

REPURPOSED TRADITIONAL MEDICINAL PLANTS AS AN IMPORTANT WEAPON FOR FIGHTING AGAINST COVID-19: PAKISTANI PERSPECTIVE

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Abstract

In present scenario, World needs prevention and control of SARS-COV₂ ailment epidemic. To manage overall sheer carrier and sufferers of covid-19 needs intensive medical assistance and adjunctive treatment plans to overcome the malady. The outbreak can be coped with support of ailment suppression through public fitness measures and adjunctive treatments for patients. In Pakistan due to scarce health care amenities, most of the rural population rely upon indigenous traditional medicinal plant (TMPs) resources. Due to lack of proper anti-covid-19 therapy, TMPs/ herbal treatments could be helpful as first line of defence. It is indispensable to securitize potent repurposed TMPs to impede viral entry, viral proliferation manifestations, inflammation and immunity booster as major weapons against the COVID-19. However, most of these TMPs are being examined in a lot of molecular docking analysis, *In vitro In vivo* experimentation and in clinical trials at various levels. Auxiliary to this, review describes current hallmark of vitamins research in efficient functioning of immune system. This overview suggested that traditional medicinal plants are safe and have enough hierarchy of evidence to use them as adjunctive treatment. This review compiles, the medicinal plants with potent bioactive compounds to devise fast and sensitive adjunctive therapy and for further planning to explore suitable candidates for drug development.

Key words: TMPs, SARS-COV₂, Manifestations, Inflammation, Adjunctive treatment and Vitamins.

Introduction

Novel Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV₂), new member of Coronaviridae family, responsible for current pandemic COVID-19 started from main seafood market Huanan, China (Sarwar *et al.*, 2020). Coronaviridae family has single-stranded, RNA genome characteristically originate respiratory and enteric malady (Hosoki *et al.*, 2020). World already faced outbreaks of SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV), nevertheless SARS-CoV₂ triggered huge pandemic with its exponential transmission rate (Arabi *et al.*, 2017; Arshad *et al.*, 2021). SARS-CoV₂ pathogenesis ranged rigorous spectrum originating from minor upper respiratory infection to acute respiratory distress pattern, pneumonia, multi-organ dysfunction, and eventually demise (Angelini *et al.*, 2013).

To diagnose sheer infection of SARS-CoV₂ reverse transcriptase and reverse real-time polymerase chain reaction (PCR) mainly used with samples variety of broncho alveolar lavage fluid, sputum, nasal and pharyngeal swabs, blood and fibro bronchoscope brush biopsies (Drosten *et al.*, 2003). However, diagnostic reliability, sensitivity increased with Computed tomography (CT), designed with distinctive markers associated with confirmed coronavirus incidence in lungs (Barati *et al.*, 2020; Pang *et al.*, 2020).

In Karachi, on 26th February, 2020, first person was identified Covid-19 positive, in extremely crowded city of Pakistan (Hanif *et al.*, 2020). Since than COVID-19 infection increased exponentially till July, 2020. After that, intensity of infection drastically decreased however, currently, Pakistan faced the second wave of infection without appropriate intervention like vaccine or antiviral / anti-COVID-19 therapy approved by world health organization (WHO) (Cucinotta & Vanelli, 2020).

Therefore, various suffering countries explored traditional medicinal plants (TMPs) /herbs containing phytochemicals, foods, nutritional microelements (vitamins), dietary supplements, herbal products as adjunctive phytotherapeutic approach (Aanouz *et al.*, 2020). In Pakistan TMPs considered as powerful part of culture heritage and performed immense contribution in catering health care (Sher & Hussain, 2009). Due to poor health care facilitation, remoteness and cold and harsh climatic conditions in rural regions majority of population relied upon indigenous TMPs resources to cure numerous disorders (Younis *et al.*, 2018). Latest research on SARS-CoV₂ advised that TMPs used to treat human immunodeficiency virus (HIV) infection could be explored for COVID-19 treatment (Devansh, 2020).

Recurrent exercised home remedies comprised of natural ingredients, such as traditional medicinal plants, phytotherapeutic nourishments, vitamins, dietary supplements for management of respiratory syndromes across the globe. Pakistan is immense manufacturer of traditional medicinal herbs (Hussain *et al.*, 2012). Pakistan served as immense producer of TMPs, most of them could have fighting potential against COVID-19. This review covers strategic identification of TMPs / supplemental adjunctive therapies that can be repurposed against prevention, manifestation, pathogenesis and recovery of SARS-CoV₂.

Methodology

Search strategy: Data hunt was operated by exploiting three searching strategies in various databases till January, 2020. Data sources include "PubMed", "Google Scholar", "Scopus" "Science Direct", "Cochrane Central Register of Controlled Trials" (CENTRAL), "ClinicalTrials.gov database" and "Web of Science" databases. Initial search of this review covers indigenous immunity booster home/

herbal teas remedies and antidepressant, anticonvulsant and anxiolytic TMPs which can be repurposed with any available evidence as preventive measures for SARS-CoV₂ outbreak. Second search portion comprised of potent indigenous traditional medicinal plants used for sore throats home/herbal remedies & respiratory congestion and Sinuses home/herbal remedies with accessible evidence (Randomized clinical trials of TPMs) against manifestation of COVID-19 (respiratory congestion and sinuses) if any.

