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Potential phytomedicines against COVID-19: A review

Muzafar Iqbal[1*], Shagufta Jabeen[2], Shamim Umer[3], Ume Hifsa Bashir[1] and Habiba Ahmad[1]

[1]Department of Botany, The Islamia University of Bahawalpur, Bahawalpur, **Pakistan**
[2]Department of Botany, Govt Degree College for Women Ahmed Pur East, Punjab, **Pakistan**
[3]Department of Botany, University of Agriculture, Faisalabad, **Pakistan**

***Correspondence:** botany618@gmail.com **Received 28-08-2020, Revised: 09-10-2020, Accepted: 15-10-2020 e-Published: 17-10-2020**

COVID-19 is a pandemic disease and has affected more than 5.8 million people across the world. Given the alarming desolation and transience of COVID-19, it is understandable to identify phytomedicine's contingency use to lead to a new indication of anti-COVID-19 drug build on evidence. To summarize the potential phyto-drugs formulae provided to treat COVID-19 patients, we designed a non-systematic review of the recent literature. Five data sources (PubMed, Embase, Web of Sciences, Google Scholar and Chinese guidelines on novel coronavirus) were preferred to identify presented potential phytomedicines for COVID-19 treatment. This literature study showed the anti-COVID-19 potential of wielded phytochemicals. The study regards plant-derived composites such as chloroquine phosphate, diammonium glycyrrhizinate, artemisinin, luteolin-7-glucoside and kaempferol as suitable agents for the COVID-19 antiviral therapy. Moreover, the use of curcumin and recommended TCMs for the expression of the nCOV-19 antigens can be a target for the future antiviral drug of the COVID-19 due to the intrinsic antiviral properties. We hope that present review will serve as a reference and guidance for the identification of potential antiviral compounds and/or drugs for COVID-19 treatment.

Keywords: SARS-CoV-2; Artemisinin; Diammoniumglycyrrhizinate; Curcumin; Crocin; Traditional Chinese medicines

INTRODUCTION

Novel coronavirus 2019 (nCoV-19) causes SARS-CoV-2 or COVID-19. It was first time aroused in December 2019 in Wuhan, a city of People's Republic of China (Xu et al., 2020a). Contingency measures were adopted by Chinese health authorities, CDC and researchers to prevent and find its potential therapy. The earliest genomic sequence of nCoV-19 was available in January 2020, which facilitated the medical specialists and researchers to rapid virus detection in patients using the RT-PCR method (Zhu et al., 2020). The earliest study about nCoV-19 was published on January 21, 2020, which showed that nCoV-19 resembles with bat coronavirus HKU9-1, and its spike protein interacts strongly with ACE2 receptor in humans (Xu et al., 2020b). World health organization (WHO) set a global health emergency first on January 30, 2020, and later on March 11, 2020, called it pandemic due to swift spread. nCov-19 is a viral strain and transmits through the human-to-human contact (Shereen et al., 2020). As of May 31, 2020, COVID-19 confirmed cases 5934936, and death has reached over 367166 worldwide (WHO, 2020).

Presently, there is no vaccine or specific antiviral agents approved against COVID-19; hence it is a big demand for researchers to discern specified antiviral remedy to cure this

deadly disease (Haq et al., 2020). Medical specialists recommended remdesivir as an emergency treatment. In addition to remdesivir, plants derived natural products such as chloroquinephosphate, ritonavir, ribavirin, arbidol, and TCM have also been practised as antiviral agents to treat COVID-19. These natural products showed effectiveness against SARS-CoV, which causes COVID-19 in humans (Dong et al., 2020).

Plant products and their derivatives have been extensively used in traditional therapy for very long to treat a wide range of infections, including viral diseases (Ganjhu et al., 2015). The importance and demand for plant-derived medicines in terms of nutraceuticals is greatly increasing (Williamson et al., 2020). Nature has provided us with a vast library of phytochemicals that act as curative agents against numerous diseases. Therefore, studies on plant-derived medicines are developing on a daily basis across the world. Many plants or their derivatives have shown antiviral potential (Jassimand Naji, 2003; Todorov et al., 2014).

