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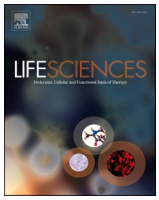

Review article

Various theranostics and immunization strategies based on nanotechnology against Covid-19 pandemic: An interdisciplinary view

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ABSTRACT

COVID-19 pandemic is still a major risk to human civilization. Besides the global immunization policy, more than five lac new cases are documented everyday. Some countries newly implement partial/complete nationwid lockdown to mitigate recurrent community spreading. To avoid the new modified stain of SARS-CoV-2 spreading, some countries imposed any restriction on the movement of the citizens within or outside the country. Effective economical point of care diagnostic and therapeutic strategy is vigorously required to mitigate viral spread. Besides struggling with repurposed medicines, new engineered materials with multiple unique efficacies and specific antiviral potency against SARS-CoV-2 infection may be fruitful to save more lives. Nanotechnology-based engineering strategy sophisticated medicine with specific, effective and nonhazardous delivery mechanism for available repurposed antivirals as well as remedial for associated diseases due to malfeasance in immuno-system *e.g.* hypercytokinaemia, acute respiratory distress syndrome. This review will talk about gloomy but critical areas for nanoscientists to intervene and will showcase about the different laboratory diagnostic, prognostic strategies and their mode of actions. In addition, we speak about SARS-CoV-2 pathophysiology, pathogenicity and host specific interation with special emphasis on altered immuno-system and also perceptualized, copious ways to design prophylactic nanomedicines and next-generation vaccines based on recent findings.

1. Introduction

It is very much true to say reality is stranger than fiction. We had studied a lot on global pandemics in novels, popular cultures, classics and most importantly in scientific journals and books [1]. Our entire generation is experiencing, documenting and victimizing in this devastating planetary massacre and earnestly waiting for a cure. Besides developing self-immunity through adaptive immunity or vaccination [2], a stable and valid therapeutic curative approach may give some hope in this primal morbid situation [3]. This pneumonic disease is well documented as the fifth pandemic after the 1918th Spanish flu, caused by H1N1 influenza A virus [4]. World Health Organization was briefing on a flare-up of unknown pneumatic flu cases in a cluster of operating dealers and vendors of Hunan Seafood market at Wuhan city, Hubei, China on the very last day of 2019 [5]. It is a city of 11 million people- a densely populated, economic and cultural hub with international airport and other well-managed connective transportations [6]. These patients were coming with fever, malaise, dry cough and dyspnea [7]. 59 cases were noted on 5th January and no one was died among them [8]. But the scenario was changed to ferocity after ten days, WHO broadcasted 282 confirmed cases among them, 4 persons in Japan, South Korea and Thailand [9] along with six death, 51 severely ill and 12 were in critical care unit in Wuhan [10]. It was primarily termed as Wuhan pneumonia by the press. This errhine virus was characterized on 7thJanuary [11], 10th January viral RNA was sequenced through NGS [12] and was published on 12th January [13]. On that day, WHO declared causative contagion is a new strain of coronavirus and temporarily coined this virus as a novel coronavirus (2019-nCov) and the pernicious malady is officially named as coronavirus disease 2019 (COVID-19) on 12 February 2020 [15]. On second March 2020, International Committee

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on Taxonomy of Virus (IGTV) placed this virus into β-coronavirus genus, Sarbecovirus subgenus, severe acute respiratory syndrome-related coronavirus species and the stain is coined as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) [16]. In the recent twenty years, another two CoVs epidemics have occurred [17]. SARS-CoV evoked a devastating epidemic get rolling from China and spread out in 24 countries with approximately 8000 cases and 800 deaths (morbidity rate of 9.6%) [18,19], and the MERS-CoV that outspread from Saudi Arabia and has approximately 2500 documented cases and 800 deaths (mortality rate of 35%) and still count as sporadic phase [19,20]. On 30th January 2020, due to high contagious nature and quickly mushrooming worldwide, WHO declared a Public Health Emergency of International Concern [21]. On that very day, SARS-Cov-2 was documented in 18 different countries [20] with human to human transmission cases and a total number of 9439 active patients among them 213 persons was died [22]. On 11th March 2020, after long assessment and characterization WHO notified Covid-19 as a new viral pandemic, following 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2) and 2009 Pandemic flu (H1N1) [23], which caused an estimated 50 million, 1.5 million, 1 million, and 300,000 human deaths [24], sequentially. But, within a few months, presently this new strain of coronavirus sickens 43,457,902 individuals and ceased 1,160,573 lives in 235 countries [25]. At present most affected countries like USA, Brazil, India, Russia, UK, Spain, and Italy. Every day near about 2 to 2.5 lakh cases was newly documented and roughly 4 to 5 thousand people were died [26]. Numbers are increasing every day and historically breaking the new record of morbidity regularly. Global mortality rate is 4.8% [27]. Besides fever (85.6%), cough (68.7%) and fatigue (39.4%) [28], which probably are the most important symptoms for COVID-19, some other symptoms are noted like dyspnea, headache, poor appetite, breathing panting, sore throat, vomiting, diarrhea, abdominal pain [29]. Recent patient report shows comorbidity is an important factor [30], over the situation and it's a high risk for heart [31], kidney, liver [32], G.I. tract [33], brain (encephalitis) [34], eye (conjunctivitis) [35,36]. Excluding SARS-Cov-2, there are four classes of coronavirus with low pathogenicity causes responsible human endemic: HCoV-OC43, HCoV-HKU1, HCoV-NL63 and HCoV-229E [37] and there is no remedial therapeutics or immunization are blessed against any human transmitting coronavirus [38] (Fig. 1).

2. Well-practiced and emerging possibilities for detecting Covid-19 infection

Symptoms of COVID-19 are very much imprecise and mimicking with common cold infection and other flu. Reports [39] depicted approximately 44% of 1099 COVID-19 patients in China admitted to hospital with a fever, whereas, 89% covid-19 positive patients express fever symptoms after hospital admission. Other symptoms like cough (68%), fatigue (38%), shortness of breath (19%), and sputum production (34%) are noticed and popularly used as diagnostic tools for other respiratory cardiothoracic diseases [39,40].

In this scenario protein, nucleic acid testing and computed tomography scan (CT scan) based imaging may be used as a potential tool for pointing out Covid-19 patients (symptomatic and asymptomatic both) and practice mass population screening to restrict its virulent spreading [41]. Molecular testing like nucleic acid and immunoprotein testing more accurately identifies a specific causative pathogen [42]. Designing molecular techniques is depending upon understanding two thumbs-one is understanding viral genomic and proteomic sequence [43]. Another is the expression of protein/genes and their cumulative or respective activity within the host throughout the contagion and lurgy tenure [44]. The proteomic and genomic structure of SARS-Cov-2 is exposed but its pathogenicity with the host immune system is still within the dilemma. WHO confirmed about 104 different strains [45], which were accessed and sequenced by using the Illumina model, that based on sequence by synthesis method [46] and Oxford nanopore sequencing model, *i.e.* encompass translocating DNA molecule within protein pore resulting in a voltage shift to identify DNA sequence [47], till mid of February 2020. Both genome sequencing is equally requisite to researchers for developing accurate primers and probe sequences for PCR [48] and other nucleic acid-based tests and kits [49]. RT-PCR diagnostic kits were designed on the SARS-Cov-2 genome sequence. Reverse transcription of viral RNA was templated into cDNA. Specific region is sequentially multiplying [50]. After a thorough assessment, researchers came upon with three conserved sequences - (1) RNA-dependent RNA polymerase gene (RdRP) gene, *i.e.* located at ORF1ab region, (2) the Envelop protein or E gene and (3) the nucleocapsid protein gene or N gene. Among the three gene E and RdRP genes have excessive detection sensitivity (3.6–3.9 copies/reaction) whereas, the N gene has lesser (8.3 copies/reaction) [51]. For specificity of the test, reaction is designed against two targets, one is for general coronavirus and another one is exclusively for SARS-CoV-2. Corman aligned a number of SARS-related viral genome sequences to develop a set of primers and probes for kits [12].

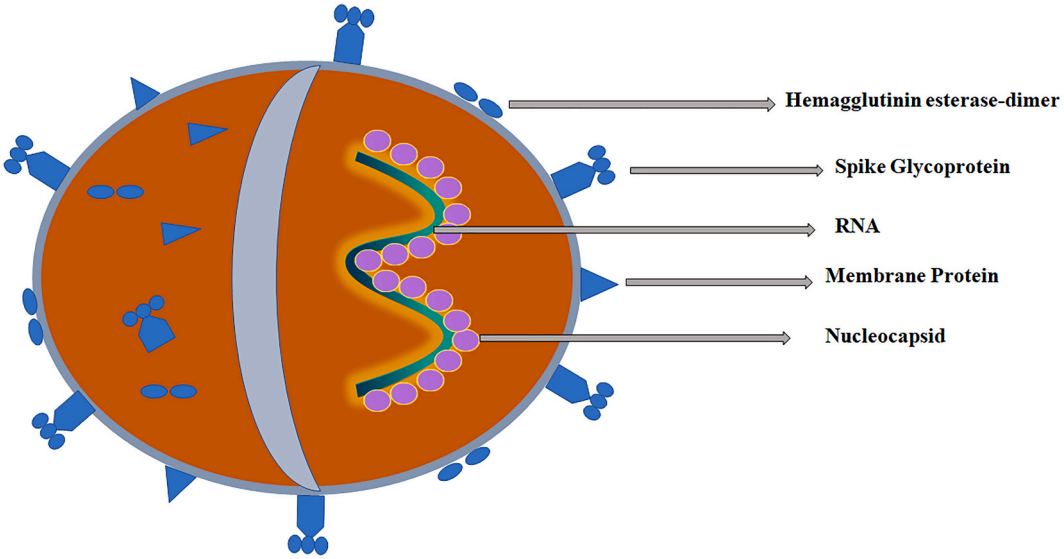

Fig. 1. Diagrammatic representation of SARS-CoV-2 structure illustrating four main structural proteins and RNA.

