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AN OVERVIEW AND COMPARISON OF CONVENTIONAL AND NANOTECHNOLOGY BASED ANTIVIRAL APPROACHES FOR COVID-19

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ABSTRACT

Since the end of 2019, the whole world was introduced to a new pandemic situation called COVID -19. This outbreak was named novel coronavirus (2019-nCov) by World Health Organization (WHO) and still, there is not any promising solution to tackle this pandemic disease. For diagnostic, preventive, control, and treatment of COVID-19, various strategies have been developed. Therefore, several antiviral agents are used against COVID-19. Antiviral agents such as M2 ion channel blockers, protease inhibitors, neuraminidase inhibitors, and fusion inhibitors are seen effective against 2019-nCov. Nowadays, many antiviral drugs used for the treatment of disease are available in form of nanoparticles and the antiviral based-nanoparticles prove to be a very powerful approach for COVID-19 treatment. Many case studies showed that nanoparticles have various advantages over conventional dosage forms such as improved efficacy and safety, etc. This review attempts to focus on the preparation and evaluation of nanotechnology-based antiviral drugs. The review includes case studies, clinical trials, and a comparison of conventional and nanotechnology-based antiviral approaches for COVID-19.

KEYWORDS: Conventional**,** COVID-19, Epidemiology, Nanotechnology.

INTRODUCTION

In December 2019, an unknown viral infection appeared in South China which spread rapidly throughout the world. This pandemic affects the economy of the countries and everyone's life. These are submicroscopic infectious entities produced via SARS-CoV-2 that replicate within the cells. These viruses contain DNA or RNA, and capsid protein with or without a lipid envelope. They are further categorized into envelope and non-envelope viruses and covid -19 is surrounded by lipid envelope (envelope viruses).[1] The structure of coronavirus is shown in **Fig. 1**.

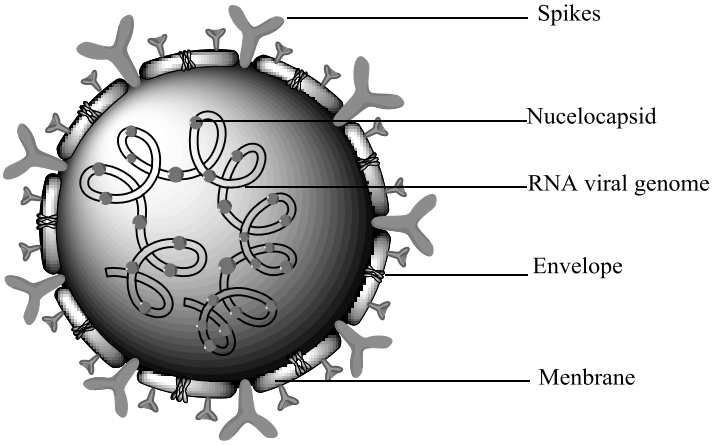

Fig. 1: Structure of Coronavirus.

A research study by the Chinese CDC observed that 80% of patients have moderate symptoms including fever, chest pain, dry cough, diarrhea, abdominal pain, dizziness, fatigue, nausea, headache, and sometimes vomiting.[2] 15% of patients have severe symptoms and

5% of patients become critically ill. Day by day progress of COVID-19 is shown in **Table no. 1**.

Table 1: Day-by-day progress of COVID-19.[3]

DAY 1	**Fever, Fatigue, Muscle pain, Dry cough.**
DAY 5	Breathing Problems, Serious health conditions.
DAY 7	These symptoms Lead to the Patient being admitted to the hospital.
DAY 8	ARDS (acute respiratory distress syndrome)
DAY 10	Move to worse condition and patient shifted move to ICU
DAY 17	The patient recovers and is discharged from the hospital.

COVID-19 is transmitted by direct means (human-to-human interaction and droplets) and by indirect means (contaminated food and objects). The major source of COVID-19 transmission is respiratory droplets, patients cough when they talk or even sneeze. These droplets cannot travel more than two meters and can't remain in the air for more than 3 hours. So, there is a requirement for the application of sanitizers, isolations, and use of disinfectants.[4] The mode of transmission of the virus is depicted with the help of a pictorial diagram in **Fig. 2**.

