Atlantic Journal of Life Sciences
Volume 2025, Article ID 22, pages 21
https://doi.org/10.71005/rqx9tt78

Review Article

Nano-Chitosan and Nanomedicine Approaches Against Pathogenic Coronaviruses

Ishrat Perveen[1], Jawad Hussain[2], Tallat Anwar Faridi[3], Sajid Hameed[4], Mehwish Najeeb[3], Saba Sabahat[5], Yasar Saleem[1], Amna Mumtaz[1], Sumbal Nazir[6], Muhammad Jalil Khalid[7], Wajid Hussain [2], Shenqi Wang [2]

[1]GenEd and Molecular Biology Labs, Food and Biotechnology Research Centre, Pakistan | [2]Huazhong University of Sciences and Technology, Wuhan 430074, China| [3]The University of Lahore, Lahore, Pakistan | [4]Department of Public Health, Green International University, Pakistan | [5]Rashid Latif Medical College, Ferozepur Road, Lahore, Pakistan| [6]Minhaj University Lahore, Lahore, Pakistan| [7]National University of Sciences and Technology, Islamabad, Pakistan

Correspondence should be addressed to Ishrat Perveen; drishrat_fbrcpcsir@hotmail.com

Received: 11 May 2025; Revised: 23 May 2025; Accepted: 12 September 2025; Published 31 October 2025

KEYWORDS

Nanomedicine
Nano-chitosan
Drugs Nanocarrier
Therapeutics
Viral infections
Coronavirus infection
Nanotherapeutics
Nano-diagnostics
Pathogenesis

ABSTRACT

Human coronaviruses (HCoVs), composed of the viruses causing severe acute respiratory illness described as the syndromes resulting from infection with respiratory coronaviruses (e.g., human immunodeficiency viruses (HIVs), whose incubation period averages 7 to 15 days and 1 to 6 months, respectively) and the newly emerged ones (e.g., human respiratory herpesvirus 6). The spread of new variants over a short period of time requires urgent and effective therapeutic strategies..This review discusses the potential of nano-chitosan biopolymeric nanoparticles as a promising therapy for combating SARS-CoV-2 and related viruses. The study examined the structural features, genome organization, and pathogenesis of the viral strains causing the current pandemic-SARS-CoV, MERS-CoV, and most recently, the viruses responsible for the current "coronavirus" syndication, namely, the newly discovered coronavirus - known as the "SAR-corona subgroup, viral genome organization, pathogenesis, and host/virus away within the SAR Coronavirus family. The role of nano-chitosan as an anti-viral agent and as a drug delivery enhancer for improved-drug bioavailability and targeted therapy is also reviewed in the context. Nano-chitosan shows a strong antiviral effect on HCoVs via enhancing drug solubility and bioavailability. Its capacity as a carrier able to transport antiviral agents, and in vaccine delivery, diagnostics, as well as in the field of therapeutic applications, is an important advance in nanomedicine. Nano-chitosan is a potential candidate for the future pandemic of coronavirus. The incorporation of nano-chitosan into therapeutic approaches may improve existing therapies as well as contribute to more effective control of viral outbreaks. Future work will be on optimizing its use and on overcoming the challenges relative to clinical application.

1. Introduction

Coronaviruses are single-stranded ribonucleic acid (ssRNA) genome viruses that cause severe enteric and respiratory diseases in humans, animals, and poultry. The common cold is one of the most common coronaviruses, affecting the URT (upper respiratory tract) and GIT (gastrointestinal tract). Several coronavirus strains have been identified, with 4-5 of them primarily affecting humans. (Zhu, 2020). Control strategies for coronaviruses are challenging because they are difficult to grow in situ. Advanced scientific methods have limited effectiveness in combating CoVs, leading to the identification of new animal and human CoVs (Noor et al., 2020). OC43 and HCoV-229E are the only viruses known to cause the common cold in humans and are considered harmless. SARS-CoV emerged in South China, Guangdong province, affecting various age groups, especially immunocompromised patients. (Summers et al., 2020).

New strains of COVID-19, including MERS-CoV and HCoV-NL63, have been identified regularly. In 2019, a unique strain of COVID-19, originating in Wuhan City, China, rapidly spread worldwide. The World Health Organization declared a worldwide health emergency, renaming it SARS-CoV-2. The virus has affected over 210 countries and resulted in significant fatalities. The emergence of SARS has shifted the focus to coronaviruses in animals that can infect humans, refocusing on zoonotic diseases. (Donnelly et al., 2019). The COVID-19 pandemic underscores the importance of understanding and strategically preparing to combat coronaviruses, as they can arise and resurface (Yasamineh et al., 2022).

This study aims to explore the potential of nanomedicine as a novel therapeutic approach to combat pathogenic coronaviruses, particularly emerging SARS-CoV-2 variants. It investigates nanotechnology-based solutions, such as nanocarriers, nano-enabled diagnostics, and nanomaterial-based vaccines, to improve diagnosis, treatment, and prevention. The study evaluates how nanomedicine can enhance antiviral drug delivery and bioavailability, with a focus on the antiviral

properties of nano-chitosan. Additionally, it analyzes control measures from past outbreaks to inform future strategies. Emphasizing integrated research in nanotechnology and virology, the study seeks to develop robust, evidence-based countermeasures against coronaviruses.

2. Origin, Epidemiology, and pathogenicity of human coronaviruses

Coronaviruses, discovered in the 1960s, cause infections in humans and animals, primarily affecting the upper respiratory tract. The first strain, HCoV-B814, was identified in 1965. These illnesses are more common during winter and spring, accounting for 35% of viral respiratory infections. Human coronaviruses, such as HCoV-OC43, HCoV-229E, HCoV-HKU1, and HCoV-NL63, cause mild-to-moderate upper respiratory tract infections and are found in specific regions. SARS-CoV and MERS-CoV pose significant risks to the human population, causing severe respiratory illnesses. The origin of SARS-CoV is uncertain, but the flying mammal, the bat, is believed to be the most likely source. Before the SARS outbreak, only a few Human Coronaviruses were recognized for producing mild ailments like the common cold. (Song et al., 2019).

The CDC in Canada sequenced the whole genome of SARS-CoV in 2003, identifying sixteen serotypes in Hong Kong, Taiwan, Mainland China, and Hanoi. The virus was distinct from previously identified CoVs. In 2004, another human coronavirus, HCoV-NL63, was identified in a seven-month-old infant with bronchiolitis and conjunctivitis. MERS-CoV, first identified in Saudi Arabia in 2012, has since spread to 27 countries with a 35.4% death rate, causing significant global concern. (Song et al., 2019). In December 2019, Wuhan, China, reported numerous cases of pneumonia of unknown cause. Clinical features and respiratory tract samples confirmed a new human coronavirus, COVID-19, causing severe pneumonia. (Huang et al., 2020). The WHO declared it a global emergency in January 2020, affecting all continents except Antarctica. (Akhter & Akhtar, 2020). The history of CoV emergence is well documented in the timeline (Figure 1).

HCoVs like NL63, 229E, HKU1, and OC43 cause mild URT infections, while SARS, MERS, and the latest COVID-19 have caused high morbidity and mortality globally. The SARS outbreak in 2002-2003 spread via close contact between humans and animals, leading to 778 deaths among 8076 infected people. The WHO identified the SARS-CoV and antibodies in animal handlers and masked palm civets, leading to the name SARS. (Liu et al., 2021). SARS-CoV patients initially experience myalgia, fever, headache, malaise, chills, and respiratory failure after a week of incubation. They then experience a non-productive cough, dyspnea, and breathing problems due to respiratory infections, leading to death. Approximately 30% to 40% of SARS-infected patients experience diarrhea symptoms. In 2005, a novel coronavirus, SARS-CoV, was isolated from horseshoe bats, indicating that bats are the probable natural host of SARS-CoV.(Fayet.al.,2022).

The SARS epidemic was primarily transmitted through the nosocomial route, with 50% of mortality rates occurring in older populations. WHO and other health institutions issued specialized instructions to control the spread. Infected individuals traveling to Canada, Singapore, Hong Kong, and Vietnam were the main drivers of the rapid spread. In Taiwan, 3032 suspected cases were confirmed, of which 246 were positive. Phylogenetic analysis of Taiwan CoV sequences showed similarities with sequences from patients in Guangdong province and Hong Kong. (Cheng et al., 2022).

The disease MERS-CoV, caused by SARS-CoV, was first isolated in the Middle East in 2012 and subsequently spread globally, including to Europe, Africa, and the Americas. The first case was found in Jeddah, and 1227 cases were reported from June 2012 to December 2015. The virus caused 549 deaths due to CoV-like symptoms, while 728 patients recovered from MERS infection (Faye et al., 2022). The MERS cases surged in March and April 2014 and decreased significantly in the third week of May 2014. Nevertheless, in May and June 2015, 186 new patients with 16 confirmed cases of MERS were identified in the public hospital in Korea (Ramadan & Shaib, 2019). The MERS outbreak infected 1621 people worldwide, resulting in 584 deaths. The highest number of deaths was in Saudi Arabia and Korea, with 186 cases reported. The outbreak was caused by travelers returning from the Middle East, with MERS spreading from one hospital to another. The outbreak lasted 12 months, and on July 6, 2015, the Saudi Arabian Ministry of Health declared the end of the epidemic. (Oh et al., 2018). The origin of MERS-CoV is unknown, but virological evidence suggests that dromedary camels were the main reservoir for transmission. Health workers and community members also contracted the virus through human-to-human transmission. The transmission of MERS-CoVs from bats to humans remains uncertain, with preliminary research suggesting it originated in bats and that it may occur through direct or indirect means. (Mostafa et al., 2020).

After MERS, endemic pneumonia of an unknown causative agent emerged in Wuhan City, Hubei Province, China, in December 2019 (Hui et al., 2020). The retrospective study showed that the first known case occurred on December 8, 2019. The Wuhan Municipal Health Commission informed the WHO and notified the public regarding the pneumonia outbreak (Wu & McGoogan, 2020). Deep sequencing of lower respiratory tract (LRT) samples revealed that the virus belonged to the Coronavirus species, and a novel strain was identified, which was then named COVID-19. The rapid spread of the disease became a pandemic after it was reported in the epicenter of Wuhan and several other provinces of Mainland China, as well as Japan, South Korea, Thailand, and the USA. (Huang et al., 2020). As of January 30, 2020, 9976 cases of COVID-19 infection had been reported in 21 countries, including the first confirmed case in the United States. (X. Zhu et al., 2020).

Following viral transmission, the coronavirus first binds to the epithelial cell membrane in the conjunctiva and oral cavity. The ACE2 protein, which is highly expressed in multiple human cells, including oral, myocardial, proximal tubular, and esophageal cells, is the primary factor in the internalization of SARS-CoVs. (Zou et al., 2020). The enzyme Furin cleaves the coronavirus S protein into S1 and S2 subunits, enabling viral entry into lung cells. SARS-CoV and SARS-CoV-2 share genetic sequences and similar structures, but SARS-CoV has a tenfold higher affinity towards ACE2 compared to previous coronaviruses, indicating a unique host cell entry mechanism. (Wrapp, 2020). Research shows that ACE2 plays a crucial role in cell signaling and that inflammation can cause tissue damage. It impairs the conversion of angiotensin II to angiotensin during viral replication, leading to clinical symptoms such as vasoconstriction, hypokalemia, and ARDS. (Gheblawi et al., 2020; Grigonyte et al., 2020; Pal & Bhansali, 2020). The release of inflammatory cytokines, including IL-6, TNF-α, IL-7, MCP-1, GCSF, IL-10, and IL-2, during coronavirus infection contributes to the severity of the infection and results in a decrease in lymphocyte count. (Diao et al., 2020; Zheng et al., 2020). The mechanism through which the coronaviruses enter cells, replicate, release, and signal molecules are released by the infected cells, as well as the induced organ damage, is shown in Figure 2 (Li et al., 2021) in detail.

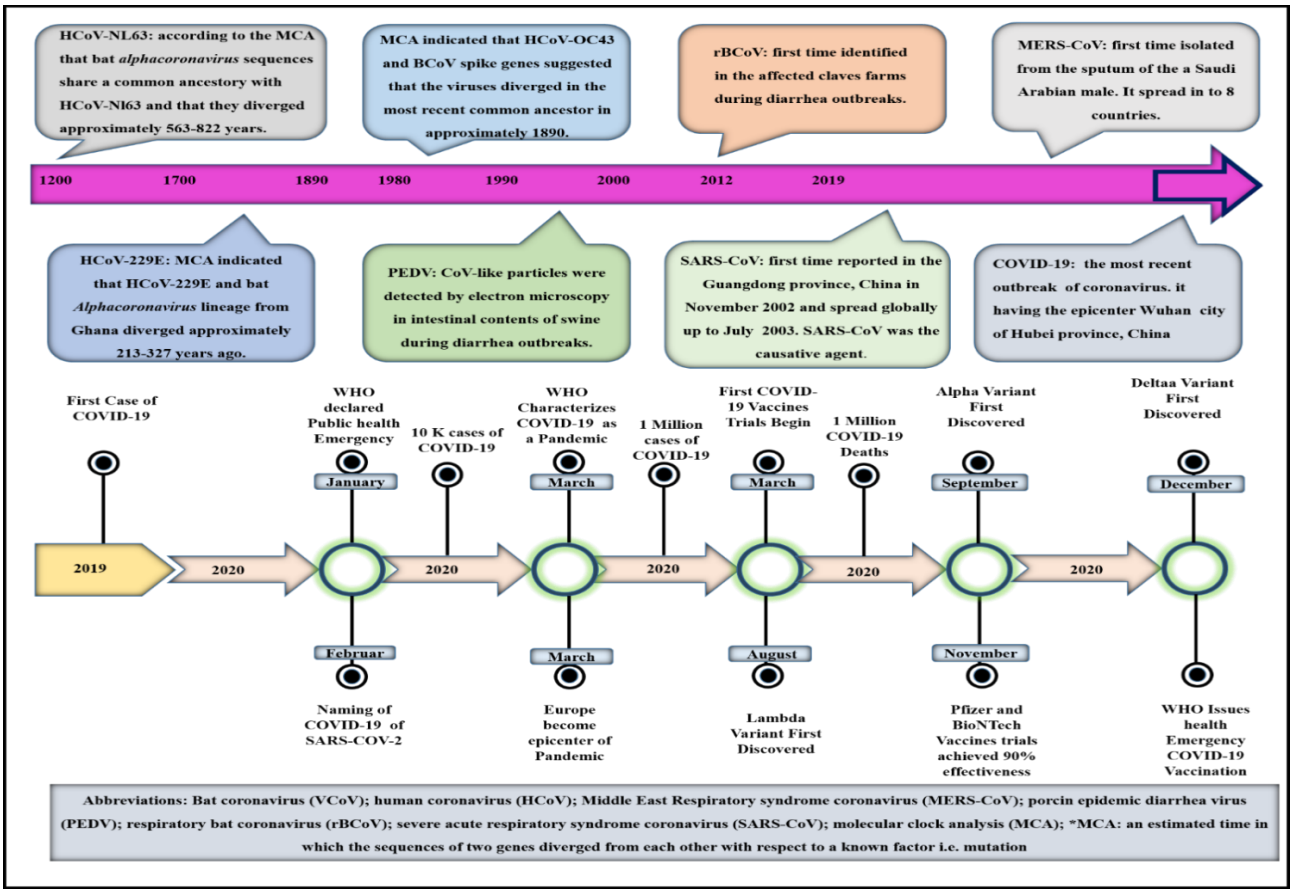

Figure 1: Timeline of the emergence and outbreaks of CoVs.