Third search strategy comprised of reported TMPs as potent antiviral and immunity enhancer (vitamins) against SARS-CoV and other viruses, having potential to fight against pathogenies of COVID-19 also recruited in randomized clinical trials (RCTs) of TPMs against COVID-19. Key words utilized for search included “Pakistani traditional medicinal plants”, “herbal remedies”, “antiviral herbal plants”, “immunity enhancer”, “vitamins”, “food plants with antiviral properties”, “herbal tea remedies”, “anti-depressant plants”, “anxiolytic”, “Sore Throats Herbal remedies”, “COVID-19 manifestation”, “Coronavirus pathogenesis”, “TMPs for covid-19 manifestation”. “Vitamin E”, “Vitamin D”, “zinc as immune-dilator”, “Medicinal plant used in SARS-COV and TMPs in vital infections”, “randomized clinical trials on Pakistani TMPs”. References of relevant articles, including review articles, were also examined for additional information. Whole search data reviewed to find out relevant papers which comply with the earlier defined criteria and answering our research question. All those paper which are not clearly covers the scope, excluded from study.

Results and Discussion

Curative home/herbal remedies against COVID-19:

Majority of confirmed COVID-19 cases encountered slight to medium respiratory infection and recovered with adjunctive COVID-19 treatment. Aged patients > 50 with comorbidities like heart disease, chronic lung problems, cancer and diabetes are at stake to experience worst form of aliment (Barati *et al.*, 2020; Sarwar *et al.*, 2020).

Most of available anti-COVID-19 therapies designed against SARS-CoV₂ manifestations appeared during infection (Trivedi, *et al.*, 2020). In Current situation, according to WHO the data majority of COVID-19 patients must confine themselves at house by self-quarantine. Until date, global community do not have particular anti-COVID-19 treatment protocol. In second wave, Pakistan faced grim reality of increased infection and demise rate. Both paramedical staff and community facing psychological complications, like depression, tension and anxiety (Bilbul *et al.*, 2020). Third wave of COVID-19 intensify the effect of infection in next generation (Children) of Pakistan with confirmed cause of spread was UK residing Pakistani area (Mumtaz & Gul, 2021). Population with poor health condition and facing poverty was the badly affected in this wave (Fisayo & Tsukagoshi, 2021).

Hence, in this regard, few effective precautionary and virus/microbes suppresser herbal remedies with evidence of antiviral, immunity improver potential are

recommended here. Selected TMPs/ herbs and food plants already used for personal care, pharyngitis, and congestion in respiratory tract and sinuses and could be potent against coronavirus pathogenesis (Ling *et al.*, 2020; Huang *et al.*, 2020). Majority of described TMPs/ herbs, food plants and vitamins in preclinical and clinical studies at different stages (Arshad *et al.*, 2021). Therefore, home remedies like herbal teas of different food/herb items have antiviral, soothing properties against respiratory tract infections, antidepressants, anxiolytic with potential to save patient from depression and anxiety of COVID-19 summarized in this section.

Antiviral and immunity booster home/ herbal teas

remedies: According to the first line recommendation of WHO against the above said issue, maintain healthy life style could help in reduced stress and boosted immune system (Ayush, 2020). In January, 2020, China’s health departments recommended few protocols to combat psychological crisis of COVID-19 (Kang *et al.*, 2020). Utilization of hot teas/ fluids of ginger & garlic could be supportive to improve the initial respiratory tract pneumonia infection (Magzoub, 2020; Mehrbod *et al.*, 2009). Virus/Microbe suppresser, immunity booster and Sore Throats home/herbal tea remedies are described in Table 1 (Nisar *et al.*, 2015). The extracts or bioactive compounds of *Allium sativum* (garlic), *Zingiber officinale* (ginger), *eucalyptus globulus* (Blue gum), *Melaleuca alternifolia* (tea tree) and *Jasminum* (jasmine) already proved antiviral potential against the influenza virus (He *et al.*, 2020; Ling *et al.*, 2020). Andrew Weil Center for Integrative Medicine, North America, suggested that polyphenol-rich plants *Matricaria chamomilla* (chamomile), *Scutellaria baicalensis* (Chinese skullcap), *Glycyrrhiza glabra* (licorice), *Allium cepa* (onions), *Malus domestica* (apples), *Solanum lycopersicum* (tomatoes), *Citrus X sinensis* (oranges), *Petroselinum crispum* (parsley), *Apium graveolens* (celery), *Curcuma longa* (turmeric root), *Camellia sinensis* (green tea), nuts and berries have diminishing potential against COVID -19 infection (Alschuler *et al.*, 2020). However, molecular docking studies confirmed the evidence of bioactive compounds which interact with viral structural and non-structural protein to suppress the infection (Li *et al.*, 2021). Ginger and licorice root both registered with clinical trials.

