Review Paper

SARS – CoV-2: A comparative analysis on Traditional Chinese and Indian Ayurvedic Medicine with Commercial Drugs

K.A. Divyashree, V. Snajuvikasini and P. Jeyavel Karthick*

Department of Biotechnology, Bannari Amman Institute of Technology, Sathyamangalam – 638 401, Erode District, Tamil Nadu, India jeyavelkarthick?@gmail.com

Available online at: www.isca.in, www.isca.me

Received 29th May 2020, revised 8th September 2020, accepted 23rd October 2020

Abstract

Coronavirus is a well-developed positive single-strand RNA virus and the hostname derived from the glycoprotein spikes and it surrounds the genome which is enclosed by nucleic capsid. Coronavirus belongs to the family Coronaviridae with six viruses. The transmission rate SARS-CoV-2 is higher than SARS-CoVI, because of the genetic recombinant of the spike protein in receptor binding domain region (RBD). The techniques for the finding and treatment of SARS-CoV-2 or COVID-19 incorporate Simple Closed Tube Molecular Test, LAMP Test, and PCR test. But, clinically RT-PCR is widely used for the detection of SARS-CoV-2. The researchers are still on research to develop effective medicines and vaccines for the disease SARS-CoV-2. First this pandemic disease arises in China and the treatment followed by them is based on Traditional Chinese Medicine (TCM) which is 92.09% more effective when compared to all other medicine throughout the world and the motility rate decreases against SARS-CoV-2. Even though our treatment is based on Ayurveda, in addition to this Commercial medicine is also combined with Ayurvedic and Chinese medicine for the treatment of SARS-CoV-2. In this review, we have comparatively analyzed the Traditional Chinese and Indian Ayurvedic Medicine with Commercial drugs.

Keywords: SARS-CoV-2, SARS, MERS, Spike protein in RBD, Diagnosis and treatment, System of medicine.

Introduction

A strange new sickness portrayed by Pneumonia, Pyrex, and inability to determine with antimicrobial treatment, developed in the Wuhan city in Hubei, territory; China in December 2019. China has recently observed an episode of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) and these in mellow examinations were quickly started and have recognized another zoonotic infection named SARS-CoV-2 or COVID-19¹.

Chinese spring festival is otherwise called the Chinese New Year or Lunar New Year, which is the most significant celebration celebrated for seven days. In 2020, China eagerly waiting for the festival falls on January 25th. Before this Chinese Spring Festival, China has faced an unexpected problem caused by an unknown virus. After the clinical investigation it was confirmed that this kind of virus belongs to the family-corona.

Coronavirus was begun from a warm blooded creature which was contended by the Shanghai Public Health Centre with the endorsement of the entire genome succession of this infection is identified with bat. This is epidemiologically connected to the Huanan seafood wholesale market in Wuhan. Then Wuhan officially declared the name of this virus as 2019-nCoV. Because of this series activity in slaughtering people, the World Health Organisation (WHO) said that Public Health Emergency of International Concern on January 31st, 2020¹². On January

20, In China, National Infectious Disease Law proposed that SARS-CoV-2 is a class B notifiable malady and alongside Frontier Health and Quarantine Law bought in that this isolate of SARS-CoV-2 flare-up².

Coronavirus has a well-developed envelope, single positivestranded RNA viruses which has a place with the family *Coronaviridae* and it is one of the largest RNA viruses in the world. Before the origin of SARS-CoV-2, there are six viruses found which belongs to the family *Coronaviridae* and caused disease in human.

It is classified into two major classes: i. A low pathogenic infection, for example, hCoV-229E, hCoV-HKU1, hCoV-NC63, and hCoV-0C43 are affirmed by Global Public Health Level. ii. High pathogenic productivity infection, for example Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) causes significant passing in numerous countries².

SARS-CoV-2 shows approximately 80% similarity in SARS based on structure and genomics. Along this lines, the International Committee on Taxonomy of Virus named COVID-19 as SARS-CoV-2 on eleventh February 2020. Due to the analysis of the transmission rate SARS-CoV-2 is higher than SARS-CoV1 because of the genetic recombinant of the spike protein in receptor binding domain region³. Over the whole world, SARS-CoV-2 caused lakhs and lakhs of death nearly

4,00,000. In India 1,65,799 cases were confirmed and 71,106 (42.88%) were hospitalized and almost 4,706 (2.83%) died. Several methods are made to predict the virus since there is no medicine is discovered for SARS-CoV-2.

