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Traditional Indian plants as the source of compounds to treat a respiratory viral infection

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Abstract

Since December 2019 world news broadcasted stories of a deadly disease caused by SARS CoV-19, which is a single-stranded positive-sense RNA virus that replicates in the cytoplasm of infected cells. Coronaviruses (CoVs) and the associated severe acquired respiratory syndrome (SARS - CoV) are potential agents to infect the respiratory tract of humans and animals. Much scientific effort has been focused on the development of vaccine and medicines to protect future outbreaks. However, the chances to rapidly develop an effective vaccine are difficult now. Due to the sudden and explosive emergence of the disease, empirical strategies have been used to treat the patients. The increasing demand for natural products as an alternative therapy for pandemic viral diseases has encouraged research into the pharmacological importance of bioactive compounds from plants, especially Indian herbs. Ethnopharmacological studies have been extremely relevant to discover promising drugs for the treatment of viral diseases. This review is intended to focus on the traditionally practised Indian medicinal plants and bioactive compounds with antiviral properties used for the treatment of respiratory associated viral infections and other retroviral infections. It may lead us to develop a broad spectrum of anti-viral for the prevention and control of these viral pathogens in the current situation.

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INTRODUCTION

Viral diseases have been increasing globally since the past few years and constitute to be a global threat to humanity. There have been various viral flare-ups, both major and minor in different landmasses of the world influencing an impressive number of individuals. All through vestige, there are records of pandemic infections, for example, smallpox and tuberculosis and the absolute most disastrous pandemics were the plagues, the Spanish flu and the pig influenza just as the avian flu. Even though various kinds of treatment techniques are accessible to fix viral ailments, inferable from their potential for transformation and advancement of new strains and obstructing different medications, infections are developing quicker. Recognizable proof of various viral components engaged with plants additionally has helped in distinguishing where they cooperate in the viral cycle, for example, entry, replication, assembly, packaging, and release.

Some plant subsidiaries of the quinone family have indicated colossal outcomes in relieving viral ailments, for example, HIV-1. Hydroxychloroquine and chloroquine have been found to have immunomodulatory impacts in reducing SARS CoV (Zhang and Zhong, 2020). In this short report, we will concentrate on various plant subordinates which are hostile to viral properties, and which will battle against ailments including HIV, SARS and furthermore.

Evidence Supporting the Efficiency of Indian Traditional Medicine System

Traditional medicine, especially herbal medicine, has been considered of immense importance globally, particularly in rural areas. Indian conventional medicinal system like Ayurveda, Siddha and Unani have an extraordinarily rich history of their effectiveness, and they are of great importance. Medicinal plants such as tulsi, aloe vera, ginger, neem, and turmeric cure several ailments. Herbs, for example, dark pepper, cinnamon, sandalwood, and ginseng, are utilized to recuperate wounds and boils. Ashwagandha, a small woody plant native to India, has shown to lower anxiety and boost the immune system. Fennel is a liquorice-flavoured plant that fights viruses, including herpes. Peppermint is also known to have anti-viral properties and is known to be powerful against respiratory syncytial infection and decreases the inflammatory compounds. Garlic also is known to be a popular remedy for several diseases and illness. It is known to possess anti-viral activity against Influenza, HIV, viral pneumonia, and rhinovirus as well as HPV. Astragalus root has been used in traditional medicine and has been shown to boost immunity and to fight against viruses like herpes virus, HCV and avian influenza H9 virus (Song *et al.*, 2007).

Some of the medicinal plants being used in Kanchipuram, Tamilnadu during the ethnobotanical survey conducted in 2003-2004 are the following: *Andrographis paniculata* (Nilavembu) – leaf paste is used to treat poison bites and leaf powder is used to treat diabetes; *Gymnema Sylvestre* (Sirukurinchan) root powder is used to treat poison bites, and leaf powder is used to treat diabetes; *Azadirachta indica* (Vembu) leaf paste is used to treat smallpox, rheumatism and skin diseases and young twigs are used as a toothbrush; *Moringa oleifera* (Murangai) the leaves are boiled and used to reduce body heat, to treat indigestion and eye diseases, and flowers are used to cool the eyes and increase sperm production; *Zizyphus mauritiana* (Ilandai) decoction of the leaf is used to get relief from body pain and bark powder is used to treat wounds; *Solanum torvum* (Sundaikkai) the juice is extracted from the leaf and is used to reduce body heat and unripe fruits are used to strengthen the body (Muthul, 2006).

