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Exploring medicinal plants as promising remedies for Respiratory Syncytial Virus infections

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Abstract

Viral infections have had a significant impact on people's health, and their frequency has increased in recent decades. Among these, the Respiratory Syncytial Virus (RSV) is most significant. It is responsible for severe acute illness, mainly in young infants. It poses a high risk for immunosuppressed individuals. It is an enveloped virus with a single-stranded, negative-sense RNA genome belonging to the family Paramyxoviridae. No safe vaccine is available for RSV. Ribavirin can be used to treat RSV, but it has serious side effects. Medicinal plants are well-known sources of therapeutic agents for the treatment of viral and other infections. Evaluation of medicinal plants is crucial for developing and synthesizing drugs for different therapeutic targets. Antiviral potential of several phytocompounds isolated from medicinal plants has been thoroughly investigated. This review intends to seek awareness of preventive and therapeutic measures of medicinal plants against RSV illness, which is a persistent cause of death in infants globally. The main focus is on the antiviral activities of various plant extracts and their natural compounds against RSV. Experimental results, including their CC_{50}, IC_{50}, and SI values, were collected from the literature and discussed for their anti-RSV activity to assess the potential activity of compounds. Various medicinal plants include *Rosmarinus officinalis, Cimicifuga foetida, Panax ginseng, Coptidis rhizoma, Glycyrrhiza uralensis, flos Lonicerae, Nauclea latifolia, Plantago asiatica, Clerodendrum trichomum, Schefflera heptophyla, Lophatherum gracile, Citrus reticulata, Blumea laciniata, Markhamia lutea, Euphorbia jolkinii, Vigna radiata, Scutelaria indica, Sargassum fusiforme,* etc., which have been used to *in vitro* or *in vivo* anti-RSV activity.

Keywords: Respiratory Syncytial Virus; Acute Respiratory Illness; Paramyxoviridae; Bronchiolitis; Cytotoxicity Concentration; Inhibitory Concentration

1. Introduction

The Respiratory Syncytial Virus (RSV) is a widespread virus responsible for severe respiratory tract infection [1]. According to a global report in 2015, the research found that approximately 33.1 million cases of acute lower tract diseases, hospitalization of 3.2 million persons, and 59600 deaths of children under five years of age have been recorded. RSV causes a predominantly high risk to infants under 1 year of age. Significant symptoms during viral infection are cold, cough, low-grade fever, coryza, reduced feeding efficiency, and difficulty breathing. Clinical symptom severity, initiated from day 3-5, reaches its peak [2]. Institute of Health Metrics and Evaluation (Washington) evaluated the mortality rate in 2010 as 2.34 lakh deaths, 25% of all acute lower respiratory infections, and 0.36 thousand deaths of infants in 2015 [3]. In temperate climates, RSV infections occur mainly during winter epidemics from November to February, but 40% of cases occur in December or January [4,5]. Seventy percent of children get RSV infection within their first year of life, and nearly all children are infected by the completion of 2 years. Globally, RSV is responsible for around 33 million incidents of acute lower respiratory tract infections during early childhood, and according to reports

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in 2015, it is estimated that almost 0.1 million deaths of children from RSV-associated sickness [6]. Acute Respiratory Infections (ARI) kill approximately 1.9 million people each year in developing countries, accounting for about 20% of all deaths in India [7]. RSV was first isolated in 1956 from a captive chimpanzee [8]. Initially, it was named Chimpanzee Coryza Agent, but its molecular and biochemical classification persisted fundamentally for a long time due to insufficient knowledge, physical instability, and pleomorphism. Researchers began a comprehensive analysis of its genome and molecular sequencing in 1981. RSV was identified as a human pathogen and discovered in infants with lower respiratory illness. RSV commonly causes pneumonia, asthma, wheezing, bronchiolitis, and chronic obstructive pulmonary disease in people of all ages, but mainly affects infants and leads to high morbidity and mortality. It also involves some immune-weakened adults [9, 10, 11]. RSV is widespread globally, but apart from this, it has a substantial effect on newborns in low-income countries where the fatality rate is high [12].

