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Review

A review on antiviral activity of the Himalayan medicinal plants traditionally used to treat bronchitis and related symptoms

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Abstract

Objectives Bronchitis is a common respiratory tract infection of humans mainly caused by *influenza virus, rhinovirus, adenovirus*, *coronavirus* and *respiratory syncytial virus.* The aim of this review was to gather fragmented literature on ethnomedicinal plants used against bronchitis in the Himalayan region and their in-vitro validation against bronchitis causing viral pathogens.

Key findings Present review contains ethnomedicines of total 55 plants from different countries of the Himalayas. Most of the literature reported was from India followed by Pakistan, China and Nepal. Familiarly used plant families for bronchitis treatment in the Himalayan region were Leguminosae (six plants) and Lamiaceae (five plants). Leaves and roots were the most common parts used in ethnomedicines against bronchitis. Of these 55 plants, only six plants have been studied *in vitro* against viral pathogens causing bronchitis. Different compounds like monoterpenoids, flavonoids, triterpenoids, iridoid glycosides, sesquiterpenes, benzoic and phenolic compounds were reportedly isolated from these plant extracts having strong antiviral potential.

Summary The Himalayan regions possess variety of ethnomedicinal plants used against respiratory diseases, but still there are only few studies related with their in-vitro validation. We invite the attention of researchers for detailed ethnopharmacological and phytochemical studies on unexplored plants used to treat bronchitis for the development of novel antiviral drugs.

Introduction

Bronchitis is a respiratory disease of humans, in which mucous membrane of the bronchial tubes become inflamed that carry oxygen from trachea to lungs. The main aetiological agents for this disease are viruses including *influenza, rhinoviruses, adenoviruses*, *coronavirus* and *respiratory syncytial virus*[1,2] while some bacteria including *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Bordetella pertussis* account for about 10% of cases.[3] Cigarette smoking, air pollution, occupational exposure to dust particles, irritants, fumes, polluted air particles and biomass fuels may also cause bronchitis.[4] Bronchitis is slowly progressive and largely irreversible disease with clinical signs and symptoms like sore throat, runny nose, airway obstruction, tiredness, sensation of tightness, burning or dull pain in the chest under the breast bone, shortness of breath, fever, sputum production and sputum tenacity.[5] According to World Health Organization report, respiratory tract infections are foremost cause of deaths among all contagious disease.[6] Viral diseases are life-threatening diseases with high degree of complications to the humans because of its rapid outbreak throughout the developing world.[7–9] Treatment of viral diseases is great challenge for the peoples even today because of different reasons like easily adaptations of virus, emergence of resistant viral pathogens, development of new viral strains, high cost and side effects of medicine, and host

resistance to antiviral drugs.[10,11] Antibiotics are ineffective against viral infections because viral envelope and set of replicating machinery are completely different than that of bacteria.[3] The common treatment for viral diseases includes antiviral drugs that do not destroy their target pathogen; instead, they inhibit their development, shorten infection and help prevent complications.[12] Bacteria involved in causing bronchitis have also shown resistance against commonly used antibiotics (azithromycin, clarithromycin, tosufloxacin, minocycline, rifamycins and telithromycin) against respiratory tract infections.[13,14] In recent years, emergence of resistant potential of viral and bacterial pathogens against commonly used drugs particularly for respiratory tract infections has increased, which is a major public health problem and great hurdle in the treatment of these diseases.[12,15] Generally, resistance of viral pathogens to chemotherapy has been shown in immune-compromised individuals.[16,17] The pathogenic resistance patterns and high cost of antiviral drugs encourage the use of medicinal plants all over the world.[18]

In Asia, the medicinal plant species are abundantly found in the Himalayan forests that play a key role in the rural livelihood, by supplying diversity of valuable products for food and medicine.[19] The Himalayan region is the largest mountain system blessed with large number of valuable medicinal plants because of its unique topographical, ecological, geographical, climatic and physiographical conditions.[20] The Himalayan medicinal plants have very immense historical background, earliest evidences and records of using plants as medicines originated from the Himalayas and can found in old texts of 'Rigveda' written 6500 year ago.[21] Local healers of the region have tremendous skills and knowledge of preparing traditional medicines for treating different kind of ailments. There is no exact figure about the number of the Himalayan medicinal plants being use for primary health care and livelihood, but most of the researchers documented that more than 10 000 Himalayan medicinal plants are supporting about 600 million people in the region.[22]

Approximately 70–80% people worldwide depend on medicinal plants to cure various human ailments including viral diseases.[12] Herbal drugs have gained much importance due to their easily adaptability, low cost and fewer side reactions on patients.[23] Various traditional medicine systems like Ayurveda and Chinese medicine have gained popularity and used in various parts of the world.[24] Most of the people in the Himalayan region used medicinal plants traditionally to treat various diseases including bronchitis. Medicinal plants are considered as an important source of various bioactive compounds having antiviral properties, yet fewer studies have been done on antiviral potential of medicinal plants.[15]

Literature is limited regarding the Himalayan medicinal plants used against viral diseases especially bronchitis. Main objectives of the present review were to gather utmost fragmented literature on the ethnomedicinal plants used to treat bronchitis in the Himalayan region and their in-vitro activity against viral pathogens and phytochemistry. This review will provide baseline information to the researchers about potential antiviral medicinal plants and will also disclose the scientific gaps in current knowledge that could lead towards the development of novel drugs for the welfare of human beings.