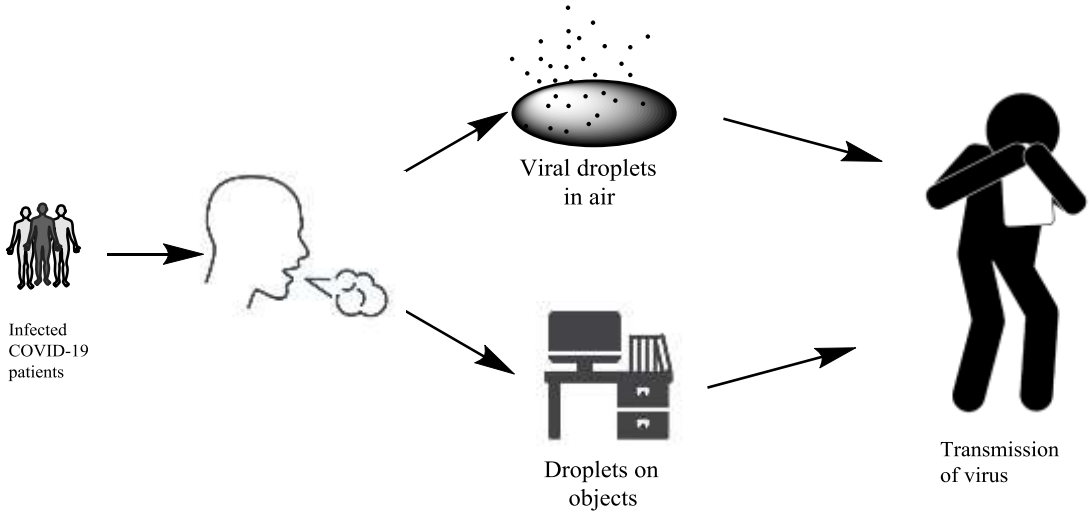

Fig. 2: Modes of transmission of SARS-CoV-2 virus.

1.1 Epidemiology

COVID-19 spread over 100 countries and there have been 428,511,601 confirmed cases of COVID-19, including 5,911,081 deaths. The whole world is affected by this pandemic resulting in great loss of life and the global economy. We have collected the data and prepared a comparison chart of current cases of coronavirus worldwide (**Fig.3**).[5]

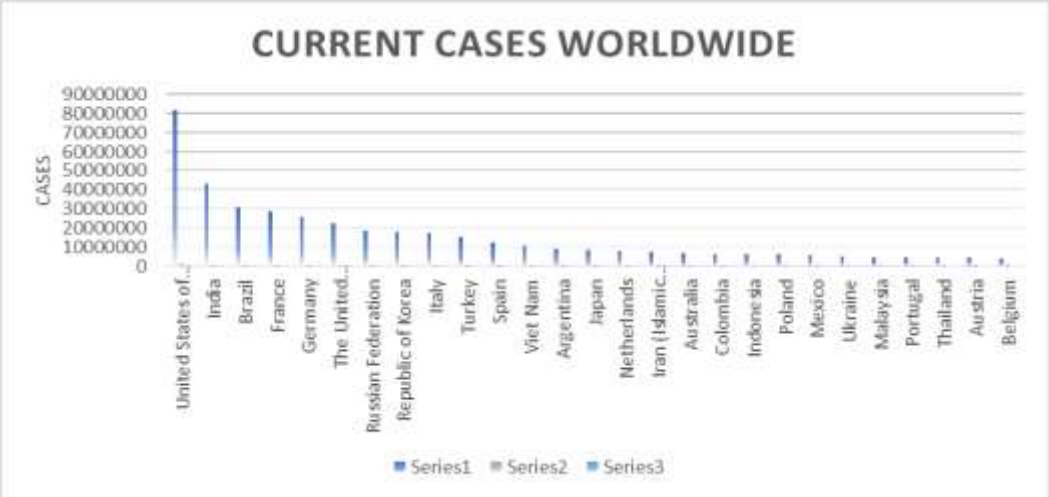

Fig. 3: Worldwide cases of COVID-19.

