Review Article

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CONCEPTUAL REVIEW ON THE POTENTIAL OF *PUNARNAVADYA GHRITA* IN TACKLING THE SYMPTOMS OF COVID-19

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ABSTRACT

COVID-19 disease has created panic among all with respect to health and economy. On 11th March 2020 WHO (world health organisation) declared novel corona virus outbreak as global pandemic. Confirmed effective remedy to prevent or treat COVID-19 is not yet established. Ayurveda, the Indian system of medicine is the oldest medicinal literature known to mankind as old as 3000 BC and is recognised as medical system by WHO. There is a need to investigate time tested potent classical Ayurvedic formulations backed by contemporary scientific studies in treating symptoms of COVID-19 disease. *Vijaya (Cannabis sativa* Linn.*)* in Ayurveda notable for its *Vyavayi* (quick absorption) and *Yogavahi* (synergetic action) properties said to be originated from ambrosia as per *Vedic* mythology. Recent scientific research on the phytochemicals of *Cannabis* plant showed promising results in decreasing the pro-inflammatory cytokine storm and to an extent halting the replication of SARS-CoV-2. We have put forward one such classical Cannabis Ayurvedic formulation *Punarnavadya Ghrita* available in market which can be useful as an alternative remedy for prophylactic and curative to the symptoms of novel corona virus disease whose individual herbal phytochemical compounds are studied through *in silico*, *in vitro* and *in vivo* methods in treating COVID-19 with positive outcomes.

Keywords: *Punarnavadya Ghrita*, Cannabis, COVID-19, SARS-CoV-2, Main protease, Cytokine storm.

INTRODUCTION

The corona virus disease 2019 pandemic has caused havoc on every aspect of public health causing social and economic disruption. Scientists across the globe are attempting to investigate anti-viral, immunity modulators and vaccines specific to COVID-19 with not much efficacy tailed by side effects like the steroid medications which are immune suppressants. Classical medicines in Ayurveda are time tested formulations which are being successfully revalidated through scientific studies by many institutes across the world of AYUSH systems. In these circumstances there is a need to encourage Ayurvedic medications which are backed by scientific research as prophylactic and symptomatic treatment measures in COVID-19. The COVID-19 disease caused by SARS-CoV-2 can be compared to *Bhuta, Rakshasa, Graha*, etc, a kind of microbes elucidated in Ayurveda which may cause *Bhutabhishangaja Jwara* (fever caused by invisible organisms), a kind of *Agantu Jwara* (fever caused by external factors) negatively effecting *Pranavaha srotas* (the vessels carrying the vitals) related to Lungs, Heart and Brain[1]. The spread of COVID-19 pandemic is compared to *Janapadodhwamsa* or *Maraka*, a broad term for epidemic in Ayurveda which cause contagious diseases through four important factors Viz. polluted air, water, land and season. It has been said that pandemic spreading by air can be easily treated than other causative factors like water, land and seasons. *Pancha-karma* (purification therapies) to detoxify, *Rasayana* (rejuvenative) therapies to improve the immune system, symptomatic treatment and anti-viral medicines to control the replication of virus or entry of virus into the body are the prime focus in treating Covid-19 like pandemic in Ayurveda[2].

Powerful medicines are required to quickly address the damage/infection caused by the Covid-19. Immune modulators, anti-inflammatory drugs and symptomatic treatment being the main focus in tackling the COVID-19 disease by AYUSH personnel,[3,4] we focused on certain attributes said in Ayurveda which are required for the quick stimulation of both body and mind for improving immune system and fitness of the body to help tackle the COVID-19 disease. *Vyavayi guna*[5] (fast diffusing quality) is a specific property of few herbs in Ayurveda which first spreads/ circulates quickly throughout the body to exert its action and then undergoes *paka* (digestion). *Sattva* (goodness) is the purest quality among the three primary attributes of mind which is said to be required for homeostasis in the neuronal impulses which triggers all the physiological functions in the body[6]. *Medhya*[7] (intellect promoting) is also a unique quality among certain herbs to help maintain the neuronal health and psychological balance. *Vajikarana-Rasayana*[8] (aphrodisiac and rejuvenative) herbs are the best in improving and maintaining energy levels, stamina and immunity. All these qualities are present in one single herb called *Vijaya* (*Cannabis sativa* Linn.)[9] and recent scientific researches done on the phytocannabinoids of *Cannabis* plant showed encouraging results in decreasing the pro-inflammatory cytokine storm and to an extent halting the replication of SARS-CoV-2 which will be explained in brief. There are more than 200 formulations[10] of *Vijaya* (*Cannabis sativa* Linn.) in Ayurveda that are mostly unexplored. So, we searched online journals for scientific research articles on Elsevier, Pub Med, Research Gate, Science Direct, Medline, Google Scholar, Semantic Scholar, Ayush research portal, etc, for Ayurvedic herbs useful in COVID-19 disease; in parallel also explored classical *Vijaya* (*Cannabis sativa* Linn.) based Ayurvedic formulations available in the AYUSH medical shops or online pharmaceutical markets having such combination of researched herbs on COVID-19.

