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Leveraging nature's pharmacy: A comprehensive review of traditional medicinal and aromatic plants against COVID-19

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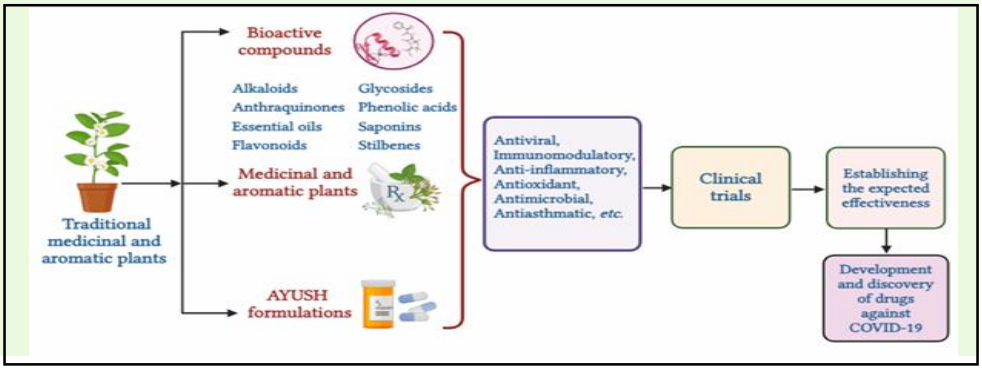
Abstract

The COVID-19 pandemic has highlighted the need for effective treatments and underscored the urgent need for effective therapeutic agents. This comprehensive review explores the potential of traditional medicinal and aromatic plants as therapeutic agents against COVID-19 and delves into the rich pharmacological potential of these plants, which have been used for centuries in traditional medicine systems worldwide. The review discusses various bioactive metabolites and plant products derived from these plants, highlighting their potential antiviral, anti-inflammatory, and immune-boosting properties. It also examines herbal formulations such as AYUSH kwath, AYUSH-64, agasthya hareetaki, and anuthalia recommended by AYUSH and other traditional medicine systems, assessing their potential efficacy against COVID-19 based on available scientific evidence including routinely used medicinal plants. Plant-based preparations include antiviral, antibacterial, and anticancer therapies and their possible therapeutics against COVID-19. Limited, unregulated clinical trials involving conventional mono and poly-herbal therapies are being conducted worldwide. Some clinical trials have reached completion, but doubts about safety and efficacy persist even with the recent invention of vaccines. Meta-analyses have shown favourable effects of herbal medicine when added to standard treatment for COVID-19. These effects include improvements in the total effective rate, time to remission from fever, coughing, fatigue, sputum production, and more. Traditional Chinese medicine (TCM) combined with conventional western medicine has shown positive outcomes in treating COVID-19. Lung CT parameters and clinical cure rates were better with TCM combined therapy for mild to moderate cases. Chinese herbal medicines combined with conventional therapy improved lung CT parameters and clinical cure rates compared to conventional therapy alone. NRICM102, composed of 10 herbs, has shown effectiveness in improving pulmonary fibrosis in animal experiments and preliminary clinical trials. However, further research is needed to fully understand their potential and address the challenges involved.



1. Introduction

Amidst the ongoing COVID-19 crisis, there has been contemplation of diverse treatment modalities that should be utilizing traditional medicine, which has been extensively employed in previous outbreaks such as SARS and H1N1 influenza (Luo *et al.*, 2020). Directives delineating the application of traditional remedies for the prevention

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and management of COVID-19 have been promulgated by India, China, and South Korea. India is confident in its own established traditional medical systems (Ayurveda, Yoga, Unani, Siddha, and Homeopathy, collectively known as AYUSH), which stand as some of the most ancient medical practices globally (Ang *et al*., 2020). These comprehensive systems are rooted in natural substances sourced from plants, animals, or minerals. AYUSH has garnered renewed attention for its role in guiding India through historical pandemics like the plague, cholera, and the Spanish flu. By adapting the traditional uses of Indian medicinal flora and concoctions, novel possibilities may potentially emerge for addressing the present COVID-19 crisis. Some of these formulations are presently undergoing clinical assessments in COVID-19 patients (Ahmad *et al*., 2021). Furthermore, several Indian medicinal plants are known to possess antiviral, immunomodulatory, antiallergic, and asthmatic properties. Many of these plants constitute key components of traditional formulations with a longstanding history of use. This analysis deliberates on plausible alternative approaches leveraging Indian traditional medicine to navigate COVID-19 by mitigating morbidity as a supplementary therapeutic intervention and for preventive purposes. It accentuates the imperative to delve deeper into evaluating botanical compounds sourced from Indian medicinal plants against SARS-CoV-2, with a focus on those exhibiting documented antiviral, immunomodulatory, and related attributes.

The researchers and members of the community have uncovered a potential method for the treatment and prevention of COVID-19 through the utilization of herbal remedies. Given the significant role of the patient's immune system in COVID-19 infection, herbal remedies possessing immunomodulatory properties could function as preventive measures and potentially therapeutic interventions for individuals with COVID-19 (Afroz Alam and Adnan Ahmad Khan, 2022; Sharma *et al*., 2009; Zhang and Liu, 2020). Herbal remedies are increasingly being recognized as crucial medications, prompting ongoing research efforts due to their noted antioxidant, anti-inflammatory, and antiviral capabilities. Given the current global apprehension, it is imperative to identify enduring solutions to curb the transmission of this pandemic. The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has a significant impact on global health, leading to high morbidity and mortality rates and remarkable cases of hospitalization. Despite the recent development and distribution of vaccines, there is still a pressing need for effective therapeutic agents to combat this disease. Traditional medicinal and aromatic plants have a long history of use in treating various ailments, including viral infections. These plants are notable wellsprings of potential drugs, including antiviral, antibacterial, and anticancer therapies. In the face of the COVID-19 pandemic, researchers worldwide have turned their attention to these plants, exploring their potential as therapeutic agents against the virus (Afroz Alam and Adnan Ahmad Khan, 2022). This comprehensive review aims to explore the potential of traditional medicinal and aromatic plants as therapeutic agents against COVID-19. It will highlight and focus on plant-based anti-COVID-19 clinical trials found in several scientific and authenticated databases. The review will also discuss the role of bioactive metabolites and plant products in combating the virus. The exploration of these plants and their bioactive compounds could provide valuable insights into the development of effective treatments for COVID-19. However, it is important to note that while many clinical trials are underway to establish these agents as credentialed sources of anti-COVID-19 medications, only a few have reached the landmark of completion. Therefore, the need for further rigorous scientific investigation is evident. This review will provide a comprehensive overview of the current state of research on the potential of traditional medicinal and aromatic plants in the fight against COVID-19, highlighting the promising leads, the challenges faced, and the future directions for this exciting field of research.COVID-19 is the disease, caused by SARS-CoV-2 virus. The virus caused an initial outbreak in Wuhan, China with affected individuals presenting with viral pneumonia. Early on, in the outbreak, metagenomic RNA sequencing shed light on this novel coronavirus, which is an enveloped virus, containing a single stranded RNA and gets its name from the crown like spikes on their surface (Figure 1) (Khan *et al*., 2020).

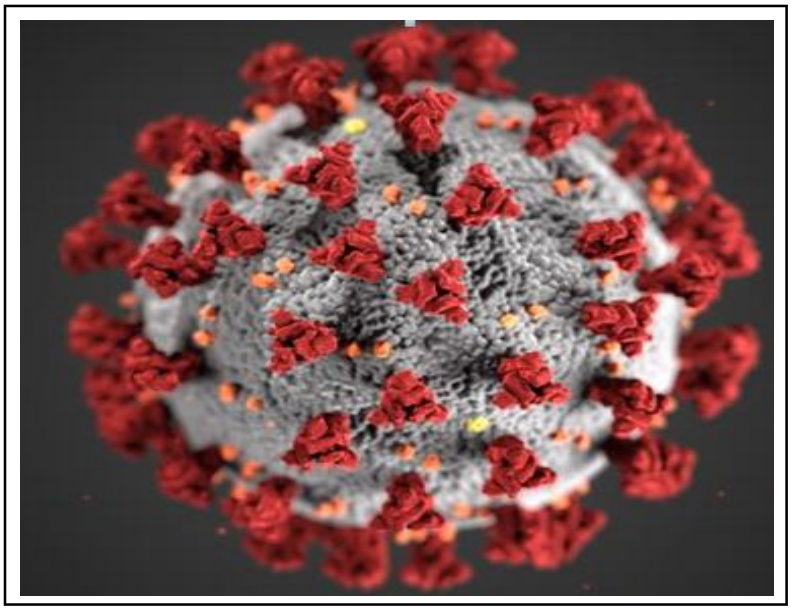

Figure 1: Corona virus- Photo credit: Alissa Eckert, MSMI; Dan Higgins, MAMS.

2. Epidemiology of COVID-19

Coronaviruses such as SARS and MERS have thrown significant challenges to public health in prior outbreaks which have primarily targeted the human respiratory system (Khan *et al*., 2020). In the latter part of 2019, a group of pneumonia instances with unidentified origins emerged in Wuhan, China (Bogoch *et al*., 2020; Lu *et al*., 2020). These instances were linked *via* epidemiology to a local market involving seafood and live animals. Initial approximations pointed to the novel coronavirus, subsequently named COVID-19 by the World Health Organization. WHO announced the disease as a global public health emergency on January 30, 2020, and declared it a pandemic on March 11, 2020 (Figure 2) (Hsieh *et al.,* 2021; Voidarou *et al.,* 2023).