World health organization said that about 3.5% covid patients died and the death rate varied due to various factors such as Age, Sex, and Health conditions. We conducted a thorough literature survey and found that the death rate is higher in elders than in middle-aged and even more common in diabetes, high blood pressure, and heart disease-related patients.[3] The data indicating death rate with respect to age and sex are tabulated in **Table 2 and 3**.

Table 2: Fatality by Age in COVID-19.

AGE	10-19	20-29	30-39	40-49	50-59	70-79	80+
DEATH RATE	0.20%	0.20%	0.20%	0.40%	1.30%	8.00%	14.80%

Table 3: Fatality Rate by SEX.

SEX	DEATH RATE
MALE	4.7%
FEMALE	2.8%

***Death Rat**e = (numbers of deaths/number of cases) = **probability of dying if infected by the virus** (%).

2. Role of nanoparticles in COVID-19

For intracellular drug delivery, various approaches such as nanoparticles, prodrugs, liposomes, microspheres, etc. have been used to increase the absorption of encapsulated drugs because of improved stability properties and retention time of drug. Various studies state that nanotechnology-based formulations demonstrate a positive outcome for the pulmonary drug delivery system (intracellular) which results in the increased therapeutic efficacy of treatment. Similarly, in the case of COVID-19, nanoparticles show potential advantages over conventional dosage forms for the delivery of drugs.[6,7]

2.1 Conventional treatment vs Nanoparticles

In recent years, there is a huge sarcastic development in the field of nanoparticle technology. These are solid particles with a size range between 10-1000nm which are encapsulated, dissolved, and entrapped within a polymer matrix. Nanoparticles are a choice of drug delivery system because of the target delivery and prolonged action of the drug.

The advantage of nanoparticles over conventional dosage forms

1. They can provide control and sustain release and increase the therapeutic efficacy of the drug.
2. By using magnetic guidance or Targeting ligands with nanoparticles used to achieve site-specific targeting.
3. Nanoparticles offer a variety of routes of administration such as oral, nasal, parenteral, transdermal, etc.
4. After parenteral administration, active and passive targeting can be achieved by altering particle size and surface characteristics.[8]

2.2 Methods for Preparation of Nanoparticles

Various research groups are now working for encapsulating the antiviral drugs used for COVID-19 in the form of nanoparticles after looking into its emerging applications.[9] The different methods that are used for the preparation of nanoparticles are:

2.2.1 Nanoprecipitation

Nanoprecipitation is easy, less complex, low energy consumption as well as more acceptable when compared to other techniques for the formulation of nanoparticles. This technique is based on dissolution and precipitation mechanisms. It involves interfacial deposition due to solvent displacement with non-solvent hence called the solvent displacement method.[9,10]

Hydrophilic and lipophilic drug entrapment is achieved with the help of nanoprecipitation. Nanoparticles are obtained by colloidal suspension in which the oil phase is slowly added to the aqueous phase with continuous stirring. In this method, drugs, and polymer are mixed with water-miscible organic solvents like methanol and acetone. Then, the above mixture is added dropwise in an aqueous solution containing surfactants, and finally, nanoparticles are obtained on the removal of the solvent under reduced pressure.[11]

2.2.2 Solvent evaporation

Solvent evaporation includes two parts (the polymer is emulsified into an aqueous phase and evaporation of polymer-solvent for the preparation of nanoparticles). Polymer and hydrophobic drugs are dissolved in organic solvent and the above mixture is emulsified in the aqueous phase to form o/w emulsion and finally, the organic solvent is evaporating under reduced pressure to obtain nanoparticles.[12]