We found a classical *Cannabis* based Ayurvedic formulation available in the market called *Punarnavadya Ghrita* from a GMP certified Ayurvedic company Charaka Hanf Pvt. Ltd.[11] taken

from *Shotha roga chikitsa prakarana* (chapter related to the treatment of inflammations) of the classical book *Bhaishajya ratnavali*[12] listed in the first schedule of drugs and cosmetics act (1940). This polyherbal infused Ghee is blended by a unique combination of five anti-inflammatory herbs indicated in *Jwara* (fever), *Kasa* (cough), *Shwasa* (shortness of breath, asthma) and *Daruna Shotha* (severe inflammation) which are the major symptoms of COVID-19. Other symptoms of COVID-19 are headache, sore throat, chest pain, loss of taste and smell, tiredness, aches, loss of appetite, nausea, diarrhoea, etc[13,14] which can be managed by the researched herbs of *Punarnavadya Ghrita* as per the properties of the individual herbs in Ayurvedic literature[15]. *In silico, In vitro* and *In vivo* research is available on the phytochemicals of these five herbal ingredients for symptomatically treating COVID-19 and also inhibiting the replication of SARS-CoV-2 with positive outcomes will be discussed below in brief.

Table 1: The herbal ingredients of *Punarnavadya Ghrita*

S. No.	Sanskrit name	Scientific name	Family	Part used
1.	*Vijaya*	*Cannabis sativa* Linn.	Cannabinaceae	Leaf
2.	*Punarnava*	*Boerhavia diffusa* Linn.	Nyctaginaceae	Root
3.	*Bhunimba*	*Andrographis paniculata* (Burm. f.) Nees.	Acanthaceae	Whole plant
4.	*Shunthi*	*Zingiber officinale* Rosc.	Zingiberaceae	Rhizome
5.	*Devadaru*	*Cedrus deodara* (Roxb.) G. Don.	Pinaceae	Heart wood[15]

Table 2: The Ayurvedic pharmacological properties of the above researched herbs

S. No.	Herbs	*Rasa* (taste)	*Guna* (qualities)	*Virya* (potency)	*Vipaka* (taste after digestion)	*Dosha* (fundamental bio-elements)
1.	*Vijaya*	*Tikta* (bitter), *Katu* (pungent)	*Laghu* (light), *Tikshna* (sharp)	*Ushna* (hot)	*Katu* (pungent)	alleviates *Kapha-Vata*
2.	*Punarnava*	*Madhura* (sweet), *Tikta* (bitter)	*Laghu* (light), *Ruksha* (dry)	*Ushna* (hot)	*Katu* (pungent)	alleviates *Kapha-pitta*
3.	*Bhunimba*	*Tikta* (bitter)	*Laghu* (light), *Ruksha* (dry), *Sara* (mobility)	*Sita* (cold)	*Katu* (pungent)	alleviates *Kapha-pitta*
4.	*Shunthi*	*Katu* (pungent)	*Laghu* (light), *Snigdha* (oily), *Grahi* (absorbent)	*Ushna* (hot)	*Madhura* (sweet)	alleviates *Kapha-Vata*
5.	*Devadaru*	*Tikta* (bitter), *Katu* (pungent)	*Laghu* (light), *Snigdha* (oily)	*Ushna* (hot)	*Katu* (pungent)	alleviates *Kapha-Vata*[15]

Scientific research on phytochemicals of the herbs of *Punarnavadya Ghrita* on SARS-CoV-2

***Vijaya (Cannabis sativa* Linn.)**

The endocannabinoid system is found in multiple systems within the human body, including the immune system. Its activation can lead to beneficial results such as decreased viral entry, decreased viral replication and a decrease in pro-inflammatory cytokines such as IL-2, IL-4, IL-6, IL-12, TNF-α or TNF-γ. Moreover, endocannabinoid system activation can lead to an increase in anti-inflammatory cytokines, mainly represented by IL-10. Overall, the cannabinoid system can potentially reduce pulmonary inflammation, increase the immunomodulatory effect, decrease PMN infiltration, reduce fibrosis, and decrease viral replication, as well as decrease the cytokine storm[16].

