

Novel Therapeutic Interventions for COVID-19 Pneumonia, Vaccine Candidates, Medicinal Plants and Healthy Immune Nutrients

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Abstract

Currently, there is no effective treatment for COVID-19-infected patients. Some recent clinical studies demonstrated that alveolar epithelial cells and capillary endothelial cells of the patients' lungs were damaged contributing to acute lung injury. Wang and colleagues reported in the journal "Cell Discovery" published on March 18, 2020 that hydroxychloroquine can prevent SARS-CoV-2 (COVID-19) replication. Seven clinical trials had been registered in the Chinese Clinical Trial Registry to test hydroxychloroquine's effectiveness against COVID-19 infection. Remdesivir, a nucleoside analogue with a broad-spectrum antiviral activity and as being in the US clinical trials with near approval for use by the US FDA has been also studied in France by Gautret, *et al.* from Marseille University. The investigators feel optimistic about the French research data. Favipiravir inhibits RNA polymerase activity by the conversion of favipiravir into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase. A clinical trial on favipiravir for the treatment of COVID-19 disease was initiated by the Third People's Hospital of Shenzhen and the Clinical Medical Research Center of the National Infectious Diseases, China on February 14, 2020 achieved the promising results. As of March 27, 2020, the 7th edition of the Chinese Clinical Guidance for COVID-19 pneumonia diagnosis and treatment published by the China National Health Commission on March 4, 2020 included an interleukin (IL)-6 receptor inhibitor (a humanized anti-IL-6 receptor antibody) "tocilizumab" as an therapeutic option for severe COVID-19 patients, patients with extensive pulmonary lesions and IL-6 level elevation. "Convalescent plasma" therapy has been working on some time by the US FDA. This is not a proven treatment but is a possible treatment. Currently, several trials on mesenchymal stem cells in treating patients with COVID-19 pneumonia are ongoing. For examples, trial sponsored by Innovative Precision Medicine Group (IPM), China. *Andrographis paniculata* is most widely used to treat cold and flu symptoms. Recently, some Asian countries claimed that *Andrographis paniculata* may kill the COVID-19 and they will initiate studies on this issue in 2020 as soon as possible.

Keywords: COVID-19; Novel Therapeutic Interventions; *Andrographis paniculata*; Chloroquine; Hydroxychloroquine; Favipiravir; Remdesivir; Interleukin-6 Receptor Inhibitor; Healthy Immune Nutrients; Mesenchymal Stem Cells; Vaccines

Abbreviations

ACE 2: Angiotensin-Converting Enzyme 2; AIDS: Acquired Immunodeficiency Syndrome; COVID-19: Coronavirus Disease-2019; FDA: Food and Drug Administration; HIV: Human Immunodeficiency Virus; INF- α : Interferon-Alpha; RdRp: RNA-Dependent RNA Polymerase; RNA: Ribonucleic Acid; SARS-CoV: Severe Acute Respiratory Syndrome-Coronavirus; TMSRSS2: Type II Transmembrane Serine Protease; US: United States

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Introduction

Patients with COVID-19 pneumonia were detected in Wuhan city, China since late December 2019. More and more cases have been identified in other areas outside Wuhan city of China and abroad, particularly in Italy, Iran and other European countries, including the United Kingdom and the United States. Since December 2019, and as of March 29, 2020, 657,140 cases of COVID-19 and 30,451 deaths have been reported [1]. Currently, there is no effective treatment for COVID-19-infected patients. Some recent clinical studies demonstrated that alveolar epithelial cells and capillary endothelial cells of the patients' lungs were damaged contributing to acute lung injury. Post-mortem transthoracic needle biopsies from a COVID-19 patient with roentgenographic bilateral ground-glass opacities that was consistent with alveolar damage and respiratory failure revealed that there were organizing-phase diffuse alveolar damage, reactive type II pneumocyte hyperplasia with denuded alveolar lining cells, intra-alveolar fibrous exudates, chronic inflammatory infiltrates, loose interstitial fibrosis and intra-alveolar loose fibrous plugs indicating organizing pneumonia [2]. Inhibition of pulmonary inflammatory response is hypothesized to be the key to cure the patients with COVID-19 pneumonia.

