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REVIEW ARTICLE

Effect of Phyto Constitutes of *Ayurveda* and *Siddha* Herbs on SARS-CoV-2/CoVID-19 Management by Modulating the Human Gut Microbiome

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Abstract

The therapeutic plants used in *Ayurveda* and *Siddha* medicine primarily function as immunomodulators to combat viral infection. The majority of the Indian states adopted an integrative approach to the treatment strategy for COVID-19 infection during the COVID-19 outbreak. A large percentage of Indians consume *Ayurvedic* and *Siddha* herbs as preventative medication or immune boosters during the COVID outbreak. ACE-2 receptor, Mpro, Nsp15, endoribonuclease, ACE-2-RBD interface, RBD complex, helicase inhibitors, and ACE-2-RBD interface are the main targets of the phytochemicals of medicinal plants, which also have the potential to limit their action and lower infection rates. The phytonutrients also preserve the permeability of the gut epithelial membrane and improve gut barrier proteins including occludin, Zo-1, and claudin. The phytonutrients also help probiotic bacteria flourish, such as *Faecalibacterium*, *Rikenellaceae, Lactobacillus* and *Lachnospiraceae*, which may lower proinflammatory cytokines and improve immunological function. A small number of opportunistic bacteria, such as *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, co-infect with the SARS-CoV-2 virus and increase the frequency of hospital stays and severity of the illness. The co-infections or secondary infections may be reduced by the antibacterial and anti-inflammatory activities of phytochemicals.

Keywords: *Ayurveda*, Co-infections, COVID-19, Human Gut Microbiota, *Siddha*

1. Introduction

A pandemic that started in late December 2019 was brought on by the SARS-CoV-2 viruses[1]. Due to the severe negative impacts on public health, the World Health Organization (WHO) identified the resulting illness as Coronavirus disease in 2019 and proclaimed it a worldwide emergency[2]. The angiotensin-converting enzyme[2] ACE-2 receptor is a known SARS-CoV-2 receptor for the entrance of the virus into host cells[3,4]. This receptor is found in several bodily cells, including the respiratory, digestive, renal, and cutaneous epithelium, suggesting that each of these organs may be a possible target for the virus[2]. The human gastrointestinal tract (GI tract) is the body's largest immunological organ and is crucial in preventing pathogen infection[5]. As documented the gut microbiota has a great impact on immune responses[6]. The SARs-CoV-2 infection causes short- and long-term changes in the ecology and dynamics of the human gut microbiome, which in turn affect the health of the human host. For the severity of the disease, microbial change promotes the growth of opportunistic pathogenic microorganisms.

The 10,000-year-old medical systems of *Ayurveda* and *Siddha* medicine both attempt to alleviate ailments by enhancing the immune system. According to Balasubramani *et al*., there are several *Ayurvedic* treatments available for increasing immunity against respiratory infections, including specific immunomodulators (known as *Rasayan*)[7]. South

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India is where the *Siddha* system of medicine is most prevalently practiced among the people also consists of several medicinal herbs that have a great impact on the immune system. In this review article, we are trying to analyze how the phytochemicals of Medicinal plants used in the *Ayurveda* and *Siddha* systems of medicine will inhibit SARS-CoV-2 viruses' infections or may reduce the severity of infection by modulating intestinal microbial populations[8].

2. Materials and Methods

The literature was looked up in three main areas. *Ayurveda*, *Siddha* medicine, and SARS-CoV-2 virus were used as search terms in the first section's literature search in PubMed, Google Scholar, and the Web of Sciences. We looked through numerous studies from the past 20 years, and those that were worthwhile we have included. Additionally, since the immune system plays a significant part in SARS-CoV-2 virus infections, we have included specific characteristics like the impact of *Ayurvedic*/*Siddha* herbs on immunity.

The effects of *Ayurvedic* and *Siddha* herbs on the human gut flora in COVID-19 patients are the subject of our narrative review. Although there are no direct indications, herbs have significant antiviral and immunomodulatory impacts on human health. Concerning the gut microbiota, we used the plant's botanical name as a keyword. We have included around 20 medicinal herbs commonly used in the prevention and treatment of COVID-19 infection. We looked through many web databases. We tried to apply insightful studies to COVID-19 patients.

3. Alteration of Gut Microbiota Diversity during the Time of SARS-CoV-2/CoVID-19 Infection

A pilot investigation that involved sequencing fecal samples from 15 patients revealed that COVID-19 infections considerably changed the fecal microbiomes, with a decrease in helpful commensals and an enrichment of opportunistic pathogens[9]. According to one study, people with SARS-CoV-2 infection experienced significant changes in the diversity of their fecal microbiome, which were characterized by an enrichment of opportunistic pathogens (*Clostridium hathewayi, Actinomyces viscous*, and *Bacteroides nordii*) and a depletion of beneficial commensals (*Faecalibacterium prausnizii,* Lachnospiraceae) bacterium[10]. SARS-CoV-2 was eliminated from respiratory samples, but gut dysbiosis and reduced symbionts persisted. By hindering host entry through ACE-2, *Bacteroidetes* species, for instance, may provide a protective role in avoiding SARS-COV-2 infection[9]. Gut bacteria protect against SARS-CoV-2 infection. The phylum *Firmicutes*, which includes *Coprobacillus, Clostridium ramosus*, and *Clostridium hathewayi*, is linked to the severity of SARS-CoV-2 infections. *Faecalibacterium prausnitzi*, which shows anti-inflammatory activity, the intake of probiotic bacteria may reduce the severity of COVID-19 infection[11].

SARs-Cov-2 severity and rate of infections depends on some specific bacteria like *Bacteroides* species (*Bacteroides dorei, Bacteroides thetota, Bacteroides massiliensis*, and *Bacteroides ovatus*). These species may restrict the capacity of SARS-CoV-2 to get into enterocytes because they were linked to a decrease in ACE2 expression in the mouse gut. These results supported those of a different study that found that patients with SARS-CoV-2 infection had less diverse gut microbiotas, greater numbers of opportunistic bacterium pathogens, and fewer butyrate-producing bacteria than H1N1 patients and healthy controls[12]. Additionally, seven bacterial strains (*Streptococcus, Fusicatenibacter, Collinsella, Dorea, Agathobacter, and Eubacterium Rumninococcus*) could be used as COVID-19 diagnostic biomarkers[12]. GI symptoms such as diarrhea, nausea, and vomiting are reported by more than 60% of patients in an article from China, which suggests that patients have microbial dysbiosis due to reduced *Lactobacillus* and *Bifidobacterium*[13].

4. Role of Probiotics in the Prevention of SARS-CoV-2/CoVID-19 Infection

There has been a lot of research on the biological impact of the gut microbiota on lung diseases like pneumonia, pleural effusion, emphysema, chronic bronchitis, and chronic obstructive pulmonary disease[14]. A Disruption in the gut microbiota is known to occur as a result of viral infections of the respiratory tract[8]. Probiotics were the most important for reducing the consequences of the COVID-19 outbreak. These were

L. casei, L. gasseri, B. longum, B. bifidum, L. rhamnosus, L. plantarum, and *B. breve*[15]. The equilibrium of the normal microbiota in the human intestine is disrupted by COVID-19 infection, according to a recent study from China, which was based on the detection of lower numbers of *Bifidobacterium* spp. and *Lactobacillus* species in patients with the illness[16]. The genus's probiotics concerning gastrointestinal dysbiosis brought on by severe acute respiratory syndrome corona virus-2, *Lactobacillus*, and *Bifidobacterium* have the biological capacity to combat it[17]. Li *et al.*, reported that giving patients a probiotic containing *Bifidobacterium longum, B. infantis, Lactobacillus acidophilus, Lactobacillus delbrueckii, Bacillus cerus, Streptococcus thermophiles*, and *Enterococcus faecium* shortened their stay in the hospital and accelerated their recovery from severe acute respiratory syndrome corona virus-2[18]. It was demonstrated by Carelli *et al.*, that the usage of a probiotic including *S. therophilus, Bifidobacterium lactis, L. acidophilus, L. helveticus, Lactobacillus paracasei, L. plantarum*, and *L. brevis* decreased the motility in COVID-19 patients[19]. According to one study, low bacterial diversity and the loss of *Bifidobacterium* genera either before or after the infection resulted in reduced pro-immunological function, which allowed SARS-Cov-2 infection to manifest symptoms[20]. Probiotics like *Lactobacillus* and *Bifidobacterium,* according to a meta-analysis, provide a slight decrease in common cold symptoms and SARS-CoV-2 infection symptoms[21].

5. Opportunistic Pathogenic Bacteria, which Enhances the secondary SARS-CoV-2/CoVID-19 Infection

In COVID-19 patients, secondary bacterial infections commonly arise and may be linked to worse outcomes. Secondary bacterial infections were substantially correlated with disease severity in a multicenter study involving 476 COVID-19 patients[22]. According to a meta-analysis of research published in 2020, 14% of SARS-Cov-2 hospitalized patients had a bacterial co-infection, and this number is close to 7% in studies that only included ICU patients[23].