In an *in vitro* study Cannabis compounds Viz. CBD, CBG and THCV exhibited anti-inflammatory activity in COVID-19-related inflammation in lung epithelial cells and pro-inflammatory activity in macrophages[17].

In an experimental study CBD (Cannabidiol), the Phytocannabinoid and its metabolite, 7-OH-CBD potently blocks SARS-CoV-2 replication in lung epithelial cells. CBD acts after 5 cellular infections, inhibiting viral gene expression and reversing many effects of SARS-CoV-2 on host gene transcription. CBD (Cannabidiol) induces interferon expression and up-regulates its antiviral signalling pathway[18]. CBD might represent as a potential anti-inflammatory therapeutic approach against SARS-CoV2-induced inflammation[19].

In an animal experimental study; the treatment of SEB-mediated ARDS mice with Delta-9 Tetrahydrocannabinol (THC), the main Phytocannabinoid led to a 100% survival, decreased lung inflammation and the suppression of cytokine storm. This was associated with immune cell apoptosis involving the mitochondrial pathway, as suggested by single-cell RNA sequencing. A transcriptomic analysis of immune cells from the lungs revealed an increase in mitochondrial respiratory chain enzymes following THC treatment. THC caused the downregulation of miR-185, which correlated with an increase in the pro-apoptotic gene targets. Interestingly, the gene expression datasets from the bronchoalveolar lavage fluid (BALF) of human COVID-19 patients showed some similarities between cytokine and apoptotic genes with SEB-induced ARDS. Collectively, this study suggests that the activation of cannabinoid receptors may serve as a therapeutic modality to treat ARDS associated with COVID-19[20].

Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, is a peptide hormone secreted mainly by the stomach. Interestingly, ghrelin possesses promising antioxidant, anti-and inflammatory effects, making it an attractive agent to reduce the complications of the SARS-CoV-2. In addition, ghrelin exerts a wide range of immunomodulatory and anti-inflammatory effects and can mitigate the uncontrolled cytokine production responsible for acute lung injury by upregulating PPARγ and down-regulating NF-κB expression. Ghrelin has also been reported to enhance Nrf2 expression in inflammatory conditions which led to the suppression of oxidative stress. The current opinion summarizes the evidence for the possible pharmacological benefits of ghrelin in the therapeutic management of SARS-CoV-2 infection. Delta-9 Tetrahydrocannabinol (THC) compound of cannabis is responsible for the stimulation and release of ghrelin[21].

High CBD (cannabidiol) Cannabis extracts are able to down-regulate the expression of the two key receptors for SARS-CoV2 in several models of human epithelia. CBD (cannabidiol) exerts a

wide range of immunomodulatory and anti-inflammatory effects and it can mitigate the uncontrolled cytokine production responsible for acute lung injury. CBD being a PPARγ agonist, it can display a direct antiviral activity and PPARγ agonists are regulators of fibroblast/myofibroblast activation and can inhibit the development of pulmonary fibrosis, thus ameliorating lung function in recovered patients[22].

***Punarnava* (*Boerhavia diffusa* Linn.)**

Main protease (Mpro) of SARS-CoV-2 is a key enzyme of corona viruses and has a pivotal role in mediating viral replication and transcription, making it an attractive drug targets to design anti-viral meds. Many phytochemicals of *Boerhavia diffusa* were tested with molecular docking study and an article was published. The ligands that showed the least binding energy were Biorobin 8.17 kcal/mol, Bioquercetin 7.97 kcal/mol and Boerhavisterol 6.77 kcal/mol. These binding energies were found to be favourable for an efficient docking and resultant inhibition of the viral main protease[23].

Bhunimba (Swertia chirata* Buch. - Ham*)

SARS-CoV-2 proteins associated with host attachment and viral replication namely, spike protein, main protease enzyme (Mpro) and RNA-dependent RNA polymerase (RdRp) are promising druggable targets for COVID-19 therapeutic research. Extensive molecular docking of the phytocompounds of *Swertia chirata* at the binding pockets of the viral proteins revealed their promising inhibitory potential. Subsequent assessment of physicochemical features and potential toxicity of the compounds followed by robust molecular dynamics simulations and analysis of MM-PBSA energy scoring function revealed amarogentin, a natural bitter terpenoids of *Swertia chirata* against SARS-CoV-2 RdRp as potential inhibitor and displayed significantly higher binding energy score[24].

