression of the viral nucleocapsid protein [60]. There are no

reports about the effect of this compound on SARS-CoV-2 activity. At least five different trials were already registered in the US Clinical Trial Register to test the influence of nitazoxanide on COVID-19. The antiviral drugs baloxavir and nucleoside analogs (tenofovor, or fludarabine phosphate R-1479) showed no apparent antiviral effect against the SARS-CoV-2 in Vero E6 cells at concentrations under 100 μM [33].

2.8. Azithromycin

Azithromycin, a macrolide derivative, is a broad-spectrum macrolide antibiotic. It is used to treat enteric, respiratory, and genitourinary bacterial infections. Azithromycin was not proved to treat viral infections. One paper in preprint service indicated that azithromycin also has anti-SARS-CoV-2 activity with EC50 of 2.12 μM and EC90 of 8.65 μM in Vero E6 cells at MOI of 0.002 [43]. The mechanism of the inhibitory effect of azithromycin on anti-SARS-CoV-2 remains to be further investigated.

Some hospitals combined azithromycin with hydroxychloroquine or chloroquine for treatment of COVID-19 [61]. An open-label non-randomized clinical trial showed that 100% patients with COVID-19 (n = 6) co-treated with hydroxychloroquine and azithromycin had no SARS-CoV-2 infection at day 6 by PCR test, compared to 57.1% patients (n = 14) treated with hydroxychloroquine alone, and 12.5% in a control group (n = 16) [32]. The data suggest that azithromycin enhanced the effect of hydroxychloroquine. A pilot uncontrolled non-comparative observational study showed that a combination of hydroxychloroquine (200 mg, orally, thrice/day for 10 days) and azithromycin (Day 1: 500 mg, Days 2-4: 250 mg daily) significantly decreased nasopharyngeal viral loading in patients (n = 80) with relatively mild COVID-19 [44]. These results further suggest a beneficial effect of co-treatment of hydroxychloroquine and azithromycin on mild COVID-19 [44]. However, high-quality, coordinated, randomized, clinical trials are urgently needed to test the effect of azithromycin and the combination of it with hydroxychloroquine or other antiviral drugs on COVID-19. More than 45 different trials for SARS-CoV-2 were already registered in the US Clinical Trial Register, which are related to the examination of azithromycin in the treatment of COVID-19.

2.9. Ivermectin

Ivermectin is derived from macrocyclic lactone avermectin, which was isolated from the bacterium Streptomyces avermitilis. It is widely used for treating parasite infestation with an excellent safety profile [62]. Ivermectin also displayed inhibitory activity against RNA viral replication [62]. Ivermectin inhibited SARS-CoV-2 replication with IC50 of 2.5 μM in Vero/hSLAM cells at an MOI of 0.1 [45]. However, this concentration is the equivalent of 2190 ng/mL, which is 50-fold the peak concentration in plasma after the single dose of 200 μg/kg that is commonly used [63], which may discourage the following clinical trials. There is no clinical report about ivermectin so far. Around three different trials for SARS-CoV-2 were already registered in the US Clinical Trial Register, which are related to examining of ivermectin in the treatment of COVID-19.

2.10. Teicoplanin

Teicoplanin, a lipoglycopeptide antibiotic, is a complex of related natural products isolated from the fermentation broth of a strain of Actinoplanes teichomyceticus [64]. It consists of five major components (A2-1 through A2-5), one hydrolysis component (A3-1), and four minor components (RS-1 through RS-4) [64]. Teicoplanin has anti-bacterial and anti-SARS-CoV activities [65]. Teicoplanin significantly prevented the entrance of 2019-nCoV-Spike-pseudoviruses into the cytoplasm in A549 cells, with an IC50 of 1.66 μM [46]. The teicoplanin homolog dalbavancin but not vancomycin also inhibited the entry of 2019-nCoV in A549 cells in a dose-dependent manner [46]. Teicoplanin also effectively repressed SARS-CoV-2 entrance into HEK293T cells and Huh7 cells, which also express ACE2 [46]. There are no animal studies or clinical reports investigating the inhibitory effect of teicoplanin on SARS-CoV-2 activity.

