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Corticosteroids versus Nanotechnology for SARS-CoV-2 Treatment

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Abstract **- Novel coronavirus or SARS-CoV-2 caused serious pandemic worldwide and led to significant mortality, morbidity and socioeconomic impact on population. To challenge this pandemic, several new approaches arose for diagnosis and treatment of COVID-19 infection. Drug repurposing is necessary action for this pandemic. According to World health organization approved that Corticosteroids are the effective drugs against viral infection and reduced mortality, but the major disadvantages are complications caused by these drugs, increased viral replication, and drug resistance. Because of its multivalent properties of Nanotechnology might become one of the possible and efficient treatment against viral infection and the major limitations are cost effective and requirement of clinical studies. This review summarizes the advantages, disadvantages, and limitations of corticosteroids from clinical studies, and then the applications of Nano medicine in diagnosis, therapy, and vaccine development for COVID-19 treatment.**

Keywords: COVID-19, Corticosteroids, Nanotechnology, vaccine Nano carriers, Drug repurposing.

Abbreviations:

SARS-CoV-2 - severe acute respiratory syndrome coronavirus-2
ssRNA+ -single strand positive RNA,
ACE2- Angiotensin-converting enzyme 2
ARDS - (Acute respiratory distress syndrome)
TCZ - (tolicizumab)
TNFα - (Tumor necrosis factor-α)
AgNPs - (Silver Nanoparticles)
AuNPs - (gold nanoparticles)

I. Introduction

Novel coronavirus disease 19 or COVID-19 caused by SARS-CoV-2 or Coronavirus belongs to *Coronaviridae* family has caused the serious pandemic situation and world health organization (WHO) announced public health emergency of international concern (PHEIC) on 31st January 2020(1,8). According to the WHO COVID-19 dashboard a total of 198,234,951 coronavirus cases are confirmed globally by 02-august-2021 and resulted in 4,22,7359 deaths (42).

SARS-CoV-2 is an enveloped virus with ssRNA+ and encodes proteins that are anti-viral targets to the host immune system which are phosphorylated nucleocapsid, envelope, spike, helicase, membrane glycoproteins, and 3-chymotrypsin like protease, and papain-like protease (15).ACE2 is a cell surface receptor in humans and its high expression is observed in the lung, heart, kidney, intestine, testis, and brain. The coronavirus spike protein binds to the ACE2 receptor and enters into the host cell. CD 147 is an extracellular matrix metalloproteinase inducer considered as another receptor for SARS-CoV-2 present mainly on epithelial cells, WBC, RBC, and endothelial cells, etc. The involvement of CD-147 by SARS-CoV-2 infection eventually influences the prostate tissue and leads to prostate cancer (21).the spike protein is made up of two subunits. The S1 subunit consists of NTD (N terminal domain), and CTD (C terminal domain) responsible for attachment to the host cells. The S2 subunit consists of pFP (potential fusion peptide), heptad repeats N and C (HR-N, HR-C), and a TM (Transmembrane domain). S2 subunit fuses with the host cell membrane and enters into the cell through endocytosis (40).

Currently, based on phylogenetic relationship, the Coronavirus is classified into four genera: α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus. α and β coronaviruses infect mainly mammals and lead to a severe respiratory syndrome in many cases. Contrastingly, the γ- and δ coronaviruses cause disease to birds. Several strains are identified in human coronavirus infection including SARS-CoV, MERS-CoV, HCoV-NL63, HCoV-229E, and HCoVHKU1 (2, 5).SARS-CoV-2 can infect the lower airways leading to pneumonia, ARDS, and in some cases, it leads to death also. In most cases, SARS-CoV-2 escaping the innate immune response at the upper respiratory tract and reaching to lower respiratory airways, and triggering cytokine storm and inflammatory response, immunological lung injury, diffuse alveolar damage. Many patients, not all who were admitted to

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the hospital required the use of supplemental oxygen therapy, assisted mechanical ventilation, and antibiotics (5, 11).

Patients with COVID-19 show clinical symptoms such as fever, dyspnea, non-reproductive cough, myalgia, fatigue, abnormal WBC count, and radiographic evidence of pneumonia, which are severe respiratory illness manifestations similar to symptoms of previous SARS-CoV and MERS – CoV infections. SARS-CoV-2 infection can remain asymptomatic or cause moderate symptoms (6).Many patients were developed severe respiratory diseases during the SARS-CoV epidemic in 2003. These patients were administrated with systematic corticosteroids. (7). COVID-19 has an initial period characterized by cough and fever, followed after around 8 days in approximately 20% of patients by the development of dyspnea with pulmonary infiltrates in about 10% of the patients (4)

