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Drug Discovery for Covid-19 – A Multidimensional Perspective

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ABSTRACT

Covid-19, a disease caused by severe acute respiratory syndrome corona virus (SARS-CoV) has challenged pharmaceutical science against viruses, globally. The disease has become a global pandemic beginning the race of new therapeutic strategies against novel corona virus (nCoV). Therefore, management of such pandemic issue is a need of the hour. Drug delivery refers to an approach adopted to transfer drug particles within the body to obtain a potent therapeutic effect. In the present study, an attempt has been taken to discuss about plant secondary metabolites (PSMs) and fungal bioactive compounds which are potent antiviral pharmaceutical agents. Also, a discussion about allopathic ingredient of plant secondary metabolites have also been done. The unique repository of Indian plants and versatility of fungal species provide broad spectrum to screen for pharmaceutical ingredients against novel corona virus. Further, screening of plant secondary metabolites by molecular docking can be a cost effective way to combat from novel corona virus. Thus, it can be said that, Multidimensional approach discussed herein may provide insights to combat antimicrobial resistance in the future. The present review will promote further research horizons in plants and fungal based therapeutics and a novel approach towards drug discovery thereby preventing the humans from suffering through severe adversities.

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INTRODUCTION

A novel pathogen, severe acute respiratory syndrome corona virus (SARS-CoV-2) has recently been identified as the cause of fatal respiratory disease called corona virus disease (COVID-19). COVID-19 originated from Wuhan, China and rapidly spread worldwide leading to global health crises (Lan *et al.*, 2020). Approximately 5 million COVID-19 cases appeared in May 2020 with 30 thousand death reports globally (Panyod *et al.*, 2020). Corona viruses, a large group of positive sense single stranded RNA viruses that cause respiratory infections in mammals, have taken a scary form with high mortality rates in many countries (Brian and Baric, 2005). Among the seven types of human corona viruses reported so far, severe acute respiratory syndrome (SARS)- CoV, Middle East respiratory syndrome (MERS-CoV), and 2019- novel corona virus (nCoV) are major concerns of scientists all over the world (Kanne, 2020). Pathologically, the response phase of the virus and host along with severe progressive symptoms are associated with disease mortality. It is marked by increased levels of cytokines and lymphopenia and decreased expression of interferons which can be life threatening related to COVID-19 (Hirano and Murakami,

2020). The disease pathology exhibits similarities with pneumonia and HIV infections involving deaths due to respiratory failure (Jayshree and Arijit, 2020).

Viruses are extremely dynamic and rapidly evolving pathogens which are difficult to treat. Their ability to generate de-novo diversity with a high mutation rate makes treatment strategy complicated (Xu *et al.*, 2020). Currently, combination therapies are the most effective treatments for infections caused by rapidly mutating viruses. There is no cure for COVID-19 in the form of a vaccine. The patients are being subjected to oxygen therapy for symptomatic relief in respiratory impairment. Non-invasive and invasive medical ventilators are being used in case of obstinate respiratory failure. Hence, due to lack of specific treatment courses for COVID-19, this review opens scope of novel drug discovery by incorporating plants and fungi based therapeutic compounds.

Different approaches for treatment

Common antiviral drugs used for infections like HIV, pneumonia, ebola are being extrapolated to drug treatments for COVID-19. The treatment has shown promising results in the form of symptoms relief but does not ensure specific approved treatment for the disease (Wu *et al.*, 2015). The crisis has urged the development of new therapies against mutating viruses to improve the clinical status of COVID-19 patients. The precedence of synthetic and natural therapies against pre-existing viral diseases in India can serve as a trace line for drug development against COVID-19.

Allopathy against COVID-19

Combinations of several antiviral drugs have been repurposed for treatment of COVID-19 and have displayed positive results. The fundamental approach for such therapy involves interruption of host-pathogen interactions. The structural and non-structural proteins of CoV are considered targets of antivirals (Coperchini *et al.*, 2020). According to Prajapat et al., seven major drug targets of nCoV include viral spike protein, nucleocapsid protein, and membrane protein, envelop protein, hemagglutinin esterase, protease and helicase. These proteins and enzymes are responsible for viral replication and host interaction (Prajapat *et al.*, 2020).

