Race to Finding COVID-19 Cure: Could Traditional Herbal Medicine Hold the "Silver Bullet"? An Appraisal of Research Evidence

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Articles Information	Abstract
	Background: The global index case of the ongoing novel 2019-nCoV infection was recorded in China in December 2019. The infection is currently considered a global public health and security threat due to its high infectivity, associated high mortality and morbidity, fast replication and mutations and lack of clinically approved drugs and vaccines for its treatment. These have spurred the global race for the discovery and development of effective and safe chemotherapeutic and chemoprophylactic agent(s) for its treatment. In order to harness the potentials and bring to the attention of stakeholders in the healthcare industry the anti-COVID-19 potentials inherent in plant-derived bioactive compounds, the present study is designed to rapidly review published basic and clinical studies on traditional medicinal plants with proven anti-COVID-19 natural compounds. **Methods:** Eight online database search engines using some COVID-19 keywords were used to search for literature from between 1 December 2019 and 15 May 2020. Of 218 hits retrieved, only 19 peer-reviewed and published works fulfilled the set criteria and were reviewed. **Results:** Using network pharmacology screening and molecular docking technology, natural bioactive compounds, quercetin, kaempferol, and luteoline were the most prevalent and effective bioactive compounds identified to directly inhibited SARS-CoV-2 protease and down-regulated inflammation. Also the few clinical studies reviewed showed that COVID-19 positive patients managed with traditional herbal remedies either alone or in combination with conventional antiviral regimen and palliative treatment experienced significant clinical improvements. **Conclusions:** Overall, these studies provided new evidence to support the possible therapeutic role traditional herbal medicine could offer in the clinical management and prevention of COVID-19. However, more robust and multicenter human trials are still required to verify the efficacy and safety of these remedies.

1. Introduction

In mid-December 2019, a pneumonia of unknown etiology was first reported in Wuhan City, the capital of Huber Province, Peoples Republic of China. Although the World Health Organization (WHO) Country Office in China was notified but this disease was not declared a global public health emergency until 30 January 2020 after it has assumed a global dimension [1, 2]. On 11 February 2020, WHO identified the causative pathogen as a novel enveloped RNA betacoronavirus2 and named it severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for sharing similar phylogenetic profile with SARS-CoV [3]. This pathogen is also known as the 2019 novel coronavirus (2019-nCoV), being a new strain of coronavirus family that was discovered in the year 2019 [4] with its clinical condition known as coronavirus disease 19 (COVID-19). COVID-19 is considered a highly infectious disease and is characterized by common and spectrum of symptoms such as fever, sore throat, cough, dyspnea, body weakness, myalgia, diarrhea, loss of smell (hyposmia) and loss of taste (hypogeusia) [4, 5, 6, 7] and ocular manifestations, such as epiphora, conjunctival congestion, or chemosis [8]. However, the disease may manifest

atypical presentations such as abdominal pain and testicular pain [9], cardiac symptoms (e.g. palpitations and chest pain resulting from underlying virus-induced myocardial injury) and neurologic presentations (including acute cerebrovascular disease, muscle injuries and acute necrotizing hemorrhagic encephalopathy as well as Guillain–Barré Syndrome) [10, 11], all supposedly resulting from "cytokines storm syndrome" [12]. However, COVID-19 complications include acute respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), acute liver injury and liver failure, acute cardiac injury, secondary infections, acute kidney injury, septic shock, rhabdomyolysis, venous thromboembolism, disseminated intravascular coagulation, *etc* [13].

According to WHO, as at 17 May 2020 nearly 4.6 million infected, 1.6 million recovery cases and 308,000 deaths have, thus, been recorded so far globally [14]. Unfortunately, till date, there are no approved effective treatment drugs for COVID-19 although there are over 700 clinical trials going on simultaneously across the globe in a bid to find an effective cure for this pandemic. Two most popular of these clinical trials being that of 4-aminoquinolone antimalarial agent, chloroquine and its congener, hydroxychloroquine, and most recently broad spectrum serine protease inhibitor antiviral agent, remdesivir, which was initially designed and developed for the clinical treatment of Ebola viral infection but recently re-purposed for COVID-19 treatment. Remdesivir, only available in the injectable form, was recently authorized by the US Food and Drug Agency (FDA) for the emergency treatment of COVID-19 patients [15]. However, clinical data emanating from the clinical trials of these drugs have been greeted with controversies such as effectiveness *vs* ineffectiveness, cost *vs* benefits, *etc*.

In view of the unique complexity of COVID-19 structure and genome sequence, its rapid mutations and absence of effective orthodox therapeutic agents, the World Health Organization (WHO) through its African Regional Office recently but cautiously welcomed and encouraged explorations into therapeutic drug repurposing, complementary and alternative medicines and new therapies development in the search for potential COVID-19 therapies, especially traditional medicinal plants which are of proven efficacy and tolerable side-effects [16]. In addition, WHO has re-committed itself towards closely working with and supporting countries engaged in the development of safe and effective indigenous knowledge and medical practice in the prevention, control and early detection of the virus, as well as timely case referral to existing and appropriate health facilities [16]. As the discovery and development of conventional therapies including drugs and vaccines may take months or years despite this scourge ravaging the world, it becomes imperative to explore and develop a more efficient and responsive treatment and control mechanisms for the disease, one of which is exploring the therapeutic potential of mono- or poly-herbal formulas in the disease management. The effectiveness of herbal therapies in the control highly infectious diseases were demonstrated during the 2003 severe acute respiratory syndrome (SARS) [17, 18, 19] and 2012 Middle East Respiratory Syndrome (MERS) outbreaks [20, 21]. Since the outbreak of COVID-19, there have been increasing evidences on the efficacy of plant products in COVID-19 treatment. Therefore, in this study, a review of the protocols and preliminary trial reports in the form of published research articles from preclinical, clinical trials and observational studies supporting the beneficial role of traditional mono- and poly-herbal formulas from Traditional Chinese Medicine, Ayurveda and African Traditional Medicine and used in the local COVID-19 treatment was undertaken.