Some methods like simple closed tube molecular test which is done in the small clinical level without the need for any sophisticated equipment, but the result is not sensitive. Another one is the Two-stage method which is enough in 100 time minimal sample than LAMP and PCR along with 1000 times sensitivity than LAMP and RT-PCR. Due to some reason this method also dropped down. The most widely and currently used method is Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)¹⁹. This outcome is anticipated by utilizing the samples of blood, sputum, defecation, alveolar lavage fluid, and nasopharyngeal swabs⁴.

With the SARS-CoV-2 outbreak, every country is in need to control the spread of the corona and safeguard mankind. Since there are no more medicines are found to cure or treat SARS-CoV-2. Some of the different fields of medicine used to treat the disease in many countries. China and India play a major role to treat SARS-CoV-2.

Traditional Chinese Medicine of China has potentially treated for SARS-CoV-2 and the Chinese government provided "integrative methods for the patients to receive TCM plus biomedicine". In India, the AYUSH medicine is most widely used to treat SARS-CoV-2 suggested by the Prime Minister of India, based on the interventional claim. In this review article, we have outline the comparative analysis of different medicinal systems involved in the treatment process.

Elucidation of SARS-CoV-2: The word "Corona" describes the meaning of "a usually coloured circle often seen around and close to a luminous body (such as the sun or moon) caused by diffraction produced by suspended droplets or occasionally particles of dust".SARS-CoV-2 produced infestation to the whole world. The new Coronavirus belongs to:

Class : Nidovirales
Group : Coronaviruses
Family : Coronaviridae
Genus : Beta-coronavirus
Sub-genres : Sarbecovirus

Coronavirus family was classified into four genera based on phylogeny: Alpha Co-V (group 1), Beta Co-V (group 2), Gamma Co-V (group 3) and Delta Co-V (group 4) within this Beta (4 lineages) A, B, C, D are recognized. SARS-CoV-2 is placed under the classification of Beta-Co-V (group 2)^{5,6}.

SARS-CoV-2 has a single stranded large positive RNA genome ranges from 26.2 - 31.7 kilobases. SARS-CoV-2 RNA genome contains 29,891 nucleotides and 9860 amino acids. It has both structural and non-structurally protein². The most significant

basic proteins are spike (S) protein (trimeric), envelop (E) protein, membrane (M) protein, and the nucleocapsid (N) protein. The most important protein which helps to enter and penetrate the human body is spike (S) protein because it can enter into Angiotensin-Converting Enzyme also called the ACE receptor. Spike protein is a transmembrane glycoprotein that mediating viral infection through the binding of the host receptor. The nucleocapsid is the most important sub-unit for the packing of the viral genome through the protein oligo polymerization^{2,5,6}.

The RNA genome of SARS-CoV-2 has seven open reading frames (ORF) that are preserved in the order of ORF1a, ORF1b, S, ORF3, E, M, N in 5' to 3' direction. Two- third fragments of the RNA genome is secured with an open reading frame (ORF). The significant open reading frame which takes in the genome furthest layer is ORF1a and ORF1b which creates the two viral replicase protein that are polyprotein known as PP1a and PP1b. PP1a and PP1b have by virally encoded chymotrypsin-like protease (3CLpro)^{2,4,6}.

This plays a major role in the main protease (M pro), spike protein, and RNA dependent RNA polymerase. SARS-CoV-2 also contains 16 Non-Structural Proteins from NSP 1 through NSP 16. Each NSP plays a vital role in their activity. These 16 NSP have come under the two proteases, named PL2 pro and 3Lpro. From NSP1 to NSP3, 3a, 3b comes under the PL2 pro and the rest NSP4- NSP16 comes under the 3Lpro⁴.

NSP1 and NSP2 play a role in gene expression in the formation of a multi-domain complex. NSP3 is the host for the gene expression. NSP5 play a vital role for the protease (M) replication. The initial stage of the target for drug development chymotrypsin-like cysteine main protease M^{pro} or 3C like protease (3CL^{pro}). NSP4 and NSP6 help for the transmembrane protein. NSP7 and NSP8 both act as primers. NSP9 is the most important non-structural protein for RNA binding protein of dimeric form for viral infection. NSP10 and NSP11 acts as a cofactor for the activation of the replication enzyme. NSP12 is a viral RNA dependent RNA polymerase, which is the most significant of each of the 16 NSP's.

