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Antiviral efficacy of medicinal plants against respiratory viruses: Respiratory Syncytial Virus (RSV) and Coronavirus (CoV) / COVID 19

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ABSTRACT

Respiratory syncytial virus (RSV) and Coronavirus disease (CoV) / Covid 19 are droplet infections caused by a group of RNA viruses infecting respiratory system and communicates through sneezing or physical contact. Due to the pandemic effect of Covid 19, it is essential to identify active components, which could be an active compound, which would be beneficial to the community such as respiratory syncytical virus (RSV) and coronavirus. 40 medicinal plants were screened basis the antiviral property pertaining to RNA virus and were dealt in detail to identify the plant which could be a source for developing a novel treatment for Respiratory Syncytical Virus and Covid 19. This review attempts to address the importance of herbs for the treatment of respiratory virus because rapid spread of the infection and preventing the use of allotropic medicine.

Keywords: Antiviral Medicinal plants, Covid 19, Corona virus, Respiratory syncytial virus, Viral inhibiting plants.

INTRODUCTION

Acute respiratory disease (ARD) are one among the most acute morbidities and mortalities in large proportion mortalities worldwide, among which acute viral respiratory tract infection accounts to 80 % [1] approximately. Among those, Influenza Virus, Respiratory Syncytial Virus (RSV), Coronavirus, Adenovirus, and Rhinovirus are some of the major viral pathogens [2]. These are highly pathogenic in nature and they emerging and reemerging coronaviruses in nature which cause epidemics or pandemics, such as the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), etc, and most recently, a novel coronavirus 2019 have posed great threat to global public health [3]. Among those, Respiratory syncytial virus (RSV) is a single-stranded RNA virus which belongs to the family Paramyxoviridae [4]. In temperate climates, the disease peaks in the winter [5]. The structure of RSV is that of a bilipid-layer-envelope surrounding a ribonucleoprotein core, with several membrane proteins, one of which functions in attachment to host cells, and one of which functions in fusion to host cells. There is only one serotype of RSV, but it is classified into two strains, "A" and "B" with differences consisting of variation in the structure, most especially the attachment protein [6]. Respiratory syncytial virus (RSV) will affect persons of all ages and is one of the major causes of serious Lower Respiratory Tract Infections in younger group of children. Children below the age group of one year are especially likely to develop lower respiratory involvement, with up to 40% of primary infections resulting in bronchiolitis [7]. Among those, coronavirus primarily targets the Human respiratory system, which is one of the major pathogens for respiratory system. Coronaviruses is from the family Orthocoronavirinae [8]. This group of viruses can cause diseases in mammals and birds. Four coronaviruses which are endemic to humans are HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1 and they are mainly associated with mild respiratory illnesses and Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and COVID-19 ((SARS-CoV-2) are present as emerging infections causing severe respiratory syndrome [9]. The genomic sequence of the COVID-19 demonstrates about 80% identity towards SARS-CoV and 50% to MERSCoV [10-11] and interestingly it has been observed that both SARS-CoV and MERS-CoV originate in bats [12].

Outbreaks of SARS-CoV and MERS-CoV are characterized and considered to be a great threat towards the public health. In November, 2002, the SARS-CoV emerged in China causing global anxiety as the outbreak rapidly spread, and by July, 2003, had resulted in over 8000 cases in 26 countries [13].

In 2012, a novel human coronavirus, which was termed as MERS-CoV, emerged in the Middle East to cause fatal human infections in three continents. This has a high fatality rate similar to SARS-CoV and its contagious ability to spread from person to person. Both viruses also have close relationships with bat coronaviruses [14-16]. During late December 2019, a cluster of patients were admitted to hospitals in the city of Wuhan Province, with an initial diagnosis of pneumonia of unknown etiology. Initially they were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, China [17-19]. On April 15, 2020, a total of 2,000,066 cases have been confirmed COVID-19 in 210 countries and territories around the world. The case fatality rate was calculated to be 6.3 % (126754 / 2,000,066) [19]. Despite this verity of the global health threat and economic burden posed by respiratory virus infection, there is no effective Covid 19 specific antiviral agents, which can manage or treat the virus. Though Ribavirin is and FDA approved drug of choice for RSV, it has its own limitations owing to several factors, including toxicity and difficulty of administration [20]. Chloroquine is effective in preventing the spread of corona virus in cell culture [21].

The conventional treatment for these disease are not yet identified and worldwide many rationale treatments are advocated along with documented side effects in patients [22]. With this rationale a suitable drug is warranted and plants with already established antiviral properties from Medicinal Plants could also be established to identify new molecules in the management of such Pandemic situation [23]. Many of those Medicinal plants are widely used in various traditional systems of medicine proving its benefit in successful management in various viral ailments [24]. Among those some are localized like Tibetan medicine and others, like Ayurveda, Siddha, Unani (AYUSH) medicines are also gaining popularity worldwide and are being increasingly used in various parts of the world [25].

Antiviral activity of herbal medicine against selected viruses

Many medicinal plants are being evaluated internationally, and are being advocated for strong antiviral activities. Among those some are being treat animals and people who suffer from viral infection [26]. Study demonstrates that during 1952 the search of antiviral agents development were started in Europe by the Boots drug company at Nottingham, England. They were the pioneres in examining the actions of 288 plants against influenza A virus in embryonated eggs. Among that they found that 12 of them suppressed virus multiplications [27]. During the past two to three decades, there are enumerable broad-based screening programmes initiated in different parts of the globe to evaluate the antiviral activity of medicinal plants both *in vitro* and *in vivo* assays [28].

