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NOVEL PERCEPTION ON THE ANTI - VIRAL EFFECT OF BIOACTIVE NATURAL MOLECULES AGAINST COVID -19

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ABSTRACT

The world community is facing unpredicted pandemic of novel Corona virus disease (COVID-19) caused by severe acute respiratory syndrome. Corona virus (SARs COV- 2) was first reported in Wuhan the capital of Hubei china. This disease spread globally with 5,794,000 conform cases in 213 countries and territories or 3,57,510 death as of May 28,2020 7:16 GMT despite worldwide efforts to contain it the pandemic is continuing to speed for want clinically proven prophylaxis and therapeutic strategies. The dimensions of pandemic require an urgent harnessing of all knowledge system available globally. The pyrolytic and therapeutic potential of traditional and complimentary medicine system such as herbal plant preparation and phytoconstituent have proved useful in attenuating infectious condition and crucial role in drug development process against COVID-19 treatment. Among the viral infections play and important role in human disease. so treatment of viral infections addition of good number of natural products with anti-corona virus activity are the major constituents of some common dietary supplements which can be exploited to improve the immunity of the general population in COVID -19 pandemic. In this review, we summaries the antiviral effect reported for several natural product and herbal medicine.

KEYWORDS: COVID-19, Anti-viral agents, Phytoconstituents.

Purpose of document

The corona virus disease (COVID-19) has been declared as a worldwide epidemic by the world health organization. To combat this deadly COVID-19, a number of conventional drug like Chloroquine, Hydroxychloroquine etc. have been tried and found with certain curative

effect in vitro. However, the clinical drug response is not very encouraging, and toxicity remains in inevitable issue causing serious adverse effect. This promoted to study the antiviral effect of bioactive natural molecules against COVID-19 treatment by Indian herbal drug Because the inherent side effects of the synthetic chemical used in allopathic drug a size able population has switched over to the traditional system of medicine (herbal medicine) for their primary health care. Other bioactive natural molecules Turmeric Ashwagandha, Clitoria ternate and Ginger. The inhibition potential of all these plant extracts are found to be larger than those of chloroquine and Hydroxychloroquine the two anti-malarial drug compound are already reported to treatment of covid-19 in vitro. Due to inherent toxicity and side effects however, they are not approved by most of the countries. Therefore our findings become very interesting towards the development of alternative herbal medicine having number apparent side effect. We except prompt action in this direction to combat with the covid-19.

Literature Findings

From literature survey we found substantial number of herbal plants and plants preparation with antiviral potential different types of viruses. Majority of the antiviral herbs were found containing active components such as flavones, alkaloids and polyphenols, which play an important role against viruses. Based on the extensive search performed, the results are presented under three sections classified as Covid-19, Antiviral, Phytoconstituents.

INTRODUCTION

A contagious virus of unknown origin, causing flu-like and respiratory symptoms, was detected in Wuhan, China, and was first reported to the WHO Country Office in China on December 31st 2019.

It was due to a novel respiratory coronavirus, the World Health Organization named officially the very famed coronavirus outbreak of 2019 as COVID-19 which stands for coronavirus disease that was discovered in 2019January 30th, 2020, WHO declared the corona virus as an epidemic in China, constituting it a public health emergency of international concern. On march 11, 2020 WHO officially declared it as global pandemic. The first case of the COVID-19 pandemic in India was reported on 30 January 2020.

- **Research and treatment**

A combination of anti-malaria, anti-swine flu and anti-HIV drugs resulted in the recovery of three patients in March the Indian Institute of Chemical Technology, the Council of Scientific

and Industrial Research (CSIR) and Cipla launched a joint venture to develop Anti-(COVID-19) drugs Indian firm, Stempeutics, announced plans to introduce a stem cell-based agent for treating COVID-19 patients. On 23 March, the National Task Force for COVID-19 constituted by the ICMR recommended the use of hydroxychloroquine for the treatment of high-risk cases till May, there were over 30 candidates of COVID-19 vaccine in development in India, many of which were already in pre-clinical tests ICMR to start clinical trials of the plasma therapy. WHO supports scientifically-proven traditional medicine viral infections plays an important role in human disease and recent outbreak in the advent of globalization and ease of travel have underscored their prevention as a critical issues is safeguarding public health. In India a majority of people rely upon traditional Indian medicine to treat human maladies due to loss cost, easier available, and without any side effect. These medicines are made by herbal plant. This study aims to assess the Indian herbal plant in pursuit of potential COVID-19 inhibitors using in silica approaches we have considered 11differnt species of these plant. Our calculated aqueous solubility, lipophilicity and binding affinity of the extracted compound suggest that the inhibition potential in the order; harsinger> aloe Vera>giloy> turmeric> neem > ashwaghandha> red onion> tulsi > cannabis > black pepper.

Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host specific interactions. In this brief report, we summarize the antiviral activities from several natural products and herbal medicines against some notable viral pathogens including coronavirus (COV), coxsackievirus (CV), human immunodeficiency virus (HIV) and respiratory syncytial virus (RSV) Coronaviruses (CoVs) are a large group of enveloped viruses with non-segmented, single-strand, and positive-sense RNA genomes. CoVs are classified in the family Coronaviridae of the order Nidovirales. The COV family consists of several species and causes upper respiratory tract and gastrointestinal infections in mammals and birds. These viruses are pleomorphic particles with sizes ranging from 80 to 120 nm in diameter. In humans, it mainly causes common cold, but complications including pneumonia and SARS can occurs and also enteric and central nervous system diseases. Two highly pathogenic microorganisms with approximately 30,000 nucleotides. The known human COV includes HCoV-229E,-OC43,-NL63, HKU1, and the more widely known severe acute respiratory syndrome coronavirus which caused a global threat with high mortality in 2003. There are no specific treatments for

COV infection and preventive vaccines are still being explored. Thus, the situation reflects the need to develop effective antivirals for prophylaxis and treatment of COV infection. We have previously reported that Saikosaponins (A, B2, C, and D), which are naturally occurring triterpene glycosides isolated from medicinal plants such as Bupleurum spp., Heteromorpha spp., and Scrophularia Scorodonia.

- **Causes**

Infection with the new coronavirus (severe acute respiratory syndrome coronavirus 2, or (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19).

Coronaviruses are large family of zoonotic viruses that cause illness, zoonotic means these viruses are able to be transmitted from animals to humans this is called a spillover.

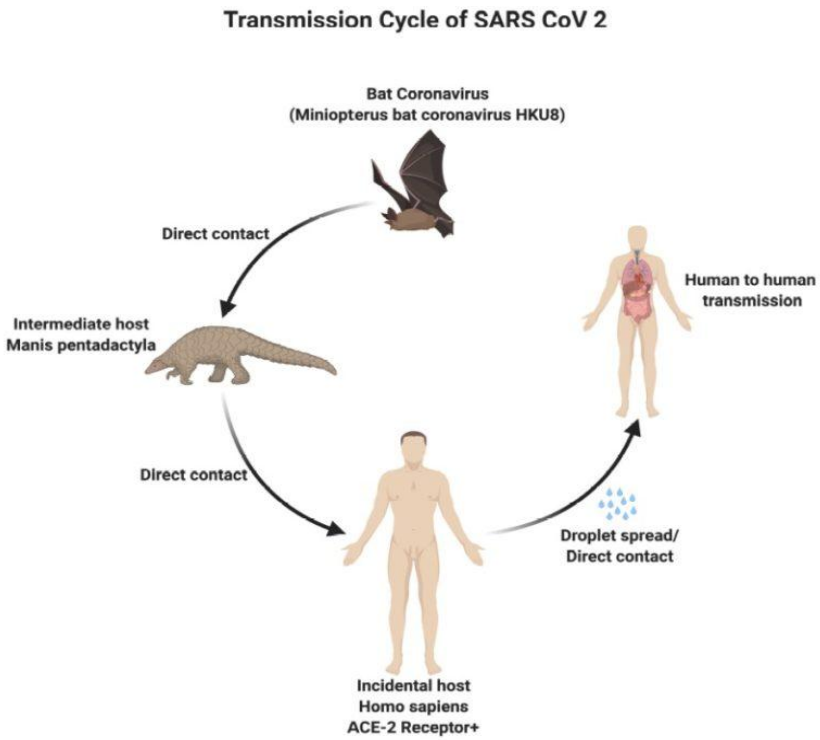
There are different types of corona viruses. Some cause very mild infections every year like common cold. In 2002, Severe acute respiratory syndrome (SARS-COV) Another was Middle east respiratory syndrome of and the most recent is the novel coronavirus named as SARS-CoV-2 and the disease it causes is called COVID-19.

The virus appears to spread easily among people, and more continues to be discovered over time about how it spreads. Data has shown that it spreads from person to person among those in close contact (within about 6 feet, or 2 meters). The virus spreads by respiratory droplets released when someone with the virus coughs, sneezes or talks. These droplets can be inhaled or land in the mouth or nose of a person nearby.

Transmission-SARS-CoV-2 is thought to spread from person to person via.

Droplet transmission: Which spread through large respiratory droplets that people sneeze, cough. When the droplets particles >5-10 μm in diameter they are referred to as respiratory droplets, and when then are < 5 μm in diameter. They are referred as droplets nuclei.

Aerosol transmission: Aerosol transmission is different from droplet transmission as it refers to the presence of microbes with in droplet nuclei which are generally considered to be particles > 5 μm in diameter can remain in the air for long periods of time and be transmitted to others over distances greater than 1m. which spread through when someone coughs or sneezes in room.



Contact transmission: Transmission of the COVID-19 virus can occur by direct contact with infected people and indirect contact with surface in the immediate environment or with object used on the infected person e.g (stethoscope or thermometer). It is through touching a contaminated surface then touching your mouth, nose or eyes.

Direct Transmission: Spreads while kissing and shaking hands etc.

- **Symptoms**

One of the factors that makes virus so deadly is its incubation period, it is a time period between when you catch a virus and when your symptoms start. For SARS-CoV-2 it is 2-14 days. Within 11.5 days taken as average a study shows that more than ninety seven percent of people who contract SARS-CoV-2 show symptoms after exposure.

It is lower respiratory tract infection, which means the most important symptoms are felt in chest and lungs.