***Bhunimba* (*Andrographis paniculata* (Burm. f.) Nees.)**

The drug compound, Andrographolide extracted from the plant *Andrographis paniculata* was analysed by *in silico* computational docking tools it successfully docked against the inhibitor region of the main protease of SARS-CoV-2 virus with docking score of -3.094357 Kcal/mol, the docking score showed great binding when compared to synthetic compounds when they are docked against Mpro such as disulfiram, tideglusib and shikonin which are -46.16 Kcal/mol, -61.79 Kcal/mol and -17.35 Kcal/mol. And it also shows great binding score when compared against recently proposed combination of three drugs namely, lopinavir, ostelmivir and ritonavir whose binding scores are -4.1Kcal/mol, -4.65 Kcal/mol and -5.11 Kcal/mol. Even some plant molecules which are studied to inhibit the main protease of SARS-CoV-2 failed to prove their binding score when compared with the Andrographolide such as kaempferol -9.41 Kcal/mol, quercetin -8.58 Kcal/mol, demethoxycurcumin -8.17 Kcal/mol, curcumin -7.31 Kcal/mol, catechin -7.05 Kcal/mol, epichatechin gallate- 7.24 Kcal/mol, zingerol -6.67 Kcal/mol and gingerol -5.40 Kcal/mol respectively. Even proposed inhibitor of Mpro such as PRD_002214 has a docking score of -10.466 Kcal/mol which proclaim that Andrographolide has better properties than other proposed inhibitors[25].

A molecular docking approach, and combined molecular dynamics and MM-GBSA based free energy calculations approach were used to study the potency of the four selected phytochemicals namely andrographolide, 14-deoxy 11, 12-didehydro andrographolide, neoandrographolide and 14-deoxy andrographolide from *Andrographis paniculata* plant against the four key targets including three non-structural proteins 3CLpro (Mpro), papain-like protease (PLpro) and RNA-directed RNA polymerase (RdRp) and a structural protein spike protein (S) of the virus which are responsible for replication, transcription and host cell recognition. Results state phytochemical neoandrographolide has the stronger binding affinity than other compounds towards spike protein-ACE2 complex (-7.8 kcal/mol), 3CLpro (-7.1 kcal/mol), PLpro (-7.3 kcal/mol) and RdRp (-7.4 kcal/mol). In this way *Andrographis paniculata* was shown to have potency against the Covid-19 and have evidenced its microscopic mechanism through rational computational modelling[26].

Experiments were done by plaque assay for viral output study using the legitimate model of human lung epithelial cells, Calu-3, to determine anti-SARS-CoV–2 activity of *Andrographis paniculata* extract and its major component andrographolide. SARS-CoV-2 at 25TCID50 (Median Tissue Culture Infectious Dose) was able to reach the maximal infectivity of 95% in Calu-3 cells. Post-infection treatment of *Andrographis paniculata* and andrographolide in SARS-CoV–2 infected Calu-3 cells significantly inhibited the production of infectious virions with the IC50 of 0.036 μg/mL and 0.034 μM, respectively, as determined by plaque assay[27].

Andrographolide from *Andrographis paniculata* and its fluorescent derivative, the nitrobenzoxadiazole-conjugated andrographolide (Andro- NBD), suppressed the main protease (Mpro) activities of 2019-nCoV. Moreover, Andro-NBD was shown to covalently link its fluorescence to Mpro. Further mass spectrometry (MS) analysis suggests that andrographolide formed a covalent bond with the active site Cys^{145} of SARS-CoV–2 Mpro. Consistently, molecular modelling analysis supported the docking of andrographolide within the catalytic pockets of viral Mpro[28].

***Shunthi* (*Zingiber officinale* Rosc.)**

SARS-CoV-2 utilises its Spike protein as a significant part of its envelop that participate in the interaction with its cellular receptor angiotensin converting enzyme 2(ACE2). Consequently, the spike protein is cleaved by extracellular catalytic domain of Transmembrane protease Serine 2 (TMPRSS2) also called as Serine protease or Hepsin leading to entry of virus into the host cell. Molecular docking study revealed that Gingerenone (-5.87 kcal/mol) and Zingiberene (-5.77 kcal/mol) have shown effective binding affinity towards ACE2. Shoagol (-5.72 kcal/mol), Zingerone (-5.79 kcal/mol) and Zingiberene (-5.52 kcal/mol) have shown higher binding with extracellular domain of serine protease TMPRSS2. Zingiberene scored significant binding energy (-6.23 kcal/mol) with Spike protein of SARS-CoV-2[29].