Methodology

Published data on traditionally used medicinal plants for bronchitis and their antiviral activity were collected from the online bibliographical databases: PubMed, Scopus, Google Scholar, Web of Science and floras of the Himalayan countries. Inside the databases, we used the keywords like medicinal plants, Himalaya, antiviral plant extracts and isolated compounds for bronchitis. Plant databases such as 'Tropicos' and 'The Plant List' (www.theplantlist.org) were searched for plant accepted names, synonyms and families.[25] Total 87 articles were reviewed for this study, which were mostly published in English. We selected only those articles, in which complete information was given regarding the traditional use of medicinal plants in the Himalayan region and their antiviral activity. Two tables were developed using Microsoft Excel 2007 and Microsoft Word 2007. Table 1 contains information on the ethnomedicinal uses of selected plants used to treat bronchitis in the Himalayan region including information such as plant name, family, local name, habit, part used, study area and recipe formulation. Table 2 consisted of antiviral activity of plant extracts, concentration (μg/ml), inhibition (%) and active compounds tested against viral pathogens. Chemical structures of compounds were drawn using ChemDraw software (CambridgeSoft\ChemOffice2004\ChemDraw).

Discussion

Ethnomedicinal plants used to treat bronchitis in the Himalayas

The Himalayan region is considered to be the rich source of medicinal plants. Local peoples have strong traditional beliefs regarding high efficacy of ethnomedicinal plants used to treat bronchitis. Traditional healers believe that ethnomedicinal plants are more effective with fewer side effects as compared to modern allopathic drugs. Present review shows that 38 families are being used in the Himalayan belt across the different countries. Most of studies related to traditional uses have been carried out in India

Table 1 Medicinal plants used to treat bronchitis in the Himalayan region

Plant/Family/Local name	Study area	Habit/Part used	Recipe
Abies pindrow (Royle ex D. Don) Royle/ Pinaceae/Raisul[30]	Nepal, Garhwal Himalayas	Tree/Bark	Extract of bark is given orally
Acacia nilotica (L.) Delile/Leguminosae/ Babool[59]	Bageshwar Valley (Kumaun Himalayas) of Uttarakhand, India	Tree/Bark	Bark's extract is used
Achyranthes aspera L./Amaranthaceae/ Lich Kura[30]	Garhwal Himalayas	Herb/Whole Plant	Plant decoction is given
Achyranthes bidentata Blume/ Amaranthaceae/Kuru[59]	Bageshwar Valley (Kumaun Himalayas) of Uttarakhand, India	Herb/Root	Juice of root is used
Acorus calamus L./Acoraceae/Bojho, Katara, Bach[60]	Terai Forest in western Nepal	Herb/Root	Juice of root is given orally
Angelica glauca Edgew./Apiaceae/ Chura[61]	Kashmir Himalaya	Herb/Root	Roots are used and combined with tonics for bronchitis
Artemisia indica Willd./Asteraceae/Tite Pati[60]	Terai Forest in western Nepal	Herb/Leaves	Leaf juice is given orally
Barleria cristata L./Acanthaceae/ Porcupine Flower, Barleria[36]	Pauri Garhwal Himalayas	Shrub/Root	Root decoction is given
Betula utilis D. Don/Betulaceae/ Bhojpatra, Bhooj, Himalayan Silver Birch[62]	Himachal Pradesh	Tree/Bark	Infusion of bark is given
Bidens pilosa L./Asteraceae/Blackjack, Spanish Needle[36]	Pauri Garhwal Himalayas	Herb/Whole Plant	Plant extract along with honey is given
Boerhavia diffusa L./Nyctaginaceae/ Pundera[30]	Garhwal Himalayas	Herb/Whole Plant	Plant infusion is given
Bombax ceiba L./Malvaceae/Simal, Semar[60]	Terai Forest in western Nepal	Tree/Bark	Bark decoction is given orally
Cannabis sativa L./Cannabaceae/ Bhang[39,59]	Vaidyas in Ukhimath Block, Uttarakhand	Herb/Leaves, Seeds	Leaves and seed extract with pepper, cumin seeds and cardamom is given
Cassia fistula L./Leguminosae/Amaltas, Raj Briksha[46]	Garhwal Himalayas	Tree/Fruit	Fruit pulp is given
Celastrus paniculatus Willd./ Celastraceae/Sankhiran[62]	Himachal Pradesh, India	Shrub/Seeds	Powder of seeds is given
Desmodium gangeticum (L.) DC./ Leguminosae/Shalparni[59]	Bageshwar Valley (Kumaun Himalayas) of Uttarakhand, India	Herb/Root	Extract of root is given
Desmodium elegans DC./Leguminosae/ Bhatul[59]	Bageshwar Valley (Kumaun Himalayas) of Uttarakhand, India	Herb/Whole Plant	Extract of plant is used
Ephedra gerardiana Wall. ex Stapf/ Ephedraceae/Ephedra, Somlata[63,64]	Pakistan, Himachal Pradesh	Shrub/Whole Plant	Powder of the crushed plant and some time its tea is used for relaxation of bronchial muscles
Euphorbia hirta L./Euphorbiaceae/Jatli-Dodal[65]	Sewa River Catchment Area in the north-west Himalaya	Herb/Whole Plant	Decoction of plant is used
Euphorbia neriifolia L./Euphorbiaceae/ Sheund[66]	Tarai Region of Kumaun, Uttarakhand, India	Shrub/Whole Plant	Cooked vegetable is given
Hedychium spicatum Sm./Zingiberaceae/ Ban-Haldi, Pankha Phool, Sara[30,40]	Garhwal Himalayas, Uttarakhand	Herb/Rhizome	Rhizome extract is taken orally
Hibiscus rosa-sinensis L./Malvaceae/ Gurhal[59]	Bageshwar Valley (Kumaun Himalayas) of Uttarakhand, India	Shrub/Stem, Flower	Extract of stem and flower is used
Hippophae rhamnoides L./Elaeagnaceae/ Buru[67]	Gilgit District of northern Pakistan	Shrub/Fruit	Syrup made from fruit mixed with *Morus nigra* L. fruit and sugar is used for bronchial congestion
Hyoscyamus niger L./Solanaceae/ Henbane, Khorasani Ajwain[62]	Himachal Pradesh, India	Herb/Seeds	Seeds is principally employed as sedative in bronchitis