2. Methods

As there were no primary data used in this review, there was no basis for obtaining ethical approval from both Institutional Human and Experimental Research Ethics Committee.

2.1 Search Methodology

Because of dearth in the number of published research articles on the pre and clinical trials involving herbal remedies in COVID-19 treatment, inclusion criteria only included data obtained from all peer reviewed published original articles while unpublished studies, commentaries and review articles were excluded. A total of eight electronic databases (MEDLINE, EMBASE, Web of Science, SCOPUS, Cochrane library, Academic Search Complete, GoogleScholar and HINARI) were searched from December 1, 2019 to May 15, 2020, using variant Medical Subject Headings (MeSH) and free-text (Text) terms to retrieve published literature using a complete list of key words such as 2019-nCoV infection, traditional herbal medicine, basic studies, clinical trials, clinical outcomes. Using these search engine tools, we got 218 hits, most of which were commentary, letters to editors and reviews. Only 19 of these hits met the criteria of original research articles.

3. Results

Using the aforementioned search engines, only 19 articles (involving 13 preclinical and 6 clinical studies) that met the set criteria of original research articles on the use of traditional herbal medicine in COVID-19 treatment were retrieved and these were from China, India and Morocco. The findings of the retrieved original articles are, thus, summarized below:

3.1. Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations [22].

This is computational investigation designed at investigating 67 secondary metabolites naturally existing in some selected Moroccan medicinal plants with already established antiviral activities that can prevent human transmission of COVID-19 infection through inhibition of 2019-nCoV main protease using molecular docking analysis. Molecular docking analysis. Molecular docking analysis used to study the binding affinity and the type of interactions between the 67 molecules retrieved and the targeted 2019-nCoV main protease showed that only crocin, digitoxigenin, and β-eudesmol exhibited significant viral protease inhibition against the coronavirus based on the binding affinity.

From pharmacological perspectives and literature search, crocin is an important carotenoid pigment and flavonoid in Crocus sativus L. (saffron) (family: Iris), with the capacity of inhibiting herpes simplex virus (HSV-1); Human Immunodeficiency virus (HIV-1) replication in vitro [23]. Similarly, aglycone cardiac glycoside, digitoxigenin, constitutes 11.25% of the quantitative phytochemicals in Nerium oleander which belongs to the Apocynaceae family. This has been demonstrated to exhibit significant antiviral (polio virus-1, Sb-1; and HIV-1 and 2) and anticancer activities [24, 25, 26] while β-eudesmol which constitutes barely 2.39% constituents of Lauris nobilis L. (family: Lauraceae) has been demonstrated to exhibit significant antibacterial and antiviral activities [27, 28].

3.2. Network pharmacology-based analysis of the role of traditional Chinese herbal medicines in the treatment of COVID-19 [29].

This is a network pharmacology method used to investigate the efficacy and molecular mechanisms of action of two Chinese herbal medicine (CHM) formulas in the prevention of COVID-19 using Gene Ontology (GO)-based functional enrichment, annotation tool and the Kyoto Encyclopedia of Genes and Genomes (KEGG). The CHM formulas obtained from the Hubei Province Diagnosis and Treatment Protocol for COVID-19 were "Formula A" which consisted of: Rhizoma atractylodis, Flos lonicerae japonicae, Pericarpium citri reticulatae, Rhizoma phragmitis communis, Folium mori [the leaf of Morus alba L. (Moraceae)], and Radix Astragali seu Hedysari; and "Formula B" which consisted of: Radix Astragali seu Hedysari, Rhizoma atractylodis macrocephalae, Radix saposhnikoviae, Cyrtomium fortunei - J. Sm., Flos lonicerae japonicae, Eupatorium fortunei Turcz., and Pericarpium citri reticulatae. Results of the study showed that the most enriched biological processes of these two CHM formulas through the GO-based functional enrichment included nuclear receptor activity, transcription factor activity, and direct ligand regulated sequence-specific DNA binding pathways while the KEGG analysis utilized most efficiently the P13K/Akt signaling pathways that are known to be central to the inhibition of viral replication.

