Phytomolecules and Novel Drug Delivery Approach for COVID-19

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Abstract Coronavirus disease 2019 (COVID-19) has been a recent pandemic where very rarely few therapeutic modalities are effective in the treatment and management of the complications. Some of the pharmacological treatment approaches still in use include hydroxychloroquine/chloroquine, repurposed antiviral medications, monoclonal antibodies or IL-6 pathway inhibitors, corticosteroids, convalescent plasma, and cell and biological therapy. It has been shown that type I and type II interferons have antiviral action, and it is thought that the human immune system contributes significantly to the viral eradication process.

Numerous herbal drugs such as tulsi, ginger, clove, dalchini, garlic, ashwagandha, giloy, black pepper, black cumin, amla, turmeric, and garlic have been cited in Ayurvedic texts for their diversified use as anti-inflammatory, antioxidant, and immunomodulatory agents. Many herbs and natural phytoconstituents are efficient home remedies for COVID-19 therapy for quick recovery and immune modulators as a preventive measure. In this chapter, we've discussed the value of natural substances in the treatment of COVID-19 as well as contemporary integrated pharmaceutical therapies that use herbal formulations and their clinical results. So many studies have been done in recent years to demonstrate the antiviral efficacies of medicinal plant extracts and secondary metabolites. We discussed the safety and effectiveness of phytomolecules, conventional medication's quality problems, and analytical challenges with a new delivery approach combined with polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. It also emphasizes

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the use of newly developed drug delivery systems of already developed therapeutic agents to address the gaps left by latent targeted administration.

Keywords COVID-19 · Phytoconstituents · Antiviral · Herbal drugs · Giloy · Ashwagandha

1 Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified in December 2019 at Wuhan, China [1]. In India, 43 million confirmed cases and 516.3 lakhs deaths have been reported till March 2022 [2].

The structural contribution of SARS-CoV-2 is an enveloped β-coronavirus with a large positive-sense, single-stranded RNA genome ranging from 26 to 32 kb in size. The four secondary components present in the virus are the spike (S) protein, envelope (E), membrane (M) protein, and nucleocapsid (N) protein. The spike protein interacts with the host cell membrane, allowing the virus to enter despite the infections [3, 4]. Angiotensin-converting enzyme 2 (ACE2) is among the potential target receptors for SARS-CoV-2 in the human body. It is distributed in various tissues such as the heart, gastrointestinal tract, vessel, intestine, liver, kidney, spleen, and skin [5, 6]. This could contribute to the possible involvement of numerous human organs in the short and long term. It was also a challenge to battle the newly evolving viruses and its variants. Viral RNA polymerase has a high risk of mutation due to the lack of capacity to proofread [7], and this function helps RNA-genome viruses establish resistance to existing antiviral drugs [8]. COVID-19 has a high replication rate because the RNA-dependent polymerase RNA (RdRP) jumps and continuously generates transcription errors [9]. Because of its high levels of mutation, COVID-19 is zoonotic pathogens that can infect different humans and animals, resulting in a broad variety of clinical characteristics ranging from acute to multi-organ failure [10, 11]. Currently, there are no appropriate therapeutic approaches available for treating COVID-19 infection, and there is an inadequate amount of research reported in this field. Non-corona viral therapies attack either the human cells or the virus themselves. Human immune system is considered to play a major role in destroying the virus and research has shown that the type I and type II interferon antiviral efficacy. Interferon-beta (IFN-β) has been proven to decrease Middle East respiratory syndrome coronavirus (MERS-CoV) replication in vitro [12]. The other targets in human cells are blocking the cell surface receptors for coronavirus binding and the cell signaling pathways that aid in viral replication. ACE2 is among the targets suggested to promote drug target therapy to avoid virus infection. Anti-ACE2 monoclonal antibodies, anti-SARS-CoV-2 neutralizing monoclonal antibodies, peptide fusion inhibitors, and anti-proteases therapy will invade cell entry via ACE2 receptors [13, 14].

The COVID-19 study has shown in recovering patients that it influences quality of life, but this deadly respiratory virus may have long-lasting adverse effects. Viral load may have been reduced for many, but some common symptoms such as cough, sore throat, and weakness may continue for weeks after fighting the disease, and even the recovered patients may return to the hospital with complaints of cardiac attacks, emotional illness, and comorbid condition. It is therefore much more important that researchers not only wait for a vaccine to conquer the COVID-19 tide but also take rigorous steps to ensure the safety for the community. In Ayurveda, Acharya Charaka clarified that Panchakarma (five purification procedures), Sadvritta (good behavior), and Rasayana dravyas (immunomodulators) of Ayurveda could be used for immune modulation, prevention, and reduction in burden of various diseases [15–17]. We have explained the importance of natural ingredients in the management of COVID and current integrated pharmacological interventions using herbal formulations with their clinical outcomes.

2 Methodology

Literature review was performed on PubMed, Google Scholar, and ScienceDirect by Boolean, and specific searches to identify terms included "coronavirus," "severe acute respiratory syndrome", "COVID-19," "novel formulations drug delivery system," and "phytoproducts" in combination with "treatment" and "pharmacology action." The data was collected from different reviews, case reports, case series, and research articles published on some of the mentioned topics. Ongoing clinical trials were cited from the official website of Clinical Trial Registry of India (CTRI).

3 Pathology and Current Pharmacological Intervention for COVID-19

Various pharmacological treatment options still going on are hydroxychloroquine/chloroquine, repurposed antiviral medications, monoclonal antibodies or IL-6 pathway inhibitors, and corticosteroids along with the convalescent plasma and cell and biological therapy.

To date, no specific medicines have been developed to prevent COVID-19, and the drugs being used are only to help in reducing the viral load and to offer symptomatic treatment. The US Food and Drug Administration (US FDA) has granted an antiviral drug remdesivir emergency use authorization, while the UK government has approved the use of low-cost steroidal medication [18] to manage respiratory conditions. India has also approved the use of immunosuppressive tocilizumab and convalescent plasma therapy off label on specific patient groups apart from oxygen or mechanical ventilation. In addition, India is also using favipiravir and

Table 1 Pharmacological target for the COVID-19

Synthetic drugs	Targets
Hydroxychloroquine sulfate/chloroquine phosphate	Inhibit terminal glycosylation
Lopinavir/ritonavir	3 cl (chymotrypsin-like protease)
Umifenovir	S-protein/ACE2, membrane fusion inhibitor
Remdesivir	RNA polymerase inhibitor
Favipiravir	RNA polymerase inhibitor
Tocilizumab	IL-6 inhibitor in cytokine storm

hydroxychloroquine as prophylaxis drugs. Hydroxychloroquine also has role with azithromycin which collapsed with time in treating COVID-19 patients [19].

