



### Abbreviations

<b>ACE-2</b>	angiotensin converting-enzyme-2
<b>3CL<sup>PRO</sup></b>	3-chymotrysin-like protease
<b>COVID-19</b>	corona Virus Disease-2019
<b>CPE assay</b>	cytopathogenic effect assay
<b>CTSL</b>	cathepsin L
<b>DENV</b>	dengue virus
<b>HCoV</b>	human coronavirus
<b>HRV-3C Protease</b>	human rhinovirus 3C protease
<b>IBV</b>	infectious bronchitis virus
<b>IFN</b>	interferon

<b>IV</b>	intravenous
<b>IVIG</b>	intravenous immunoglobulin
<b>MERS-CoV</b>	Middle East Respiratory Syndrome-coronavirus
<b>MHV</b>	mouse hepatitis virus
<b>PL<sup>PRO</sup></b>	papain-like protease
<b>N protein</b>	nucleocapsid protein
<b>Nsps</b>	non-structural proteins
<b>RdRp</b>	RNA-dependent RNA polymerase
<b>SARS-CoV</b>	Severe Acute Respiratory Syndrome-coronavirus
<b>S protein</b>	spike protein
<b>TCM</b>	Traditional Chinese Medicine
<b>TMPPSS2</b>	transmembrane protease serine type 2

#### 1.1. Conventional medications used for the coronavirus

Currently, there is not a custom-made medication for the treatment of the COVID-19. The development of a vaccine for SARS-CoV-2 is under progress, and there is a substantial effort to design a medication specific for it. Yet, it will require some time to prove the efficacy and safety of any new agents. Drugs such as ribavirin and corticosteroids have significant side-effects.<sup>6,7</sup> The systemic use of ribavirin through intravenous or oral administration may cause dose-dependent anemia and bone marrow suppression.<sup>6</sup> The aerosol application of ribavirin is associated with nausea, headaches, and rarely to bronchospasm.<sup>6</sup> In a retrospective cohort study with SARS patients, the researchers verified that corticosteroid therapy was associated with a 20-fold increase in adverse effects.<sup>7</sup> Monoclonal antibody therapies for the CoV are still under investigation. Although not yet proven to be effective for the COVID-19, broad-spectrum antiviral medications and drugs used for the treatment of retrovirus-associated diseases may be repurposed to control the actual CoV infection. The drug recommendations for the COVID-19 such as lopinavir, ritonavir, nebulized  $\alpha$ -interferon, chloroquine or hydroxychloroquine, ribavirin, and interferon (IFN) are being made based on retrospective cohort studies, historically controlled studies, case reports and case series that resulted from the SARS-CoV-1 and MERS-CoV outbreaks.<sup>8</sup> In a systematic review requested by the WHO (2006), the investigators examined the published literature on ribavirin, corticosteroids, lopinavir/ritonavir, type 1 interferon (IFN), intravenous immunoglobulin (IVIG), and SARS convalescent plasma from both in-vitro studies and SARS patients.<sup>9</sup> From the 72 reviewed studies, the authors concluded that it was not possible to determine if the treatments indeed benefitted the patients during the SARS outbreak of 2002-03, and actually, some could have been harmful.<sup>9</sup> Thus, the efficacy and safety of these drugs also need to be assessed by future clinical trials.<sup>10</sup>

#### 1.2. Herbal medicine and the treatment of the SARS-CoV-1 infection

In 2002, the SARS mortality in mainland China was the lowest (7%) when compared with the 15%–27% of other areas such as Canada (17%), France (14%), Malaysia (40%), Philippines (14%), Thailand (22%), Hong Kong (17%), Taiwan (11%), Singapore (14%), and Vietnam (8%).<sup>11</sup> It was suggested that the lower mortality rate in mainland China and the relatively rapid response in controlling the SARS 2002 outbreak could have been due to the inclusion of herbal formulations from Traditional Chinese Medicine (TCM) in the treatment protocols.<sup>12,13</sup> A statistical study showed a significant low fatality rate caused by the SARS-CoV-1 in Beijing when compared with Hong Kong and Singapore.<sup>13</sup> Many hospitals in mainland China used a combination of TCM and conventional (Western) medicine, while Hong Kong and Singapore essentially

used conventional drugs throughout the research period.<sup>13</sup> Thus, the researchers suggested that the use of an integrative approach could more effectively control the infection and reduce the number of deaths.<sup>13</sup> The Beijing You-an Hospital, for example, reported that the death rate of severe patients was 15.4% when a drug-herbal combination was used, and it was 47.7% when only conventional medications were applied.<sup>14</sup> Also, one study reported on the administration of a TCM herbal formula to 3160 hospital workers as a preventive measure. Within a two-week period, none of the herb consumers contracted the SARS-CoV-1, and adverse effects were infrequent and mild.<sup>15</sup> The short period of follow-up is an obvious weakness of this study. Yet, the subject definitely deserves further investigations.

#### 1.3. Potential benefits of herbal medicine-based treatments for the CoV infection: stand-alone herbal use, drug-herbal combination, symptomatology management, and preventive care

After the outbreak of 2002, there was a surge in research focusing on drug discovery and testing of new medications, herbs, natural and synthetic compounds for the SARS-CoV. Like the conventional drugs, a series of studies investigating the use of herbs for the SARS-CoV-1 were published in the form of case studies, controlled and uncontrolled clinical studies, systematic reviews, meta-analyses, and one randomized double-blind and placebo-controlled clinical pilot study.<sup>16–26</sup> These studies attracted the interest of researchers and encouraged more investigations on the potential of herbs-compounds for the management of the CoV infection.<sup>5,22,24,25,27</sup> Peer-reviewed papers examined how TCM participated in an integrative treatment approach and showed that the combination of herbs with conventional medications was more effective than the use of conventional drugs alone.<sup>14,16,17,19,20,23–25,27,28</sup> Herbs were seen to significantly lower the average daily dosage of drugs such as methylprednisolone and hydrocortisone in severe cases ( $p < 0.05$ ), and to reduce the serious side effects caused by some medications.<sup>14,24</sup> Although there was some conflicting evidence on the mortality and cure rates, in general, the studies showed that the herbs helped reduce the symptoms of the CoV such as dyspnea, non-productive cough, fatigue, and malaise.<sup>14,18,21,22,24</sup> In one study, the mean duration of these symptoms, except for headaches and myalgias, was relatively shortened and their intensity lowered in the patients treated with herbal compounds along with conventional drugs.<sup>14</sup> In another research, patients receiving an integrative treatment showed a likelihood of a complete or partial pulmonary infiltrate resolution, a shorter defervescence time, and higher CD4<sup>+</sup> lymphocyte count.<sup>24</sup> In a small clinical study, the use of TCM herbal medicine as a standalone treatment strategy showed promising results to control fever and pulmonary infiltration.<sup>18</sup> Another paper warranted the

use of TCM in the SARS-CoV clinically cured and discharged patients from the hospital that presented with sequelae such as impairment of heart, lungs, liver, hypo-immune status, and psychological problems.<sup>29</sup> Other articles reported the preventive function of TCM herbs in strengthening the immune system to reduce the number of possible onsets of infectious cases.<sup>15,30</sup> One recent article revealed that three out of four patients with the SARS-CoV-2 infection showed improvement with a combination of Kaletra (lopinavir/ritonavir) and *arbidol* associated with the Chinese medicine formula *Shu Feng Jie Du* capsule.<sup>31</sup> In an animal model, this formula protected against acute lung injury through the suppression of the MAPK/NF- $\kappa$ B pathway.<sup>32</sup> Many other herbal formulas have been proposed to prevent and treat the SARS-CoV-1 infection, and many formulations are also currently being researched and suggested for the SARS-CoV-2 (reviewed in).<sup>30,33,34</sup> Limitations of the above-mentioned studies include a small number of participants of some investigations, the poor quality of some studies mentioned by systematic reviews, a low number of controlled clinical trials, and a lack of investigations on drug-herbal interaction. However, one of the advantages of the TCM rationale is to use diagnostic patterns of differentiation to select the remedies for treatment that can be prescribed according to the individual clinical presentation. In general, TCM doctors utilize herbal formulas for the SARS-CoV infection that are composed of herbs known to have a broad-spectrum antiviral, anti-inflammatory, immune-modulatory, and anti-toxicity effects, among other actions. Also, the comorbidities, age, constitution, and many other relevant factors during the diagnostic process are taken into account.

Collectively, these research articles offer a broader perspective on new treatment possibilities that should be explored. There is an urgent need to find therapeutic options in support of the current protocols to assist in the prevention, treatment, control of symptomatology, and decrease the severity of SARS-CoV infections. Herbs are generally consumed as teas prepared from raw herbs, water and ethanol extracts, dry extracts, pills, powder, liposomal, and other forms. Natural products can also be a source of “drugs” in the form of compounds, derivatives, and other refined substances obtained from them. With this review, we aimed to investigate the antiviral properties and mechanisms of action of herbs and natural compounds against the SARS-CoVs. We hope to inspire a fruitful cooperation among medical scientists and clinicians for developing novel and more efficacious therapeutic agents as well as treatment protocols in an integrative medical approach to fighting coronaviruses.

## 2. Methodological approach

Pubmed was searched for articles in English that investigated the antiviral properties of the Traditional Chinese Medicine (TCM) herbs or natural compounds against the SARS-coronavirus (CoV). The herbs refer to their unaltered and whole form while the natural compounds are active components isolated from the herbs. The articles were screened and selected for the primary experimental and/or clinical evidence of the herbs and natural compounds to effectively target the CoV infection. Particularly, we paid attention to the mechanisms of action and/or signaling pathways involved in the activity of such herbs and natural products that could support the ability to contrast the SARS-CoV infection. Keywords were used to include studies published out of the outbreak in China in 2002–03 (SARS-CoV-1), as well as any publications on the novel 2019 coronavirus (SARS-CoV-2). During the search, the Pubmed “similar articles” section was also screened, and the list of bibliographic references in each article was examined for additional relevant papers. Articles that investigated exclusively conventional drugs or

synthetic substances for SARS-CoVs were not included.

**Primary search parameters:** (coronavirus OR “corona virus” OR SARS OR “severe acute respiratory syndrome” OR SARS-CoV OR 2019-nCov OR nCoV-2019 OR nCoV-19 OR COVID-19) AND (herb OR herbs OR “herbal medicine” OR “herbal medicines” OR “Chinese medicine” OR “medicinal herb” OR “medicinal herbs” OR “medicinal herbal extract” OR “natural compounds”). The search was done at the beginning of March of 2020 but it was last repeated on April 6 of 2020 due to the large number of papers being currently published on the coronavirus subject.

## 3. Results

The Pubmed search rendered 201 articles and, after the secondary searches, 43 relevant papers were located. The articles revealed many known and new herbs, natural compounds, and derivatives studied for the SARS-CoV and related viruses. Some of these studies also included conventional drugs and synthetic compounds. Although it is impossible to precisely quantify, we estimated that these 43 articles screened and tested 45,000+ substances, although some were in duplicate. A general hand-count resulted in 450+ herbs and natural compounds with antiviral properties, though some were also duplicated. Drawing the exact numbers was not possible because of the way that some papers displayed the results. From the 43 articles, 31 demonstrated the mechanism(s) of action by which some of the herbs-compounds specifically acted against the SARS-CoVs and associated viruses. The molecular mechanisms refer to the inhibition or blockade of the main SARS-CoV and host protein pathways that are important for the whole process of viral replication. Data were extracted from the articles to provide a summary for the readers, as organized in [Table 1](#) according to the date of publications, the goal of each study, and results. Due to the large amount of data reported by the 43 articles, [Table 1](#) aimed to provide the readers with a quick synopsis of each paper, yet it does not reflect all the accounted results. The mechanism(s) of action of the herbs-natural products reported in the reviewed articles were summarized in [Fig. 1](#).

## 4. Discussion

We organized the discussion to progressively facilitate the understanding of the extracted data and to specifically explain the mechanisms of action found in the articles. We first clarify the overall methodologies of the papers, the broader antiviral properties, and then the more explicit molecular mechanisms of the antiviral herbs and natural compounds.

