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An Ethno Botanical Perspective of Sustainable Prevention of Covid-19

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Abstract

A pandemic outbreak of Coronavirus has been declared by the WHO in March of 2020 as a result of the early occurence of Coronavirus-19 in China. Since then, COVID19 continued to devastate people all around the world. Human civilization has witnessed one of its greatest crises by facing 180 million of confirmed cases with 38.9 lakh deaths across the world till end of June 2021. Angiosperms include wide-ranging secondary metabolites and metabolic proteins with huge ethnomedicinal values. Though the definite mode of action of the majority of these chemical substances are yet to be known, screening of some valuable metabolites from plant and comprehensive analysis will generate treasures of effective natural medicines in the future. Natural medicines obtained from plant based products are generally safe, well-tolerated with negligible side effects, and extremely absorptive in character by the immunogenic pathway of the human body. Application of these natural drugs along with the conventional treatment may help to minimize the death rates as well as infection rates in the future. Plants are the storehouse of antimicrobial metabolites which have also long been utilized as traditional medicines against different viral infections. Appropriate method of action of these conventional medicines may be a prospective resource of successful anti-COVID drug for future implications. Highly developed bioinformatic tools have opened up an innovative field in speculating these repurposed drugs as a prospective COVID mitigator. The present review briefly summarizes the effect of different plant-derived medicinal compounds against Covid-19 has been discussed along with their targets against SARS CoV2. This review will surely provide an insight into the different plant-derived metabolites for their potential use against Covid-19 in the upcoming days.

Keywords: Medicinal plants; secondary metabolites; sustainable covid-19 prevention

1. Introduction

The earth is dismantle due to a further severe deadly disease by Corona virus that caused outbreak three time between 2002 and 2019 in the form of SERS, MERS, and SARS-COV-2.These were responsible for severe respiratory syndrome (SARS) in 2002, Middle East respiratory syndrome (MERS) in 2012, and now the severe acute respiratory syndrome Coronavirus-2 (SARS-COV-2) first identified in Wuhan, Hubei province, China, in 2019 [1, 2]. Among these three forms SARS-COV-2 or Covid 19 has more dangerous than the previously spreading SARS and MERS corona viruses. This is the successive pandemic next the influenza pandemic in 1918 universally well-known as Spanish flu [3]. After the first happening of Covid-19 in China, World Health Organization had stated novel corona viral outburst as pandemic on March, 2020. Since then, COVID-19 continued to devastate people all around the world. Human civilization has witnessed one of its major crises by facing 180 million of confirmed cases with 38.9 lakh deaths across the world till end of June 2021. Plants have varied secondary metabolites and metabolic proteins with enormous ethnomedicinal values. Although the definite method of act of the majority of these phytochemicals is yet to be discovered, screening of some efficient plant metabolites and thorough analyses of these will generate treasures of effective natural medicines in the future [4]. Plant based medicines are generally non-hazardous, well-tolerated with least side effects, and extremely absorptive in nature by the immunogenic pathways of the human body [5]. Application of these natural drugs along with the conventional treatment may help to minimize the death rates as well as infection rates in the future. Plants are the storehouse of antimicrobial metabolites which have also long been utilized as traditional medicines against different viral infections. Accurate mode of action of these long-established medicines may possibly be a probable source of successful anti-COVID drug for implications in future. A new area of research has opened up in predicting these previously used drugs as COVID mitigators using advanced bioinformatics [6]. Researchers of entire world are still involved to decipher the origin of virus, disease incident and its severity, and development of treatment strategies against the 26 to 32 kb single-stranded positive-sense RNA genome virus [7]. The

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nucleocapsids of the virus are helical and have distinctively shaped particles made from glycoproteins which project from the envelope surface to appear as crowns or coronas [8, 9]. Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Omicron (B1.1.529) are different variants of SARS-COV-2 [10]. These variants are initially designated as Variant under Monitoring (VUM) and after that these are mentioned as Variant of Concern (VUC), if required, after detailed interpretation by WHO [11]. It was already known that human coronaviruses cause gentle forms of common cold-like symptoms [12]. But now it jump from animal to human and is having respiratory complications [13]. Common symptoms of this disease are fatigue, muscle pain, sore throat, dry cough, high fever, respiratory problems etc. But in some cases, it may lead to pneumonia, severe respiratory set of symptoms, kidney malfunction and even death [14]. This virus is more prone to affect person who be ill with cardiovascular diseases, chronic respiratory diseases, diabetes or cancer [15]. The virus initially targets for entry in the host system through the attachment with spike protein with the Angiotensin-converting Enzyme-2 (ACE-2), which is present on the exterior of the cells of alveoli of the lungs [16]. Due to its rapid transmission rate and high mortality rate, the World Health Organization declared the SARS COV-2 as pandemic and it was considered as global health emergency on 30th January 2020 [17]. But, till date there has no proper drug to cure this disease. Some repurposing drugs like favipiravir, remdesivir, lopinavir, ritonavir, nebulized alpha interferon chloroquine, hydroxychloroquine, ribavirin and interferon (TFN) have been recommended for COVID-19 treatment they have direct or indirect adverse side effects [3, 18]. In this regard, different phytochemicals may be able to play a vital role in obtaining the necessary drugs to resist these deadly viruses across the globe. Phytochemicals, such as flavonoids, alkaloids, and peptides can be used against SARS COV-2 in sustainable approaches [19].

Plants provide us an essential medicine in the form of natural quinines which prove its effectiveness in alleviate the symptoms of coronavirus without side effects based on its biocompatibility which operating as a self-defense against stress induced by environmental triggers and pathogens [20]. A thorough understanding of the pathways of plant's secondary metabolites along with their conservation status, ecology and ethnobotany is important for drug development for recent medical calamities. Its magnitude lies in the fact that WHO concludes 80% of the world population depend on medicinal plant-based treatment [21]. It has been seen that there is a plethora of medicinal plants already employed against respiratory viruses. The trials on Traditional Chinese Medicine including dried fruit extract of *Forsythiae fructus* are ongoing as a part of the world's race to develop useful treatment for COVID-19 [3]. *Monochoria hastate* (L.) Solms also effectively relieve SARS-COV-2 infection by altering the main proteases of the pathogens [22]. Therefore, it is no doubt that medicinally important plants could be employed as a potent weapon against COVID-19 in a non-hazardous way. Thus, this review paper highlights the harbal and ethnobotanical treatment approaches and their lively phytochemicals for treatments against SERS-COV-2 infections which is shown in figure-1.