In contrast, *Pseudomonas aeruginosa,* human adenovirus, human rhinovirus, and herpes simplex virus were only discovered in symptomatic patients. *Streptococcus pneumoniae, Klebsiella pneumoniae, Hemophilus influenza, Escherichia coli, Staphylococcus aureus, Aspergillus*, and Epstein Barr Virus (EBV), for example, were found in both symptomatic and asymptomatic patients[16]. Hospital-Acquired Pneumonia (HAP) was discovered in approximately 11.5% of COVID-19 patients, according to Yang and colleagues[24]. Sepsis, bacterial meningitis, and severe bacterial pneumonia are just a few organ and system failures that have been associated with bacterial co-infection. *K. pneumoniae* was discovered in COVID-19 patients in 34% of cases. The most prevalent bacterial species among the 108 COVID-19 patients in Saudi Arabia were K. pneumoniae and *A. baumannii,* both of which were resistant to every antibiotic tested[25]. One of the most common gram-negative bacterial species associated with significant hospital-acquired illnesses in various hospitals is *Pseudomonas aeruginosa*. It is additionally referred to as a typical respiratory opportunistic pathogen. According to one study, *P. aeruginosa* was the most prevalent co-infecting pathogen and could boost quorum sensing for prolonged colonization and bacterial co-infection during the crucial COVID-19 Pneumonia period[26].

6. Role of *Ayurveda* and *Siddha* in the Management of COVID-19

In its COVID-19 strategic preparedness and response plan, the World Health Organization has also advised including traditional medicine. The goal should not be to just deploy this workforce as a backup plan, but rather to use its therapeutic management ability to enhance the care provided by modern medicine. As outlined in the National Health Policy, which advocates for integrative health practices to meet national goals and objectives, plurality is one of the guiding principles of the Indian health system.

Panchakarma (five operations of purification), *Rasayana chikitsa* (immune-modulator therapy), and *Sadvritta* (good conductor) are the three main *Ayurvedic* treatments for epidemic conditions[27]. The *Rasayana chikitsa* is the most popular treatment among these. Several substances and herbs have *Rasayana*-like properties. In healthy people, *Rasayana* may be taken either as a prophylactic medication or as a preventative strategy[28]. *Rasayana dravyas* like *Withania somnifera* (L.), *Tinospora cordifolia*, *Phyllanthus emblica*, *Andrographis paniculate*, *Ocimun sanctum*, *Boerhavia diffusa*, and *Piper longum* L are examples.

The *Siddha* system of medicine is largely practised in Tamil-speaking countries and southern India. The Ministry of AYUSH of the Indian government released therapeutic guidelines for AYUSH practitioners to prevent and manage the COVID-19 pandemic, including the use of *Kabasura kudineer*, a polyherbal *Siddha* formulation that has typically been prescribed and supplied to treat *lyasuram*, which is characterized by fever and flu-like symptoms[29]. The combination of *Zingiber officinale, Phyllostachys longa, Syzygium aromaticum, Pyrethrum anacyclus, A. Solanum perianth, Coleus amboinicus, Justica adhatoda, Ferminalia chebulaassurance alappa, Cyperus rotundus, Andrographis pariculata, Cissrpelos pareina, Tinospora coridifolia,* and *Clerodendrum serratum* usually suggested for prevention and treatment of COVID-19.

Table 1. Effects of *Ayurvedic* and *Siddha* herbs on covid 19 and gut microbial alteration

Sl. No.	Name of the plant	Phytochemicals	Effects on Covid 19 patients	Impact on human gut microbiota and pathogenic opportunistic bacteria	References
1	*Withania somnifera* (L.) (*Ashwagandha*)	Withanolide I, Withanolide-G, Withanolide-M, Withaferin, Withanone	According to one duckling study, withanolides showed a binding affinity for PLpro and Spike proteins. Withaferin may bind to spike proteins, interfering with the viral S-protein's ability to attach to host receptors and inhibiting the release of ACE-2 into the lungs. Another substance in the *W. somnifera*, withanone, docked exceptionally effectively in the AEC-2 complex's binding interface.	Ashwagandha root powder may work by increasing *Lactobacilli* and decreasing *E. coli.*	40-44
2	*Tinospora cordifolia* (*Guduchi*)	Berberine, Cordioside	Secondary metabolites of *T. cordifolia* exhibit a high affinity for blocking the primary protease of the SARS-COV-2 virus. According to a different study, six components of *T. cordifolia* may be able to prevent the SARs CoV-2 protein from interacting with the human receptor ACE-2 protein.	Berberine alters the population of intestinal bacteria by reducing *Clostridium* cluster XIva and Iv	45-47
3	*Phyllanthus emblica* L (*Amalaki*)	PhyllaemblicineG7, Piceatannol	The phytochemicals of *P. emblica* (Piceatannol and Phyllaemblicine G7) both show a high affinity for the spike protein.	It shows antimicrobial activity against *S. aureus*	48,49

Table 1. Continued...

			In addition to possessing a strong affinity for the ACE2 protein, they also inhibit the enzyme activity of TMPRSS2, which cuts the spike protein and contributes to the development of SARS-CoV-2 and MERS COV.		
4	*Glycyrrhiza glabra* L (*Mulethi*)	Glycyrrhizin, tannins, coumarins, estrogens, phytosterols, glycosides, glycyrrhizic acid	*G. glabra* L. has demonstrated good results in preventing SARS-CoV-2 viral replication.	Glycyrrhizic acid promotes the population of *Desulfovibrio vulgaris* and *Clostridium sordelli*	50,51
5	*Asparagus racemosus* (*Shatavari*)	Asparoside-D, Racemoside A, Racemoside C, Asparoside C, Asparoside F, Kaempferol	The phytoconstituents (Asparoside-C, Asparoside-3, and Asparoside F) of *Asparagus racemosus* were investigated for their ability to inhibit SRBD and IN SP15 endoribonuclease. According to the study, asparasides C, D, and F may have some influence on both proteins and may also have some effect on SARS-COV-2. According to a different study, the saponins Racemoside A and Racemoside C interact with the S-protein's RBD and prevent it from interacting with ACE2. By interacting with the s-protein, it stops that protein from interacting with other structural proteins.	Kaempferol increases the beneficial bacteria such as Prevotellaceae and Rumninococaceae and reduces the richness of Proteobacteria	52-54
6	*Andrographis paniculate* (*Bhuineem*)	Alkaloids, saponins, flavonoids, and steroids andrographolide	*A. paniculate* was more likely to affect a target protein specific to a virus. Specifically, 3CL pro was examined *in silico*, and the findings were supported by *in vitro* research. However, the results demonstrated that andrographolide's IC_{50} when inhibiting 3CL pro was higher than its IC_{50} when inhibiting the formation of infectious virions.	Andrographolide administration significantly increases the abundance of beneficial intestinal bacteria including *Lachospiraceae, Rumnococcaceae*	5,55,56

Table 1. Continued...

7	*Ocimun sanctum* L (*Tulsi*)	Flavonoids, polyphenol	The findings indicated that Tulsi's flavonoids and polyphenolic chemicals may be able to covalently attach to the primary protease's catalytic residue, cys145, and so permanently inhibit the viral enzyme.	1% of clove powder and 3% Tulsi extract causes the growth of *Lactobacillus* bacteria	57,58
8	*Boerhaavia diffussa* L (*Punarnava*)	Boeravisterol, Boeravinone J, boerhavi sterol, kaempferol, quercetin, trans-caftaric acid	Boeravisterol was chosen as a remedy because the major proteases of SARS and MERS share structural similarities. Comparative docking of these ligands was also performed on the MERS and Mpro, but it was shown that the binding energies for these targets were not conducive to spontaneous binding.	*Boerhaavia diffussa* L. shows antimicrobial effects against *S. aureus, B. subtilis, S. faecalis, M. lutcus, K. pneumoniae, P. vulgaris, Marcescens,* and *S. flexneri*	59,60
9	*Piper longum* L (*Pippali*)	Piperolactam A, piperlongmine, piperine, piperolactam	A phytoconstituent of *P. longum* called piperolactam A is a powerful inhibitor of s-protein. This inhibitor prevents the s-protein from adhering to the cell surface receptor, which prevents viruses from attaching to the host.	It shows antimicrobial activity against *Mycobacterium* Piperlongamine shows antibiotic properties against gram-negative bacteria like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*	61-63
10	*Terminalia chebula* (*Haritaki*)	Pyrogallol, tannins, anthraquinone, ethaedioic acid, glucopyranose, terpinenols	The aqueous extract of *T. chebula* may have inhibitory effects on the SARS-CoV-2's 3CLpro protease activity, according to an in-silico study. Because the inhibitor of this enzyme activity has the potential to prevent viral replication within cells, it may protect against the COVID-19 virus.	The fruit extracts show inhibitory activity against *C. perfringens* and *E. coli*	64-66
11	*Curcuma longa* L (*Haldi*)	Curcumin	Curcumin can stop SARS-COV-2 from entering lung cells by interfering with the way S-protein interacts with ACF-2. This shows that curcumin can prevent SARs-CoV-2 viral entry and reproduction, which is also connected to the activation of NRF-2 pathways (nuclear factor erythroid-related factor 2).	Curcumin increases the abundance of Prevotellaceae, Bacteroidaceae, and Ricknellaceae	67-69

Table 1. Continued...