Phytomedicines are less understood compared to conventional drugs, but several scientific analyses have been ongoing to evaluate their antiviral effects more precisely. This study aims to show the potential therapeutic plants and their derivatives effective against nCoV-19 disease.

MATERIALS AND METHODS

Approach, literature search and data collection

We carried out a non-systematic review of the literature to collect the most relevant information about efficient phytomedicines against COVID-19. Articles were extricated employing PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Web of Science (https://www.webofknowledge.com/) Google Scholar (http://scholar.google.com/) and Chinese guidelines on novel coronavirus (https://www.evidenceaid.org/chinese-guidelines-on-novel-coronavirus/), searching by terms "COVID-19", "SARS-CoV-2", "2019-nCOV phyto-drugs against COVID-19" and "COVID-19 phytomedicines" in title and keywords.

RESULTSAND DISCUSSION

Potential phyto-drugs against COVID-19

Plants have been the natural source of a variety of phytochemicals and led to drug discovery against various diseases. Interestingly, plant products have also been used as the earliest line of treatment against SARS-CoV-2. Chloroquine phosphate was used as a cure for COVID-19 (Qiu et al., 2020). It is analogue of quinine and extracted first from the bark of cinchona. Chloroquine phosphate is generally used as anti-malarial treatment. But, its use as an antiviral drug to prevent COVID-19 has been shown in China, and it significantly alleviated the COVID-19 symptoms and induced regulatory effects on immunity (Gao et al., 2020).

Diammonium glycyrrhizinate, a herbal compound obtained from *Glycyrrhiza glabra*, has been employed effective antidote of COVID-19 (Ding et al., 2020). *Glycyrrhiza glabra* has very long been used to treat coughs, digestive disorders and hepatitis B (Sharma and Agrawal, 2013).). It also has anti-inflammatory activity and used to manage liver infection **(**Siracusa et al., 2011).

Artemisinin, a herbal derivative of *Artemisia annua,* has been recently suggested for a clinical trial to employ as a COVID-19 therapy (Haq et al., 2020). Artemisinin has been commercialized earlier as an anti-malarial drug (Efferth et al., 2008). Previous reports show that *Artemisia annua* has a strong potential to alleviate SARS-CoV and Herpes Simplex virus infections (Li et al., 2005; Karamoddini et al., 2011). Furthermore, Luteolin-7-glucoside and Kaempferol, herbal compounds obtained from *Olea europaea* and *Anethum graveolens* respectively, were predicted as an efficient treatment for COVID-19 based on molecular docking experiment (Khaerunnisa et al., 2020). A recent study by Aanouz et al. (2020) based on nCoV-19 main Protease (M^{pro}) analysis shows that Crocin (A compound derived from *Crocus sativus*), β- Eudesmol (obtained from *Lauris nobilis*) and digitoxigenin (extracted from *Nerium oleander*) be efficient inhibitors against COVID-19. Previous reports also confirm the antiviral potential of *Crocus sativus* (Soleymani et al., 2018)*, Lauris nobilis* (Loizzo et al., 2008) and *Nerium oleander* (Avci and Dik, 2014).

Moreover, 5, 7, 30, 40 - Tetrahydroxy2'-(3, 3-dimethylallyl) isoflavone, a compound from *Psorothamnus arborescens,* showed significant results by inhibiting SARS-CoV-2 $3CL^{pro}$ (ulQamar et al., 2020).

Table 1: Recommended TCM for COVID-19 treatment (NHC, 2020)

Stage of infection	Symptom(s)	Recommended TCM
Clinical observation period	Tiredness with fever	Shu Feng Jie Du Capsule , Lian Hua Qing Wen Capsule, Jin Hua Qing Gan Capsule
	Fatigue with gastrocolic discomfort	Huo Xiang Zheng Qi Shui
Clinical therapy period (Disease established patients)	General case	Qing FeiPai Du Tang
	Mild case	Qing FeiPai Du Tang
	Severe case	Xi Yan Ping Injection, Re Du Ning Injection, Xue Bi Jing Injection , Qing FeiPai Du Tang , Tan Re Qing Injection, Xing Nao Jing Injection
	Critical case	Tan Re Qing Injection , Xue Bi Jing Injection, Re Du Ning Injection, Shen Fu Injection, Shen Mai Injection, Sheng Mai Injection, An Gong Niu Huang Pill, Su He Xiang Pill