Table 1 (*Continued*)

Plant/Family/Local name	Study area	Habit/Part used	Recipe
Indigofera tinctoria L./Leguminosae/ Neel[65]	Sewa River Catchment Area in the north-west Himalaya	Shrub/Whole Plant	Extract of plant is used
Jurinea ceratocarpa (Decne.) Benth. & Hook.f./Compositae/Turjit, Chholmong[68]	Nubra Valley – a cold arid zone of Himalaya	Shrub/Leaves	Leaf extract is given
Justicia adhatoda L./Acanthaceae/Asuro, Ross, Benkar, Brehankar, Baiker[60,70]	Terai Forest in western Nepal, Allai Valley, western Himalaya, Pakistan	Shrub/Whole Plant	Dried powder of entire plant parts is given. Roots and leaves are either given in decoction or powder form
Lantana camera L./Verbenaceae/ Phoolwari[70]	Kumaun Himalayas of Uttarakhand	Shrub/Whole Plant	Decoction is given
Musa balbisiana Colla./Musaceae/Ban Kera[71]	Sikkim Himalayas of India	Herb/Leaves	Syrup is made from leaves and given
Myrica esculenta Buch.-Ham. ex D. Don/ Myricaceae/Kafal, Kaphal[30]	Nepal Himalaya	Tree/Bark	Bark decoction is used
Myrtus communis Linn/Myrtaceae/ Manoo[69]	Allai Valley, western Himalaya, Pakistan	Shrub/Whole Plant	Plant is taken internally in the treatment of bronchial congestion
Oberonia falconeri Hook.f./Orchidaceae/ Hirvi Chapti Amri[30]	Garhwal Himalayas	Herb/Whole Plant	Plant extract is given
Ocimum sanctum L. (*Ocimum tenuiflorum* L.)/Lamiaceae/Tulsi[70]	Kumaun Himalayas of Uttarakhand	Herb/Leaves	Leave juice is used
Ocimum basilicum L./Lamiaceae/ Niazbo[51,72]	Morgah Biodiversity Park, Rawalpindi, China	Herb/Leaves	Decoction of leaves is given
Origanum vulgare L./Lamiaceae/Ban Tulsi[61]	Western Himalaya, India	Herb/Leaves	Tea is made from leaves and used
Oroxylum indicum (L.) Kurz/ Bignoniaceae/Sonpatha[66]	Tarai Region of Kumaun, Uttarakhand, India	Tree/Bark	Decoction of bark is given
Papaver somniferum L./Papaveraceae/ Posht[37]	Kashmir Himalaya, India	Herb/Flowers	Syrup made from sepals and ovary given to the kids for the cure of bronchitis
Perilla frutescens (L.) Britton/Lamiaceae/ Bhang, Jeera[30]	Garhwal Himalayas	Herb/Whole Plant	Plant extract or powder of dried plant parts is used
Pinus roxburghii Sarg./Pinaceae/Chir Pine[36]	Pauri Garhwal Himalayas	Tree/Bark	Saw dust is given
Piper Longum L./Piperaceae/Pipla[71]	Sikkim Himalayas of India	Herb/Fruit	Mature and dried fruits are taken orally
Plantago major L./Plantaginaceae/ Jabai[69]	Allai Valley, western Himalaya, Pakistan	Herb/Roots	Decoction of roots is used
Punica granatum L./Lythraceae/ Anar[27,73]	Neelam Valley, Azad Jammu Kashmir, Kumaun Himalayas of Uttarakhand	Shrub/Whole Plant	Decoction of flower bud is given
Rheum nobile Hooker. f. & Thomson/ Polygonaceae/Kenjo[74,75]	Himachal Pradesh India	Herb/Roots	The watery extract of roots is given orally
Rhododendron anthopogon D. Don/ Ericaceae/Dhoopi[75]	Himachal Pradesh India	Shrub/Flowers, Leaves	Given orally
Tagetes minuta L./Asteraceae/Genda[65]	Sewa River Catchment Area in the north-west Himalaya	Herb/Flowers	Volatile oil of flower is used
Taxus wallichiana Zucc./Taxaceae/ Himalayan Yew[76]	India, Nepalese Himalaya	Tree/Leaves	Leaves extract is given
Terminalia chebula Retz./Combretaceae/ Harad[59]	Bageshwar Valley (Kumaun Himalayas) of Uttarakhand, India	Herb/Fruit	Fruit powder is used
Thymus linearis Benth./Lamiaceae/Ban-Ajwain[77]	Himachal Pradesh, India	Herb/Whole Plant	Plant infusion or syrup is used
Toona ciliate M. Roem/Meliaceae/ Toon[70]	Kumaun Himalayas of Uttarakhand	Tree/Bark	The extract of stem bark is given

Table 1 (*Continued*)