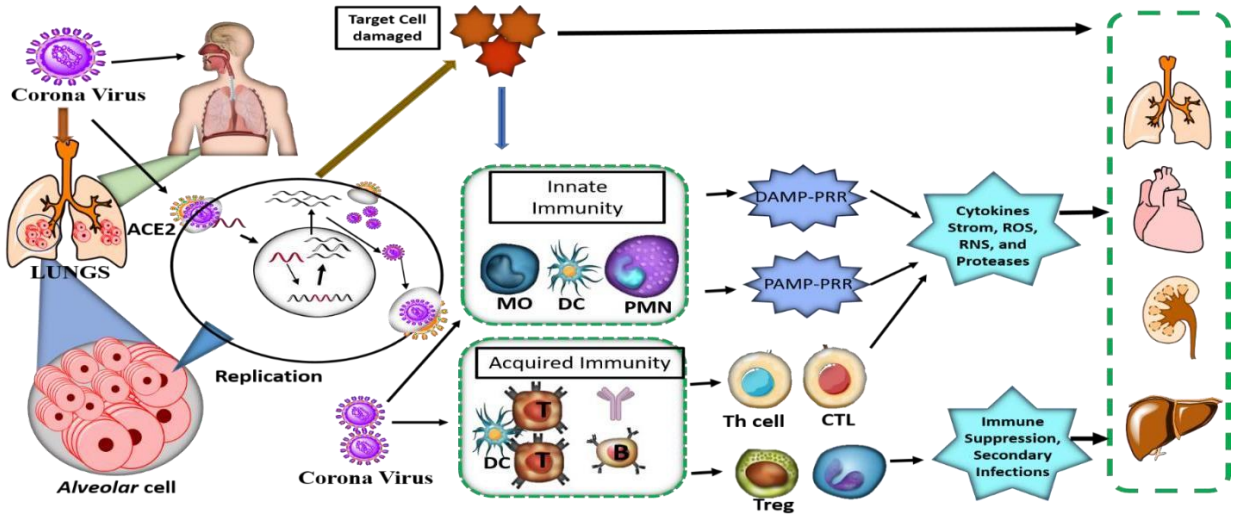

Figure 2: The diagram illustrates the development and disease process of coronaviruses, including the SARS virus's entry into cells via the ACE2 receptor, reproduction, assembly, and exit. The inflammatory molecules released by infected cells, which act as signaling molecules for innate immune responses, are activated. Sometimes the severity of infections results in organ injury. Reproduced from ref. (Li et al., 2021). S, spikes; ACE2, angiotensin-converting enzyme-2; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; PRR, pattern recognition receptors; ROS, (reactive Oxygen Species); DC (dendritic cells); B(B-lymphocytes); T(T-lymphocytes); MO, (Monocytes); CTL, (Cytotoxic T lymphocytes); RNS, (Reactive nitrogen species).

3. Classification and structure

3.1. Virion structure and genome organization

Recent studies on cryo-electron microscopy and tomography have shown that the CoVs are spherical with a 125nm diameter. The club-shaped projections or spikes originating from the virion's surface have noticeable properties that define the appearance of the virion (Figure 3A) (Saville et al., 2022). The virion envelope contains the nucleocapsid in helical symmetry. The nucleocapsid contains a single-stranded, positive-sense RNA genome. The virion has four structural proteins: an envelope protein (E), a membrane protein (M), a nucleocapsid protein (N), and a Spike protein (S). The coding of these proteins is attributed to the 3' end of the viral genome, as shown in Figure 3B (Saville et al., 2022). The "S" protein (spike) of the coronavirus virion (about 150 kDa) uses the N-terminal signal sequences to access the endoplasmic reticulum and is highly glycosylated. It provides a specialized structure to the CoV virion, making it distinctive among viruses. (Saville et al., 2022). The class I fusion protein, made of trimeric S glycoprotein, helps in the mediation of the attachment of the virion to cell receptors. Most coronaviruses cleave the furin-like protease, forming S1 and S2 proteins. S1 forms the receptor-binding domain, while S2 shapes the virion's stalk in the spike. The M protein is a major structural protein in CoVs, measuring about 25-30 kDa, and contains three transmembrane domains that give the virion its shape. The ectodomain N-terminal is glycosylated, and the end domain C-terminal is extended about 6 to 8 nm from the virion. Most M proteins have a single deletion due to co-translational processing in the ER. (Li et al., 2023).

The M protein dimer within the virion adopts multiple conformations, facilitating both membrane curvature and nucleocapsid binding. The E proteins, with molecular weights of 8-12 kDa, share a standard structure and are present at low copy numbers. As transmembrane proteins, they are instrumental in virion assembly and release. The E protein also functions as an iron channel in SARS-CoV, although its full role remains to be elucidated (Naqvi et al., 2020). The N protein, comprising N- and C-terminal domains, exhibits RNA-binding activity in vitro. As the sole protein component of the nucleocapsid, its binding is dependent on an optimal RNA concentration. Extensive phosphorylation of the N protein induces conformational changes that amplify the genome-packaging signal. A fifth protein, hemagglutinin-esterase (HE), interacts with sialic acids on surface glycoproteins to promote viral propagation and entry, working in concert with the S protein. The HE protein also associates with nsp3 to facilitate the replication-transcription complex (RTC) and package the genome into new viral particles. The coronavirus genome, organized with Rep1a and Rep1b genes, encodes the various proteins required to assemble a complete virion (Q. Zhang et al., 2021).

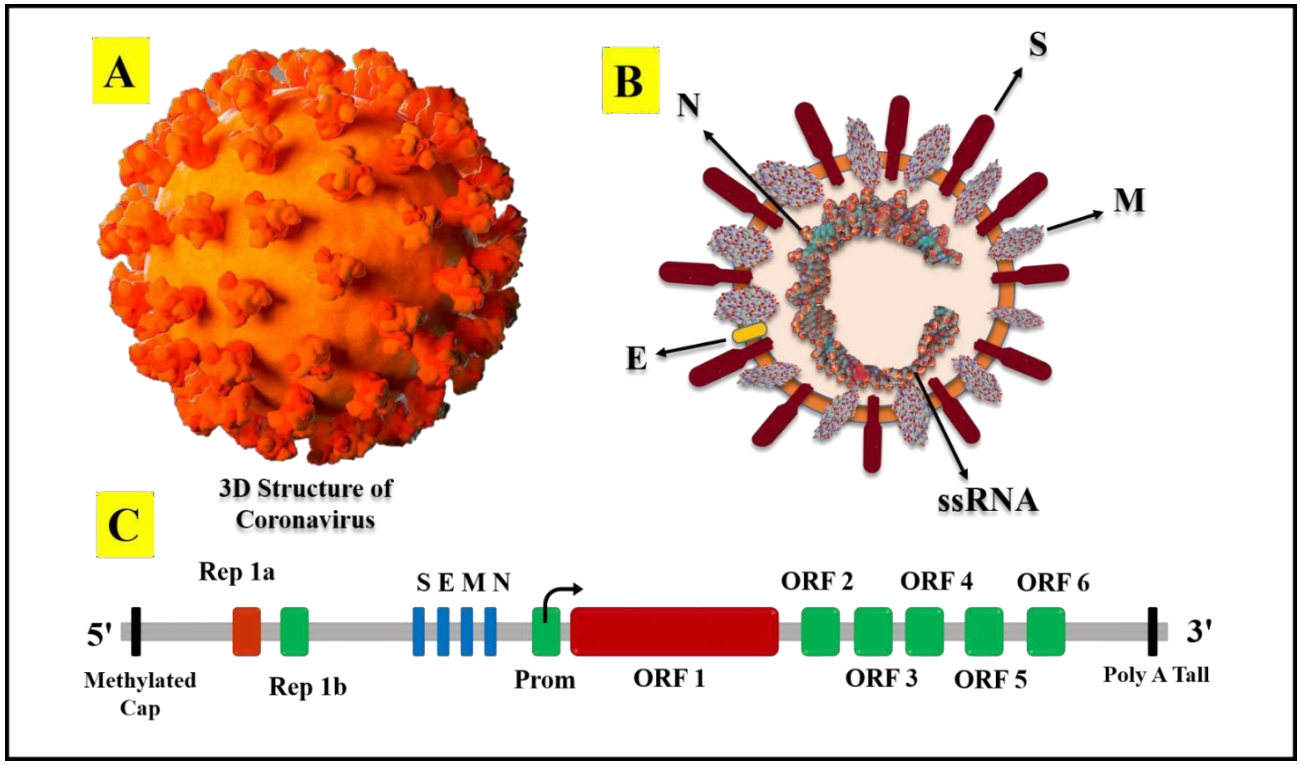

Figure 3: Illustration of the coronavirus virion and its genomic organization, including the basic proteins. A) The 3D structure of the CoV virion, reproduced from ref. (Saville et al., 2022); B) The ssRNA genome with nucleocapsid (N) protein, transmembrane protein (M), and spikes (S) proteins. There is also another protein named E protein (membrane-spinning protein) in the virion structure of the coronaviruses. C) The genomic organization of CoV with Rep1a and Rep1b and other necessary genes codes for different proteins for making a complete virion structure. Reproduced from ref. (Q. Zhang et al., 2021) (CC BY 4.0).

3.2. Life Cycle

Developing a comprehensive understanding of SARS infection routes and the underlying pathobiology of coronaviruses would facilitate the advancement of rational treatment approaches that specifically target the virus's life cycle. Initially, the coronavirus attaches to cellular receptors via its spike proteins; thus, changes in the spikes facilitate fusion of the cell membrane with the virion. Following fusion, the nucleocapsid is released into the cell, then the viral genome's 5' end ORFs (ORF1a and ORF1ab) are translated into pp1a and pp1ab proteins (Figure 3C). The ORF1a gene encodes 3C-like proteases and

papain-like proteases (PLP) that convert pp1a and pp1ab into fully functional replicase proteins. ORF1a X domain encodes ADP-ribose activity, while ORF1b encodes RdRp and helicase enzymes. These enzymes are essential for the metabolism of coronavirus RNA and interfere with host cell processing. During infection, RNA replication and transcription occur, with replicated RNA serving as a template for genomic RNA. This RNA gives rise to subgenomic messenger RNAs (mRNAs) with 75-80-nucleotide leader sequences at the 5' end.(Jackson et al. 2022). The negative and positive-stranded RNAs produced through specific discontinuous transcription are not entirely understood. However, it is believed that subgenomic mRNA synthesis occurs via transcription-regulated sequences, with transcription initiation from each mRNA (Malone et al., 2022). The viral proteins are produced by translating the mRNA, and the downstream ORF encodes the E protein of MHV, called ORF-5b. ORF 5b is interrupted by the ribosomal entry site. E and M protein translations are organized through post-translational modifications, sending them to the Golgi, an intracellular compartment on the ER, which is assumed to be a site for budding. These two types of proteins are expressed even when other viral proteins are absent or when RNA is insufficient for virus-like particle production. The distribution of viral spike proteins occurs at the intracellular and plasma membranes, promoting interactions with "M" proteins and cell-to-cell fusion during viral assembly. In contrast, nucleocapsid proteins and genomic RNA form a helical structure, leading to vesicle formation and virus transport into the cell surface (Figure 4). (Khan et al., 2023).

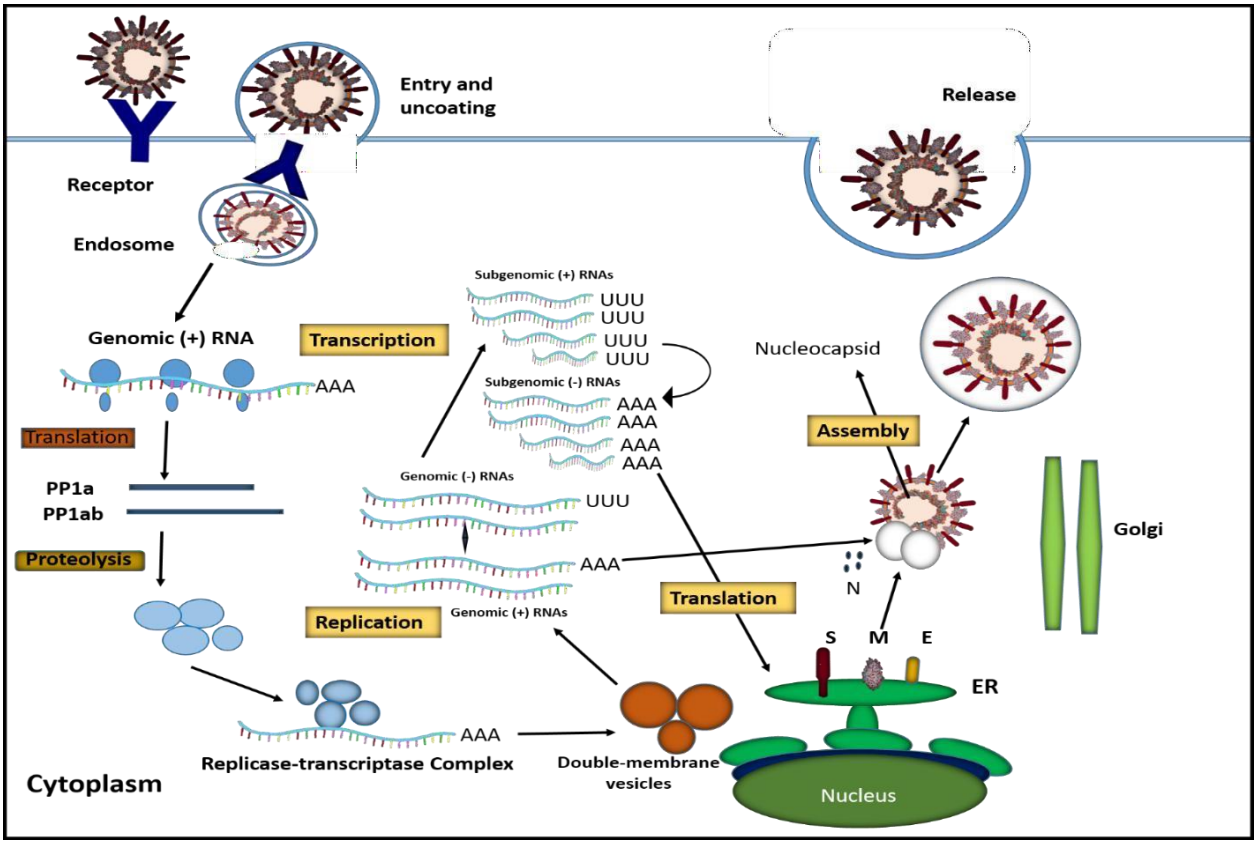

Figure 4: The coronavirus's genome ssRNA encodes for two large polyproteins, pp1a and pp1ab, which are proteolytically cleaved into sixteen proteins (non-structural), including 3CLpro, Plpro, Helicase, Exonuclease (ExoN), and RdRp. In addition, transcription of 9-12 ORFs was observed, encoded by subgenomic RNAs. The entry of coronavirus into the host cell results in the translation of the ORF1a and ORF1ab viral RNAs, leading to the production of the basic proteins and the genomic part of the virions. The virion structural proteins assemble in the Golgi bodies and endoplasmic reticulum intermediate compartments, leading to the release of mature virions. (Trougakos et al., 2021).

3.3. Human CoVs and Cytokines Production

The body's immune cells, using PRRs (pattern recognition receptors), detect pathogen-associated molecular patterns (PAMPs) and initiate the immune response when viruses enter the body (Lebeau et al., 2020). TNF-α, IL-6, and IL-1 are produced via signaling pathways and are secreted by mast cells, macrophages, epithelial cells, and endothelial cells during the immune response. Cytokines can rapidly increase, leading to cytokine storms, which pose significant risks to life and safety (Tavakolpour et al., 2020). In the case of CoV infection, CD+ T cells are activated via alveolar epithelial cells (AECs), which are classified into T helper cells 1 and 2. Th1 cells produce primary cytokines, *i.e.,* TNF-β, IL-2, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The coronavirus enters the bloodstream, activating GM-CSF and triggering the production of inflammatory monocytes, eosinophils, neutrophils, and other immune cells. This leads to increased cytokine levels through secondary cytokines. However, rapid escalation can cause cytokine storms, posing significant risks to life and safety (Zhou et al., 2020).