Still, eleven nucleic acid-based methods and eight antibody-based techniques had used and accepted by the National Medical Products Administration (NMPA) for SARS-CoV2 detection [48].

3. Clinical approaches for better prognosis of Covid-19 - a fortuner in site

Center for disease control and prevention (USA) appraised with one-step reverse transcription polymerase chain reaction (RT-PCR assay) [53]. That can evaluate specific quantitative information on SARS-CoV-2. To increase more accuracy in screening, three-step screening is instigated. One is to detect the E gene region of all SARS-related viruses. Next is against the RdRP gene by using two different probes and two different primers, exclusive to the step one positive sample as per Chaite, Germany [54]. On other hand, Sheikhzadeh et al. nominated a minutely different strategy, by using primers of the N gene for initial screening and ORFb gene for authentication [51,55,56]. Antibody testing and CT scan are used as temporary tools for clinical diagnosis. Chest CT scan followed by radiological analysis revealed, abnormal features, that can be a diagnostic tool [57]. Normal CT scan can able to find 56% covid-19 patients in early stages (0–2 days) [58]. Extreme lung involvement is usually highest near 10th day after visualizing the first symptom. Researchers documented distinguished ground-glass opacity within four days and severity is gradually increased with time and irregular shaped crazy-paving pattern is visualized in CT images [58]. Those images maybe resemble with pneumonic lung injury and lower specificity (25%), but a cardinal life-supporting tool for both symptomatic and asymptotic covid-19 patient to qualitative analysis of thoracic and pulmonary damage [60] (Fig. 2).

Both RT-PCR and CT scan are eminent and high-priced techniques that required well-equipped laboratory facilities and trained technicians. But they were unable to detect virion, after the infection tenure [61]. Multiplex panel and serological analysis with proteins can facilitate to point-out both patients and recovered individuals [62]. These point-to-care tests were very much economical and a very much useful tool for mass scale primary screening in areas with underdeveloped laboratory facility or lack of RT-PCR kits [63]. Loop-mediated isothermal amplification technique (LAMP) is a newly developed high sensitivity nanoprobe mediated technique, can detect SARS-CoV-2 nucleic acids accurately [64]. Reverse transcriptase LAMP (RT-LAMP) uses DNA polymerase and four to six primers to recognize and tie-up with six specific target regions on the viral genome [65]. This technique is operated with two inner and two outer primers [66]. Due to an increased primer number than RT-PCR, this simple-operative technique shows greater accuracy without thermal cycles and modern laboratory set-up [67]. Results can be visualized easily with minimal background noise [68]. But primer standardization is needed. Isothermal amplification techniques can be multiplexed at the amplification stage and may be used as polymeric beads with specific optical identity for unique barcoding specific for capturing unique genome or antigen and emits detectable fluorescence [49]. Like cystic fibrosis, designing a specific barcoded-multiplex panel against the Covid-19 genome is commercially beneficial and provides accurate results in huge scale tests in a quicker time with lesser infrastructure [68]. As it is primarily designed for research purposes, it had some difficulty with readout and interpret complex barcode emissions [49]. Researchers now using quantum dots for barcoding to more financially inexpensive but technically (91–95%) accurate instrument for diagnosis [72]. That can be excited through

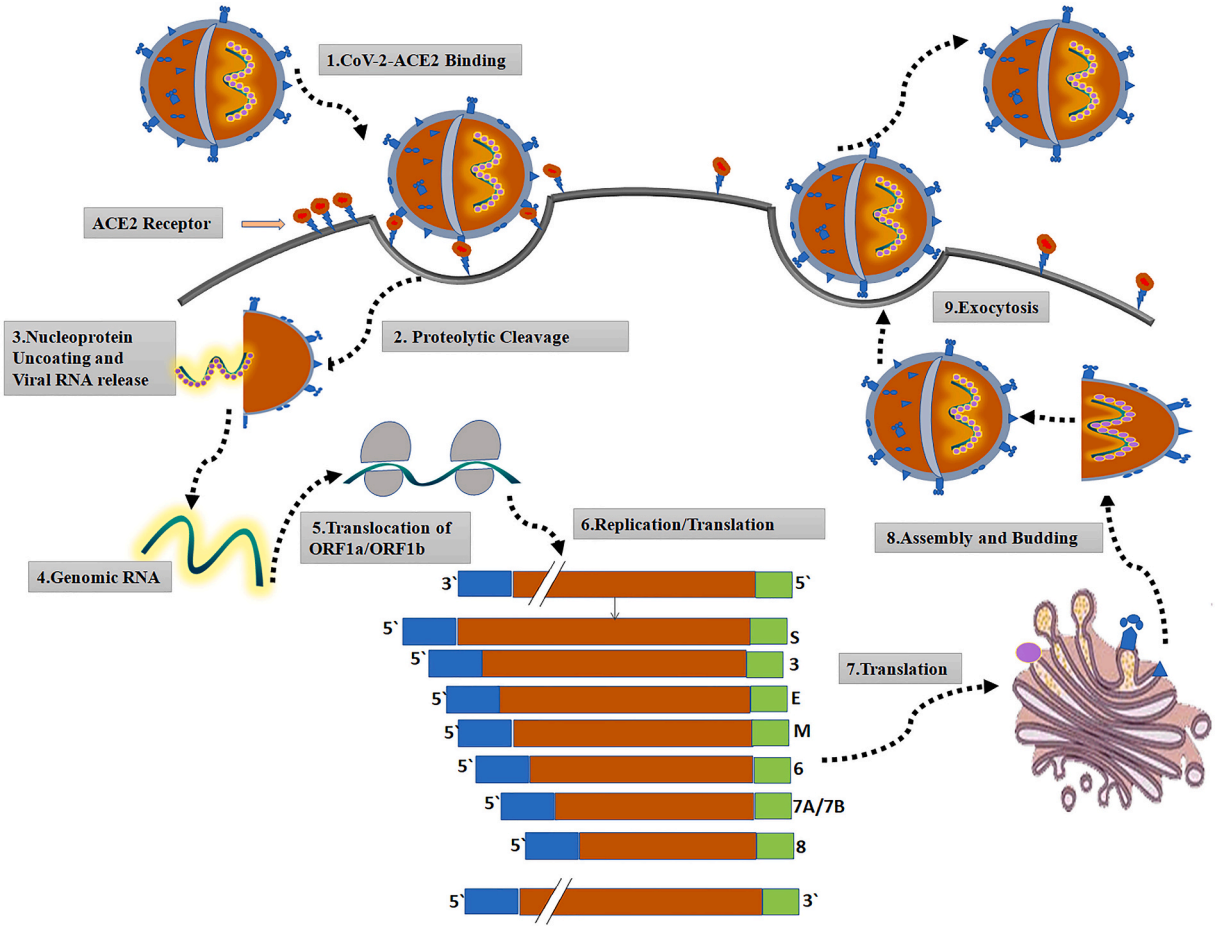

Fig. 2. Pictorial representation of key steps for entry and multiplication mechanism of SARS-CoV-2.

battery and emission can be captured and analyzed with a smartphone with camera [73]. SHERLOCK, an efficient technique, that can detect as low as 2000 copies/ml in serum proven its importance in Zika virus and can be used for Covid-19 diagnosis [74]. Covid-19 patients have depicted a sharp increase in C-reactive protein [75], D-dimer and lower platelets [76], lymphocytes and leukocytes [77]. Patients also elicited SARS-CoV2 IgG and IgM antibodies after 5–7 days of virus inoculation [78]. Therefore designing multiplex test with both antibody and small molecular markers can be beneficial for huge population screening [79]. The lateral flow antigen detection method is a very easy and popular assay. This wide commercially available nitrocellulose membrane-based detection technique used gold nanoparticles for visualization. It contains two lines, one is coated with capture antibodies and the others with coated with gold nanoparticle antibody conjugates. Specific antigens from patients sample used as antigen source and flows to capturing antibody, which is observed by color illuminated by gold nanoparticle in both lines [42]. The qualitative result is visualized in red and blue colors [81]. This method proved a high clinical sensitivity, specificity and accuracy (57%, 100% and 69% respectively) for IgM and 81%, 100% and 86% for IgG antibody [82]. RT-LAMP mediated lateral flow assay effectively detects nucleic acid (previously used in MERS-CoV) [83]. Therefore design, develop and commercialize lateral flow assays against SARS-CoV-2 nucleic acid, IgG and IgM may be useful for mass scale point of care testing where sophisticated Covid-19 testing is impossible. HIV testing microfluidic based attachment device for smartphone, successfully proved clinical sensitivity (100%) [84] and specificity (87%) [85]. Adopting this nano based detection method and design a similar device targeting RNA and protein sequences unique for SARS-CoV-2, may be very useful [86]. Besides these abovementioned well developed and developing methods, a nano based thermal monitoring device is also beneficial for cheap and frequent screening [87]. At this global pandemic scenario, ready to use, a swift and economically affordable diagnostic method with high accuracy was urgently needed for rapid testing followed by proper administration to restrict further outbreak. Recently, clustered regularly interspaced short palindromic repeats (CRISPR) based unique point-of-care diagnostic kit specific for Covid-19 was introduced. FnCas9 Editor Linked Uniform Detection Assay simply FELUDA, can readout SARS-CoV2 nucleotide sequence, nucleobases and their variants through employing a highly accurate FnCas9 based enzymatic binding and subsequent cleavage. FELUDA can detect low copy numbers of nucleic acid and accurately detects single-nucleotide variations (SNVs). Affinity based FELUDA assay may be a game-changer in the field of rapid point-of-care diagnostic even in developing panels of mutation scanning siRNA on a microchip for simultaneous and larger population screening. FELUA was developed by CSIR-IGIB, India and will be marketed by TATA Sons., received regulatory approvals from the Drug Controller General of India. It has been reported as high-quality benchmarks with 96 percent sensitivity and 98 percent specificity for detecting the novel coronavirus [88,89] (Fig. 3).