Auxiliary to herbal teas, citrus tea and honey also have capability to suppress the symptoms of infection (Abdelkhalek *et al.*, 2020; Das *et al.*, 2019; Schuhmacher *et al.*, 2003). Shaikh Zayed Hospital & Services Institute of Medical Sciences, Services Hospital Lahore, Pakistan registered clinical trial with no NCT04347382, HNS-COVID-PK, (phase 3 study) to evaluate effectiveness of *Nigella sativa* (black seed) and natural honey in management of COVID-19 infection (Ashraf *et al.*, 2020b). Few anti-depressant/ anxiety suppressor TMPs of Pakistan with bioactive compounds having pharmacological evidence are also added in this review.

Few anti-depressant/ anxiety suppressor TMPs of Pakistan with bioactive compounds having pharmacological evidence presented in Table 2.

Table 1. Virus/Microbe suppresser, immunity booster and Sore Throats home/herbal tea remedies.

S #	Home/herbal tea remedies	Recommended ingredients of remedy	Possible effect	Reference
1.	Turmeric tea	Ginger, garlic and turmeric	Have antiviral and healing properties to improve the initial infection of respiratory tract	(Magzoub, 2020; Mehrbod <i>et al.</i> , 2009; Nisar <i>et al.</i> , 2015)
2.	Herbal teas	Ginger, cinnamon, peppermint with honey	Have antiviral and immunity boosting properties	(Khan <i>et al.</i> , 2020; Hong <i>et al.</i> , 2012; Schuhmacher <i>et al.</i> , 2003)
3.	Hot tea	Licorice root and marshmallow root with honey	Have antiviral & antimicrobial properties and capable of developing soothing effect against inflammation and pain of mucous membranes	(Fukuchi <i>et al.</i> , 2016; Popovych <i>et al.</i> , 2019; Watanabe <i>et al.</i> , 2014)
4.	Ginger tea	Ginger with honey	Have antiviral properties and supportive to improve the infection and immunity	(Magzoub, 2020; Nisar <i>et al.</i> , 2015)
5.	Chamomile teas	Eucalyptus, chamomile with honey	Have capability to suppress viruses and the signs of antiviral diseases	(Abdelkhalek <i>et al.</i> , 2020; Popovych <i>et al.</i> , 2019)
6.	Herbal teas	Lemon with honey	Antimicrobial and immunity boosting properties	(Nagoor Meeran <i>et al.</i> , 2021; Watanabe <i>et al.</i> , 2014)

Medicinal plants (TMPS) of Pakistan with pharmacological evidence, used for Depression and Anxiety problem are present in Table 2

Sore throats home/herbal remedies: Sore throat common sign of COVID-19 infection, but not confirmed indication pneumonia infection. Hence, utilization of saline gargles supports patient in loosening mucous of respiratory tract as first line of defense. In addition to it, hot fluid /extract of licorice root and marshmallow root with honey might be capable of increasing soothing effect against inflammation and pain of mucous membranes (Popovych *et al.*, 2019). Licorice root is under evaluation in a Clinical trial with COVID-19 patients, for its potent bioactive compounds in Iran (Safa *et al.*, 2020). Home/herbal teas remedies of sore throat already presented in Table 1. However, Pakistani plants having bioactive compounds used as food source, already evaluated against different viruses and SARS-CoV might be valuable identification against SARS-CoV₂. TMPs screened for bioactive compounds as phyto therapy against infectious pathogens and reported the presence of various phytoconstituents like phenols, steroids, flavonoid. In Egypt *Nigella sativa* (black seeds), *Matricaria chamomilla* (chamomile) and natural honey in liquid formulation utilized as adjunctive treatment for positive patients and results of that case study confirmed the early recovery with above mentioned TMPs in addition to standard health care procedures (El Sayed *et al.*, 2020). Agha Khan University Hospital Karachi, Pakistan registered clinical trial (NCT04341688) of *Azadirachta indica* (Neem) leaf extract as gargling agent/ nasal douche checked for effectiveness in dropping intra-oral viral load with COVID -19. Trial is in experimentation phase (Khan *et al.*, 2020). Molecular docking analysis of *Withania somnifera* L., confirmed the maximum binding free energy against SARS-CoV2 enzyme named “Mpro” required for viral integrity (Prasanth *et al.*, 2020).

List of Pakistani food plants used as antiviral agents given in Table 3 most of them are being studied at different preclinical and clinical evaluation stages for identification of suitable candidates for anti-COVID medication.

Respiratory congestion and sinuses home/herbal remedies: During respiratory congestion vaporizers, humidifier, steam inhalers along with congestion remover agents or oils, such as, hybrid mint, eucalyptus leave or oilibanum can be helpful for breathing difficulties.

