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Review Paper

ANTIVIRAL ACTIVITY OF INDIAN MEDICINAL PLANTS: PRVENTIVE MEASURES FOR COVID-19

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Abstract

Viral diseases, including the emerging (COVID-19) and chronic viruses, are causing increasing worldwide health concerns. Consequently, the discovery of new antiviral agents from plants has assumed more urgency than in the past. A number of indigenous Indian drugs of plant origin are known to have antimicrobial and anti-inflammatory activity, although only a few have been studied for their antiviral properties and immunomodulatory effects. COVID-19, a new strain of coronavirus (CoV), was identified in Wuhan, China, reportedly at the end of 2019. The COVID-19 (Coronavirus disease 2019) spreads primarily through droplets of saliva or droplets discharged from the nose. No specific therapies are yet available, though a number of research groups internationally are actively engaged in developing these. Thus, so far definitive treatments regarding COVID-19 are lacking. This review covers three different aspects of preventive measures based upon traditional Indian medicinal plants. Firstly, we can develop an efficient viral inactivation system by utilising naturally occurring bioactive compounds from medicinal plants and infusing these in nanofibre-based respiratory masks. Our strategy would be the development of three-layered masks impregnated with these compounds for viral deactivation. Secondly, we can assess naturally occurring bioactive compounds like kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate found in Indian medicinal plants to determine the best potential COVID-19 M^{pro} inhibitors, using molecular docking studies. Last but not least, as a third preventive measure, we can prepare COVID-19 herbal tea at our home by combination of five immune booster Indian medicinal plants *viz*., vasak, tulsi, pippali, green tea and sunthi.

Key words: Antiviral, Indian medicinal plants. COVID-19, respiratory masks, molecular docking, immune booster.

INTRODUCTION

Plants have been a major source of medicine for human kind. According to available information, a total of at least 35,000 plants species are widely used for medicinal purposes. The demand for traditional medicinal herbs is increasing very rapidly, mainly because of the undesirable side-effects of some synthetic chemical drugs. The World Health Organization (WHO) has pointed out that traditional medicine provides important contribution to its health goals. India has a rich tradition of herbal medicine as evident from Ayurveda. Charak Samhita and Sushruta Samhita are the two most famous treatises of Ayurveda where uses of 700 herbal drugs have been described. Some of them have been shown to have antiviral activity. Viral diseases, including chronic and emerging viruses, constitute rapidly escalating worldwide health concern. Due to the global disease burden caused by viral infections there is an urgent need for novel and more effective antiviral drugs. Medicinal herbs and their bioactive constituents come in the centre of interest, since they may provide feasible treatment options for the population of developing countries, where the majority of the population cannot afford expensive chemical drugs of western medicine.

The novel coronavirus 2019 (COVID-19), causing the unexpected pandemic, has caused severe panic among people worldwide. The new strain of CoV was identified reportedly at the end of 2019 and initially named 2019-nCoV, had emerged during an outbreak in Wuhan, China [1]. The Emergency Committee of the World Health Organization (WHO) declared an outbreak in China on January 30, 2020. The advent of COVID-19 has kept the whole world on tenterhooks, causing unprecedented panic. Countries are maximising their efforts to minimise infection and combat the virus. Most countries were unprepared for a pandemic of this magnitude, and may not be able to prevent transmission and undertake treatment efficiently. In this situation, vaccine(s) can greatly reduce morbidity and mortality. However, the potential problem will persist till the development of effective viral vaccine(s). Individuals close to the point of outbreak would be in immediate danger of exposure till development of vaccine(s).

This review covers three different aspects of preventive measures based upon utilisation of traditional Indian medicinal plants. Firstly, we can develop an efficient viral inactivation system by using naturally occurring bioactive compounds from medicinal plants and infusing these into nanofibre-based respiratory masks. Our aim would be the development of three-layered masks impregnated with these compounds

for viral deactivation. Secondly, we can assess naturally occurring bioactive compounds like kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate found in Indian medicinal plants to find out which of these appear to be the best potential COVID-19 M^{pro} inhibitors, using molecular docking studies. Last but not least, as a third preventive measure, we can prepare COVID-19 herbal tea at our home by combination of five immune booster Indian medicinal plants *viz*., vasak, tulsi, pippali, green tea and sunthi.