➢ **Most common symptoms**

- Fever
- Dry cough
- Tiredness

➢ **Less common symptoms**

- Aches and pains
- Sore throat
- Diarrhea
- Conjunctivitis
- Headache
- Loss of taste or smell
- A rash on skin, or discoloration of fingers or toes

➢ **Serious symptoms**

- Difficulty breathing or shortness of breath
- Chest pain or pressure
- Loss of speech or movement

➢ **Diagnosis**

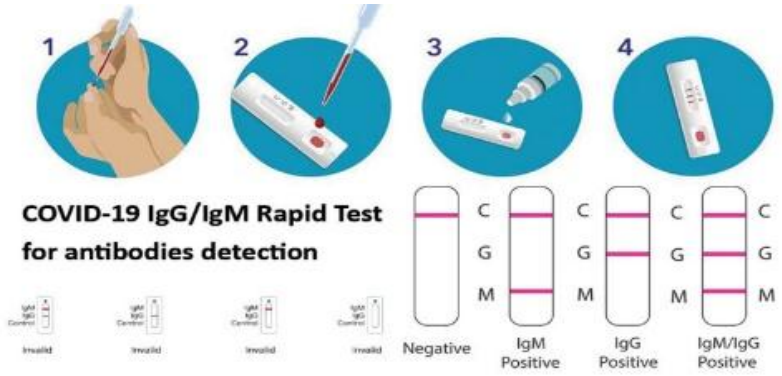
COVID-19 can be diagnosed similarly to other conditions caused by viral infection using a blood, saliva or tissue sample. However, most common is a cotton swab test. This test retrieves a sample from the inside of your nostrils i.e. nasopharyngeal swab.

Diagnostic kits

1. Rapid diagnostic tests based on antigen detection- One type of rapid diagnostic test (RDT) detects the presence of viral proteins (antigens) expressed by the COVID-19 virus in a sample from the respiratory tract of a person. If the target antigen is present in sufficient concentrations in the sample, it will bind to specific antibodies fixed to a paper strip enclosed in a plastic casing and generate a visually detectable signal, typically within 30 minutes. The antigen(s) detected are expressed only when the virus is actively replicating; therefore, such tests are best used to identify acute or early infection.

2. Rapid diagnostic tests based on host antibody detection: There is another, more common type of rapid diagnostic test marketed for covid-19 antibodies in the blood of people believed to have been infected with COVID-19. Antibodies are produced over days to weeks after infection with the virus. The strength of antibody response depends on several factors, including age, nutritional status, severity of disease, and certain medications or infections like HIV that suppress the immune System. In some people with COVID-19, disease confirmed by molecular testing (e.g. reverse transcription polymerase chain reaction: RT-PCR), weak, late

or absent antibody responses have been reported. The majority of patients develop antibody response only in the second week after onset of symptoms. This means that a diagnosis of COVID-19 infection based on antibody response will often only be possible in the recovery phase.



3. Abbott ID NOW COVID-19 - Abbott ID covid-19 is portable light weighted(3kg), small toster size covid -19 test device which can be various locations including physician's office, clinic or mobile units. The test is an automated assay that delivers positive results in just five minutes and takes only 13 minutes to show the negative results, using the ID NOW™ molecular platform. The ID NOW™ molecular platform of the test is an instrument-based, isothermal system for rapid qualitative identification of infectious diseases. Its isothermal nucleic acid amplification technology facilitates accurate test results in few minutes. The test detects nucleic acid from the RNA of SARS-CoV-2 virus present in nasal, nasopharyngeal or throat swabs, as well as the swabs eluted in viral transport media, collected by the healthcare providers from the suspected Covid-19 patient.

Current Status of Vaccines

Vaccines are the most effective strategy for preventing infectious disease since they are more cost-effective than treatment, and reduce morbidity and mortality without long-lasting effects. Vaccines are the most effective strategy for preventing infectious disease since they are more cost-effective than treatment, and reduce morbidity and mortality without long-lasting effects. Nonetheless, there are social, clinical and economic hurdles for vaccine and vaccination programs including (a) the willingness of the public to undergo vaccination with a novel vaccine, (b) the side effects and severe adverse reactions of vaccination, (c) the potential difference and/or low efficacy of the vaccine in populations different from the clinical trials' populations and (d) the accessibility of the vaccines to a given population (including the cost and availability of the vaccine). The following describes the current status of vaccine development against COVID-19 through various approaches:

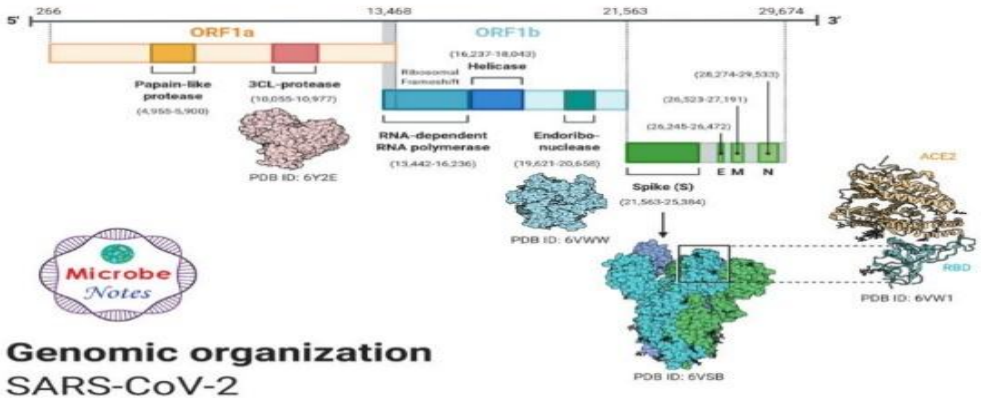
1. Recombinant Subunit Vaccine: In general, subunit vaccines are advantageous over other types of vaccines in that they are highly safe and have fewer side effects by inducing the immune system without introducing infectious viruses. Subunit-based vaccine development studies have also reported enhancement of T cell immune responses and generation of high titer neutralizing antibodies in vivo. Clover Biopharmaceuticals is testing a recombinant subunit vaccine based on the trimeric S protein (S-Trimer) of the SARS-CoV-2. The S protein contains three S1 heads and a trimeric S2 stalk. Clover Biopharmaceuticals confirmed the generation of a nativelike trimeric viral spike in mammalian cell culture-based expression system and the detection of antigen-specific neutralizing antibodies in the sera of fully-recovered COVID-19 patients.