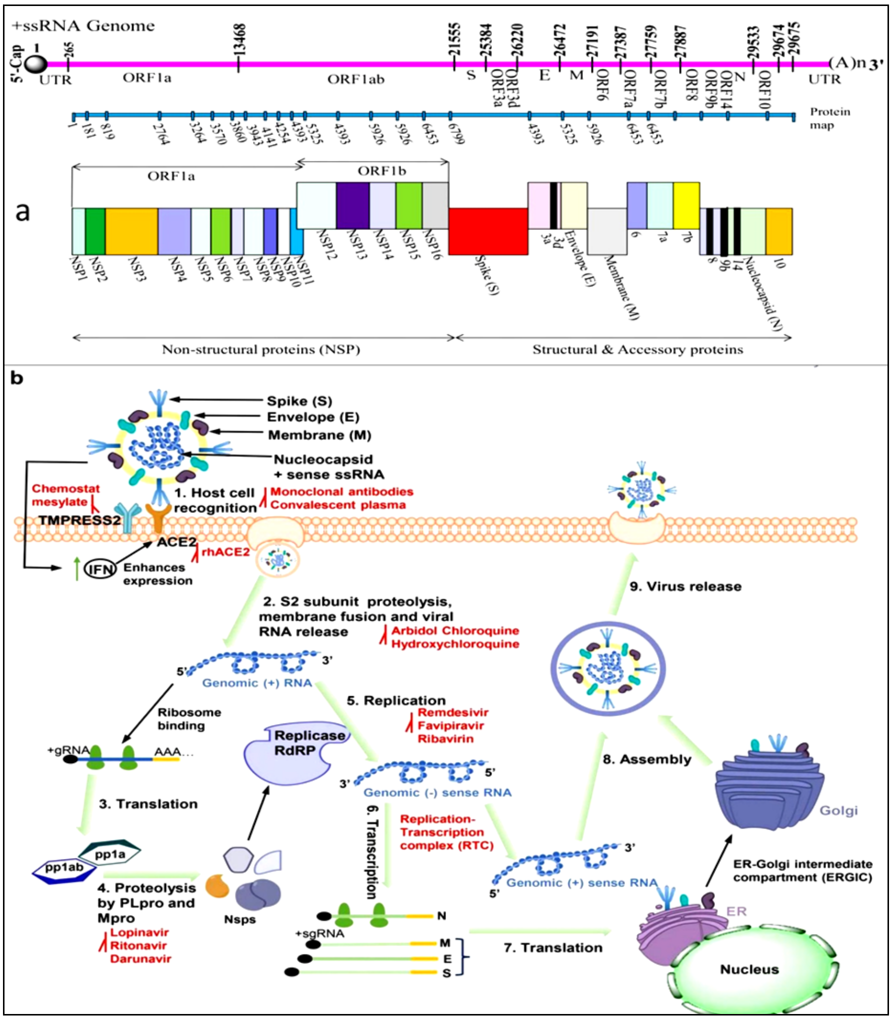

Fig 1: Potential targets for SARS-CoV-2 and its whole-genome composition.

There are 16 nonstructural proteins (NSPs) encoded by the viral genome and structural proteins that are required for replication/transcription and in the assembly of new virions. During attack, SARS-CoV-2 first and foremost enters lymphatic epithelial cells and type II pneumocytes, targeting the body's natural reaction by generating interferons (IFNs. ACE2 protein is activated by IFN, and it functions as a receptor for virus attachment to host cells. The S1-S2 boundary leads to proteolytic cleavage due to interaction between ACE2 and S protein and serine 2 (TMPRSS2) cleavages the S2′ site mediated by transmembrane protease, further fusion host cell plasma membrane inducing the viral. Viral polypeptides (pp1a and pp1ab) are synthesized by the host machinery by means of the ssRNA in the viral genome. These polypeptides are then cleaved by the PLpro and Mpro proteins to produce Nsps. A series of subgenomic messenger RNAs encoding accessory and structural proteins are produced from these Nsps by replication transcription complex (RTC). Virus particles are formed from viral genomic RNA and proteins in the ER-Golgi intermediate compartment (ERGIC. The viral particles are then released from the cell when the vesicle-containing virus fuses with the plasma membrane. A red highlight indicates antiviral molecules that have target sites [110].

2. Plant-based Traditional Treatments against Bacterial, Fungal, Protozoal and Nematode Infection

Plants contain a range of molecules with medicinal characteristics. Though the complete mechanism of action of these drugs is still unidentified, depending on primary available data and computational screening approaches natural therapeutics can largely be classify and describe. Respiratory disorder like asthma, pneumonia, COPD, pleurosis and other acute respiratory infections like SARS, MERS and SERS-COV-2 are the common respiratory tract disease occur due to diverse viral, bacterial, environmental and life style factors. The familiar pharmacological approaches are run either by synthetic drugs likes hydroxychloroquine, remdesivir, darunavir, ivermectine, lopinavir, arbidol, ritonavir etc. [18]. Apart from these synthetic drugs, a huge amount of ethnomedicinal application is commonly used for treatment of disease. These plant products are commonly applied in the form of either crude extracts from roots, stems, flowers, fruits, and seeds or as pure active compounds with different solvents like water, alcohol etc. The common application of ethnomedicinal plants and their active components are described in tabulated form (Table-1).

Table 1: Different antiviral plants and their role against different viruses

Biologial Name (Common Name)	Family	Role against Virus	Reference
Allium sativum (Garlic)	Amaryllidaceae	Influenza A and B, pneumonia	[26]
Andrographis paniculata (Kalmegh)	Acanthaceae	Dengue virus sero type 1 and Hepatitis B virus	[27]
Justicia adhatoda (Vasak)		Influenza virus; asthma	[28]
Strobilanthes Cusia (Assam Indigo)		HCoV-NL63	[29]
Artimisia annua (Annual wormwood)	Asteraceae	HSV, Malaria, EBV, CMV, HCV; SARS-CoV	[3]
Artemisia spp		influenza, human immunodeficiency virus (HIV), herpes, simplex virus (HSV), hepatitis, and coxsackievirus infections	[30]
Azadirachta indica (Neem)	Meliaceae	DEN 2	[25]
Aglaia sp.		MERS-CoVandHCoV-229E	[31]
Camellia sinensis (Tea plant)	Theaceae	Herpes Simplex Virus	[25]
Dioscorea sp. (Yam)	Dioscoreaceae	adenovirus, herpes virus, rhinovirus, influenzavirus, corona virus, dengue virus; in traditional medicine in different diseases like asthama, cough etc.	[32]
Ficus benjamina (weeping fig)	Moraceae	HSV	[3,33]
Glycyrrhiza glabra (Licorice)	Fabaceae	Influenza virus, Corona virus type A and Hepes simplex virus	[3,33]
Atropa belladonna (belladonna)	Solanaceae	HSV and influenza virus	[34]
Phyllanthus urinaria (Chamber/leaf flower)	Euphorbiaceae	HSV-1 and 2 ; HBV	[25]
Sambucus nigra (Elder berry)	Adoxaceae	Influenza virus type A and B; HSV-1	[3]
Prunus dulcis (Almond)	Rosaceae	Herpes Simplex Virus	[35]
Pelargonium sidoides	Geraniaceae	HCov-229E corona virus	[36]
*Heteromporpha*spp.	Apiaceae	HCov-229E	[37]
Stephania tetrandra	Menispermaceae	HVoV-0C43v	[38]

Table 2: Ethnomedicinal plants and their role against different viruses causing respiratory syndrome

