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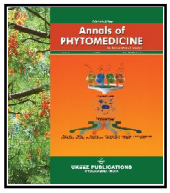

Review Article : Open Access

Emerging pharmacological interventions: A COVID-19 perspective

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Abstract

The current COVID-19 pandemic caused by SARS-CoV-2 is believed to be due to zoonotic emergence. The infection leads to a variety of conditions, from mild discomfort to severe respiratory disorder requiring intensive care monitoring and at times even becoming life-threatening. The advent of multiple mutations led to variants wherein the severity and contagiousness of the disease have varied. In the initial days of the pandemic, supportive care measures such as providing oxygen for ventilation and using antivirals effective against various respiratory diseases were the pharmacological interventions used. Ongoing clinical trials are helping identify the most effective repurposed antiviral drug or a combination of such drugs to be effective against the SARS-CoV-2 infection.

Researchers and healthcare personnel are putting in tremendous efforts to urgently identify prospective preventive, diagnostic and therapeutic strategies on priority. Various research institutions and pharmaceutical companies put in intensive efforts and within a short duration, many vaccines were available that helped develop population immunity, thus preventing the severity of infection even when people got infected. Candidates for therapy include the use of: (i) medicinal aromatic plant, or active phytoconstituents, individually or as a combination; (ii) nanotechnological tools to encapsulate the drugs/plant phytoconstituents; (iii) food fortification with the prepared nanoparticles, amongst some prospective strategies. As phytomedicine is gaining significance in holistic wellbeing, the research and development in the field of polyherbal have intensified. Combinational therapy is being propagated through promising results obtained by multiple researchers. In most studies, compounds used had proven potential *via in vitro* or *in vivo* studies against viruses similar to SARS-CoV-2. Further, the infection rates and the severity of the disease have been drastically reduced, with population immunity being developed due to the use of vaccines. An array of vaccines ranging from DNA, mRNA, sub-unit, viral vector and virus-like particles, are already in various stages of clinical trials, with over 12.3 billion doses being delivered globally.

This is a review of scientific work conducted toward developing pharmacological interventions against COVID-19. The data represented provides a resource to researchers and healthcare providers to help control the infection and the pandemic.

1. Introduction

Since ancient times it has been believed that food can be as effective as medicine and the same is communicated through verses such as "unave marundhu, marundhe unavu" (Karpagam *et al.,* 2022).The advent of synthetically produced pharmaceuticals saw a dip in consumption of natural plant-derived healers, though, in recent times, the multiple adverse reactions to these pharmaceuticals have led to a reacceptance of alternative medicine for holistic wellbeing (Palzer, 2009). Complementary and alternative medicine (CAM) for diagnosis, treatment and prognosis, in recent years, has been much sought after, especially under the pandemic threat (Tirant *et al.*, 2018). WHO reports that 170 out of 194 member nations still depend on 40,000-70,000 traditional herbal plants as medicine. Anand *et al.* (2020) have suggested that 25% of modern-day medications are directly or indirectly obtained from plants. Most plant-derived chemical components typically comprise many chiral centres, so their industrial production is challenging. This structural complexity is the reason for the pharmacological attributes of plant-derived drugs (Biswas *et al.*, 2021; Khare *et al.*, 2021; Chowdhury *et al.*, 2021).

Plants generate as by-products secondary metabolites possessing a wide range of pharmacological functions. These phytoconstituents result in improvising persistent diseases as they possess pharmacological applications, though they may have low effectiveness.These components are beneficial for health and have been termed nutraceuticals. De Felice defines nutraceuticals as 'food or a part of food that provides medical or health benefits, which include prevention and treatment of diseases and are dietary supplements delivering nutrients (Sohaimy, 2012). Nutraceuticals contain the active phytochemicals in concentrations more than those found in food, and thus provide therapeutic effects.

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Akobundu *et al.* (2004) classified nutraceuticals based on their function and composition into three main categories, *viz.* (i) nutrients, (ii) herbals or phytochemicals (iii) dietary supplements. Nutraceuticals rich in nutrients, *e.g.*, carbohydrates, amino acids, fatty acids, vitamins and minerals, provide calorific needs and supplement body functionality. The protective category of biomolecules; namely, vitamins and minerals, are required in the diet and not biosynthesised, providing health advantages (Mc Clements, 2012). Pro- and prebiotics and antioxidants are dietary supplements used as nutraceuticals that comprise several bioactive ingredients constituted together as a powder, tablet, liquid, or any other dosage form (Espín *et al.*, 2007).

Bioavailability is the number of biomolecules or bioactive components that are absorbed and available in blood circulation for causing an effect and is of prime importance in determining their efficiency (Esfanjani *et al.*,2018; Rapaka and Coates, 2006). It is affected by the route of administration, being maximum for the intravenous route and as nutraceuticals are primarily consumed through the oral route, their bioavailability is low due to first-pass metabolism, solubility in the gut, reduced permeability and inadequate gastric retention, among other reasons (Bell, 2001). Poor solubility leads to compound instability and crystallisation of the active constituents during formulation and is often challenging (Augustin and Sanguansri, 2012). To prevail over these limitations, an alternative could be to prepare a suitable delivery system using nanotechnology. The efficiency, biological activity and solubility of the compounds can be enhanced by reducing the particle size of the delivery system, thereby increasing the surface area per unit molecule. The use of nanosized delivery molecules helps control the release of the nutraceutical and improvises bioavailability, along with protecting the active constituents of the nutraceuticals from manufacturing to the distribution phase, thus enhancing the product's characteristics (Prasad *et al.*, 2019). These nanonutraceuticals, due to their small size, lead to a larger surface area and are thus able to reduce the challenges of *in vivo* drug delivery. Javeri (2011) reformulated silymarin, a drug used for therapy of liver disorders and cirrhosis, into nanoliposomes, which led to increased bioabsorption. The production of nanomaterials involves not only the task of incorporating the bioactive compounds but also characterization and the study for efficiency in entrapment, stability and release of the nutraceutical along with analysing its therapeutic/diagnostic function (de Souza Simo˜es *et al.*, 2017). Acevedo-Fani *et al.* (2017) have explored the significant contribution that nanoemulsionscan offer to novel nutraceutical delivery systems and nano-encapsulated herbs, spices and active phytoconstituents have been evaluated for their medicinal properties with promising results.

Since early 2020, a global health crisis has emerged due to the novel acute respiratory condition arising due to infection from SARS-CoV-2 or coronavirus leading to COVID-19. This virus is a member of the coronaviridae family and Nidovirals order, the coronavirus genus. It is an RNA virus that can potentially cause disease in both animals and humans alike, though it is a zoonotic virus that was transmitted to humans from animals and back (Hafeez *et al.*, 2019). The virus leads to respiratory and/or gastrointestinal tract infection, characterised by fever, bad throat, fatigue, dyspnea and lymphopenia. The SARS-CoV-2 variant is 79% similar to SARS-CoV, while the similarity is 50% with MERS-CoV, as per genome sequencing results. Its primary receptor is angiotensin-converting enzyme 2 (ACE2), expressed on the respiratory epithelium, vascular endothelium and immune cells as alveolar monocytes and macrophages.

The current review aims to present emerging pharmacological interventions in the context of the current SARSCoV-2 COVID -19 pandemic.