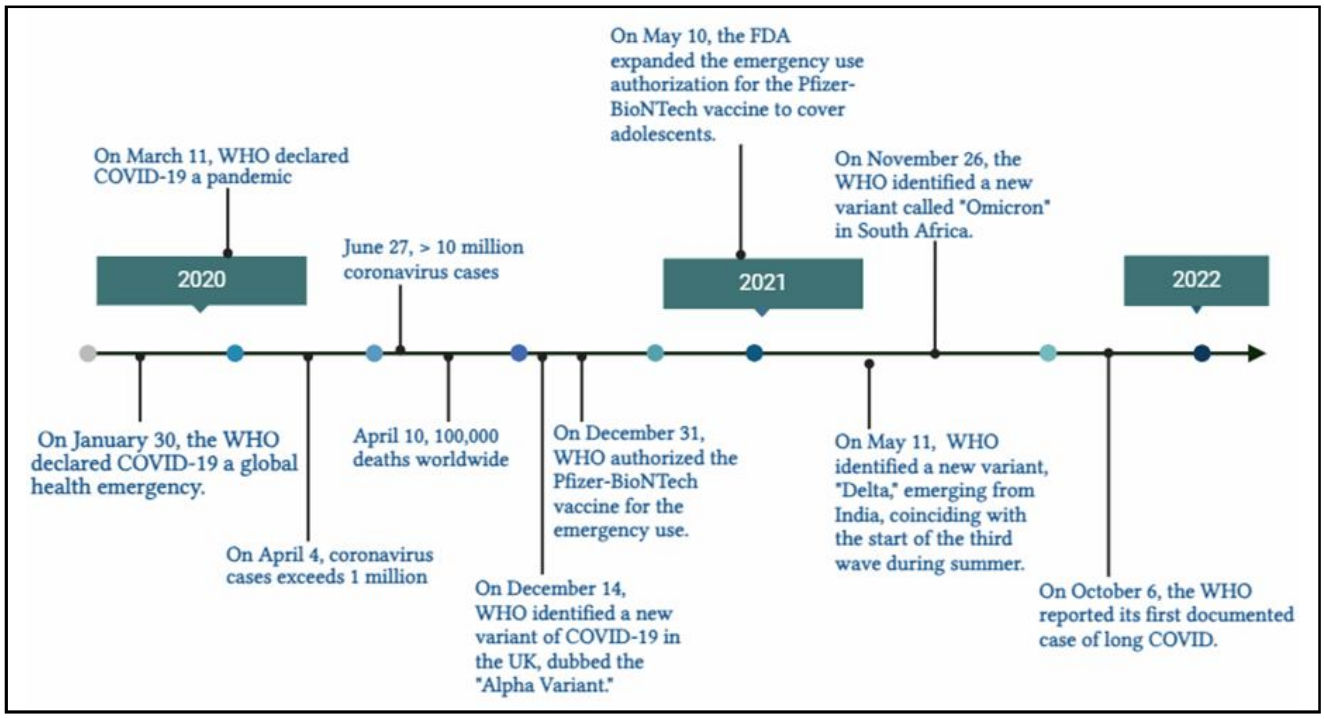

Figure 2: Epidemiology of COVID-19.

3. Bioactive metabolites and plant products against COVID-19

Medicinal plants and herbs, characterized by their diverse bioactive constituents, have been historically employed for various health conditions, including the combat against pathogens such as SARS-CoV-2. Phytochemicals obtained from these botanical sources present auspicious antiviral properties, acting on different phases of viral infections ranging from cellular entry to replication and dissemination. Types of phytoconstituents currently under scrutiny for their effectiveness against COVID-19 encompass flavonoids, essential oils, alkaloids, phenolic acids, stilbenes, anthraquinones, saponins, glycosides, and tannins. Further, exploration of these phytoconstituents shows potential for the development of efficacious therapeutic agents against COVID-19 (Table 1 and Figure 3).

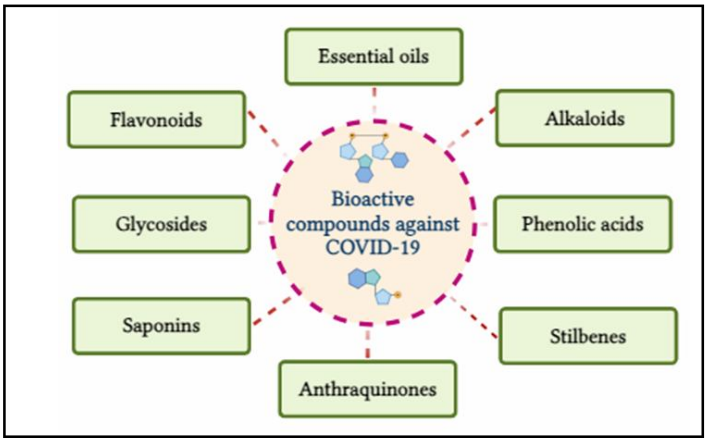

Figure 3: Bioactive metabolites against COVID-19.

Table 1: Bioactive metabolites and its functions against COVID-19

Bioactive metabolite	Phytochemical	Function	References
Flavonoids	Quercetin, procyanidin-β-2,7-dimethoxyflava n-42-o-β-d-glucopyranoside, amentoflavone, hidrosmin, galloca the chingallate, diosmin, pectolinaren, kaempferol, isoquercetin, hesperetin, and myricetin	Impede viral cell entry and replication	Ngwa *et al*., 2020; Chauhan and Karla, 2020
Essential oils	Dithymoquinone	Disrupt viral envelopes, thereby hindering attachment to host cells	Kulkarni *et al*., 2020
Alkaloids	Resoquines anguinarine, quinine, chelidonine, cinchonine, isoquinoline, hartmine, coptisine, berberine, palmatin, tetradine and emetine	Demonstrate antiviral effects by targeting viral replication	Jahan and Onay, 2020; Srivastava *et al*., 2020; Bleasel and Peterson, 2020
Phenolic acids	Broussochalcone a, papyriflavonol a, 32-(3-methyl but-2-enyl)-32,42,7-trihydroxy flavane, brousso flavan a, kazinol f, and kazinol j	Obstruct the viral entry into host cells	Park *et al*., 2017
Stilbenes	Resveratrol, transresveratrol, piceatannol and pinosylvin	Intervene in viral entry mechanisms	Pandey *et al*., 2020; Wahedi *et al*., 2020
Anthraquinones	Emodin, aloin a and b, rubiadin, aloe-emodin, pseudohypericin, damnacanthal and chryosphanic	Inhibit crucial viral proteins	Das *et al*., 2022; Khan *et al*., 2020
Saponins	Glycyrrhizic acid and ginsenoside	Interfere with viral particles and fusion	Sumathi and Vidhya, 2022
Glycosides	Focus on host cell proteins, and tannins exhibit antioxidant characteristics	Inhibit viral activity	Sumathi and Vidhya, 2022

4. Mechanism of actions of plant products against COVID-19

Various botanical derivatives have been scrutinized for their efficacy in combatting COVID-19 through diverse pathways. The flavonoids, alkaloids, and polyphenols present in botanicals (*Camellia sinensis*, *Glycyrrhiza glabra*, and *Sambucus nigra*) have exhibited direct antiviral properties by impeding viral replication and adhesion to host cells. In addition, specific botanical extracts like polysaccharides from myco-medicinal fungi and plants like *Astragalus membranaceus* might regulate the immune response, assisting the organism in combating viral infections and diminishing inflammation. Conversely, substances like curcumin from *Curcuma longa*, resveratrol from *Vitis vinifera*, and quercetin from various fruits and vegetables possess antiinflammatory attributes that could potentially mitigate the excessive inflammation instigated by COVID-19 (Ngwa *et al*., 2020; Chauhan and Karla, 2020). Additionally, botanical antioxidants such as vitamins C and E, flavonoids, and carotenoids sourced from diverse outlets could counteract the oxidative stress incited by the virus. Compounds like quercetin and epigallocatechin gallate (EGCG) from *Camellia sinensis* have exhibited promise in modulating the ACE2 receptor, utilized by the SARS-CoV-2 virus for cellular entry. Furthermore, certain plant-derived protease inhibitors, like those found in catechins from *Camellia sinensis* and *Glycyrrhiza glabra*, may impede viral replication by blocking viral proteases. Illustrations comprise berberine, present in botanicals like *Hydrastis canadensis* and *Berberis vulgaris*, which has shown antiviral effects against analogous coronaviruses by disrupting viral RNA replication (Jahan and Onay, 2020; Srivastava *et al*., 2020; Bleasel and Peterson, 2020). Nevertheless, it is imperative to acknowledge that despite the potential of these mechanisms, clinical substantiation endorsing the efficacy and safety of botanicals specifically for COVID-19 remains restricted. Furthermore, disparities in the composition and potency of natural products underscore the necessity for standardized formulations and rigorous clinical trials to authenticate their potential in the prevention or treatment of COVID-19 (Srivastava *et al*., 2020).

5. Therapeutic potential of medicinal and aromatic plants in COVID-19 management

Numerous plants are acknowledged for their capacity to enhance the immune system, such as *Ocimum basilicum* L., *Zingiber officinale* Roscoe, *Allium sativum* L., *Cinnamomum* spp., *Tinospora cordifolia* (Willd.) Miers among others. These botanical species and seasonings are frequently employed to manage respiratory conditions (Singh *et al*., 2016). Common culinary components like turmeric, clove, ginger, cinnamon, and black pepper are esteemed for their immune-boosting attributes in combatting viral infections (Srivastava *et al*., 2020). This manuscript explores the antiviral capabilities of sixteen widely used medicinal and aromatic plants in Ayurveda and Unani medicine. These botanicals are frequently integrated into herbal concoctions designed to bolster immunity against SARS-CoV-2 during the current pandemic. Many of these plants constitute essential elements of herbal remedies targeting respiratory disorders (Afroz Alam and Adnan Ahmad Khan, 2022).

5.1 *Cassia fistula* L. (Golden shower tree)

Cassia fistula L. (Fabaceae) is a widely distributed botanical species present in tropical, subtropical, and semi-arid regions across the globe. Its medicinal attributes have been highly regarded since ancient

times, as evidenced in historical texts focusing on therapeutic flora. The extraction of medicinal compounds from the leaves, tender shoots, and flowers of *C. fistula* is a common practice. Several anthraquinones, notably chrysophanol, rhein, and physcion, have been identified within this plant, particularly in its fully developed leaves (Dickert *et al.,* 1981). Chrysophanol is an anthraquinone found in various medicinal plants, including Chinese herbal medicines. It has been studied for its pharmacological effects, which include purgation, antiinflammation, immunoregulation, antihyperlipidemia, and anticancer properties. Rhein is another anthraquinone with diverse biological activities. It is absorbed mainly in the intestines and is widely distributed in various tissues and organs. Like chrysophanol, rhein can be transformed into other anthraquinones, potentially influencing its effects. Moreover, investigations have delved into the antiviral properties of *C. fistula*. Ethanol extracts derived from its fruits have displayed inhibitory effects against foot and mouth disease virus (FMDV), while extracts from pods and bark exhibited toxicity towards ranikhet disease virus (RDV) and vaccinia virus (VV) (Sundararaju and Saritha, 2006). Notably, hot water extracts from the plant's leaves and young pods have demonstrated inhibitory effects against the infectious bovine rhinotracheitis virus (IBR) (Kainsa and Kumar, 2012). Given the observed potential in combating viral infections, further exploration into the properties of *C. fistula* made it possible to address coronavirus infections.