Phytochemicals	Plant Name	Family	References
Polyphenols	*Alnus japonica*	Betulaceae	[18,43]
	Anthemis hyaline	Asteraceae	
	Psoralea corylifolia	Fabaceaea	
	Cassia tora		
	Paulownia tomentosa	Paulowaniaceae	
	Taxillus chinensis	Loranthaceae	
Sibiriaester A, Sibiriaester B	*Armeniaca sibirica*	Rosaceae	[3]
Cineole	*Lanxangia tsaoko*	Zingiberaceae	
Menthalactone, maniladiol, Spicatoside	*Mentha haplocalyx*	Lamiaceae	
Isoforsythoside, Forsythoside	*Forsythia suspensa*	Oleaceae	
Sarsasapogenine,sarsaapongenin	*Anemarrahena asphodeloides*	Asperagaceae	
Arctiin,Arctigenin	*Arctium lappa*	Capriforaceae	
Disogenin	*Dioscorea opposita*	Dioscoreaceae	[3,32]
Andrographolides	*Andrographis paniculata*	Acantahaceae	[17,27]
Chloroquine	*Cinchona officinalis*	Rubiaceae	[17,20]
Withanione	*Withania somnifera*	Solanaceae	[17]
Flavonoids	*Citrus sinensis*	Rutaceae	[42,56]
	Pyrrosia lingua	Polypodiaceae	[18,43]
Biflavonoids	*Torreya nucifera*	Taxaceae	[18,44]
Ephedrine	*Ephedra sinica*	Ephedraceae	[45]
	Ephedra herba		[46]
Luteoline	*Gala chinensis*	Anacardiaceae	[43]
	Lophtherum gracile	Poaceae	[3]
Glycyrrhizic acid derivatives Glycyrrhizin	*Glycyrrhiza glabra*	Fabaceaea	[3,36]
	Glycyrrhiza radix		[43]
Griffithsin	*Griffithsia* sp.	Wrangeliaceae	[3,43]
Sinigrin,Indigi beta sitosterol, Aloe-emodin, Hesperetin	*Isatis indigotica*	Brassicaceae	
Lycorine	*Lycoris radiata*	Amaryllidaceae	
Benzylisoquinoline	*Lindera aggregate*	Lauraceae	
Theaflavin	*Camellia sinensis*	Theaceae	[43]
Stryspinoside,chlorogenicacid,loganinaglycone,caffeic acid	*Lonicera japonica*	Caprifoliaceae	[47]
Reserpine	*Rauwolfia serpentina*	Apocynaceae	
Platycodin D	*Platycodon grandiflorum*	Campanulaceae	[38]
Thymoquinone	*Nigella sativa*	Rananculaceae	[17,42]
β-sitosterol, luteoxanthin, violaxanthin	*Urtica dioica*	Urticaceae	[48]

Table 3: Ethnomedicinal plant derived phytochemicals and its mechanism of action against SARS-Cov-2

Plant Name	Metabolites	Target of Plant Metabolites	Reference
Artemisia annua (Asteraceae)	artemisinin and its derivatives (Sesquiterpene lactone)	spike glycoprotein	[30]
Calamus scipionum (Arecaceae)	Myricetin (Polyphenols)	SARS-CoV helicase activity	[43]
Scutellaria baicalensis (Lamiaceae)	Scutellarin (Polyphenols)	SARS-CoV helicase activity	
Broussonetia papyrifera (Moraceae)	3'-(3-methylbut-2-enyl)-3',4,7-trihydroxyflavane (polyphenols)	SARS-CoVPLpro	
Torreyanucifera (Taxaceae)	Quercetin (Flavonid)	SARS-CoVPLpro and prevent host cell entry	[3,43]
Arisaema tortuosum (Araceae)	Luteoline phlorotannins (flavonoids)	spike protein; probably act as TMPRESS2 inhiobitors	[3, 18]
*Scutellaria baicalenis*root (Lamiaceae)	Baicalein,baicalin (Flavonoid)	Act as RNA dependent RNA polymerase inhibitors of SARS-CoV-2	[83]
Andrographis paniculata (Acanthaceae)	Naringenin (Flavonoid)	SARS-CoV-2 3CLpro	[84]
Sophora alopecuroides (Fabaceae)	Oxysophoridine (aklkaloids)	Exact mode of action is not known but it may be broad spectrum anti RNA virus chemical	[85]
Cinchona officinalis (Rubuaceae)	Chloroquine (alkaloid)	SARS-CoV-2 cell replication	[43]
Ocimum sanctum (Lamiaceae)	Tulsinol A, B,C,D,E,F,G and dihydrodieuginol B (Neolignans)	Act on ACEII	[17]
Withaniasominifera (Solanaceae)	Withanone (terpene)	main protease (Mpro)	[86]
Ginkgo biloba (Ginkgoaceae)	Ginkgolide A (terpene)	anti SARS CoV-2 protease activity	[18]
Curcuma longa (Zingiberaceae) *Azadirachta indica* (Meliaceae)	Curcumin (diarylheptanoids), nimbin(triterpenoid)	target Spike protein and ACE-2	[87]
Andrographis paniculata (Acanthaceae)	Andrographolide (diterpenoid)	Main proteases	[18]

3. Plants with Antiviral Properties; An Overview

From the beginning of human civilization plants are used medicinally all over the world. A large portion of population of developing countries including India even today depends on traditional plants for their health requirements. Plants synthesize hundred of chemicals known as phytochemicals which can be employ against common to rare infectious and non-infectious diseases. Hundreds of phytochemicals which have potent biological action have been recognized [23].

According to WHO, 'infectious diseases are the sixth leading cause of premature deaths in the World.'[23]. Communicable diseases are caused by different viruses, bacteria, fungi and protozoa etc. Among these viral infections are of great importance because of their diversity and high rate of mutation. Modern system of medical biology generally used different antimicrobial therapy to deal with different infectious diseases. But, gradual increasing resistances of microorganisms to this type of chemical compounds, scientists are search for different treatments. In this approach medicinally valuable plants may be capable of be most excellent weapon owing to their strong capability to alleviate different infectious diseases including the diseases caused by viruses. The chemical substances or metabolites obtained from plants act against virus differently i.e. their mechanism of action differs from one another. They inhibit virus particles either targeting their envelope or membrane or inhibiting viral replication cycle or inhibiting their entrance in to host cells or destroy essential enzymes for viral encoding [24, 25]. Under this heading we will enlist some anti-viral plants.

4. Plant Based Remedies for Viral Respiratory Infections (VRI)

The majority of human illnesses are caused by viral respiratory infections (VRI). There are many benefits that antiviral plants can provide for patients who have acute bronchitis, acute respiratory syndrome, common colds, influenza, and viral pharyngitis. A number of plants with antiviral properties have also been experimented for their ability to combat respiratory viruses. The herb is known to be applied traditionally to cure viral flu caused by influenza viruses [39], respiratory viruses [40], and more recently for two disease outbreaks caused by coronaviruses (SARS-CoV in 2002 and MERS-CoV in 2012). Additionally, Rajasekaran *et al*. (2013) [41] also showed that fifty tropical plants, which originate from rainforests, possess anti-influenza virus activity. There was a significant ability to inhibit viral neuraminidase and hemagglutination by the plants tested, despite their minimal cytotoxicity. Plant extracts which were reported previously to combat with coronaviruses can be effective this time because SARS-CoV-2 is also belongs to beta genus of coronavirus. In this review article we make an elaborate table to accommodate the plants which have activity against SARS-CoV.