DISCUSSIONS

(I) Development of efficient viral inactivation systems by infusing naturally occurring active compounds them into nanofiber-based respiratory masks.

In this review, firstly we discuss various aspects of controlling infection, and mitigating effects on how to manufacture a more effective of respiratory protective equipment and masks to prevent any aerosol with microbes. Respiratory and facial protection is required for those infectious microorganisms that are usually transmitted via droplets/aerosols [2]. Transmission of COVID-19 infection occurs mainly through sneezing or coughing where infectious particles, *viz*. aerosol droplets of varying sizes, may be inhaled. Extensive studies have provided useful information on the management of respiratory infection outbreaks with a high risk of human to human transmission [3]. The use of medical masks to health care providers committed to patient care in high-risk situations are recommended by Centres for Disease Control and Prevention (CDC) [4] and the World Health Organization (WHO) [5] guidelines. To reduce the transmission of COVID-19 to the general population also, it is of advantage to use personal respiratory protective equipment. Respirators and masks, eye protectors and gloves are considered appropriate personal protective equipment for prevention of COVID-19 transmission. The efficiency of filtration in respirators and masks depends on filter characteristics, *viz*. fibre diameter, charge of fibres, packing density, filter thickness, as well as on properties of the particles to be filtered out - diameter, density and velocity.

A large proportion of respiratory masks have larger pore size than viruses (SARS-CoV-2 = approximately 120 nm); this constitutes a key challenge for researchers to devise means of deactivating the pathogen before entering the human system. Hence the need

for efforts to develop universal virus negation systems which are easy to use. Research needs to be focused on treatment of filters with substances possessing established antimicrobial properties. We propose to develop efficient viral inactivation systems by utilising active compounds derived from/ extracts from Indian medicinal plants and infusing them into nanofibre-based respiratory masks, *i.e.* to develop fibrous filtration with three-layered masks using compounds/ extracts from medicinal plants [6] for viral deactivation (Figure 1).

The active constituents/ extracts may be infused through the electrospinning process into the layers constituting the masks. These masks provide the wearer with an extra mode of protection in addition to the physical barrier. For those viral particles, too small to be held back by the mask, adding antiviral filter layers will prove beneficial in deactivating the viruses. The infused compounds destroy the virus by contact inhibition by disruption of virus cell walls or by immobilisation (Figure 1).