4. Anatomy and life cycle of SARS-CoV-2

SARS-CoV-2 is a pleomorphic, encapsulated, spherical virus with positive sensed single-stranded ribonucleic acid as a genetic material [90]. Observation with transmission electric microscopical (TEM) studies illustrates an 80–160 nm spherical nano-sized virion with well-organized nucleic acid bilayer with club-shaped spike proteins on their surface [91]. Genomic RNA is 26.4–31.7 kb in size [92], possibly the largest among all known RNA viruses [93]. RNA is linked with nucleoprotein and hemagglutinin-esterase protein [94]. Viral genome encoded structural proteins like membrane glycoproteins (M), envelope proteins (E), nucleocapsid proteins (N) and spike glycoproteins (S) occurs in 5′-3′–S, E, M, N order [94]. Papain-like protease (PLpro), coronavirus main protease (3CLpro) and proteins for specific replication are translated from specific genomic regions [95]. CoVs genome encodes some accessory proteins like HE protein, 3a/b protein, 4a/b proteins [96]. A Covid-19 genome contains a minimum of 6 Open reading frames (ORFs), that helps in sub-genomic mRNA translations like 3CLpro, PLpro and Mpro [97]. Three to four structural proteins are predominant in coronavirus membrane [98,99]. Membrane glycoprotein is a transmembrane protein three time spans membrane bilayer [100]. A typical CoV contains six ORFs in its genome. All the accessory and structural proteins are translated from the sgRNAs of CoVs. Four main structural proteins are encoded by ORFs 10, 11 on one-third of the genome near the 3′-terminus. The phenotypic and genetic structure is vital for COVID-19 pathogenesis. COOH- terminal domain is within virion and NH2-terminal domain is located outward [101]. It maintains the membrane integrity of virus. Spike glycoprotein is a polymer made transmembrane protein with 7 mm wide head and 23 nm long body, that forms a homotrimeric structure peek out from the viral surface. The entry of coronavirus into host cells is mediated by spike glycoprotein. ORF 1a and 1b encode replication enzymes consisting of 16 non-structural proteins (nsp1–16) that are highly conserved among the coronaviruses. Main protease (Mpro, also known as 3CLpro) is one of the important nsp encoded by ORF 1a and 1b, plays an essential role in the processing of polyproteins and control the replication of coronavirus [102]. Spike proteins have two host-binding functional subunits [103]. S1 subunit is responsible for binding with host cell receptors through the receptor-binding domain [104]. Receptor binding enables conformation changes in the S2 subunit that permits fusion peptide to enter into host cell membrane [105]. HR1 or the heptad region1 located in the S2 subunit forms a homotrimeric orientation that opens three highly conserved hydrophobic grooves on the outer surface region that enable an association with heptad repeat 2 (HR2). This six-helix bundle (6-HB)

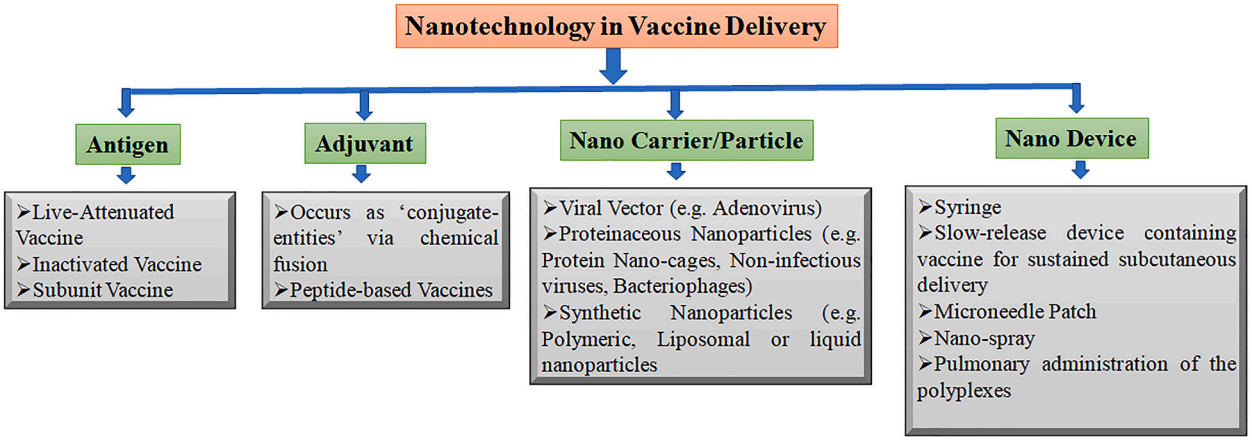

Fig. 3. Efficacy of nanotechnology in various field of vaccine development against Covid-19.

structure is set up over the fusion process and helps bring the viral and cellular membranes into close proximity for viral fusion and entry into target cells. Envelop protein is the smallest in size and performed a structural role in membrane assembly and budding [101]. Preliminary conformational investigation of the receptor (ACE2) binding site of the spike protein is accomplished. This investigation is suggesting that while it is somewhat conserved, it appears to be more variable than KRSFIEDLLFNKV [107]. Lastly, nucleocapsid protein is copiously expressed, dominant, very much stable and highly immunogenic protein. Usually attached with siRNA [108]. Targeting SARS-CoV-2 surface S protein by using neutralizing antibodies (nAbs) is a good remedial to attenuate infection by crosslinking the virus through developing nAbs-sometimes nAbs developed for other coronavirus shows effectivity in the present scenario due to structural similarities [104]. Nano-packaging nAbs have increased adjuvant functions and better efficacy by compiling with other effective immuno-suppressor and repurposed anti-viral medicines [110].

Shang J [104,110] deciphered underplayed molecular entry mechanism of SARS-CoV-2 within the human cells. Like SARS-CoV, SARS-CoV-2 recognize and bind with human ACE2 (hACE2) receptor but with much higher affinity [111,112]. Crystal structure of SARS-CoV-2 attached with hACE2 demonstrated some minute but practically notable differences, that favor receptor-binding domain (RBD) of this new virus have a significantly higher binding affinity due to its spikes are pre-activated with furin and hidden RBDs potentiate not only much efficient receptor binding and cellular engulfing but also evading immune system [113]. It was previously examined and documented that the amino acid GLN498 of SARS-CoV-2 interacts with ACE2 at the ASP38, TYR41, GLN42, LEU45, and LYS353 amino acids, while LEU455 of the virus has interaction with ASP30, LYS31, and HIS34 [114]. Similar interlinkage was noted in SARS-CoV-2, PHE486 with GLN24, LEU79, MET82, TYR83, and LEU472. GLN493 was interlinked with ACE2 LYS31 and HIS34 and forms a H-bond with GLU35 [115]. The amino acid ASN501 has a similar type of interaction with ACE2 LYS353, GLY354 and ASP355, while H-bond interaction was visualized with TYR41. Another similar study was also deciphered LYS417 amino acid of SARS-CoV-2 bridged a salt bridge interaction with ASP30 of ACE2. This positively charged patch facilitated electrostatic potential on the surface of RBD [116], which potentiates the higher binding affinity of SARS-Cov-2.

Human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) split the spike proteins and helps receptor binding [117]. ACE2 receptors, the major functional receptor for SARS-CoV-2 infection, are frequently found in every part of both lung and small intestine epithelium, which make them more prone to damage. SARS-Cov-2 infection is aided with furin-mediated pre-cleavage at S1/S2 site in infected cells [118]. That promotes, TMPRSS2 and TMPRSS4, the two mucosa specific serine 2, mediated fucogenic activity and stimulated its entry into the host cell [115]. ACE2 is a dimer of two sub-units. Among them, an arch shaped peptidase helix interplayed polar interaction with the RBD domain of SARS-Cov-2 spike protein [115]. Another helix-loops sub-unit attaches with antiparallel strands and modulate peptidase domain to RBD. Those peptidase domains of ACE2 are useful candidates for designing novel therapeutic inhibitors [119].