SARS-CoV infection primarily affects tracheal cells and areas of acute lung damage (ARDS). In laboratory conditions, the virus triggers the production of chemokines, leading to inflammatory damage. SARS-CoV attaches to angiotensin-converting enzyme 2 (ACE2) and is present in alveolar epithelial type II cells. When infecting mononuclear macrophages, peripheral blood mononuclear cells, and dendritic cells, the virus cannot replicate but stimulates

cytokine production. (Khalil et al., 2022). SARS-CoV increases the production of antiviral cytokines IFN-α, IFN-γ, and TNF-β, leading to increased expression of inflammatory cytokines. It manipulates macrophages to generate IFN, causing lung damage. Severe infections result in elevated levels of pro-inflammatory cytokines IL-1, IL-6, IL-12, IFN-γ, transforming growth factor-β, and chemokines CCL2, CXCL9, CXCL10, and IL-8 in patients' serum. Overall, SARS-CoV infection in macrophages, DCs, and AECs leads to a significant increase in cytokines and chemokines, playing a crucial role in SARS disease development. This has been shown in Figure 5 (A) (Liu et al., 2021).

MERS-CoV, the etiological agent of MERS, binds to dipeptidyl peptidase 4 on the surface of angiotensin-converting enzyme, leading to infection and symptoms such as cough and fever. The infection process is similar to SARS-CoV, but with a delayed response characterized by robust cytokine activation, including IL-6, IL-1β, IL-8, and IFN-γ. MERS-CoV exclusively replicates in activated human T cells, and further research is needed to understand its replication in other cell types. MERS-CoV triggers the synthesis of cytokines and chemokines when infecting macrophages, dendritic cells (DCs), and monocyte THP-1 cells. However, dendritic cells (DCs) and mononuclear macrophages do not produce interferon-alpha-beta (IFN-αβ), leading to elevated IFN levels. Severe MERS-CoV infections exhibit elevated levels of cytokines, including IFN-α, and chemokines CCL5 and CXCL10 compared to moderate illnesses. SARS-CoV manipulates macrophages to induce IFN production, leading to severe lung damage. Transforming growth factor-β, chemokines, and pro-inflammatory cytokines are elevated in the blood serum of patients with severe infections compared to non-critical patients. (Shah et al., 2020).

Dendritic Cells and macrophages are the preferred cells for replication of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which, in turn, leads to the abnormal release of pro-inflammatory cytokines and chemokines, the leading cause of increased mortality in MERS-infected people. The delayed response in MERS cases results in weakened immune cells and reduced antiviral effects. MERS-CoV replication in different cells, the release of cytokines, and apoptosis are shown in Figure 5 (B) (Liu et al., 2021).

SARS-CoV-2 primarily targets the respiratory system, causing symptoms such as fever and exhaustion, and can lead to severe complications, including heart damage, ARDS, and secondary infections. The virus invades and replicates within AT2 cells, alveolar macrophages, and dendritic cells (DCs) (Abassi et al., 2020). A consistent feature of SARS-CoV-2 and MERS-CoV infection is the dysregulation of cytokine levels (Huang et al., 2020). Studies demonstrate that ICU patients exhibit significantly elevated concentrations of numerous cytokines, including G-CSF, IFN-γ, IL-7, IL-1RA, IL-1β, IL-9, IL-8, IP-10, and IL-10, as well as increased levels of MCP1, MIP-1α, PDGF, and TNF-α (Huang et al., 2020; Ruan et al., 2020). This critical state is characterized by pronounced cytokine release, which can trigger a cytokine storm and induce widespread organ damage. Although SARS-CoV-2 can trigger the production of anti-inflammatory Th2 cytokines such as IL-10 and IL-4, the precise immunomodulatory mechanisms are not fully elucidated. The viral capacity for extra-pulmonary infection remains an active area of investigation. The replication cycle of SARS-CoV-2 within host cells, subsequent cytokine release, and induction of apoptosis (Figure 5C).

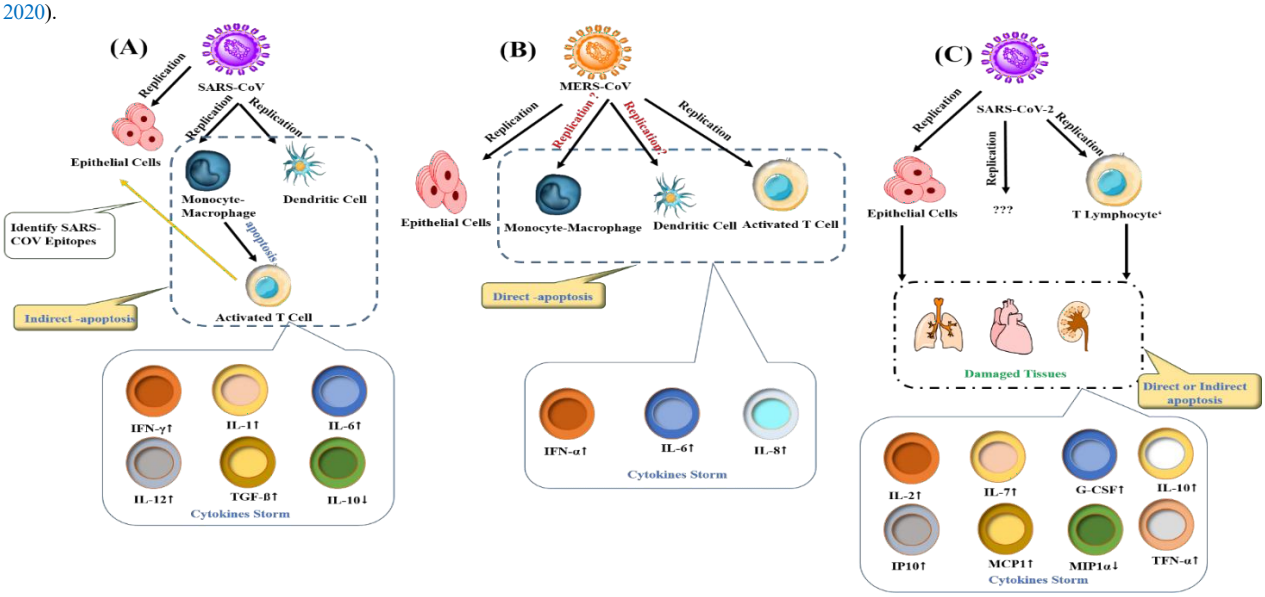

Figure 5. Illustration of different cytokine production during HCoV infections. (A) The SARS virus infects and replicates in epithelial cells, monocytes/macrophages, and DCs, leading to cytokine production by activated T cells and indirect apoptosis. (B) MERS-CoV infection and replication in epithelial and activated T cells and production of different cytokines. MERS-CoV replication in monocytes, macrophages, and DCs remains poorly understood. (C) Replication of SARS-CoV-2 in epithelial cells and T cells triggers the release of large amounts of cytokines, which damage the kidneys, heart, and lungs. Although it is still under investigation whether SARS-CoV-2 can infect and replicate in them. Reproduced from ref. (Liu et al., 2021) (CC BY-NC 3.0).

3.4. Reservoirs and Transmission

Coronaviruses like SARS-CoV and MERS-CoV are primarily found in bats, but SARS was initially isolated from raccoon dogs, Chinese ferret badgers, and masked palm civets. These hosts were unexpected, and no evidence of SARS-CoVs in palm civets has been found worldwide. MERS-CoV was initially found in bats, but the same serotype was found in dromedary camels. In Qatar, MERS-CoV was isolated from swab samples, and in Saudi Arabia, dromedary camels have specific genetic links to viruses that primarily cause outbreaks in humans. Infected camels link the viruses to humans through zoonotic

transmission, causing infections. However, SARS-CoV without an intermediate host involvement does not cause SARS infection in humans. (Schindell et al., 2022). SARS-CoV and MERS-CoV are primarily transmitted nosocomially, with 43-100% of cases linked to hospitals. Family members are responsible for 22 to 39% of SARS transmission, while MERS-CoV transmission is 13-21%. The most common transmission route is from one patient to another, with infected individuals to healthcare workers accounting for 62.79% and 33-42.2%, respectively. The primary transmission route is likely due to the spread of viruses after incubation periods and symptom emergence. Infected individuals are often superspreaders of the virus, driving further transmission. The coronavirus reservoir and routes of transmission, like SARS and MERS, have been illustrated in Figure 6 (Kane et al., 2023).

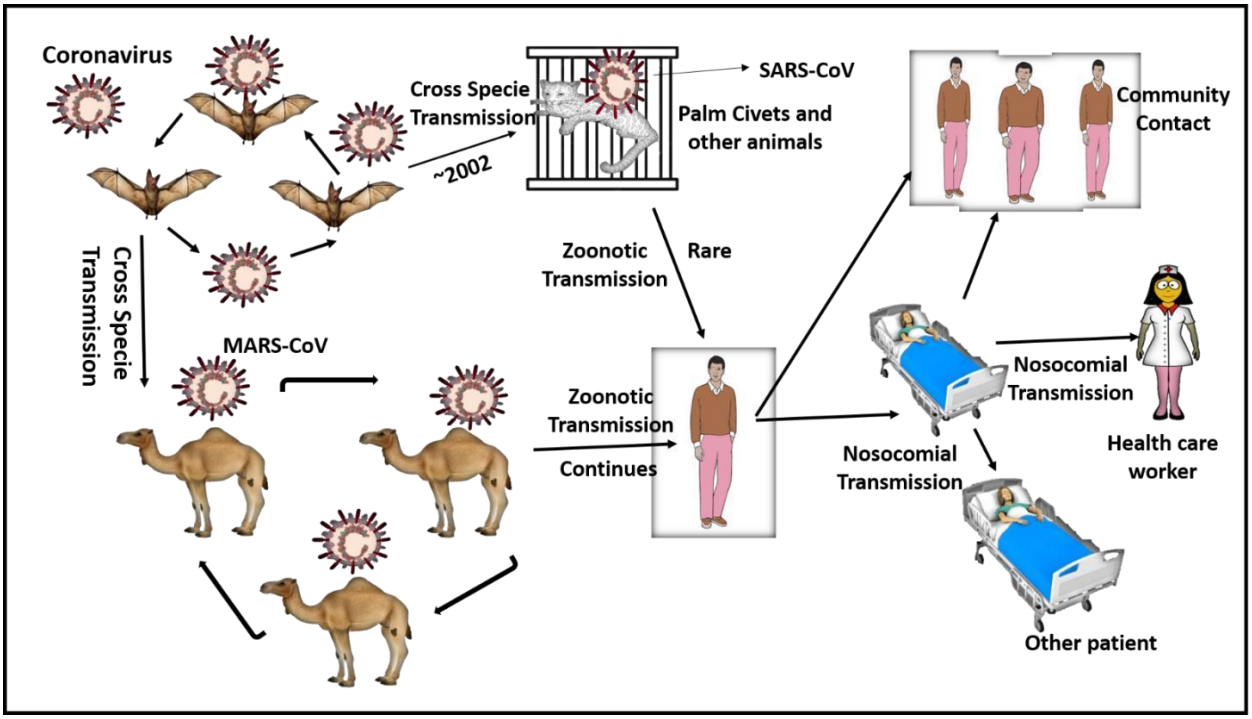

Figure 6. Bats harbor a wide range of viruses, including coronaviruses; the SARS-CoVs and MERS-CoVs are among the best-known CoVs. The SARS-CoVs crossed the species barrier into palm civets. Similarly, MERS-CoV crossed the species barrier from bats to the dromedary camel. Evidence suggests that MERS-CoV is transmitted through zoonotic and nosocomial routes and infects large numbers of the population, including healthcare workers, as well as close healthy individuals. Reproduced from ref. (Kane et al., 2023) (CC BY 4.0).

3.5. Diagnosis, treatment, prevention, and control

The investigation and diagnosis of coronaviruses depend on the method of collection, which can be stool samples or electron microscopy. For Bovine coronavirus (BCV), SN antibodies are the main target, while acute infection samples are collected after the disease onset. ELISA is used to test for SN antibodies and for BCV and ECV coronavirus antigens. RT-PCR and indirect immunofluorescence assays are used for foal coronavirus categorizations, while real-time PCR is used for human coronaviruses . Northern blotting is used to analyze the proteome and viral genomic RNA of ECV-infected cells. Phylogenetic analysis and nucleotide sequences help determine the relationship between ECV and group II coronaviruses. Several diagnostic methods have been developed for COVID-19. These include immunoassays that detect specific antibodies, such as IgM and IgG, in blood samples (Cassaniti et al., 2020). To confirm positive results, polymerase chain reaction (PCR) testing is used on various sample types, including blood, sputum, feces, and bronchoalveolar lavage fluid. However, the CDC has recommended swab-based testing as the standard for diagnosis. This recommendation is supported by evidence showing a high viral load in throat swabs at the onset of infection, making them a convenient choice for early COVID-19 detection (La Marca et al., 2020; Zou et al., 2020).Primary supportive treatment for coronavirus infections consists of drug combinations, such as interferon (IFN) and ribavirin, which have been used against SARS and MERS. Oxygen and broad-spectrum antibiotics are also part of the supportive treatment. In SARS outbreaks, ribavirin and corticosteroids were used in combination to reduce inflammation. IFN-α, in combination with thymosin or immunoglobulin, was administered to promote T cell growth. The deletion of Nsp14 encoding sequences in coronaviruses results in increased ribavirin sensitivity against coronaviruses, although the underlying mechanism is uncertain (Hemida, 2021). Control measures are necessary for patients with high fever, including antipyretic medication treatment if the temperature exceeds 38.5°C. Warm water showers and antipyretic patches are preferred as preventive measures. Basic medications include ibuprofen orally and acetaminophen orally. The chances of hypoxia increase as the infection focuses on the lungs. Nasal catheters and oxygen should be given to the patient, and non-intrusive or obtrusive mechanical ventilation should be provided in crises (Xu et al., 2022).

Interferons (IFNs) have shown efficacy against MERS-CoV in laboratory studies, but their impact on people remains uncertain. Combining IFN with ribavirin enhances treatment effectiveness. However, IFNα2b and ribavirin therapy did not result in survival in MERS patients. Combining ribavirin and IFNα2b led to complete recovery. Lopinavir, lopinavir, and 3CLpro are commonly recommended for most MERS cases. Drugs like cyclosporine A, chlorpromazine, chloroquine, and loperamide are used to limit the CoV virus reproduction. Plasma and antibody therapy are crucial for

COVID-19 treatment due to safety, minimal technological requirements, and reliance on recovered patients. Monoclonal antibodies have shown efficacy in neutralizing MERS-CoV spike proteins, but further research is needed to determine their comprehensive impact on the virus (Khalili et al., 2020).

Coronaviruses (CoVs) are divided into four groups: Human coronaviruses are typically categorized into α and β-CoVs, while Delta-, Gamma-, Beta-, and Alpha-CoV are the most common in the group. The pandemic COVID-19 derives from SARS-CoV-2, a β-coronaviruses group member. The virus has a single-stranded RNA structure with a positive sense, containing multiple open reading frames (ORFs) encoding various proteins. The replicase gene of SARS-CoV-2 contains two overlapping polyproteins crucial for replication and transcription processes. The 5'-UTR section of the RNA contains ORF1a/b, which constitutes over two-thirds of the RNA. Coronaviruses act as the main protease, breaking down polyproteins during digestion. The S protein binds to the ACE2 receptor on the host cell, and the genomic RNA (sgRNA) enables the cap-dependent translation of ORF1a, leading to the synthesis of polyprotein pp1a. The structural proteins are incorporated into the endoplasmic reticulum membranes and transported to the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). The genome generates virions, which are transported to the plasma membrane for release. This is depicted in Figure 7 (Yasamineh et al., 2022).
Host-driven strategies and therapies have been used to treat coronaviruses, targeting enzymes such as cathepsin L, cathepsin B, and transmembrane protease serine 2 to prevent entry. Protease inhibitors such as camostat have been used to reduce SARS-CoV entry in mice, thereby increasing survival. Vaccination is another potential treatment method, with various vaccines, such as viral vectors, recombinant proteins, inactivated viruses, and live attenuated viruses, being used. Recombinant DNA subunit vaccines containing the receptor-binding domain have been developed to reduce lung pathology in MERS infection models. These vaccines can reduce viral load and lung pathology five weeks after MERS-CoV onset. The scientific community has made significant efforts in vaccine development, with over 12 COVID-19 preventive vaccines approved by the CDC, including Pfizer, CanSino, and CoronaVac vaccines, and some under clinical trials (Jamkhande et al., 2021).