There are many types of therapies that are introduced to mitigate the COVID-19 infection and its complications such as ARDS and hyper inflammatory conditions. Corticosteroids and nanomaterial's are the most promising therapies for SARS-CoV-2 infection. The use of corticosteroids to the COVID-19 patients is controversial, but some studies suggesting administration of corticosteroids at low doses to treat patients with pneumonia and ARDS may prevent lung injury and cytokine storm (11). There is still no clinical evidence available to support or to oppose corticosteroid treatment for COVID-19 pneumonia (3).Nanotechnology and Nanomedicine have multivalent properties to treat viral infections which are (a) antimicrobial properties (b) enhanced and efficient drug delivery (c) useful for the preparation of Nano-based vaccination and (d) accuracy in the diagnosis etc. (22, 28).

Most of the work on Nanotechnology has been done for the diagnosis and treatment of viral infections. Those strategies might become possible therapies for COVID-19 infection. This review represents the therapeutic approaches of corticosteroids and nanomedicine to combat the SARS-CoV-2 infection and along with the clinical database of corticosteroid treatment.

II. Corticosteroid Therapy for COVID-19

Cholesterol is the precursor molecule for all types of steroid hormones such as corticosteroids, androgens, estrogens, and progestogens. Corticosteroids are classified into glucocorticoids and mineralocorticoids released by the adrenal gland cortex present on the above kidney. Glucocorticoids regulate diverse cellular functions including development, cognition, homeostasis, metabolism, and inflammation. Glucocorticoids are the most prescribed drugs in the world because of their immune-modulatory actions such as inflammatory and autoimmune diseases like asthma, allergy, inflammatory bowel disease, septic shock rheumatoid arthritis, etc. (1, 5)

During the early stages of the COVID-19 pandemic, the use of corticosteroids was discouraged due to experience with previous studies of SARS and MERS pneumonia mainly due to undocumented benefit and side effects and fearing potentials of increased viral replication during treatment.Along with advantages, glucocorticoids also cause adverse effects associated with high dose and long term use. These are hypertension, growth retardation, obesity, cataracts, glaucoma, necrosis, skin atrophy, and diabetes. Patients who are under long-term glucocorticoid therapy develop tissue-specific resistance (3).

Corticosteroids such as dexamethasone, methylprednisolone, hydroxycortisone, calcifediol, hydroxychloroquine, 25-hydroxy vitamin D3, and cyclosporine A have been used in the treatment of COVID-19 and showed reduced mortality. In some cases, patients have treated with tocilizumab a monoclonal antibody along with corticosteroids also shown fast recovery and reduced mortality (9).

A recovery trail was conducted in National Health Service organizations, United Kingdom on COVID -19 patients during March 19 to June 8, 2020. A total 11,303 patients among them, 4321 had undergone usual care and 2104 had undergone the dexamethasone treatment or randomization. There was an observed reduction in mortality in dexamethasone group (22.9%) when compared to the usual care group (25.7%) and patients who are receiving mechanical ventilation with dexamethasone and usual care groups showed the death incidence 29.3% and 41.4% respectively. Hospital time duration also reduced in dexamethasone group and less risk was observed in patients who required mechanical ventilation in dexamethasone group when compared to usual care group. Side effects were observed in 4 patients such as two of patients showed hyperglycemia, one of gastrointestinal haemorrhage and one of psychosis (11).

Jonathan A and C. Sterne 2020 conducted a meta-analysis from 7 clinical randomized trials with 1703 patients who are confirmed with COVID-19 from different countries. These patients were administrated with corticosteroids. Seven trails are named separately and dose and type of corticosteroid administrated and vary from one trail to other trail and are represented in table no: 1

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S.No	Name of the trail	Concentration and dose	Mortality
1.	DEXA-COVID-19	Dexamethasone and high dose (20mg/day)	60 day mortality was observed
2.	CoDEX	Dexamethasone and high dose (20mg/day)	Ventilator free days
3.	RECOVERY	Dexamethasone and low dose (6mg/day)	28 day mortality
4.	CAPE COVID	Hydroxycortisone and low dose (50-200mg/day)	21 day mortality
5.	COVID STEROID	Hydroxycortisone and dose (200mg/day)	28 day mortality
6.	REMAP-CAP	Hydroxycortisone and dose 50mg/6 hours	28 days mortality
7.	Steroids-SARI[a]	Methylpredinosolone and high dose 40mg/12 hours	30 day mortality

*Dexamethasone therapy for patients with ARDS caused by COVID-19[1], *COVID-19 dexamethasone[2], *Randomized evaluation of COVID-19 therpay[3], *Community acquired pneumonia evaluation of corticosteroids in coronavirus disease[4], *Hydrocortisone for COVID-19 and severe hypoxia[5], *Randomized evaluation of COVID-19 therapy[6], *Glucocorticoid therapy for COVID-19 critically ill patients with severe respiratory failure[7].