3.3. Molecular basis for treating COVID-19 with official Chinese herbal formula LCTE [30].

This is another network pharmacology method used to investigate the effectiveness and the underlying molecular mechanisms of the Chinese herbal formula, lung-cleaning and toxicity-excluding soup (LCTE) for the prevention of COVID-19 using: (i). three comprehensive Chinese herbal databases (Traditional Chinese Medicine Systems Pharmacology database, Encyclopedia of Traditional Chinese Medicine, and SymMap); (ii). human gene-disease associations (GDAs) repository (DisGeNET); (iii). ADME filtration test; and (iv). protein enrichment analysis. KEGG pathway and Disease Ontology (DO) enrichments were used to predict the general in vivo effects of LCTE. The LCTE formula is a mixture of 20 herbal ingredients and one mineral material (Rudis Gypsi Miscueris). The 20 herbal ingredients are: Rhizoma atractylodis macrocephalae, Rhizoma pinelliae, Radix bupleuri, Pericarpium citri reticulatae, Flos farfarae, Poria cocos, Radix glycyrrhizae, Cinnamomi ramulus, Radix scutellariae, Pogostemon cablin, Herba ephedrae, Rhizoma discoreae, Rhizoma belamcandae, Rhizoma zingiberis recens, Herba asari, Semen armenniacae amarum, Rhizoma alismatis, Fructus aurantii immaturus, Polyporus umbellatus, Radix asteria, and Radix gypsi micueris. The study showed that the 20 herbal composite ingredients contained 207 secondary metabolites with the two

most prevalent and effective natural compounds (kaempferol and quercetin) directly inhibiting SARS-CoV-2 protease and down-regulate inflammation. The results of the KEGG pathways and DO pathways also showed that the top 30 enriched KEGG pathways were related to viral infections and inflammation/cytokines signaling which were known to be closely related to pneumonia caused by coronavirus, thus, lending credence to LCTE's usefulness in COVID-19 treatment.

3.4. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus [31].

This is a two-step network pharmacology screening analysis of 26 Chinese herbal plants traditionally used in the folkloric treatment of viral infection, immune/inflammation reactions and hypoxia. It utilized an in silico integrative model of absorption, distribution, metabolism and excretion (ADME) screening/filtration test. The herbs screened are: Forsythiae fructus, Licorice, Mori cortex, Flos chrysanthemi, Flos farfarae, Flos lonicerae japonicae, Chrysanthemum morifolium, Radix peucedani, Rhizoma fagopyri cymosi, Tamaricis cacumen, Erigeron breviscapus, Radix bupleuri, Rhizoma coptidis, Houttuyniae herba, Hoveniae dulcis semen, Flos inulae, Eriobotryae folium, Hedysarum multijugum maxim, Lepidii seu Descurainiae semen, Ardisiae japonicae herba, Asteris radix et rhizoma, Euphorbiae helioscopiae herba, Ginkgo semen, Anemarrhenae rhizoma, Epimrdii herba, and Fortunes bossfern rhizoma.

Herbs with documented antiviral activities were initially sought via literature search and later confirmed using the Traditional Chinese Medicine Systems Pharmacology (TCMSP), the Encyclopedia of Traditional Chinese Medicine (ETCM) and SymMap databases; classic usage catalogue cross-reference; and network pharmacology analysis to predict in vivo general effects of these herbs. Bioactive compounds retrieved from herbs that are traditionally administered orally were subjected to an in silico integrative model of ADME screening and then protein-molecular docking analysis through protein-protein interaction analysis and enriched KEGG pathways. Results of the study showed that 115 overlapping natural compounds were identifiable from the 26 Chinese herbs screened. Using ADME filtration test, only 13 out of the 115 natural compounds were screened via the top 15 enriched KEGG pathway that are related to antiviral, immune/inflammatory

responses and hypoxia response which showed them to be highly efficacious in inhibiting the viral replication, indicating that these Chinese herbs could be highly beneficial in the treatment of 2019-nCoV and related viruses.

3.5. An artificial intelligence system reveals liquiritin inhibits SARSCoV-2 by mimicking type I interferon [32].

Using an artificial intelligence of enriched Gene Ontology (GO) pathways and gene set enrichment analysis (GSEA), a group of Chinese scientists from Peking University and Chinese Academy of Military Medical Sciences, Beijing, China, investigated the potential inhibitory effect of liquiritin in Vero E6 cell culture. In vivo single intravenous toxicity study at a dose of 150 mg/kg for 7 days and repeated intraperitoneal toxicity study at 300 mg/kg/day of liquiritin for 10 days were also conducted. Liquiritin (one of the main flavonoids in Glycyrrhiza uralensis; family: Fabaceae) is documented with biological effects such as antidepressant, neuroprotective, anti-inflammatory and cardioprotective effects. Results of the study showed that while liquiritin exhibited high safety profile, it significantly inhibited of SARS-CoV-2 replication in Vero E6 cells with the EC50 value of 2.39 μM. Liquiritin's anti-SARS-CoV-2 activity was mediated via type I interferon signaling pathway, and inhibition of viral genome replication, thus, highlighting liquiritin as a potential therapeutic alternative for COVID-19 treatment.

3.6. Investigating the mechanism of Qing-Fei-Pai-Du-Tang for the treatment of novel coronavirus pneumonia by network pharmacology [33].

This study aimed at providing a treatment for COVIDS-19 infection investigated the relationship between Qing-Fei-Pai-Du-Tang (QFPDT) targets and COVID-19-related-pneumonia and the therapeutic mechanisms of its multiple components on COVID-19 via multiple targets. QFPDT is a combination of four Chinese classic Traditional Chinese herbal formulas that ancestral traditional use and whose use has been supported both by classical texts and by the clinical experience of later physicians The meridian tropisms, compounds and targets of each constituent herb in QFPDT were collected from Encyclopedia of Traditional Chinese Medicine (ETCM), Traditional Chinese Medicine Systems Pharmacology (TCMID) and Natural Product Activity and Species Source (NPASS) databases. Open-source virtual bioinformatics software,

Cytoscape, was used to construct and analysis networks while functional enrichment analysis of targets were applied. Results of the study showed that among QFPDT's 790 putative targets, 232 were co-expressed with angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2. The important targets identified were enriched on two classes of disease pathways of viral infection and lung injury. Thus, QFPDT's chief target in the lung involves up-regulation of a series of proteins co-expressed with ACE2 in COVID-19 and a series of signaling pathways involved in balancing immunity and eliminating inflammation, ACE2 being the cell receptor COVID-19 uses to invade human cells. Thus, QFPDT may act as an antiviral agent against COVID-19 by targeting ribosomal proteins that are essential for its replication through inhibition of viral mRNA translation and a group of proteins that interact with viral proteins. QFPDT is, however, predicted to be 90% effective in treating COVID-19 infection.