Chloroquine and hydroxychloroquine, two very old and popular anti-malarial, anti-inflammatory and anti-thrombosis [120] medicine, were efficiently 90% suppress SARS-Cov-2 infection in Vero E6 cells [121]. Similarly, it was supported by several *in vitro* as well as *in vivo* studies and clinical trials [122]. Being the first potent anti-Covid-19 agent, chloroquine and hydroxychloroquine, *i.e.* less toxic but more effective, have been portrayed as a gamechanger medicine and attracted global popularity but also trolled as dangerous gibberish [123]. SARS-CoV-2 interacts and endocytosed within a human host cell is mediated by angiotensin-converting enzyme-2 or ACE2. It is well reported in Covid-19 as like other viral infections ACE2 expression is tremendously augmented [124]. Chloroquine and hydroxychloroquine reduce glycosylation of ACE2 by increasing endosomal pH through increasing pH of acidic vesicles like endosomes, endolysosomes, Golgi bodies and lysosomes [125]. That effectively terminates spike protein biding of the causative virus, cell fusion and contagious process. Coincidently, chloroquine and hydroxychloroquine, as an established immuno-suppressor, can restrict hypercytokinaemia by suppressing IL-1β, IL-6, IL-12 [126]. They also suppress acid dependent protease, TLRs, IFN-1, and receptor mediated autophagy [127]. Covid-19 patients with acute respiratory distress syndrome were recovered in significant numbers with hydroxychloroquine and chloroquine treatment and the success rate is increased in combinational treatment with azithromycin in clinical trials. Besides their efficacy, those two medicines have a long list of side effects due to toxicity in the GI tract, liver, kidney, heart, retina, spleen, cardiac muscles, systematic immunity and metabolism, some of them are chronic even fetal. Previously chloroquine and hydroxychloroquine are used in studying cellular nano-medicine uptake mechanisms. Nobel metal nanoparticle AuNP and AgNP coated with hydroxychloroquine and chloroquine have the very least amount of toxic effects and other side effects and increases tissue specificity [128]. Polymeric iron nano-chloroquine phosphate is previously synthesized by Muhmmad Usman and it shows high efficacy and low ramification in malaria treatment [129] by interfering endosome-lysosome fusion, general endocytosis trafficking, calthrine coated endocytosis and receptor mediated endocytosis. Polymeric nanosphere with azithromycin and chloroquine phosphate was previously developed and shows its efficacy as a combinational therapy against malaria. Therefore, these nano-medicines, due to similar effectivity, can be used as a singular or combinational therapeutics on Covid-19 patients (Fig. 4).

Camostat mesilate, is a protease inhibitor, developed by the Japanese in 1980s and used as an effective medicine in chronic pancreatitis and reflux esophagitis treatment. Previous studies on camostat mesilate treatment in SARS-CoV infected animal model significantly increase survival rate (≅ 60%). Underneath molecular study depicted, this medicine can bind and blocked endosomal protease activity of TMPRSS2, through which SARS-CoV-2 enters into the host cell like MARS and SARS [130]. A similar effect was also noted with ammonium chloride treatment in an infected *in vitro* study. Combinational therapy with E-64, an inhibitor for cathepsin B/L, camostat mesilate can inhibit endosomal protease mediated Covid-19 virus entry effectively by restricting both proteases. Camostat mesilate, within a nano packaging in nanosphere previously noted as high efficacy single and combinational medicine [131] in various diseases like pancreatic fibrosis [132]. Therefore, developing particular nano based delivery system through using these medicines may be a safe, unhazardous, therapeutic approach against Covid-19.

After ACE2 receptor and spike protein mediated fusion of viral envelop with cell membrane followed by endocytosis of hole membrane bound virion within the human host cell, the viral RNA released into the host cytoplasm. Two viral replicase poly-proteins namely pp1a and 1ab are translated from viral genomic DNA. These newly translated poly-proteins are cleaved by proteases with chymotrypsin-like activity into a small complex that triggers (−) RNA generation through both replication and transcription processes. By using (−) RNA genome as a template, new full length (+) RNA is produced through replication. A pack of 7–9 sub-genomic mRNAs including all codons is required to encode structural proteins like S, M and N by using discontinuous transcription method. Newly transcribed mRNAs are translated and viral nucleocapsids are amalgamated with genomic RNA and R proteins. After that genomic compounds are assembled with structural proteins and come with a packed virion formation within the lumen region of endoplasmic reticulum and Golgi apparatus. Complete virus particles then spread from the infected cells through exocytosis. These newly released viruses are capable of infect neighboring cells, tissues and organs like lower respiratory tract, liver, kidney, small intestine and even T cells. Virions are multiply in number and can capable of crucial

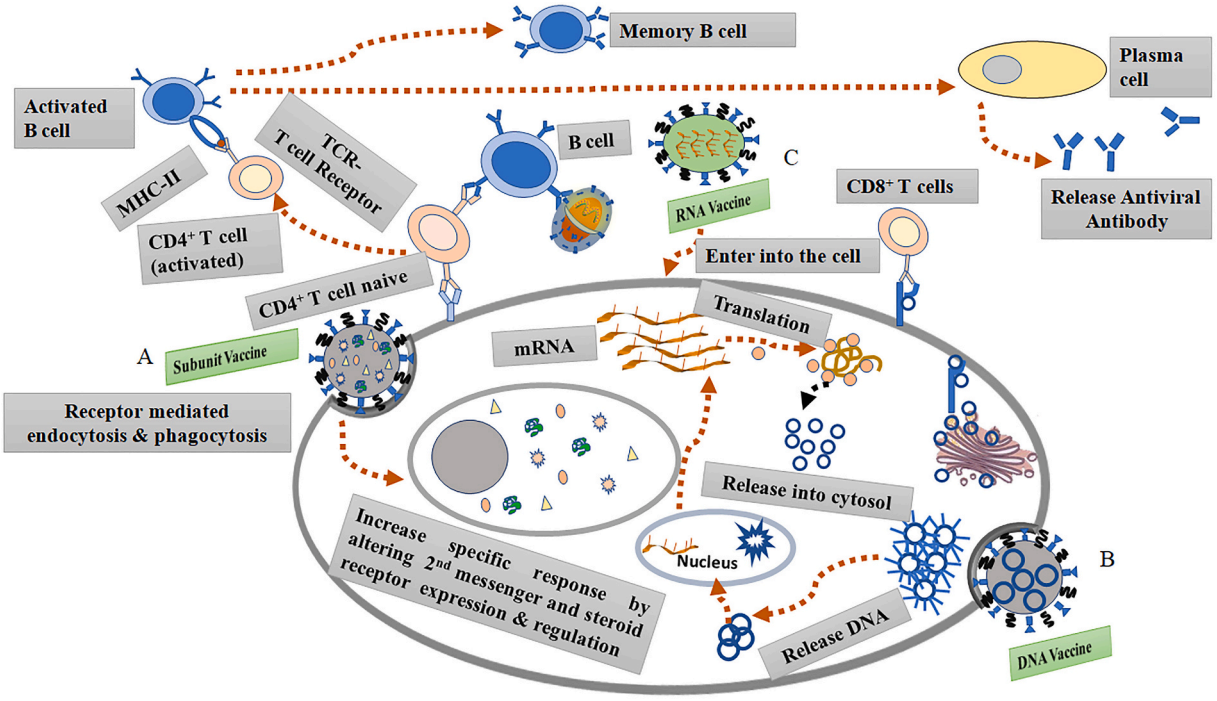

Fig. 4. Schematic representation of vaccine mechanism developed by using nano platform. (A) Representation probable mode of action of subunit vaccine. Key steps of DNA vaccines (B) and RNA vaccine.

damage to infected organs. That can be diagnosed as the symptomatic sign for infected individuals and this basic transfection procedure is still valid for the second web of Covid-19 pandemic.

Umifenovir-marketed as Arbidol, a small indole derived molecule, is a wide spectrum antiviral medicine popular in China and Russia for the remedy of influenza A/B and other respiratory infections like para-influenza, avian influenza virus A and SARS-CoV. A survey by Wang [133] demonstrated Umifenovir treatment increases patient improvement and survival rate. This observation was supported by one *in vitro* finding that portrayed inhibition of SARS-CoV-2 infection within the host by interacting multiple stages of host lifecycle as well as block viral entry by impeding viral attachment through proteolytic cleavage and detached from early endosome as well as endolysosomes [134]. Nano-crystallization of Umifenovir may be a better option for oral administration against Covid-19.

Baricitinib, an anti-inflammatory drug, can inhibit Janus kinase and is approved for rheumatoid arthritis treatment. It was documented in Italy, Baricitinib treatment, in 12 patients, significantly improved all clinical characteristics and respiratory functions within one to two weeks. Reduced C-reactive protein (CRP) and fever, the validated Modified Early Warning Score (MEWS), peripheral capillary oxygen saturation (SpO2), the ratio of the partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO2/FiO2) status was notably improved. None of them required any critical care support [134]. Researchers established viral entry is associated with calthrine mediated endocytosis with the help of AP2 associated protein kinase1 (AAK1) and G-associated protein kinase (GAK). High plasma concentration of Baricitinib can efficiently not only suppress all three endocytosis processes of Covid-19 entry but also inhibit inflammation and excess cytokine production by blocking JAK1/2 [132]. Artificial intelligence, AI-based algorithm study supported above findings and demonstrated therapeutic efficacy of Baricitinib is higher than other JAK/NAK inhibitors like fedratinib, ruxolitinib [139]. Presently few clinical trials as single or combinational dose (only Baricitinib or Baricitinib + fedratinib/ruxolitinib) of 2–4 mg/day for two weeks can establish its better efficacy against SARS-CoV-2 infection. Poly-lactic-*co*-glycolic-acid-nanoparticle of Baricitinib is a FDA approved biodegradable, semi-synthetic, polymer developed from nano-precipitation method that can show 93% sustained release during 24 h and increase solubility rate [139] in *in vitro* studies. So nano-encapsulation of this drug may more effectively inhibit Covid-19 entry. According to recent reports on self-assembled nanoparticles and surface functionalized gold nanoparticles documented as a good therapeutic index by restricting SARS-CoV-2 entry [141]. Aurora B kinase inhibitor loaded PLGA nanoparticles revealed increased efficacy and reduced toxicity as compared to its free form which produced intolerable side effects in phase II clinical trials [142]. There are also some lipid nanoparticles encapsulated mRNA, which has shown excellent therapeutic properties on SARS-CoV-2, in clinical trials [143]. Researchers have recently reported the use of cholesterol-modified hydroxychloroquine (Chol-HCQ) loaded liposomes that lowered the dose and toxicity of hydroxychloroquine and also inhibited the proliferation of rat lung fibroblasts, thereby, reducing pulmonary fibrosis. This strategy can be adopted to have dual benefits in SAR-COV-2 patients, which show viral load and pulmonary fibrosis [144,145]. Iron oxide nanoparticles (IONPs) were previously approved by the US food and drug administration (FDA) for anemia treatment and studies have also demonstrated its antiviral activity *in vitro*. A promising *in silico* based docking study elucidated interaction potency of IONPs (Fe_2O_3 and Fe_3O_4) with the spike protein receptor binding domain (S1-RBD) of SARS-CoV-2. Similar docking analysis was also performed with hepatitis C virus (HCV) glycoproteins E1 and E2. Comparing both studies revealed that both Fe_2O_3 and Fe_3O_4 interacted efficiently with the SARS-CoV-2 S1-RBD and HCV glycoproteins, E1 and E2. Fe_3O_4 formed a more stable complex with S1-RBD whereas Fe_2O_3 favored HCV E1 and E2. These interactions of IONPs are expected to be associated with viral proteins conformational changes and hence, viral inactivation [146].