### 4.1. Methodologies used in the studies

Generally, drugs with antiviral properties against the SARS-CoV are tested through in-vitro infected cell lines accompanied by the cytopathic effect (CPE) assay. Since the investigations with SARS-CoVs require a Biosafety Level 3 (BSL-3) laboratory equipped to contain dangerous pathogens,<sup>35</sup> very often researchers use pseudotyped viruses known for their inability to replicate. Different viruses can be used as models to study the SARS-CoV such as the mouse hepatitis virus (MHV), HCoV-OC43, HCoV229E, or HIV-luc/SARS pseudotyped virus, to name a few. Experiments with HCoV-OC43, hepatitis, and HIV viruses require a Biosafety Level 2 (BSL-2) lab making them easier to test.<sup>35</sup> So, the viruses used as models for the SARS-CoV and that provide a proximity for testing are RNA viruses such as hepatitis C, HIV, different CoVs of the *Coronaviridae* family, different strains of SARS-CoV, and similar viruses. The influenza viruses are also RNA viruses, yet their manipulation requires a BSL-3 lab. Furthermore, in the studies, different

**Table 1**  
**Summary of the forty three (43) studies that reported antiviral activity of herbs and natural compounds against the SARS-CoV and other related viruses.** Out of the 43 articles, thirty one (31) investigated the mechanisms of action by which the herbs-compounds exerted the antiviral activity, and are marked with a \*. These molecular mechanisms refer to the action on the coronavirus-host protein pathways (See Fig. 1).

Studies	Tested substances - drugs, medicinal herbs, natural compounds, and synthetic substances	Results - Herbs and natural compounds with antiviral properties
<b>Cinatl et al., 2003</b> <sup>51</sup>	<i>Ribavirin</i> , 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin were tested for their antiviral properties against CoV isolates (FFM-1 and FF-M2).	Glycyrrhizin or GL (from <i>Glycyrrhiza radix</i> ): the most active in inhibiting the replication of SARS-associated virus with few toxic effects. <i>Ribavirin</i> and <i>mycophenolic acid</i> did not affect the replication of the SARS-CoV.
* <b>Yi et al., 2004</b> <sup>69</sup>	Extracts from 121 Chinese herbs from small molecule libraries that exhibited antiviral activities were screened and tested.	TGG ( <i>tetra-O-galloyl-β-D-glucose</i> , from <i>Galla Chinensis</i> ) and <i>luteolin</i> avidly binded to SARS-CoV Spike-2 (S2) protein without cytotoxic effects. <i>Quercetin</i> also showed antiviral activity with low cytotoxicity.
<b>Chen et al., 2004</b> <sup>12</sup>	20 commercially antimicrobial agents and the bioactive compounds from “ <i>Qing Fei Jie Du Tang</i> ” (“Clear the lung and detoxify decoction”) were screened and tested against SARS-CoV isolates: <i>glycyrrhizin</i> (from <i>Glycyrrhiza uralensis</i> ), <i>baicalin</i> (from <i>Scutellaria baicalensis</i> ), <i>chlorogenic acid</i> (from <i>Flos lonicerae</i> ) and <i>artesanate</i> (from <i>Artemisia apiacea</i> ). Additional tested drugs: <i>acyclovir</i> , <i>ganciclovir</i> , <i>cidofovir</i> , <i>foscarnet</i> , <i>ribavirin</i> , <i>IFN-α-2a</i> , <i>IFN-α-2b</i> , <i>IFN-β1a</i> , leukocytic <i>IFN-α</i> , <i>amantadine</i> , <i>rimantadine</i> , <i>zidovudine</i> , <i>stavudine</i> , <i>nevirapine</i> , <i>abacavir</i> , <i>ritonavir</i> , and <i>lopinavir</i> .	<i>Glycyrrhizin</i> , <i>baicalin</i> , <i>chlorogenic acid</i> , <i>IFN-β-1a</i> , leukocytic <i>IFN-α</i> , <i>ribavirin</i> , <i>lopinavir</i> , and <i>rimantadine</i> showed antiviral activity. The combination of <i>ribavirin</i> with the IFNs revealed potentially synergistic action against the SARS-CoV. <i>Baicalin</i> instead of <i>glycyrrhizin</i> should be used for prophylaxis or treatment.
<b>Wu et al., 2004</b> <sup>36</sup>	More than 10,000 compounds were screened and tested to identify antiviral agents against the SARS-CoV. The tested substances included approximately 200 FDA-approved drugs, more than 8000 synthetic compounds, around 1000 TCM herbs, and 500 protease inhibitors.	Approximately 50 compounds showed antiviral activity against the SARS-CoV. The most potent compound was <i>Valinomycin</i> . 15 compounds related to <i>Reserpine</i> showed antiviral activity against the SARS-CoV. The extracts of <i>eucalyptus</i> , <i>Lonicera japonica</i> , and <i>ginsenoside-Rb1</i> showed antiviral activities against the SARS-CoV at a higher concentration (100 μM). The following drugs and compounds did not show antiviral activity against SARS-CoV: <i>AG7088</i> , <i>Pentoxifylline</i> , <i>melatonin</i> , <i>vitamin C</i> , <i>AZT</i> , <i>didanosine</i> , <i>nevirapine</i> , <i>ritonavir</i> , <i>lopinavir</i> , <i>saquinavir</i> , and <i>ribavirin</i> . <i>Ritonavir</i> and <i>Saquinavir</i> did not inhibit SARS-CoV 3CL <sup>PRO</sup> .
<b>Hoever et al., 2005</b> <sup>11</sup>	The anti-SARS-CoV activity of 15 <i>glycyrrhizin</i> derivatives (from <i>Glycyrrhiza radix</i> ) was tested.	Seven (7) <i>Glycyrrhizin</i> (GL) derivatives inhibited SARS-CoV replication in-vitro at lower concentrations when compared to GL. Chemical structure modifications to GL caused from a 10-fold to a 70-fold increase in activity against the SARS-CoV.
* <b>Lin et al., 2005</b> <sup>61</sup>	Water extract of <i>Isatis indigotica</i> , its 5 major compounds, and 7 phenolic compounds were tested as SARS-CoV 3CL <sup>PRO</sup> inhibitors ( <i>indigo</i> , <i>indirubin</i> , <i>indicant</i> , <i>β-sitosterol</i> , <i>sinigrin</i> , <i>aloe-emodin</i> , <i>hesperidin</i> , <i>quercetin</i> , <i>naringenin</i> , <i>daidzein</i> , <i>emodin</i> , and <i>chrysophanol</i> ).	<i>Isatis Indigotica</i> significantly inhibited SARS 3CL <sup>PRO</sup> . Of the 5 compounds, <i>sinigrin</i> , <i>β-sitosterol</i> , and <i>indigo</i> dose-dependently inhibited 3CL <sup>PRO</sup> . <i>Sinigrin</i> was more efficient than <i>indigo</i> and <i>β-sitosterol</i> . <i>Aloe-emodin</i> and <i>hesperidin</i> also dose-dependently inhibited the cleavage activity of 3CL <sup>PRO</sup> . <i>Indigo</i> , <i>sinigrin</i> , and <i>hesperidin</i> showed low cytotoxicity.
* <b>Chen et al., 2005</b> <sup>37</sup>	A library of 720 natural compounds was screened for inhibitory activity against SARS-CoV 3CL <sup>PRO</sup> . Green, Oolong, Pu'er, and black teas were investigated for the same inhibitory property.	<i>Tannic acid</i> , the polyphenols 3- <i>isothaeflavin-3-gallate</i> , and <i>theaflavin-3,3'-digallate</i> (TF3) found in teas potently inhibited 3CL <sup>PRO</sup> . The extract from Pu'er and black teas were more potent in inhibiting 3CL <sup>PRO</sup> than green or oolong teas. <i>Caffeine</i> , <i>theophylline</i> (TP), <i>epigallocatechin gallate</i> (EGCG), <i>epicatechin</i> (EC), <i>catechin</i> (C), <i>epicatechin gallate</i> (ECG), and <i>epigallocatechin</i> (EGC) did not inhibit 3CL <sup>PRO</sup> at concentrations up to 100 μM.
* <b>Chen et al., 2005</b> <sup>38</sup>	26 <i>Isatin</i> derivative compounds (from <i>Isatis Indigotica</i> ) were examined for inhibitory activity against SARS-CoV 3CL <sup>PRO</sup> .	<i>Some Isatin</i> compounds are potent and selective inhibitors against the SARS-CoV 3CL <sup>PRO</sup> . <i>Isatin</i> 4a and 4k were especially more potent.
<b>Li et al., 2005</b> <sup>67</sup>	200 Chinese medicinal herbal extracts historically used for the treatment of virus-induced infections were screened for antiviral activities against the SARS-CoV. Interferon-α (IFN-α) was used as a positive control.	<i>Lycoris radiata</i> , <i>Artemisia annua</i> , <i>Pyrrosia lingua</i> , <i>Lindera aggregate</i> , and the compound <i>Lycorine</i> (from <i>L. radiata</i> ) showed moderate to potent antiviral activity in a dose-dependent manner. <i>Lycoris radiata</i> was the most potent. Inhibition of the four herbs was stronger than the control IFN-α.
* <b>Liu &amp; Zhou, 2005</b> <sup>40</sup>	The study screened and tested 8078 compounds from the Marine Natural Products Database (MNPd) and 9127 compounds from the Traditional Chinese Medicine Database (TCMD) to evaluate their molecular docking affinity to the SARS-3CL <sup>PRO</sup> .	18 compounds, 7 compounds from MNPd and 11 compounds from TCMD showed anti-SARS-CoV 3CL <sup>PRO</sup> activity (M3927, M4367, M4890, M5410, M5789, M6601, M6602, T1434, T1441, T2826, T2831, T4744, T537, T5656, T6791, T8593, T3091, T5242).
* <b>Zhou et al., 2006</b> <sup>41</sup>	A series of 23 <i>Isatin</i> derivatives (from <i>Isatis indigotica</i> ) were synthesized and tested against the SARS-CoV 3CL <sup>PRO</sup> .	<i>Isatin</i> compound 5f was the most selective inhibitor against SARS CoV 3CL <sup>PRO</sup> . It was also a potent inhibitor against HRV-14 3C protease, and it may be used as a broad-spectrum antiviral agent.
* <b>Chen et al., 2006</b> <sup>42</sup>	8 <i>quercetin-3-β-galactoside</i> derivatives were synthesized and studied for their binding affinity to SARS-CoV 3CL <sup>PRO</sup> .	<i>Quercetin-3-β-galactoside</i> was identified as a new class of drug and a potent inhibitor of SARS-CoV 3CL <sup>PRO</sup> .
* <b>Ho et al., 2007</b> <sup>72</sup>	312 controlled Chinese medicinal herbs were screened for its inhibitory activity against the SARS-CoV Spike (S) protein. Due to a similar chemical structure, <i>emodin</i> was compared to the promazine, an anti-psychotic drug shown to inhibit the replication of SARS-CoV.	<i>Rhei Radix et Rhizoma</i> , <i>Polygoni multiflora radix</i> , and <i>Polygoni multiflora Caulis</i> inhibited the CoV S protein. Also, <i>emodin</i> , an <i>anthraquinone</i> compound derived from <i>Rheum officinalis</i> and <i>Polygonum multiflorum</i> significantly blocked the S protein/ACE-2 interaction in a dose-dependent manner. When compared to <i>emodin</i> , <i>promazine</i> exhibited a higher inhibition, yet differences between them were not significant.