Antiviral drugs being developed or evaluated for COVID-19 treatment include Remedesivir, Lopinavir, Ritonavir and Oseltamivir. Remedesivir is currently under clinical trials whereas Lopinavir, Ritonavir and Oseltamivir are FDA approved drugs used in HIV and influenza respectively (Foo *et al.*, 2020). Additionally, development of new antivirals poses formulation challenges such as low solubility of active compounds. Drug solubility is necessary for improved bioavailability in case of oral antivirals (Kazmierski, 2011). Among COVID-19 antivirals, Remedesivir, Lopinavir and Ritonavir show limited solubility in aqueous solution. As approved by FDA, cyclodextrins can be used as indicative pharmaceutical ingredients to increase solubility of antivirals for oral as well as parenteral drug formulations (Foo *et al.*, 2020).

Since January 2020, when SARS-CoV genome sequence was released, scientists have been struggling to find cues for COVID-19 vaccine development based on mRNA and non-living subunit vaccine concepts. Non-living subunit vaccines lack immunogenicity and require adjuvants to restore immunity. Another way to tackle the infection could be using monoclonal antibiotics. Monoclonal antibodies can specifically target the virus and exhibit long term effects.

These monoclonal antibodies would additionally require excipients in formulation for structural stability of antibodies during storage and transport (Serno *et al.*, 2010). Overall, allopathy treatments for COVID-19 show direct action on virus proteins and enzymes but extensive research and trials are necessary for formulation development. Hence, there seems to be a long way before development of a stable and ubiquitously responsive COVID-19 vaccine.

Homeopathy against COVID-19

Homeopathy is often marked under the halo of criticism and called pseudoscience. Arsenic has been reported to be beneficial for several viral infections. Arsenic Album-30, diluted arsenic oxide is a prophylactic homeopathic drug. According to the Directorate of AYUSH, the prophylactic medicine can be used to prevent nCoV infection.

The argument was extremely criticised by Taiwan Medical News in February 2020 due to lack of clinical data and action mechanism (Ali and Alharbi, 2020).

However, the study conducted by Mathie *et al.* (2013) Arsenic Album can provide symptomatic relief by effectively reducing fever, runny nose, throat infection in patients with symptoms of swine flu (Mathie *et al.*, 2013).

Overall, it is necessary to evaluate clinical effectiveness of Arsenic Album in terms of patient data and research should be done to determine mode of action. Based on success of homeopathy over similar communicable diseases like influenza, it can be a potential add on therapy along with other drug molecules.

Natural therapeutic agents against COVID-19

Plants have been used as a source of therapeutic agents to improve human health since ancient times. Different antiviral compounds have been produced from numerous plant varieties and incorporated in many studies. Scientists have been trying to screen different plant based therapeutics and secondary metabolites to find potential antiviral compounds against COVID-19. Plant metabolites have capability to target enzymes involved in CoV replication and impede cellular signaling pathways (Chitemerere and Mukanganyama, 2014).

Plant secondary metabolites (PSMs) can affect important processes of viruses such as nucleic acid synthesis, quorum sensing and stabilization of cytoplasmic elements (Sun *et al.*, 2014; Radulovic *et al.*, 2013; Mogosanu *et al.*, 2015). Moreover, due to increased risk of drug resistance and evolution of superbugs, researchers have started exploring plant based therapeutics against human pathogens such as CoV.

According to study conducted by Bhuiyan *et al.* numerous varieties of antiviral compounds were screened from 219 medicinal plants related to 83 plant families. Most of these antiviral compounds were found to include polyphenols (Bhuiyan *et al.*, 2020). The polyphenols have been reported to exhibit antiviral properties against HIV, influenza and ebola virus. These compounds help in disturbing signaling pathways and inhibiting papain like protease to prevent coronavirus infection progression (Annunziata *et al.*, 2020; Chowdhury *et al.*, 2018).

Among different categories of polyphenols, papyriflavanol has shown impressive effect against SARS CoV (Park *et al.*, 2017). Alternatively, flavonoids like apigenin and quercetin, had shown antiviral properties against SARS CoV (Ryu *et al.*, 2010; Kim *et al.*, 2014). Another type of PSM called alkaloids are promising therapeutic compounds against HIV, herpes, influenza and Newcastle disease virus (NDV) (Islam, 2020).

Different alkaloids such as Ipecac, Macetaxime and Tylophorine were found antiviral against SARS CoV by affecting protein synthesis, RNA synthesis and inhibiting protease enzyme (Islam, 2020). Some other alkaloids have been associated with intercalation of nucleic acids and inhibition of nucleocapsid and spike proteins (Wink, 2020). Saponins are another important class of PSM as they are omnipresent in different plants and exhibit antiviral properties against NDV, influenza, Simian virus, Epstein barr virus (EBV) and dengue virus.

Additionally, diterpenes, sequesterpenes and hemi terpenes have displayed anti-SARS CoV activity (Wink, 2020). Overall, these studies suggest that plant derived secondary metabolites displaying active against different viruses have scope of being extrapolated to drug discovery for COVID-19.