To prevent the spread of coronaviruses and control future outbreaks, preventive measures should be adopted. In animals, infected animals should be separated from healthy ones, and recovered ones should be placed separately to avoid stress. Individuals should wear protective gear during animal handling to prevent cross-contamination. Bedding materials should be buried to kill pathogens. Farms should be cleaned with detergents and sanitizers, and daily-use equipment should be kept clean to prevent contamination. Animals should also be used for vaccine production and for advancing immunology, biotechnology, virology, and genetic engineering against human coronaviruses. Antibiotics used for secondary infection should be effective as supportive care for infected individuals. Control steps and preventive measurements, including good management and biosecurity, are essential for fighting against coronaviruses in both humans and animals. Biosecurity and biosafety instruction should be implemented to control bio-threats and future outbreaks (Bielecka-Oder, 2018).
Standard operating protocols should be strictly followed to minimize infection spread, and awareness about testing and quarantine procedures should be advertised (Ashraf, 2020). Domestic checks on traveling history and individuals' tracing can help reduce COVID-19 spread. Collective cultural traits also play a significant role in controlling COVID-19 (Frey et al., 2020).

3.6. Nanotherapeutics Application to Combat SARS-CoV-2
Nanotechnology is a crucial aspect of pharmaceutical research, particularly in nanomedicine, which focuses on managing, diagnosing, preventing, managing, and treating diseases (Table 1) . It is considered a potential solution for mitigating the COVID-19 pandemic. Nanomaterials, including POC (Point-of-Care) devices, have advantages such as chemical stability, robust electrical conductivity, and the ability to induce Localized Surface Plasmon Resonance (LSPR), enhancing detection sensitivity and specificity. Nanoparticles would prevent the development of COVID-19 by preventing the entry of the virus and protein fusion inside infected cells. Immunotherapy interventions, such as convalescent plasma and monoclonal antibodies, are also important to treatment, as they have a good overall safety profile, have comparatively low technological needs, and can be sourced via recovered patients. In particular, monoclonal antibodies proven to work with the MERS-CoV spike proteins, and DDP4-targeted antibodies have already proven effective in labs. More work is, however, required to completely establish the therapeutic efficiency of antibody treatments against coronaviruses (Wibowo et al., 2024). Nanotechnology has additionally been used in the fight against pandemics to create even more personalized protective equipment, antiviral coatings, and ultra-sensitive nanoproducts like nano-sensors. Such newer technologies are crucial to protect healthcare workers with infections by means to boost more effective and safer therapeutics and immunizations as possible ways to stimulate the immune responses (Singh & Sodhi, 2023).
When antimicrobials and therapeutics are designed and nanoparticles (NPs) are used as delivery vectors, nanomedicine may be used to individualize therapeutic delivery (e.g., by avoiding host defenses such as mucociliary clearance and phagocytic alveolar macrophages). One example is micro/nanocarriers with a polyethylene glycol (PEG) coating, which confer stealth properties by reducing biological binding and cellular uptake. (Mohammed & Yahia, 2022). Because of the physicochemical properties of nanomedicines, interactions between host cells and coronaviruses can be altered. Nanoparticles, whether virally or antibody-conjugated, will help defend against new coronaviruses or variants of the new coronavirus as they emerge.
More than this, an organic nanoparticle can be used as an efficient carrier for antiviral drugs, thereby increasing their potency. One major drawback of traditional antivirals is their lack of specificity, which can cause host cell damage and cytotoxicity. Nanoencapsulation offers a solution to these off-target effects, establishing the path forward to safer anti-COVID-19 and other anti-viral treatment solutions. One such method is a survey in which artificial, multilayered exenatide-loaded nanoparticles targeting type 2 diabetes were produced using the layer-by-layer method. Another promising development is the I3-01v9 SApNP platform, which—when introduced by S2G-HR2—effectively stimulated T-cell immunity, highlighting its potential as a basis for a next-generation COVID-19 vaccine. (Campos et al., 2008).

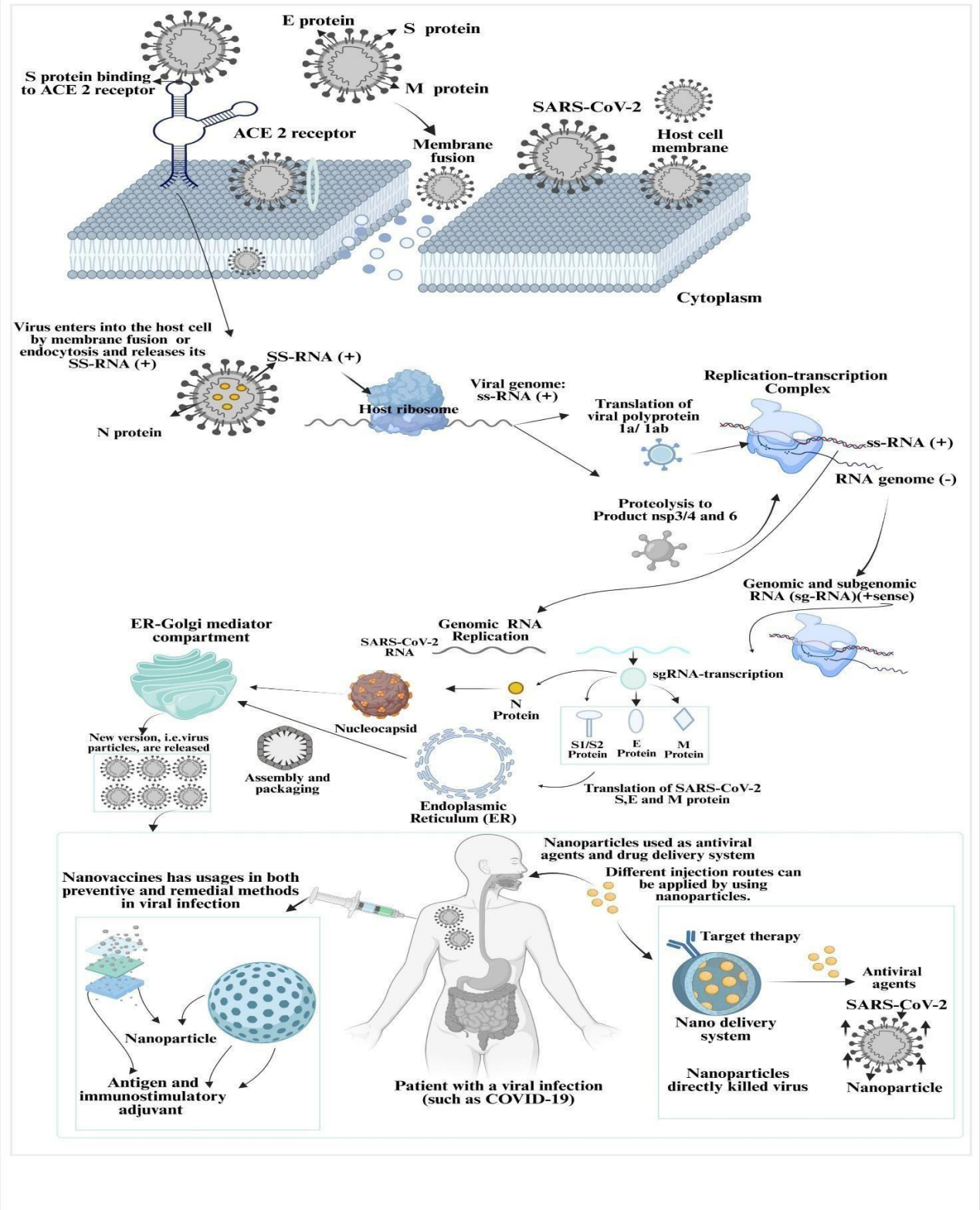

Figure 7: The role of nanotechnology in developing novel vaccines, treatment methods, and enhancing the delivery and safety of antiviral medicines to suppress SARS-CoV-2 reproduction. It depicts the effectiveness of I3-01v9. The SApNPs introduced by S2G-HR2 are a promising vaccine candidate for stimulating T-cell immunity. It also depicts the nonstructural and structural proteins of the SARS-CoV-2 virus, including the ACE2 receptor on target cells, and demonstrates the entry and replication processes within specific cells. (Yasamineh et al., 2022).

.

Table 1: Advanced Diagnostic Nanomaterials for SARS-CoV-2 Detection and Management.

Sr. No.	Nanomaterials	Applications	Mechanism of action (Test duration/ Target/ LOD)	References
1	Small interfering RNA-Lipid nanoparticles.	Viral genome Inhibition	Adjunctive vaccine Therapy	(Idris et al., 2021)
2	Spike protein NPs	Vaccines' Immunoglobulin Response to SARS-CoV- • Significant neutralizing immunoglobulin response.	Spike Proteins in Viral Infections Bind to cell receptors. • Prevent reinfection. • Stimulate neutralizing antib thatdies. • Vaccines use this mechanism	(Rasmi et al., 2022a)
3	IONPs	Optical Magnetic Diagnostic Biosensor	1 h 40 min/RdRp/0.4 fM	(Tian et al., 2020)
4	Metallic NPs	Antimicrobial, Antiviral, & face masks	Face Mask Filtering System • Nanofibrous matrix made of cellulose acetate and polylactic acid. • Contains nanosheets and NPs of graphene sheets and CuO, respectively. Electrospinning-based generation.	(Chue-Gonçalves et al., 2021)
5	Glycyrrhizic acid nanoparticles	Suppress viral proliferation; reduce inflammation	Target the lungs to alleviate inflammation & decrease viral load	(Zhao et al., 2021)
6	Gold NPs	LSPCF Diagnostic Probe	Nucleocapsid protein-based serum, (N.A.) 1 pg/ml	(Huang et al., 2009)
7	Dendrimers	Encapsulate drugs, strongly interact with the virus.	COVID-19 Treatment	(Asdaq et al., 2021)
8	Exosomes	Binds the target and prevents viral uptake in the cells, and inhibits replication	Blocks the replication & entry of SARS-CoV-2	(Hassanpour et al., 2020)
9	Titanium oxide nanoparticles	Surface proteins and the viral capsid are engaged to prevent replication.	Inactivates the virus by degrading the protein envelope.	(Shukla et al., 2021)
10	Gold nanoparticles	Deforms and collapses the virus & viral capsid.	Exhibit potential to compromise the structural SARS-CoV-2 integrity and inhibit membrane fusion.	(Asdaq et al., 2021)
11	Chitosan NPs/nano-polymer	Direct Infection Medication Administered • Administer medications to the infection location.	"Saquinavir Administration in COVID Patients" • Direct pulmonary delivery. • Controls viral spread.	(Chowdhury et al., 2021)
12	Carbon quantum dots	Blockage of SARS-CoV-2 entry	S1 Protein Interaction and Entry of SARS-CoV-2 • The interaction with S1 protein. • May block SARS-CoV-2 from entering host cells.	(Vahedifard & Chakravarthy, 2021a)
13	Nitric Oxide nanoparticles	Produce peroxynitrite, leading to cytotoxicity and suppression of viral replication.	Counteract SARS-CoV-2 effects on endothelial cells	(Cavalcanti & Cajubá de Britto Lira Nogueira, 2020)
14	Carbon nano fullerenes	"Preventing Viral Entry and Reproduction" • Inhibiting necessary targets.	"Preventing Viral Entry and Reproduction" • Inhibiting necessary targets.	(Skariyachan et al., 2021a)
15	Nanofibers	Mask Use: Optimal Breathability & Filtration • Provides filtering efficacy.	Nanofiber Membrane in Masks • Efficiently retains virus particles. • Enhances breathability. • Provides comfort and reduces fatigue.	(Pandey et al., 2020)
16	Polymeric nanoparticles	Block the onset of infection.	Binds to the ACE2 receptor and prevents the angiotensin's cleavage.	(Vahedifard & Chakravarthy, 2021b)
17	Gold NPs	Lateral flow Diagnostic immunoassay	15min. / IgG & IgM / N.A.	(Li et al., 2020)

18	Silver NPs	AgNPs in Mouthwash and Nasal Rinse decrease viral infection rate.	AgNPs Solution for Oral and Nasal Rinsing" • Reduces viral load. • Temporarily lowers transmission risk.	(Almanza-Reyes et al., 2021)
19	Polymeric NPs	NPs Permeation and Assimilation • Facilitates sustained antiviral agent release. • Allows treatment for days/weeks.	Carrier of antiviral drugs in colloidal form	(Khalil et al., 2011)
20	RBD-mi3 Mosaic nanoparticles	Heterologous antigen delivery	Antibody-based Response for Viral Proteins' Neutralization	(Cohen et al., 2021)
21	Ferritin-based NPs	Anti-viral vaccines	Fexplicitlyparticles Activate CD4+ T Cells • Facilitated by RNA. • Generate TNF-α & IFN-γ. • Effective against MERS-CoV.	(Rasmi et al., 2022b)
22	Poly-LA nanoparticles	Delivery system.s for antiviral drugs	Ensuring Safe and targeted administration of chloroquine	(Vahedifard & Chakravarthy, 2021b)
23	Gold NPs	Colorimetric diagnostic assay	30min / RdRp /0.5 ng	(Kumar et al., 2021)
24	Graphene oxide	Graphene Oxide's Virus Deactivation • Applied in textiles, filters, and masks.	Graphene Oxide's Hydrophobic Properties • Prevents bacteria penetration of the facemask's protective layers. • Readily recyclable through photocatalysis or heat treatment.	(Ghaemi et al., 2021)
25	Gold NPs	Electrochemical diagnostic immunosensor	N.A. /Antigen/ 90fM.	(Wan Mahari et al., 2020)
26	PLGA- PEG-DX600	Human ACE2 inhibition	Blocks viral entry by inhibiting interaction with ACE2 receptors	(Keshmiri Neghab et al., 2020)
27	PLGA	Exploring Nanocarriers for Medication Delivery • Precision targeting.	The inflammation is being alleviated by administering lopinavir directly to the affected site.	(Tan et al., 2021)
28	Copper NPs	The substance is used as a facial barrier in facemasks to shield against SARS-CoV-2.	Copper's antiviral and antibacterial properties, including reactive oxygen species generation and viral genetic degradation, make it a potential candidate for antiviral masks that may aid in preventing viral transmission.	(Foffa et al., 2022)
29	Lipid nanoparticles	Safe Antiviral Medication Delivery • Target specific antiviral medications. • Shield DNA/RNA vaccines from nucleases.	Aerosol Use in Remdesivir Administration • Administers remdesivir directly to lungs. • Delivers mRNA and DNA plasmid vaccinations.	(Mufamadi et al., 2023; Abdool Karim & de Oliveira, 2021; Tian et al., 2020)
30	ZO-NPs	Inhibition of viral replication	Suppressing RdRNP Production Inhibits SARS-CoV-2 Replication • Effectively inhibits virus replication.	(Sarkar & Das Mukhopadhyay, 2021)
31	Adjunctive therapy to vaccines	Induces an immune response by the production of antibodies	Nano-vaccines' Potential for SARS-CoV-2 • Potential for targeted vaccines.	(Rashidzadeh et al., 2021)
32	Carbon nanotubes	Carbon nanotubes	Remdesivir Administration Overview • Ensures accurate delivery. • Binds to S protein, major protease, RdRNP, and ACE2. • Prevents viral entry and replication.	(Skariyachan et al., 2021b; Keshmiri Neghab et al., 2020)
33	Carbon nanotubes	Virus removal from the PPE surface	Lithography is a technique that coats a metallic surface with carbon nanotubes,	(Kashyap & Saha, 2020)

			securely attaching them to the most vulnerable area of PPE, thereby eliminating SARS-CoV-2 in healthcare professionals.	
34	Graphene oxide	Modifies Virus Receptor Proteins	S protein-ACE2 receptor interaction prevents viral entry into hosts. • Inhibits the reproduction of virus.	(Unal et al., 2021)
35	MnFe3O4 & QDs Nanospheres	Fluorescence-linked immunoassay	N.A./ IgG/ 4pg	(Guo et al., 2020)
36	Au@SiO2 NPs	Lateral flow diagnostic immunoassay	15 min./ IgG & IgM/N.A.	(Rabiee et al., 2024)
37	Gold NPs	PPT Diagnostics	N.A./ RNA/0.22 p.m.	(Qiu et al., 2020)
38	Quartz wafer embedded piezoelectric crystal	Piezoelectric immunosensor	Sputum (Antigen)/N.A./ 0.6 µg per ml	(Zuo et al., 2020)
39	SA-DNPs	LFA	ORF1ab/12 copies per25µl	(Zhu et al., 2020)
40	Graphene NPs	FET	1.6 × 101 pfu/ml/ Antigen/N.A	(Seo et al., 2020)
41	Gold NPs	Colorimeter assay	0.18ng/µl/ RNA/10 min.	(Moitra et al., 2020)
42	IgG-coupled QD NPs	Fluorescence-linked immunosorbent assay	4 pg/ml/ IgG & IgM/ 15 min.	(Derakhshan et al., 2021)
43	Selenium NPs	LFA Immunoassay	N/A/ IgM & IgG/10 min.	(Bayin et al., 2021)

* LSPCF: Localized surface plasmon coupled fluorescence; PPT: plasmonic photothermal; ZIF: Zeolite Imidazole Framework; ROS: Reactive Oxygen Species; NPs: Nanoparticles; Zinc Oxide Nanoparticles: ZnO NPs; α: alpha lineage (B.1.1.7) & δ: delta lineage (B.1.617); LA: Lactic acid; PLGA: Poly Lactic-co-Glycolic Acid; ZO-NPs: Zinc Oxide Nanoparticles; SiO2@AU@QD nano-tagged particles.