5.2 *Cinnamomum cassia* (L) J. Presl (Cinnamon)

Cinnamomum, known as Cinnamon in common parlance, holds significant value in traditional medical systems such as Ayurveda and Unani due to its wide-ranging therapeutic applications. Obtained from the inner bark of young branches, it has been a fundamental ingredient in global culinary practices for generations. The presence of numerous phytochemicals like cinnamaldehyde and eugenol in cinnamon contributes to its antioxidative, antimicrobial, antiviral, antidiabetic, antihypertensive, antitumor, gastroprotective, and immunomodulatory attributes (Shen *et al*., 2012). Research indicates that the extract of cinnamon bark can potentially augment both cell-mediated and humoral immunity, showcasing its prospective role as an immunostimulant. Recent studies have exhibited encouraging results in diminishing the infectivity of herpes simplex virus-1 (HSV-1) using cinnamon extract, especially essential oil, implying its plausible effectiveness against other viral infections such as SARS-CoV-2 Notably, all kinds of herpes viruses, including HSV-1, are highly sensitive to essential oils from various sources, such as citronella, clove, and oregano (Moshaverinia *et al*., 2020). The elevation of serum immunoglobulin levels and enhancement of both cell-mediated and humoral immunity have been attributed to cinnamon. Particularly, cinnamaldehyde has been recognized as a potent modulator of immune responses mediated by monocytes/macrophages, accomplished by inhibiting PI3K, PDK1, and NF-κB activation of signalling components (Kwon *et al*., 2010). An extract containing 10% cinnamon deactivated 99.9% to 100% of the virus after only 10 min of intermittent mixing. These results were observed after 24 h of incubation 22-hydroxy cinnamaldehyde, derived from the bark of Cinnamon, demonstrates anti-inflammatory properties through the inhibition of nitric oxide production *via* the repression of NF-κB activation (Lee, 2015). Furthermore, the ethanolic extract of Cinnamon showcases notable anti-inflammatory effects by diminishing the activation of Src/spleen-tyrosine-kinase-mediated NF-κb. Trans-cinnamaldehyde and p-cymene is two compounds found in cinnamon extract that contribute significantly to its anti-inflammatory effects (Yu and Yang, 2012). The anti-inflammatory activity of Cinnamon is evident in its capacity to reduce the expression of inducible cyclooxygenase-2 (COX-2), inhibit nitric oxide (NO) production and synthesis (iNOS), as well as lower the levels of lipopolysaccharide-induced tumour necrosis factor-á (Hong *et al*., 2012).

5.3 *Glycyrrhiza glabra* L. (Liquorice)

Glycyrrhiza glabra L., commonly known as liquorice or licorice. The chemical composition of the plant is varied, encompassing a diverse array of compounds including sugars, polysaccharides, proteins, amino acids, minerals, resins, pectins, gums, sterols, tannins, coumarins, flavonoids, and glycosides (Wang *et al*., 2015). Notably, glycyrrhizin is responsible for its sweetness, a triterpenoid saponin, which is approximately 50 times sweeter than sucrose (Rizzato *et al*., 2017; Yu *et al*., 2015). Liquorice also comprises flavonoids that impart its characteristic yellow colour, in conjunction with numerous volatile compounds contributing to its distinct aroma. *G. glabra* showcases a wide spectrum of pharmacological actions, such as antioxidant, anti-inflammatory, antitussive, antiulcer, antimicrobial, anticarcinogenic, antimutagenic, hepatoprotective, neuroprotective, sedative, antidepressant, and antiviral effects. The antiviral properties are ascribed to two triterpenoids, glycyrrhizin, and 18α-glycyrrhetinic acid, which impede viral replication, adhesion, and penetration. Furthermore, glycyrrhizin modulates cellular signalling pathways such as protein kinase C and nuclear factor κB, thereby hindering viral dissemination. Specifically, glycyrrhizin has exhibited promise against severe acute respiratory syndrome virus (SARS) by affecting cellular signalling pathways and transcription factors crucial for viral replication, hence limiting viral transmission (Wang *et al*., 2015). glycyrrhizic acid is effective against the SARS virus. In a hamster model, prophylactic treatment with licorice showed protection against weight loss, reduced lung viral load, and improved lung pathology. It also reduced the expression of pro-inflammatory cytokines.

5.4 *Piper nigrum* L. (Black pepper)

Piper is a member of the Piperaceae family and commonly referred to as the 'monarch of condiments'. Specifically, *Piper nigrum* possesses remarkable biological characteristics, with its bioactive components being employed in various sectors such as preservation, medicine, and perfumery. Piperine, a principal alkaloid extracted from this botanical specimen, is extensively utilized in traditional medical frameworks like Ayurveda, Unani, Siddha, and Tibetan medicine (Tiwari *et al*., 2020). Research endeavours have also delved into the plausible antiviral traits of *P. nigrum*. Investigations employing chloroform and methanolic extracts against vesicular stomatitis virus (VSV) and human parainfluenza virus (HPV) discovered that the chloroform extract, containing elevated alkaloid levels, manifested superior antiviral efficacy (Priya and Saravana, 2017). Moreover, molecular docking analysis suggested that piperine effectively impedes specific viral constituents, such as the VP35 interferon inhibitory domain of the Ebola virus and methyltransferase of the Dengue virus, outperforming the conventional antiviral Ribavirin (Nag and Chowdhury, 2020). Additionally, bioactive compounds like piperidine and piperanine obtained from *P. nigrum* have exhibited promising effectiveness against COVID-19, hinting at their prospective utility as therapeutic agents against this pathogen.

Black pepper amplifies the number and efficacy of leukocytes, thereby reinforcing the organism's capacity to counteract malignant cells and intruding microorganisms. Piperine-IIa, extracted from black pepper, comprises galacturonic acid, galactose, arabinose, and rhamnose monosaccharides, as well as refined polysaccharides possessing anti-complement properties. Piperine, the principal component found in black pepper, demonstrates a substantial decrease in the synthesis of IL6 and PGE2, which are crucial proinflammatory mediators, within human fibroblast-like synoviocytes upon IL1β activation. The noteworthy reduction of PGE2 holds significance as it plays a key role in the onset of pain (Mujumdar *et al*., 1990). Furthermore, the efficacy of piperine is evident in its remarkable suppression of oedema volume escalation in carrageenan-induced experiments, underscoring its capacity to effectively target the initial phases of inflammation (Singh *et al*., 2008).

5.5 *Zingiber officinale* Roscoe (Ginger)

Zingiber officinale Roscoe, commonly known as ginger. It harbours a variety of bioactive components encompassing phenols, alkaloids, and steroids, with zingiberol standing out as the primary aromatic element derived from its rhizome. Furthermore, it comprises compounds like 4-gingerol, 6-gingerol, 8-gingerol, 10-gingerols, 6-shogaols, and 14-shogaols (Ali *et al*., 2008). The bioactive constituents have demonstrated potent inhibitory effects against various viruses, including herpes simplex virus (HSV), Chikungunya virus, Influenza virus, Human respiratory syncytial virus, and SARS-CoV-2 (Sulochana *et al*., 2020). For instance, Wahab *et al*. (2009) reported that lyophilized ginger juice exhibits antiviral efficacy against hepatitis C virus, with significant control observed at a concentration of 100 µg/ml. Additionally, Ahkam *et al*. (2020) conducted a molecular docking analysis that highlighted the potential of compounds such as gingerenone A, geraniol, gingerol, shogaol, zingiberenol, zingiberene, and zingerone in averting SARS-CoV-2 infection. These bioactive elements interact with the spike protein and main protease (Mpro) of the virus, impeding viral attachment to the ACE2 receptor and replication within the host cell. This indicates the efficacy of ginger constituents as therapeutic agents against SARS-CoV-2 (Afroz Alam and Adnan Ahmad Khan, 2022). Gingerol, the primary constituent found in ginger, has been shown to reduce the synthesis of nitric oxide (NO) by mononuclear cells in the organism, potentially by directly influencing NO production. Its mechanism involves downregulating the expression of inducible nitric oxide synthase (iNOS) and TNF-α by interfering with the NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) and protein kinase C signalling pathways (Amri and Touilboukoffa, 2016).

5.6 *Syzygium aromaticum* L. (Clove)

Syzygium aromaticum L., known as clove. Clove includes a variety of active compounds like flavonoids, hydroxybenzoic acids, hydroxycinnamic acids, and hydroxyphenylpropenes. Eugenin, a different phytochemical derived from clove, has been recognized for its antiherpes simplex virus properties. Its hindering impact on viral DNA replication is achieved by acting as a specific inhibitor of HSV-1 DNA polymerase, while eugenol restrains viral proliferation and diminishes infection, according to (Reichling *et al*., 2009). Experimental research involving clove extracts demonstrated a reduction in nitric oxide (NO) synthesis, which was linked to the antioxidant properties of clove and specific constituents present within it. The influence of clove on the production of macrophage cytokines, such as IL-6 and TNFα, is predominantly reliant on dosage and displays biphasic trends. Nevertheless, the impact on IL-12 is deemed insignificant, suggesting a limited immunomodulatory effect (Dibazar and Dineshmandi, 2015). Cloves demonstrate anti-inflammatory and immunomodulatory properties through diverse mechanisms, such as the inhibition of the NF-κB pathway, suppression of neutrophil and macrophage chemotaxis, and hindrance of prostaglandin synthesis and cyclooxygenase II enzyme expression. The presence of eugenol in cloves further enhances these effects by diminishing the production of pro-inflammatory cytokines like IL-6 and TNF-α (Han and Parker, 2017; Barboza *et al*., 2018).

5.7 *Trigonella foenu - graecum* L. (Fenugreek)

Fenugreek belongs to the Fabaceae family. The composition of its seeds comprises carbohydrates (45-60%), predominantly galactomannans, in addition to proteins, lipids, alkaloids (trigonelline, choline), polyphenols (isovitexin, rhaponticin), saponins, and essential minerals such as calcium and iron. Computational investigations involving bioactive compounds derived from fenugreek have been recognized as potential inhibitors of the main protease (Mpro) and spike (S) receptor of SARS-CoV-2. These specific proteins are known to play essential roles in facilitating the virus's entry into host cells, as well as its processes of replication and transcription. Research conducted by Sen *et al*. (2020) highlighted the notable binding affinities of quercetin and luteolin, both present in fenugreek, towards the main protease (Mpro) and spike (S) receptor of SARS-CoV-2, respectively (Sen *et al*., 2020). Fenugreek is renowned for its capacity to regulate the immune system. Research has indicated a significant augmentation in the cell quantities of the thymus, bone marrow, and spleen when fenugreek is present. When administered in lower dosages, it amplifies delayed hypersensitivity reactions, whereas, higher dosages lead to increased responses in plaque-forming cell (PFC) tests, demonstrating enhanced humoral immunity. Furthermore, fenugreek notably boosts the phagocytic capability of macrophages (Rizwanul *et al*., 2003).