Table 1 (continued)

Studies	Tested substances - drugs, medicinal herbs, natural compounds, and synthetic substances	Results - Herbs and natural compounds with antiviral properties
*Wang et al., 2007 <sup>43</sup>	The Traditional Chinese Medicine Database (TCMD) was used to screen more than 10,458 natural molecules. MDL28170 was used as a template as it was shown to inhibit CTSL activity during the entry of the SARS-CoV into the target cell.	MOL 736 ( <i>Aurantiamide acetate</i> from <i>Artemisia annua</i> ) inhibited the activity of CTSL in the molecular docking analysis. MOL 736 was more “matchable” than MDL28170.
*Wen et al., 2007 <sup>52</sup>	221 phytochemicals were evaluated for activity against the SARS-CoV. <i>Niclosamide</i> and <i>valinomycin</i> were used as controls for their potent anti-SARS-CoV replicative activity.	20 newly identified phytochemicals exhibited significant levels of anti-SARS-CoV activity: 10 <i>diterpenoids</i> , 2 <i>sesquiterpenoids</i> , 2 <i>triterpenoids</i> , 5 <i>lignoids</i> , and <i>curcumin</i> , <i>Betulinic acid</i> and <i>savinin</i> were competitive inhibitors of SARS-CoV 3CL <sup>PRO</sup> .
*Lau et al., 2008 <sup>39</sup>	The antiviral and immunomodulatory effects of the water extract of <i>Houttuynia cordata</i> were investigated using a murine model.	<i>Houttuynia cordata</i> (HC) exhibited antiviral and immunomodulatory properties that can help prevent the SARS-CoV infection. HC inhibited SARS-CoV 3CL <sup>PRO</sup> and RdRp, and it was non-toxic after administration to lab animals (16 g/kg).
*Kim et al., 2008 <sup>93</sup>	The effects of 22 medicinal herbal extracts were evaluated for their antiviral activity against CoV (MHV-A59), porcine epidemic diarrhea virus (PDEV), and vesicular stomatitis virus (VSV) in-vitro.	<i>Cimicifuga rhizome</i> , <i>Melia cortex</i> , <i>Coptidis rhizome</i> , <i>Phellodendron cortex</i> , and <i>Sophora subprostrata radix</i> inhibited MHV activity, and reduced viral RNA synthesis, and S and N protein expression. <i>Coptidis rhizome</i> completely abolished MHV production. RNA synthesis was significantly decreased suggesting that the underlying antiviral mechanism might be RdRp inhibition.
Chen et al., 2008 <sup>112</sup>	Formulas-herbs from the TCM classical medical texts <i>Shang Han Lun</i> and <i>Wen Bing Tiao Bian</i> were screened for their possible antiviral activity against the SARS-CoV (strain FFM1) and HCoV 229E. Several other herbs in addition to a popular vegetable <i>Toona sinensis</i> (AKA <i>Cedrela sinensis</i> ) were suggested by experienced by TCM doctors for testing.	Only TSL-1, the extract of <i>Toona sinensis Roem</i> was found to have anti-SARS-CoV activity.
Zhuang et al., 2009 <sup>68</sup>	The water extract of 7 medicinal herbs was tested for anti-SARS-CoV and anti-ACE-2 properties: <i>Forsythiae fructus</i> , <i>Scutellaria radix</i> , <i>Bupleuri radix</i> , <i>Astragali radix</i> , and <i>Glycyrrhizae radix</i> , and 4 fractionated samples of <i>Cinnamomi cortex</i> (CC) and <i>Caryophylli Flos</i> (CF). The 4 fractions were ethanol (Fr.1), n-butanol (Fr.2), aqueous (Fr.3), and ethylacetate (Fr.4) extractions. Eight (8) compounds isolated from CC were also tested.	Only the extracts of <i>Cinnamomi cortex</i> (CC) and <i>Caryophylli Flos</i> (CF) showed slight to moderate antiviral activity. All CC and CF fractions showed inhibitory activity, but CC/Fr. 2 was the most potent. The CC fractionated compounds procyanidin A2 and procyanidin B1 showed moderate anti-SARS-CoV activity. The compounds did not affect ACE-2.
*Ryu et al., 2010 (a) <sup>44</sup>	12 phytochemicals (8 <i>diterpenoids</i> and 4 <i>biflavonoids</i> ) were isolated from <i>Torreya nucifera</i> and examined for their anti-3CL <sup>PRO</sup> activity. <i>Abietic acid</i> , <i>apigenin</i> , <i>luteolin</i> , and <i>quercetin</i> were also evaluated.	The ethanol extract of <i>Torreya nucifera</i> exhibited inhibitory activity against 3CL <sup>PRO</sup> . From the diterpenoids, <i>ferruginol</i> (3) was the strongest anti-SARS-CoV 3CL <sup>PRO</sup> . Among the isolated bioflavonoids, <i>amentoflavone</i> (9) was the most potent inhibitor of SARS-CoV 3CL <sup>PRO</sup> . <i>Apigenin</i> , <i>luteolin</i> , and <i>quercetin</i> were also strong inhibitors.
*Ryu et al., 2010 (b) <sup>45</sup>	Isolated <i>quinone-methide triterpenes</i> ( <i>celastrol</i> , <i>pristimerin</i> , <i>tingenone</i> , <i>iguesterin</i> ) from <i>Tripterygium regelii</i> , and the semi-synthetic <i>dihydrocelastrol</i> were evaluated for anti-SARS-3CL <sup>PRO</sup> activity. <i>Curcumin</i> was used as a positive control which is known to inhibit 3CL <sup>PRO</sup> .	<i>Tripterygium regelii</i> remarkably inhibited SARS-CoV 3CL <sup>PRO</sup> activity (>70% inhibition at 30 µg/ml). <i>Celastrol</i> , <i>pristimerin</i> , <i>tingenone</i> , and <i>iguesterin</i> showed potent anti-SARS-3CL <sup>PRO</sup> activity, and <i>dihydrocelastrol</i> also showed SARS-3CL <sup>PRO</sup> inhibitory activity, although less.
*Kim et al., 2010 <sup>59</sup>	19 TCM herbal extracts were evaluated for antiviral activity against MHV-A59. The extracts were also tested against the John Howard Mueller strain of MHV (MHV-JHM), porcine diarrhea virus (PEDV), and vesicular stomatitis virus (VSV). Ribavirin was used as a control.	<i>Sophorae radix</i> , <i>Acanthopanax cortex</i> , <i>Sanguinobae radix</i> , and <i>Torilis fructus</i> showed in-vitro antiviral activity reducing or completely inhibiting MHV-A59. All 4 herbs were stronger CoV inhibitors than ribavirin. <i>Sophorae radix</i> had the highest selectivity index. <i>Sophorae radix</i> , <i>Acanthopanax cortex</i> , and <i>Torilis fructus</i> reduced mRNA7 and N protein synthesis, while <i>Sanguinobae radix</i> only decreased N protein synthesis without significant reduction in intracellular RNA levels.
*Schwarz et al., 2011 <sup>35</sup>	<i>Emodin</i> was investigated for anti-SARS-CoV 3a protein in-vivo and in-vitro.	<i>Emodin</i> is a potent inhibitor of 3a ion channel of SARS-CoV and HCoV-OC43. In the plaque reduction assay emodin showed antiviral property in a dose-dependent manner. <i>Emodin</i> at 100 µM inhibited viral release by 20% and with 100 µM it completely inhibited viral release.
*Wen et al., 2011 <sup>64</sup>	More than 200 extracts from Chinese medicinal herbs were evaluated for anti-SARS-CoV activity. <i>Valinomycin</i> was used as reference control with high inhibition. For the SARS-CoV 3CL inhibition assay, <i>niclosamide</i> was used as a reference control.	The herbal extracts of <i>Gentiana radix</i> (GSH), <i>Dioscorea rhizome</i> (DBM), <i>Cassiae semen</i> (CTH), <i>Loranthi ramus</i> (TCH), and CBE and CBM (extracts from <i>Rhizoma cibotii</i> , the root of <i>Cibotium barometz</i> ) were potent inhibitors of SARS-CoV with little or no cytotoxicity. Although the <i>valinomycin</i> was more potent, these 6 herbs significantly inhibited SARS-CoV. CBM and DBM showed significant inhibition of SARS-CoV 3CL <sup>PRO</sup> activity.
Yin et al., 2011 <sup>113</sup>	<i>Houttuynia cordata</i> (HC) was investigated in-vitro, in-vivo and in-ovo for antiviral properties against the avian infectious bronchitis virus (IBV). Also, the effect of HC on cell apoptosis induced by IBV was investigated.	<i>Houttuynia cordata</i> had more than 90% inhibition rate against the IBV infection, and decreased more than 90% apoptotic cells caused by the virus. The inhibitory effects of HC on IBV infection in-ovo protected the SPF embryos from death with no adverse effects. However, the treatment of chickens with HC did not fully protect against IBV.
*Yu et al., 2012 <sup>65</sup>	The researchers examined 64 purified natural compounds against the SARS-CoV helicase (nsP13) protein and the HCV helicase.	<i>Myrecetin</i> and <i>Scutellarin</i> (from <i>Scutellaria Baicalensis</i> ) potently inhibited the SARS-CoV helicase protein in-vitro by affecting ATPase activity by more than 90% at a concentration of 10 µM, but with no unwinding activity or cytotoxicity. Other compounds such as <i>myricitrin</i> , <i>amentoflavone</i> , <i>diosmetin-7-O-Glc-Xyl</i> , and <i>taraxerol</i> also inhibited nsP13.
Chang et al., 2012 <sup>53</sup>	23 compounds were isolated from <i>Euphorbia nerifolia L.</i> , including 22 <i>triterpenoids</i> and 1 <i>flavonoid glycoside</i> , and tested for their antiviral activity against the human coronavirus (HCoV-229E). <i>Actinomycin D</i> was used as a positive control.	13 new compounds were isolated from <i>Euphorbia nerifolia L.</i> for the first time. <i>3β-Friedelanol</i> exhibited more potent anti-viral activity (132.4%) than the positive control, <i>Actinomycin D</i> (69.5%).

(continued on next page)

Table 1 (continued)