2.2.3 Emulsification/solvent diffusion

The solvent diffusion method is an enhanced version of the solvent evaporation method. The encapsulated polymer is added to a partially water-miscible solvent. For the formation of nanoparticles, the above mixture is emulsified in an excess amount of aqueous phase-containing stabilizers. This will lead to precipitation of polymer and finally nanoparticles obtained by evaporation of solvent according to its boiling point or by filtration.[9]

2.2.4 Supercritical fluid technology

Supercritical fluid technology is a widely used technique in the last two decades. Supercritical fluids are more eco-

friendly solvents and supercritical CO_2 and H_2O are commonly used for the preparation of varieties of NP. Supercritical fluids can avoid the drawback of conventional methods and can produce NP with high purity.[9,13]

2.2.5 Dialysis

Dialysis is the most ideal approach for the preparation of small, narrow-size nanoparticles with help of amphiphilic material, block, and graft copolymers. For the preparation of NP, drug, polymer, and surfactants are mixed with organic solvents which are placed within the dialysis tube and a nonsolvent miscible solution passes through the dialysis tube for the formation of micro nanoparticles.[14,15]

2.2.6 Salting out method

The salting-out method separates the water-miscible solvent from the aqueous solution with the help of the salting-out effect. In this method, polymer and drug dissolved in organic solvent and then emulsified in an aqueous gel containing salt out the agent for the formation of oil/water emulsion and further added the above mixture in aqueous solvent for the formation of nanoparticles.[12]

2.2.7 Polymerization method

This method involves the conversion of monomers into polymers for the formation of nanoparticles.

2.2.8 Interfacial polymerization

Interfacial polymerization is the polymerization method used for the preparation of polymer nanoparticles. Monomers are dissolved at the interface of two phases (dispersed and continuous phase). Interfacial crosslinking reactions such as polycondensation and polyaddition are used for the preparation of nano-sized hollow polymer particles. Monomers polymerization with oil/water interface of fine o/w micro-emulsion to form oil-containing nanoparticles.[9,16]

2.2.9 Emulsion polymerization

This is the fastest method for the high scale nanoparticles preparation and this method involves two stages (continuous organic and aqueous phase). In the continuous organic phase, dispersion of monomer into an insoluble solvent containing surfactants, organic polymers, etc. This phase is not widely used because of toxic surfactants, organic polymers, and non-biodegradable polymers used for the production of nanoparticles.

In continuous aqueous phase, monomers are mixed with an aqueous solution that doesn't require the use of surfactants and emulsifiers. These monomers are introduced with high-energy rations or ultraviolet light to form monomer ions and these ions interact with each other to form a chain of monomers (polymers).[9]

2.2.10 Mini-emulsion Polymerization

The most commonly used ingredients used for the formulation of mini-emulsions are monomer blends, stabilizers, water, and surfactants. Mini-emulsions are prepared by homogenization of two immiscible liquids with the help of high shearing forces such as ultrasonication or high-pressure homogenization.[17,18]

2.2.11 Micro-emulsion polymerization

These are the most effective and new approaches for the preparation of nanoparticles where emulsions and micro-emulsions are almost similar in every aspect but differ when compared kinetically (particle size and the average number of chains per particle are smaller in micro-emulsion).[9]

2.2.12 Controlled/living radical polymerization

Controlled/living radical polymerization provide new opportunities by using the old polymerization technique where controlled/living radical polymerization is more environment-friendly method and C/LRP can overcome the limitation of the old polymerization technique which include uncontrol molar mass, molar mass distribution, and the end-functionalities.[16]

All the techniques are summarized in Fig. 4.

