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Antiviral activity of plant and herbal extracts against air borne viruses

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ABSTRACT

Airborne diseases are becoming a great threat to human kind due to its highly infectious mode of transmission. Medicinal plants have been traditionally used to cure many pathogenic diseases including diseases caused by viruses. Plants contain bioactive compounds which are capable of inhibiting the growth of most pathogens and also show antiviral activity. Since these plants are of natural origin, these biochemicals possess minimum toxicity and their possibility of causing allergies to an individual is also low. Biochemicals showing antiviral properties have been found in various parts of the plants like roots, stem, leaves, flowers, etc. This review focuses on the antiviral properties of plants against air borne viruses - Influenza, Rhino virus, SARS, HSV and RSV, which mainly affect the respiratory tract.

Keywords: *Airborne Diseases, Active Components, Herbs, Antiviral Agents*

1. INTRODUCTION

An airborne disorder is any disease which is caused by a microorganism, transmitted through the air. Many clinically important airborne diseases are caused by bacteria, viruses and fungi [1]. These organisms may be transmitted through sneezing, coughing, spraying of liquids, spread of dust, talking, or any activity that results in the generation of aerosolized particles [2].

The spread of infectious diseases is of global concern because of many social and economic reasons. It is seen that seasonal influenza kills 200–500 thousand people annually. In 2009-2010, influenza A (H1N1) had caused 17,000 deaths worldwide, many among whom were healthy adults [4,5]. In 2002-2003, severe acute respiratory syndrome (SARS) killed more than 700 people and spread into 37 countries causing a cost of $18 billion in Asia [6].

Due to advancements in the molecular biology in the last 20 years, unique features in the viral structures and replication cycles have been identified as potential targets [10]. Viruses have a unique strategy at each replication step beginning with entering the host cell, transcription, translation, assembly of viral genome/proteins, and the cellular release of progeny virions [11]. The airborne viral diseases mostly cause severe acute respiratory tract infections (SARIs) and can be RNA viruses or DNA viruses. Many drugs are being used to treat these viral infections. Some of the common drugs used are Pleconaril, Ribavirin, Zanamivir, etc [7,8]. Pleconaril prevents viral replication by inhibiting viral uncoating and blocking viral attachment to host cell receptors, thus interrupting the infection cycle. Zanamivir competitively inhibits influenza virus neuraminidase (NA). Ribavirin is a nucleoside analogue whose mechanisms of action are poorly understood and probably not the same for all viruses; however, its ability to alter nucleotide pools and the packaging of mRNA appears important[9]. Due to development of viral resistance towards current antiviral agents, there is a need for new effective compounds against viral infections.

Traditionally, plant derived medicines have been used to treat many of the viral infections in Ayurveda, Traditional Chinese medicines, etc. The antiviral activities of extracts from grape, apple, strawberry and other fruit juices where reported to show activity against HSV, poliovirus type 1, coxsackievirus B5 and echovirus, back in 1970s.In 1995, 12 out of 100 British Colombian medicinal plants, showed significant antiviral effect against corona viruses, respiratory syncytial virus (RSV), para-influenza virus type 3 (PI3), herpesvirus type 1 (HSV-1) and retavirus. In 1998, out of 800 Chinese herbal medicines detected for antiviral activities against HIV, more than 100 plants exhibited anti-HIV activities. Most of these studies used aqueous or ethanolic extraxts of these plants. Recently research has been done to identify compounds in plants which are capable of being extracted to be used as antiviral agents [10].

This review discusses about the antiviral compounds present in plant extracts which show antiviral properties against some of the common airborne viral infections.

2. COMMON ANTIVIRAL COMPOUNDS IN PLANTS AND THEIR EXTRACTION PROCESS

The broad-spectrum antiviral nature of plant extracts could be associated with a single phytochemical, or a number of different plant constituents. The common Indian herbs which are antiviral and are effective against many viruses, these are aloevera, Onion, Garlic, sweet basil, ginger, etc. Aloe-emodin and de-glycosylated aloin extracted from aloevera inactivated the viruses, it prevents virus adsorption and replication. It suggests that aloe-emodin is directly virucidal to enveloped viruses [14]. Organosulfur compounds present in onion and garlic are responsible for affecting virus cycle at different stages[15]. Quercetin is one of the organosulfur compounds present in onion [16]. Quercetin can affect entry and attachment of the Enterovirus and Influenza virus on the host cell [17,18]. Organosulfur compounds like allicin, diallyl trisulphide and ajoene are main chemicals which has antiviral property to garlic [19]. These compounds also have the ability to inhibit RNA polymerase, hence inhibit viral replication and also alter signalling pathways [20]. The replication has been affected by organosulfur compounds in a wide range of viruses like polio-virus, SARS virus, and HIV.