5.8 *Withania somnifera* L. (Ashwagandha)

Withania somnifera, also referred to as Ashwagandha. Its primary bioactive compounds comprise withaferins, steroid lactones, and steroid alkaloids, predominantly derived from the withanolide group. One particular component, Withaferin A, emerges as a potent antiviral substance combating infectious bursal disease virus (IBDV), herpes simplex virus (HSV), HIV-1, and HPV. As a result, *W. somnifera* shows potential as an enhancer of the immune system through the augmentation of T, B, and NK cell levels while modulating Th-1/Th-2 immunity (Shi *et al*., 2016). Vetvicka and Vetvickova, (2011) emphasized the herb's capacity for immune modulation, along with its rejuvenating and revitalizing characteristics. Iuvone *et al*. (2003) made a discovery indicating that the extract of *W. somnifera* elevated the production of nitric oxide in a manner dependent on the dosage, thereby enhancing the ability of macrophages to destroy pathogens and malignant cells. The enzyme nitric oxide synthase, which plays a role in generating inflammatory molecules that impede the growth of pathogens, exhibited an increase in secretion when exposed to *W. somnifera* extract. Furthermore, certain glycosylated forms of withanolides and sito-indosides in the extract stimulated the phagocytic function, resulting in a rise in the quantity and movement of macrophages. Rasool and Varalakshmi (2009) documented that

the *W. somnifera* extract effectively suppressed the proliferation of lymphocytes induced by mitogens, as well as the complement system and reactions of delayed-type hypersensitivity.

5.9 *Ocimum tenuiflorum* L. (Holy Basil)

Ocimum tenuiflorum or *Ocimum sanctum* commonly referred to as Holy Basil or Tulsi. The phytoconstituents found in *O. Sanctum* have exhibited anti-COVID-19 properties, with a mere three out of the 46 active phytoconstituents demonstrating a favourable reaction against the virus. These active compounds consist of vicenin (a type of flavonoid), isorientin 4'-O-glucoside 2"-O-p-hydroxybenzoate (a flavone), and ursolic acid (a natural triterpene compound). In comparison to the native ligand N3 designed for the SARS-CoV-2 Mpro, these substances exhibited notable binding affinity (Shree *et al*., 2022). Specifically, Vicenin showcased the highest binding energy at 8.97 kcal/mol, engaging with specific residues through carbon and π-donor hydrogen bonding, π-sulfur bonding, and allyl interactions. Isorientin formed interactions with certain residues through positively charged hydrogen bonds and hydrophobic interactions, displaying a binding energy of 8.55 kcal/mol. Ursolic acid, with a binding energy of 8.52 kcal/mol, bonded to residues *via* alkyl and π-alkyl interactions, along with carbon-hydrogen bonding. Significantly, these compounds have demonstrated the ability to hinder the synthesis of viral proteins (Shree *et al*., 2022). The extracted essence derived from fresh leaves of *O. sanctum* has demonstrated the ability to regulate the humoral immune response in rodents by impacting immune receptivity *via* cellular mechanisms and GABAergic pathways (Kumar, 2023). In a clinical trial involving healthy participants, Tulsi was found to enhance the levels of interferon-γ, interleukin-4, T-helper cells, and Natural killer cells. The administration of Tulsi seed oil (3 ml/kg, i.p.) resulted in an increase in antisheep RBC antibody levels and a reduction in histamine levels within mast cells, indicating a modulation of the humoral immune response. When Tulsi aqueous extract was orally administered, there was a notable enhancement in antibody synthesis (Kumar, 2023).

5.10 *Tinospora cordifolia* Willd. Miers (Giloy)

Tinospora cordifolia, known as Guduchi or Giloy. The stems contain a wide array of bioactive compounds like alkaloids, diterpenoids, and glycosides. Berberine, the primary component of *T. cordifolia*, has a historical application as a natural dye and for the management of parasitic and fungal infections. Its efficacy has been observed in combating the SARS-CoV-2 virus. Similarly, other elements such as â-sitosterol, tetrahydropalmatine, octacosanol, and choline have also displayed antiviral properties against SARS-CoV-2 (Ahsan *et al*., 2023). Furthermore, berberine and β-sitosterol offer additional advantages, where berberine aids in reducing cholesterol levels and â-sitosterol exhibits anti-inflammatory characteristics. Studies involving molecular docking have indicated the potential of *T. cordifolia* to function as an inhibitor for the 3CLpro (main protease) enzymes of SARS-CoV-2 (Ahsan *et al*., 2023). Notably, constituents like berberine, β-sitosterol, octacosanol, tetrahydropalmatine, and choline show promise as inhibitors against these targets. Consequently, the extract derived from the stems of *T. cordifolia*, containing compounds like berberine and β-sitosterol, presents a viable option as an antiviral medication targeting SARS-CoV-2. This is attributed to its ability to impede 3CL protease activity, thereby regulating viral replication and propagation (Ahsan *et al*., 2023). Dhama *et al*. (2016) investigated the immunomodulatory impacts of *T. cordifolia*, commonly used as an adjunct in tumour immunotherapy. Their research revealed that palmatine, a key constituent of *T. cordifolia*, diminishes the expression of B-cell lymphoma-2, resulting in programmed cell death *via* caspase-mediated DNA fragmentation. Moreover, the octacosanol configuration of palmatine contributes to its capacity to hinder angiogenesis and the spread of cancer cells. *T. cordifolia* inhibits the activity of vascular endothelial growth factor genes by obstructing NF-κB, thus impeding the development of fresh blood vessels and offering defence against neuroblastoma. The aqueous ethanolic extract of the plant's stem exhibits anti neuroblastoma characteristics by regulating cellular proliferation indicators. Furthermore, *T. cordifolia* boosts the expression of mortalin and the RelA subunit of NF-κB, suggesting potential benefits in alcohol metabolism and liver well-being through its antioxidative and metabolic regulatory effects (Ahsan *et al*., 2023). *T. cordifolia* extract inhibits the activity of C3 convertase in the complement system, a factor implicated in the production of anaphylatoxins, therefore preventing the release of proinflammatory anaphylactic peptides. Furthermore, the extract has been shown to enhance IgG levels in a manner that correlates with the dosage administered (Ahsan *et al*., 2023).

5.11 *Achyranthes bidentata* Blume (Chaff flower)

Achyranthes bidentata Blume, also known as "Niu Xi" or "Ox Knee," is a perennial plant. The antiviral activity of sulfated *A. bidentata* polysaccharide (ABPS) is significant. The researchers explored its efficacy against the VR2332 strain of porcine reproductive and respiratory syndrome virus (PRRSV) in MARC-145 cells obtained from African green monkey kidneys. In MARC-145 cells, sulfated ABPS demonstrated significant antiviral activity, even at lower doses than unmodified ABPS (Liu *et al*., 2013). The effect of *Achyranthes bidentata* polysaccharide (ABP) on the immune system was studied in young piglets with underdeveloped immune systems. The study observed improved lymphocyte proliferation and increased levels of serum immunoglobulins (IgG, IgM, and IgA), IL-2, and IFN-γ. Furthermore, ABP treatment improved the number of peripheral T-cells and splenic lymphocytes (Chen *et al*., 2009).

5.12 *Cydonia oblonga* Mill. (Quince)

Cydonia oblonga Mill. commonly referred to as quince. It is celebrated for its strong aroma and adaptability in culinary applications, in addition to providing nutritional advantages owing to its abundant fibre, vitamin C, and antioxidant composition. *In vitro* studies revealed that phenolic compounds derived from the fruit of *C. oblonga* exhibited noteworthy antiviral properties against the influenza virus (A/PR/8/34 strain) at a concentration of 0.5 mg/ml, effectively impeding the aggregation of erythrocytes. Moreover, it was postulated that extensively polymerized procyanidins, even when not absorbed by the gastrointestinal tract, could potentially aid in the inactivation of the influenza virus in the pharynx (Yaermaimaiti *et al*., 2021). In a separate study, Yaermaimaiti *et al*. (2021) undertook a procedure to isolate bioactive constituents from the extract of *C. dichotoma* fruit, discovering seven botanical compounds with moderate antiviral efficacy against the influenza virus A/Hanfang/359/95 (H3N2), such as rosmarinic acid, balanophonin, evofolin B, and coniferyl aldehyde. Nevertheless, investigations into the antiviral properties of *C. oblonga* against SARS-CoV-2 have not yet been carried out.

5.13 *Embelia ribes* Burm. (False black pepper)

Embelia ribes Burm recognized as False Black Pepper or Vidanga. Through the presence of bioactive constituents like embelin, quercitol, and volatile oils, *E. ribes* demonstrates a diverse array of pharmacological actions, including activities such as antiparasitic, anti-inflammatory, anticancer, and antidiabetic effects. Hossan *et al.* (2018) examined the ethyl acetate extract originating from the fruits of *E. ribes* by utilizing a variety of influenza strains (H1N1, H3N2, and H5N2) within MDCK cells. The results of their study unveiled promising antiviral characteristics present in both the fruit extract of *E. ribes* and embelin, a component derived from the aforementioned fruit. The calculated selectivity index (SI) and IC_{50} values demonstrated a noteworthy potential for these extracts. More specifically, the H5N2 strain displayed an increased vulnerability to embelin, showcasing an SI of 31, while the H3N2 virus strain illustrated a higher level of resilience with an SI of 5. Inflammation encompasses the process of cleaving the transmembrane protein TNF-α *via* TNF-á converting enzyme, subsequently liberating it within the extracellular milieu. The study conducted by Dhanjal *et al.* (2014) noted a reduction in the release of TNF-α upon administration of *E. ribes*, indicating its potential as an anti-inflammatory and immunomodulatory agent.