Remdesivir, Galidesivir, Sofosbuvir, Tenofovir, Ribavirin are popular FDA approved antiviral drugs popularly use in many viral infections like paramyxoviruses, pneumonia viruses, filoviruses [147] and that can binds with SARS-CoV-2-RNA dependent RNA polymerase and inhibit viral genome multiplication [148]. Remdesivir, a nucleoside analog can suppress Covid-19 replication in *in vitro* culture and animal models [133]. Clinical trials within 237 patients do not satisfy eligibility criteria

for a single medicine. But in combination with Favipiravir (Emory Institute for Drug Development, EIDD-2801, 1931) and dexamethasone may be a useful way to treat Covid-19. Favipiravir has already established its high efficacy as nano encapsulated medicine against H1N1 treatment [150]. Similarly, combinational therapy within nanosphere packaging of abovementioned drugs may be a good efficient way in Covid-19 treatment. EIDD-2801, a ribonucleoside analog, previously established significant potentiality against RNA virus infections like influenza, Ebola. Various epithelial cell lines and mice models are infused with MERS, SARS and SARS-CoV-2 and the report noted early treatment can reduce viral replication and restrict lung injury. Analysis with a single drug in SARS-CoV-2 infected HAE, Calu-lung cell and mice model depicted a serious reduction in viral loads by stopping replication through affecting RNA dependent RNA polymerase and leading to error catastrophe by initiating numerous error in the replication process. That increase mutation rate and hampered RNA synthesis and required protein expression [151].

5. Altering host immune response by SARS-CoV-2 infection induces fetal abnormalities

It is usual to turn on the host immune system against every antigen including pathogen. Similar to other pathogenic interactions SARS-CoV-2 elevated innate and adaptive immune response and it is sustained damage to local and systematic tissue by activating cellular and humoral responses [152]. When virus enters into the host body, a highly efficient innate immune response is played as the first line of defense. Extensively elevated innate immunity mediated response, surprisingly imbalanced adaptive immune response, which releases monstrous amount of cytokine and chemokines [153]. So-called cytokine storm or hypercytokinaemia is lethal and this uncontrolled phenomenon is definitely due to complete breakdown of host immune mechanism, results badly injure lung as well as other organs. That, in turn develops acute respiratory distress syndrome, septic shock and multiple organ failure and systematic damages like renal, cardiovascular, neuroendocrine, gastric and intestinal system [154]. Statistical documentation revealed, only 5% of covid-19 patients suffer this much severity and the majority (80%) patient population have only mild to moderate symptoms [155]. At the time of viral infection, pattern recognition receptors, like TLRs (7 and 8) in ssRNA, RLRs, NLRs of the innate immune system recognize the pathogenic virus. All are well expressed in epithelial cells and alveolar macrophages [156]. Receptor recognition induces abductor protein mediated transcription factors like IRF, NF-KB, AP-1, antiviral chemokines and interferons [157]. That, in turn, attracts cells eminent factors of the innate immune system like polynuclear leukocytes, monocytes, NK cells, dendritic cells, MIG-10, IP-10, MCP1, MIP1A, G-CSF, GM-CSF, CCL3, tumor necrosis factor-α (TNF-α) and various interleukins like IL-1β, IL-2, IL-6, IL-8, IL-10, IL-17 [158,159]. Significant similarity is also noted in the autopsy report of dead Covid-19 patients [160]. SARS-CoV-2 badly targets both types I and type II pneumocytes, alveolar macrophages. Studies of Blanco-Melo elucidated SARS-CoV-2 activates a peculiar phenomenon by reduced viral immuno-mediators like IFN-I, IFN-II and IFN-III response and significantly induced IL-1B, IL-6, TNF, IL1RA and other chemokines [161]. Serum report of critical Covid-19 patients has supported the above findings [162]. These severe and deceased reports also pointed to a significant decrease in the numbers of circulating $CD4^+$ cells, $CD8^+$ cells, NK cells, B cells, basophils, eosinophils and monocytes. That results hyperinflammatory pathogenesis like response [163]. Based on multicenter cohort study, by Huang, I revealed severe Covid-19 patients with extreme Hs-CRP and pro-calcitonin level in serum has a high threat of mortality due to lung injury and multi-organ failure [164]. Meta-analysis study by analysts [165], from 10,798 Chinese covid-19 patients pointed out IL6 levels progressively increase with the severity of disease condition. Serum IL6 level was 2.9 times higher in critical patients than mild [166]. After Tocilizumab, an Il6 blocker treatment in 20 patients surprisingly increase the recovery rate [167].

Change to the adaptive immune response is still very less known to researchers and clinicians for Covid-19. The number of CD4 and NK cells is decreased with increasing disease severity in circulation. CD4 mediated protective response is very low and cytotoxic $CD8^+$ T cells are more abundant (80%). Circulating CD8 analysis of Covid-19 patients at critical condition depicted anomalous phenotype in freakily functioning $CD8^+IFN\text{-}\gamma^+GM\text{-}CSF^+T$ cells and dismantled $Tim3^+Pd1^+$, $NKG2^+CD107a^+IFN\gamma^+grzB^+$ [168]. As a result, a flawed response was played, which cannot control viral replication or eliminate infected cells. But can trigger exacerbated inflammatory response leading to cytokine storm mediated ARDs and organ failure-like consequences [169]. Lymphopenia syndrome was noticed in Covid-19 patients that affecting $CD3^+T$ cells [170]. Precisely, it was reported as IL6 and IL8 were inversely correlated with perforin content in both NK cells and CD3 cells and anticorrelated with increasing myeloid-derived suppressor cells [171]. $CD4^+T$ cells were numerically lower in ICU patients but they surprisingly increased CD69, CD38, CD44 and HLA-DR associated with $Thr17CD4^+CCr6^+$ production in huge content [172]. OX40, which played as a promoter of various cytokines in T cells, had been reported as remarkably overexpressed in critical patients [173]. An activation induced co-stimulatory molecule 41BB was significantly hiked expression *i.e.* vital for cytotoxic activity of $CD8^+T$ cells in ICU patients [174]. $CD14^+CD16^+$ monocyte cell population was increased in notable high percentage in the peripheral blood circulation of Covid-19 ICU patients with severe-pulmonary-syndrome that was the main reason for high GM-CSF secretion [175]. Primate model study by previous researcher [175] documented virus can be replicate within lungs for 10 days and post infection which is most crucial at day 14 and sometimes continues till day 28. Samples of 452 severe Covid-19 patients study in Wuhan portrayed a very miserably lower number of whole T cell numbers including T helper cells, T regulatory cells and T suppressor cells. In extremely terrible cases, the number of memory T cells was also decreased but astonishingly naïve T cell percentage was enormously increased. Underlying studies were reveled CD147, binds to S1 domain and enables to host cell entry of Covid-19 virus. Besides CD147, CD26 also helps SARS-CoV-2 entry into T cells that causes T cell infection and induced cell death by apoptosis [176]. Consequently, dysfunctional memory T cell, which is responsible for specific antigen response, by SARS-CoV-2 infection satisfying huge naïve T cell response, that promotes a massive and highly coordinated cytokine release and hyper inflammation [177]. Dysfunctional and reduced memory T cell numbers forecasted a possible recurrence of the disease [178]. Covid-19 patients suffered Lymphopenia because SARS-CoV-2 can also infect lymphocytes that have a nominal number of ACE2 receptors on their surface [179]. That is responsible for specific receptor mediated endocytosis of virus followed by lymphocyte cell death and damage lymphatic organ [180]. CD147 or Basigrin or EMMPRIN a receptor widely expressed on host cells as well as in memory CD4+ T cells and NK cells acts as a novel route for SARS-CoV-2 invasion. After entering into a specific memory T cell, SARS-CoV-2 induces cell death mechanism. That limits vaccine longevity and host-immunity. Possibly this is the prime and only reason for recurrent infection. Azithromycin, Meplazumab shows high affinity with CD147, recent study was suggested treatment with these drugs significantly increase the memory T cell population. Therefore, coding combinational and targeted therapeutics specially nanosphere, micelle containing drug load and affected cell specificity may be a use full way to increase immunity by increasing memory T cell population [180,181,182].

A transcriptomics study by Wen et al. demonstrated notable changes in B cell population [183]. Naïve B cells were decreased in number whereas peripheral blood mononuclear cells were remarkably increased in plasma [184]. Alteration in B cell receptors is surprisingly noted. IGHV2-23, IGHV3-7, IGHV3-15, IGHV3-30 and IGKV3-11 (previously noted as a target for the vaccine) receptors are prime [183]. IGHV3-23-IGHJ4 stays as monoclonal stage with SARS-CoV-2 specificity [184].

