*Journal of Ayurvedic and Herbal Medicine 2020; 6(3): 149-153*


***Research Article***

ISSN: 2454-5023
J. Ayu. Herb. Med.
2020; 6(3): 149-153

www.ayurvedjournal.com
Received: 23-08-2020
Accepted: 19-09-2020

# *In-silico* screening of active molecules from medicinal plant resources for controlling SARS-CoV-2 infection

**Rajdeep Ghosh[1], Satadru Palbag[2], Debasish Ghosh[3*]**

***1*** GSL Medical College and General Hospital, NH 16, Lakshmipuram, Rajahmundry-533296
**2** ISM Drugs Control, 205, Vivekananda Road, Kolkata-700006. India
**3** Vishwanath AyurvedMahavidhyalaya And Hospital, 94, Grey Street, Kolkata, India

## ABSTRACT

The entire human population is under treat of SARS-Cov-2 virus causing life threatening complicacies. Three proteins namely papain-like protease (PLpro), 3C-like protease (3CLpro) and spike protein isolated from the virus have been targeted for formulating the antiviral medicament. Ayurvedic medicinal plants with established antiviral efficacy are great choice to design immediate treatment strategies in this trying time. Here, 9 active molecules from ayurvedic medicinal plant resources were selected, out of which only 6 have screened through ADME analysis and molecular docking was performed with the three viral proteins to understand their antiviral performances in in silico model. Outcome of this study will surely open up a floodgate of thousand new possibilities in exploiting the existing natural herbs in COVID 19 treatments.

**Keywords:** ADME analysis, Antiviral activity, Medicinal Plants, Molecular Docking, SARS-CoV-2, Viral proteins

## INTRODUCTION

At the beginning of 2020, a new novel SARS-CoV-2 viral disease with flu or influenza like symptoms has introduced a global pandemic causing a mammoth human loss. The epicenter of the disease is believed to be Wuhan province of China [1]. The zoonotic transmission of the contagious disease quickly transformed its course into human to human transmission, resulting in rapid spread of the disease in a very short time span. On 30th January, 2020, declaration of a public health emergency and temporary recommendations by the Director-General of the World Health Organization (WHO)emerged a global concern on the pandemic issue [2]. Thespecific vaccines and antiviral agents needed to overcome the emergency, demands adequate research and time to serve the population. A number of medicines has been surfaced in the meanwhile as an effective mean of disease control, but failed to sustain for long due to the quick alteration of the virus nature and character [3-5].

Among the SARS-CoV-2 encoded proteins reported till date, three proteins namely papain-like protease (PLpro), 3C-like protease (3CLpro) and spike protein play pivotal role in invasion, infection establishment and replication of the virus inside the host body. Being mandatory tool for the virus in disease causing and continuing the life cycle, these proteins draw special attention to the scientific community in preventing and treating the viral infection. For example, Successful inactivation or structural alteration of viral 3C-like protease (3CLpro) or spike (S) protein hold promises in arresting the viral life cycle progression and entry into the host body respectively. Thus, working on drug designing, these proteins are considered as target molecules to fight against the notorious virus SARS-Cov-2 [6-11].

In search of a suitable and sustainable alternative to cope up with the newly emerged scenario, the traditional medical systems are of special attention. Ayurveda is considered by many scholars to be the oldest healing science. In Sanskrit, Ayurveda means “The Science of Life.” The knowledge originated in India more than 3000 years ago and is often called the “Mother of All Healing.” The knowledge of plant sciences resides in several Nighantus which may be termed as Ayurvedic Lexicons. Several plants in Ayurveda exhibits potent antibacterial, antifungal and antiviral activities through several stages of research by means of modern scientific community. In day to day practice or home remedies we used these plants from generations after generation for the management of several viral diseases, such as for the management of viral fever or common cold, specially for juvenile patients we usually administers basil leaves juice as a normal house hold remedy. We also use ginger and black piper infusion for the treatment. Modern science supports the antiviral activities of several ayurvedic plants through several published papers. Till date in

***Corresponding author:**
***Dr. Debasish Ghosh***
Vishwanath Ayurved Mahavidhyalaya And Hospital, 94, Grey Street, Kolkata, India
*Email:* *drdghosh71@gmail.com*

