




## RESEARCH ARTICLE

# Promising traditional Indian medicinal plants for the management of novel Coronavirus disease: A systematic review

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Traditional Indian medical practices (Ayurveda, Siddha, Unani, and homeopathy) are a vast reservoir of knowledge about medicinal plants. The promising pharmacological properties of these plants have paved the way for developing therapy against novel Coronavirus (CoV) infection. The current review will summarize published works of literature on the effects of traditional Indian medicinal plants against acute respiratory infection (COVID-19, SARS, Influenza, and Respiratory syncytial virus infection) and registered clinical trials of traditional Indian herbal medicines in COVID-19. The current study aims to comprehensively evaluate the data of traditional Indian medicinal plants to warrant their use in COVID-19 management. PubMed, Embase, and Cochrane databases were searched along with different clinical trial databases. A total of 22 relevant traditional Indian medicinal plants (35 relevant studies) were included in the current study having potential antiviral properties against virus-induced respiratory illness along with promising immunomodulatory and thrombolytic properties. Further, 36 randomized and nonrandomized registered clinical trials were also included that were aimed at evaluating the efficacy of herbal plants or their formulations in COVID-19 management. The antiviral, immunomodulatory, and thrombolytic activities of the traditional Indian medicinal plants laid down a strong rationale for their use in developing therapies against SARS-CoV-2 infection. The study identified some important potential traditional Indian medicinal herbs such as *Ocimum tenuiflorum*, *Tinospora cordifolia*, *Achyranthes bidentata*, *Cinnamomum cassia*, *Cydonia oblonga*, *Embelin ribes*, *Justicia adhatoda*, *Momordica charantia*, *Withania somnifera*, *Zingiber officinale*, Camphor, and *Kabusura kudineer*, which could be used in therapeutic strategies against SARS-CoV-2 infection.

## KEYWORDS

Ayurvedic medicine, COVID-19, homeopathy, medicinal plants, respiratory syncytial virus infections, SARS virus, Unani medicine

## 1 | INTRODUCTION

Infections caused by viruses pose a great challenge due to their wide spectrum of clinical presentations (Zou et al., 2020). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease (COVID-19) reported to affect more than 8 million people worldwide and has shown significantly high morbidity and mortality rates within a very short period (WHO, Situation Report–150, 2020). The critical cases of coronaviruses (CoV) are linked to severe acute respiratory infection (SARI), aberrant immune response (L. Chen et al., 2020; C. Huang et al., 2020; Z. Xu et al., 2020), and thrombosis (Connors & Levy, 2020; Helms et al., 2020). At present, there is no drug therapy available for this disease. The research is currently focused on three strategies, first to test broad-spectrum antiviral drugs, second in silico screening, and finally repurposing of drugs (Wu et al., 2020).

Apart from these strategies, alternate medicines, for instance, traditional Indian medicines can be explored to find effective drug therapy against the current pandemic. There is a dearth of suitable therapeutic strategies for COVID-19; therefore, it is imperative to peruse all the available options. Traditional Indian medicinal practices, for instance, Ayurveda, Siddha, Unani, and Homeopathy are some of the oldest practices that emerged in the first two centuries (common era). Thus, Indian traditional medicine is a vast reservoir of medicinal plants. Pharmacopoeia Commission for Indian Medicine & Homoeopathy (PCIM & H) contained the Pharmacopoeias and formularies of traditional Indian medicinal plants (Pharmacopoeia commission for Indian medicine & Homoeopathy, 2020). Practitioners have been using traditional Indian medicinal plants extensively for their antiviral, immunomodulatory, and thrombolytic activities for ages (Arora et al., 2011).

Influenza, CoV, and Respiratory syncytial viruses (RSV) all belong to the category of SARI and imposed a great burden on our healthcare (Boncristiani, Criado, & Arruda, 2009). These viruses affect both upper and lower respiratory tracts. The complications in these diseases range from fever to pneumonia with high morbidity and mortality (V. C. Cheng, Tang, Wu, Chu, & Yuen, 2004; Thompson & Zambon, 2009).

The study aimed to review the efficacy of traditional Indian medicinal plants in these viral-induced respiratory illnesses (COVID-19, SARS, RSV, and Influenza). Further, the study also reviewed the registered clinical trials of traditional Indian herbal medicines and their formulations against COVID-19.

### 1.1 | Similarities between CoVs and other viruses

In novel coronavirus, the positive single-stranded RNA of length 30 kb is encircled in a nucleocapsid (N protein). An important protein present on the virus called spike protein S is a final determinant of its entry into the cell (de Wit, van Doremalen, Falzarano, & Munster, 2016) leading to dysregulation of multiple pathways (Figure 1).

RSV is a single-stranded, negative-sense RNA virus whose receptors included toll-like receptor-4 (TLR-4), heparan sulfate

proteoglycans (HSPGs), and CX3 chemokine receptor 1 (CX3CR1), which are present at the cell surface. These receptors bind with viral RSV glycoprotein and restrain the virus to the surface of the cell. Nucleolin cell surface proteins help in the virus entry by activating the fusion of host and virus-cell membranes. Furthermore, the virus hijacks the cellular machinery for its replication. RNA-dependent replication cycle plays an important role in RSV multiplication (Griffiths, Drews, & Marchant, 2017; Ye & Wang, 2018).

The influenza virus is a single-stranded RNA virus (Rossman & Lamb, 2011) encoding 11 proteins (Blackburne, Hay, & Goldstein, 2008; Tumpey et al., 2007). The hemagglutinin (HA) protein of the virus complex binds to the sialic acid residues present on the alveolar epithelium of the target cell to carry out the endocytosis process. The entry of the virus into the lysosome triggers the acidification that activates the matrix protein-2 viral channel resulting in membrane fusion leading to the detachment of the ribonucleoprotein core of the virus. The ribonucleoprotein is then transported to the nucleus for viral replication (Herold, Becker, Ridge, & Budinger, 2015; Rust, Lakadamyali, Zhang, & Zhuang, 2004).

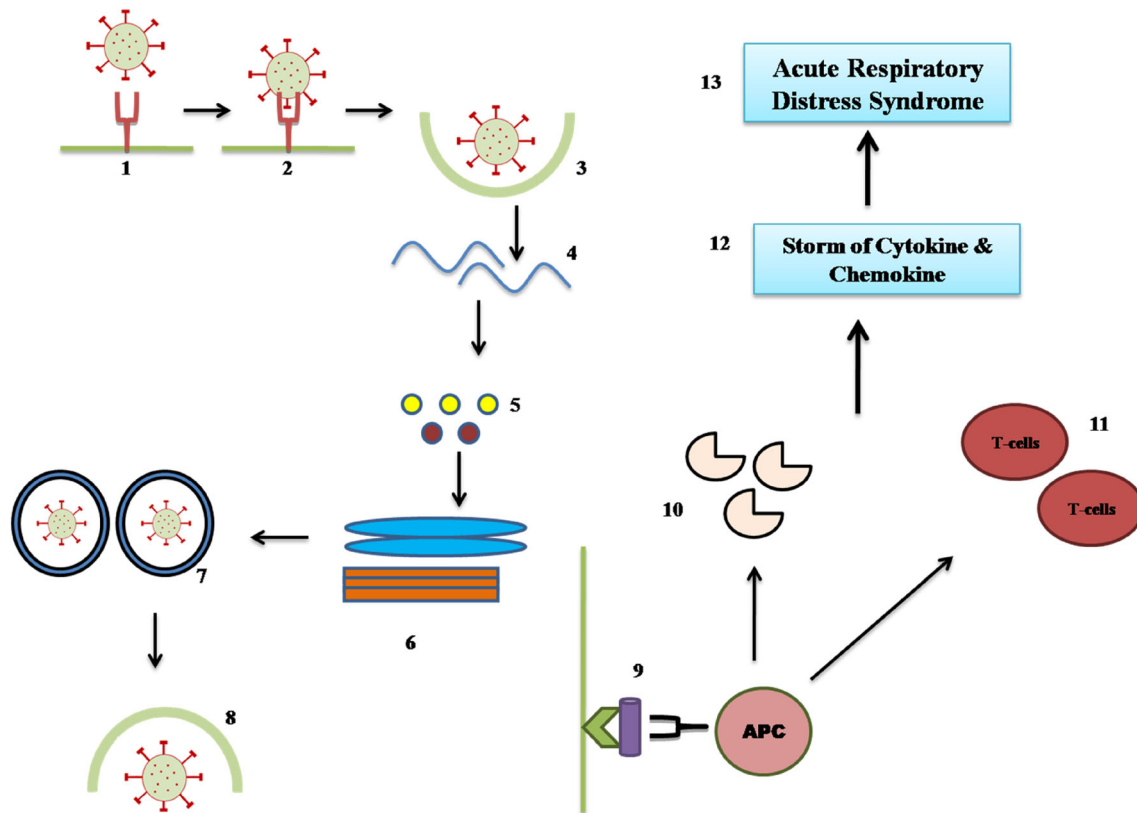
COVID-19, influenza, and RSV viruses exhibit a broad range of respiratory illnesses from asymptomatic to severe disease and death. The transmission factors for these viruses are common such as droplets, aerosols, and fomites (Figure 2) (Killingley & Nguyen-Van-Tam, 2013; Thompson & Zambon, 2009).

## 2 | METHOD

### 2.1 | Search strategy

Our study is a systematic review and follows the PRISMA guidelines (Moher et al., 2009). The PubMed, Embase, and Cochrane databases were searched using the following Mesh terms “medicinal plants” OR “herbal medicine” OR “ayurvedic medicine” OR “Unani medicine” OR “Siddha medicine” OR “homeopathy” OR “antiviral agents” OR “alternate medicine” AND “COVID-19” OR “coronavirus” OR “Influenza, Human” OR “Respiratory Syncytial Virus Infections.” The present study includes clinical trials (randomized and nonrandomized), in silico, in vitro, and in vivo studies that evaluated the traditional Indian medicinal plants in viral-induced respiratory illness like COVID-19, SARS, MERS, influenza, and RSV. Pharmacopoeias and formularies of Ayurveda, Siddha, Unani, and Homoeopathy systems of medicine along with traditional Indian medicinal plants databases were also searched. Plant names have been verified and upgraded with the online available databases such as the International plant name index (International Plant Names Index, 2020), plant list (The Plant List, 2013), and Indian medicinal plants database (Indian Medicinal Plants Database, National Medicinal Plants Board, 2020).

The Clinical trial databases were searched for the registered clinical trials of traditional Indian medicinal plants in COVID-19 included ClinicalTrials.gov, Clinical Trial Registry-India (CTRI), International Clinical Trials Registry Platform (ICTRP), European Union Clinical Trials



**FIGURE 1** Pathophysiology of Coronaviruses. (1) SARS-CoV & SARS-CoV-2 interact with ACE-2 receptor, MERS-CoV binds to DPP4 receptor; (2) Proteolytic cleavage at SARS-CoV S protein at S2 position; (3) Membrane fusion followed by endocytosis; (4) Viral genome released; (5) Polyprotein and Structural protein released; (6) Viral replication takes place, Nucleocapsid formed from genomic RNA and nucleocapsid protein and ultimately ERGIC generate viral particle; (7) Double-layer vesicles contain viral particle formed; (8) Vesicles fuse with plasma membrane and release virus; (9) Viral peptide presentation to antigen-presenting cells and antigen-presenting cells present antigen to T-cells (CD4+ and CD8+); (10) B-cells activated and expanded, releasing antibodies; (11) Clonal expansion of T-cells, which further releases cytokines and chemokines; (12) Storm of Cytokines and Chemokine shoot up; (13) This results in ARDS which may lead to mortality [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Register, UMIN-Clinical Trials Registry (UMIN-CTR), and Australian New Zealand Clinical Trials Registry (ANZCTR) using keywords “medicinal plants” OR “herbal medicine” OR “Ayurvedic medicine” OR “Unani medicine” OR “Siddha medicine” OR “homeopathy” AND “COVID-19” OR “coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR “severe acute respiratory syndrome-coronavirus-2.”

## 2.2 | Types of studies

There was no restriction for study selection. In silico, in vitro, and in vivo studies were included that evaluated efficacy of traditional Indian medicinal plants in viral-induced respiratory illnesses. For clinical trial data, randomized and nonrandomized clinical trials were included. Only articles in the English language were included. The databases were searched in the data range between January 1, 2000 and May 26, 2020. Only published articles were included along with all registered Clinical trials of Indian traditional medicinal plants in COVID-19.