It plays many vital activities and it is responsible for the replication process. It has high polymerase activity which causes fever, tiredness, and dry cough. NSP13 is for helicase activity, NSP14 for exoribonuclease action, NSP 15 for endoribonuclease action and NSP16 for the methyl transferase action. From NSP12 - NSP16 have 80-85% similarity of the human protein. The viral protein of SARS-CoV-2 attack macrophages alveoli packed TNF alpha interleukin 1 and interleukin 6 which cause high fever for the human being 7.

Since more information about the virus is an unpredictable one. Hence, the clinicians and the scientist have not found any drug or vaccine for this virus.

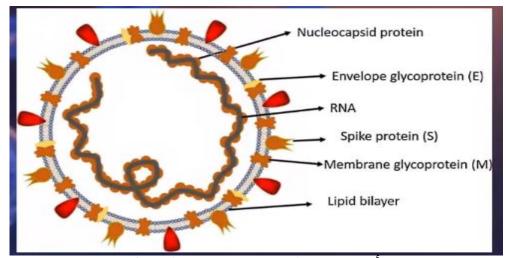


Figure-1: Common structure of SARS-CoV-2⁵.

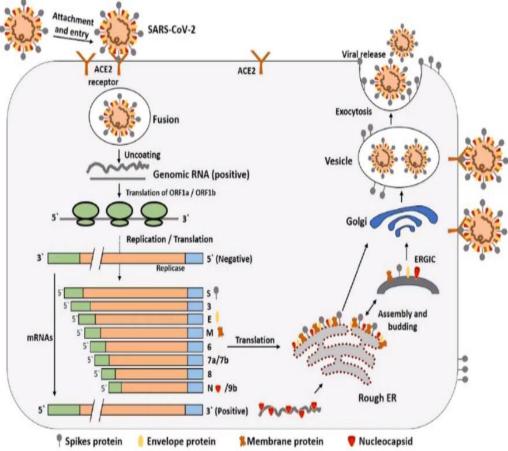


Figure-2: Mechanism of nCoV-2 on human cell⁵.

Outline of Traditional Chinese and Indian Ayurvedic Medicine with Commercial Drugs

In this part, we have reviewed that the Traditional Chinese and Indian Ayurvedic Medicine with commercial drugs. With the outbreak of SARS-CoV-2, all the kind of medicine which was

used in SARS and MERS are analyzed to treat SARS-CoV-2 throughout the world. Since there is no more drugs or vaccine are found to treat or cure disease. Some kinds of medicines are there to prevent SARS-CoV-2. China plays a major role to treat SARS-CoV-2. It is one of the world's leading exporter's of the botanical ingredients. China exports moreover the USA,

Germany, Japan, etc. Almost 3,100 Traditional Chinese Medicine (TCM) combinations related medicine were developed. At least 60,000-70,000 cases were treated by TCM. Usage of herbal plants an ingredient for the formulation of Traditional Chinese Medicine. Around the world, herbal-based products are used for many viral diseases. In China, the herbal plant comprises around 80% of Traditional Chinese Medicine products ^{9,10}.

There are currently no pharmacological treatments for SARS-CoV-2. Due to the urgent need for effective treatments, there has been increased interest in repurposing currently available drugs for immediate use. The antiretroviral lopinavir/ritonavir is a protease inhibitor, which is utilized for the treatment of HIV and is a potential for the treatment of SARS-CoV-2. There has been no proof from randomized preliminaries of the viability of lopinavir/ritonavir in rewarding SARS or MERS. Remedisivir is a broad-spectrum antiviral medication is being tested as a specific treatment for SARS-CoV-2 and also provided by Emergency use authorization in the U.S. for those hospitalizations with severe disease. Ribavirin also used to treat SARS-CoV-2 as RNA dependent RNA polymerase inhibitor. Hydroxychloroquine and a related drug, chloroquine, are currently used as a possible treatment for SARS-CoV-2. This is the illness caused by the new coronavirus. These medication have not yet been affirmed by the Food and Drug Administration (FDA) utilization⁶.

An ancient writing is related to "holistic and natural" approach to mental and physical health and it is termed as Ancient Indian Medical system. Indian government recommended AYUSH methodology to treat SARS-CoV-2. AYUSH includes Siddha, Ayurveda, Yoga, Unani, Homeopathy, Naturopathy. The world's oldest medicine is termed as Indian Avurvedic medicine and also reminds as India's traditional health care system. Ayurvedic treatment not only includes plants but it may also include animals, metals, minerals, etc. It was developed more than 3,000 years ago in between 2500 and 500 BC in India. More than 60,000 plant species were used throughout the world. Almost 28,000 plants were well documented and more or less 3,000 species were estimated¹³.