It is useful to know what drug should be given at what time and stage of the disease for, e.g., tocilizumab when the levels of IL-6 (IL-6 is among the main cytokine storm mediators) are significantly high. The drug tocilizumab is still under investigation as a treatment for COVID-19, but the outcomes of phase-three trials have reportedly shown no clinical or mortality advantage [20]. The use of antiviral drugs (lopinavir and ritonavir) for further treatment was investigated in the beginning phases against COVID-19; however, both have wasted favors [21]. Patients only have supporting treatment like IV fluids, ventilation systems, and steroids. The convalescent plasma therapy showed mild improvement but did not reveal better results in overall condition. The function of the anticoagulants has become increasingly important in patients with mild and severe disease or with low risk of internal bleeding are also being prescribed [22] (Table 1).

4 Overview of the Phytoproducts

Ayurveda is a 5000-year-old medicine system that originated in India. Some theories stated that it is one of the oldest healing sciences. In Ayurveda, integrated therapy includes phytoproducts (mostly obtained from nature that involves metal and mineral products), diet, and exercise, meditation, and lifestyle modification. Because of its potential usefulness and safety, the use of traditional compounds was also found for this perspective in view of the medicinal benefits. Some of the potent bioactive compounds including curcumin, *Withania* alkaloids, cannabidiol, etc. are a perfect example of the bioactive compound's multi-mechanistic mode of action for favorable therapy. It acts against infectious diseases including inflammatory diseases, neurological diseases, cardiovascular diseases, pulmonary diseases, metabolic diseases, liver diseases, and cancers. There has been increasing evidence on the antiviral efficacy of the traditional compounds, and also Ayurvedic therapy and home remedies support to increase the immune system preventing the viral disease from spreading.

4.1 Ashwagandha

Withania somnifera (WS), widely known as ashwagandha, is an Ayurvedic herb that has recently gained recognition as a treatment for anxiety and stress in India. WS is classified as an anti-inflammatory supplement with antioxidant and immunomodulatory bioactives. The WS is also classified as an adaptogen, indicating its capacity to control physiological processes and stabilize the response of the body to stress [23]. Generally, traditional medical practitioners were using natural constituents of the WS plant called withanolides to treat various diseases. Withaferin shows real potential as a treatment modality to treat or prevent COVID-19 spread due to the recorded interaction with the host receptor binding of the viral S-protein; however, there is a lack of effect on ACE2 expression in the respiratory system [24]. Research investigated that WS extract-treated rats responded better to symptoms of induced chronic stress, similar to those of standard benzodiazepines [25]. The results of this specific study show that herbal supplementation is equally effective in anxiety management as are standard prescription drugs in a rodent model, without the harmful adverse effects. In people with mild cognitive impairment, WS may be effective in improving both immediate and general memory as well as improving cognitive function, recognition, and speed for processing of information. WS root extract is also being used as a rejuvenating agent for enhanced muscle strength, fatigue resistance, exercise recovery, and as an energy booster. In healthy athletic adults, the oral administration (high concentration) of WS root extract improves cardiovascular dynamics by increasing the maximum levels of oxygen and thus improving cardiorespiratory endurance as well as improving quality of life (QOL) in healthy adults [26].

4.2 Tulsi

Ocimum sanctum is not only an immunity boosting herb; it is also the most commonly found plant in Indian households. There are different variants of tulsi like Rama tulsi, Krishna tulsi, and Vana tulsi that can be consumed for different health benefits. Active phytoconstituents of tulsi have been proven to significantly inhibit the key protease COVID-19 [27]. Compounds such as ursolic acid, carnosol, rosmarinic acid, cirsilineol, apigenin, eugenol, and cirsimaritin present in *Ocimum sanctum* increase the concentration of hemoglobin and increase the sheep red blood cell agglutinin titer; decrease the activity of cyclo-oxygenase-2, lipoxygenase-5, and NF-3B pathway; and increase the IL-2, IFN-γ, and TNF-alpha regulations [28]. Tulsi improves the defense mechanism against infection by boosting immune reaction. Several studies stated that tulsi extracts have antimicrobial (including antibacterial, antiviral), antioxidant, anti-inflammatory, cardio-protective, analgesic, antipyretic, and immune-modulatory properties [29].

Tulsi is known as the Elixir of Life in Ayurveda for its healing capacity and promising potential to cure various conditions, i.e., bronchitis, pyrexia, rheumatism, asthma and microbial infections, gastric and hepatic disorders, etc. The role of tulsi in post COVID-19 control to treat pain, diarrhea, cough, and fever which are common symptoms associated with COVID-19 is still not clear. Tulsi has significant importance and role in boosting the immune system that assists the human body to fight against unwanted microbial strangers including bacteria and viruses. This study confirmed that the use of tulsi extract against COVID-19 is due to inhibition of replication of SAR-CoV with ACE2 blocking properties [30].

4.3 Curcumin

Curcumin is said to be one of the most effective Ayurvedic herbs as it has bioactive compounds with medicinal properties. Curcumin may even have promising impacts toward COVID-19 infection through its ability to alter the diverse molecular components that lead to SARS-CoV attachment and internalization to organs [31]. Curcumin may also regulate pathways for regulating cellular activities such as inflammation, apoptosis, and transcription of RNA. In infection with COVID-19, curcumin may also suppress pulmonary edema and associated pathways to fibrosis. The anti-inflammatory and immunomodulatory activity of curcumin together with proof of this phytochemical's anti-fibrotic and pulmonary protective activity on the lung tissue renders it a suitable candidate for the management of post COVID-19. Curcumin has reported strong inhibitory effects on NF-kB and other pro-inflammatory cytokines that can be particularly useful as an adjunct in preventing the destructive cytokine storm [32]. Curcumin as an antiviral and anti-inflammatory agent can be helpful in both the prevention and treatment of new emerging COVID-19 symptoms. Nonetheless, excellently designed clinical trials are needed to demonstrate curcumin's possible effectiveness against post COVID-19 complication.

4.4 Cannabidiol

Cannabidiol (CBD), a non-psychotropic phytocannabinoid, has the potential for so many rationales to limit the severity and disease progression. High cannabidiol levels can reduce the expression of the two main SARS-CoV2 receptors in several human epithelial models [33–35]. Cannabidiol has a wide range of immunomodulatory and anti-inflammatory effects and can reduce the excessive production of cytokines responsible for acute lung injury. It can demonstrate direct antiviral activity as a PPARγ agonist which is a regulator for activation of fibroblast/myofibroblast and can prevent the development of pulmonary fibrosis [34]. Significant protective function for CBD during ARDS can expand CBD by reducing cytokine storm,

protecting lung tissues, and re-establishing inflammatory homeostasis as part of COVID-19 therapy [34, 35].

Recent results suggesting the ability of CBD in the treatment of acute respiratory distress syndrome (ARDS) in a follow-up study indicate that CBD can improve the symptoms of ARDS through upregulation of apelin, a peptide with an important role in the central and peripheral regulation of immunity, CNS, metabolic, and cardiovascular system [36].