Basis this the medicinal plants were screened basis their antiviral potential, basis which can inhibit the RNA virus, which could be of beneficial in developing a drug in the management of Covid 19 / RSV. The suggestive plants which can be further subjected for detailed evaluation 40 medicinal plants were found to be effective basis the antiviral properties and are tabulated in Table 1.

Table 1: Medicinal Plants demonstrating active antiviral properties against various viruses

S. No.	Botanical Name	Family Name	Antiviral benefit	Phytochemical composition	References
1	*Acacia modesta* Wall	Mimosoideae	HCV	4-hydroxy benzoic acid, palmitone, dihydroflavonols, catechins, chalones, anthocyanidins, Quercetin, kaempherol, terpenoids, essential oils, Lupeol, Betulin, αamyrin, pentacyclic triterpenes, βs itosterol, Neurolathyrogen and α-amino-β-oxalylaminopropionic	[29, 30]
2	*Allium sativum* L.	Alliaceae	H1N1, Influenza B, HSV 1, HSV 2	Ajoene, allyl alcohol, Diallyl disulphide, Diallyl disulfide (DADS), diallyl sulfide (DAS), Alliin Organo sulfur compounds like Allicin, Diallyl trisulfide, Ajoene	[31-33]
3	*Allium porrum* L.	Alliaceae	Adenovirus	Dipropyl disulfide and Dipropyl trisulfide quercetin, Zalcitabine, Allicin, Ribavirin	[34]
4	*Amaryllis belladonna* L.	Amaryllidaceae	RSV	Phenanthridine Lycorine Tazetine	[35]
5	*Andrographis paniculata* (Burm.f.) Nees	Acanthaceae	HIV	Andrographaloide, Neoandrographolide, 1,5-dimethyl-1,5-cyclooctadiene and 2-hydroxyethyl benzoate	[36, 37]
6	*Artemisia annua* L.	Asteraceae	CMV, HSV-1, HSV-2, EBV, HBV, HIV-1, HIV-2, HCV, Influenza virus	Artemisinin, Artesunate, Scopoletin	[38]
7	*Blumea laciniata* (Wall. ex Roxb.) DC.	Asteraceae	HSV-1 & RSV	Borneol, β-caryophyllene, Germacrene D, sabinene	[39, 40]
8	*Blumea laciniata* (Wall. ex Roxb.) DC.	Asteraceae	RSV	Protocatechuic acid, chrysoeriol, apigenin, 4-hydroxy-3,5-dimethoxbenzoic acid, scopolet.	[40, 41]
9	*Boerhavia diffusa* L.	Nyctaginaceae	RNA Virus	Punarnavine, 2-glucopyranose-4-hydroxy-5-[P-hydroxyphenyl]- propionyldiphenyl methane, steroids, triterpenoids, alkaloids and flavonoids.	[42,43]
10	*Bryonia alba* L.	Cucurbitaceae	Human CoV, H1N1,	Bryonicine, Saponarin, Vitexin, Isovitexin, lutonarin, Isoorientin, Glycosides 22-deoxocucurbitosides A and B, Arvenin IV	[36, 44]