2.11. Emetine and Homoharringtonine

Emetine could be extracted from root of a plant Cephaelis ipecacuanha (Brot.) Willd. It has been used as an anti-protozoal drug and an expectorant. It also exhibited antiviral activity, but with potential cardiotoxicity [33]. Emetine inhibited SARS-CoV-2 replication with EC50 of 0.5 μM in Vero E6 cells [33]. Remdesivir (6.25 μM) in combination with emetine (0.195 μM) may achieve 64.9% inhibition in viral yield, suggesting that synergy between remdesivir and emetine [33]. The concentrations of emetine can be almost 300 times higher in the lungs, which indicated that emetine could be much more effective as an anti-coronavirus agent than as an anti-protozoal drug [66]. There are no animal studies, clinical reports or registered clinical trials evaluating the effect of emetine on COVID-19. Homoharringtonine, a cytotoxic plant alkaloid derived from evergreen shrub Cephalotaxus fortune HOOK, has been used to treat chronic myeloid leukemia [33]. Homoharringtonine inhibited SARS-CoV-2 with EC50 of 2.10 μM in Vero E6 cells [33]. There are no studies reporting its effect on SARS-CoV-2 in preclinical in vivo models and clinical trials.

2.12. Others

There are lots of compounds which do not belong to natural products or their derivatives or mimics, but exhibited anti- SARS-CoV-2 activity. We briefly list them here for an overview. Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex or their synthetic analogs. They are involved in various physiological processes, such as regulation of inflammation. They also could suppress lung inflammation in patients with COVID-19 [67]. At least two different trials were already registered in the Chinese Clinical Trial Register and more than 21 different trials in the US Clinical Trial Register to test corticosteroids in the treatment of COVID-19. Humanized antibodies, Tocilizumab and Bevacizumab were also used to treat severe complications related to SARS-CoV-2 [22]. There are more than 29 and 3 clinical trials which were already registered in the US Clinical Trial Register to test tocilizumab and bevacizumab, respectively, in the treatment of COVID-19. An immunomodulating drug, fingolimod, is also tested in several clinical trials registered in US Clinical Trial Register (NCT04280588).

Ibrutinib and acalabrutinib created by scientists are known as Bruton's tyrosine kinase (BTK) inhibitors. They have been used to treat indolent B-cell malignancies and chronic graft versus host disease [68]. A clinical report suggested that ibrutinib may protect against pulmonary injury in SARS-CoV-2 infected patients with Waldenstrom's Macroglobulinemia [68]. The authors described that patients (n = 5) with high dose of ibrutinib (420 mg/day) experienced no dyspnea and required no hospitalization compared to a patient (n = 1) with low dose of ibrutinib (140 mg/day), who experienced progressive dyspnea and hypoxia prompting hospitalization [68]. A clinical trial examining the benefit of BTK-inhibitor acalabrutinib was initiated in COVID-19 patients in pulmonary distress (NCT04346199).

Dipyridamole is an antithrombotic agent by inhibiting phosphodiesterase, and then increasing intracellular cAMP/cGMP [69]. Dipyridamole suppressed CoV-2 replication in Vero E6 cells with IC50 of 0.1 μM [69]. In a clinical trial, dipyridamole (50 mg/time, thrice per day orally) treatment (n = 14) decreased D-dimers level, enhanced lymphocyte and platelet recovery in the circulation, and improved clinical outcomes compared to the control group (n = 16) [69]. It is worth noting that all patients in this study received ribavirin, glucocorticoids, and oxygen treatment [69]. High-quality, coordinated, randomized, large clinical trials are urgently needed to confirm the results in this study.

Omeprazole, oxprenolol hydrochloride, clemizole hydrochloride, alprostadil, dolutegravir, sulfadoxine, opipramol dihydrochloride, and quinidine hydrochloride monohydrate have anti-SARS-CoV-2 activity with EC50s of 17.06, 20.22, 23.94, 5.39, 22.04, 35.37, 5.05, and 5.11 μM in Vero E6 cells at an MOI of 0.002 [43]. The effect of these compounds on SARS-CoV-2 activity in preclinical in vivo models and their effects in clinical trials remains to be investigated.

3. Traditional Medicine Products (with Focus on TCM)

Traditional medicine has been used to fight against various diseases, including pandemic diseases, for thousands of years. It has also played an important role in SARS and H1N1 influenza [70]. Recently, some countries, including China, South Korea, Japan and India, have issued traditional medicine treatment guidelines on the prevention and treatment of COVID-19 [71]. Probably the most prominent traditional medicine worldwide is TCM, which has been used for more than five thousand years [16]. In China, more than 85% of SARS-CoV-2 infected patients were receiving TCM treatment [72]. TCM treatment for COVID-19 was based on syndrome differentiation, according to which individual treatment was administered. According to the theory of TCM, the "targeted organ location" of COVID-19 is the lung, and its core pathogenesis is "dampness and plague" caused by external "cold-dampness", which impairs "lung" and "spleen". The "dampness and plague" can transform to "heat" because of dysfunction of "Qi", which is a kind of vital force [73]. Therefore, the main principle of TCM treatment for COVID-19 is to strengthen "Qi" to protect patients from external pathogens, decrease "wind" and discharge "heat", and improve "dampness" [74]. In this part, we reviewed publications regarding the TCM treatment of COVID-19 (Table 2).