3.7. Medicinal herbal extracts of Sophorae radix, Acanthopanacis cortex, Sanguisorbae radix and Torilis fructus inhibit coronavirus replication in vitro [34].

This is a preclinical in vitro study that evaluated the antiviral including anti-coronavirus activity of 19 traditional medicinal herbal extracts using plaque assay, concentration of extract required to inhibit 50% of the replication [EC50] of mouse hepatitis virus (MHV) A59 strain (MHV-A59), and 50% cytotoxic concentration [CC50] of each extract. Northern and western blot analyses were also conducted to evaluate antiviral activity on viral entry, viral RNA and protein expression, and release in MHV-infected DBT cells. Sophorae radix, Acanthopanacis cortex and Torilis fructus were reported to have reduced intracellular viral RNA levels with comparable reductions in viral proteins and MHV-A59 production. The extracts also reduced the replication of the John Howard Mueller strain of MHV, porcine epidemic diarrhea virus and vesicular stomatitis virus in vitro.

Sanguisorbae radix significantly reduced coronavirus replication via decreased viral protein synthesis without concomitant reduction in intracellular viral RNA levels. The EC50 values of the four extracts ranged from 0.8-3.7 µg/ml while the CC50 values ranged from 156.5-556.8 µg/ml. Acanthopanacis cortex and Torilis fructus exerted their antiviral activities in MHV-A59-infected cells by increasing anti-inflammatory pathway (increased cyclooxygenase-2 expression via

extracellular signal-related kinase (ERK) and p38 signaling pathway. These results, thus, highlighted the promising anti-coronavirus potential of Sophorae radix, Acanthopanacis cortex, Sanguisorbae radix and Torilis fructus. However, in a more recent study, the mechanism of the anti-coronavirus effect of Radix sophorae flavescentis was reported to have been mediated via multiple pathways which included type I interferon, NF-κB signaling pathway, ERK signaling pathway, PI3K/Akt signaling pathway, and matrine [35].

3.8. Exploring the active compounds of Da-Yuan-Yin in treatment of novel coronavirus (2019-nCoV) pneumonia based on network pharmacology and molecular docking method [36].

This study investigated the possible anti-COVID-19 potential and mechanism(s) of actions of the active compounds of the traditional Chinese poly-herbal formula, Da-Yuan-Yin (composition: Semen Arecae, Magnoliae officinalis cortex, Fructus Tsaoko, Rhizoma Anemarrhenae, Radix Paeoniae Alba, Radix Scutellariae, and Radix Glycyrrhizae), using Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), UniProt and GeneCards database, compound-putative target network and molecular docking techniques. Results showed that the compound-target network contained 141 compounds and 267 corresponding targets, and the key targets involved PTGS2, HSP90AA1, ESR1, AR, NOS2, etc. The results of molecular docking showed that quercetin, kaempferol, baicalein and other core compounds exhibited significant binding activities to angiotensin converting enzyme II (ACE2) receptors. Therefore, suggesting that these compounds could be regulating multiple signaling pathways involving ACE2 receptors and acting on targets such as PTGS2, HSP90AA1 and ESR1 to cause its anti-COVID-19 effect.

3.9. Exploring material basis and mechanism of Lianhua Qingwen Formula against coronavirus based on network pharmacology [37].

This is another Chinese study that investigated the bioactive compounds and mechanism of action of a traditional Chinese poly-herbal formula, Lianhua Qingwen Formula (LQF) (consisting of 11 Chinese herbs, gypsum and menthol), for the treatment of COVID-19. Using TCMSP, Batman, Swiss Target Prediction and other databases, the chemical components and targets of LQF were retrieved and coronavirus disease targets were screened by GeneCards. "Chinese herb-component-

target-disease" interaction network map was constructed using Cytoscape software and potential target interactions, and the action mechanism was predicted through enrichment analysis and molecular docking techniques. The study showed that 100 active ingredients, 636 drug targets, and 347 disease targets were retrieved, and obtained 67 drug-disease common targets. The key targets involved PTGS2, IL6, CASP3, MAPK1, EGFR, ACE2, etc. While its GO enrichment analysis revealed a total of 1946 entries which basically involved T cell activation, viral receptors, and inflammatory responses, its KEGG pathway enrichment analysis revealed 166 signaling pathways, including renin-angiotensin system, Toll-like receptor signaling pathway, JAK-STAT signaling pathway, T cell receptor signaling pathway, and TNF signaling pathway. The molecular docking results showed that kaempferol, quercetin and luteolin had strong binding affinity for Mpro while glycyrrhetinic acid, stigmasterol, and indigo had strong binding affinity for ACE2 receptors.

3.10. Exploring active compounds of Jinhua Qinggan granules for prevention of novel coronavirus pneumonia (COVID-19) based on network pharmacology and molecular docking [38].