5. Bioactive Plant Derived Chemicals and their Mechanism of Action against SARS-Cov-2

On or after its discovery in 1960 coronaviruses turned fatal three times-SARS on 2003, MESRS on 2012 and recently the SARS-CoV 2 on 2019. Its genomic sequences became available within few days but till date, no proper drugs are not arrived to treat it properly. Because it is time consuming process to develope a safe and efficient process to develop safe and efficient drugs [19]. On the other side, artificial drugs may possibly have adverse effect. As an instance, it is observed that use of remdesivir amplified the intensity of liver enzyme which in turn can damage liver tissue [18]. If we look back our past it is evident that people from ancient time are relying in medicinal plant to treat themselves. It is very difficult to develop an antiviral medicine because have to be proceed against virus with no effect on the host cell metabolic activity. So, researchers often turn to plant metabolites to treat different viral infections like Dengue virus, influenza virus, hepatitis virus due to its efficacy and lower toxicity to host cells. Different *in vitro* studies show that different antiviral phytochemicals can also be effective against SARS-CoV 2 as they were proven against SARS-CoV-1. The phytochemicals which have anti SARS-CoV-1 activities are flavones, flavonoles, fatty acids, tannins, terpenes and alkaloids [19]. Alkaloids have broad spectrum antiviral activities even in case of inhibiting the infection of corona viruses [49]. Withanone obtained from *Withania somnifera* can prevent SARS virus entrance into host cell by acting on ACE-2-RBD (Receptor-Binding Domain) complex [17]. It is evident by using in silico methodology andrographolides from Andrographis paniculata can act against SARS-CoV-2 proteases [17] which is shown in figure-2.

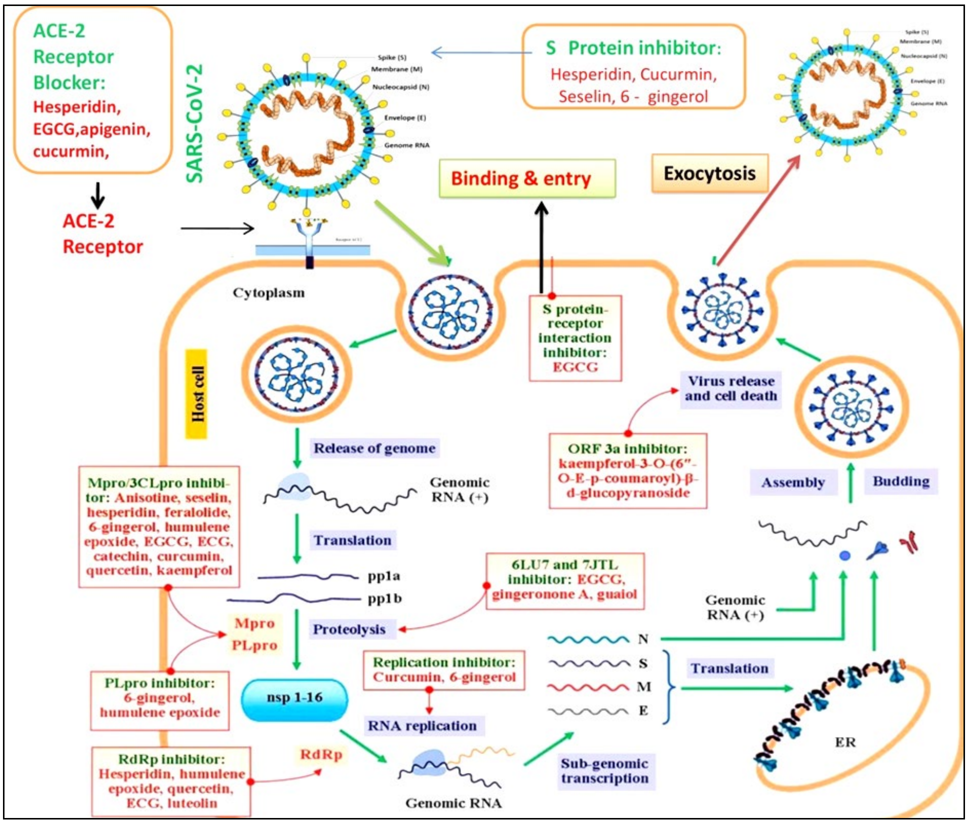

Fig 2: Impact of bioactive metabolites obtained from medicinally important plants on molecular targets of various steps of multiplication process of SARS-CoV-2. ACE2, angiotensin converting enzyme 2; N, Nucleocapsid; S, M, E:,spike, membrane, envelope proteins; pp1a, pp1b, nonfunctional polypeptides; nsp, nonstructural proteins; Mpro, main protease; 3CLpro, 3-chymotrypsin like protease; PLpro, papain like protease; RdRp, RNA dependent RNA polymerase; RNA (+), positive-sense RNA; and ER, endoplasmic reticulum [111].

5.1. Plant Metabolites as Preventor of Viral Replication, Immune Modulators and Prophylactic Agents

Alkaloids are diverse chemical compounds mainly characterized by heterocyclic nitrogen compounds and are alkali by nature [50]. Green plants are the principal reservoir of alkaloids (e.g., morphine, strychnine, quinine, ephedrine, nicotine) a type of secondary metabolites. They also have potential drug activity [51]. The most well-known nucleic acid intercalation alkaloids are isoquinoline, emetine, sanguinarine, berberine, beta-carboline. These DNA alkaloids or RNA alkaloids readily restrain their further replication. This apparatus is equipped to hold back SARS CoV 2 by plant-derived alkaloids [52]. Tomatidine steroidal alkaloid extracted from immature and full-grown green tomato plants exhibit remarkable effects against Chikungunya virus (CHN), as well as flaviviruses like dengue virus (DENV) and zika virus (ZIKV) [53]. The screening of these antiviral alkaloids against SARS CoV-2 may provide more insight into their mechanism of action and efficacy in the future. The specific drug against Covid-19 is still elusive. In such a situation, immunomodulators have a positive effect on this disease. The nonspecific inflammation of different organs such as liver, kidney including neurological and cardiovascular complications are prominent due to massive “cytokine storm” [54]. A preliminary experiment with alcoholic extraction of *Humulus lupulus* and (hop) *Cinnamum verum* (cinnamons) bark exhibit a number of optimistic immunomodulation effects [55]. Flavonoids, xanthones, proanthocyanidins and secoiridoids have potential natural therapeutic activity against SARS CoV-2 by blocking ACE 2 [56]. Vitamin C (citric acid) has a prominent role in scavenging oxidative damage due to ACE 2-S-protein interaction [57]. Essential oils obtained from lemon and Geranium has considerably adversely affected the expression of human ACE 2 receptors in epithelial cells [58]. In several cases, plant derived compounds showed enhanced effectiveness than artificially made substances [59]. Lectins are the carbohydrate-binding proteins present predominantly in many parts of plants, fruits, and vegetables. Among these lectins mainly mannose-binding lectins found to be act as potent antiviral proteins [60]. Nutritionists also recommended *Glycyrrhiza radix* (Licorice), *Zingiber officinalis* (Ginger), and *Ocimum sanctum* (Tulsi) as immunomodulatory drugs during the Covid-19 pandemic [61].

