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

BUSHRA ARSHAD1,2

1Pakistan Council for Science and Technology, Ministry of Science and Technology Islamabad, Pakistan
2Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan

Corresponding author’s email: bushraarshad1988@gmail.com

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 phytherapeutic 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, phytherapeutic 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-CoV\textsubscript{2} 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 TMPs) 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 TMPs 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 ailment (Barati et al., 2020; Sarwar et al., 2020).

Most of available anti-COVID-19 therapies designed against SARS-CoV\textsubscript{2} 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 (Magzoub, 2020; Mehrbod et al., 2009). Utilization of hot teas/ fluids of ginger & garlic could be supportive to improve the initial respiratory tract pneumonia infection (Mehr, 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 anitviral 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 Mattricaria 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 (Abdelkhalak 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.
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 phytotherapy 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 olibanum 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 (TMPs) 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 1. Virus/Microbe suppresser, immunity booster and Sore Throats home/herbal tea remedies.

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

Medicinal plants (TMPs) of Pakistan with pharmacological evidence, used for Depression and Anxiety problem are present in Table 2
<table>
<thead>
<tr>
<th>No.</th>
<th>Botanical Name</th>
<th>Family</th>
<th>Local Name</th>
<th>Part Used</th>
<th>Pharmacological Properties</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alpinia officinarum L</td>
<td>Zingiberaceae</td>
<td>Shamu</td>
<td>Leaves, Roots</td>
<td>Antidepressant, Anticonvulsant, Antibacterial, Anti-inflammatory</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>2</td>
<td>Cannabis Sativa L</td>
<td>Cannabaceae</td>
<td>Bhang</td>
<td>Whole Plant</td>
<td>Antiviral, Antibacterial, Anticonvulsant, Analgesic</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>3</td>
<td>Citrus limon (L.) Osbeck</td>
<td>Rutaceae</td>
<td>Nimboo</td>
<td>Leaves</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>4</td>
<td>Hypericum perforatum L</td>
<td>Hypericaceae</td>
<td>Bhang</td>
<td>Whole Plant</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>5</td>
<td>Jasminum grandiflorum L</td>
<td>Oleaceae</td>
<td>Bahawalpur</td>
<td>Flowers &amp; Fruits</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>6</td>
<td>Withania somnifera L</td>
<td>Solanaceae</td>
<td>Sirin</td>
<td>Leaves &amp; Roots</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>7</td>
<td>Ziziphus jujube L</td>
<td>Rhamnaceae</td>
<td>Bakhra</td>
<td>Whole Plant</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>8</td>
<td>Tribulus terrestris L</td>
<td>Zygophyllaceae</td>
<td>Bakhta</td>
<td>Flowers</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>9</td>
<td>Verbena officinalis L</td>
<td>Verbenaceae</td>
<td>Shambuy</td>
<td>Whole Plant</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
<tr>
<td>10</td>
<td>Ziziphus jujube Mill</td>
<td>Rhamnaceae</td>
<td>Bari</td>
<td>Leaves, Roots &amp; Fruits</td>
<td>Antioxidant, Antiviral, Antibacterial, Anticonvulsant</td>
<td>Bahawalnagar</td>
</tr>
</tbody>
</table>