Corticosteroids were associated with lower mortality among critical ill COVID-19 patients who were and were not received invasive mechanical ventilation at randomization. Lower mortality was stronger in patients who were administrated only with corticosteroids when compared to the patients who were received corticosteroids with vasoactive medication at randomization.There is no specificity was observed between corticosteroids and mortality among gender, age, and duration of symptoms.In the RECOVERY trail, absolute death risk was reduced by 12.1% those who were under invasive mechanical ventilation treated with low dose dexamethasone and found that higher dose of corticosteroids was associated with greater benefit than a lower dose of corticosteroids. These finding are contrast among patients with influenza, for whom mortality and hospital acquired infections may be increased by the administration of corticosteroids. There are several limitations in the above studies which are number of patients participated in thus study, long term mortality and discharge mortality was not studied, trails conducted only on adults etc. (11).

A study was conducted from March 17 and April 2020 on 186 patients who were administrated with TCZ (123-admitted into conventional hospitals and 63 – into critical/semi-critical care units) showed a survival rate of 79%. Nonsurvivors received fewer doses of CS with the combination of TCZ and showed a greater increase of IL-6, and worse LDH plasmatic levels when compared to the survivors. Out of 186, 153 patients who received TCZ and CS in combination, CS were most commonly given as iv pulses of methylprednisolone at 125 mg 3 days at day +11, immediately followed by or overlapped with iv TCZ at day +12, at 8 mg/Kg (single dose). Only a minority of our patients (7.5%) received a second or third TCZ infusion, which does not appear to be related to lower mortality. It seems reasonable to propose a sequential combined therapy with effective antiviral drugs as a first step, and thereafter, immunomodulatory treatment in those patients with COVID-19 who progress into the advanced stage with severe pulmonary failure and systemic hyperinflammatory syndrome. The use of dexamethasone or alternative CS are currently recommended as an immunomodulatory agents for the treatment of patients with severe COVID-19 requiring supplemental oxygen. This study is retrospective in nature and the efficacy of TCZ in the general population with COVID-19 infection was not measured, inflammatory parameters were analysed only in some number of patients (1).

Nicola Veronese et al. 2020 studied 542 Chinese patients (conducted between the end of 2019 and February 2020) from 4 studies and diagnosis confirmed by RT-PCR from throat swab samples. All patients showed pneumonia from mild to more complicated forms and one convalescent patient. Among 4 studies, two showed negative impact with the use of corticosteroids; patients experienced double risk of being admitted in ICU as well as increased proliferation of virus when compared to the controls. One study did not report any benefit after using methylprednisolone (30-80mg/day) on clinical outcomes (137 patients) and one study (201 patients) with different stages of pneumonia and ARDS were due to COVID-19, treated with methylprednisolone (standard doses) significantly reduced the risk of death by 62%. Different studies suggesting different perspectives on the use of corticosteroids for COVID-19 patients. Patients with MERS-CoV pneumonia were not showing any signs of improvement after the corticosteroid therapy and another study reported that there is no difference in the 90-day mortality and delayed MERS-CoV RNA clearance (7).

Activation of the VDR (Vitamin D signalling receptor) pathway can decrease cytokine/chemokine storm, change the neutrophil activity, reduce the coagulation, regulates the renin-angiotensin system, stimulates epithelial repair, and maintain

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the integrity of the pulmonary epithelial barrier are the beneficial effects to treat patients with ARDS. Lower concentrations of 25 (OH) D3 in circulation also reported that it is associated with SRAS-CoV-2 infection and ARDS. Total 76 patients with SARS-CoV-2 infection were assessed for eligibility in this pilot study for randomization. Along with the calcifediol, patients have received the combination of hydroxychloroquine (400mg every 12h of the first day and 200mg for every 12h for the next 5 days), Azithromycin (500 mg orally for 5 days), and ceftriaxone (2g intravenously) (standard care therapy). Among the 76 patients, 50 were administrated with calcifediol and 26 were not treated with calcifediol (2:1 randomization).Among 50 patients one patient only required ICU admission, no one died and out of 26 patients (controls) 13 people required ICU admission and two patients have died and all other people are in conventional hospitalization. Among all 26 had a history of hypertension (11 received calcifediol and 15 did not).This pilot study suggested that treating the COVID-19 patients with a high dose of 25 hydroxy Vitamin D3 significantly reduced the need for ICU treatment of patients who required hospitalization due to COVID 19 infection. Using corticosteroid (dexamethasone) and calcifediol, to the COVID-19 infected patients has potent inflammatory actions, and recently has been shown to reduce the mortality in hospitalized patients on COVID-19 who required respiratory assistance. These randomized clinical and observational studies revealed that chloroquine and hydroxychloroquine are no longer effective for COVID-19 treatment due to its less safe and less efficient (6)