However, natural saline nasal sprays of xylitol showed maximum activity to recover congestion. Keeping in consideration the importance of congestion remover, clinical trial is registered by Pakistan to check the effectiveness of neem for viral clearance in COVID -19 patients (Khan *et al.*, 2020). Ethno-medicinal exploration contributes a lot to find new therapeutics drugs from TMPs. Most of the modern drugs are also derived from plants sources (Sher & Hussain, 2009). From last few years, phyto-chemical for respiratory disorders are extensively studied due to trending of phyto-therapeutic practiced in many parts of the world. Approximately 13,000 Pakistani TMPs have been investigated in previous 5 years for their efficacy evaluation against respiratory disorders. Evaluated TMPs with enough potential against respiratory congestion and sinuses might be beneficial against symptoms of COVID -19. List of repurposed Traditional Medicinal Plants (TPMs) with mechanism of action against COVID-19 manifestation (respiratory congestion and sinuses) are given in Table 4.

Similarly already available antiviral TMPs could be repurposed against viral proliferation and pathogenesis (Shinwari *et al.*, 2020). Some TMPs in nanoparticles formulation served as synergistic antiviral (Hameed *et al.*, 2019). So, nanoparticles formulation could also be beneficial against corona virus (Shinwari *et al.*, 2020). However, accessible evidence based statistics on TMPs increasing day by day. Here, in Table 5 TMPs reported as potent antiviral against SARS-CoV and other viruses.

Vitamins: Efficient defense system plays chief role to fight against infection and help in proficient working of cells. Any deficiency of vitamins/ immunity boosters might cause invasion of pathogen. Vitamins improve body’s protection, by reinforcing mucosal barriers of skin, immune system of each body cell and antibody manufacturing (Kapoor *et al.*, 2020). So, 70% of fat soluble Vitamins like A, E and 30% of water soluble vitamin C, play role in boosting the mucosal barrier of skin function. Similarly, vitamins like retinol, B complex, tocopherol and D perform function synergistically within immune cells and studies proved that retinol has ability to enhance immunity against viruses mainly influenza (Patel *et al.*, 2019). As a whole, all vitamins, (fat and water soluble) beneficial for antibody manufacturing with exception of ascorbic acid.

Table 2. Traditional Medicinal Plants (TMPs) of Pakistan with pharmacological evidence, used for Depression and Anxiety proflin (Khan et al., 2019).