5.14 *Justicia adhatoda* L. (Malabar nut)

Justicia adhatoda L. commonly known as Adhatoda, Malabar nut, is a botanical species affiliated with the Acanthaceae. The different constituents of the plant, encompassing leaves, roots, and flowers, are utilized in traditional herbal medicine as a consequence of their rich reservoir of bioactive elements such as alkaloids and flavonoids. Acknowledged for its bronchodilator, expectorant, and anti-inflammatory attributes, Adhatoda is extensively employed for alleviating respiratory ailments like asthma, bronchitis, coughs, and colds, with alkaloids like vasicine and vasicinone purportedly serving as the primary agents contributing to these remedial effects (Khandelwal *et al*., 2024). Chavan and Chowdhary (2014) conducted an investigation into the efficacy of methanolic leaf extract derived from *J. adhatoda* against a prevalent influenza strain in MDCK cells. The findings from their research indicated a reduction in levels of hemagglutinin (HA) as well as the replication of the virus. Thakur (2007) investigated the effects of an alcoholic extract derived from the leaves of Adhatoda on splenic lymphocytes, peritoneal macrophages, and haematological parameters in Swiss albino mice. The research noted a rise in splenic lymphocytes, blood lymphocytes, total white blood cell count, and peritoneal macrophages. Furthermore, Adhatoda displayed a protective impact against myelosuppression triggered by cyclophosphamide, resulting in a significant increase in white blood cell count. These results cumulatively propose that Adhatoda showcases immunostimulant properties (Jinyavarghese *et al*., 2005). Investigations were carried out separately on the anti-inflammatory properties of specific compounds like vasicine, vasicinone, vasicine acetate, 2-acetyl benzylamine, and vasicinolone using paw oedema models induced by carrageenan and complete freund's adjuvant (CFA). Vasicinone, when administered at a dosage of 10 mg/kg over four days post-CFA injection, displayed the highest inhibition rate (63.94%), whereas vasicine, administered at a dosage of 20 mg/kg six h following carrageenan injection, exhibited the most potent anti-inflammatory characteristics (59.51%) (Khandelwal *et al*., 2024). Vasicine, a pyrrole-quinazoline alkaloid present in the alkaloid fraction of *A. vasica* has been identified as a promising therapeutic agent against inflammation-related ailments due to its substantial occurrence in the alkaloid fraction. The alkaloid fraction exerts its anti-inflammatory effects by regulating the expression of pro-inflammatory cytokines, reducing mRNA levels, and suppressing nitric oxide production. Further investigation through scientific inquiry and clinical trials shows potential for the utilization of *A. vasica* as a beneficial anti-inflammatory treatment (Khandelwal *et al*., 2024).

5.15 *Momordica charantia* L. (Bitter gourd)

Momordica charantia L., known as bitter melon or bitter gourd. Rich in vitamins, minerals, and antioxidants, bitter melon has been widely adopted in traditional medicine systems worldwide for its well-established properties against diabetes, inflammation, microorganisms, viruses, and cancer (Mukherjee and Karati, 2023). Ethanolic extracts originating from the foliage and stems of *M. charantia* display noteworthy inhibition towards HSV-1 and SINV viruses. Of particular interest, the research posits that the antiviral efficacy is primarily attributed to photosensitizers as opposed to momordicin I or II. Furthermore, diverse proteins and steroids obtained from *M. charantia* showcase antiviral characteristics. It is noteworthy that momordicin offers direct safeguarding to infected myocardial cells from coxsackie virus (CVB3) and hinders CVB3 RNA transcription and translation (Mukherjee and Karati, 2023). Studies conducted by Chao *et al.* (2014) and colleagues delved into the potential of wild bitter gourd, a type of *M. charantia* in alleviating inflammatory reactions in mice induced with sepsis. Their findings suggested that wild bitter gourd comprises components that stimulate PPARα and PPARγ, known for their anti-inflammatory properties (Mukherjee and Karati, 2023). Examination of different parts of the gourd such as the fruit, seeds, leaves, stems, and flowers, demonstrated that the fruit segment displayed significant suppression of inflammatory agents like PGE2 and nitric oxide. The main focus of this investigation was to assess the anti-inflammatory attributes of wild bitter gourd fruit utilizing animal models of inflammation (Mukherjee and Karati, 2023).

5.16 *Allium sativum* L. (Garlic)

Garlic scientifically known as *Allium sativum*. The garlic essential oil is known for its antiviral features, but there has been limited study in this area. Ajoene and allicin, two major compounds present in garlic, have strong antiviral properties against Herpes simplex virus types 1 and 3, as well as Para influenza virus. Ajoene's antiviral action involves decreasing adhesive contact and leukocyte fusion, whereas allicin inhibits a variety of thiol enzymes. Garlic essential oil has shown promise in combating viruses by eliminating their surface receptors and disrupting their genetic material through processes such as RT-PCR and hemagglutination (Okoro *et al*., 2023). The anti-inflammatory activities of aged black garlic (ABG) were related to a direct decrease in toll-like receptor 4 (TLR4) signalling activation inside macrophages, which was accompanied by decreased nuclear NF-κB levels and increased cytoplasmic NF-κB and I-B levels in LPS-activated RAW264.7 cells (Okoro *et al*., 2023). The application of garlic essential oil to stress-free mice increased leukocyte and erythrocyte counts, perhaps improving immunological function. Garlic essential oil reduced inflammation caused by sodium hydroxide in rats by lowering TNF-α levels. A single application of garlic essential oil lowered pro-inflammatory cytokines IFN-γ and TNF-α in mice on a high-fat diet (HFD). Furthermore, treatment with garlic powder reduced oxidative damage, inflammation, and obesity-induced

apoptosis in the testicular tissues of obese rats, while simultaneously improving testosterone levels (Okoro *et al*., 2023).

6. AYUSH recommended formulations

The AYUSH system, which includes Ayurveda, Yoga, Unani, Siddha, and Homeopathy, encompasses a range of recommended formulations and constituents with traditional applications for wellness and disease prevention. The following are examples of commonly recommended formulations, along with their constituent substances (Figure 4).

6.1 AYUSH kwath

Ayush kwath is an Ayurvedic combination that includes four medicinal plants: *Ocimum sanctum* Linn., *Cinnamomum zeylanicum* Breyn., *Zingiber officinale* Rosc., and *Piper nigrum* Linn. This formulation is known for its potent antiviral, thrombolytic, anti-inflammatory, and immune-modulatory effects. As a result, the Indian government has approved it as an immune-enhancing supplement to battle COVID-19 (Gautam *et al*., 2022).

6.2 Samshamani vati

Guduchi Ghana vati, also known as Samshamani vati, is used to treat fevers. Its formulation includes an aqueous extract of *Tinospora cordifolia*, which is known for its immunomodulatory effects and efficacy in viral infections. The combination of *Alstonia scholaris*, *Picchoriza, Swertia chirayita*, and *Caesalpinia crista* is useful in treating asthma and stimulating the immune system.

6.3 AYUSH-64

AYUSH-64 constitutes a tablet formulation containing *Picrorhiza kurroa* (rhizomes), *Swertia chirayita* (whole plant), *Alstonia scholaris* (bark), and *Caesalpinia crista* (seed pulp). These components are recognized for their antiviral, antiasthmatic, immune-enhancing, and antimalarial characteristics. Owing to its antimalarial properties, AYUSH-64 is proposed to exhibit efficacy in populations with a high susceptibility to coronavirus infection. Consequently, the AYUSH endorses the utilization of this tablet for individuals afflicted with COVID-19, with a prescribed intake of two 500 mg tablets twice daily for 30 days in lukewarm water for asymptomatic cases, and two 500 mg tablets thrice daily for 30 days in lukewarm water for mild COVID-19-positive patients (Sruthi *et al*., 2023).

6.4 Agasthya hareetaki

Agasthya hareetaki, recognized as Avaleha kalpana in the field of Ayurveda, is a concoction composed of more than 15 botanical components, such as *Inula racemosa*, *Piper longum*, *Piper chaba*, *Mucuna prurita*, *Sida cordifolia*, among others. This particular herbal blend has been traditionally utilized for the treatment of respiratory infections. Owing to the diverse advantageous attributes of its constituents, which encompass antiasthmatic, antioxidant, anti-inflammatory, antiviral, and immunomodulatory properties, it is advised for the alleviation of symptoms associated with COVID-19. AYUSH recommends a daily intake of 5 g of Agasthya hareetaki, to be consumed twice a day along with lukewarm water, for the management of COVID-19 manifestation (Sruthi *et al*., 2023).

6.5 Anuthalia

Anuthaila is a compound of about 25 herbs in Ayurvedic oil preparation, which includes *Aquilaria agallocha* (heartwood), *Aegle marmelos* (root), *Berberis aristata* (stem), *Asparagus racemosus* (root), *Cedrus deodara* (heartwood), *Cinnamomum zeylanicum* (stem bark), *Cinnamomum tamala* (leaf), *Coleus vettiveroides* (root), *Cyperus rotundus* (rhizome), *Desmodium gangeticum* (whole plant), *Cyperus scariosus* (rhizome), *Embelia ribes* (fruits), *Elettaria cardamomum* (seed), *Glycyrrhiza glabra* (root), *Hemidesmus indicus* (root), Nelumbo nucifera (flower), *Leptadenia reticulata* (root), *Nymphaea stellata* (flower), *Santalum album* (heartwood), *Pluchea lanceolata* (root), *Solanum indicum* (whole plant), *Uraria Picta* (whole plant), *Solanum surattense* (whole plant), *Vetiveria zizanioides* (root), *Sesamum indicum* (oil), and *Vitex negundo* (seed). The efficacy of *L. reticulata* and *S. indicum* against conditions such as asthma, bronchitis, cough, and respiratory infections validates the use of Anuthaila for COVID-19. Moreover, Anuthaila has a historical application in nasya therapy for addressing concerns like skin dryness, hair graying, and muscle disorders in the cervical region. AYUSH suggests the daily administration of two drops of Anuthaila into each nostril to manage symptoms associated with COVID-19 (Sruthi *et al*., 2023).

6.6 Chyawanprash

Chyawanprash, an Ayurvedic nutritional supplement, comprises concentrated essences of botanicals and minerals, featuring Amla fruit as its primary component, well-known for its revitalizing properties aimed at enhancing physical strength, endurance, and overall vigour. Various scientific investigations have underscored the diverse health benefits associated with Chyawanprash, including its antioxidant, antibacterial, antiviral, anti-inflammatory, antiallergic, and antithrombotic attributes (Sharma *et al*., 2019). Research indicates its potential to act synergistically with antitubercular medications in managing pulmonary tuberculosis while also potentially mitigating allergic reactions through the reduction of plasma histamine levels and IgE release. Furthermore, Chyawanprash has exhibited the capacity to enhance NK cell function, elevate immune system markers, and enhance phagocytic activity, thereby displaying its immunomodulatory effects (Sharma *et al*., 2019).