2. DNA Vaccine: DNA vaccines represent an innovative approach by direct injection of plasmids encoding the antigens, accompanied with a wide range of immune responses. Recently, various DNA vaccine platforms have been developed to improve the efficacy of vaccines by using electroporation to deliver plasmids and adding adjuvant to enhance the immune responses. This vaccine platform has advantages that can produce therapeutic antibodies and activate immune cells by delivering the vaccines intradermally into the patient In vivo Pharmaceuticals is preparing for phase I trials in the U.S.A. and China with support from the Coalition for Epidemic Preparedness Innovations (CEPI).

3. mRNA Vaccine: mRNA vaccines are rapidly developing technologies to treat infectious diseases and cancers. mRNA-based vaccines contain mRNAs encoding the antigens, which are translated at the host cellular machinery by vaccination. mRNA vaccines have advantages

over conventional vaccines, by the absence of genome integration, the improved immune responses, the rapid development, and the production of multimeric antigens. Moderna's mRNA vaccine is designed in silico, which enables the rapid development and evaluation of vaccine efficacy. Moderna Inc. is preparing a phase I study with financial support from CEPI.

4. Other Vaccine Approaches: Genexine Inc. is developing a COVID-19 vaccine using Hyleukin-7 platform technology. Hyleukin-7 platform enhances the immune responses by fusion of interlekin-7 (IL-7) to hyFc, designed to hybridize IgD and IgG4 for long-acting effects of Fc fusion proteins. IgD has a flexible hinge structure that maximizes biological activity of Fc-fusion protein. IgG4 has an unexposed junction site that minimizes adverse immunogenicity by preventing antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Genexine Inc. has reported the improved vaccine efficacy showing the accumulation of pulmonary T cells and the increase of plasma cytoid dendritic cells by treatment of Fc-fused IL-7 in influenza A virus infection model.



Understanding the genomic organization of corona virus

The genome of SARS-CoV-2 is a single-stranded positive-sense RNA of 30kb (29891 nucleotides) encoding 9860 amino acids. The G + C content is 38%.

There are 12 functional open reading frames (ORFs) along with a set of nine Sub genomic mRNAs carrying a conserved leader sequence, nine transcription regulatory sequences, and 2 terminal untranslated regions.

The genome of this virus lacks the haemagglutinin-esterase gene, which is characteristically found in lineage A β CoV.

Two-thirds of viral RNA, mainly located in the first ORF translates two polyproteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP), while the remaining ORFs encode accessory and structural proteins.

The 16 non-structural proteins include two viral cysteine proteases, namely, NSP3 (papain-like protease) and NSP5 (main protease), NSP12 (RNA-dependent RNA polymerase, NSP13 (helicase), and other NSPs which are likely involved in the transcription and replication of the virus.

The rest part of the viral genome codes for four structural proteins E, M, S, and E along with a number of accessory proteins that interfere with the host immune response.

The organization of the coronavirus genome is 5′-leader-UTR-replicase-S (Spike)–E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTR-poly (A) tail with accessory genes interspersed within the structural genes at the 3′ end of the genome.

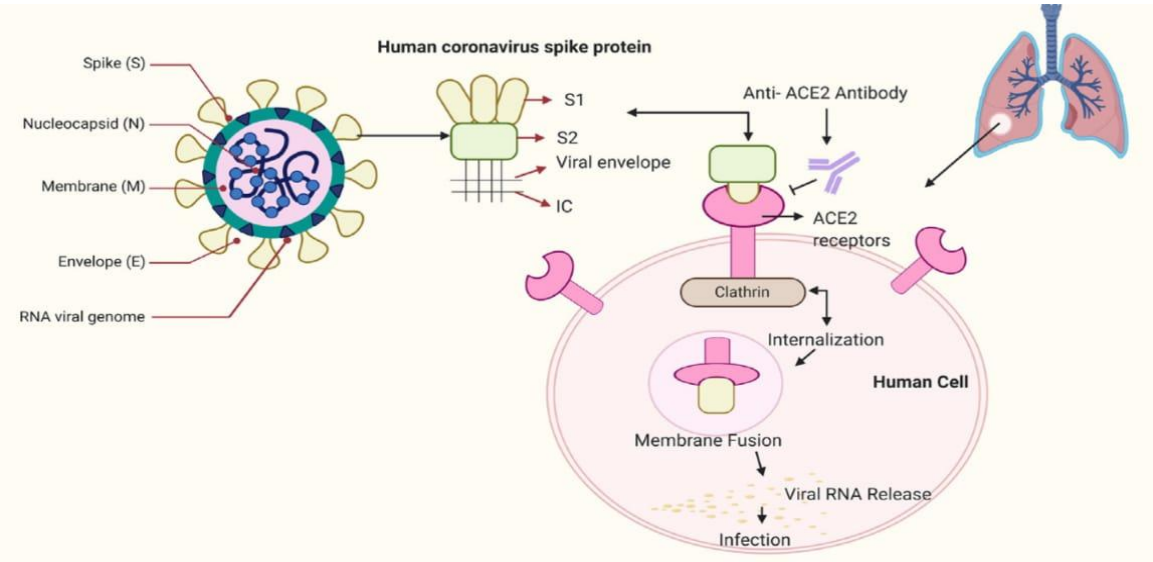
SARS-CoV-2 is closer to the SARS-like bat CoVs in terms of the whole genome sequence.