1.1. Structure of RSV

RSV is a non-segmented, enveloped, negative-strand RNA genome, as shown in **Figure 1**. Its genome contains 10 genes, which encode 11 proteins [13]**.**

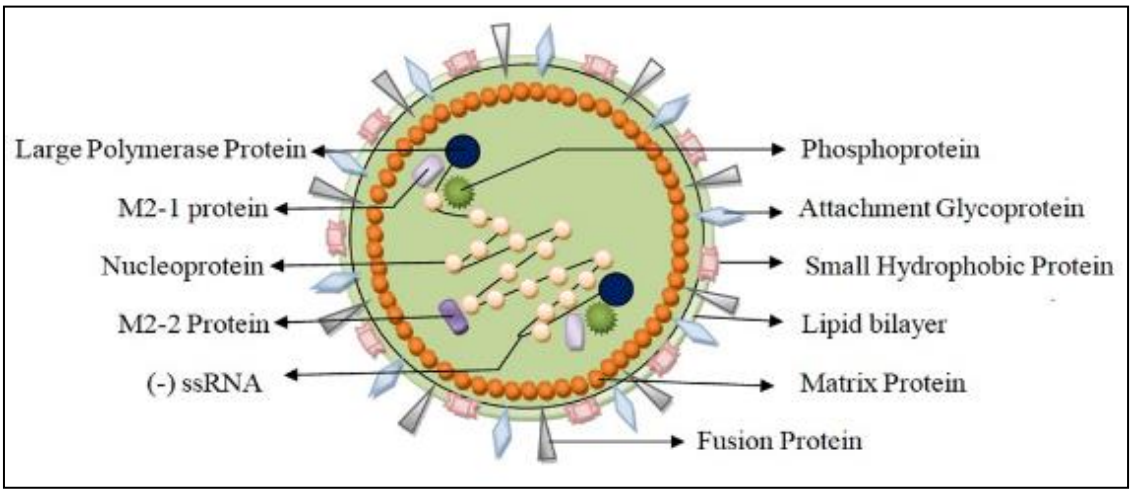

Figure 1 Structure of RSV

1.1.1. Signs and Symptoms

After an RSV infection, symptoms may range from a mild cold to severe breathing problems [14].

1.2. Transmission of RSV

RSV infection spreads from one person to another through respiratory droplets from coughing and sneezing, or by touching contaminated surfaces **(Figure 2)**. RSV persists on the non-porous surface at room temperature for three to thirty hours [14]**.** The virus enters the host body and replicates in the upper respiratory tract, the nasopharynx. After that, it infects the epithelial cells and spreads throughout the lungs. The pathophysiology of RSV involves epithelial cell damage and necrosis. Sometimes, it is associated with inflammation and the proliferation of host cells. For the RSV infection, the incubation period is generally from 4-5 days [15].

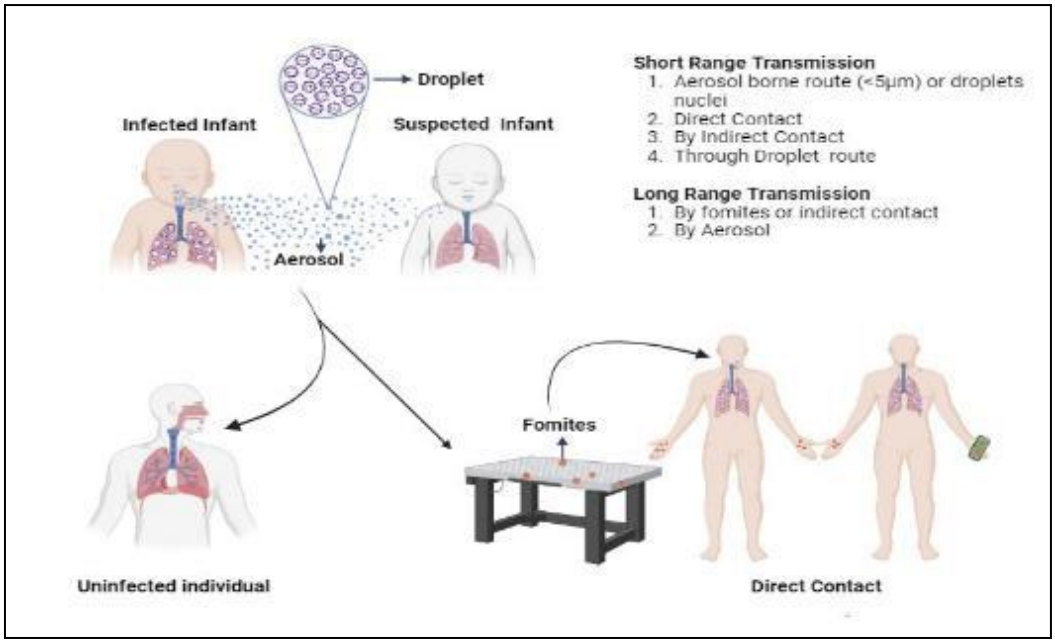

Figure 2 Transmission route of RSV

1.3. Diagnostic Techniques for RSV

For the detection of RSV, there are several techniques, including viral isolation in tissue culture, immunological methods (like ELISA, direct and indirect immunofluorescence staining), molecular assays (Reverse Transcription PCR, Real-Time PCR, and RT-LAMP), and chromatographic and optical immunoassays, primarily RT-PCR used for the detection of viral nucleic acid [16].