11	*Camellia sinensis* (L.) Kuntze	Theaceae	Bovine CoV, HIV	Epigallocatechin gallate, Epigallocatechin, Epicatechin gallate, Epicatechin, Catechin	[45]
12	*Citrus reticulata* Blanco	Rutaceae	SARS-CoV-2, Dengue Virus serotypes 1-4, HBV, HCV	Tangeretin, Nobiletin, Hesperetin, Tangeretin, Naringenin, Nobiletin	[46]
13	*Curcuma zedoaria* (Christm.) Roscoe	Zingiberaceae	H1N1, Influenza B virus	Germacrone, Curcumin	[47-49]
14	*Echinacea purpurea* (L.) Moench	Asteraceae	H1N1, HSV-1, Influenza	Caffeic acid Cichoric acid alkylamides	[50, 51]
15	*Elephantopus scaber* L.	Asteraceae	RSV	3,4-dihydroxy benzaldehyde, p-coumaric acid, Vanillic acid, Syringic acid, Isovanillic acid, p-hydroxybenzoic acid, Ferulic acid, 3-methoxy-4-hydroxyl cinnamic aldehyde, Tricin 2-hydroxybenzolate acid	[40, 52]
16	*Eupatorium perfoliatum* L.	Asteraceae	H1N1, Influenza virus	Caffeic acid derivatives, Flavonoids, Sesquiterpene Lactones, Tannins.	[36]
17	*Galanthus nivalis* L.	Amaryllidaceae	SARS-CoV	Ethyl-a-D-glucopyranoside, Ethyl-a-D-ribo-side, Ethyl linoleate. *O* N^4-hydroxycytidine, *N*-(4-fluorophenylsulphonyl)-L-valyl-L-leucinal.	[53]
18	*Glycyrrhiza glabra* L.	Fabaceae	Kaposi's sarcoma-associated virus, HAV, HBV, CoV, Influenza virus, HIV-1, SARS	Glycyrrhizic acid, Glycyrrhizin, Glycyrrhetinic acid, Chalcone	[54, 55]
19	*Houttuynia cordata* Thunb.	Saururaceae	SARS-CoV	Houttuynoside A (1) and Houttuynamide A, Anthocyanins,	[56]
20	*Isatis indigotica* L.	Brassicaceae	H1N1, SARS-CoV, Foot-and-mouth disease, Rabies,	Epigoitrin, Indirubin	[57-61]
21	*Justicia adhatoda* L.	Acanthaceae	Influenza	Alkaloids, lignans, flavonoids, and terpenoids (Iridods, Diterpenoids, and Triterpenoids)	[36, 62]
22	*Laggera pterodonta* (DC.) Benth.	Asteraceae	H1N1, H9N2	Pterodontic acid	[63]
23	*Lindera aggregata* (Sims) Kosterm.	Lauraceae	SARS-CoV	Benzylisoquinoline alkaloids	[64]
24	*Lycoris radiata* (L'Her.) Herb.	Amaryllidaceae	SARS-CoV	Lycorine	[64]
25	*Mussaenda pubescens* Dryand	Rubiaceae	RSV	Triterpene esters, 3-palmitoyllupeol, 3-benzoylepi-betulin and β-sitosterol	[40, 65]
26	*Narcissus tazetta* L.	Amaryllidaceae	RSV, Influenza A (H1N1, H3N2, H5N1) and Influenza B virus, Japanese encephalitis, Dengue, Yellow Fever, HIV Type 1	Pseudolycorine, Galanthamine,1-hydroxygalanthine. Isoquinolone derivatives	[66]
27	*Ocimum tenuiflorum* L.	Lamiaceae	Orthomyxovirus, Paramyxovirus	Eugenol, Methyl eugenol, Cirsilineol, Circimaritin, Isothymusin, Apigenin, Rosameric acid, Terpenoid compounds	[36, 67]
28	*Phyllanthus amarus* Schum. & Thonn.	Euphorbiaceae	HBV	Lignins alkaloids, Hydrolysable tannins, Flavanoids, Ellagic acid, polyphenols.	[68, 69]
29	*Piper longum* L.	Piperaceae	HBV	Pentenoyl Piperidine, Piperolactam A, Pirrolidine, Turmerone, Piperine Demethoxycurcumin Bisdemethoxycurcumin, Glycosides longumosides A and B,	[70]
30	*Piper nigrum* L.	Piperaceae	Human Para influenza virus	Polyphenols, Piperidine, Piperine	[70, 71-74]
31	*Pyrrosia lingua* (Thunb.) Farw.	Polypodiaceae	SARS-CoV	Chlorogenic acid, Flavonoids	[75, 76]
32	*Rosmarinus officinalis* L.	Lamiaceae	hRSV, H1N1, Influenza B virus	Rosmarinic acid, Carnosol, Carnosic	[77-80]
33	*Schefflera heptaphylla* (L.)	Araliaceae	RSV, H1N1	Two highly active pure triterpenoids	[81]
34	*Schefflera heptaphylla* (L.)	Araliaceae	H1N1, CVB3, HSV-1	Dicaffeoylquinic acids	[82]

35	*Scrophularia scorodonia* L.	Scrophulariaceae	HSV-1, VSV, PV-1	Iridoids, Phenylpropanoids, Scorodioside, Phenolic acids, Flavonoids, Saponins.	[75, 83]
36	*Scutellaria indica* L.	Lamiaceae	RSV	Scutellarin, Luteolin, Naringenin, Wogonoside, Apigenin, Hispidulin, Wogonin, Chrysin	[40]
37	*Selaginella sinensis* (Desvaux) Spring	Selaginellaceae	RSV	Alkaloid, Phenolic compounds, Terpenoid, Amentoflavone	[84]
38	*Solanum nigrum* L.	Solanaceae	HCV	Alkaloids, Saponins, polyphenols, tannins, terpenoids, Solasolidine	[30, 85]
39	*Withania somnifera* (L.) Dunal	Solanaceae	H1N1	Alkaloids, Withasomnine, Visamine, Amino acids, Withaferin A	[86-88]
40	*Zingiber officinale* Roscoe	Zingiberaceae	HCV	6-gingerol, 6- paradols and 6-shogaol	[36, 85]

CMV – Cytomegaloviruses, CoV – Corona virus, CVB3 - Coxsackie B3, EBV - Epstein-Barr virus, HAV - Hepatitis A virus, HBV - Hepatitis B virus, HCV - Hepatitis C virus, HSV 1 - Herpes simplex virus 1,, HSV 2 - Herpes simplex virus 2, HIV - Human Immuno Deficiency Virus, HIV-1 - Human Immuno Deficiency Virus 1, HIV-2 - Human Immuno Deficiency Virus 2, hRSV – Human Orthopneumovirus, H1N1 -Influenza A virus, H9N2 - Avian influenza A virus, PV-1 - Poliovirus Type 1, RSV - Respiratory Syncytial Virus, SARS - Severe Acute Respiratory Syndrome, SARS-CoV - Severe Acute Respiratory Syndrome- Corona virus, VSV - Vesicular stomatitis virus,

From the table it is evident that the medicinal plant belongs to 22 families, which are found to be effective in antiviral property ingredients basis various studies carried out by various authors. Methanolic extract of *A. modesta* demonstrated a dose dependent inhibition against arachidonic acid induced platelet aggregation at a dose of 2.5 mg/ml provided IC50 was 0.80 mg/ml, which is beneficial in viral infections causing platelet aggregation. Further compounds like long chain alcohols [octacosanol, nonaeicosanol and hentriacontanol], hydrocarbons [hentriacontane and octacosane], 4-hydroxy benzoic acid, palmitone, dihydroflavonols, catechins, chalones, anthocyanidins, Quercetin, kaempherol, mono-, sesqui-, di, tri-, tetra-terpenoids, essential oils, phytosterols, Lupeol, Betulin, αamyrin, pentacyclic triterpenes, βsitosterol, Neurolathyrogen and α-amino-β-oxalylaminopropionic acid are being reported for its therapeutic benefit. RNA expression using acetone extract exhibiting antiviral activity against HCV at a concentration of 100 µg, when evaluated via real time RT-PCR [89].