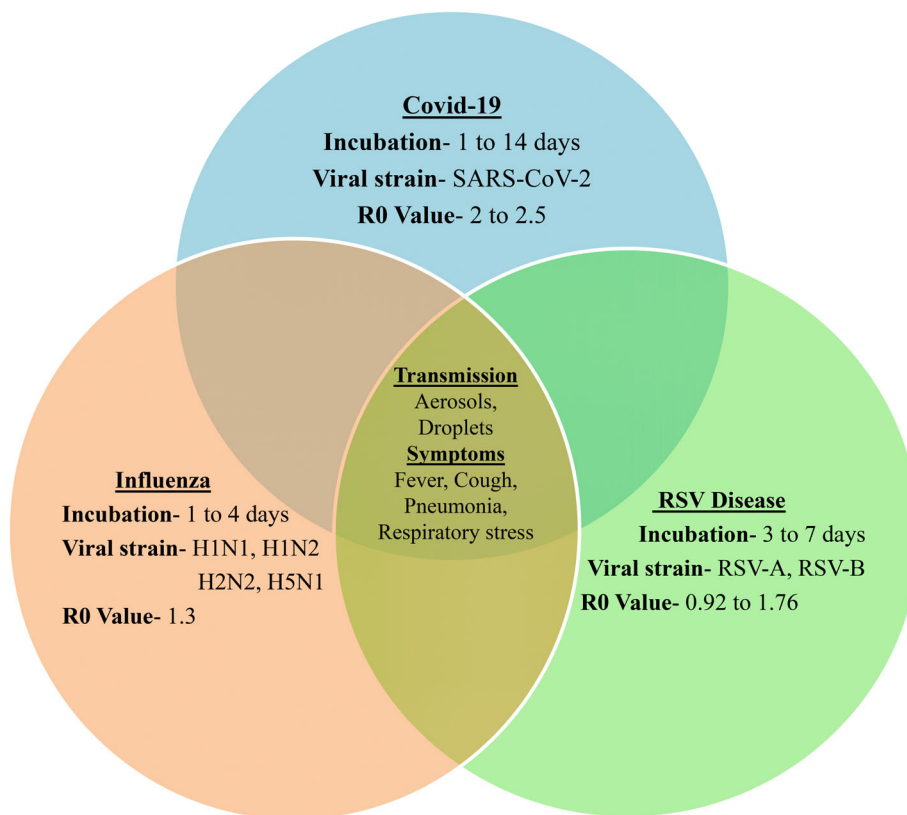
## 2.3 | Types of outcome measures

The studies which evaluated the antiviral activity of traditional Indian medicinal plants in viral-induced respiratory infections were included in the study. For clinical trials, the primary outcomes' measures were disease severity, mortality rate, clinical symptoms, number of serious patients, and number of days of hospitalization. The secondary outcomes that were evaluated were the number of days of clinical symptoms, comparative assessment of the severity of COVID-19 in herbal treated, and control groups.

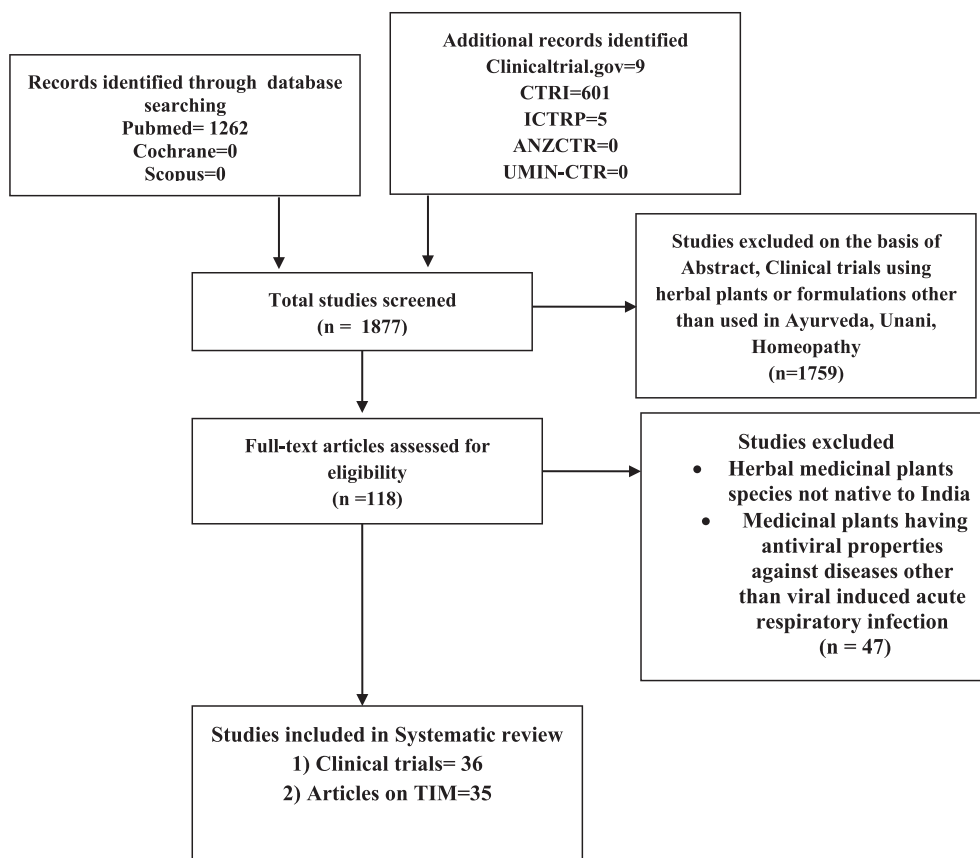
## 2.4 | Study selection

The eligibility of the studies was assessed independently in an unblinded standardized manner. Disagreements between reviewers were resolved by consensus. A total of 1,877 studies were searched using the mentioned criteria out of which 71 studies were scrutinized for the study (Figure 3).

**FIGURE 2** Common features in COVID-19, RSV disease, and Influenza: Transmission factors and symptoms showed inside the Venn diagram are similar in all these diseases [Colour figure can be viewed at wileyonlinelibrary.com]



**FIGURE 3** Flow diagram for literature search. (\*TIM—traditional Indian medicine; CTRI, Clinical trial registry India; ICTRP, International Clinical Trials Registry Platform; ANZCTR, Australian New Zealand Clinical Trials Registry, University Hospital medical information network clinical trial registry)



### 3 | RESULTS

#### 3.1 | Potential traditional Indian medicinal plants for viral-induced severe acute respiratory infection—A preclinical perspective

##### 3.1.1 | *Acacia arabica* (Lam.) Willd. (Leguminosae)

*Acacia arabica* is also known as gum arabic tree. It has many medicinal roles in Ayurveda and is used in the management of several health diseases, for instance, asthma, inflammation, cough, flu (Singh, Satapathy, & Prasad, 2020), Peste des petits ruminants (PPR) virus (Balamurugan et al., 2008), and goatpox virus (Bhanuprakash et al., 2008).

Ghoke et al. (2018) evaluated the antiviral activity of the leaves extract of *Acacia arabica* against the Influenza A virus subtype H9N2 (H9N2) using *in ovo* model in three different experimental procedures that is, virucidal, prophylactic, and therapeutic. The most suitable non-toxic dose of each extract of this compound was evaluated using viral load along with haemagglutination level and real-time PCR (polymerase chain reaction). The study reported that its polyphenolic content and crude extract expressed promising antiviral activities against viral infections. Table 1 presents traditional Indian medicinal plants with antiviral properties.

##### 3.1.2 | *Achyranthes bidentata* Blume (Amaranthaceae)

*Achyranthes bidentata* is commonly known as ox knee and is indigenous to the hilly districts of India, China, and Japan. It is widely used as antiarrhythmic, laxative, ecobolic, antihypertensive, antiviral, antispasmodic, anticoagulant, and antitumor (Devi et al., 2007).

*Achyranthes bidentata* was found to be effective in bronchitis, which is a type of bronchial tube inflammation caused by certain viruses like coronaviruses, influenza, rhinovirus, and adenovirus (Peiris et al., 2003). The root extract was found to be effective in bronchitis, cough, asthma, pneumonia, and fever (Singh et al., 2014).

The sulfated *Achyranthes bidentata* polysaccharide (ABPS) has a potent antiviral activity. The potency of ABPS was evaluated against porcine reproductive and respiratory syndrome virus (PRRSV) strain that is, (VR2332) in MARC-145 (African green monkey kidney-derived cells) cells. The sulfated form showed antiviral activity even at lower concentrations when compared to nonmodified ABPS in MARC-145 cells (C. Liu et al., 2013).

The immunomodulatory effect of *Achyranthes bidentata* polysaccharide (ABP) was evaluated in underdeveloped piglets. The study illustrated increased lymphocyte proliferation, serum IgG (Immunoglobulin type G), IgM, IgA, IL-2 (Interleukin type-2), and IFN- $\gamma$  (Interferon-gamma) levels. Moreover, it also increased the production of peripheral T-cells and splenic lymphocytes (Q. Chen, Liu, & He, 2009). Table 2 presents traditional Indian medicinal plants with immunomodulatory properties.

*Achyranthes bidentata* polypeptide k (ABPPk) has a potential thrombolytic activity. It can prevent oxidative damage of brain endothelial cells caused by ischemia and also leads to NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and plasminogen activator inhibitor-1 activation. ABPPk inhibited the neutrophils, basophils, and eosinophils infiltration along with the activation of various MMP-2/-9 (matrix metalloproteinases) in the ischemic penumbra and alleviated neurological functions (Q. Cheng et al., 2019). Table 3 presents traditional Indian medicinal plants with thrombolytic properties.

##### 3.1.3 | *Aloe vera* (L.) Burm.f. (Xanthorrhoeaceae)

Traditionally, *Aloe vera* acts as an antioxidant, antibacterial (Nejatzadeh-Barandozi, 2013), and antiviral. The activity of ethanol extract of *Aloe vera* was evaluated against influenza A virus in Madin-Darby canine kidney (MDCK) cells. The extract significantly inhibited autophagy induced by the viral strain (J. G. Choi et al., 2019). C. T. Huang et al. (2019) assessed the antiviral efficacy of Aloin (*Aloe vera* derivative) against Influenza A virus subtype H1N1 (H1N1) in MDCK cells. Aloin significantly decreased viral infections. Also, when H1N1 induced mice were treated with Aloin, the viral load and mortality significantly decreased. These results supported the application of the derivative in clinical use.

Neuraminidase (NA) is an enzyme that hydrolyses sialic acid residue of viruses and receptors of the host. It also helps in virus movement and plays an important role in escaping viruses from the host cell after replication. Aloin inhibited the NA, which further leads to immune suppression, and inhibition of virus replication. Aloin increased the immunity along with an increased hemagglutinin-specific T-cell response to the infection (C. T. Huang et al., 2019). *Aloe vera* aqueous gel extract from leaves showed a significant immunomodulatory effect by increasing the cell viability of infected macrophages (Farahnejad et al., 2011).

##### 3.1.4 | *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae)

Generally called Kariyat, *Andrographis paniculata* is a herb that is harvested annually and has a common occurrence throughout India (Rajagopal, Kumar, Deevi, Satyanarayana, & Rajagopalan, 2003).

Sornpet et al. (2017) studied the crude extract of *Andrographis paniculata* in Influenza A virus subtype H5N1 (H5N1) strain using MDCK cells. The study observed a significant decrease in the virus titer in the treatment group. Enmozhi et al. (2020) observed andrographolide (an *Andrographis paniculata* extract) fitted with the inhibitor site of one of the proteases that play a central role in the SARS-CoV-2 virus that is, main protease (Mpro). *In silico* studies highlighted Andrographolide scored high in the docking study. The docking affinity of the compound was found to be significantly higher than the synthetic compounds like disulfiram, tideglusib, and a combination of lopinavir, oseltamivir, and ritonavir. The *in silico* study of

