Phytonanoparticles and COVID-19

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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 antiviral biological activity.

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

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 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. Phytonanotechnology, 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 (Arionang 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, Phyllanthus niruri and Tinospora cordifolia (Sharma et al., 2019)
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 serrulate (Sharifi-Rad et al., 2014) extending anti-inflammatory properties can be considered against SARS-CoV-2 (COVID-19) and SARS-CoV-2 (Haggag et al., 2019). They transform disease diagnosis, immunization, prophylaxis and treatment of various viruses with antiviral compounds specifically against monkey pox, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (SARS-CoV-2) (Figure 1). These biosynthesized phytonanoparticles have 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 inflammatory potential can be considered against various viruses with anti-inflammatory potential can be considered against SARS-CoV-2 transmission or blockage. This present review encompasses the inflammatory potential can be considered against various viruses with anti-inflammatory potential can be considered against SARS-CoV-2 transmission or blockage.

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).

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 CeO₂, CuO, ZnO, TiO₂, ZrO₂, In₂O₃, and CuO. PhSH, and Fe₃O₄. 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).

**Figure 2:** Green nanoparticles extending potential antiviral activity.
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, taeburine 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 extracelular 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.     | Cinnamonum cassia Lauraceae | Bark | Ag | - | SEM, UV Vis absorption spectroscopy, FTIR | H7N3 influenza A virus | Fatima, et al., 2016 |
| 4.     | Andrographis paniculata Acanthaceae | - | Ag | Andrographolide | 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 immunodeficiency, 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 virulent 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 ½ MNTD 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 ½ MNTD 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 antiviral activity than the citric acid capped AgNPs (Patel *et al*., 2012). Inflammatory cytokines (IL-1α, IL-6, IL-8, TNF-α) are released by the cells. Nanoparticles alter the balance of cytokines like IL-1β, IL-6, IL-8, and TNF-α, respectively (Yang *et al*., 2016). From reports, it is evidenced that 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-inflammatory, 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

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 aequous 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. Including, 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-inflammatory, 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 nanomaterials 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       | root               | Ag, Au, Ag-Au    | Bimetallic          | FTIR, DLS, AFM, XRD, Zeta potential             | Ageing, vigor immunity, mental functions             | Amina et al., 2020 |
| 2.      | Hypoxis hemerocallidea   | -                  | Au               | Hypoxoside          | UV-Vis Spectropt hotometer, FTIR                | HIV/AIDS, hypertension, diabetes, psoriasis, ulcers, urinary infections, tuberculosis, asthma | Elbagory et al., 2019 |
| 3.      | Dictyota mertensii        | -                  | Ag               | -                   | FTIR, DLS, XRD, Zeta potential                   | Antioxidant, antiproliferative, immuno-modulatory effect | Fernandes-Negreiros et al., 2018 |

FTIR: Fourier Transform Infra-Red spectroscopy, SEM: Scanning electron microscope, TEM: Transmission electron microscope, EDX: 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-xB) pathways crucially contribute in the process of inflammation by enhancing the quantity 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-alpha (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-xB via extra cellular signal-regulated, mitogen-activated protein kinase (MAPK) signalling pathway (Nandipati et al., 2017). On that account, hindrance of NF-xB 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 consequent 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, phytomonanoparticles can be exploited considerably for their anti-inflammatory potency (Table 3).
Green nanoparticles extending potential anti-inflammatory activity

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, scopoline | 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 triloboides 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. Phytomonoparticles 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, phytomonoparticles 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.

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