Studies	Tested substances - drugs, medicinal herbs, natural compounds, and synthetic substances	Results - Herbs and natural compounds with antiviral properties
*Park et al., 2012 <sup>63</sup>	Seven <i>tanshinone</i> isolates from <i>Salvia miltiorrhiza</i> were investigated for SARS-CoV 3CL <sup>PRO</sup> and PL <sup>PRO</sup> inhibition, and deubiquitinating (DUB) enzyme activities. <i>Tanshinones</i> : <i>tanshinone IIA</i> (1), <i>tanshinone IIB</i> (2), <i>methyl tanshinonate</i> (3), <i>cryptotanshinone</i> (4), <i>tanshinone I</i> (5), <i>dihydrotanshinone I</i> (6), and <i>rosmariquinone</i> (7).	The ethanol extract from <i>Salvia Miltiorrhiza</i> inhibited both proteases SARS-3CL <sup>PRO</sup> (60%) and PL <sup>PRO</sup> (80%) at 30 µg/ml. The <i>tanshinone</i> compounds (1-7) showed marked inhibitory activity against the SARS-CoV 3CL <sup>PRO</sup> and PL <sup>PRO</sup> . The isolate <i>tanshinone I</i> (5) exhibited the most potent inhibitory activity toward deubiquitinating.
*Park et al., 2013 <sup>46</sup>	The study investigated 9 <i>phlorotannins</i> (1-9) isolated from the edible algae <i>Ecklonia cava</i> for their anti-SARS-3CL <sup>PRO</sup> inhibitory activity. Isolated compounds: 1. <i>Phloroglucinol</i> , 2. <i>Triphloretol</i> , 3. <i>Eckol</i> , 4. <i>Dioxinodehydroeckol</i> , 5.2- <i>phloroecol</i> , 6.7- <i>phloroecol</i> , 7. <i>Fucodiphloroethol</i> , 8. <i>Dieckol</i> , 9. <i>Phlorofucofuroeckol</i> .	Isolates 2-9 of <i>Ecklonia cava</i> showed SARS-CoV 3CL <sup>PRO</sup> inhibitory activity in a dose-dependent and competitive manner with no toxicity. <i>Dieckol</i> (8) showed the most potent anti-SARS-CoV 3CL <sup>PRO</sup> activity.
*Cho et al., 2013 <sup>95</sup>	The study investigated the SARS-CoV PL <sup>PRO</sup> inhibitory activities of the methanol extract of <i>Paulownia tomentosa</i> fruits and its 12 flavonoid (1-12) isolates.	Most compounds (1-12) from <i>P. tomentosa</i> inhibited SARS-PL <sup>PRO</sup> in a dose-dependent manner in-vitro. All the newly discovered geranylated flavonoid compounds (1-5) ( <i>tomentin A</i> , <i>tomentin B</i> , <i>tomentin C</i> , <i>tomentin D</i> , <i>tomentin E</i> ) showed better inhibition than their parent compounds.
*Schwarz et al., 2014 <sup>65</sup>	The researchers tested the inhibitory activity of the <i>flavonols kaempferol</i> , <i>kaempferol glycosides</i> , and <i>acylated kaempferol glucoside derivatives</i> against the SARS-CoV 3a protein in-ovo. Other flavonoids such as <i>quercetin</i> , <i>naringenin</i> , and <i>genistein</i> were also tested.	Five (5) <i>kaempferol glycosides</i> ( <i>kaempferol</i> , <i>juglanin</i> , <i>tilioside</i> , <i>afzelin</i> , and <i>Kaempferol-3-O-<math>\alpha</math>-rhamnopyranosyl(1 <math>\rightarrow</math> 2) [<math>\alpha</math> rhamnopyranosyl(1 <math>\rightarrow</math> 6)]-<math>\beta</math>-glucopyranoside)</i> inhibited 3a protein. <i>Juglanin</i> was a potent 3a protein inhibitor and produced nearly complete inhibition (10 µM) or complete inhibition (20 µM). The <i>kaempferol glycosides tilioside</i> and <i>afzelin</i> , although less potent than <i>juglanin</i> , also inhibited 3a protein. <i>Quercetin</i> , <i>naringenin</i> , and <i>genistein</i> did not affect 3a protein.
*Liu et al., 2014 <sup>47</sup>	A series of 5-sulfonyl isatin derivatives (from <i>Isatis indigotica</i> ) were designed, synthesized and evaluated for anti-SARS-CoV 3CL <sup>PRO</sup> activity.	A series of compounds showed inhibitory activity against SARS-3CL <sup>PRO</sup> . Compounds 7a-m, 7i and 7k showed the highest inhibition. Among the compounds 8, 8k1 and 8k2 were the most potent. Compounds 3f and 3h showed high inhibitory activities (95.32% and 95.37%).
*Song et al., 2014 <sup>96</sup>	The methanol extract of <i>Tribulus terrestris</i> fruits and the fractioned 6 cinnamic amides (1-6) and ferulic acid (7) were investigated for anti-SARS-CoV PL <sup>PRO</sup> activity. Compounds: 1. <i>N-trans-caffeoyltyramine</i> , 2. <i>N-trans-coumaroyltyramine</i> , 3. <i>N-trans-feruloyltyramine</i> , 4. <i>terrestriamide</i> , 5. <i>N-trans-feruloyloctopamine</i> , 6. <i>terrestimine</i> , and 7. <i>ferulic Acid</i> .	<i>T. terrestris</i> showed potent activity against SARS-CoV PL <sup>PRO</sup> . Compounds 1-6 displayed significant PL <sup>PRO</sup> inhibitory activity. <i>Terrestimine</i> (6) was the most potent, and ferulic acid was inactive against PL <sup>PRO</sup> up to 200 µM.
Chiu et al., 2016 <sup>62</sup>	The study evaluated the activities of ethyl acetate (EA) fraction of <i>Houttuynia cordata</i> and three of its flavonoids, <i>quercetin</i> , <i>quercitrin</i> , and <i>rutin</i> against the SARS-CoV and Dengue using the MHV and DEN-2 virus models. The compounds were compared with <i>Cinanserin hydrochloride</i> which was proven to neutralize SARS-CoV in-vitro.	The EA fraction of <i>Houttuynia cordata</i> inhibited both MHV and DEN-2 in-vitro. HC exerted antiviral activity with no cytotoxicity in-vitro and in-vivo. <i>Quercetin</i> also inhibited both MHV and DEN-2. <i>Quercitrin</i> inhibited DENV-2, but not MHV. <i>Rutin</i> did not show an inhibitory effect on both viruses.
*Park et al., 2016 <sup>48</sup>	The isolates of <i>Angelica keiskei</i> , 9 <i>anlylated chalcones</i> (1-9) and 4 <i>coumarins</i> (10-13) were examined for their anti-SARS-CoV 3CL <sup>PRO</sup> and PL <sup>PRO</sup> activity. Compounds: <i>isobavachalcone</i> (1), <i>4-hydroxyderricin</i> (2), <i>xanthoangelol</i> (3), <i>xanthoangelol F</i> (4), <i>xanthoangelol D</i> (5), <i>xanthoangelol E</i> (6), <i>xanthoangelol B</i> (7), <i>xanthoangelol G</i> (8), <i>xanthokeistal</i> (9), <i>psoralen</i> (10), <i>bergapten</i> (11), <i>xanthotoxin</i> (12), <i>isopimpinellin</i> (13).	The ethanol extract of <i>Angelica keiskei</i> significantly inhibited 3CL <sup>PRO</sup> (75% inhibition at 30 µg/ml) and PL <sup>PRO</sup> (88% at 30 µg/ml). All of the isolated compounds (1-13) except the <i>coumarin</i> derivatives (10-13) showed a dose-dependent inhibitory activity against the SARS-CoV 3CL <sup>PRO</sup> . <i>Chalcone 6 (xanthoangelol E)</i> exhibited the most potent anti-SARS 3CL <sup>PRO</sup> and PL <sup>PRO</sup> inhibitory activity. All 13 isolates also showed potent activity against <i>ubiquitin</i> and <i>ubiquitin-like</i> proteins.
*Park et al., 2017 <sup>90</sup>	The study investigated the inhibitory activity of <i>Broussonetia papyrifera</i> -derived polyphenols against SARS-3CL <sup>PRO</sup> and PL <sup>PRO</sup> in-vitro. Isolated compounds: <i>broussochalcone B</i> (1), <i>broussochalcone A</i> (2), <i>4-hydroxyisolonchocarpin</i> (3), <i>papyriflavonol A</i> (4), <i>30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavane</i> (5), <i>kazinol A</i> (6), <i>kazinol B</i> (7), <i>brousoflavan A</i> (8), <i>kazinol F</i> (9), <i>kazinol J</i> (10). Additionally, <i>isoliquiritigenin</i> , <i>kaempferol</i> , <i>quercetin</i> and <i>quercetin-<math>\beta</math>-galactoside</i> were also tested.	All polyphenols (1-10) were potent inhibitors of SARS-PL <sup>PRO</sup> , more than against 3CL <sup>PRO</sup> . Compound 4 ( <i>papyriflavonol A</i> ) was the most potent against SARS-CoV PL <sup>PRO</sup> and presented the highest deubiquitination and deISGylation inhibitory activity.
*Kim et al., 2019 <sup>108</sup>	The study evaluated the antiviral properties against the compounds isolated from <i>Stephania tetrandra</i> and other related species of <i>Menispermaceae</i> against the HCoV-OC43. Compounds: <i>bis-benzylisoquinoline alkaloids-tetrandine</i> (TET), <i>fangchinoline</i> (FAN), and <i>cepharanthine</i> (LEP).	<i>Stephania tetandra</i> , TET, FAN, and LEP significantly inhibited HCoV-OC43 replication in a time- and dose-dependent manner with no cytotoxicity even with high concentrations. The three compounds inhibited S and N protein expression, and experiments indicated that they can be applied for the prevention and treatment of HCoV infection. Compounds also reduced the expression of the cytokines IL-1 $\beta$ , IL-6 and IL-8.
Weng et al., 2019 <sup>109</sup>	The study investigated the antiviral activity of ethanol extract of <i>Sambucus FormosanaNakai</i> stem and some phenolic constituents against the HCoV-NL63 in-vitro. Phenolic acid constituents: <i>caffeic acid</i> , <i>chlorogenic acid</i> , <i>coumaric acid</i> , <i>ferulic acid</i> , and <i>gallic acid</i> .	<i>S. FormosanaNakai</i> inhibited HCoV-NL63 virus yield, plaque formation, and viral attachment with low toxicity in a concentration-dependent manner. The in-vitro antiviral activity was ranked according to virus yield reduction: <i>caffeic acid</i> > <i>chlorogenic acid</i> > <i>coumaric acid</i> . <i>Caffeic acid</i> was the strongest inhibitor of HCoV-NL63 and powerfully reduced the viral attachment to the cell surface and plaque formation.
Shen et al., 2019 <sup>60</sup>	A 2000-compound library of FDA-approved drugs and pharmacologically active compounds were screened for an in-vivo and in-vitro study to assess the broad-spectrum antiviral properties against the HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59. Control: dimethyl sulfoxide (DMSO)	The in-vitro antiviral activity of 36 compounds against wild-type HCoV-OC43 was confirmed. 17 compounds inhibited HCoV-NL63, 13 compounds inhibited MERS-CoV, and 12 compounds inhibited MHV-A59. 7 compounds were identified as broad-spectrum inhibitors of the 4 CoVs in-vitro in a dose-dependent manner ( <i>lycorine</i> , <i>emetine</i> , <i>monensin sodium</i> , <i>mycophenolate mofetil</i> , <i>lycophenolic acid</i> , <i>phenazopyridine</i> , and <i>pyrvinium pamoate</i> ). All 7 compounds significantly inhibited HCoV-OC43 (90% inhibitory effect). <i>Lycorine</i> (from <i>Lycoris radiata</i> ) was the most potent antiviral compound against all 4 viruses.


Table 1 (continued)

Studies	Tested substances - drugs, medicinal herbs, natural compounds, and synthetic substances	Results - Herbs and natural compounds with antiviral properties
*Tsai et al., 2020 <sup>114</sup>	This study investigated the antiviral activity of the methanol extract of <i>Strobilanthes cusia</i> leaf and its chemical components against the anti-HCoV-NL63. The researchers also investigated the anti-RdRp and anti-PL <sup>PRO</sup> activity of the compounds. <i>S. cusia</i> components: $\beta$ -sitosterol, indirubin, tryptanthrin, betulin, indigodole A, and indigodole B.	<i>S. cusia</i> potentially inhibited virus yield and viral infectivity of HCoV-NL63-infected cells in a concentration-dependent manner. Tryptanthrin showed the strongest antiviral activity. It prevented the early and late stages of viral replication and significantly inhibited RdRp and PL <sup>PRO</sup> 2 activity. Indigodole B was the second-highest to reduce HCoV-NL63. Both tryptanthrin and indigole B showed low cytotoxicity.
*Zhang et al., 2020 <sup>50</sup>	A literature search for natural compounds with confirmed anti-SARS-CoV or MERS-CoV activity was conducted. The resulting compounds were cross-checked with the TCM Systems Pharmacology Database. The study aimed to identify compounds that would be potentially protective against the SARS-CoV-2 (2019).	The antiviral activity of 115 natural compounds was confirmed. After Absorption, Distribution, Metabolism, and Excretion (ADME) evaluation, thirteen (13) compounds were found to have anti-SARS-CoV-2 (2019) activity. 125 herbs contained one or more of these 13 compounds. Of these 125 herbs, 26 are classically cataloged to treat viral respiratory infections. For all plants analyzed, nearly half of the top 30 pathways are related to antiviral, immune, inflammatory and hypoxia responses indicating that these herbs are suitable for antiviral use. Molecular docking identified a series of compounds that inhibited 3CL <sup>PRO</sup> , PL <sup>PRO</sup> and S protein (see Fig. 1). TCM classical treatments used for viral respiratory infections might contain direct anti-2019-nCoV compounds.
*Khan et al., 2020 <sup>49</sup>	Database of natural and synthetic molecules and 16 FDA-approved drugs were screened and tested for their inhibitory activity against SARS-CoV-2 3CL <sup>PRO</sup> .	Remdesivir, Saquinavir, Darunavir, and the natural compounds flavone and coumarin derivatives exhibited inhibitory activity against SARS-CoV 3CL <sup>PRO</sup> . Saquinavir showed the highest binding affinity.
*Wu et al., 2020 <sup>2</sup>	Molecular docking simulations were performed to identify the drugs, herbs, natural compounds, and synthetics that would inhibit/block 3CL <sup>PRO</sup> , PL <sup>PRO</sup> , RdRp, helicase, Spike protein, ACE-2, and other protein pathways of the SARS-CoV-2. Several databases were screened such as the FDA approved drug database (ZINC drug database) containing 2924 compounds, TCM herbs and natural products database including reported common antiviral components with 1066 substances, and database of commonly used antiviral drugs containing 78 antiviral compounds. The complete genome of the Wuhan-Hu-1 SARS-CoV was downloaded from the NCBI nucleotide database and used for this study. Studies on the homology encoded proteins of the SARS-CoV-2 in comparison with the SARS-CoV-1 were performed.	<b>For the mechanisms of action of the herbs and natural compounds on SARS-CoV-2, see Fig. 1.</b> <b>Drugs that may inhibit SARS-CoV-2 PL<sup>PRO</sup>:</b> ribavirin, valganciclovir, $\beta$ -thymidine (antiviral); doxycycline, chloramphenicol, cefamandole, tigecycline (antibacterial); chlorphenesin carbamate (muscle relaxant); and levodropropizine (anti-tussive), and others. Also, $\iota(+)$ -Ascorbic acid, glutathione, hesperidin and sildenafil (for erectile dysfunction) showed potential as PL <sup>PRO</sup> inhibitors. <b>Drugs that may inhibit 3CL<sup>PRO</sup>:</b> lymecycline, chlorhexidine, demeclocycline, doxycycline, tigecycline, oxytetracycline (antibacterial); alfuzosin, nicardipine, telmisartan (anti-hypertensive); and conivaptan (used for hyponatremia), and others. Montelukast (asthma medication) and lutein also showed potential as 3CL <sup>PRO</sup> inhibitor. <b>Potential drugs inhibitors of SARS-CoV-2 RdRp:</b> valganciclovir (antivirus), itraconazole (anti-fungal); chlorhexidine, cefibuten, cefuroxime, novobiocin (antibacterial); atovaquone (antimalarial), chenodeoxycholic acid (gall-dissolving drug); cortisone (anti-allergic); fludarabine, idarubicin (anti-tumor); silybin (hepatoprotective); pancuronium bromide (muscle relaxant); dabigatran etexilate (anti-coagulant), and others. <b>Drugs that would inhibit SARS-CoV-2 helicase protein:</b> lymecycline, cefsulodine, rolitetracycline (antibacterial); itraconazole (anti-fungal); saquinavir (anti-HIV-1); dabigatran (anti-coagulant); and canrenoic acid (diuretic). <b>Possible SARS-CoV-2 anti-Spike protein drug inhibitors:</b> rescinamine, iloprost, prazosin (anti-hypertensive); poconazole, itraconazole (anti-fungal); sulfasalazine, azlocillin, penicillin, cefsulodin (antibacterial); and dabigatran etexilate (anti-coagulant). <b>Drugs that may inhibit Nsp1, Nsp3c, and ORF7a:</b> piperacillin, cefpiramide, streptomycin, lymecycline, and tetracycline. <b>Potential host ACE-2 inhibitors:</b> troglitazone (anti-diabetes), losartan (anti-hypertensive), ergotamine (analgesic), cefmenoxime (anti-bacterial), and silybin (hepatoprotective). <b>Potential TMPRSS2 inhibitors:</b> pivampicillin, hetacillin, cefoperazone, and clindamycin (antibacterial).