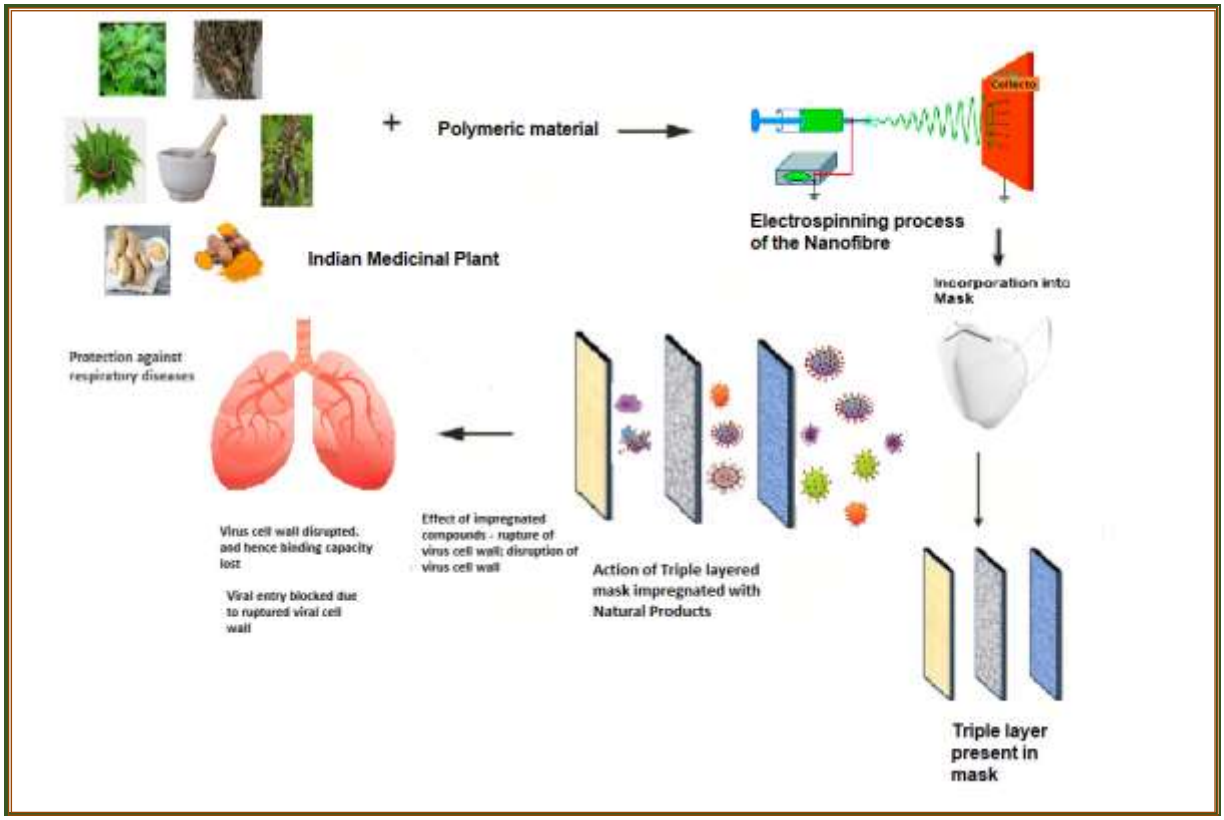
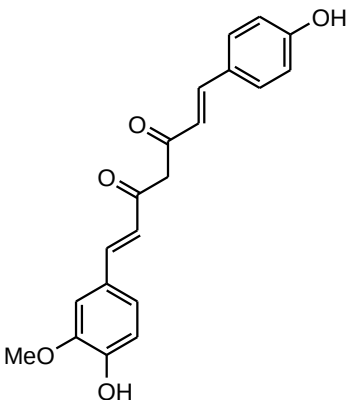
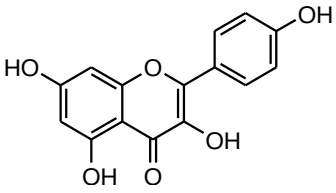
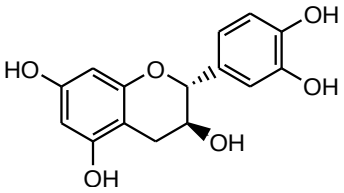


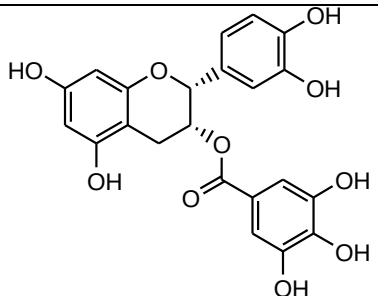
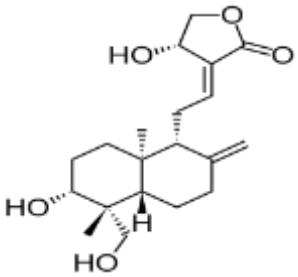
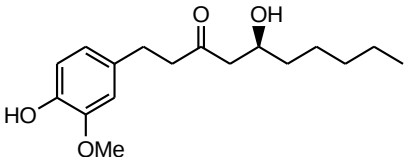
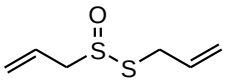
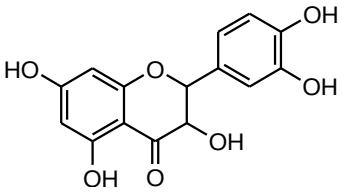
Figure 1. Flow diagram for preparation of Mask with medicinal plant filter for prevention and deactivation of the viruses.

