Annals of Phytomedicine, Volume10, Special Issue1 (COVID-19): S222-S230, 2021

DOI: http://dx.doi.org/10.21276/ap.covid19.2021.10.1.20

Annals of Phytomedicine: An International Journal
http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

Special Issue1 (COVID-19)

# Phytonanoparticles and COVID-19

**Santwana Palai◆, Ritun Patra* and Manaswini Dehuri****

*Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar-751003, Odisha, India*

* *Department of Veterinary Anatomy and Histology, College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar-751003, Odisha, India*

** *Department of Veterinary Parasitology, College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar-751003, Odisha, India*

## Article Info

**Article history**
Received 1 May 2021
Revised 17 June 2021
Accepted 18 June 2021
Published Online 30 June 2021

**Keywords**
Green nano-based drugs
COVID-19
SARS-CoV-2
Plasma therapy
Antiviral therapy

## Abstract

The novel coronavirus disease (COVID-19) pandemic has grasped the entire world due to its high rate of spread with serious public health concern. The scientific community has applied all possible therapeutic strategies to defeat the virus, still the situation is not in control. So, as a fresh approach, the "phytonanoparticles" can be used as a powerful gadget against COVID-19 because it can be formulated to perform directly concerning the infection, enhancing drug delivery system or by the way of stimulating the immunity of the patient. The plant extract bioactive can offer its antioxidant, anti-inflammatory, immunomodulatory effect for prophylaxis and treatment of SARS-CoV-2. Selective drug targeting of these plant compounds is needed for augmenting drug stability, solubility, increasing drug half-lives in the blood and reducing adverse effects in non-target organs. Green nano-based drugs use plant extract as a bioreduction and capping agent at room temperature. The green nanoparticles can be aimed to decrease the oxidative stress and systemic inflammation of COVID-19 with increased activity and lesser toxicity to normal cells. This review work summarises the antiviral, immunomodulatory, anti-inflammatory potential of green nanoparticles biosynthesised with plant derived molecules with advanced delivery systems which has a possibility to act as efficient potential remedy against coronavirus. This review discusses the scientific explorations of phytonanoparticles which can protect human lives from the devastation of SARS-CoV-2 because of its enhanced anticoronavirus biological activity.

## 1. Introduction

The challenge of SARS-CoV-2 persistence is due to the possibility of antigenic variants that evade immunity conferred by infection or vaccine. SARS-CoV-2, like SARS-CoV-1, is impossible to be eradicated. SARS-CoV-2 is apparently more transmissible than SARS-CoV-1 and, hence does not respond to the same transmission controls. It causes mortality due to oxidative stress, systemic inflammation and increased pro-inflammatory cells along with infiltration of T-helper cells and macrophages resulting in cytokine storm (Palai *et al*., 2020). It has the potential to spread to billions of people who are now uninfected on the planet, as well as the many millions who join the population each year as a new birth cohort. The remarkable and unprecedented pace at which COVID-19 vaccine production, clinical trials, emergency use authorization in less than a year, are the direct result of previous exploration of novel dissemination platforms for HIV and other viruses (Richman, 2021).

When nanomaterials are designed to contain traditional antiviral properties, nanoparticle-based delivery systems can solve problems associated with traditional drug therapies in the treatment of viral infections (Singh *et al*., 2017). Green synthesis of metal and metal oxide nanoparticles from plant leaf extracts is a plant-based eco-friendly and greener nano-access than traditional nanoparticle assembly using radioactive and unsafe materials. Phyto-nanotechnology, which uses extracts from various plant parts such as seeds, leaves, flowers, and roots to make different nanoparticles, produces phyto-nanoproducts that are inexpensive, risk-free, and energy efficient. The prepared biological nanomaterials are used in the preparation of novel pharmaceuticals for imaging, medication delivery, diagnosis, and treatment. As a result, green nanoparticles may be a key element in developing novel treatments for a variety of viral epidemic diseases (El Shafey, 2020).

Medicinal plants contain secondary metabolites like alkaloids, polyphenols, flavonoids, tannins, *etc.* acting as reducing agent for biosynthesis of nanoparticles. During the production of nanoparticles, they act as reducers, stabilisers, or both (Aritonang *et al*., 2019). Various plants or their extracts are used for green synthesis of Au, Ag or Zn like nanoparticles with antiviral, immunomodulatory, anti-inflammatory activities. These plant-based green nanoparticles are emerging source of new antiviral agents where its secondary metabolites reduce respective metal ions.

The biosynthesis of Ag nanoparticles with extracts of *Curcuma longa* (Yang *et al*., 2016), *Malephora lutea* (Haggag *et al*., 2019), *Cinnamomum cassia* (Fatima *et al*., 2016), *Andrographis paniculate, Phylanthus niruri* and *Tinospora cordifolia* (Sharma *et al*., 2019 )

**Corresponding author: Dr. Santwana Palai**
*Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, OUAT, Bhubaneswar-751003, Odisha, India*
**E-mail: palaisantwana@gmail.com**
**Tel.: +91-9438298384**

and *Panax ginseng* (Sreekanth *et al.*, 2018 ) showed their antiviral efficacy with reassuring results against HSV-1, HAV-10, and CoxB4 virus (Haggag *et al.*, 2019 ), H7N3 influenza A virus (Fatima *et al.*, 2016), chikungunya virus (CHIKV), herpes simplex virus, vaccinia, monkey pox virus, influenza virus, respiratory syncytial virus, human immunodeficiency virus, hepatitis B virus, alphavirus, togaviridae (Sharma *et al.*, 2019 ), influenza A virus (strain A/PR/8) (Sreekanth *et al.*, 2018). Large sized nanoparticles have higher level of cytotoxicity while small size nanoparticles are more efficient because having large surface areas for direct interaction with proteins of viral envelope. Also, nanoparticles with smaller size can interfere in viral replication by interacting with the viral genome and antiviral plant extracts and compounds can limit virus transmission or block infection.

The biosynthesis of nanoparticles using plant extracts like *Asparagus racemosus* (Amina *et al.*, 2020), *Hypoxis hemerocallidea* (Elbagory *et al.*, 2019) and alga like *Dictyota mertensii* (Fernandes-Negreiros *et al.*, 2018) with metal ions like Ag/ Au/ Ag-Au show immunomodulatory effects in ageing, HIV/AIDS, psoriasis, ulcers, hypertension, asthma, diabetes, tuberculosis improving vigour immunity and mental functions.

The synthesis of Ag nanoparticles using plant extracts like *Cestrum nocturnum* (Keshari *et al.*, 2020), *Lippia nodiflora* (Sudha *et al.*, 2017), *Malus domestica* (Nagaich *et al.*, 2016), *Blighia sapida* (Akintola *et al.*, 2020), *Erythrina suberosa* (Mohanta *et al.*, 2020) has shown therapeutic activity acting as local anaesthetic, analgesic, anodyne, cardiotonic, laxative and diuretic in conditions of yellow fever, epilepsy, ophthalmia, conjunctivitis, edema by douching free radicals and reactive oxygen.