Plant/Family/Local name	Study area	Habit/Part used	Recipe
Trifolium pratense L./Leguminosae/ Trepatra, Chita-Batta[67]	Gilgit District of northern Areas	Herb/Flower	Powder of dried flowers is given
Urtica dioica L./Urticaceae/Jalbang[69]	Allai Valley, western Himalaya	Herb/Roots, Leaves	The juice of the roots or leaves mixed with honey or sugar is given
Verbascum thapsus L./Scrophulariaceae/ Mullein, Akalbir, Cows Lungwort[30]	Garhwal Himalayas	Herb/Whole Plant	Plant extract is used
Viola pilosa Blume./Violaceae/Kaura[30]	Garhwal Himalayas	Herb/Whole Plant	Decoction of plant is given orally
Viola canescens Wall./Violaceae/ Banafsha[75]	Neelum Valley, Azad Jammu Kashmir	Herb/Leaves, Flowers	The decoction of leaves and flowers is given
Zingiber officinale Roscoe./ Zingiberaceae/Aduwa, Suntho[60]	Terai Forest of western Nepal	Herb/Rhizome	Rhizome is chewed in bronchial infections

while rarely from Pakistan, China and Nepal due to less availability of published data (Table 1). Possible reasons for the high availability of ethnomedicinal data from India are; medicinal plants from India have been reported to be very useful in curing various human ailments including bronchitis, rich medicinal plants diversity as Himalaya region is mostly covered by India,[26] most popular traditional systems of this country like Ayurveda, Siddha and Unani, strong traditional believe and dependency of local community on medicinal plants for curing diseases.[26] The most widely used plant families for the treatment of bronchitis in the Himalayan region are Leguminosae (six plants), Lamiaceae (five plants) and Asteraceae (four plants). High number of medicinal plants in these families might be due to their higher abundance in the study area, presence of most active secondary metabolites like flavonoids in the Leguminosae[27]; monoterpenoids, flavonoids and triterpenoids of Lamiaceae[28]; and sesquiterpene lactones in the Asteraceae.[29] Plants belonging to these families are not only used to treat bronchitis but also for many other human diseases in the Himalayan region.[30–32] These families are not only preferred in the Himalayan region but in other countries as well for medicinal purposes due to antimicrobial activity of their plants.[33,34] Medicinal plants used to treat bronchitis in the Himalayan region are mostly herbs (58%) as compared to shrubs (24%) and trees (18%) because they are easily collected, their higher abundance and efficacy against different human pathogens and popularity in traditional medicine system.[35,36] Mostly whole plants are used traditionally in recipe formation to treat bronchitis, which is major threat to the conservation status of these medicinal plants. Almost all plant parts are found to have antiviral activity but most preferred plant parts used are leaves, roots, bark and flowers (Table 1). Different additives like water, sugar and honey are used in the recipe formation in order to reduce the bitter taste of plants as well as to reduce their toxic effects.[37,38] Mixture of some plants is also used for recipes formulation in order to increase their efficacy due to synergistic effect of various compounds in these plants.[39,40] As an example, leaves and seed extract of *Cannabis sativa* with pepper, cumin seeds and cardamom are given orally to treat bronchitis (Table 1). Powder, infusion, decoction and extract are common techniques for recipe formation in the Himalayan region. The most preferred techniques are decoction and extract in the study area that might be due to their easy administration or efficacy of dissolved bioactive compounds in extract.

Antiviral activity of isolated compounds from plants

Data available on the Himalayan plants show that of 55 ethnomedicinally used plants, only six plants have been reportedly studied for their in-vitro activity against viral pathogens causing bronchitis. Whole plant and its different parts like leaves, flowers, aerial parts and rhizomes have been used for the preparation of extracts. Different solvents like aqueous, ethanol and methanol have been reportedly used for the extract preparation (Table 2). Methanol and ethanol are most preferable solvents for plant extraction due to their polar nature that ensures the release of wide variety of bioactive compounds from plants. Plants extracted with these solvents have been reported for their good antimicrobial activity.[41,42] The plant extracts have been taken in different concentrations ranging from 6.25 μg/ml to 10 000 μg/ml, which showed strong inhibition ranges from 16.67% to 100% against adenovirus and influenza virus. Cos *et al.*[43] studied the anti-infective potential of natural product and defined the criteria for good activity as 100 μg/ml for extracts and essential oils while 10 μg/ml for pure compounds and drugs. Among various techniques used for the detection of viral inhibition, dye uptake assay and cytopathic effect reduction assay

Table 2 In-vitro screening of antiviral plants against viruses causing bronchitis

Plant name	Part used	Extract/ Compound/ Control drug	Chemical class	%age of composition of major comp. in the extracts	Concentration (μg/ml)	Inhibition (%)	Viral type	Techniques
Hyoscyamus niger	Flower	Methanol		18.7	40	50	*Influenza* A	Dye uptake assay[78]
		Acyclovir				No effect		
		Amantadine HC			16.8	50		
Justicia adhatoda	Leaves	Methanol	Vasicine	0.026	10 000	100	*Influenza*	Simultaneous assay[50]
		Aqueous	Alkaloids	0.023	5000	16.67		
					10 000	33		
Ocimum basilicum	Whole plant	Aqueous			174.1	50	*Adenovirus* (ADV-3)	Cytopathic effect reduction assay[28]
		Ethanol			>1000			
		Linalool	Monoterpenoids	>95	24.4			
		Apigenin	Flavonoids	>95	11.1			
		Ursolic acid	Triterpenoids	>95	>200			
		2′,3′-Dideoxycytidine			26.7	50		
		Aqueous			129.6	50	*Adenovirus* (ADV-8)	
		Ethanol			>200			
		Linalool		>95	26.4			
		Apigenin		>95	8.0			
		Ursolic acid		>95	4.2			
		2′,3′-Dideoxycytidine			12	50		
		Aqueous			129.1	50	*Adenovirus* (ADV-11)	
		Ethanol			91.9			
		Linalool		>95	16.9			
		Apigenin		>95	20.9			
		Ursolic acid		>95	24.5			
		Hot aqueous			2500	32		
		Methanol			78	28		
		Hydro-methanol			1250	30		
		2′,3′-Dideoxycytidine			28.2	50		
Plantago major	Whole plant	Aqueous			>1000	50	*Adenovirus* (ADV-3)	XTT assay [10]
		Aucubin	Iridoid glycoside	NA	>200			
		Baicalein	Flavonoids		>20			
		Baicalin			>50			
		Luteolin			>25			
		Caffeic acid	Phenolic		14.2			
		Chlorogenic acid	compounds		76.0			
		Ferulic acid			>100			
		p-coumaric acid			>200			
		Oleanolic acid	Triterpenoids		>40			
		Ursolic acid			>20			
		Vanillic acid	Benzoic compounds		>200			
		ddC			5.3			
		Aqueous			>1000	50	*Adenovirus* (ADV-8)	
		Aucubin			>200			
		Baicalein			>20			
		Baicalin			>50			
		Caffeic acid			>200			
		Chlorogenic acid			108			
		Ferulic acid			52.5			
		Luteolin			>25			
		Oleanolic acid			>40			
		p-coumaric acid			>200			
		Ursolic acid			>20			