A study by Jadhav *et al.* (2012) with 24 plant extracts showed 5 of them to have anti-viral activity. *Azadirachta indica* Linn. bark aqueous extract demonstrated potent entry inhibitor activity against HSV-1 infection. *Ocimum basilicum* aqueous and ethanol extracts containing ursolic acid exhibited potent anti-HSV-1 activity *in-vitro*. The aqueous extract and tannins from the pericarp of *P. granatum* had shown anti-HSV-1 and HSV-2 activities *in-vitro*, respectively. The acetone, ethanol, and methanol extracts of *Phyllanthus urinaria* Linn. inhibited HSV-2 infection by disturbing the early stage of virus infection and by decreasing the virus infectivity. Putranjivain A, isolate of *Euphorbia jolkini,* inhibited both the virus entry and late-stage replication of HSV-2 *in-vitro.*

Molecular Mechanism of Action of Anti-Virals Derived From Plants

Herbal medicine and purified products provide a precious resource for new anti-viral drug development. Identification of the anti-viral mechanism from these natural agents has shed light on where they interact in the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus-host –specific interactions Figure 1.

Viral Entry Inhibitors

Rhizophora apiculate, leaf extract contains an acid polysaccharide, mainly composed of galactose, galactosamine and uronic acid. It was shown to completely inhibit the binding of HIV-1 to the cells at a concentration of 100 mg/ml. Further, it can be presumed to block this attachment by forming a shield between the gp120 glycoprotein viral envelope and the CD4 cell surface receptor. The compounds 6,8-diprenylaromadendrin and 6,8-diprenylkaempferol extracted from *Vaticaastrotricha* have been found to inhibit HIV-1 entry. These extracts were reported to prevent syncytia formation in the HIV-infected cells. The root extract of *Pelargonium sidoides* contains polyphenolic compounds that inhibit the HIV-1 entry by interfering with the function of the envelope proteins (Helfer *et al.*, 2014).

The saponin-rich methanolic extract of *Buple urumkaoi* roots was able to block HCV infection by neutralizing free virus particles and abolishing viral attachment and entry/fusion. The terpenoid, SSa blocked HCV entry, while SSb2, the least abundant

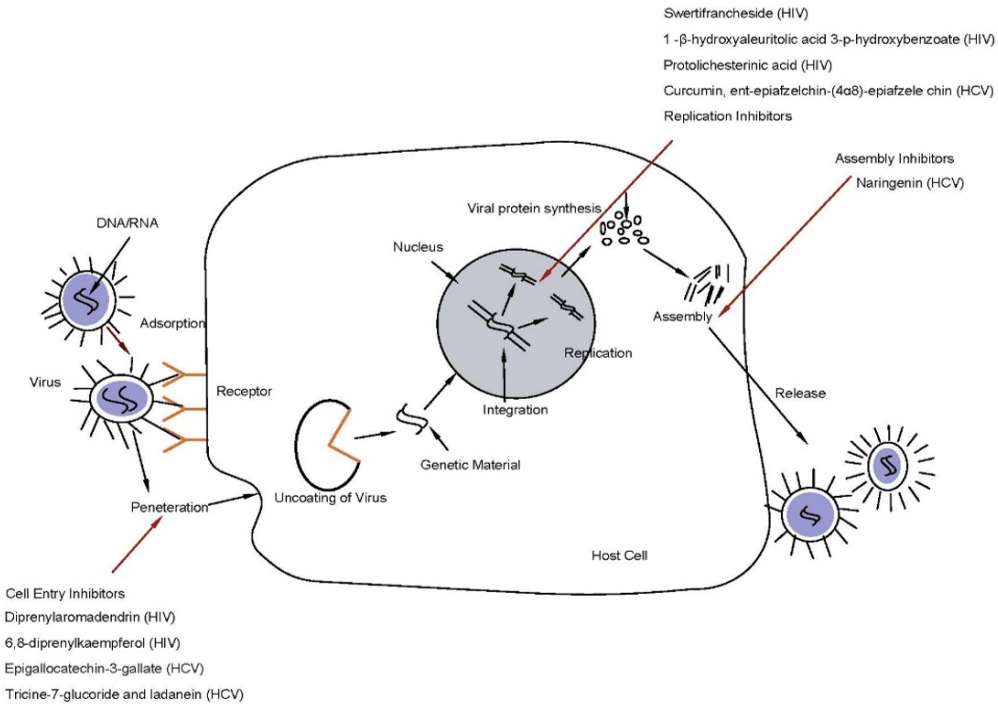

Figure 1: Molecular mechanism of antiviral phytochemicals derived from Plants

saikosaponin, was found to be most effective as it inhibited multiple events of the entry cycle including, neutralization of virus particles, inhibiting attachment, and preventing entry/fusion. Green tea catechins, especially, epigallocatechin-3-gallate targets viral cell entry, and NS3/4A-independent preliminary stage of the viral replication cycle in both the hepatoma cell lines and the primary human hepatocyte. It was also preventing viral attachment to the target cell as well as transmission from cell to cell between adjacent cells (Ciesek, 2011).