S #	Botanical name	Family	Local name	Part used	Pharmacological properties	Chemical Compounds Identified	Location
1.	<i>Albizia lebbek</i> (L.) Benth	Leguminosae	Sirin	Leaves & Roots	Antidepressant, Anticonvulsant and anxiolytic	Alkaloids, saponins A, B and C, beta carotene, ascorbic acid, melacacidin, tocopherils, catechin lebbecacidin, beta amyrrin, friedelin, ergosterol, and β -sitosterol, and terpenoids	Mianwali
2.	<i>Cannabis Sativa</i> L.	Cannabaceae	Bhang	Leaves, Flowers & Whole plant	Antidepressant, Anticonvulsant, anxiolytic. Sedative, Antidementia	Uracil and quebrachitol cannabidiol, dronabinol, acetyl stigmaterol, cannabigerol, volatile oils, tetrahydro-cannabinolic acid, resins, cannabichromenic acid, cannabidiolic acid, α -spinasterol, anandamide, cannabichromene, chrysoeriol and β -sitosterol	Bannu
3.	<i>Citrus limon</i> (L.) Osbeck	Rutaceae	Nimboo	Leaves	Anticonvulsant Sedative, anxiolytic and antidepressant	Linalool, α -terpineol, Flavonoids linalyl acetate, acetate geranyl, volatile oils, nerolidol, acetate neryl, farnesol, ascorbic acid sabinene, myrcene, cineol and geraniol Limonene, -pinene, β - pinene, α -Terpinene, Linalool, Citronellol, β -Elemene, α -Phyllylandrene	Bahawalpur
4.	<i>Hypericum perforatum</i> L.	Hypericaceae	Bulhsana	Whole plant	Anticonvulsant sedative, Anxiety suppresser antidepressant	Chlorogenic acid, tannins, phenolic acids, Hyperoside, amino acids adhyperforin Quercitrin, isoquercitrin, Rutin, Hypericin, essential oil Kaempferol, flavonoids Biapigenin and Hyperforin, hyperoside, and naphthodianthrones	Gujrat
5.	<i>Jasminum grandiflorum</i> L.	Oleaceae	Chanbeli	Whole plant	Antidepressant Anticonvulsant	Benzyl alcohol, Rutin, Linalool, kaempferol, quercetin, saponins, β -primeveroside, α -Terpineol, kaempferol, Indole, cis-Jasnone, hesperidin Methyl jasmonate, methyl anthramilate, Benzyl benzoate, cardiac glycosides, β -rutinoside, Methyl oleate, oleuropein and daucosterol and essential oils	Bahawalpur
6.	<i>Withania somnifera</i> (L.) Dunal	Solanaceae	Paneer doda	Whole plant	Antidepressant Anxiolytic and Antiparkinson	Sommiferinine, Glycoproteins, Withanolides, amino acids, withaferins, glycosides, Withamine, flavonoids isopellerterine aniferine, glucose, Anahygrine ,aniferine, Cuscohygrine, β -Sisterol, pseudo-withamine Chlorogenic acid, Scopoletin, cuscohygrine choline, , pseudotropine, Sommiferinine, Tropanol, iron, tropine, minerals, and condensed tannins	Bahawalnagar
7.	<i>Ocimum basilicum</i> L.	Lamiaceae	Niazbo	Leaves, Flowers, Stem	Antidepressant Anxiety suppresser memory Enhancer and Sedative,	Essential oil, Cineole, α -guaiene flavonoids, β -farnesene geraniol, germacrene, Terpenoids, linalool polyphenols, metil eugenol, cadinol, sabinene, β -elemene, methyl chavicol, β -caryophyllene α -bisabolol, neral, quercetin, myricetin, kaempferol, and eugenol	Bahawalnagar
8.	<i>Tribulus terrestris</i> L.	Zygophyllaceae	Bakhra	Fruits, Bark and leaves	Anxiolytic, Antidepressant, sedative	Flavonoids, quercetin-3-O-gent-7-O-glu glycoproteins, Tigogenin , Saponins, 25R, S-5 α -spiro-2 α ,3 β -dihydroxyl-3-O- β -d-glc-(1 \rightarrow 4)- β -d-gal neotigogenin, rutin, tannins chlorogenin, Methyl pseudo - diosgenin Isoterrestrosin B(I) alkaloids caffeoyl, Gracillin ruscogenin, kaempferol, kaempferol -3-O-rutinoside tribulosid, ter restribisamide, quercetin, β -sitosterol, stigmaterols, harmane, norharmane N-trans-coumaroyltyramine and tribulusterine	Bahawalnagar
9.	<i>Verbena officinalis</i> L.	Verbenaceae	Shamkay	Whole plant	Antidepressant, Anticonvulsant, anxiolytic and sedative	Diterpenes, Verbenin, 3 α ,24-dihydroxy-urs-12-en-28-oiic acid, aminoacids, flavonoids, oleanolic acid, verbenalin, apigenin castanoside, E, hastatoside, Alkaloids, phytosterols 4 -dodecyl-1,2-benzenediol, alpha -sitosterol, ursolic acid, kaempferol, aucubin, hastatoside luteolin, verbascoside, scutellarein, limonene, phenolic compounds and spathulenol	Battagram
10.	<i>Ziziphus jujube</i> Mill	Rhamnaceae	Beri	Leaves, Roots and fruits	Sedative and hypnotic Anxiolytic Anti-seizure	Isobutyric acid, Zizybeoside I and II, Deoxysugars, Chrysoeriol, Swertisin, Mucilages , Quercetin, Jujubasaponin IV, Lotoside I and II, Zizyphus, nucleosides saponin I and II catechin, sovaleric acid, quercetin-3-O-robinobioside, cerebrosides, rutin, n -Nonanal, quercetin-3-O- α -L-arabinosyl-(1 \rightarrow 2)- α -L-rhamnoside, Tridecyl methyl ketone, flavonoids, Linoleic acid, Vitamin E, γ -Sitosterol and p-coumaric acid	Bahawalnagar

Table 3. List of Pakistani food plants used as antiviral agents.