6.7 Triphala

Triphala, a widely recognized herbal formulation in Ayurveda, is composed of equal proportions of *Phyllanthus emblica* L., *Terminalia bellerica* (Gaertn.) Roxb., and *Terminalia chebula* Retz, typically consumed in powdered form for gastrointestinal and invigorating purposes. It encompasses a wide array of medicinal attributes, such as antioxidative, anti-inflammatory, antineoplastic, antimicrobial, and antidiabetic effects. Studies have revealed that the alcoholic extract of Triphala exhibits distinct antimicrobial properties and comprehensive efficacy against bacteria that are resistant to antibiotics. Moreover, Triphala extract has shown effectiveness in ameliorating arthritic and inflammatory conditions by diminishing the expression of inflammatory mediators through the inhibition of NF-κB. It also inhibits the generation of inflammatory mediators and intracellular free radicals in activated macrophages, thus ameliorating inflammation and oxidative stress while boosting cell-mediated immune responses. Clinical research has indicated the capability of Triphala to enhance T cells and NK cell activation, although levels of cytokines remain unaltered. Furthermore, the individual constituents of Triphala demonstrate immunomodulatory characteristics. In conclusion, Triphala emerges as a potent herbal concoction with a variety of therapeutic advantages (Kushwaha *et al*., 2023).

7. Unani approaches

7.1 Triyaq-e-Araba

Triyaq-e-Araba is an important Unani formulation used for detoxification. It contains *Laurus nobilis* L. berries, *Bergenia ciliate* (Haw.) Sternb. stem, *Aristolochia indica* L. roots, and *Commiphora myrrha* (Nees) Engl. Several investigations have demonstrated its effective antiviral effects, including efficacy against SARS-CoV. Bergenia ciliate has been demonstrated to be effective against influenza virus-A and herpes simplex virus-1 (HSV-1), with its active component, bergenin, also being effective against hepatitis C virus and HIV. Based on these findings, Triyaq-e-Araba has the potential to be an effective antiviral drug, suggesting that it could be used to treat COVID-19 (Ahmad *et al*., 2018).

7.2 Roghan-e-Baboona

Roghan-e-Baboona is a Unani remedy with antiasthmatic properties and is used to treat inflammatory diseases. The main constituent is obtained from *Matricaria chamomilla* L. This mixture, which contains *M. chamomilla* flowers, has shown effective in treating acute viral nasopharyngitis and sore throat (Srivastava *et al*., 2010).

7.3 Arq-e-Ajeeb

Arq-e-Ajeeb is a liquid composition that contains thymol, menthol, and camphor. Thymol has shown potential as a topical antiviral treatment for herpes infections, and menthol is known for its anti-inflammatory effects. Arq-e-Ajeeb has historically been used successfully by Unani practitioners to treat Nazla wabai (Swine flu), suggesting that it could be used to treat COVID-19 based on these findings (Sharifi-Rad *et al*., 2017).

7.4 Khamira-e-Banafsha

Khamira-e-Banafsha is a semi-solid Unani formulation made by infusing *Viola odorata* L. flowers into the base of sugar or honey. It is traditionally used to treat respiratory diseases like as colds, coughs, bronchitis, and fevers, acting as an expectorant and antipyretic. According to studies, *V. odorata* can lower viral load and improve the efficacy of antiretroviral medicines, as well as potentially improve lung health by reducing alveolar wall thickness and bleeding. Based on this evidence, Khamira-e-Banafsha may be used to treat COVID-19 symptoms (Gerlach *et al*., 2019).

7.5 Laooq-e-Sapistan

Laooq-e-Sapistan, is a renowned sugar-based Unani formulation extensively used in India. Its main constituent, the jelly-like mass of mature fruit from *Cordia myxa* L., is known for its antiviral and antitussive properties. Ziziphus fruit contains betulinic acid, which has been demonstrated to enhance immunity by down-regulating IFN-ã levels, making it a possible treatment agent for viral infections. Furthermore, another component, *Viola odorata* L., has been shown to lower viral loads. These data suggest that Laooq-e-Sapistan could be useful in treating COVID-19 symptoms, according to AYUSH formulations (Gerlach *et al*., 2019).

7.6 Sharbat-e-Sadar

Sharbat-e-Sadar, is an Unani syrup formulation, that is widely used to treat common colds, coughs, and respiratory diseases. *Trachyspermum ammi* (L.) Sprague, a key constituent, has been demonstrated to neutralize Japanese encephalitis virus antibodies while also stimulating B-cell proliferation *via* a glycoprotein component. *Adhatoda vasica* Nees inhibits HIV-Protease, but *Bombyx mori* enhances immunological responses to viral infections. Additional ingredients include *Glycyrrhiza glabra* L., *Ficus carica* L., *Onosma bracteatum* Wall, and *Ziziphus jujuba* Mill. also have antiviral and immunomodulatory effects (Lü *et al*., 2018).

7.7 Khameera marwareed

Khameera marwareed is a semi-solid Unani formulation composed of compounds and sugar, utilized as an immunomodulator. Studies suggest that it enhances the immune system by promoting a T helper 1 (Th1) type cytokine response, thereby equipping the body to better combat viral infections. Additionally, its constituents exhibit potent antiviral effects by inhibiting viral replication (Khan *et al*., 2009).

7.8 Asgandh safoof

Asgand, scientifically known as *Withania somnifera* (L.) Dunal, is a widely recognized medicinal plant in India. In the Unani system of medicine, its root powder is utilized as an immunomodulator. Studies indicate that extracts from its roots notably increase the counts of CD4+ and CD8+ cells, as well as enhance blood parameters like white blood cell (WBC) and platelet counts. Furthermore, research suggests that aqueous suspensions of Asgand possess significant inhibitory activity against the proliferative response of T-lymphocytes induced by mitogens. Additionally, it has been observed to disrupt connections between the viral S-protein receptor binding domain and the host ACE2 receptor, potentially preventing the entry of SARS-CoV-2. This evidence supports the potential preventive use of Asgand safoof against COVID-19 (Balkrishna *et al*., 2020).

7.9 Habb-e-Bukhar

Habb-e-Bukhar, a polyherbal tablet formulation within the Unani system of medicine, is traditionally used for conditions like elephantiasis and malarial fever. Its primary ingredient, cinchona bark, contains quinine, which has garnered interest in some countries as an experimental treatment or potential drug for COVID-19. Additionally, *Tinospora cordifolia* (Willd.) Miers, another component of Habb-e-Bukhar, has been noted for its potent antiviral effects against HSV and its suggested immune-enhancing properties. Thus, existing literature supports the potential use of Habb-e-Bukhar in the management of COVID-19 (Devaux *et al*., 2020).

7.10 Sharbat-e-Toot Siyah

Sharbat-e-Toot Siyah comprises *Morus nigra* L. juice blended with a sugar base, commonly employed to address tonsillitis and sore throat. Studies indicate its anti-inflammatory and analgesic properties, along with its ability to inhibit pro-inflammatory cytokines. Recent findings suggest that it enhances immunomodulatory activity (Lim and Choi, 2019).

7.11 Laook-e-Katan

Laook-e-Katan is a semi-solid Unani formulation made from *Linum usitatissimum* L. seeds and sugar. These seeds are rich in alpha-linolenic acid and are known for their antiviral, anti-inflammatory, and immunomodulatory properties (Miccadei *et al*., 2016).

8. Siddha approaches

8.1 Adathodai manapagu

Adathodai manapagu comprises leaves of *Adathoda vasica*, containing abundant alkaloids like vasicine, a prevalent active constituent in various cough remedies. Throughout centuries, this botanical has been employed in Ayurveda for addressing respiratory disorders. Additionally, its extract is recognized for enhancing the immune system's reactivity (Sruthi *et al*., 2023).

8.2 Kabasura kudineer

Kabasura kudineer, a Siddha formulation, exhibits efficacy in addressing common respiratory conditions such as influenza and the common cold. Furthermore, kabasura kudineer is recommended by Siddha experts for addressing fever, intense phlegm, and dry cough. This formulation comprises 15 herbal components, including *Zingiber officinale* (rhizome), *Syzygium aromaticum* (flower bud), *Piper longum* (fruit), *Tragia involucrate* (root), *Hygrophila auriculata* (root), *Anacyclus pyrethrum* (root), *Terminalia chebula* (fruit rind), *Coleus aromaticus* (leaf), *Justicia adhatoda* (leaf), *Costus speciosus* (root), *Clerodendron serratum* (root), *Tinospora cordifolia* (stem), *Andrographis paniculata* (whole plant), *Cyperus rotundus* (root tuber), and *Sida acuta* (root). These constituents play a distinct role in managing respiratory tract infections, allergies, and viruses, while also possessing immunomodulatory properties. Consequently, the Ministry of AYUSH has recommended the utilization of kabasura kudineer for alleviating symptoms associated with COVID-19. AYUSH has also proposed the use of nilavembu kudineer and kaba sura kudineer as antiviral agents (60 ml, twice daily after meals), along with adathodai manapagu (10-20 ml with warm water, twice daily after meals) for addressing COVID-19 symptoms in adults (Sruthi *et al*., 2023).

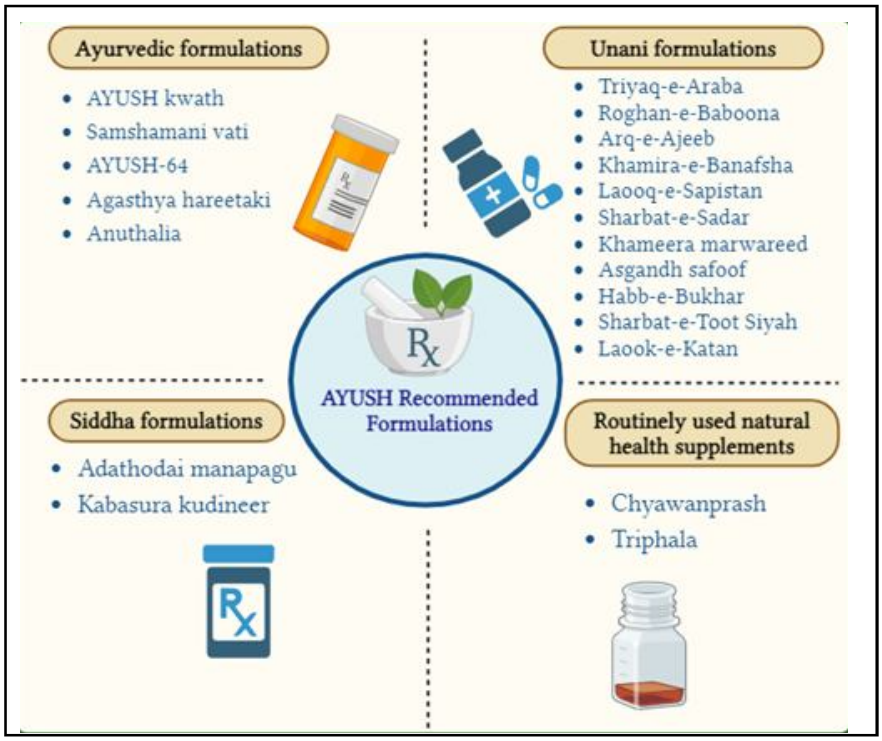

Figure 4: AYUSH formulations.

