AN INSIGHT INTO POTENTIAL PHYTOPHARMACEUTICALS FOR COVID-19
(Short Title: MANAGEMENT OF COVID-19 USING PHYTOPHARMACEUTICALS)
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ABSTRACT
Novel coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has triggered respiratory disease outbreak worldwide and is affecting more than 200 countries. This pathogenic SARS-CoV-2 can have serious complications not only on the respiratory system but also affects the heart and nervous system. Currently, there is no specific treatment for COVID-19 and the vaccine administration is also in their trial stages in healthcare workers. The non-specific drugs recommended for COVID-19 that have shown efficacy are Hydroxychloroquine, Remdesivir, Lopinavir, Tocilizumab, Darunavir, Chloroquine, Interferon-alpha, Favipiravir, Umifenovir, Corticosteroids, etc. However, their disadvantages are their adverse effects like fatigue, extrapyramidal disorders, vertigo, ataxia, confusion, neurosis, seizure, etc. Natural plants have shown promising antiviral and immunomodulatory effects which are now being validated on experimental models. The objective of our research study is to focus on the phytopharmaceuticals that can contribute to the prevention and control of COVID-19. For achieving this target, a survey questionnaire was also designed and circulated to the community to understand the extent of the usage of herbs in management of COVID-19.

Keywords: Anti-viral, Botanicals, COVID-19 survey, Immunomodulatory activity, SARS-Cov-2.

1. Introduction
The outbreak of coronavirus occurred in Wuhan Hubei in China at the end of December 2019, which led to the rapid dissemination of the Coronavirus (COVID-19) growing into a pandemic that is accountable for the ongoing global health emergencies. The coronavirus cases were reported to the WHO Country Office on December 31, 2019 leading to the awareness of earlier unknown Coronavirus in January, 20201. The word 'Corona' came from Latin, which means 'Crown'2. To date, till the end of January 2021, over 93 million COVID-19 cases and over 2 million deaths have been reported by World Health Organization3. There is currently no clear COVID-19 treatment and the vaccines are in emerging stage. Hydroxychloroquine, Remdesivir, Lopinavir, Tocilizumab, Darunavir, Chloroquine, Interferon-alpha, Favipiravir, Umifenovir, Corticosteroids, etc. are the non-specific drugs approved for COVID-19 that have shown efficacy. Their downside, however, is their adverse effects, such as fatigue, extrapyramidal disorders, vertigo, ataxia, confusion, neurosis, seizures, etc. Natural plants have shown promising antiviral and immunomodulatory effects that are currently validated on animal models.

1.1 Severity of COVID-19
Fever, dry cough, and weakness are the most common symptoms of COVID-19. Pains and aches, migraine, respiratory irritation, sore throat, conjunctivitis, diarrhea, lack of taste or scent, or a skin rash/ finger/toe discoloration are some less frequent signs that occur in certain patients. Typically, these symptoms are mild and often there are chances to progress towards damaging the organs4. Effect on CNS-
Viral infection can severely affect the nervous system's function and structure. Viral CNS infection can cause extreme encephalitis and toxic encephalopathy leading to acute demyelinating lesions.5

Effects on CVS-
Impacts of COVID-19 are not only on the lungs but also can have severe effects on the CVS system. Patients with pre-existing CVS disease having a greater mortality rate. In 40% of COVID-19 cases, patients have CVS disease, in which 16.7% of patients developed arrhythmia, 7.2% cases developed an acute cardiac injury. Around 8.7% of patients developed shock and some cases are also seen having myocarditis.6

Effects on organs-
Severe immune reactions during COVID-19 disease could also lead to rapid cytokine release that can contribute to multiple organ failures and ischemic stroke.7

2. Role of nature in prevention and treatment of COVID-19
Nature provides a comprehensive chemical library to explore and create diverse medicines for the treatment of different diseases. Because of their natural source, protection, and cost-effectiveness as compared to artificial drugs, these natural products can be effective integrative medicines in the battle against viruses. Some phytochemicals groups, such as flavonoids, alkaloids, and peptides have been tested and recognized as anti-viral bioproducts. Such agents have been known for not only playing an important role in the battle against COVID-19 but also in preventing the viral attack. Thus, in the management of COVID-19, the phytoconstituents have been recognized to offer a significant role.9,10 Certain herbs with their active constituents and validated activities on the established models are shown in Table 1.