This study investigated the bioactive compounds and their anti-COVID-19 mechanisms on SARS-CoV-2 3CL hydrolase and ACE2 receptors in another Chinese herbal remedy, Jinhua Qinggan granules, for treatment of COVID-19 using network pharmacology and molecular docking techniques. The study showed that the poly-herbal remedy contained 154 compounds and 276 targets with its key targets involving PTGS2, HSP90AB1, HSP90AA1, PTGS1, NCOA2, etc. While its GO function enrichment analysis revealed 278 entries, including ATP binding, transcription factor activation and regulation of apoptosis process, the KEGG pathway enrichment screened 127 signaling pathways, including TNF, PI3K/Akt and HIF-1 signaling pathways related to lung injury protection. Also, its molecular docking analysis showed that formononetin, stigmasterol, β-sitosterol, anhydroicaritin and other key compounds had strong binding affinity with SARS-CoV-2 3CL hydrolase and ACE2, thereby highlighting the potential anti-COVID-19 role of Jinhua Qinggan granules.

3.11. Study on active compounds from Huoxiang Zhengqi oral liquid for prevention of coronavirus disease 2019 (COVID-19) based on network pharmacology and molecular docking [39].

This is another Chinese study that investigated Chinese poly-herbal oral liquid mixture, Huoxiang Zhengqi (consisting of 10 medicinal plants: Atractylodes chinensis, Citrus reticulata, Magnolia officinalis, Angelica dahurica, Poria cocos, Pinellia ternata, Glycyrrhiza uralensis, Pogostemon cablin and Pinellia ternata) for its anti-COVID-19 potential using network pharmacology and molecular docking techniques. The 10 herbal plants were searched and retrieved from Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and analysis platform while the corresponding target genes were searched and retrieved on UniProt database and Cyoscape software was used for the virtual construction of herb-bioactive compound-target network. The underlying mechanisms of anti-COVID-19 action of these natural bioactive compounds were also predicted using GO function and KEGG pathway enrichment analyses.

Results of the study showed that 123 bioactive compounds with their corresponding 257 action targets were identified from the 10 herbs screened. The key gene targets identified included PTGS2, AR, CAMSAP2, HSP90AB1, PPARG and NOS2. The GO analysis resulted in 178 biological processes (BP) entries and 36 cellular component (CC) entries and 64 molecular function (MF) entries while its KEGG pathway enrichment analysis identified key bioactive compounds such as quercetin, isohamnetin, irisolidone, kaempferol, wogonin and biacalein as sharing strong affinity for COVID-19 ACE2 receptors. However, quercetin, isohamnetin, and irisolidone exhibited strongest affinity for PTGS2, HSP90AB1, AR and CAMSAP2 highlighting the anti-COVID-19 chemopreventive and chemotherapeutic potentials of these bioactive compounds.

3.12. Potential material basis of Kangbingdu granules for treatment of coronavirus disease (COVID-19) based on network pharmacology and molecular docking technology [40].

The study investigated the anti-COVID potential of the Chinese poly-herbal formula, Kangbingdu granules, made from 9 Chinese herbs (Radix isatidis, Fructus forsythiae, Gypsum fibrosum, Rhizoma anemarrhenae, Rhizoma phragmitis, Radix rehmanniae praeparata, Pogostemon cablin, Rhizoma acoritataninowii and Radix curcumae)

which were searched and retrieved on TCMSP database and subjected to other network pharmacology and molecular docking techniques. The corresponding targets were searched on UniPort database while medicinal material-compound-target network was constructed using Cytoscape software. Enriched GO functional analysis and KEGG pathway enrichment analysis were used to predict the possible anti-COVID-19 mechanisms of actions. The study revealed that from the 8 Chinese herbs screened, 75 bioactive compounds and 255 of their corresponding gene targets were identified. GO enrichment analysis revealed 65 biological processes, 36 cell component and 60 molecular function entries. KEGG pathway enrichment analysis also revealed 131 possible pathways and the molecular docking revealed 22 possible compound-target binding affinities. Of the topmost 15 key bioactive compounds identified, bicuculline, luteoline and quercetin exhibited the most significant binding affinities on SARS-COV2 3CL hydrolase and ACE2 receptors via PTGS2, HSP90AB1 and PTGS1 targets.

3.13. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach [41].

This study evaluated the extremely bitter labdane diterpenoid, Andrographolide, isolated from the stem and leaves of Andrographis paniculata, as a potential SARS-COV-2 Mpro (main protease) inhibitor using in silico studies which included molecular docking, target analysis, toxicity prediction and ADME prediction. The study revealed that while Andrographolide exhibited significant binding to SARS-CoV-2 Mpro, the computational approaches also predicted good pharmacokinetic and pharmacodynamics property, target accuracy and good toxicity prediction for Andrographolide, highlighting its therapeutic potential as an effective anti-COVID-19 agent.

3.14. Treatment efficacy analysis of traditional Chinese medicine for novel coronavirus pneumonia (COVID-19): an empirical study from Wuhan, Hubei Province, China [42].