The synthesis of Ag or Au nanoparticles using plant extracts like *Atropa acuminata* (Rajput *et al.*, 2020), *Nigella sativa* (Alkhalaf *et al.*, 2020), *Astragalus tribuloides* (Sharifi-Rad *et al.*, 2020), *Prunus serrulate* (Singh *et al.*, 2018), *Phyllanthus niruri* (Gajapriya *et al.*, 2020), *Sambucus nigra* (Moldovan *et al.*, 2016) extending anti-inflammatory activity in disease conditions of arthritis, scarlet fever, encephalitis conjunctivitis, joint pain, Parkinson's disease muscle spasms, pancreatitis, hepatitis B virus, diarrhoea, epilepsy pain disorders, dyspepsia, vaginitis, tumors, malaria, hypertension, fever through supporting the immune system against infections.

The main biologically active compounds like alkaloids, terpenoids and flavonoids present in medicinal plants like herbs or spices extend antiviral, immunomodulatory, antioxidant and anti-inflammatory properties can be considered for advanced antiviral plant-based drugs (Palai *et al*., 2020). These biosynthesized phytonanoparticles are cost effective, easy for handling, non-toxic and easily penetrate the host cell.

These phytonanoparticles can complement the recommended prophylaxis and treatment of (COVID-19) and evolve as natural antiviral compounds specifically against SARS-CoV. These phytonanoparticles exhibit antioxidant properties, support the immune system against infections of various viruses with anti-inflammatory potential can be considered against SARS-CoV-2 transmission or blockage. This present review encompasses the potentials of phytonanoparticles derived from medicinal plant extracts with their metallic nano-counterpart against respiratory viruses like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diseases which have no specific treatment. This article aims to help scientists and researcher to formulate nano-based plant medicines or nano-based plant medicated masks, clothes, gloves, *etc*., for prophylaxis of COVID-19 (Figure 1).

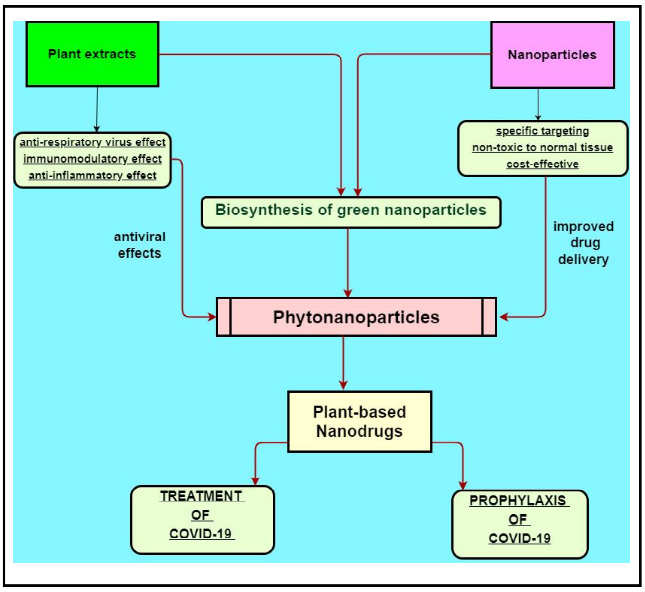


**Figure 1: Phytonanotherapeutic approaches for COVID-19.**

## 2. Nanoparticles acting as nanomedicines

The manipulation of materials at the nanoscale created opportunities for medical science to address long-standing issues such as drug-resistant bacteria, vaccine production, and cancer (Manuja *et al.*, 2012). Various nanotechnological methods, such as nanomaterials, nanomedicine, nanovaccines and nanotheranostics have been created to provide a better alternative to medical problems (Mohanty *et al.*, 2014). They transform disease diagnosis, immunization, medications and prophylactic measures. Loading substances can be coupled with nanoparticles using a variety of methods, including physical encapsulation, chemical conjugation, and adsorption. Depending on the requirement, a suitable loading nanosubstance is used. They may distribute chemicals such as medications, chemotherapeutic agents, or imaging agents; biological substances such as antibodies, antigens, RNA, or DNA by endocytosis; and light and heat to their target cells as required (El-Sayed and Kamel, 2020).

### 2.1 Advantages of nanotechnology in medicine

Using nanotechnology in medicine improved the medication half-life cycle by refining drug internalisation, lessening drug degradation or clearance, and creating slow-release pathways for loaded medications. The positive charges promote nanoparticles internalisation, negative charges prolong nanoparticles circulating time in the blood circulation. They improve medication bioavailability, water solubility of hydrophobic preparations, alter pharmacokinetics and precisely administer the medications, and reduce side effects and required doses (El-Sayed and Kamel, 2020). Nanoparticle-mediated delivery systems are efficient due to various benefits such as no enzyme degradation, prolonged life, simple delivery along with adjuvants, precise targeting of cells by receptor-ligand connections, and enhancement of immune system, which are economical, rapid, and reliable.

## 2.2 Antiviral potential and mechanism of nanoparticles

The recent coronavirus 2019 outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) results in COVID-19 which has shown its merciless impact on human health and the economy. More than two decades have passed after pandemics outbreak like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), no effective treatment against the CoV family is found, indicating the need for newer therapeutic targets. This alternative, healthy, and biocompatible antiviral agents should be capable of decreasing infection spread and mitigate economic losses. Metallic nanoparticles enable the improvement of pharmacological properties (Vahedifard and Chakravarthy, 2021). Like silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs) have exceptional antimicrobial and antiviral properties (Gurunathan *et al.*, 2020).

Silver nanostructures have been shown to improve biofilm inhibition, anticancer, and anti-inflammatory properties. Because of their potential to impair the permeability of microbial cell membranes, silver nanoparticles have antimicrobial activity. The association of AgNPs with HIV-1 is size-dependent, and bound particles have normal spatial relationships. AgNPs preferentially associate with the gp120 subunit of the viral envelope glycoprotein, and this association of AgNPs and glycoproteins prevents the virus from attaching to host cells, demonstrating a potent activity against certain viruses such as the influenza virus (Galdiero *et al.*, 2011) (Figure 2).

Antiviral activity of AgNPs against Kaposi's sarcoma-associated herpesvirus, human oncogenic-herpesviruses, and Epstein-Barr virus was demonstrated by reactivating viral lytic replication *via* reactive oxygen species production and autophagy (Gurunathan *et al.*, 2019).

Gold nanoparticles are used as drug carriers in the diagnosis and treatment of cancer, as well as in the treatment of malaria and filaria. AuNPs that have been functionalized inhibit the influenza virus, HSV, and HIV. By multivalent interactions, AuNPs can enhance antiviral effects. AuNPs inhibited the entry of porcine reproductive and respiratory syndrome virus into host cells by particularly inhibiting virus replication and protein expression (Bai *et al.*, 2018).