biochemical and immunological assays are applied, and the investigations are developed with a multi-layered methodology. Although the methodologies of the included articles in this review are varied and complex, there is a coherence and a certain commonality in designing the experiments. Ultimately, the goal is to identify the substances with antiviral properties against the SARS-CoV. In addition to detecting the antiviral properties, some studies also aspired to uncover the specific molecular mechanism(s) by which herbs-natural compounds would act against the SARS-CoV. Researchers used complementary techniques to identify these mechanism(s) such as fluorescence resonance energy transfer

(FRET), SARS-CoV 3CL protease (3CL<sup>PRO</sup>) and papain-like protease (PL<sup>PRO</sup>) inhibition assays, SARS-CoV RdRp assay, SARS-CoV PL deubiquitination and deISGylation assays, and many others.<sup>36–39</sup> Several studies on drug discovery screened a database of hundreds or even thousands of existing substances to identify the best possible options for the CoV treatment (Table 1). To help determine the mechanisms of action, computer molecular docking simulations are often the choice because it is precise in locating the potential remedies. These docking analyses allow scientists to discover the capacity of small-molecule ligands to bind to three-dimensional proteins of the virus and host cells. The present

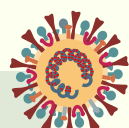
Coronavirus-Host Target Proteins		HERBS AND NATURAL COMPOUNDS
<b>A</b>	<b>S PROTEIN</b>	TGG (tetra-O-galloyl-β-D-glucose, from <i>Galla Chinensis</i> ) and luteolin; <i>Cimicifuga</i> rhizome, <i>Melia</i> cortex, <i>Coptidis</i> rhizome, <i>Phellodendron</i> cortex, and <i>Sophora subprostrata</i> radix; Compounds extracted from <i>Stephania tetandra</i> : bis-benzylisoquinoline alkaloids-tetrandine (TET), fangchinoline (FAN), and cepharanthine (LEP); Dihydrotanshinone I; Licoflavonol (from <i>Glycyrrhiza uralensis</i> ), cosmoisin (from <i>Scutellaria baicalensis</i> ), neohesperidin (from <i>Citrus aurantium</i> ), mangostin (from <i>Garcinia mangostana</i> ), kouitchenside D (from <i>Swertia kouitchensis</i> ), excoecariatoxin (from <i>Excoecaria agallocha</i> ), phyllaemblicin G7 (from <i>Phyllanthus emblica</i> ), and piceatannol (from <i>Vitis vinifera</i> ).
	<b>ACE-2</b>	Phyllaemblicin G7 (from <i>Phyllanthus emblica</i> ), xanthones (from the plants of <i>Swertiagenus</i> ), neohesperidin and hesperidin (from <i>Citrus aurantium</i> ).
	<b>S/ACE2 Interaction</b>	Emodin/ <i>Rhei Radix et Rhizoma</i> , <i>Polygoni multiflora</i> radix, and <i>Polygoni multiflora</i> Caulis; Hesperidin.
	<b>TMPRSS2</b>	Phyllaemblicin G7, neoandrographolide, kouitchenside I, and others.
	<b>CATHEPSIN L</b>	MOL 736 (Aurantiamide acetate from <i>Artemisia annua</i> ).
<b>B</b>	<b>3CL<sup>PRO</sup></b>	<i>Isatis Indigotica</i> , sinigrin, beta-sitosterol, indigo, aloe-emodin, and hesperidin; Tannic acid, 3-isothaflavin-3-gallate (TF2B), theaflavin-3,3'-digallate (TF3); Isatin derivatives (especially 4o and 4k); 18 natural compounds from MNPD and TCMD; Isatin compound 5f; Quercetin-3-β-galactoside; Betulinic acid and savinin; <i>Houttuynia cordata</i> ; <i>Torreya nucifera</i> / amentoflavone, apigenin, luteolin and quercetin; <i>Tripterygium regelii</i> / quinone-methide triterpenes - celastrol, pristimerin, tingenone, and iguesterin; and dihydrocelastrol; CBM (dried rhizome of <i>Cibotum barometz</i> ); DBM ( <i>Dioscorea</i> rhizome); <i>Salvia Miltiorrhiza</i> and its tanshinone compounds; <i>Ecklonia cava</i> and its isolates, especially dieckol; 5-sulfonyl isatin derivatives (especially compounds 7i, 7k, 8k1 and 8k2, and others); <i>Angelica keiskei</i> and its compounds, especially xanthoangelol E (chalcone 6); <i>Broussonetia papyrifera</i> polyphenols, especially papyriflavonol A (4); Coumaroyltyramine, Cryptotanshinone, Desmethoxyreserpine, Dihomo-γ-linolenic acid, Kaempferol, Lignan, N-cis-feruloyltyramine, Quercetin, Sugirol, and Tanshinone lia; Flavone and coumarin derivatives; Andrographolide derivatives, chrysin-7-O-β-glucuronide and cosmoisin (from <i>Scutellaria baicalensis</i> ), betulonal (from <i>Cassine xylocarpa</i> ), andrographiside and andrograpanin (from <i>Andrographis paniculata</i> ), 2β-hydroxy-3,4-seco-friedelolactone-27-oic acid, isodecortinol and cerevisterol (from <i>Viola diffusa</i> ), neohesperidin (from <i>Citrus aurantium</i> ), 2,2-Di(3-indolyl)-3-indolone (from <i>Isatis indigotica</i> ), theaflavin 3,3'-di-O-gallate (from <i>Camellia sinensis</i> ), rosmarinic acid (from <i>Salvia verticillata</i> ), kouitchenside I and oleanolic acid (from <i>Swertia</i> genus), and others.
	<b>PL<sup>PRO</sup></b>	<i>Salvia Miltiorrhiza</i> and its tanshinone compounds; <i>Paulownia tomentosa</i> flavonoid derivative compounds; <i>Tribulus terrestris</i> and its compounds; <i>Angelica keiskei</i> and its compounds, especially xanthoangelol E (chalcone 6); <i>Broussonetia papyrifera</i> polyphenols, especially papyriflavonol A (4); <i>Tryptanthrin</i> (from <i>Strobilanthes cusia</i> ); Coumaroyltyramine, Cryptotanshinone, Kaempferol, Moupinamide, N-cis-feruloyltyramine, Quercetin, Tanshinone IIa; Platycodin D (from <i>Platycodon grandiflorus</i> ), chrysin and baicalin (from <i>Scutellaria baicalensis</i> ), neohesperidin (from <i>Citrus aurantium</i> ), sugetriol-3,9-diacetate (from <i>Cyperus rotundus</i> ), phaitanthrin D and 2,2-di(3-indolyl)-3-indolone (from <i>Isatis indigotica</i> ), Epigallocatechin gallate (from <i>Camellia sinensis</i> ), piceatannol (from <i>Vitis vinifera</i> ), rosmarinic acid (from <i>Salvia verticillata</i> L.), magnolol (from <i>Magnolia officinalis</i> ), and others.
	<b>RdRp</b>	<i>Houttuynia cordata</i> ; <i>Cimicifuga</i> rhizome, <i>Melia</i> cortex, <i>Coptidis</i> rhizome, <i>Phellodendron</i> cortex, and <i>Sophora subprostrata</i> radix; <i>Tryptanthrin</i> (from <i>Strobilanthes cusia</i> ); Betulonal (from <i>Cassine xylocarpa</i> ), gnidicin and gniditrin (from <i>Gnidia lamprantha</i> ), 14-deoxy-11,12-didehydroandrographolide and andrographiside (from <i>Andrographis paniculata</i> ), theaflavin 3,3'-di-O-gallate (from <i>Camellia sinensis</i> ), baicalin (from <i>Scutellaria baicalensis</i> ), and others.
	<b>N protein</b>	<i>Cimicifuga</i> rhizome, <i>Melia</i> cortex, <i>Coptidis</i> rhizome, <i>Phellodendron</i> cortex, and <i>Sophora subprostrata</i> radix; <i>Sophorae</i> radix, <i>Acanthopanax</i> cortex, and <i>Torilis fructus</i> (↓ mRNA7 and N protein synthesis); <i>Sanguinobae</i> radix (only ↓ N protein synthesis); Compounds extracted from <i>Stephania tetandra</i> : bis-benzylisoquinoline alkaloids-tetrandine (TET), fangchinoline (FAN), cepharanthine (LEP).
	<b>Helicase</b>	Myrecetin/Scutellarin (from <i>Scutellaria Baicalensis</i> ); Flavonoids from different sources (α-glucosyl hesperidin, hesperidin, rutin, quercetagenin 6-O-β-D-glucopyranoside and homovitinexin), xanthones (kouitchenside H, kouitchenside A, kouitchenside D), triptexanthoside D (from <i>Swertia</i> genus), and others.
	<b>Nsp1, Nsp3c &amp; ORF7a</b>	Platycodin D (from <i>Platycodon grandifloras</i> ), wogonoside (from <i>Scutellaria baicalensis</i> ), Vitexin (from <i>Vitex negundo</i> ), andrographolide derivatives, and xanthones (from <i>Swertia</i> genus).
	<b>3a protein</b>	Emodin; Kaempferol glycosides (juglanin, kaempferol, tiliroside, afzelin, kaempferol-3-O-α-rhamnopyranosyl (1→2)[α-rhamnopyranosyl (1→6)]-β-glucopyranoside).