1.3.1. Prevention and Treatment

Administration of humanized monoclonal antibodies is prophylactic for high-risk young children. Recently, no licensed vaccines have been available for RSV protection. Since Sept 2016, more than 40 vaccines have been preclinically developed; over 15 are in clinical trials [17]. The formalin-inactivated RSV vaccine was developed in the 1960s and failed due to low antibody affinity and avidity for neutralizing epitopes, as well as its poor ability to activate TLRs on B cells. The subunit vaccine Novavax was developed in February 2016 and completed its phase II trial. It includes the transplacental transfer of maternal antibodies in baboons, but the Novavax vaccine fails to protect the infants. Two antivirals for RSV are palivizumab for prophylaxis and Ribavirin for treatment in high-risk children. However, palivizumab offers no benefit for active infection, and Ribavirin has some side effects and limited efficacy [18].

1.4. Medicinal plants as therapeutic agents

Novel antiviral medication development is challenging due to the rapid variation in viral strains. Viral resistance to antiviral medications is becoming more common; virus persistence remains a challenge that must be overcome. The emergence of viral resistance to therapeutic agents increased the need for bio-compounds for the treatment of viral infections. Traditional herbal remedies offer a promising therapeutic alternative, particularly when specific vaccines or antiviral medications are unavailable. There is growing interest in ethnobotanical therapies, which are generally considered safer than synthetic pharmaceuticals and often demonstrate versatile therapeutic effects [19]. Therefore, medicinal plants could be used as a source of antiviral therapy. Organic extracts of plants and their compound proved to be equally beneficial. Table 1 lists some typical literature-based medicinal plants that showed antiviral activity against RSV.

Table 1 Literature-based medicinal plants contain anti-RSV activity by using different assays

Medicinal Plant	Family	Some Important Phytochemicals	Assays used	Antiviral effect	Reference
Rosmarinus officinalis	Lamiaceae	Rosmarinic acid, Camphor, Caffeic acid, Ursolic acid, Betulinic acid, Carnosic acid, and Carnosol	MTT assay, Plaque-reducing assay, qRT-PCR	Inhibition of viral replication	[20, 21]
Cimicifuga foetida	Ranunculaceae	25-O-acetylcimigenol xyloside, Norvisnagin, Isoferulic acid, 25-anhydrocimigenol-3-O-b-xyloside, Acetylacteol-3-O-arabinoside, Cimicinol, Cimicifol, Foetidinol, Angelicain, Isoimperatorin 15a-hydroxyfoetidinol-3-O-b-xyloside, and Cimifugin	XTT assay, Plaque-reducing assay	Inhibited the cytopathic effects of RSV	[22, 23]
Panax ginseng	Araliaceae	Ginsenoside, Phenolic compounds, Saponins, and Polysaccharides	Cell viability assay, Immunoplaque assay, RT-PCR	Inhibits RSV-induced ROS formation in A549 cells	[24]
Coptidis rhizoma	Ranunculaceae	Berberine, Coptisine, Jaterorrhizine, Palmatine, Coptisine, Epiberberine, Worenine, and Magnoflorine	Real-time PCR, Detection of cytokine by the Immunoblot assay	Inhibition of viral replication	[25, 26]
Laminaria japonica	Laminariaceae	Phlorotannins, Fucoidans, and Fucoxanthin	Detection of IRF3 by Western blot assay, CCK-8 Cytotoxicity Assay, RSV inhibition assay	Extract of *L. Japonica* up-regulates IRF3 signaling mediated interferon- α production for inhibiting the activity of RSV	[27]
Glycyrrhiza uralensis	Leguminosae	Glycyrrhizin, 18β-GA, Saponins, Liquiritigenin, Flavonoid C-glycosides, Prenylated Dihydrostilbene, Bisepoxylignans, and Gallates	XTT-assay Plaque-reducing assay, qRT-PCR, RT-PCR, ELISA	Inhibit viral penetration	[28, 29]
Lonicerae flos	Caprifoliaceae	3,5-Dicaffeoylquinic acid, Cynaroside, Rutin, Hyperoside, Iridoids, Chlorogenic acid, Caffeic acid	Cytotoxicity assay, *In Vivo* Assay, CPE assay	Anti-RSV activity	[30, 31]
Aesculus hippocastanum	Hippocastanaceae	α and β escin, Coumarins (esculin, esculetin, scopoletin, and fraxetin), Flavonoids, Phytosterol	Cytopathic effect assay, *In-vivo* assay	Virucidal and Antiviral Activities against RSV	[32, 33]
Nauclea latifolia	Rubiaceae	Tramadol, Latifoliamide, Naucleamide, and 10-Hydroxy-strictosamide	MTT assay, fluorescent microscopy, Plaque reduction assay	Anti-RSV activity with reduction of RSV plaque-forming units	[34, 35]