Anxiety and PTSD linked to COVID-19 are likely to be a major long-term problem arising from the current pandemic. Research assumes that CBD, a product with reported anxiolytic properties extracted from *Cannabis sativa* may be a therapeutic alternative for the treatment of anxiety disorders linked to COVID-19. Anxiety, stress, depression, and sleep disorders are consistently the primary reasons individuals use CBD in the regional over-the-counter. Observational and preclinical evidence also support the therapeutic value of CBD in enhancing sleep (increased duration of sleep/quality and decrease in nightmares) and depression, frequently followed by anxiety. Together with these CBD characteristics, it is an attractive new therapeutic choice for COVID-19-related PTSS that merits study and testing through carefully regulated randomized controlled trials.

Immune support or boosting is one of the most common claims for CBD. Immunomodulation can be mediated by cannabinoid receptors or by various other pharmacological targets. These net effects can be summarized as anti-inflammatory and for a number of immune-mediated disorders, including autoimmune conditions and neurodegeneration, are the sought-after therapeutic effects of CBD [33].

4.5 Giloy

Tinospora cordifolia, a very important medicinal plant, is also known as Guduchi in Sanskrit and Galo in Gujarati. Giloy stems are widely used in folk and Ayurvedic systems of medicine. The chemical constituents of *T. cordifolia* are classified into different classes that include alkaloids, steroids, glycosides, diterpenoid lactones, polysaccharides, aliphatic compounds, phenolics, and sesquiterpenoids. It appears that *T. cordifolia* improves the phagocytic function. It will also occur without affecting the humoral or cell-mediated immune system. It is categorized as Rasayana and used for its anti-inflammatory, immunomodulatory, anti-allergic, and anti-diabetic properties, etc. [37]. The whole plant is utilized medicinally; however, the stem is approved and useful in medicine as listed by the Ayurvedic Pharmacopeia of India. This is due to higher alkaloid content in the stems than in the leaves. *Guduchi Ghana* (concentrated form of decoction) is the secondary *Kalpana* (formulation) derived from the primary *Kalpana*, i.e., *Kwatha* (decoction). Several research works have been carried out regarding the anti-inflammatory activity of the decoction, alcohol extract, and water extract of the stem of Giloy. The water extract of the plant is found to be more potent than the other extract. Hence, it has been planned to study

the comparative anti-inflammatory activity of classically prepared and market samples of *Guduchi Ghana.*

Until now, three countries, including India, China, and South Korea, have issued guidelines on traditional regimens for the prevention and management of COVID-19.

The Indian Traditional System of Medicine is one of the oldest systems of medical practice in the world. India has the exclusive distinction of its own recognized traditional medicine: Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH). Approaches of these systems are holistic, and the pharmacological modalities are based on natural products of plants, animals, and/or mineral origin. After the successful treatment of plague, cholera, and Spanish flu with the help of AYUSH, to combat the current deadly pandemic of COVID-19, repurposing the traditional uses of Indian medicinal plants and formulation is a need [21, 38].

AYUSH suggested a few known traditional formulations of immunity modulators, which were in use for centuries in some allergic conditions and respiratory disorders. The Government of India has listed a few of them as prophylactic measures in red zones and containment zones as well as for corona warriors. A few of them are under clinical trials now for COVID-19 patients. Some antiviral medicinal plants are listed (Table 2).

Some homeopathic formulations like arsenic album, *Bryonia alba*, and *Rhus toxicodendron* were also used for management of COVID-19.

Ashwagandha, Giloy, ginger, cinnamon, tulsi, black pepper, black cumin, amla, turmeric, garlic, flax seeds, etc. are routinely used common Indian medicinal plants for management of COVID-19 (Table 3).

5 Prospective Phyto-ingredients for COVID-19 and Their Possible Mode of Action

The emergence of infectious diseases caused by novel viral strains that are resistant to common antiviral drugs is a major worldwide issue. Interestingly, herbal medicines, also known as phytomedicines derived from traditional Chinese, Japanese, Indian, and European herbal medicine systems, are promising candidates for the discovery and development of novel antiviral drugs. Therefore, in recent years, a huge number of experiments confirming the antiviral efficacies of medicinal plant extracts and secondary metabolites (i.e., such as flavonoids, naphthodianthrones, and anthraquinones) have been conducted. Particularly, in the last two decades, a number of medicinal plant extracts and/or related physiologically active ingredients have been reported to exhibit antiviral activities. Some of the phytochemicals proven effective against the viruses or symptoms related to what is shown by COVID-19 along with mode of action are discussed in this section.

Chinese traditional medicine (TCM) is highly recommended by the government of China for the eradication of SARS-CoV-2. It was reported that the following medicinal plants and their derived formulations have been used in 23 provinces of

Table 2 Potential traditional Indian/AYUSH formulations for the management of COVID-19 [38]

Sr no.	Type and name of formulations	Constituents	Sources	Activity
	Ayurvedic approaches			
1	AYUSH KWATH ("AYUSH Kudineer" or "AYUSH Joshanda") [39–50]	*Ocimum sanctum* L. leaves, *Cinnamomum verum* J. Presl. stem barks, *Zingiber officinale* Roscoe rhizomes *Piper nigrum* L. fruits	Powder and tablet	Boost immunity; antiviral remedies
2	Samshamani Vati (Guduchi Ghan Vati) [51–53]	*Tinospora cordifolia* (Willd.) Miers (family Menispermaceae)	Powder extract	Antipyretic and anti-inflammatory remedy
3	AYUSH-64 [54–56]	*Alstonia scholaris* (L.) R. Br. bark, *Picrorhiza kurroa* Royle ex Benth. rhizomes, *Swertia chirayita* (Roxb.) H. Karst. whole plant, *Caesalpinia crista* L. seed pulp	Tablet	Antiviral, anti-asthmatic, and immune boosting
4	Agastya Haritaki (Avaleha kalpana)	More than 15 herbal ingredients including Chitrak, Apamarga, Haritaki, Shankhpushpi, Kachur, Dashamoola, and Pushkarmool	Avaleha	Antiviral, anti-asthmatic, anti-inflammatory, and immunomodulatory activities
5	Anuthaila	*Leptadenia reticulata* *Ocimum sanctum* L. *Sesamum indicum* L. oil *S. indicum* seeds with *Trachyspermum ammi* (L.) Sprague seeds	Oil	Anti-allergic Anti-fever, cough, malaria; migraine and respiratory infections; lung disease
	Unani approaches			
6	Tiryaq-e-Arba [57–59]	*Laurus nobilis* L. berries, *Bergenia ciliata* Sternb. stem, *Aristolochia indica* L. roots, *Commiphora myrrha* (Nees) Engl.	Powder form	Detoxifying agent; potent antiviral agent against SARS-CoV, hepatitis C, HIV virus
7	Roghan-e-Baboona [60]	Flowers of *Matricaria chamomilla* L	Liquid preparation	Anti-asthmatic and inflammatory and against acute viral nasopharyngitis, as well as for sore throat
8	Arq-e-Ajeeb [61, 62]	Thymol, menthol, and camphor	Liquid preparation	Topical antiviral agent; anti-inflammatory; proven against swine flu