2. Nanotechnology-based delivery systems

Nanomedicine is an upcoming field as it improvises on drug characteristics such as solubility, sustained and more prolonged action and targeted effects to the tissue of concern, thereby preventing adverse reactions. The size and shape of the nanoparticles influence their pharmacokinetics involving cellular internalization and biodistribution (Gratton *et al.*, 2008). Thus, nanostructured drug-delivery systems (NDDS) are formulations wherein active drugs/ biomolecules are encapsulated/incorporated/intercalated/adsorbed to cause pharmacological action. The size, composition, charge and pH can be modified to increase the efficacy of target-cell interaction (Ribeiro *et al.*, 2019). Various biomaterials are being encapsulated for various applications (Ribeiro *et al.*, 2017). NDDS to be used as antivirals are designed to reduce drug toxicity by reducing the concentration of drug delivered and maintaining prolonged drug release, thus not affecting the efficacy (Lembo and Cavalli, 2010). Different NDDS-based systems have been used for viral infections such as HIV, hepatitis and herpes zoster, comprising polymers, lipids, metals and inorganic nanoparticles (Sivasankarapillai *et al.*, 2020). Using such biochemicals for entrapping nanoparticles is pocket-friendly, reproducible, biocompatible and biodegradable (Ribeiro *et al.*, 2018). Different biopolymers used for making nanoparticles include heparin, starch, cellulose, gelatin, PVP (polyvinyl-pyrrolidone), PVA (poly-vinyl acetate), chitosan and many more (Mohammed *et al.*, 2017).

Nanoparticles can be synthesised using various techniques as (i) desolvation (Fu *et al.*, 2018); (ii) microemulsion (Kupper *et al.*, 2017), (iii) spray-drying (Jiang *et al.*, 2017); (iv) electro spraying (Bakhsheshi-Rad *et al.*, 2017); (v) freeze-drying (Iwao *et al.*, 2018); (vi) layer-by-layer self-assembly surfactant assemblies (Shiraki and Daikoku, 2020); and (vii) supercritical fluid extraction (Wölfel *et al.*, 2020). Amongst the mentioned methods, the simplest one for manufacturing protein-based nanoparticles is the desolvation method which utilises organic solvents mixed with constant stirring in an aqueous solution. The flow rate and amount of desolvating agent are used to determine the dimensions of the nanoparticles formed by this method (Ungaro *et al.*, 2017). For heat labile and pressure-sensitive molecules, the preferred method for forming dried porous nanoparticles is the freeze-drying method. In this method, the time required for nanoparticle formation is extensive, with bigger-sized nanoparticles being formed and the process is expensive (Sivasankarapillai *et al.*, 2020). Using the electrospray technique, nanoparticles are obtained by a process involving electrostatic force used to break liquid surfaces. It is a single-step, multipurpose and reliable procedure (Liu *et al.*, 2020). Nanoemulsions are produced by dispersing in the presence of emulsifiers or surfactants, a biopolymer in two immiscible liquid phases. This leads to optically transparent, thermodynamically stable nanoparticles with high drug encapsulation (Kupper *et al.*, 2017).

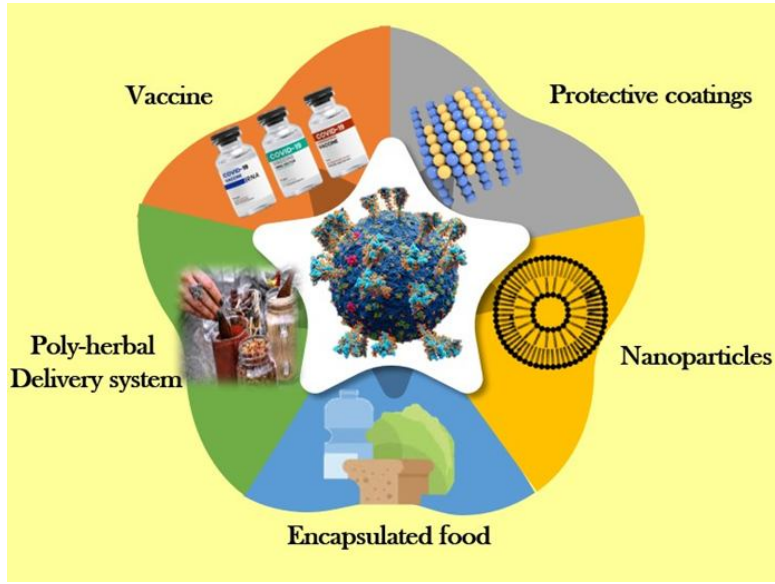

Figure 1: Applications of nanotechnology based pharmacological interventions.

Table1: Nanostructured drug-delivery systems

Drug	Nanotechnological preparation	Matrix	Reference
Remdesivir	Dendrimer	PEG	Starpharma, 2020
Tocilizumab	Nanoparticles	Gold	Lee *et al*., 2014
IL-6 Ab	Nanoparticles	Chitosan-hyaluronic acid	Lima *et al*., 2018
IL1 receptor antagonist	Nanoparticles	Chitosan	Xiao *et al*., 2013
Dexamethasone	Liposomes		Deshantri *et al*., 2019
	Nanoparticles	Chitosan	Yu *et al*., 2020
Hydrocortisone sodium succinate	Nanoparticles	Hydrocortisone sodium succinate	Gulin-Sarfraz *et al*., 2019

In the current health crisis due to the SARS-CoV-2 infection, nanotechnology-based pharmacological interventions can be of immense help in prevention, diagnosis and therapy. Preventive vaccination using nanobased technology to enhance immunity can lead to curbing infection. Further, designing personal protective equipment (PPE) and efficient antiviral disinfectants to be applied as surface coatings to inactivate the SARS-CoV-2 virus will also limit its spread. Nanobased sensors with high specificity and sensitivity can be designed for the early detection of infection (Figure 1). Antiviral drugs can be encapsulated to enhance their efficacy and potency, reduce toxicity and have sustained-release properties (Campos *et al.*, 2020). Many such NDDS have been developed; some are presented in Table 1.

2.1 Nanoencapsulated plant products

Medicinal and aromatic plants (MAPs) from across the globe have been investigated for their potential as antiviral. In the past two years since the pandemic, the plants possessing potential as an immunity booster and having properties to prevent the virus from infecting a host cell or preventing its replication are being researched for equivalent properties against SARS-CoV-2.

Conventional medicines using plants and their phytoconstituents across various geographic locations and habitats have been suggested as promising sources of natural drugs for antiviral therapy against COVID-19 infection. Researchers have revisited many plants and their active phytochemicals in the past two years for a therapeutic hunt for COVID-19. A few MAPS having anti-SARS-CoV-2 potential are depicted in Table 2

The phytoconstituents are also being modified into new drug delivery systems involving nanotechnological techniques with added benefits (Figure 2). Some nanoencapsulated phytoconstituents are hereby discussed.

2.1.1 Curcumin (*Curcuma longa* L.)

The dried rhizomes of *Curcuma longa* L. are rich in polyphenolic compounds; namely, curcuminoids, with E-1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, or curcumin, being the most prominent one. Curcumin bears the potential of being an exceptional anti-inflammatory, antioxidant, antimicrobial, antiviral, antitumor and immunomodulator (Mehrotra and Jadhav, 2021).