Even though, everyone known fact is that there is no more system of medicine has any approved evidence for SARS-CoV-2 based on the treatment.

Traditional Chinese Medicine: With the outbreak of SARS-CoV-2, the use of all the plants as an herbal ingredient for the formulation of the Traditional Chinese Medicine. In China, the herbal plant plays a major in the field of medicine of about 80% of the product. China is one of the most significant exporters of natural fixings all throughout the world. Traditional Chinese Medicine brings great hope for the treatment and prevention of SARS-CoV-2 in China. It assumes a key job in the treatment of numerous pandemic maladies and accomplished a striking impact on SARS-CoV-2. There is some Traditional Chinese

Medicine which does not just restrain the viral replication yet it can keep from disease, expanding body insusceptible reaction, and remove the provocative tempest.

Based on clinical studies, overall symptoms of the infected patient showed that the particular herbs and herbal formulated medicine potentially increase the time of recovery from SARS-CoV-2 and also shows natural plant medicine effectively fight against the SARS-CoV-2 and its conditions. China's Heilongjiang University treated 102 SARS-CoV-2 infected patients and similarly compared their outcomes. They found that Traditional Chinese Medicine has some potential benefits to treat SARS-CoV-2. Outcomes show that decreased symptoms and body temperature within 2 days. Further, it shows an increase in clinical cure rate and immune system markers such as lymphocyte of about 70 percent⁹.

Traditional Chinese Medicine is prescribed based on the infected patient's condition and physical strengthening. The concentrate contained in Chinese herbs to the specific forsythia, honeysuckle, and *Scutellaria baicalensis* are utilized to treat cold, hack with fever, and sore throat ¹². The formulation medicine that suggest to treat SARS-CoV-2 is qingfei paidu concoction, gancaoganjiang concoction, sheganmahuang concoction, and quingfei touxie fuzheng concoction. From this formulation of TCM quingfei paidu has been officially approved by the General Office of National Health ⁹.

The formulation of qingfei paidu concoction was majorly used to treat SARS-CoV-2 and it shows 92.09% when compared to the rest¹¹.

Indian Ayurvedic Medicine: The most basic and important herbal plant in the AYUSH system is Tulsi. The word Tulsi is in the language of Sanskrit which means "Incomparable one". The only which shows many medicinal capabilities according to Charaka Samhita, to balance various mechanisms and to increase the life span. The medicinal practitioners of an ayurvedic system of 250,000 herbal plants are registered when compared to about 700,000 modern medicines. In this proportion, Ayurveda has 2000 plants, Siddha 1300, Unani 1000, Homeopathy 800, Tibetan 500, Modern 200, and Folk 4500¹⁴.

In India, Tulsi assumes a significant job in each house which is planted and simple to devour. It is used as a pain reliever, and to treat diarrhoea, cough, and fever. Tulsi treats numerous viral ailments, for example, Newcastle sickness infection, Vaccinia infection, and irresistible bursal ailments. It helps to cure respiratory parameters and relief of the symptoms of Asthma. It has both physiological and psychological functions. Tulsi plays a role in increasing anti-oxidant molecules to boost up the Defence mechanism of the immune system, enzyme, and to protect the cell and membrane. Tulsi also used to treat the basic symptoms of SARS-CoV-2¹⁵.

Some therapeutic approach for SARA-CoV2 by symptomatic management are Agastya Haritaki is a powder of Ayurveda consume 5grams twice a day to treat Upper Respiratory Infections (URI), AYUSH-64 is a tablet of Ayurveda consume twice a day to treat a respiratory infection, Anuthaila is ayurvedic oil which taken through nostrils of 2 drops to treat respiratory infections, Adathodai Manapagu is an aqueous of Siddha to cure fever, Bryonia Tablet is under Homeopathy to treat lung infections, Rhus toxico dendron is a tablet of Homeopathy to treat lung diseases such as Asthma and Chronic. Eupatorium Sempervirens is a tablet of Homeopathy to treat asthma¹⁷. The two important herbs used first to treat SARS-CoV-2 were Ashwagandha and Yashitumadhu. It is provided by the Ayurvedic stream of medicine¹⁶.