Table 2 (*Continued*)

Plant name	Part used	Extract/ Compound/ Control drug	Chemical class	%age of composition of major comp. in the extracts	Concentration (μg/ml)	Inhibition (%)	Viral type	Techniques
		Vanillic acid			>200			
		ddC			10	50		
		Aqueous			>1000	50	*Adenovirus* (ADV-11)	
		Aucubin			>200			
		Baicalein			>20			
		Baicalin			>50			
		Caffeic acid			>200			
		Chlorogenic acid			13.3			
		Ferulic acid			23.3			
		Luteolin			>25			
		Oleanolic acid			>40			
		p-coumaric acid			43.8			
		Ursolic acid			>20			
		Vanillic acid			>200			
		ddC			14			
Verbascum thapsus	Aerial parts	Methanol	Phenylethanoid and lignan glycosides		6.25	50	*Influenza* A	Dye uptake assay [50]
Zingiber officinale	Rhizome	ar-curcumene	Sesquiterpenes		20.4	50	*Rhinovirus* IB	Plaque reduction test [30]
		β-Sesquiphellandrene			0.90			
		α-Zingiberene			1.90			
		β-Bisabolene			14.3			
		Flavan	Flavonoids		0.27			
		4, 6-Dichloroflavan			0.02			
		Flavan 5			0.02			

were the most common techniques (Table 2). These techniques are also used in other countries for in-vitro antiviral study.[44,45] *Zingiber officinale* has been investigated using plaque reduction test. In plaque reduction assay, crude fractions (pg per plate) were derived from the dose–response curve and from this the specific activity in units lg, where one unit of activity (1 u) was defined as the activity that reduced the number of plaques by 50% as compared to the virus controls. Flavan 5 was used as the positive control in the plaque reduction test.[30]

Medicinal plants are the good source of various chemical compounds that provide basis for the development of new chemotherapeutic agents against various human pathogens.[10,46] The mechanism of antiviral potential of plants extract or compounds varies among different viruses. Some phytochemical compounds of plants target viral envelope or membrane protein; others inhibit the formation of viral genome or stop attachment of virus to the host cellular machinery for reproduction while some destroy enzymes necessary for viral encoding.[15,47]

Acute respiratory infections (ARI) remain serious problem and leading cause of death in young children throughout the world especially in developing countries. Most frequently reported viruses include rhinovirus, respiratory syncytial virus, influenza virus A and bocavirus. Anders *et al.*[48] demonstrated a high burden of ARI during the first year of life in southern Vietnam. Emerging drug-resistant potential of influenza virus led towards identification of novel antiviral agents. First-generation influenza antiviral agents such as amantadine and rimantadine act on viral M2 protein and stated as ion channel blockers. However, their side effects are associated with patient nervous system and gastrointestinal tract. Moreover, rapid emergence of viral resistance limited the benefits and usefulness of adamantanes in the prevention and treatment of influenza. Complementary and alternative medicines with ethnopharmacological background suggest novel platform for the development of antiviral drugs. Antiviral potential compounds present in medicinal plants work either alone or in synergistic manner. Effectiveness of several medicinal plants extracts is directly associated with synergistic properties of therapeutically active compounds and their derivatives. However, slight cytotoxicity observed in plant extracts investigated might be due to the presence of cytoprotective components. These phytocompounds and extracts could serve as potential source for the development of innovative

antiviral drugs. Present review reported plant extracts likely to be promising candidates in the race of developing third-generation anti-influenza drugs, thus challenging the neuraminidase drug-resistant viruses in an effort to protect human health and the global economy.[49]

Present review showed that the Himalayan plants contain several bioactive substances like monoterpenoids, flavonoids, triterpenoids, iridoid glycosides, sesquiterpenes, benzoic and phenolic compounds having strong antiviral activity. Among traditionally used medicinal plants of the Himalayan region, phytochemicals of only four plants (*Justicia adhatoda*, *Ocimum basilicum*, *Plantago major* and *Zingiber officinale*) have been directly checked against viral pathogens (Table 2).