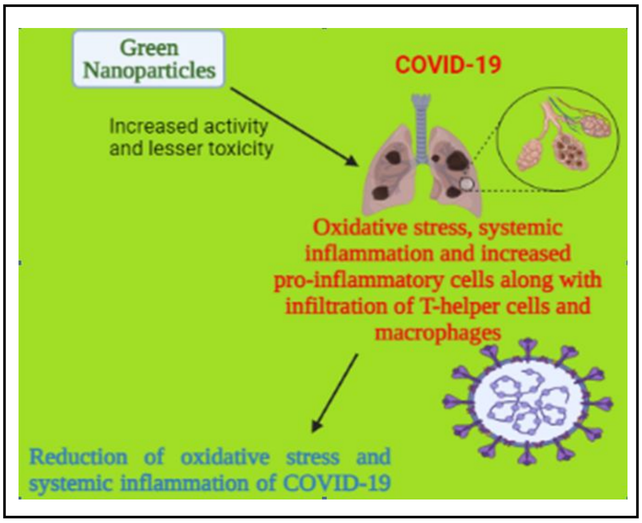


**Figure 2: Green nanoparticles extending potential antiviral activity.**

## 2.3 Green nanoparticles and their characterization

Green synthesis of nanoparticles is gaining popularity because of its sustainability, eco-friendliness, and low cost. Green-mediated synthesis refers to the production of submicron-sized particles from biogenic materials. Green metal nanoparticles include Ag, Au, Cu, Cd, Pt, Pd, Fe, and other metal oxides such as $CeO_2$, $Cu_2O$, ZnO, $TiO_2$, $ZrO_2$, $In_2O_3$, and CuO, PbS, and $Fe_3O_4$. These nanoparticles are primarily distinguished by their crystallinity, surface morphology, basic surface area, size distribution, compositional structure, particle size, and elemental composition. Spectroscopic (UV-visible absorption spectroscopy (UV-vis), x-ray diffraction (XRD), fourier transform infrared (FTIR), energy dispersive spectroscopy (EDX) and microscopic (atomic force microscopy (AFM), transmission electron microscopy (TEM) and scanning electron microscopy (SEM) analysis, and other methods are often used to characterise metal and metal oxide nanoparticles. Characterization of green nanoparticles is essential for understanding the origin, behaviour, and functional properties (Anukiruthika *et al.*, 2020).

## 2.4 Stability, safety and toxicology of green nanoparticles

Phytonanoparticles are advantageous over expensive and environmentally unsound physical and chemical approaches due to its scalability, cost-effectiveness, biocompatibility, environmental friendliness, and medicinal claims. The extract of the plant, *i.e.*, the secondary metabolite is responsible for comprehensible mechanisms in the green synthesis of nanoparticles conferring anticipated assets like particle size distribution, inhibition competence, shape, growth trend, *etc*. The specific applications of green nanoparticles for commercial scale should be recommended by properly addressing the toxicity, if any to humans and the environment (Maniam *et al.*, 2020; Karupannan *et al.*, 2020).

Nanoparticles synthesised from plant extracts outperform standard methods of synthesis due to low processing cost, less detrimental effect and cleaner materials with less waste proving biosynthesis of nanoparticles is nearly an ideal process. These are specifically targeted nanotherapeutic delivery systems with high purity and yield from natural resources. Yet, the changes occurring in the physicochemical and structural properties of nanomaterials during its synthesis with decrease in their size may result in minor toxicological effects. These characteristics should be considered when designing the synthesis of nanoparticles formulating nanodrugs. Novel nanoformulations incorporating a synergistic mixture of plant-based drugs and synthetic drugs may extend drug circulation cycles, have synchronised drug release, and provide a higher efficacy to toxicity ratio, allowing them to enter clinical trials. Efficient formulation targeting techniques, assessment of NP targeting effectiveness, and compliance with international toxicology and biocompatibility criteria could pave the way for clinically feasible phytochemical-based therapies (Khan and Gaurav, 2018).

Phytonanotechnology potentially enhances the efficacy of parenterally administrated curcumin by enhancing its solubility (Bisht *et al.*, 2007). These "green" extracts change the properties and behaviours of the nanoparticles. Zeta potentials show the brittleness of nanoparticles due to particle aggregation. Chemically synthesised nanomaterials are not always healthy. The AuNPs derived from golden rod extract were less toxic than nanoparticles synthesized without plant leaf extracts (Botha *et al.*, 2019).

### 2.5 Mode of administration of green nanoparticles

Oral route is a safer path for administering phytomedicines because it improves patient compliance along with manufacturing benefits. Increasing drug hydrophilicity with higher water solubility results in a faster drug dissolution and drug permeation rate across the cell membrane. Change of route can improve absorption, therapeutic efficacy, bioavailability and degradation of nano-phytomedicines (Gunasekaran *et al*., 2014).

The trans-dermal application of plant *Artemisia annua* was improved through solid lipid nanoparticles mixing, where increased oil deposition results in increased bioactivity. This increased oil infusion rate is due to the effective penetration, moisturising and restructuring properties of plant oil and smaller particle size of plant extract (Aziz and Setapar, 2020). The medicinal plant *Radix salvia* enriched with nanoparticles has shown to increase bioavailability due to particle size reduction through biosynthesis of nanoparticles (Su *et al*., 2008). Vitamin D, C, and E nanoparticle formulation of *Swertia japonica* extract and sunflower can be used as a transdermal topical and oral therapeutic agent, intradermal and subcutaneous parenteral injection.

Unlike traditional medicine therapies, nanoparticles having size range of 50 nm can enter the body quickly and cause a variety of reactions across the oral and mucous membranes. These nanosystems can deliver active constituents at the optimal concentration leading to the desired action (Pattabhiramaiah *et al*., 2020).

## 3. Green nanoparticles extending potential antiviral effects

The silver nanoparticles (AgNPs) used against H1N1 influenza A virus, herpes simplex virus (HSV), monkeypox virus, hepatitis B virus (HBV), human immunodeficiency virus (HIV), adenovirus, tacaribe virus, *etc*., augments its potential as an antiviral agent. AgNPs inhibit the differentiation process of the HIV-1 virus. It occurs by combining of AgNPs to the disulfide bond that is present in the cluster of differentiation 4(CD4) binding domain inside the envelope made up of glycoprotein of this virus. Furthermore, the high binding affinity character of AgNPs with the double-stranded HBV can be conveniently used to prohibit the genesis of hepatitis B virus RNA and extracellular virions. Strong antiviral potential of AgNPs is authenticated by their capacity to hinder the multiplication of virus within the host cell either in the way of inhibition of the reproduction or by obstructing the virus entry into the cell of the host by multiple interaction with the glycoprotein receptor present on viral envelop (Salleh *et al.,* 2020) (Table 1).