This is an empirical retrospective study combining clinical data and network pharmacology technology to assess the effectiveness of Traditional Chinese Medicine (TCM) {Qingfei Paidu decoction (QFPDD) and Chinese National Health Commission (NHC) - recommended} in COVID-19 pneumonia. The study involved a total of 54 confirmed COVID-19 pneumonia in-patients resident in Wuhan city and receiving traditional

Chinese herbal formulas, TCM in the Jihe-based Infectious Disease Department, China, from 24 January 2020 to 17 February 2020. The patients' personal information including patients' age, gender, symptoms, temperature, use of TCM and diagnostic results during the hospital stay were collected through the facility's Hospital Information System. Patients' clinical characteristics, TCM use and pre-admission and discharge diagnostic results were the measuring endpoints for the study. Network pharmacology and molecular docking techniques were also utilized to determine the bioactive compounds in the TCM constituent herbal ingredients and their corresponding mechanism(s) of anti-COVID-19 action. The study showed that the average hospital stay of the treated patients was roughly 9 days. Comparing the pre-admission and discharge blood test parameters, the TCM treatment profoundly improved the patients' immunity against SARS-CoV-2 infection as indicated by a profound increase in the total leukocyte counts, neutrophil and lymphocyte differentials and platelet counts, while the erythrocytes count, hemoglobin concentration and hematocrit decreased during the TCM treatment.

The network pharmacology study revealed that QFPDD contained 21 traditional Chinese herbs and 16 traditional Chinese herbs in NHC - recommended formulas. These included Pogostemon cablin (Blanco), Atractylodes lancea (Thunb.) DC., Scutellariae Radix, Chaihu Radix Bupleuri, Fructus forsythiae, gypsum, Atractylodes lancea (Thunb.) DC., Polygoni Cuspidati Rhizoma Et Radix, Verbenae herb, Ephedra herba, Lepidii Semen Descurainiae Semen, buffalo horn, Panax ginseng C. A. Mey., Aconiti lateralis radix praeparata, Hedysarum multijugum Maxim., Ophiopogon japonicus (Linn. f.) Ker-Gawl and Panacis Quinquefolii Radix. Of the 32 herbs selected due to duplication, only 29 were picked for network pharmacology study due to the fact that information on Ophiopogon japonicus (Linn. f.) Ker-Gawl., gypsum, and buffalo horn could not be retrieved from the TCMSP database. From these, 201 compounds in NHC-recommended formulas and 288 compounds in the QFPDD were discovered, of which kaempferol, β-sitosterol, stigmasterol, quercetin, luteolin, genkwanin, diop, isorhamnetin were the most common bioactive compounds. There were 204 putative sites in NHC-recommended formulas, and 240 targets in QFPDD, with the most significant binding affinities of kaempferol, quercetin, luteolin, galangin, luteolin, isorhamnetin being

CYP1B1, ABCG2, CA7, CA4 and ESR2, respectively.

3.15. Guideline on diagnosis and treatment of COVID-19 (Trial 6th edition) [43].

This is a Chinese government sponsored preliminary clinical trial of a larger scale multicenter clinical trials of a Chinese poly-herbal decoction, Qingfei Paidu decoction (QPD), which contains 21 kinds of traditional Chinese medicine and are mainly derived from 4 different classical prescriptions originated from Shang Han Lun: (i). Ma Xing Shi Gan Tang, (ii). Xiao Chai Hu Tang, (iii). She Gan Ma Huang Tang and (iv). Wu Ling San. Its main ingredients are Ephedrae herba, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Semen armeniacae amarum, Gypsum fibrosum, Cinnamomi ramulus, Alisma orientale (Sam.) Juz rhizomes (Alismatis Rhizoma), Polyporus squamosus, Atractylodis macrocephala Koidz rhizomes, Poria cocos, Radix bupleuri chinensis, Radix Scutellariae, Pinelliae Rhizoma Praepratum cum Zingibere et Alumine, Zingiberis Rhizoma Recens, Asteris Radix et Rhizoma, Flos farfarae, Belamcandae chinensis rhizome, Asari radix et rhizoma, Dioscorea opposita Thunb. rhizome, Aurantii Fructus Immaturus, Citri Reticulatae Pericarpium, and Pogostemonis herba, in the clinical management of confirmed COVID-19 patients. Of the 701 confirmed COVID-19 cases treated with QPD, 130 cases were successfully cured and discharged, clinical symptoms of 51 cases resolved, 268 cases of symptoms improved, and 212 cases had stable symptoms without deterioration. The effective cure rate of QPD in COVID-19 confirmed patients was, therefore, estimated to be over 90%.

3.16. Traditional Chinese medicine for COVID-19 treatment [44].

This is a very preliminary Chinese human trial of a Chinese poly-herbal decoction, Qingfei Paidu decoction (QPD), which consisted of Ephedrae herba, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Semen armeniacae amarum, Gypsum fibrosum, Cinnamomi ramulus, Alisma orientale (Sam.) Juz rhizomes (Alismatis Rhizoma), Polyporus squamosus, Atractylodes macrocephala Koidz rhizomes, Poria cocos, Radix Bupleuri chinensis, Radix Scutellariae, Pinelliae Rhizoma Praepratum cum Zingibere et Alumine, Zingiberis Rhizoma Recens, Asteris Radix et Rhizoma, Flos farfarae, Belamcandae chinensis rhizome, Asari radix et rhizoma, Dioscorea opposita Thunb. rhizome, Aurantii Fructus Immaturus, Citri Reticulatae Pericarpium, and Pogostemonis herba, that evaluated its effectiveness and role as an add-on adjuvant therapy in the clinical management of a confirmed male COVID-19 patient. QPD was added as an adjuvant to the antiviral combination therapy of oseltamivir phosphate capsule, intravenous ganciclovir, and inhalational recombinant human interferon a1b, already initiated in the patient's care due to persisting high fever and chest computer tomography "ground glass" appearance of both lungs which were equally enlarged and of very high density. The presence or absence of fever, asthenia, cough and the rales of two lungs were used as clinical endpoints. Following 6 days of this treatment with the QPD add-on, the patient's clinical state improved significantly and was subsequently discharged home and continued 7 doses of the prescription post-discharge.

