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From Phytochemicals to Phytomedicines: Potential Roles of Plant-Based Biomolecules in the Covid Era

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ABSTRACT

The current pandemic of the Corona virus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has urged for the invention and implementation of effective drugs and vaccines to mitigate the adversity worldwide. Numerable studies are going on to identify and evaluate the efficacy of several synthetic drugs and vaccines. In this scenario, identification and use of plant-derived biomolecules against SARS-CoV-2 could be highly beneficial. Furthermore, upscale production of such plant metabolites and plant-based vaccines can help in controlling the pandemic. Several previous studies have reported the success of plant-based traditional medicines in immunity enhancement and decreasing viral loads. Thus, in depth researches involving the phytochemicals could reveal their roles and level of efficacy against SARS-CoV-2. Considering the present scenario, this review article presents the perspectives of using the phytochemicals in mitigating SARS-CoV-2, and the possible evolution of these phytochemicals into phytomedicines.

KEY WORDS: PHYTOCHEMICALS, SECONDARY METABOLITES, SARS-COV-2, COVID-19.

INTRODUCTION

The Coronaviruses (CoVs) family (Coronaviridae) consists of single-stranded RNA viruses and has been reported since the 1960s (Adhikari et al. 2020). These viruses can infect a wide array of hosts, including cattle, camels, bats, and humans (Boopati et al. 2019). The newly discovered severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus, previously known as novel corona virus, which cause the COVID-19 disease belong to the CoVs family (Prasad et al. 2020). As of present no vaccine has been officially available for the human consumption to curb or to treat the COVID-19 disease. Although, some vaccines in their trial stages are showing promising results, they are still to clear some more trial phases before getting available in the market.

In this scenario, a rampant search is going on to find chemicals or compounds of antiviral capacity, which is evident by the number of studies getting published recently. Apart from vaccines, development of effective drugs or the use of already existing drugs is the most practiced methods to treat COVID-19. For instance, different nucleoside analogs like ribavirin, favipiravir, and remdesivir, anti-HIV drugs like, ritonavir and lopinavir and reverse-transcriptase inhibitor drugs like azvudine are in use for treating COVID-19 patients (Wang et al. 2020; Chen et al. 2020; Harrison 2020). Although, much of the attention is given in discovering synthetic drugs and searching for a potent active pharmaceutical ingredient (API), use the plant-based biomolecules against COVID-19 is largely unexplored.

Plants are the producers of innumerable phytochemicals and bioactive metabolites having huge pharmacological attributes such as, antimicrobial, antioxidant, anti-hypertension, anti-diabetic, anti-inflammatory,

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anticancer, and immunomodulatory activity (Patel et al. 2020; Adnan et al. 2020; Patel et al. 2018). In addition, some phytochemicals are reported to have antiviral properties and are capable of inhibiting viral replications (Ben-Shabat et al. 2015; Arunkumar et al. 2019). Thus, finding out a potent phytochemical(s) by exploiting various technological interventions, which could be effective in controlling SARS CoV-2 and treating COVID-19 will be absolutely crucial. In this review, such plant-based biomolecules having antiviral properties and can thereof be extrapolated to use against SARS CoV-2 are highlighted. Also, the importance and the potential therapeutic applications of novel phytochemicals are discussed.

Plant-derived bioactive compounds and their effectiveness against SARS CoV-2:

The present scenario: Numerous plants are there with vital medicinal properties that can inhibit the viruses like, Middle East respiratory syndrome coronavirus (MERS-CoV), Human coronavirus 229E (HCoV-22E9), and SARS-Cov due to the presence of various bioactive compounds (Siddiqui et al. 2020). Previously, use of traditional plant-based medicines in China have successfully aided in treating the SARS-CoV during the pre-COVID-19 times (Lau et al. 2005). Although, like most of the traditional medicine practices, the exact mode or composition of the treatment is unknown, the role of phytochemicals and plant secondary metabolites of the used plant parts could be the best fit candidates to attain the results (O'Connor 2015). Studies involving plant secondary metabolites production and applications have revealed their efficacy in treating various diseases.