Plantago asiatica and Clerodendrum trichotomum	Plantaginaceae, Lamiaceae	Phenylethanoid glycosides- calceorioside, Acteoside, Isomartynoside, and Desrhamnosyl acteoside	HPLC analysis, Immunoblot analysis, qRT-PCR, Syncytium formation assay, *In vivo* assay	Blocked syncytia formation and reduced RSV replication, transcription, and protein synthesis	[36]
Schefflera heptaphylla	Araliaceae	3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, 3α-hydroxylup-20(29)-ene-23,28-dioic acid, 3-epi-betulinic acid, and 3-O-sulfate	Plaque reduction assay, CPE reduction assay, Direct virucidal assay, MTT reduction assay.	In the early period, the fusion of the virus and the cell was inhibited, and at the late stage, virus replication was inhibited	[37, 38]
Citrus reticulata	Rutaceae	Limonene, Hesperidin, Tangeritin, Sinensetin, 5-O-demethylnobiletin, Nobiletin, 5-hydroxymethylfurfural, and Nitroisobutylglycerol	HPLC analysis, q Real-Time PCR, MTT Assay, CPE Reduction assay, Western blot assay, Attachment Inhibitory Assay	*In Vivo*, a study showed RSV-induced lung inflammation and RSV replication were inhibited by tangeretin	[41, 42]
Blumea laciniata	Asteraceace	Borneol, β-caryophyllene, Germacrene D, Sabinene, Protocatechuic acid, Chrysoeriol, Apigenin, 4-hydroxy-3,5-dimethoxybenzoic acid, and Scopolet	Cytotoxicity assay, CPE reduction assay	*In vitro*, a study showed antiviral activity against RSV	[43, 44]
Markhamia lutea	Bignoniaceae	Verbascoside, Isoverbascoside, Luteoside A, Luteoside B, Luteoside C, Forthysioside B, Myricoside, and Myricoside	Thin Layer Chromatography, 2D-Nuclear Magnetic Resonance spectrometry, CPE Plaque neutralization assay	It shows potential effectiveness by acting intracellularly on RSV using the *in vitro* CPE method or Plaque neutralization assay.	[45]

Vigna radiata or green gram, belongs to the Fabaceae family. Over 3500 years have passed since mung beans have been widely consumed as a traditional cuisine. In India, China, Bangladesh, the Philippines, Thailand, Southeast Asia, and Western nations, these versatile legumes are enjoyed in multiple forms, ranging from raw additions to salads to cooked vegetable dishes, and in some regions constitute a fundamental part of the daily diet. According to WHO, consuming phytocompounds may potentially improve healthcare perspectives and aid in recovery from various chronic degenerative ailments like Alzheimer's disease, Diabetes, Arthritis, CVD, and Cancer [46]. Secondary metabolites in plants as bioactive compounds defend against herbivores, predators, microbes, and viral pathogens. Mung bean sprouts exhibit significant antioxidant properties, which are associated with their effective antiviral potential [47]**.** It is a crucial pulse consumed globally and used as traditional medicine, especially in Asian countries. Seeds and sprouts of this pulse are rich in nutrients and have bioactive properties. In mung beans, biochemical constituents are organic acids, polyphenolics, flavonoids, amino acids, phenolic acids, carbohydrates, and lipids [48]. The significance of methanolic extracts of *Vigna radiata* was compared with the standard drug Ribavirin using an MTT assay. Direct virus inactivation and inhibition of virus replication methods. From this finding, methanolic extracts of *Vigna radiata* sprouts showed lower selective indices (14.18 and 12.82) for virucidal and prophylactic activity than Ribavirin (23.39 and 21.95) [47]**.**