Fungal bioactive against COVID-19

Fungi are ubiquitous organisms with repositories of different medicinal bioactives as antiviral compounds. Fungal fruiting bodies capable of synthesizing secondary metabolites have a long history of therapeutic applications. Different fungi and their metabolites have been found effective in showing antiviral properties against known disease causing viruses (Table 1) (Dine *et al.*, 2008). *Ganoderma*, the most researched fungal genera is considered to be an antiviral precursor. Their mycelia and fruiting body have been known to synthesize ganoderic acid and triterpenoids as secondary metabolites which have antiviral properties (Eo *et al.*, 1999).

Additionally, different antiviral bioactive compounds include lignin derivatives, proteins and polysaccharides (Clevenger *et al.*, 2017). These compounds can be produced *in-vitro* by culturing mycelium hyphae in highly nutritious liquid medium. Genome based studies have also revealed fungi consists of gene clusters capable of producing therapeutic secondary metabolites (Linnakoski *et al.*, 2018). Therefore, regulation of gene clusters in culture medium should be diligently optimized for screening of antiviral metabolites.

Apart from *Ganoderma,* different endophytic fungi can be utilized for discovery of novel antiviral compounds. Endophytic fungi grow on living plants through mutualistic symbiosis relationship. These fungi are known for their defense mechanisms against unfavourable environmental conditions (Kusari *et al.*, 2014). They have been recognized as a rich source of secondary metabolites, released when the host plant is under pathogen attack. Therefore, defense chemicals and secondary metabolites of these fungi, exhibit wide chemical variety with different biological relevance.

Moreover, secondary metabolites of endophytic origin have been hypothesized to evolve with a variety of changes due to their extreme environmental growth conditions (Deshmukh *et al.*, 2018). Based on the hypothesis, it is probable that these compounds can broaden the spectrum of their virus targets. Overall, fungal metabolites and bioactives hold great potential in novel drug discovery. Their direct mechanism of action over replication of viral particles and scalability has been underutilized so far.

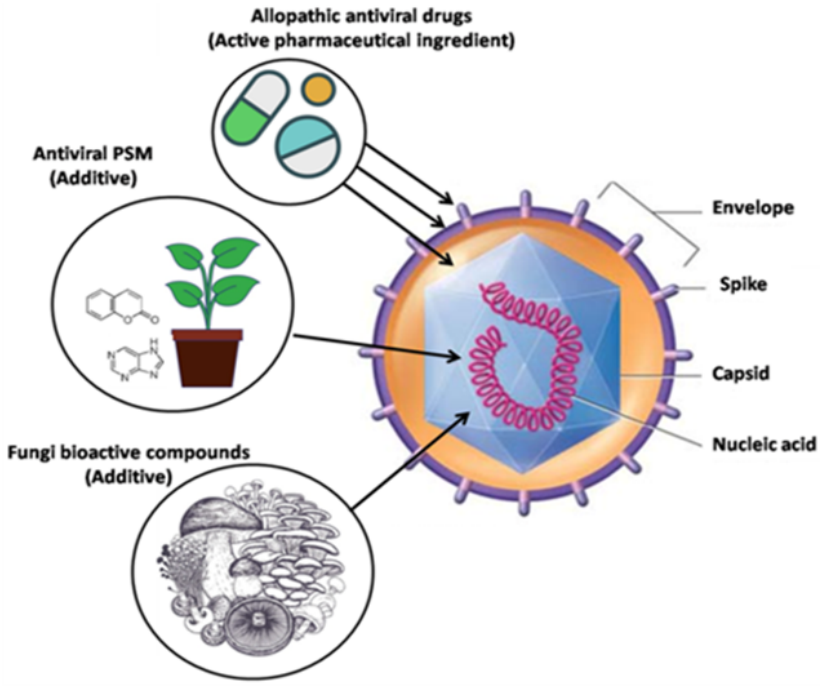

Figure 1: A prospective strategy to develop pharmaceutical formulation for novel corona virus (nCoV) by amalgamation of allopathic and natural compounds

Table 1: Characteristic fungi phylum and order which are known for their secondary metabolites having antiviral properties against various disease causing viruses

Virus	Fungi phylum	Fungi order
Hepatitis C virus	Basidiomycota	Agaricales, Polyporales
HIV	Ascomycota	Amphisphaeriales, Chaetothyriales, Diaporthales, Eurotiales, Hypocreales, Microascales, Ophistomatales, Pleosporales
	Bsiodiomycota	Agaricales, Boletales, Cantherellales, Polyporales
Influenza virus	Ascomycota	Sordaliales
	Basidiomycota	Agaricales
Zika virus	Ascomycota	Eurotiales
Respiratory syncytial virus	Basidiomycota	Agaricales

Drug discovery for COVID-19: Future insights

Despite several attempts for drug discovery against COVID-19, researchers have not been successful towards specific, stable and most effective treatment.