Studies against the viral receptors by using the molecular docking technique revealed phytocompound 6-gingerol proves anti-viral efficiency against SARS CoV-2 by showing the highest binding affinity ranging from -2.8764 KJ/mol to -15.7591 KJ/mol with various COVID-19 viral protein targets including Viral proteases, RNA binding protein, Spike protein[30]. A molecular docking study showed that the nine phytochemicals of *Zingiber officinale* are potential inhibitors against the main protease enzyme (6LU7) of COVID-19[31].

***Devadaru* (*Cedrus deodara* (Roxb.) G. Don)**

The bark of *Cedrus deodara* contains large amounts of taxifolin[32,33], a flavonoid, also called dihydroquercetin was tested using molecular docking on main protease (Mpro) of SARS-CoV-2 in an *in-silico* study and binding affinity to Mpro was

assessed. It was subjected to molecular dynamics simulation and predicted activity (IC_{50}) using 3D-QSAR analysis. Study suggests taxifolin potential inhibitory activity against SARS-CoV-2 Mpro with IC50 value 9.63 μM[34].

Essential oil from pine needles of *Cedrus deodara* was determined, and twenty-three components, representing 95.79% of the oil, were identified by gas chromatography mass spectrometry. The main components include α-terpineol (30.2%), linalool (24.47%), limonene (17.01%), anethole (14.57%) and caryophyllene (3.14%)[35].

Alpha-terpineol, a monoterpenoid has the strongest inhibitory effects on the ACE2 protein in human body and PDB6LU7 protein in the SARS-CoV-2 in a molecular docking simulation study. Docking of α-terpineol -ACE2 has DS (docking score energy) of −11.0 kcal.mol^{-1} and RMSD (root mean square deviation) of 1.97 Å, while the site-site bonding interaction exhibiting the length of the binding of compound with amino acid between -OH of α-terpineol and amino acids Asn 103 is 2.25 Å and 2.08 Å for Gln 101. Docking of α-terpineol -SARS-CoV-2 has DS (docking score energy) -10.9 kcal.mol^{-1} and RMSD (root mean square deviation) of 1.16 Å. Results show strongest inhibitory effects of α-terpineol on ACE2 and PDB6LU7 proteins (main protease of the SARS-CoV-2)[36]. Another Mpro of novel corona virus docking analysis with α -terpineol showed two hydrogen bonds with GLU166; three hydrophobic alkyl and pi-alkyl bonds with MET49, MET165, and HIS41 residues; and five van der Waals forces with TYR54, LEU167, GLN189, ARG188, and ASP187 with a binding energy value of -5.43 kcal/mol and 105.43 μM inhibitory constant[37].

Linalool, a monoterpenoid is capable of binding to ACE2 and PDB6LU7 proteins and has quite good interactions with amino acid Asn 210 of ACE2 protein, and Gly 143 as well as Cys 145 of PDB6LU7 protein. Docking of Linalool -ACE2 has DS (docking score energy) of -10.9 kcal.mol^{-1}, RMSD ((root mean square deviation) of 1.77 Å, and site-site bonding interaction between -OH and amino acid Asn 210 is 1.96 Å. Docking of Linalool -SARS-CoV-2 has DS (docking score energy) of -11.1 kcal.mol^{-1}, and RMSD (root mean square deviation) of 1.18 Å, and site-site bonding interactions between –OH and amino acid Gly 143 and Cys 145 are 2.89 Å and 2.82 Å, respectively. Results exhibit the significant inhibition of linalool on ACE2 and PDB6LU7 proteins (main protease of the SARS-CoV-2)[38].

The docking study of Mpro with d-limonene, a monoterpenoid has utilized an energy value of -5.18 kcal/mol and 159.51 μM inhibitory constant and 12 hydrophobic bonds were formed with MET49, PRO52, TYR54, MET165, HIS41, CYS44 and ARG188 and three van der Waals interactions with HIS164, GLN189, and ASP187 residues, the active sites of protein (Mpro of novel corona virus). The molecular interaction analysis using Autodock 4.2 software resulted in favourable interactions of limonene as a possible inhibitor of main protease of SARS-CoV-2[39].

Anethole is an aromatic polyphenol related to lignols. It has been docked against the S1 receptor binding domain of the spike (S) glycoprotein of SARS-CoV-2 in an *in-silico* studies. A receptor-binding domain (RBD) is a short immunogenic fragment from a virus that binds to a specific endogenous receptor sequence to gain entry into host cells. Results prove Anethole exhibited good inhibition of RBD region of SARS-CoV-2 spike protein[40].