12	*Embelia ribes* Burm (*Vidang*)	Embelin, Quercetin	Embelin, a significant phytoconstituent of *E. ribes,* was investigated in the creation of a plant-based influenza agent due to the presence of its binding site in the viral haemagglutinin RBD. Quercetin is a crucial polyphenol. Quercetin exhibits a variety of antiviral effects against HCV and H1N1 influenza viruses.	Embelin shows significant antibacterial activity against *S. aureus, S. pyrogenes, Shigella flexneri, Shigella sonnei* and *P. aeruginosa*	70,71
13	*Adatoda vasica* Nees	Vascicine, anisotine	Increased negative binding affinities for C and O -glycosides were found for HLF-1alpha, IL-6, Janus kinase 1/3, TNF-alpha, and TGF-beta in A. vasica's phytoconstituents, which are crucial mediators of hypoxic inflammation and several respiratory diseases. Additionally, it was found that vasicine inhibits the 3 CL protease.	*Adatoda vasica* has an inhibitory effect against *Klebsiella pneumoniae*	72,73
14	*Phyllanthus amarus* Schum (*Bhumi Amalaki*)	Lignans, Phyllanthin, Hypophyllanthin, Ninphyllin, Flavanone, glycoside	When *P. amarus* root extracts were tested in vitro for their capability to inhibit the HCV-NS3 protease enzyme, *P. amarus* leaf extract showed this ability to inhibit NS5B. The structures of SARS-CoV-2 and NS3 protease are similar.	Phyllanthin along with Norfloxacin as well as Ethidium bromide shows antimicrobial activity against *S. aureus*	74-76
15	*Zingiber officinale* (*Chukku*)	Zingiberene, zingerone, gingerenone, gingerol	In this computer simulation study, the main phytochemical in ginger interacts with the human ACE-2 protein and the RBD of the COVID-19 spike protein at their active locations to provide antiviral properties and prevent the propagation of COVID-19 sickness.	The ginger juice enhances the growth of *Firmicutes* to *Bacteroidetes* ratio, *Proteobacteria,* and *Faecalibacterium*. Decrease of *Prevotella* to *Bacteroidetes* ratio, *Rumnicoccus* bacteria	77,78

Table 1. Continued...

16	*Syzygium aramaticum* (*Lavangam*)(Clove)	Eugenol	Along with *Eucalyptus globulus*, *Cymbopogon citratus*, and *Zingiber officinale*, clove is presently used as a medicinal plant to prevent and treat the SARs-CoV-2 linked sickness.	Eugenol along with other Phyto constitute a lower *Escherichia-Shigella* ratio and *Campylobacter* population	28,79
17	*Tragia involucrate* (*Sirukaanjuriven*)	Costunolide, iridin, quercetin, orientin	This is because plant extract is a component of *Siddha* medication. When tested against the viral spike glycoprotein, the *Siddha* medication formulation displayed encouraging results.	Quercetin enhances the population of gut microbiota like *Porphyromonadaceae, Oxalobacteraceae* and reduces the populations of *Actinobacteria*	80,81
18	*Anacyclus pyrethrum* (*Agragaram*)	Alkaloids, tannins, flavonoids, coumarins	Anti-inflammatory and antioxidant activities can be seen in water-soluble polysaccharides extracted from *Anacyclus pyrethrum* root extract.	Methanol extract of A pyrethrum shows antimicrobial activity against *S. sanguis, S. aureus* and *P. aeruginosa*	82,83
19	*Solanum erianthum* (*Karimulli*)	Astorvosides, neosolaspigenin-6-0 aminopyrans	Infections with the human herpes virus type 1, influenza viruses A and B, viral hepatitis, and HIV have all been successfully treated using *Solanum erianthum.*	The water acetone and water-ethanol extracts of *S. torvum* show the highest antimicrobial activity against *B. cereus*, LMG	84,85

7. Result

7.1 Effects of *Ayurveda* and *Siddha* Medicinal Plant Extracts on the Diversity of Gut Microbiota and Antimicrobial Effects

Ayurveda and *Siddha* medicine is taken in the form of formulation (mixture of various plant extracts) and basically, it is used for the prevention of COVID-19 infection during the time of lockdown in India. The Department of AYUSH clearly instructed that people should consume *Kadha*, a mixture of *Ayurvedic*/*Siddha* formulations, during the first COVID wave in India. Immunity plays a great role in the severity of COVID-19, the main aim of taking the *Ayurvedic*/*Siddha* formulation is to boost our immunity. Many states like Kerela used *Ayurveda* and conventional medicine, to reduce the severity of COVID-19 infections. As described previously almost all the medicinal herbs used in *Ayurveda* and *Siddha* medicine are effective against COVID-19 viruses. The plant extracts also enhance the growth of beneficial gut microbiota and inhibit the growth of pathogenic, opportunistic bacteria. Probiotic bacteria like Lactobacillaceae, Desulfovibrionace, Lachnospiraceae, Ruminococcaceae, Prevotellaceae, Bacteroidaceae, Rikenellaceae, Porphyromonadaceae and Oxalobacteraceae (Table 1).

Ayurveda and *Siddha* medicinal herbs show antimicrobial activity against *Clostridium perfringen, S. aureus, S. faecalis, M. lutcus, K. pneumoniae, Shigella flexneri, Pseudomonas aeruginosa, Prevotella to Bacteroidetes, Rumnicoccus, Actinobacteria, S. sanguis, S. aureus* and *P. aeruginosa* (Table 1).

7.2 The Phyto Constitute of *Ayurveda* and *Siddha* Medicine Altered the Gut Barrier Functions

The intestine is the inhabitants of the human gut microbiome and the diversity and the population of gut microbiome depend on the intestinal mucosal barriers.

The composition and activities of the tight junction proteins (Occludin, Zo-1, and Claudin) are crucial for intestinal barrier function. Intestinal permeability and the microbial composition of the gut are mostly maintained by tight junctions[30]. Under pathological conditions, the structure and the function of the tight junction will be altered. This will cause the loss of homeostasis of the species. The phytochemicals found in *Ayurvedic* and *Siddha* remedies primarily enhance tight junction protein concentration, epithelial cell structure, colonic epithelial barrier repair, and gut microbial diversity (Table 2).

7.3 Mechanisms of Action

7.3.1 Modulation of ACE-2 Receptors

The extracts potentially interfere with the ACE-2 receptors, which are the entry points for the SARS-CoV-2 virus into host cells. This modulation can reduce the virus's ability to infect the host.

7.3.2 Reduction of Pro-inflammatory Cytokines

Consumption of these medicinal plant extracts has been associated with reduced levels of pro-inflammatory cytokines (e.g. IL-6, TNF-alpha, IL-1beta), which are typically elevated in severe COVID-19 cases. This anti-inflammatory effect is crucial in managing the severe inflammatory response seen in COVID-19 patients.

7.3.3 Direct Interaction with Viral Components

Some phytochemicals exhibit a high binding affinity for viral proteins, inhibiting the virus's ability to attach and enter host cells. For example, Withanolides from Ashwagandha bind to spike proteins and ACE-2

Table 2. The effects of Phyto constitute of *Ayurvedic* and *Siddha* herbs on the gut barrier functions

Sl. No.	Name of the medicinal plants	The name of the Phyto constitutes	Effects on gut barriers functions	References
1	*Withania somnifera*	Ashwandhanoilide	Modulates intestinal gut permeability and intestinal absorption.	86
2	*Tinospora cordifolia*	Berberine	Increases the ZO-1 and occuludin.	87
3	*Glycyrrhiza glabra* L	Glycyrrhic acid	Increases the ZO-1 and occuludin.	87
		Diammonium glycyrrhizinate	Encourages the expression of the proteins that make up tight junctions (Claudin, Occludin, and Zo-1).	88
4	*Asparagus racemosus, Syzygium aramaticum*	Kaempferol	Assembles tight junction proteins (Zo-1, Zo-2, Occludin, Claudin-1, Claudin-3, and Claudin-4) to improve intestinal barrier function.	89
5	*Embelia ribes Burm, Asparagus racemosus, Syzygium aramaticum Tragia involucrate*	Quercetin	Enhancing the production of the Zo-2 occludin and claudin-1 protein.	90
6	*Ocimun sanctum* L.	Thymol	Increase the expression of critical tight junction proteins to preserve barrier function.	91
7	*Terminalia chebula*	Ellagic acid	Regulates mucin secretion and maintains the tight junction function integrity.	92
8	*Curcuma longa* L.	Curcumin	Increases ZO-1, Occludin, and Claudin-5 protein expression.	93
9	*Curcuma longa* L.	Eucalyptol	Occludin-1 and Zo-1, two tight junction-associated proteins, had their induction reversed.	94
10	*Zingiber officinale*	Ginsenoside	Ensuring that the TJ multiprotein complex remains properly assemble.	95
11	*Syzygium aramaticum*	Eugenol	Improves the barrier function.	96

receptors, potentially blocking the virus's entry into cells.