Immunoassays use various nanoparticles, such as quantum dots, colloidal gold, magnetic nanoparticles, carbon nanotubes, and rare earth nanoparticles to detect various targets. The US FDA has approved 49 antigen detection devices for SARS-CoV-2, primarily using colloidal gold nanoparticles and Lateral Flow Assays (LFAs), and employing immunoassays to detect various targets, including quantum dots, colloidal gold, magnetic nanoparticles, carbon nanotubes, and rare-earth nanoparticles. These devices induce color changes or detect fluorescent, electrochemical, or magnetic signals when antibodies bind to the antigen. Colloidal gold nanoparticles are the most common form of LFA, offering affordability and a straightforward approach to result interpretation. Fluorescence-based detection techniques, *i.e.,* rare-earth nanoparticles, specifically quantum dots, offer lower detection thresholds and improved sensitivity compared to the colorimetric method of detection. However, the interpretation requires specialized fluorescence reading instruments. Magnetic LFA quantifies changes in the stray magnetic field induced by magnetic nanoparticles, offering exceptional sensitivity and a low detection threshold. Hybrid nanoparticles, *i.e.,* silica-based LFA and QD-loaded mesoporous silica, have demonstrated a substantial enhancement in detection sensitivity compared to commercially available colloidal gold-based LFA. This improvement has the potential to aid early identification of SARS & SARS-CoV-2 infections. (Xu et al., 2022).

3.7. Nano-Chitosan mediated therapeutic Potentials against SARS-CoV-2

Nanotechnology is becoming increasingly popular in the realm of respiratory medication administration. Nano chitosan has the potential to be used for the precise delivery of therapies that target and combat COVID-19 (Wang et al., 2023). Chitosan derivatives and composites, particularly due to their antimicrobial properties, are promising polymers for biomedical applications, originating from the abundant chitin polymer. The review examines the antiviral activity and mechanisms of action of chitosan derivatives, highlighting their importance in combating COVID-19. It also discusses challenges and potential future solutions for addressing the pandemic. (Gopal et al., 2023). Chitosan, a natural nanoparticle, has been used during the recent health crisis to deliver medications to specific body locations, targeting the lungs of affected individuals. Nanoparticles offer significant benefits in biotechnology, medicine, drug delivery, sensors, DNA labeling, and connecting bulk materials. (Yee Kuen & Masarudin, 2022).

Using nanotechnology, point-of-care testing (POCT) for COVID-19 diagnosis is now possible, a welcome development since laboratory infrastructure is not required. One key element of this technology is the perpendicular flow of antigens through a test strip. Commercial lateral flow immunoassays work by using a nitrocellulose strip with antibodies and immunoreagents immobilized to gold nanoparticles. Such a platform helps provide the correct, quick diagnosis needed to guide appropriate treatment. (Yee Kuen & Masarudin, 2022).

Additionally, a nanotechnology-based optical biosensor can detect coronavirus in patient samples within about 30 minutes, providing a rapid, reliable alternative to traditional tests. This new method can discriminate specifically between coronaviruses and influenza viruses. It is also a non-human diagnostic and can be effectively used to treat and monitor the coronavirus strain in animal reservoirs. (Gopal et al., 2023).

3.8. Mechanism of action

Previously reported work shows that the physical properties of chitosan can be controlled through polymer blending. The researchers report that this is the first time target nanoparticle sizes and morphological features, crucial for their use as drug vehicles, have

been obtained. By adjusting the ratios of chitosan to added materials, the quality and performance of the final composition may be accurately controlled. As a biocompatible, cationic natural polysaccharide, chitosan has high basicity and mucoadhesive properties and is used extensively as a polymer for nanotechnological applications, especially for drug delivery. Chitosan processing requires careful determination of the required chemical and physical properties, along with UV-Vis Spectroscopy, Zeta Potential, and Size Measurements, to evaluate the resultant nanoparticles. These properties are then characterised using several different techniques, including Transmission Electron Microscopy (TEM), Field Emission Scanning Electron Microscopy, Atomic Force Microscopy (AFM), and Fourier Transform Infrared Spectroscopy (Safer & Leporatti, 2021). These methods were used to understand the effects of processing on bonding and flow properties and to corroborate our understanding of these effects. There are only a few examples of the development of chitosan nanoparticles for the drug delivery of the antiviral agent. Previously, we have developed and tested the delivery of Bay41-4109—an antiviral drug—in chitosan NPs synthesized via the chitosan-tripolyphosphate (TPP) gelation method for the treatment of antiviral-related diseases. The high interaction of polymers and drugs allows for high drug loading and capacity. Bay41-4109 was determined to be located throughout amorphous chitosan nanoparticles (Huanbutta et al., 2023).

The nanoparticles, as studied by TEM, are 150-200 nm in size. The cellular absorption of drugs was improved by electrostatic interactions between positively charged chitosan molecules and the negatively charged cell membrane. The chitosan nanoparticles were employed in an in vivo study because of their mucosal adhesion properties for sustained drug delivery. The nanoparticles also prolonged the time the drug remained in circulation. The in vivo results demonstrated that Bay41-4109 nanoparticles showed improved bioavailability, suggesting that oral administration of these nanoparticles for the treatment of HBV may be a viable option in the future. (Hoang et al., 2022).

Enveloped viruses connect to a cell surface receptor via several of their envelope glycoproteins. For example, alphaviruses have a large spike glycoprotein complex, and rhabdoviruses have a trimeric glycoprotein (G protein) complex, both of which are examples of viruses that contain a single species of enveloped glycoprotein complex responsible for both receptor binding and fusion. The primate lentiviruses have a single virally encoded envelope protein (Env: gp120/gp41), but they acquire a variety of cellular proteins during assembly, including MHC class II antigens. Although these accessory proteins are not obligatory for virus infectivity, they may help bind host cell receptors and be immunogenic, potentially eliciting antibodies with clearly detectable antiviral activity. The paramyxoviruses contain several proteins involved in both binding and fusion, while even more complex viruses, such as herpes, may have multiple VAPs and fusion proteins. (Klasse et al., 1998).

Virus surface glycoproteins, which outnumber other surface molecules such as glycolipids and phospholipids, comprise most of the surface. Single-pass type 1 integral membrane proteins (e.g., CD4), multispanning proteins (e.g., amino acid transporters), and glycophosphatidylinositol (GPI)-linked proteins (e.g., low-density lipoprotein receptor (LDLR)-related protein) can serve as representatives of many different protein classes. Many viral receptors are members of the immunoglobulin superfamily, many of which are involved in recognition events. In addition, some receptors act as transporters, glycocalyx components, or adhesion molecules. Different receptors have been identified for retroviruses, including CD4 and multimembrane-spanning transporters, as well as an LDLR-related (glycolipid-anchored) protein, which all seem to bind similar SU-TM complexes.

Nevertheless, a recurring theme in this type of interaction has been the proposal that three key residues in CD4, the ecotropic MuLV receptor (cationic amino acid transporter), and ALV receptor (LDLR-related protein) contain one aromatic residue and at least one charged residue (Klasse et al, 1998), suggesting similar mechanisms for effective viral receptor binding. (Klasse et al., 1998).

3.9. Antiviral Properties

Chitosan nanoparticles have the potential to treat COVID-19 due to their enhanced drug-delivery properties. However, their practicality in clinical settings is being evaluated through examination or ongoing studies. Current knowledge of antiviral treatment comes from studies of viruses such as SARS-CoV-1, MERS-CoV-2, and Ebola. Patients with COVID-19 require complete immobilization, consistent medical care, and adequate calorie and water intake to prevent dehydration. Regular monitoring of vital signs, oxygen consumption, blood tests, C-reactive protein levels, and urine testing is also necessary. (Pyrć et al., 2021).
Chitosan, a plant-derived antiviral drug, inhibits plant viral infection by affecting its concentration, molecular weight, and poly-cationic properties. It has been shown to inhibit local tissue death induced by tobacco mosaic virus (TMV). The presence of large amounts of oxidized groups and acetylation justified the antiviral activity of the products of chemical hydrolysis of the chitosan chains. (Safarzadeh et al., 2021). It has been shown that an equivalent of chitosan sulfate can prevent HIV-1 infection in animal cells, as it prevents the virus from binding to cells and prevents the reverse transcriptase enzyme from binding to the poly (A) template. In addition, an electrostatic interaction between the chitosan anionic derivatives and the positively charged gp120 molecule helps prevent viral fusion with the cell membrane. Findings from a study confirm the potential of chitosan derivatives in antiviral practice. (Dilnawaz et al., 2024).

3.10. Drug Delivery Applications of Nano-chitosan:

Chitosan nanoparticles are a developed delivery system of antivirus drugs. By facilitating control over drug release profiles and bioavailability, which may lead to reduced dosing, their use improves therapeutic efficacy through enhanced restorative capacity.

Chitosan, as a natural polymer, provides a good candidate for nanoparticle fabrication. As a result, nanoparticles are known to be low-toxic, highly biocompatible, and biodegradable. Both their ease of manufacture and their usefulness as drug delivery systems (DDSs) make them particularly beneficial. Furthermore, chitosan is generally recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA). These properties have led to the study of chitosan nanoparticles for drug delivery via various routes, including oral, nasal, pulmonary, buccal, ophthalmic, mucosal, and vaginal administration.

They have also been tested for gene transfer, vaccine delivery, and advanced cancer therapy. Several studies have suggested that chitosan nanoparticles could serve as new therapeutic tools against viral infections. (Boroumand et al., 2021).

A nanocomposite including curcumin and chitosan (CuCs) was proven to have a synergistic effect as a virus entry and multiplier inhibitor in human hepatoma cells Huh7 (Pyrć et al., 2021). Antimicrobial coatings, such as metallic nanoparticles, can effectively control COVID-19 transmission at the network level. These coatings can help limit the spread of serious illnesses. Researchers should contact other researchers for more information on the use of nanoparticles in COVID-19 treatment (Dilnawaz et al., 2024).

Chitin and chitosan interact with viruses via electrostatic interactions, causing physical damage and exerting direct antiviral effects. Their cationic charges interact with the capsid proteins' anionic charges, facilitating virus disintegration. Chitosan neutralizes viruses by binding to their tail fibers or disrupting their replication process, with its effectiveness influenced by factors like molecular weight, deacetylation degree, concentration, and environmental pH (Gopal et al., 2023). Chitin and chitosan polymers enhance antiviral immune responses by activating innate immune cells such as NK cells and macrophages, increasing phagocyte numbers, generating reactive oxygen species, releasing nitric oxide, increasing myeloperoxidase activity, and increasing neutrophil movement. (Yee Kuen & Masarudin, 2022).Chitin microparticles, smaller than 40 µm, have immunomodulatory properties and are detected by pattern recognition receptors. They trigger immune responses in vertebrates, enhancing TH1 cell-mediated immunity and inducing IL-10 generation by macrophages. This reduces pro-inflammatory cytokine production, enabling advantageous innate and adaptive immune responses against viral infections. Increased secretion of pro-inflammatory cytokines triggers TH1-type cellular responses and IgG2c isotype switching, resulting in potent immune responses. (Singh & Sodhi, 2023). A study on HIV infection found that DNA/chitin microparticles increased HIV-specific antibodies and virus-specific T cells, suggesting chitin's ability to enhance adaptive immune responses. Inactivated hemagglutinin and genetically modified HA proteins from H1N1 and H5N1 influenza viruses can trigger both mucosal and systemic immune responses, resulting in immunity after vaccination. (Beach et al., 2024).

3.11. Clinical Trials and Effectiveness:

It was found that when mice were inoculated with chitin microparticles through their noses, followed by inoculation with the influenza virus, NK cell multiplication in lymphoid tissues expressing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) was enhanced. Results showed that this nasal spray reduced viral load, superfluous cytokine production, clinical manifestations in patients with H5N1 and H1N1 viruses, and increased the effectiveness of the illness. (Khalili et al., 2020; Shah et al., 2020).

Much like several current viral vaccines and viral agents designed to prevent healthcare locally, chitin micro-particles are effective mucosal adjuvants so long as they help to activate immunity, reduce viral burden, and induce the adaptive response following viral invasion. (Beach et al., 2024). Chitosan is an antibacterial, antioxidant, and immunomodulatory compound. It produces type I interferon by activating the cGAS-STING signaling pathway, thereby inducing dendritic cell proliferation through mitochondrial stress. It also activates the NLRP3 inflammasome through phagocytosis, reactive species production, potassium ion consumption, and lysosome rupture. This results in activation of cellular TH1-types and cellular IgG2c isotype switching, as both are efficient responses to viral infections (Tousian & Khosravi, 2023).

Mucosal vaccines can activate an immune response in humans using chitosan polymers, such as nano- and microparticles, hydrogels, powders, and solutions. Combining chitosan with inactivated influenza vaccines has the potential to enhance the vaccine's ability to elicit an immune response and generate antibodies against multiple virus strains. TMC is more positively charged and can therefore direct immune responses to become TH1 responses and promote antibody production. Full-attenuated influenza virus and H3N2 subunit antigen delivered nasally enhances antigen absorption, leading to increased immunological responses. (Safarzadeh et al., 2021).

When used as adjuvants and carriers of viral antigens, chitosan nanoparticles include HbSag, H1N1, IBV, and HA. This improves the body's immune response by activating antibodies and immune cells. Such chitosan-based structures are particularly effective as intranasal formulations or vehicles for inducing both Th1- and Th2-mediated immune responses, leading to robust immunity (Ait Hamdan et al., 2023).

Chitosan is a substance with desirable properties, which is why it is used in medicine, particularly for targeted drug delivery. It is pretty biocompatible and can protect therapeutic cargo from the perils of stomach acid and blood flow-related fragmentation. Additionally, it forms a marvelous polymer that produces drug-delivery systems due to its ease of forming at the mucous membrane and its ability to deliver the target to the colon, making it an even better choice. (Hutchinson et al., 2023).