Caryophyllene, a sesquiterpene is a component in the essential oil of Devadaru (*Cedrus deodara* (Roxb.) G. Don.) and is also abundant in *Vijaya* (*Cannabis sativa* Linn.). Pi-alkyl interactions of Caryophyllene with PHE 294 were observed with an affinity of -7.2 could be a potential inhibitor of SARS-CoV-2 main protease[41].

DISCUSSION

Punarnavadya Ghrita is a potent anti-inflammatory classical medication mentioned in *Shotha* (anti-inflammatory) chapter in the book *Bhaishajya Ratnavali* indicated in *Jwara* (fever), *Kasa* (cough), *Shwasa* (shortness of breath, asthma) and *Daruna Shotha* (severe inflammation) which are also the prime symptoms observed in COVID-19 as per WHO. It is prepared from the goodness of Bilona A2 Cow Ghee and infused with the *Rasayana* (rejuvenating) herb *Vijaya* (*Cannabis sativa* Linn.) which is *Vyavayi* (fast acting) and having *Yogavahi* (synergetic action). *Vijaya* (*Cannabis sativa* Linn.) has *Grahi* (Absorbent), *Dipana* (appetiser), *Pachana* (digestive) and *Ruchya* (improves taste) properties[9] which can quickly correct the metabolism of impaired digestion, the root cause leading to complications in most of the diseases (*Rogah Sarve api mandagnou*)[42] said by *Vagbhata*. *Ojas* (immunity) is the *Upadhatu*[43] of *Sukra dhatu* (tissues and components of reproductive system present in both males and females)[44] which is circulated all over the body[45] along with *Rasa dhatu* (blood plasma). This may be the Ayurvedic explanation why plasma donation was once an off-label recommendation for patients to recover fast from COVID-19 as the *Ojas*/ antibodies (immune components) are in circulation with blood plasma, but was discontinued from COVID-19 treatment guidelines as the antibodies in donor's plasma were not sufficient enough for patient recovery and also researchers hypothesized the risk of developing new variants of Virus. *Sukra* is the par excellence of well digested food said in *Charaka samhita*[46] which is later converted to *Ojas* (immune system components). Diminished *Sukra* may lead to various diseases and even death so, one should preserve the *Sukra dhatu* by indulging in wholesome food and lifestyle; hence potent *Vajikarana* (aphrodisiac) and *Sukra Stambhana*[47] (drugs prolonging ejaculation time) herbs like *Vijaya* (*Cannabis sativa* Linn.) can improve *Ojas* (immune system). *Vijaya* (*Cannabis sativa* Linn.) is a *Vata-Kapha* alleviating herb which according to *Acharya Charaka* is an essential *Dosha karma* for curing *Shwasa* (breathing difficulty/asthma)[48]. The cytokine storm is one of the major side effects of SARS-CoV-2 virus infection. Pro-inflammatory cytokines like interleukins, TNF-α and TNF-γ are involved in the inflammation of alveoli and damage the lungs. The endocannabinoid system inside the mammalian bodies controls these IL-2, IL-4, IL-6, IL-12 interleukins along with Tumour Necrosis Factor alpha and gamma (TNF-α, TNF-γ). Interleukin IL-10 called human cytokine synthesis inhibitory factor (CSIF) is a protein that inhibits the synthesis of a number of pro-inflammatory cytokines is also increased by the activation of the endocannabinoid receptors related to Phytocannabinoids of *Vijaya* (*Cannabis sativa* Linn.)[16]. *In vitro* experiment with CBD (cannabidiol), a major Phytocannabinoid was effective in stopping the replication of SARS-CoV-2 in lung epithelial cells[19]. CBD (cannabidiol) is a known anti-inflammatory and immune modulator molecule. CBD (cannabidiol) being an agonist at PPAR-γ receptor (peroxisome proliferator-activated receptor) reduced pulmonary inflammation and fibrosis in animal models of asthma. High CBD (cannabidiol) extracts have been reported to downregulate Angiotensin-converting enzyme 2 (ACE2) and Transmembrane Serine Protease 2 (TMPRSS2) receptors, viral gateways in oral, lung and intestinal epithelia constituting important routes of SARS-CoV2 invasion. In an animal study, CBD (cannabidiol) caused marked amelioration of the pulmonary function by acting at adenosine A2 receptor site and reducing of leukocyte migration into the lung, accompanied to a marked inhibition of both pro-inflammatory cytokines (TNF-α, IL-6) and chemokines (MCP-1 and MIP-2)[22]. THC (delta-9