Allium sativum has a strong inhibitory effect on virus multiplication, due to the flavonoid composition, which is also observed to block the formation of protein and genetic materials in the virus, which minimizes influenza A and B viral infections and also effective against cytomegalovirus, rhinovirus, HIV, herpes simplex virus 1, herpes simplex virus 2, viral pneumonia, and rotavirus. It is also observed to significantly minimize the occurrence of the common cold virus. Compounds like Ajoene, allyl alcohol, and diallyl disulfide are found effective against HIV infected cells. Organosulfur compounds like allicin, diallyl trisulfide, and ajoene are the main chemicals which impart antiviral property. Diallyl disulfide (DADS), diallyl sulfide (DAS), and alliin considerably reduced inflammation during dengue virus infection. Quercetin is well-known to act against the entry of the virus in the host cell. For example, Hemagglutinin and neuraminidase are envelope glycoproteins responsible for entry of the Influenza virus. This glycoprotein helps in attachment and membrane fusion of the virus to the host cell. The process of membrane fusion further facilitates the release of the viral ribonucleic proteins into the cytosol. Ribonucleic protein is then transported into the nucleus, which is the site for genome replication. In an interesting study, quercetin was observed to interact with Haemagglutinin protein, which resulted in the inhibition of virus entry into the cell. Similarly, quercetin reduced Enterovirus infection by blocking viral attachment stage of viral infection. It is also an inhibitory effect on quercetin on viral replication. Further, quercetin derivative have been proved to inhibit the translation of polio-virus RNA. The process of formation of multiple copies of polio-virus using the minus-RNA strand was blocked by quercetin. This was attributed to a reduction in viral RNA polymerase, an enzyme essential to initiate the formation of the viral genome. Similarly, quercetin was observed to inhibit the translation process of the hepatitis C virus. SARS-CoV protease, which is required for multiplication of the SARS virus, was inhibited in the presence of quercetin. It is also observed that quercetin derivatives can increase zinc uptake, which can inhibit RNA Polymerase. This will be beneficial in Covid 19 treatment since absorption of zinc will help to destroy the viral protein. Quercetin also has the potential to disrupt the activation of RNA polymerase by reducing the processing of polyprotein by Rhinovirus proteases. Therefore, the application of quercetin is efficient in enhancing the immune response in the host cells. It has been observed that during the replication process, RNA viruses, including Rhinovirus release protease which attack host cells by cleaving eukaryotic initiation factor (eIF)-4GI and eIF4GII. This ultimately blocks cap-dependent host cell protein synthesis and therefore facilitates viral multiplication. Quercetin has the ability to reduce the cleavage of eIFG4II and minimize the formation of viral capsid protein. This affects the replication of RhinoVirus replication. Similarly, allicin is the chemical present, which also can act against Virus. Allicin can pass through the phospholipid membrane of the cell and can further contribute in inhibiting viral multiplication. It can modulate the immune system in response to viral infection. It has been proved that it blocks the release of pro-inflammatory cytokines like Interleukine 6 (IL-6) and Tumor Necrosis Factor-α (TNF-α). Apart from inhibiting cytokines, allicin has a property to alter transcription of the nuclear factor kappa B (NF-κB) and DNA binding activity. It has a high amount of selenium and sulphur, which impart antioxidant effect by reacting with intracellular thiol compounds [90].

Chemical compounds like quercetin, zalcitabine, allicin, and ribavirin are found in *A. porrum*, which are effective against adenovirus. By MTT assay and PRD (Plaque reduction) methods exhibited the highest level of antiviral activity [91]. *A. belladona* has been identified with Twenty-six different Amaryllidaceae alkaloids, among those 1-*O*-acetylcaranine, 3-*O*-acetylhamayne, buphanamine were found to be effective in *in vitro* screening against parasitic protozoa *Plasmodium falciparum*) using methanol extract, which emphasis its benefit in Covid 19 with the report of beneficial of Chloroquine [92].

Andrographaloide *from A. paniculata* are active against HIV, selected pathogenic bacterial organism and possess immune-regulating activities. Alcoholic (90 %) extract demonstrated antiviral activity cell line A549 against Simian Retro Virus (SRV) by RT-PCR analysis, and was nontoxic and comparable with standard drug, Lamivudine, which could benefit in the management of Covid. Immuno-stimulant activity was described by its ability which induces lymphocytes cell proliferation using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Interestingly at a lower concentration of 1 µg/mL the extract stimulated 38 % of lymphocyte cell proliferation, which is quiet promising for further evaluation on Covid 19 [93].