VIRUS REPRODUCTION



INHIBITION OF VIRUS REPRODUCTION



Fuzimoto & Isidoro, 2020

**Fig. 1.** Herbs and natural compounds able to inhibit the SARS-CoV-host protein pathways. Panel A corresponds to the proteins involved in the internalization of the CoV into the host cells; Panel B corresponds to further processes involved in translation, transcription, replication, assembly and egress from the host cells.



review located fourteen (14) studies that included this methodology.<sup>2,36,38,40–50</sup> Importantly, the studies investigating the antiviral properties and molecular mechanism(s) of conventional drugs and herbs-natural compounds against the SARS-CoV adopt the same (or very similar) experimental models and methodologies. As a matter of fact, some of these studies include and compare conventional drugs, whole herbs, natural and synthetic compounds in the same research.<sup>2,12,36,51</sup> For example, in a recently published study (2020), databases consisting of 2924 FDA-approved drugs, 1066 TCM herbs and natural products, and 78 antiviral compounds were analyzed by computational molecular docking against the SARS-CoV-2.<sup>2</sup>

Also, we verified that some studies tested the herbs and natural compounds using conventional drugs or other agents known for their antiviral action as a template or positive control.<sup>43,52,53</sup> Some examples are given such as *niclosamide* and *valinomycin*,<sup>52</sup> *actinomycin D*,<sup>53</sup> MDL28170<sup>43</sup>, and *curcumin*.<sup>44</sup> *Niclosamide* is an anti-parasitic drug and it was shown to inhibit dengue virus infection by hindering endosomal acidification.<sup>54</sup> *Valinomycin* is a potent antibiotic, and it blocked the entrance of poliovirus into the host cells.<sup>55</sup> *Actinomycin D* is a chemotherapy drug used for cancer, and it obstructed influenza virus RNA synthesis in-vivo.<sup>56</sup> MDL28170 is a compound known to inhibit the Cathepsin-L endosomal protease activity thus preventing the coronavirus cell entry.<sup>57</sup> Finally, *curcumin*, a compound extracted from *Curcuma longa*, ameliorated severe pneumonia caused by influenza A virus in-vitro and in-vivo, downregulated inflammatory cytokines and inhibited NF- $\kappa$ B signaling macrophages.<sup>58</sup> Worthy of note, one study took a step further on pharmacokinetics and assessed the absorption, distribution, metabolism, and excretion (ADME) of the orally administered herbs and natural compounds.<sup>50</sup>

#### 4.2. Antiviral properties of herbs and compounds against the SARS-CoV

The ideal therapeutic choices for the SARS-CoV need to show antiviral properties, have low cytotoxicity, few side effects, and good bioavailability. In general, the studies that used cell-based assays and additional techniques examined some of these requirements to elect the potential candidates (Table 1). As mentioned, the selected 43 studies showed antiviral properties of many herbs and natural compounds. Remarkably, in some experiments, various herbs even exceeded the antiviral properties of some conventional drugs at certain dosages and concentrations while presenting low cytotoxicity. For example,  $\beta$ -*Friedelanol* extracted from *Euphorbia nerifolia* L. exhibited a more potent antiviral activity than the positive control, actinomycin D.<sup>53</sup> In another study, *ribavirin* did not affect viral replication while *glycyrrhizin* extracted from *Glycyrrhiza radix* was the most active in inhibiting the clinical isolates of the CoV (FFM-1 and FF-M2).<sup>51</sup> A high concentration of *glycyrrhizin* (4000 mg/L) completely blocked the CoV replication with no toxic effects, yet the mechanism of action was not clarified.<sup>51</sup> However, in another research, *baicalin* isolated from *Scutellaria Baicalensis* was suggested for the SARS-CoV instead of *glycyrrhizin*. A small intravenous dosage of *baicalin* can achieve a much higher serum concentration when compared to *glycyrrhizin*.<sup>12</sup> In this case, the use of *baicalin* at 48h and 72h (EC<sub>50</sub> 12.5–25 and 25–50  $\mu$ g/ml) against 10 strains of SARS-CoV in the rRhK4 cell line surpassed *ribavirin* (EC<sub>50</sub> 12.5–200 and 50–200  $\mu$ g/ml) as well as *glycyrrhizin* (EC<sub>50</sub> > 400  $\mu$ g/ml).<sup>12</sup> Also, the herbs *Sophorae radix* (EC<sub>50</sub> 0.8  $\mu$ g/ml), *Pulsatillae radix* (EC<sub>50</sub> 6.1  $\mu$ g/ml), *Acanthopanax cortex* (EC<sub>50</sub> 0.9  $\mu$ g/ml), *Sanguisorbae radix* (EC<sub>50</sub> 3.7  $\mu$ g/ml), *Punicae cortex* (EC<sub>50</sub> 11.0  $\mu$ g/ml) and *Torilis fructus* (EC<sub>50</sub> 0.8  $\mu$ g/ml) were more potent inhibitors of MHV-59/CoV than *ribavirin* (EC<sub>50</sub> 17.5  $\mu$ g/ml).<sup>59</sup> In another study, a series of herbal

compounds showed strong antiviral activity against 4 types of CoVs when compared with several conventional drugs. *Lycorine* (EC<sub>50</sub> 0.15, 0.47, 1.63 and 0.31  $\mu$ M) and *emetine* (EC<sub>50</sub> 0.30, 1.43, 0.34 and 0.12  $\mu$ M) potently inhibited HCoV-OC43, HCoV-NL63, MERS-CoV and MHV-A59, in contrast with *chloroquine* (EC<sub>50</sub> 0.33, 4.89, 16.44 and 15.92  $\mu$ M), *valinomycin* (EC<sub>50</sub> 4.43, 1.89, 6.07 and 6.78  $\mu$ M), and *loperamide* (EC<sub>50</sub> 1.86, 6.47, 4.82 and 10.65  $\mu$ M), respectively.<sup>60</sup> Many other herbs and natural compounds exerted a strong replicative inhibition of the SARS-CoV and related viruses such as the-aflavins (IC<sub>50</sub> 3–9.5  $\mu$ M),<sup>37</sup> *Isatis indigotica* (IC<sub>50</sub> 53.8  $\mu$ g/ml),<sup>61</sup> isatins (from IC<sub>50</sub> 0.37+  $\mu$ M),<sup>38,41,47</sup> *Houttuynia cordata* (IC<sub>50</sub> 0.98  $\mu$ g/ml),<sup>62</sup> *diekol* from *Ecklonia cava* (IC<sub>50</sub> 2.7  $\mu$ M),<sup>46</sup> *hesperidin* (IC<sub>50</sub> 8.3  $\mu$ M),<sup>61</sup> *tanshinone* compounds from *Salvia Miltiorrhiza* (from IC<sub>50</sub> 0.7+  $\mu$ M),<sup>63</sup> *amentoflavone* extracted from *Torreya nucifera* (IC<sub>50</sub> 8.3  $\mu$ M),<sup>44</sup> the isolates *celastrol*, *pristimerin*, *tingenone*, *iguesterin* from *Tripterygium regelii* (IC<sub>50</sub> 2.6–10.3  $\mu$ M)<sup>45</sup>, *Gentiana radix*, *Dioscorea rhizome*, *Cassiae semen*, *Loranthi ramus*, and CBE and CBM (from *Rhizoma Cibotii*, the dried *rhizome Cibotium barometz*) (EC<sub>50</sub> 5.39 to >10  $\mu$ g/ml)<sup>64</sup>, *Myrecetin* and *Scutellarin* (from *Scutellaria Baicalensis*) (IC<sub>50</sub> 2.71 and 0.86  $\mu$ M, respectively),<sup>65</sup> and *juglanin*, a *Kaempferol-arabinoside* present *Kaempferia galangal* L. (IC<sub>50</sub> 2.3  $\mu$ M).<sup>66</sup> *Lycoris radiata*, *Pyrrosia lingua*, *Artemisia annua*, *Lindera aggregate*, and *lycorine* provided from moderate to potent antiviral activity with *Lycoris radiata* being the strongest (EC<sub>50</sub> 2.4  $\mu$ g/ml).<sup>67</sup> In contrast, other natural substances only exerted a moderate effect on the SARS-CoV such as *Cinnamoni cortex* and *Caryophylli Flos* (IC<sub>50</sub> < 100  $\mu$ g/ml).<sup>68</sup> The studies provided a long list of herbs, isolates, and derivatives to fuel the discussion on the clinical use and future development of antiviral remedies for the SARS-CoVs. Although the majority of the available studies focused on the SARS-CoV-1, three recent articles by Zhang et al. (2020), Khan et al. (2020), and Wu et al. (2020) presented an extended list of antiviral candidates specifically for the SARS-CoV-2.<sup>2,49</sup> Zhang et al. (2020), for example, listed the following herbs with antiviral activity against the SARS-CoV-2: *Forsythiae fructus*, *Licorice* (*Glycyrrhiza radix*), *Mori cortex*, *Chrysanthemi flos*, *Farfarae flos*, *Lonicerae japonicae flos*, *Mori follum*, *Peucedami radix*, *Rhizoma fagopyri cymosii*, *Tamaricis cacumen*, *Erigeron breviscapus*, *Radix bupleuri*, *Coptidis rhizoma*, *Houttuynniae herba*, *Hoveniae dulcis semen*, *Inulae flos*, *Eriobotryae folium*, *Hedysarum multijugum maxim.*, *Lepidii semen descurainiae semen*, *Ardisiae japonicae herba*, *Asteris radix et rhizoma*, *Euphorbiae helioscopiae herba*, *Ginkgo semen*, *Anemarrhenae rhizoma*, *Epimrdii herba*, and *Fortunes bossfern rhizoma*. A comprehensive summary of herbs-compounds with antiviral properties is reported in Table 1.

Regarding the cytotoxicity of the natural agents, many articles reported on their low or absent *in-vitro* cell toxicity. For instance, TGG (EC<sub>50</sub> 4.5  $\mu$ M) and *luteolin* (EC<sub>50</sub> 10.6  $\mu$ M) were more potent inhibitors of the wild-type SARS-CoV than *glycyrrhizin* (EC<sub>50</sub> > 607.6  $\mu$ M), while presenting low/no cytotoxicity (TGG CC<sub>50</sub> 1.08  $\mu$ M, SI 240; and *luteolin* CC<sub>50</sub> 0.155  $\mu$ M, SI 14.62).<sup>69</sup> *Quercetin* also showed antiviral activity against the HIV-luc/SARS pseudo-typed virus with low cytotoxicity (EC<sub>50</sub> 83.4  $\mu$ M; CC<sub>50</sub> 3.32 mM).<sup>69</sup> A variety of potent antiviral compounds exhibited substantially higher selectivity index (SI) than the control *valinomycin* (SI 41.4), also revealing little or no toxicity. These included *ferruginol* (SI 58), *dehydroabieta-7-one* (SI 76.3),  $8\beta$ -*hydroxyabieta-9(11),13-dien-12-one* (SI > 510),  $7\beta$ -*hydroxydeoxycryptojaponol* (SI 111),  $3\beta,12$ -*diacetoxyabieta-6,8,11,13-tetraene* (SI 193), *pinusolidic acid* (SI 159), *forskolin* (SI 89.8), *betulinic acid* (SI 180) and *savinin* (SI 667).<sup>52</sup> The water extract of *Houttuynia cordata* expressed strong antiviral activity against the SARS-CoV and was considered non-toxic to animals upon oral administration of 16 g/kg.<sup>39</sup> In addition to exerting a potent antiviral property, *myricetin* and *scutellarin* were non-toxic when tested against breast-derived epithelial MCF10A cells at

2  $\mu\text{M}$  dosages.<sup>65</sup> For the confirmed anti-HCoV-OC43 compounds *tetrandrine* (TET), *fangchinoline* (FAN) and *ceparanthine* (CEP) extracted from *Stephania tetrandra*, the  $\text{IC}_{50}/\text{CC}_{50}/\text{SI}$  were 0.33/13.41/40.19  $\mu\text{M}$ , 1.01/11.54/11.46  $\mu\text{M}$ , and 0.83/11.26/13.63  $\mu\text{M}$ , respectively.<sup>70</sup> Further clinical studies would verify the efficacy and safety of these compounds for humans through pharmacokinetics and cytotoxicity analyses.