Natural metabolites derived from plants are broadly used against Covid-19 as a prophylactic substance. The arrival of the newest computer mediated techniques permit analysing various natural substances to evaluate their efficiency as medicinal probiotics [62]. *Curcuma longa*, *Ocimum basilicum*, *Thymus vulgaris*, *Rosmarinus officinalis*, *Juniperus communis*, *Melissa officinalis*, and *Mentha piperita* were proved to be extremely effectual crude antiviral agent [63]. Green tea (*Camellia sinensis*) due to the presence of an excessive amount of catechins has long been known as an antioxidant, anti-inflammatory, anti-infection as well as broad anti-viral agent [64]. In recent times, it has been establish that epigallocatechin largely present in green tea fruitfully inhibit SARS CoV 2 attack [65]. Another natural wonder compound curcumin extracted from Curcuma showed an attenuation effect against Covid-19 by activating pro-inflammatory angiotensin II-AT1 receptor signaling pathways [66]. A programmed modeling-mediated observation showed that curcumin could be active as an immunomodulator by lowering "cytokine storm" in infected person [67].

5.2. Recent Development and Mechanistic Aspects of Using Phytochemicals against SARS-CoV-2

After SARS-CoV and MERS CoV another devastating viral infection is SARS-CoV-2 which is first originated in Wuhan city of China in December 2019 [18]. On 30th January WHO declared it as a matter of Public Health Emergency of International Concern and also declared as epidemic [68]. On 13th January full genome analysis was completed [69]. Complete genome sequencing and phylogenetic studies confirms that the corona virus that cause Covid-19 is beta corona virus belongs to the same subgenus as severe acute respiratory syndrome (SARS) their clad is different. Both the viruses use the same receptor namely Angiotensin Converting Enzyme-2 for their host cell's entry. Due to their similarity, the Corona virus Study Group of the International Committee on Taxonomy of Viruses named the viruses that cause covid-19 as Severe Acute Respiratory Syndrome Corona virus-2 (SARS CoV-2) [70]. SARS-CoV-2 is a pleomorphic or spherical shaped linear single stranded positive sense RNA virus [18, 68]. Size of the genome of this virus is 26.4-31.7 KB in length and considered to be as one of the largest genomes compare to the other RNA viruses. It also contains a crown like surface glycoprotein [18]. The genome i.e. RNA produce four structural proteins, sixteen non-structural proteins and ten accessory proteins [71]. These four structural proteins are Spike protein (S), Envelope protein (E), Membrane protein (M) and Nucleocapsid protein [69]. S protein binds with Angiotensin Converting Enzyme-2 of human cells and facilitate the virus to entering the host cells [69]. E protein which is integral ion channel protein, plays important role in human cell disruption, immune evasion, pathogenesis, virion production exit [71]. Amongst the nonstructural proteins RNA dependent RNA polymerase (nsp12), Helicase (nsp13), Papain-like protease (nsp3), main protease (nsp5) which is also known as 3-C-like protease (3CLpro) and 2' O methyl transferase (nsp16) are important. This structural protein may have role in transcription, replication and pathogenesis of the virus. All of these proteins can be target of antiviral drugs and vaccines. Coronaviruses are zoonotic virus [72] and can infect the animal like turkeys, mice, cats, dogs, rats, horses, cattle and pigs. Sometimes these animals spread this virus to human [14]. SARS-CoV-2 is transfered all the way through respiratory droplets during cough and sneezes and enters the body through mouth and nose. It may be transmitted indirectly by touching surfaces or objects which are already contain virus but probably they are not main source of infection. Corona virus attack cells of gastrointestinal tract and respiratory tract of their hosts. After entering the cell, they multiply with the help of RNA dependent RNA polymerases enzymes [14]. After binding with the host plasma membrane, the virus inject its RNA only and its envelope and capsid part stay behind the cell. As it is positive sense RNA virus its RNA directly acts as mRNA. After entering the host cells, it replicates and transcribed with the help of different structural proteins like main protease (nsp5), papain-like protease (nsp3) and non-functional protein like RNA dependent RNA polymerase (RdRp) [69, 72]. Our immune system also helps in assemble of newly generated virion particles. Development of new-fangled virion particles take place into the cavity of Golgi intermediate compartment complex (ERGIC) [18]. New virion particles released from cell by exocytosis [3]. SARS-CoV-2 affected patients can be suffered from asymptomatic form to non-severe symptomatic form to acute bilateral pneumonia. In last case patient have to be admitted in Hospital [18, 73]. Before this SARS-CoV outbreak corona viruses rarely cause lower respiratory infection and symptoms are like as cold. Patients affected with SARS-CoV generally shows symptoms like dry cough, sore throat, breathlessness, fever, fatigue, lymphopenia and elevated lactate dehydrogenase level [73, 74].

SARS-CoV-2 is an enveloped virus with positive sense RNA and its genome is largest among the RNA viruses. It is the causal agent of Covid-19. Its envelope contains hemagglutinin esterase. SARS-CoV-2 completes its life cycle following attachment, penetration, biosynthesis, maturation, and release [75]. RNA encodes 29 proteins; four of them are structural proteins, namely the membrane (M), spike (S), envelope (E) and nucleocapsid (N) proteins [17, 76]. Among these four structural proteins, nucleocapsid (N) proteins are very important in RNA packaging and host cell entry. It has immunogenic property [77]. S protein also helps the virus to attach with host cell. S protein has two sub units, namely S1 and S2. S1 binds directly with peptidase domain (PD) of ACE-2 receptor with the help of its receptor binding domain (RBD). Furthermore, S 2 associated with membrane fusion [78]. Corona viruses enters/inoculates and replicates in host cells/alveolar type II cells [79] by using three proteins-papain like protease (ACE-2), and spike protein (TMPRSS2) of host cells and the 3 chymotrypsin-like protease (3CLpro), within SARS-CoV-2 [19]. Papain like protease (PLpro) and 3CLpro helps the virus to evade the host immune system. 3 CLpro also plays an important role in producing viral functional protein along with RNA-dependent RNA polymerase (RdRp), helicase, single-stranded RNA-binding protein (ssRBP), exoribonuclease, endoribonuclease, ribose methyltransferase etc. [80]. As a result of immune reaction to SARS-CoV an antiviral environment is established surrounding the infected cells via expression of IFN-stimulated genes those are induced by Type I interferons (IFN-alpha and beta) [81]. Mpro of SARS-CoV-2 plays an important role in machinery of viral replication [82]. After entering the host cells virus genome or genetic material bind with the host's ribosome to produce large polyproteins. Then these polyproteins are altered by the proteolysis. Methyltransferase (nsp 16) and helicase (nsp 13)- the two nonstructural protein of SARS-CoV-2 also play an important role in causing disease [72].