Table 2. Traditional medicine products fighting COVID-19 (with focus on traditional Chinese medicine—TCM).

Traditional Medicine	Constituents	In Vitro and In Vivo Studies	Clinical Studies	Registered Clinical Trials
Lian Hua Qing Wen Capsule (LHQWC)	*Forsythiae Fructus* (Chinese name: Lianqiao), *Lonicerae Japonicae Flos* (Jinyinhua), *Ephedrae Herba* (Mahuang), *Armeniacae Semen Amarum* (Kuxingren), *Isatidis Radix* (Banlangen), *Dryopteridis Crassirhizomatis Rhizoma* (Mianmaguanzhong), *Houttuyniae Herba* (Yuxingcao), *Pogostemonis Herba* (Guanghuoxiang), *Rhei Radix et Rhizoma* (Dahuang), *Rhodiolae Crenulatae Radix et Rhizoma* (Hongjingtian), *Glycyrrhizae Radix et Rhizoma* (Gancao), menthol and *Gypsum Fibrosum* (Shigao)	Inhibit SARS-CoV-2 replication in Vero E6 cells (100 TCID50) with an IC50 of 411.2 µg/mL, and reduce mRNA levels of pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1 and CXCL-10/IP-10) in Huh-7 cells infected by CoV-2 [75].	NA	ChiCTR: >11 USCTR: 0
Shuang Huang Lian Oral Liquid (SHLOL)	*Lonicerae Japonicae Flos* (Jinyinghua), *Forsythiae Fructus* (Lianqiao) and *Scutellariae Radix* (Huangqin)	NA	The cases had poor response to other medicine (oral moxifloxacin, cefotaxime, arbidol and oseltamivir) but responded well to SHLOL [76].	ChiCTR: >1 USCTR: 0
Qingfei Paidu Decoction (QPD)	*Gypsum Fibrosum* (Shigao), *Cinnamomi Ramulus* (Guizhi), *Ephedrae Herba* (Mahuang), *Glycyrrhizae Radix et Rhizoma* (Gancao), *Pinelliae Rhizoma* (Banxia), *Asteris Radix et Rhizoma* (Ziwan), *Farfarae Flos* (Kuandonghua), *Belamcandae Rhizoma* (Shegan), *Asari Radix et Rhizoma* (Xixin), *Scutellariae Radix* (Huangqin), *Aurantii Fructus Immaturus* (Zhishi), *Dioscoreae Rhizoma* (Shanyao), *Alismatis Rhizoma* (Zexie), *Polyporus* (Zhuling), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Poria* (Fuling), *Bupleuri Radix* (Chaihu), *Citri Reticulatae Pericarpium* (Chengpi), and *Pogostemonis Herba* (Guanghuoxiang)	NA	The effect of QPD on COVID-19 is inconclusive because there was no control group [77].	ChiCTR: >2 USCTR: 0
Scutellariae Radix	NA	Inhibit activity of a main protease of SARS-CoV-2, 3C-like protease (3CLpro) and CoV-2 replication in Vero cells with an EC50 of 0.74 µg/mL [78].	NA	ChiCTR: >7 USCTR: 0

NA: not applicable.

According to the opinions and frontline experiences of medical experts in China, there are several different herbal formulae which are recommended for COVID-19 treatment in the light of their clinical classification in Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) published by the China National Health Committee [79]. A study in preprint service showed that this guideline-based TCM treatment plus routine treatment (antiviral and antibiotic drugs, nutritional support and mechanical ventilation) may have more beneficial effects compared to only routine treatment on severe COVID-19 [80]. This clinical trial is a small pilot (n = 42), which need further large clinical study to confirm the adjunctive therapeutic effect on COVID-19.