Panax ginseng is the most powerful adaptogenic herb used in herbal medicine in East Asian nations. Over 5000 years ago, it was discovered in the mountains of Manchurian, China. Adaptogens fall under the family of neutraceuticals. These are naturally occurring bioactive substances that can maintain metabolic processes and regulate homeostasis [49]**.** It prevented RSV-infected oxidative cellular stress, enhanced IFN-γ production to boost immunity, and decreased virus titer in the lungs of an investigational murine model [24]**.**

Rosmarinus officinalis (Rosemary) is a perennial aromatic herb belonging to the mint family, Lamiaceae; it is an evergreen, dense herb reaching 90–200 cm in height, with hairy, sticky, needle-like leaves. It contains a cymose inflorescence with pale blue colored flowers. It comprises active biological compounds, essential oils, terpenes, camphor, carnosol, carvacrol, carvone, limonene, luteolin, rosmarinic acid, and salicylates. Rosemary has bioactive compounds with antioxidant, anti-inflammatory, antimicrobial, antitumor, and anti-proliferative properties. It is a medicinal plant native to the Mediterranean region and globally cultivated [50]. Active constituent carnosic acid exhibits intense anti-RSV activity. It was effective against both type A and B strains of RSV. Carnosic acid effectively inhibited the replication of respiratory syncytial virus in a concentration-dependent manner [20].

Scutellaria indica is an annual herb belonging to the Lamiaceae family, has significant therapeutic and nutritional benefits. It is mainly found in Japan, Korea, China, Indo-China, and Taiwan. It is a small perennial herbaceous plant that typically grows 15-30cm tall, with erect shoots arising from a prostrate base [51], [52]. Respiratory syncytial virus is inhibited by the natural metabolites (polyphenols) of *Blumea laciniata* and *Scutellaria indica,* of which IC_{50} ranges between 12.5-32 µg/mL [53].

Blumea laciniata is an aromatic, herbaceous annual plant. It is widely distributed across South and Southeast Asia, including Bangladesh, and grows as a winter weed. According to various research findings, *Blumea laciniata* possesses anti-proliferative, antiviral, antibacterial, and radical-scavenging properties, with different solvents used for the extraction (Aqueous, Ethanol, and methanol [54]). A strong inhibitory effect of the *Blumea laciniata* extract was observed against the RSV [55].

Glycyrrhiza glabra is a well-known perennial herb that belongs to the family Fabaceae (also called Leguminosae). The word glycyrrhiza originated from Greek, where glykos means "sweet" and rhiza means "root." *G. glabra* contains several bio-constituents, including carbohydrates, proteins, mineral salts (P, Na, K, Cu, Si, Se, Mn, Zn, Fe, Ca, and Mg), resins, vitamins, phytosterols, and pectin. Various phytoconstituents have also been isolated- mostly triterpenes, flavonoids, and saponins. Saponins are constituents responsible for sweetness and are found as glucuronides, while aglycones are found as oleananes [56]. *G. glabra* contains a component known as glycyrrhizic acid, which has anti-RSV activity.

Citrus reticulata is a shrub from the Rutaceae family that can reach up to 20 feet. It has glossy leaves and aromatic flowers and is a good source of essential oil. It produces round-shaped sweet fruit with aromatic pulp and a light yellow-orange color [57]. Due to their significant therapeutic benefits and antioxidant properties, their peels and fruits are the most popular. They are also rich in minerals and bioactive components [58]. In the research findings by Xu *et al.* (2013), a cytopathic reduction assay was used to assess *in vitro* anti-RSV activity. They used supercritical fluid extracts of *Citrus reticulata*, with an IC_{50} of 12.5-25.0 µg/mL. They also isolated five polymethoxylated flavanones (5-O-demethylnobiletin, Tangeretin, Nobiletin, 6-methoxytangeretin, and Sinesetin). These five polymethoxy flavanones had efficient activity against RSV [41]. The RSV-induced inflammatory response was significantly reduced by tangeretin compound.

Plantago asiatica belongs to the Plantaginaceae family, a perennial herb commonly used as a traditional remedy in countries such as China, Japan, and Korea. Using *Plantago asiatica* extracts, numerous diseases, including chronic constipation, bronchiolitis, and cholesterolemia, have been cured [36]. Plant extracts of both (*P. asiatica and C. trichotomum*) substantially decreased RSV replication, transcription, and translation and prevented syncytia formation when seeded to HEp2 and A549 cell lines.