**Chemical Compounds Identified**

- Alkaloids, flavonoids, Linoleic acid, Vitamin E, γ-Sitosterol and p-coumaric acid
- Benzyl alcohol, Rutin, Linalool, kaempferol, quercetin, β-sitosterol, Ursolic acid, kaempferol, aucubin, rutinoside, Methyl oleate, oleuropein and rutin, gallic acid, rutin, quercetin, quercitrin, isoquercitrin, Rutin, Hypericin, essential oil, tannins, Flavonoids, chlorogenin, Methyl pseudo tigogenin, rutin, naphthodianthrones
- Benzyl alcohol, Rutin, Linalool, kaempferol, quercetin, β-sitosterol, Ursolic acid, kaempferol, aucubin, rutinoside, Methyl oleate, oleuropein and rutin, gallic acid, rutin, quercetin, quercitrin, isoquercitrin, Rutin, Hypericin, essential oil, tannins, Flavonoids, chlorogenin, Methyl pseudo tigogenin, rutin, naphthodianthrones
- Benzyl alcohol, Rutin, Linalool, kaempferol, quercetin, β-sitosterol, Ursolic acid, kaempferol, aucubin, rutinoside, Methyl oleate, oleuropein and rutin, gallic acid, rutin, quercetin, quercitrin, isoquercitrin, Rutin, Hypericin, essential oil, tannins, Flavonoids, chlorogenin, Methyl pseudo tigogenin, rutin, naphthodianthrones
<table>
<thead>
<tr>
<th>Plant name/ Part used</th>
<th>Family</th>
<th>Common name</th>
<th>Active compound</th>
<th>Effective against virus</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Azadirachta indica</em> A. Juss./ Leaves</td>
<td>Meliaceae</td>
<td>Neem, Nintree or Indian lilac</td>
<td>Glycosides, Polysaccharides, Flavanoids, Phenols, Anthocyanin, Tannins, Saponins, and Alkaloids</td>
<td>Newcastle and Hepatitis</td>
<td>Mohamed <em>et al</em>., 2020</td>
</tr>
<tr>
<td><em>Hyoscyamus niger</em> L. Seeds</td>
<td>Solanaceae</td>
<td>Black henbane-stinking nightshade, Kharasani</td>
<td>alkaloids, scopine, flavonoids, tannins, 3-phenylacetoxy-6,7-epoxytropane, terpenes, saponins, apocapalone, carbohydrates, skimmianine, cardiac glycosides</td>
<td>Influenza A</td>
<td>(Devi &amp; Thakur, 2011)</td>
</tr>
<tr>
<td><em>Melissa officinalis</em> L. Entire plant</td>
<td>Lamiaceae</td>
<td>Lemon balm balm, or Balm mint</td>
<td>caffeic acid, Terpinene, gallic acid, phenol, quercetin, flavon-glycoside acid, Quinon, flavonoids, ferric reducing ability and Condensed tannin</td>
<td>Simplex Herpes, Semliki and Newcastle</td>
<td>(Akram <em>et al</em>., 2018)</td>
</tr>
<tr>
<td><em>Moringa oleifera</em> Lam./ Seeds/Leaves/ fruits</td>
<td>Moringaceae</td>
<td>Moringa, Horseradish tree</td>
<td>Alkaloid, β-sitosterol, Flavonoid, Saponin, Steroid, glucosides Tannin, sitosterol and glycerol</td>
<td>Epstein- Barr virus</td>
<td>(Saleem <em>et al</em>., 2020)</td>
</tr>
<tr>
<td><em>Morus alba</em> L./ Root and leaves</td>
<td>Moraceae</td>
<td>Toot, White mulberry</td>
<td>p-Hydroxybenzoic acid, mulberroside C, Caffeic acid Quercetin 3-rutinoside, cyclomorusin, Kaempferol 3-O-rutinoside eudraflavone B hydroperoxide, Total flavonols, oxydihydromorusin, Coumaric acid, leachianone α-acetyl-amyrin and Total anthocyanins</td>
<td>Herpes virus</td>
<td>(Du <em>et al</em>., 2003)</td>
</tr>
<tr>
<td><em>Nigella sativa</em> L./ Seed</td>
<td>Ranunculaceae</td>
<td>Kalonji, Black cumin, Kalojeera,</td>
<td>Thymohydroquinone, resins, oleic acid, Steroids, carvacrol tannins, t-anethol dithymoquinone flavonoids, α-pinene coumarins, linoleic acid, glycosidal cardiac glycosides, melanzhenin, saponins reducing sugars, diterpenes, palmitic, stearic acid. α-sitosterol and proteins</td>
<td>Murinecy tomegalovirus</td>
<td>(Ahmad <em>et al</em>., 2013)</td>
</tr>
<tr>
<td><em>Phyllanthus emblica</em> L./ Fruits</td>
<td>Leiothrichidae</td>
<td>Amla, Gooseberry</td>
<td>Tannins, Anthocyanosides, Phlobatannins, Chlorogenic acid, Saponins, Proteins and amino acids, Steroids, Emblicanin A, Flavonoids, Phenolic flavonoids, Gibberellins 1Terpenoids, Ellagic acid, Alkaloid and Anthraquinones</td>
<td>HIV</td>
<td>(Andleeb <em>et al</em>., 2020)</td>
</tr>
<tr>
<td><em>Withania somnifera</em> L. Dunal/ Root</td>
<td>Solanaceae</td>
<td>Ashwagandha, Indian ginseng</td>