Table 2: MAPS with anti-SARS-CoV-2 potential

Medicinal/aromatic plants	Phytoconstituents	Activity against	References
Camellia sinensis	Theaflavin	RNA-dependent RNA polymerase	Lung *et al.*, 2020
	Myricetin 3-O-beta-D-glucopyranoside	Binds to SARS-CoV-2 3CL protease	Ul Qamar *et al.*, 2020
Zingiber officinal	6-Gingerol, 8-Gingerol, and 10-Gingerol	Binds to SARS-CoV2 PLprotease	Goswami *et al.*, 2020
Andrographis paniculata	Andrographolide	Binds to SARS-CoV-2 3CLprotease	Enmozhi*et al.*, 2020
Scutellaria baicalensis	Baicalin and baicalein	SARS-CoV-2 3CL protease	Su *et al.*, 2020
Azadirachta indica	Meliacinanhydride	Main protease inhibitor	Umar *et al.*, 2021
	Nimolicinol	Main protease inhibitor	Parida *et al.*, 2020
	Nimbin	Interact with protease	Gurung *et al.*, 2020
Anthocephalus cadamba	Oleanic acid	Main protease inhibitor	Teli *et al.*, 2021
Myrica cerifera	Myricitrin	SARS-CoV-2 3CL protease inhibitor	Ul Qamar *et al.*, 2020
Withania somnifera	Quercetin	Binds to PLpro and 3CLpro	Parida *et al.*, 2020 Khaerunnisa *et al.*, 2020
	Somniferine 2,3-Dehydro-somnifericin	Binds with NSP15	
	Anaferine	Binds with NSP10 and 165	
	27-Deoxy-14- hydroxy withaferin A	Protease inhibitor	
	27-Hydroxy withanone, 12-Deoxy witha-stramonolide, 27-Deoxy withaferin A, 2,3-Dihydro withaferin A	Interferes with spike protein	
	27-Hydroxy withanolide B	Binds with NSP10	
	Witha-stramonolide, Withanolide R, Withanolide A, Withanolide B	Binds with NSP12D2	
	27-Hydroxy Withanolide B	Binds with NSP9	
Glycyrrhiza uralensis	Licoleafol	SARS-CoV-2 3CL protease inhibitor	Ul Qamar *et al.*, 2020
Tinospora cordifolia	Cordioside Berberine	Main protease inhibitor	Pandit and Latha, 2020 Srivastava *et al.*, 2020
Catharanthus roseus	Vindolinine	Binds with NSP15	Parida *et al.*, 2020
Cinnamomum verum	Camphorating D	Blocks signalling pathway	Khanal *et al.*, 2020
	Bonducellpin D	Inhibits Mpro	Gurung *et al.*, 2020
Piper nigrum	Moupinamide	Inhibits PLpro	Mani *et al.*, 2020
Curcuma longa	Demethoxy-curcumin	Mpro inhibitor	Khaerunnisa *et al.*, 2020
Aloe vera	Aloenin	Interacts with protease	Pandit and Latha, 2020
Nigella sativa	Limonin	Binds with NSP16	Parida *et al.*, 2020

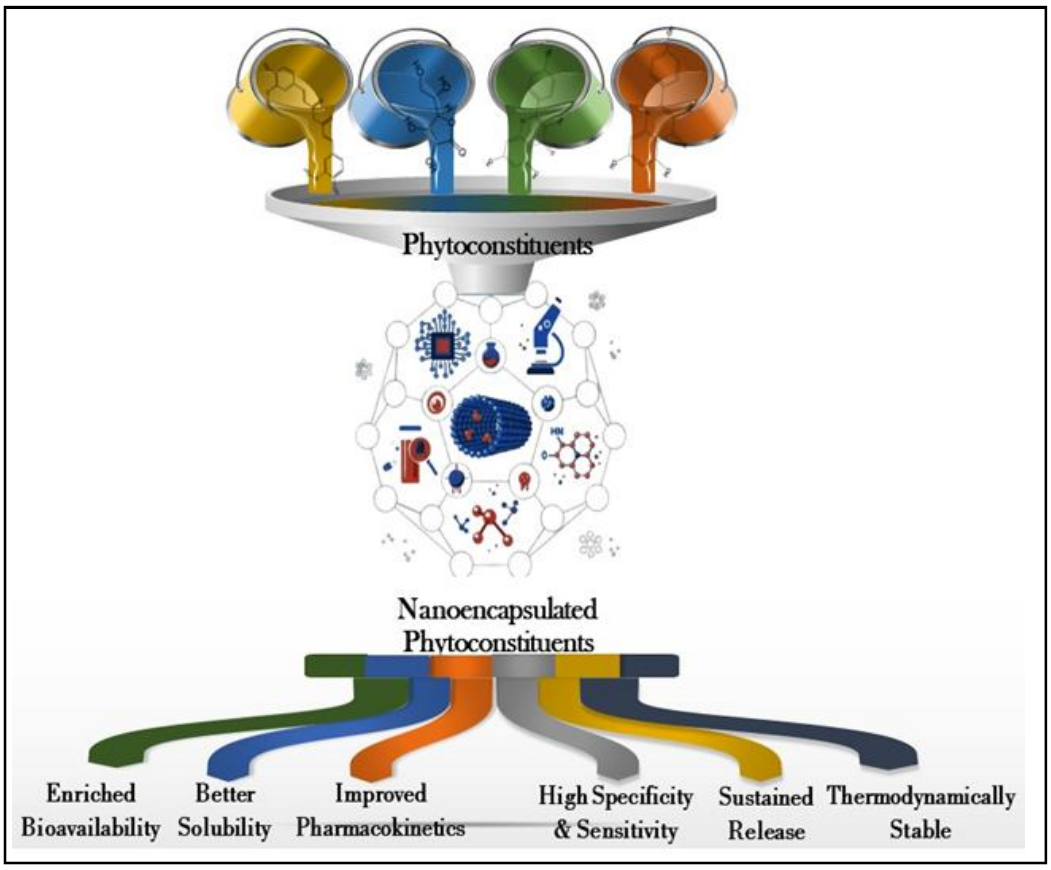

Figure 2: Advantages of nanoencapsulated phytoconstituents.

Curcumin possesses anticytokinetic properties, which modulate inflammation as the synthesis of IL-1, TNF-α, IL-8, transcription factors as nuclear factor kappa B (NF-kB) and activator protein-1 (AP-1) are inhibited, thereby restricting lung tissue damage during infections of the respiratory system (Avasarala *et al.*, 2013). In contrast to nelfinavir, a synthetic antibiotic, curcumin shows a greater binding affinity towards SARS-CoV-2 Mpro (Khaerunnisa *et al.*, 2020). Infection of the host cell can be minimised because it irreversibly inhibits aminopeptidase N/CD13 (Shim *et al.*, 2003). *In silico* studies further suggest that curcumin inhibits the entry of SARS-CoV-2 into target cells, as it binds with great affinity to the SARS-CoV-2 nucleocapsid and proteins as NSP 10 (Suravajhala *et al.*, 2020).