**TABLE 1** Antiviral properties of traditional Indian medicinal plants

Sr. No.	Indian medicinal plant	Common name	Component and dose of plant used	Assay used	Action	References
1.	<i>Acacia arabica</i>	Gum arabic tree, Babul	Leaves (polyphenol); 135 mg/0.1 ml	H9N2 strain in embryonated chicken eggs;	Antiviral	Ghoke et al., 2018
2.	<i>Achyranthes bidentata</i>	Ox knee, putkanda	Sulfated <i>Achyranthes bidentata</i> polysaccharide (sABPS) roots; 0.244–0.488 µg/ml Root extract	PRRSV strain in MARC-15 cells —	Decrease viral titer Effective in bronchitis, fever, and pneumonia	C. Liu et al., 2013 Singh et al., 2014
3.	<i>Aloe vera</i>	Aloe, chhota-kanvar	Ethanol extract of leaves; 25 or 250 µg/ml  Aloin extracted from leaves; 100 µM aloin (in vitro); 2.5 mg/kg body weight (in vivo)	H1N1 in MDCK cells;  H1N1 in MDCK cells and in mice	Antiviral;  Immunomodulator and Antiviral;	J. G. Choi et al., 2019  C. T. Huang et al., 2019
4.	<i>Andrographis paniculata</i>	Kariyat, Nilavembu kudineer	Andrographolide  Ethanol and water extract of leaves; 8.2 µg/ml (ethanol extract), 380.3 µg/ml (water extract)	SARS-CoV-2 in silico study;  H5N1 strain in MDCK cells	High druggability and target accuracy;  Antiviral;	Enmozhi, Raja, Sebastine, & Joseph, 2020  Sornpet, Potha, Tragoolpua, & Pringproa, 2017
5.	<i>Bergenia ciliata</i>	fringed elephant's ears, Pasanabheda (Sanskrit)	Methanolic extract of rhizome; 8 to 10 µg/ml	H1N1 strain in MDCK and Varo cell	High IC50 activity	Rajbhandari et al., 2009
6.	<i>Cinnamomum cassia</i>	Cinnamon, Dalchini	Nanoparticles of bark; 50, 100, and 200 µg/ml	H7N3 strain in varo cells	Antiviral	Fatima, Zaidi, Amraiz, & Afzal, 2016
7.	<i>Curcuma longa</i>	Turmeric, haldi	AgNPs from rhizomes; 0.12 nM and 0.24 nM  crude extracts of <i>Curcuma longa</i> ; 69.3 µg/ml (ethanol extract), 142.3 µg/ml (water extracts)  Curcumin; 30 µM curcumin or MAC  Curcumin; 50 mg/kg body weight	RSV strain in Hep-2 cells  H5N1 virus infection  PR8, H1N1 strain in MDCK cell  Acute Respiratory Distress syndrome; in vivo study	Immunomodulator and Antiviral;  Immunomodulator and Antiviral;  Antiviral;  Antiviral;	X. X. Yang, Li, & Huang, 2016  Sornpet et al., 2017  Richart et al., 2018  Avasarala et al., 2015
8.	<i>Cydonia oblonga</i>	Quince	Ethanol extract of Fruit; 0.5 mg/ml (as phenolics)	A/PR/8/34 strain in chicken erythrocyte Suspension;	Antiviral	Hamazu, Yasui, Inno, Kume, & Omanyuda, 2005
9.	<i>Embelia ribes</i> <i>Burm</i>	False black pepper, white-flowered embelia a	Ethyl acetate extract of Fruit; 0.2 µg/ml	H1N1, H3N2, H5N2 in MDCK cells	Antiviral	Hossan et al., 2018
10.	<i>Glycyrrhiza glabra</i>	liquorice	Glycyrrhizin component; 4,000 mg/L	FFM-1 and FFM-2 in Vero cells;	Block replication, adsorption and penetration;	Cinatl et al., 2003

(Continues)

TABLE 1 (Continued)

Sr. No.	Indian medicinal plant	Common name	Component and dose of plant used	Assay used	Action	References
			Water soluble Glycyrrhetic acid conjugates; 50 $\mu$ M	H1N1 in MDCK cells;	Decreased viral titer;	Liang et al., 2019
			Constituents of roots; 1.70 $\mu$ g/ml (methanol extract), 0.33 $\mu$ g/ml (aglycone-enriched fraction)	H1N1 strain in MDCK cells;	NA inhibition	Grienke et al., 2014
11.	<i>Hypericum perforatum</i>	St. John's wort	Methanol and Ethyl acetate; 78.13 $\mu$ g/ml ( <i>H. perforatum</i> ethyl acetate), 39.06 $\mu$ g/ml ( <i>H. perforatum</i> water) 480–120 mg/kg (in vivo)	IBV strain in CEK cells and SPF chickens;	Antiinflammatory, immunomodulator, decreased mRNA expression and viral titer;	H. Chen et al., 2019
			Ethanol extract of dry plant; 30 $\mu$ g/ml (in vitro), 110 mg/kg (in vivo)	H1N1 strain in A549 cells and Balb/c mice;	Antiinflammatory, immunomodulator;	N. Huang et al., 2013
			<i>Hypericum perforatum</i> extract (HPE) 50–200 mg/kg	influenza A virus (IAV) in Balb/c mice	Immunomodulator and decreased viral titer;	Xiuying et al., 2012
12.	<i>Jatropha curcas</i>	purging nut, jablota	Aqueous and methanolic extract leaf; 15 mg to 1 mg/ml. (methanol extract), 25 and 5 mg/ml (aqueous extract)	H1N1 strain in MDCK cell	Block viral adsorption	Patil et al., 2013
13.	<i>Justicia adhatoda</i>	Malabar nut	Methanolic extract of leaf; 10 mg/ml	Standard influenza strain in MDCK cells	Reduction in HA, block viral attachment and replication	Chavan & Chowdhary, 2014
14.	<i>Momordica charantia</i>	Bitter cucumber	Seeds; 1.401 mg/ml	H1N1, H3N2, H5N1 strains in MDCK cells	Decreased viral titer	Pongthanapisith, Ikuta, Puthavathana, & Leelamanit, 2013
15.	<i>Ocimum tenuiflorum</i>	Holy basil, Thai basil, Tulsi	Leaves (crude extract, terpenoid and polyphenols); 135 mg/0.1 ml	H9N2 strain in embryonated chicken eggs;	Antiviral;	Ghoke et al., 2018;
			Phytocompounds- Apigenin;	H1N1 in silico study;	High binding energy;	Alhazmi, 2015
16.	<i>Psoralea corylifolia</i>	Bawchan seed	Bakuchiol, a naturally occurring phenolic isoprenoid; 12.5–100 $\mu$ M	H1N1 and H3N2 strains in MDCK cells	Immunomodulator and antioxidant	Shoji et al., 2015
17.	<i>Syzygium cumini</i>	Jambolan, java plum Indian blackberry	Aqueous crude extract of leaves and bark; 1.28 $\mu$ g/ml and 8.69 $\mu$ g/ml*	H5N1 in MDCK cells	Antiviral	Sood et al., 2012
18.	<i>Tinospora cordifolia</i>	Heart-leaved moonseed, Gulbel	Berberine, Isocolumbin, Magnoflorine, and Tinocordiside	SARS-CoV-2 proteins under in silico studies	Antiviral	Sagar & Kumar, 2020

TABLE 1 (Continued)

Sr. No.	Indian medicinal plant	Common name	Component and dose of plant used	Assay used	Action	References
			(1,4)-alpha-D-glucan (alpha-DG) drug; 10 mg/kg	Lung and Spleen of Endotoxin-Stimulated Juvenile Rats	Immunomodulator; Antiviral	Velazquez, Kimura, Torbati, Ramachandran, & Totapally, 2009
19.	<i>Viscum album</i>	Mistletoe	Aqueous extract of leaves; 1 µg/ml (aqueous extract)	HPIV2 strain in Vero cells	Reduced viral replication	Karagöz, Onay, Arda, & Kuru, 2003
20.	<i>Withania somnifera</i>	Ashwagandha	Withaferin A	In silico study	High binding affinity to NA	Cai et al., 2015
21.	<i>Woodfordia fruticosa</i>	Fire Flame Bush, Red Bell Bush, ban-mahendi (hindi)	Gallic acid extracted from flowers; 100 µg/ml	Hella, HRV2 and HRV3 cells	Inhibit viral replication and antioxidant	H. J. Choi, Song, Bhatt, & Baek, 2010
22.	<i>Zingiber officinale</i>	Ginger	Aqueous extract of Fresh ginger rhizomes; 300 µg/ml Aqueous extract of ginger rhizomes; 10% concentration of aqueous extract	HRSV strain in HEp-2 and A549 cell lines; H9N2 strain in embryonated chick eggs;	Antiviral; Antiviral;	Chang, Wang, Yeh, Shieh, & Chiang, 2013 Rasool et al., 2017

Abbreviations: H1N1, H3N2, H5N1, H7N3, H9N2, Influenza A virus subtypes; HPIV-2, human parainfluenza virus type 2; HRV, Human rhinovirus; IAV, influenza A virus; IBV, Infectious Bronchitis Virus; MDCK, Madin-Darby canine kidney; PRRSV, porcine reproductive and respiratory syndrome virus; RSV, Respiratory Syncytial Virus Infection; SPF, Specific pathogen free.

andrographolide showed significantly high druggability, permeability, solubility, and target accuracy.

*Andrographis paniculata* has also been observed to inhibit increased levels of NOD-like receptor protein-3 (NLRP3), caspase-1, and interleukin-1 $\beta$  molecules involved in SARS-CoV mechanism (Y. T. Liu, Chen, et al., 2020; Z. Liu, Xiao, et al., 2020).

The hot water extract of *Andrographis paniculata* illustrated significant immunomodulatory activity through its multitarget efficacy in esophageal cancer management (Yue et al., 2019). HN-02 (a mixture of different *Andrographis paniculata* extract) ameliorated cyclophosphamide-induced immune suppression and stimulated the humoral and cell-mediated immunity (Naik & Hule, 2009). Andrographolide regulated the macrophage activation via mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling along with targeted antibody secretion (Wang et al., 2010).

### 3.1.5 | *Bergenia ciliata* (Haw.) Sternb. (Saxifragaceae)

*Bergenia Ciliata* is commonly known as fringed elephant's ears, is native to China, and the Himalayas, and is commonly used in the management of fever, diarrhea, and chest infection (Saha & Verma, 2011).

Rajbhandari et al. (2009) assessed the antiviral potency of methanol extract of *Bergenia ciliata* rhizome against human influenza virus

A/WSN/33 (H1N1) in MDCK and Vero cells. The extract significantly inhibited the virus strain with the concentration ranging from 30 to 50  $\mu\text{g ml}^{-1}$  that significantly lowers the cell viability by 50% and half-maximal inhibitory concentration ( $\text{IC}_{50}$ ) values from 8 to 10  $\mu\text{g ml}^{-1}$ .

One of the studies evaluated the immunostimulatory activity of lyophilized ethanol extract of *Bergenia ciliata* leaves. The findings illustrated the increased production of CD69, a human transmembrane glycoprotein that is involved in lymphocyte growth and function (Tumova & Vokurková, 2018).

### 3.1.6 | *Cinnamomum cassia* Nees ex Blume (Lauraceae)

Traditionally, Cinnamon is used as a healthy herbal spice. It is extracted from the inner bark of a tree that belongs to *Cinnamomum* (Bae, Nam, & Park, 2002).

Fatima et al. (2016) determined the antiviral properties and characteristics of Cinnamon silver (Ag) nanoparticles against influenza virus infection in Vero cells. The nanoparticles illustrated significant antiviral properties in treated groups along with a significant safety profile. This possible strategy of synthesized nanoparticles may be an option for the effective treatment of virus infections.

Koh et al. (1998) determined two cinnamaldehyde derivatives that is, 2'-hydroxycinnamaldehyde (HCA) and 2'-benzoxy-cinnamaldehyde (BCA) from *Cinnamomum cassia* and evaluated their immunomodulatory



TABLE 2 Traditional Indian medicinal plants as immunomodulators

Sr. No.	Plant name	Component	Immunologic RESPONSE	Reference
1.	<i>Achyranthes bidentata</i>	Achyranthes bidentata polypeptide k (ABPPk) from roots	Increased lymphocyte level of IgA, IgG, IgM, IL-2, and IFN- $\gamma$ and also increased splenic lymphocytes and peripheral T-cells	Q. Cheng et al., 2019
2.	<i>Andrographis paniculata</i>	HN-02, (andrographolides + 14-deoxyandrographolide +14-deoxy-11,12-didehydroandrographolide) crude powder	Improved macrophage phagocyte system-innate immunity Ameliorate humoral response in Hemagglutination antibody (HA) titer against sheep red blood cells	Naik & Hule, 2009
3.	<i>Andrographis paniculata</i>	Andrographolide	In vivo—Decreased production of anti-HBs antibody and number of IL-4 inducing splenocytes In vitro—decreased the macrophages activation induced by LPS or IL-4, cytokine expression of M1 and M2, IL-12/IL-10 ratio and mannose receptor (CD206)	Wang et al., 2010
4.	<i>Andrographis paniculata</i>	Hot water extract of raw herb	Regulated the population of regulatory T cells, production of cytokines in model of esophageal tumorigenesis Significantly increased the tumors apoptosis by suppressing the growth of cell line-based xenografts In vitro—proliferation of human peripheral blood mononuclear cells, as well as TNF- $\alpha$ and IFN- $\gamma$ productions	Yue et al., 2019
5.	<i>Aloe Vera</i>	Aqueous gel extract from leaves	Increased cell viability of infected macrophages	Farahnejad, Ghazanfari, & Yaraee, 2011
6.	<i>Aloe Vera</i>	Aloin from leaves	Boosted host immunity with enhance the hemagglutinin-specific T cell response	C. T. Huang et al., 2019
7.	<i>Bergenia ciliata</i>	Ethanol leaves extract	CD69 increased on lymphocytes	Tumova & Vokurková, 2018
8.	<i>Cinnamomum Cassia</i>	2'-hydroxycinnamaldehyde (HCA) and 2'-benzoxycinnamaldehyde (BCA) from stem bark using methanol	Lymphoproliferation suppressed and T-cell differentiation stimulated	Koh et al., 1998
9.	<i>Curcuma longa</i>	Aqueous extract of dried rhizome	Stimulative effect on proliferation of PBMC and production of cytokine	Yue, Chan, Hon, Kennelly, et al., 2010; Yue, Chan, Hon, Lee, et al., 2010
10.	<i>Curcuma longa</i>	Curcuminoids and alpha-turmerone from dried rhizome using ethanol	Production of cytokines and PBMC proliferation stimulated	Yue, Chan, Hon, Kennelly, et al., 2010; Yue, Chan, Hon, Lee, et al., 2010
11.	<i>Cydonia oblonga</i>	peel, pulp and seeds hot water extract	IL-13, TNF- $\alpha$ , Leukotriene C(4) and prostaglandin, COX-2 reduced in BMMC	Kawahara & Iizuka, 2011
12.	<i>Cydonia oblonga</i>	whole crushed	Reduced level of IL-8 and TNF- $\alpha$ in human mast cells	Huber et al., 2012
13.	<i>Embelia ribes</i>	Embelin (present in berries of plant) - in silico study	TNF-alpha decreased	Dhanjal et al., 2014
14.	<i>Glycyrrhiza glabra</i>	Aqueous root extract	HA titer and antibody-secreting cells in mouse spleen	Mazumder, Pattnayak, Parvani, Sasmal, & Rathinavelusamy, 2012
15.	<i>Hypericum perforatum</i>	Hyperforin	Enhances immunity by modulating phagocytosis	Brondz & Brondz, 2012
16.	<i>Hypericum perforatum</i>	ethanol extract of dry plant	Suppresses IFN- $\gamma$ and monocyte chemotactic protein	N. Huang et al., 2013
17.	<i>Jatropha curcus</i>	Aqueous methanolic extract and its derivatives	Increased level of lymphocytes, macrophages cells, and antibody titer	Abd-Alla, Moharram, Gaara, & El-Safty, 2009