However, mutations are observed in NSP2 and NSP3 and the spike protein, that play a significant role in infectious capability and differentiation mechanism of SARS-CoV-2 Besides, two strains, namely L-type and S-type, are discovered. The L-type, derived from the S-type, is found to be more aggressive and contagious.

Replication and mechanism of SARS cov-2:-

It has been confirmed that the SARS-CoV-2 uses the same cellular entry receptor, ACE2, as SARS-COV. Human ACE2, found in the lower respiratory tract of humans, works like the cell receptor for SARS-COV and regulates both the cross-species and human-to-human transmission. The virion S-glycoprotein present on the surface of coronavirus attaches to the receptor, ACE2 on the surface of human cells. It has been shown that S protein and ACE2 binding efficiency is 10- to 20- fold higher than that of SARS-CoV. In the case of SARS-CoV, the cleavage of trimer S protein is initiated by the cell surface-associated transmembrane protease serine 2 (TMPRSS2) and cathepsin.

At the same time, the possible molecules facilitated membrane invagination for SARS CoV-2 endocytosis are still unclear.



However, it has been observed that the SARS-CoV-2 may readily transmit while causing less severe human infection rather than human SARS-CoV. S glycoprotein includes two subunits, S1 and S2.S1 is responsible for the determination of the virus-host range and cellular tropism via Receptor Binding Domain (RBD), while S2 facilitates virus-cell membrane fusion by two tandem domains, heptad repeats 1 (HR1) and heptad repeats 2 (HR2). The genomic RNA of coronavirus of approximately 30,000 nucleotides encodes structural proteins and nonstructural proteins of the virus that have a critical role in viral RNA synthesis (called replicase-transcriptase proteins).At least one niche-specific protein, nonstructural protein 2 (nsp2), and one structural protein, the nucleocapsid protein (N), are involved in viral RNA synthesis. The expression of the coronavirus replicase-transcriptase protein genes is mediated by the translation of the genomic RNA. The replicase-transcriptase proteins are encoded in open-reading frame 1a (ORF1a) and ORF1b and are synthesized initially as two large polyproteins, pp1a and pp1ab. The synthesis of pp1ab involves programmed ribosomal frameshifting during translation of ORF1a. During or after synthesis, these polyproteins are cleaved by virus encoded proteinases with papain-like (PLpro) and chymotrypsin-like folds into 16 proteins. NSP1 to NSP11 are encoded in ORF1a, and NSP12 to NSP16 are encoded in ORF1b. The replicase-transcriptase proteins, together with other viral proteins and, possibly, cellular proteins, assemble into membrane-bound replication-transcription complexes (RTC). These complexes accumulate at perinuclear regions and are associated with double-membrane vesicles. Hydrophobic transmembrane domains are present in NSP3, NSP4, and NSP6 likely serve to anchor the nascent pp1a/pp1ab polyproteins to membranes during the first step of RTC formation. Finally, the virion containing vesicles fuse with the plasma membrane of the cell to release the virus. The virus then attaches a new cell, and the cycle is repeated.

Treatment

All the patients are treated in isolation. Once coronavirus infection is confirmed treatment is supportive, making sure of adequate oxygen supply, managing fever and ventilator.

Vaccines and treatment options for COVID-19 are currently investigated around the world.

Several antiviral and antibacterial drugs are used including combination therapy.

Various drugs are under trial therefore researches are focusing on the best ways of protection against virus before the vaccine can be made available.

Herbal medicine is used parallelly to treat various diseases and therefore each possibility of natural source for treatment of COVID-19 should be exposed.

Herbal medicine

Modern medicine today utilizes active compounds isolated from higher plants, and about 80% of these active ingredients indicate a positive correlation between their modern therapeutic use and the traditional uses. Indian herbs have been used as a treatment and preventive strategy for several diseases, including respiratory viral infections. The benefit of using these herbs in viral respiratory infections is to build immune stimulating and inflammation modulating effects of manage the immune system.