9. Routinely used medicinal plants

9.1 *Curcumin longa* L. (Turmeric)

The aqueous solution derived from *Curcuma longa* displayed encouraging immunomodulatory effects in an animal model with cyclophosphamide-induced immunosuppression, leading to a decrease in spleen mass and changes in haematological indicators. These findings indicate the potential of turmeric as an immunomodulating agent. Moreover, the turmeric solution exhibited antiviral properties against the dengue virus and H5N1, resulting in reduced viral levels in both experimental and animal trials (Sornpet *et al*., 2017). Additionally, the turmeric solution showed antiallergic effects by modulating Th1/Th2 cells and decreasing levels of allergy-related cytokines and immunoglobulins, suggesting its potential in treating conditions such as asthma and food allergies. Several studies have also emphasized the anti-inflammatory effects of turmeric, whether administered alone or in conjunction with other substances (Lee *et al*., 2020).

9.2 *Linum usitatissimum* L. (Flax seed)

The heteropolysaccharide derived from the hull of flax seeds exhibits immunomodulatory properties and potential as a therapeutic agent against the hepatitis B virus. It boosts the expression of TNF-α, NO, and IL mRNA, thereby triggering immune reactions in murine macrophages, and concurrently shows antiviral effects by obstructing hepatitis B virus antigens and impeding DNA replication. Moreover, it holds potential as an immunostimulant and an adjuvant for vaccines (Liang *et al*., 2019). In the realm of insulin resistance linked to obesity, it showcases anti-inflammatory and immunomodulatory characteristics, particularly through the reduction of TNF-α level.

Additionally, components of flax seeds amplify Th2-related cytokines and the levels of serum anti-ova IgG1 and IgE, while diminishing Th1-related cytokines and anti-ova IgG levels, suggesting comprehensive immunomodulatory effects. The phenolic elements found in flax seeds also exhibit immunomodulatory properties, notably through the suppression of cell-mediated immune responses (Palla *et al*., 2015).

9.3 *Nigella sativa* L. (Black cumin)

Bioactive compounds derived from *Nigella sativa* L. have exhibited promise as inhibitors of COVID-19 in computational molecular studies. Notably, nigellidine and á-hederin have displayed considerable affinity at the active sites linked to the virus, surpassing the efficacy of conventional medications such as chloroquine, hydroxychloroquine, and favipiravir (Salim and Noureddine, 2020). Furthermore, the ethanol-based seed extract demonstrates dual functionality by suppressing immune response to phytohemagglutinin and enhancing immune response in non-phytohemagglutinin-stimulated cell proliferation. Additionally, the thymoquinone-enriched oil obtained from *N. sativa* has demonstrated the ability to inhibit cytokine signalling molecules and prostaglandin E2 (PGE2) production in T-lymphocytes, while simultaneously promoting PGE2 release in adrenocarcinomic human alveolar basal epithelial A549 cells (Koshak *et al*., 2018).

9.4 *Phyllanthus emblica* L. (Amla)

Amla has proven effective in mitigating chromium-induced immunosuppression, resulting in the restoration of lymphocyte proliferation and the synthesis of crucial immune signaling molecules like IL-2 and INFγ. The phenolic compounds derived from emblica have been identified as promoters of splenocyte proliferation, with specific compounds such as geraniin and isocorilagin displaying significant immunostimulatory properties (Liu *et al*., 2012). Moreover, ethanolic extracts of amla demonstrate strong anti-inflammatory characteristics through the reduction of pro-inflammatory cytokine levels and the elevation of anti-inflammatory cytokines. Furthermore, a compound isolated from emblica, namely 1,2,4,6-tetra-O-galloyl-β-d-glucose, has exhibited antiviral activity against HSV by deactivating HSV-1, consequently impeding early viral infection mechanisms like attachment, penetration, intracellular multiplication, and gene expression n (Xiang *et al*., 2011).

10. Clinical outcomes, treatment, and prevention of COVID-19 from the medicinal herbal formulations

Although specific herbal treatments have been traditionally employed for handling respiratory ailments and boosting immune responses, their immediate effectiveness against COVID-19 remains subject to scrutiny (Table 2 and Figure 5). There is persistent curiosity and examination in this domain; however, definite proof concerning the efficacy of herbal compounds against COVID-19 is still pending.

Table 2: Data regarding completed clinical trials on AYUSH drugs for COVID-19

(Source: www.ctri.nic.in; www.clinicaltrails.com).

Clinical trial number	Study design	Study title	Outcomes
CTRI/2020/04/024883 ZINGIVIR-H	Interventional (Other) completed	'Clinical research on the safety and efficacy of ZingiVir-H as an add-on therapy in COVID-19 patients'	Administration of ZingiVir-H in conjunction with conventional treatment among verified COVID-19 individuals led to notably enhanced rates of recovery when juxtaposed with those who were administered a placebo.
CTRI/2020/05/ 025161/Herbal formulation-Aayudh advance	Interventional (randomized, parallel-group, active-controlled trial) completed.	To study the effectiveness of herbal formulation - Aayudh advance as a supplementary treatment for the coronavirus 2019 (COVID-19) infected patients'	When co-administered with conventional treatment, the safety profile of "Aayudh advance" was established to be impeccable, devoid of any discernible pharmacolo-gical interactions. It exhibited effectiveness as a virucidal agent, leading to a decrease in viral burden, and a boost in recuperation rates in comparison to solely employing standard care in COVID-19 patients with mild symptoms.
CTRI/2020/05/ 025215/Kabasura kudineer	Interventional (randomized, parallel-group Trial) completed.	'Effectiveness of Siddha medicine, kabasura kudineer, and vitamin C-zinc supplementation in the management of mild COVID-19 patients'	The efficacy of co-administering vitamin C and zinc in the treatment of COVID-19 is currently not well established. Therefore, a research investigation will be conducted to examine the relative effectiveness of this combination in promoting the reversal of SARS-CoV-2 infection when compared to kabasura kudineer.
CTRI/2020/05/ 025275/Ayurveda Rasayana along with conventional guidelines for health care workers	Interventional (randomized, parallel-group Trial) completed.	'Role of chyawanprash in the Prevention of COVID-19 in healthcare workers'	The study did not identify any adverse effects.

CTRI/2020/05/025276/ Ayurveda protocol	Interventional (single arm Trial) completed.	'Effect of ayurvedic intervention in COVID-19 positive cases'	The therapeutic protocol in Ayurveda, which includes Sanshamani, Nagaradi Kwath, Amalaki Churna, and golden milk, resulted in an improvement in the patient's physical vigor.
CTRI/2020/05/025397/ Purified aqueous extract of cocculus hirsutus (AQCH)	Interventional (randomized, parallel-group Trial) completed.	'A study to evaluate the effect and safety of a phyto-pharmaceutical drug in the treatment of coronavirus infection'	Patients with COVID-19 demonstrated advancements in their clinical condition corresponding to the gravity of the illness.
CTRI/2020/05/025425/ Chayapanprash (an ayurvedic herbal preparation)	Interventional (single arm trial) completed.	Ayurvedic intervention (chyawanprash) in the prevention of the COVID-19 pandemic among healthcare personnel.	This solution was recognized as a potential safe preventive measure for COVID-19.
CTRI/2020/06/025527/ Amrta karuna syrup	Interventional (randomized, parallel-group, active-controlled trial) closed to recruitment	'Clinical trial on immunity and antiviral for quarantine patients of COVID-19'	The formulation was discovered to possess immunomodulatory properties.
CTRI/2020/06/025556/ Virulina→ along with standard treatment protocol	Interventional (randomized, parallel-group, placebo-controlled Trial) completed.	'A clinical trial to know the effect of Virulina® along with standard treatment in COVID-19-positive patients'	The formulation was observed to enhance patients' immunity and alleviate symptoms.
CTRI/2020/06/025590/ Astha 15 capsule	Interventional (randomized, parallel-group, placebo-controlled trial) completed.	'A clinical trial to evaluate the safety and efficacy of polyherbal capsule Astha-15 used as an add-on therapy with standard care of therapy as an immunity booster in the suspected and COVID-19-diagnosed patients'	An improved rate of recovery was noted.
CTRI/2020/06/025592/ Immunity kit	Interventional (single arm Trial) completed.	'Use of herbal medicine like tulsi, amruth (giloy), turmeric, and ashwagandha as add-on treatment in COVID-19 patients'	After incorporating the Ayurvedic formulation as an additional treatment, there was an enhanced recovery observed in terms of COVID-19 patients' signs and symptoms.
CTRI/2020/06/026221/ Arogya Kashayam-20	Interventional (randomized, parallel-group, active-controlled trial) completed.	'Intervention of ayurvedic medicine (arogya kashayam) in COVID-19 -positive cases (asymptomatic and mild symptomatic)'	The Unani regimen was deemed effective in addressing the mild symptoms of COVID-19.
CTRI/2020/06/026227/ Khameera marwareed Tiryaq-e-Arba Unani joshanda/ decoction behidana (Cydonia oblonga) 3 gm, unnab (Zizyphus jujube) 5 in number, sapistan (Cordia myxa) 9 in numbers	Interventional (non-randomized, multiple arm trial) completed.	'A study on unani regimen for prevention of high/ moderate risk population of COVID-19'	Enhancement was observed in the immune status of COVID-19 patients.
CTRI/2020/06/025801/ Tab. Bresol and tab. Septilin	Interventional (randomized, parallel-group, active-controlled trial) completed.	'Role of herbal immunomodulators in mild COVID-19 confirmed cases'	The utilization of herbal immunomodulators as supplementary treatment resulted in an enhanced recovery rate among COVID-19 patients.
CTRI/2020/07/026337/ Add-on personalized Ayurveda intervention to ICMR guideline on Covid-19	Interventional (randomized, parallel-group trial) completed.	'The COVID-19 study with Ayurveda add-on to ICMR guideline'	The effectiveness of the treatment was assessed by determining the average duration of patients' hospital stays until they tested negative for COVID.