TABLE 2 (Continued)

Sr. No.	Plant name	Component	Immunologic RESPONSE	Reference
18.	<i>Justicia adhatoda</i>	Chloroform, methanolic and diethyl ether extracts from leaves	Increased percentage of neutrophil adhesion, and it also leads to delayed type hypersensitivity in rats	Vinothapooshan & Sundar, 2011
19.	<i>Momordica charantia</i>	polysaccharide extract from dried fruit extract using ethanol	Increased the production of serum haemolysin, thymus index, spleen index, and natural killer cell cytotoxicity	Deng et al., 2014
20.	<i>Ocimum sanctum</i>	Petroleum ether seeds extract	Balanced both cell and humoral-mediated immune response	Mediratta, Sharma, & Singh, 2002
21.	<i>Ocimum sanctum</i>	Aqueous leaves extract	Enhanced the lymphocyte and neutrophil counts along with increase in phagocytic index and phagocytic activity	Mukherjee, Dash, & Ram, 2005
22.	<i>Psoralea corylifolia</i>	Ethanol seeds extract	Stimulated antibody-dependent cellular cytotoxicity, NK cell activity, antibody complement-mediated cytotoxicity during development of tumor, and inhibition of growth of tumor	Latha, Evans, Panikkar, & Jayavardhanan, 2000
23.	<i>Tinospora cordifolia</i>	ethyl acetate, water fractions and hot water stem extract	Increased phagocytosis percentage	U. Sharma et al., 2012
24.	<i>Tinospora cordifolia</i>	G1-4A (polysaccharide)	Upregulation of IL- $\beta$ , IL-12, TNF- $\alpha$ , IFN- $\gamma$ , IL-10 and nitric oxide	Gupta, Rajan, & Kulkarni, 2017
25.	<i>Tinospora cordifolia</i>	Guduchi Imp from dry stem powder using water	Significantly increased anti-guduchi Imp IgG and IgA, anti-OVA IgG and IgA after administration of guduchi Imp	Aranha & Venkatesh, 2018
26.	<i>Tinospora cordifolia</i>	Aqueous extract	Increased the production of TNF- $\alpha$ , IFN- $\gamma$ and IL-1 $\beta$ in cyclophosphamide-treated mice	Alrumaihi et al., 2019
27.	<i>Viscum album</i>	Peptide Iscador (isotonic injectable Preparation and concentrated plant extract)	Natural killer cell activity enhanced, antibody dependent cellular cytotoxicity stimulated	Kuttan & Kuttan, 1992
28.	<i>Viscum album</i>	Iscador M (= mali from apple tree mistletoe) and Iscador P (= pini, from pine mistletoe)	Normalization of initial immune indices	Chernyshov et al., 2000
29.	<i>Withania somnifera</i>	Methanol Root extract	Increased circulating antibody titer and number of plaque forming cells in spleen, Phagocytic action of peritoneal macrophages increased	Davis & Kuttan, 2000
30.	<i>Withania somnifera</i>	<i>Withania somnifera</i> (WS) extract and Withaferin A	Reduction in phagocytosis, up-regulation of TLR6, restoration of phagocytic activities	J. Kumar, Mitra, Hussain, & Kaul, 2019
31.	<i>Woodfordia fruticosa</i>	Ethanol Flowers extract	Stimulation of macrophages, bone marrow cells and nonspecific immune responses	Shah & Juvekar, 2010
32.	<i>Zingiber officinale</i>	Essential oil extract	Recovered the humoral immune activity in immunosuppressed mice	Carrasco et al., 2009
33.	<i>Zingiber officinale</i>	Ethanol rhizome extract	Regulated expression of IL-33 and IL-27	Jafarzadeh et al., 2014

Abbreviations: ABPPk, *Achyranthes bidentata* polypeptide k; COX-2-cyc, loxygenase-2; HA, Hemagglutination antibody; IFN- $\gamma$ , Interferon gamma; IgA, IgG, IgM, Immunoglobulins; IL-2, IL-4, IL-12/IL-10, IL-13, IL- $\beta$ , IL-12, IL-33 and IL-27, Interleukins; LPS, Lipopolysaccharides; PBMC, peripheral blood mononuclear cell; TLR 6, Toll like receptors 6; TNF- $\alpha$ , Tumor necrosis factor alpha.

**TABLE 3** Thrombolytic properties of traditional Indian medicinal plants

Sr. No.	Plant name	Component	Thrombolytic activity	Reference
1.	<i>Achyranthes bidentata</i>	Achyranthes bidentata polypeptide k (ABPPk) from roots	Inhibited oxidative damage induced in endothelial cells of brain, enhanced the tissue factor activation, plasminogen activator inhibitor –1 and MMP-2/9 activation	Q. Cheng et al., 2019
2.	<i>Cinnamomum Cassia</i>	Active compounds obtained from methanol extract of twigs	Cinnamic alcohol, methoxycinnamaldehyde, eugenol, coniferaldehyde, amygdalactone, and hydroxycinnamaldehyde effective in inhibition of platelet coagulation	Kim et al., 2010
3.	<i>Curcuma longa</i>	Aqueous extract	Clot lysis activity (32.94 ± 3.663%)	I. N. Khan et al., 2011
4.	<i>Cydonia oblonga</i>	Aqueous extract of leaves	Decreased plasma concentration of thromboxane B2 and increased 6-keto-prostaglandine F1 $\alpha$	Zhou et al., 2014
5.	<i>Embelia Ribesm</i>	Ethanol fruit extract	Reduced adenosine diphosphate and thrombin-induced platelet aggregation Inhibit malondialdehyde production	Jagtap, Sancheti, & Phadke, 2012
6.	<i>Glycyrrhiza glabra</i>	Glycyrrhetic acid	Inhibit factor Xa and platelet aggregation	Jiang, Wang, Shen, Xiao, & Li, 2014
7.	<i>Justicia adhatoda</i>	Methanolic leaves extract	Lysis of almost 80% clot	Shahriar 2013
8.	<i>Momordica charantia</i>	Seed extract	Role of seed extract in intrinsic pathway of blood coagulation cascade enhanced the clotting time of blood	Manjappa et al., 2015
9.	<i>Tinospora cordifolia</i>	Caps HT2, a herbal formulation	Inhibited platelet aggregation, increased the synthesis of lipoprotein lipase enzyme, and delaying calcification of plasma	Mary, Babu, & Padikkala, 2003
10.	<i>Withania somnifera</i>	Withaferin A (WFA)	Increased bleeding time in an in vivo and ex vivo, prevented PAI-1 production induced by TNF- $\alpha$ , decreased PAI-1/t-PA ratio significantly	Ku & Bae, 2014
11.	<i>Zingiber officinale</i>	Aqueous roots extract	Lowered serum PGE(2), TXB(2), decreased in serum cholesterol	Thomson et al., 2002

Abbreviations: ABPPk, Achyranthes bidentata polypeptide k; MMP-2/9, Matrix metalloproteinase-2/9; TNF- $\alpha$ , Tumor necrosis factor alpha; PGE(2), Prostaglandin E2; TXB(2), Thromboxane B2.

effects. The study concluded that these derivatives have the potency to block the proliferation of lymphocytes and T-cells differentiation by inhibiting the signaling pathway of cell growth.

Thirteen compounds were extracted from *Cinnamomum cassia* out of which hydroxycinnamaldehyde, methoxycinnamaldehyde, amygdalactone, eugenol, coniferaldehyde, and cinnamic alcohol were active compounds that significantly inhibited arachidonic acid-induced platelets aggregation and a thromboxane A2 induced aggregation in the preliminary testing (Kim et al., 2010).

### 3.1.7 | *Curcuma longa* L. (Zingiberaceae)

Curcumin belongs to the ginger family and is prepared from *Curcuma longa* rhizomes. It has various noted pharmacological properties like antiinflammatory, antioxidant, antibacterial, and antiviral (Araújo & Leon, 2001).

Sornpet et al. (2017) used the crude extracts of *Curcuma longa* against H5N1 virus infection to evaluate its antiviral activity in MDCK cells. The study found that the treatment of Curcumin exhibits a significant rise in the level of TNF- $\alpha$  (tumor necrosis factor) and IFN- $\beta$  at mRNA level in cells, which indicates its role in inhibiting virus replication.

X. X. Yang et al. (2016) used Curcumin-modified silver nanoparticles (cAgNPs) to evaluate its effectiveness against RSV infection in human epithelial type 2 (HEp-2) cells and found decreased viral loads in the cell line.

Avasarala et al. (2015) observed the antiviral efficacy of curcumin in a rodent model of acute pneumonia (Acute Respiratory Distress Syndrome). Curcumin significantly alleviated the fibrosis and inflammation in the lungs.

Richart et al. (2018) evaluated the synergic virucidal activity of curcumin and monoacetylcurcumin (a structural analog of curcumin) against influenza virus infection in MDCK cells. The combination

significantly inhibited viral NA activity and PI3K/Akt (phosphatidylinositol 3-kinase (PI3K)/protein kinase B) pathway (important for viral replication) thereby decreasing viral replication.

Alpha-turmerone (*Curcuma longa* extract) showed a significant immunomodulatory effect in human peripheral blood mononuclear cells (PBMC). Alpha-turmerone triggered peripheral blood mononuclear cells (PBMCs) proliferation and the release of various cytokines, for instance, TNF- $\alpha$ , IFN- $\gamma$ , and IL-2 (Yue, Chan, Hon, Kennelly, et al., 2010; Yue, Chan, Hon, Lee, et al., 2010). Polar fractions of *Curcuma longa* hot water extracts modulated the cytokine production and showed stimulatory effects on PBMCs that further advocated its use as an adjuvant in cancer therapy (Yue, Chan, Hon, Kennelly, et al., 2010; Yue, Chan, Hon, Lee, et al., 2010).

I. N. Khan et al. (2011) determined the thrombolytic activity of *Curcuma longa* in an in vitro thrombolytic model. The study found that *Curcuma longa* exhibited moderate clot lysis activity that was  $32.94 \pm 3.663\%$  as compared to streptokinase (standard) that showed  $86.2 \pm 10.7\%$  clot lysis effect.

### 3.1.8 | *Cydonia oblonga* Mill. (Rosaceae)

*Cydonia oblonga*, commonly known as Quince, mainly found in sub-Himalayan regions is effective against diabetes, inflammation, cancer, and ailments related to the heart and brain (R. Sharma, Joshi, & Rana, 2011).

Phenolic extract of Quince fruit significantly decreased the influenza viral titer (hemagglutinin =27) when compared to the control group (HA = 210). One of the components of phenolic extract that is, procyanidins was found to have strong antiviral activity and prevent infection in the throat (Hamauzu et al., 2005).

*Cydonia oblonga* increased thrombolysis and shortened euglobulin lysis time. It also reduced the arterial and venous thrombus weights in a dose-dependent manner. Furthermore, treatment of *Cydonia* decreased the thromboxane B2 (TXB2) level and increased the level of 6-keto-prostaglandin F1 $\alpha$  (6-keto-PGF1 $\alpha$ ) in plasma (Zhou et al., 2014).