Artemisinin derived from *A. annua*, which can be metabolized in the liver by microsomal cytochrome P 450 monooxygenase enzymes,

CYP2B6 and CYP3A4 is active against malaria and other viral diseases. It provides a good *in vitro* and *in vivo* evidence as antiviral against DNA viruses like cytomegaloviruses, human herpesvirus 6, herpes simplex viruses 1 and 2, Epstein-Barr virus and Hepatitis B virus. On the contrary, it was not potent against Polyomaviruses and papilloma viruses., RNA viruses such as HIV 1 and 2, hepatitis C virus, influenza virus etc. Further artesunate exerted synergistic inhibition of antiviral drugs clinically also exert cross-resistance to ganciclovir-resistant HCMV. Specific terpenoides and lignoids with activity against SARS [94]. Alcoholic extract was found to be effective against 2005 SARS-CoV. Like SARS-related coronavirus strain, SARS-CoV-2 is also member of the same subgenus and the similarities between these two virus, conclude that artemisinin derivatives could be beneficial drug for further evaluation [95].

Human RSV was inhibited by aqueous extract derived from the following plants namey, *B. laciniata, E. scaber, L. pterodonta, M. pubescens, S. octophylla* and *S. utellaria indica* [96]. Root extracts of *B. diffusa* was very potential against potato virus X. Further a purified glycoprotein (70 - 80% protein and 8–13% carbohydrates; Mol. Wt 16 – 20 kDa) from *B. diffusa* exhibited strong antimicrobial activity against RNA (ribonucleic acid) bacteriophages and also active against tobacco mosaic virus [97].

B. alba demonstrated a very good inhibitory effects against human coronavirus 229E and influenza A virus, which was mainly through interference in early stage of viral replication, such as absorption and penetration and attenuating aberrant pro-inflammatory cytokine production. These two viruses are cultured in human cells, human fetal lung fibroblasts MRC-5 and A549 cells, respectively [98].

The beneficial effects of *C. sinensis* are mainly attributed to the presence of a type of polyphenols known as catechins and formed by several isomers including (-) - epigallocatechin gallate (EGCG), (-) - epigallocatechin, (-) - epicatechin gallate, (-) -epicatechin, and (+) - catechin. The catechins have a wide range of antiviral activity against a variety of viruses that act by interfering with its replication cycle. Polyphenolic catechins from *C. sinensis* demonstrated potential inhibitors of HIV reverse transcriptase (RT). EGCG attenuates neuronal damage mediated by HIV infection in the presence of IFN-gamma both *in vitro* and *in vivo* and mildly reduce activated microgliosis and enhance neuron survival [99].

C. reticulata contains several methoxy flavonoids, such as hesperetin, tangeretin, naringenin, and nobiletin which perform low binding energy which are comparable with the reference ligands, lopinavir and nafamostat to the three essential receptors. Hesperetin is used in SARS-CoV-2 which binds with ACE2 receptor, Naringenin is beneficial against Dengue virus (DENV) serotypes 1-4, which Inhibits virus infection and replication Tangeretin in Hepatitis C virus (HCV) reduces HCV secretion in infected cells *in vitro* and *in vivo*. Nobiletin in Hepatitis B virus (HBV) Inhibits HBsAg production and HBV replication in *vitro* and *in vivo*. With this benefit this can be tried to combat beta coronavirus, included SARS-CoV-2 [100].

A major component of essential oil, Germacrone, extracted from the rhizome of *C. zedoaria,* inhibited influenza virual multiplication and was active against H1N1 and H3N2, Influenza A and B viruses, in a dose-dependent manner. On evaluation of the viral protein expression and RNA synthesis were decreased both in MDCK and A549 cell lines treated with germacrone. Further it also exhibited an inhibitory role on viral replication cycle and interestingly it also had an effective protection of mice from lethal infection and viral load / titres of the lung were markedly reduced. Germacrone and Oseltamivir in combination exhibited an additive effect on the inhibition of influenza viral infection, both *in vitro* and *in vivo*. Further Curcumin and Curcumol can also inhibit NF-κB and TGF-β_1/Smads signaling pathways [101].

Methanol and aqueous extracts derived from *E. purpurea* partially protected Influenza A virus and Herpes simplex virus type 1, Caffeic acid, a constituent prevented replication of vesicular stomatitis virus, a membrane containing RNA virus in a mouse cell line. Hexane root extract was active against herpes simplex virus, and was identified due to Cichoric acid present in it. The aqueous fraction containing caffeic acid derivatives and alkylamides showed impressive activity against HSV and influenza. Ethanol extract was as active against HSV [102].

β sesquiphellandrene, is one of the important sesquiterpene compounds showing anti-rhinoviral activity which is found in *E. scaber* Further phenolic acids and flavonoids are also isolated from various fractions. Out of which 3,4-dihydroxy benzaldehyde, p-coumaric acid, vanillic acid, syringic acid, isovanillic acid, p-hydroxybenzoic acid, ferulic acid, 3-methoxy-4-hydroxyl cinnamic aldehyde, tricin, syringic acid, E-3-(3-ethoxy-4-hydroxyphenyl) acrylic acid, 2-hydroxybenzolate acid, are phenolic compounds, which were purified by ethanol fraction. Towards the activity against RSV a new dicaffeoyl derivative, 1α, 2β-O-dicaffeoylcyclopentan-3β-ol showed *in vitro* inhibition which was quite promising Similarly methyl esters of four dicaffeoylquinic acids 4, 5 –di-O-caffeoylquinic acid, 3, 4, di-O-caffeoylquinic acid also possessed strong activity against RSV activity with a marked $IC_{50,}$ which was lower than that of ribavirin [103], which could be subjected for further evaluation.