(continued)

Table 2 (continued)

Sr no.	Type and name of formulations	Constituents	Sources	Activity
9	Khamira-e-Banafsha [63, 64]	Decoction of flowers of *Viola odorata* L. to a sugar or sugar with honey base	Semisolid	Treatment of ailments of respiratory system and chest diseases, bronchitis, whooping cough; decrease viral load
10	Laooq-e-Sapistan [65, 66]	Ripe fruit of *Cordia myxa L.* and Ziziphus *mauritiana* fruit and *Viola odorata L.*	Semisolid sugar-based polyherbal Unani formulation	Treatment of cold and cough, whooping cough, and phlegm; antiviral and antitussive immunity booster
11	Sharbat-e-Sadar [67, 68]	*Trachyspermum ammi* Sprague, *Adhatoda vasica Bombyx mori*, etc.	Unani syrup	Common cold, cough and respiratory diseases; immunomodulator
12	Khamira Marwareed [69]	Compound sugar-based semisolid	Compound sugar-based semisolid	Immunomodulator; antiviral
13	Asgandh Safoof [68]	Asgand (*Withania somnifera*) root extract	Suspension	Immunomodulation and antiviral
14	Habb-e-Bukhar [70, 71]	Cinchona bark, *Tinospora cordifolia*	Poly herbal tablet	Elephantiasis and malarial fever; antiviral
15	Sharbat-e-Toot Siyah [72]	*Morus nigra L.* juice	Liquid/juice with sugar base	Treat tonsillitis and sore throat; analgesics; immunomodulatory activity
16	Laooq-e-Katan [73]	*Linum usitatissimum L.* seed	Sugar-based semisolid	Antiviral, anti-inflammatory, and immunomodulatory activities
	Siddha approaches			
17	Nilavembu Kudineer [74]	Nilavembu Kudineer polyherbal formulation	Polyherbal formulation	Immunomodulator activity against the dengue fever and chikungunya, malaria, typhoid and viral fever
18	Ahatodai Manapagu [75]	*Adhatoda vasica* Nees. leaves	Juice, syrup	To treat respiratory disorders and immunomodulator activity
19	Kabasura Kudineer [40, 76, 77]	Kabasura Kudineer herbs	More than herbs liquid formulation	Common respiratory complaints; for severe phlegm, dry cough, and fever; COVID-19 symptomatic management

China and proved effective for the treatment of COVID-19. These include *Agastache rugosa, Astragalus membranaceus, Radix platycodonis, Atractylodis rhizoma, Cyrtomium fortunei, Lonicerae japonicae, Glycyrrhiza uralensis, Fructus*

Table 3 Routinely used common Indian medicinal plants and traditional Indian formulations for the management of COVID-19

Sr. no.	Type and name of formulations	Part used	Sources/forms	Activity
1	*Allium sativum L.* (garlic) [78]	*A. sativum* peel	Oil	Immunomodulatory activity; antiviral; anti-inflammatory
2	*Cinnamomum verum J. Presl.* (cinnamon) or *Cinnamomum zeylanicum Blume* [39]	*C. verum* bark *C. zeylanicum* bark	Essential oil and powder; bark extract	Antioxidant, immunostimulant, and antiviral activity; immunomodulatory activity
3	*Curcuma longa L.* (turmeric) [79, 80]	*C. longa* oleo resins	Extract	Immunomodulatory activity; allergic disorders; antiviral; anti-inflammatory
4	*Linum usitatissimum L.* (flaxseed) [81]	Heteropolysaccharide and phenolic compound from flaxseed	Extract	Immunomodulatory; immunostimulant and vaccine adjuvant
5	*Nigella sativa L.* (black cumin) [82]	Seed of *Nigella sativa*	Seed extract	Inhibitors of COVID-19-associated disorder like obstructive lung diseases; immunosuppressive activity and immunomodulator
6	*Ocimum sanctum L.* (tulsi) [41]	*Ocimum sanctum* leaves	Oil/leaves	Antioxidant; immunomodulator; anti-allergic and anti-asthma
7	*Phyllanthus emblica L.* [83] (amla)	Fruits of *Phyllanthus emblica*	Fruit extract	Antioxidant; immunomodulator
8	*Piper nigrum L.* (black pepper) [84]	Piperamides isolated from *P. nigrum* fruits	Fruit extract	Antioxidant; immunomodulator; anti-allergic and anti-asthma
9	*Tinospora cordifolia* (Willd.) Miers (giloe) [85, 86]	*T. cordifolia* silver nanoparticles	Stem; leaves extract	Proven against chikungunya virus; immunity booster; anti-inflammatory
10	*Withania somnifera (L.) Dunal* (ashwagandha) [87]	*W. somnifera* formulation (supplemented with minerals)	Leaves extract	Antiviral and immunomodulatory
11	*Zingiber officinale Roscoe* (ginger) [40]	*Z. officinale* extract	Soft gel capsule; oil	Antiviral and immunomodulatory

(continued)

Table 3 (continued)

Sr. no.	Type and name of formulations	Part used	Sources/forms	Activity
12	Chyawanprash [88, 89]	Polyherbal health supplement with amla fruit base and nutrient rich herbs and minerals	Semisolid *paka* preparation	Antioxidant, free radical scavenging, antibacterial, antiviral, anti-inflammatory, anti-allergic, and antithrombotic effects; pulmonary tuberculosis; immunomodulatory
13	Triphala [90, 91]	Polyherbal Ayurvedic medicine consisting of equal proportions of fruits of *Phyllanthus emblica L., Terminalia bellirica* (Gaertn.) *Roxb.* and *Terminalia chebula Retz.*	Powder churna; tablet; capsules	Digestive disorders; antioxidants, anti-inflammatory, antineoplastic, antimicrobial, antidiabetic, etc.
14	Rooh Afza Sharbat [92, 93]	Seeds of khurfa (*Portulaca oleracea L.*), kasni (*Cichorium intybus L.*), angoor (*Vitis vinifera L.*), nilofar (*Nymphaea alba L.*), Neel Kamal (*Nymphaea nouchali Burm. f.*), kamal (*Nelumbo nucifera Gaertn.*), Gaozaban (*Borago officinalis L.*), badiyan (*Coriandrum sativum L.*), fruits/juices of santara (*Citrus sinensis (L.) Osbeck*), ananas (*Ananas comosus (L.) Merr.)*, seb (*Malus domestica* (Suckow) Borkh., berries (*Rubus fruticosus L.*), vegetables like palak (*Spinacia oleracea L.*), gazar (*Daucus carota L.*), and pudina (*Mentha arvensis L.*)	Concentrated squash prepared as sugar syrup	Refreshing; antiviral, immunomodulatory, and anti-allergic against respiratory disorders

forsythiae, Saposhnikoviae divaricata, and *Rhizoma atractylodis*. Although most of the treatments were found to lack proper statistical designs, effectiveness of these trials could be questioned. However, some TCM formulations and their possible mode of actions reported against novel coronavirus are listed in Table 4.