### 3.1.9 | *Embelia ribes* Burm.f. (Primulaceae)

*Embelia Ribes* commonly called white-flowered embelia or false black pepper was found in northern western ghats of Maharashtra state of India. The National Medicinal Plant Board put it on a priority species list for cultivation. It has great importance in traditional medicine as analgesic, antiinflammatory, antibacterial, and antioxidant (Mhaskar et al., 2011).

Hossan et al. (2018) assessed ethyl acetate extract of *Embelia ribes* fruits using different strains of influenza (H1N1, H3N2, and H5N2) in MDCK cells. Selectivity index (SI) and IC<sub>50</sub> values of the fruit extract of *Embelia ribes* and Embelin (*Embelia ribes* extract) have shown potential antiviral properties of these extracts. H5N2 strain was the most vulnerable to embelin (SI = 31), while the H3N2 virus strain was more resistant (SI = 5).

During inflammation, TNF- $\alpha$  converting enzyme cleaves the transmembrane protein that is, TNF- $\alpha$  to release it in the extracellular space. *Embelia Ribes* was found to reduce the secretion of TNF- $\alpha$  thereby act as an antiinflammatory and immunomodulatory agent (Dhanjal et al., 2014).

Adenosine diphosphate and thrombin-induced platelet aggregation were significantly reduced by ethanol extract of *Embelin ribes* and moreover, it also inhibited malondialdehyde production in platelets. Arteriovenous shunt and stasis-induced thrombosis were significantly reduced by embelin in rats (Jagtap et al., 2012).

### 3.1.10 | *Glycyrrhiza glabra* L. (Leguminosae)

*Glycyrrhiza glabra*, locally known as “liquorice” and “mulaithi,” is found mainly in the Punjab and Sub-Himalayan regions of India (Shibata, 2000). This herb is employed abundantly in traditional Indian medicine as antiinflammatory and antiviral agents (Damle, 2014).

Glycyrrhizin extracted from *Glycyrrhiza glabra* showed potency in inhibiting adsorption, penetration, and replication of SARS-CoV in Vero cell lines (SI = 67). The extract exhibited the virucidal property by inhibiting the cellular signaling pathways of the virus. Moreover, glycyrrhizin and glycyrrhetic acid, an aglycone metabolite, increased nitrous oxide expression (Cinatl et al., 2003).

Grienke et al. (2014) determined the antiviral efficacy of *Glycyrrhiza glabra* roots extract. The study used NA inhibition in chemiluminescence (CL)-based assay along with additional tests. Out of different compounds, three compounds showed promising results (Tanimoto Combo value >0.70).

Liang et al. (2019) evaluated 18 water-soluble  $\beta$ -cyclodextrin (CD)-G (*Glycyrrhiza glabra* conjugates) for antiviral activities in A/WSN/33 (H1N1) virus. A total of six conjugates showed potential antiviral activity when evaluated in a cytopathic effect assay.

The aqueous root extract of *Glycyrrhiza glabra* is a potent immunomodulator that significantly increased HA titer and antibody-secreting cells along with Zinc in a mouse spleen (Mazumder et al., 2012).

The glycyrrhetic acid showed antithrombotic activity by inhibiting the platelet aggregation and the factor involved in the clotting pathway that is, factor Xa in the rat venous stasis model (Jiang et al., 2014).

### 3.1.11 | *Hypericum perforatum* L. (Hypericaceae)

Generally known as St John's Wort, *Hypericum perforatum* is a herb, which grows mainly in Asia, Africa, and Australia and has antiinflammatory, antidepressant, anxiolytic, and nootropic activities (V. Kumar, Singh, & Bhattacharya, 2001).

H. Chen et al. (2019) assessed *Hypericum perforatum* ethyl acetate (HPE) extract in specific pathogen-free (SPF) chicken embryos along with kidney cells using infectious bronchitis strain (IBS-M41). Under in vitro conditions, HPE significantly reduced viral titer and mRNA

expression. Under in vivo conditions, HPE ameliorated IBS-M41-induced inflammation in the trachea and in the kidney that could be attributed to its immunomodulatory effect and antiviral effect. *Hypericum perforatum's* components, for instance, hyperoside, quercitrin, quercetin, pseudohypericin, and hypericin, were found to be potential anti-IBV (Infectious Bronchitis Virus) agents.

N. Huang et al. (2013) studied ethanol extract of *Hypericum perforatum* against H1N1 strain in A549 human bronchial alveolar epithelial cells and mice. In cell lines, *Hypericum perforatum* suppressed IFN- $\gamma$  and monocyte chemotactic protein. In mice, the treatment group showed a minor reduction in viral titer.

Xiuying et al. (2012) observed significant antiviral potency of *Hypericum perforatum* extracts in Influenza A Virus (IAV)-induced mice. The expression of IL-10 and IFN- $\gamma$  increased, whereas expression of TNF- $\alpha$  and IL-6 decreased significantly. It resulted in decreased lung index and viral load.

Hyperforin (*Hypericum perforatum* extract) significantly increases immunity by modulating phagocytosis. It has an important antibiotic along with immunomodulatory properties administer to individuals exposed to Gram-positive *Coccaceae*, including methicillin-resistant *Staphylococcus aureus* (Brondz & Brondz, 2012).

### 3.1.12 | *Jatropha curcas* L. (Euphorbiaceae)

Commonly known as purging nut, it is mainly cultivated in drier sites of central and western parts of India. It has a medicinal value in tumors and certain infections (Dahake, Roy, Patil, Rajopadhye, & Chowdhary, 2013).

Patil et al. (2013) assessed the aqueous and methanolic extract of *Jatropha curcas* leaves against the Influenza A (H1N1) virus in MDCK cells. The aqueous and methanolic extract of *Jatropha curcas* showed more potent antiviral activity in the simultaneously treated group and postpenetration exposure group than the prepenetration exposure group. The study concluded that the extracts of *Jatropha curcas* at the time of simultaneous exposure may exert their effect by inhibiting the absorption of viruses in the cells, mediated by sialic acid.

The aqueous methanolic extracts and derivatives of *Jatropha curcas* illustrated a significant increase in antibody production, lymphocyte, and macrophage cells, in SPF chicks of 1 day old. These chicks were observed to be protected against the Newcastle disease virus (Abd-Alla et al., 2009).

### 3.1.13 | *Justicia adhatoda* L. (Acanthaceae)

*Justicia adhatoda* generally known as Malabar nut is a herb that grows in the open tree canopy in tropical to subtropical areas mainly in the Indo-China region. It acts as an antimicrobial, antiinflammatory, and beneficial for cardiovascular diseases (Dhankhar et al., 2011). Chavan and Chowdhary (2014) assessed the activity of methanolic leaf extract of *Justicia adhatoda* against standard influenza strain in MDCK cells and found a reduction in HA and virus replication.

Administration of *Justicia adhatoda* extracts in Wistar rats enhanced the adhesion of neutrophils to nylon fibers. Moreover, the test samples also induced delayed-type hypersensitivity reactions in erythrocytes of sheep that showed its immunomodulatory activity in the host (Vinothapooshan & Sundar, 2011).

The methanolic fraction of *Justicia adhatoda* exhibited a significant thrombolytic activity (53.23%) using streptokinase as the standard (Shahriar, 2013).

### 3.1.14 | *Momordica charantia* L. (Cucurbitaceae)

*Momordica charantia* is found mainly in some parts of Asia and Africa and used for its edible fruit. It acts as an antidiabetic, anticancer, and anti-infectious agent (Grover & Yadav, 2004).

Pongthanapisith et al. (2013) assessed the antiviral efficacy of *Momordica charantia* against H1N1 and H3N2 viral infections. The study concluded that the purified protein from the seeds of *Momordica charantia* significantly inhibited H1N1 and H3N2 and also its subtypes under in vitro conditions without exhibiting any cytotoxicity. The plant has a broad range of antiviral activity and can be used as a treatment option for various emerging viral infections.

Administration of polysaccharides of *Momordica charantia* in cyclophosphamide-induced immunosuppressed mice significantly enhanced the secretion of serum hemolysin. Moreover, it normalizes the thymus index, spleen index, and natural killer (NK)-cell cytotoxicity (Deng et al., 2014).

The seed extract of *Momordica charantia* prolonged the clotting time of activated partial thromboplastin time through blood coagulation cascade (Manjappa et al., 2015).

### 3.1.15 | *Ocimum tenuiflorum* L. (Lamiaceae)

*Ocimum tenuiflorum* is widely distributed in India and its medicinal roles have been mentioned in Indian Ayurveda (Wealth of India, 1991). There are different parts of *Ocimum tenuiflorum* used for the treatment of several ailments like asthma, bronchitis, cough, cold, and digestive disorders (Ghosh, 1995).

An in silico study concluded the potential role of *Ocimum tenuiflorum* extracts in inhibition of ACE-2 (angiotensin-converting enzyme –2) receptor of SARS-CoV-2 (Varshney, Varshney, & Nath, 2020).

Out of different extracts, crude extract and terpenoid extract of *Ocimum tenuiflorum* exhibited a significant reduction in copy numbers of viruses genome at the lowest dose tested. The crude and terpenoid extract prepared from the *Ocimum tenuiflorum* leaves had strong antiviral potency against the H9N2 virus (Ghoke et al., 2018).

Alhazmi (2015) evaluated the antiviral properties of all phytochemicals isolated from *Ocimum tenuiflorum* plant using a protein of H1N1 strain under in silico study. The study reported that Apigenin has good binding properties in comparison to Oseltamivir and Zanamivir. Therefore, this compound needs further investigation under in vitro as well as in vivo conditions.

Intraperitoneal administration of seed oil extract from *Ocimum tenuiflorum* at the dose of 3 ml/kg in sensitized rats exhibited significant augmentation of antibody titer and reduction in the release of histamines from peritoneal mast cells and also inhibited the migration of leukocyte (Mediratta et al., 2002). Aqueous extract of *Ocimum tenuiflorum* showed significant immunomodulatory potential by increasing the lymphocytes and neutrophils population. It also augmented the phagocytic index as well as phagocytic activity (Mukherjee et al., 2005).

### 3.1.16 | *Psoralea corylifolia* L. (Leguminosae)

*Psoralea corylifolia* is a plant used in Indian traditional medicine. (+)-(S)-Bakuchiol is a phenolic isoprenoid that is isolated from *Psoralea corylifolia* seeds and helpful in traditional Indian medicine to cure numerous diseases (Z. Chen et al., 2010; H. L. Chen, Feng, & Li, 2010; Poláková, Fauger, Sayag, & Jourdan, 2015).

Shoji et al. (2015) examined the antiviral activity of Bakuchiol in MDCK cells. The study found that (+)-(S)-Bakuchiol and its enantiomer (–)-(R)-Bakuchiol significantly prevented the activity of influenza A viral infection by inhibiting the mRNA expression and protein expression of the virus. (+)-(S)-Bakuchiol showed more potency as compared to (–)-(R)-Bakuchiol. These results showed that it may be used as a good antiviral candidate against viral infectious diseases.

Administration of *Psoralea corylifolia* extract inhibited the cancer cell growth and induced the antibody-dependent cellular cytotoxicity, NK-cell activity, antibody complement-mediated cytotoxicity, and activation of B-cells for the production of antibodies (Latha et al., 2000).

### 3.1.17 | *Syzygium cumini* (L.) Skeels (Myrtaceae)

Generally called jambolan or java plum, *Syzygium cumini* has a potential activity in respiratory illness, diabetes, and inflammation (Ayyanar & Subash-Babu, 2012).

Sood et al. (2012) determined the antiviral efficacy of crude extracts of leaves and bark of *Syzygium cumini* against the avian influenza virus (H5N1) in MDCK cells. Cytopathic effect (CPE) reduction assay, yield reduction assay, and egg-based *in ovo* assay were used to examine the virucidal, pre- and postexposure antiviral activities of the extracts. The complete inhibition of the virus was shown by bark and leaves extracts. The efficacy was further supported by egg-based *in ovo* assay and virus yield reduction assay.

### 3.1.18 | *Tinospora cordifolia* (Willd.) Miers (Menispermaceae)

*Tinospora cordifolia*, generally called heart-leaved moonseed, is a shrub that mainly grows in higher altitudes of India. It is found to be efficacious in ameliorating diabetes, inflammation, oxidation, cancer, and

immune imbalance (Ayurvedic Pharmacopoeia Committee, 2001; Parthipan, Aravindhan, & Rajendran, 2011; Rana, Thakur, Sood, Sharma, & Sharma, 2012; Upadhyay, Kumar, Kumar, & Mishra, 2010).

An *in silico* study concluded four natural compounds (*Berberine*, *Isocolumbin*, *Magnoflorine*, and *Tinocordiside*) of *Tinospora cordifolia* showed high binding affinity toward four important targets of SARS-CoV-2 that are responsible for attachment (6VSb, 6M0J) and replication (6M71, 6Y84). The reported efficacy of the natural compounds is either equivalent or superior to some of the important antiviral drugs such as Favipiravir, Lopinavir, and Remdesivir (Sagar & Kumar, 2020).