Viral replication inhibitors

Since most of the traditional medicines are plant-derived natural viral replication inhibitors, the recorded that Swertifrancheside, a flavanone-xanthone glucoside isolated from *Swertia franchetiana*, 1-β-hydroxyaleuritolic acid, 3-p-hydroxybenzoate a triterpene isolated from roots of *Maprounea Africana* and protolichesterinic acid, an aliphatic α-methylene-γ-lactone isolated from the lichen *Cetraria islandica* were found to be potent inhibitors of the DNA polymerase activity involved in the replication mechanism of HIV-1 reverse transcriptase. Aqueous and ethanolic extracts of *Ocimum basilicum*, and its compounds like linalool, apigenin and ursolic acid, have shown to interfere with a viral infection of coxsackievirus and enterovirus. Tricyclic coumarin from the stem bark of *Calophyllum brasilience* inhibits both replications in acute and chronic infections by suppressing NF-κB activation in HIV-1 (Kudo, 2013).

Naturally, derived herbal products such as ent-epiafzelchin-(4αà8)-epiafzelechin extract from *Cassia javanica* has been shown to inhibit HSV replication (Cheng, 2006). Curcumin has been shown to play an essential role in inhibiting viral replication by suppressing the Akt-SREBP-1 pathway in HCV replication. Ladanein isolated from *Marrubium peregrinum* has also been shown to block viral replication in HSV viruses. Influenza viruses cause respiratory infections which leads to conditions such as pneumonia. Plant-derived inhibitors such as extracts of dandelion have shown to inhibit viral NP RNA levels and polymerase activity. Chalcones from *Glycyrrhiza inflate*a and Xanthones from *Polygala karensium* acted against influenza A virus and served as a nucleic acid inhibitor (Haid, 2012).

Viral assembly inhibitors

Prunella vulgaris aqueous extracts are known to inhibit post virion binding event. *Citrus paradisi* contains a flavanone compound called Naringenin that inhibits the Hepatitis C virus protein responsible for its assembly after replication of the RNA. *Acacia nilotica* also inhibits the virion assembly (Jiaa *et al.*, 2008).

Retrovirus and HIV

Retrovirus belongs to the virus family with substantial medical importance. On top of that, the endogenous retroviruses contain some parts of the vertebrate genome. Bioinformatics studies proved that these viruses evolved during the period of the Palaeozoic era, which is between 460 and 550 million years ago, which provides the oldest evidence for the formation or presence of a virus. Sometimes the virus leaves traces in the genomes of the host as endogenous viral elements (EVs), which helped in locating the history of viruses. HIV-1 and HIV-2 belong to the class of retroviral lentiviruses. Transmission of cross-species from other primates to humans was possibly induced by blood mixing from harvesting and treating 'bushmeat.' HIV-1 was first detected in 1983, and HIV-2 was first reported in 1985. HIV-1 was derived from the chimpanzee simian immunodeficiency virus (SIVcpz), while HIV-2 is genetically like the sooty manu virus (SIVsmm). As a result, HIV-1 and HIV-2 are vastly different; their nucleic acid sequences are homologous to just around 40 per cent. Both HIV-1 and HIV-2 are pathogenic in humans unlike SIV, which does not induce immunodeficiency in its native primate host. The virus has the three critical open frames (gag, pol, and env) along with six small additional genes encoding various accessory and regulatory proteins. Accessory proteins are Vif, Vpr and Vpu and regulatory proteins are Tat, Rev and Nef.

Mode of action

The HIV-1 cell entry cycle starts with a virus envelope attachment to a permissive host cell. HIV-1 envelope proteins usually bind to the CD4-receptor expressing cells. Chemokine co-receptor binding is required for the entry of HIV-1 to facilitate the final conformational changes needed for membrane fusion. Upon membrane fusion, the viral material is released into the cell. Initially, the transcription mechanism leads to the early formation of regulatory HIV-1 proteins like Tat and Rev. Tat binds to the TAR site (Transactivation Response Element) at the origin of HIV-1 RNA in the nucleus and triggers transcription and more extended RNA transcript formation. Rev promotes the transcription of longer RNA transcripts and the expression of structural and enzymatic genes, and inhibits the synthesis of regulatory proteins, thus promoting mature viral particle formation (Fanales-Belasio *et al.*, 2010).