Discovery of de-novo antiviral formulations, vaccines and therapeutic antibodies would require extensive research and pharmacovigilance. Since ancient times, India has held a repository of natural therapeutic compounds in Ayurveda. However, lack of clinically relevant data for properties of ayurvedic compounds has posed great challenges to incorporate the field into drug discovery.

The existence of plant secondary metabolites in therapeutic research has created a directory of antiviral compounds which can be screened for efficacy against COVID-19. Screening of antiviral plant secondary metabolites through molecular docking can be a cost effective way of drug discovery in a timely manner. Endophytic fungi lie under the similar group of potential antiviral sources. The detailed understanding of precise molecular targets and antiviral mechanisms can open different ideas for COVID-19 drug discovery.

The traditional Hindu medicinal regime based on the potential of historical roots to balance bodily systems is continuously being explored for COVID-

19 treatments. According to a report by The Hindu, a blend of ayurvedic and allopathic could be potential therapy against COVID-19. As stated by AYUSH ministry, ayurveda can boost immunity and prevent disease progression from mild to severe stage (Awasthi, 2020). Additionally, it has been reported that China has used traditional plant based formulations to treat SARS-CoV in Guangdong (2002-2003).

The bioactive properties of therapeutic plants have been repurposed to treat COVID-19 (Li *et al.*, 2020). Similarly, plant secondary metabolites can be used along with allopathy to discover a new class of therapeutic compounds against COVID-19 (Figure 1). PSMs can be used as functional additives to improve bioavailability of allopathic formulations. Research studies involving plant secondary metabolites could be performed in a systematic way to deduce their mechanism of action. Overall, the amalgamation of antiviral allopathic compounds, plant based therapeutics and/or fungi bioactive compounds can provide new scope of drug discovery against COVID-19.

CONCLUSIONS

The world is struggling to find a stable treatment for COVID-19. Scientists are trying to repurpose the existing pharmaceutical findings to relieve patients from fatal respiratory dysfunction. The existing treatments are either based on using drugs for symptomatic relief or using ventilators to aid respiration at severe stage. According to researchers, traditional Chinese plants formulations have shown anti-SARS-CoV activity when provided to COVID patients. In India, allopathic drugs have been utilized to treat various viral infections in history but marking most effective allopathic drug requires intensive research trails which requires a lot of time. In parallel terms, homeopathy has been criticized for lack for clinical data and action mechanism. However, plant based therapeutics and fungal bioactive remain are not explored for antiviral potential with nCoV. In present scenario, our study focuses on developing research perspectives for de novo drug discovery. The study describes amalgamation of plant secondary metabolites (PSM) and fungal bioactive compounds along with allopathic formulations to expand the scope of drug discovery in current scenario of global pandemic.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

REFERENCES

Ali, I., Alharbi, O. M. L. 2020. COVID-19: Disease, management, treatment, and social impact. *Science of The Total Environment*, 728:138861.

Annunziata, G., *et al.* 2020. May Polyphenols Have a Role Against Coronavirus Infection? An Overview of in vitro Evidence. *Frontiers in Medicine*, 7:240.

Awasthi, P. 2020. Goa to be the first state to integrate allopathy with Ayurveda to treat COVID-19 patients. The Hindu.

Bhuiyan, F. R., *et al.* 2020. Plants Metabolites: Possibility of Natural Therapeutics Against the COVID-19 Pandemic. *Frontiers in Medicine*, 7:444.

Brian, D. A., Baric, R. S. 2005. Coronavirus genome structure and replication. pages 1–30. Springer, Berlin, Heidelberg. In Coronavirus replication and reverse genetics.

Chitemerere, T. A., Mukanganyama, S. 2014. Evaluation of cell membrane integrity as a potential antimicrobial target for plant products. *BMC Complementary and Alternative Medicine*, 14(1):278.

Chowdhury, P., *et al.* 2018. Theaflavins, polyphenols of black tea, inhibit entry of hepatitis C virus in cell culture. *Plos one*, 13(11):e0198226.

Clevenger, K. D., *et al.* 2017. A scalable platform to identify fungal secondary metabolites and their gene clusters. *Nature Chemical Biology*, 13(8):895–901.