Table 1: List of herbs and their activities

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of Plant</th>
<th>Active Constituent</th>
<th>Parts used</th>
<th>Pharmacological Activities</th>
<th>Probable mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ashwagandha (Withania somnifera)</td>
<td>Steroidal Lactones- Withaferins Withanolides Alkaloids- Cuscohygrine Anahygrine Isopelletierine Anaferine Saponins11</td>
<td>Plant’s root or leaves.</td>
<td>Antiviral activity against COVID-19</td>
<td>Molecular docking of Withanone and Withaferin-A (obtained from the alcoholic extract of Ashwagandha leaves) is found to block transmembrane protease serine 2 enzyme which shows that it can block the entry of SARS-CoV-2 inside the cell. Withanone also down regulated the expression of enzyme in MCF7 cell line13.</td>
</tr>
<tr>
<td>2.</td>
<td>Turmeric (Curcuma longa)</td>
<td>Curcumin Desmethoxycurcumin bisdemethoxycurcumin volatile oils14</td>
<td>Rhizome</td>
<td>Anti-influenza activity, Inhibition of hemagglutination</td>
<td>Curcumin shows anti-influenza activity against influenza viruses PR8, H1N1, and H6N1 by inhibiting NF-κB signaling and reduced the viral load of influenza virus using MDCK virus-infected cells. Also inhibits hemagglutination using chicken erythrocytes15.</td>
</tr>
<tr>
<td>3.</td>
<td>Kalmegh (Andrographis paniculata)</td>
<td>Andrographolide Neo-andrographolide Deoxyandrographolide andrographiside16</td>
<td>Whole plant</td>
<td>Antiviral and Anti-influenza activity17,18</td>
<td>In vitro studies of andrographolides showed anti-influenza activity within the canine kidney cell line infected with H5N1, H9N2, or H1N1. It shows decreased lung viral titers in-vivo and anti-hemagglutinin activity19.</td>
</tr>
</tbody>
</table>
### 4. Clove (Syzygium aromaticum)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Plant Part</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eugenol, Eugenol acetate, Eugenin</td>
<td>Flower buds</td>
<td>Antiviral activities of Eugenin</td>
</tr>
<tr>
<td>β-carisofilenol</td>
<td></td>
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</tr>
</tbody>
</table>

The compound Eugenin derived from clove oil has shown antiviral activity against herpes virus strains by inhibiting viral DNA synthesis in virus infected Vero cells.23,24

### 5. Tulsi (Ocimum sanctum)

| Flavonoids, Eugenol | Whole plant | Immunomodulatory and ACE Ihblocking properties |

Dihydrodieugenol B & Tulsinol A, B, C, D, E, F, G in tulsi extract inhibits main protease and papain like protease of SARS CoV-2 in silico studies.25 In vitro studies of tulsi extracts inhibited H9N2 virus replication using embryonated chicken eggs.26

### 6. Patha (Cissampelos pareira)

| Hyatine, Hayatinine, Hayatidine, Bisbenzylisoquionline, Berberines | Root | Anti-oxidant activities, Immunomodulato r activity, Anti-inflammatory, Heptoprotective action |

Alcoholic extract (AFCP) has shown potent inhibition of all four types of DENV'S (dengue virus) in cell-based assay by inhibiting NS1 antigen secretion. Decreased viral load and downregulated TNF-α using AG129 mouse model.29 AFCP has a major immunosuppressive effect by reducing antibody production.30

### 7. Liquorice (Glycyrrhiza glabra)

| Glabridin, Glycyrrhizinic acid | Root/Ste m | Antiviral activity, Antioxidant activity, immunom oactive, anti-inflammatory activity |

GLR (glycyrrhizic acid) in liquorice extract has been reported to effectively inhibit the replication of two Coronavirus associated with SARSclinical isolates (FFM-1 & FFM-2) inside Vero cells.32 A study was conducted showing antioxidant activities of liquorice in 4 groups of growing Kunming mice.33

### 8. Bhumyamalaki (Phyllanthus amarus)

| Lignans, Glycosides, Ellagitanins, Phenylpropanoids, Amarin, Germanin, Corilagin, Flavonoids, Alkaloids | Whole plant | Antipyretic, Antiviral activity Immunomodulato r activity |

Aqueous and methanolic extracts of bhumyamalaki showed anti-viral effect against dengue virus by blocking the virus adsorption thereby hindering viral entry into the Vero cells.35 Berberine strongly suppressed viral replication which is antagonistic towards influenza A/FM1/1/47 (H1N1) inside A549 cells & in mouse lungs by suppressing the regulation of NF-κB and TLR7 signaling and decrease production of cytokines.36 Respiratory swelling & minimal tissue damage, inflammation including pulmonary embolism caused in mice through viral illness is reduced by Berberine.37