The Lian Hua Qing Wen Capsule (LHQWC), a TCM formula, has been used to treat influenza and exhibited broad-spectrum antiviral effect and immune regulatory activity [75]. LHQWC is constituted by 11 kinds of traditional Chinese herbs, including *Forsythiae Fructus* (Chinese name: Lianqiao, the dried fruit of *Forsythia suspensa* (Thunb.) Vahl), *Lonicerae Japonicae Flos* (Jinyinhua, the dried flowers or flower buds of *Lonicera japonica* Thunb.), *Ephedrae Herba* (Mahuang, the dried herbaceous stem of *Ephedra sinica* Stapf, *Ephedra equisetina* Bge., *Ephedra intermedia* Schrenk et C. A. Mey), *Armeniacae Semen Amarum* (Kuxingren, the dried mature seed of *Prunus armeniaca* L. var. ansu Masim., *Prunus sibirica* L., *Prunus mandshurica* (Maxim.) Koehne or *Prunus armeniaca* L.), *Isatidis Radix* (Banlangen, the dried root of *Isatis indigotica* Fort), *Dryopteridis Crassirhizomatis Rhizoma* (Mianmaguanzhong, the dried rhizome and remnants of leaf stems of *Dtyopteris crassirhiaoma* Nakai), *Houttuyniae Herba* (Yuxingcao, the fresh or dried aerial portion of *Houttuynia cordata* Thunb), *Pogostemonis Herba* (Guanghuoxiang, the dried aerial portion of *Pogostemon cablin* (Blanco) Benth), *Rhei Radix et Rhizoma* (Dahuang, the dried root and rhizome of *Rheum palmatum* L. or *Rheum tanguticum* Maxim. ex Balf, or *Rheum officinale* Baill), *Rhodiolae Crenulatae Radix et Rhizoma* (Hongjingtian, the dried root and rhizome of *Rhodiola crenulata* (Hook. f. et Thoms.) H. Ohba.), and *Glycyrrhizae Radix et Rhizoma* (Gancao, the dried root and rhizome of *Glycyrrhiza uralensis* Fisch), along with menthol and a traditional Chinese mineral medicine *Gypsum Fibrosum* (Shigao). LHQWC significantly inhibited SARS-CoV-2 replication in Vero E6 cells (100 TCID50) with an IC50 of 411.2 μg/mL, and reduced mRNA levels of pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1 and CXCL-10/IP-10) in Huh-7 cells infected by CoV-2 [75]. There are no in vivo studies or clinical reports to test the effect of LHQWC on COVID-19. At least 11 different trials were already registered in the Chinese Clinical Trial Register to test the effect of Lian Hua Qing Wen Capsule/Granule on COVID-19.

There is one case report showing the first family case (parents and their daughter) of COVID-19, whereby patients were co-treated by western medicine and Chinese traditional patent medicine Shuang Huang Lian Oral Liquid (SHLOL) [76]. SHLOL, containing extract of three Chinese herbs (*Lonicerae Japonicae Flos* (the dried flowers or flower buds of *Lonicera japonica* Thunb), *Forsythiae Fructus* (the dried fruit of *Forsythia suspensa* (Thunb.) Vahl) and *Scutellariae Radix* (the dried root of *Scutellaria baicalensis* Georgi)), which is usually used to treat cold and cough with fever. These patients were treated using the SHLOL after there were no effects of other treatments (oral moxifloxacin, cefotaxime, arbidol and oseltamivir) [76]. Three cases had poor response to other medicine but responded well to SHLOL [76]. The authors already initiated a clinical trial to examine the effect of SHLOL on COVID-19 (ChiCTR2000029605).

Another case report showed that Qingfei Paidu Decoction (QPD) exhibited a beneficial effect on patients with COVID-19. QPD is consisting of *Gypsum Fibrosum* (Chinese name: Shigao), *Cinnamomi Ramulus* (Guizhi, the dried tender branches of *Cinnamomum cassia* Presl), *Ephedrae Herba* (Mahuang), *Glycyrrhizae Radix et Rhizoma* (Gancao), *Pinelliae Rhizoma* (Banxia, the dried tuberous rhizome of *Pinellia ternate* (Thunb.) Breit), *Asteris Radix et Rhizoma* (Ziwan, the dried root and rhizome of *Aster tataricus* L.), *Farfarae Flos* (Kuandonghua, the dried flower bud of *Tussilago farfara* L.), *Belamcandae Rhizoma* (Shegan, the dried rhizome of *Belamcanda chinensis* (L.) DC.), *Asari Radix et Rhizoma* (Xixin, the dried root and rhizome of *Asarum heterotropoides* Fr. Schmidt var. mandshuricum (Maxim.) Kitag., *Asarum sieboldii* Miq., *Asarum sieboldii* Miq.var. seoulense Nakai), *Scutellariae Radix* (Huangqin), *Aurantii Fructus Immaturus* (Zhishi, the dried young fruit of *Citrus aurantium* L., and its cultivar *Citrus sinensis*