The chief minister inaugurated a scheme called Aarogyam to boost the immunity of people over Tamilnadu and handed over packets of Nilavembu Kudineer and Kabasura Kudineer on the advice of medical experts. The mainly used ayurvedic medicine to treat SARS-CoV-2 is Vishasura Kudineer in the form of a tablet which consists of the polyherbal formulation of Siddha of 60ml twice a day to treat fever. Another significant one, right now used to treat SARS-CoV-2 Kabasura Kudineer which likewise as a tablet to treat all the side effects of infections, for example, fever, hack, sore throat, and brevity of breath ¹⁷.

In Siddha medication Nilavembu Kudineer is a decoction based polyherbal Siddha plan which is endorsed for fever of obscure inception. Like that covers Kabasura Kudineer has played the job of anticipation of coronavirus these days in famous ways. A few investigations have uncovered that Kabasura Kudineer because of its mitigation properties helps in decreasing growing noticeable all around section while antibacterial and antipyretic properties ease fever. Kabasura Kudineer or churnam has various healing aspects and immunomodulatory properties.

Commercial Drugs: Commercial drugs are the mixture of substances used in the manufacture of medicinal products and that substances are intended to furnish the pharmaceutical activities in the diagnosis, cure, mitigation, treatment, or prevention of disease. Some commercial drugs are Plaquenil, Aralen, Azithromycin, Remedesivir, Ribavirin, Ritonavir, and Lopinavir.

In India, the Plaquenil, Aralen, and Azithromycin are widely used in the treatment of SARS-CoV-2 because it can inhibit the RNA dependent RNA polymerase (RdRp). Remedesivir was originally developed to treat viral diseases like Ebola and Marburg virus disease but the drug was ineffective for these viral diseases. Still the drug Remedesivir is used for the treatment of SARS-CoV-2 in the country of USA. Ribavirin is otherwise called tribavirin, is an antiviral medication used to treat Respiratory Syncytial Virus (RSV) infection, hepatitis C, and further more used to treat plague ailment SARS-CoV-2. The antiretroviral medicate Lopinavir is a protease inhibitor, which hinders the processing chemical cytochrome P4503A is

the fundamental proof of the adequacy of the medication against coronavirus. Some more drugs used for the disease are Sofosbuvir, Favipiravir, Ruxolitinib, Darunavir, Arbidol, Eculizumab, Fedratinb, etc¹⁷⁻¹⁹.

These are some drugs that have been concluded for the treatment of SARS-CoV-2 and still, researches have not found accurate drugs to treat and heal this epidemic disease SARS-CoV-2.

Conclusion

From the above review, we have observed that all kinds of medicinal system were attempted to discover the drug. The researchers have found that various kinds of medicine for the treatment of epidemic disease SARS-CoV-2 but, there are no more effective medicine to heal the disease completely. Traditional Chinese medicine is about 92.09% more effective than commercial and Indian Ayurvedic Medicine for the treatment of SARS-CoV-2 infected patients. The main motive of all the systems of medicine is to control the motility rate.

We concluded that the system of medicine depends on the natural environmental conditions. The experimental researches are carrying out for the development of vaccine and drug to overcome this dreadful disease.

References

- **1.** Penghui Ya and Xiliang Wang (2020). COVID-19: A new challenge for human beings. *Springer Nature*, https://doi.org/10.1038/s41423-020-0407-x.
- 2. Qingmei Han, Qingqing Lin, Shenhe Jin and Liangshun You (2020). Coronavirus 2019-nCoV: A brief perspective from the front line. Elsevier, https://doi.org/10.1016/j.jinf.2020.02.010.
- 3. Matthew J. Binnicker. (2020). Emergence of a Novel Coronavirus Disease (COVID-19) and the Importance of Diagnostic Testing: Why Partnership between Clinical Laboratories, Public Health Agencies, and Industry is Essential to Control the Outbreak. *American Association for Clinical Chemistry*, https://doi.org/10.1093/clinchem/hvaa071/5741389.
- **4.** Mohamed El-Tholot, Haim H. Bau and Jinzhao Song (2009). A Single and Two-Stage, Closed-Tube, Molecular Test for the 2019 Novel Coronavirus (COVID-19) at Home, Clinic, and Points of Entry. *Research-gate*, https://doi.org/10.26434/chemrxiv.11860137.v.
- **5.** Muhammad Adnan Shereen, Suliman Khan, Abeer Kazmi, Nadia Bashir, Rabeea Siddique (2020). COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*, https://doi.org/10.1016/j.jare.2020.03.005.