Curcumin, an organic molecule, is poorly soluble in water, and thus its bioavailability gets restricted, leading to instability in body fluids and rapid metabolism. Feng *et al.* (2017) demonstrated enhanced water solubility of nanoencapsulated curcuminoids and liposomal curcumin. Further, Dos Santos *et al.* (2019) suggested that curcumin nanoparticles exert enhanced antioxidant and cytotoxic effects against tumor and non-tumor cell lines. Liposomal curcumin inhibited the nuclear factor-kappaB pathway and the downregulation of inflammatory cytokines as transforming growth factor-β, tumor necrotic factor-α, IL-6 and IL-8 after thoracic irradiation (Sadeghi *et al.*, 2019). Liu *et al.* (2013), by the one-step solid dispersion method, synthesised monomethyl poly (ethylene glycol)-poly (ε-caprolactone) copolymer (MPEG-PCL) curcumin loaded micelles. The loading capacity of the micelles was 14.8%, with an encapsulation efficiency of 98.9%. These micelles showed sustained release *in vitro* at pH 7.4, with 60% of entrapped curcumin being released in 7 days. Hu *et al.* (2018) developed inhalable curcumin-loaded in large porous microparticles to treat idiopathic pulmonary fibrosis with the microparticles significantly diminishing lung injuries, hydroxyproline concentration and collagen I synthesis. It also inhibited TNF-α, TGF-β1, NF-κB p65, and MMP9 and showed higher antifibrotic activity (Amini *et al.*, 2018). Lung injuries during SARS-CoV-2 infection are similar to idiopathic pulmonary fibrosis, so that these microparticles can cause therapeutic advantage in COVID-19. Collagen deposition and expression of myofibroblasts reduce with curcumin and it thus is preventive for the development of pulmonary fibrosis (Li *et al.*, 2020). Kandeel and Al-Nazawi (2020) observed that a combination of vitamin C, curcumin and glycyrrhizic acid was effective in pulmonary fibrosis resulting from SARS-CoV-2. Clinical trials by Tahmasebi *et al.* (2020) and Valizadeh *et al.* (2020) for nanoencapsulated curcumin helped significantly in diminishing common symptoms associated with COVID-19 like cough, fever and dyspnea.

The charge on the nanoparticles modulates the efficiency and cellular uptake of nanoparticles and it was concluded by Lee *et al.* (2016) that a positive charge leads to the higher uptake efficiency by alveolar macrophages. Such studies suggest that curcumin could be used as a therapeutic and prophylactic agent in inhibiting the attachment of viruses with the host cells.

2.1.2 Thymoquinone (*Nigella Sativa* L.)

One of the primary compounds in the seeds of *Nigella sativa* L., a plant with vari*ous* medicinal properties with a good safety profile, is thymoquinone (Imran *et al.,* 2019). Quinones are compounds having double substitution for the ketonic group, and thus are very reactive (Goyal, 2017).

As per Ahmad *et al.* (2020) study, thymoquinone has been shown to possess a strong binding affinity for the SARS-CoV-2-ACE2 interface, the site through which the virus infects the host cell. Besides thymoquinone, other active constituents of *N.sativa* are dithymoquinone, thymol, thymohydroquinone, p-cymene, 4-terpineol and tanethole and all of these docks well against the S protein-ACE2 receptor interface. This binding can thus be a strategy to disrupt viral entry as it prevents virus-host interactions. Amongst the pharmacological effects produced by *N.sativa* are its properties as anti-inflammatory, antidiabetic, antihistaminic, antioxidant, antiviral, bronchodilatory, immunomodulatory and antitussive actions (Maideen, 2020). Idrees *et al.* (2020) studied *N. sativa* for its potential against the causes and symptoms of COVID-19. Studies showed the effects of the phytochemicals with anti-SARS-CoV activity and concluded *N.sativa* to be very promising. Through, molecular simulation studies, Kadil *et al.* (2020) depicted the inhibitory activity of thymoquinone against SARS-CoV-2 protease. In animal models with induced sepsis leading to kidney and liver failures; thymoquinone showed therapeutic activity. Similar pathological conditions are present in COVID-19 pneumonia, and thus the possibility of causing relief in COVID-19 (Alkharfy *et al.*, 2020; Guo *et al.*, 2020).

Thymoquinone has poor oral bioavailability, as it is only slightly soluble in water (Pathan *et al.*, 2011). Thymoquinone-loaded nanostructured lipid carriers were studied for their pharmacokinetics and bioavailability using a high-pressure homogenisation method. The nanoparticles exhibited sustained release of the phytoconstituent at a slow rate and the concentration attained was in the therapeutic window. The absorption was better through the intravenous route, while the bioavailability was better *via* oral administration (Zakarial *et al.*, 2020; Rathore *et al.*, 2020).

2.1.3 Resveratrol (*Vitis vinifera* L.)

Resveratrol is a polyphenol compound (3,5,4'-trihydroxystilbene) found in fruits as grapes (*Vitis vinifera*), Mulberry (Morus *nigra),* Peanuts (*Arachis hypogaea*), amongst many others.The pharmacological properties endowed in this phytoconstituent include being an antioxidant and free radical scavenger, antiviral, antiplatelet, anticarcinogenic, anti-inflammatory, cardioprotective and immunomodulator (Baur and Sinclair, 2006). Pasquereau *et al.* (2021) tested *in vitro* activity of seven drugs/nutraceuticals against HCoV-229E. Extensively used drugs such as lopinavir/ritonavir and chloroquine showed EC_{50}values of 8.8 µM and 5 µM, respectively, while the EC_{50} = 4.6 µM for resveratrol was suggestive of a favorable antiviral effect. It also showed the best selectivity index of 45.65. The phytoconstituent has immunomodulatory effects and in animal models, it attenuates lung injury (Baur and Sinclair, 2006) along with a reduction in levels of inflammatory biomarkers such as tumor necrosis factor and C-reactive protein (Koushki *et al.,* 2018).

Resveratrol undergoes extensive metabolism in the gastrointestinal tract, leading to poor oral bioavailability and a noticeably short half-life of a few minutes, though its metabolic byproducts as sulfate metabolites have a half-life of about 8 h. Due to these reasons, the compound cannot attain effective levels to depict antiviral activity during oral administration (Baur and Sinclair, 2006), leading to the development of nanotechnology-based formulations (Lin *et al.*, 2020). Electrospinning technology was used to synthesise resveratrol-loaded polyvinylpyrrolidone and hydroxypropyl-β-cyclodextrin nanofibers. The nanofibers possessed good antioxidant activity and skin penetration ability compared to pure resveratrol. In HaCaT keratinocytes, the nanofibers suppressed particulate matter-induced expression of COX-2 and MMP-9 proteins known to lead to inflammation. Thus, improved solubility and physicochemical properties of these nanofibers hold antiviral potential for tropical application.

2.1.4 Gingerol (*Zingiber officinale* Roscoe)

6-gingerol, the most active constituent of fresh ginger, is a phenolic compound with a broad spectrum of therapeutic values (Butt and Sultan, 2011). A potent immunomodulator, it is known to affect the secretion of inflammatory cytokines levels (Akinyemi *et al.*, 2018), and in macrophages, it leads to the inhibition of lipopolysaccharide (LPS)-induced inflammatory responses (Villalvilla *et al.*, 2014). Kardan *et al.* (2019) and Yocum *et al.* (2020) also demonstrated the beneficial activity of gingerol in cases of allergic asthma and allergic rhinitis. The phytoconstituent in ginger depicts suitable pharmacokinetic parameters along with good biodistribution, contributing to its advantage as a therapeutic agent (Li *et al.*, 2019). When delivered *via* the oral route, the constituents are absorbed and distributed well in the body tissue (Simon *et al.*, 2020).

Using a modified thin-film dispersion method, spherical/oval gingerol proliposomes were prepared which were reported to be physicochemically stable with good release of gingerol under *in vitro* conditions with five times enhanced oral bioavailability (Wang *et al.*, 2018).Goswami *et al.* (2020), through *in silico* studies, have demonstrated good inhibitory activity of gingerols against SARS-CoV-2 PLprotease. Thus, nanoencapsulation of this immune system modulating phytoconstituent can be a candidate for COVID-19 therapy.