Table 2. Frequently utilized TCM plants for COVID-19 prevention

Herbal plant	Herbal plant (Chinese Pin Yin)	Applicable region	Reference
Glycyrrhizae uralensis	Gancao	23 provinces covered Central (including Wuhan), Northeast, North, South, East, Northwest, and Southwest China.	Luo et al., 2020
Lonicerae japonicae flos	Jinyinhua		
Astragalusme mbranaceus	Huangqi		
Saposhnikoviae divaricata	Fangfeng		
Fructus forsythia	Lianqiao		
Rhizoma atractylodis macrocephalae	Baizhu		
Cyrtomium fortune J. Sm	Guanzhong		
Atractylodis rhizoma	Cangzhu		
Agastache rugosa	Huoxiang		
Radix platycodonis	Jiegeng		
Ophiopogon japonicus	Maidong	Eight regions in northern China (Shanxi, , Beijing, Tianjin, Henan, Shaanxi, Gansu,Shandong and Hebei)	Xuet al., 2020
Scrophularia ningpoensis	Xuanshen		
Rhizoma phragmitis	Lugen		
Adeinopho rastricta Miq	Shashen		
Dendrobium nobile Lindl.	Shihu		
Atractylodis rhizoma	Cangzhu	Five regions in southern China (Wuhan , Jiangxi, Hubei, Hunan and Yunnan)	
Eupatorium fortunei Turcz.	Peilan		
Agastache rugosa	Huoxiang		
Astragalusmembranaceus	Huangqi	Beijing, Shaanxi,Tianjin, Shandong, Hebei, Shanxi, Henan, Hubei, Jiangxi, Hunan, Gansu and Yunnan	

The use of 5,7,30, 40 -tetrahydroxy-2'-(3, 3-dimethylallyl) isoflavone has also found in TCM records and has been effectively employed as an antileishmanial agent (Salem, and Werbovetz, 2006; Xie et al., 2011). Curcumin, a derivative of *Curcuma longa*, also needs to conduct further studies to explore its potential as a COVID-19 treatment (Rocha and de Assis, 2020; Zahedipour, et al., 2020). In various studies carried out in humans, curcumin showed an excellent safety profile (Aggarwal et al., 2013).

Medicinal herbs, notably those used in TCM, have created substantial curiosity because they comprise bio-active constituents that can be utilized to synthesize formal medicines with no or minimal concomitants against several diseases (ulQamar et al., 2019). The government of China also highly valued TCM in its contingency campaigns to control COVID-19. For instance, the Health Commission officially acknowledged that TCMs could be employed conjointly with conventional medicines in the management of COVID-19. For this, NHC has published six versions Guidelines of Diagnosis and Treatment against COVID-19 (NHC, 2020). According to the latest 6th edition of Guideline, NHC recommended TCMs for the COVID-19 patient in the health observation stage as a deterrent. These include Huo Xiang Zheng Qi Shui, Xi Yan Ping Injection, Re Du Ning Injection, Qing FeiPai Du Tang, ShuFengJie Du Capsule, JinHua Qing Gan Granule, Xue Bi Jing injection, Xing Nao Jing Injection,LianHua Qing Wen Capsule and Tan Re Qing Injection (Xu et al., 2020a). Along with these, Shen Fu Injection, Shen Mai Injection, Su He Xiang Pill, An Gong Niu Huang Pill and Sheng Mai Injection could be used in critical condition (Table 1). Regularity analysis of TCM used revealed *Glycyrrhizae uralensis, Atractylodes macrocephala, Astragalus membranaceus, Agastache rugosa*, *Saposhnikoviae divaricata, Lonicerae japonicae flos , Radix platycodonis, Cyrtomium fortune J. Sm*, *Fructus forsythia* and *Atractylodis rhizoma* among ten most used herbs in COVID-19 therapy (Luo et al., 2020). Xu et al. (2020) accounted that Yu Ping Feng and *A. membranaceus* were used for reinforcing vital *qi* (a term indicating boosting of host defense capability in TCM). *Scrophularia ningpoensis* and *Ophiopogon japonicus* were most frequently employed in northern China for nourishing *yin*. At the same time, *A. rugosa* and *A. macrocephala* were used in southern China to combat COVID-19 (Table 2).