Plants against Retroviral infection

The water extract of *Eclipta prostrate*, containing ecliptol, orobol, wedelolactone and four terthiophene compounds exerts inhibitory activity against HIV-1 protease. The black elderberry (*Sambucus nigra*) contains catechins, proved for reducing the symptoms and effects of HIV by blocking the enzymes. *Momordica charantia* (bitter melon) is widely available in India and has the compound α- and β- momorcharins which had the potential to inhibit HIV replication. *Gymnema Sylvestre* (Sirukurinja) is native to southern India, and the ethanolic extract of this plant inhibits the reverse transcriptase of HIV at 200μg/ml. In contrast, methanolic extract inhibits the DNA polymerase of Hepatitis B. Flavonoids from *Desmos sp. (*Annonaceae), and *Chrysanthemum morifolium* have shown to have an anti-viral response against HIV-1. *Anisomeles indica* produces a compound ovatodiolide which has shown some amount of anti-viral activity. *Glycyrrhiza glabra* containing the compound glycyrrhizin can cure HIV-1 by decreasing its replicator activity. Illicinone-A from *Illicium verum* and *Andrographis paniculata* leaf extracts upon MT-4 cell assay showed inhibition of HIV protease and reverse transcriptase. Seed extract from *Areca catechu* contains a compound procyanidin that inhibits protease of HIV (Song *et al.*, 2007).

SARS (Severe Acute Respiratory Syndrome)

Severe Acute Respiratory Syndrome is a respiratory infection caused by a coronavirus (SARS- CoV). The illness was found to be highly contagious and sometimes, even fatal. SARS-CoV contains 3-Chymotrypsin-like protease (3CL^{pro}) that mediates the proteolytic processing of replicase polypeptides, 1a and 1ab into the functional protein. Therefore, it was being focused on the development of anti-viral drugs against SARS.

Anti-viral compounds against SARS

Root extracts of *Isatis indigotica* were found to have anti-viral properties against SARS. The root contains indigo, indirubin, indican (indoxyl-beta-D-glucoside), beta-sitosterol, gamma-sitosterol, sinigrin. The cell-free cleavage assay suggested that the root extract of *I. indigotica* had a dose-dependent anti-3CL^{pro} effect with an IC$_{50}$ of 53.8 $\pm$ 4.2μg/mL and 191.6 $\pm$ 8.2 μg /mL for cell-based cleavage assay. The cell-based assay had shown that hesperetin (IC$_{50}$: 8.3 μM) and sinigrin (IC$_{50}$: 217 μM) could be used as potential inhibitors for SARS-CoV 3CL^{pro}.In another study, 33 carbohydrate-binding proteins containing mannose, N-acetyl glucosamine, glucose, galactose, N-acetyl galactosamine specific plant lectins were studied for their anti-viral activity against SARS-CoV infection in vitro (Els *et al.*, 2007). It was found that the mannose-binding lectins had the most anti-viral activity against SARS-

CoV. N-acetyl glucosamine specific lectin isolated from stinging nettle and tobacco plant also had active anti-viral activity against SARS-CoV.

In 2005, two glycyrrhizin derivatives were reported as having anti-SARS-CoV activity and hence the anti-SARS-CoV activity of 15GL derivatives was experimented. It was found from the experiments that when 2-acetamido-β-D-glucpyranosylamine was introduced into the glycoside chain of GL, it increased anti-SARS-CoV activity to about ten-fold when compared to the GL activity (Hoever, 2005). Glycyrrhizin hinders virus replication, adsorption, and penetration. It was also reported that Glycyrrhizin was most efficacious when given during and after the adsorption period (EC_{50} 300 mg/L). The compounds derived from *Artemisia annua, Lycoris Radiata, Pyrrosia lingua,* and *Lindera aggregate* have exhibited anti-viral activity against SARS-CoV, this was found in Vero cell-based CPE/MTS screening. Further analysis of the structure and activity determined that lycorine is an active component in the alkaloid portion of the *Lycoris Radiata*. Plant extracts of eucalyptus, *Lonicera japonica*, and Ginsenoside-Rb1, were recently reported to show activity against the SARS-CoV at the concentration of 100M. It was found that four extracts of Chinese herbs used in traditional Chinese medicine exhibited anti-SARS-CoV activity in Vero cell-based assays. *L. radiata* was found to show the best potency (EC_{50}: $2.4\pm0.2\mu$g/ml). The results indicate that these herb extracts, especially from *Lycoris Radiata*, might be potent and efficient candidates for anti-viral medicine. The study reported that six phyto extracts, one each from *Rhizomaci botii, Gentiana radix, Dioscoreae rhizoma, Cassiae semen, and Loranthi ramus,* and two extracts from *Rhizomacibotii* were proved for effective anti-SARS-CoV activity by inhibiting the replication of SARS-CoV. The research was recorded on SARS-CoV 3CLproinhibitors from *Tripteryguim regelii* (Celastraceae). It was found that the bark methanol (95%) extracts of this plant can significantly inhibit SARS-CoV 3CLproactivity (>70% inhibition at 30lg/mL). Subsequent bioactivity-guided fractionation of the $CHCl_3$extracts resulted in the identification of four quinone-methide triterpenoid derivatives – celastrol, pristimererin, tingenone, and iguesterin (Li and Shi-You, 2005).