2.1.5 Kaempferol (Vegetables and fruits)

The polyphenol is present in abundance in various vegetables and fruits such as beans, broccoli, cabbage, cauliflower, chia seeds, cumin, moringa leaves, fennel and garlic, is 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) or kaempferol. It displays numerous pharmacological characteristics such as antidiabetic, anticarcinogenic, anti-inflammatory, antimicrobial, antioxidant, antitumor, cardio and neuroprotective (Imran *et al.*, 2021). Both *in vitro* and *in silico* studies confirm the interaction of the phytoconstituent with SARS-CoV-2 main protease 3CLpro (Khan *et al.*, 2021). Kaempferol bears structural resemblance with flavonoids such as myricetin, dihydromyricetin, scutellarein, 5,6 dihydroxyflavone, 6,7 dihydroxyflavone, herbacetin, baicalein and others and all these compounds have been reported by Dai *et al.* (2020) to inhibit 3CLpro strongly. The IC_{50} value depicting inhibition of SARS-3 CLpro was 116.3 µM with kaempferol (Jo *et al.*, 2020). Thus, this phytoconstituent protects host cells from virus-induced cell death, implying its use for COVID-19 treatment.

Qian *et al.* (2019) observed that kaempferol reduces endotoxin-induced inflammatory responses, similar to those seen during SARS-

CoV infection. It was observed that an increase in K63-linked polyubiquitination of factor 6 is associated with receptors for TNF and IL-1, leading to higher activation of other downstream signal pathways.

Pharmaceutic nanotechnological approaches such as complexes with phospholipid or emulsifying formulations are known to enhance the low bioavailability of kaempferol (Chen *et al.*, 2010). *In vitro* and *in vivo* effects of different nanostructured lipid carriers with N-trimethyl chitosan delivered *via* oral route were examined by Du *et al.* (2019), and the pharmacokinetic properties were improved. The impediments in the specificity, absorption and bioavailability can be negated using nanoparticles like gelatin encapsulated kaempferol (Khatoon *et al.*, 2022).

2.2 Phytoconstituent co-encapsulation in nanoparticles

Huang *et al.* (2019) formulated curcumin and resveratrol co-loaded liposomes by mixing the components in 5:1, wherein small-sized 77.50 nm liposomes with 80.42% encapsulation efficiency and low polydispersity index were obtained. The liposomes exhibited intense 2,2-diphenyl-1-picrylhydrazyl scavenging activity and lipid peroxidation inhibitory activity. Techniques such as fluorescence and infrared spectroscopy determined that in the hydrophobic acyl-chain region of the liposomes; curcumin was located while orientated to the polar head groups was resveratrol which improvised the pharmacokinetic properties of the combination liposomes against those entrapped with individual components.

A similar experiment was conducted by Zhang *et al.* (2019) wherein α-tocopherol and resveratrol, having different solubilities, were nanoencapsulated into zein nanoparticles. Resveratrol was encapsulated at the portion between the hydrophobic core and the surface of zein particles. The encapsulated zein particles showed better stability of both the constituents.

Natural polyphenolic compounds as curcumin and rutin hold antibacterial, antitumor, antioxidant, anti-inflammatory and chemo-preventive medicinal properties, amongst many others. Nanoparticles containing both curcumin and rutin were prepared using the solvent evaporation method. The oral bioavailability of both the components, curcumin and rutin, increased to 3.06 and 4.24 folds, respectively, as compared to their pure drugs (Negahdari *et al.*, 2021).

2.3 Nanoencapsulated food

The nanoencapsulated bioactive components discussed have been utilised mainly for enriching the bioavailability of minerals, vitamins, polyphenols, omega (ω)-3 fatty acids and so on. These macro and micronutrients play an immense role in boosting immunity and are being discussed as a modality of combating COVID-19. A significant setback to meeting these requirements through the diet is the poor bioavailability of these compounds, as they are susceptible to low pH in the gastrointestinal tract. Thus, the futuristic opportunities to build immunity could be to use nanoencapsulated active compounds for fortification in food to impart greater bioavailability and provide targeted delivery along with sustained release during viral infections like COVID-19 (Tripathy *et al.*, 2021).

The role of vitamin D as an immunomodulator has been researched and shown to abate the cytokine storm by diminishing INF γ and TNF-α release and, through T-cell induction regulating the adaptive immune response (Cantorna *et al.*, 2015). Golfomitsou *et al.* (2018) added vitamin-D3 encapsulated in soya lecithin to milk and its products as lassi as a supplement for COVID-19. The vitamin-D3 nanoparticles exhibited good stability with acceptance from subjects during sensory evaluation.

Omega (ω)-3 fatty acids are potent immune enhancers, leading to the proliferation and activation of T-cells, macrophages and neutrophils (Gutiérrez *et al.*, 2019). A rich source of omega (ω)-3 fatty acids is fish oil; however, many do not prefer the flavor and aroma. Hence, as an alternative, Ojagh and Hasani (2018) encapsulated these fatty acids in liposomes made from soybean phospholipids. These liposomes were used in bread, making it a healthy food option. The bread scored well during the sensory assessment and adding liposomal ω-3 fatty acids did not lead to an unfavourable texture.

Another essential nutrient for immunosurveillance that controls the proliferation and differentiation of immune cells, cell-mediated immunity as well as cytokine production is iron. Its deficiency affects T-cell maturation, macrophage differentiation and the functionality of natural killer cells. Gutiérrez *et al.* (2016) formulated iron-fortified yoghurt using sorbitan mono-oleate lauryl alcohol and glycerol to encapsulate iron. As iron is essential for the proper functioning of the immune system, nanoencapsulated iron may be used against coronavirus (Lange and Nakamura, 2020).

Feng *et al.* (2020) prepared nanoemulsions that contained fat-soluble vitamin E integrated into fish and meat-based food products. Due to the small size and better distribution of the vitamin within nanoemulsion, these nanoparticles enhanced stability, thus providing higher antioxidant activity to the fish and meat food products. The role of vitamin E is significant in providing immunity as it enhances activity as well as mitogenesis of T-cells, increases secretion of IL-2 and also augments NK cell function, resulting in minimising the risk of infections (Wu and Deydani, 2019), which can be effective against SARS-CoV-2 too (Shi *et al.*, 2020).

3. Polyherbal delivery systems

Plants have served and continue to serve as an essential basis of medication since the hunter-gatherer days. Plant natural products have evolved themselves to form modern-day medicine. Plants are the offerors of many ingredients for the treatment of COVID-19. The plant-based Rasayanas are well known for their immunomodulatory and rejuvenating properties, which can be helpful in the management of COVID-19. *In vitro* as well as clinical studies have confirmed the immunomodulatory actions of plant-based Rasayana drugs like *Tinospora cordifoloia* (Guduchi), *Emblica officinale* (Amalaki), *Withania somnifera* (Ashwagandha) (Balasubramani *et al.*, 2011). Plant-based formulations have been projected for protective and remedial purposes to battle COVID-19. These formulations contain gold nanoparticles (Swarna bhasma), silver nanoparticles (Rajat bhasma), copper nanoparticles (Tamra bhasma), iron nanoparticles (Lauha bhasma), and tin nanoparticles (Vanga bhasma) (Kar *et al.*, 2020). Studies reported that metal nanoparticles possess virucidal action, which may destroy the viral envelope or inhibit viral reproduction. Soni *et al.* (2020) and Gauri *et al.* (2020) elucidated the antiviral property of bhasma as, it affects the conformation of spike protein and disrupts the outermost layer of the coronavirus. It was also observed that Rajat bhasma has the potential to inhibit the replication cycle of coronavirus, whereas Tamra bhasma exhibits virucidal potential by degrading SARS-CoV-2 capsid.