Chitosan does not show optimal efficacy as a drug carrier and relies on several structural factors. The most important three are (degree of deacetylation and substitution, molecular weight, porosity, particle size, and compression force). These parameters directly influence the functional groups that facilitate electrostatic interactions, on which we base drug loading and release. (Tousian & Khosravi, 2023). Chitosan itself is highly positively charged, making it best suited for the formation of nano- and micro-particles. Examples include a study that loaded rifampicin, an anti-tubercular drug, into chitosan nanoparticles, which are virtually drinkable as a dry powder. The resulting design necessitated the slow release of drugs over 24 hours, without any detrimental impacts on cells or organs. (Ait Hamdan et al., 2023; Tousian & Khosravi, 2023).

The virus SARS-CoV-2 is a positively charged nanoparticle. This provides it with a strong electrochemical advantage over previously emerging SARS-associated sequences, due to polybasic arginine-containing motifs on its capsid and spike proteins. One suggested countermeasure leverages this property when cationic polymers are used. To illustrate this, nanofibers composed of chitosan embedded in PPEs used by healthcare workers might counter and, by extension, suppress the release of viruses into the environment, thereby diminishing transmission. (Kianpour et al., 2022).

To further demonstrate chitosan's usefulness, scientists have developed antiviral analogs that prevent infection by low-pathogenic human coronaviruses in cell cultures and in living organisms, both in vitro and in vivo. They do so by binding directly to the viral spike protein and interfering with contact to host cell receptors. In support, it has lately been asserted that the research on impeccable designs of snow-white airways epithelium arrangement could effectively subdue both SARS-CoV-2 and MERS-CoV (Hu et al., 2021).

Chitosan nanoparticles can be used to deliver the vaccines. Scientists have developed an intranasal DNA vaccine encoding the SARS-CoV nucleocapsid protein, with chitosan NPs as the vaccine delivery agent. The rationale behind this strategy was to improve vaccination by attaching the DNA vaccine directly to the nasal-resident dendritic cells, which play a critical role in antigen presentation and T-cell activation. This approach has been successful, as it led to much higher rates of systemic and mucosal IgG and mucosal IgA antibodies targeting the N protein than in controls. (Iqbal et al., 2003).

Other nanomaterials promise to be useful in addition to chitosan. The article reviewed a clinical trial in India that tested the use of intravenous silver nanoparticles (AgSept, AgSept1, AgSept2) as the adjunctive treatment of moderate to severe COVID-19 pneumonia. When combined with regular care, the intervention led to a significant improvement in patient survival among the 40 participants. This observation suggests potential applications of silver nanoparticles in treating pneumonia caused by the virus, where there are few treatment

options, as well as establishing their general efficacy in COVID-19 treatment. (Wieler et al., 2023).

Nano-chitosan is a vaccine adjuvant and a method for delivering medications, siRNA, and peptides via the intranasal route. It boosts the immune system, passes through mucosal lining cells, and modifies antigen molecules to enhance the immune response. Novochizol™ nanoparticles in aerosol formulations can efficiently deliver anti-COVID-19 medications to the lungs of ill patients, effectively targeting them. (Tousian & Khosravi, 2023). The development of multivalent antigens in vaccines is gaining interest, with current vaccine candidates using nanoparticles that can elicit antibodies against multiple virus strains over time. However, focusing on conserved non-receptor binding domain epitopes may limit antigenic evasion. To identify new targets, protein nanoparticles with coronavirus prefusion-stabilized spike (CoV_S-2P) trimers were created from MERS-CoV, SARS-CoV-1, SARS-CoV-2, hCoV-HKU1, and hCoV-OC43. The immunogenicity of these nanoparticles was evaluated in female mice. Monotypic SARS-CoV-1 nanoparticles produced cross-neutralizing antibodies against MERS-CoV, protecting against MERS-CoV infection. The use of mosaic nanoparticles with different CoV_S-2P trimers generated antibodies targeting diverse cross-group antigens, protecting against MERS-CoV infection in both male and female mice. The study's findings will provide valuable insights for future vaccines against all types of coronaviruses. (Hutchinson et al., 2023).

3.12. Discussion and Critical Analysis

The use of nanochitosan in nanomedicine offers several advantages over existing antiviral approaches for treating HCoVs, such as SARS-CoV, MERS-CoV, and the recently emerged SARS-CoV-2. By developing new concepts and processes for fighting viruses, nanotherapeutics overcome many of the limitations of traditional treatments. (Bhattacharjee et al., 2022). This section is intended to evaluate nanotherapeutics relative to current methods critically, discuss relevant literature and clinical issues, examine the risk-benefit profile of nanomaterials as therapeutics, and provide a global perspective on nanomaterials in therapeutics.

3.13. Nanomedicine vs. Traditional Antiviral Therapies

Traditional antiviral medications, such as protease inhibitors (for example, ritonavir and lopinavir) and nucleoside analogues (for instance, remdesivir), have long been the basis of viral infection therapy. However, significant limitations of these agents include their generally low broad-spectrum activity and development of rapid drug resistance. For instance, one popular antiviral against COVID-19 is remdesivir, which has been shown to decrease viral replication in cell cultures and improve clinical outcomes in some patients. However, its efficacy is also modest, particularly in patients with more severe disease or high viral loads. (Blair, 2023).

On the other hand, nanomedicine leads to fewer nonspecific therapies, as Alghareeb et al. (2025) and Biswas et al. (2025) Reported that the application of nano-chitosan as a natural nanoparticle, for the specific targeting of infected cells and tissues, might reduce the systemic adverse effects that are typically linked to traditional antiviral drugs. For example, in the case of pulmonary infections, nanoparticles (nano-chitosan) can be used to enhance the solubility and bioavailability of antiviral agents, thereby improving their therapeutic effectiveness. This is in marked contrast to traditional drug preparations, which are poorly soluble and incompletely absorbed, leading to reduced effectiveness.

3.14. Comparative Clinical Efficacy

Nanomedicine-based vaccines have distinct advantages over traditional vaccine platforms, especially those using nanoparticle adjuvants such as nanochitosan. Even though the mRNA-based vaccines mRNA-1273 and mRNA-1273.3 from Pfizer Inc./BioNTech SE and Moderna Inc., respectively, have achieved exceptionally high efficacy against SARS-CoV-2, these data suggest that classical vaccines, including mRNA vaccines, require booster doses and are logistically limited by the need for ultracold chain storage. A primary advantage of nanomaterials is their ability to enhance immune responses through mechanisms such as slow antigen release and increased vaccine stability. For example, nano-chitosan was successfully employed in nanoparticle-based vaccines to induce high antigen presentation and also induction of high cellular and humoral immunity, as shown by (Bezbaruah et al., 2022).

Because they are comprised of nanoparticles, the vaccines are also more stable and shelf-stable, meaning they do not require cold-chain logistics or refrigeration for transport, as most vaccines do. Thus, the application of nanotechnology to vaccines offers opportunities to improve efficacy and potentially address challenges in international distribution.

3.15. Safety and Toxicity Concerns

While the potential of nanomedicine is promising, there are two potential safety and long-term toxicity issues with nanoparticles. Even though nanochitosan was biocompatible and biodegradable, other researchers indicated that chitosan nanosuspension is safe for topical ocular application (no side effects). However, chitosan nanoparticles might biodegrade and accumulate in organs and tissues, potentially becoming toxic to cells, especially after multiple or prolonged exposure. (Ewii et al., 2025; Farjadian et al., 2019). Moreover, studies by Park & Kim (2019) Suggest that nanoparticles may, in some people, trigger immune system activation and thus lead to inflammation or hypersensitivity. These data highlight the critical need for comprehensive safety assessments and long-term clinical studies to delineate the risk profile of medical nanomaterials fully. In contrast, the clinical safety of conventional drug therapy is well established, having undergone years of intensive clinical testing and routine clinical implementation. While both treatments can also cause side effects, the risks are fairly well characterized. This enables the expression of a rational risk-benefit profile and the justification of their use, in particular when no alternative treatments exist. The long-term effects of traditional vaccines and antivirals are well established, so we can more easily predict outcomes in most clinical settings.

3.16. Manufacturing Challenges and Regulatory Hurdles

The production of nanomedicines imposes challenges different from those of conventional medicines. A primary challenge is the mass production of nanoparticles with reproducible size, shape, and quality. Although Zhang & Zhang (2021) and Zhang & Zhang (2007) have shown that nanoparticles, such as nanochitosan, can be synthesized using various methods, scaling up some of these techniques for global distribution is technically challenging. Secondly, regulatory systems for the approval of nanomedicines are still in development. Profit-seeking pharmaceutical companies submit these products for review and evaluation by regulatory agencies that apply a much more rigorous level of scrutiny to judge their safety, effectiveness, and manufacturing reproducibility than that applied to traditional medications.

By contrast, a regulatory pathway for classical interventions, such as antiviral drugs and vaccines, is well-defined and established. Even this standard process was accelerated during public health emergencies such as the COVID-19 pandemic to ensure these drugs could be deployed quickly. Nanomedicine, on the other hand, is stymied by a paucity of harmonized international regulations and the inherent complexity of nanomaterials, which requires extensive preclinical and clinical testing to evaluate potential side effects.

3.17. **Risk-Benefit Evaluation**

A risk-benefit analysis for nanomedicine must carefully weigh the potential of the innovative field against uncertainties in clinical benefits and safety. While nanomedicines such as nanochitosan provide significant benefits in targeted delivery, improved bioavailability, and enhanced logistics of vaccine delivery, potential uncertainties and the lack of scalable manufacturing regarding the long-term safety of vaccines are of great concern. Clinical studies such as Karahmet Sher et al. (2024) It is necessary to support evidence on the short- and long-term therapeutic effectiveness and potential toxicity of nanomedicine interventions for the treatment of viral infections. In contrast, for conventional therapies, there is a well-defined risk-benefit ratio based on a long clinical history. Their disadvantages, however -- including reduced effectiveness against emerging viral variants and a constant threat of drug resistance -- underscore the need for alternative methods, such as nanomedicine.

In conclusion, nanomedicine, specifically Nano chitosan, is a promising approach for advancing antiviral therapy through targeted delivery and improved drug bioavailability, as well as for novel vaccine development. However, major roadblocks in scalable manufacturing, regulatory approval, and long-term safety need to be resolved before these nanotherapeutics achieve widespread clinical adoption. However, nanomedicine has shown great potential compared with other fields, but this potential can be realized only if these massive challenges are overcome. Future work will need to focus on the development and optimization of nanoparticle formulations, the design of large-scale clinical trials, and the creation of concrete regulatory guidance to ensure the safe and effective use of nanomedicine for the treatment of viral infections.

3.18. Conclusion and Future Prospective

Nano-chitosan is a new and promising product for the treatment of human coronavirus infections, including the new strains. Its unique properties, such as improved bioavailability, targeted drug delivery, and immune system modulation, make it a valuable tool against current and future viral pandemics. The incorporation of nanochitosan into therapeutic intervention strategies could significantly enhance the efficiency and specificity of viral treatments. However, further research is necessary to optimize its use in the clinic, establish its safety, and investigate its role in combination with other therapies, such as vaccines and antiviral drugs. The future of nanomedicine against viral infections is bright, and balancing supply is vital; nano-chitosan plays a vital role in its exciting innovations.

Declarations

Ethics approval and consent to participate

Not applicable.

Ethical consideration

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

No applicable

Author's Contribution

Conceptualization, W.H., S.W., methodology, J.H., I.P., Software, S.S., Validation, Y.S., M.N. and I.P., formal analysis, S.S., and I.P., investigation, S.S., S.H. and S.W., resources, I.P., data curation, W.H., S.S., and H.R. writing, editing, & review of original draft: I.P, Supervision and project administration, W.H., S.W. ; S.N., S.M.,A.M & Y.S., revised the final revision of the manuscript, and M.N drew all the figures. All authors have approved and reviewed the manuscript.

Funding

This work has not received any funding

Data Availability

No new data were generated or analyzed in this study. All data supporting this review are available within the published articles cited herein.

References

Ait Hamdan, Y., El Amerany, F., Desbrières, J., Aghrinane, A., Oudadesse, H., & Rhazi, M. (2023). The evolution of the global COVID-19 epidemic in Morocco and understanding the different therapeutic approaches of chitosan in the control of the pandemic. *Polymer Bulletin*, *80*(10), 10633–10659. crossref

Akhter, S., & Akhtar, S. (2020). Emerging coronavirus diseases and future perspectives. *Virusdisease*, *31*(2), 113–120. crossref

Alghareeb, S., Ekenna, I., Asare-Addo, K., Conway, B. R., & Adebisi, A. O. (2025). Chitosan nanoparticles for nasal drug delivery. *Journal of Drug Delivery Science and Technology*, *105*, 106623. crossref

Almanza-Reyes, H., Moreno, S., Plascencia-López, I., Alvarado-Vera, M., Patrón-Romero, L., Borrego, B., Reyes-Escamilla, A., Valencia-Manzo, D., Brun, A., Pestryakov, A., & Bogdanchikova, N. (2021). Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: In vitro and in vivo. *PLOS ONE*, *16*(8), e0256401. crossref

Asdaq, S. M. B., Ikbal, A. M. A., Sahu, R. K., Bhattacharjee, B., Paul, T., Deka, B., Fattepur, S., Widyowati, R., Vijaya, J., Al mohaini, M., Alsalman, A. J., Imran, Mohd., Nagaraja, S., Nair, A. B., Attimarad, M., & Venugopala, K. N. (2021). Nanotechnology Integration for SARS-CoV-2 Diagnosis and Treatment: An Approach to Preventing Pandemic. *Nanomaterials*, *11*(7), 1841. crossref

Ashraf, B. N. (2020). Economic impact of government interventions during the COVID-19 pandemic: International evidence from financial markets. *J Behav Exp Finance*, *27*, 100371. crossref

Bayin, Q., Huang, L., Ren, C., Fu, Y., Ma, X., & Guo, J. (2021). Anti-SARS-CoV-2 IgG and IgM detection with a GMR based LFIA system. *Talanta*, *227*, 122207. crossref

Beach, M. A., Nayanathara, U., Gao, Y., Zhang, C., Xiong, Y., Wang, Y., & Such, G. K. (2024). Polymeric Nanoparticles for Drug Delivery. *Chemical Reviews*, *124*(9), 5505–5616. crossref

Bezbaruah, R., Chavda, V. P., Nongrang, L., Alom, S., Deka, K., Kalita, T., Ali, F., Bhattacharjee, B., & Vora, L. (2022). Nanoparticle-Based Delivery Systems for Vaccines. *Vaccines*, *10*(11), 1946. crossref

Bhattacharjee, R., Dubey, A. K., Ganguly, A., Bhattacharya, B., Mishra, Y. K., Mostafavi, E., & Kaushik, A. (2022). State-of-art high-performance Nano-systems for mutated coronavirus infection management: From Lab to Clinic. *OpenNano*, *8*, 100078. crossref

Bielecka-Oder, A. (2018). Safety and Security Regulations Against Biological Threats. In V. Radosavljevic, I. Banjari, & G. Belojevic (Eds.), *Defence Against Bioterrorism* (pp. 151–176). Springer Netherlands.crossref

Biswas, R., Mondal, S., Ansari, M. A., Sarkar, T., Condiuc, I. P., Trifas, G., & Atanase, L. I. (2025). Chitosan and Its Derivatives as Nanocarriers for Drug Delivery. *Molecules*, *30*(6), 1297. crossref

Blair, H. A. (2023). Remdesivir: A Review in COVID-19. *Drugs*, *83*(13), 1215–1237. crossref

Boroumand, H., Badie, F., Mazaheri, S., Seyedi, Z. S., Nahand, J. S., Nejati, M., Baghi, H. B., Abbasi-Kolli, M., Badehnoosh, B., Ghandali, M., Hamblin, M. R., & Mirzaei, H. (2021). Chitosan-Based Nanoparticles Against Viral Infections. In *Frontiers in Cellular and Infection Microbiology* (Vol. 11). crossref