CHLOROQUINE

Chloroquine (chloroquine phosphate) is a drug used to forestall and treat malaria. It belongs to the class of drugs, 4-aminoquinoline. This drug is used not only for malaria, but also found to be effective in treating diseases like amebiasis, rheumatoid arthritis and lupus erythematosus. Chloroquine (CQ) is a synthetic derivative of the alkaloid quinine. Quinine is derived from the bark of many species of Cinchona trees. According to the ethnobotanical study of indigenous knowledge on medicinal plants used by the village people of Thoppampatti, Dindigul district, Tamilnadu, India, it was found that the herb *Acalypha indica* L., also known as Indian acalypha or kuppaimeni, produced quinine as one of its many chemical compounds (Sivasankari *et al.*, 2014).

Chloroquine analogues as immunomodulators

Chloroquine analogues, as an adjuvant treatment, control immune activation with other antiretroviral agents in the viral infection (e.g., HIV-1). The analogues minimize systemic activation of the T cell and HIV/AIDS immune hyperactivation. As an endosomal inhibitor, chloroquine blocks Toll-like receptor (TLR) mediated activation of plasmacytoid dendritic cells (PDC) and myeloid differentiation primary response gene 88 (MyD88) signalling by the reduction in the level of interleukin-1 receptor-associated kinase 4 (IRAK-4) and IFN regulatory factor 7 (IRF-7) and by IFN-α synthesis inhibition (Martinson *et al.*, 2014).

Anti-malarial action

Forty-six therapeutic herbs which are utilized to cure malaria and numerous different infections in Madagascar have been exposed to biological analysis to determine some of the most bioactive components in tackling *Plasmodium falciparum*. Dihydrocordobimine RS, cordobimine and monterine were extracted from *Crematosperma sp.* They were shown to possess anti-malarial activity against CQ resistant *P. falciparum* FcB1. Helenalin- [(2- hydroxyethyl-3-methyl) acrylate] extracted from *Vernoniopsis caudate* was shown to exhibit anti-malarial activity with an IC_{50} value of 0.2 μM against chloroquine-resistant *P. falciparum* FcB1. Fresh samples of *Ulva fasciata, Enteromorpa compressa, Enteromorpha intestinalis, Chaetomorpha antennina, Chaetomorpha indica, Helimida gracilus, Gracilaria edulis* and *Sargassum wightii* were collected from the Kanyakumari district of Tamilnadu, India. The methanolic extracts were subjected to in-vitro anti-plasmodium activity against *Plasmodium falciparum*. The anti-plasmodial activity was corroborated to the occurrence of sugars and phenolic compounds.

Anti-HIV effects of chloroquine

Chloroquine can curtail the in-vitro replication and growth of HIV. This potential was verified by saturating cells with high doses of chloroquine before infection to imitate the medication build-up in the

body tissue of patients undergoing extensive therapy and via maintaining HIV-infected cells in continuous incubation with chloroquine concentrations detected in the blood of patients excessively treated with this medicine. CQ was found to prevent the X4, R5, and X4/R5 strains of HIV-1 infection in lymphocytic and monocytic cells, HIV-1 subtype C and HIV-2. The fundamental pathway of CQ-inhibition of HIV tends to be an impact on gp120 (glycoprotein) at a post-transcription stage (Savarino *et al.*, 2003).

Chloroquine for treating SARS-CoV

Chloroquine interferes with the ability of the SARS virus replication. The drug reaches acidic endosome initially. However, its pH is enhanced by the drug's molecular structure. To break the cell membrane, expel the genetic material and initiate the replication, several viruses (including SARS-CoV) acidify endosomes. This crucial process is blocked by chloroquine. The drug also stops SARS-CoV from attaching itself to the angiotensin-converting enzyme-2 receptor (ACE2) on primate cells (Martin *et al.*, 2005). The adverse effects of chloroquine consumption include anaemia, blurred vision, nausea, stomach cramps, headache, diarrhoea.

HYDROXYCHLOROQUINE

Apart from chloroquine, hydroxychloroquine is another synthetic derivative of quinine. Hydroxychloroquine or hydroxychloroquine sulphate is also used as an anti-malarial drug and in treating diseases like rheumatoid arthritis, systemic lupus erythematosus and porphyriacutaneatarda. Hydroxychloroquine is a less toxic amino-quinoline and has an N-hydroxy-ethyl side chain instead of N-diethyl group of chloroquine (Zhang and Zhong, 2020).