Chloroquine and hydroxychloroquine

Chloroquine, a potential broad-spectrum antiviral agent found in 2006, can interfere with the virus's ability to replicate in two ways. First, the drug enters compartments called "endosomes" within the cell membrane. Endosomes tend to be slightly acidic, the chemical structure of the drug boosts their pH, making the compartments more basic. Many viruses acidify endosomes in order to breach the cell membrane, release their genetic material and initiate replication. Chloroquine blocks this critical step. Second, chloroquine also prevents SARS-CoV from plugging into a receptor called "angiotensin-converting enzyme 2 (ACE 2)" on primate cells, demonstrated in the 2005 report [3,4]. The virus sets off a chemical process that alters the structure of the ACE 2 receptor and allows the virus to infect when the virus inserts its spike protein into the ACE 2 receptor. Chloroquine blocks COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC_{50}) of 1.13 μ M and a half-cytotoxic concentration (CC_{50}) greater than 100 μ M. An appropriate dose of chloroquine is to be undermined in this process. The investigators expect that whatever pertained to SARS-CoV-1 might apply to SARS-CoV-2 (COVID-19) [3,4].

In February 2020, Manli Wang, a virologist in a research group of the Chinese Academy of Sciences demonstrated that chloroquine successfully inhibited the spread of SARS-CoV-2 (COVID-19) in cultured human cells. Preliminary reports from China, South Korea, and France indicated that the treatment was effective in COVID-19-infected patients. Some hospitals in the United States have initiated administering chloroquine in treating severely COVID-19-infected patients. Additionally, the United States Food and Drug Administration (US FDA) is organizing a large clinical trial to formally evaluate the chloroquine's effects [3,4]. The US FDA will take all steps to ensure chloroquine remains available for patients who take it to treat severe and life-threatening illnesses, such as lupus. Nevertheless, due to the overdose of chloroquine can contribute to acute poisoning or death in humans and a short supply of chloroquine in China, Wang's research team also studied the closely related drug "hydroxychloroquine" that shares a similar chemical structure and reveals lower toxicity in animals than chloroquine and also remains widely available in treating lupus and rheumatoid arthritis. Wang and colleagues reported in the journal "Cell Discovery" published on March 18, 2020 that hydroxychloroquine can prevent SARS-CoV-2 (COVID-19) replication. Seven clinical trials had been registered in the Chinese Clinical Trial Registry to test hydroxychloroquine's effectiveness against COVID-19 infection [3,4]. The University of Minnesota, United States is studying whether taking hydroxychloroquine can protect persons living with COVID-19-infected patients from catching the virus themselves [5]. According to the American Society of Health-System Pharmacists, both chloroquine and hydroxychloroquine have been in short supply since earlier March 2020. Nevertheless, on March 19, 2020, a drug company from Germany donated 3 million tablets of chloroquine phosphate to the US federal government.

In a single protocol was studied from early March 2020 to March 16, 2020, thirty-six French COVID-19-confirmed patients were included to receive 600 mg of hydroxychloroquine daily. Azithromycin was added to the treatment protocol depending on their clinical

presentation [6]. Nasopharyngeal swabs for testing their viral load were performed daily in a hospital setting. Absence and presence of COVID-19 at Day6-post inclusion was considered the end point. Eight patients presented with lower respiratory tract symptoms, 22 cases presented with upper respiratory tract infection, whereas 6 cases were asymptomatic. Twenty cases were treated and demonstrated a significant decrease of the viral load at Day6-post inclusion, whereas adding azithromycin to hydroxychloroquine was significantly more efficient in viral load reduction [6].