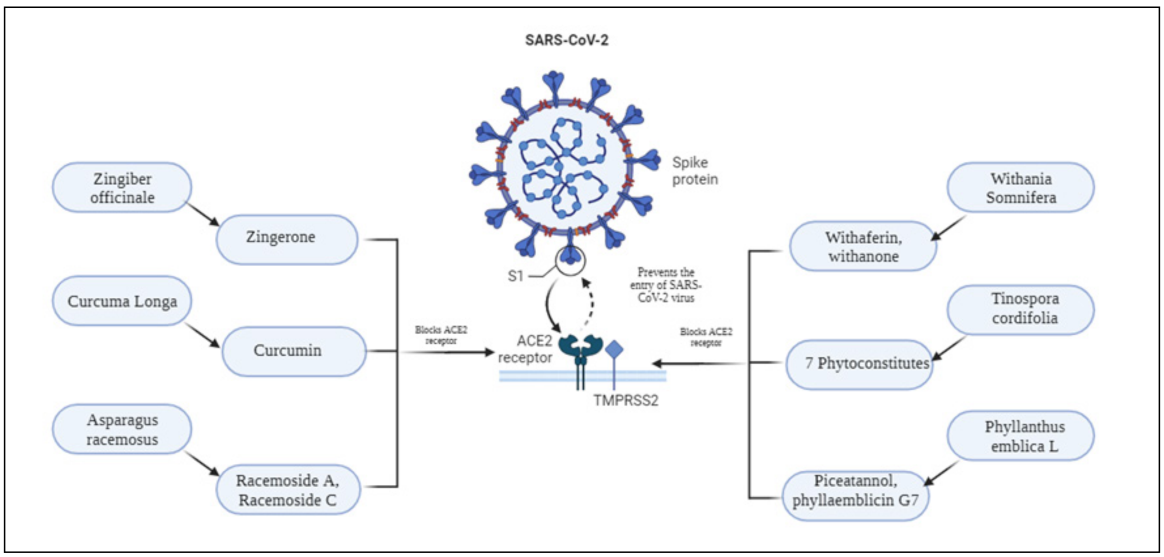
Andrographolide from *Andrographis paniculata* shows inhibition of the main protease (3CLpro) of SARS-CoV-2, which is crucial for viral replication.

7.3.4 Anti-inflammatory Effects

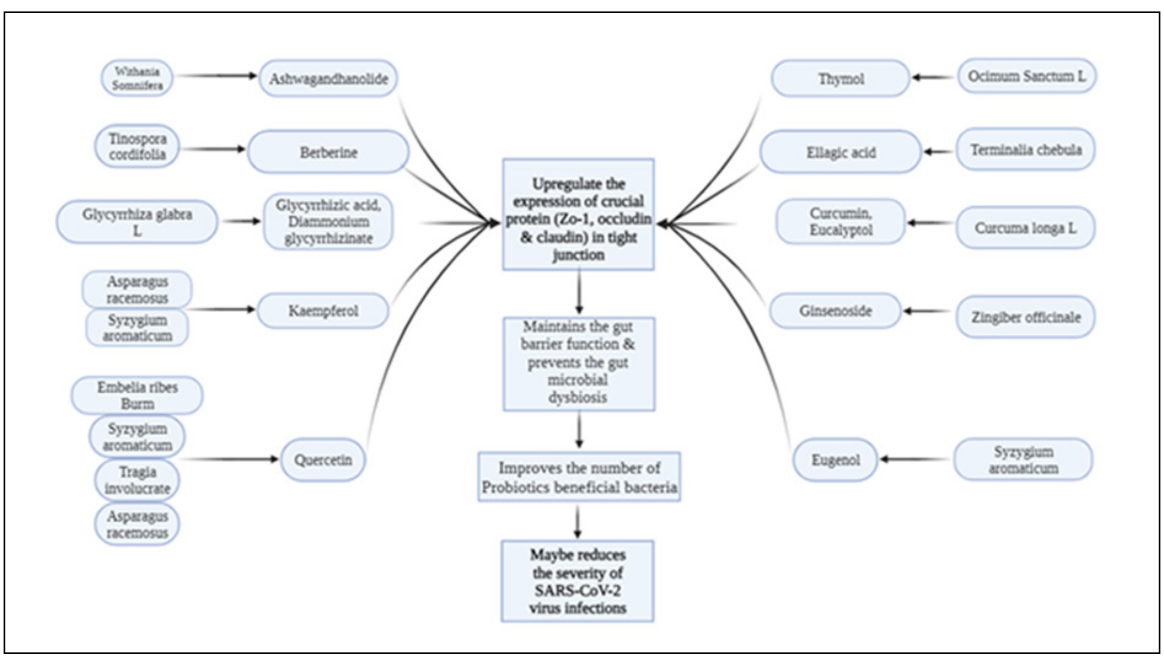
Consumption of these medicinal plants also reduces the expression of pro-inflammatory cytokines such as TNF-alpha, IL-6, and IL-1beta, which are elevated in COVID-19 patients. For instance, *Lactobacillus mucosae* and *Lactobacillus rhamnosus* decrease the expression of these cytokines, thereby mitigating inflammation.

7.3.5 Immune Modulation

The extracts promote the production of regulatory T cells (Tregs), which play a critical role in controlling the immune response and preventing the progression of COVID-19 from mild to severe stages. For example, *F. prausnitzii* and *Bifidobacterium longum* enhance



(a)



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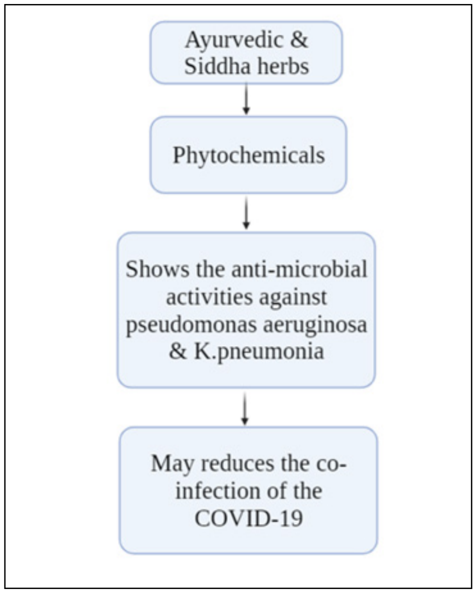

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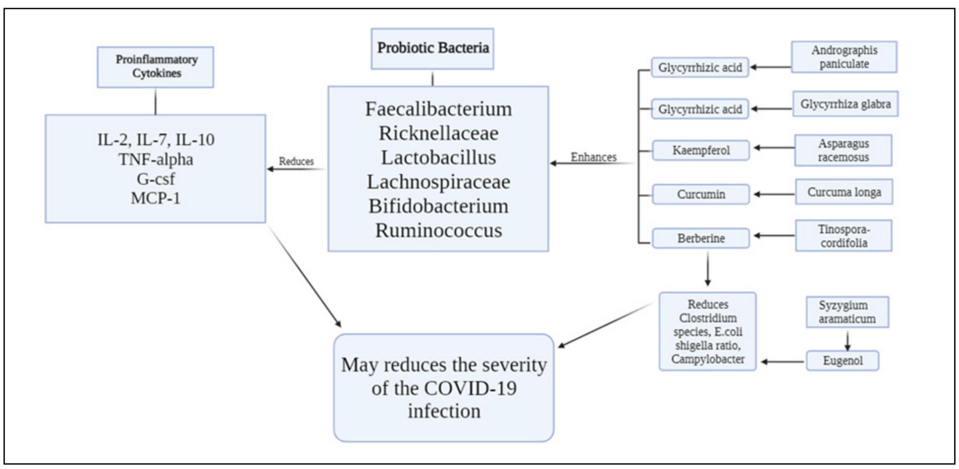

(d)

Figure 1. The mechanism through which Phyto consists of *Ayurvedic* and *Siddha* medicinal plants regulates SARS-COV-2 infections by modulating human gut microbiota. **(a).** Effects of Phyto constitutes of *Ayurvedic* and *Siddha* herbs on ACE-2 receptors. **(b).** Effects of Phyto constitutes of *Ayurvedic* and *Siddha* herbs on gut barrier functions. **(c).** Effects of Phyto constitute on pathogenic micro-organisms. **(d).** Effects of Phyto constitutes of *Ayurvedic* and *Siddha* herbs on probiotic bacteria.

the production of Tregs, contributing to a balanced immune response (Figure 1a,1b, 1c and 1d).