Asian and African continent, herbal medicines are effectively practiced and serving the mankind in disease control [12]. Literature say, > 250,000 higher plant species reserve the unexplored active molecules of enormous medicinal importance [13]. The plant based natural products not only exhibit potential antimicrobial efficacy that limits the chances of microbial infections onto the host body, but also imparts an immune-modulatory role which strengthen the host immune system to fight against the pathogen. The multifaced approach of the plant based medicines provide better protection to the host in terms of disease control. For instance, in 2003, SARS outbreak in China was successfully controlled by the traditional herbal treatments [14-20].

However, the impressive medicinal properties of thousands of plants,impose critical challenge in deciding the appropriate ones effective against SARS-Cov-2. Based on the established evidences available in scientific literature, 9 medicinal plants with significant antiviral efficacy were selected for this study. Traditional utility, availability and disease curing ability were the primary criteria followed for this selection. To determine their possible exploitation in combating SARS-Cov-2, a two-step screening protocol has been followed. Initially, the active components of the selected herbs, playing pivotal role in pathogen control have been screened through network pharmacology analysis that ensures their medicinal application for treating illness. Further, the most suitable compounds were docked with the important viral protein molecules, ensuring the antiviral potency of these compounds at molecular level. The entire study has been performed in *in silico* model to achieve conclusion in short time span.

## METHODOLOGY

***Plant selection:*** The medicinal plants selection was based on the established efficacy in treating viral infections with cough and cold, flu or influenza like symptoms. Ayurvedic plants in table 1 have been selected by us through the support of the data as available in the articles, published in the English language from Web of Science, Cochrane Library, AMED, CISCOM, EMBASE, MEDLINE, Scopus, and PubMed by using relevant keywords including plants possessing antiviral activity, the antiviral effects of plants, and plants used in viral disorders.

**Table 1:** Selected Medicinal plants with antiviral potency and the related active compounds**.**

| Traditional name | Botanical name | Active component | References |
|---|---|---|---|
| Neem | *Azadirachta indica* | Azadirachtin | [21] |
| Pipul | *Piper longum* | Piperine | [22] |
| bhuiamlaki | *Phyllanthus niruri* | Phyllanthin | [23] |
| Tulsi | *Ocimumsanctum* | Ursolic acid | [24] |
| | | | |
| Haldi | *Curcuma longa* | Curcumin | [25] |
| Durva | *Cynodondactylon* | Hexadecanoic acid | [26] |
| Ginger | *Zingiber officinale* | α, β zingiberene | [27] |
| Anantamool | *Hemidismus indicus* | Hexatriacontane | [28] |
| Parijat | *Nyctanthes arbor-tristis* | Nicotiflorin | [29] |

***Network pharmacology analysis:*** Considering the oral intake as most preferable route of drug administration, ADME (absorption, distribution, metabolism and excretion) screening was performed using SwissADME online tool. The parameters used for this screening study includes drug likeness, solubility, bioavailability, GI absorptionof the active components of the medicinal herbs. The screening of the herbs wasbased on their fitness in Veber, Egan and Lipinski's rule of five [30].

***Molecular docking:*** Molecular docking is a bioinformatic modelling that involves the interaction of two or more molecules to give the stable adduct. Depending upon binding properties of ligand and target, it predicts the three-dimensional structure of any complex.

The 3D structure of the 6M0J.pdb (spike protein), 6W9C.pdb (papain-like protease) and 7BQY.pdb (3C-like protease) were downloaded from the protein data bank. The molecular docking and visualization using discovery studio are performed as followed by Sribalan *et al.,* 2016 and Banuppriya *et al.,* 2018 [31, 32]. Molecular docking was performed using the Autodock 4.2 software. The 3D structures of molecules were optimized using Chemdraw 13.0 using MMFF 94 (Maximum number of interactions: 5000, minimum RMS gradient: 0.100). All avoidable water and ligand were removed from the protein and the default docking parameters were fixed and performed.