5.3. Inhibition of SARS-CoV entry by phytochemicals

A promising avenue for finding a suitable drug candidate is to inhibit viral entry by plant-derived compounds. Prior to inflowing the host cell SARS-CoV-2 an interaction takes place between S protein of virus and host cell receptor angiotensin converting enzyme 2 (ACE 2). ACE 2 is a type I membrane protein located in lung, kidney, intestine and heart. So, SARS-CoV can invade kidney, intestine and heart cells besides alveolar type II cells [79, 88] So, those phytochemicals which have activity against S protein ACE 2 intercation can be used against Covid 19 beacause they can inhibit viral entrance in host cells [3]. The Flavonoids quercetin and isorhamnetin have great affinity to ACE 2 and inhibit virus entry by blocking spike protein attachment to this receptor [75]. A variety of glycosylated quercetin derivatives, such as quercetin-3-glucuronide-7-glucoside and quercetin-3-vicianoside, can be extracted from *Piper longum, Curcuma longa*, and *Artemisia absinthium* to achieve anti-corona virus protection [19]. Among the quercetin, luteoline and etra-O-galloyl-beta-D-gucose, activity against human immunodeficiency virus (HIV)-luc/SARS pseudo-typed virus, quercetin shows lower cytotoxicity effect. FDA also approved quercetin as drug ingredient against COVID-19 [3]. Hesperidin, emodin, and chrysin act as strong inhibitor of SARS-CoV S protein and ACE 2 interaction [88]. Curcumin and nimbin have binding affinity with SARS-CoV-2 spike protein and ACE 2 of human [89]. SARS-CoV 2 binds with ACE 2 of human with the help of S protein Receptor-Binding Domain (RBD). Withanone from *Withania somnifera* acts on this ACE2-RBD complex and obstruct the access of SARS-CoV-2 entry. *Ocimum sanctum* extraction also have ACE 2 blocking property [17]. Chebulagic acid, piperin, mangiferin, thebaine, berberine-these antiviral phytochemicals inhibit SARS-CoV 2 entry by binding with Spike protein and ACE-2 [18]. In the study, anthraquinone compounds, rhein, emodin and a flavonoid, chrysin, isolated from the genus *Rheum* and *Polygonum*, were tested for their effectiveness against SARS-CoV which is shown in figure-3.

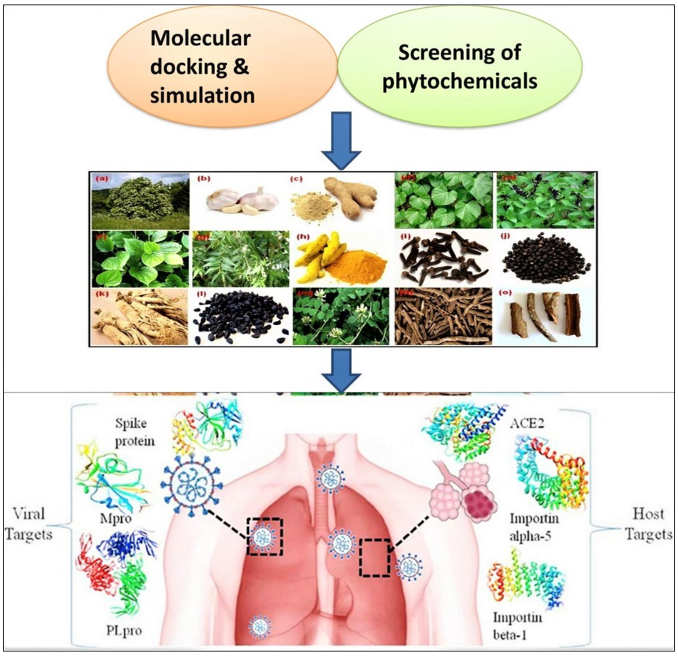

Fig 3: Plants phytochemical act as inhibitors of SARS-CoV 2

5.4. Inhibition of Replication in SARS-CoV

SARS-CoV 2 mRNA replicates when it gets entry the host cell by hijacking the copying machinery. The viral proteinase Mpro or 3CLpro plays a major role in the replication process. Viral replication can be restricted using different phytochemicals targeting this proteinase [88]. Bioactive molecules that target SARS-CoV helicase can also be used as SARS-CoV inhibitors [3].

The anti-SARS-CoV action of glycyrrhizin obtained from *Glycyrrhiza glabra* root was observed by inhibiting the replication with an EC50 value of 300 µg/ml. Lycorine, an alkaloid isolated from the stem cortex of *Lycoris radiata*, inhibits SARS-CoV with an EC50 value of 15.7 nM [90]. It was also observed that lycorine inhibit viral replication at lower concentration that of glycyrrhizin [3]. Aescin a bioactive compound from Aesculus hippocastanum have anti SARS-CoV activity with EC50 value of 6.0 µM and CC50 value of 15 µM. An alkaloid, reserpine obtained from *Rauvolfia serpentina* dried root inhibits SARS-CoV replication. EC50 and CC50 value for reserpine was observed 3.4 µM and 25 µM respectively [3, 90]. The anti SARS-CoV activity of reserpine and aescin was confirmed by enzyme linked immunosorbent assay (ELISA), Western blot analysis, immunofluorescence and flow cytometry assays. They act against SARS-CoV in two ways-by resisting viral entry into the cell and additionally interfering with 3CLpro enzyme activity [3]. Aloe-emodin isolated from *Aloe vera*, *Cassia angustifolia* and *Rheum emodi* have anti SARS-CoV activity. It resists viral replication by inhibiting the cleavage activity of SARS-CoV 3CLpro. Sinigrin is one type of glucosinolate, found in different species of Brassicaceae as well as Isatis Indigotica interact with the 3 CLpro activity have IC50 value 217 µM and CC50 value >10,000 µM [90]. Quercetin a flavonol have anti 3CLpro and PLpro properties along with its inhibitory property against viral cell entry [88]. Other flavonoids such as apigenin, Amentoflavone and luteoline obtained from *Torreya nucifera* of Taxaceae act against SARS-CoV 3CLpro. The IC 50 values of this 3CLpro inhibitor are 280.8, 8.3 and 20.2 mM respectively. Scutellarein from *Scutellaria baicalensis* and myricetin from *Isatis tinctoria* also active against SARS-CoV 3CLpro [92]. Besides their activity against SARS-CoV 3 CLpro they also act against SARS-CoV helicase activity *in vitro* by affecting the activity of helicase. Due to their low IC50 values, 2.71 +/- 0.19 mM and 0.86 +/-0.48 mM correspondingly and no cytotoxic activity against breast cancer cell lines, myricetine and scutellarein could be good inhibitor of SARS-CoV [3]. Kaempferol inhibit SARS-CoV-2 3CLpro enzyme activity. It was observed an experiment on SARS-CoV recombinant protease that Theaflavin-3, 30-digallate with an IC50 value of 9.5 M significantly decreases the 3CLpro activity [75].

Terpenoids such as ferruginol, pinusolidic acid, αcadinol from *Chamaecyparis obtuse* var *formosona* significantly inhibit 3CL protease activity in the concentration between 3.3 and 10 µM. cedrane-3β, 12-diol and betulonic acid from *Juniperus formosona* and cryptojaponol and 7 β-hydroxydeoxy cryptojaponol also have same effect on SARS-CoV 3 CL protease [92]. The strong activity of terpenoid on 3CLpro activity was confimed through docking studies. From different studies it was establish that most of the terpenoids show their inhibitory effect on SARS-CoV replication at EC50 between 3.8 and 7.5 mM and an CC50 value greater than 250 mM. ELISA studies also confirmed that terpenoids block virus S protein and further stimulate inhibition of copying action [3].