Justicia adhatoda L

Justicia adhatoda is a well-known plant in Ayurvedic and Unani medicine, a shrub which is widespread throughout the tropical regions of south-east Asia. Leaves of this plant have been used extensively for the treatment of respiratory disorders. Simultaneous assay of leaves showed 33% reduction at a concentration of 10 000 μg/ml in aqueous extract and 16.67% reduction was observed from 1000 μg/ml to 5000 μg/ml, whereas 100% reduction was observed in methanolic extract at a concentration of 10 000 μg/ml. As the concentration decreased, inhibition also found to be decreased from 33.34% at 1 mg/ml to 16.67% at 5000 μg/ml. These data suggest that aqueous and methanolic extracts may directly interfere with protein envelope of viruses and not with sialic acid receptor at the cell surface. Only methanolic extract inhibited influenza virus infection by blocking viral attachment and inhibiting viral hemagglutinin (HA) protein. Vasicine alkaloids have been isolated from leaves, with percentage composition of 0.026% in methanol and 0.023% in aqueous extract which may be responsible for activity.[50]

Ocimum basilicum L

Sesquiterpenoid compounds like farnesol, caryophyllene, flavonoids such as apigenin (Figure 1), monoterpenes like linalool (Figure 2), cineole, fenchone, carvone, myrcene, geraniol and thujone, and triterpenoids such as ursolic acid (Figure 3) have been reportedly isolated from *Ocimum basilicum*. These compounds have been reported to inhibit various viral infections of DNA and RNA viruses.[28,51] Only three types of secondary metabolites apigenin, linalool and ursolic acid have been checked directly against different types of human adenovirus involved in bronchitis. Among these ursolic acid showed maximum inhibition (50%) against adenovirus (ADV-8) at minimum concentration (4.2 μg/ml). Composition of all the isolated compounds is >95%. 2′,3′-Dideoxycytidine is used as positive control and similar activity of ursolic acid (Table 2). Triterpenoid saponins of oleanane group inhibited the viral activity by inhibiting DNA synthesis, while urasane group inhibited viral protein capsid.[52] Other compounds need further investigation against viral pathogens involved in bronchitis. Toxicological studies showed that higher doses of plant cause stomach irritation.[53]

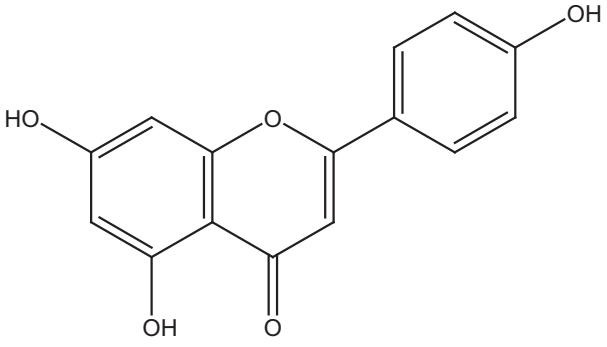

Figure 1 Apigenin.[79]

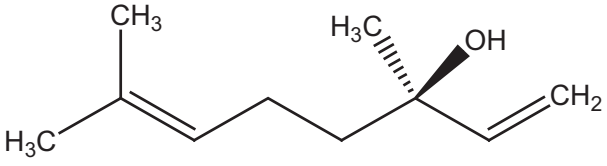

Figure 2 Linalool.[80]

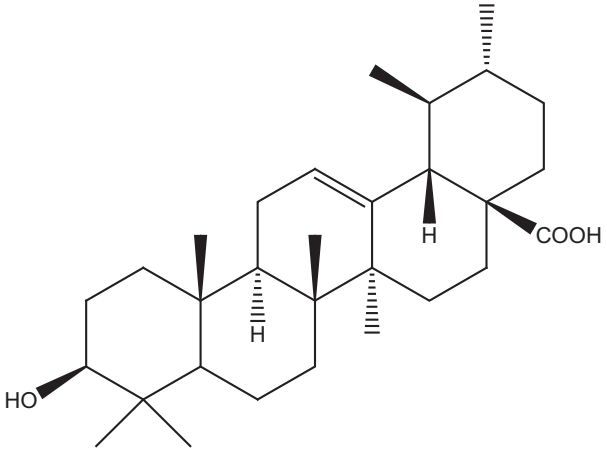

Figure 3 Ursolic acid.[81]

Plantago major L

Phytochemicals isolated from *Plantago major* contain five classes of biologically active compounds: aucubin

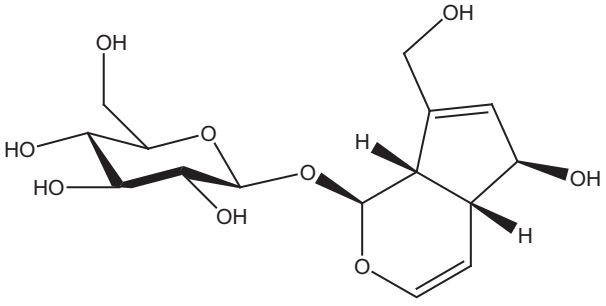

Figure 4 Aucubin.[82]

(Figure 4) belongs to class iridoid glycoside, baicalein, baicalin and luteolin are derivatives of flavons (Figure 5), and vanillic acid (Figure 6) belongs to benzoic compounds and derivatives of cinnamic acid (Figure 7) like caffeic acid, chlorogenic acid, ferulic acid, *p*-coumaric acid, triterpenes ursolic acid (Figure 3) and oleanolic acid (Figure 8). In-vitro antiviral activity of these compounds has been checked against three types of human adenovirus at different concentrations. Although all compounds showed similar inhibition against adenovirus, but chlorogenic acid and caffeic acid had shown 50% inhibition against adenovirus at minimum concentration of about 13.3 and 14.2 μg/ml, respectively (Table 2). The strong antiviral activity of phenolic compounds might be correlated with the presence of two hydroxyl groups on chlorogenic acid and caffeic acid than ferulic acid and *p*-coumaric acid with only one hydroxyl group. Phenolic compounds found effective for their antiviral activity not only against adenoviruses but also against many other viral pathogens.[10,46] Many bioactive chemical classes like flavonoids, triterpenes, sesquiterpenes,