Hydroalcoholic extracts from the aerial parts of *E. perfoliatum* inhibited the growth of H1N1 and Influenza virus with an inhibitory concentration (IC50) of 7µg/mL and 14µg/mL, and a selectivity index (SI) of 52 and 26, respectively, and the antiviral activity might be due to polyphenolic compounds which protect cells from IAV infection by inhibiting viral attachment to the host cells. Hence it appears to be a promising compound for the pandemic evaluation for covid 19 [104].

Compounds from *G. nivalis* namely *O* N^4-hydroxycytidine, calpain inhibitors (*N*-(4-fluorophenylsulphonyl)-L-valyl-L-leucinal), aglycon derivatives and mannose-specific plant lectins inhibit SARS-CoV replication with an EC_{50} of 1 µM and selectivity index of ≥100. The effect was comparable with drugs like Vancomycin, Eremomycin and Teicoplanin [105].

Glycyrrhizic acid from *Glycyrrhiza glabra* demonstrated inhibition on the replication of SARS-CoV *in vivo* and also increased interferon-γ production. Kaposi's sarcoma-associated viral elimination via apoptosis and anti-viral effects are also being described against DNA and RNA viruses, like Hepatitis A virus, Hepatitis B virus, Coronavirus, Influenza virus, HIV-1 etc. [106].

H. cordata is a promising source for many flavonoid molecules including anthocyanins, flavones and flavanones. Aqueous extract increases the proliferation of mouse splenic lymphocytes significantly and dose-dependently and increased the proportion of CD4(+) and CD8(+) T cells. It also possessed significant inhibitory effects on SARS-CoV 3C-like protease (3CL (pro)) and RNA-dependent RNA polymerase (RdRp), which are very beneficial on the drug development [107].

Epigoitrin, a natural alkaloid from *I. indigotica*, protects against influenza infection and also relieves stress. Further interestingly it also elevated mitochondria antiviral signaling (MAVS) protein expression and subsequently increased the production of IFN-β and interferon inducible transmembrane 3 (IFITM3), thereby helping to fight viral infections, which could assist in reducing the susceptibility to influenza virus via mitochondrial antiviral signaling [108].

In vitro antiviral effect of *J. adhatoda* methanolic and aqueous extracts demonstrated inhibition of Influenza virus by Hemagglutination assay with 100% at the concentration of 10 and 5mg/ml respectively with an inhibition of 33% and 16.67% n the simultaneous assay. These results suggest the strong basis against influenza virus, which inhibits viral replication, attachment, and can be further evaluated as viral prophylaxis [109].

In vitro antiviral activity of pterodontic acid, derived from *L. pterodonta*, inhibits Influenza A viral replication by blocking nuclear export of viral RNP complexes, and attenuating the inflammatory response by inhibiting and activation by NF-κB pathway. In addition, in H1N1 it significantly attenuates the expression of pro-inflammatory molecules like IL-6, MIP-1β, MCP-1, and IP-10 and also downregulate expression of cytokines and chemokines which are induced by the Avian Influenza A virus (H9N2) [110].

L. aggregata exhibited a significant inhibition against SARS-CoV strain with an EC50 of 2.4 ± 0.2 and CC50 values range from 886.6 ± 35.0 µg/ml. [111]. Similarly, Lycorine isolated from *Lycoris radiata* L. initially used for certain other indication, showed strong anti-SARS-CoV activity.

Pseudolycorine, Galanthamine, and 11-hydroxygalanthine are isolated from *N. tazetta*. Isoquinolone derivatives were active against RNA containing flavivirous namely Japanese encephalitis, Dengue and Yellow Fever. It is also effective against Lentivirus namely Human Immuno Deficiency virus Type 1 [113] (Bjarne Gabrielsen, *et. al.,* 1992).

In vitro cytotoxicity with aqueous extract of *O. tenuiflorum* revealed moderate inhibitory activity Orthomyxovirus, whereas alcohol extract demonstrated moderate inhibitory activity against Paramyxovirus, Methanol and chloroform extracts showed significant inhibition of orthomyxovirus. Further crude extract and terpenoid compounds showed significant virucidal activity in comparison with virus control and maintained its effect for longer period of time of up to 72 h post-incubation, suggesting antiviral properties to control viral infections [114].

P. amarus exerts antiviral effect by interacting with transcription factors C/EBP α and β and also HBV enhancer 1thereby inhibiting the HBV polymerase activity and mRNA transcription. *In vitro* study of *P. amarus* at a dosage of 1 mg/ml^{-1} concentration was inhibiting the secretion of HBsAg. This disruption against HBV polymerase activity, mRNA transcription, and replication supports its role as an antiviral agent. Extracts were found active against both HBV and WHV surface antigens namely HBsAg and WHsAg which were inhibited by their corresponding antibodies. In addition it also inhibited, WHV DNA-polymerase activity *in vitro*, in a dose-dependent manner. This activity could be attenuated due to inhibition of Immune complexes and virus replication, which are normally restricted to Liver parenchymal cells. Flavonoid compound ellagic acid present in *P. amarus* inhibits immunotolerance against hepatitis B virus e-antigen [115]. Therapeutically HBV infections can be halved by *P. amarus* towards the spreading of virus and improving the immune complexes which could restore to normal liver in its cellular functions.