Clerodendrum trichotomum belongs to the Lamiaceae family (also called Verbenaceae). It is a deciduous shrub widely distributed in Japan, China, South Korea, and the Philippines. *Clerodendrum trichotomum* extract possesses valuable broad-spectrum properties, including anti-hypersensitivity, anti-asthmatic, and antioxidant [36].

Nauclea latifolia, also known as the African pincushion tree, is widely used in traditional medicine to treat conditions such as epilepsy, pain, and malaria across several regions of Africa. *Nauclea latifolia,* also known as the African pincushion tree, is widely used in traditional medicine to treat conditions such as epilepsy, pain, and malaria across several regions of Africa [35]. *In vitro*, screening of aqueous root bark extracts of the plant *Nauclea latifolia* revealed remarkable, promising antiviral activity against the RSV A2 strain by using the time course assay and viral-induced cytopathic effect assay [34].

Lophatherum gracile belongs to the Gramineae family. In *Lophatherum gracile*, phenolic compounds (phenolic acids and flavonoids) are present and are known for their bioactivities, including antitumor, antiviral, antibiosis, and antioxidant activities. It is well known for treating lung inflammation and cough-associated diseases. Numerous Flavone-C-glycosides isolated from the *Lophatherum gracile* plant showed potent effects against RSV using an *in vitro* CPE reduction method [40].

Scutellaria baicalensis is extensively recognized as potentially active against RSV. It consists of three crucial flavonoid compounds named baicalin, baicalein, and wogonin, which are responsible for antiviral activity. Researchers have demonstrated that baicalin usually prevents the expression of IL-6 and IL-8 cytokines mediated by RSV and stimulates oxidative stress and signal transduction cascades. It was also observed that IFb1 expression in RSV-infected cells was boosted by baicalein [59].

Sargassum fusiforme is a brown algae belonging to the family Sargassaceae. It is a warm-temperature annual alga with a widespread distribution along the eastern coast of Asia [60]. The Human Epithelial cell line was treated with a non-cytotoxic dose of *Schefflera fusiforme* extract, which markedly decreased RSV-induced cell demise, its replication, transcription, translation, and syncytia formation. Additionally, an *in vivo* study found that oral administration of SFE considerably enhanced RSV reduction in the lungs of BALB/c mice [61].

Schefflera heptaphylla belongs to the Araliaceae family*.* Evaluation of aqueous extracts using different parts (leafstalks, bark, and leaves) of the plant *Schefflera heptaphylla* was more efficient than Ribavirin. SI of leaf extracts and leaf stalks demonstrated higher potency. A non-cytotoxic dose of *Schefflera heptaphylla* was determined to be high for leafstalk, leaf, and bark extracts (CC_{50}: 510 µg/mL, 1000 µg/mL, and 850 µg/mL), indicating that this plant shows significantly less toxicity to cells. Ribavirin's CC_{50} value was 62.5, indicating greater cytotoxicity [38]. The *Schefflera heptaphylla* plant was screened for isolated caffeoylquinic acid derivatives with antiviral activity against RSV. These compounds inhibit syncytia formation and prevent virus attachment to the cells [37].

Markhamia lutea belongs to the family Bignoniaceae, commonly known as the Nile Tulip*.* Different parts of *M. lutea are* used as folk medicine and possess pharmacological properties [62].

Aesculus hippocastanum belongs to the family Hippocastanaceae. Seed extracts of *Aesculus hippocastanum* contain secondary metabolites such as hydroxycoumarins, triterpenoid saponin glycosides, flavonoids, proanthocyanidins, and sterols. These compounds exhibit various activities, including antibacterial, hepatoprotective, antidiabetic, and anti-neuropathy. *In vivo*, the study of the plant's seed extract revealed a decrease in lung inflammation, as measured by reduced inflammatory cell infiltration. *In vitro*, the study used to evaluate antiviral properties [32].

Cimicifuga foetida is found in forest regions at elevations ranging from 1700 to 2300 meters above sea level. It comes under the family Ranunculaceae*.* The antiviral effect of *Cimicifuga foetida* against the RSV has been attributed to the active constituent known as cimicifugin. The study findings indicate that cimicifugin demonstrated anti-RSV activity in A549 and HEp-2 cell lines. It's IC_{50} (5.4 µg/mL and 38.6 µg/mL), CC_{50} (246.1 µg/mL and 250.1 µg/mL), and SI values (45.7 and 6.4) as shown in **Table 2**. The study suggests that RSV-induced plaque formation in A549 cells was inhibited in a time- and dose-dependent manner. The results of ELISA analysis indicate that cimicifugin can inhibit the attachment and internalization of the RSV virus by triggering antiviral cytokines [22]. In A549 cells, RSV-induced plaque formation was

reduced by less than 10% using a 300 μg/mL concentration of *Cimicifuga foetida* Rhizoma hot water extract. So, higher extract concentration could lead to significantly reduced RSV-induced morbidity as well as mortality [63].