Campos, A. C., Groth, A. K., & Branco, A. B. (2008). Assessment and nutritional aspects of wound healing. *Current Opinion in Clinical Nutrition and Metabolic Care*, *11*(3), 281–288. crossref

Cavalcanti, I. D. L., & Cajubá de Britto Lira Nogueira, M. (2020). Pharmaceutical nanotechnology: which products are been designed against COVID-19? *Journal of Nanoparticle Research*, *22*(9), 276. crossref

Cheng, C.-C., Fann, L.-Y., Chou, Y.-C., Liu, C.-C., Hu, H.-Y., & Chu, D. (2022). Nosocomial infection and spread of SARS-CoV-2 infection among hospital staff, patients and caregivers. *World Journal of Clinical Cases*, *10*(34), 12559–12565. crossref

Chowdhury, N. K., Deepika, Choudhury, R., Sonawane, G. A., Mavinamar, S., Lyu, X., Pandey, R. P., & Chang, C.-M. (2021). Nanoparticles as an effective drug delivery system in COVID-19. *Biomedicine & Pharmacotherapy*, *143*, 112162. crossref

Chue-Gonçalves, M., Pereira, G. N., Faccin-Galhardi, L. C., Kobayashi, R. K. T., & Nakazato, G. (2021). Metal Nanoparticles against Viruses: Possibilities to Fight SARS-CoV-2. *Nanomaterials*, *11*(11), 3118. crossref

Cohen, A. A., Gnanapragasam, P. N. P., Lee, Y. E., Hoffman, P. R., Ou, S., Kakutani, L. M., Keeffe, J. R., Wu, H.-J., Howarth, M., West, A. P., Barnes, C. O., Nussenzweig, M. C., & Bjorkman, P. J. (2021). Mosaic nanoparticles elicit cross-reactive immune responses to zoonotic coronaviruses in mice. *Science*, *371*(6530), 735–741. crossref

Derakhshan, M. A., Amani, A., & Faridi-Majidi, R. (2021). State-of-the-Art of Nanodiagnostics and Nanotherapeutics against SARS-CoV-2. *ACS Applied Materials & Interfaces*, *13*(13), 14816–14843. crossref

Diao, B., Wang, C., Tan, Y., Chen, X., Liu, Y., Ning, L., Chen, L., Li, M., Liu, Y., Wang, G., Yuan, Z., Feng, Z., Zhang, Y., Wu, Y., & Chen, Y. (2020). Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Frontiers in Immunology*, *11*, 827. crossref

Dilnawaz, F., Acharya, S., & Kanungo, A. (2024). A clinical perspective of chitosan nanoparticles for infectious disease management. *Polymer Bulletin*, *81*(2), 1071–1095. crossref

Dinarello, C. A. (2007). Historical insights into cytokines. *European Journal of Immunology*, *37 Suppl 1*, S34—45. crossref

Donnelly, C. A., Malik, M. R., Elkholy, A., Cauchemez, S., & Van Kerkhove, M. D. (2019). Worldwide Reduction in MERS Cases and Deaths since 2016. In *Emerging infectious diseases* (Vol. 25, Issue 9, pp. 1758–1760).crossref

Ewii, U. E., Attama, A. A., Olorunsola, E. O., Onugwu, A. L., Nwakpa, F. U., Anyiam, C., Chijioke, C., & Ogbulie, T. (2025). Nanoparticles for drug delivery: Insight into in vitro and in vivo drug release from nanomedicines. *Nano TransMed*, *4*, 100083. crossref

Farjadian, F., Ghasemi, A., Gohari, O., Roointan, A., Karimi, M., & Hamblin, M. R. (2019). Nanopharmaceuticals and Nanomedicines Currently on the Market: Challenges and Opportunities. *Nanomedicine*, *14*(1), 93–126.crossref

Faye, M. N., Barry, M. A., Jallow, M. M., Wade, S. F., Mendy, M. P., Sy, S., Fall, A., Kiori, D. E., Ndiaye, N. K., Goudiaby, D., Diamanka, A., Niang, M. N., & Dia, N. (2022). Epidemiology of Non-SARS-CoV2 Human Coronaviruses (HCoVs) in People Presenting with Influenza-like Illness (ILI) or Severe Acute Respiratory Infections (SARI) in Senegal from 2012 to 2020. *Viruses*, *15*(1), 20. crossref

Foffa, D., Dunne, E. M., Nesbitt, S. J., Butler, R. J., Fraser, N. C., Brusatte, S. L., Farnsworth, A., Lunt, D. J., Valdes, P. J., Walsh, S., & Barrett, P. M. (2022). Scleromochlus and the early evolution of Pterosauromorpha. *Nature*, *610*(7931), 313–318. crossref

Frey, C. B., Chen, C., & Presidente, G. (2020). Democracy, Culture, and Contagion: Political Regimes and Countries Responsiveness to Covid-19. *Covid Economics*, *18*, 1–20.

Ghaemi, N., Sverdlov, A., Shelton, R., & Litman, R. (2021). Efficacy and safety of mij821 in patients with treatment-resistant depression: Results from a randomized, placebo-controlled, proof-of-concept study. *European Psychiatry*, *64*(S1), S334–S335. crossref

Gheblawi, M., Wang, K., Viveiros, A., Nguyen, Q., Zhong, J.-C., Turner, A. J., Raizada, M. K., Grant, M. B., & Oudit, G. Y. (2020). Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circulation Research*, *126*(10), 1456–1474. crossref

Gopal, J., Muthu, M., Pushparaj, S. S. C., & Sivanesan, I. (2023). Anti-COVID-19 Credentials of Chitosan Composites and Derivatives: Future Scope? *Antibiotics*, *12*(4), 665. crossref

Grigonyte, A. M., Harrison, C., MacDonald, P. R., Montero-Blay, A., Tridgett, M., Duncan, J., Sagona, A. P., Constantinidou, C., Jaramillo, A., & Millard, A. (2020). Comparison of CRISPR and Marker-Based Methods for the Engineering of Phage T7. *Viruses*, *12*(2). crossref

Guo, Y.-R., Cao, Q.-D., Hong, Z.-S., Tan, Y.-Y., Chen, S.-D., Jin, H.-J., Tan, K.-S., Wang, D.-Y., & Yan, Y. (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. *Military Medical Research*, *7*(1), 11. crossref

Hassanpour, M., Rezaie, J., Nouri, M., & Panahi, Y. (2020). The role of extracellular vesicles in COVID-19 virus infection. *Infection, Genetics and Evolution*, *85*, 104422. crossref

Hemida, M. G. (2021). The next-generation coronavirus diagnostic techniques with particular emphasis on the SARS-CoV-2. *Journal of Medical Virology*, *93*(7), 4219–4241. https://doi.org/10.1002/jmv.26926 crossref

Hoang, N. H., Thanh, T. Le, Sangpueak, R., Treekoon, J., Saengchan, C., Thepbandit, W., Papathoti, N. K., Kamkaew, A., & Buensanteai, N. (2022). Chitosan Nanoparticles-Based Ionic

Gelation Method: A Promising Candidate for Plant Disease Management. In *Polymers* (Vol. 14, Issue 4).crossref

Wu, H. C., Chen, Y. F., Cheng, M. J., Wu, M. D., Chen, Y. L., & Chang, H. S. (2021). Investigations into chemical components from Monascus purpureus with photoprotective and anti-melanogenic activities. *Journal of Fungi*, 7(8), 619.crossref

Huanbutta, K., Sriamornsak, P., Suwanpitak, K., Klinchuen, N., Deebugkum, T., Teppitak, V., & Sangnim, T. (2023). Key Fabrications of Chitosan Nanoparticles for Effective Drug Delivery Using Flow Chemistry Reactors. *International Journal of Nanomedicine*, *18*. crossref

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497–506. crossref

Huang, D. W., Sherman, B. T., & Lempicki, R. A. (2009). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nature Protocols*, *4*(1), 44–57. crossref

Hui, D. S., E, I. A., Madani, T. A., Ntoumi, F., Kock, R., Dar, O., Ippolito, G., McHugh, T. D., Memish, Z. A., Drosten, C., Zumla, A., & Petersen, E. (2020). The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis*, *91*, 264–266. crossref

Hutchinson, G. B., Abiona, O. M., Ziwawo, C. T., Werner, A. P., Ellis, D., Tsybovsky, Y., Leist, S. R., Palandjian, C., West, A., Fritch, E. J., Wang, N., Wrapp, D., Boyoglu-Barnum, S., Ueda, G., Baker, D., Kanekiyo, M., McLellan, J. S., Baric, R. S., King, N. P., … Corbett-Helaire, K. S. (2023). Nanoparticle display of prefusion coronavirus spike elicits S1-focused cross-reactive antibody response against diverse coronavirus subgenera. *Nature Communications*, *14*(1), 6195. crossref

Idris, A., Davis, A., Supramaniam, A., Acharya, D., Kelly, G., Tayyar, Y., West, N., Zhang, P., McMillan, C. L. D., Soemardy, C., Ray, R., O'Meally, D., Scott, T. A., McMillan, N. A. J., & Morris, K. V. (2021). A SARS-CoV-2 targeted siRNA-nanoparticle therapy for COVID-19. *Molecular Therapy*, *29*(7), 2219–2226. crossref

Iqbal, M., Lin, W., Jabbal-Gill, I., Davis, S. S., Steward, M. W., & Illum, L. (2003). Nasal delivery of chitosan–DNA plasmid expressing epitopes of respiratory syncytial virus (RSV) induces protective CTL responses in BALB/c mice. *Vaccine*, *21*(13–14), 1478–1485. crossref

Jackson, C. B., Farzan, M., Chen, B., & Choe, H. (2022). Mechanisms of SARS-CoV-2 entry into cells. *Nature Reviews Molecular Cell Biology*, *23*(1), 3–20. crossref

Jamkhande, A., Khairnar, M. R., Gavali, N., Patil, Y., Kapare, S. S., & Bhosale, K. P. (2021). A review of approved COVID-19 vaccines. *Roczniki Panstwowego Zakladu Higieny*, *72*(3), 245–252. crossref

Kane, Y., Wong, G., & Gao, G. F. (2023). Animal Models, Zoonotic Reservoirs, and Cross-Species Transmission of Emerging Human-Infecting Coronaviruses. *Annual Review of Animal Biosciences*, *11*(1), 1–31. crossref

Karahmet Sher, E., Alebić, M., Marković Boras, M., Boškailo, E., Karahmet Farhat, E., Karahmet, A., Pavlović, B., Sher, F., & Lekić, L. (2024). Nanotechnology in medicine revolutionizing drug delivery for cancer and viral infection treatments. *International Journal of Pharmaceutics*, *660*, 124345. crossref

Kashyap, U., & Saha, S. K. (2020). Enhanced Design of PPE Based on Electrostatic Principle to Eliminate Viruses (SARS-CoV-2). *Transactions of the Indian National Academy of Engineering*, *5*(2), 337–341. crossref

Keshmiri Neghab, H., Azadeh, S. S., Soheilifar, M. H., & Dashtestani, F. (2020). Nanoformulation-Based Antiviral Combination Therapy for Treatment of COVID-19. *Avicenna Journal of Medical Biotechnology*, *12*(4), 255–256.

Khalil, B. A., Shakartalla, S. B., Goel, S., Madkhana, B., Halwani, R., Maghazachi, A. A., AlSafar, H., Al-Omari, B., & Al Bataineh, M. T. (2022). Immune Profiling of COVID-19 in Correlation with SARS and MERS. *Viruses*, *14*(1), 164. crossref

Khalil, N. M., Carraro, E., Cótica, L. F., & Mainardes, R. M. (2011). Potential of polymeric nanoparticles in AIDS treatment and prevention. *Expert Opinion on Drug Delivery*, *8*(1), 95–112. crossref

Khalili, J. S., Zhu, H., Mak, N. S. A., Yan, Y., & Zhu, Y. (2020). Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID-19. *Journal of Medical Virology*, *92*(7), 740–746. crossref

Khan, D., Terenzi, F., Liu, G., Ghosh, P. K., Ye, F., Nguyen, K., China, A., Ramachandiran, I., Chakraborty, S., Stefan, J., Khan, K., Vasu, K., Dong, F., Willard, B., Karn, J., Gack, M. U., & Fox, P. L. (2023). A viral pan-end RNA element and host complex define a SARS-CoV-2 regulon. *Nature Communications*, *14*(1), 3385. crossref

Kianpour, M., Akbarian, M., & Uversky, V. N. (2022). Nanoparticles for Coronavirus Control. *Nanomaterials*, *12*(9), 1602. crossref

Klasse, P. J., Bron, R., & Marsh, M. (1998). Mechanisms of enveloped virus entry into animal cells. In *Advanced Drug Delivery Reviews* (Vol. 34, Issue 1). crossref

Kumar, M., Joshi, M., Patel, A. K., & Joshi, C. G. (2021). Unravelling the early warning capability of wastewater surveillance for COVID-19: A temporal study on SARS-CoV-2 RNA detection and need for the escalation. *Environmental Research*, *196*, 110946. crossref

Lebeau, G., Vagner, D., Frumence, É., Ah-Pine, F., Guillot, X., Nobécourt, E., Raffray, L., & Gasque, P. (2020). Deciphering SARS-CoV-2 Virologic and Immunologic Features. *International Journal of Molecular Sciences*, *21*(16). crossref

Li, C., He, Q., Qian, H., & Liu, J. (2021). Overview of the pathogenesis of COVID-19 (Review). *Experimental and Therapeutic Medicine*, *22*(3), 1011.crossref

Li, L., Huang, T., Wang, Y., Wang, Z., Liang, Y., Huang, T., Zhang, H., Sun, W., & Wang, Y. (2020). Response to Char's comment: Comment on Li et al: COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of Medical Virology*, *92*(9), 1433–1433. crossref

Li, X., Yuan, H., Li, X., & Wang, H. (2023). Spike protein mediated membrane fusion during SARS-CoV-2 infection. *Journal of Medical Virology*, *95*(1). crossref

Liu, D. X., Liang, J. Q., & Fung, T. S. (2021). Human Coronavirus-229E, -OC43, -NL63, and -HKU1 (Coronaviridae). In *Encyclopedia of Virology* (pp. 428–440). Elsevier. crossref

Liu, T., Feng, M., Wen, Z., He, Y., Lin, W., & Zhang, M. (2021). Comparison of the Characteristics of Cytokine Storm and Immune Response Induced by SARS-CoV, MERS-CoV, and SARS-CoV-2 Infections. *Journal of Inflammation Research*, *14*, 5475–5487. crossref

Malone, B., Urakova, N., Snijder, E. J., & Campbell, E. A. (2022). Structures and functions of coronavirus replication–transcription complexes and their relevance for SARS-CoV-2 drug design. *Nature Reviews Molecular Cell Biology*, *23*(1), 21–39. crossref

Mohammed, M. I., & Yahia, I. S. (2022). Towards multifunctional applications of Fullerene-filled (PVA-PEG) polymeric nanocomposite films: structural, optical, and electrical properties. *Physica Scripta*, *97*(6), 65813.crossref

Moitra, P., Alafeef, M., Dighe, K., Frieman, M. B., & Pan, D. (2020). Selective Naked-Eye Detection of SARS-CoV-2 Mediated by N Gene Targeted Antisense Oligonucleotide Capped Plasmonic Nanoparticles. *ACS Nano*, *14*(6), 7617–7627. crossref

Møller, A.-S. W., Haug, R. O. K. B. F., Westvik, G. B. J. A. B., & Kierulf, P. (2005). Chemokine production and pattern recognition receptor (PRR) expression in whole blood stimulated with pathogen-associated molecular patterns (PAMPs). *Cytokine*, *32 6*, 304–315. crossref

Mostafa, A., Kandeil, A., Shehata, M., El Shesheny, R., Samy, A. M., Kayali, G., & Ali, M. A. (2020). Middle East Respiratory Syndrome Coronavirus (MERS-CoV): State of the Science. *Microorganisms*, *8*(7), 991. crossref