## RESULTS AND DISCUSSIONS

***Network pharmacology analysis:***

The selected ayurvedic herbs presented in Table 1 were subjected to ADME screening and results are presented in Table 2. Analyzing the data presented in Table 2, the low bioavailability and GI absorption of azadirachtin, hexatriacontane and nicotiflorin restricts the oral administration of Neem, Anantamool and Parijat in SARS-Cov-2 treatment. In contrast, the higher bioavailability of piperin, phyllanthin, ursolic acid, curcumin, hexadecanoic acid and zingiberene signifies their possible utilization in the mentioned purpose. Furthermore, better fitting into Lipinski, Egan and Veber filter of these molecules strengthen their medicinal applicability compared to the other molecules. Among these 6 molecules, piperine and curcumin is of greater importance due to their high solubility in aqueous medium that facilitates better GI absorption (Table 2).

**Table 2:** Pharmacology Network analysis through ADME screening of the active molecules in selected ayurvedic herbs**.**

| Plant resource | Name of the Active Molecules | GI Absorption | Bioavailability | Solubility (in water) | Drug likeness | | |
|---|---|---|---|---|---|---|---|
| | | | | | Lipinski filter | Egan filter | Veber filter |
| *Azadirachtaindica* (Neem) | Azadirachtin | Low | 17% | Moderately soluble | No | No | No |
| *Piper longum*(Pipul) | Piperine | High | 55% | Soluble | Yes | Yes | Yes |
| *Phyllanthus niruri* (bhuiamlaki) | Phyllanthin | High | 55% | Moderately soluble | Yes | Yes | No |
| *Oscimumsanctum(Tulsi)* | Ursolic acid | Low | 56% | Poorly soluble | Yes | No | Yes |
| *Curcuma longa*(Haldi) | Curcumin | High | 55% | Soluble | Yes | Yes | Yes |
| *Cynodondactylon (Durva)* | Hexadecanoic acid | High | 56% | Moderately soluble | Yes | Yes | No |
| *Zingiber officinale* (Ginger) | Zingiberene | Low | 55% | Moderately soluble | Yes | Yes | Yes |
| *Hemidismus indicus* (Anantamool) | Hexatriacontane | Low | 17% | Insoluble | No | No | No |
| *Nyctanthes arbor-tristis*(Parijat) | Nicotiflorin | Low | 17% | Soluble | No | No | No |

**Molecular docking:** The six active molecules with higher possibility of oral administration were then docked with three target protein molecules isolated from SARS-CoV-2. Inhibition of these target proteins directly restricts the viral activity like defending host immunity, replication and infection establishment into the host body (Zhang *et al*., 2020).The binding energy and inhibition constantbetween the target-ligand molecules determine the stability of the 3Dcomplex (Table 3).

**Table 3:** Interaction of active molecules with target proteins

| Plant resource | Active components | binding energy (Kcal/mol) | | | Inhibition constant (µM) | | | Interacted amino acids | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | PLpro | 3CLpro | spike | PLpro | 3CLpro | spike | PLpro | 3CLpro | spike |
| *Piper longum*(Pipul) | piperine | -5.93 | -7.8 | -6.17 | 45.19 | 1.92 | 6.65 | TYR273, GLY163 | TYR54, GLN189, GLN192 | TRP48, GLN340, THR334 |
| *Phyllanthus niruri* (bhuiamlaki) | Phyllanthin | -4.2 | -5.37 | -4.1 | 827.56 | 111.41 | 985.88 | LEU162, GLY16, TYR264, ASN267 | HIS164, GLY143 | VAL343, HIS345, THR347, ASN51, TRP349, TRP349 |
| *Oscimumsanctum(Tulsi)* | Ursolic acid | -5.82 | -6.72 | -5.76 | 54.25 | 11.89 | 59.8 | TYR264, TYR273, GLY163, THR301 | GLU166, HIS164, ARG188, THR190 | SER47, ALA348, TRP349, TRP349, HIS378 |
| *Curcuma longa*(Haldi) | Curcumin | -6.99 | -7.31 | -5.64 | 7.48 | 4.4 | 73.49 | GLN250, ASN267 | HIS41, GLN189, GLN192, THR190, PRO168, GLU166 | GLU406, GLU402, SER47, HIS378, HIS378 |
| *Cynodondactylon (Durva)* | Hexadecanoic acid | -2.62 | -4.45 | -1.68 | 11.98 mM | 546.72 | 58.44 mM | TYR273, THR301 | GLN192, MET49, | ASN51, TRP349 |
| *Zingiber officinale* (Ginger) | zingiberene | -5.4 | -6.65 | -4.99 | 109.21 | 13.38 | 218.33 | TYR264, GLY163 | GLN192, THR190, GLN189, HIS41, ARG188, ASP187, TYR54 | SER44, SER44, ASP350, ASP382, ASP382, TYR395, HIS401 |