In addition to these formulations, many herbal extracts have been proposed as supplements to treat symptoms of COVID-19. For example, *Tinospora cordifolia* extract having an immunomodulatory effect against human immunodeficiency virus is effective to treat related symptoms. Similarly, herbal extracts of *Anthemis hyalina, Nigella sativa*, and *Citrus sinensis* decreased the coronavirus replication and downregulated TRP genes that may be involved in the survival of coronavirus in epithelial cells in a study conducted by Ulasli et al. [94]. Likewise, medicinal plants

Table 4 Phytochemicals from some medicinal herbs and their mode of action against treatment of COVID-19

Herbs	Phytochemicals	Mode of action	Reference
Isatis indigotica	Phenolic compounds like aloe emodin, hesperidin, quercetin, and naringenin in plant extract	Inhibition of the cleavage activity of SARS-3CLpro enzyme	[95]
Houttuynia cordata	Phenolic quercetin 7-rhamnoside in plant extract	Inhibition of viral RNA-dependent RNA polymerase activity (RdRp)	[96]
Multiple herbs	Isobavachalcone, herbacetin, helichrysetin, quercetin, 3-β-glucoside	Inhibition of cleavage activity of MERS-3CLpro enzyme	[97]
Glycyrrhizae Radix	Glycyrrhizin	Inhibition of viral attachment and penetration	[98]
Litchi chinensis and *Rheum palmatum* (Chinese rhubarb)	Flavonoids such as rhoifolin, pectolinarin, epigallocatechin gallate, gallocatechin gallate, quercetin, and herbacetin	Inhibition of SARS-3CLpro activity	[99, 100]
Scutellaria baicalensis	Baicalin	Inhibition of angiotensin-converting enzyme (ACE)	[101]

such as *Heteromorpha* spp. and *Scrophularia scorodonia* possess various phytochemicals, for example, saikosaponins, a derivative of triterpene-oleanane found abundantly across many angiosperm families. It is reported to possess medicinal functions such as modulation of immune function, anti-inflammation, anti-hepatoma, and antimicrobial effects; therefore, it has been shown to be active against measles, herpes simplex, influenza, varicella zoster, and human immunodeficiency viruses and related symptoms. A study conducted by Cheng et al. [102] indicated that saikosaponin B2 has potent antiviral property against infection caused by human coronavirus 229E, and possible mode of action includes inhibitory effect on attachment, penetration, and replication of the novel coronavirus. Similarly, *Zingiber officinale*-derived phytochemical, 6-gingerol, showed promising anti-coronavirus properties due to its high binding affinity against multiple SARS-CoV-2 targets, namely, RNA-binding protein, proteases, and spike proteins.

6 Herbal Formulations Used in Market for COVID-19

In this pandemic condition of COVID-19, it's a requirement of human being for using herbal remedies to boost the innate and acquired immunity to fight against viruses. To boost the "immune system," ways like active lifestyle, healthy diet, physical exercise, relaxation, and sound sleep are needed. Home remedies also played a vital role as immunity modulator agents. Ayurveda treatises have described

several herbal drugs like tulsi, ginger, clove, dalchini, turmeric, garlic, and Marich as effective home remedies for viral infections, as COVID-19 therapy for speedy recovery, and as immunity modulators as a preventive solution [103]. Herbal medicine includes herbs, herbal materials (like plant parts) or preparations, processed and finished herbal products, and active ingredients [104].

Many herbal extracts are proposed as supplements to treat COVID-19 symptoms by different modes of action. For example, *Tinospora cordifolia* extract having an immunomodulatory effect against human immunodeficiency virus is used to treat related symptoms. Herbal extracts of *Anthemis hyalina*, *Nigella sativa*, and *Citrus sinensis* decreased the coronavirus replication and downregulated TRP genes. Likewise, plants such as *Heteromorpha* spp. and *Scrophularia scorodonia* have phytoconstituents, for example, saikosaponins, which has been proven to be active against measles, herpes simplex, influenza, varicella zoster, and human immunodeficiency viruses and like symptoms.

COVID-19 is emerging as a very severe danger to global health. Unfortunately, no agents (even currently approved remdesivir) are showing clinical efficacy against SARC-CoV-2 and its complications, thus needing a drug repurposing strategy or newer drug delivery systems. Pharmaceutical research shows a key role by implementation of novel formulations for old phytocompounds that are able to enhance the delivery of bioactives to the site of infection and also to improve safety by minimizing the side effects for phytomolecules like dietary supplements, herbal compounds, medical gas mixtures, etc.

6.1 Dietary Supplements, Micronutrients, and Herbal Medicines

Several dietary supplements, micronutrients, nutraceuticals, probiotics, and herbal medicine formulations were suggested as repurposed compounds for the management of COVID-19. Although evidence of their benefit in viral infections (e.g., influenza, common cold, or SARS) is limited, different ongoing trials are currently investigating the efficacy of several dietary supplements and herbal compounds in COVID-19 when used alone or in combination with "traditional" repurposed agents. Notably, medicinal products are well defined for specific indications, and they must follow specific legislation to demonstrate quality, efficacy, and safety to obtain marketing authorization. Dietary supplements, nutraceuticals, and herbal products do not follow a similar procedure, given that marketing authorization may be required. Thus, their efficacy remains poorly supported, and open questions sometimes remain on safety. As regards Chinese herbal medicine, different meta-analyses of randomized controlled trials reported a better outcome in patients treated with Chinese herbal medicine in association with traditional western medicine compared to traditional Western medicine alone, although significant biases in included studies existed. Herbal formulations exhibit a wide range of pharmacological functions,

including anti-inflammatory, antiviral, antipyretic, expectorant, anti-asthmatic, and antitussive effects. Licorice root (Gancao, Glycyrrhizae Radix) was the most commonly administered compound. Different formulations of Chinese herbal products exist, including decoction, granule, capsule, oral liquid, pill, and injection, with decoction being the most commonly used. However, it is noteworthy that more evidence in terms of not only efficacy but also, above all, safety are required for these compounds. We focused on novel pharmaceutical formulations of dietary supplements and herbal medicines (namely, zinc, essential oils, and glycyrrhizin) developed and implemented in COVID-19 setting.

6.2 Zinc Supplementation

Zinc exhibits a wide variety of direct and indirect antiviral activities against different species, including rhinovirus and influenza virus, enhancing both immune and adaptive immunity, as well as affecting virus attachment and replication. Although the efficacy of zinc supplementation in treating the common cold caused by rhinoviruses is debated, it is important to underline that intranasal zinc gluconate gel formulations exist, potentially providing for direct micronutrient delivery at the site of infection. The administration of intranasal zinc formulations could also be repurposed as adjuvant treatment in patients affected by COVID-19, particularly concerning the prevention of disease transmission and the treatment of nasal symptoms. However, zinc toxicity involving the olfactory system was found in preclinical models, and several cases of zinc-induced anosmia syndrome were reported.