Coperchini, F., *et al.* 2020. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine & Growth Factor Reviews*, 53:25–32.

Deshmukh, S. K., *et al.* 2018. Marine Fungi: A Source of Potential Anticancer Compounds. *Frontiers in Microbiology*, 8:2536.

Dine, R. S. E., *et al.* 2008. Anti-HIV-1 Protease Activity of Lanostane Triterpenes from the Vietnamese MushroomGanoderma colossum. *Journal of Natural Products*, 71(6):1022–1026.

Eo, S. K., *et al.* 1999. Antiherpetic activities of various protein bound polysaccharides isolated from Ganoderma lucidum. *Journal of ethnopharmacology*, 68(1-3):175–181.

Foo, L. S. W. C., *et al.* 2020. Combating Coronavirus: Cyclodextrins In Treatment & Prevention. On Drug Delivery.

Hirano, T., Murakami, M. 2020. COVID-19: A New Virus, but a Familiar Receptor and Cytokine Release Syndrome. *Immunity*, 52(5):731–733.

Islam, M. T. 2020. Natural products and their derivatives against coronavirus: A review of the

non-clinical and pre-clinical data. Phytotherapy Research. Page:1-22.

Jayshree, S., Arijit, P. 2020. COVID 19: Growth analysis, similarity study with HIV and its prevention through flavone rich natural foods. *Global Journal of Infectious Diseases and Clinical Research*, 6(1):003–007.

Kanne, J. P. 2020. Chest CT findings in 2019 novel coronavirus (2019-NCoV) infections from Wuhan, China: Key points for the radiologist. *Radiology*, 295(1):200241.

Kazmierski, W. M. 2011. Antiviral Drugs: From Basic Discovery through Clinical Trials. page 480.

Kim, D. W., *et al.* 2014. Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia. *Journal of enzyme inhibition and medicinal chemistry*, 29(1):59–63.

Kusari, S., *et al.* 2014. Biotechnological potential of plant-associated endophytic fungi: hope versus hype. *Trends in Biotechnology*, 32(6):297–303.

Lan, J., *et al.* 2020. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, 581(7807):215–220.

Li, Y., *et al.* 2020. Traditional Chinese herbal medicine for treating novel coronavirus (COVID-19) pneumonia: protocol for a systematic review and meta-analysis. *Syst Rev*, 9:75.

Linnakoski, R., *et al.* 2018. Antiviral Agents From Fungi: Diversity, Mechanisms and Potential Applications. *Frontiers in Microbiology*, 9:2325.

Mathie, R. T., *et al.* 2013. Homeopathic treatment of patients with influenza-like illness during the 2009 A/H1N1 influenza pandemic in India. *Homeopathy*, 102(3):187–192.

Mogosanu, G., *et al.* 2015. Prevention of Microbial Communities: Novel Approaches Based Natural Products. *Current Pharmaceutical Biotechnology*, 16(2):94–111.

Panyod, S., *et al.* 2020. Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective. *Journal of Traditional and Complementary Medicine*, 10(4):420–427.

Park, J. Y., *et al.* 2017. Evaluation of polyphenols from Broussonetia papyrifera as coronavirus protease inhibitors. *Journal of enzyme inhibition and medicinal chemistry*, 32(1):504–512.

Prajapat, M., *et al.* 2020. Drug targets for corona virus: A systematic review. *Indian journal of pharmacology*, 52(1):56.

Radulovic, N. S., *et al.* 2013. Antimicrobial plant metabolites: structural diversity and mechanism of action. *Current medicinal chemistry*, 20(7):932–952.

Ryu, Y. B., *et al.* 2010. Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. *Bioorganic & medicinal chemistry*, 18(22):7940–7947.

Serno, T., *et al.* 2010. Inhibition of Agitation-Induced Aggregation of an IgG-Antibody by Hydroxypropyl-β-Cyclodextrin. *Journal of Pharmaceutical Sciences*, 99(3):1193–1206.

Sun, S., *et al.* 2014. Bacterial Quorum Sensing Inhibition Activity of the Traditional Chinese Herbs, Ficus carica L. and Perilla frutescens. *Chemotherapy*, 60(5-6):379–383.

Wink, M. 2020. Potential of DNA Intercalating Alkaloids and Other Plant Secondary Metabolites against SARS-CoV-2 Causing COVID-19. *Diversity*, 12(5):175.

Wu, H., *et al.* 2015. Strategies for combating bacterial biofilm infections. *International journal of oral science*, 7(1):1–7.

Xu, J., *et al.* 2020. Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*, 12(2):244.