8. Discussion

About one out of every three SARS-COV-2 patients who are in critical or severe circumstances will develop a severe, life-threatening case of ARDS[31]. It is proven that bacterial dysbiosis is found after COVID-19 infection along with loss of intestinal barrier function[20]. The bacteria enter the bloodstream, travel through the circulation to different host tissues or organs, and ultimately set off a chain reaction of inflammatory factors that develop into severe sepsis and result in ARDS[89]. The first organ to suffer damage following bacterial translocation is the lung, demonstrating that intestine infection is what causes acute lung injury. Acute Respiratory Distress Syndrome

(ARD) patients in clinical trials have greater intestine bacterial levels in bronchoalveolar lavage fluid, which is proportional to the level of systemic inflammation[32]. As mentioned in Table 2 the phytoconstituent of *Ayurveda* and *Siddha* herbs maintain the tight junction-associated protein and decrease the gut wall permeability enhancing the probiotic population. The probiotic bacteria populations like *Faecalibacterium, Ricknellaceae, Lactobacillus* and *Lachnospiraceae*, may be enhanced after the consumption of *Ayurveda* and *Siddha* medicinal plant extract consumption (Table-1). The COVID-19 infection is marked by systemic inflammation and multiple organ failure. The level of interleukins (IL-2, IL-7, IL-10), G-CSF, MCP-1, and TNF-alpha among other inflammatory mediators was observed to be higher in critically ill individuals[33]. Intake of both *Lactobacillus mucosae* and *Lactobacillus rhamnosus* also reduced the expression of tumor necrosis factors alpha, IL-beta, MCP-1, and IL-8[34]. Consumptions of *F. prausnitzii and B. longum* induce the Foxp3 and T reg cell production[35]. According to one study, the introduction of T-reg cells may help to prevent COVID-19 disease from progressing from mild to severe and even treat severe patients. Regs can inhibit a variety of immune cells, including $CD8^+$, $CD4^+$, T cells, monocytes, and B cells, controlling undesirable immune responses at various stages of transplant, allergy, and autoimmune rejection[36]. COVID-19 infections are associated with increases in proinflammatory cytokines like IL-6, TNF-alpha, IL-1beta, and IL-17[94] of *Ruminococcus* species that inhibit the secretions of TNF-alpha[38]. *Lachnospiraceae* reduces the secretion of proinflammatory cytokines(96). As prescribed herbal supplementation is given as a preventive measure or along with conventional therapy. Previously we have discussed *P. aeruginosa* and *K. pneumoniae* infections are very common during SARS-CoV-2 infections. Maybe the co-infections cause different organ failure, and multiorgan failure and increase the duration of hospital stay(25,26). *Ayurvedic* and *Siddha* medicinal plant supplementation have shown antimicrobial activity against Pseudomonas aeruginosa and *K. pneumoniae* (Table 1).

9. Conclusion

By blocking the enzyme activity of TMPRSS-2, which has a strong binding affinity to ACE2 protein and Mpro (Main proteases), ACE-RBD-interface, Nsp-15 endoribonuclease, RBD complex, and CL protease, medicinal plants used in *Ayurvedic* and *Siddha* medicine directly lower COVID infections. Additionally, the phytochemicals strengthen the gut barrier functions and proteins while repopulating the gut bacteria. The probiotic bacterial population may grow as a result of the phytoconstituents, which lowers the concentration of proinflammatory cytokines. Overall, we can say that the medicinal plant extracts used in *Ayurveda* and *Siddha* may lessen the severity of SARS-CoV-2 infections. Direct investigation may provide additional in-depth illumination in this area.

10. Need for Further Studies

While our findings suggest that *Ayurveda* and *Siddha* plant extracts benefit gut microbiota and improve gut barrier integrity, further research is essential to validate and expand upon these results. Rigorous clinical trials are necessary to confirm the efficacy and safety of these plant extracts in COVID-19 patients. Mechanistic studies should investigate the exact pathways through which these extracts modulate gut microbiota and enhance gut barrier function. Additionally, the long-term impact of these extracts on gut health and immune function, including potential side effects, needs to be examined. Comparative studies are needed to identify the most effective formulations and standardize treatment protocols. Research should also include diverse populations to understand the generalizability of the findings. Exploring the synergistic effects of these extracts when combined with conventional COVID-19 treatments can provide insights into integrated treatment approaches. Advanced gut microbiome analysis using next-generation sequencing techniques will help comprehensively characterize the changes in microbial communities. Addressing these areas through further research will build a robust evidence base to support the use of *Ayurveda* and *Siddha* plant extracts in managing COVID-19, ultimately contributing to the development of effective integrative treatment strategies.

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12. References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8). https://doi.org/10.1056/NEJMoa2001017 PMid:31978945 PMCid:PMC7092803
2. Jamshidi P, Hajikhani B, Mirsaeidi M, Vahidnezhad H, Dadashi M, Nasiri MJ. Skin manifestations in COVID-19 patients: Are they indicators for disease severity? A systematic review. Front Med. 2021; 8. https://doi.org/10.3389/fmed.2021.634208 PMid:33665200 PMCid:PMC7921489
3. Li W, Moore MJ, Vasllieva N, Sui J, Wong SK, Berne MA, *et al*. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Lette. 2003; 426:40-4. https://doi.org/10.1038/nature02145 PMid:14647384 PMCid:PMC7095016
4. Ayittey, Foster Kofi, et al. Updates on Wuhan 2019 novel coronavirus epidemic. J Med Virol. 2020; 92(4):403. https://doi.org/10.1002/jmv.25695
5. Shi TH, Huang YL, Chen CC, Pi WC, Hsu YL, Lo LC, *et al*. Andrographolide and its fluorescent derivative inhibit the main proteases of 2019-nCoV and SARS-CoV through covalent linkage. Biochem Biophys Res Commun. 2020; 533(3):467-73. https://doi.org/10.1016/j.bbrc.2020.08.086 PMid:32977949 PMCid:PMC7447262
6. Geva-Zatorsky N, Sefik E, Kua L, Pasman L, Tan TG, Ortiz-Lopez A, *et al*. Mining the human gut microbiota for immunomodulatory organisms. Cell. 2017; 168(5):928-43. https://doi.org/10.1016/j.cell.2017.01.022 PMid:28215708 PMCid:PMC7774263
7. Balasubramani SP, Venkatasubramanian P, Kukkupuni SK, Patwardhan B. Plant-based *Rasayana* drugs from *Ayurveda*. Chin J Integr Med. 2011; 17:88-94. https://doi.org/10.1007/s11655-011-0659-5 PMid:21390573
8. Dhar D, Mohanty A. Gut microbiota and COVID-19-possible link and implications. Virus Res. 2020; 285. https://doi.org/10.1016/j.virusres.2020.198018 PMid:32430279 PMCid:PMC7217790
9. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, *et al*. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterol. 2020; 159(3):944-55. https://doi.org/10.1053/j.gastro.2020.05.048 PMid:32442562 PMCid:PMC7237927
10. Zuo T, Zhan H, Zhang F, Liu Q, Tso EYK, Lui GCY, *et al*. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterol. 2020; 159(4):1302-10. https://doi.org/10.1053/j.gastro.2020.06.048 PMid:32598884 PMCid:PMC7318920
11. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, *et al*. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A. 2008; 105(43):16731-6. https://doi.org/10.1073/pnas.0804812105 PMid:18936492 PMCid:PMC2575488
12. Gu S, Chen Y, Wu Z, Chen Y, Gao H, Lv L, *et al*. Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza. Clin Infect Dis. 2020; 71(10):2669-78. https://doi.org/10.1093/cid/ciaa709 PMid:32497191 PMCid:PMC7314193
13. Xu K, Cai H, Shen Y, Ni Q, Chen Y, Hu S, *et al*. Management of corona virus disease-19 (COVID-19): The Zhejiang experience. Infect Microb Dis. 2020; 2(2):55-63.
14. Han MK, McLaughlin VV, Criner GJ, Martinez FJ. Pulmonary diseases and the heart. Circul. 2007; 116(25). https://doi.org/10.1161/CIRCULATIONAHA.106.685206 PMid:18086941
15. Baud D, Dimopoulou Agri V, Gibson GR, Reid G, Giannoni E. Using probiotics to flatten the curve of coronavirus disease COVID-2019 pandemic. Front Public Health. 2020; 8. https://doi.org/10.3389/fpubh.2020.00186 PMid:32574290 PMCid:PMC7227397
16. Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, *et al*. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Res. 2020; 285. https://doi.org/10.1016/j.virusres.2020.198005 PMid:32408156 PMCid:PMC7213959
17. Sundararaman A, Ray M, Ravindra PV, Halami PM. Role of probiotics to combat viral infections with emphasis on COVID-19. Appl Microbiol Biotechnol. 2020; 104:8089-104. https://doi.org/10.1007/s00253-020-10832-4 PMid:32813065 PMCid:PMC7434852
18. Li Q, Cheng F, Xu Q, Su Y, Cai X, Zeng F, *et al*. The role of probiotics in coronavirus disease-19 infection in Wuhan: A retrospective study of 311 severe patients. Int Immunopharmacol. 2021; 95. https://doi.org/10.1016/j.intimp.2021.107531 PMid:33714884 PMCid:PMC7934664
19. Ceccarelli G, Borrazzo C, Pinacchio C, Santinelli L, Innocenti G Pietro, Cavallari EN, *et al*. Oral bacteriotherapy in patients with COVID-19: A retrospective cohort study. Front Nutr. 2021; 7. https://doi.org/10.3389/fnut.2020.613928 PMid:33505983 PMCid:PMC7829198
20. Hazan S, Stollman N, Bozkurt HS, Dave S, Papoutsis AJ, Daniels J, *et al*. Lost microbes of COVID-19:

Bifidobacterium, *Faecalibacterium* depletion and decreased microbiome diversity associated with SARS-CoV-2 infection severity. BMJ Open Gastroenterol. 2022; 9(1). https://doi.org/10.1136/bmjgast-2022-000871 PMid:35483736 PMCid:PMC9051551

21. Kang EJ, Kim SY, Hwang IH, Ji YJ. The effect of probiotics on prevention of common cold: A meta-analysis of randomized controlled trial studies. Korean J Fam Med. 2013; 34(1):2-10. https://doi.org/10.4082/kjfm.2013.34.1.2 PMid:23372900 PMCid:PMC3560336
22. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, *et al*. COVID-19 with different severities: A multicenter study of clinical features. Am J Respir Crit Care Med. 2020; 201(11). https://doi.org/10.1164/rccm.202002-0445OC 5PMid:32275452 PMCid:PMC7258639
23. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: A systematic review and meta-analysis. J Infect. 2020; 81(2):266-75. https://doi.org/10.1016/j.jinf.2020.05.046 PMid:32473235 PMCid: PMC7255350
24. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5):475-81. https://doi.org/10.1016/S2213-2600(20)30079-5 PMid:32105632
25. Said KB, Alsolami A, Moussa S, Alfouzan F, Bashir AI, Rashidi M, *et al*. COVID-19 Clinical profiles and fatality rates in hospitalized patients reveal case aggravation and selective co-infection by limited gram-negative bacteria. Int J Environ Res Public Health. 2022;19(9):5270. https://doi.org/10.3390/ijerph19095270 PMid:35564665 PMCid:PMC9101447
26. Qu J, Cai Z, Liu Y, Duan X, Han S, Liu J, *et al*. Persistent bacterial coinfection of a COVID-19 patient caused by a genetically adapted pseudomonas aeruginosa chronic colonizer. Front Cell Infect Microbiol. 2021; 11. https://doi.org/10.3389/fcimb.2021.641920 PMid:33816347 PMCid:PMC8010185
27. Pandey G. Pt. Kashinath Sastri Vidhyotini Hindi commentarator of Caraka Samhita of Agnivesa-1st volume, Sutra Sthan Viddhishonitama Adhayay chapter 24 verse 17-18; 2006.
28. Kanyinda JNM. Coronavirus (COVID-19): A protocol for prevention and treatment (Covalyse®). Eur J Health Sci. 2020; 2(3). https://doi.org/10.24018/ejmed.2020.2.4.340
29. Meenakumari R, Thangaraj K, Sundaram A, Sundaram MM, Shanmugapriya P, Mariappan A, *et al*. Clinical outcomes among COVID-19 patients managed with modern and traditional *Siddha* medicine - A retrospective cohort study. J *Ayurveda* Integr Med. 2022; 13(2):100470. https://doi.org/10.1016/j.jaim.2021.06.010 PMid:34188417 PMCid:PMC8226037
30. Kim YH, Cho KH, Moon BS. Banhabaikchulcheunma-tang Down-regulates LPS-induced production of pro-inflammatory cytokines. J Physiol Pathol Korean Med. 2009; 23(01):192-8.
31. Sofía D la B, Giannina I, Carolina RM, Gabriela R, Cecilia P. Acute pancreatitis associated with SARS-CoV-2 infection in a pediatric patient. Andes Pediatrica. 2021; 92(6).
32. Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, *et al*. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol. 2016; 1(10):16113. https://doi.org/10.1038/nmicrobiol.2016.113 PMid:27670109 PMCid:PMC5076472
33. Upadhyay J, Tiwari N, Ansari MN. Role of inflammatory markers in corona virus disease (COVID-19) patients: A review. Exp Biol Med. 2020; 245(15):1368-75. https://doi.org/10.1177/1535370220939477 PMid:32635752 PMCid:PMC7441343
34. Yang WT, Li QY, Ata EB, Jiang YL, Huang H Bin, Shi CW, *et al*. Immune response characterization of mice immunized with Lactobacillus plantarum expressing spike antigen of transmissible gastroenteritis virus. Appl Microbiol Biotechnol. 2018; 102(19). https://doi.org/10.1007/s00253-018-9238-4 PMid:30056514 PMCid:PMC7080198
35. Qiu X, Zhang M, Yang X, Hong N, Yu C. *Faecalibacterium prausnitzii* upregulates regulatory T cells and anti-inflammatory cytokines in treating TNBS-induced colitis. J Crohns Colitis. 2013; 7(11):e558-68. https://doi.org/10.1016/j.crohns.2013.04.002 PMid:23643066
36. Feng Z, Yu Q, Yao S, Luo L, Zhou W, Mao X, *et al*. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. Nat Commun. 2020; 11(1):4968. https://doi.org/10.1038/s41467-020-18786-x PMid:33009413 PMCid:PMC7532528
37. Darif D, Hammi I, Kihel A, El Idrissi Saik I, Guessous F, Akarid K. The pro-inflammatory cytokines in COVID-19 pathogenesis: What goes wrong? Microbial Pathogenesis. 2021; 153. https://doi.org/10.1016/j.micpath.2021.104799 PMid:33609650 PMCid:PMC7889464
38. An J, Lee H, Lee S, Song Y, Kim J, Park IH, *et al*. Modulation of pro-inflammatory and anti-inflammatory cytokines in the fat by an aloe gel-based formula, QDMC, is correlated with altered gut microbiota. Immune Netw. 2021; 21(2):e15. https://doi.org/10.4110/in.2021.21.e15 PMid:33996171 PMCid:PMC8099612
39. Valcheva R, Hotte N, Gillevet P, Sikaroodi M, Thiessen A, Madsen KL. Soluble dextrin fibers alter the intestinal microbiota and reduce proinflammatory cytokine secretion in male IL-10-deficient mice. J Nutr. 2015; 145(9). https://doi.org/10.3945/jn.114.207738 PMid:26180249