Hydroxychloroquine in treatment of malaria

Hydroxychloroquine may inflict its impact through concentrating in the parasite's acid vesicles. It is effective against the erythrocytic types of chloroquine susceptible strains of *Plasmodium falciparum, P. malariae, P. ovale,* and *P. vivax*. A group of traditional healers and herbologists belonging to the Dharmapuri village were interviewed regarding the commonly used plants or herbs in treating malaria. The ethyl acetate and methanol extracts were tested for anti-plasmodial and cytotoxic activities in vitro. The obtained plant samples were assayed against the chloroquine-sensitive strain of *Plasmodium falciparum*. The extracts of *Aegle marmelos, Piper nigrum, Lantana Camara, Momordica charantia, Phyllanthus amarus and Leucas Aspera* showed excellent anti-malarial activity having IC_{50} below 20μg/ml (Kamaraj *et al.*, 2012). The plants *A. zeylanica* leaf and *E. ribes* showed promising anti-malarial activity insensitive and resistant to *P. falciparum* strains. *Plumbago zeylanica* had also demonstrated strong anti-malarial activity with IC_{50} of 24.05μg/mL.

Hydroxychloroquine is the treatment of Rheumatoid arthritis

A randomized 36-week, placebo-controlled trial was conducted to test the potency of hydroxychloroquine (HCQ) in treating the disease. The patients had been randomly administered HCQ orally or an approximate amount of placebo pills with a dose of approximately to 7 mg/kg every day. After around 36 weeks, the joint index, the pain index and the physical function index significantly increased in the group receiving HCQ than that of the placebo group. There has been no psychological progress or notable variations in the side effects among HCQ or placebo. In-vitro studies have suggested various activities of chloroquine and hydroxychloroquine to be used as anti-rheumatic agents like intercalation into DNA, antioxidant activity, inhibition of phospholipases (Fox, 1993).

Hydroxychloroquine as a treatment for COVID-19

Studies have demonstrated that hydroxychloroquine (HCQ) seems to have a wide array of protective role against a variety of dengue virus, Ebola virus, and SARS-CoV-1, etc. HCQ may tamper with viral particle adhesion to its cell surface receptor or even with the pH-dependent endosome-mediated viral entry to impede their reproductive stage. Interference with the post-translational modification of viral proteins or impairment of maturation of viral protein by pH modulation is observed. So far, 15 clinical trials were conducted in China to test the efficacy and safety of HCQ and CQ in treatment of COVID-19. The clinical study findings demonstrated the short-term effectiveness of HCQ in treating COVID-19 that could efficaciously maximize the results of lung imaging, facilitate virus-negative conversion as well as lessen the course of the disease (Zhang and Zhong, 2020). Side effects of hydroxychloroquine include atrioventricular block, pulmonary hypertension, hypoglycaemia, hyper skin pigmentation and psoriasis aggravation.

CORONA VIRUS

CoV is an enveloped positive-sense ss-RNA virus of the *Coronaviridae* family. It causes upper respiratory tract and gastrointestinal infections in mammals and birds. It causes the common cold in humans, although complications could arise such

as pneumonia and SARS. The known human CoV (HCoV) includes HCoV-229E, -OC43, -NL63, -HKU1 and the more widely known severe acute respiratory syndrome CoV (SARS-CoV) that posed a globally high mortality threat in 2003 and 2020.

Mechanism of action

The receptor-binding sites on the SARS-CoV-2 Spike (S) proteins bind to human ACE2 receptor, which confirms the virus-cell linkage. Peng *et al.* (2020) acknowledged these critical characteristics on the N-terminal protein SARS-CoV-2 S domain that binds another host-cell receptor. The attributes of SARS-CoV-2 that can induce human infection comprises the S1B receptor binding motifs (RBMs) connected to the ACE2 receptor and the S1A domain, which offers additional host interactions.

Progression of Coronavirus in the body

There are three stages of the pathogenesis of CoV-stage I asymptomatic incubation period; stage II, non-sense symptomatic period; stage III severe respiratory symptomatic stage. A study published in the Zhou *et al.* (2020) reports that COVID-19 resides 21 days in the body after the infection and the transition rate from the first infection to severe conditions occurs within a span of 4 to 9 days. Symptoms (fever, cough, sore throat) appear during the early three days due to viral entry in the upper respiratory system. By the 4^{th} day, the disease reaches the lungs and causes acute respiratory disease. During days 8 to 15, viruses move to the circulatory system, i.e. blood and fatal complications such as sepsis, and multiple organ failure may develop.