Alcohol extract of *P. longum* possessed *in vitro*. Activity against HBV. Six new compounds, two new glycosides longumosides A and B and two new amide alkaloids erythro-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]-piperidine, threo-1-[1-oxo-9(3,4-methylenedioxyphenyl)-8,9-dihydroxy-2E-nonenyl]-piperidine, as well as two compounds 3β,4α-dihydroxy-2-piperidinone, 5,6-dihydro-2(1H)-pyridinone, were also able to demonstrate antiviral activity *in vitro*. Piperine was able to demonstrate remarkable inhibiton against HBV and also against the secretion of HBsAg (Hepatitis B virus surface antigen) and HBeAg (Hepatitis B virus e antigen). Interestingly their Selectivity Index (SI) values were 15.7 and 16.8, respectively, which is also well established as a drug to improve bioavailability [116].

Anti-viral activity of *P. nigrum* in chloroform extract showed higher activity than methanolic extract against Human Para influenza virus on HeLa cell line and was due to the presence of Piperidine [117]. It also contains Piperine and the need to incorporate this compound into formulations and adjunctive therapy is to enhance the bioavailability of various (chemo) therapeutic drugs [118]. *P. lingua* exhibited significant inhibition effects on virus-induced CPE against SARS-CoV and a dose dependent antiviral activity was determined in serial dilutions of compounds [119].

Marked antiviral activity by Amantadine was revealed from the methanol extract of *R. officinalis* which inhibited the replication of enterovirus and was effective than Amantadine, a common antiviral agent with higher therapeutic index and greater safety [96]. Further various compounds were also tested on the chemical compounds from *R. officinalis*, out of which carnosic acid displayed a potent anti-hRSV activity and was illustrating effect against both A- and B-type viruses. It suppressed the replication of hRSV and suppressed viral gene expression without inducing type-I interferon production or affecting cell viability, suggesting that it can directly affect viral factors, in a concentration-dependent manner. Carnosic acid after injection of 8 hours also in a time course analysis demonstrated an effective blockage on hRSV gene expression suggesting that it can inhibit the replication of hRSV directly [120].

Interestingly *S. heptaphylla* exhibited potent antiviral activity against RSV. Fractionation and isolation from *S. heptaphylla* identified two triterpenoids, namely 3*α*-hydroxylup-20(29)-ene-23,28-dioic acid and 3-*epi*-betulinic acid 3-*O*-sulfate. These two triterpenoids demonstrated a wide range of antiviral avtivity agaist RSV by cytopathic effect (CPE) reduction method with an IC_{50} value of 6.25 µg/mL. Further for Influenza A (H1N1) virus, Coxsackie B3 (Cox B3) virus and Herpes simplex virus type 1 (HSV-1) respectively the IC_{50} values were 25 to 31.3, 12.5 to 20 and 18.8 and 25 µg/mL, respectively. Newer compounds like three caffeoylquinic acid derivatives, namely 3-O-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid and 3,5-di-O-caffeoylquinic acid also were effective against RSV with of 2.33µM and 1.16 µM respectively by plaque reduction assay. Dicaffeoylquinic acids against HEp-2 cells exhibited minimal cytotoxicity with a median cytotoxic concentration (CC50) higher than 1000 µM and maximal non-cytotoxic concentration (MNCC) of the two dicaffeoylquinic acids were about 96.7 µM, suggesting its non-cytotoxicity against RSV. But it was not having antiviral activity against influenza A (Flu A), Coxsackie B3 (Cox B3), and Herpes simplex type one (HSV-1) viruses. Moreover, they could not inhibit RSV attachment to host cells, thereby can not protect HEp-2 cells from RSV infection, which further reinforce that hose compounds exerted their anti-RSV effects by inhibiting virus cell fusion in early stage, and at the end stage by inhibiting cell to cell fusion of RSV replication cycle [121].

S. scorodonia was effective in *in vitro* against certain strains of virus namely, Herpes simplex type I (HSV-1), Vesicular stomatitis virus (VSV) and Poliovirus type 1, where Scorodioside showed 47.8 % inhibition at 500 µ/ml [122].

Amentoflavone and three other flavonoids isolated from the ethanol extract of *S. sinensis*. illustrated activity against RSV, with an IC50 of 5.5 µ/ml. It is also interesting that the contents of amentoflavone in nine species of *Selaginella* were it was high in *S. sinensis* and the content was 1.13% [123].

Methanol and chloroform extracts of *S. nigrum* (SN) exhibited a marked inhibition of Hepatitis C Virus (HCV) against HCV NS3 protease by transfecting HCV NS3 protease plasmid into liver cells. Among those two extracts, chloroform extract in a dose dependent manner was able to decrease the expression or function of HCV NS3 protease and on the contrary GAPDH remained constant, which can be advocated with interferon as a better option to treat chronic HCV [124].

Withaferin A an active constituent of *W. somnifera* can attenuate the neuraminidase of H1N1 influenza. Further alcoholic extract is potential and increase the total WBC count and increase the bone marrow cellularity, which is very vital in the pandemic of viral infection to improve the immunity [125].

Z. officinale extract *in vitro* in HepG2 cell line (Hepatocellular carcinoma) was effective against HCV. Viral replications were

inhibited which were detected by amplification of viral RNA segments and further inhibited viral replication inside the HCV-infected HepG2 cells with an inhibitory dose of 100µg/ml. *Z. officinale*, rhizome are reported to contain pungent vanillyl ketones. These including [6]-gingerol and [6]-paradol, compounds which are being credited to have marked therapeutic and preventive health benefits, including anti-cancer and antiviral properties [126].