Table 2 Potent activities of some medicinal plant extracts against RSV and their CC_{50}, IC_{50}, and Selective Index in the different cell lines used

Plant Extracts	Solvent Extracts/Compounds	Cell-Line used	CC_{50} (μg/mL)	IC_{50} (μg/mL)	SI	Reference
Radix glycorrhyzae	Water extract	HEp-2	2010.4	74.8	26.9	[28]
		A549	1945.3	70.7	27.5	
Radix glycorrhyzae Preparata		HEp-2	2549.8	131.6	19.4	
		A549	2144.8	80.1	26.8	
Plantago asiatica	Aqueous extract	HEp-2	938.4	39.82	23.5	[36]
Clerodendrum trichotomum		HEp2	764.2	27.9	27.3	
Nauclea latifolia	Aqueous extract	HEp-2	187.35	58.15	3.2	[34]
Euphorbia jolkinii	Jolkinol A	HEp-2	38.4	4.8	8.0	[64]
Vigna radiata	Methanolic extract	Vero	220.96 *	17.23*	12.8	[47]
Rosmarinus officinalis	Carnosic acid	A549	130.8	6.51	20.1	[20]
		HEp-2	130.8	6.71	19.5	
Cimicifuga foetida	Water extract	HEp-2	3000	67.3	44.6	[22]
		A549	3000	31.0	96.7	
Flos lonicerae	3,5-Dicaffeoylquinic acid	HEp-2	>200	0.035 ± 0.001	>5700	[30]
Aesculus hippocastanum	Seed Extracts	HEp-2	100	13.3 ± 0.4	7.5	[32]
		A549	100	14 ± 1.2	7.1	
		Vero	100	7.5 ± 0.6	13.3	
	β-escin	HEp-2	100	1.6 ± 0.3	62.5	
		A549	100	2.4 ± 0.8	41.6	
		Vero	100	1.5 ± 0.5	66.7	
Schefflera heptaphylla	3,4-Di-O-caffeoylquinic acid	HEp-2	1160†	2.33†	500	[37]
	3,5-Di-O-caffeoylquinic acid		1300†	1.16†	1116	
Laminaria japonica	Polysaccharide extract	HEK293	1760	5.27	334	[27]
Markhamia lutea	Verbascoside	HEp-2	0.80	76.9	85	[45]
	Isoverbascoside		0.62	51.4	84	
	Luteoside A		0.87	77	89	
	Luteoside B		3.4	>67	>19	
Sargassum fusiforme	Aqueous extracts	HEp-2	659.24	45.34	14.53	[61]

Lophatherum gracile	Ethanolic extracts	HEp-2	> 200.0	20.0	>10.0	[39]
Citrus reticulata	Nobiletin	HEp-2	252.1±1.9†	15.4±0.8†	16.4	[41]
	Tangeretin		417.2 ±1.3†	8.3±1.1†	50.3	

* -mg/mL, † -µM, CC_{50}-50% Cytotoxicity Concentration, IC_{50}-50% Inhibitory Concentration, SI=50% Cytotoxicity Concentration/50% Inhibitory Concentration

In vitro study of *Coptidis rhizome* showed GFP expression and reduced viral replication. Anti-RSV activity was assessed using dried bark aqueous extracts of *Coptidis rhizoma* in the HEp-2 cell line. Water extracts of *Coptidis rhizoma* had a CC50 of 19.2 ± 2.1 µg/mL. RSV-GFP replication was 50% reduced by *Captidis rhizoma* extracts (CRE), with an EC_{50} of 0.48±0.11 g/mL. In BALB/c mice, oral administration of CRE could mediate an anti-RSV response by inducing the expression of pro-inflammatory cytokine IL-6 and IFN-β signaling [25].

Glycyrrhiza uralensis belongs to the Leguminosae family. Hot-water extraction of licorice plants reduced RSV-induced plaque formation in upper and lower respiratory cell lines (HEp-2 and A549). Secretion of IFN-β was enhanced by using extracts of *Glycyrrhiza uralensis* dose-dependently. IFN-β performs several functions, including preventing viral penetration, replication, translation, and assembly [28].