Cyclosporine A (CsA) is a calcineurin inhibitor and also has the properties of inhibiting the IL-2 production, and a suppressor of T cell immune response. CsA promotes anti-inflammatory cytokine IL-10 and inhibits the pro-inflammatory cytokines such as IL-1ß, IL-12, and TNF-α. CsA has also shown in vitro antiviral replication against several coronaviruses such as SARS-CoV and MERS-CoV.In A pilot study, out of 209 adult patients, 105 patients were administrated with CsA group and 104 were controls. All patients received medical care until recovery or death. In the 28 days protocol, 149 patients were discharged from the hospital and 60 died. Out of 149, 82 received CsA plus steroids and 67 received steroids alone and out of 60 deceased patients, 23 were administrated with CsA plus steroids and 37 steroids alone. Results showed significantly lower mortality in CsA+steroids which is more remarkable in patients with moderate to severe pneumonia. The use of corticosteroids for COVID-19 is always remarkable. According to some author's suggestions, even corticosteroids reduced lung inflammation, due to its immunosuppressive activity it can also cause a rebound of the viraemia which was proven in the MERS treatment. Corticosteroids when administrated at early stages improved the clinical conditions of the patients with ARDS. The corticosteroids used in this study either prednisone or methylprednisolone were given at low doses of 0.5-1.0 mg/kg per day for up to 10 days (this regimen is equivalent to the low doses of dexamethasone). The addition of CsA to the standard treatment provides additional improving outcomes and reducing mortality. No observed nephrotoxicity when compared to the studies with prolonged use of CsA.In COVID-19 patients CsA can inhibit the NET (neutrophil extracellular traps) mechanism and it could be helpful to prevent alveolar damage and preserve normal lung function. CsA is a potent inhibitor of cyclophilins, essential enzymes in the cycle of coronavirus (antiviral activity). (10).

Tang, Xiao, et al. 2021 conducted a single-blind trial during the early days of the COVID-19 pandemic. In this trial, only physicians were aware of the treatment procedure, not the patients. The last patient in this study enrolled in the trial on March 31, 2020, and terminated the trial on April 15, 2020. Out of 213 patients, 127 were excluded, and eventually, 86 patients were randomized (43 methylprednisolone group and 43 control group respectively). During hospitalization, 67 patients in both groups were administrated with antiviral agents, and antibiotics are given to 61 patients. 70 patients required nasal cannula oxygen therapy, 3 used high flow nasal cannula oxygen therapy a, 4 received mechanical ventilation and 2 underwent extracorporeal membrane oxygenation. After 7 days of randomization with methylprednisolone treatment, CD3+T cells, CD8+ T cells, and NK cells after 14 days were significantly lower in the methylprednisolone group when compared to the control group. On day 7 CD11b+ myeloid cells increased in the methylprednisolone group. And this treatment group doesn't show any effect on CD19+ B cells and the other immune cells. 4 patients were shown clinical deterioration with respiratory failure (3).

A study revealed that treatment with corticosteroids (methylprednisolone) reduced the risk of death. Corticosteroid therapy was associated with delayed clearance of viral RNA from respiratory secretions. A study gave an opposite result that early use low dose of methylprednisolone may not obtain any clinical benefits in the patients of COVID-19, even prolonged the virus shedding. A pathological study of a patient who died from COVID-19 pneumonia reveals bilateral diffuse alveolar damage with cellular fibromyxoid exudates, interstitial lymphocyte infiltrates, and multinucleated syncytial cells in the intra alveolar spaces.Clinical studies suggest that dysregulation of immune response; especially T cells might be highly involved in the pathological process of COVID-19. Reduction in CD8+ cells counts as one of the predictors of mortality. However, methylprednisolone did extend the virus shedding time and hospital days in patients without acute respiratory failure. Treatment of corticosteroid for viral pneumonia has a potential risk of secondary infections and

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other long term complications such as bacterial pneumonia or invasive fungal infection (3).

After revising many clinical studies, it is not clear corticosteroids to use in the COVID-19 treatment. More studies are required to use of corticosteroids in anti-viral therapy. Advantages, disadvantages and limitations of corticosteroids are represented in the Table number 2.