(1,4)-alpha-D-glucan (alpha-DG) drug was extracted from *Tinospora cordifolia* and its antiviral efficacy was evaluated in the lungs of *E. coli* endotoxin-stimulated juvenile rats. Quantification of protein using enzyme-linked immunosorbent assay (ELISA) showed a decline in pro-inflammatory and anti-inflammatory cytokines in a drug-treated group when compared to endotoxemia (Velazquez et al., 2009).

G1-4A a polysaccharide of *Tinospora cordifolia* effectively activated macrophages via TLR4-MyD88 dependent pathway and plays an important role in innate immunity (Gupta et al., 2017).

*Tinospora cordifolia* aqueous extract efficiently ameliorated cyclophosphamide-induced immunosuppression in a rodent model (Alrumaihi et al., 2019).

Further, as a herbal formulation, *Tinospora cordifolia* prevented platelet aggregation, increased the production of lipoprotein lipase enzyme, and delayed plasma calcification. This process resulted in inhibition of atherogenicity (Mary et al., 2003).

### 3.1.19 | *Viscum album* L. (Santalaceae)

*Viscum album* belongs to the family *Viscaceae* and it has various therapeutic roles as a traditional Indian medicinal plant in many diseases like asthma, vertigo, lumbago, and hypertension (Duke, 1987; Zarkovic, Zarkovic, Grainca, Kissel, & Jurin, 1997).

Different extracts of *Viscum album*, for instance, distilled water, chloroform, ethanol, acetone, and petroleum ether were examined for antiviral potential against human parainfluenza virus type 2 (HPiV-2) growths in Vero cells. The study observed that out of five extracts, the aqueous extract was the most potent selective inhibitor followed by chloroform extract (Karagöz et al., 2003).

The peptide of the *Viscum album* at 2 micrograms/ml enhanced the NK-cell activity in animals. It also induced antibody cellular cytotoxicity and increased the antibody titer in peptide-treated animals (Kuttan & Kuttan, 1992). Children who were exposed to radioactive fallout when treated with *Viscum album* resulted in the regulation of immune indices in the controlled range (Chernyshov et al., 2000).

### 3.1.20 | *Withania somnifera* (L.) Dunal (Solanaceae)

*Withania somnifera* (Ashwagandha) has several medicinal roles like anti-inflammatory, antioxidant, and immunomodulatory (Malik et al., 2007; Mishra, Singh, & Dagenais, 2000).

It has an active component Withaferin A (WA) that acts as an antiviral agent. Withaferin A decreased activity of NA in H1N1 influenza. The docking and molecular dynamics simulation studies found that Withaferin A has a high binding affinity toward NA and showed several important molecular relationships with the residues that are important in the course of simulations (Cai et al., 2015).

*Withania somnifera* extract and Withaferin A significantly decreased the toxicity mediated by zinc oxide nanoparticles under in vivo conditions. The extracts also restored TLR6 and phagocytic activities (J. Kumar et al., 2019). Administration of *Withania somnifera* extract in mice increased the number of plaque-forming cells, circulation of antibody titer in mice spleen, and phagocytosis activity of macrophages (Davis & Kuttan, 2000).

As a thrombolytic agent, Withaferin A increased bleeding time and inhibited aggregation of platelets, the formation of thrombus, and fibrin polymerization (Ku & Bae, 2014).

### 3.1.21 | *Woodfordia fruticosa* (L.) Kurz (Lythraceae)

*Woodfordia fruticosa* is found throughout the region of India, East Asia, and some parts of Africa. The flower of the plant has a medicinal role in diseases like menorrhagia, stomach troubles, and liver diseases (Das et al., 2007).

Gallic acid was prepared from the flower of *Woodfordia fruticosa* and evaluated for its antiviral potential against human rhinoviruses (HRVs). It was administered at different time points that is, during and after infection of HRV in human epithelioid carcinoma cervix cells. Finally, it inhibited the infection of two types of human rhinovirus without showing any cytotoxicity (H. J. Choi et al., 2010).

Ethanol extract of *Woodfordia* exhibited significant immunomodulatory activity by exhilarating the nonspecific immune responses. The extract significantly increased bone marrow cell proliferation and ameliorated cyclophosphamide-induced myelosuppression (Shah & Juvekar, 2010).

### 3.1.22 | *Zingiber officinale* Roscoe (Zingiberaceae)

Generally known as Ginger, *Zingiber officinale* acts as an antiemetic, antiviral, and antibacterial agent (Ali, Blunden, Tanira, & Nemmar, 2008). Chang et al. (2013) evaluated the antiviral efficacy of fresh ginger against HRSV (human respiratory syncytial virus)-induced infection in two important cancer cell lines that is, A549 and HEp-2 cell lines in a dose-dependent manner. The extract is effective against the HRSV-induced infection by blocking the attachment of virus and internalization. Another study used an aqueous extract against the antiavian influenza virus (H9N2) in chick embryos. The study observed that the ginger aqueous extract significantly exhibited antiviral activity against H9N2 (Rasool et al., 2017).

Administration of ginger essential oil orally for a week induced humoral immunity (with sheep red blood cells) in immunosuppressed mice (Carrasco et al., 2009). Jafarzadeh et al. (2014) showed that the administration of extract of ginger in the experimental mice model of

autoimmune encephalomyelitis decreased the IL-27 and IL-33 expression and also modulated the disease severity.

*Zingiber officinale* has thrombolytic activity. In one of the studies, the use of 500 mg/kg of the ginger extract significantly decreased the serum level of prostaglandin-E(2) and platelet thromboxane-B(2) levels. The higher doses of the ginger extract significantly decreased the serum cholesterol level (Thomson et al., 2002).

## 3.2 | Potential traditional Indian herbs and formula used in clinical trials

### 3.2.1 | Kashaya (decoction)

One of the studies depicted that silver nano-particles of *Piper longum* fruit extract has potential antibacterial activity and cytotoxicity activity against MCF-7 (breast cancer cell lines) cell lines (Reddy, Vali, Rani, & Rani, 2014) while *Tinospora cordifolia* has promising antiviral, immunomodulatory, and thrombolytic properties (Alrumaihi et al., 2019; Gupta et al., 2017; Mary et al., 2003; Velazquez et al., 2009).

### 3.2.2 | ZingiVir H (a poly herbomineral drug)

ZingiVir H tablets showed a significant role against respiratory infections, acute bronchitis, RSV, and Influenza virus (Clinical Trial of Ayurvedic Medicine Zingivir-H Tablet Starts on COVID-19 Patients, 2020). A total of seven studies have been registered for Ayurvedic drugs, which include kashaya (decoction) of *Tinospora cordifolia*, ZingiVir H, MyVir tablets, Dabur Chyawanprash, Shanshamani Vati or Sudarshana Ghanavati or Ashwagandha, Yashtimadhu tablet, Guduchi tablet. These Ayurvedic formulations consist of polyherbal drugs that act as an immune booster and fight against infectious diseases. Supportive data are scarce for the use of Ayurvedic drugs against COVID-19. However, the Ministry of AYUSH published guidelines for safety precaution of its use against COVID-19 (Biswakarma & Wadhawan, 2020).

### 3.2.3 | Dabur Chyawanprash with milk

Dabur Chyawanprash is a formulation of herbals that are broadly used as a dietary supplement in India. The popularity of herbal remedies is now extended after the occurrence of COVID-19. It has been used for health benefits from ancient times for boosting the immunity of the body. Dabur Chyawanprash is a composition of more than 40 herbs that are clinically tested and found to enhance two times immunity from common routine infections (Phelamei, 2020).

Various existing works of the literature showed the useful effects of IgG and colostrums found in milk against respiratory tract infections. Previous studies reported that dietary bovine colostrums decreased the human RSV infection and increased the CD8+ T-cell response during infection (den Hartog et al., 2014; M. L. Xu, Kim, Wi, & Kim, 2015).

### 3.2.4 | Aayudh Advance

Aayudh Advance acts as a sniper's shot toward pathogens. Due to pathogens, normal cells of the body can die and can make more harm to the body, which leads to deterioration of health. So Aayudh Advance helps in fighting against pathogens (Aayudh advance, 2020). It was found in a human clinical trial that Aayudh Advance decreased the viral load in the body by 300% and remarkably increased the recovery of patients without showing any side effects or adverse effects. Therefore Aayudh Advance can be used for the treatment of viral diseases (CTRI, CTRI/2020/05/025161).

### 3.2.5 | Samshamani Vati

Samshamani Vati is recommended for the treatment of fever and anemia at a dose of 500 mg twice a day (Maurya, Kumar, Bhatt, & Saxena, 2020).

### 3.2.6 | Anu taila nasal drops

According to the traditional Ayurveda, Anu taila is recommended as a nasal drop to regulate the mucus discharge and other symptoms related to COVID-19. Maharishi Charak has shown the importance of Anu taila in the treatment of congestion of nasal route (Shukla & Tripathi, 2017).

### 3.2.7 | Sudarshana Ghana Vati

Sudarshana Ghana Vati is broadly used for the treatment of fever in different dosage forms. Previous studies showed its significant activity against *Staphylococcus aureus* and also equally beneficial against other diseases like *Salmonella Typhi*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Kiran, Vivek, Deepak, & Khemchand, 2017).

### 3.2.8 | AYUSH-64

Administration of AYUSH-64 for 1 week showed significant improvement in symptoms of Influenza. The study did not report any adverse drug reaction (Gundeti et al., 2020).

### 3.2.9 | Kabasura kudineer

In silico study of 74 compounds depicted that Kaba Sura Kudineer Chooranam (KSKC) has the potency to inhibit the main protease of COVID-19 (Lakshmanan, Moulishankar, & Suresh, 2020).

### 3.2.10 | Vitamin C

Vitamin C can be beneficial in the management of viral diseases due to its proven antiviral and immunomodulatory activities (Righi et al., 2020).

### 3.2.11 | Zinc supplementation

Zinc acts as an antiviral against various viral diseases like papillomavirus, herpes simplex virus, RSV, human immunodeficiency virus (HIV), and hepatitis C virus. Zinc showed its effect by inhibiting the fusion with the membrane of the host, decreasing the function of viral polymerase, and blocking the release of viral particles (Ishida, 2019; Read, Obeid, Ahlenstiel, & Ahlenstiel, 2019; Skalny et al., 2020; Suara & Crowe, 2004).

### 3.2.12 | Camphor

In silico study depicted that camphor has a good affinity for the protease of COVID-19 and ACE-2 receptor (Omar, Bouziane, Bouslama, & Djemel, 2020).

### 3.2.13 | Ayush kwath

Ayush kwath is an Ayurvedic formulation consisting of four medicinal plants (*Ocimum sanctum* Linn., *Cinnamomum zeylanicum* Breyn., *Zingiber officinale* Rosc., and *Piper nigrum* Linn.). The formulation has important antiviral, thrombolytic, antiinflammatory, and immunomodulatory activities. Therefore, it has been recommended by the Government of India as an immune booster against COVID-19 (Gautam, Gautam, Chhetri, & Bhattarai, 2020).

### 3.2.14 | Arsenic Alba-30

Arsenic Alba-30 is an important Unani medicine, known for its biological and antioxidant activities. It acts at the subcellular and cellular levels by regulating certain genes that are involved in the enzymatic activity to prevent oxidative damage and genotoxic effects induced by arsenic trioxide (Kundu, Mitra, & Bukhsh, 2000).

### 3.2.15 | Joshanda

“Joshanda” (decoction) means boiling and “Andah” means prepared by; therefore, it means prepared by boiling. The preparations were used predominantly for influenza, common cold, cough, fever, and respiratory ailments (I. Ahmad, Shamsi, & Shadab, 2020). One of the important preparations called Tiryag-e-Arba consists of



*Gentiana lutea* L., *Aristolochia longa* L., *Commiphora myrrha* (Nees) Engl, and *Laurus nobilis* L. This preparation is mainly used as an immune booster to fight epidemics (A. A. Khan, Bashir, & Akhtar, 2020).

Khameera Marwareed, an Unani formulation, contains three constituents of animal origin, 11 constituents of plant origin, and one constituent of mineral origin (S. Ahmad et al., 2010). These are recommended for the clinical manifestations of infectious diseases (Ansari, Ahmed, Ahmed, & Khan, 2020).

### 3.2.16 | *Bryonia alba* L

*Bryonia alba* L contains several pharmacologically important constituents such as bryonidine, saponarin, vitexin, isovitexin, lutonarin, iso-orientin, glycosides 22-deoxocucurbitosides A and B, and arvenin IV and has significant antiviral activity against human coronavirus and H1N1 (Manvi & Prasad Garg, 2011).