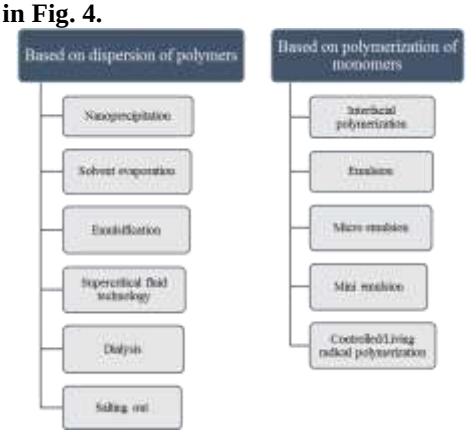

Fig. 4: Methods for the preparation of nanoparticles.[9]

2.3 Types of Nanoparticles

These are classified into organic, inorganic, and carbon-based nanoparticles. The various types, their materials, and their specific characteristics are summarized in **Table 4**. Thereafter, the characterization nanoparticles are briefed in **Table 5**.[19]

Table 4: Various nanoparticles, their characteristics, and material used.

Type	Characteristics	Material used	Ref
ORGANIC NANOPARTICLES Dendrimers, Liposomes, Ferritin, Micelles etc.	Biodegradable, non-toxic, Sensitive towards thermal and electromagnetic radiation (heat and light)	Chitin, Polyamidoamine, Polyethyleneimine, Chitosan, Gelatin, Albumin etc.	[19,20]
INORGAINIC NANOPARTICLES Metal based nanoparticles Metal oxides based Nanoparticles Ex- Cerium oxide	Synthesized from metals of nanometric sizes by destructive or constructive methods. Stable, Biocompatible and have magnetic properties to provide a target delivery	Cobalt, Iron, Gold, etc. Chromium dioxide, Maghemite, Cobalt ferrite etc.	[19,20]
CARBON-BASED NANOPARTICLES Carbon nanotubes Carbon nanofibers Carbon black	Honeycomb-like structure with hollow cylinders called hollow tubes. Made up of cone or cup-shaped Amorphous, spherical shape, 20-70 nm diameter.	Completely made up of Carbon.	[9,19]

Table 5: Characterization of nanoparticles.[12]

Parameters	Characterization methods
Particle size	Photon correlation spectroscopy (PCS) Electron microscopy (SEM and TEM) Scanning electron microscopy Transmission electron microscopy
Structure and Crystallinity	X-ray diffraction method (XRD)
Molecular weight	Gel permeation chromatography
Surface charge and electronic mobility	Zeta potentiometer Laser Doppler Anemometry
Specific surface area	Sorptometer (Single and multi-point method) Static secondary ion mass spectrometry
Surface hydrophobicity	water contact angle Rose Bengal (dye) binding
Stability of drug	atomic force microscopy Critical flocculation temperature
Carrier-drug interaction	Differential scanning calorimetry
In vitro release	Franz Diffusion Cell

2.4 Nanoparticles-based Antiviral therapy

Various NP-based studies are conducted to determine the effect of antiviral drugs in COVID-19 in several ways including blocking viral replication, deactivating the virus, or blocking receptor sites. Antiviral drugs include favipiravir, ribavirin, chloroquine phosphate, ritonavir, etc. for prevention, diagnosis, and treatment of COVID-19 (**Fig. 6**).[6,21,22]