**Table 1: Green nanoparticles extending potential antiviral effect**

| Sr.No. | Name of plant and family | Parts of plant used | Metal used for NP | Bioactive compounds | Characterisation | Pharmacological effect/virus against which has action | References |
|---|---|---|---|---|---|---|---|
| 1. | *Curcuma longa* Zingiberaceae | Rhizome | Ag | Curcumin | UV-vis spectrometer, SEM, TEM | Antioxidant, anticancer activity, radicals scavenging | Yang *et al.*, 2016 |
| 2. | *Lampranthus coccineus* Aizoaceae | Aerialparts | Ag | - | TEM,UV-Visible spectroscopy, FTIR | HSV-1, HAV-10, CoxB4 virus | Haggag *et al.*, 2019 |
| 3. | *Cinnamomum cassia* Lauraceae | Bark | Ag | - | SEM, UV Vis absorption spectroscopy, FTIR | H7N3 influenza A virus | Fatima, *et al.*, 2016 |
| 4. | *Andrographis paniculata* Acanthaceae | - | Ag | Andrograph olide | FTIR spectroscopy, SEM, DLS | Chikungunya virus, Alphavirus, Togaviridae | Sharma *et al.*, 2019 |
| 5. | *Phyllanthus niruri* Phyllanthaceae | - | Ag | Alkaloids, diterpenoid lactones, glycosides, steroid | FTIR, SEM, DLS | Herpes simplex, vaccinia, monkey pox, influenza, respiratory syncytial, human immunodeficiency, hepatitis B virus | Sharma *et al.*, 2019 |
| 6. | *Tinospora cordifolia* Menispermaceae | - | Ag | Alkaloids, diterpenoid lactones, glycosides, steroids | FTIR, SEM, DLS | Herpes simplex, vaccinia, monkey pox, influenza, respiratory syncytial, human immuno-deficiency, hepatitis B virus | Sharma *et al.*, 2019 |
| 7. | *Panax ginseng* Araliaceae | Roots | Ag | Ginsenosides, polysaccharides, amino acids | TEM, UV vis, XRD, FTIR, EDX, FFT | Influenza A virus (strain A/PR/8). | Sreekanth *et al.*, 2018 |

SEM: Scanning electron microscope, TEM: Transmission electron microscope, FTIR: Fourier transform infrared spectroscopy, DLS: Dynamic light scattering, UV vis: UV-visible spectroscopy, XRD: X-ray diffraction, EDX: Energy- dispersive X-ray analysis, FFT: Fast Fourier Transform.

### 3.1 Green nanoparticles against chikungunya

*Tinospora cordifolia* and *Andrographis paniculata* derived AgNPs when used on vero cells to test their antiviral potency against chikungunya virus revealed outstanding result. Since long cinnamon is being used as both medicine and spice (Sharma *et al*., 2018). Neither the anti-influenza activity nor the AgNPs synthesis using cinnamon have been documented earlier. In vero cells, the evaluation of antiviral potential of green synthesized AgNPs from cinnamon bark extract in case of virulant avian influenza virus subtype H7N3 though revealed inhibiting chikungunya virus capability, but the effectiveness was less than *Tinospora cordifolia* and *Andrographis paniculata* derived AgNPs. This conclusion in favour of green synthesized AgNPs stating its antiviral potentiality was proved *via* estimating the vero cell viability following infection of chikungunya virus along with treatment using MNTD (maximum non-toxic dose) and ½MNTD of AgNPs produced from plant extract. These out-turns of this experiment suggested that *Andrographis paniculata* aqueous extract derived AgNPs exerts remarkable potential against chikungunya virus. The contaminated cells without the treatment exhibited around 25% cell viability and this was enhanced to nearly 81% and 67% following application of MNTD and ½MNTD of *A. paniculata* synthesized AgNPs, respectively (Galdiero *et al*., 2011). The principal phyto-constituent present in *A. paniculata* extract is andrographolide which is famous for bearing inhibiting capacity in opposition to many viruses. The effect of AgNPs of *Phyllanthus niruri* against chikungunya virus was examined and it was observed to combat chikungunya virus infection at a lower extent as compared to *Tinospora cordifolia* and *Andrographis paniculata* derived AgNPs (Sharma *et al.*, 2019).

### 3.2 Green nanoparticles against herpes simplex virus-2

The silver nanoparticles remodulated using tannic acid was applied in both *in vitro* and *in vivo* conditions at a dose rate that is not harmful to the host cells for treatment of HSV-2 infection in order to assess its antiviral effect. It was noted that the action of AgNPs in the absence of tannic acid remodulation was slow and inefficient whereas the modification of AgNPs employing tannic acid imparted highest efficiency of inhibitory effect against the virus (Orlowski *et al*., 2013). This occurred exclusively due to direct interaction of remodulated tannic acid-AgNPs and virions of herpes simplex virus-2. On the other hand, prior treatment of the cells with the remodulated tannic acid-AgNPs did not reveal any inhibition upon HSV-2 entry (Akhtar and Shukla, 2009). This suggests that the effect of remodulated tannic acid-AgNPs either on binding of this virus to the surface receptors of the cell or on cellular entry factor is null (Orłowski *et al.*, 2018).

## 4. Green nanoparticles extending potential antirespiratory virus activity

### 4.1 Green nanoparticles against respiratory syncytial virus

Reports reveal that the AgNPs capped with curcumin have better antiviral activity than the citric acid capped AgNPs. This may be due to amiable characteristics of both AgNPs and curcumin. Thus, the curcumin AgNPs (cAgNPs) can exert high grade antiviral effect against RSV (respiratory syncytial virus) infection. The mechanism behind this significant effect is direct inactivation of RSV by cAgNPs before its entry into the cell. In addition to this, cAgNPs are capable to turn down the infectivity of virus to some extent when used either before or after RSV infection. However, the analysis of decrease in titers of virus of the cell before and after treatment revealed that it was comparatively less effectual from that of the virus pre-treatment analysis. It authenticates that the inhibitory effect of cAgNPs against virus was mainly due to head-on deactivation of RSV (Yang *et al.*, 2016).

### 4.2 Green nanoparticles against H7N3 influenza virus

The green synthesis method was applied to develop silver nanoparticles using an extract from cinnamon bark. As compared to the aqueous distillation of cinnamon bark, the silver nanoparticles synthesized by using cinnamon as the reducing agent manifested the enhancement of its potency to fight with H7N3 influenza virus in both the cases of prior and after penetration exposures. Cinnamon as well as the nanoparticles reduced from it was reported safe for vero cells (Skehel and Wiley, 2000). Cinnamon based nanoparticles are still under observation in the form of *in vivo* studies for approval of their antiviral effects against influenza virus.

Thus, the phyto-fabricated silver nanoparticles, because of their safe and multifactorial benefits can be fruitfully applied against those highly mutating viruses for which normal schedule treatment fails. The mechanism behind the antiviral function of nanoparticles is required to be further explored in order to manufacture better antiviral therapeutics (Fatima *et al.*, 2016).