Remdesivir

Remdesivir, a nucleoside analogue with a broad-spectrum antiviral activity and as being in the US clinical trials with near approval for use by the US FDA has been also studied in France by Gautret, *et al.* from Marseille University. The investigators feel optimistic about the French research data [7]. Previous studies conducted by the researchers from the University of Alberta, Canada and Gilead Sciences, Inc. involving cell cultures and animal models has demonstrated that remdesivir can block the replication of a variety of coronaviruses, hypothesized by blocking the RNA-dependent RNA polymerase, a particular enzyme that is required for viral replication [8]. Remdesivir potently blocks COVID-19 infection at low-micromolar concentration and has a high selectivity index (half-maximal effective concentration (EC_{50}), 0.77 μ M; half-cytotoxic concentration (CC_{50}) > 100 μ M; SI > 129.87) [9]. A previous study in the US reported that remdesivir treatment demonstrated promising results [10]. For evaluating the efficacy and safety of remdesivir in patients with COVID-19 disease, a randomized placebo-controlled, double-blind, multicentric phase III clinical trial was initiated on February 6, 2020 in China. The subjects in the study group received an initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days through intravenous infusion in addition to routine treatment. The control group received routine treatment and the same dose of a placebo. By the end of April 2020, the clinical trial is expected to be concluded [11-14]. Remdesivir was developed by the US pharma giant Gilead Sciences, Inc. and previously was tried to treated Middle-East-Respiratory Syndrome (MERS) and Ebola. The Credit Suisse pharma team declares that remdesivir is the most advanced novel drug in treating patients with COVID-19 disease but concerning about the supply [15].

Other compound candidates

On February 4, 2020, investigators in China announced that darunavir inhibited COVID-19 viral replication at a concentration of 300 μ M *in vitro* and its inhibition efficiency was 280-fold that in the control group. Type II transmembrane serine protease (TMSPSS2) inhibitors and BCR-ABL kinase inhibitor-imatinib are other potential drugs. TMSPSS2 inhibitors would block the entry of the cellular protease, TMPRSS2 into the target cells via ACE 2 receptor in organ with having high ACE 2 expression, such as kidney and intestine. Imatinib inhibits the fusion of virions with the endosomal membrane (anti-coronal activity) [16]. On January 25, 2020, 30 drugs with potential antiviral activity against COVID-19 performed through the drug screening in silicon and an enzyme activity test, cinanserin, cyclosporin A, TDZD-8, PX-12, tideglusib, ebselen, shikonin, carmofur, disulfiram, chalcone, polydatin, deoxyrhapontin, montelukast, raltegravir, maribavir, elvitegravir, bortezomib, abacavir, presatovir, enzaplatovir, fosamprenavir, tipranavir, darunavir, atazanavir, remdesivir, ritonavir, carfilzomib, lopinavir, saquinavir, and indinavir were reported by a joint research team of the Shanghai Institute of Materia Medica and Shanghai Tech University [16].

The 6th edition of China national Guidelines for COVID-19 treatment, issued on February 18, 2020, recommends interferon- α (IFN- α), lopinavir/ritonavir, ribavirin, chloroquine phosphate and arbidol for treatment agents. IFN- α is administered via vapor inhalation at a dose of 5 million Units (and 2 ml of sterile water for infection) for adults, 2 times daily. Lopinavir/ritonavir is administered orally at a dose of 400 mg/100 mg for adults, 2 times daily. Ribavirin is administered via intravenous infusion at a dose of 500 mg each time for adults, 2 to 3 times daily in combination with IFN- α or lopinavir/ritonavir. Chloroquine phosphate is administered orally at a dose of 500 mg (300 mg for chloroquine) each time for adults, 2 times daily. Arbidol is administered orally at a dose of 200 mg, each time, 3 times daily. Arbidol

effectively inhibits COVID-19 infection at a concentration of 10 - 30 μM *in vitro*. The duration of all treatment options is no more than 10 days [16].

Favipiravir

On February 15, 2020, favipiravir, a new type of RNA-dependent RNA polymerase (RdRp) inhibitor that was first approved in Japan in March 2014 for establishing preparedness against the possible outbreak of novel or re-emerging influenza virus infections was approved for treatment of COVID-19 disease in China. Currently, favipiravir is undergoing clinical trials in treating COVID-19 disease. In addition to favipiravir's anti-influenza virus activity, it can block the replication of alpha-, arena-, bunya-, filo-, flavi-, and other RNA viruses. Favipiravir inhibits RNA polymerase activity by the conversion of favipiravir into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase. A clinical trial on favipiravir for the treatment of COVID-19 disease was initiated by the Third People's Hospital of Shenzhen and the Clinical Medical Research Center of the National Infectious Diseases, China on February 14, 2020 achieved the promising results. The preliminary results from a total of 80 patients with COVID-19 disease, including the control group and the experimental group demonstrated that favipiravir had more potent antiviral activity than that of lopinavir/ritonavir. Favipiravir treatment group demonstrated no significant adverse reactions and had significantly fewer adverse effects than the lopinavir/ritonavir group [16].