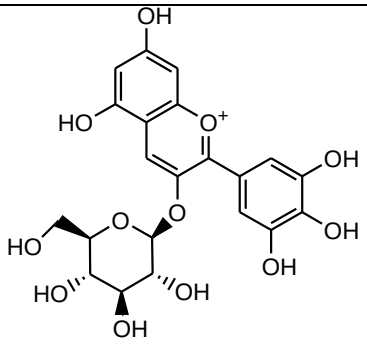
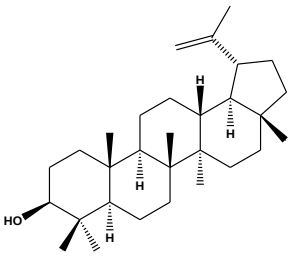
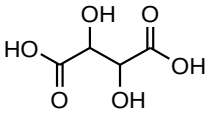
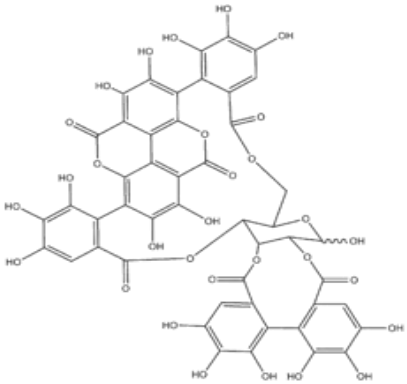
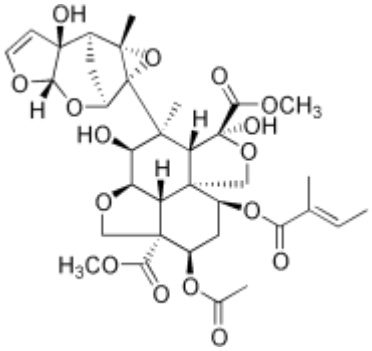
(II) Assessment of bioactive compounds found in medicinal plants as potential COVID-19 M^{pro} inhibitors, using molecular docking studies

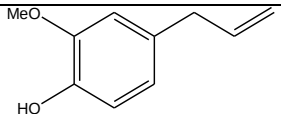
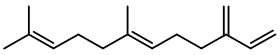
In order to rapidly discover lead compounds for clinical use, an international group of scientists (from Shanghai Tech University in Shanghai, Tsinghua University in Beijing, Chinese Academy of Sciences in Wuhan, Nankai University in Tianjin, and the University of Queensland in Brisbane, Australia) initiated a program of combined structure-assisted drug design, virtual drug screening and high-throughput screening to identify new drug leads that target the COVID-19 virus main protease (M^{pro}). M^{pro} is a key CoV enzyme, which plays a pivotal role in mediating viral replication and transcription, making it an attractive drug target for this virus. They identified a mechanism-based inhibitor, N3, by computer-aided drug design and subsequently determined the crystal structure of COVID-19 virus M^{pro} in complex with N3. Once they had this structure, they could use it as a model to identify more lead M^{pro} inhibitors. This work is published in *Nature*, 2020 in the paper titled, "Structure of M^{pro} from COVID-19 virus and discovery of its inhibitors" [7]. They analysed a large number of compounds and identified the following six compounds as the best options - ebselen, disulfiram, tideglusib, carmofur, shikonin, and PX-12. This protease represents a potential target for the inhibition of CoV replication; Xu et al. has predicted Nelfinavir to be a potential inhibitor of 2019-nCov main protease by an integrative approach combining homology modelling, molecular docking and binding free energy calculation [8]. Molecular docking studies have been carried out by Joseph and co-workers (2020) to assess the natural product andrographilide as potential COVID-19 M^{pro} inhibitor [9]. In our perspective great attention has to be paid to secondary bioactive metabolites secreted by plants in tropical regions that may be developed as medicines [10, 11] using similar molecular docking approaches. Among other compounds the studies can focus on active antiviral phyto-compounds from Indian medicinal plants such as kaempferol, quercetin, luteolin-7-glucoside, demethoxy-curcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechin-gallate, gingerol and allicin as potential inhibitor candidates for COVID-19 M^{pro}. Some of these phyto-compounds of Indian medicinal plants, which may be investigated along with sources, structures and their reported pharmacological properties are given in Table I.

Table I:- Phyto-compounds of Indian medicinal plants – Sources, Structures and their reported Pharmacological properties.

Sl. No.	Medicinal plants	Part used	Active antiviral phyto-compound with molecular structure	Reported Pharmacological property
1	Turmeric (*Curcuma longa*)	Rhizome	Demethoxy curcumin ($C_{20}H_{18}O_5$) 	Antiviral properties [13,14]
2	Spinach (*Spinacia oleracea*), Cabbage (*Brassica oleracea*)	Leaves	Kaempferol ($C_{15}H_{10}O_6$) 	Antiviral properties [12]
3	Green tea (*Camellia sinesis*)	Leaves	Catechin ($C_{19}H_{18}O_8$)  Epicatechin gallate ($C_{22}H_{18}O_{10}$)	Immunomodulatory and Anti-inflammatory effect on lungs [15, 16]