3.17. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment [45].

This is a retrospective Chinese clinical studies investigating the effectiveness of a traditional Chinese herbal formulation, Shufeng Jiedu Capsule (SFJDC) (2.08 g given 8 hourly per oral route and active ingredients being quercetin, rutin, kaempferol, iquiritigenin, liquiritin, resveratrol, emodin, and rhein) as an add-on adjuvant therapy in confirmed in-patient COVID-19 patients already on oxygen therapy, mechanical ventilation, antibiotics, antivirals (lopinavir 400 mg/ritonavir 100 mg, 12 hourly, per oral route), arbidol (200 mg, 8 hourly, per oral route), and intravenous immunoglobulin therapy. SFJDC is made from eight traditional Chinese medicinal materials including Polygonum cuspidatum, Fructus forsythia, Radix isatidis, Radix bupleuri, Dahurian patrinia herb, Verbena leaves, Rhizoma phragmitis and liquorice root. Four patients (3 males and 1 female; 2 under 35 years of age and 2 over 60 years of age) diagnosed with 2019-nCoV pneumonia according to the WHO interim guidance were recruited into the study between 21 January 2020 and 24 January at Shanghai Public Health Clinical Center, Shanghai, China. Clinical presentations such as fever, cough, nasal congestion, sore throat, dizziness, fatigue, rhinnorhea, constipation; respiratory rate; lung auscultations; radiological findings such unilateral or bilateral pneumonitis; and laboratory tests (real-time RT-PCR, nasal and throat swab) were used as clinical endpoints. Treatment was for 6-15

days. After treatment, 3 of the treated patients had significant improvements in the COVID-19 pneumonia-related symptoms. Of these 3 patients, 2 patients were subsequently confirmed 2019-nCoV negative and discharged after two consecutive tests, while 1 was virus negative at the first test. The remaining patient who severe pneumonia also showed signs of clinical improvement as at the cutoff date for data collection. Thus, the study highlighted the potential role of SFJDC as adjuvant therapy in the management of COVID-19 patients.

3.18. Clinical features and treatment of COVID-19 patients in northeast Chongqing [46].

This is a more robust retrospective clinical study which investigated the effectiveness of traditional Chinese herbal formulation, Shufeng Jiedu Capsule (SFJDC), as an add-on/adjuvant therapy to conventional antiviral therapy (lopinavir 400 mg/ritonavir 100 mg, 12 hourly, per oral route), arbidol (200 mg, 8 hourly, per oral route) and intravenous interferon therapy in COVID-19 patients. The study recruited 135 confirmed COVID-19 patients with the median age of 47 years, 53.3% male and 46.7% female all from northeast Chongqing were hospitalized in Chongqing University Three Gorges Hospital in northeast Chongqing, China, from 23 January to 8 February 2020. Clinical features of pneumonia, laboratory and radiological imaging findings, and treatment outcomes were the measuring clinical endpoints.

All the 135(100%) COVID-19 patients received antiviral combination therapy (lopinavir/ritonavir and interferon), while 59(43.7%) and 36(26.7%) were administered antibiotics and corticosteroids, respectively. In addition, 124(91.85%) of the patients received traditional Chinese herbs (TCH). The Chinese herbals used to treat the COVID-19 patient as add-on primarily included glycyrrhiza, ephedra, bitter almond, gypsum, reed root, amomum, and trichosanthes, whose primary functions were to relieve fever, relieve cough and increase immunity. Results showed that 43(31.9%) patients had underlying diseases: primarily hypertension (13[9.6%]), diabetes (12[8.9%]), cardiovascular disease (7[5.2%]), and malignancy (4[3.0%]). Of these cases admitted, there were 95(70.4%) mild cases and 40(29.6%) severe cases. Common clinical features the patient presented with included pyrexia (120[88.9%]), cough (102[76.5%]), and fatigue (44[32.5%]) while radiological examination with chest computed

tomography (CT) scans showed bilateral patchy shadows or ground glass opacity in the lungs of all the patients. Following this treatment, 42.9% of the admitted patients were discharged home following significant clinical and laboratory improvement in the patients while 1 patient with underlying diabetes mellitus died of COVID-19 complications. Overall, the study suggested that early introduction of lopinavir / ritonavir and interferon and the add-on TCH into early clinical management of COVID-19 associated pneumonia could be highly beneficial in the overall clinical outcome of treated COVID-19 patients.

3.19. Role of Homoeopathy in COVID-19 Management- A Clinical Experience [47].

This is an empirical Indian human trial involving the use of capsules of an Ayurvedic medicinal plant, Arsenicum album 30, in the prevention of COVID-19 infections in patients already undergoing homoeopathy. The study was conducted within the facilities of Ahmedabad Homoeopathic Medical College (AHMC), Ahmedabad, Gujarat, India between January and February 2020. The study involved and recruited 420 participants from over 100 Indian families with no COVID-19 related symptoms but already on homoeopathic treatment for chronic ailments such as bronchial asthma, hypertension and diabetes mellitus. The patients were orally administered Arsenicum album 30 capsules on daily basis for 6 weeks and followed up for 8-12 weeks for possible development of COVID-19 symptoms such as fever, non-productive cough, and throat pain/itching, body ache, headache, shortness of breath, diarrhea, nausea and runny nose that were used as measuring clinical endpoints for COVID-19 infection.