CONCLUSION

It is concluded that the present review can be employed as a reference in the potential Phyto-therapy treatment against COVID-19. More clinical investigations are considered necessary to evaluate the effectiveness and safety of phyto-drugs and provide scientific substantiation. The integration of phytomedicines into conventional therapy may be an alternative, economic, and straightforward approach for COVID-19 treatment.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed in all parts of the paper. MI Designed, wrote and reviewed the manuscript. SJ and SU collected information and wrote the review paper. UHB and HA reviewed and corrected the review paper. All authors read and approved the final version.

REFERENCES

Aanouz, I., Belhassan, A., El Khatabi, K., Lakhlifi, T., El Idrissi, M., &Bouachrine, M. (2020). Moroccan Medicinal plants as inhibitors of COVID-19: Computational investigations. J BIOMOL STRUCT DYN, 1-12. https://doi.org/10.1080/07391102.2020.1758790.

Aggarwal, B. B., Gupta, S. C., & Sung, B. (2013). Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. *Br J Pharmacol*, *169*(8), 1672-1692. https://doi.org/10.1111/bph.12131.

Avci, O., &Dik, B. (2014).Determination of in vitro antiviral activity of Nerium oleander distillate against to parainfluenza-3 virus. *Anim Vet Sci*, *2*(5), 150-153.

Ding, H., Deng, W., Ding, L., Ye, X., Yin, S., & Huang, W. Glycyrrhetinic acid and its derivatives as potential alternative medicine to relieve symptoms in non-hospitalized COVID-19 patients. *J Med Virol.*https://doi.org/10.1002/jmv.26064.

Dong, L., Hu, S., &Gao, J. (2020). Discovering

drugs to treat coronavirus disease 2019 (COVID-19). *Drug DiscovTher*, 14(1), 58-60. https://doi.org/10.5582/ddt.2020.01012.

Ganjhu, R. K., Mudgal, P. P., Maity, H., Dowarha, D., Devadiga, S., Nag, S., &Arunkumar, G. (2015). Herbal plants and plant preparations as remedial approach for viral diseases. *Virusdisease*, *26*(4), 225-236. https://doi.org/10.1007/s13337-015-0276-6.

Gao, J., Tian, Z., & Yang, X. (2020). Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*.https://doi.org/10.5582/bst.2020.01047.

Haq, F. U., Roman, M., Ahmad, K., Rahman, S. U., Shah, S. M. A., Suleman, N., ...&Ullah, W. Artemisia annua: trials are needed for COVID-19. *Phytother Res.*https://doi.org/10.1002/ptr.6733.

Jassim, S. A. A., &Naji, M. A. (2003). Novel antiviral agents: a medicinal plant perspective. *J ApplMicrobiol*, *95*(3), 412-427. https://doi.org/10.1046/j.1365-2672.2003.02026.x.

Karamoddini, M. K., Emami, S. A., Ghannad, M. S., Sani, E. A., &Sahebkar, A. (2011). Antiviral activities of aerial subsets of Artemisia species against Herpes Simplex virus type 1 (HSV1) in vitro. *Asian Biomed*, *5*(1), 63-68. https://doi.org/10.5372/1905-7415.0501.007.

Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., &Soetjipto, S. (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. *Prepr.*https://www.preprints.org/manuscript/202003.0226/v1.

Lau, J. T., Leung, P. C., Wong, E. L. Y., Fong, C., Cheng, K. F., Zhang, S. C., ... &Ko, W. M. (2005). The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory syndrome transmission, relieve influenza-related symptoms, and improve quality of life: a prospective cohort study. *J Altern Complement Med*, *11*(1), 49-55. https://doi.org/10.1089/acm.2005.11.49.

Li, S. Y., Chen, C., Zhang, H. Q., Guo, H. Y., Wang, H., Wang, L., ... & Li, R. S. (2005). Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antivir Res*, *67*(1), 18-23. https://doi.org/10.1016/j.antiviral.2005.02.007.