40. Kumar P, Berwal R. Supplementation of Ashwagandha root powder improving gut micro flora and immune response of broilers. Pharm Innov. 2019; 8(10):114-18.
41. Saggam A, Limgaokar K, Borse S, Chavan-Gautam P, Dixit S, Tillu G, *et al*. *Withania somnifera* (L.) Dunal: Opportunity for clinical repurposing in COVID-19 management. Front Pharmacol. 2021; 12. https://doi.org/10.3389/fphar.2021.623795 PMid:34012390 PMCid:PMC8126694
42. Balkrishna A, Nain P, Chauhan A, Sharma N, Gupta A, Ranjan R, *et al*. Super critical fluid extracted fatty acids from *Withania somnifera* seeds repair psoriasis-like skin lesions and attenuate pro-inflammatory cytokines (TNF-α and IL-6) release. Biomolecules. 2020; 10(2):185. https://doi.org/10.3390/biom10020185 PMid:31991752 PMCid:PMC7072271
43. Straughn AR, Kakar SS. Withaferin A: A potential therapeutic agent against COVID-19 infection. J Ovarian Res. 2020; 13:79. https://doi.org/10.1186/s13048-020-00684-x PMid:32684166 PMCid:PMC7369003
44. Khanna K, Kohli SK, Kaur R, Bhardwaj A, Bhardwaj V, Ohri P, *et al*. Herbal immune-boosters: Substantial warriors of pandemic COVID-19 battle. Phytomed. 2021; 85. https://doi.org/10.1016/j.phymed.2020.153361 PMid:33485605 PMCid:PMC7532351
45. Thakkar SS, Shelat F, Thakor P. Magical bullets from an indigenous Indian medicinal plant *Tinospora cordifolia*: An *in silico* approach for the antidote of SARS-CoV-2. Egypt J Pet. 2021; 30(1):53-66. https://doi.org/10.1016/j.ejpe.2021.02.005 PMCid:PMC7901307
46. Jena S, Munusami P, Balamurali MM, Chanda K. Computationally approached inhibition potential of *Tinospora cordifolia* towards COVID-19 targets. VirusDis. 2021; 32:65-77. https://doi.org/10.1007/s13337-021-00666-7 PMid:33778129 PMCid:PMC7980128
47. Tian Y, Cai J, Gui W, Nichols RG, Koo I, Zhang J, *et al*. Berberine directly affects the gut microbiota to promote intestinal farnesoid X receptor activation. Drug Metab Dispos. 2019; 47(2). https://doi.org/10.1124/dmd.118.083691 PMid:30409838 PMCid:PMC6323626
48. Adak S, Chakraborty D, Maji HS, Basu S, Roy P, Mitra S, *et al*. Comparison of the antimicrobial activity of the phyto-constituents obtained from the stem bark and leaf extracts of *Phyllanthus emblica* L. against different strains of *Staphylococcus aureus* and *Salmonella typhi*. Res J. Pharmacol. Pharm. 2018; 10(2):53-60. https://doi.org/10.5958/2321-5836.2018.00009.5
49. Glowacka I, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, *et al*. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011; 85(9). https://doi.org/10.1128/JVI.02232-10 PMid:21325420 PMCid:PMC3126222
50. Sharma H, Yunus GY, Agrawal R, Kalra M, Verma S, Bhattar S. Antifungal efficacy of three medicinal plants *Glycyrrhiza glabra*, *Ficus religiosa*, and *Plantago* major against oral *Candida albicans*: A comparative analysis. Indian J Dent Res. 2016; 27(4):433-6. https://doi.org/10.4103/0970-9290.191895 PMid:27723643
51. Qiu M, Huang K, Liu Y, Yang Y, Tang H, Liu X, *et al*. Modulation of intestinal microbiota by glycyrrhizic acid prevents high-fat diet-enhanced pre-metastatic niche formation and metastasis. Mucosal Immunol. 2019; 12(4):945-57. https://doi.org/10.1038/s41385-019-0144-6 PMid:30755716
52. Chikhale RV, Sinha SK, Patil RB, Prasad SK, Shakya A, Gurav N, *et al*. *In-silico* investigation of phytochemicals from *Asparagus racemosus* as plausible antiviral agent in COVID-19. J Biomol Struct Dyn. 2021; 39(14):5033-47. https://doi.org/10.1080/07391102.2020.1784289 PMid:32579064 PMCid:PMC7335809
53. Patel CN, Goswami D, Jaiswal DG, Parmar RM, Solanki HA, Pandya HA. Pinpointing the potential hits for hindering interaction of SARS-CoV-2 S-protein with ACE2 from the pool of antiviral phytochemicals utilizing molecular docking and Molecular Dynamics (MD) simulations. J Mol Graph Model. 2021; 105: 107874. https://doi.org/10.1016/j.jmgm.2021.107874 PMid:33647752 PMCid:PMC7897937
54. Qu Y, Li X, Xu F, Zhao S, Wu X, Wang Y, *et al*. Kaempferol alleviates murine experimental colitis by restoring gut microbiota and inhibiting the LPS-TLR4-NF-κB Axis. Front Immunol. 2021; 12. https://doi.org/10.3389/fimmu.2021.679897 PMid:34367139 PMCid:PMC8339999
55. Sa-Ngiamsuntorn K, Suksatu A, Pewkliang Y, Thongsri P, Kanjanasirirat P, Manopwisedjaroen S, *et al*. Anti-SARS-CoV-2 activity of *Andrographis paniculata* extract and its major component andrographolide in human lung epithelial cells and cytotoxicity evaluation in major organ cell representative. J Nat Prod. 2021; 84(04):1261-70. https://doi.org/10.1021/acs.jnatprod.0c01324 PMid:33844528
56. Wu H, Wu X, Huang L, Ruan C, Liu J, Chen X, *et al*. Effects of andrographolide on mouse intestinal microflora based on high-throughput sequence analysis. Front Vet Sci. 2021; 8:702885. https://doi.org/10.3389/fvets.2021.702885 PMid:34485430 PMCid:PMC8416444
57. Mohapatra PK, Chopdar KS, Dash GC, Mohanty AK, Raval MK. *In silico* screening and covalent binding of phytochemicals of *Ocimum sanctum* against SARS-CoV-2 (COVID 19) main protease. J Biomol Struct Dyn. 2023; 41(2):435-44. https://doi.org/10.1080/07391102.2021.2007170 PMid:34821198
58. Islam R, Sultana N, Bhakta S, Haque Z, Hasan A, Siddique MP, *et al*. Modulation of growth performance, gut morphometry, and cecal microbiota in broilers by clove (*Syzygium aromaticum*) and tulsi (*Ocimum sanctum*)

supplementation. Poult Sci. 2023; 102(1):102266. https://doi.org/10.1016/j.psj.2022.102266 PMid:36370662 PMCid:PMC9660731

59. Sumanth M, Mustafa SS. Antistress, adoptogenic and immunopotentiating activity roots of *Boerhaavia diffusa* in mice. Int J Pharmacol. 2007; 3(5):416-20. https://doi.org/10.3923/ijp.2007.416.420
60. Surya UR, Praveen N. A molecular docking study of SARS-CoV-2 main protease against phytochemicals of *Boerhavia diffusa* Linn. for novel COVID-19 drug discovery. VirusDis. 2021; 32:46-54. https://doi.org/10.1007/s13337-021-00683-6 PMid:33758772 PMCid:PMC7971947
61. Singh C, Singh SK, Nath G, Rai NP. Anti-mycobacterial activity of *Piper longum* L. fruit extracts against multi drug resistant *Mycobacterium* spp. Internat J Phytomed. 2011; 3(3).
62. Naika R, Prasanna KP, Ganapathy PSS. Antibacterial activity of piperlongumine an alkaloid isolated from the methanolic root extract of *Piper longum* L. Pharmacoph. 2010; 1(2):141-8.
63. Rohaim MA, El Naggar RF, Clayton E, Munir M. Structural and functional insights into non-structural proteins of coronaviruses. Microb Pathog. 2021; 150:104641. https://doi.org/10.1016/j.micpath.2020.104641 PMid:33242646 PMCid:PMC7682334
64. Kim HG, Cho JH, Jeong EY, Lim JH, Lee SH, Lee HS. Growth-inhibiting activity of active component isolated from *Terminalia chebula* fruits against intestinal bacteria. J Food Prot. 2006; 69(9):2205-9. https://doi.org/10.4315/0362-028X-69.9.2205 PMid:16995525
65. Rubab I, Ali S. Dried fruit extract of *Terminalia chebula* modulates the immune response in mice. Food Agric Immunol. 2016; 27(1). https://doi.org/10.1080/09540105.2015.1055554
66. Upadhyay S, Tripathi PK, Singh M, Raghavendhar S, Bhardwaj M, Patel AK. Evaluation of medicinal herbs as a potential therapeutic option against SARS-CoV-2 targeting its main protease. Phytother Res. 2020; 34(12):3411-19. https://doi.org/10.1002/ptr.6802 PMid:32748969 PMCid:PMC7436756
67. Shen L, Liu L, Ji HF. Regulative effects of curcumin spice administration on gut microbiota and its pharmacological implications. Food Nutr Res. 2017; 61. https://doi.org/10.1080/16546628.2017.1361780 PMid:28814952 PMCid:PMC5553098
68. Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, *et al*. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An *in silico* study for drug development. J Biomol Struct Dyn. 2020. https://doi.org/10.26434/chemrxiv.12094203
69. Thimmulappa RK, Mudnakudu-Nagaraju KK, Shivamallu C, Subramaniam KJT, Radhakrishnan A, Bhojraj S, *et al*. Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19. Heliyon. 2021; 7:E06350. https://doi.org/10.1016/j.heliyon.2021.e06350 PMid:33655086 PMCid:PMC7899028
70. Radhakrishnan N, Gnanamani A, Mandal AB. A potential antibacterial agent Embelin, a natural benzoquinone extracted from *Embelia ribes*. Biol Med. 2011; 3(2 Special Issue).
71. Bachmetov L, Gal-Tanamy M, Shapira A, Vorobeychik M, Giterman-Galam T, Sathiyamoorthy P, *et al*. Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity. J Viral Hepat. 2012; 19(2):e81-8. https://doi.org/10.1111/j.1365-2893.2011.01507.x PMid:22239530
72. Rahaman L, Ghosh S, Nath N, Sen A, Sharma BK. Extracts of *Adhatoda vasica* Nees and vasicine inhibits biofilm formation of *Klebsiella pneumoniae*. IOSR J Pharm Biol Sci. 2018; 13(2).
73. Thangaraju P, Sudha TYS, Pasala PK, Hari TYS, Venkatesan S, Thangaraju E. The role of Justicia adhatoda as prophylaxis for COVID-19 – Analysis based on docking. Infect Disord Drug Targets. 2021; 21(08):1-7. https://doi.org/10.2174/1871526521666210119120643 PMid:33463480
74. Ribeiro AMB, Sousa JN de, Costa LM, Oliveira FA de A, dos Santos RC, Silva Nunes AS, *et al*. Antimicrobial activity of *Phyllanthus amarus* Schumach. and Thonn and inhibition of the NorA efflux pump of *Staphylococcus aureus* by Phyllanthin. Microb Pathog. 2019; 130:242-6. https://doi.org/10.1016/j.micpath.2019.03.012 PMid:30876871
75. Bafna K, Krug RM, Montelione GT. Structural similarity of SARS-CoV2 Mpro and HCV NS3/4A proteases suggests new approaches for identifying existing drugs useful as COVID-19 therapeutics. ChemRxiv. 2020. https://doi.org/10.26434/chemrxiv.12153615
76. Harikrishnan H, Jantan I, Alagan A, Haque MA. Modulation of cell signaling pathways by *Phyllanthus amarus* and its major constituents: Potential role in the prevention and treatment of inflammation and cancer. Inflammopharmacol. 2020; 28. https://doi.org/10.1007/s10787-019-00671-9 PMid:31792765
77. Wang X, Zhang D, Jiang H, Zhang S, Pang X, Gao S, *et al*. Gut microbiota variation with short-term intake of ginger juice on human health. Front Microbiol. 2021; 11. https://doi.org/10.3389/fmicb.2020.576061 PMid:33708178 PMCid:PMC7940200
78. Haridas M, Sasidhar V, Nath P, Abhithaj J, Sabu A, Rammanohar P. Compounds of citrus medica and *Zingiber officinale* for COVID-19 inhibition: *In silico* evidence for cues from *Ayurveda*. Futur J Pharm Sci. 2021; 7(01):1-9. https://doi.org/10.1186/s43094-020-00171-6 PMid:33457429 PMCid:PMC7794642
79. Júnior CDS, Martins CCS, Dias FTF, Sitanaka NY, Ferracioli LB, Moraes JE, *et al*. The use of an alternative feed additive, containing benzoic acid, thymol, eugenol,