Results of this study showed that of the 420 patients recruited, 402 patients were followed up and completed the study while 17 were lost to follow up and untraceable. 100% of the fully treated patients did not develop any form of symptoms neither during the treatment nor follow-up periods. Although 17 patients were untraceable and lost to follow-up, none of their name was published in the list of positive cases published by Indian government authority and were, therefore, considered benefited from the preventive homoeopathic Arsenicum album 30 remedy. Based on these finding, Arsenicum album 30 remedy was considered an effective chemoprophylaxis against COVID-19 infection.

4. Discussion

Since the emergence of COVID-19 (also known as SARS-CoV-2, or 2019-nCoV), clinicians and researchers have made concerted efforts to deeply understand the pathogenesis and clinical characteristics of this infection with the view of discovering, designing and developing effective therapeutic drugs as there are no effective antiviral drugs available yet for SARS-CoV-2 treatment [42]. Although over 700 different clinical trials currently ongoing worldwide, it might take several months to years to develop efficacious drugs and vaccines against SARS-CoV-2 infection apparently due to the genomic structure and complexity of the novel virus while still considering the safety and efficacy of such drugs [48, 49]. However, with the exception of remdesivir which has only obtained emergency use authorization (EUA) from the FDA, no other drugs or biologics have proven to be relatively effective for either the prevention or treatment of critically ill COVID-19 patient [15, 50]. Remdesivir, based on preliminary data, has been shown to offer faster recovery time and shortened hospital stay of in patients with severe form of the disease although further large scale multicenter studies are currently ongoing to further assess its efficacy and safety as a choice drug in the disease treatment [34].

Similarly, orthodox antiviral agents such as lopinavir, ritonavir, umifenovir, ribavirin, α-interferon and interferon beta-1b, treatment with antibiotics, and palliative support with oxygen and mechanical ventilation are provisionally used in COVID-19 treatment [51, 52, 53]. Nonetheless, the efficacy and safety profile of these drugs remain major concerns as clinical data on their use in COVID-treatment are still preliminary and would require more robust and large scale validations as the number of COVID-19-associated deaths continue to increase exponentially worldwide [54]. It is against this backdrop that recently there have been public calls for "alternative" remedies (such as herbal therapies, teas, essential oils, tinctures, etc) to prevent or treat COVID-19 [55]. In most traditional medicine systems such as Traditional Chinese Medicine, Ayurveda, Traditional Japanese Medicine (Kampo), Traditional Korean Medicine, Unani and African Traditional Medicine, Traditional Aboriginal Medicine, etc., thrive in use of local herbs to treat diseases according to certain combinatorial principles. This principle was exemplified in all of the different anti-COVID-19 herbal formulas evaluated in the studies (pre-clinical and clinical) reviewed. In in vitro studies reviewed, network pharmacology which is a cost-effective network-based drug discovery and development that has been used to evaluate "compound-proteins/genes-disease" pathways and are capable of describing complexities among biological systems, drugs, and diseases from a network perspective, were adopted. This technology together with molecular docking techniques has been successfully used in the screening and discovery of effective plant derived antiviral agents [56, 57]. Similarly, these techniques were used in the screening and identification of bioactive natural compounds from herbal formulas of Chinese, Indian and African origin, with quercetin, kaempferol, luteolin and other flavonoids being the most common anti-COVID principles identified from the in vitro studies reviewed, although these bioactive compounds have previously being reported to have their potential target sites for the inhibition of 2019-nCov and other coronaviruses replication. This viral replication hindrance is known to be mediated via Cov 3C-like protease inhibition and prevention of ACE2-dependent 2019-nCOV infection thereby preventing 2019-nCOV infection [24, 39, 58, 59, 60, 61]. Similarly, other flavonoids in these herbal remedies such as baicalin, scutellarin, hesperetin, glycyrrhizin and liquiritin have previously been identified as natural compounds targeting ACE2 receptor and as such may exert antiviral effects treating and preventing the COVID-19 [62, 63, 64]. These bioactive compounds have also been reported to exert anti-oxidative stress, anti-inflammation, anti-apoptosis, antitussive and expectorant activities [65, 66, 67, 68].

These therapeutic potentials are particularly important in the treatment of severe cases of COVID-19, because the host inflammatory response is a major cause of lung damage and its associated mortality and morbidity. These appeared to be the therapeutic potentials utilized in all of the clinical trials reviewed. Similarly, it was also observed that many of the medicinal plants contained in the poly-herbal formulas utilized in the clinical studies, including Herba ephadrae, Semens armeniacae amarum), and Bupleurum chinense DC (bupleuri radix) contain active ingredients such as L-ephedrine, D-pseudoephedrine, L-methylephedrine and amygdalin which are known not only to inhibit the interaction of the 2019-nCoV virus S protein with ACE2 but also relieve pulmonary congestion and viral pneumonia [69, 70].

5. Conclusions

There is no doubt that the current pandemic has given rise to many small-sized, uncontrolled clinical trials, involving traditional mono- and poly-herbal remedies in different regions of the world and only providing empirical data from these studies. However, it has become imperative to conduct more robust, high-quality and evidence-based basic medical researches and human trials to determine the efficacy and safety profiles of these poly-herbal formulas, so that their therapeutic potentials in the clinical management of COVID-patient could be optimally utilized.

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