## 5. Green nanoparticles extending potential immunomodulatory effects

An appropriate balance of Th1/Th2 (T-helper cells type 1 or type 2) is maintained by the normal immune system in the body for exhibition of an appropriate immune response. But, a preferential activation of T helper cells either type 1 or type 2 causes immune alterations and disturbs the equilibrium of the immune system. Additionally, multi wall carbon nano tubes can particularly reduce the monocytes proficient for phagocytosis and stimulate attachment of the monocytes those are un-proficient for phagocytosis in blood stream. For innate immune system toll-like receptor acts as a receptor. Thus, the innate immunity can be activated by modulating toll-like receptors which will result in powerful adaptive immunity. Triggering of the toll like receptor pathways is able to bring about persistent inflammation and ROS. NF-κB pathway is an alternative chief controller of defence system of the body. As a prime controller of expression of gene of pro-inflammation, NF-κB mediates genesis of cytokines like IL-1β, IL-6, IL-8, and TNF-α (Jiao *et al.*, 2014).

Induction of human inflammatory diseases may be occurred due to activation of NF-κB (Wang *et al.*, 2012). From reports, it is evidenced that activation of NF-κB signalling pathway in Tohoku Hospital Pediatrics-1cells is caused by negatively charged poly (acrylic acid) conjugated GNP (Patel *et al.*, 2012). Inflammatory cytokines including IL-8 and TNF-α are released by the cells. Nanoparticles could harmonize the immune cells homeostasis together with the alteration of balance of Th1/Th2 and monocyte equilibrium (Zhu *et al.*, 2012). Nanoparticles have the ability to interact with the cells of both innate and adaptive immunity, strike the cell function and thus interrupt the immune system. Nanoparticles can induce inflammation which is a key response of immune system. It is confirmed by the production of cytokines/chemokines. Nanoparticles cause oxidative stress which is ascribed as the prime downstream event of inflammation. In comparison to normal particles, nanoparticles possess larger surface areas and powerful oxidative abilities. As a result, nanoparticles can lead to oxidative damage which is a crucial factor for immunity variation. A number of nanoparticles are revealed to induce ROS production when analyzed in *in vitro* and *in vivo* environments magnifying functioning of immune system or inflammatory response. Tissue damage caused by free radicals renders a vital role in inflammatory diseases (Liu *et al.*, 2013).

Bacterial infection stimulates macrophages and NK cells to liberate pro-inflammatory cytokines (TNF-alfa, IL-1beta). These cytokines serve in infiltration of immune cells into the affected tissue. On the other hand, some cases of chronic/persistent inflammation can lead to unwanted complications. In case of chronic inflammation, the genesis of high levels of pro-inflammatory modulators is hastened by persistent recruitment of innate and adaptive immune cells. Several nanomaterials can be used with favourable result in immune modulation application. The gene expression analysis study reported that injection of gold nanoparticles in rats impacted the degree of expression of many cytokines, *viz.*, TNF-alfa, IL-1beta, and IL-6 (Khan *et al.*, 2013). Conversely, an anti-inflammatory reaction was manifested by citrate-gold nanoparticles due to down regulation of inflammatory cells response by IL-1beta both *in vitro* and *in vivo*. However, biosynthesized nanoparticles were analyzed for their immunomodulatory activities against cell culture models of macrophages and NK cells (Amina *et al.*, 2020) (Table 2).

**Table 2: Green nanoparticles extending potential immunomodulatory effects**

| Sr. No. | Name of plant and family | Part of plant used | Metal used for NP | Bioactive compounds | Characterisation | Pharmacological effect/virus against which has action | References |
|---|---|---|---|---|---|---|---|
| 1. | *Asparagus racemosus* Asparagaceae | root | Ag, Au, Ag-Au Bimetallic | steroidal saponins flavonoid, tannins | FTIR, DLS, AFM, XRD, Zeta potential | Ageing, vigor immunity, mental functions | Amina *et al.*, 2020 |
| 2. | *Hypoxis hemerocallidea* Hypoxidaceae | - | Au | Hypoxoside | UV-Vis Spectrop hotometer, FTIR | HIV/AIDS, hypertension, diabetes, psoriasis, ulcers, urinary infections, tuberculosis, asthma | Elbagory *et al.*, 2019 |
| 3. | *Dictyota mertensii* Dictyotaceae | - | Ag | - | FTIR, DLS, XRD, Zeta poteintial | Antioxidant, antiproliferative, immunomodulatory effect | Fernandes-Negreiros *et al.*, 2018 |

FTIR: Fourier Transform Infra-Red spectroscopy, SEM: Scanning electron microscope , TEM: Transmission electron microscope, EDX: X-ray diffractometer, XRD: X-ray diffraction.

## 6. Green nanoparticles extending anti-inflammatory activity

Inflammation is a leading defence mechanism to any infection in the biological system. But, several diseases like cancer, arthritis, and neurological disorders can be caused due to unrestricted inflammation (Singh *et al.*, 2017). Macrophages, the cells playing key role in inflammation influence the control of multiple inflammatory pathways. The nuclear factor-kappa B (NF-κB) pathways crucially contribute in the process of inflammation by enhancing the quantum of cytokines and different mediators of inflammation like nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) induced by lipopolysaccharides (LPS) (Rius-Pérez *et al.*, 2020). LPS activate macrophage which in turn leads to production of different pro-inflammatory cytokines, *i.e.*, NO, PGE2 and tumour necrosis factor-α (TNF-alfa). Researchers have revealed from their studies that extracellular signal-regulated kinase (ERK), jun kinase (JNK) and p38 MAPK are actively involved in the inflammatory mediators derived NF-κB *via* extra cellular signal-regulated, mitogen-activated protein kinase (MAPK) signalling pathway (Nandipati *et al.*, 2017). On that account, hindrance of NF-κB transcription factor *via* inhibition of MAPK may render possibility to treat different inflammatory diseases. Though, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids are commonly used curative agents against inflammation but they may bring about consequential side effects. Thus, invention of alternative compound with at par result without any side effect is the demand of the current time.

A study in RAW264.7 cells subjected to induction by lipopolysaccharide (LPS) revealed that appearance of inflammatory mediators, *viz.*, nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) can be turned down by nanoparticles. Moreover, LPS-induced stimulation of NF-jB signalling pathway through p38 MAPK was suppressed remarkably by nanoparticles in RAW 264.7 cells (Singh *et al.*, 2018).

A study employed European black elderberry fruits extract to synthesize silver nanoparticles to estimate its biological activity (capability to prevent oxidative damage) in different systems such as HaCaT cells exposed to UV-B radiation, carrageenan-induced paw edema in rats and psoriasis lesions in human (David *et al.*, 2014). Hence, phytonanoparticles can be exploited considerably for their anti-inflammatory potency (Table 3).