Interleukin-6 inhibitors

As of March 27, 2020, the 7th edition of the Chinese Clinical Guidance for COVID-19 pneumonia diagnosis and treatment published by the China National Health Commission on March 4, 2020 included an interleukin (IL)-6 receptor inhibitor (a humanized anti-IL-6 receptor antibody) "tocilizumab" as an therapeutic option for severe COVID-19 patients, patients with extensive pulmonary lesions and IL-6 level elevation [17]. High IL-6 level is observed in COVID-19 patients for at least 2 weeks after disease onset. This IL-6 inhibitor demonstrated the positive outcomes in 21 severe COVID-19 patients with severe pulmonary inflammation. There are several ongoing or planned studies for the US Food and Drug Administration (FDA)-approved IL-6 inhibitors in patients with COVID-19 as the following: 1) NCT04310228 (multicenter, open label, randomized control trial (3 arms)), favipiravir+tocilizumab, compared with favipiravir alone or tocilizumab alone, date of primary completion-May 2020); 2) NCT04306705 (retrospective cohort study (3 arms), tocilizumab with standard of care, compared with continuous renal replacement therapy with standard of care or standard of care alone, date of primary completion-May 2020); 3) NCT04322188 (observational, case-control study, siltuximab, compared with standard of care, date of primary completion-May 2020); 4) NCT04317092 (single-arm, multicenter, phase II, observational cohort study, tocilizumab, no comparator, date of primary completion-December 2020); 5) NCT04321993 (open label, phase II, non-randomized study, lopinavir/ritonavir, hydroxychloroquine sulphate, baricitinib, sarilumab, no comparator; date of primary completion-February 2021); 6) NCT04315298 (double blind, phase II/III, randomized control trial (3 arms), high dose sarilumab, low dose sarilumab, compared with placebo, date of primary completion-March 2021); 7) NCT04320615 (multicenter, open label, randomized control trial (4 arms), intravenous tocilizumab, subcutaneous tocilizumab, subcutaneous sarilumab, compared with standard medical care, date of primary completion-June 2021); 8) NCT04320615 (multicenter, double blind, phase III, randomized control trial, tocilizumab, compared with placebo, date of primary completion-August 2021) [17]. A trial "COVACTA" on tocilizumab will recruit about 330 COVID-19 patients around the world, with expected start date sometime in early April 2020 [18]. A drug company in the US has announced the initiation of a randomized controlled clinical trial of sarilumab, an antibody to the interleukin (IL)-6 receptor, to evaluate whether the modification of the lung inflammatory response by therapeutic intervention provides the benefit to COVID-19-infected patients [16].

Although none of the IL-6 inhibitors are mentioned by the World Health Organization (WHO), the Society of Critical Care Medicine, and the European Society of Intensive Care Medicine, a number of professional bodies have included tocilizumab as a therapeutic option for selected severe COVID-19 patients as the following: 1) Chinese Clinical Guidance for COVID-19; 2) The Italian Society of Infectious Diseases

and Tropical Diseases COVID-19 Guidelines; 3) Michigan Medicine (University of Michigan); and 4) The Society for Immunotherapy of Cancer. Several other US FDA-approved IL-6 inhibitors currently are in trials: ALX-0061, ARGX-109, BMS945429 (ALD518), clazakizumab, CPSI-2364, elsilimomab, FE301, FM101, olokizumab (CDP6038), olokizumab, sirukumab (CNT0136) and sirukumab. Other promising drugs includes Janus kinase (JAK) inhibitors (baricitinib, inositol-requiring transmembrane kinase/endoribonuclease (IRE1 α)), tylophorine based compounds, and tracolimus [19].

Convalescent plasma

“Convalescent plasma” therapy has been working on some time by the US FDA. This is not a proven treatment but is a possible treatment. The immunoglobulins in the previously COVID-19-exposed individuals’ circulating virus-free convalescent plasma could potentially provide a benefit to severely COVID-19-infected patients [20].