Ocimum basilicum (OB), also known as sweet basil, is a well-known medicinal herb. In the present study, extracts and purified components of OB were used to identify possible antiviral activities against DNA viruses. The results show that crude aqueous and ethanolic extracts of basil and selected purified components, namely apigenin, linalool and ursolic acid, exhibit a broad spectrum of antiviral activity [21]. Fresh rhizome of *Z. officinale* (Ginger) has been proven with an antiviral effect against many viruses. Allicin is an active ingredient present in ginger which consists of anti-influenza cytokines. Hence, *Z. officinale* is effective as an antiviral agent against influenza A-H1N1[22]. Essential oil of *Z. officinale* is affected against Herpes simplex virus type 2 (HSV-2) mainly before adsorption probably by interacting with the viral envelope [23].

Preparation of herbal extract is a crucial step in achieving high quality outcome. This involves determination and extraction of quality and quantity of the active component before performing the efficacy test. The first step involved in the preparation of herbal extract is the selection of solvent. The type of plant, part of plant to be extracted, nature of the bioactive compounds, and the availability of solvent are the factors which determine the choice of solvent [24-26]. After selection of solvent, appropriate extraction methods are used for obtaining bioactive compound. Some of the extraction methods include maceration, digestion, decoction, infusion, percolation, Soxhlet extraction, superficial extraction, ultrasound-assisted, and microwave-assisted extractions. After extraction, photochemical screening takes place [24,27]. Phytochemical screenings are preliminary tests conducted to detect the presence of both primary and secondary metabolites in an extract [24]. The next step involves separation and purification of the extracted component. This can be done using various chromatographic techniques such as paper chromatography, thin-layer chromatography, gas chromatography, and high-performance liquid chromatography [28].

3. HUMAN RHINOVIRUS (HRV)

Human rhinoviruses (HRVs) are the most common cause of the common cold. They are small about 27 nm belonging to the Enterovirus genus of Picornaviridae family [31]. Although they were thought to cause minor upper respiratory tract illness, they are now associated with other conditions like chronic pulmonary disease, asthma development, severe bronchiolitis in infants and children and fatal pneumonia in elderly and immunocompromised adults [32-36]. 3 species of HRV are identified, namely, HRV A, HRV B, HRV C which consists of over 150 antigenically distinct types [40].

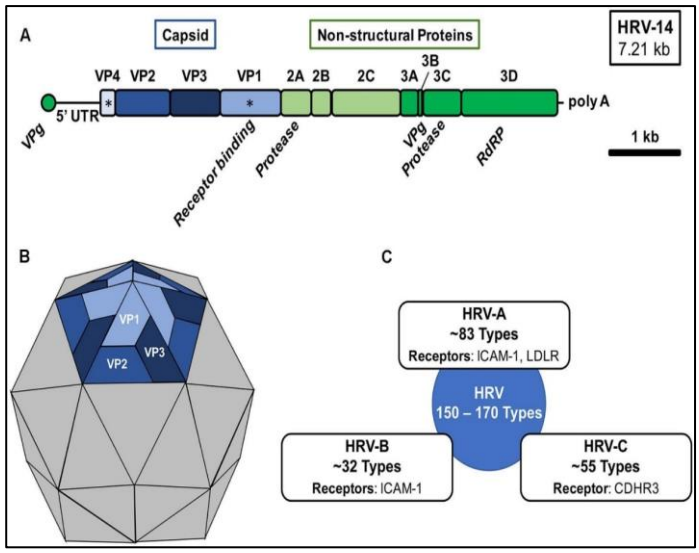

Fig. 1: Human rhinovirus genomic organization, virion structure, and species [40].

3.1 Structure

HRVs are positive-sense, single-stranded-RNA (ssRNA) viruses of approximately 7,200 bp. The viral genome consists of a single gene and its proteins are translated as a single polypeptide, which is then cleaved by virally encoded proteases to produce 11 proteins. The viral capsid containing four proteins; VP1, VP2, VP3, and VP4; encases the RNA genome, while the other non-structural proteins are involved in viral genome replication and assembly [31,37,38,40].

The VP1, VP2, and VP3 proteins are responsible for the virus' antigenic diversity, while VP4 anchors the RNA core to the capsid [39,40]. There are 60 copies each of the four capsid proteins, which gives the virion an icosahedral structure, with a canyon in VP1 that serves as the site of attachment to cell surface receptors [41-43]. More than 90% of known HRV serotypes, the "major group," utilize the cell surface receptor intercellular adhesion molecule 1 (ICAM-1), while the "minor group" attaches to and enters cells via the low-density lipoprotein receptor (LDLR) [44-46]. Some of the major-group HRVs also use heparan sulfate as an additional receptor [47-49].

3.2 Potential targets

There is currently no approved treatment for rhinovirus infections. A few synthetic drugs like Pleconaril, Itraconazole and Niclosamide have shown some activity against the virus by binding to the capsid, protease, inhibition of oxysterol-binding protein and inhibiting viral entry by neutralizing the acidic endosome, respectively [51-54].