**Table 3: Green nanoparticles extending potential anti-inflammatory activity**

| Sr. No. | Name of plant and family | Part of plant used | Metal used for NP | Bioactive compounds | Characterisation | Pharmacological effect/ virus against which has action | References |
|---|---|---|---|---|---|---|---|
| 1 | *Atropa acuminata* Solanaceae | Leaf | Ag | Alkaloids, atropine scopolamine | UV-V is, XRD, HRTEM, EDAX, DLS | Arthritis, muscle spasms, joint pain, conjunctivitis, encephalitis, scarlet fever, pancreatitis, Parkinson's disease | Rajput *et al*., 2020 |
| 2 | *Nigella sativa* Ranunculaceae | Seeds | Ag | PUFA | SEM, UV-V is | Diabetes, Diabetic Neuropathy | Alkhalaf *et al*., 2020 |
| 3 | *Astragalus tribuloides* Fabaceae | Root | Ag | Saponins, phenolics, flavonoid | UV-Vis, FTIR, XRD, TEM | Tumors, throat, liver, chest back pains, regenerate the tissues and heal wounds | Sharifi-Rad *et al*., 2020 |
| 4 | *Prunus serrulata* Rosaceae | Fresh fruit extract | Ag, Au | Amygdalin, prunasin | UV-Vis, FE-TEM, EDX, DLS, FTIR, XRD | Cancer, arthritis, neurological diseases | Singh *et al*., 2018 |
| 5 | *Phyllanthus niruri* L. Euphorbiaceae | Leaves | Ag | | UV-Vis | Hepatitis B virus, diarrhea, epilepsy pain disorders, dyspepsia, vaginitis, tumors, malaria, hypertension, fever | Gajapriya *et al*., 2020 |
| 6 | *Sambucus nigra* Adoxaceae | Fruits extract | Ag | Anthocyanins | TEM | Colds, arthritis, asthma, constipation | Moldovan *et al*., 2018 |

FTIR: Fourier Transform Infra-Red spectroscopy, SEM: Scanning Electron Microscope, TEM: Transmission Electron Microscope, EDX: X-ray diffractometer, XRD: X-ray diffraction, PUFA - polyunsaturated fatty acid.

## 7. Conclusion

The latest coronavirus 2019 outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) has no effective treatment indicating the need for newer therapeutic targets. Nanotechnology so far has been utilized in the identification and therapeutic management of several viral diseases. Thus, it may furnish a fresh beginning with fabrication of plant extracts for redressing pre-existing medicaments and therapies against COVID-19 in a renovative approach in terms of mitigating problems of side effects, inferior stability and low bioavailability. Phytonanoparticles are likely to play an important role in COVID-19 prevention, diagnosis, recovery and vaccine with its antiviral, immunomodulatory and anti-inflammatory activities. The biosynthesis of green nanoparticles employing plant extract is easy, coherent, economical, and an eco-friendly substitute to broad-spectrum antiviral agents. Nano-based plant medicaments can be designed to act on the targeted tissues with release of the nanodrug at a required rate. It could be helpful to optimize the competence of treatment thus minimizing the duration and dose of the treatment to defeat the virus. As these green nanomaterials are beneficial in a multi-dimensional way. Still till now, it has not been explored to full extent which is the demand of the current situation as it may be helpful to overcome the SARS-CoV-2 pandemic condition. At different juncture of COVID-19 pathogenesis, phytonanoparticles can contribute significantly in form of inhibiting viral entry into the host cell or defusing the initial attachment of infected cell protein with the virus. Green nano-based drugs can be a supplement or replacement for COVID-19 therapy or prophylaxis of healthcare personnel and the general public. *In vivo* studies in detail are essentially required to know the outcomes and mode of functioning of these plant green nanoparticles at the molecular level before their practice as remedial agents and safely configure antiviral drugs. The outcomes of these analysis can help pharmacologists and biomedical engineers engaged in nanotechnology to explore efficient plant-based nanodrugs and it can be fruitfully used as upcoming COVID-19 infection treatment with an aim of control drug delivery and release, nullifying the adverse effects in an economic and eco-friendly way.

## Conflict of interest

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

## References


**Akintola, A.O.; Kehinde, B.D.; Ayoola, P.B.; Adewoyin, A.G.; Adedosu, O.T.; Ajayi, J.F. and Ogunsona, S.B. (2020).** Antioxidant properties of silver nanoparticles biosynthesized from methanolic leaf extract of Blighiasapida. In: IOP conference series: Materials Science and Engineering, (Vol. 805, No. 1, p. 012004). IOP Publishing.

**Akhtar, J. and Shukla, D. (2009).** Viral entry mechanism: Cellular and viral mediators of herpes simplex virus entry. FEBS J., **276**:7228-7236.

**Alkhalaf, M.I.; Hussein, R.H. and Hamza, A. (2020).** Green synthesis of silver nanoparticles by *Nigella sativa* extract alleviates diabetic neuropathy through anti-inflammatory and antioxidant effects. Saudi Journal of Biological Sciences, **27**(9):2410-2419.

**Amina, M.; Al Musayeib, N.M.; Alarfaj, N.A.; El-Tohamy, M.F. and Al-Hamoud, G.A. (2020).** Antibacterial and immunomodulatory potentials of biosynthesized Ag, Au, Ag-Au bimetallic alloy nanoparticles using the asparagus racemosus root extract. Nanomaterials, **10**(12):24-53.

**Anukiruthika, T.; Priyanka, S.; Moses, J.A. and Anandharamakrishnan, C. (2020).** Characterization of green nanomaterials. In: Ahmed S., Ali W. (eds) Green Nanomaterials. Advanced Structured Materials, Vol 126, Springer, Singapore. https://doi.org/10.1007/978-981-15-3560-4-3.

**Aritonang, H.F.; Koleangan, H. and Wuntu, A.D. (2019).** Synthesis of silver nanoparticles using aqueous extract of medicinal plants (*Impatiens balsamina* and *Lantana camara*) fresh leaves and analysis of antimicrobial activity. International Journal of Microbiology, https://doi.org/10.1155/2019/8642303.

**Aziz, Z.A.A. and Setapar S.H.M. (2020).** Nanotechnology: An effective approach for enhancing therapeutics and bioavailability of phytomedicines. Functional bionanomaterials, In: Thangadurai D., Sangeetha J., Prasad R. (eds) Functional Bionanomaterials. Nanotechnology in the Life Sciences. Springer, Chem., **47**-71. https://doi.org/10.1007/978-3-030-41464-1-3.

**Bai, Y.; Zhou, Y.; Liu, H.; Fang, L.; Liang, J. and Xiao, S. (2018).** Glutathione-stabilized fluorescent gold nanoclusters vary in their influences on the proliferation of pseudorabies virus and porcine reproductive and respiratory syndrome virus. ACS Appl. Nano Mater, **1**:969-976.

**Bisht, S.; Feldmann, G.; Soni, S.; Ravi, R.; Karikar, C.; Maitra, A. and Maitra, A. (2007).** Polymeric nanoparticle - encapsulated curcumin (nanocurcumin): A novel strategy for human cancer therapy. Journal of Nanobiotechnology, **5**(1):1-18.