In Table 3, the binding energy and the inhibition constant between active molecule and protein interactions denotes promising activities of piperine, ursolic acid, curcumin and zingiberene in combating the SARS-CoV2 virus. Piperine (from Pipul) blocks the 3CLpro and spike protein of

the virus, thus capable of restricting the virus entry and multiplication inside the host body. Similarly, ursolic acid (from Tulsi) and zingiberene (from Zinger) show promising interactionswith 3CLpro protein and expected to be active in inhibiting viral replication inside the host cell. Again, curcumin (from Haldi) actively binds with PLpro and 3CLpro proteins, thus arrests the viral efficacy against host immunity and multiplication inside the host cell (Fig 1). comparing the antiviral efficacy, piperine and curcumin are most preferable followed by ursolic acid and zingiberene. It is noteworthy to mention, the *in-silico* performances of phyllanthin and hexadecanoic acid found against SARS-CoV 2 are not promising and thus not recommended for COVID 19 treatment.

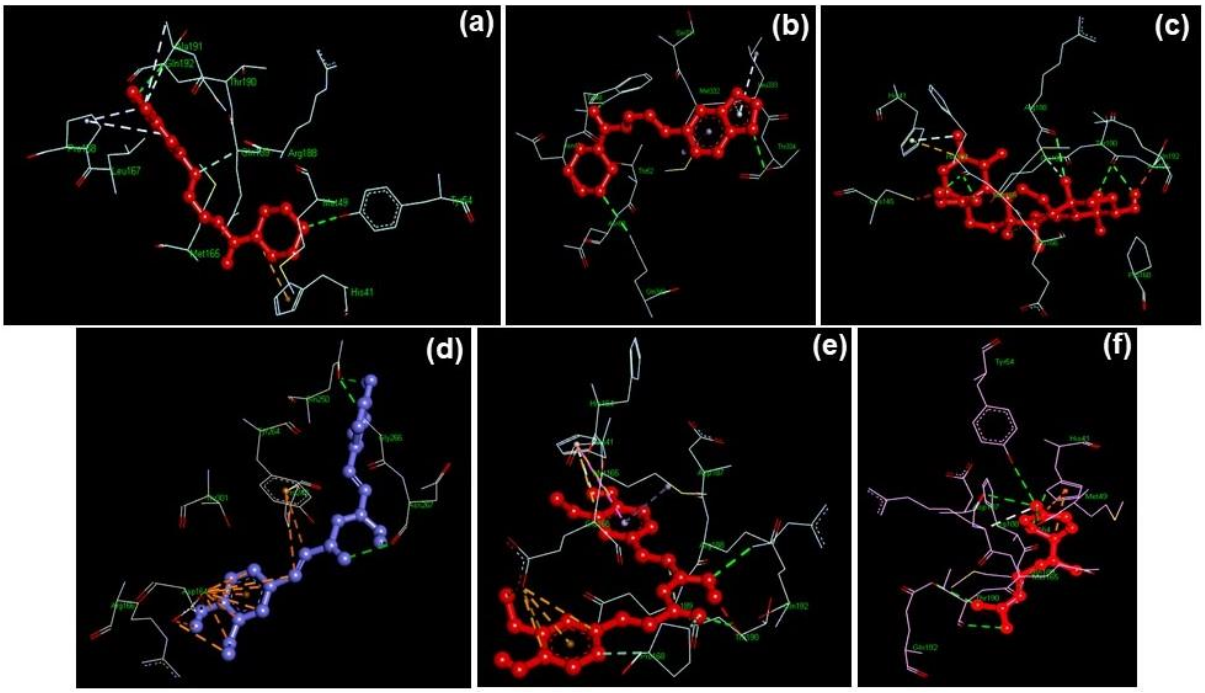


**Figure 1:** Pictorial presentation of molecular docking between Piperineand (a) 3CLpro (b) Spike protein; Ursolic acid and (c) 3CLpro; Curcumin and (d) PLpro (e) 3CLpro; Zingiberene and (f) 3CLpro protein.