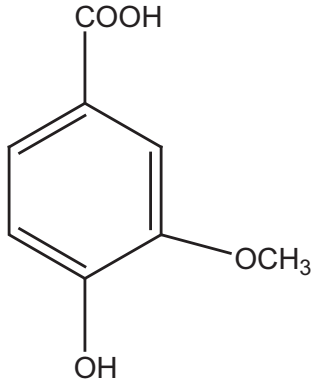

Figure 6 Vanillic acid.[84]

phenolic and benzoic compounds isolated from many other plants have been investigated for their antiviral activity.[10,15,28,47,51] Toxicological studies showed no toxicity of methanolic extract with doses up 2 g/kg body weight in an acute toxicity assay. Contrary to this result, another study suggested that oral administration of an aqueous extract (1000 mg/kg body weight) of leaves had shown highest reduction in the total acidity of gastric fluid in rats.[54] Another study reported that oral administration of aqueous extract (2000 mg/kg) of *Plantago major* for total 40 days did result in mortality of model organism.[52]

Zingiber officinale Roscoe

Three types of sesquiterpene derivatives (Figure 9) ar-curcumene, β-sesquiphellandrene, α-zingiberene and β-bisabolene and two types of flavonoids (Figure 10) flavan and

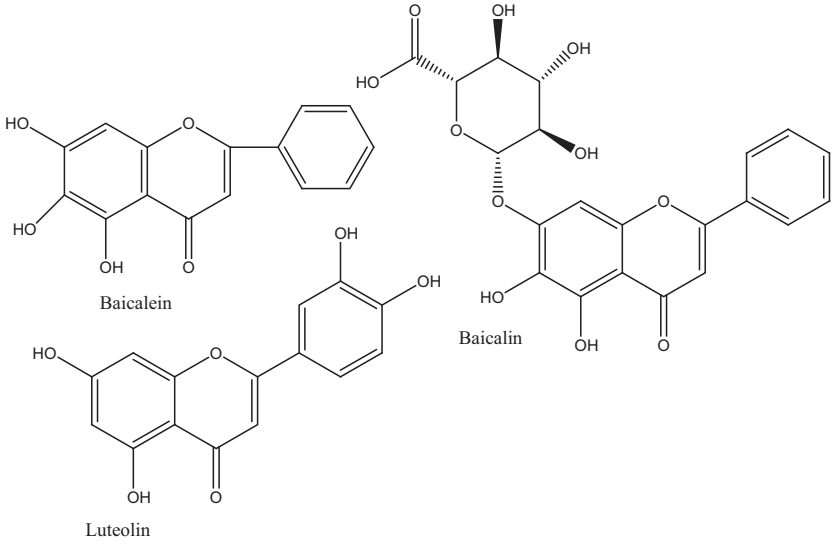

Figure 5 Derivatives of flavons.[83]

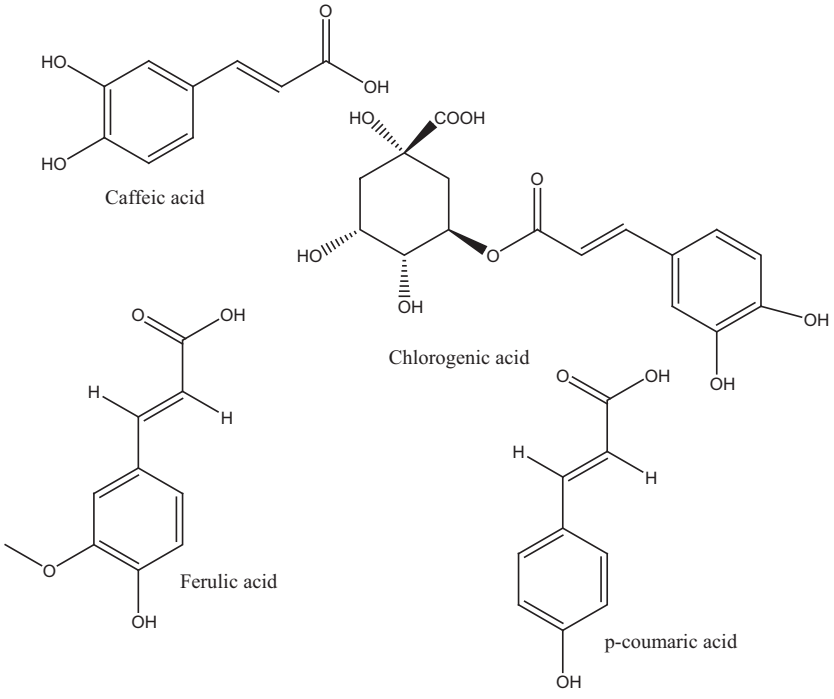

Figure 7 Derivatives of cinnamic acid.[10]

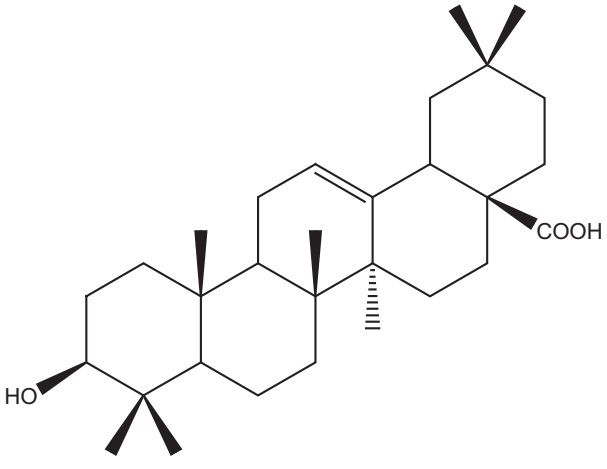

Figure 8 Oleanolic acid.[85]