6.3 Essential Oils

Essential oils (EOs) include a complex mixture of volatile phytochemicals from diverse classes, including monoterpenes, sesquiterpenes, and phenylpropanoids, showing anti-inflammatory, immunomodulatory, bronchodilatory, and antiviral properties. EOs usually contain about 20–60 components showing widely different concentrations, of which two or three are present at higher concentrations (20–70%; major components) compared to the others (retrieved in trace amounts), thus determining the biological properties of the compound. The chemical profiles of the EOs differ not only in the number and type of molecules but also in their stereochemical structures and can be very different according to the selected method of extraction. Notably, EOs exhibited in vitro activity against several viruses, including influenza and other respiratory viral infections. Different EOs have been investigated through different repurposing approaches (including the in silico approach, in vitro assays, molecular docking) against COVID-19, being eucalyptus oil from *Eucalyptus globulus*, jensenone, and eucalyptol as major components and garlic oil, coupled with several single major components (viz., farnesol, anethole, cinnamaldehyde,

carvacrol, geraniol, cinnamyl acetate, L-4-terpineol, thymol, pulegone, eugenol, menthol, and carvacrol) the most promising compounds. EOs are usually used by external application (gargles or inhalation), with the respiratory tract exhibiting the most rapid route of administration, followed by the dermal pathway. However, unfavorable chemical properties of EOs—namely, poor solubility, solvent toxicity, high volatility, low bioavailability, and physicochemical instability (responsible for degradation of EOs components)—limit their use as active compounds in several formulations. Consequently, the search for different novel formulations arose as an urgent need for pharmaceutical research in this area, also in order to potentially improve and implement the use of EOs in viral infections, including COVID-19, leading to the development of many nanotechnology-based carriers, namely, liposomes, dendrimers, nanoparticles, nanoemulsion, and microemulsion. Encapsulation of bioactive and major compounds of EOs represents a feasible approach to modulate drug release, increase the physical stability of the active substances, protect them from interactions with the environment, decrease their volatility, enhance their bioactivity, reduce toxicity, and improve patient compliance and convenience. Currently, there are different ongoing trials investigating EOs in the management of COVID-19, including their efficacy for anosmia recovery in post-COVID infection.

6.4 Glycyrrhizin

Glycyrrhizin or glycyrrhizic acid is a natural product isolated from the roots (Glycyrrhizae Radix) of the plants *Glycyrrhiza glabra* (typically cultivated in Europe, henceforth called European licorice) and *G. uralensis Fisch* and *G. inflata Bat* (used in the Chinese pharmacopeia). It has been demonstrated to exhibit antiviral (based on cytoplasmic and membrane effects) and anti-inflammatory/immunomodulatory properties (through the activation of multiple pathways involving Toll-like receptors and inhibition of pro-inflammatory cytokines), inhibiting in vitro isolates of SARS-associated coronavirus and other respiratory viruses.

However, the extensive first-pass metabolism strongly reduces plasmatic exposure of glycyrrhizic acid, with the consequent achievement of inadequate serum concentrations, well below the IC50 for SARS-CoV. To overcome this issue, different pharmaceutical approaches have been explored: (a) the modification of chemical structure of glycyrrhizic acid, in order to develop amide derivatives and amino-acid conjugates that may considerably enhance the activity against SARS-CoV but with increased cytotoxicity, and (b) the development of drug delivery systems consisting of the encapsulation of glycyrrhizic acid into nanoliposomes, hyalurosomes, or niosomes. The latter formulations not only may improve plasmatic bioavailability and exposure of glycyrrhizic acid but also facilitate the transportation and delivery of co-transported drugs, given the amphiphilic properties of vesicles, allowing for the enhancement of poorly soluble drugs and increasing the passive diffusion through cellular membranes of co-transported agents.

As previously mentioned, hydroxychloroquine, a repurposed drug widely used in the first phase of the COVID-19 pandemic, is one of the compounds combined with glycyrrhizic acid in novel nano-formulation by virtue of the potential antiviral and anti-inflammatory synergism coupled with an improvement in delivery (Table 5).

7 Intention for Newer Novel Drug Delivery Approach

7.1 Gap or Loopholes for Phytomolecule in Terms of Safety and Effectiveness; Quality Issues, and Analytical Challenges for the Traditional Medicines [105]

- The current case study of Villena-Tejada M et al. [106] reported an association between 17 medicinal plants' uses and prevention and treatment of the respiratory symptoms related to COVID-19; the major plants were eucalyptus, ginger, spiked pepper, chamomile, garlic, etc. It was observed that the population in the present study had used a greater number of plants for disease prevention when respondents were older and if one of the friends or family members came out from COVID-19. It was also found that respondents who achieved technical or higher education were using less plants for its treatment. The latent use of medicinal plants for respiratory conditions was approved but more and more research is essential to get solid confirmation of their effectiveness and standardized process to isolate compounds to achieve their potential pharmacological use. A few studies are necessary to determine proper effective forms and their doses and potential combination of these plants [106].
- Phytoformulations, especially homeopathic formulations, are prepared by dilutions in such a way that no single detectable molecule is present in the final formulation, which results in controversy.
- Non-evidential rationale to determine the biological effects of solutions containing unmeasurable starting material led to criticism.
- Challenge is for a pharmacologist to validate the therapeutic claims of homeopathic-typed phytomedicines through experiments. Low acceptance of these formulations is due to the absence of standardized protocols to justify their pharmacological potential.
- The time and processes required to develop an herbal medicine of prime quality and consistency for therapeutic use with sufficient safety data is extremely protracted. This is due to the nature of medicinal plants having multiple phytochemicals, getting easily affected by agronomic factors [107].
- Even identifying, isolating, and producing reference standards required for the standardization of medicinal plants is difficult, compared to straight synthetic chemical entities. Standardization of herbal products based on bioactive markers remains vital to ensure consistency and efficacy for different batches.