**Botha, T.L.; Elemike, E.E.; Horn, S.; Onwudiwe, D.C.; Giesy, J.P. and Wepener,V. (2019).** Cytotoxicity of Ag, Au and Ag-Au bimetallic nanoparticles prepared using golden rod (*Solidago canadensis*) plant extract. Scientific Reports, **9**(1):1-8.

**David, L.; Moldovan, B.; Vulcu,A.; Olenic, L.; Perde-Schrepler, M.; Fischer-Fodor, E. and Filip, G.A. (2014).** Green synthesis, characterization and anti-inflammatory activity of silver nanoparticles using European black elderberry fruits extract. Colloids and Surfaces B: Biointerfaces, **122**: 767-777.

**El Shafey, A.M. (2020).** Green synthesis of metal and metal oxide nanoparticles from plant leaf extracts and their applications: A review. Green Processing and Synthesis, **9**(1):304-339.

**Elbagory, A.M.; Hussein, A.A. and Meyer, M. (2019).** The *in vitro* immunomodulatory effects of gold nanoparticles synthesized from *Hypoxishemero callidea* aqueous extract and hypoxoside on macrophage and natural killer cells. International Journal of Nanomedicine, **14**:9007.

**El-Sayed, A. and Kamel, M. (2020).** Advances in nanomedical applications: diagnostic, therapeutic, immunization, and vaccine production. Environ. Sci. Pollut. Res., **27**:19200-19213. https://doi.org/10.1007/s11356-019-06459-2.

**Fatima, M.; Sadaf Zaidi, N.U.S.; Amraiz, D. and Afzal, F. (2016).** *In vitro* antiviral activity of *Cinnamomum cassia* and its nanoparticles against H7N3 influenza A virus. Journal of Microbiology and Biotechnology, **26**(1): 151-159.

**Fernandes Negreiros, M.M.; Araújo Machado, R.I.; Bezerra, F.L.; Nunes Melo, M.C.; Alves, M.G.C.F.; Alves Filgueira, L.G. and Rocha, H.A.O. (2018).** Antibacterial, antiproliferative, and immunomodulatory activity of silver nanoparticles synthesized with fucans from the alga, *Dictyota mertensii* Nanomaterials, **8**(1):6.

**Gajapriya, M.; Arivarsasu, L. and Rajeshkumar, S. (2020).** Green synthesis of *Phyllanthus niruri* mediated silver nanoparticles and it is anti-inflammatory activity. Drug Invention Today, **13**(4):4.

**Galdiero, S.; Falanga, A.; Vitiello, M.; Cantisani, M.; Marra, V. and Galdiero, M. (2011).** Silver nanoparticles as potential antiviral agents. Molecules, **16**:8894-8918.

**Gurunathan, S.; Qasim, M.; Choi, Y.; Do, J.T.; Park, C.; Hong, K. and Song, H. (2020).** Antiviral potential of nanoparticles: Can nanoparticles fight against coronaviruses?. Nanomaterials, **10**(9):1645.

**Gurunathan, S.; Qasim, M.; Park, C.H.; Arsalan Iqbal, M.; Yoo, H.; Hwang, J.H. and Hong, K. (2019).** Cytotoxicity and transcriptomic analysis of biogenic palladium nanoparticles in human ovarian cancer cells (SKOV3). Nanomaterials, **9**(5):787.

**Gunasekaran, T.; Haile, T.; Nigusse, T. and Dhanaruju, M.D. (2014).** Nanotechnology: an effective tool for enhancing bioavailability and bioactivity of phytomedicine. Asian J. Trop. Biomed., **1**:1-7.

**Haggag, E.G.; Elshamy, A.M.; Rabeh, M.A.; Gabr, N.M.; Salem, M.; Youssif, K.A. and Abdelmohsen, U.R. (2019).** Antiviral potential of green synthesized silver nanoparticles of *Lampranthus coccineus* and *Malephora lutea*. International Journal of Nanomedicine, **14**:6217.

**Jiao, Q.; Li, L.; Mu, Q. and Zhang, Q. (2014).** Immunomodulation of nanoparticles in nanomedicine applications. Bio. Med. Research International, Article ID 426028, 19 pages, https://doi.org/10.1155/2014/426028

**Keshari, A.K.; Srivastava, R.; Singh, P.; Yadav, V.B. and Nath, G. (2020).** Antioxidant and antibacterial activity of silver nanoparticles synthesized by *Cestrum nocturnum*. Journal of Ayurveda and Integrative Medicine, **11**(1):37-44.

**Khan, H.A.; Abdelhalim, M.A.K.; Alhomida,A.S. and Al-Ayed, M.S. (2013).** Effects of naked gold nanoparticles on proinflammatory cytokines mRNA expression in rat liver and kidney. Bio. Med. Research International, 590730, doi:10.1155/2013/590730.

**Khan, T. and Gurav, P. (2018).** Phytonanotechnology: Enhancing delivery of plant based anticancer drugs. Frontiers in Pharmacology, **8**:1002.

**Kumaran, A.; Ho, C.C. and Hwang, L.S. (2018).** Protective effect of *Nelumbo nucifera* extracts on beta amyloid protein induced apoptosis in PC12 cells, *in vitro* model of Alzheimer's disease. Journal of Food and Drug Analysis, **26**(1):172-181.

**Liu, H.; Yang, D.; Yang, H.; Zhang, H.; Zhang, W.; Fang, Y. and Xi, Z. (2013).** Comparative study of respiratory tract immune toxicity induced by three sterilisation nanoparticles: Silver, zinc oxide and titanium dioxide. Journal of hazardous materials, **248**:478-486.

**Manuja, A.; Kumar, B. and Singh, R.K. (2012).** Nanotechnology developments: opportunities for animal health and production. Nanotechnol. Dev., **2**:4.

**Maniam, G.P.; Govindan, N.; Rahim, M.H.A. and Yusoff, M.M. (2020).** Plant extracts: Nanoparticle sources. In: Phytonanotechnology challenges and Prospects, 41-49. https://doi.org/10.1016/B978-0-12-822348-2.00003-6.

**Mohanta, Y.K.; Panda, S.K.; Jayabalan, R.; Sharma, N.; Bastia, A.K. and Mohanta, T.K. (2017).** Antimicrobial, antioxidant and cytotoxic activity of silver nanoparticles synthesized by leaf extract of *Erythrina suberosa* (Roxb.). Frontiers in Molecular Biosciences, **4**:14.

**Mohanty, N.; Palai, T.; Prusty, B. and Mohapatra, J. (2014).** An overview of nanomedicine in veterinary science. Vet. Res., **2**:90-95.

**Moldovan, B.; David, L.; Achim, M.; Clichici, S. and Filip, G.A. (2016).** A green approach to phytomediated synthesis of silver nanoparticles using *Sambucus nigra* L. fruits extract and their antioxidant activity. Journal of Molecular Liquids, **221**:271-278.