#### 4.3. The SARS-CoV and host protein pathways

In the past years, a lot of progress was made in understanding how the coronavirus invades the host cells and replicate. CoVs are enveloped positive-sense RNA viruses and possess the largest genome of all RNA viruses (30 kilobase genomes).<sup>71</sup> Potential therapies against the CoV can be divided into two categories. They can block signaling pathways of human cells that are required by the virus to replicate, or they can act directly on the virus.<sup>2</sup> In the first case, therapies could inhibit or block the virus from binding to human cell receptors, preventing the viral entry and the spreading from cell to cell. In the second instance, the therapies could act on structural and functional proteins, enzymes, or the genetic material of the virus to inhibit RNA synthesis, replication or virus self-assembly.<sup>2</sup>

The CoV Spike (S) glycoprotein, which binds to the ACE-2 receptor of the human host, is essential for viral attachment and cell entry, and it is also involved in the fusion process.<sup>72–74</sup> Stopping the virus entry through a blockade of the S protein is important because it hinders the propagation of the virus at an early stage and prevents drug resistance.<sup>69</sup> After receptor binding, the second important step for viral entry is the fusion of the viral envelope with host cellular membranes that frees the virus genome into the cytoplasm.<sup>74</sup> The membrane fusion can happen directly with the host cell membrane (cell-surface non-endosomal pathway) or with endosome membrane (endosomal pathway).<sup>75</sup> Cathepsin L (CTSL), an endosomal protease is known to process the SARS-CoV S protein and to participate in the activation of membrane fusion.<sup>57,74</sup> The CoV membrane fusion happens through a three-step process which includes receptor binding and induced conformational changes of the S protein, followed by the CTSL proteolysis within the endosomes.<sup>57</sup> So, the S protein and CTSL play an important role in the internalization of the CoV, and are considered attractive targets for the development of new drugs. In addition, the host transmembrane protease serine-type 2 (TMPRSS2) activates the S protein and was shown, in-vitro, to induce virus cell-membrane fusion.<sup>76</sup> 3-Chymotrypsin-like protease (3CL<sup>PRO</sup> or nsp5), papain-like protease (PL<sup>PRO</sup> or nsp3), RNA-dependent RNA polymerase (RdRp or Nsp12), and helicase protein (nsp13) are the main targets for developing RNA synthesis and replication inhibitors.<sup>2</sup> Two-thirds of the CoV RNA is translated into two large polyproteins, pp1a and pp1ab that encode 16 non-structural proteins (nsp1–nsp16)<sup>75</sup>. These polyproteins are cleaved by the proteases PL<sup>PRO</sup> and 3CL<sup>PRO</sup>, a step necessary for the transcription, translation, and replication processes leading to new virions inside the host cells.<sup>75,77</sup> The cleavage of protein precursors releases key replicative enzymes such as RdRp and the helicase protein. The role of both 3CL<sup>PRO</sup> and PL<sup>PRO</sup> is to process the polyproteins to generate the various viral proteins. To be noted, PL<sup>PRO</sup> has the additional function of stripping ubiquitin and ISG15 from the host cell proteins to help the CoV escape the innate immune system.<sup>77</sup> The ubiquitin-like protein ISG15 is an interferon-induced protein that is believed to have an important role in the host antiviral defense.<sup>78</sup> RdRp is an indispensable enzyme for replicating the genome and the transcription cycle of RNA viruses.<sup>79</sup> Helicases are motor proteins that separate and rearrange nucleic acid duplexes in processes powered by adenosine triphosphate (ATP) hydrolysis.<sup>80</sup> The helicase protein

unwinds double-stranded DNA and RNA into single strands so they can be copied.<sup>81</sup> DNA helicases play a crucial role in replication, recombination and repair, and RNA helicases are instrumental for transcription, translation and RNA splicing.<sup>80</sup> The Nucleocapsid (N) protein is a multifunctional structural protein that is involved in the CoV life cycle and cellular response.<sup>82</sup> The N protein plays a key role in viral core formation, viral assembly, viral envelope formation and budding, and genomic mRNA replication and RNA synthesis.<sup>82</sup> It also participates in a series of cell processes that support the CoV pathogenesis.<sup>82</sup> The encoded ORF 3a protein is a transmembrane protein and it is believed to form an ion channel that modulates viral release.<sup>83</sup> Among the CoV virulence factors, Nsp1, Nsp3c, and ORF7a interfere with the host's innate immune response and assist the CoV immune escape.<sup>2</sup> The main target proteins that would intervene with the SARS-CoV-2 replicative process include Nsp1, Nsp3 (Nsp3b, Nsp3c, Papain-like protease (PLpro), and Nsp3e), Nsp7-Nsp8 complex, Nsp9-Nsp10, and Nsp14-Nsp16, E channel (E protein), ORF7a, Spike, angiotensin-converting-enzyme 2 (ACE-2), C-terminal RNA binding domain (CRBD), N-terminal RNA binding domains (NRBD), helicase, RdRp, and TMPRSS2.<sup>2</sup> All these proteins are potential candidates for designing new antiviral drugs capable of interfering with different phases of the viral life cycle.

##### 4.3.1. Herbal medicine and the inhibition/blockade of the coronavirus-host target protein pathways

During previous years, many drugs have been researched as inhibitors of the coronavirus-host protein pathways. For example, the combination of ritonavir and lopinavir exhibited some clinical signs of effectiveness against the SARS-CoV. However, molecular docking simulations failed to prove that these drugs could indeed interact significantly with 3CL<sup>PRO</sup>.<sup>84</sup> Remdesivir, a drug developed for Ebola and Marburg diseases, has been researched as an RdRp inhibitor which would hinder the CoV nucleic acid production. Thus, it is currently being considered as a repurposed drug for the SARS-CoV-2.<sup>85</sup> Likewise, many herbs and natural compounds have been investigated for their ability to interfere with these same virus protein pathways. Fig. 1 (panels A and B) summarizes our current knowledge on the herbs-natural compounds able to inhibit CoV 3CL<sup>PRO</sup>, PL<sup>PRO</sup>, RdRp, helicase protein, S protein, N protein, 3a protein, Cathepsin L, the virulence factors (Nsp1, Nsp3c, and ORF7a), and blockade the S protein/ACE-2 interaction.

In many studies, the herbs-natural compounds significantly and potently inhibited some of these protein pathways. For example, four studies showed that *Isatis indigotica*, its compounds *isatin*, *sinigrin*, *beta-sitosterol*, *indigo*, *aloe-emodin*, *hesperidin*, and other compounds and derivatives are potent SARS-CoV 3CL<sup>PRO</sup> inhibitors.<sup>38,41,47,61</sup> In molecular docking analyses, *hesperidin* demonstrated the potential to inhibit 3CL<sup>PRO</sup>, helicase protein, S protein, ACE-2 receptor, and S protein/ACE-2 interaction.<sup>2</sup> *Neohesperidin* can also inhibit all these proteins except for the S protein/ACE-2 interaction.<sup>2</sup> *Phaitanthrin D* and *2,2-di(3-indolyl)-3-indolone* also from *Isatis indigotica* inhibited the SARS-CoV PL<sup>PRO</sup>.<sup>2</sup> *Isatis indigotica* has a long history in the treatment of viral infections. In one article, *Isatis indigotica* isolate *lariciresinol-4-O- $\beta$ -D-glucopyranoside* inhibited influenza A (H1N1) virus-induced pro-inflammatory response in-vitro.<sup>86</sup> *Indirubin*, an alkaloid extracted from *Isatis Indigotica* reduced the H1N1 susceptibility in an animal model, lowered the mortality rate, and alleviated lung injury. It also promoted the expression of interferon- $\beta$  (IFN- $\beta$ ) and interferon (IFN) inducible transmembrane 3, and preserved the function and morphology of mitochondria after the infection.<sup>87</sup> *Epigoitrin*, another alkaloid from *Isatis indigotica*, reduced H1N1 infection in a stress-induced susceptible model in-vivo and in-vitro, evidenced by low mortality rate, improved inflammation, a decreased viral replication in the lungs and increased production of IFN- $\beta$  and IFN-

inducible transmembrane 3.<sup>88</sup> Moreover, the crude extract of *Isatis indigotica* prevented viral attachment to the target cells in an in-vitro model of influenza.<sup>89</sup> Thus, *I. Indigotica* has several isolates of proved antiviral activity and may target different proteins pathways. Other herbs-natural compounds that showed potential inhibition of both SARS-CoV 3CL<sup>PRO</sup> and PL<sup>PRO</sup> were *Salvia miltiorrhiza* and its *tanshinone* compounds,<sup>63</sup> *Angelica keiskei* and its compounds,<sup>48</sup> and *Broussonetia papyfera* polyphenols.<sup>90</sup> The water extract of *Salvia miltiorrhiza*, for example, demonstrated potent activity against HIV-1 integrase activity in-vitro and viral replication in-vivo with no cytotoxicity.<sup>91</sup>

*Houttuynia cordata* showed antiviral activity by inhibiting the SARS-CoV 3CL<sup>PRO</sup> and RdRp, and stimulated the proliferation of CD4<sup>+</sup> and CD8<sup>+</sup> T cells in-vitro.<sup>39</sup> *Houttuynia cordata* is a widely used TCM herb for respiratory diseases, bacterial and viral infections. In an animal study with influenza H1N1, *Houttuynia cordata polysaccharides* ameliorated pneumonia and intestinal injury through inhibition of inflammation, protection of intestinal barrier and regulation of mucosal immunity.<sup>92</sup> In another research, *Cimicifuga rhizome*, *Melia cortex*, *Coptidis rhizome*, *Phellodendron cortex*, and *Sophora subprostrata radix* were able to inhibit the SARS-CoV RdRp, S and N proteins.<sup>93</sup> One of the main isolates of *Coptidis rhizome* and *Phellodendri cortex* is *berberine*. *Berberine*, a natural isoquinoline alkaloid isolated from plants of the *berberis* species, exerted anti-inflammatory, antibacterial, antifungal, and anti-helminthic properties.<sup>94</sup> As an example, *berberine* reduced viral replication, pulmonary inflammation, necrosis, inflammatory cell infiltration, and pulmonary edema caused by the infection in a murine model of H1N1.<sup>94</sup> Other herbs-compounds that also inhibited PL<sup>PRO</sup> were *Paulownia tomentosa* flavonoids,<sup>95</sup> *Tribulus terrestris* and its compounds,<sup>96</sup> *Platycodin D* (from *Platycodon grandiflorus*), and *sugetriol-3,9-diacetate* (from *Cyperus rotundus*).<sup>2</sup> Herbs and natural compounds able to inhibit the PL<sup>PRO</sup>'s deubiquitinating (DUB) and deISGylating activities would also increase their effectiveness against the CoV.<sup>48,63,90</sup> In this context, all the 13 isolates from *Angelica keiskei* showed potent inhibitory effects on deubiquitination (from 2.6 to 73.3  $\mu$ M) and deISGylation (from 1.1 to 33.1  $\mu$ M).<sup>48</sup> Similarly, all the 10 compounds extracted from *Broussonetia papyfera* and the substances *isoliquiritigenin*, *kaempferol*, *quercetin*, and *quercetin- $\beta$ -galactoside* exhibited moderate deubiquitination and deISGylation inhibition effects (from 7.6 to 136.9, and from 8.5 to 71.7, respectively).<sup>90</sup>

*Rhei Radix et Rhizoma*, *Polygoni multiflora radix*, *Polygoni multiflora Caulis*, and especially the compound *emodin* extracted from these plants exerted strong antiviral activity (IC<sub>50</sub> 1–10  $\mu$ g/ml; *emodin* IC<sub>50</sub> 200  $\mu$ M) and blocked the SARS-CoV S protein/ACE-2 interaction.<sup>72</sup> In a different study, *emodin* inhibited the SARS-CoV 3a protein and S protein.<sup>35</sup> Thus, *emodin* could hinder the SARS-CoV by blocking both viral entry and release. Interestingly, *Emodin* increased the survival rate in an animal model of H1N1 infection, reducing edema, pulmonary viral titer and inflammatory cytokines, and improved lung histopathological changes.<sup>97</sup> *Emodin* was shown to inhibit influenza A virus and influenza viral pneumonia through the Nrf2, TLR4, p38/JNK, and NF-K $\beta$  pathways.<sup>97</sup> Moreover, *juglanin*, a *kaempferol* derivative from *Kaempferia galangal L.* completely blocked the SARS-CoV 3a protein.<sup>66</sup>