3.3 Herbs active against HRV

Some of the plants which are already proved to show activity against Rhinovirus are ginger, garlic, echinacea and liliaceae[55-57]. The dried rhizomes of *Zingiber officinale* contains many sesquiterpenes which have shown antirhinoviral activity with beta-sesquiphellandrene being the most active [56].

Quercetin, which is an active component present in onion, also has the potential to disrupt the activation of RNA polymerase by reducing the processing of polyprotein by Rhinovirus proteases.[20] Echinacea have also shown antiviral activity against HRV with the potential targets being capsid proteins and replication [55].

4. SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Severe acute respiratory syndrome (SARS) emerged as a global and regional health threat in 2002-2003, causing approximately 800 deaths [58]. A cooperative worldwide effort rapidly led to the identification of the disease-causing virus as a novel SARS coronavirus (CoV). At present, the newly identified SARS-CoV-2 has caused a large number of deaths with a huge number of confirmed cases worldwide, posing a serious threat to public health [59].

4.1 Structure

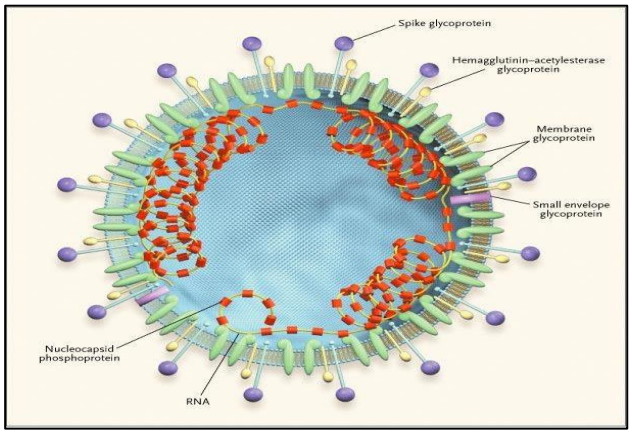

Fig. 2: Structure of SARS Coronavirus Virion (Adopted from NEJM sources-perspective SARS Associated coronavirus 2003) [72]

The structure of SARS-related coronavirus is characteristic of the coronavirus family as a whole. The size of the virus particles is in the range 80–90 nm. The viruses are large, pleomorphic and spherical particles with bulbous surface projections[60]. The envelope of virus consists of a lipid bilayer where the membrane (M), envelope (E) and spike (S) proteins are anchored[61]. M protein is the most abundant structural protein in SARS virus and it also defines the shape of the viral envelope [62].

It is the central organiser for assembly of virus, interacting with all other major coronaviral structural proteins. E protein is the smallest of the major structural proteins, it is abundantly expressed inside the infected cell during replication, but only a small portion is incorporated into the virion envelope [63].

The spike proteins provide the virus with its bulbous surface projections of virus. The spike protein's interaction with its complement host cell receptor, angiotensin-converting enzyme 2 (ACE2) receptor is central in determining the tissue tropism, infectivity, and species range of the virus[64]. There is the nucleocapsid inside the envelope, which is formed from multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous manner. The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host [65]. RNA-dependent RNA polymerase (RdRp) regulates viral replication hence making it essential for the virus survival [66].

4.2 Possible targets

The possible target against which the antiviral drugs or components can act are RNA-dependent RNA polymerase, Receptor ACE2 (angiotensin-converting enzyme 2), Non-structural proteins such as 3-chymotrypsin-like protease also known as 3C-like protease ($3CL^{pro}$), papain-like protease, Spike protein, Helicase and other Miscellaneous protein such as Interferon alpha and beta[67-71].

4.3 Herbs active against the SARS virus

There are many proven herbs against these targets of SARS virus. Herbs such as Cimicifuga rhizoma, Broussonetia papyrifera, Green tea, Cinnamomi Cortex, Ginger rhizome, Licorice roots, Lycoris radiata, Isatis indigotica and Torreya nucifera were found to have antiviral activity against SARS virus. The table 1 shows the active component and inhibiting action of each herbs.