### 3.2.17 | *Gelsemium sempervirens*

*Gelsemium sempervirens* is used in homeopathic medicines and might be promising against COVID-19 (Dey, Dey & Sihag 2020). The known pharmacological action of antimony potassium tartrate is well documented and it is used especially as an anthelmintic in animals (Antimony Potassium Tartrate - an overview|ScienceDirect Topics, 2020). The documented toxicological studies of antimony potassium tartrate give a detailed picture of its toxicological and pathophysiological effects as well as its harmful dosage. Homeopathic dilutions are much safer and well below their toxic proportions (Antimony Potassium Tartrate [UK PID], 2020). There is a substantial basis to consider Homeopathic administration of antimony potassium tartrate for prophylaxis as well as an add-on treatment of COVID-19 infection (Deodhar & Deodhar, 2020). *Crotalus horridus* from rattlesnake venom may be able to inhibit the replication of HIV (P., 2015).

### 3.2.18 | *Neolamarckia cadamba*

*Neolamarckia cadamba* is used predominantly in Indian traditional medicine for cough, fever, gastrointestinal ailments, and skin diseases (Umachigi et al., 2007).

### 3.2.19 | AOIM-Z tablet

AOIM-Z tablet is manufactured by Solumiks Herbaceuticals and has antioxidant and immunomodulatory properties. It enhances the host defense and is used against respiratory tract infections (Aoim-Z tablets, 2020).

### 3.2.20 | Ayurvedic kadha

Ayurvedic kadha consists of basil, cinnamon, black pepper, dry ginger, and raisins are effective as an immune booster (Ministry of AYUSH, 2020).

## 3.3 | Clinical trials on traditional Indian medicinal plants and their formulations

Numerous clinical trials are under investigation to elucidate the efficacy of traditional Indian medicinal plants against COVID-19. In the majority of the clinical trials, traditional Indian medicines against COVID-19 are studied as add-on therapy in addition to standard of care medicines or as a prophylactic/preventive measure in a high-risk population. Traditional Indian medicines are studied as stand-alone in asymptomatic patients or patients with mild to moderate disease (Refer to Table 4).

A total of 32 clinical trials of traditional Indian medicines are registered with Clinical Trial Registry-India (CTRI). Ayurveda interventions include: decoction of *Tinospora cordifolia* stem and *Piper longum* fruit as add-on to standard of care (CTRI, CTRI/2020/04/024882), a poly herbo-mineral drug ZingiVir H as an adjuvant therapy (CTRI, CTRI/2020/04/024883), MyVir tablets to ameliorate immunity in quarantine patients (CTRI, CTRI/2020/05/024967), Chyawanprash as a preventive remedy (CTRI, CTRI/2020/05/024981; CTRI, CTRI/2020/05/025275), supplemental treatment of Aayudh Advance (herbal formulation consisting of essential oils) (CTRI, CTRI/2020/05/025161), effect of Shanshamani Vati or Sudarshana Ghanavati or Ashwagandha in prevention of infection in containment areas (CTRI, CTRI/2020/05/025069), Guduchi ghanvati in prevention of infection in containment areas (CTRI, CTRI/2020/05/025213), AOIM-Z Tablets for prevention of COVID-19 infection in high risk healthy police personnel (CTRI, CTRI/2020/05/025222), and efficacy of Kiratikta and Ashwagandha Churna with Yoga modalities in management of COVID-19 patients (CTRI, CTRI/2020/05/025341). Two randomized controlled trials to assess the potency and safety of Ayush-64 as an add-on to standard therapy are registered (CTRI, CTRI/2020/05/025156; CTRI, CTRI/2020/05/025214). A randomized exploratory clinical study evaluates the immune-stimulatory potential of Ayurveda management protocol (Tablet Samshamani Vati, application of Anutaila to each nostril, gargle with warm water mixed with rock salt and turmeric, Ayush preventive guidelines for COVID-19 with Yoga and Pranayama) (CTRI, CTRI/2020/05/025171). A pilot study is evaluating the efficacy of Ayurveda protocol: *Tinospora cordifolia* with a decoction of *Zingiber officinale*, *Terminalia chebula*, *Tinospora cordifolia*; powder of *Phyllanthus emblica* with water; and golden milk (milk with *Curcuma longa*) (CTRI, CTRI/2020/05/025276). Another randomized trial evaluates the effect of the Ayurvedic treatment regime (pure ashwagandha, pure giloy extract, pure tulsi extract, anu taila drops, and nasal drop powder Swasari Ras) in COVID-19 (CTRI, CTRI/2020/05/025273). Three observational studies that

**TABLE 4** Clinical trials of traditional Indian medicinal plants in COVID-19

Trial registration	Study design/n/Site	Intervention/comparator agent	Therapy type
1	CTRI/2020/04/024882 Nonrandomized, active controlled trial N = 60 Haryana	Kashaya (decoction) of <i>Tinospora cordifolia</i> stem added with finely powdered dried <i>Piper longum</i> fruit Standard of care	Add-on to standard of care
2	CTRI/2020/04/024883 Other N = 112 Karnataka	ZingiVir H (a poly herbomineral drug)	Add-on therapy
3	CTRI/2020/05/024967 Single arm trial N = 30 Karnataka	MyVir tablets Standard treatment as per hospital protocol for COVID 19 Cases	Standalone
4	CTRI/2020/05/024981 Randomized, parallel group trial N = 600 Gujarat, Maharashtra, Rajasthan,	Dabur Chyawanprash twice daily followed by milk Milk (twice daily)	Preventive remedy
5	CTRI/2020/05/025161 Randomized, parallel group, active controlled trial N = 120 Gujarat	Herbal formulation—Aayudh Advance As standard treatment suggested by WHO	Supplemental treatment
6	CTRI/2020/05/025171 Randomized, parallel group trial N = 50,000 New Delhi	Samshamani Vati, Anutaila, rock salt and turmeric, Ayush preventive guidelines Conventional preventive medicine guidelines	Preventive remedy
7	CTRI/2020/05/025069 Single arm trial N = 1,324 New Delhi	Shanshamani Vati or Sudarshana Ghanavati or Ashwagandha	Preventive remedy
8	CTRI/2020/05/025093 Other N = 1,200 Andhra Pradesh	Yashtimadhu tablet	Preventive remedy
9	CTRI/2020/05/025166 Randomized, parallel group trial N = 1,200 Andhra Pradesh	Ashwagandha tablet	Preventive remedy
10	CTRI/2020/05/025088 Randomized, parallel group trial N = 1,200 Andhra Pradesh	Guduchi tablet	Preventive remedy
11	CTRI/2020/05/025156 Randomized, parallel group, active controlled trial N = 60 Maharashtra	AYUSH-64 Standard treatment for COVID-19 infection	Add-on to standard treatment
12	CTRI/2020/05/025213 Single arm trial N = 1,500 Himachal Pradesh	Guduchi ghanvati	Preventive remedy
13	CTRI/2020/05/025214 Randomized, parallel group, active controlled trial N = 80 Chandigarh	AYUSH 64 Conventional standard therapy as per ICMR/WHO parameters	Add-on to standard of care
14	CTRI/2020/05/025298 Nonrandomized, active controlled trial N = 21,500 Tamil Nadu	Kabasura kudineer Nilavembu kudineer Personal Sanitation and Environmental Sanitation	Prophylaxis
15	CTRI/2020/05/025215 Randomized, parallel group trial N = 50 Tamil Nadu	Kabasura Kudineer Vitamin C, zinc supplementation	Add-on
16	CTRI/2020/05/025222 Single arm trial N = 275 Maharashtra	AOIM-Z Tablets	Preventive remedy
17	CTRI/2020/05/025276 Single arm trial N = 50 New Delhi	SanshamaniVati ( <i>Tinosporacordifolia</i> ) with Nagaradikwath (Decoction of <i>Zingiberofficinale</i> , <i>Terminaliachebula</i> , <i>Tinosporacordifolia</i> ), AmalakiChurna (Powder of <i>Phyllanthusemblica</i> ), Golden Milk (milk with <i>Curcuma longa</i> )	Standalone

(Continues)

TABLE 4 (Continued)

	Trial registration	Study design/n/Site	Intervention/comparator agent	Therapy type
18	CTRI/2020/05/025273	Randomized, parallel group, placebo-controlled trial N = 120 Rajasthan	Pure Ashwagandha, Pure Giloy Extract, Pure Tulsi Extract, AnuTaila drops, Nasal Drop Powder SwasariRas Placebo therapy placebo of same dosage form by Oral/nasal route	Standalone
19	CTRI/2020/05/025275	Randomized, parallel group trial N = 200 New Delhi	Ayurveda Rasayana along with conventional guidelines for health care workers. Conventional guidelines for health care workers as per the WHO	Preventive remedy
20	CTRI/2020/04/024857	Cluster-randomized trial N = 100 Maharashtra	ArsAlb, Camphora, <i>Bryonia alba</i> , <i>Helleborusniger</i> , <i>Justicia Adhatoda</i>	Standalone
21	CTRI/2020/04/024905	Randomized, parallel group, placebo-controlled trial N = 100 Uttar Pradesh	Arsenic Album, <i>Bryonia Alba</i> , Gelsemium, AntimoniumTartaricum, <i>Crotalus Horridus</i> Placebo	Add-on
22	CTRI/2020/04/024947	Randomized, parallel group, active-controlled trial N = 100 Maharashtra	Cadamba drug therapy	Standalone
23	CTRI/2020/04/024925	Randomized, parallel group, placebo-controlled trial N = 100 Maharashtra	Homoeopathic medicines will be given as adjuvant to the standard care Placebo	Add-on to standard treatment
24	CTRI/2020/04/024926	Single-arm trial N = 100 Uttar Pradesh	Arsenic Album, <i>Bryonia Alba</i> , Gelsemium, Antimonium Tartaricum, <i>Crotalus horridus</i>	Standalone
25	CTRI/2020/05/024986	Single-arm trial N = 10,000 New Delhi	Arsenic album 30c	Preventive remedy
26	CTRI/2020/05/025254	Nonrandomized, multiple arm trial N = 40,000 Uttar Pradesh, Karnataka, Telangana, Jammu & Kashmir, Maharashtra, New Delhi	Unani Joshanda (Decoction) and Tiryaaq-e-Arba Unani Joshanda (Decoction) and Khameera Marwareed	Prophylaxis
27	CTRI/2020/05/025205	Cluster randomized trial N = 33,000 Chennai, Delhi, Andhra Pradesh, Hyderabad, Jaipur, Kolkata, Kerala, Uttar Pradesh, Mumbai, Noida, Gujarat	Arsenicum album 30C The control group clusters will receive no treatment. However, this will be under observation similar to medicine group.	Preventive remedy
28	CTRI/2020/05/025272	Cluster randomized trial N = 800 Kerala	Arsenicum album 30 Placebo	Prophylaxis
29	CTRI/2020/05/025341	Randomized, parallel group trial N = 30 Uttar Pradesh	Kiratiktadi Kwath, Ashwagandha churna, Yoga exercises, Immuno-booster Ayush Kwath as ministry of ayush guidelines Modern treatment as per UP Govt. norms to asymptomatic and mild cases	Standalone
30	CTRI/2020/05/025338	Single-arm trial N = 40 New Delhi	Ayush 64	Standalone
31	CTRI/2020/05/025332	Randomized, parallel group, active-controlled trial N = 400 Mumbai	Ashwagandha ( <i>Withania somnifera</i> ) Hydroxychloroquine	Prophylaxis

TABLE 4 (Continued)

	Trial registration	Study design/n/Site	Intervention/comparator agent	Therapy type
32	CTRI/2020/05/024969	Randomized, parallel group, placebo-controlled trial N = 100 Uttar Pradesh	Homoeopathic medicine Placebo	Add-on to standard treatment
33	NCT04387643	Observational model: Other Time perspective: Prospective N = 52 Jaipur, India	Dietary supplement: Ayurvedic Kadha	Preventive
34	NCT04395976	Randomized, open label, parallel assignment trial N = 120 London, UK	Ayurveda (each participants will be treated with individualized care)	Prophylaxis
35	NCT04345549	Open-label single-group assignment N = 18 United Kingdom	Individualized Ayurveda	Supportive care
36	NCT04351542	Randomized trial N = 32 United Kingdom	Dietary supplement: Ayurveda Usual care	Supportive care

evaluate the intake of Yashtimadhu, Ashwagandha, and Guduchi tablets as a preventive measure are registered (CTRI, CTRI/2020/05/025093; CTRI, CTRI/2020/05/025166; CTRI, CTRI/2020/05/025088).

A nonrandomized population-based prospective study will evaluate the effectiveness of Unani medicine as a prophylactic in the population at a high risk of COVID-19. The interventions are (1) Unani Joshanda (decoction) and Tiryaq-e-Arba, (2) Unani Joshanda (decoction) and Khameera Marwareed (CTRI, CTRI/2020/05/025254).

There are two trials registered, which aimed to evaluate the effect of Siddha intervention in COVID-19. The first trial evaluates the effect of Kabasura kudineer Nilavembu kudineer as a prophylactic measure in a high-risk population (CTRI, CTRI/2020/05/025298) and the other assesses the effect of Kabasura kudineer supplementation to manage asymptomatic COVID-19 patients (CTRI, CTRI/2020/05/025215).