Table 2: Some of advantages, disadvantages and limitations of corticosteroid therapy for COVID-19

Advantages	Disadvantages	Limitations
1. Anti-inflammatory effect 2. Low mortality 3. Reduced days of hospitalization **4.** Reduced requirement of invasive mechanical ventilation	1. Hyperglycaemia 2. Gastrointestinal haemorrhage 3. Psychosis 4. Hospital acquired infections 5. Double risk of being administrated in ICU 6. Delayed RNA clearance and extended the viral shedding time 7. Nephrotoxicity when prolonged use of CsA 8. Increased hospital stay	1. Most studies done with less number of patients which does not allow for firm conclusion to be drawn 2. Long term mortality and post discharge were not studied 3. Trails were only conducted on adults not on children's 4. Some studies does not measured the inflammatory cytokines 5. Patients with other medical complications such as HIV, long term use of immune suppressive agents, pregnant and breast feeding women, hypertension, glaucoma, hypokalemia are excluded from the many studies 6. Not detected the quantity of viral load in many studies.

III. Nanotechnology for COVID-19 Therapy

Nanoparticles (NPs) are very small sized particles range from 1 and 100nm and with high surface to volume ratio, suitable for various biological applications including health care. NPs are synthesized from various types of inorganic and organic substances are silica, gold, silver, graphene and liposomes, micelles, proteins/peptides and dendrimers etc. Because of their high absorbing capacity, NP's become powerful materials in diagnostics and therapeutic approaches. NP's are able to deliver the drugs to the target site and protect from degradation within the body (14). Nanotechnology plays a crucial role in the drug delivery, administration, and they can serve as adjuvants to the antigens used in vaccines to boost immune response. SARS-CoV-2, spreading very quickly, it is necessary to require drug repurposing and multipronged scientific approaches which are largest testing capacity methods must be accurate, need of therapeutic drugs to reduce the effects of the virus, mortality and morbidity, and then vaccines to produce antibodies lead to eventual herd immunity (18).Nano particles become the most promising therapeutic approaches in the COVID-19 treatment because of its antimicrobial properties. Selective target of modified Nano particles with properties such as bioavailability, biodegradability and not to generate reactive oxygen species (ROS) are suitable for anti-viral therapy (27).Several inorganic Nano particles have capable to deliverthe drugs for treatment of viral infections. Gold and silica NPs were used in nanovaccines against influenza A virus and HIV respectively. Target cellular entry, binding to the viral genome, aberrant viral transcription, triggering of ROS and activation of signalling pathway properties made NPs to use against SARS-CoV-2 (28).

Drug repurposing against COVID-19 will reduce the mortality rate. The combination of drugs with NPs may enhance their biocompatibility and physicochemical properties (19). Different applications of Nanotechnology in anti-viral treatment are depicted in the picture 1:

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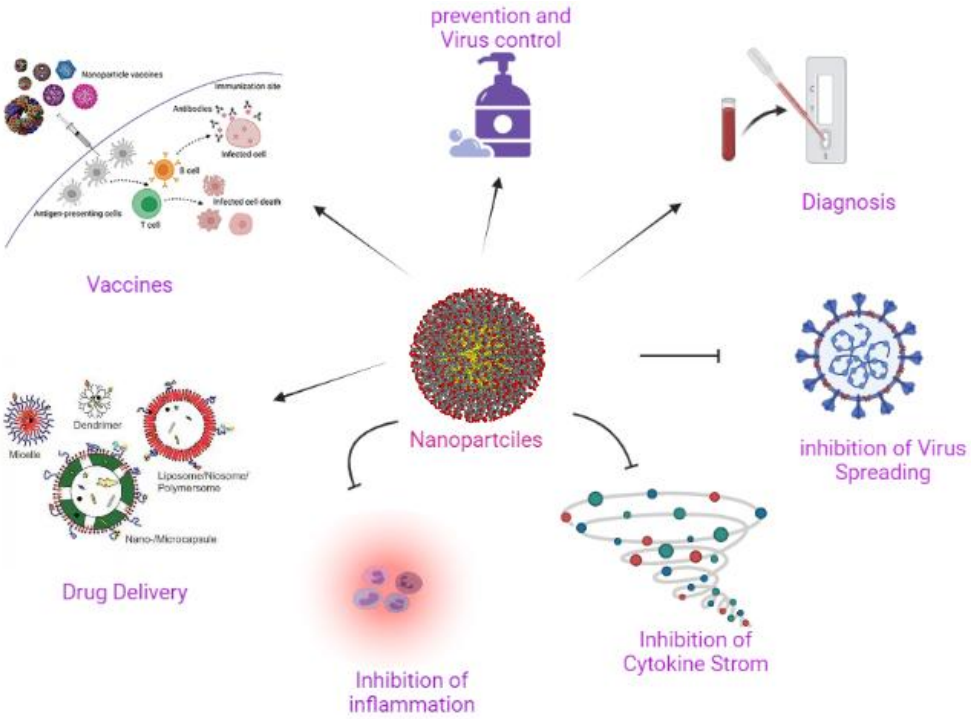