Another interesting research investigated the SARS-CoV 3CL<sup>PRO</sup> inhibitory effects of black, Pu'er, green and oolong teas. The authors concluded that *tannic acid*, *3-isothaflavin-3-gallate* (TF2B), and *theaflavin-3,3'-digallate* (TF3) were potent SARS-CoV 3CL<sup>PRO</sup> inhibitors, and that the black and Pu'er teas were more potent at their inhibitory properties than the green and oolong teas.<sup>37</sup> However, *Caffeine*, *Epigallocatechin gallate* (EGCG), and *epigallocatechin* (EGC) did not inhibit 3CL<sup>PRO</sup>.<sup>37</sup> In another study,<sup>2</sup> the researchers verified that *theaflavin 3,3'-di-O-gallate* (TF3) from *Camellia sinensis* green

tea effectively inhibited SARS-CoV RdRp and 3CL<sup>PRO</sup>, and *epigallocatechin gallate* (also from *C. sinensis*) blocked PL<sup>PRO</sup>. Also, three different *theaflavins*, *theaflavin* (TF1), *theaflavin-3'-monogallate* (TF2), and *theaflavin-3-3'-digallate* (TF3), major polyphenols from black tea, were tested against the hepatitis C virus (HCV). The researchers deduced that the *theaflavins* are inhibitors of the HCV entry, thus able to inhibit cell-to-cell spread.<sup>98</sup> Another paper reported that *theaflavin* derivatives (particularly from black tea) could inhibit HIV-1 entry into target cells by blocking the retroviral envelope glycoprotein 41 (gp41) that is involved in the internalization of the host cells.<sup>99</sup>

The compound *MOL 736, aurantiamide acetate* derived from the herb *Artemisia Annuu*, was found to be a CTSL inhibitor during the SARS-CoV infection.<sup>43</sup> *Artemisia Annuu* together with its isolates *artemisinin* and *artesanate* have been extensively studied as therapeutic agents for malaria, cancer, and schistosomiasis.<sup>100–102</sup> *Artemisinin* and *artesanate* exhibited antiviral properties against the cytomegalovirus, herpes simplex type 1, Epstein-Barr, hepatitis B and C viruses, and bovine diarrhea virus.<sup>102</sup> In another research, *Myrecetin* and *scutellarin*, the latter extracted from *Scutellaria Baicalensis*, hindered the SARS-CoV helicase protein activity.<sup>65</sup> *Baicalin* from *S. baicalensis* also demonstrated inhibition potential of the SARS-CoV PL<sup>PRO</sup> and RdRp in molecular docking simulations.<sup>2</sup> Likewise, the flavonoid *cosmosiin* from *S. baicalensis* can inhibit the SARS-CoV 3CL<sup>PRO</sup> and Spike protein, and *wogonoside* from the same herb displayed the capacity to inhibit the SARS-CoV Nsp1, Nsp3c, and ORF7a.<sup>2</sup> Decreasing the coronavirus virulence factors would attenuate the severity of disease and give the immune system a better fighting chance. *S. baicalensis*, a very popular herb used in TCM for common cold, fever, and influenza has been extensively researched for many ailments and demonstrated great potential in the treatment for acute lung injury induced by influenza virus A in an animal model.<sup>103</sup> Besides the antiviral properties, the flavonoid-enriched extract from *S. Baicalensis* also showed anti-inflammatory and anti-complement activities.<sup>103</sup> Also, *wogonin*, an isolate extracted from *S. baicalensis*, displayed antiviral activity against the influenza infection through the modulation of the cyclic adenosine monophosphate (AMP) pathway.<sup>104</sup> Another herb of interest is *Andrographis paniculata*, known for its anti-inflammatory and antibacterial properties.<sup>105</sup> Its derivatives *andrographiside*, *andrograpanin* and *andrographolide* can inhibit SARS-CoV 3CL<sup>PRO</sup>, while the former can also hinder RdRp, and the latter can additionally restrain Nsp1, Nsp3c, and ORF7a.<sup>2</sup> *Neoandrographolide* can inhibit TMPRSS2 making *Andrographis paniculata* another herb that can target multiple protein pathways. In another example, *andrographolide* inhibited influenza A-virus induced inflammation through the NF-K $\beta$  and JAK-STAT signaling pathways in a murine model.<sup>106</sup>

Panels A and B in Fig. 1 illustrate the potential of many natural substances as drug and therapeutic candidates for the SARS-CoVs. Some herbs and natural compounds significantly and potently inhibited one or more protein pathways, thus interfering in different phases of the viral life cycle. Noteworthy, SARS-CoV-2 is highly homologous to the SARS-CoV-1.<sup>2</sup> In genomic homology analyses, the SARS-CoV-2 displayed the highest genome sequence identity to the SARS-CoV-1 of 79–80%, and a similarity to MERS-CoV of 50%.<sup>2,3</sup> Most of the proteins from the SARS-CoV-1 and the SARS-CoV-2 exhibited an homology of 72%–99%.<sup>2</sup> The proteins 3CL<sup>PRO</sup>, PL<sup>PRO</sup>, and RdRp of the SARS-CoV 1 and 2 are highly analogous, and the homology of the spike-receptor binding domain (RBD) sequence between the two viruses is 76%.<sup>2</sup> Though the SARS-CoV-2 is sufficiently divergent from the SARS-CoV-1 to be considered a new type of human coronavirus, the receptor-binding domain structure of both is similar, and the SARS-CoV-2 can bind to the ACE-2 receptors of the host.<sup>3</sup> These studies indicate that, even with the mutations, therapeutic agents that intervene with



the SARS-CoV-1 and host pathways can, to some extent, be therapeutically useful for the SARS-CoV-2.

#### 4.4. Limitations of the studies

Some limitations in the studies were observed. In our search, we did not see follow up studies as a result of past herbal and natural compounds discovery. Although not part of the goal of the studies, we also missed investigations on drug-herbal interaction while treating CoVs. As a critical warning, when combining a conventional drug with a natural product it is mandatory to rule out any possible interference with pharmacokinetic and pharmacodynamic processes. For instance, coadministration of lopinavir/ritonavir is not recommended with certain herbal medicines (e.g., *St. John's wort* or *Hypericum perforatum*) that may substantially reduce its plasma concentrations.<sup>107</sup> *Glycyrrhizin*, which inhibits SARS-3CL<sup>PRO</sup>, could compete with the *Kaleta* (lopinavir/ritonavir). Agents that block RdRp such as *Coptidis rhizome*, *Phellodendron cortex*, and ritonavir could interfere with each other. Also, the interaction between ACE-2 inhibitor drugs and natural substances that potentially block ACE-2 receptors or the S protein/ACE-2 interface should be considered. However, not all drug-herbal interactions are harmful and their combination may also be beneficial. Moreover, only three (3) studies researched and/or discussed drug synergism which is very important to elect useful routes of clinical action.<sup>12,62,108</sup>

#### 4.5. Critical considerations

Important considerations include the fact that some studies used water and ethanol extract with good results in inhibiting the SARS-CoV and host proteins.<sup>39,44,53,61,63,67,68,72,109</sup> For example, the water extract of *Isatis indigotica* and the ethanol extract of *Torreya nucifera* significantly inhibited SARS-CoV 3CL<sup>PRO</sup>. Also, the ethanol extract of *Salvia miltiorrhiza* significantly inhibited SARS-CoV 3CL<sup>PRO</sup> and PL<sup>PRO</sup>. Thus, the use of whole herbs may effectively treat the viral infection as opposed to only the exclusive creation of “drugs” from herbal compounds and derivatives. However, since the extraction of the active components of the ingested whole herbs depends on the health of the digestive system of the patients, the use of isolates and derivatives from the herbs may offer advantages of a more targeted approach. The efficacy of natural substances also depends on the mode of administration. Furthermore, studies highlighted that the herbs and natural compounds acted as the antiviral agents in a dose- and concentration-dependent manner. Thus, verifying concentrations and dosage thresholds of isolated compounds and derivatives to act as independent drugs is essential for efficacy and safety. The clinical efficiency of natural substances may also vary according to the stage of pathogenicity of the infection. For example, bis-benzylisoquinoline alkaloids tetrandrine (TEN), fangchinoline (FAN) and cepharanthine (CEP) demonstrated antiviral activities against the HCoV-OC43 at an early stage of infection.<sup>108</sup> Therefore, these substances acted not only in a concentration- and dose-dependent manner but also in a time-dependent manner. All these ideas deserve future investigations. Apart from sequelae of coronaviruses infections, there is evidence of reactivation of cases of the SARS-CoV-2. A recent study showed that from 55 patients with a history of epidemiological exposure to the COVID-19, 5 patients (9%) who were discharged from the hospital had the SARS-CoV-2 reactivation.<sup>110</sup> Symptoms of the reactivated patients included fever, cough, sore throat and fatigue. One patient had progressive lymphopenia and neutrophilia.<sup>110</sup> Therefore, clinical therapeutic procedures need to also envision possible sequelae and viral reactivation. Additional measures to promote detoxification and increase the immune-

modulatory capabilities of the patients with SARS-CoVs should be explored. Many herbs have been potentially proven useful for this purpose.

## 5. Conclusion and perspectives

The investigation on the CoV treatments represents a big challenge for researchers due to the fast dissemination of the disease and the impossibility to perform randomized clinical treatment trials that are dangerous and pose ethical problems in face of a life-threatening condition.<sup>105</sup> Some conventional drugs are tried in infected patients through compassionate use programs.<sup>3</sup> Thus, there is an urgent need to explore and discover new treatment options for SARS-CoV-2 and similar pathogens. Approximately 450+ herbs and natural compounds reviewed here have shown their activity as antiviral substances against the SARS-CoV and related viruses. More specifically, many of them demonstrated the ability to inhibit the coronavirus-host protein pathways and interfere in different stages of the coronavirus life cycle such as viral entry into the host cell, membrane fusion, the processes of transcription, translation, replication, viral assembly, and viral release. The evidence on these herbs and natural compounds' properties was acquired utilizing the same or very similar methodologies as with the research on conventional drugs. The data suggest that these herbs-compounds offer a huge potential as therapeutic options to support the SARS-CoV treatment protocols.

Composing complementary and synergistic herbal remedies that could inhibit/block several viral-host protein pathways would surely render powerful allies in the fight against the SARS-CoV-2 infection. The study of synergistic combinations of conventional drugs and natural substances would also be of great value. Regardless, many herbs and modified herbal formulas habitually used by master herbalists for viral infections might be hitting some of the target proteins of the coronavirus and host. One herbal formula containing several herbs, that in turn comprise dozens or even hundreds of compounds, may target different pathways, some of which not yet known. It is highly credible that the herbal formulas used for the SARS-CoV-2 may inhibit multiple protein pathways while mediating antiviral, anti-inflammatory, antipyretic, immune-modulatory, anti-complement, anti-pulmonary fibrosis, anti-toxicity, and analgesic responses. However, further post-drug discovery research would provide a more in-depth perspective on the efficacy and safety of these herbs and isolated substances for standalone use, herbal-herbal, or drug-herbal combination. As a warning, the results of the in-vitro studies may not correspond to the same clinical effects if applied to human patients. The use of herbs and natural compounds may also represent enormous support for the conventional medical system, alleviating the work of medical staff and hospital workers actively fighting in the front-line against the COVID-19. Thus, this review also indicates the importance of considering the combination of conventional drugs and herbal medicine in an integrative and collaborative medical approach.

#### Availability of data and material

All data generated or analyzed during this study are included in this published article.

#### Ethics approval and consent to participate

Not applicable.



## Consent for publication

Not applicable.

## Funding

The authors declare that they obtained no funding for this study.

## Authors' contributions

ADF designed and carried out the literature searches, drafted the entire article, and prepared the table, graphical abstract, and figure. CI revised and finalized the figure and manuscript, adding comments and references. Both authors revised the manuscript in different phases of its preparation, and they have read and approved the final version.

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## Declaration of competing interest

The authors declare that they have no competing interests.

## Acknowledgements

Not applicable.

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