For instance, the alkaloid lycorine derived from *Lycoris radiate* possesses antiviral activity against different types of viruses, including Herpes simplex virus, Poliomyelitis virus, and SARS-CoV (Li et al. 2005). Similarly, the alkaloid quinine obtained from *Cinchona officinalis* plants is hugely effective in the treatment of malaria from many decades (Achan et al. 2011). Furthermore, the structural analog of quinine, hydroxychloroquine (HCQ) has been used to treat COVID-19 patients along with the antibiotic azithromycin (Gautreta et al. 2020). Cinatl et al. (2003) reported that glycyrrhizin, a saponin from *Glycyrrhiza glabra* can inhibit the viral replications and can be effective against SARS-CoV infection. Similarly, the water extract of the herb *Houttuynia cordata* was found to exhibit antiviral activity against SARS-CoV by inhibiting the viral RNA-dependent RNA polymerase (RdRp) and 3C-like protease (3CLP) (Lau et al. 2008). As SARS-CoV and SARS-Cov-2 share high similarities, the use of glycyrrhizin or *H. cordata* extracts could be a possible alternative to treat COVID-19.

Flavonoids like Myricetin from the Chinese bayberry plants *Myrica rubra* and Scutellarein from the herb *Scutettaria baicalensis* showed antiviral effects on the SARS-CoV virus (Yu et al. 2012). Likewise, flavones from the coniferous tree *Torreya nucifera*, including apigenin, quercetin, amentoflavone, and luteolin have been reported to have 3CLP inhibitory properties (Ryu et al. 2010). Additionally, bioactive compounds such as, hesperetin, emodin, and sinigrin obtained from the herb *Isatis tinctoria* exhibited 3CLP inhibitory properties (Lin et al. 2005).

Lectins are a class of plant secondary metabolites having crucial roles in plant immune responses, thus can be potential antiviral compounds. In the pre-COVID-19 times, 33 numbers of different plant-derived lectins showed antiviral activity against SARS-CoV virus (Keyaerts et al. 2007). Agglutinin, a lectin obtained from *Galanthus nivalis* was reported to show antiviral activity against the Feline coronavirus (Hsieh et al. 2010). Further, a natural occurring stilbene derivative resveratrol was reported to inhibit MERS-CoV infection (Lin et al. 2017).

Albeit, huge number of phytochemicals and the plant bioactive compounds have been studied for their antiviral properties (Table 1), no extensive research has been done to isolate the API and then exploit it into meaningful bio-therapeutics. Recently, the AYUSH ministry of India has recommended the people to consume a cocktail of medicinal plant parts/extracts containing as many as 15 plants, including ginger, clove, black pepper, and others (Ministry of Ayush PIB 2020). Moreover, Siddiqui et al. (2020) reviewed the potential role of about 40 medicinal plants in contributing towards the treatment of COVID-19. Thus, these available data suggest that there is a need of collaborating the researches to examine the synergistic effect of such plant-derived biomolecules and other synthetic drugs against SARS-CoV-2 to get the best solution in winning against COVID-19.

Plant biotechnology-based advancements and solutions: Since last decade, plant biotechnology has taken a leap into the future by adopting new cutting-edge technologies and inventions. Processes like targeted metabolic pathway engineering, enhancement of phytopharma capacity and production of recombinant enzymes, hormones, and vaccines has been realized via biofarming (Rosales-Mendoza 2020). The advantage of producing these transgenic or transient recombinants is that they follow the required post-transcriptional and post-translational modifications, unlike in bacterial systems and they are devoid of the animal pathogens (Takeyama et al. 2015). In *Nicotiana benthamiana* plants, the human Type-I collagen was produced and commercialized. Furthermore, vaccines for diseases like influenza, rabies, and hepatitis-B were produced in plant systems and underwent clinical trials (Takeyama et al. 2015). Recombinant N-terminal of S-glycoprotein of swine-transmissible gastroenteritis coronavirus obtained from the leaf extracts of transgenic *Arabidopsis thaliana* and *Solanum tuberosum* lines exhibited antiviral activities against SARS-CoV virus (Gómez et al. 1998; Gómez et al. 2000).