It is a natural, thoughtful and a holistic form of medicine. It does not just treat the isolated signs and symptoms of disease but treats the WHOLE of you - physically, mentally and emotionally. Human body has great potential to naturally and safely heal itself - herbal medicine will help to harness this potential in order to bring the body back to an optimum state of balance and harmony. Herbal medicine is all about the promotion of health and the prevention of disease herbal medicine is the oldest form of medicine and has been tried, tested and trusted throughout the ages and even today it is still used by many cultures as their only form of medicine.

India has always been a rich reservoir of medicinal plants because of several agroclimatic zones. Therefore, in the present work, we have chosen a multitude of Indian herbal plants such as Harsingar (Nyctanthes arbor-tristis), Giloy (Tinospora cordifolia), Aloe Vera (Aloe barbadensis miller), Turmeric (Curcuma longa), Neem (Azadirachta indica), Ashwagandha (Withania somnifera), Ginger (Zingiber officinale), Red Onion (Allium cepa), Tulsi (Ocimum

sanctum), Cannabis (Cannabis sativa) and Black Pepper (Piper nigrum). The pharmacological importance of these plants is well documented in the literature12-14. We have selected a few extracted compounds of these herbal plants and evaluated their inhibition properties against COVID-19 main protease in silico. We have obtained encouraging responses from most of these medicinal plants in general. The inhibition potentials of Harsingar, Aloe Vera and Giloy are particularly interesting. Therefore, we believe that this study should offer some insights into the development of alternative drugs for this novel coronavirus.

Phytoconstituent health against COVID-19 treatment

Herbal remedies have long been used to treat infections and viruses, such as the common cold, influenza, fever, and even herbes.

1. Unexposed asymptomatic group

This group will include persons who currently do not have any related symptom nor have any associated risk factor and co-morbidities. These apparently healthy people may be the most suitable for building of immunity so that infection-related pathogenesis can be countered to keep them healthy. Preventive interventions here can include both pharmacological as well as non-pharmacological strategies.

Among the non-pharmacological interventions healthy lifestyles, adequate physical activity, sufficient sleep, care of retainable and non-retainable urges, sadvritta, and avoidance and isolation from infected persons are vital. Fumigation of homes, shelters and living-place by Ayurvedic herbs such as garlic (Allium sativum) peel, turmeric (Curcuma longa) powder, Carom or Ajwain (Trachyspermum ammi) seeds and Loban (resin of Styrax benzoin and Boswellia species) may also be a useful strategy for disinfection. In addition, community

based Swarna Prashana and mass prophylaxis through rasayana having the predominant effects upon respiratory tract can be useful.

Rasayana may include Brahma Rasayana, Chyavanprasha or Amrit Bhallataka.

The rationale for choice of rasayana drugs can be traced back to Samhita classics of Ayurveda as well as in contemporary research. Rasayana act as antioxidant, antistress, anti-inflammatory, anti-microbial, vaccine adjuvant, and confer immunity against diseases. Further, according to Ayurveda classics, rasayana therapy, along with physical and social distancing from infected persons, constitute a core strategy to overcome epidemic and infectious diseases. Building immunity requires time. There may be some asymptomatic carriers who could transmit the virus to other apparently healthy people. Hence, physical and social distancing for all would be essential to avoid any transmission.

2. Exposed asymptomatic (quarantined)

This group comprises of people who are without apparent symptoms, but at risk due to contact history. They need to be quarantined carefully. Specific prophylaxis for this group may include Sanjeevani vati and Chitrakadi vati and combination of Guduchi (Tinospora cordifolia), Shunthi (Zingiber officinale) and Haridra (C. longa). This choice of medicines is aimed at maintenance of agni as well as aam pachana in order to prevent the progression of pathogenesis in its initial sanchaya-prakopa-prasara stage. Sanjivani vati is widely used against communicable diseases, fever due to infection and sannipataj jvara, cold, cough, and indigestion. It also strengthens and rejuvenates the immune system. This group may also be provided with decoction of a combination of Ayurvedic herbs including T. cordifolia, Z. officinale, C. longa, Ocimum sanctum, Glycyrrhiza glabra, Adhatoda vasica, Andrographis paniculata, Swertia chirata, Moringa oleifera, Triphala and Trikatu. These herbs are proposed for the reason that these are known to be broad-spectrum antivirals and protease inhibitors.

3. With mild COVID-19 symptoms

This category relates to people found positive to SARS-CoV-2 and are having mild URTI symptoms. They are required to be carefully isolated and monitored for any progression of the disease, along with giving adequate therapy to arrest the symptoms and balancing the vitiated doshas to control disease progression. Formulations like Lakshmi Vilas Rasa, Pippali rasayana, Sanjeevani vati, C. vati, Go jihvaadi Kashaya, Vyaghri haritaki, Kantakaari Avaleha, Dashamul kwath, Sitopaladi, Talishadi, and Yashtimadhu may be the most suitable drugs to

be used at this stage in an integrative model. Those patients showing progression of the disease may immediately require shifting to ICU.