**CONCLUSION**

The antiviral efficacy of the active molecules from natural resources has been studied here in *in silico* model. The interactions between the active molecules and the target protein of SARS-Cov 2 virus, ensures the higher probability of their successful utilization in overcoming the pandemic situation.

The important finding of this work can be summarized as:

- Piperine (from Pipul) interacts with the 3CLpro and spike protein of the virus, that ensures inhibition of the virus entry and multiplication inside the host body.
- Ursolic acid (from Tulsi) and zingiberene (from Ginger) are expected tosuccessfully arrest viral replication by interacting with 3CLpro protein, that is mandatory for viral replication.
- Curcumin (from Haldi) blocks PLpro and 3CLpro proteins, thus capable of restricting the viral efficacy against host immunity and multiplication inside the host cell.

The *in-silico* study outcomes can be taken further for *in vivo* study and clinical trials for dose determination, immunomodulation efficacy and many more prior to recommendation for SARS-CoV 2 treatment by the scientific community.The results show enormous scope and promise as effective medication for SARS-CoV2 infection. Further, we suggest, along with independent application of these active molecules, their synergistic application is also recommended in *invivo* study and clinical trials, which may show greater efficacy in controlling the viral infection.

**REFERENCES**


1. Paraskevis D, Kostaki EG, Magiorkinis G, Panayiotakopoulos G, Sourvinos G, Tsiodras S. Full-genome evolutionary analysis of the novel corona virus (2019- nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect Genet Evol2020;79:104212.
2. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV).
3. As cited from the website, https://www.mohfw.gov.in/ (dated 1st April, 2020)
4. As citedfromthewebsite,https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf(dated 1st April, 2020)
5. As cited from the microwebsite http://ayush.gov.in/covid-19(dated 1st April, 2020)
6. Bhoj VG, Chen ZJ. Ubiquitylation in innate and adaptive immunity. Nature2009;458(7237):430-7.
7. Isaacson MK, Ploegh HL. Ubiquitination, ubiquitin-like modifiers, and deubiquitination in viral infection. Cell Host Microbe 2009;5(6):559–70.