According to Sarkar and Mukhopadhyay (2021), Ayurvedic bhasma formulations with immunomodulatory effects can be used as an adjuvant for vaccines. These herbal-based immunomodulators may be injected laterally with the vaccines that may elicit a quicker and stronger response against COVID-19 infection. They further established the possible use of Swarna bhasma with gold nanoparticles as an adjuvant with vaccines, providing more decisive immunomodulatory action by elevating IL-1β, IL-6 and IFN-γ. The other preparations of bhasma such as Yashada bhasma also revealed similar prospects when administered along with vaccines.

As per the findings of Rastogi *et al.* (2022), interventions of Ayurveda were pragmatically proposed for preventive, curative and prophylactic action of formulations against severe, moderate and mild cases of COVID-19. In their exhaustive study, 120 COVID-19 RTPCR confirmed patients with mild, moderate and severe symptoms were selected and divided into two groups, *viz.*, control study and intervention group. In the control study group, standard medications such as paracetamol, hydroxychloroquine and methylprednisolone were administered, whereas in the intervention group, *Ayurcov* medication comprised mainly curcuma, potassium alum, rock candy along with other ayurvedic components was administered. They were also supplemented with standard medicines. Surprisingly, the results showed that significant proportions of patients with *Ayurcov* were relieved of symptoms early compared to the control group.

Furthermore, the study group presented a significant decrease in the RT-PCR Ct values. Also, the functional status of the interventional group was better than the control group, with a lower risk of adverse reactions. Similar positive outcomes were observed in the clinical trial studies presented by Sankhe *et al.* (2021) on *Ayurcov.*

Balkrishna *et al.* (2021) conducted a comparative study on 59 patients suffering from COVID-19 with mild symptoms who were selected to be administered allopathic medicines in combination with ayurvedic treatment or only ayurvedic medicines. Forty-one patients were administered a combination of azithromycin, vitamin C and antihistamines along with plant-based Rasayana such as giloy ghanvati (GG), divya swasari ras (DSR) and ashwagandha capsule (AC), while another group of 18 was only given ayurvedic formulations. The study's results suggested that 88.33% of patients who were only on ayurvedic medicines were relieved of the symptoms within 13 days, while amongst those on combination therapy, 48.78% of patients felt relief in the same duration.

In another study, Balkrishna *et al.* (2021) studied coronil, a tri-herbal formulation comprising *Withania somnifera*, *Ocimum sanctum* and *Tinospora cordifolia* and observed that the formulation helped prevent SARS-CoV-2 stimulated pathologies in rescued humanised zebrafish. It inhibits the interaction of ACE-2 with recombinant spike protein on the virus and significantly lowers the elevated cytokines such as IL-β, IL-6, and TNF-α in A549 cells, in a dose-dependent manner.

A placebo-controlled, randomised, double-blind pilot clinical trial was conducted with a formulation comprising giloy ghanvati (*Tinospora cordifolia*), ashwagandha (*Withania somnifera*), tulsi ghanvati (*Ocimum sanctum*) and swasari ras-a-herbo-mineral formulation. It was an oral formulation administered for seven days, twice per day. Besides the polyherbal, the subjects were also administered four drops of Anu taila (a nasal drop) daily before breakfast. The control group was given a placebo. RT-qPCR was used to estimate the viral load, and quantification of IL-6, TNF-α and hs-CRP was conducted. By day seven, 100 % recovery was observed in the treatment group, while it was 60.0 % in the placebo group. The IL-6, hs-CRP, and TNF-α were 2.5, 12.4, and 20 times lesser in the treatment group compared to the placebo group on day 7 (Devpura *et al.*, 2021).

An extensive study was accomplished by Qing *et al.* (2020) to learn about the interaction of herbs and chemical drugs and it revealed that Chinese medicines, along with western medicines, play a vital part in preventing the progress of the disease and enhancing the patients' recovery. Xia *et al.* (2020) performed clinical studies to prove that lymphocyte percentage, serum alanine transaminase, aspartate transaminases, amyloid A, creatine kinase enzyme and blood urea nitrogen in the combined therapy recovered faster than those treated with only western medicines. According to Fu *et al.* (2021), integrated administration of granules of Toujie Quwen, prepared from sixteen different Chinese medicines, up-regulated the CD^{4+}/CD^{8+} expression along with lymphocytes in 37 patients with COVID-19. This suggested the optimistic function of combined therapy in modulating immune cells and enhancing the recovery rate of patients. A comparative study by Song *et al.* (2019) indicated a reduction in the mortality rate of 710 patients with severe pneumonia by 8.8% when administered with Xuebijing injection with a regular treatment strategy and reduced ICU hospitalisation by four days.

Thus, polyherbal delivery systems can be an excellent pharma cological intervention against COVID-19.

4. Vaccines as preventive medicine

Antibodies are immune mediators exerting a combined effect, thereby neutralising the viral particles for faster recovery from disease. For many viral diseases, the detrimental action of killer lymphocytes (NK cells) governs the healing rate. Literature supports that protective action against COVID-19 is associated with antibodies against the spike proteins and its ability to bind to ACE receptors or prevent replication (Piccoli *et al.*, 2020).

As preventive measures are better than therapeutic modalities, a better approach to end the pandemic was to develop vaccines. Despite numerous studies on SARS-CoV-2, due to the high mutation rate, there exist many unanswered questions, and it is challenging to forecast the type of immune response a vaccine will elucidate against the virus. According to Lurie (2020), developing a vaccine is an expensive and extensive process with a high failure rate. It involves exploring manifold candidates with several years of challenging work to obtain a licensed vaccine ready for production.

The first COVID-19 vaccine was administered to a volunteer in March 2020 during a clinical trial. Later in the year, more than 100 vaccines proceeded to human trials. As of June 2022, the number has increased to 166. These are currently being tested in clinical trials, whereas around 198 vaccines are in preclinical development (WHO, 2022). These anti-SARS-CoV-2 vaccines target the whole CoV-2 virus or fragments of the viral surface. All the different vaccines can be congregated based on the scientific platform to exert effective action, and thus every vaccine has its characteristics, making it unique in terms of efficacy and side effect. It is of utmost importance to compare the effectiveness and time of the protective response provoked by the different vaccines to grade them as superior (Akst, 2020).

4.1 Nucleic acid vaccines

Nucleic acid vaccines are derived from DNA or RNA, leading to the synthesis of viral proteins that stimulates an immunological response. DNA and RNA-based vaccines have a peculiarity in ease of construction that permits their rapid development. Such vaccines can be introduced into the human cells to produce copies of the genome that elicit immunostimulatory mechanisms (Piyush *et al.*, 2020). Development of nucleic acid anti-SARS-CoV-2 vaccines, as compared with traditional vaccines, hold preference due to the high potency of mRNA, activation of both CD4+ and CD8+ T-cells and simplicity in the design of structural modification of mRNA (Schlake *et al.*, 2018; Pardi, 2016; Lim *et al.*, 2015). In relation to safety and cost of production, nucleic acid vaccines possess many advantages over the other types of vaccines.