Serological reports of Covid-19 patients notably revealed 96.8% of patients can capable of seroconversion from IgG to IgM within 20 days of the first symptom [183,186]. SARS-CoV-2 specific IgG is present in all patients after 17–19 days of first symptom onset and 94.1% of the patient population can generate specific IgM approximately within 20–22 days [186]. Due to enormous alikeness in genomic sequence with SARS-CoVs and MERS-CoVs, SARS-CoV-2, like the other two viruses, can display a similar mechanism for dogging host-antiviral-immune defense *via* suppressing interferon (IFN-1). sIgA or secretory immunoglobulin A is the fundamental warrior of mucosal defense, which is a major entry route for SARS-CoV-2. Researchers demonstrated the presence of IgA in Covid-19 patient serum [187]. Therefore, investigating on causative agent for sIgA on Covid-19 patients and use it as a neutralizing agent for the virus in respiratory tract mucosa.

6. Covid-19 immunopathogenesis: the root of exhausted immune response leading toward cytokine storm

Hypercytokinaemia is a key factor for immuno-pathological response resultant vascular permeability, plasma leakage and severe vascular coagulation, frequently noticed among 5% of Covid-19 patients, who had sustained lethal or very severe respiratory symptoms and required life supporting critical care treatment. One RT-PCR and NGS studies on 41 admitted Covid-19 patient in Wuhan City Hospital shows elevated IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF (granulocyte-macrophage colony-stimulating factor), INF-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα and VEGF levels in plasma collected from non-ICU patients and severely extreme level of IL-2, IL-6, Il-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, MIP-1β and TNF-α in ICU patients [188]. That portrayed cytokine storm, which is potentiated with disease severity. The phenomenon is quite similar to viral sepsis; specific components of innate immune systems recognize an invading pathogen then swiftly trigger appropriate immune responses. Sometimes, depending on the condition to cure outrageous pathogenic burden, this process is loudly augmented. That veiled elevation can worsen host tissue, but that also influences a protective regulatory mechanism that restricts immune hyperactivity after an infection point and restored to normal homeostasis [189]. Cytokines, a group of secreted proteins with a very short half-life (value range), have played crucial role in the activation of statutory signals that specify, multiply and resolve immune response through recruiting various lymphatic cells at sites of inflammation [190]. Activated on an extreme level, cytokines stimulated systematic activities and colony-forming factors at infection sites, which is sequentially promote granulopoiesis within the bone marrow and gradually surged in neutrophil and monocyte production and mobilization [191]. As a circumstantial repercussion of extensive T cell response or high innate recognition, that collapse resolve mechanism and depicted as a gigantic cytokine level in plasma and serum resultant collateral system damage [192]. This physiological injury is termed as cytokine storm, cytokine release syndrome or hypercytokinaemia in clinical physiology [193]. Analogous cytokine spike is also documented in chronic auto-immune diseases (Juvenile idiopathic arthritis, lupus *etc.*) certain cancer and patients treating with chemo medicines [194]. In response to viral infection, myelopoiesis is triggered and it is followed by monocyte mobilization and a hike in monocyte population in bone marrow [195].

It is still unclear that Covid-19-cytokine storm is an effect of immune hyperactivity or a failure of immune response because of continual viral replication and associated immune dysregulation. Like conventional viral immune-response models, Covid-19-cytokine storm can significantly alter target tissue and the host physiology toward fetal direction by spread to multiple organs. Hallmark symptoms of cytokine storm are persistent fever, fatigue, headache, respiratory failure, loss of blood pressure, vasodilatory shock, capillary leak syndrome, edema, renal injury and disseminated intravascular coagulation (DIC). There are some reports on cytokine antagonists were fortunately reduced cytokine level in severely ill Covid-19 patients and help in their recovering process [196]. Cytokine neutralization with (Interleukin) IL-1, TNF, IL-6, IL-17, IL-12/13, GM-CSF and IFNγ inhibitor, may be a useful candidate in Covid-19 cytokine storm therapy and it is also proven its efficacy in ICU admitted patients with critical condition like sepsis [197].

7. Patient profiling and use as diagnostic markers

By using a machine learning model with 20 blood parametric of 366 Covid-19 patients depicted severity of patients with a proteomic risk score and that correlated with gut microbiota, which resembles to pro-inflammatory cytokines [198]. Metabolomics analysis of some potent amino acid related pathways like aminoacyl-tRNA biosynthesis pathway, arginine biosynthesis pathway, valine, leucine and isoleucine biosynthesis pathways from fecal samples of 987 patients revealed a pattern that harmonized with disease extremity [199]. Hence, Paley et al. predicted intestinal microbiota and associated metabolites may be used as further analysis and characterized as an indicator to forecast susceptibility of SARS-Cov-2 with an individual or entire population [199,200].

Histopathological findings were resemblance to previous SARS and MARS affected patients. Biopsy analysis of lung, liver and heart tissue isolated from a 50 year old male Covid-19 patient by Xu [200] demonstrated bilateral alveolar injury associated with cellular fibro myxoid exudates. Exfoliation of pneumocytes and formation of the hyaline membrane in section of right lung and sections of left lung displayed pulmonary edema with hyaline membrane formation, which specifically pointed toward acute respiratory distress syndrome (ARDS) [200]. Interstitial mononuclear inflammatory infiltrates, lymphocytes, multinucleated syncytial cells with atypical enlarged pneumocytes featuring huge sizable nuclei, amphiphilic granulated cytoplasm associated with prominent nucleoli were noted at intra-alveolar space. That prescribed as cytopathic-like changes but no intracellular or intracytoplasmic viral inclusion was pinpointed [202]. Liver sections were portrayed as lite micro-vesicular steatosis with mild lobular formation with portal activity [203]. But heart section was more or less healthy with a slight interstitial mononuclear inflammation [204]. Similar analysis with a lung tissue isolated from 72 years of female Covid-19 patient with diabetic history by Wang, revealed diffuse alveolar damage, denuded alveolar cell lining with hyperplasia by type II pneumocyte. Intestinal fibrosis exodus with intra-alveolar organizing fibrin was dominant [205]. Intra-alveolar loose fibrous plugs of organizing pneumonia, chronic inflammatory infiltrates with loose interstitial fibrosis were also visualized [206]. Staining with Anti-Rp3NP of SARS-CoV2 visualized the virus on alveolar epithelial space in huge numbers, but the lesser amount in the interstitial region and blood vessels [207].

After virus detection on 4/5 days from nasopharyngeal swab IgM and IgG were demonstrated as notably increased [208] still 20th day in very mild symptomatic patient. $CD3^{-}CD19^{+}CD27^{hi}CD38^{hi}$ B cells, $CD4^{+}CXCR5^{+}ICOS^{+}PD1^{+}$ T helper cells, $CD8^{+}$, $CD38^{+}$, $HLA\text{-}DR^{+}$ cytotoxic T cells were expressed in high content and MCp1/CCL2 in low content in day 7 blood sample [209]. Whereas NGS study from blood sample of 149 hospitalized serious Covid-19 patients by Mathew and colleagues [210] depicted naïve ($CD45RA^{+}CD27^{+}CCR7^{+}CD95^{-}$), central memory ($CD45RA^{-}CD27^{+}CCR7^{+}$), effector memory ($CD45RA^{-}CD27^{-}CCR7^{+}$)/($CD45RA^{-}CD27^{-}CCR7^{-}$), $CD39^{+}$ and ($CD45RA^{+}CD27^{-}CCR7^{-}$) EMRA T cells were increased but ($CD45RA^{-}CD27^{+}CCR7^{-}$) effector T cell was decreased. In acute infection condition $KI67^{+}HLA\text{-}DR^{+}CD38^{+}$ non naïve CD8 T cell population was increased significantly [210].

8. Cellular pathways triggered by SARS-Cov-2

Viral spike proteins of SARS-Cov-2 bind with angiotensin converting enzyme II (ACE2) [211] to enter into host cells. S1 receptor mediated cellular entry is also depended upon S2 mediated fusion governed by