Similarly, in *Lactuca sativa* and *N. benthamiana* the stable expression of S-glycoprotein of the SARS-CoV virus was achieved, which served as a potential oral vaccine (Li et al. 2006). Another study reported the consumption of transgenic tomatoes expressing S-glycoprotein of SARS-CoV was successful in producing the virus-specific IgA in mice (Pogrebnyak et al. 2005). Many organizations related to manufacturing phytopharma based drugs have already commenced the development of plant-based vaccines against COVID-19 (Rosales-Mendoza 2020). On the other hand, the rapid sequencing of SARS-CoV-2 virus strains and availability of the data in public domains have triggered the epitome mapping studies that ultimately could result in developing new and potent vaccine against SARS-CoV-2. Interestingly, different efficient plant biomolecules and phytochemicals are often present in lower concentration. Thus, bio-firming of these chemicals via targeted metabolic engineering in the *in vitro* cultures could result in their boosted production and recovery (Kayser 2018). Moreover, plant biotechnology along with targeted metabolic pathway engineering leading to the upscale production of antiviral phytochemicals against SARS-CoV-2 could emerge as a big solution to the current COVID-19 pandemic.

Table 1. List of the bioactive compound from plants and their effect on viruses.

Plant Name	Product	Virus Type	Effect	Reference
Euphorbia jolkinin *Reseda luteola* *Aesculus hippocastanum*	Tetra-O-galloyl-β-d-glucose luteolin	SARS-CoV	Antiviral	Yi et al. 2004
Rauvolfia serpentina *Scrophularia scorodonia* *Heteromorpha* spp.	Aescin, reserpine	SARS-CoV	Viral replication inhibitor	Wu et al. 2004
Bupleurum spp.	Saikosaponins	HCoV 229E	Disruption of host penetration and surface attachment	Cheng et al. 2006
33 different plant spp.	Lectins	SARS-CoV, Feline coronavirus	Viral S-glycoprotein inhibition	Keyaerts et al. 2007
Rheum spp. *Polygonum* spp.	Emodin	SARS-CoV	Blocking of S-glycoprotein and ACE2 interaction	Ho et al. 2007
Toona sinensis *Malus* spp., *Camellia* spp.,	Leaf extract	SARS-CoV, HCoV 229E	Viral replication inhibitor	Chen et al. 2008
Allium spp.	Quercetin	SARS-CoV	Antiviral	Park et al. 2012
Euphorbia neriifolia	Ethanolic extract	SARS-CoV	Antiviral	Chang et al. 2012

CONCLUSION

The COVID-19 pandemic is unprecedented and has asked for the scientific solution in solidarity. Be it traditional or synthetic, any drug showing potential against the SARS-CoV-2 is highly welcomed in these trying times. Considering this fact, the plant-based biomolecules that exhibit antiviral properties should be explored and an exhaustive research on this could unearth new possibilities. To upscale the production and recovery of the valuable phytochemicals use of plant biotechnology and metabolic engineering can facilitate the initiative. Furthermore, production of plant-based vaccines and their successful clinical trials will not only help in controlling the global pandemic, but also can be hugely cost effective. Moreover, evaluating the synergistic effects of the phytochemicals and synthetic drugs could prove to be a successful strategy to curb COVID-19 and be a roadmap for future studies.

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REFERENCE

Achan, J., Talisuna, A.O., Erhart, A., Yeka, A., Tibenderana, J.K., Baliraine, F.N., Rosenthal, P.J. and D'Alessandro, U. 2011. Quinine, an old antimalarial drug in a modern world: role in the treatment of malaria. Malar J. 10: 144.

Adhikari, S.P., Meng, S., Wu, Y.-J., Mao, Y.-P., Ye, R.-X., Wang, Q.-Z., Sun, C., Sylvia, S., Rozelle, S., Raat, H. and Zhou, H. 2020. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infect. Dis. Poverty. 9: 29.

Adnan, M., Patel, M., Deshpande, S., Alreshidi, M., Siddiqui, A.J., Reddy, M.N., Emira, N. and De Feo, V. 2020. Effect of adiantum philippense extract on biofilm formation, adhesion with its antibacterial activities against foodborne pathogens, and characterization of bioactive metabolites: An in vitro-in silico approach. Front. Microbiol. 11: 1–19.