Picture 1: Applications of Nanotechnology in anti-viral treatment

IV. Nanotechnology Role in the Diagnosis of COVID-19

Accurate and early detection of COVID-19 infection spread is more essential during this pandemic situation. Molecular diagnosis with NPs has emerged as a promising strategy for the detection of COVID-19 accurately. Extraction of RNA from COVID-19 using high affinity silica coated iron oxide nanoparticles gave the accurate identification. Serological methods by colloidal gold NPs are superior methods to detect the SARS –CoV-2 antibodies instead of the virus. Gold Nanoparticles can able to detect the IgM and IgG antibodies derived from the SARS-CoV-2 quickly. Chiro-immunosensors based on chiral AuNPs (CAu-NPs)-quantum dot (QDs) nanocomposites using exciton-plasmon interaction showed enhanced sensitivity for viral RNA detection. Chaperone-mediated ferritin NPs, Self-assembling protein Nanoparticles (SAPN), AgNPs, Lumazine synthase NPs, spike protein NP's, AuNPs, Lumazine synthase NPs are being used in diagnosis of viral RNA (15).

RT-PCR methods are highly sensitive and highly specific for the detection of viral RNA based on the exponential increase of RNA. However, this methods still having some limitations including time consuming process, low extraction efficiency and contamination leads to false result. NPs such as Metal NPs, Metal Nano islands (NIs), polymeric NPs, quantum dots (QDs), silica NPs and polymeric NPs applied in RT-PCR, ELISA (enzyme-linked immunosorbent assay) and reverse transcription loop-mediated isothermal amplification (RT-LAMP) showed greater efficiency in the diagnosis of viral genome. Most of these diagnostic methods are depend on electrochemical, fluorescence, colorimetric and optical detection techniques (18).

NPs can improve the detection, increase signal amplification, sensitivity in PCR analysis. AuNPs are used in the preparation of rapid IgM/IgG antibody test kit for COVID – 19. Serology protein based test is widely accepted and standard method to detect the viruses in the body fluids and it is based on specific antigen or antibody. Carbon nanotubes, silica nanoparticles, polymeric nanoparticles and quantum dots are successfully used in the virus detection. Increased surface area to volume ratio of Nanoparticles would improve the interaction between analyte and sensor, decrease the detection time and increase the detection limit.AuNPs are precise for diagnosis because of their electrical, photonic and catalytical properties. Modified AuNPs with thiol group on surface can efficiently interact with target molecules (20, 26).

V. Nanotechnology Role in the Treatment of COVID-19

Nanomaterials or NPs can overcome the drug resistance and are advantage for the anti-viral treatment. In addition to its antiviral properties, NPs also act as promising antiviral drug carriers (30).Cyclodextrins conjugated with Nanoparticles could reduce the drug associated toxicity for COVID-19 and these are highly biocompatible. Due to its electrical, thermal and bio availability properties, Carbon Nano tubes (CNTs) can raise the local cellular temperature using photodynamic thermal effect and inhibit the COVID-19 viral replication.

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Negatively charged silica surfaces and gold particle surfaces has shown good interaction with RBD of SARS-CoV-2 S protein. (14).

Natural peptide inhibitors were found against the SARS-CoV-2 RBD. These peptide inhibitors bind to ACE2 receptor in host cell and prevent the binding of virus to ACE2, which is the main entry path of the virus. Conjugating natural peptide inhibitors with natural compounds show effective anti-viral action (29). Peroxy nitrate derived from NO (Nitric oxide) nanoparticles inhibit the RNA replication and prevent the SARS-CoV infection as well as virulence in endothelial cells. Noncoding RNAs such as microRNA, siRNA and shRNA can regulate viral gene expression. These noncoding RNAs encapsulated with NPs protect them from enzymes within the host body. Dose dependent Octadecylamone and decamethasone encapsulated with Nano diamond particles showed promising results on declining of iNOS, TNF-α, and macrophage infiltration in mice (31).

Occupying the virus ligand sites on host cell surfaces, diminish the viral attachment. Recently Carbon dot nanomaterials derived from ethylenediamine/citric acid and modified boronic acid ligands showed inhibition and inactivation of HCoV-229E by interacting with its entry receptors on host cell surface (32).A molecular docking study revealed that iron oxide nanoparticles can able to interact efficiently with S1-RBD of the SARS-CoV-2 and promotes the antiviral therapy by changing the conformation of viral protein (15).