Table 1: Antiviral herbs against SARS virus

S no.	Effective herbs	Active components (AC)	Inhibiting action on viral proteins	References
1	*Cimicifuga rhizoma*	Ferulic and isoferulic acids	Inhibits CoV production via reductions in viral RNA synthesis and viral protein expression.	[73,74]
2	*Broussonetia papyrifera*	Polyphenols	Inhibition of cysteine proteases	[75]
3	Green tea	Epigallocatechin gallate, epicatechingallate and gallocatechin-3-gallate	Interaction with catalytic residues of major protease (Mpro)	[76]
4	Cinnamomi Cortex	Procyanidins and butanol extract	Inhibits the internalization of TfR indicating the interference of clathrin-dependent endocytosis.	[77]
5	Ginger rhizome	6-gingerol	Highest binding to Viral protease, RNA binding protein and Spike protein.	[78]
6	Licorice roots	Glycyrrhizin	It affects cellular signalling pathways such as protein kinase C; casein kinase II; and transcription factors such as activator protein1 and nuclear factor κB	[79,80]
7	*Lycoris radiata*	Lycorine	Modulates host factors instead of directly targeting viral factors.	[81,82]
8	*Isatis indigotica*	Phenolic compounds	SARS 3CL protease inhibitor	[84]
		myricetin, scutellarein	non-structural protein 13 (nsP13) helicase	[83]
9	*Torreya nucifera*	Amentoflavone	SARS 3CL protease inhibitor	[85]

5. HUMAN RESPIRATORY SYNCYTIAL VIRUS (RSV)

Human respiratory syncytial virus (RSV) is one of the most common viruses which infects children and elderly. The most common clinical scenario caused due to RSV infection is an upper respiratory infection, bronchiolitis in young children, a lower respiratory tract illness with small airway obstruction, and in rare cases can progress to pneumonia, respiratory failure, apnea, and death[86-88].Human respiratory syncytial viruses are found within the genus Orthopneumovirus, family Pneumoviridae, order Mononegavirales[90].

5.1 Structure

Structurally, RSV is an enveloped, spherical virus with a diameter of approximately 150 nm. Filamentous species have also been observed which are of several micrometres in length. Both spherical and filamentous virions are infectious [91]. RSV is a single stranded, negative strand, membrane bound RNA virus. The RNA genome codes for key internal structural proteins(matrix protein [M] and nucleoprotein [N]), proteins required for a functional polymerase complex (phosphoprotein [P] and polymerase [L]), non-structural proteins involved in evasion of the innate immune response (NS-1 and NS-2), externally exposed transmembrane glycoproteins (small hydrophobic protein [SH], glycoprotein [G], and fusion protein [F]), and the regulatory M2 proteins (M2-1 antitermination protein and M2-2, involved in transcription/replication regulation)[89,92-94].

5.2 Possible targets

Main focus during the development of therapeutics for a particular viral infection is targeting various surface proteins, enzymes that are involved in the replication, attachment and fusion of virus. The RSV genome encodes many proteins, out of which the fusion (F) protein is the most common target. The F protein is the viral surface protein that binds to the respiratory epithelial surface and it's binding is capable of inhibiting the virus from fusing and entering the respiratory epithelial cell [95]. Some of the fusion inhibitors are in the phase II clinical trial [97,98]. RSV nucleocapsid is another common target. The nucleocapsid contains 5 different proteins which are the nucleo (N)-protein, the phospho (P)-protein, the large polymerase protein (L-protein or RNA polymerase), and regulatory proteins called M2-1 and M2-2[95]. These are efficient mediators of RSV transcription and replication processes.[96] Inhibition of nucleocapsid mRNA also indirectly targets the nucleocapsid of RSV by preventing its formation and eventually inhibiting viral replication[96].One therapeutic drug is such that it is a nucleoside analogue that targets the RSV polymerase and inhibits replication by chain termination [95,90]. One of the novel mechanisms have emerged from in vitro testing which targets the third surface protein, the SH-protein, which most likely is involved in RSV pathogenicity rather than replication [99].

5.3 Herbs active against RSV

Herbs that show antiviral activity against RSV are *Cimicifuga foetida, Terminalia chebula, Plantago asiatica, Clerodendrum trichotomum,* echinacea, *Blumea laciniata, Elephantopus scaber, Laggera pterodonta, Mussaenda pubescens, Schefflera octophylla, Scutellaria indica and Selaginella sinensis.* The table 2 shows the active component and inhibiting action of each herbs.

Table 2: Antiviral herbs against RSV

S no.	Effective herbs	Active components (AC)	Inhibiting action on virus	References
1	*Cimicifuga foetida*	Cimicifugin	Inhibits RSV attachment and internalization and stimulates epithelial cells to secrete IFN-β to counteract viral infection.	[100, 101]
2	*Terminalia chebula*	hydrolyzable tannins: chebulagic acid and punicalagin	Inactivate RSV particles and also block viral entry-related events, including binding and fusion.	[102]
3	*Plantago asiatica*	Phenylethanoid glycosides	The active compound significantly reduced RSV replication, RSV gene transcription, RSV protein synthesis, RSV-induced cell death and also blocked syncytia formation.	[103, 104]
4	*Clerodendrum trichotomum*			
5	Echinacea	Caffeic acid derivatives, alkylamides and certain types of polysaccharides	Inhibits the membrane proteins as potential targets. Also stimulates the secretion of pro-inflammatory cytokines.	[105]

6. INFLUENZA VIRUS

Influenza viruses belong to the Orthomyxoviridae family, and are classified as A, B, and Thogotovirus. Influenza A viruses circulate in several species, including humans, horses and related animals, swine, and birds, while type B affects only humans. Influenza caused by types A and B is indistinguishable; in contrast, type C causes mild respiratory symptoms. The genomes of all influenza viruses are composed of eight single-stranded RNA segments. These RNAs are negative-sense molecules, meaning that they must be copied into positive-sense molecules in order to direct the production of proteins [106].