Targets to develop anti-viral drugs against coronavirus

Due to the pandemic situation caused by SARS CoV-2, some empirical strategies must be followed to patients suffering from COVID-19. There are three main pathways to assess the solution: adapt to an already approved drug, push an experimental drug through a clinical trial or create a new medicine or vaccine entirely. Some conventional approaches addressed are to block the viral entry in the first stage, by the developing TMPRSS2 inhibitor, Spike protein vaccine, ACE receptor blocker and soluble ACE2 receptor.

Muralidharan *et al.* (2020) made use of enhanced sampling molecular simulations of available structure models of SARS-CoV-2 S-protein binding with the ACE2 receptor to generate configurations for ensemble docking. Through docking analysis, it was found that three of the interface-binding compounds, nitrofurantoin, isoniazid pyruvate, and eriodictyol were shown to prefer residues belonging to the ACE2 receptor portion of the interface. It was hypothesized that these interactions might limit the interaction of S-protein with the ACE2 receptor. Analysis through computational methods showed that the binding energy of the combination of drugs such as lopinavir, oseltamivir and ritonavir against the SARS-CoV-2 protease is stronger than that of each drug docked against the protein separately (Muralidharan *et al.*, 2020).

Therapeutics for Corona

There seem to be hardly any specific treatments for infection with CoV, and preventive vaccines are all under the investigative process. Chemoprophylaxis and immune prophylaxis can be taken care of in three major categories: anti-viral drugs, chloroquine, hydroxychloroquine, and vaccination. Until more precise therapies are available, more broad-spectrum anti-viral that includes prescription therapy substitutes should be considered like Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), RNA synthesis inhibitors.

Bioactive compounds in Indian medical practice system to treat coronavirus

Naturally occurring compounds can be administered as a good source for therapeutics to tackle many illnesses. Quercetin is known to inhibit the Hepatitis C virus generation in an HCV culture, epigallocatechin-3-gallate (EGCG), a principal active constituent in green tea, purged HIV replication by deteriorating semen derived enhancer of virus infection(SEVI). Nicotinamide is found to be rich in soya bean and serves as a potent ACE2 inhibitor with an IC_{50} value of 84nM. It has been proved that the soya bean possesses a vigorous ACE2 inhibitor activity. Glycyrrhizin derived from liquorice roots found in India and is also known as mulethi, has proved to possess inhibitory properties. It has shown successful results in treating SARS by inhibiting viral adsorption and penetration.

Five components of Phlorotannins such as phloroglucinol, eckol,7-phloroeckol, phlorofucofuroeckol, dieckol were isolated from the ethanol extract of *Ecklonia cava.* It was reported that phlorofucofuroeckol, dieckol were able to inhibit the viral replication in Vero cells strongly. The five geranylated flavonoids such as tomentin A, tomentin B, tomentin C, tomentin D and tomentin E were isolated from the methanolic extract of the fruit of *Paulownia tomentosa* that contains 3,4-dihydro-2H-pyran moiety, which strongly inhibits the SARS-CoV replication at papain-like protease (PLpro). Ranavelli *et al.* (2015) isolated alkaloids from hydroalcoholic extract of *Croton Echinocereus* leaves (Euphorbiaceae), namely, cory-

dine and norisoboldine, which showed inhibition of reverse transcriptase enzyme activity of HIV at 100μg/ml and 450μg/ml respectively. Another opiate alkaloid, papaverine isolated from *Papaver somniferum*, can inhibit the HIV replication and protein production.

A recent report by Sampangi-Ramaiah *et al.* (2020) from the medicinal plants-based compound survey to inhibit SARS CoV-2 main protease by molecular docking has shown many of the Indian herbal plants with high binding affinity against COVID-19 6LU7 and 6Y2E proteases. Apigenin is a flavonoid widely found in many medicinal plants such as chamomile. Apigenin derivatives 7-O-β-D-glucopyranoside and apigenin 7-Oβ D-(4' caffeonyl)-glucuronide isolated from herbs *Kummerowi astriata* and *Chrysanthemum morifolium*, respectively have been proven to activate anti-HIV activity. They repress HIV expression by impeding viral entry and replication. Ursolic acid is a pentacyclic triterpenoid, present in *Ocimum sanctum* (Tulsi) and *Swertia chitara.* Its derivative sageone, is present in high amounts in aqueous and ethanolic root and shoot extract of *Salvia apiana* and exhibits anti-viral property. The anti-viral activity of *Salvia officinalis* is mediated by safficinolide and sageone diterpenoids found in aerial parts. Neeraj *et al.* (2014) isolated ursolic acid from *Canscora decussate* and *Clitorea ternatea* Shankupushpi. The genus *Cucurbita pepo* (pumpkin) seeds have anti-viral and hepatoprotective activity. *Momordica charantia* (Bitter gourd) extract is used in anti-viral therapy by inhibiting the herpes simplex virus-I and HIV-I due to the presence of ribosome-inactivating protein. *Momordica indica* (small bitter gourd or spine gourd) is a rich source of triterpenoids, alkaloids, saponins, oleanolic acid and alpha-spiranosterolhederagenin.