Encapsulation of chloroquine/hydroxychloroquine with in the Nano carriers such as liposomes, polymeric NPs etc., can able to deliver the cargo to the respiratory system and decline complications such as myopathy, retinopathy and heart diseases. Combination therapy using nanomaterial can increase the therapeutic effects as well as minimize the effective dose of drugs. In one of the antiviral study, lopinavir/ritonavir encapsulated with PLGA NPs showed effective antiviral activity and reduced effective dose of the drug (33).

Nanodrugs shows double-edged sword. From one side is about their toxicities and on the other hand efficacy of drugs or direct inhibition of viral docking and replication. Several therapeutic drugs against COVID-19 are under the research and many of corticosteroid drugs show slightly adverse effects. Dexamethasone incorporated in liposomal nanomaterials has shown greater efficacy in multiple myeloma. Dexamethasone without nanomaterial also showed reduction in the ARDS condition in clinical trials of COVID-19. Anti-fibrotic effects of dexamethasone can be potentiated by reformulating it as a nanomedicine and enable to target the alveolar macrophages or of phagocytes at inflammation sites. But this technology is expensive, reduces the mortality and cost reduction in hospitalization (17).

Chloroquine drug can able to block the ACE 2 receptor though the suppression of PICALM which prevents the binding of SARS-CoV-2 on the human cells. Therefore, Chloroquine encapsulated inside the polymeric NPs can effectively deliver the drug to the target site and most commonly used NPs encapsulating the Chloroquine are PLA (poly Lactic acid) polymeric NPs (34).

Not only drug delivery but NPs can also interfere directly with the receptor binding and cell entry of viruses. Curcumin cationic carbon dots (CCM-CDs) with ~1.6 nm diameter showed 50% inhibition efficiency at 125 μg/ mL in the PEDV (porcrine epidemic diarrhea virus) which is a corona virus model. This carbon dots also reduced the cell apoptosis and suppressed the reactive oxygen species (ROS) accumulation. Nanoparticles with smaller size have large surface area than larger size particles which can lead to direct interactions with envelope proteins of virus and inhibition (3).

NPs especially metallic NPs, associated with the tumorgenicity, free radical generation, mutagenicity and penetration into the brain, hence it is necessary to evaluate the toxicity, size dose dependency, biodistribution and bioavailabilty and then the route of administration. Another important aspect is associated with the cell death mechanisms provoke by Nanoparticles is cross-reaction with the efficacy of drugs against a virus such as autophagy, ferroptosis, etc. (33).

Haung et.al found a peptide, named as pregnancy –induced hypertension (PIH). This PIH could mimic the structure of HR2 and interact with HR1 and inhibit the formation of 6-HB (six helix bundle) leads to inhibition of cell fusion process. When PIH was immobilized on the surface of AuNRs (gold nanorods), showed a 10-fold higher inhibitory activity and exhibited excelled biocompatibility (39). Porous silicon NPs (SiNPs) are extremely biocompatible and biodegradable were able to prevent the infection of viral particles to host cells and also able to act as scavengers of free virus particles. Binding of SiNPs with virions is universal for different enveloped viruses, making them potential agents against SARS-CoV-2 as well (40).

Transmissible gastroenteritis virus (TGEV), a member of the coronavirus family infectivity is significantly reduced in the presence of AgNWs (Silver Nanowires) and AgNPs below toxic level concentration (30).Silver NPs bind to RNA viral genome and activate mitochondrial signaling pathways and proteins which show antiviral activity (37). Nano encapsulated drugs work more efficiently in activating intracellular mechanism which causes damage to viruses and

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reduce the viral transcription, translation and replication (24).The NPs of tocilizumab and adalimumab antibody therapies are under clinical trials which may show the enhanced stability, prolonging retention after injection and specific target.

The NPs of GAG (Glycosominoglycan) suppresses the IL – 6, TNF – α and IL - 1β cytokines through electrostatic interactions of positively charged amino acids of cytokine with negatively charged sulfate group of GAG. (26)AgNPs acts as anti-viral against enveloped and non-enveloped viruses by fixing on graphene oxide sheets (GO) with low toxicity. GO-AgNPs ruptures the virus by interacting with positively charged lipid membrane of virus with negatively charged GO – AgNPs. PEG – ZnO NPs (Poly Ethylene Glycol Zinc Oxide Nano Particles) promote antiviral activity and cerium dioxide NPs used in synthesis of Nano vaccines. SiNPs act as Nanothernostics and controls the viral infections like Hepatitis B, Human Immuno deficiency Virus, Human papilloma virus etc., based on fluorescent detection of nucleic acid hybridization. In many studies, Iron Oxide NPs (IONPs), Selenium NPs (SeNPs), graphene oxide (GO), Zanamivir modified selenium (SeNPs – ZNV) and Titanium nano particles (TiNPs) showed anti-viral activity (23).Drugs encapsulated with in polymeric nanostructured materials prevent the degradation of drug and uptake by the reticulo endothelial system and may be become powerful tool against COVID-19 (20).