World Health Organization (WHO), has clearly stated on usage of traditional medicine as a primary health care need as first step medication states that 80% of people from India, 85% from Burma and 90% from Bangladesh are found to use herbal based products as their primary stage of health care management. Basis this many novel comounds are being idenfitied from those palnts and are also subjected to various antiviral studies, worldwide. Understanding this scenario, in this review, we are evaluating various approaches currently available or under development for antiviral medicine which can be recommended for the management / control and treatment for RSV and Covid 19. Nowadays, the risk of epidemic and pandemic spread of virus is panicking and is spreading among continents and countries, very quickly. Though there are viral drugs available, due to the pandemic situation of Covid 19, no confirmed drug is available and with the existing antiviral and symptomatic treatment is advocated. Due to mutagenic activity of viral ailments, they are found to be difficult to control and there are still relatively few drugs for treatment of viral diseases [127]. Ribavirin is one such drug approved for the treatment of Respiratory Syncytial Virus which are beneficial for children against bronchiolitis [128]. As on the current prevailing scenario, there is no specific antiviral therapy available for covid 19. Since with the emergence of SARS-CoV which has triggered a largest thrust of antiviral research for corona, on this basis a detailed review against antivirals specific to SARS-CoV could provide a lead to identify novel therapy for the humans [129]. Though currently many antiviral agents which were effective against SARS, like Ribavirin, Lopinavir-Ritonavir, and Oseltamivir, were not showing any progressive proof against Covid 19 [130] provided the general strategies which are advocated include bed rest and supportive treatment, including antiviral therapy [131], antibiotics, immunomodulating therapy and nutritional supplements like zinc and Vitamin C [132, 133]. Another study demonstrated that Remdesivir and Chloroquine are highly effective in the control of corona infection *in vitro*, but cinically there are many challenges [21, 134]. Chloroquine is effective in preventing the spread of corona virus in cell culture. Favorable inhibition of virus spread was observed when the cells were either treated with chloroquine prior to or after corona infection. Synthetic drugs which are being prescribed for viral infections are seldom proving unsatisfactory results and limited narrow spectrum of activity, toxicity and resist antiviral strains [135, 136]. The medicinal plants dealt with are well established towards their antiviral activity and in specific to RNA virus, which can be further screened and could be a possible solution to treat Covid 19 and also can be coprescribed along with the existing which required further evaluation and also, could reduce the dosage by its bioavailability, which is an well-established fact.

Medicinal plants were screened and evaluated basis their antiviral property with special emphasis to Respiratory syncytial virus and RNA virus in order to identify the probable medicinal plants, which could be a right candidate in controlling the Covid 19. Basis this, the study was carried out and interestingly, *A. belladonna, B. laciniata, E. scaber, S. indica, S. sinensis* and *S. heptaphylla, M. pubescens* were effective against Respiratory syncytial virus. *A. paniculata, A. annua and Glycyrrhiza glabra* were effective against Human Immuno Deficiency Virus. *A. modesta, A. annua, C. reticulata, S. nigrum* and *Z. officinale* were found to be effective in treating Hepatis C. Influenza was found to be inhibited by *Allium sativum, A. annua, B. alba, C. sinensis, C. zeodaria, E. purpurea, E. perfoliatum, I.indigotica, Piper nigrum, S. heptaphylla, Rosmarinus officinalis, Schefflera heptaphylla, Glycyrrhiza glabra, Justicia adathoda, Laggera pterodonta Withania somnifera.* Sesquiterpene Lactones from *E. perfoliatum* is effective against H1N1 virus. Similarly, *A. porrum* against Adenovirus and Purnavine from *B. diffusa* and Scorodioside, from *S. scorodonia* are effective against RNA virus. It is also interesting to note that lutonarin, Isoorientin, from *B. alba*, Epicatechin, Catechin from *C. sinensis* and Glycyrrhizin and Glycyrrhizic acid from *G. glabra* are found to be effective in Human Coronavirus, which we can also revisit in finding a novel candidate to fight the pandemic. Nobiletin, from *C. reticulata*, Houttuynoside A and Houttuynamide from *H. cordata*, Epigoitrin, Indirubin from *I. indigotica*, Benzylisoquinoline alkaloids from *L. aggregata*, Lycorine from *L. radiata*, Glucopyranoside from *G. nivalis* Glycyrrhizin from *Glycyrrhiza glabra* and Chlorogenic acid from *P. lingua* are also proven to be effective against SARS-CoV, which is further supporting to evaluate and identify new molecules in the management of viral disease. These observations clearly elucidate that the viral property of those plants could be suggestive in selecting a novel compound and further evaluating, which can through in-depth knowledge, which could help in identifying the right candidate against the viral pandemic.

CONCLUSION

Communicable diseases are very common in spreading the pandemic of Covid 19 and can be a concern to all age groups worldwide. Ever since ages, most of the viral diseases are being considered as intractable to selective antiviral drug, the reason behind is that it has replicative cycle of the virus which are being assumed to be closely interwoven with normal cell metabolism, further it attempts to suppress virus reproduction which could severely harm or doomed to kill the uninfected cell as well. The current review substantiates the usage of herbal drugs and compounds which are mainly having antiviral property with special activity against RNA virus and plants in general are considered to be with lesser side effects, relatively low cost and additional important advantage of their easy availability The current review demonstrates medicinal plants, and compounds like Lycorine, Sabinene, Apigenin, Naringenin, Andrographoloide, Artesunate, Scopoletin, Glycyrrhizin, Carnosic acid and similar active compounds which were identified from the selected list of plants screened in this study, which could help in developing a novel drug in the management of Respiratory syncytial virus and Covid 19, which is the need of the hour.

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