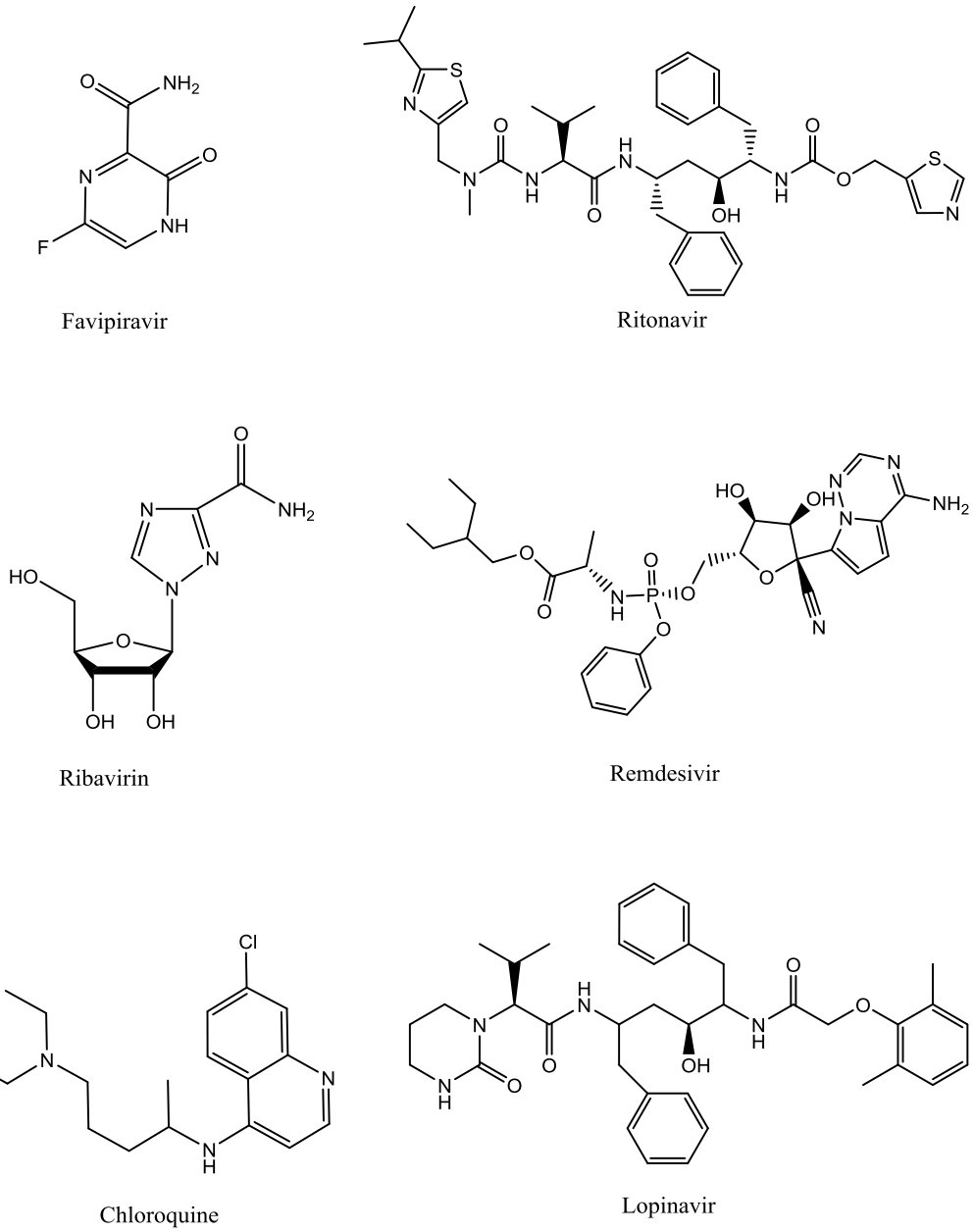

Fig. 6: Antiviral drugs used in COVID-19.

Favipiravir

Many efforts have been made by researchers to tackle this pandemic condition through the development of oral and vaccine therapy against Novel Coronavirus (COVID-19). Antiviral drugs show a great impact against COVID-19. RNA-dependent RNA polymerase (RdRp) is the core element essential for coronavirus replication and plays an important role in this viral lifecycle. Favipiravir produce their antiviral activity by inhibiting RNA-dependent RNA polymerase against Covid-19. They produce their therapeutic effect at a higher concentration of EC50 = 61.89 M.[21,23]

Chloroquine

The U.S. Food and Drug Administration allows the emergency use of chloroquine and hydroxychloroquine against Novel Coronavirus. Chloroquine increases the lysosomal and endosomal PH. Invitro, the acidic PH of lysosomal and endosomal helps in cell fusion and initiates cell division. Thus, chloroquine inhibits these critical steps to produce their antiviral activity. Chloroquine showed its antiviral activity by inhibition of viral enzymes such as DNA and RNA polymerase, glycosylation of viral protein, assembly of the virus, viral transport, and also include inhibition of ACE2 receptor by binding on the surface of the cell membrane to prevent binding with the virus.[6,24]