Andrographis paniculata, locally known as Kalmegh, predominantly grows in Southeast Asia and the Indian subcontinent, with little distribution globally. It belongs to the Acanthaceae family; this herb contains an array of pharmacologically active compounds, with its chemical profile featuring diterpenes, flavonoids, diterpenoids, lactones, and glycosides [19]. It exhibits diverse therapeutic properties, including antibacterial, antiviral, antimalarial, fever-reducing, heart-strengthening, liver-protective, and anticancer effects. The principal bioactive component isolated from *Andrographis paniculata* is andrographolide, a diterpene lactone with significant antiviral activity against multiple viral pathogens [65].

Flos lonicerae is a member of the family Caprifoliaceae. For a long time, it has been known as traditional Chinese medicine and has been utilized in China [31]. The study tested against RSV showed intense anti-RSV activity, with a selective index>20; the IC_{50} value was 50 µg/mL [66]. *In vitro* study includes crude extracts (hot aqueous extracts), methanol extracts, a Vacuum Liquid Chromatography fraction of methanol extracts, and an isolated compound of the *Flos lonicerae*, which were used to check the cytotoxicity and antiviral activity in the HEp2 cell line. *In Vivo*, a study using the CJ-4-16-4 compound in a cotton rat model showed that the viral titer in lung tissues decreased with compound administration [30].

Epigallocatechin gallate (EGCG), a catechin in green tea, exhibits antiviral activity against multiple viruses, including RSV. The mechanism involves EGCG's ability to interfere with RSV's fusion with host cell membranes, thereby blocking viral entry and subsequent replication within host cells. Studies have shown that curcumin, the active compound in the traditional Indian spice turmeric, exhibits significant antiviral activity against RSV by inhibiting the viral RNA polymerase, which is essential for viral replication. Additionally, resveratrol, a polyphenol naturally found in foods such as grapes, various berries, and peanuts, has been shown to inhibit RSV replication by targeting multiple enzymes involved in viral replication, particularly those associated with RNA synthesis [67].

Research studies have demonstrated that purified Ephedra Herb extract (EFE), free of ephedrine alkaloids, combined with Cinnamon Bark extract, prevents RSV infection by targeting the viral G attachment protein. These botanical compounds specifically bind to the G protein's central conserved domain (CCD), effectively preventing the virus from attaching to its target receptor, CX3CR1, on host cells. The antiviral efficacy of Ephedra Herb extract (EFE) was demonstrated by its half-maximal inhibitory concentration (IC_{50}) of 0.566 µg/mL and its half-maximal cytotoxic concentration (CC_{50}) of 374.9 µg/mL. The resulting selection index was 662, calculated from these values, indicating a notably high therapeutic window [68].

A list of traditional Chinese medicines found to have strong anti-RSV effects. These include *Patrinia villosa, Paeonia suffruticosa, Callicarpa nudiflora, Isatis indigotica*, *Sarcandra glabra, Selaginella sinensis, Forsythia suspense, Lonicera japonica, Polygonum multiflorum, Sophora flavescens, Tinospora capillipes, Artemisia capillaries, Ipomoea cairica, Polygonum cuspidatum,* which are Chinese herbs identified with their SI, IC_{50}, and CC_{50} ranging between 15.4 to 32.1, 9.2 to 16.7 µg/mL, 200 to >1000 µg/mL, showing the higher antiviral effects compared to the approved drug Ribavirin. It inhibits infection with an IC_{50} of 2.6 µg/mL. An isolated compound from the *Sophora flavescens* (Anagyrine and Sophoranol) and *Scutellaria baicalensis* (Wogonin and Scutellarein) inhibits RSV infections [69].

2. Conclusion

RSV is a common respiratory virus that causes illnesses such as bronchiolitis and pneumonia in infants. 80% of children are infected with this virus during their first year. Most infections involve the upper respiratory tract, but some patients have severe acute respiratory disease. It is responsible for morbidity and mortality in the young. However, there is no effective vaccine available to treat RSV. The available drug, Ribavirin, has limited efficacy against this virus. So, medicinal plants are the best options to treat RSV infection because of their easy availability, fewer side effects, low cytotoxicity, and lower cost as compared to synthetic drugs. Consequently, natural pharmacotherapy may be a suitable substitute for treating viral-related illnesses. This review focused on the various literature-based medicinal plants responsible for antiviral effects against RSV. These plants exhibit significant CC_{50}, IC_{50}, and Selective Index values for anti-RSV activity using MTT, XTT, plaque reduction, and plaque neutralization assays.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest related to this review article.

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