CTRI/2020/07/026371/1. Kabasura kudineer 2. Shakti drops 3.Turmeric plus tablets	Interventional (Others) completed.	'Kabasura kudineer, shakti drops, and turmeric plus in the management of COVID-19'	The addition of Ayurvedic medicines led to an improved recovery rate regarding the signs and symptoms of stage 1 and 2 COVID-19 cases, thus enhancing the quality of life for these patients.
CTRI/2020/07/026433/1. Dashamula kwatha and pathyadi kwatha with trikatu churna 2. Sansamani vati 3. AYUSH 64 4. Yastimadhu Ghanavati	Interventional (randomized, parallel group, active controlled trial) completed.	'Effect of ayurveda medicine in COVID-19 mild symptoms'	There were no adverse reactions observed, and signs and symptoms showed improvement.
CTRI/2020/07/026570/ Cap. IP	Interventional (randomized, parallel group trial) completed.	'Safety and efficacy of ayurvedic capsule in mild to moderate	COVID-19 infection' Enhancement was noted in the respiratory symptoms of COVID patients.

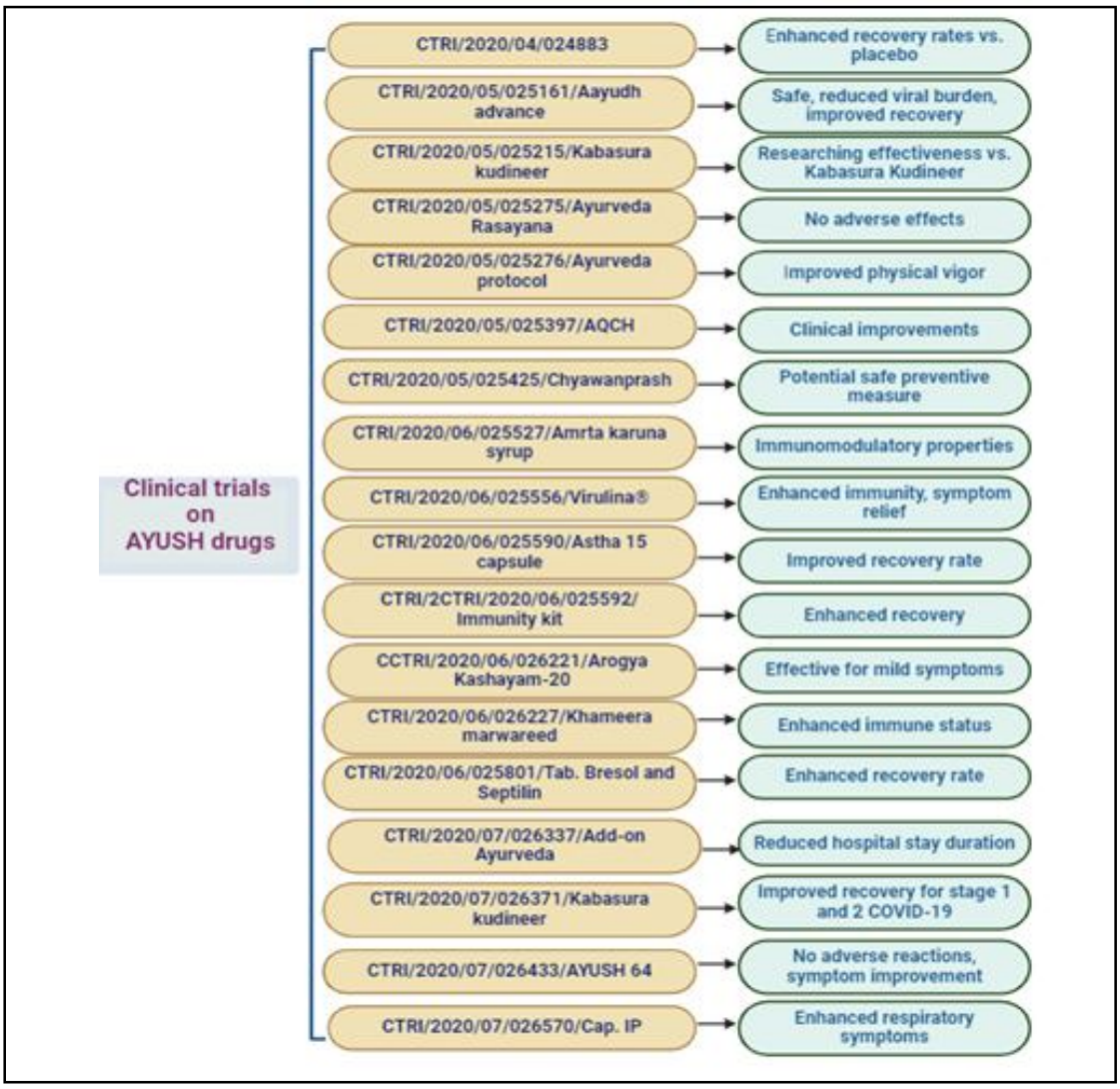

Figure 5: Clinical trials on AYUSH drugs for COVID-19 and their outcomes.

11. Regulatory challenges and the integration of traditional medicine into mainstream healthcare

India has a rich tradition of Ayurveda, Unani, and other traditional systems of medicine. These systems have been effectively incorporated into the healthcare system. Ayurvedic hospitals and clinics coexist alongside modern medical facilities. Patients can choose between conventional treatments and Ayurvedic therapies. India has established research institutes dedicated to studying traditional medicine. These institutes contribute to evidence-based practices and promote integration (Table 3).

Table 3: Regulatory challenges and the integration of traditional medicine into mainstream healthcare

Regulatory framework	Opportunities	Challenges	References
Research and evidence	Traditional medicine offers a rich repository of knowledge about plant-based remedies, herbal formulations, and holistic approaches. Integrating this knowledge can enhance healthcare outcomes.	The lack of standardized training, quality control mechanisms, and evidence-based practices pose barriers to the integration of traditional medicine into mainstream healthcare.	Michael *et al.*, 2024
Regulation and training	Establishing clear regulations for traditional medicine practitioners ensures safety, quality, and accountability. Training programs can bridge the gap between traditional and modern healthcare practices.	Balancing the need for regulation with the diverse nature of traditional healing practices is complex. Differentiating between formal and informal practices is essential.	von Schoen-Angerer *et al.*, 2023
Awareness and collaboration	Raising awareness among healthcare providers and the public about the benefits of traditional medicine fosters acceptance and collaboration.	Power struggles between traditional and orthodox health practitioners can hinder effective integration. Building inter professional collaboration is crucial.	Michael *et al.*, 2024
Risk-based regulation	A risk-based regulatory approach can address the full range of traditional, complementary, and integrative healthcare (TCIH) products. It ensures safety while allowing flexibility.	Determining risk levels for different TCIH products and providing clear guidance require careful consideration by health authorities.	von Schoen-Angerer *et al.*, 2023
Global perspective	The WHO Traditional Medicine Strategy aims to integrate traditional medicine into global healthcare systems. Collaboration among stakeholders can drive progress.	Striking a balance between cultural diversity and evidence-based practices remains a challenge. Advocacy for TCIH research and funding is essential.	von Schoen-Angerer *et al.*, 2023

12. Future prospects

12.1 Plant-based vaccines

Recombinant plant-based vaccines

Researchers are investigating the use of plant-based platforms to produce vaccines. For example, the CoVLP vaccine, which is produced in plants and displays the prefusion spike glycoprotein of the original strain of SARS-CoV-2, has shown promising results. CoVLP, combined with an adjuvant (Adjuvant system 03 [AS03]), demonstrated efficacy in preventing symptomatic COVID-19.

Expanding vaccine options

As more plant-based vaccines undergo clinical trials, additional options for COVID-19 vaccination may be explored.

12.2 Traditional herbal medicines

Anti-COVID-19 trials

Several clinical trials are evaluating traditional herbal medicines for their potential as anti-COVID-19 agents. While not all trials have been completed, ongoing research aims to validate the efficacy of plant-based remedies.

Bioactive metabolites

Researchers are exploring bioactive metabolites derived from plants. These compounds may have antiviral, anti-inflammatory, and immunomodulatory properties relevant to COVID-19 management.

12.3 Quality and safety data

Completeness of data

Incorporating quality and safety data into human trials is crucial. Researchers need comprehensive information on the safety profiles of plant-based formulations.

Authentication and standardization

Efforts are ongoing to authenticate and standardize plant materials used in clinical studies. Ensuring consistency and quality is essential.

12.4 Systems biology and computational tools

Target identification

Advances in systems biology and computational tools aid in identifying drug targets should be worked out. Researchers analyze complex interactions between plant compounds and human pathways.

Polypharmacology

The shift from "one-disease, one-target" to polypharmacology recognizes that natural products can interact with multiple human physiology targets.

12.5 Nanoformulations of phytochemicals

Researchers are exploring nanoformulations of phytochemicals. These optimized delivery methods enhance efficacy and safety, potentially improving treatment outcomes.

12.6 COVID-19 research

Clinical studies continue to investigate the efficacy and safety of traditional medicines, isolated compounds, functional foods, nutraceuticals, and herbal preparations against SARS-CoV-2. These studies include plant-based products used in Chinese medicine and Ayurveda.

13. Conclusion

The absence of authorized vaccines or pharmaceuticals for the treatment of SARS-CoV-2 presents a substantial peril to the

worldwide populace. In light of the documented immunomodulatory and anti-inflammatory attributes of numerous botanicals in combatting viral infections, such as COVID-19, it is crucial to subject them to rigorous testing. Traditional medicines exhibit potential owing to their longstanding utilization, ancient citations, and scientific validation concerning their safety and effectiveness. The AYUSH Ministry of India has consistently advocated for the exploration of herbal remedies for COVID-19, underpinned by evidence of their immune-boosting, anti-inflammatory, and antiviral properties. While awaiting the validation of pharmaceuticals or vaccines through clinical trials, these herbal treatments could potentially provide some alleviation. Notably, a significant proportion of financial resources for clinical trials are allocated to AYUSH interventions, with a focus on disseminating findings to guide policy development and facilitate global scientific partnerships. Research institutions are urged to give priority to the investigation into medicinal plant species for potential lead molecule development against SARS-CoV-2 and COVID-19. It's crucial for herbal drug manufacturers and research institutions, both nationally and globally, to strategize for further preclinical and clinical research on these promising therapeutic avenues.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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