Ribavirin

Ribavirin is a guanosine nucleotide analog used for the treatment of various viral infections such as herpesvirus, poxvirus, hepatitis C virus, RSV, and some viral fevers by inhibiting the replication of RNA and DNA. The ribavirin also affects RNA capping by affecting

guanosine which is required to prevent RNA degradation. Ribavirin inhibits the formation of natural guanosine by inhibiting inosine monophosphate dehydrogenase which is crucial for the production of the guanine precursor required for the formation of natural guanosine. Ribavirin also produces its antiviral activity by inhibiting RNA- dependent RNA polymerase which makes it effective against SARS- CoV-2. It requires a high concentration (1.2 g to 2.5 g every hour orally) to produce its antiviral effect.[25–27]

Lopinavir/Ritonavir

Lopinavir is the protease inhibitor used for the treatment of human immunodeficiency virus (HIV). In 1996, Ritonavir was approved in the United States as a second protease inhibitor for the treatment of HIV. Ritonavir was originally used as an HIV protease inhibitor to inhibit cytochrome p450-3A4. Ritonavir is used along with Lopinavir to improve the biological half-life of Lopinavir. Several studies show that the combination of Lopinavir/Ritonavir reduces the death rate among SARS patients and is later on used for the treatment of acute respiratory illness and produce antiviral activity against Covid-19 by inhibiting viral replication.[28–31]

Remdesivir

Remdesivir has been approved by various medical regulators for the treatment of COVID-19. These are monophosphoramidate nucleoside prodrugs that intracellularly convert into active metabolite NTP (nucleoside triphosphate). Remdesivir triphosphate active metabolite of remdesivir targets the steps responsible for the replication of viral RNA genome or affect highly conserved element of SARS-CoV-2. They formed synthetic compounds which mimic the physiological properties of endogenous nucleosides that are required for the replication of viral RNA. These nucleotide analogs compete with these endogenous nucleotides and produce antiviral activity against SARS-Cov 2, MERS-CoV, Hendra virus, etc.[2,32]

3. Case studies of antiviral drugs for COVID-19

The various case studies are related to the administration of antiviral drugs and their outcome are discussed in **Table 6**:

3.1 Case Study 1

Table no. 6

Case studies	Outcome	Reference
3.1.1 Favipiravir **Open-label control study** Mid to moderately high risk 80 Covid-19 Patients received favipiravir or LPV/RTN for 14 days along with interferon-a through Aerosol inhalation. **Case report:** In the first case, young healthy males with mild Covid-19 received only supportive care alone. In the second case, 60-year-old men with diabetes and hypotension received supportive care with favipiravir.	Favipiravir showed effective treatment against Covid-19 in viral clearance and disease progression. Reduction in illness observed with supportive care only. Favipiravir showed effective results in reducing temperature and improving oxygenation.	[21,33] [34]
3.1.2 Lopinavir/ritonavir **Case report** A 54-year-old Korean men tested positive for Covid-19 with mild symptoms received Lopinavir/Ritonavir. **Retrospective observational study:** 17 patients with mild Covid-19 patients Received ARB (arbidol) and 17 received LPV/RTN + ARB and 5 received LPV/RTN	Lopinavir/ritonavir effectively reducing the symptoms and viral loads. Administration of ARB seems effective against mild symptoms where LPV/RTN is effective against severe symptoms	[35] [36]
3.1.3 Remdesivir **Case report** 40-year-old men with Covid-19 received supportive care with chloroquine for 5 days and received remdesivir on day 9 Of hospitalization. **Open-label, phase 3 randomized controlled trial:** 1063 patients with covid-19 received Remdesivir or placebo for 10 total days During hospitalization where study states	Remdesivir seems effective in reducing symptoms in Covid-19 patients. Time to recover and primary endpoint is better in patients group received remdesivir	[37] [38]