Table 5 Clinical trial on photoproducts on COVID-19 (ctri.nic.in)

Sr no.	CTRI No.	Intervention	Clinical outcome of the phytoproducts	Sample size
1	CTRI/2020/04/024882	Kashaya of Tinospora cordifolia added with 2 gm dried powder of *Piper longum* fruit	Assess the effect of the Ayurveda drug combination of *Tinospora cordifolia* and *Piper longum* in the progression of the disease, its severity, and clinical outcome	60
2	CTRI/2020/05/024981	Dabur Chyawanprash	Comparative assessment of the severity of COVID-19, changes in quality of life, assessment of incidence, and severity of disease	600
3	CTRI/2020/05/025171	1. *Guduchi Ghana Vati* 2. Anu Taila 3. Rock salt and turmeric	Improvement in *Bala* of an individual resulting in immune-stimulation, improvement in quality of life	50,000
4	CTRI/2020/05/025069	Sudarshana Ghana Vati or ashwagandha	Effectiveness of such preventive measures and Ayurveda advocacies	1324
5	CTRI/2020/05/025093	Yashtimadhu tablet/ ashwagandha tablet/ Guduchi tablet	Comparative assessment of occurrence of COVID-19 infection, assessment of severity, assessment of subjects not requiring hospitalization, severity of symptoms	1200
6	CTRI/2020/05/025178	Tab Samshamani Vati, Herbal tea, Anu Taila (into nostrils), Haridra Khanda	Improvement in *Bala* of an individual resulting in immune-stimulation leading to nondevelopment of symptoms of COVID-19, improvement in quality of life	140
7	CTRI/2020/05/025156	AYUSH-64 as add-on to standard treatment	Clinical cure rate, duration of fever and each of the respiratory symptoms. Improvement in hematological and laboratory parameters, required invasive or noninvasive oxygen, progressed to multi-organ failure	60
8	CTRI/2020/05/025222	AOIM-Z Tablets	Prevention of incidence of COVID-19 infection, comparative assessment of occurrence of COVID-19 infection, assessment of severity, assessment of subjects not requiring hospitalization	275

(continued)

Table 5 (continued)

Sr no.	CTRI No.	Intervention	Clinical outcome of the phytoproducts	Sample size
9	CTRI/2020/05/025341	Kwath (Kiratiktadi Kwath) and ashwagandha Churna along with yoga exercises (pranayama, Surya Namaskar	Management of mild and asymptomatic cases of COVID-19, rate of recovery	30

- Development of evidence-based validated methods and advancements in the traditional system to justify its measurable dilutions, which may help to understand the mechanism of action and these formulations.
- Due to the variation in the formulations existing for medicinal plants, there are ample safety and toxicity studies related to the formulation of importance. Due to so many challenges, it is highly unlikely to build up new products from scratch in time for emergency use during COVID-19 pandemic type of crises. In emergency time, generally accelerated approvals for therapeutic molecules with proven safety with lowest risk of toxicity and having potential for benefits are considered [108].

7.2 Potentials of Novel Herbal Drug Delivery System for Traditional Medicines

- The novel drug delivery technology in herbal medicine may help to increase the efficacy of targeted active phyto-ingredient and even to reduce its side effects; untoward effects are likely to happen in phytomedicine, as people don't know their limited dose and dosing frequency, and, of course, herbs may contain polyphytocompounds which may be less targeted to provide effectiveness and more to give side effects.
- Earlier times, herbal medicines were not being taken risk for development as novel formulations due to their lack of scientific justifications and their processing problems, like standardization, extraction, and even identification of key components in polyherbal complex systems. Modern phytopharmaceutical research may be able to solve the scientific needs like pharmacokinetics determination, mechanism and mode of action, site of action, accurate dosing and dosage regimen, etc. of herbal medicines within novel drug delivery system, examples nanoparticles, microemulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles, etc.
- New drug delivery is an interdisciplinary approach that combines polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. Novel drug systems can deliver a herbal drug constituent with significant efficacy. Some constituents have an optimal concentration range, which can bring its maximum

benefit, and above or below its concentration range may be toxic or unsafe or may have less or slow effect in severe disease. Henceforth, a multidisciplinary way of delivering key phytoconstituents to targeted site tissues, for required amount for required time by controlling the pharmacokinetics, pharmacodynamics, nonspecific safety and toxicity, immunogenicity, biorecognition and efficacy of drugs came in existence.

A few case studies may be presented for reference [109].

Phytopharmaceuticals are pharmaceuticals using traditional compounds derived from botanicals instead of chemicals. Natural ingredients are more easily and more readily metabolized by the body. Therefore, they produce fewer, if any, side effects and provide increased absorption in the bloodstream resulting in more thorough and effective treatments. Pharmaceuticals made from chemical compounds are prone to adverse side effects. The human body will have a tendency to reject certain chemical compounds which do not occur naturally. These rejections occur in the form of side effects; some may be as mild as minor headaches and others as severe as to be potentially lethal. It is important to note that, while phytopharmaceuticals produce fewer to no side effects, chemical interactions with other prescription drugs can occur.

Furthermore, as they are single and purified compounds, they can be easily standardized making it easier to incorporate them in modern drug delivery systems compared to herbs.

8 Lipid-Based Drug Delivery Systems Have Proven Their Potential in Controlled and Targeted Drug Delivery

Pharmacosomes are amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipids. They impart better biopharmaceutical properties to the drug, resulting in improved bioavailability.

Phytosomes are novel compounds comprising of lipophilic complexes of components of plant origin like *Silybum marianum*, *Ginkgo biloba*, ginseng, etc. with phospholipid [110]. They are also called as phytolipid's delivery system. It has high lipophilicity and improved bioavailability and therapeutic effects. These are advanced forms of herbal extract having improved pharmacokinetic and pharmacological parameters, advantageous in treatment of acute liver diseases, either metabolic or infective origin. Phytosomes have wide potential in cosmetology in Indian Ayurvedic medicines to combat serious ailments using both benefits like novel drug delivery and phytosomes.

Novel drug delivery systems like mouth dissolving tablets; mucoadhesive systems; sustained, controlled, prolonged, and extended release formulations; transdermal dosage forms; micro/nanoparticles; microcapsules; implants; etc. are exhaustively researched. A few have reached the market as well (Table 6).

Table 6 Case studies of successful herbal novel drug delivery systems

Form of medicine	Solution of problem by mechanism of improvement	Results
Asoka Lifescience Limited Res-Q, the world's first poly-herbal mouth dissolving tablet	Dissolves in the mouth by mixing with the saliva and gets absorbed; drug reaches the blood directly and the first pass metabolism is bypassed; imparts increased efficacy for lung problems and other respiratory ailments	Relief from respiratory distress within 15 min; resembles the efficacy of Sorbitrate, a revolutionary mouth dissolving drug used in cardiac distress
Patented orally administrable matrix tablet/microcapsule in 2-piece capsule for the controlled release or stable storage of a granulated herb	A granulated herb and a carrier, the formulation release of 75% of the active in between 4 and 18 h	Steady supply of the active components for a sustained period So convenient oral dosage form for user compliance
Process and product US patented new stable *Gingko biloba* extract formulation in the form of sustained-release microgranules	Poor flowability and compressibility properties can be improved by excipients (pellets can be prepared by extrusion-spheronization, fluid air bed process, or a coating-pan method)	Product and process is improved without costly equipment
Palatal mucoadhesive tablet of sage, *Echinacea, Lavender,* and *Mastic gum*	Sustained release abilities of buccal tablets having mucoadhesive polymers	Effective in reducing oral malodor and VSC levels
Transdermal films of boswellic acid (*Boswellia serrata)* and curcumin (*Curcuma longa)*	Targeted action, avoids the first pass metabolism, no pain associated with injection, may be sustained drug delivery	Targeted action with patient compliance and effectiveness; new version of Ayurvedic turmeric *poultice* or *lepa*
Effect and mechanism of Shuanghua aerosol (SHA) checked on upper respiratory tract infections in children from 3 to 14 years	SHA has obvious anti-inflammatory and antiviral effects and has proven good curative effect in treating infantile upper respiratory tract infections	SHA has obvious anti-inflammatory and antiviral effects and has proven good curative effect in treating infantile upper respiratory tract infections
Microparticles of Gugulipid—oleo-gum resin of *Commiphora wightii* using chitosan, egg albumin, sodium alginate, ethyl cellulose, cellulose acetate, gelatin, and beeswax	Optimum physicochemical characteristics and HPLC showed distinct separation of E- and Z-guggulsterone; confirming entrapment of Gugulipid in microparticle	Good release can be achieved