Loizzo, M. R., Saab, A. M., Tundis, R., Statti, G. A., Menichini, F., Lampronti, I., ...&Doerr, H. W. (2008). Phytochemical analysis and in vitro antiviral activities of the essential oils of seven Lebanon species. *Chem Biodivers*, *5*(3), 461-470. https://doi.org/10.1002/cbdv.200890045.

NHC,*2020. http://www.nhc.gov.cn/xcs/s3574/202002/f12a62d10c2a48c6895cedf2faea6e1f.* shtml. 2020.

Qiu, T., Liang, S., Dabbous, M., Wang, Y., Han, R., &Toumi, M. (2020). Chinese Guidelines Related to Novel Coronavirus Pneumonia. https://www.preprints.org/manuscript/202004.0207/v1.

Rocha, F. A. C., & de Assis, M. R. (2020).Curcumin as a potential treatment for COVID-19. . *Phytother Res*. https://doi.org/10.1002/ptr.6745.

Salem, M. M., &Werbovetz, K. A. (2006).Isoflavonoids and Other Compounds from Psorothamnusarborescens with Antiprotozoal Activities. *J Nat Prod*, *69*(1), 43-49. https://doi.org/10.1021/np0502600.

Sharma, V. A. R. S. H. A., &Agrawal, R. C. (2013).Glycyrrhizaglabra-a plant for the future. *Mintage J Pharm Med Sci*, *2*(3), 15-20.

Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., &Siddique, R. (2020). COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res.*https://doi.org/10.1016/j.jare.2020.03.005.

Siracusa, L., Saija, A., Cristani, M., Cimino, F., D'Arrigo, M., Trombetta, D., ...&Ruberto, G. (2011). Phytocomplexes from liquorice (Glycyrrhizaglabra L.) leaves—chemical characterization and evaluation of their antioxidant, anti-genotoxic and anti-inflammatory activity. *Fitoterapia*, *82*(4), 546-556. https://doi.org/10.1016/j.fitote.2011.01.009.

Soleymani, S., Zabihollahi, R., Shahbazi, S., &Bolhassani, A. (2018).Antiviral effects of saffron and its major ingredients. *Curr Drug Deliv*, *15*(5), 698-704. https://doi.org/10.2174/1567201814666171129210654.

Todorov, D., Hinkov, A., Shishkova, K., &Shishkov, S. (2014). Antiviral potential of Bulgarian medicinal

plants. *Phytochem Rev*, *13*(2), 525-538. https://doi.org/10.1007/s11101-014-9357-1.

ulQamar, M. T., Maryam, A., Muneer, I., Xing, F., Ashfaq, U. A., Khan, F. A., ... &Siddiqi, A. R. (2019). Computational screening of medicinal plant phytochemicals to discover potent pan-serotype inhibitors against dengue virus. *Sci Rep*, *9*(1), 1-16. https://doi.org/10.1038/s41598-018-38450-1.

WHO, 2020.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200531-covid-19-sitrep-132.pdf?sfvrsn=d9c2eaef_2

Williamson, E. M., Liu, X., &Izzo, A. A. (2020).Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *Br J Pharmacol*, *177*(6), 1227-1240. https://doi.org/10.1111/bph.14943.

Xie, G., Zhou, J., & Yan, X. (2011). Encyclopedia of Traditional Chinese Medicines: Molecular Structures, Pharmacological Activities, Natural Sources and Applications; Volume 6: Indexes.

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., ...&Hao, P. (2020b). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci*, *63*(3), 457-460. https://doi.org/10.1007/s11427-020-1637-5.

Xu, X., Zhang, Y., Li, X., & Li, X. X. (2020a).Analysis on prevention plan of corona virus disease-19 (COVID-19) by traditional Chinese medicine in various regions.*Chin Herb Med,* 2020:1-7.

Zahedipour, F., Hosseini, S. A., Sathyapalan, T., Majeed, M., Jamialahmadi, T., Al-Rasadi, K., &Sahebkar, A. Potential effects of curcumin in the treatment of COVID-19 infection. *Phytother Res.*https://doi.org/10.1002/ptr.6738.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., &Niu, P. (2020).A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.*https://doi.org/10.1056/nejmoa2001017.