6.1 Structure

Influenza A is defined by its surface proteins hemagglutinin (HA) and neuraminidase (NA) of which there are 18 HA and 11 NA. Influenza B viruses are categorized into two lineages (B/Yamagata and B/Victoria). The surface of both A and B viruses contains HA, NA, and the M2 proteins.

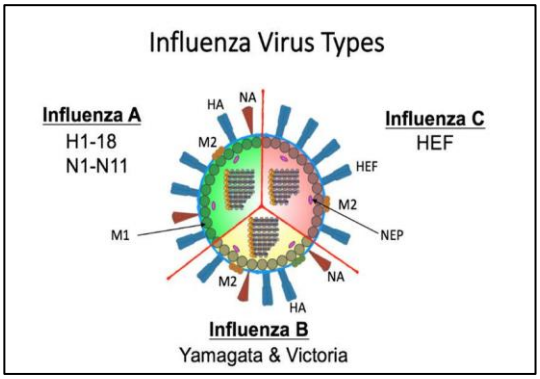

Fig. 3: Schematic of Influenza A, B and C virus structure [113]

Internally, A and B viruses both have eight genomic segments. Influenza C viruses have only one external spike protein (HEF) which functions both in viral entry and egress and an ion channel M2 protein. Type C viruses have 7 internal genomic segments. M1 protein line the envelope internally adjacent nuclear export protein (NEP) proteins for type A, B, and C viruses. The genomic segments are encapsidated by the NP protein and form the ribonucleocapsid with the polymerase proteins Polymerase acidic (PA), Polymerase basic 1 (PB1), and Polymerase basic 2 (PB2) [110].

6.2 Possible Targets

Target for drugs that prevent virion release:

M2 Ion Channel Inhibitors: The antiviral component act by binding to a specific pocket on the viral M2 protein, stabilizing its closed conformation and preventing the virus from releasing the ribonucleoprotein complex to the cytoplasm after fusion, thus halting the viral cycle [108].

Neuraminidase Inhibitors**:** The antiviral drugs prevent the cleavage of sialic acid, inhibiting virion release and preventing the dissemination of new viral particles to other cells.