4. With moderate to severe COVID-19 symptoms

This category may be the population where the moderate to severe symptoms are already present and the patients also belong to high risk groups. These patients require tertiary care from the beginning itself but can also be co-prescribed with Ayurveda medicines in order to reduce the impact of the pathology and to buy more time to have intensive management. Recommended formulations here may include P. rasayana, Laghu Vasant Malati, Sanjeevani vati, Tribhuvan keerti rasa, Brihata Vata Chintamni rasa, Mrityunjaya rasa, and Siddha makardhvaja rasa. The key criterion for choosing rasa aushadhi in category 3 and 4 as noted above is the urgency of initiation of therapeutic actions. Rasaaushadi are shown to have better bioavailability and absorption through sublingual and oral route accounting to the nano size of their particles. For example, suvarna bhasma has been found to get absorbed well through sublingual administration when mixed with black pepper powder and ghee.

Studies on coronavirus using medicinal plants are rather minimal in India, a **study has shown anti-mouse coronaviral activity** (a **surrogate of SARS CoV**) **by the plants**

indigofera tinctoria - नी लका

Vitex trifolia-स भालू

Gymnema sylvestre-गुड़मार

Abutilon indicum-कंघी

Leucas aspera- गोफा

Cassia alata- दादमुदन

Sphaeranthus indicus- गोरखमुंडी

Clitoria ternatea- अपरा जता

Clerodendruminerme Gaertn-संकु पी

Pergulariadaemi - ढोली धी

Evolvulus alsinoides - शंखपुपी

Among them Vitex trifolia and Sphaeranthus indicus have been found to reduce inflammatory cytokines using the NF-kB pathway, a pathway that has been implicated in respiratory distress in SARS-CoV.

1. **Clitoria ternatea (अपरा जता)** has been identified as a metalloproteinase inhibitor, ADAM17, a metalloproteinase that is involved in ACE shredding can be targeted using this plant. The plants Glycyrrhiza glabra (मुलेठ) and Allium sativum (Garlic) have been known to target the viral replication of SARS-CoV, arising as promising candidates against SARS CoV-
2. **Clerodendrum inerme Gaertn, (batraj)** another herb has been found to have the potential to inactivate the viral ribosome, this can be further investigated for its utility as a drug targeting SARS-CoV2 protein translation.

Similarly, Strobilanthes Cusia (Assam Indigo) blocked the viral RNA genome synthesis and induced papain like protease activity targeting the HCoV.

1. **Indigofera tinctoria**

Synonyms: Anila tinctoria var. Normalis Kuntze, Indigofera bergii Vatke

Biological Source: Nili (leaf) consists of Dried leaf of Indigofera tinctoria Linn belongs to the Family Fabaceaea.Indigofera tinctoria is a shrub, 1.2-1.8 m high, found through out and widely cultivated in many parts of the country.

Phytochemical Constituents

A galactomannan, composed of galactose and mannose in molar ratio of 1:1.52, isolated from seeds and partially characterized Flavonoids, terpinoids, alkaloids and glycosides1,9,7 Indigotine, Indiruben, rotenoids.

2. Vitex trifolia

Most of the species of the genus Vitex are widely used in traditional Indian systems of medicine. Around 270 plant species of genus Vitex have been reported worldwide. Vitex trifolia belongs to the family Lamiaceae. V. trifolia is an aromatic coastal deciduous shrub or small plant growing from 1–4 m tall.

Phytochemical constituents

The plant contains polyphenolic compounds, flavonoids, proteins, tannins, phytosterols, and saponins. Fruits of V. trifolia consist of essential oil, Vitex trifolia A-G, monoterpenes along with diterpenes, dihydrosolidagenone, beta-sitosterol-3-Oglucoside, terpineol, alpha-pinene, 3,6,7-trimethylquercetagetin, hexanic, and dichloromethanic were extracted from stem.

3. Gymnema sylvestre-

Synonyms-Gymnema sylvestre G. sylvestre is a large, more or less pubescent, woody climber. It is occasionally cultivated as medicinal plant. Leaves are opposite, usually elliptic or ovate (1.25–2.0inch × 0.5–1.25 inch).

Flowers are small, yellow, in umbellate cymes. Follicles are terete, lanceolate, upto 3inches in length.

4. Abutilon indicum

Synonyms- Sida indica L.

Biological source- Abutilon indicum is a small shrub in the family Malvaceae, native to tropic and subtropical regions and sometimes cultivated as an ornamental. It is found in Karnataka and Tamil Nadu.

Chemical constituents

If whole plant of Abutilon indicum has resulted in the isolation of two new compounds, abutilin. A (1) and (R)-N-(1′-methoxycarbonyl-2′-phenylethyl)-4-hydroxybenzamide (2), as well as 28 known compounds.

5. Leucas aspera

Leucas aspera commonly known as 'Thumbai' is distributed throughout India from the Himalayas down to Ceylon. The plant is used traditionally as an antipyretic and insecticide. Medicinally, it has been proven to possess various pharmacological activities like antifungal, antioxidant, antimicrobial, antinociceptive and cytotoxic activity.

Family-Lamiaceae

6. Cassia alata

Name- Senna alata(L.) Roxb.

Synonyms- Cassia alata L.

Senna alata is an important medicinal tree, as well as an ornamental flowering plant in the sub family-Caesalpinioideae.It also known as emperor's candlesticks.

Chemical Constituents

Cassia alata which were identified as chrysoeriol, kaempferol, quercetin, 5,7,4'-trihydroflavanone, kaempferol-3-O-beta-D-glucopyranoside, kaempferol-3-O-beta-D-glucopyran-(1-->6)-beta-D-glucopyranoside, 17-hydrotetratriacontane, ndotriacontanol, n-triacontanol, palmiticacidceryl...alata.