and piperine, improved growth performance, nutrient and energy digestibility, and gut health in weaned piglets. J Anim Sci. 2020; 98(5). https://doi.org/10.1093/jas/skaa119 PMid:32280983 PMCid:PMC7229883

80. Kumar MP, Sundaram KM, Ramasamy M. Coronavirus spike (S) glycoprotein (2019-ncov) targeted *Siddha* medicines *Kaba Sura Kudineer* and *Thontha Sura Kudineer* - *In silico* evidence for corona viral drug. Asian J Pharm Res Health Care. 2020; 12(01):20-7. https://doi.org/10.18311/ajprhc/2020/25103
81. Xie J, Song W, Liang X, Zhang Q, Shi Y, Liu W, *et al.* Protective effect of quercetin on streptozotocin-induced diabetic peripheral neuropathy rats through modulating gut microbiota and reactive oxygen species level. Biomed. Pharmacother. 2020; 127: 110147. https://doi.org/10.1016/j.biopha.2020.110147 PMid:32559841
82. Canli K, Yetgin A, Akata I, Altuner EM. Antimicrobial activity and chemical composition screening of *Anacyclus pyrethrum* root. Indian J Pharm Educ Res. 2017; 51(3). https://doi.org/10.5530/ijper.51.3s.22
83. Kerboua KA, Benosmane L, Namoune S, Ouled-Diaf K, Ghaliaoui N, Bendjeddou D. Anti-inflammatory and antioxidant activity of the hot water-soluble polysaccharides from *Anacyclus pyrethrum* (L.) roots. J Ethnopharmacol. 2021; 281:114491. https://doi.org/10.1016/j.jep.2021.114491 PMid:34364970
84. Kalinina TS, Zlenko DV, Kiselev AV, Litvin AA, Stovbun SV. Antiviral activity of the high-molecular-weight plant polysaccharides (Panavir®). Int J Biol Macromol. 2020; 161:936-8. https://doi.org/10.1016/j.ijbiomac.2020.06.031 PMid:32534094 PMCid:PMC7287457
85. Elizalde-Romero CA, Montoya-Inzunza LA, Contreras-Angulo LA, Heredia JB, Gutiérrez-Grijalva EP. Solanum fruits: Phytochemicals, bioaccessibility and bioavailability, and their relationship with their health-promoting effects. Front Nutr. 2021; 8. https://doi.org/10.3389/fnut.2021.790582 PMid:34938764 PMCid:PMC8687741
86. Gowtham HG, Murali M, Singh SB, Shivamallu C, Pradeep S, Shivakumar CS, *et al.* Phytoconstituents of *Withania somnifera* unveiled Ashwagandhanolide as a potential drug targeting breast cancer: Investigations through computational, molecular docking and conceptual DFT studies. PLoS One. 2022; 17(10). https://doi.org/10.1371/journal.pone.0275432 PMid:36201520 PMCid:PMC9536605
87. Li Q, Cui Y, Xu B, Wang Y, Lv F, Li Z, *et al.* Main active components of Jiawei Gegen Qinlian decoction protects against ulcerative colitis under different dietary environments in a gut microbiota-dependent manner. Pharmacol Res. 2021; 170. https://doi.org/10.1016/j.phrs.2021.105694 PMid:34087350
88. Li Y, Liu T, Yan C, Xie R, Guo Z, Wang S, *et al.* Diammonium glycyrrhizinate protects against nonalcoholic fatty liver disease in mice through modulation of gut microbiota and restoration of intestinal barrier. Mol Pharm. 2018; 15(9). https://doi.org/10.1021/acs.molpharmaceut.8b00347 PMid:30036479
89. Suzuki T, Tanabe S, Hara H. Kaempferol enhances intestinal barrier function through the cytoskeletal association and expression of tight junction proteins in Caco-2 cells 1-3. J Nutr. 2011; 141(1):87-94. https://doi.org/10.3945/jn.110.125633 PMid:21068182
90. Suzuki T, Hara H. Quercetin enhances intestinal barrier function through the assembly of zonnula occludens-2, occludin, and claudin-1 and the expression of claudin-4 in caco-2 cells. J Nutr. 2009; 139(5):965-74. https://doi.org/10.3945/jn.108.100867 PMid:19297429
91. Omonijo FA, Liu S, Hui Q, Zhang H, Lahaye L, Bodin JC, *et al.* Thymol improves barrier function and attenuates inflammatory responses in porcine intestinal epithelial cells during lipopolysaccharide (LPS))-induced inflammation. J Agric Food Chem. 2019; 67(2):615-24. https://doi.org/10.1021/acs.jafc.8b05480 PMid:30567427
92. Peng B, Xue L, Yu Q, Zhong T. Ellagic acid alleviates TNBS-induced intestinal barrier dysfunction by regulating mucin secretion and maintaining tight junction integrity in rats. Int J Food Sci Nutr. 2023:476-86. https://doi.org/10.1080/09637486.2023.2230525 PMid:37455358
93. Wu S, Guo T, Qi W, Li Y, Gu J, Liu C, *et al.* Curcumin ameliorates ischemic stroke injury in rats by protecting the integrity of the blood brain barrier. Exp Ther Med. 2021; 22(1). https://doi.org/10.3892/etm.2021.10215 PMid:34055082 PMCid:PMC8145684
94. Kim DY, Kang MK, Lee EJ, Kim YH, Oh H, Kim S Il, *et al.* Eucalyptol inhibits amyloid-β-induced barrier dysfunction in glucose-exposed retinal pigment epithelial cells and diabetic eyes. Antioxidants. 2020; 9(10):1000. https://doi.org/10.3390/antiox9101000 PMid:33076507 PMCid:PMC7602655
95. Wu XX, Huang XL, Chen RR, Li T, Ye HJ, Xie W, *et al.* Paeoniflorin prevents intestinal barrier disruption and inhibits lipopolysaccharide (LPS))-induced inflammation in Caco-2 cell monolayers. Inflam. 2019; 42:2215-25. https://doi.org/10.1007/s10753-019-01085-z PMid:31473900
96. Ibrahim D, Eldemery F, Metwally AS, Abd-Allah EM, Mohamed DT, Ismail TA, *et al.* Dietary eugenol nanoemulsion potentiated performance of broiler chickens: Orchestration of digestive enzymes, intestinal barrier functions and cytokines related gene expression with a consequence of attenuating the severity of *E. coli* O78 infection. Front Vet Sci. 2022; 9. https://doi.org/10.3389/fvets.2022.847580 PMid:35812892 PMCid:PMC9260043