4.1.1 DNA vaccine

In vitro synthesis of DNA is typically carried out by plasmid DNA with eukaryotic expression elements encoding specific proteins/ antigens. The type of plasmid and vector selection depend on the desired product (Rauch *et al.*, 2018). DNA vaccines for infectious diseases caused by cytomegalovirus, Zika virus, HIV, Influenza virus, Human hepatitis virus, Ebola virus, and MERS-CoV are already in preclinical trials, and some have progressed to clinical studies (Gary and Weiner, 2020). DNA vaccines are highly immunogenic and can produce a higher titer of antibodies when administered along with the inactivated vaccine using an electroporation device.

INO-4800, a vaccine against SARS-CoV-2, developed by INOVIO Pharma, Korean Institute of Health and International Vaccine Institute, is an example (Kaur and Gupta, 2020). The safety, immunogenicity and tolerability of INO-4800 were investigated in an open-label, non-randomised, phase-I study against COVID-19 volunteers of Kansas City and Philadelphia. It was observed that this vaccine exhibits optimal development speed and thermal stability. Despite several advantages, INO-4800 faces many challenges, such as insufficient immunogenicity, the requirement for larger volumes, and the use of special electroporation devices, which is a financially heavy burden (Tregoning and Kinnear, 2015). As per the McGill COVID-19 vaccine tracker team (2021), TAK-919 (Moderna formulation), ZyCoV-D (Zydus Cadila), and AG0301 (An Ges formulation) are the other varieties of DNA-based vaccines synthesised and are in the clinical trial. As of 21st June 2022, seven DNA candidate vaccines have entered phase-I clinical trial, whereas five vaccines have entered phase-II, with four vaccines in phase-III (WHO, 2022). Inside the cells, DNA vaccines can stimulate innate immune responses related to inflammasome and TLR9/MyD88 (Suschak *et al.*, 2016).

In silico studies revealed genetic similarities and differences between SARS-CoV-2 and earlier infections caused by SARS-CoV and MERS. These studies provided a foundation for the prospective candidate epitopes to be considered that have helped hasten the development of vaccines against SARS-CoV-2 (Lucchese, 2020; Lee and Koohy, 2020).Th_1, Th_2, CD^{4+} and CD^{8+} T cells and antibodies are induced using DNA-based technology against several antigens providing a balanced Th_1/Th_2 response (Silveira *et al.*, 2021).

4.1.2 m-RNA vaccine

mRNA is a nominal information carrier provides minimum interaction with the host genome and is considered safe for use, alongwith the added advantage of quick synthesis. mRNA can be expressed to any protein molecule, which suggests flexibility with respect to the generation of vaccines for cancer and infectious diseases (Schlake *et al.*, 2012). It is well known that mRNA vaccines elicit humoral immune response *via* B cell activation, leading to proliferation and differentiation into memory cells or plasma cells actively secreting antibodies (Palm *et al.*, 2019).The proposal for using mRNA as a direct delivery system to manipulate gene expression and production of focused protein was put forward in late 1980. Malone *et al.* (1989) were the first to demonstrate that mRNA can be transfected to NIH_3T_3 fibroblast using N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride, a cationic lipid.

One chief advantage of mRNA-based vaccines is using the cell's protein translation system to produce accurately folded and perfectly functional proteins. The other advantages include stability, cost-effectiveness, ease of preparation and no requirements of purification steps. However, these vaccines require ultracold temperature for their storage which limits their distribution worldwide, alongwith the need for booster shots which are mandatory for maintaining threshold immunity (Turner *et al.*, 2021). Further, it has been observed that immune stimulation of the cells due to vaccines is weakened in the absence of interaction of vaccines with endosomal RNA receptors. Therefore, using opriate liposomes and complexing mediators increases cells' uptake, enhancing delivery to the cytoplasmic translation machinery and preventing degradation of mRNA (Schlake *et al.*, 2012).

SARS-CoV-2 mRNA vaccines developed by BioNTech/Pfizer, AstraZeneca/Shenzhen Kangtai, Arcturus, Moderna, Chulalongkorn University, Curevac and the Academy of Military Sciences of China have entered clinical trials. Amongst these, Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273) and Cure Vac were the vaccines developed in a concise period (Tang *et al.*, 2021). As of 21st June 2022, 37 candidate mRNA vaccines have entered clinical trials, amongst which three have entered phase-IV clinical trials (WHO, 2022). The Pfizer-BioNTech was the first vaccine against coronavirus approved by the FDA for commercial use on 23rd August 2021 and the first one to get approval for use in children aged 5-11 on 29th October 2021 (FDA 2021).

Myocarditis was an adversity reported post mRNA vaccines during the current pandemic. Mevorach *et al.* (2021) investigated suspected myocarditis patients among people vaccinated with the BNT162b2 mRNA vaccine (Pfizer-BioNTech) in Israel compared with unvaccinated controls for six months. Post-vaccination patients with suspected myocarditis were a mere 136 during the surveillance of 5 million vaccinated individuals. Amongst these suspected cases, a single patient succumbed to death. The ratio of the occurrence of myocarditis among fully vaccinated patients to unvaccinated people was 2.35, and the highest rate was found in males aged between 16 and 19 years. A similar study by Witberg *et al.* (2021) revealed that 54 cases among 2.5 million vaccinated individuals in Clalit Health Services showed myocarditis, as per the CDC's international definition.

4.2 Subunit vaccine

Subunit vaccines comprise surface proteins, such as the antigenic spike S proteins in SARS-CoV-2, made *in vitro* and administered. These are safer vaccine candidates with significantly fewer side effects as they do not possess any active viral component. Due to the lower potential for an immunological response, these vaccines must be

given in multiple doses along with adjuvants (Khuroo *et al.*, 2020). According to Ning *et al.* (2020), the virus can enter the cell by endocytosis through S-protein by binding to the hACE2 receptor. Hence, the S-protein and its fragments are the prime targets for developing a vaccine. As of June 2022, 54 total candidate vaccines have entered the clinical trials, of which only one vaccine has entered phase-IV leaving 21 in phase-III, 6 in phase-II, and 15 in phase-I clinical trials (WHO, 2022).

NVX-CoV2373 is a nanoparticle-based vaccine eliciting immune response based upon the recombinant expression of the stable pre-fusion S-protein expressed stably in the Baculovirus system (Coleman *et al.*, 2020; Tu *et al.*, 2020). FDA provided fast track designation to Novavax for the vaccine NVX-CoV2373, to be tested in clinical trials. Dunkle *et al.* (2022) conducted a phase 3, placebo-controlled, observer-blinded, randomized trial in Mexico and the US (United States), where 29949 participants underwent randomization, of which 19965 received NVX-CoV2373 and 9984 were administered a placebo. They observed 90-95% efficacy of the vaccine in preventing infection. Chooa and Teoa (2021) demonstrated an 89.7% efficacy rate with systemic and minor local adverse effects such as pain at the injection site, headache, tenderness, fatigue and myalgia.

The multi-epitope vaccines were established considering that they should be highly antigenic, immunogenic and promiscuous with B-cell epitopes. Higher binding affinity towards MHCs (major histocompatibility complex) and confirmational globularity of structure were also considered.