(L.) Osbeck), *Dioscoreae Rhizoma* (Shanyao, the dried rhizome of *Dioscorea opposite* Thunb), *Zingiberis Rhizoma Recens* (Shengjiang, the fresh rhizome of *Zingiber officinale* (Willd.) Rosc), *Armeniacae Semen Amarum* (Kuxingren), *Alismatis Rhizoma* (Zexie, the dried tuberous rhizome of *Alisma orientalis* (Sam.) Juzep), *Polyporus* (Zhuling, the dried sclerotium of *Polyporus umbellatus* (Pers.) Fries), *Atractylodis Macrocephalae Rhizoma* (Baizhu, the dried rhizome of *Atractylodes macrocephala* Koidz), *Poria* (Fuling, the dried sclerotium of *Poria cocos* (Schw.) Wolf), *Bupleuri Radix* (Chaihu, the dried root of *Bupleurum chinense* DC.), *Citri Reticulatae Pericarpium* (Chengpi, the dried mature pericarp of *Citrus reticulate* Blanco and its culticars), and *Pogostemonis Herba* (Guanghuoxiang, the dried aerial portion of *Pogostemon cablin* (Blanco) Benth) [77]. In the treatment of the QPD group (*n* = 701), 130 cases were discharged, and the clinical symptoms of 51 and 268 cases disappeared and improved, respectively [77]. However, the effect of QPD on COVID-19 is inconclusive because there was no control group. There are two clinical trials registered in the Chinese Clinical Trial Register (ChiCTR2000030883, ChiCTR2000030806) to investigate the effect of QPD on COVID-19.

Scutellariae Radix (the dried roots of *Scutellariae baicalensis* Georgi; Chinese name: Huangqin), has been widely used to treat viral infection-related symptoms in China [78]. The ethanol extract of *Scutellariae Radix* inhibited activity of a main protease of SARS-CoV-2, 3C-like protease (3CLpro) and SARS-CoV-2 replication in Vero cells with an EC50 of 0.74 µg/mL [78]. A major component of *Scutellariae Radix*, baicalein, strongly inhibited SARS-CoV-2 3CLpro activity with an IC50 of 0.39 µM [78]. Baicalein inhibited viral replication by docking in the core of the substrate-binding pocket of SARS-CoV-2 3CLpro by interacting with two catalytic residues (the crucial S1/S2 subsites and the oxyanion loop) to prevent the peptide substrate approaching the active site [81]. There are at least seven clinical trials registered in the Chinese Clinical Trial Register to investigate the effect of *Scutellariae Radix* or its components on COVID-19.

In addition, the effects of self-made herbal preparations such as Xin Guan-1 Formula, Xin Guan-2 Formula, Qing Yi-4, and commercially available Tan Re Qing Injection, Xue Bi Jing Injection, Re Du Ning Injection, Shen Qi Fu Zheng Injection, Shen Fu Injection, Xi Yan Ping Injection, Shuang Huang Lian Oral Liquid, Kang Bing Du Granules, Jing Yin Granule, Jin Yin Hua Tang, Ke Su Ting Syrup/Ke Qing Capsule, and Gu Biao Jie Du Ling are examined in the clinical trials registered in the Chinese Clinical Trial Register [72].

Through thousands of years of development, TCM has carved out its own theory and practice. In fact, one classic medicinal book *Shanghan Zabing Lun*, which was compiled by ZHANG Zhongjing around 220 AD, even described how to fight against pandemic diseases. The theory of TCM to treat COVID-19, including concepts like "dampness and plague" and "Qi" among others, are difficult to be understood and accepted by other countries except China, Japan and Korea. Therefore, to verify the potential effect of TCM formulae on COVID-19, high-quality, coordinated, randomized, large clinical trials are needed. In addition, the Chinese medicine formulae are composed of many Chinese herbs which contain complicated chemical compositions. Thus, a systemic evaluation approach needs to be developed to assess diverse traditional Chinese medicine products.