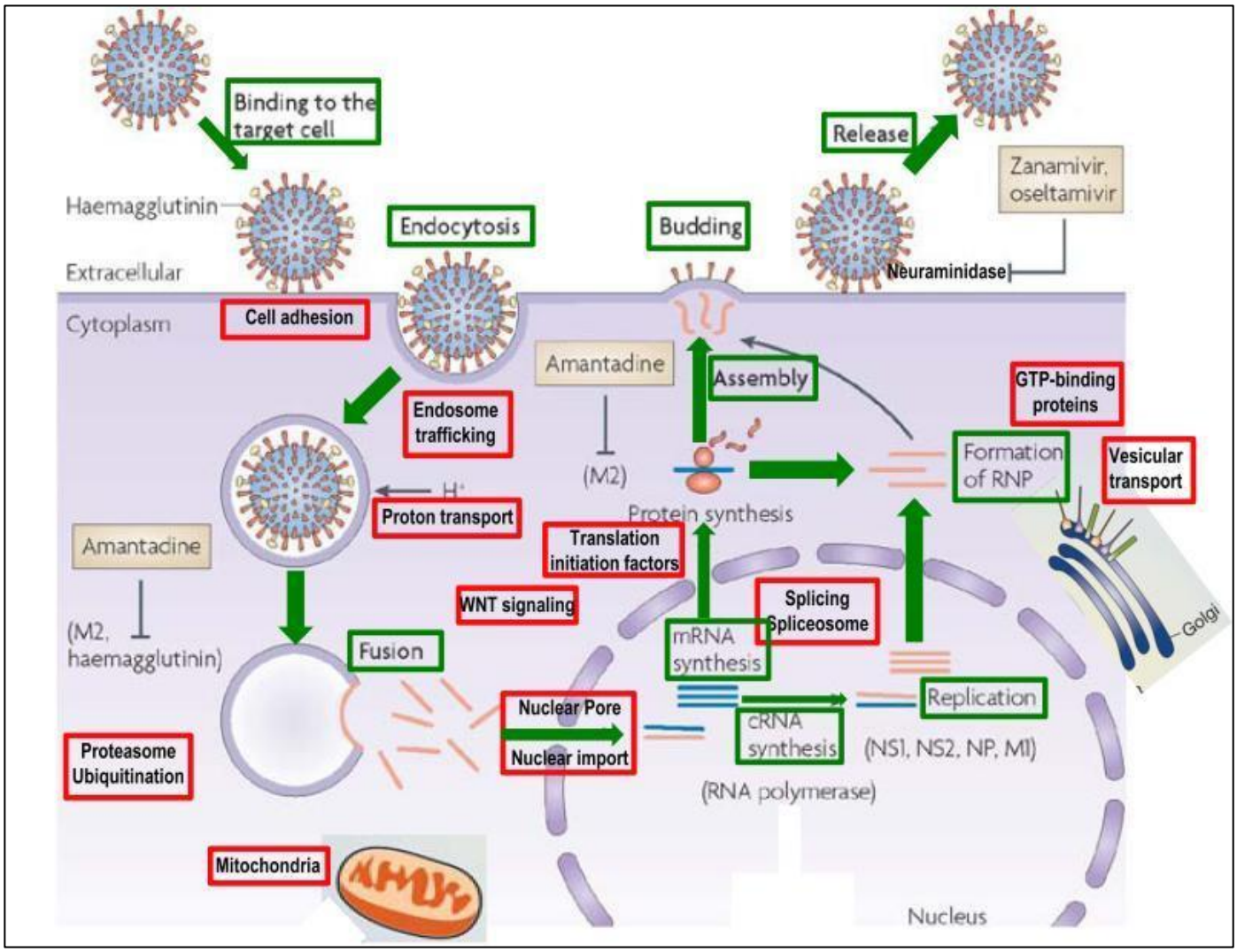

Fig. 4*:* Cellular targets for anti-influenza drugs in the context of the replication cycle of influenza virus [110]Targets for drugs that attack viral components

Inhibitors of Viral Binding and Fusion: Inhibit influenza A virus entry by binding to the HA stem region, interfering with viral fusion. Viral Polymerase Inhibitors: Viral polymerase is a protein that remains highly conserved among the various influenza strains, making it a therapeutic target of interest [108]. Nucleoprotein Inhibitors: Nucleoprotein binds to viral RNA and forms part of the ribonucleoprotein complex. It is essential for the synthesis of viral RNA and also participates in the nuclear export of viral ribonucleoproteins and in cytoplasmic trafficking [108].

6.4 Herbs active against the virus

Table 3 shows the herbs along with their active components and part used which are active against the various influenza viruses.

Table 3: Antiviral herbs against various types of Influenza

S no.	Herb	Part Used	Dose	Active Component	Activity	References
1.	Cinnamon bark	bark	120 mg/day	Cinnamic aldehyde, tanin	Influenza A	[109,115]
2.	Apricot kernel	seed	-	Amygdalin		[109,124]
3.	Licorice	roots	Tincture 3-5 ml	Glycyrrhizin	H2N2, H5N1,	[109,116]

					influenza A	
4.	*Punica granatum*	fruit	-	Polyphenols	Influenza A (H1N1)	[109,117]
5.	Berries extract	berry	-			
6.	*Clinacanthus siamensis*	Leaf	-	-	INFLUENZA	[109,118] [109,119]
7.	*Psidium guajava Linn.* (guava tea)	leaf	-	tannins	H1N1, H5N1.	[109,120]
8.	*Epimedium koreanum*	Aerial part	-	quercetin	H1N1, H5N2, H7N3	[109,121, 123]
9.	*Scutellaria baicalensis*	Stem and leaves	-	flavone	H1N1, H3N2	[109,122, 124]

7. HERPES SIMPLEX VIRUS TYPE 1 (HSV-1)

All the known human herpesviruses are grouped under 3 herpes sub-families α-, β-, and γ-herpesviruses based on their

biological properties. Herpes simplex virus type 1 (HSV-1, causes cold sores) and type 2 (HSV-2, causes genital herpes) and varicella-zoster virus (causes chickenpox and shingles) come under α-herpesvirus subfamily and is capable of establishing lifelong latent infections within the peripheral nervous systems of their hosts [125].

7.1 Structure

Herpes has genome up-to 240kbp and they are double stranded DNA viruses. The genetic component of the virus in enclosed in a complex T = 16 icosahedral capsid that is 1,250 Å in diameter [126]. The nuclear capsid is surrounded by a proteinaceous layer called as the tegument, which in turn is surrounded by a protein-containing lipid bilayer known as the envelope [126].

The spikes present on the envelope of herpes simplex virus (HSV) contains several glycoproteins. It contains in its envelope at least 11 glycoproteins, 5 of which function in viral entry. Glycoproteins gB, gC, gD, gH, gE are known to be present on the envelope out of which gB, gC and gD are seen to be present in highest concentration. The penetration of attached virus into the cell is done by the glycoprotein gB. It is also essential for virus infectivity. Glycoprotein D (gD) is essential for virus infectivity and is responsible for binding to cellular membrane proteins and subsequently promoting fusion between the virus envelope and the cell [127]. Two proteins which bind to HSV-1 gD have been identified. The protein responsible for virus entry into human lymphoid cells is termed as the herpesvirus entry mediator A (HveA). The protein responsible for the entry of virus into mucosal epithelial cells is termed as the poliovirus receptor-related protein 1 (HveC) [128].