<td>Alkaloid, Glycoside, Phenol, Protein, Tannin, Starch and Phyto-sterols</td>
<td>Bursal disease virus, simplex virus type 1 &amp; 2</td>
<td>(Prasanth <em>et al</em>., 2020)</td>
</tr>
<tr>
<td><em>Zingiber officinale</em> Roscoe whole plant</td>
<td>Zingiberaceae</td>
<td>Adrak, Ginger</td>
<td>Alkaloids, Photo-boatinns, Flavonoids, Steroids, Tannins, Saponins, Glycosides and Terpenoids</td>
<td>Rhino-virus IB</td>
<td>(Magzoub, 2020)</td>
</tr>
<tr>
<td>Botanical name / Part used</td>
<td>Family</td>
<td>Traditional consumption</td>
<td>Mechanism</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td>Abies pindrow Royle ex D. Don / Leaves</td>
<td>Pinaceae</td>
<td>Cough, breathing complaints, bronchospasms (asthma) and other lung disorders</td>
<td>Highly effective against cough and breathing issues persuade by increased level of histamine. Bronchosphasms, effective to suppress /prevent the symptoms of asthma and lungs distress attacks like chemical drug named cromoglycate</td>
<td>(Sher &amp; Hussain, 2009)</td>
<td></td>
</tr>
<tr>
<td>Achyranthes aspera L. / Leaves</td>
<td>Amaranthaceae</td>
<td>Pneumonia and bronchospasms (asthma)</td>
<td>Preventer of allergic rhinitis, other allergies, inflammation. Impedes action of histamine, neurotransmitters essential in the cascade of rhinitis and Broncho protective</td>
<td>(Bhosale et al., 2012)</td>
<td></td>
</tr>
<tr>
<td>Althaea officinalis L. / Flowers, fruits, leaves, roots,</td>
<td>Malvaceae</td>
<td>(Bronchospasms) Asthma and bronchitis</td>
<td>Cough inhibitor stimulated by citric acid during cough impulse</td>
<td>(Šutovská et al., 2009)</td>
<td></td>
</tr>
<tr>
<td>Artemisia scoparia Waldst. &amp; Kitam / Entire plant</td>
<td>Compositae</td>
<td>Cough, chest distress</td>
<td>Anti-asthmatic effect</td>
<td>(Hongrui et al., 2000)</td>
<td></td>
</tr>
<tr>
<td>Carum carvi L. / Seeds, leaves and flowers</td>
<td>Apiaceae</td>
<td>Cough, loose bowels and bronchitis</td>
<td>Broncho expander and nerve impulse blocker effect, anti-allergic</td>
<td>(Gilani et al., 2005)</td>
<td></td>
</tr>
<tr>
<td>Ephedra gerardiana Wall. ex Stapf / Stem</td>
<td>Ephedraceae</td>
<td>Bronchospasm Asthma/breathing disorders</td>
<td>Have Anti-allergic properties in mice model</td>
<td>(Chaitanya et al., 2014)</td>
<td></td>
</tr>
<tr>
<td>Justicia adhatoda L. / Entire plant</td>
<td>Acanthaceae</td>
<td>Whooping cough, bronchitis, bronchial asthma</td>
<td>Inhibitor of hyper -stativity reaction, anti - incendiary, antitussive, Antihistamine, bronchodilator and lung healer</td>
<td>(Gheware et al., 202; Hussain et al., 2016)</td>
<td></td>
</tr>
<tr>
<td>Ocimum basilicum L / Leaves and seeds</td>
<td>Lamiaceae</td>
<td>Bronchitis, cough, cold</td>
<td>Inhibitor of calcium channels and muscarinic receptors to initiation bronchodilation and vasodilation.</td>
<td>(Janbaz, Hamid, &amp; Qadir, 2014)</td>
<td></td>
</tr>
<tr>
<td>Onosma borysthenica Klokov / Entire plant</td>
<td>Boraginaceae</td>
<td>Bronchitis/ lung infections</td>
<td>Have Antihistamine and anti-incendiary properties</td>
<td>(Patel et al., 2011)</td>
<td></td>
</tr>
<tr>
<td>Taxus baccata L. / Bark</td>
<td>Taxaceae</td>
<td>Breathing complaints</td>
<td>Bronchodilator and suppresser of hyper -sensitivity reaction provoked in Broncho spasm</td>
<td>(Patel et al., 2008)</td>
<td></td>
</tr>
<tr>
<td>Trachyspermum ammi (L.) Sprague / Seeds and oil</td>
<td>Apiaceae</td>
<td>Bronchospasm Bronchitis, chills and cough</td>
<td>Antihistamine, bronchodilator and muscle spasms suppresser</td>
<td>(Gilani et al., 2008)</td>
<td></td>
</tr>
<tr>
<td>Ziziphus jujuba Mill / Fruits</td>
<td>Rhamnaceae</td>
<td>Whooping cough/ Bronchitis</td>
<td>Antihistamine and suppresser of hyper -sensitivity, anti - allergic properties against milk induced eosinophilia and leukocytosis</td>
<td>(Naik et al., 2013)</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. TMPs reported as potent antiviral against SARS-CoV and other viruses.