Plant name/ Part used	Family	Common name	Active compound	Effective against virus	Reference
<i>Azadirachta indica</i> A. Juss./ Leaves	Meliaceae	Neem, Nimtree or Indian lilac	Glycosides, Polysaccharides, Flavonoids, Phenols, Anthocyanin, Tannins, Saponins, and Alkaloids	Newcastle and Hepatitis	Mohamed <i>et al.</i> , 2020)
<i>Hyoscyamus niger</i> L. Seeds	Solanaceae	Black henbane-stinking nightshade; Kharasani	alkaloids, scopine, flavonoids, tannins, 3-phenylacetoxy-6,7-epoxytropane, terpenes, saponins, aospopolamine, carbohydrates, skimmianine, cardiac glycosides	Influenza A	(Devi & Thakur, 2011)
<i>Melissa officinalis</i> L. Entire plant	Lamiaceae	Lemon balm balm, or Balm mint	caffeic acid, Terpinene, gallic acid, phenol, quercetin, flavon-glycoside acid, Quinon, flavonols, ferric reducing ability and Condensed tannin	Simplex Herpes, Semliki and Newcastle	(Akram <i>et al.</i> , 2018)
<i>Moringa oleifera</i> Lam./ Seeds	Moringaceae	Moringa, Horseradish tree	Alkaloid, β -sitosterol, Flavonoid, Saponin, Steroid, glucosides Tannin, sitosterol and glycerol	Epstein- Barr virus	(Saleem <i>et al.</i> , 2020)
<i>Morus alba</i> L./ Root and leaves	Moraceae	Toot, White mulberry	<i>p</i> -Hydroxybenzoic acid, mulberroside C, Caffeic acid Quercetin 3-rutinoside, cyclomorusin, Kaempferol 3- <i>O</i> -rutinoside eudraflavone B hydroperoxide, Total flavonols, oxydihydromorusin, Coumaric acid, leachianone α - acetyl-amyryn and Total anthocyanins	Herpes virus	(Du <i>et al.</i> , 2003)
<i>Nigella sativa</i> L./ Seed	Ranunculaceae	Kalonji, Black cummin, Kalojeera,	Thymohydroquinone, resins, oleic acid, Steroids, carvacrol tannins, t-anethol dithymoquinone flavanoids, α -pinene coumarins, linoleic acid, glycosidal cardiac glycosides, melanthigenin, saponins reducing sugars, diterpenes, palmitic, stearic acid. α -sitosterol and proteins	Murinecy tomegalovirus	(Ahmad <i>et al.</i> , 2013)
<i>Phyllanthus emblica</i> L./ Fruits	Leiotohrichidae	Amla, Gooseberry	Tannins, Anthocyanosides, Phlobatannins, Chlorogenic acid, Saponins, Proteins and amino acids, Steroids, Emblicanin A, Flavonoids, Phenolic flavonoids, Gibberellins I Terpenoids, Ellagic acid, Alkaloid and Anthraquinones	HIV	(Andleeb <i>et al.</i> , 2020)
<i>Withania somnifera</i> L. Dunal/ Root	Solanaceae	Ashwagandha, Indian ginseng	Alkaloid, Glycoside, Phenol, Protein, Tannin, Starch and Phyto-sterols	Bursal disease virus, simplex virus type 1 & 2	(Prasanth <i>et al.</i> , 2020)
<i>Zingiber officinale</i> Roscoe whole plant	Zingiberaceae	Adrak, Ginger	Alkaloids, Pholo-botannins, Flavonoids, Steroids, Tannins, Saponins, Glycosides and Terpenoids	Rhino-virus IB	(Magzoub, 2020)

Table 4. List of repurposed Traditional Medicinal Plants (TPMs) with mechanism of action against COVID-19 manifestation (respiratory congestion and sinuses).

Botanical name / Part used	Family	Traditional consumption	Mechanism	Reference
<i>Abies pindrow</i> Royle ex D. Don Royle / Leaves	Pinaceae	Cough, breathing complaints, bronchospasm (asthma) and other lung disorders	Highly effective against cough and breathing issues persuaded by increased level of histamine. bronchospasm, effective to suppress /prevent the symptoms of asthma and lungs distress attacks like chemical drug named cromoglycate	(Sher & Hussain, 2009)
<i>Achyranthes aspera</i> L. / Leaves	Amaranthaceae	Pneumonia and bronchospasm (asthma)	Preventer of allergic rhinitis, other allergies, inflammation. Impedes action of histamine, neurotransmitters essential in the cascade of rhinitis and Broncho protective	(Bhosale <i>et al.</i> , 2012)
<i>Althaea officinalis</i> L./ Flowers, fruits, leaves, roots,	Malvaceae	(Bronchospasm) Asthma and bronchitis	Cough inhibitor stimulated by citric acid during cough impulse	(Šutrovská <i>et al.</i> , 2009)
<i>Artemisia scoparia</i> Waldst. & Kitam/ Entire plant	Compositae	Cough, chest distress	Anti-asthmatic effect	(Hongrui <i>et al.</i> , 2000)
<i>Carum carvi</i> L./ Seeds, leaves and flowers	Apiaceae	Cough, loose bowels and bronchitis	Broncho expender and nerve impulse blocker effect, anti-allergic	(Gilani <i>et al.</i> , 2005)
<i>Ephedra Gerardiana</i> Wall. ex Stapf / Stem	Ephedraceae	Bronchospasm Asthma/breathing disorders	Have Anti-allergic properties in mice model	(Chaitanya <i>et al.</i> , 2014)
<i>Justicia adhatoda</i> L. / Entire plant	Acanthaceae	Whooping cough, bronchitis, bronchial asthma	Inhibitor of hyper-stativity reaction, anti - incendiary, antitussive, Antihistamine, bronchodilator and lung healer	(Gheware <i>et al.</i> , 202; Hussain <i>et al.</i> , 2016)
<i>Ocimum basilicum</i> L/ Leaves and seeds	Lamiaceae	Bronchitis, cough, cold	Inhibitor of calcium channels and muscarinic receptors to initiation bronchodilation and vasodilation.	(Janbaz, Hamid, & Qadir, 2014)
<i>Onosma borysthenica</i> Klokov/ Entire plant	Boraginaceae	Bronchitis/ lung infections	Have Antihistamine and anti- incendiary properties	(Patel <i>et al.</i> , 2011)
<i>Taxus baccata</i> L. / Bark	Taxaceae	Breathing complaints	Bronchodilator and suppresser of hyper -sensitivity reaction provoked in Broncho spasm	(Patel <i>et al.</i> , 2008)
<i>Trachyspermum ammi</i> (L.) Sprague / Seeds and oil	Apiaceae	Bronchospasm Bronchitis, chills and cough	Antihistamine, bronchodilator and muscle spasms suppresser	(Gilani <i>et al.</i> , 2008)
<i>Ziziphus jujuba</i> Mill/ Fruits	Rhamnaceae	Whooping cough/ Bronchitis	Antihistamine and suppresser of hyper -sensitivity, anti - allergic properties against milk induced eosinophilia and leukocytosis	(Naik <i>et al.</i> , 2013)