Oleanolic acid (OA) is a pentacyclic triterpenoid, mostly present on Oleaceae families such as olive plant, *Lantana Camara* and *Lisgustrum licudum*. Some of the culinary spices are a source of oleanolic acids such as thyme and clove plants, apple, grape, elderberry, and sage. It has pharmacological characteristics such as anti-diabetic, anti-inflammatory, hepato-protective, anti-hypertensive, and antioxidant (Betty *et al.*, 1915).

Alcoholic and aqueous extracts of *Salvia officinalis* are rich in the flavonoids- rosmarinic acid and luteolin 7-glucoside. Caffeic acid and 3-caffeoylquinic acid are obtained from the methanolic extract of the same plant. Several flavonoids like epigallocatechin gallate, quercetin, rutin, epicatechin, chlorogenic acid, ellagic acid and luteoline 7-glucoside as well as several volatile compounds like borneol, cineole, and camphor have been identified in the infusion extract. Tylophorine compounds are naturally occurring phenanthroindolizidines and phenanthroquinolozidines mainly present in *Tylophora indica* as potent in-vitro inhibitors of entero-pathogenic CoV. Tylophorins such as tylophorinine and 14-hydroxytylophorine were isolated from *T. atrofolliculata* and *T. ovata*, respectively. These compounds could also inhibit other CoV like SARS CoV in Vero 76 cells (Hernandez *et al.*, 2016).

Natural Plant Compounds as Potential Inhibitor of COVID-19 Main Protease (M^{pro})

A research was conducted to rapidly discover compounds for clinical use, targeting COVID-19 virus main protease (M^{pro}) responsible for replication and transcription. Six compounds such as ebselen, disulfiram, tideglusib, carmofur, Shikonin, PX-12 possibly inhibit $M^{pro,}$ and the IC_{50} value ranges from 0.67-21.4μM. Cinanserin served as a strong enzymatic inhibitor, indicating that it may possess multi-drug targets in averting viral infection. Ebselen and N3 showed strongest anti-viral activity. Cepharanthine, ergoloid and hypericin are also found to have high affinity with S-protein (Jin *et al.*, 2020).

Molecular docking was used by Khaerunnisa *et al.* (2020) and aimed to evaluate bioactive compounds found in medicinal plants as potential COVID-19 M^{pro} inhibitors. The study stated that nelfinavir and lopinavir could be reported as probable treatment choice because they are said to possess high affinity (ΔG) values. Kaempferol, quercetin, luteolin-7-glucoside, apigenin-7-glucoside, dimethoxy curcumin, catechin, and epicatechin-gallate were some of the other compounds that tend to have high potency to function as COVID-19 M^{pro} inhibitors.

In another study, 67 aromatic compounds from different medicinal plants were docked against coronavirus spike protein. Among them, crocin from *Crocus sativus*, digitoxigenin from *Nerium oleander* and β-eudesmol from *Laurisnobilis* had significant anti-viral potential based on their excellent interaction with spike protein targets (Aanouz *et al.*, 2020). It has been documented that Traditional Chinese Medicine herbal extracts can impede the enzymatic action of SARS 3CLpro. Herbal substances like sinigrin (IC_{50}: 217μM), indigo (IC_{50}: 752μM), aloe-emodin (IC_{50}: 366μM), hesperetin (IC_{50}:8.3μM), quercetin (IC_{50}: 73μM), herbacetin and pectolinarin were capable in hindering the activity of SARS 3CLpro. Chinese *Rhubar*b extracts, *Houttuynia cordata* water extract, flavonoid extract from litchi seeds and beta-sitosterol extracted from *Isatis indigotica* root were some of the TCM extracts that were

reported.

CONCLUSION

Given that several viruses exist despite effective vaccines as well as successful anti-viral therapies, it seems impossible to eliminate such viral infections. Natural compounds act as an effective source of biodiversity for devising new anti-virals, identifying new structure-property relationship, as well as developing beneficial preventive / treatment strategies against many viral illnesses. Many ayurvedic and Siddha substances have strong anti-viral activity, and their findings will, therefore, assist with the manufacturing of derivative products and curative leads. Since several types of research in this field are in the initial preparatory status, further investigation is promoted in evaluating the biologically active ingredients, addressing the pathways involved as well as assessing the effectiveness and promising uses in-vivo to create and enhance effective antiviral therapies. The natural compounds will continue to play a crucial role and lead to the production of anti-virals with the best potency.

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Conflict of Interest

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