- **6.** Sunil Kumar Verma (2020). In search of feasible interventions for COVID-19 pandemic. *Preprints*, https://doi.org/10.20944/preprints 202003.0353.v1.
- 7. Manisha Prajapat, Phulen Sarma, Nishant Shekhar, Pramod Avti, Shweta Sinha, Hardeep Kaur, Subodh Kumar, Anusuya Bhattacharyya, Harish Kumar, Seema Bansal, and Bikash Medhi. (2020). Drug target for corona virus: A systemic review. *Indian journal of pharmacology*, https://doi.org/10.4103/ijp.IJP_115 20.
- 8. Sivaraman. D. and Pradeep P.S. (2020). Revealing antiviral potential of Bio-active therapeutics targeting SARS-CoV-2- polymerase (RdRp) in combating COVID-19: Molecular Investigation on Indian traditional medicines. Preprints, https://doi.org/10.20944/preprints202003.0450.v1.
- **9.** Jun-ling Ren., Ai-Hua Zhang and Xi-Jun Wang (2020). Traditional Chinese Medicine for COVID-19 treatment. Elsevier, https://doi.org/10.1016/j.phrs.2020.104743.
- 10. LUO Hui., TANG Qiao-ling, SHANG Ya-xi., LIANG Shibing., YANG Ming., Nicola Robinson, and LIU Jian-ping. (2020). Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chinese Journal of Integrative Medicine, https://doi.org/11655-020-3192-6.
- 11. Ruocong Yang, Hao Liu, Chen Bai, Yingchao Wang, Xiaohui Zhang, Rui Guo, Siying Wu, Jianxun Wang, Elaine Leung., Hang Chang, Peng Li, Tiegang Liu, Yi Wang (2020). Chemical Composition and Pharmacological Mechanism of Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction against Coronavirus Disease 2019 (COVID-19); in silico and experimental study. *Journal Pre-Proof*, https://doi.org/10.1016/j.phrs. 2020.104820.
- 12. Li Ni., Ling Zhou, Min Zhou, Jianping Zhao and Dao Wen Wang (2020). Combination of western medicine and Chinese traditional patent medicine in treating a family case of COVID-19 in Wuhan. © Higher Education Press and Springer-Verlag GmbH Germany, part of Springer Nature, https://doi.org/10.1007/s11684-020-0757-x.

- **13.** Dharmendra kumar Maurya and Deepak Sharma (2020). Evaluation of traditional ayurvedic preparation for prevention and management of the novel Coronavirus (SARS-CoV-2) using molecular docking approach. preprints, https://doi.org/10.26434/chemrxiv.12110214.
- **14.** Pandey M.M., Subha Rastogi and Rawat A. K. S. (2020). Indian Traditional Ayurvedic System of Medicine and Nutritional Supplementation. Hindaw. https://doi.org/10.1155/2013/376327.
- **15.** Sai Sailesh Kumar Goothy, Srilatha Goothy, Anita Choudhary, Potey G G, Hirok Chakraborty, Arun HS Kumar and Mahadik V.K. (2020). Ayurveda's Holistic Lifestyle Approach or the Management of Coronavirus disease (COVID-19): Possible Role of Tulsi. *International Journal of Research in Pharmaceutical Science*, https://doi.org/10.26452/ijrps.v11iSPL1.1976
- **16.** Sangeeta Ojha. (2020). COVID-19 treatment: India to test for Ayurvedic drugs within a week. www.livemint.com
- 17. Balachandhar Vellingiri, Kaavya Jayaramayya, Mahalaxmi Iyer, Arul Narayanasamy, Vivekanandhan Govindasamy, Bupesh Giridharan, Singaravelu Ganesan, Anila Venugopal, Dhivya Venkatesan, Harsha Ganesan, Kamarajan Rajagopalan, Pattanathu K.S.M. Rahman, Ssang-Goo Cho, Nachimuthu Senthil Kumar, Mohana Devi Subramaniam (2020). COVID-19: A promising cure for the global panic. *Elsevier*, https://doi/org/10.1016/j.scitotenv.2020.138277.
- 18. Min Zhou., Xinxin Zhang., Jieming Qu. (2020). Coronavirus disease 2019 (COVID-19): a clinical update.
 © Higher Education Press and Springer-Verlag GmbH Germany, part of Springer Nature, https://doi.org/10.1007/s11684-020-0767-8.
- **19.** Kit San Yuen., Zi -Wei Ye, Sin-Yee Fung, Chi-Ping Chan, and Dong-Yan Jin. (2020). SARS-CoV-2 and COVID-19: the most important research questions. *Springer Nature remains neutrals*, https://doi.org/10.1186/s13578-020-00404-4.