Arunkumar, G., Mudgal, P.P., Maity, H., Dowarha, D., Devadiga, S., Nag, S. and Arunkumar, G. 2015. Herbal plants and plant preparations as remedial approach for

viral diseases. Virus disease. 26: 225–236.
Ben-Shabat, S., Yarmolinsky, L., Porat, D. and Dahan, A. 2019. Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies. Drug Deliv. Transl. Res. 10: 354–367.
Boopathi, S., Poma, A.B. and Kolandaivel, P. 2020. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. J. Biomol. Struct. Dyn. 1–10.
Chang, F.R., Yen, C.T., Ei-Shazly, M., Lin, W.H., Yen, M.H., Lin, K.H. and Wu, Y.C. 2012. Anti-human coronavirus (anti-HCoV) triterpenoids from the leaves of Euphorbia neriifolia. Nat. Prod. Commun. 7: 1415–1417.
Chen, C.J., Michaelis, M., Hsu, H.K., Tsai, C.C., Yang, K.D., Wu, Y.C., Cinatl, J. and Doerr, H.W. 2008. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. J. Ethnopharmacol. 120: 108–111.
Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X. and Zhang, L. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507–513.
Cheng, P.W., Ng, L.T., Chiang, L.C. and Lin, C.C. 2006. Antiviral effects of saikosaponins on human coronavirus 229E in vitro. Clin. Exp. Pharmacol. Physiol. 33: 612–616.
Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H. and Doerr, H.W. 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 361: 2045–2046.
Gautret, P., Lagier, J.C., Parola, P., Hoang, V.T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V.E., Tissot Dupont, H., Honoré, S., Colson, P., Chabrière, E., La Scola, B., Rolain, J.M., Brouqui, Pand Raoult, D. 2020. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open- label non-randomized clinical trial. J. Antimicrob. Agents. 56(1): 105949.
Gómez, N., Carrillo, C., Salinas, J., Parra, F., Borca, M.V. and Escribano, J.M. 1998. Expression of immunogenic glycoprotein S polypeptides from transmissible gastroenteritis coronavirus in transgenic plants. Virology. 249: 352–358.
Gómez, N., Wigdorovitz, A., Castañón, S., Gil, F., Ordás, R., Borca, M. V. and Escribano, J. M. 2000. Oral immunogenicity of the plant derived spike protein from swine-transmissible gastroenteritis coronavirus. Arch. Virol. 145: 1725–1732.
Harrison, C. 2020. Coronavirus puts drug repurposing on the fast track. Nat Biotechnol. 38: 379–381.
Ho, T.Y., Wu, S.L., Chen, J.C., Li, C.C. and Hsiang, C.Y. 2007. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antivir. Res. 74: 92–101.
Hsieh, L.E., Lin, C.N., Su, B.L., Jan, T.R., Chen, C.M., Wang, C.H., Lin, D.S., Lin, C.T. and Chueh, L.L. 2010. Synergistic antiviral effect of *Galanthus nivalis* agglutinin and nelfinavir against feline coronavirus. Antivir. Res. 88:25–30.
Kayser, O. 2018. Ethnobotany and medicinal plant biotechnology: from tradition to modern aspects of drug development. Planta. Med. 84: 834–838.
Keyaerts, E., Vijgen, L., Pannecouque, C., Van Damme, E., Peumans, W., Egberink, H., Balzarini, J., and Van Ranst, M. 2007. Plant lectins are potent inhibitors of coronaviruses by interfering with two targets in the viral replication cycle. Antivir. Res. 75: 179–187.
Lau, K.M., Lee, K.M., Koon, C.M., Cheung, C.S., Lau, C.P., Ho, H.M., Lee, M.Y., Au, S.W., Cheng, C.H., Lau, C.B., Tsui, S.K., Wan, D.C., Waye, M.M., Wong, K.B., Wong, C.K., Lam, C.W., Leung, P.C. and Fung, K.P. 2008. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. J. ethnopharm. 118(1): 79–85.
Lau, T.F., Leung, P.C., Wong, E.L., Fong, C., Cheng, K.F., Zhang, S.C., Lam, C.W., Wong, V., Choy, K.M. and Ko, W.M. 2005. Using herbal medicine as a means of prevention experience during the SARS crisis. Am. J. Chin. Med. 33: 345–356.
Li, H.Y., Ramalingam, S. and Chye, M.L. 2006 Accumulation of recombinant SARS-CoV spike protein in plant cytosol and chloroplasts indicate potential for development of plant-derived oral vaccines. Exp. Biol. Med. 231: 1346–1352.
Li, S.Y., Chen, C., Zhang, H.Q., Guo, H.Y., Wang, H., Wang, L., Zhang, X., Hua, S.N., Yu, J., Xiao, P.G., Li, R.S. and Tan, X. 2005. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antivir. Res. 67:18–23.
Lin, C.W., Tsai, F.J., Tsai, C.H., Lai, C.C., Wan, L., Ho, T.Y., Hsieh, C.C. and Chao, P.D. 2005. Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. Antivir. Res. 68: 36–42.
Lin, S.C., Ho, C.T., Chuo, W.H., Li, S., Wang, T.T. and Lin, C.C. 2017. Effective inhibition of MERSCoV infection by resveratrol. BMC. Infect. Dis. 17:144.
O'Connor, SE. 2015. Engineering of secondary metabolism. Annu. Rev. Genet. 49: 71–94.
Park, H.R., Yoon, H., Kim, M.K., Lee, S.D. and Chong, Y. 2012. Synthesis and antiviral evaluation of 7-O-arylmethylquercetin derivatives against SARS-associated coronavirus (SCV) and hepatitis C virus (HCV). Arch. Pharm. Res. 35: 77–85.
Patel, M., Ashraf, M.S., Siddiqui, A.J., Ashraf, S.A., Sachidanandan, M., Snoussi, M., Adnan, M. and Hadi, S. 2020. Profiling and role of bioactive molecules from puntius sophore (freshwater/brackish fish) skin mucus with its potent antibacterial, antiadhesion, and antibiofilm activities. Biomolecules. 10: 920.
Patel, M., Sachidanandan, M. and Adnan, M. 2018. Serine arginine protein kinase 1 (SRPK1): A moonlighting