The capsid shell is made of four distinct proteins that lie on a T = 16 icosahedral lattices. The major capsid protein, VP5 (149 kDa), makes up both capsomere structures, the pentons and hexons, which contain five and six VP5 monomers, respectively [129]. The capsid-associated tegument complex (CATC—previously termed CCSC and CVSC), is composed of pUL17, pUL25, and pUL36 and binds to the triplexes and hexons. pUL25 plays an important role in retention of DNA within the nucleocapsid. Moreover, pUL25 is essential for genome release [126]. The virus encodes variety of genes and produces different polypeptides and later uses these polypeptides for majority of functions such as entry into the cell, regulation of gene expression, replication and packaging of viral DNA into virions [130].

7.2 Possible targets

Antiviral therapy is the targeting different enzymes, fusion inhibitors, glycoprotein-receptor interactions to inhibit the initial steps of viral entry, attachment, and fusion. The replication of the viral structure is the most common target for the therapeutic drugs used against HSV-1 as replication is highly ordered process and any changes in the process leads to unfavourable results [131].

HSV-1 DNA Replication inhibitors: DNA polymerase plays an important role in the DNA synthesis of HSV-1 virus and thus becoming an important target for the development of antiviral drugs. The polymerase enzyme is sensitive for proper base pairing which approves for the use of nucleoside and pyrophosphate analogs as anti-HSV-1 agents [131]. Thus, the termination of the chain extension can be achieved by integration of either of the two analogs into the DNA chain. Acyclovir (ACV) which is one of the oldest antiviral drugs functions as a substrate for viral DNA polymerase, competing with deoxyguanosine triphosphate for incorporation into the elongation chain [131].

HSV-1 Fusion inhibitors: The envelope containing glycoproteins present on the exterior structure of HSV1 are also targeted which block the fusion of the virus with the cell membrane [131]. Docosanol is the drug which uses this mechanism [131].

Glycoprotein receptor targeting: Potential role in HSV-1 therapy**:** Glycoproteins gB, gD, gH and gL are essential for the coordination of attachment and fusion of the virus with the cell [131]. The amino acid sequence of gD is highly sequenced and therefore glycoprotein targeted therapeutic can prove to be highly beneficial. Glycoproteins gB, gD, gH-gL are ideal targets for the therapeutic process due to their unique properties. This target is yet to be clinically marketed for individuals with HSV-1 [131].

Another class of potential antivirals are Hydrolyzable tannins without specific glycoprotein-receptor targets. They inhibit the interactions HSV-1 glycoproteins and the cell surface glycosaminolgycans they normally bind to [131].

7.3 Herbs active against the virus

A large number of compounds extracted from medicinal plants are said to be effective against viruses. Naturally occurring biochemicals such as phenolics, polyphenols, terpenes (e.g., mono-, di-, tri-), flavonoids, sugar-containing compounds are found to be promising anti-herpetic agents [132]. Table 4 shows some of the medicinal plants effective in destroying HSV-1 virus.