(continued)

Table 6 (continued)

Form of medicine	Solution of problem by mechanism of improvement	Results
Sustained release implant of danshen (*radix Salvia miltiorrhiza*) extract using chitosan	In the CS/gelatin (1:2) matrix, drug release was effectively controlled by the drug amount loaded in the matrix Film degradation was being seen in rats	Implant for the promotion of anastomosing and healing of muscles and tissues at the organic incision site in abdominal cavities
Nanoparticles of TCH (traditional Chinese herbs) *peach seed, safflower, angelica root, Szechuan lovage rhizome, Rehmannia* root, red peony root, leech, gadfly, earthworm, and ground beetle	The thrombolytic effects of nanoparticles of TCHs are much more intense than their non-nanoparticle form	Improve their absorption and distribution in the body, and so enhance their efficacies
ArthriBlend—SR is a proprietary clinically validated blend of glucosamine sulfate, Boswellin (*Boswellia serrata* extract), and Curcumin C3 Complex (curcuminoids from *Curcuma longa*) natural actives for joint care applications	Slow release profile of 80–90% active ingredient release, in an 8-h period Sustained release technology benefits the continuous management of symptoms of arthritis	Support healthy joints and connective tissues in the body Relevant to the bioavailability of glucosamine

9 Novel Technologies for Drug Delivery Approach [111]

Novel drug delivery systems (NDDS) will be a boon for the better and target-specific delivery of repurposed drugs. Currently ongoing research exemplify the execution of NDDS in prevention and treatment of COVID-19 as well as in the vaccine development process. Here, emphasis is on how NDDS of already developed therapeutic agents in the form of improved convenient delivery systems (dosage forms) fill the void spaces for latent targeted delivery. Therefore, NDDS and nanotechnology intervention in product development may play a vital safeguard to humanity in this difficult era.

- *Novel drug delivery system (NDDS) for the delivery of vaccines*
  - Transdermal vaccine
  - Oral vaccine
  - Intranasal vaccine
  - Biosynthetic nanoparticle-based vaccines
- *NDDS in antiviral therapy*
  - Microemulsions
  - Liposomes and ethosomes

  - Microspheres
  - Iontophoresis

- *Repurposing of drugs*
  - Hydroxychloroquine
  - Remdesivir
  - Tocilizumab
  - Azithromycin
  - Convalescent plasma

- *NDDS for drugs in treatment of COVID-19*
  - Nanoparticles of drugs
  - Intranasal delivery nanoparticles

Plant-based supplements which are used in different countries other than India:

1. *Echinacea purpurea*: Purple coneflower is one of the most popular herbal medicines in form of extracts, tinctures, teas, and sprays used in Europe and North America due to several bioactive compounds present like chicoric acid and caffeic acids, alkylamides, and polysaccharides. A preliminary in vitro study found that Echinaforce®, an *E. purpurea* preparation, inactivated SARS-CoV-2 in a clinical trial in Iran on 100 adults based on chest computed tomography (CT) scan or x-ray analysis.
2. *Curcuma longa*: Curcumin is an alkaloid from rhizomes of turmeric and is used for treatment for hypertension, which is the most common comorbidity in COVID-19 patients (23.7%) as per studies used across the globe.
3. Cinchona bark (Cinchona species): Quinine alkaloids isolated from cinchona bark found in the Andean mountain forests, which were the most wanted drugs in the society for COVID-19 treatment.
4. Xanthorrhizol: Java turmeric *or Curcuma xanthorrhiza* Roxb. is a herbal plant widely used as an immunosuppressant in the treatment for COVID-19. This plant is commonly found growing in Southeast Asian countries like Indonesia, Thailand, Philippines, Sri Lanka, and Malaysia; however, using xanthorrhizol for treatment and prevention in COVID-19 still requires more evaluation, especially in the clinical trial setting [112, 113].
5. *Andrographis paniculata*: A few in vitro studies suggest that andrographolide isolated from andrographis might bind the main protease of SARS-CoV-2, thereby inhibiting its replication, transcription, and host cell recognition as observed in small clinical trial in Thailand; when given 3 times per day in 12 people with mild-to-moderate COVID-19 symptoms, marked improvement was observed after patients started taking the low dose (60 mg) andrographis, and all patients recovered after 3 weeks.
6. *Sambucus nigra:* Elder berry fruits growing in North America, Europe, and parts of Africa and Asia and having rich chemical profile including anthocyanins, fla-

vonols, and phenolic acids. Owing to its antioxidant, anti-inflammatory, antiviral, antimicrobial, and immune-stimulating effects, sales of supplements containing elder berry has been doubled shortly after the COVID-19 pandemic began in the United States.

10 Conclusion and Future Aspects

The active constituents of Ayurvedic/AYUSH origin for COVID-19 patients can be utilized in a better form with enhanced efficacy by involvement of modern dosage delivery forms. Phytotherapeutics require a scientific policy to deliver the key components in a novel active manner to boost patient compliance and reduce repeated administration. Novel drug delivery systems utilized for formulations of COVID-19 may not only reduce the frequent administration to conquer noncompliance but may also help to improve the therapeutic value by reducing side effects and toxicity and by increasing the bioavailability at required sites.

The medicinal plant species mentioned and categorized for preclinical and clinical investigation may be further taken up by research organizations on priority basis, which may result in the development of key marker molecules against SARS-CoV-2 and COVID-19.

By seeing the potential of AYUSH medicines and medicinal plants' diversity in India, the herbal drug manufacturers and various government and nongovernment research organizations have developed essential strategies for proceeding with preclinical and clinical research on these promising therapeutic remedies.

The potential use of various medicinal plants for respiratory and other symptomatic conditions were successfully acknowledged to be positive as a prevention and remedy for COVID-19, but more and more research is needed to have solid proof of their effectiveness for specific isolated compounds with budding pharmacological use. Furthermore, studies are needed to determine effective and safe doses, forms of formulation, and their effective combinations of medicinal plants. This may open up a new market for Ayurvedic pharmaceuticals.

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