Mufamadi, M. S., Ngoepe, M. P., Nobela, O., Maluleke, N., Phorah, B., Methula, B., Maseko, T., Masebe, D. I., Mufhandu, H. T., & Katata-Seru, L. M. (2023). Next-Generation Vaccines: Nanovaccines in the Fight against SARS-CoV-2 Virus and beyond SARS-CoV-2. *BioMed Research International*, *2023*, 1–11. crossref

Noor, A. U., Maqbool, F., Bhatti, Z. A., & Khan, A. U. (2020). Epidemiology of CoViD-19 Pandemic: Recovery and mortality ratio around the globe. *Pak J Med Sci*, *36*(COVID19-S4), S79–S84. crossref

Oh, M. D., Park, W. B., Park, S. W., Choe, P. G., Bang, J. H., Song, K. H., Kim, E. S., Kim, H. B., & Kim, N. J. (2018). Middle East respiratory syndrome: what we learned from the 2015 outbreak in the Republic of Korea. *Korean J Intern Med*, *33*(2), 233–246. crossref

Pal, R., & Bhansali, A. (2020). COVID-19, diabetes mellitus and ACE2: The conundrum. *Diabetes Research and Clinical Practice*, *162*, 108132. crossref

Pandey, D., Bansal, S., Goyal, S., Garg, A., Sethi, N., Pothiyill, D. I., Sreelakshmi, E. S., Sayyad, M. G., & Sethi, R. (2020). Psychological impact of mass quarantine on population during pandemics—The COVID-19 Lock-Down (COLD) study. *PLOS ONE*, *15*(10), e0240501.crossref

Park, S.Y., & Kim, C.G. (2019). Biodegradation of micro-polyethylene particles by bacterial colonization of a mixed microbial consortium isolated from a landfill site. *Chemosphere*, *222*, 527–533. crossref

Pyrć, K., Milewska, A., Duran, E. B., Botwina, P., Dabrowska, A., Jedrysik, M., Benedyk, M., Lopes, R., Arenas-Pinto, A., Badr, M., Mellor, R., Kalber, T. L., Fernandez-Reyes, D., Schätzlein, A. G., & Uchegbu, I. F. (2021). SARS-CoV-2 inhibition using a mucoadhesive, amphiphilic chitosan that may serve as an anti-viral nasal spray. *Scientific Reports*, *11*(1), 20012. crossref

Qiu, J., Shen, B., Zhao, M., Wang, Z., Xie, B., & Xu, Y. (2020). A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. *General Psychiatry*, *33*(2), e100213. crossref

Rabiee, N., Ahmadi, S., Akhavan, O., & Luque, R. (2024). Correction: Rabiee et al. Silver and Gold Nanoparticles for Antimicrobial Purposes against Multi-Drug Resistance Bacteria. Materials 2022, 15, 1799. *Materials*, *17*(12), 2841. crossref

Ramadan, N., & Shaib, H. (2019). Middle East respiratory syndrome coronavirus (MERS-CoV): A review. *Germs*, *9*(1), 35–42. crossref

Rashidzadeh, H., Danafar, H., Rahimi, H., Mozafari, F., Salehiabar, M., Rahmati, M. A., Rahamooz-Haghighi, S., Mousazadeh, N., Mohammadi, A., Ertas, Y. N., Ramazani, A., Huseynova, I., Khalilov, R., Davaran, S., Webster, T. J., Kavetskyy, T., Eftekhari, A., Nosrati, H., & Mirsaeidi, M. (2021). Nanotechnology Against The Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2): Diagnosis, Treatment, Therapy and Future Perspectives. *Nanomedicine*, *16*(6), 497–516. crossref

Rasmi, Y., Mosa, O. F., Alipour, S., Heidari, N., Javanmard, F., Golchin, A., & Gholizadeh-Ghaleh Aziz, S. (2022a). Significance of Cardiac Troponins as an Identification Tool in COVID-19 Patients Using Biosensors: An Update. *Frontiers in Molecular Biosciences*, *9*. crossref

Rasmi, Y., Mosa, O. F., Alipour, S., Heidari, N., Javanmard, F., Golchin, A., & Gholizadeh-Ghaleh Aziz, S. (2022b). Significance of Cardiac Troponins as an Identification Tool in COVID-19 Patients Using Biosensors: An Update. *Frontiers in Molecular Biosciences*, *9*. crossref

Safarzadeh, M., Sadeghi, S., Azizi, M., Rastegari-Pouyani, M., Pouriran, R., & Haji Molla Hoseini, M. (2021). Chitin and chitosan as tools to combat COVID-19: A triple approach. *International Journal of Biological Macromolecules*, *183*, 235–244. crossref

Safer, A.-M., & Leporatti, S. (2021). Chitosan Nanoparticles for Antiviral Drug Delivery: A Novel Route for COVID-19 Treatment. *International Journal of Nanomedicine*, *Volume 16*, 8141–8158. crossref

Sarkar, P. K., & Das Mukhopadhyay, C. (2021). Ayurvedic metal nanoparticles could be novel antiviral agents against SARS-CoV-2. *International Nano Letters*, *11*(3), 197–203. crossref

Saville, J. W., Berezuk, A. M., Srivastava, S. S., & Subramaniam, S. (2022). Three-Dimensional Visualization of Viral Structure, Entry, and Replication Underlying the Spread of SARS-CoV-2. *Chemical Reviews*, *122*(17), 14066–14084. crossref

Sawicki, S. G., Sawicki, D. L., & Siddell, S. G. (2007). A contemporary view of coronavirus transcription. *J Virol*, *81*(1), 20–29. crossref

Schindell, B. G., Allardice, M., McBride, J. A. M., Dennehy, B., & Kindrachuk, J. (2022). SARS-CoV-2 and the Missing Link of Intermediate Hosts in Viral Emergence - What We Can Learn From Other Betacoronaviruses. *Frontiers in Virology*, *2*. crossref

Seo, G., Lee, G., Kim, M. J., Baek, S.-H., Choi, M., Ku, K. B., Lee, C.-S., Jun, S., Park, D., Kim, H. G., Kim, S.-J., Lee, J.-O., Kim, B. T., Park, E. C., & Kim, S. Il. (2020). Rapid Detection of COVID-19 Causative Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor-Based Biosensor. *ACS Nano*, *14*(4), 5135–5142.crossref

Shah, V. K., Firmal, P., Alam, A., Ganguly, D., & Chattopadhyay, S. (2020). Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. *Frontiers in Immunology*, *11*. crossref

Shukla, B. K., Tyagi, H., Bhandari, H., & Garg, S. (2021). Nanotechnology-Based Approach to Combat Pandemic COVID 19: A Review. *Macromolecular Symposia*, *397*(1). crossref

Singh, C. K., & Sodhi, K. K. (2023). The emerging significance of nanomedicine-based approaches to fighting COVID-19 variants of concern: A perspective on the nanotechnology's role in COVID-19 diagnosis and treatment. *Frontiers in Nanotechnology*, *4*. crossref

Skariyachan, S., Gopal, D., Deshpande, D., Joshi, A., Uttarkar, A., & Niranjan, V. (2021a). Carbon fullerene and nanotube are probable binders to multiple targets of SARS-CoV-2: Insights from computational modeling and molecular dynamic simulation studies. *Infection, Genetics and Evolution*, *96*, 105155. crossref

Skariyachan, S., Gopal, D., Deshpande, D., Joshi, A., Uttarkar, A., & Niranjan, V. (2021b). Carbon fullerene and nanotube are probable binders to multiple targets of SARS-CoV-2: Insights from computational modeling and molecular dynamic simulation studies. *Infection, Genetics and Evolution*, *96*, 105155. crossref

Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., Qu, Y., Zhu, H., Zhao, W., Han, Y., & Qin, C. (2019). From SARS to MERS, Thrusting Coronaviruses into the Spotlight. *Viruses*, *11*(1), 59. crossref

Summers, J., Cheng, H.-Y., Lin, H.-H., Barnard, L. T., Kvalsvig, A., Wilson, N., & Baker, M. G. (2020). Potential lessons from the Taiwan and New Zealand health responses to the COVID-19 pandemic. *The Lancet Regional Health. Western Pacific*, *4*, 100044. crossref

Tan, Q., He, L., Meng, X., Wang, W., Pan, H., Yin, W., Zhu, T., Huang, X., & Shan, H. (2021). Macrophage biomimetic nanocarriers for anti-inflammation and targeted antiviral treatment in COVID-19. *Journal of Nanobiotechnology*, *19*(1), 173. crossref

Tavakolpour, S., Mahmoudi, H., Mirzazadeh, A., Balighi, K., Darabi-Monadi, S., Hatami, S., GhasemiAdl, M., & Daneshpazhooh, M. (2020). Pathogenic and protective roles of cytokines in pemphigus: A systematic review. *Cytokine*, *129*, 155026. crossref

Tian, B., Gao, F., Fock, J., Dufva, M., & Hansen, M. F. (2020). Homogeneous circle-to-circle amplification for real-time optomagnetic detection of SARS-CoV-2 RdRp coding sequence. *Biosensors and Bioelectronics*, *165*, 112356.crossref

Tousian, B., & Khosravi, A. R. (2023). Chitosan-based pulmonary particulate systems for anticancer and antiviral drug carriers: A promising delivery for COVID-19 vaccines. *Results in Chemistry*, *6*, 101146. crossref

Trougakos, I. P., Stamatelopoulos, K., Terpos, E., Tsitsilonis, O. E., Aivalioti, E., Paraskevis, D., Kastritis, E., Pavlakis, G. N., & Dimopoulos, M. A. (2021). Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications. *Journal of Biomedical Science*, *28*(1), 9. crossref

Unal, M. A., Bayrakdar, F., Nazir, H., Besbinar, O., Gurcan, C., Lozano, N., Arellano, L. M., Yalcin, S., Panatli, O., Celik, D., Alkaya, D., Agan, A., Fusco, L., Suzuk Yildiz, S., Delogu, L. G., Akcali, K. C., Kostarelos, K., & Yilmazer, A. (2021). Graphene Oxide Nanosheets Interact and Interfere with SARS-CoV-2 Surface Proteins and Cell Receptors to Inhibit Infectivity. *Small*, *17*(25). crossref

Vahedifard, F., & Chakravarthy, K. (2021a). Nanomedicine for COVID-19: the role of nanotechnology in the treatment and diagnosis of COVID-19. *Emergent Materials*, *4*(1), 75–99. crossref

Vahedifard, F., & Chakravarthy, K. (2021b). Nanomedicine for COVID-19: the role of nanotechnology in the treatment and diagnosis of COVID-19. *Emergent Materials*, *4*(1), 75–99.crossref

Wan Mahari, W. A., Peng, W., Nam, W. L., Yang, H., Lee, X. Y., Lee, Y. K., Liew, R. K., Ma, N. L., Mohammad, A., Sonne, C., Van Le, Q., Show, P. L., Chen, W.-H., & Lam, S. S. (2020). A review on valorization of oyster mushroom and waste generated in the mushroom cultivation industry. *Journal of Hazardous Materials*, *400*, 123156. crossref

Wang, Z., Zhang, B., Ou, L., Qiu, Q., Wang, L., Bylund, T., Kong, W.-P., Shi, W., Tsybovsky, Y., Wu, L., Zhou, Q., Chaudhary, R., Choe, M., Dickey, T. H., El Anbari, M., Olia, A. S., Rawi, R., Teng, I.-T., Wang, D., … Kwong, P. D. (2023). Extraordinary Titer and Broad Anti-SARS-CoV-2 Neutralization Induced by Stabilized RBD Nanoparticles from Strain BA.5. *Vaccines*, *12*(1), 37. crossref

Wibowo, Y. G., Ramadan, B. S., Taher, T., & Khairurrijal, K. (2024). Advancements of Nanotechnology and Nanomaterials in Environmental and Human Protection for Combatting the COVID-19 During and Post-pandemic Era: A Comprehensive Scientific Review. *Biomedical Materials & Devices*, *2*(1), 34–57. crossref

Wieler, L., Vittos, O., Mukherjee, N., & Sarkar, S. (2023). Reduction in the COVID-19 pneumonia case fatality rate by silver nanoparticles: A randomized case study. *Heliyon*, *9*(3), e14419. crossref

Wrapp, D. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, *367*.crossref

Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*, *323*.

Xu, C., Lei, C., Hosseinpour, S., Ivanovski, S., Walsh, L. J., & Khademhosseini, A. (2022). Nanotechnology for the management of COVID-19 during the pandemic and in the post-pandemic era. *National Science Review*, *9*(10). crossref

Yasamineh, S., Kalajahi, H. G., Yasamineh, P., Yazdani, Y., Gholizadeh, O., Tabatabaie, R., Afkhami, H., Davodabadi, F., farkhad, A. K., Pahlevan, D., Firouzi-Amandi, A., Nejati-Koshki, K., & Dadashpour, M. (2022). An overview on nanoparticle-based strategies to fight viral infections with a focus on COVID-19. *Journal of Nanobiotechnology*, *20*(1), 440. crossref

Yee Kuen, C., & Masarudin, M. J. (2022). Chitosan Nanoparticle-Based System: A New Insight into the Promising Controlled Release System for Lung Cancer Treatment. *Molecules*, *27*(2), 473. crossref

Zhang, H., & Zhang, H. (2021). Entry, egress and vertical transmission of SARS-CoV- **2**. *Journal of Molecular Cell Biology*, *13*(3), 168–174. crossref

Zhang, Q., Xiang, R., Huo, S., Zhou, Y., Jiang, S., Wang, Q., & Yu, F. (2021). Molecular mechanism of interaction between SARS-CoV-2 and host cells and interventional therapy. *Signal Transduction and Targeted Therapy*, *6*(1), 233.crossref

Zhang, S., & Zhang, Z. Y. (2007). PTP1B as a drug target: recent developments in PTP1B inhibitor discovery. In *Drug Discovery Today* (Vol. 12, Issues 9–10). crossref

Zhao, Z., Xiao, Y., Xu, L., Liu, Y., Jiang, G., Wang, W., Li, B., Zhu, T., Tan, Q., Tang, L., Zhou, H., Huang, X., & Shan, H. (2021). Glycyrrhizic Acid Nanoparticles as Antiviral and Anti-inflammatory Agents for COVID-19 Treatment. *ACS Applied Materials & Interfaces*, *13*(18), 20995–21006.crossref

Zheng, M., Gao, Y., Wang, G., Song, G., Liu, S., Sun, D., Xu, Y., & Tian, Z. (2020). Functional exhaustion of antiviral lymphocytes in COVID-19 patients. In *Cellular & molecular immunology* (Vol. 17, Issue 5, pp. 533–535).crossref

Zhou, Y., Fu, B., Zheng, X., Wang, D., Zhao, C., qi, Y., Sun, R., Tian, Z., Xu, X., & Wei, H. (2020). Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. *BioRxiv*. crossref

Zhu, N. (2020). A Novel Coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.*, *382*. crossref

Zhu, X., Wang, X., Han, L., Chen, T., Wang, L., Li, H., Li, S., He, L., Fu, X., Chen, S., Xing, M., Chen, H., & Wang, Y. (2020). Multiplex reverse transcription loop-mediated isothermal amplification combined with nanoparticle-based lateral flow biosensor for the diagnosis of COVID-19. *Biosensors and Bioelectronics*, *166*, 112437. crossref

Ziebuhr, J., Thiel, V., & Gorbalenya, A. E. (2001). The autocatalytic release of a putative RNA virus transcription factor from its polyprotein precursor involves two paralogous papain-like proteases that cleave the same peptide bond. *Journal of Biological Chemistry*, *276*(35), 33220–33232.ref

Zou, X., Chen, K., Zou, J., Han, P., Hao, J., & Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine*, *14*(2), 185–192. crossref

Zuo, H., Deng, S., Huang, Z., & Li, H. (2020). Numerical Investigation of Binary Fluid Flow through Propped Fractures by Lattice Boltzmann Method. *International Journal of Geomechanics*, *20*(7). crossref