Tetrahydrocannabinol), the main Phytocannabinoid in an animal study prevented mortality from ARDS (acute respiratory distress syndrome) by inducing apoptosis in immune cells responsible for increase in pro-inflammatory molecules, leading to the suppression of cytokine storm[20]. Ghrelin, a peptide hormone whose secretion is stimulated by THC (delta-9 Tetrahydrocannabinol) can decrease the uncontrolled cytokine production responsible for acute lung injury by upregulating PPARγ and down-regulating NF-κB expression. Ghrelin also enhance transcription factor Nrf2 expression in inflammatory conditions which can suppress oxidative stress[21].

Apart from *Vijaya* other herbs are, *Punarnava* (*Boerhavia diffusa* Linn.) a *Sopha hara* (anti-inflammatory), *Hridya* (Cardiotonic) herb indicated in *Kasa* (cough), *Shwasa* (dyspnoea/asthma), *Angamarda* (tiredness)[49] having *Kapha-Pitta* alleviating property included in *Vayahsthapana daseimani* (list of anti-ageing drugs) in *Charaka Samhita*[50]. *In silico* experiment on Main protease (Mpro) of SARS-CoV-2 with the phytochemicals of *Punarnava* (*Boerhavia diffusa* Linn.) Viz. Biorobin, Bioquercetin and Boerhavisterol were found to be effective in inhibiting viral main protease which mediates viral replication and transcription[23]. This signifies the preliminary antiviral property of *Punarnava* (*Boerhavia diffusa* Linn.).

Bhunimba is controversial between two plants, *Swertia chirata* which grows in north (Himalayan region) and *Andrographis paniculata* which grows in southern parts of India. Commonly *Andrographis paniculata* is used as a substitute for *Swertia chirata* as both plants have similar medicinal properties according to Ayurvedic community[51,52]. *Bhunimba* is a famous *Jwaraghna* (antipyretic) & blood purifying herb having *Kapha-Pitta* alleviating property prescribed in *Aruchi* (loss of taste), *Kasa* (cough), *Shwasa* (dyspnoea/asthma) and *Sopha* (inflammatory)[53]. As per the contemporary research *Andrographis paniculata* (Burm. f.) Nees. was taken as *Bhunimba* in the present formulation *Punarnavadya Ghrita* which was also approved by directorate of AYUSH. *In silico* experiments on main protease (Mpro) of SARS-CoV-2 with the phytochemical Andrographolide of *Andrographis paniculata*, a well-known antiviral showed strong binding affinity towards SARS-CoV-2 proteins associated with host attachment and viral replication namely, spike protein, main protease enzyme (Mpro), papain-like protease (PLpro) and RNA-dependent RNA polymerase (RdRp)[26,28]. An *in vitro* study with the model of infected human lung epithelial cell and Calu-3 with *Andrographis paniculata* extract and phytochemical Andrographolide was able to inhibit the infectious SARS-CoV-2 virion production displaying IC50 of 0.036 μg/mL and 0.034 μM, respectively with a high safety margin for major human organs viz. lung, brain, liver, kidney and intestine in cell culture models[27].

Shunthi (*Zingiber officinale* Rosc.) is a *Sopha hara* (anti-inflammatory), *Hridya* (Cardiotonic), *Swarya* (voice promoting), *Vrishya* (aphrodisiac) and *Kapha-Vata* alleviating herb which is indicated in *Kasa* (cough), *Shwasa* (dyspnoea/asthma), *Hikka* (hiccups), *Pinasa* (rhinitis) and various gastro-intestinal ailments like *Vibandha* (constipation), *Ajirna* (indigestion), *Mandagni* (low appetite), *Sula* (pain in abdomen), *Hrillasa* (nausea), *Anaha* (abdominal distension/ bloating), etc[54]. *In silico* experiments with the phytochemicals of *Shunthi* (*Zingiber officinale* Rosc.) displayed effective binding energies towards angiotensin converting enzyme (ACE2) cellular receptor and the spike protein, Mpro of SARS-CoV-2 whose interactions are responsible to the entry of virus into the host. This shows the preliminary antiviral property of the API's (Active Pharmaceutical Ingredient) of *Shunthi* (*Zingiber officinale* Rosc.).