**Nagaich, U.; Gulati, N. and Chauhan, S. (2016).** Antioxidant and antibacterial potential of silver nanoparticles: Biogenic synthesis utilizing apple extract. Journal of Pharmaceutics, Article ID 7141523: 8. https://doi.org/10.1155/2016/7141523.

**Nandipati, K.C.; Subramanian, S. and Agrawal, D.K. (2017).** Protein kinases: mechanisms and downstream targets in inflammation-mediated obesity and insulin resistance. Molecular and Cellular Biochemistry, **426**(1-2):27-45.

**Or³owski, P.; Kowalczyk, A.; Tomaszewska, E.; Ranoszek-Soliwoda, K.; Wêgrzyn, A.; Grzesiak, J. and Krzyzowska, M. (2018).** Antiviral activity of tannic acid modified silver nanoparticles: Potential to activate immune response in herpes genitalis. Viruses, **10**(10):524.

**Pattabhiramaiah, M.; Rajarathinam, B. and Shanthala, M. (2020).** Nanoparticles and their application in folklore medicine as promising biotherapeutics. In Functional Bionanomaterials, pp:73-110. Springer, Cham.

**Palai, S.; Dehuri, M. and Patra, R. (2020).** Spices boosting immunity in COVID-19. Ann. Phytomed., **9**(2):80-96. DOI: 10.21276/ap.2020. 9.2.7

**Patel, J.K.; Clifford, R.L.; Deacon, K. and Knox, A.J. (2012).** Ciclesonide inhibits TNFα - and IL-1β-induced monocyte chemotactic protein-1 (MCP-1/CCL2) secretion from human airway smooth muscle cells. The American Journal of Physiology: Lung Cellular and Molecular Physiology, **302**(8):785-792.

**Rajput, S.; Kumar, D. and Agrawal, V. (2020).** Green synthesis of silver nanoparticles using Indian belladonna extract and their potential antioxidant, anti-inflammatory, anticancer and larvicidal activities. Plant Cell Reports, **39**(7):921-939.

**Richman, D.D. (2021).** COVID-19 vaccines: Implementation, limitations and opportunities. Glob. Health Med., **3**(1):1-5. doi:10.35772/ghm.2021.01010.

**Rius-Pérez, S.; Pérez, S.; Martí-Andrés, P.; Monsalve, M. and Sastre, J. (2020).** Nuclear factor kappa B signaling complexes in acute inflammation. Antioxidants and Redox Signalling, **33**(3):145-165.

**Salleh, A.; Naomi, R.; Utami, N.D.; Mohammad, A.W.; Mahmoudi, E.; Mustafa, N. and Fauzi, M.B. (2020).** The potential of silver nanoparticles for antiviral and antibacterial applications: A mechanism of action. Nanomaterials, **10**(8):15-66.

**Karupannan, S.K.; Dowlath, M.J.H. and Arunachalam, K.D. (2020).** Phytonanotechnology: Challenges and future perspectives, In Micro and Nano Technologies, Phytonanotechnology, Elsevier, 303-322. https://doi.org/10.1016/B978-0-12-822348-2.00015-2

**Sharifi-Rad, M.; Pohl, P.; Epifano, F. and Álvarez-Suarez, J.M. (2020).** Green synthesis of silver nanoparticles using *Astragalus tribuloides* delile root extract: Characterization, antioxidant, antibacterial, and anti-inflammatory activities. Nanomaterials, **10**(12):2383.

**Sharma, V.; Kaushik, S.; Pandit, P.; Dhull, D.; Yadav, J.P. and Kaushik, S. (2019).** Green synthesis of silver nanoparticles from medicinal plants and evaluation of their antiviral potential against chikungunya virus. Applied Microbiology and Biotechnology, **103**(2):881-891.

**Singh, L.; Kruger, H.G.; Maguire, G.E.M.; Govender, T. and Parboosing, R. (2017).** The role of nanotechnology in the treatment of viral infections. Ther. Adv. Infect. Dis., **24**(4):105-131. doi:10.1177/20499361177-13593.

**Singh, P.; Ahn, S; Kang, J.P.; Veronika, S.; Huo, Y.; Singh, H. and Yang, D.C. (2018).** *In vitro* anti-inflammatory activity of spherical silver nanoparticles and monodisperse hexagonal gold nanoparticles by fruit extract of *Prunus serrulata*: A green synthetic approach. Artificial Cells, Nanomedicine, and Biotechnology, **46**(8):2022-2032.

**Skehel, J.J. and Wiley, D.C. (2000).** Receptor binding and membrane fusion in virus entry: The influenza hemagglutinin. Ann. Rev. Biochem., **69**:531-569.

**Sreekanth, T.V.M.; Nagajyothi, P.C.; Muthuraman, P.; Enkhtaivan, G.; Vattikuti, S.V.P.; Tettey, C.O. and Yoo, K. (2018).** Ultra-sonication-assisted silver nanoparticles using *Panax ginseng* root extract and their anti-cancer and antiviral activities. Journal of Photochemistry and Photobiology B: Biology, **188**:6-11.

**Su, Y.L.; Fu, Z.Y.; Zhang, J.Y.; Wang, W.M.; Wang, H. and Wang, Y.C. (2008).** Microencapsulation of *Radix salvia* miltiorrhiza nanoparticles by spray-drying. Powder Technol., **184**:114-121.

**Sudha, A.; Jeyakanthan, J.and Srinivasan, P. (2017).** Green synthesis of silver nanoparticles using Lippianodiflora aerial extract and evaluation of their antioxidant, antibacterial and cytotoxic effects. Resource-Efficient Technologies, **3**(4):506-515.

**Vahedifard, F. and Chakravarthy, K. (2021).** Nanomedicine for COVID-19: The role of nanotechnology in the treatment and diagnosis of COVID-19. Emergent Mater, **4**:75-99. https://doi.org/10.1007/s42247-021-00168-8

**Wang, S.Z.; Ma, F.M. and Zhao, J.D. (2012).** Expressions of nuclear factor-kappa B p50 and p65 and their significance in the up-regulation of intercellular cell adhesion molecule-1 mRNA in the nasal mucosa of allergic rhinitis patients. European Archives of Oto-Rhino-Laryngology, **270**(4):1329-1334.

**Yang, X.X.; Li, C.M. and Huang, C.Z. (2016).** Curcumin modified silver nanoparticles for highly efficient inhibition of respiratory syncytial virus infection. Nanoscale, **8**(5):3040-3048.

**Zhu, M.; Li, Y.; Shi, J.; Feng, W.; Nie, G. and Zhao, Y. (2012).** Exosomes as ext rapulmonary signalling conveyors for nanoparticle induced systemic immune activation. Small, **8**(3):404-412.

**Citation** Santwana Palai, Ritun Patra and Manaswini Dehuri (2021). Phytonanoparticles and COVID-19. Ann. Phytomed., Volume10, Special Issue1 (COVID-19): S222-S230. http://dx.doi.org/10.21276/ap.covid19.2021.10.1.20