### 9. Mamira (Coptisteeta)

| Berberine (8.5%) | Rhizome | Anti-viral Antimicrobial, Anti-inflammatory, Anti-oxidant activity |

Berberine strongly suppressed viral replication which is antagonistic towards influenza A/FM1/1/47 (H1N1) inside A549 cells & in mouse lungs by suppressing the regulation of NF-κB and TLR7 signaling and decrease production of cytokines. Respiratory swelling & minimal tissue damage, inflammation including pulmonary embolism caused in mice through viral illness is reduced by Berberine.37

### 10. Giloy (Tinospora cordifolia)

| Berberine, Isocolumnin, Magnoflorine, Tinocordiside β-sitosterol, Coline, Tetrahydropalmatine Oc tansol, Cordifolioside A | Stem | Immunomodulato r activity, anti-inflammatory, anti-allergic, anti-viral activity |

Natural compounds like Berberine, Magnoflorine, and Isocolumnin, and Tinonoriside have been shown to inhibit SARS-CoV-2 virus target proteins viz surface glycoprotein, RNA polymerase in silico studies suggesting its interference in viral attachment and replication.42,43

Apart from the above-mentioned herbs used in raw forms, certain herbal formulations have also been developed and are being used for the management of COVID-19.44 Ayush-64, a polyherbal preparation, which has been in practice since 1980 is used under multiple conditions such as inflammation, fevers and joint pains. It has been patented by the Ayurveda and Siddha
The composition of Ayush-64 and therapeutic actions of its major ingredients are given below in the table-2.

Table 2: Ayush-64 composition and uses of its major ingredients

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Part Used</th>
<th>Extract</th>
<th>Chemical Constituents</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Katuka (Picrorhizakurroa)</td>
<td>Rhizome</td>
<td>Aqueous rhizome</td>
<td>Picroside I, II; Apocynin; Kutki sterol; D-mannitol&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Cardioprotective&lt;sup&gt;48&lt;/sup&gt;, Immunostimulatory activity&lt;sup&gt;39&lt;/sup&gt;, Healing Potential&lt;sup&gt;30&lt;/sup&gt;.</td>
</tr>
<tr>
<td>2</td>
<td>Sapthachada (Alstoniascholaris)</td>
<td>Bark</td>
<td>Aqueous bark extract</td>
<td>Alpha-amyrin; Lupanol acetate; Stigmasterol; Betasitosterol; Campesterol&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Anti-inflammatory and analgesic effects&lt;sup&gt;52&lt;/sup&gt;, Antibacterial activity&lt;sup&gt;53&lt;/sup&gt;.</td>
</tr>
<tr>
<td>3</td>
<td>Kiratatikta (Swertia chirata)</td>
<td>Whole plant</td>
<td>Aqueous extract of the whole plant</td>
<td>Amarogentin; Swertiamarin; Mangiferin; S qoside; Amaroswerin; Gentipicrin&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Antiviral activity&lt;sup&gt;55&lt;/sup&gt;, Antieptic effect&lt;sup&gt;56&lt;/sup&gt;, Antipyretic Potential&lt;sup&gt;57&lt;/sup&gt;, Anticarcinogenic activity&lt;sup&gt;58&lt;/sup&gt;.</td>
</tr>
<tr>
<td>4</td>
<td>Kuberakshi (Caesalpinabiabondulcella)</td>
<td>Seed</td>
<td>Fine Powdered seed pulp</td>
<td>Homo-isoflavonoids; Caesalpinianone; 6-O-methylcaesalpinianone&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Immunomodulatory activity&lt;sup&gt;60&lt;/sup&gt;, Antibacterial activity&lt;sup&gt;61&lt;/sup&gt;, Anti-inflammatory, antipyretic, and analgesic properties&lt;sup&gt;62&lt;/sup&gt;.</td>
</tr>
</tbody>
</table>

Another formulation, AyushKwath, advised by The Ministry of Ayushhas been recognized to boost the immune system against viruses, including the novel coronavirus that causes COVID-19. The composition of AyushKwath and therapeutic actions of its major ingredients are given below in the table-3.