Table 5. TMPs reported as potent antiviral against SARS-CoV and other viruses.

Plant name and Part used	Family	Common name	Active compound	Effective against virus	Ref
<i>Artemisia Annua</i> L./ Entire Plant	Compositae	Annual Wormwood	Phenols, flavonoids, 4-Terpeneol, Artemisinin, deoxyartemisinin, Chamazulene, artemisinic acid, Linalool, arteannuin-B, stigmasterol, friedelin, Friedelan -3- β -ol, artemetin, α - and β -thujones quercetagenin, 5, 6,3',5'-tetramethoxy cardomonin, caruifolin D and Polysaccharides	Severe acute respiratory syndrome coronavirus	(Notka <i>et al.</i> , 2004)
<i>Ficus benjamina</i> L./ leaves	Moraceae	Banyan	Amino acids Flavonoids, Tannins, Phenol, Vitamin C, Terpenoids, Phlobatanins and Chloride	<i>P. aeruginosa</i> <i>E. coli</i> and <i>B. cereus</i>	(Ashraf <i>et al.</i> , 2020a)
<i>Glycyrrhiza glabra</i> L./ Root	Leguminosae	Licorice	Glabridin, Licochalcone A, Glycyrrhetic acid, Liquiritin apioside, 18 β -Glycyrrhetic acid, Isoliquiritigenin Liguiritigenin, Glycyrrhizin, Isoliquiritin and Liguiritin	HIV, RSV, herpes viruses, and (SARS-CoV)	(Yeh <i>et al.</i> , 2013)
<i>Hyphaene thebaica</i> (L.) Mart./ Fruit	Areaceae	Doum Palm	luteolin, limonen, luteolin <i>O</i> - β -glucoside and kaempferol, nicotiflorin, vitexin/ <i>O</i> -glucuronide, octylacetate, Quercetin 3- <i>O</i> - β -4Cl-D-glucopyranoside apigenin 7- <i>O</i> - β -glucuronide	Polio virus type 1& 2 and (HSV-1,2)	(Hameed <i>et al.</i> , 2019)
<i>Justicia Adhatoda</i> L./ Leaves	Acanthaceae	Bansa, Malbar nut, Adhatoda	Phenols, tannins, alkaloids, anthraquinone saponins, flavonoids, and reducing sugars	Influenza, Herpes simplex -2 & 1, Antimicrobialefficacy of drugs mixed and bio-synthesized with gold nano-particles	(Emmanuel <i>et al.</i> , 2017; Kimet <i>et al.</i> , 2020; Yoshikawa <i>et al.</i> , 1997)
<i>Lycoris radiata</i> (L'Ha) Herb / Stem	Amaryllidaceae	Red Spider lily	Ferric-Reducing Antioxidant capability, procyanidins, Phenols, Flavonoid Epicatechin and Glycosides	Severe acute respiratory syndrome-associated coronavirus	(Shen <i>et al.</i> , 2019)
<i>Phyllanthus urinaria</i> L./ Root, leaf , leaves flower	Phyllanthaceae	Shatterstone, Stone breaker herb	Taninos, Flavonoides, Quercetin, Astragaln, Catechin Limonene, p-Cymene, Astragaln, Niruriflavone, Galocatechin and Rutin	Type 1 & 2 Herpes simplex virus	(Porter & Bode, 2017)
<i>Sambucus nigra</i> L/ Flowers fruits	Adoxaceae	Elderberry European elder	Flavonoids Polyphenols. Flavonoids Cyanidin and Luteolin	Influenza (A & B), Type 1 herpes simplex virus, HIV, hepatitis	(Porter & Bode, 2017; Akram <i>et al.</i> , 2018; Li <i>et al.</i> , 2019)

Vitamin D: Vitamin D (active form cholecalciferol) serves antimicrobial function in different pathways to reduce microbe induced demise risk. Vitamin D also helps to improve natural immunity of person through biomolecules like antimicrobial peptides, cathelicidin, LL-37 against bacteria, viruses (either encased or not), and fungi (Balla *et al.*, 2020). Covid-19 pneumonia confirmed the elevated concentration of cytokines mainly pro-inflammatory, C-reactive protein, acute respiratory distress syndrome (ARDS), ultimately organ failure. However, literature data proved that Vitamin D administration might diminish cytokine storm hazard by deregulation of interlinking renin-angiotensin system and ACE proteins (Kapoor *et al.*, 2020; Martineau *et al.*, 2017; Gautam *et al.*, 2020).