Mesenchymal stem cells

Currently, several trials on mesenchymal stem cells in treating patients with COVID-19 pneumonia are ongoing. For examples, trial sponsored by Innovative Precision Medicine Group (IPM), China, Wuhan Houshenshan Hospital, Wuhan, China, Tianjin Haihe Hospital, VCANBIO CELL and GENE ENGINEERING CORP, LTD., China, Shenzhen Third People’s Hospital, and Fifth Affiliated Hospital, Sun Yat-Sen University, China (NCT04252118); trial on human umbilical cord mesenchymal stem cell treatment for COVID-19-pneumonia patients sponsored by Wuhan Union Hospital, China and Wuhan Hamilton Bio-technology Co., Ltd., China (NCT04273646); trial on inhalation of mesenchymal stem cell exosomes in treating COVID-19-pneumonia patients sponsored by Ruijin Hospital, China, Shanghai Public Health Clinical Center, Wuhan Jinyintan Hospital, Wuhan, China, and Cellular Biomedicine Group Ltd. (NCT04276987); trial on human umbilical cord mesenchymal stem cells for treatment of COVID-19-pneumonia patients sponsored by Puren Hospital Affiliated to Wuhan University of Science and Technology and Wuhan Hamilton Bio-technology Co., Ltd. (NCT04293692); trial on dental pulp mesenchymal stem cell treatment for COVID-19-pneumonia patients sponsored by CAR-T (Shanghai) Biotechnology Co., Ltd. (NCT04302519); and trial on mesenchymal stem cells in treating patients with COVID-19 pneumonia sponsored by Beijing 302 Hospital, VCANBIO CELL and GENE ENGINEERING CORP, LTD., China, Wuhan Huoshenshan Hospital, Wuhan, China, Tianjin Haihe Hospital, Shenzhen Third People’s Hospital, Fifth Affiliated Hospital, Sun Yat-Sen University, China, Wuhan Union Hospital, China, and West China Hospital (NCT04288102) [13].

Promising medicinal plants

Andrographis paniculata (Green chiretta) (Figure 1), a medicinal plant, known as “Indian echinacea” is an herb used in traditional Chinese medicine and ayurveda. *Andrographis paniculata* is native to India and Sri Lanka but is naturalized in many tropical countries, such as Thailand, Malaysia, Java and Borneo where it grows isolated patches on roadside, near drain, in between wall cracks, lowlands, hillside, coastlines and other cultivated or disturbed areas, such as wastelands. It is a bitter-tasting herb rich in compounds known as andrographolides that is hypothesized to have antiviral, anti-inflammatory, and antioxidant properties. This herb is said to act as a natural immune-booster [21]. Other major bioactive compounds are flavonoids, polyphenols, and diterpenoids [22]. *Andrographis paniculata* is most widely used to treat cold and flu symptoms and is also used to treat other diseases and symptoms, such as human immunodeficiency-virus infection (HIV)/acquired immunodeficiency syndrome (AIDS), infections, parasitic infestations, sinus infections, cancer, rheumatoid arthritis, hepatic problems, cardiac diseases, anorexia, allergies, ulcers, and skin diseases. Nevertheless, there is not enough scientific evidence to support the use of *Andrographis paniculata* for most of these health benefits. Some preliminary studies demonstrated that *Andrographis paniculata* may offer the health benefits, such as upper respiratory tract infections and ulcerative colitis.



Figure 1: *Andrographis paniculata* (Green chiretta). (Source: indiamart.com).

Andrographis paniculata may trigger adverse side effects like fatigue, headache, nausea, diarrhea, and allergic reaction. *Andrographis paniculata* should not be administered intravenously due to possible acute renal injury. Individuals using some medications, such as anti-hypertensive medicines, chemotherapy drugs, blood-thinning drugs, etc. should consult a clinician before using *Andrographis paniculata*. Little is known about the safety of using *Andrographis paniculata*. There is no single recommended dose of *Andrographis paniculata* due to various dose studies. Some previous studies revealed that for relief of sore throat, a dose of 3 - 6 grams *Andrographis paniculata* was used once a day. For ulcerative colitis, *Andrographis paniculata* extract, 1,200 - 1,800 milligrams was used once a day for eight weeks. For common cold, a combination product (4 - 5.6 milligrams Andrographolide and 400 milligrams Siberian ginseng) was used three times daily, whereas another previous study demonstrated using Andrographis extract (KalmCold) 200 milligrams once a day for 5 days [23]. Recently, some Asian countries claimed that *Andrographis paniculata* may kill the COVID-19 and they will initiate studies on this issue in 2020 as soon as possible. Meanwhile a joint research team of the Shanghai Institute of Materia Medica and Shanghai Tech University conducted a research and demonstrated that Chinese herbal medicines, such as *Radix Sophorae Tonkinensis* and *Rhizoma Polygoni Cuspidati* may contain ingredients against COVID-19. Until now, it has been difficult to get the polymerase complex that contains multiple proteins to function in a test tube [16].