Homeopathic interventions include Arsenic alba, Camphor, *Bryonia alba*, *Helleborus niger*, *Justicia Adhatoda*, Arsenic Album, Gelsemium, Antimonium Tartaricum, *Crotalus horridus*; Cadamba drug therapy; Arsenic Album 30c (CTRI, CTRI/2020/04/024857; CTRI, CTRI/2020/04/024905; CTRI, CTRI/2020/04/024947; CTRI, CTRI/2020/04/024925; CTRI, CTRI/2020/04/024926; CTRI, CTRI/2020/05/024986; CTRI, CTRI/2020/05/025205; CTRI, CTRI/2020/05/025272; CTRI, CTRI/2020/05/024969).

A total of four clinical trials of traditional Indian medicines are registered with ClinicalTrials.gov. The first trial is an observational study to evaluate the effect of dietary supplement Ayurvedic Kadha in protecting health care workers against COVID-19 (ClinicalTrials.gov, NCT04387643). The second trial is to study Ayurveda as prophylaxis for suspected COVID-19 patients (ClinicalTrials.gov, NCT04395976). Two trials are registered to study the effect of Ayurveda as supportive care in the management of flu-like symptoms (ClinicalTrials.gov, NCT04345549; ClinicalTrials.gov, NCT04351542).

## 4 | DISCUSSION

Despite a large number of drugs under evaluation, currently, there is no standard therapy for COVID-19 (Sanders, Monogue, Jodlowski, & Cutrell, 2020). An important strategy could be the use of herbal medicines that shows potential pharmacological activity against the acute viral infections that mainly persist in the lower respiratory tract. Studies are supporting the use of traditional Chinese medicines (TCM) in ameliorating clinical symptoms in COVID-19. The National Health Commission of China reported that traditional Chinese medicine was found effective in more than 60,000 confirmed cases of COVID-19 (National Health Commission of the People's Republic of China, 2020). The Chinese medicinal plants have been studied extensively in COVID-19, for instance, *Sangju yin*, *Yinqiao san*, *Maxinshigan Tang*, and *Baihegujin Tang* (Z. Xu et al., 2020).

Correspondingly, the Indian subcontinent is a huge repository of medicinal herbs that have been in use to counteract numerous virus-related infections of the respiratory tract for ages. There is an unmet need for antiviral agents against COVID-19 that must be effective, safe, and cost-effective (Mitjà & Clotet, 2020).

The current review puts light on some of the important traditional Indian medicinal herbs that can be a potential antiviral agent against SARS-CoV-2. For instance, in silico studies revealed the potential role of extracts of *Andrographis paniculata*, Camphor, *Ocimum tenuiflorum*, and Kabasura kudineer in inhibition of COVID-19. Andrographolide (*Andrographis paniculata*) fitted well with Mpro of SARS-CoV-2 with high druggability and permeability (Enmozhi et al., 2020) that has a vital role in posttranslational modification of replicase protein in SARS-CoV-2 (Peele et al., 2020). Another important drug target is the ACE-2 receptor that is the entry gate for SARS-CoV-2 and SARS-CoV. The inhibition of this receptor can prevent the orchestrated multiple organ damage induced by these coronaviruses (Li, Tang, Li, & Liu, 2020). In silico studies concluded that Camphor (Omar

et al., 2020), *Ocimum tenuiflorum* extract (Varshney et al., 2020), and Kabusura kudineer (Lakshmanan et al., 2020) bind with the ACE-2 receptor of the coronaviruses that supports their promising role in drug development for COVID-19. The four natural compounds of *Tinospora cordifolia* are found to bind with the important proteins of SARS-CoV-2 (Sagar & Kumar, 2020).

*Glycyrrhiza glabra* inhibited the cellular pathways of SARS-CoV and prevented its adsorption, penetration, and replication. The findings strongly suggest the use of this herb for the treatment of SARS-CoV-2 infection (Cinatl et al., 2003).

Apart from these medicinal herbs, which were evaluated against SARS-CoV-2 and SARS-CoV in different *in silico* and *in vitro* studies, numerous other traditional Indian medicinal herbal plants proved efficacious against other types of acute respiratory infections. For instance, *Acacia arabica* decreased the viral titer of Influenza A virus *in ovo* model (Ghoke et al., 2018) while *Aloe vera* extracts inhibited the viral-induced autophagy and H1N1 infection, thereby reducing mortality under *in vitro* condition (C. T. Huang et al., 2019). *Bergenia ciliata* decreased H1N1 proliferation (Rajbhandari et al., 2009) and Cinnamon silver (Ag) nanoparticles showed antiviral activity against influenza with a significant safety profile (Fatima et al., 2016). In RSV infection, silver nanoparticles of *Curcuma longa* decreased the viral load (X. X. Yang et al., 2016) and also the viral titer in influenza by inhibiting PI3K signaling pathway (Richart et al., 2018). *Cydonia oblonga* and *Embelia ribes* significantly lowered the viral load of different types of Influenza virus under *in vitro* conditions (Hamauzu et al., 2005; Hossan et al., 2018). *Hypericum perforatum* inhibited IFN- $\gamma$  and chemotactic protein in influenza (N. Huang et al., 2013) while *Jatropha curcas* inhibited the absorption of H1N1 (Patil et al., 2013). *Justicia adhatoda*, *Momordica charantia*, *Psoralea corylifolia*, *Syzygium cumini*, *Withania somnifera*, and *Zingiber officinale* inhibited the virus titer of different types of Influenza viruses (Cai et al., 2015; Chavan & Chowdhary, 2014; Pongthanapith et al., 2013; Rasool et al., 2017; Shoji et al., 2015; Sood et al., 2012). *Viscum album* significantly reduced the replication of HPIV2 virus under *in vitro* conditions (Karagöz et al., 2003). Though these traditional Indian medicinal plants have not been evaluated against SARS-CoV-2, they provide compelling evidence to assess their efficacy against the virus.

The severity of the novel coronavirus infection is associated with high expression of IFN- $\gamma$ -induced protein-10, macrophage inflammatory protein 1 $\alpha$ , monocyte chemo-attractant protein-1, granulocyte-colony stimulating factor, TNF- $\alpha$ , IL-2R, IL-6, and interstitial mononuclear inflammatory infiltrates (L. Chen et al., 2020; C. Huang et al., 2020; Z. Xu et al., 2020). The traditional Indian medicinal plants have a promising immunomodulatory activity, for instance, *Achyranthes bidentata* increased the lymphocyte proliferation and release of certain cytokines (Q. Chen et al., 2009) while *Andrographis paniculata* and *Aloe Vera* can activate the humoral and innate immunity on exposure to viral infections (C. T. Huang et al., 2019; Naik & Hule, 2009). *Bergenia ciliata* and *Cinnamomum Cassia* affect the lymphocyte growth and functions (Koh et al., 1998; Tumova & Vokurková, 2018), whereas *Curcuma longa* increased the PBMC proliferation (Sormpet et al., 2017). *Hypericum perforatum* alters the

production of cytokines (N. Huang et al., 2013) while *Jatropha curcas* was found to activate antibody secretion and lymphocyte activation against the Newcastle disease virus (Abd-Alla et al., 2009). *Justicia adhatoda* can activate delayed-type hypersensitivity (Vinothapooshan & Sundar, 2011) while *Momordica charantia* ameliorated the cyclophosphamide-induced immunosuppression in rats (Deng et al., 2014). *Ocimum tenuiflorum* can affect the neutrophil and lymphocyte population (Mukherjee et al., 2005), whereas *Psoralea corylifolia* induced the NK-cell activity and antibodies-dependent cytotoxicity in cancer cells (Latha et al., 2000). *Tinospora cordifolia* activated the innate immune response via TLR4-MY88 axis (Gupta et al., 2017) and ameliorated cyclophosphamide-induced immunosuppression in rats (Alrumaihi et al., 2019). *Viscum album* regulated immune indices in radioactive exposed children (Chernyshov et al., 2000) while *Withania somnifera* has a beneficial role in humoral immunity (Davis & Kuttan, 2000). *Woodfordia fruticosa* is useful in immunocompromised conditions (Shah & Juvekar, 2010), and *Zingiber officinale* induced humoral immunity in immunosuppressed mice (Carrasco et al., 2009). These medicinal plants exhibit significant immunomodulatory activity that could be beneficial in ameliorating the cytokine storm induced by the SARS-CoV-2 virus.

Also, the severity of the disease is associated with a high prevalence of clinically relevant thrombosis in COVID-19 patients. Numerous COVID-19 patients develop ARDS that results in life-threatening thrombotic complications (Connors & Levy, 2020; Helms et al., 2020). The traditional medicinal plants showed significant thrombolytic activity, which is attributed to the decreased thromboxane B2 (TXB2), serum level of prostaglandin-E(2), factor Xa, and increased level of 6-keto-prostaglandin F1 $\alpha$  (6-keto-PGF1 $\alpha$ ) that improved blood circulation and reduced weight of thrombus. For instance, *Achyranthes bidentata* can activate plasminogen activator inhibitor-1 in brain ischemia (Q. Cheng et al., 2019) while *Cinnamomum cassia* inhibited arachidonic acid and thromboxane A2-induced platelet aggregation (Kim et al., 2010). *Cydonia oblonga* dose-dependently reduced venous and arterial thrombus along with decreased thromboxane B2 (TXB2) and increased level of 6-keto-prostaglandin F1 $\alpha$  (6-keto-PGF1 $\alpha$ ) (Zhou et al., 2014). *Embelin ribes* inhibited malondialdehyde production in platelets and also reduced arteriovenous shunt and stasis induced thrombosis in rats (Jagtap et al., 2012). *Justicia adhatoda*, *Momordica charantia*, *Tinospora cordifolia*, and *Withania somnifera* exhibit significant thrombolytic activity (Ku & Bae, 2014; Manjappa et al., 2015; Mary et al., 2003; Shahriar, 2013). *Zingiber officinale* significantly decreased the serum level of prostaglandin-E(2) and platelet thromboxane-B(2) levels (Thomson et al., 2002).

Apart from preclinical studies, numerous traditional Indian herbal medicines are considered to be evaluated under clinical trials. These studies attempt to establish the safety and efficacy of traditional Indian herbal medicines. The potential use of these traditional Indian medicinal plants cannot be proposed for the management of mild or moderate or in critical conditions but these plant products can be used as an add-on therapy. More mechanism-based studies are required to identify the effective components of these plants that could be effective against SARS-CoV-2 (Xu & Zhang 2020).

## 5 | CONCLUSION

1. Our study found 22 potential traditional Indian medicinal plants and 36 clinical trials of traditional Indian medicinal plants currently registered in different clinical trial databases for the development of drug therapies against COVID-19.
2. The most promising traditional Indian medicinal plants for the management of COVID-19 are *Ocimum tenuiflorum* and *Tinospora cordifolia* as these herbal plants exhibited significant binding affinity, immunomodulatory, and thrombolytic activities.
3. Further, *Achyranthes bidentata*, *Cinnamomum cassia*, *Cydonia oblonga*, *Embelin ribes*, *Justicia adhatoda*, *Momordica charantia*, *Withania somnifera*, and *Zingiber officinale* exhibit significant antiviral properties against different viruses known to cause acute respiratory infection. These herbs also exhibit significant immunomodulatory and thrombolytic activities.
4. *In silico* studies showed that traditional Indian herbal formulas such as Camphor and Kabusura kudineer found to bind with the important protease of the SARS-CoV-2 thereby could be promising for the treatment of the viral disease.
5. The potential use of these traditional Indian medicinal herbs cannot be proposed for the management of mild, moderate, or critical COVID-19. These types of recommendations need more supportive studies. But these plant traditional Indian medicinal products can be used as an add-on therapy.
6. Further, the clinical trials have undertaken some of the potential Indian herbs and formulas against COVID-19. There is an urgent need for prospective cohort studies to further determine the potential of these traditional Indian medicines. Since there is the availability of the population sample of COVID-19, a sequence of prospective studies with well-designed studies should start producing authentic proof for this herbal prevention of COVID-19 or related respiratory infectious diseases shortly.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR'S CONTRIBUTION

Rahul Soloman Singh, Ashutosh Singh—Conception or design of the work, Data collection, Data analysis and interpretation; Harpinder Kaur, Gitika Batra—Data collection, Data analysis and interpretation; Phulen Sarma—Drafting the article, Critical revision of the article, Data analysis; Hardeep Kaur, Anusuya Bhattacharyya, Amit Raj Sharma, Subodh Kumar, Sujata Upadhyay, Vinod Tiwari—Data collection, Data analysis; Pramod Avti, Ajay Prakash—Drafting the article, Critical revision of the article; Bikash Medhi—Conception or design of the work, Drafting the article, Critical revision of the article, Final approval of the version to be published.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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