transmembrane serine protease II (TMPRSS2) and cathepsin B/L activity. Genes of both ACE2 and TMPRSS2 are dominantly expressed in conjunctiva, cornea, respiratory tree (alveolar epithelial type II gall-bladder and common bile ducts of adults but notably absent in fetal tissues) [212]. RNAseq studies matched with to human atlas revealed cathepsin B/L is upregulated in 70–90% ACE2 expressing cells. Similar other studies revealed newborn, children and younger populations have null to low risk for Covid-19 infection and reported or chance of disease severity is less [213]. Whereas the high rate of disease transmission and severity is visualized in adults, smokers, chronic obstructive pulmonary disease (COPD), hypertension, idiopathic pulmonary fibrosis, sarcoidosis or scleroderma associated intestinal lung disease and asthma patients. Survey reports, RNAseq data, CEL files microarray analysis followed by Affymetrix analysis and RMA bioinformatics analysis cumulatively revealed ACE2 and TMPRSS2 genes are nil in fetal baby whereas children and younger population have very reduced in number and progressively increased expression with ages and extensively high in adults and patients suffering abovementioned diseases [214]. It is clearly indicated ACE2 and TMPRSS2 play an important role not only in SARS-CoV2 entry, pathogenesis but also in the activation of altered immune response and fatal intercellular pathways. NF-κβ, a common regulator of both immune responses, is widely activated through phosphorylation then trans localize within the nucleus and instigate a wide variety of gene transcription including pro-inflammatory cytokines, chemokines and various pro-apoptotic proteins including CD95. Similarly, SARS-CoV, SARS-CoV-2 triggers massive IL6 and TNFα expression through activating NF-κβ pathways. SARS-Cov-2 activated ACE2 downstream signal modulators like Ras-ERK-AP1 axis, CCL2 axis that ends with fibrosis, enormous inflammations and specific/nonspecific myocardial markers like hs-cTnI, lactate dehydrogenase, creatine kinase, creatine kinase MB [215]. That can be used as a potential tool to evaluate level of Cov-2 progression and affectivity in heart and other crucial organs [216]. The central nervous system is reported as an acute target for Covid-19 infection. It can be either directly injured by crossing blood-brain barrier followed by immense hypercytokinaemia or target sensory nerve ends results in anterograde or retrograde axonal transport by motor kinesins and dyneins [217]. Due to elevated inflammation rate and edema and lower brain oxygen saturation level, the nervous system switches to anaerobic mitochondrial respiration. That affects olfactory bulb swelling, drowsiness due to edema and headache. These are an indication of upcoming severe brain damage. Infection in microglia, astrocyte affect gigantic brain injury, sometime fetal. Beside nervous system, predominant ACE2-SARS-CoV-2 interaction was noticed by analyzing RNA nucleocapsid protein in the capillary epithelium of intestinal and reproductive organs like duodenum, small intestine, pancreases, liver, rectum, placenta, uterus [218]. This forecasted multi-organ failure and disease severity. Nano-based imaging tools with specific S protein binding domain and fluorescence property can be very useful in *in vivo* recognition of SARS-CoV-2. Nanoparticles show efficacy in various medical imaging procedures like AuNPs as contrast in CT-scan/X-ray, dendrimer-gadolinium/iron oxide NPs in MRI, carbon nanotubes with or without fluorophores, Cu^{64}/IN^{111} radioisotope in nucleic content, quantumdot crystal nanos in biosensor and in colorimetric identification from body fluids, liposomes, and micelles. Therefore, nano-based *in vivo* imaging tools with specific S protein binding domain for virus recognition and biomedical imaging property can be very useful in diagnosis rate disease spread within various organ in the patient body and also estimate resultant systemic organ injury.

Restricting those targeted pathways may be a potent therapeutic strategy against the cytokine storm of Covid-19 patients. A few potential candidates like, caffeic acid phenethyl ester, Bay 11-7082, partheno-loide, Artesunate can effectively use as a potential candidate in Covid-19 treatment. As per previous studies, nanoparticles like Sunitinib, CDDO-Me, caffeic acid cyclohexylamide (CGA-JK3), graphite nanoparticle (GN), gold nanoparticle (AuNPs), graphene oxide nanoparticle (GNO), zinc oxide nanoparticles (ZO-NPs), silica coated nano iron (SiO_2-Fe) could effectively reduce interleukins and chemokine level by down-regulating NF-κβ activation in several diseases such as viral infection, auto immuno-disorders, cancer immunity, viral sepsis, viral influenza and hypercytokinaemia. They have proven their maximum efficacy in minimal dose with the least side effects due to tissue specificity. They can also use as an effective therapy for critical Covid-19 patients. In case of previous SARS treatment, siRNAs, RNA aptamers, antisense oligonucleotides used as useful tool. Design siRNAs (M1/M2) against SARS-CoV2 M-protein, E-protein, N-proteins, RNA polymerase, and the replicase coding region can be a good therapeutic target to restrict viral replication.

8.1. *Global immunization - presently a hallucinating fantasy*

History guides toward large scale immunization policy is the only way to relief from this global pandemic. In the present Covid-19 pandemic, some vaccines are still in underdeveloped condition and a few are continuing clinical trials. We are using medieval approaches like quarantine, physical distancing and the century-old process of using face covering to restrict present viral outbreak. Today, previously mentioned policy is globally well-practiced and reported as effectively suppresses massive rate of viral spreading but still not met the goal. Present situation is still in severe catastophic [219]. That put a remarkably huge impact on the global economy. Global death rate due to the direct and indirect effect of Covid-19 is progressively increasing each and every day. Coronavirus pandemic is forecasted some about 10 years ago, but our planet is still not ready to overcome this catastrophe [220]. Recovered Covid-19 patients show high amount of SARS-CoV-2 specific and protective host immune response [221]. A study on Covid-19 induced *Rhesus macaques* model depicted protective immunity was developed and the previous SARS-CoV-2 infection acts as a safeguard from subsequent exposures [222]. Clinical studies evidenced significant efficacy of plasma containing neutralizing antibodies derived from covid-19 winner patient on SARS-CoV-2 infected patient with severe ARDs and multiple organ injury [223]. These crucial findings unquestionably suggest not only design an effective, authenticate and specific vaccine with the least side effect but also ensure its large scale industrial manufacture, unbiased distribution policy and global administration. Because it is still the only way to quell this pandemic and calling off all restrictions with lockdowns, even if the second web of infection is globally continuing.

According to various studies, structural protein S and N are probably the most preferred target for developing vaccines [224]. T cell responses against S, M and N protein are predominant and long lasting [225]. S protein was a target for SARS-CoV-2 CD8+T cell responses but it is not dominant, whereas SARS-CoV-2 M is recognized and elucidates reactivity against other antigens like nsp6, ORF3a and N can trigger 50% of total CD8+T cell response [226]. *In silico* analysis with referencing ViPR database and immuno-epitope database give a positive boost up in vaccine development procedure [227]. Most of the target epitope regions are from S and N protein regions. SARS-CoV-2 is an encapsulated single-strand RNA with spike like glycoprotein projection from outer coating. Among four major structural proteins S, E, M and N; S1 and S2 domain of S protein is the most promising target for vaccine development. Sequencing S1, RBD and more conserved S2 domain and presently use those epitopes in devolving immunization procedure [228]. SARS-Cov-2 S protein is well glycosylated and *in silico* analysis depicted its glycosylated part is more organized confirmation. Peptide epitope glycosylation is required for ACE2 receptor mediated entry [229]. Therefore, DNA/RNA vaccine has glycosylation capability may be a potential candidate.

Other than Live-attenuated and inactivated popular vaccine techniques, next-generation vaccines were also in underdeveloped state and that is only enabled through advancement in nanotechnology. Viruses are naturally occurring biological nanoparticles [230]. They are structurally and functionally more similar to nanoparticles - that's why using

nanotechnology in repurposed immuno-engineering and vaccine development is very effectively useful.

8.2. Strategy I: nucleic acid based vaccine

DNA and mRNA-based vaccines were frequently used in vaccine development by packaging it in various nano-based biological, natural, synthetic delivery systems or live/attenuated viral vectors [231]. Nanotechnology based engineered genetic, nucleotide and protein codes for *in situ* viral protein expression are a useful approach to trigger safe immune responses for required immunization. Both DNA and mRNA vaccines are in the list of potential developing vaccines; even some of them are in different progressive stages of clinical trials (Table 1). Besides their good accuracy and efficacy in the context of physical well-being, pathological safety, quick and stable positive quantifiable immunogenicity as well as reactogenicity; no candidate from this vaccine is still qualifying clinical trials but they are evidencing significant progression and success. Nucleic acid based vaccine can trigger both $CD4^+$ and $CD8^+$ T cell responses [232], that undoubtedly played a crucial role in the annihilation of SARS-CoV-2. Some potential candidates from Moderna-NIAID, BioNTech-Fosun Pharma-Pfizer, Curevac, Arcturus/Duke-NUS, Imperial College London and People's Liberation Army (PLA) academy of Military Sciences-Walvax Biotech are using mRNA mediated technology for vaccine development [233].

Moderna-NIAID coded vaccine is a lipid nanoparticle (LNP) packed mRNA-1273, which is accurately enciphered for an intact, stabilized and perfused spike protein of SARS-CoV-2. Presently this underdeveloped vaccine is in Phase III clinical trial and significantly documented positive response, even for elderly individuals, in two doses at 28 days apart through intermuscular administration [234].

BioNTech-Fosun Pharma-Pfizer scripted a highly potent 3LNP encapsulated mRNA vaccine. This kind of LNP packed vaccines is well proven effectivity in treating influenza, Ebola and Zika. Central mRNA is developed by compiling two nucleoside-modified mRNA with uridine mRNA and self-amplifying mRNA and it is denoted as BNT162 and BNT162b1. This specifically tailored mRNA is specific for RBD region of S1 subunit of SARS-CoV-2. Currently, this underdeveloped vaccine is registered in Phase III clinical trial and significantly documented effective response in two doses at 28 days apart through intermuscular administration [235].

CureVac's vaccine candidate is CVnCoV. It utilizes optimized mRNA, developed by using CureVac's RNA optimizer that can turn on human natural immunity against SARS-CoV-2. Presently this nano-packed mRNA vaccine is successfully continuing stage II clinical trial with 8 μg dual-dose for 28 days interval [236].

Lunar-CoV19 (ARCT-021) is a potent vaccine from Arcturus therapeutics, Duke University and NUS, Singapore and presently is in Phase 2 clinical trial. Preclinical data depicted a single administration of this nano vehicle packed Arcturus' STARR tailored mRNA based vaccine significantly hike in neutralizing antibody level even over 50 days and enriched efficacy is due to self-replicating nature of customized mRNA of the vaccine [237].