8. Mukherjee P, Shah F, Desai P, Avery M. Inhibitors of SARS-3CLpro: virtual screening, biological evaluation, and molecular dynamics simulation studies. J Chem Inf Model 2011;51(6):1376-92.
9. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, *et al*. Angiotensinconverting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450-4.
10. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020.
11. Tian HY. 2019-nCoV: new challenges from coronavirus. Zhonghua Yu Fang Yi Xue Za Zhi 2020;54:E001.
12. Bishop FL, Lewith GT. 2010. Who uses CAM? A narrative review of demographic
13. characteristics and health factors associated with CAM use. Evid Based Compl Alt Med.7(1):11-28.
14. Zaker, M. Natural Plant Products as Eco-friendly Fungicides for Plant Diseases
15. Control- A Review. The Agriculturists. 2016, 14, 134-141.
16. Chen Z, Nakamura T. Statistical evidence for the usefulness of Chinese medicine in the treatment of SARS. Phytother Res 2004;18(7):592–4.
17. Lai L, Han X, Chen H, Wei P, Huang C, Liu S, *et al*. Quaternary structure, substrate selectivity and inhibitor design for SARS 3C-like proteinase. Cur Pharm Des 2006;12(35):4555–64.
18. Wang SQ, Du QS, Zhao K, Li AX, Wei DQ, Chou KC. Virtual screening for finding natural inhibitor against cathepsin-L for SARS therapy. Amino Acids 2007;33 (1):129–35.
19. Kesel AJ. Synthesis of novel test compounds for antiviral chemotherapy of severe acute respiratory syndrome (SARS). Curr Med Chem 2005;12 (18):2095–162.
20. Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YS, *et al*. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci U S A 2004;101(27):10012–7.
21. Liu B, Zhou J. SARS-CoV protease inhibitors design using virtual screening method from natural products libraries. J Comput Chem 2005;26(5):484–90.
22. Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA, *et al*. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J Med Chem 2005;48(4):1256–9.
23. Badam L, Joshi SP, Bedekar SS ('In vitro' antiviral activity of neem (Azadirachtaindica.A.Juss) leaf extract against group B coxsackieviruses. J Commun Dis 1999;31:79-90.
24. Jiang ZY, Liu WF, Zhang XM, Luo J, Ma YB, Chen JJ. Anti-HBV active constituents from Piper longum. Bioorg Med Chem Lett 2013;23:2123-2127.
25. Liu S, Wei W, Shi K, Cao X, Zhou M, Liu Z In vitro and in vivo anti-hepatitis B virus activities of the lignan nirtetralin B isolated from *Phyllanthus niruri* L. J Ethnopharmacol 2014; 157: 62-68.
26. Ghoke SS, Sood R, Kumar N, Pateriya AK, Bhatia S, Mishra A, Dixit R, Singh VK, Desai DN, Kulkarni DD, Dimri U, Singh VP Evaluation of antiviral activity of Ocimum sanctum and Acacia arabica leaves extracts against H9N2 virus using embryonated chicken egg model. BMC Complement Altern Med 2018;18:174.
27. Sornpet B, Potha T, Tragoolpua Y, Pringproa K. Antiviral activity of five Asian medicinal plant crude extracts against H5N1 avian influenza virus. Asian Pac J Trop Med 2017;10: 871-876.
28. Murali KS, Sivasubramanian S, Vincent S, Murugan SB, Giridaran B, Dinesh S, Gunasekaran P, Krishnasamy K, Sathiskumar R Anti-chikungunya activity of luteolin and apigenin rich fraction from Cynodondactylon. Asian Pac J Trop Med 2015;8:352-358.
29. Rassol A, Khan MUR, Asad Ali M, Anjum AA, Aslam A, Mustafa G, Masood S, Ali MA, Nawaz M Anti-avian influenza virus H9N2 activity of aqueous extracs of Zingiber officinalis (Ginger) and Allium sativum (Garlic) in chick embryos. Pak J Pharm Sci 2017;30:1341-1344.
30. Bonvincini F, Lianza M, Mandrone M, Poli F, Gentilomi GA, Antognoni F Hemidesmus indicus (L.) R. Br. Extract inhibits the early step of herpes simplex type 1 and type 2 replication. New Microbiol 2018;41:187-194.
31. Shastry JLN DravyaGunaVijnana, Chaukhamba Orientalia, Varanasi, India 2009, 1,
32. Dasgupta A, Dey D, Ghosh D, Lai TK, Bhuvanesh N, Dolui S, Velayutham R, Acharya K Astrakurkurone, a Sesquiterpenoid From Wild Edible Mushroom, Targets Liver Cancer Cells by Modulating Bcl-2 Family Proteins. IUBMB Life 2019;71: 992-1002.
33. Sribalan R, Banuppriya G, Kirubavathi M, Jayachitra A, Padmini V. Multiple biological activities and molecular docking studies of newly synthesized 3-(pyridin-4-yl)-1H-pyrazole-5-carboxamide chalcone hybrids. Bioorg. Med Chem Lett 2016;26:5624-5630.
34. Banuppriya G, Sribalan R, Fathima SAR, Padmini V. Synthesis of β-Ketoamide Curcumin Analogs for Anti-Diabetic and AGEs Inhibitory Activities. Chem Biodiversity 2018;15: E1800105.

**HOW TO CITE THIS ARTICLE**
Ghosh R, Palbag S, Ghosh D. *In-silico* screening of active molecules from medicinal plant resources for controlling SARS-CoV-2 infection. J Ayu Herb Med 2020;6(3):149-153.