Plant lectins specifically mannose binding lectins with EC50 ranging from 0.45 to >100 g/ml and CC50 value with 50 to 100 g/ml show good anti coronavirus activity. They block the SARS-CoV entry into the host cell probably interacting with the glycans on the spike protein [93]. Lentin lectin extract from *Lens culinaris* restrain SARS-CoV by inhibiting the contact of ACE2 and S trimer [94]. So, it can be concluded that different phytochemicals such as alkaloids, flavonoids, terpenoids and plant lectins could be used as drug candidate against SARS-CoV.

6. Plant Based Vaccine against Covid 19

Immunization with vaccine is the most efficient strategy to prevent the spread of any viral disease. Virologists have developed some effective vaccines, but production or supply lags far behind the present demand across the globe. Plant-derived vaccines (PDVs) based on tailored virus like particles (VLPs) can be a realistic substitute in this case. A brief explanation about the effectiveness of the first plant-derived Covid 19 vaccine, CoVLP is discussed. PDVs and VLPs are also reviewed briefly, along with their benefits and drawbacks.

6.1. Virus like Particles (VLPs) as the Possible Alternative for Conventional Vaccines

VLPs are the self-assembling, non-replicative, non-pathogenic supramolecular particles used to target specific host and drug delivery system [95]. Literally VLPs have a very wide sense of application i.e., any acellular body which have similarity with viruses can be grouped under VLPs. They have several positive features in development of vaccines. As the VLPs be deficient in the complete genome apart from the "epitope" they are not capable to create any disease in host cell, furthermore, the protein cover are in utmost cases engineered from different viruses. Thus, inappropriateness with coat protein is one more point for its ineffectiveness. Lipid envelop coat is observed to be very useful transporter for VLPs. The relatively improved consistency of lipid organization in cellular surroundings makes them pompous deliverance method. Another important factor is the size, due to very low size, delivery system by VLPs become more efficient as readily taken up by antigen presenting cell (APC), which in turn help in activation of T cell for cytotoxicity and eventually boost up immunity [96].

6.2. Plants as Vaccine Production System with Delivery Mechanism

Plants hold an easy but efficient production powerhouse due to its uniform and proliferous growth patterns. It is very facile to manage cultural parameters within plant cell culture system *in vitro*. Biopharmaceuticals generated by plant cell cultures also exhibit superior stability than animal cell culture system. *Nicotiana tabacum* 1 (NT1) and tobacco bright yellow (BT 2) cell lines are widely used for production of plant derived pharma products [97]. Although suspension culture of *Daucus carota, Oryza Sativa, Lycopersicon esculentum* as well as Glycine max also recently been used for the molecular farming of vaccines and other medicinal components of human interest [6]. Interestingly, microalga *Chlamydomonas induration* now popularly maneuvered for vaccine aquaculture and production of different adjuvants [97].

6.3. Covid-19 Vaccine Created from Plants

The whole scientific community across the world are deploying their hard work to build up a vaccine that can beat all the hurdles and available for every living human being on this Earth. The phase I clinical trial report of a plant derived Covid 19 vaccine, CoVLP by Medicago Inc, Canada brings new hope to save the human races in a green way [98]. This technology utilizes *Nicotiana benthamiana* plant system for the vaccine production and disarmed *Agrobacterium tumefaciens* for transfer of episomal DNA containing gene for SARS CoV-2 spike protein. This is the first reported plant derived Covid 19 vaccine which set up a new path for war against Covid 19. The platform used by the Medicago Inc is well characterized and proved to be efficient previously against seasonal influenza and hemagglutinin vaccine against Avian races [98]. The vigorous and well interpreted experimental design comprising 180 ELISA (against nucleocapsid of SARS CoV-2) negative volunteers from two cities (Montreal and Quebec City) of Canada were tested [98].

Covid 19, caused by SARS-CoV 2 has spread all over the world in a time of only six months. It becomes deadliest pandemic after Spanish flu which took 50 million lives. Researchers throughout the world are trying to design an appropriate vaccine along with the development of proper drugs. In this context plants might be a potential alternative to develop a vaccine. Plants are used as bioreactor for developing vaccines. They are source of continuous and bulk production in a stipulated time. Plant-based vaccines can be placed under third generation vaccine. Plant based vaccines produced a strong immune response in humans and animals [99]. The World's first approved plant-based vaccine was for New Castle disease Virus (NDV). A single-chain fragment variable monoclonal antibody (scFvmAb) obtained from plant is used in the production of a recombinant Hepatitis B virus (HBV) vaccine; the only other licensed plant-based vaccine [100]. Though some plant-based vaccines namely swine influenza, rabies, and hepatitis-B are in clinical trial phase. Among them vaccine against influenza is front runner [101]. Generally, vaccines for SARS-CoV-2 should be based on inactivated or killed SARS-Cov-2 strains. But this is a time-consuming process and may have adverse effects. Best alternative method is producing subunit vaccines based on individual proteins or as virus-like particles (VLPs). SARS-CoV enters the host cell by interaction of Spike protein of the virus and ACE-2 of host cells. So, major vaccine candidates against SARS-CoV aim S protein. If this strategy will successful then it will be possible to hold back virus entrance into the cells. It also stimulate neutralizing antibody responses or antibody-dependent cell-mediated cytotoxicity (ADCC) or cross-presentation to reach protective cellular immunity. Virus-like particles or VLPs show its effect by using SARS-CoV-2 antigen as vaccines. VLPs boost strong cellular and humoral immunity due to their size, targeting the adaptive immune system and sequenced proteinaceous structure which act as danger signals [102]. We are trying to represent a current status of different vaccines those are developing all over the World for Covid 19 is mentioned here in the following Table-4.

Table 4: Current status of different vaccines those are developing all over the World for Covid 19.

Type of Vaccine	Name of Vaccine	Developer	Phase of Trial/Approved	Dosasge	Success Rate	Reference
Viral vectored vaccines	ChAdOx1	Oxford-AstraZeneca	2 and 3/Approved in Brazil and emergency use in UK, EU,Indiaetc	2 doses in 4 weeks gap	76%	[3,103]
	Inactivated (formaldehyde inactivated + alum)	Sinovac	3/Approved in China	2 doses in 2 weeks gap		[3,103]
	Oral COVID-19 Vaccine	Vaxart	Pre-Clinical	-	-	[103]
	Non-replicating Viral Vector	Bharat Biotech	3/Approved for emergency use in India	2 doses in 4 weeks gap	77.8%	[3,103]
	Ad26	Johnson & Johnson	3/use in emergency in U.S., E.U.	Single dose	64-72%	[3,103]
	Adenovirus Type 5 Vector	CanSino	3/Approved in China	Single dose	65.28%	[3,103]
	Inactivated viral vaccine/Inactivated	Sinopharm	3/Approved in china, U.A.E, Bahrain	2 doses in 3 weeks gap	78.1%	[3,103]
RNA vaccines	LNP-Encapsulated mRNA (mRNA-1273)	Moderna	3/Approved in Switzerland, emergency use in U.S, E.U,	2 doses in 4 weeks gap	>90%	[3,103]
	BNT162/mRNA	Pfizer/BioNTech	2,3/Approved in several countries, emergency use in U.S., E.U	2 doses in 3 weeks gap	91.3%	[3,103]
	Adeno-based Gam-COVID-Vac/Non-replicating viral vector	Gamaleya	Emergency use in Russia	2 doses in 3 weeks gap	91.6%	[3,103]
Protein Sub unit vaccine	VLP Recombinant Sub-unit, Full length S trimer	Novavax	3/-	2 doses in 3 weeks gap	89.7%	[3,103]
	Virus Like Particle (VLP) vaccine	Medigaco	Pre-Clinical	-	-	[103]
Live Attenuated Vaccine	Deoptimized live attenuated virus	Serum Institute of India	Pre-clinical	-	-	[103]