Devadaru (Cedrus deodara (Roxb.) G. Don) is a *Sopha hara* (anti-inflammatory), *Jwaraghna* (antipyretic), blood purifying and *Kapha-Vata* alleviating herb indicated in *Kasa* (cough), *Shwasa* (dyspnoea/asthma), *Hikka* (hiccups), *Pinasa* (rhinitis) and various gastro-intestinal ailments like *Vibandha* (constipation), *Ajirna* (indigestion), *Adhmana* (abdominal distension/ bloating), etc[55]. *In silico* studies on the flavonoid taxifolin of *Devadaru* (*Cedrus deodara* (Roxb.) G. Don) inhibited the Mpro of SARS-CoV-2 significatly[34]. Also; Monoterpenoids of *Cedrus deodara* Viz. Alpha-terpineol, Linalool and D-limonene displayed strong inhibitory effect against main protease of the SARS-CoV-2. While Alpha-terpineol, Linalool also inhibited angiotensin converting enzyme (ACE2) cellular receptor[36-39]. Anethole, a polyphenol displayed good inhibition of RBD region of SARS-CoV-2 spike protein[40]. This signifies the preliminary antiviral property of certain phytochemicals of *Devadaru* (*Cedrus deodara* (Roxb.) G. Don).

Ghee is promoter of *Ojas* (immune booster) conductive to *Rasa dhatu* (blood plasma) and *Sukra dhatu*[56] (tissues of reproductive system) commonly consumed for its *Bala* (strength), *Swarya* (Voice promoting), *Medhya* (intellect), *Pushti* (nourishment), *Ayushya* (longevity) and *Vayahsthapana* (anti-ageing) properties[57]. Ghee improves digestive power, acts as *Jwaraghna* (antipyretic), *Visha hara* (removes toxins from body) and *Rakshoghna* (ward off various infectious micro-organisms)[58]. Due to its unique quality *Samskarasya anuvartanat*[59] (assimilate the properties of other herbs infused in it), makes Ghee a good base material for powerful medications to fight against such viruses. Moreover; medicated Ghee (*Sneha kalpana*) has a unique methodology of preparation to incorporate both non-polar (fat soluble) and polar (water soluble) compounds of the respective herbs used for infusion which can be compared to liposomal drug delivery having quick absorption and greater bioavailability[60]. Also; the phytochemicals in infused Ghee preparations (*Sneha kalpana*) move across the BBB (blood brain barrier) easily by simple diffusion[61].

Excess mucus/phlegm secretions in throat, nostrils, sinus cavities, trachea, etc, may increase the severity of bacterial, viral or fungal infections developing in the body especially in the lungs. All the five herbs of *Punarnavadya Ghrita* have *Kapha Dosha* alleviating property and are *Shotha hara* (anti-inflammatory) in common which can decrease the excess mucus and helps to recover from respiratory ailments like *Shwasa* (breathing difficulties), *Kasa* (cough). The formulation is placed in *Shotha roga chikitsa Prakarana* (chapter related to the treatment of inflammations) which conveys its potent anti-inflammatory potential to control the cytokine storm.

Evidence based research is the prerequisite for establishing the efficacy of any drug which also applies to age old time tested Ayurvedic medicines and are being revalidated accordingly. As per the available contemporary research placed above, the five herbal ingredients showed favourable preliminarily results towards symptoms of COVID-19. More intense research is needed to establish these herbs as an alternate remedy for symptomatic treatment of COVID-19. In Ayurveda polyherbal combinations are much more effective than single herbs. Also; whole herb (full spectrum) if used as medicines will have an entourage effect with negligible side effects when compared to extracts and isolated phytochemicals. So, we postulate the combination of these herbs in the form of *Punarnavadya Ghrita* may act in synergy to amplify the benefits which needs to be further scientifically evaluated with proper clinical trials.

CONCLUSION

Pre-clinical studies like *in silico, in vitro* and *in vivo* studies on phytochemicals of the herbs Viz. *Vijaya* (*Cannabis sativa* Linn.)*, Punarnava* (*Boerhavia diffusa* Linn.), *Bhunimba* (*Andrographis paniculata* (Burm. f.) Nees.)*, Shunthi* (*Zingiber officinale* Rosc.) and *Devadaru* (*Cedrus deodara* (Roxb.) G. Don.) showed encouraging results in tackling symptoms of COVID-19 disease and to an extent may stop the replication of SARS-CoV-2. *Punarnavadya Ghrita* is a combination of these researched herbs, a classical Ayurvedic formulation available in market having anti-inflammatory properties which as an alternative remedy can be useful for symptomatic treatment of indicated diseases Viz. fever, cough, breathing difficulties and severe inflammation which needs further scientific evaluation.

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