Table 3: AyushKwath composition and uses of its major ingredients

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Parts Used</th>
<th>Main chemical constituents</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tulsa (Oenium sanctum)</td>
<td>Leaves</td>
<td>Ascorbic acid, Volatile oils (Eugenol)&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Cough; Fever; Diarrhea; Pain; Anti-viral; Pneumonia; Asthma&lt;sup&gt;64,65,66&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Cinnamon (Cinnamomumzeylanicum)</td>
<td>Stem</td>
<td>Cinnamaldehyde, Cumin aldehyde Eugenol, Benzaldehyde&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Anti-oxidant; Cough; Fl; Indigestion; Headache&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Ginger (Zingiberofficinale)</td>
<td>Rhizome</td>
<td>Zingiberene; Zingiberol&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Anti-viral; Anti-pyretic; Analgesic; Anti-oxidant; Anti-hypertensive&lt;sup&gt;70&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Black pepper (Piper nigrum)</td>
<td>Fruit</td>
<td>Piperidine; Piperine; Piperetine; Chavicine&lt;sup&gt;71&lt;/sup&gt;</td>
<td>In Respiratory, digestive disorders; Cold; Asthma; Diarrhoea&lt;sup&gt;72&lt;/sup&gt;.</td>
</tr>
</tbody>
</table>

Considering the facts learned from the literature survey and increasing growth rate of new corona cases, we felt there is a need to understand the choices of the community for the natural remedies being taken during the time of COVID-19. So, a questionnaire was designed to find out the frequency of usage of different types of herbs for prevention as well as management of COVID-19. The survey also tried to determine the extent of use of some of the alternative remedies like usage of warm water, inhalation of steam, application of oils on the body, and consumption of a healthy diet containing sprouts, protein-rich food. Data were collected from the patients suffering from COVID-19 as well as from the healthy people who were using the herbs in their day to day lives. In total, 80 survey forms were circulated in the community to gather data that included patients and healthy volunteers. The designed questionnaire is mentioned below in Fig 1.
RESULT & DISCUSSION-
The data was collected from 80 volunteers using a questionnaire survey. Their responses have been summarized below:

- 30% of the individuals were found to be suffering from COVID-19 infection out of which only 10% were hospitalized and the remaining 20% were home quarantined.
• Out of 30% of confirmed COVID patients, 15% of patients had symptoms like cough, cold, running nose, sore throat, shortness of breath, loss of smell, and low oxygen levels. And another half of COVID patients were found to be asymptomatic.
• From the co-morbidity assessment, we found that only 5% of COVID patients were suffering from diabetes and only 2% were having the liver disease as a risk factor.
• Most of the healthy volunteers as well as patients who were home quarantined were using botanicals not only as a precautionary measure but also for the treatment of COVID-19. Figure 2 below shows the frequency use of the herbs in the prevention and management of COVID-19 infection and Figure 3 shows other than herbs, the frequency use of alternative therapy for the prevention and management of COVID-19 infection.

![Pie chart showing the percentage usage of herbs (n=80)](image1)

![Pie chart showing the percentage of alternative remedies (n=80)](image2)

It was observed that most of the individuals had been using these top six herbs regularly that are: Ginger (71%), Turmeric (64%), Tulsi (60%), Giloy (51%), Black-pepper, and clove (35%). Along with the herbs, other alternative remedies were also followed by the individuals for the preventing and treatment of COVID-19 like drinking warm water (84%), inhalation of steam (54%), protein-rich diet (39%), and applying oil on the body (15%).

**Conclusion**
COVID-19 is spreading worldwide and creating chaos in the lives of people and also putting a financial burden by introducing various health-related complications. Since vaccine administration are in a preliminary stage and no specific treatment is available, we have tried to explore those botanicals and their formulations that could be effective in the management of COVID-19. For this purpose, we have conducted a questionnaire survey that investigated demographic information (age, gender); dietary habits information (daily consumption of definite foods, food frequency); lifestyle habits information (habit of smoking and drinking alcohol) followed by enquiring to what degree volunteers are using herbs in day to day lives for the prophylaxis and therapy of COVID-19. The survey was conducted from the 15th to the 31st of November 2020. The most preferred herbs were found to be Ginger, Turmeric, Tulsi, and Giloy. It was also inferred that some people are also using other alternative precautionary measures along with herbs like drinking warm water, taking steam, application of oils, taking healthy food. Our paper has shown insight on herbs that have shown efficacy in reported studies. Thus, it can be concluded that the above-mentioned herbs can be used as a treatment against the SARS-CoV-2 virus. The active constituents present in these herbs can be tested and validated in a future scenario as potential biomolecules for the management of COVID-19.

**CONFLICT OF INTEREST**
The authors declare no conflict of interest, financial or otherwise.

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