4. Discussion and Conclusions

So far, no specific drug has been discovered for COVID-19 therapy. The whole world is in a rush to find treatments for COVID-19. For this review, many published pre-clinical studies, clinical treatment experience, clinical trials, descriptive reports and case series were summarized that investigated the effect of natural products, their derivatives and mimics, as well as traditional medicine products on COVID-19. Clinical and in vitro antiviral studies indicated that chloroquine, hydroxychloroquine, remdesivir, favipiravir, LPV/RTV and arbidol may exhibit potent therapeutic effects on COVID-19. Randomized, large and placebo-controlled clinical trials were registered to further confirm their effects on COVID-19. It is observed the existence of a synergistic effect of the combination of hydroxychloroquine and azithromycin or nitazoxanide as well as combination of arbidol and LPV/RTV, which also remains to be further investigated in the large clinical studies. There are clinical trials

registered to test ribavirin, galidesivir, oseltamivir, darunavir and nitazoxanide in the treatment of COVID-19, although these compounds did not exhibit anti-CoV-2 activity in vitro or there are no related reports. It is reported that β-D-N4-hydroxycytidine, teicoplanin, ivermectin, emetine and homoharringtonine displayed in vitro anti-Cov-2 activity. There are, however, no clinical reports or registered clinical trials to investigate their effect on COVID-19.

It is implicated that some TCM treatments may exhibit beneficial effect on COVID-19. Among the TCM formulae, Lian Hua Qing Wen Capsule, Shuang Huang Lian Oral Liquid, and Qingfei Paidu Decoction were reported to exhibit beneficial effects on COVID-19. Randomized, large and placebo-controlled clinical trials were initiated to investigate their effect. In addition, the ethanol extract of a Chinese herb *Scutellariae Radix* and its main constituent baicalein inhibited SARS-CoV-2 replication in vitro. There are several clinical trials registered to test the effect of this herb or its components on COVID-19. TCM treatment of COVID-19 was based on syndrome differentiation. Mild and severe symptoms were treated by different TCM formulae. Moreover, TCM appeared to regulate human immune function and strengthen the resistance to epidemic diseases before infection [82]. Thus, the effect of TCM formulae on different phases of COVID-19 remains to be investigated, along with an assessment of the prevention effect of pre-treatment with TCM formulae. Although TCM formulae have been used clinically in China for thousands of years, their safety should be also carefully evaluated when treating patients with COVID-19 because formulae contain many complicated chemical compounds, which may affect the efficacy of standard treatment because of herb–drug interaction. The TCM treatment for COVID-19 should be applied under the guidance of TCM practitioners. The mechanism of TCM efficiency on COVID-19 remains to be further dissected. Although it is very difficult to fully understand the molecular mechanism of action of the complicated constituents of TCM formulae, we may consider that TCM might possibly exhibit therapeutic effects by inhibiting the viral replication, blocking the infection, regulating the immune response and decreasing the inflammatory storm [77]. In addition, it is valuable to point out that the studies about TCM treatment on COVID-19 were performed only in China, where the B type of SARS-Cov-2 is the most common type [83]. Since A and C types were found in significant proportions outside China, that is, in Europeans and Americans [83], they may have a different response to TCM treatment.

COVID-19 has now been declared a pandemic and no specific drug could be used for treating it. Therefore, new medicines for the management of COVID-19 are urgently needed. Currently, drug repurposing (such as the ongoing efforts with chloroquine, hydroxychloroquine, remdesivir and so on) is an important strategy to quickly develop an effective treatment for COVID-19, because it will potentially shorten overall drug development timelines and lower development costs [84]. It is of great urgency to also develop new medicines (including searching for new active natural products) to combat this difficult-to-treat new disease at the same time, since repurposed drugs may ultimately not yield a significant clinical benefit [85].

As reviewed in this paper, there is a synergistic effect of the combination of hydroxychloroquine and azithromycin or nitazoxanide as well as combination of arbidol and LPV/RTV on COVID-19. Therefore, carefully combined cocktails may be very effective to treat COVID-19, as was the case for HIV in the 1990s (LPV/RTV) [85]. The synergistic effect could be explained by the different mechanisms of action of these drugs: for example, hydroxychloroquine inhibits SARS-CoV2 replication and azithromycin has anti-inflammatory activities which probably down-regulate cytokine storm in patients with COVID-19. Therefore, it is worthwhile to emphasize the exploration of a logical combination of drugs to manage COVID-19.

Because of the urgency of treating patients with COVID-19, large-scale randomized controlled studies were almost impossible at the beginning when the disease appeared [86]. The published treatment data to date are derived exclusively from observational data, small clinical trials, or poorly designed clinical studies with potential biases in evaluating the effectiveness of treatment for COVID-19. Randomized, double-blind and placebo-controlled large clinical trials are needed to provide reliable evidence for potential effective treatments.

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