That remdesivir group has more clinical Improvement (65%).		
3.1.4 Chloroquine **Pilot study** In Vietnam, 10 patients received Chloroquine to acquire safety data on the application of chloroquine against Covid-19. **Open-label, clinical trial:** 194 patients with Covid-19 received Chloroquine to study the efficacy of chloroquine for treatment of Covid-19.	Chloroquine showed effective results in reducing the symptoms associated with Covid-19. Data states that patients received chloroquine has better recovery and reduced death rate.	[39] [40]
3.1.5 Ribavirin **Retrospective Cohort study** In 115 patients with Covid-19. 44 patients from 115 patients received ribavirin intravenously (Treatment group) and 71 patients with only supportive care (control group). 17% of patients died in the treatment group as compared to 26% in the control group. Recovery in 12 ± 4 days in the treatment group and 14 ± 3.5 days in the control group. **Clinical trial** 80 patients received ribavirin treatment for 5 days and screened for temperature, and oxygen level with the help of a thermometer and pulse oximeter.	patients receiving ribavirin resulting in less death ratio and less recovery time. patients treated with Ribavirin results in reducing viral loads and symptoms.	[41] [42]

Adverse outcome pathway

This highly infectious and life-threatening infection called Covid-19 spread rapidly to a larger extent. Various antiviral drugs have been studied for their therapeutic efficacy against SARS-CoV-2. In vitro in vivo efficacy and pharmacokinetic parameters have been studied to ensure the safety of these drugs. Covid-19 are variable RNA viruses thus new varieties of these structure appears easily where Conventional treatment is less effective on these new types of viruses. Various studies have been conducted on various antiviral drugs to develop multimodal therapies. With the help of nanotechnology-based treatment, we can overcome these problems.[6]

Future perspective

Nanotechnology-based medicines are the most interesting area for researchers in which most of the research are conducted in the last two decades with 1500 patients and several clinical trials. Nanotechnology-based medicine promises improved approaches that are absent in conventional methods with reduced side effects and reduced toxicity. This novel delivery system also contributed to the advancement of personalized medicines with diagnostic and therapeutic benefits. Nanoparticles are commonly used in the treatment of diseases such as cancer, tuberculosis, malaria, and HIV. Nano-diagnostics are more often frequently used to enhance the reliability and sensitivity of diagnostic tests.[43,44]

CONCLUSION AND DISCUSSION

Due to this pandemic called Covid-19, people facing economic, health, and environment-related problems and many researchers develop methods to control this pandemic. The above review states that nanotechnology-based medicine has a greater impact as compared to conventional drug delivery systems in terms of duration of action, site-specific with the help of targeted ligands, efficacy, high stability, low toxicity, etc. In Nanotechnology-based antiviral drugs, antiviral drugs act on critical steps required for the life cycle of SARS-CoV-2. These are some groups of antiviral drugs such as protease inhibitors, transcription inhibitors, and fusion inhibitors responsible for their therapeutic activity and also responsible for reducing viral load against Covid-19. Antiviral drugs such as ritonavir, chloroquine, ribavirin, favipiravir, etc. provide a great opportunity for treatment of Covid-19.

Abbreviation

2019-nCov: Novel coronavirus, WHO: World Health Organization, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, DNA and RNA: Deoxyribonucleic acid and Ribonucleic acid, MERS-CoV-2: Middle east respiratory syndrome coronavirus 2, NP: nanoparticles, CDC: Center for disease control and prevention, CO2: Carbon dioxide, H2O: Dihydrogen Monoxide(Water), EC50-Half Maximal Effective Concentration, PH: Potential of Hydrogen, ACE2-receptor: Angiotensin-Converting Enzyme 2, HIV: Human Immunodeficiency virus, XRD: X-ray diffraction method, SEM and TEM: Scanning electron microscope

and transmission electron microscope, RdRp: RNA dependent RNA polymerase, RSV: Respiratory syncytial virus, NTP: Nucleoside triphosphate, LPV/RTN: Lopinavir/Ritonavir, C/LRP: controlled/living radical polymerization.

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