VI. Nanotechnology Role in the Vaccines Development for COVID-19

In this pandemic situation, vaccines become the most promising solution to reduce the spread of SARS-CoV-2. An mRNA vaccine loaded with liposomal nanoparticles is under the clinical trials against SARS-CoV-2.Vaccines are now vital to develop an immediate immune response against COVID-19 disease. Delivering mRNA vaccines encapsulated in LNPs (lipid Nanoparticles) can translate into protein and enhance the specific immune response in host body (36). SaRNA (Self-amplifying RNA) is a n639ew type of RNA vaccine contain the viral replicase enzyme, which allow the replication of sub genomic mRNA. In a study on mice injected with saRNA encapsulated with LNPs triggered the high concentration of SARS-CoV-2 specific antibody and this antibody has the ability to neutralize both a pseudo type and wild type SARS-CoV-2 (37).

Spike protein mRNA of SARS-CoV-2 encapsulated in liposomes helps to protect from degradation of gastric juices, which was developed in Pfizer and Moderna vaccines. Inhalation or nasal spray administration of nanoparticles provides an attractive administration route and beneficial because the primary route of COVID-19 virus is respiratory tract(38). Nano vaccines work to control release of antigens or adjuvants, prolonged self-life or by mimicking the morphological characteristics of viruses. Larger surface of NPs allows surface functionalization through cross linking (14).

CRISPR/Cas13d RNA endonuclease with guided RNA used to inhibit/ degrade viral genome and synthesis of mRNA in targeted manner. Lipid nanoparticles encapsulated with genetic material used in vaccines It protects DNA or RNA against degradation of enzyme, efficient cell uptake, and release of genetic material into target cells (32).Fabricated nanovaccines prepared from biodegradable and synthetic PLGA (Poly Lactic co Glycolic Acid) and DEPE – PEG, deliver viral antigen and STING agonists, adjuvant in a virus like fashion. It is safe and effective against Middle East Respiratory Syndrome Coronavirus. Capsid like hollow NPs lowers systematic, reactogenicity, pH – responsive release profile and prominent local immune activation (20).

The combination of AgNP and GO used to treat the member of corona virus family known as feline corona virus. This combination of NPs also enhances the production of IFN – stimulating genes (ISGs) and interferon – α (IFN – α) which inhibits the virus proliferation. vSelenium NPs combined with Arbidol (ARB) highly effective against virus. These NPs inhibited the cell entry of influenza virus. Cell entry also blocked by cationic chitosan nanoparticles by targeting dendritic cells (DCs).PAMAMs (Polyamidoamines) one of the type of cationic NPs, binds to ACE2 receptors and prevent viral docking and these are promising strategy for COVID-19 infection (35).

Major limitations of NPs are generation of oxidative stress, Apoptosis, cytotoxicity, and mutagenesis. Hepatotoxicity, neurotoxicity, renal failure, pulmonary fibrosis, micro nuclear formation, damage of cellular membrane, uncontrolled cellular signaling and carcinogenesis are the adverse effects caused by nanoparticles. Carrying capacity, manufacturing, and cost effective are also major limitations of Nanoparticles to be used in the anti-viral therapy (23).

VII. Conclusion

Global health emergency by novel coronavirus affecting peoples life in every region of the world. In this current pandemic situation, diagnosis and treatment are crucial to battle the spreading of the virus. There is a lack of effective treatment procedures against COVID-19. Corticosteroids with low to moderate doses showed beneficial effects and reduced mortality in many clinical studies, but adverse effects also appeared such as prolonged hospitalization, delayed viral clearance, secondary and hospitalized infections. Multivalency

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of the COVID-19 requires multivalent antiviral treatments. Nanomedicine becomes a more suitable application for antiviral therapy which is targeted delivery of drugs, interruption of viral docking in many in vitro and preclinical studies, and accuracy in diagnosis. Nanotechnology is also used for, to safe delivery of vaccines into the host body. The observations from many clinical studies of corticosteroid treatment described in this review justify further investigations to determine the optimal dose, time of administration, and duration to improve the clinical outcomes and to overcome the adverse effects caused by corticosteroids. In this review we represented the role of Nanotechnology from various anti-viral studies and much clinical work is required to study the nanoparticles efficacy in COVID-19 diagnosis and treatment.

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