Table 4: Antiviral herbs using HSV-1

Plant	Active Component	Mode of Action	Inhibitory Concentration	Selectivity index	References
Podophyllum peltatum	podophyllotoxin	Not Available	Not Available	Not Available	[133]
Ocimum Basilicum	Ursolic acid	Not Available	IC50 = 6.6 mg/L	SI = 15.2	[21]
Ceratostigma willmottianum	Not Available	Inhibits viral absorption mechanism, HSV-1 gD gene replication and also HSV-1 gD gene transcription	IC50 = 29.46 mg/L	SI = 36.56	[134]
Melaleuca alternifolia	Isoborneol	Inhibits the glycosylation of viral glycoproteins gB without hampering the host cell glycosylation process	Not Available	Not Available	[135]
Solanum torvum	Torvanol A, torvoside H	Not Available	IC50 (Torvanol A) = 9.6 µg/ml, IC50 (torvoside H) = 23.2 µg/ml	Not Available	[136]
Moras alba root	Mulberroside C	Not Available	IC50=75.4 µg/ml	Not Available	[137]
Phyllanthus urinaria	1,3,4,6-tetra-O-galloyl-beta-D-glucose	Not Available	IC50 = 19.2 ± 4.0 µM	Not Available	[138]
Lamiaceae Species (runella, peppermint, rosemary and thyme)	Rosmarinic acid, apigenin- and luteolin-derivatives	Ethanolic extracts affected the virus prior to and during adsorption and also blocked viral attachment to the host	IC50 = 0.05–0.82 µg/ml	Not Available	[139]
Melissa officinalis	Monoterpenaldehydes citral a, citral b and citronellal	Melissa oil inhibited the virus before adsorption and prior to infection of the cell.	plaque formation was significantly reduced by 98.8% for HSV1	High selectivity index	[140]
Swertia chirata	Not Available	Not Available	Not Available	Not Available	[141]
Limonium sinense	Samarangenin B	Inhibits HSV-1 α gene expression, including expression of the ICP0 and ICP4 genes by blocking β transcripts such as DNA polymerase mRNA, and by arresting HSV-1 DNA synthesis and structural protein expression in Vero cells	IC50 = 25.0 ± 8.7 µg/ml.	SI = 13.2	[142]
Melia azedarach L	Tetranortriterpenoid 1-cinnamoyl-3,11-dihydroxymeliacarpin (CDM)	CDM modulates the NF-κB signaling pathway by slowing down its activation in HSV-1 infected conjunctival cells which leads to the accumulation of p65 NF-κB subunit in the cytoplasm of uninfected treated Vero cells	Not Available	Not Available	[143]
Prunella vulgaris	Lignin–carbohydrate complex (PPS-2b)	Interferes with the binding and penetration of the virus in the vero cells by blocking it.	Not Available	Not Available	[144]
Scoparia dulcis L.	Scrophulariaceae	Inhibits the viral replication but it does not show a direct virucidal effect on the virus	Not Available	SI = 16.7	[145]
Tanacetum vulgare	Spiroketalenol ether derivative	Involves blocking the virus entry and arresting the synthesis of HSV-1 gC.	Not Available	Not Available	[146]

Apart from these herbs some of the common medicinal herbs can also be effective in the treatment. These common herbs help in boosting one's body immunity against these viruses.

8. IMMUNITY BOOSTING PLANTS

Many plants have been used in Ayurveda which helps to boost our immune system and held fight microbial infections [147]. Tulsi which is known as "The queen of herbs in Ayurveda" has shown to boost defenses against infective threats by enhancing immune responses in nonstressed and stressed animals [148-153]. Garlic contains numerous compounds that have the potential to influence immunity. Immune cells, especially innate immune cells, are responsible for the inflammation necessary to kill pathogens [154]. Curcumin, from turmeric also helps to improve the immune function by inducing synthesis of glutathione in alveolar epithelial cells and antioxidants generally suppressing the production of IL- in bronchial epithelial cells [155]. Quercetin, which is found in onions, is efficient in enhancing the immune response in the host cells [156]. Roots (mostly), stems, leaves of ginseng, and their extracts have been used for maintaining immune homeostasis and enhancing resistance to illness or microbial attacks through effects on immune system [157].

Elderberry is rich in flavonoids and boosts the immune system to fight against flu, cold and other respiratory infections. The presence of one of the antioxidant compounds in the ginger root have potential anti-inflammatory as well immune-boosting characteristics, which helps in enhancing the normal metabolic activities in the human body, fight against infections and toxins to shield against harmful effects of bacteria, virus and any other diseases [158]. Other plant extracts such as licorice, Echinacea have also shown to boost immunity due to the polysaccharides present in them [155]. The antiviral effect of ginger is observed in RSV infection, this is due to decreasing plaque formation in respiratory mucosal cell lines. High concentration of *Z. officinale* could stimulate mucosal cells to secrete IFN-β which are responsible in counteracting viral infections by reducing viral attachment and internalization [159].

9. CONCLUSIONS AND DISCUSSION

According to the current study, HRV is being treated using synthetic drugs. Not much research has been done on plants showing activity against Rhino virus. However, it is observed that garlic which are some basic herbs included in everyday diet have also shown some anti-rhinoviral activity and can be further assessed for determining their active components. Ginger has also shown activity against SARS along with 8 other effective herbs with known active components and possible targets. Echinacea is seen to show activity against RSV along with HRV with certain types of polysaccharides as their active component which needs to be researched upon.

Out of the 9 herbs mentioned, which show antiviral activity against Influenza viruses, licorice is the most effective showing activity against 3 strains of influenza and also upon SARS virus with Glycyrrhizin being the common active component. Common herbs such as tulsi has shown activity against influenza as well as HSV. Other than tulsi, a collection of 14 different plants show anti-herptic activity capable of destroying the HSV virus. As a result, it is obvious to conclude that plants continue to be a rich source of compounds with anti-herpetic activity. It is also important to study mechanism of action of different plants with virucidal activity which will help in the development of new therapeutics. Antiviral component extraction from plants can prove to be of great importance and has a good scope in research. Knowledge of the active compounds in plants along with their possible targets and mode of action can help in preparing a mixture of herbal extracts which can be converted into antiviral aerosols and sprays; provided the activity of the compounds is by inhibiting or killing the virus in the respiratory tract.

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