7. Sphaeranthus indicus

Biological name - sphaeranthus indicus Linn.

Family - Asteraceae.

Synonyms-Munditika, Mundi

Sphaeranthus indicus Linn. (Asteraceae)is widely used in the Ayurvedic system of medicine in various conditions like epilepsy, mentalillness, hemicrania, jaundice. Chemical constituents-Essential oil, obtained by steam distillation of the whole herb, contain socimene, α-terpinene, methyl-chavicol, α-citral, geraniol, α-ionone, β-ionone, δ-cadinene), p-methoxycinnamaldehyde and an alkaloid sphaeranthine.

8. Clitoria ternatea

Name-pigeonwings, bluebellvine, bluepea, butterflypea, cordofanpeaand Darwinpea, is a plant species family-Fabaceae synonym-In India, it is revered as a holy flower, used in daily puja. chemical constituent-Clitoria ternatea plant. kaempferol-3-glucoside, quercetin, quercetin3-2G-rhamnosylrutinoside, quercetin-3-neohesperidoside, quercetin-3-rutinoside, quercetin-3-glucoside, myricetin-3-neohesperidoside, myricetin-3-rutinoside and myricetin-3-glucoside

9. Evoloulus alsinoides

Name: Evolvulus alsinoides

Biological name: Evolvulus alsinoides, the nela kuriji, is flowering plant from the family Convolvulaceae.

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Chemical Constituents: Plant contains an alkaloid evolvine; β-sitosterol, stearic, oleic and linoleic acid, betaine, pentatriacontane and triacotane.

10. Pergulariadaemia

Biological name: Pergulariadaemia(Forssk.)Chiov.

Synonyms-P.daemia(Forssk.) Blatt

Chemical Constituents- Most commonly found phytochemicals from the leaves of P.daemiaare flavonoids alkaloids, terpenoids and carbohydrate. In Asia, Himalayan forests are abundantly flourished with rich medicinal plant species and a study has documented the presence of ethnomedicinal plants against bronchitis.

The study screened the antiviral plant properties against bronchitis, which showed that Hyoscyamus niger, (Khurasani ajwain), Justicia adhatoda (अड सा) and Verbascum thapsus reduced infections caused by influenza viruses. The molecular mechanism by which these plants target influenza virus can be studied to understand if they attack any molecules overlapping between SARS-CoV-2 and the Influenza viruses. Hyoscyamus niger was found to be a bronchodilator and also had inhibitory effects on Ca2+ channel This could be used to target the Ca2+channels that trigger various downstream pathways upon viral infection.

Most importantly, various medicinal plants have shown inhibitory effects against ACE, and these include Coriandrum sativum (ध नया), Boerhaavia diffusa (पुननवा), Cynara scolymus (artichoke), Coscinium fenestratum (Harichandan), Punica granatum (अनार), Cassia occidentalis (Coffee Senna) and. Embeliaribes (Vidanga). Among them, Punica granatum showed a competitive mode of action while the rest were non-specific inhibitors.

One of the tropical species in the Acanthaceae family, Andrographis paniculata (kalmegh) present in South Asia has a strong treating capacity of viral respiratory infections in Ayurvedic and other medicinal systems Salacia oblonga (Saptrangi) another plant from Tamil

Nadu has also displayed suppressive effects on angiotensin II, AT1 signal, which was related to lung damage.

CONCLUSION

Many plants have also shown inhibitory actions towards HIV proteases, these plants can be promising drugs for COVID-19. They include, Acacia nilotica (Gum Arabic), Eugenia jambolana (जामुन), Euphorbia granulate. Some plants like Ocimum sanctum, Ocimum kilim and scharicum, Solanum nigrum, Vitex negundo have been known to target the reverse transcriptase activity of HIV and can be studied for activity against SARS-CoV-2 as well. Further, Sambucus Ebulus (Tasaar) has been known to inhibit the activity of enveloped viruses and can also be used to target this virus. These medicinal plants can be used to ameliorate the symptoms of COVID-19. Though many medicinal plants have been identified, a lot of research has to be carried out for the development of drug specific to SARS-CoV-2. Therefore, it is important to explore the effect of these prescribed traditional medicines on SARSCoV- 2.

COVID-19 has emerged as the most intense and petrifying viral infection to be handled by the human race. This increase in infection was mainly due to the ability of this virus to recombine, mutate, block the immune system of the host cells and infect multiple species as well as cell types. Various natural phytoconstituents can form part of anti- Respiratory syncytial virus medications by inhibiting viral attachment, viral penetration, inhibiting viral internalization, syncytial formation, alleviation of airway inflammation, and stimulation of interferon secretion and immune system reducing the increased susceptibility of the cell to the invasion of RSV. The importance of a few Indian medicinal plants that have been used for several decades in the treatment of various respiratory conditions. It highlights the pathways that the plant-based medicines may target to reduce the disease burden. Thus, proactive investments in researches based on Indian medicinal plant derived vaccines or drugs to treat COVID-19 would emerge as a source of light to overcome this fatal infection. Using medicinal herbs along with allopathic medicine i.e. If traditional knowledge is combined with modern medicine culture, there is a hope that we will get the promising results not only in combating COVID but also many other fatal diseases.

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