				
4	Kalmegha (*Andrographis paniculate*)	Leaves	Andrographolide ($C_{20}H_{30}O_5$) 	Antiviral properties [6] Potential inhibitor of SARS-CoV-2 main protease [9]
5	Ginger, Sunthi - dried ginger (*Zingiber officiale*)	Rhizome	6-Gingerol ($C_{17}H_{26}O_4$) 	Antiviral properties [17]
6	Garlic (*Allium sativum*)	Bulb	Allicin ($C_6H_{10}OS_2$) 	Proteolytic and hemagglutinating activity and viral replication [18]
7	Onion (*Allium cepa*) Chilli pepper (*Capsicum annum*)	Bulb	Quercetin ($C_{15}H_{10}O_7$) 	Antiviral properties [12]
8	Shankupushpam (*Clitoria ternatea*)	Flower	Delphinidin-3-O-glucoside ($C_{21}H_{21}O_{12}$)	Antiviral properties [6]

				
9	Kuntze (*Strobilanthes cusia*)	Leaves	Lupeol ($C_{30}H_{50}O$) 	Inhibitory action towards HCoV-NL63 [6]
10	Madhunashini (*Gymnema sylvestre*)	Leaves	Tartaric acid ($C_4H_6O_6$) 	Inhibition of viral DNA synthesis [6]
11	Dadima (*Punica granatum*)	Fruit	Punicalagin ($C_{48}H_{28}O_{30}$) 	Inhibited viral glycoprotein and Anti-HSV-1 [6]
12	Neem (*Azadirachta indica*)	Leaves	Azadirachtin ($C_{35}H_{44}O_{16}$) 	Active against coxsackievirus virus B-4 [19]
13	Tulsi (*Ocimum*	Leaves	Eugenol ($C_{10}H_{12}O_2$)	Antiviral

	tenuiflorum)		 α -Farnesene ($C_{15}H_{24}$) 	properties [20]

(III) Preparation of Herbal tea to check COVID-19

As an initial preventative measure against COVID-19, we can prepare herbal tea at our home by combination of five immune booster Indian medicinal plants, *viz*. vasak (*Justicia adhatoda*) leaves, tulsi (*Ocimum tenuiflorum*) leaves, pippali (*Piper longum*) fruit, green tea (*Camellia sinesis*) leaves and sunthi (*Zingiber officiale*) rhizome. .

CONCLUSION

Currently COVID-19, emerging initially in the human population in China and rapidly spreading throughout the world, has become a grave threat to global health, worldwide. All countries are taking precautionary measures against the virus: Governments through their officials are continuing efforts to minimise human contact by facilitating countrywide lockdown of public places; various steps like social distancing and self-quarantine which limit social interactions are being implemented to ensure the safety of the citizens. These steps reduce the risk of spreading the COVID-19 to people by interrupting the transmission chain and slow down the influx of new COVID-19 cases in a particular time period. Slowing the influx of new COVID-19 cases will significantly reduce the strain on national healthcare systems by limiting the number of severely afflicted people who need hospital care. These measures give time to scientists to develop preventive measures and ultimately lead to the preparation of drugs and vaccines to actively combat the disease. In this review, we have proposed three different aspects of preventive measures based upon traditional Indian medicinal plants. Firstly, we can develop an efficient viral inactivation system by utilising naturally occurring bioactive compounds/ extracts from medicinal plants and infusing these into nanofibre-based respiratory masks. Our aim would be the development of three-layered masks

impregnated with these compounds for viral deactivation. Secondly, we can assess naturally occurring bioactive compounds like kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, and epicatechin-gallate found in Indian medicinal plants to determine the best potential COVID-19 M^{pro} inhibitors, using molecular docking studies. This implies, that further research is necessary to investigate the potential uses of the medicinal plants containing these compounds. Last of all but not least as a home remedy we can prepare COVID-19 herbal tea as a preventive measure against corona virus by combination of five immune booster Indian medicinal plants *viz*., vasak, tulsi, pippali, green tea and sunthi. Citizens practicing self-hygiene and social distancing only and passively waiting in solitude to wait for the light at the end of the tunnel, is not enough. It is time for all scientists, clinicians, pharmacologists to join hands together and to proactively develop methods to prevent infection and devise cures for COVID19.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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