7. The Requirement of Bioinformatics in the Improvement of Antiviral Agents from Medicinal Plants

Although plants and its metabolites are potent inhibitor of different types of diseases including viral diseases are not reach to the synthetic drugs in terms of uses. One of the most significant reasons behind it is the lack of availability of these plant-based drugs than synthetic drugs. This can be overcome with the help of plant biotechnology. Plant biotechnology of medicinal plants provides us lots of information regarding medicinal plants and their activities against different pathogens like bacteria, fungi, virus etc. [3]. Plant biotechnology can also contribute in combating SARS-CoV-2 by time bound production of diagnostic reagents to identify disease and recovery from disease, developing vaccine to prevent disease and different antivirals phytochemicals to treat SARS-CoV symptoms [102]. Different information obtained from these studies is available in different databases and web sources but not in orderly manner. Computational biology can resolve this problem and bioinformatics tools help in analyzing the available data to find out proper drug to treat diseases. It also, helps in deciphering genetic pathway by which plants produce its secondary metabolites [3]. SARS-CoV 2 infection may cause idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and COVID-19. IPF and COPD develop due to the increase of angiotensin-converting enzyme 2 or ACE2. For the determination of genetic relationships among SARS-CoV-2, IPF, and COPD both microarray and RNA-seq data sets from the GEO database of the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih. gov/geo/) were used [79]. Different phytochemicals like Isothymol, Limonene, P-cymene, Thymol and γ-terpinene block virusentry into host cells by inhibiting angiotensin converting enzyme 2 (ACE-2) activities [3]. Since the Covid 19 pandemic began several databases, web servers (Virus-CKB), D3Targets-2019-nCoV, COVID-19 Docking Server and tools (MolAICal) are in use for the development of in silico drug development against SARS-CoV-2 [104]. For the effective information about therapeutic plants and its metabolic pathways databases like the Arabidopsis information resources (TAIR), the International Ethnobotany Database (ebDB) and Medicinal Plant Database for Drug Designing (MPD3) can be access. MPD3 also give us information about phytochemicals, their structure, and action along with their reference [3]. Analyzing a plant database consist of 32, 297 potential antiviral phytochemicals It was observed that nine of them can inhibit viral replication by acting on SARS-CoV-2 3CLpro [105]. On the other hand, from molecular docking studies show that stilbene based natural compound, mainly resveratrol along with quercetin, fisetin and kaempferol act against SARS-CoV-2 spike protein. Hence, they may be used as potent drug against SARS-CoV-2 [3].

8. Challenges and Future Perspective

Plants are the great reservoir of the phytochemicals. Different antiviral substances can be isolate from plants. The antiviral activities of *Acacia arabica*, *Chenopodium ambrosioides* and *Zingiber officinale* have been already established. Not only antiviral substances but also anticancer, antioxidant, antibacterial etc are found in plants [106]. From ancient past human are dependent on plants for their treatments against infectious and other diseases. They are cost effective with minimum toxicity [17]. According to WHO 80% of World population are dependent on plant-based medicine for their treatment [3]. On the way to conquer this deadly disease i.e. Covid 19 World urgently require for an appropriate drug or vaccine. In this circumstance plants once more can be a good choice over the different synthetic repurposed drugs. It has been found that Phytochemicals such as emodin, reserpine, myricetin, scutellarin etc. can be effectively used against coronaviruses [3]. Plant metabolites even can be more effective than currently used repurposed drugs, such as flavipir, remdesivir etc. Phytochemicals halt SARS-CoV-2 infection by targeting papain-like protease, 3CL protease or inhibiting the fusion of S protein of corona viruses and ACE2 of the host [18]. But phytochemicals have some limitations compare to the synthetic drugs because their mechanistic aspects which is important to know before their proper applications are less understood [3]. So, modern scientific approach should be followed to establish phytochemicals as widely accepted drug candidates [23].

Vaccines are the best solution to overcome any pandemic diseases. So, different vaccines are developed throughout the world to restrict the SARS-CoV-2, the causal agent of Covid 19 disease. Many of them are in different tier of clinical trial phase or in use in different countries. We have already discussed about these vaccines in previous section. We also found plant-based vaccines among them. Though these plants-based vaccines may be good weapon against covid 19 but they are in clinical trial phase. Among the plant-based vaccines Medicago's CoVLp vaccine show good prospect [107]. The advantages of Plant based vaccines are they are cost effective, easy to apply and efficient to combat with Covid 19 [101]. But the limitations of plant-based vaccines are the selection of antigen and expression in host plant, proper selection of dose and maintaining GMP protocol for vaccine development [100].

9. Conclusion

Conclusive Remarks and Future Outlook

The repeated incidence of the COVID-19 pandemic disturbe societal activities and impose huge stress on the healthcare system globally. Although, some vaccines were developed to contain the disease, in most cases they protect the infection to a certain percentage. Several antiviral medicines have been screened to study their effectiveness but this process needs several steps for final recognition of the drug [108]. Massive increase in cases of Covid 19 pandemic completely destabilizes health as well as socio economic condition of the world. Moreover, flora is the great reservoir of diverse metabolites and plant-derived medicine are used by tradition to cure different viral infections. Natural medicines would be nonhazardous, as majority of them have a long ethno-pharmaceutical lineage and therefore has reasonably less possibility of adverse reactivity. Although, the COVID-19 pandemic has led several researchers to screen plant-based products to use as repurposed drugs against SARS CoV2 [109]. Mass vaccination and strict implication of social protocols is the only way to save the human races in this critical situation. In this current condition, multifaceted approach of vaccine production is needed to meet the need. The discovery of CoVLP in this condition brings a new hope to increase the production in future. May many other plants derived vaccines will grab the market in future but low potential yield of protein than mammalian cell culture is a big question to be addressed. Allergic reactions against different plant derived products are rare but not completely absent. Hence, this will also be relevant with universal application of CoVLP (or other PDVs) in future. Finally, speedy transformation in SARS CoV-2 genome generate several novel variants those have the abilities to evade NAbs effect and capable of masking immune response. Detailed work has to be carried out to fix all these queries in future. Though the expansion of our natural drug needs much further consistency, still this is an immediate requirement for any future healthcare emergencies to mankind [109]. Even in such a situation, a multifaceted approach should be taken to find out a possible way out for sustainable management of such infections. In such situations only time will tell us the sustainable efficacy of CoVLP and all the vaccines against Covid 19 in future.

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