4, 6-dichloroflavan have been isolated from *Z. officinale* and investigated for their antiviral activity. All these compounds showed 50% inhibition against viral pathogens at different concentrations. 4, 6-Dichloroflavan was considered to be the most effective compound as it showed 50% inhibition against rhinovirus at very lowest concentration about 0.02 μg/ml (Table 2). The lipophilic nature of 4, 6-dichloroflavan has been attributed to its antirhinoviral activity as *Z. officinale* is known to contain various lipophilic secondary metabolites.[30] Dichloroflavan isolated from other natural products has also been investigated against rhinovirus and showed its strongest ability to bind with most sensitive rhinovirus IB at their receptor sites. Many bioactive compounds isolated from higher plants have been checked for their antiviral activity particularly for their antirhinoviral activity. Available data showed that most of the antirhinoviral activity of plants attributed to the presence of flavonoids compounds.[55,56] Administration of aqueous extracts either individually or in combination altered the relative weights of the heart, liver and kidney of the animals which is an indication of a toxic effect.[57,58]

Verbascum thapsus L

Methanolic extract of *Verbascum thapsus* showed strong efficacy about 50% at minimum concentration of 6.25 μg/ml against *influenza* A virus. Phenylethanoid and lignan glycosides have been isolated from methanolic extract of *V. thapsus*. Phytoconstituents responsible for anti-influenza viral activity depend on the amount of active compounds present in the plants which alternatively depends on the geographical distribution, collected season, climatic and ecological condition at the site of plant collection. Further fractionation and separation of extract(s) may reveal potent antiviral activity from this plant. No toxicity has been observed for higher doses.[53]

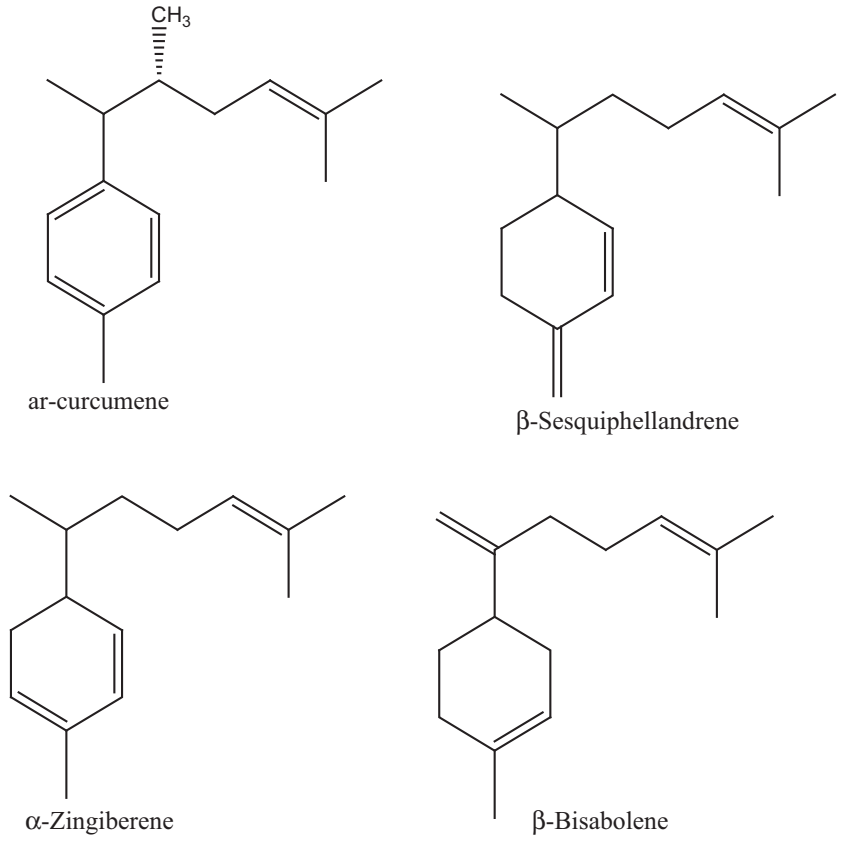

Figure 9 Derivatives of sesquiterpenes.[30]

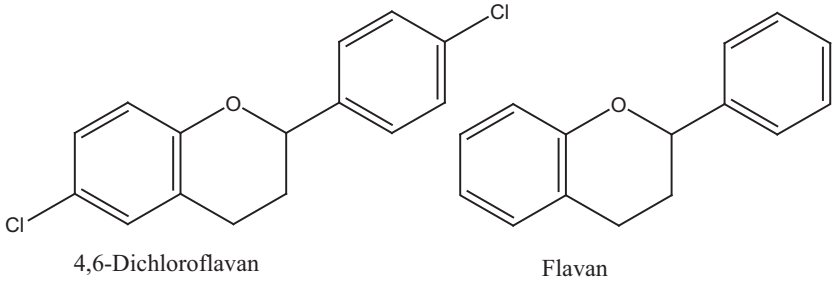

Figure 10 Flavonoids.[55]

Conclusions and Future Considerations

The Himalayan region contains variety of medicinal plants traditionally being used by the local people to treat bronchitis. However, literature is scanty regarding recipe formulation techniques, effective dosage and side effects of the Himalayan medicinal plants used against bronchitis. Therefore, it is necessary to carry out detailed ethnomedicinal studies covering all aspects which could be helpful for the patients and researchers. In addition, more focus should be given to widely distributed plants that might lead towards extraction of novel compounds due to geographical variation. Most of the ethnomedicinal studies were reported from India, and it is highly recommended that research activity in regard to antiviral medicinal plants should also be carried out in other countries of the Himalayan region. Very few plants have been screened *in vitro* and *in vivo* against viral pathogens involved in bronchitis. It is imperative to screen unexplored plants in detail not only for their in-vitro and in-vivo activity but also for their phytochemistry, toxicology and mechanism of actions.

Declarations

Conflicts of interest

The Authors have no conflicts to report.

Disclosure statement

The study had no ethical approval requirements.

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