protein with theranostic ability in cancer prevention. Mol. Biol. Rep. 46: 1487–1497.

PIB. 2020. Press Information Bureau, India. https://pib.gov.in/newsite/ PrintRelease.aspx?relid=200005.

Pogrebnyak, N., Golovkin, M., Andrianov, V., Spitsin, S., Smirnov, Y., Egolf, R. and Koprowski, H. 2005. Severe acute respiratory syndrome (SARS) S protein production in plants: development of recombinant vaccine. Proc. Natl. Acad. Sci. USA. 102: 9062–9067.

Prasad, A., Muthamilarasan, M. and Prasad, M. 2020. Synergistic antiviral effects against SARS-CoV-2 by plant-based molecules. Plant Cell Rep. 39:1109–1114.

Rosales-Mendoza, S. 2020. Will plant-made biopharmaceuticals play a role in the fight against COVID-19? Expert. Opin. Biol. Ther. 20(6): 545-548.

Ryu, Y.B., Jeong, H.J., Kim, J.H., Kim, Y.M., Park, J.Y., Kim, D., Nguyen, T.T., Park, S.J., Chang, J.S., Park, K.H., Rho, M.C. and Lee, W.S. 2010. Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. Bioorganic. Med. Chem. 18: 7940–7947.

Siddiqui, A.J., Danciu, C., Ashraf, S.A., Moin, A., Singh, R., Alreshidi, M., Patel, M., Jahan, S., Kumar, S., Alkhinjar, M., Badraoui, R., Snoussi, M. and Adnan, M. 2020. Plants-Derived Biomolecules as Potent Antiviral Phytomedicines: New Insights on Ethnobotanical Evidences against Coronaviruses. Plants. 9: 1244.

Takeyama, N., Kiyono, H. and Yuki, Y. 2015. Plant-based vaccines for animals and humans: recent advances in technology and clinical trials. Ther. Adv. Vaccines. 3: 139–154.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W. and Xiao, G. 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 30: 269–271.

Wu, C.Y., Jan, J.T., Ma, S.H., Kuo, C.J., Juan, H.F., Cheng, Y.S., Hsu, H.H., Huang, H.C., Wu, D., Brik, A., Liang, F.S., Liu, R.S., Fang, J.M., Chen, S.T., Liang, P.H. and Wong, C.H. 2004 Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc. Natl. Acad. Sci. USA. 101: 10012–10017.

Yi, L., Li, Z., Yuan, K., Qu, X., Chen, J., Wang, G., Zhang, H., Luo, H., Zhu, L., Jiang, P., Chen, L., Shen, Y., Luo, M., Zuo, G., Hu, J., Duan, D., Nie, Y., Shi, X., Wang, W., Han, Xu, X. 2004 Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J. Virol. 78: 11334–11339.

Yu, M.S., Lee, J., Lee, J.M., Kim, Y., Chin, Y.W., Jee, J.G., Keum, Y.S. and Jeong, Y.J. 2012. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorganic. Med. Chem. Lett. 22: 4049–4054.