4.3 Virus like particles

Other than subunit vaccines, protein-based anti-SARS-CoV-2 vaccines comprising only the viral shell mimicking the virus structure and lacking an active genome, thus making them non-infectious, are an alternative (Callaway, 2020). Virus-like particle (VLP) vaccines present numerous copies of the same antigen on the surface leading to strong immunogenicity against the empty viral surface. These vaccines provide a good safety profile as they lack a pathogenic viral genome, and thus do not multiply, reducing the risk of being infectious. However, this property of the vaccine characterises complications in the development because of the challenging assembly of the viral structure (Zhao *et al.*, 2020).To evaluate the immunogenic effect of the virus-like particle vaccine, BALB/c mice were administered with 0.4 micrograms and 4 micrograms of vaccine either alone or in combination with alum with the interval of 2 weeks. The results suggested that mice immunised with either low or high doses showed considerable anti-S-binding immunoglobulin (IgG and IgG1) after booster doses (Syed *et al.*, 2021). According to the McGill, COVID19 vaccine tracker team (2021), several VLP vaccines are generated; listed few are Coronavac (Sinovac), BBIBP-CorV (Sinopharm), BBV152-Covaxin (Bharat Biotech), AZD1222-Vaxzevria (Oxford/AstraZeneca). Until June 2022, only six vaccines have been developed that belong to this class, with 2 progressing to phase-III clinical trials (WHO 2022).

4.4 Viral vector

Viruses invade the host and overpower its protein-synthesising machinery, enforcing the synthesis of viral proteins coded by the viral genetic code, leading to multiple copies of the virus. These viral proteins, thus synthesised are immunogenic and lead to an immune response by the cells (Chen and Li, 2020).

A viral vector vaccine is based on a similar principle, wherein the host cells are exposed to weakened viruses that are avirulent and cannot cause COVID-19. However, they stimulate and elicit the host's immune system, thus providing immunity against the disease (Rauch *et al.* 2018). In the case of a prior immunisation through a similar viral vector-based vaccine, the hosts existing immunity prevents the replication of the newly introduced viral vector, thereby preventing it from developing immunogenicity against the second viral vector (Zhi, 2006).

Viral vector vaccines are commonly administered intramuscularly, though, in the current pandemic, several studies are being conducted for nasal administration of the vaccine (Forni and Mantovani, 2021). A successful attempt could lead to a potential vaccine that would help induce a mucosal immune response with the potential of neutralising the virus and consequently inhibiting its capacity to enter the host cells. Currently, 21 non-replicating and four replicating viral vector candidate SARS vaccines are in clinical trial phases. Amongst these, four nonreplicating candidate vaccines have been approved and have entered phase-IV trial, whereas two replicating candidate vaccines have successfully cleared phase-II clinical trial (WHO, 2022).

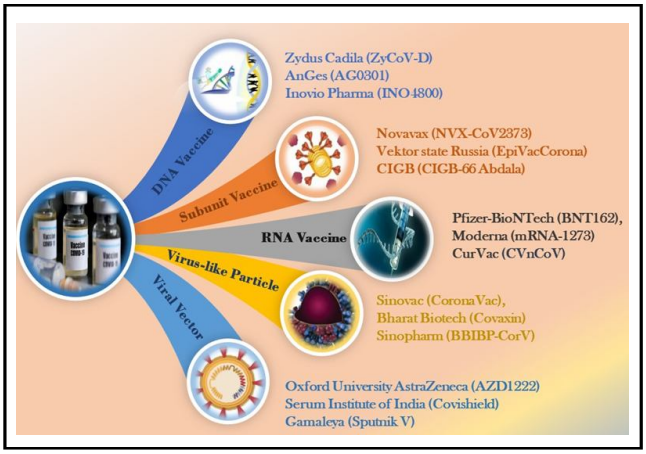

Figure 3: Vaccines as preventive medicine for COVID-19.

An extensively studied and developed human adenovirus type 5 vectored vaccine can induce mucosal immunity and is effective for a broad host range with robust infectivity high expression of proteins, and increased safety (Guo *et al.*, 2015). According to Shim *et al.* (2012), adenoviruses encoded SARS-CoV spike proteins, when administered intranasally and sublingually, as compared to intramuscularly, exert a more robust $CD8^+$ cell response and more remarkable ability to neutralise IgA and antibodies. It was observed that a solitary injection of the MERS-CoV-S protein-coding human adenovirus type 5 (HAdV-5) or HAdV-41 vectored vaccines provoked systemic and mucosal immunity in rats (Guo *et al.*, 2015). Further, Jung *et al.* (2018) boosted these subjects with S nanoparticles to detect the vaccine-induced IgG neutralising antibodies that are S-specific, along with tracking of Th_1 and Th_2 immune responses for protection of adenoviral transduced mice from MERS-CoV. A replicating faulty MVA (modified vaccinia virus Ankara) was used to express viral antigens in mammals. It was a potential stimulator of chemokines, inflammatory cytokines and lymphocyte and monocyte migration. It was notified that MVA-SARS-CoV elicited a high immunogenic response by producing neutralising antibodies in

rabbits, monkeys and mice (Delaloye *et al.*, 2009). In 2019, scientists at Hong Kong and Xiamen University successfully developed a nasal-spray vaccine for influenza, which was further taken as an initiative to develop a vaccine against coronavirus spike proteins.

5. Conclusion and future prospects

Good health requires a robust immune system that recognises changes in the body's microenvironment and adapts to these changes by eliciting a strong defensive attack. The immune system's functionality is facilitated by macro and micronutrients that provide immunocompetence and nurture innate and adaptive immune responses. Enrichment of the immune system and its functionality is the key to combating infections caused by SARS-CoV-2, a novel and highly contagious coronavirus.

Treatment involving several antiviral drugs already in use was the modality used in the initial phase of the pandemic. The drugs used included interferon α, Remdesivir, Lopinavir, Ritonavir, Ribavirin, Chloroquine phosphate and Arbidol. The dosage of drugs used to curb infection is often high leading to severe adverse reactions.

The use of plants and their products has been widely accepted across civilisations since time immemorial. Thus, the risks of toxicity due to synthetic drugs, and the low solubility of these drugs, can be resolved by using biopolymeric nanoparticles containing plant phytoconstituents. Besides negating the adverse reactions to the use of drugs, an advantage of using nanoparticles is that the concentration of phytoconstituents is comparatively low with the continuous release of active components over a more extended time. Nanotechnology-based techniques can be developed to target the viral proteases on SARS-CoV-2, *viz*., 3CLpro and PLpro, the viral S protein or the RNA polymerase, will effectively prevent infection. The viral replication can be impacted by designing nanoparticles that modulate the expression of cytokines responsible for the 'storm'.The use of more than one phytoconstituents encapsulated in nanoparticles has shown more encouraging results compared to nanoparticles with single constituents. Advantages of using nanoemulsions, nanofibers and nanoparticles can also be extended to their use in food wherein these are fortified into the food item.

The end of the pandemic was forecasted with population immunity, wherein protection from the infection can be achieved through vaccination or an earlier infection. Over the past two years, several vaccines have cleared clinical trials and are being administered to prevent aggressive infection.

Various pharmacological interventions have been cited in this review which appear very promising and initial results depict good effectiveness. This challenging time requires joint efforts from academicians, healthcare professionals, pharmaceutical companies and regulators. Concerted efforts will indeed facilitate the victory of humanity over this catastrophe.

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Conflict of interest

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

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