Vaccine candidates

Trials on several vaccine candidates, currently are also ongoing, for examples; phase I trial sponsored by Moderna Therapeutics, CanSino Biologics, Arcturus Therapeutics (Preclinical stage), BioNTech (Preclinical stage), CureVac (Preclinical stage), GlaxoSmithKline (Preclinical stage), Inovio Pharmaceuticals (Preclinical stage), Johnson and Johnson (Preclinical stage) and Pfizer (Preclinical stage), Sanofi (Preclinical stage). Usually, vaccine development takes more than 5 years and requires much capital investment. There is no guarantee of success though the traditional pharma giants' experience involving seasonal flu, particularly their specializing in mRNA molecules that are used to instruct the human body to produce its own response to combat a range of diseases [24].

Healthy immune nutrients

In the face of pathogens, some nutrients have been demonstrated to support immunity. A healthy diet, such as micronutrients, protein, and essential fats will health individuals to be more resilient and healthier. For examples, having sufficient vitamin A is associated with immunity to infections and illness. Vitamin C is currently getting a lot of attention in the time of the COVID-19 pandemic, both positive and negative. Some previous studies demonstrated that vitamin C might assist in reduction of symptoms of colds and shorten their illness duration and might assist in preventing the occurrence of colds in individuals prone to higher levels of stress and athletes when regularly taken [25-27]. Currently, several trials on vitamin C effects and COVID-19 are undergoing in China, such as in Hubei (NCT04264533, ChiCTR2000029768 <http://www.chistr.org.cn/showproj.aspx?proj=49131>), Shaanxi and Hubei (ChiCTR2000029957 <http://www.chictr.org.cn/showproj.aspx?proj=49633>), Hubei and Shaanxi (ChiCTR2000030135 <http://www.chictr.org.cn/showproj.aspx?proj=50002>) [13]. Vitamin D is a principal immune regulator and has demonstrated promise for assisting several auto-immune conditions. Vitamin E has immunomodulatory and anti-inflammatory effects. Bioflavonoids from plants can reduce upper-respiratory-tract infections, indicated by previous research. Trial on alpha lipoic acid and COVID-19 is also undergoing in China (ChiCTR2000029851 <http://www.chictr.org.cn/showproj.aspx?proj=49534>) [13].

Other foods that might boost the immune system, based on previous studies are: 1) non-dairy, unsweetened dark chocolate (containing theobromine, an antioxidant); 2) blueberries (containing anthocyanin, a type of flavonoid, an antioxidant); 3) curcumin or turmeric; 4) fish rich in omega oil (containing omega-3 fatty acids); 4) broccoli; 5) sweet potatoes; 6) spinach (containing carotenoids, flavonoids, vitamin C, vitamin E, antioxidants); 7) ginger (antioxidant); 8) garlic (a common home remedy for the prevention of colds); 9) matcha or green tea (containing flavonoids-may reduce the risk of a viral infection, small amount of caffeine); 10) kefir (an antioxidant); 11) sunflower seeds (containing rich vitamin E, an antioxidant); 12) almonds (containing rich vitamin E, an antioxidant); 13) kiwifruit and orange (containing rich vitamin C-may reduce the duration of common cold and improve immune function); and 14) red bell pepper [28].

Conclusion

In conclusion, currently, there are no finally verified antivirals and vaccine candidates specific to COVID-19. Further preclinical and clinical trials are urgently needed to successfully treat patients with COVID-19 disease and preventing individuals from COVID-19 infection. *In vitro* and *in vivo* studies are needed before beginning the clinical trials on killing effects of *Andrographis paniculata* on COVID-19 for clinical safety and its efficacy in patients with COVID-19 infection. In addition to taking the various boosting-healthy-immune-system foods mentioned above during the COVID-19 pandemic, the individuals should follow the guidance for maintaining a balance diet: 1) eat fruits and veggies, 2) eat smaller meals more frequently and 3) drink plenty of fluids.

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