A lot of discrepancies regarding function of vitamin D among scientist, but large study conducted with more than ten thousand patients confirmed effectiveness of its supplementation against ARDS (Martineau *et al.*, 2017; Shakoor *et al.*, 2021). Thus, these vitamins (protective nutrients) could be administered in critically ill COVID-19 patients, as adjunctive therapy against infection. A lot of research and clinical trials being in process, to confirm cholecalciferol as anti COVID-19 beforehand its prescription to patients.

Zinc: Zinc (trace element) inevitable, for proper functioning of immune system and synthesis antibody and leukocytes. COVID-19 pathogenies involves infection of ciliated epithelium and disruption in mucociliar clearance (Alexander *et al.*, 2020). Studies revealed that good amount of zinc, can intensify ciliary beat rate which in turn cause instabilities in the integrity of the respiratory assembly (Alexander *et al.*, 2020; Skalny *et al.*, 2020). Furthermore, enhanced ciliary clearance, beneficial for both viral clearance and turning down of proliferation rate. A *ex-vivo* research on chronic obstructive pulmonary disease (COPD) revealed zinc concentration has reverse relation with epithelium seepage respiratory tract (Junaid *et al.*, 2020; Shakoor *et al.*, 2021). Although, zinc supplementation improvises lung integrity and reduce the viral entry risk into blood. Viral entry could be affected by zinc relayed altered gene expression (zinc-metalloenzyme). If zinc binding has its effects on the molecular structure of ACE-2, thus its binding affinity towards virus, should also be checked. However, in different published reviews, antiviral capability of zinc has been demonstrated (de Almeida Brasiel, 2020). As coronavirus extremely reliant on the host metabolism, so, zinc could avert fusion with the host membrane, declines the viral enzyme functions (polymerase), harms 2nd stage of protein expression and processing (Rahman & Idid, 2021). Zinc supplementation can help patients by decrease respiratory tract infections and increasing the ability of leukocytes to fight against infection. Literature studies reveled that symptom severity and period of common cold has been lowered, by zinc intake (de Almeida Brasiel, 2020; Shakoor *et al.*, 2021).

Vitamin C (Ascorbic Acid): Ascorbic acid an essential micro nutrient and required for metabolic processes within the human body. It has antioxidant properties and scavenges free radicals, to avoid cellular injuries. It also

involved in immunity related biological processes (Hoang *et al.*, 2020; Shakoor *et al.*, 2021). Furthermore, vitamin C emerges potent antiviral properties, particularly for influenza viruses (Kivrak *et al.*, 2021). Literature data illustrated, positive affect of ascorbic acid on growth, development and in functionality of white blood cells (T lymphocytes) and NK (natural killer) cells and plays vital role in immunity against viral agents (Shakoor *et al.*, 2021; Ojha, 2021). Ascorbic acid also serves as re-modulating agent of the cytokine network during systemic inflammatory diseases (Holford *et al.*, 2020; van Gorkom *et al.*, 2018). At present, keeping in mind, all the characteristics of ascorbic acid, China has initiated phase II clinical trials (NCT04264533) with high doses of vitamin C, in severe or critically ill COVID-19 patients (Ilie *et al.*, 2020). Furthermore, its rich amount (1.5 mg/kg bodyweight) has been clinically practiced for last century in an international health organization (NIH panel) which authenticates its efficacy and safety of high dose with least adverse effects (Cheng, 2020; Kim *et al.*, 2018). Clinical trial revealed that ascorbic acid has significant potential to suppress pneumonia, respiratory tract infections and demise (Kim *et al.*, 2018).

Conclusion

Information provided here could be exploited to devise guidelines regarding beneficial Pakistani preventive, therapeutic and immunity booster TPMs for daily use as a solution to deal with immense pressure of infection on hospitals and paramedical staff challenge. As Pakistan is a developing country and most of its population lives in rural areas where Pakistani Traditional herbal medicines serves as sole therapy. This article prepared to keep idea of gathering details of potent indigenous TMPs, which could be repurposed for COVID-19, and few of them being analyzed pre-clinically or clinically (in silico, clinical trials) for other viral infection in both treatment and supportive approach. Auxiliary to this, enlisted TMPs have potent phytochemicals with evidence of pharmacological effectiveness could studied *In vitro*, *In vivo*, clinical trial to achieve reliable medication against coronavirus. However, some of TMPs are already in clinical trial registered by Pakistan and this study might be benchmark for further aid for researchers to find best economical ethnobotanical candidates for COVID-19 cure.

Acknowledgements

I am thankful to Ministry of Science and Technology Pakistan for providing basic resources to conduct this review.

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