<table>
<thead>
<tr>
<th>Plant name and Part used</th>
<th>Family</th>
<th>Common name</th>
<th>Active compound</th>
<th>Effective against virus</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisia Annua L./ Entire Plant</td>
<td>Compositae</td>
<td>Annual Wormwood</td>
<td>Phenols, flavonoids, 4-Terpineol, Artemisinin, deoxyartemisinin, Chamaazulene, artemisinic acid, Linalool, arteannuin-B, stigmasterol, friedelin, Friedelan -3-β-ol, artemetin, α- and β-thujones quercetugentin, 5, 6,3',5'-tetramethoxy cardamonin, caruifolin D and Polysaccharides</td>
<td>Severe acute respiratory syndrome coronavirus (Notka et al., 2004)</td>
<td></td>
</tr>
<tr>
<td>Ficus benjamina L./ leaves</td>
<td>Moraceae</td>
<td>Banyan</td>
<td>Amino acids Flavonoids, Tannins, Phenol, Vitamin C, Terpenoids, Phlobatanins and Chloride</td>
<td>P. aeruginosa E. coli and B. cerus (Ashraf et al., 2020a)</td>
<td></td>
</tr>
<tr>
<td>Glycyrrhiza glabra L./ Root</td>
<td>Leguminosae</td>
<td>Licorice</td>
<td>Glabridin, Licochalcone A, Glycyrrhetic acid, Liquiritin apioside, 18β-Glycyrrhetinic acid, Isoliquiritigenin Liquiritigenin, Glycyrrhizin, Isoliquirit and Liquiritin</td>
<td>HIV, RSV, herpes viruses, and (SARS-CoV) (Yeh et al., 2013)</td>
<td></td>
</tr>
<tr>
<td>Hyphaene thebaica (L.) Mart./ Fruit</td>
<td>Arecaceae</td>
<td>Doum Palm</td>
<td>luteolin, limonen, luteolin O-β-quercetin and kaempfero, nicotiflorin, vitexin7-O-glucuronoide, octylacetate, Quercetin 3-O-β-4Cl-D-glucopyranoside apigenin 7-O-β-glucuronoide</td>
<td>Polio virus type 1 &amp; 2 and (HSV-1,2) (Hameed et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>Justicia Adhatoda L./ Leaves</td>
<td>Acanthaceae</td>
<td>Bansa, Malbar nut, Adhatoda</td>
<td>Phenols, tannins, alkaloids, anthraquinone saponins, flavonoids, and reducing sugars</td>
<td>Influenza, Herpes simplex -2 &amp; 1, Antimicrobials efficacy of drugs mixed and bio-synthesized with gold nano-particles (Emmanuel et al., 2017; Kimet et al., 2020; Yoshikawa et al., 1997)</td>
<td></td>
</tr>
<tr>
<td>Lycoris radiate (L.'Ha) Herb / Stem</td>
<td>Amaryllidaceae</td>
<td>Red Spider lily</td>
<td>Ferric-Reducing Antioxidant capability, procyanidins, Phenols, Flavonoid Epicatchin and Glycosides</td>
<td>Severe acute respiratory syndrome-associated coronavirus (Shen et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>Phyllanthus urinaria L./ Root, leaf, leaves flower</td>
<td>Phyllanthaceae</td>
<td>Shatterstone, Stone breaker herb</td>
<td>Taninos, Flavonoids, Quercetin, Astragalin, Catechin Limone, p-Cymene, Astragalin, Niruflavone, Galloacatechin and Rutin</td>
<td>Type 1 &amp; 2 Herpes simplex virus (Porter &amp; Bode, 2017)</td>
<td></td>
</tr>
<tr>
<td>Sambucus nigra L./ Flowers fruits</td>
<td>Adoxaceae</td>
<td>Elderberry European elder</td>
<td>Flavonoids Polyphenols, Flavonoids Cyanidin and Luteolin</td>
<td>Influenza (A &amp; B), Type 1 and 2 Herpes simplex virus, HIV, hepatitis (Porter &amp; Bode, 2017; Akram et al., 2018; Li et al., 2019)</td>
<td></td>
</tr>
</tbody>
</table>
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 mucociliary 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 improves 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 Brasil, 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 revealed that symptom severity and period of common cold has been lowered, by zinc intake (de Almeida Brasil, 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 antioxidiant 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 (Kivvak 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.

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References