DNA vaccines are more stable than mRNA vaccines. But uncoated DNA is also easily dissolved by secreted nuclease [238]. That is the major restriction for cell or tissue specific delivery DNA vaccine delivery [239]. Nano-based carriers may be an enriched solution to overcome this limitation. Catatonic charged lipid based nanoparticles, natural polymers, synthetic polymers, inorganic nanosphere and particles are may be potential encapsulation tools for DNA packaging. Polymeric nanocarriers facilitate controlled and organ specific release and prevent biological inactivation. Polylactic-*co*-glycolic acid is a FDA approved copolymer [240], can facilitate antigen specific drug delivery. Composite nanoparticles like polyethyleneimine containing PLGA, glycol chitosan containing PLGA are well documented nano-vehicle with DNA

Table 1
List of candidate vaccine against Covid-19.

Sr. no	Developer organization	Vaccine platform	Vaccine type	Present clinical trial stage and registration number	Number of dose	Interval timing for booster dose	Route of administration
1	University of Oxford/AstraZeneca	Non-replicating viral vector	ChAdOx1-s	Phase-III/ ISRCTN89951424 & NCT04516746	Single	N/A	Intermuscular injection.
2	Beijing Institute of Biotechnology/ CanSino Biological Inc.	Non-replicating viral vector	Adenovirus type 5 vector	Phase-III/NCT04526990 & NCT04540419	Single	N/A	Intermuscular injection.
3	BioNTech/FosunPharma/Pfizer	mRNA	3 liposome nano particle packed customized BNT162mRNAs with self-annealing capability.	Phase-III/NCT04368728	Double	28 days	Intermuscular injection.
4	Moderna/NIAID	mRNA	Liposome nano particle packed customized mRNA-1273, *i.e.* specifically coded against S protein of SARS-CoV-2	Phase-III/ ChiCTR2000034780 & NCT04470427	Double	28 days	Intermuscular injection.
5	Gamaleya Research Institute	Non-replicating viral vector	Adeno-based (rAd26-S + rAd5-S)	Phase-III/NCT04530396	Double	21 days	Intermuscular injection.
6	Janssen Pharmaceutical Companies	Non-replicating viral vector	Ad26COVS1	Phase-III/NCT04505722	Double	56 days	Intermuscular injection.
7	SinoVac	Inactivated	Inactivated	Phase-III/NCT04456595 & 669/UN6.KEP/EC/2020	Double	14 days	Intermuscular injection
8	Wuhan Institute of Biological Products/SinoPharm	Inactivated	Inactivated	Phase-III/ ChiCTR2000034780	Double	14 days or 21 days	Intermuscular injection
9	Novavax	Protein subunit	Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Phase-IIb/NCT0453339	Double	21 days	Intermuscular injection
10	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Science	Protein subunit	Adjuvanted recombinant protein (RBD-dimer)	Phase-II/NCT04466085	Double or triple	0, 28 or 0, 28, 56 days	Intermuscular injection
11	CureVac	mRNA	mRNA	Phase-II/NCT04515147	Double	28 days	Intermuscular injection

loading facilitate very negligible amount of systematic toxicity with accurate target specificity and also attenuate other non-specific protein interactions [241]. DNA delivery is now used in vaccine development procedure. Nano-based electroporation technology [242] mediated DNA delivery mechanism was employed in coding of INO-4800, a customized DNA vaccine against SARS-CoV-2, which is jointly developed by INOVIO Pharmaceuticals and International Vaccine Institute, by using nanotechnology based highly sophisticated delivery mechanism [243]. This vaccine is intradermally administrated through nano based similar functioning device named CELLECTRA®2000. Presently it is in phase1/2 trial and vaccine participants will receive one intradermal injection of 1.0 mg IN0-4800 first on day 0 and second after 28 days interval [244]. Another candidate of DNA vaccine from Osaka University-AnGes-Takara Bio is presently in Phase1/2 trial. This vaccine contains a customized inactivated circular nano sized plasmid DNA, which can express SARS-CoV2 specific proteins that can stimulate immuno-response and buildup memory T cells and give protection from the respective disease without pathogenicity [245]. Plasmid DNA and adjuvant are encapsulated in nano based packaging for organ specific and effective delivery [246]. ZyCoV-D is a similar plasmid DNA based vaccine candidate from Zydus Cadilla Healthcare limited. It is presently in Phase I/II clinical trials and significantly translates viral proteins that can trigger cellular and humoral immune response [247]. GX-19, circular plasmid DNA based vaccine candidate from Genexine Consortium presently in Phase I/II. S1 and S2 spike protein of SARS-CoV-2 is coded in this pGX27-S1S2 named plasmid DNA and it can induce both $CD4^{+}$ and $CD8^{+}$T cell responses significantly without any pathogenic activity [248] (Table 2).

8.3. Strategy II: peptide based subunit vaccines

Protein based vaccines are made up of an isolated purified protein from virus or similar viruses like particles or engineered peptides, subunits, that can mimic respective pathogenic virus and it is lack of viral genome or non-structural proteins [249]. Many nucleic acid based vaccines encode a whole genome or whole structural motifs. Encapsulating whole S-protein can trigger a broad spectrum of both humoral and cellular immune responses due to large repository of potent epitopes [250]. Previous vaccine development projects against SARS and MARS group of coronavirus; widely experienced similar prejudices from antibody dependent infection enhancement and that can cause life threatening allergic infection due to establishment of non-neutralizing antibody pool, which gradually increases infection [251]. Therefore to bypass this kind of uncanny side effects, it is good to develop a specific peptide epitope based vaccine. Recent *in silico* studies depicted specific B and T cell epitope series of SARS-CoV-2 and it is presently confirmed by comparing with serological analysis from Covid-19 patients and winners may be played a crucial role in peptide based highly sophisticated vaccine designing [252].

Peptide vaccines are the simplest form of nano-sized vaccine, which can be easily administrated at specific tissue and cell of interest by loading with appropriate nano vehicle [253]. Previously it had been established efficacy in SERS, MERS, influenzas and other chronic diseases like cancer [254]. Peptide vaccine required specific adjuvants and delivery mechanisms for optimized efficacy. NVX-CoV2373 is vaccine candidate from Novavax Inc. This customized peptide vaccine was created by using Novavax's recombinant nanoparticle technology to generate specific spike protein and packed with saponin-based Matrix-M adjuvant [255]. As a whole, peptide vaccines can efficiently turn on specific immune responses and significantly enhance protective neutralizing antibody expression. Developer organizations recently broadcasted Phase III clinical trial of the specific vaccine is presently continuing in United Kingdom and positive result was noted [256].

Chinese Academy of Sciences in collaboration with Anhui Zhifei-Longcom Biopharmaceuticals coded a similar peptide vaccine. This vaccine is made up of adjuvanted recombinant RBD-dimer protein of S1

Table 2
List of potential chemical componds benefical for Covid-19 treatment.

Sr. no	Name of the drug	Nature of the drug	Mode of action
1	Chloroquine and hydroxychloroquine	Anti-malarial, anti-inflammatory and anti-thrombosis medicine	• Chloroquine and hydroxychloroquine reduce glycosylation of ACE2 by increasing endosomal pH through increasing pH of acidic vesicles like endosomes, endolysosomes, Golgi bodies and lysosomes. That effectively terminates spike protein biding of the causative virus, cell fusion and contagious process. • As an established immuno-suppressor, can restrict hyper-cytokinaemia by suppressing IL-1β, IL-6, IL-12. • Covid-19 patients with acute respiratory distress syndrome recovered in significant numbers with hydroxychloroquine and chloroquine treatment and the success rate is increased in combinational treatment with azithromycin.
2	Camostat mesilate	A protease inhibitor used against chronic pancreatitis and reflux esophagitis.	• It can bind and blocked endosomal protease activity of TMPRSS2, through which SARS-CoV-2 enters into the host cell. • Combinational therapy with E-64, an inhibitor for cathepsin B/L, camostat mesilate can inhibit endosomal protease mediated Covid-19 virus entry effectively by restricting both ACE2 and TMPRSS2 proteases.
3	Umifenovir or Arbidol	A small indole derived anti-viral molecule.	• It can inhibit SARS-CoV-2 infection within the host by interacting multiple stages of host lifecycle as well as block viral entry by impeding viral attachment through proteolytic cleavage and detached from early endosome as well as endolysosomes.
4	Baricitinib	Anti-inflammatory drug	• High plasma concentration of Baricitinib can inhibit calthrine mediated endocytosis with the help of AP2 associated protein kinase1 (AAK1) and G-associated protein kinase (GAK). That in turn restrict endocytosis processes of Covid-19 entry. • Also suppress inflammation and excess cytokine production by blocking JAK1/2
5		Anti-viral drugs	

(*continued on next page*)

Table 2 (*continued*)

Sr. no	Name of the drug	Nature of the drug	Mode of action
	Remdesivir, Galidesivir, Sofosbuvir, Tenofovir, Ribavirin		• They can binds with SARS-CoV-2-RNA dependent RNA polymerase and inhibit viral genome multi-replication
6	Sunitinib, CDDO-Me, caffeic acid cyclohexylamide (CGA-JK3)	Anti-inflammatory drugs	• They can effectively reduce interleukins and chemokine level by downregulating NF-κβ activation in several diseases such as viral infection, auto immuno-disorders, cancer immunity, viral sepsis, viral influenza and hypercytokinaemia.

subunit of SARS-CoV-2 spike protein [257]. Presently it is in Phase II clinical trial. Similar two peptide vaccines from Sanofi Pasteur/GSK and Kentucky Bioprocessing. Inc. is presently in Phase II clinical trial. They are sequentially using baculovirus derived S protein and RBD based polypeptide as vaccine load with nano-sized vehicle for specific effective delivery [258]. Vaccine candidates from Vaxine Pty Ltd-Medytox use Advax adjuvant based packaging for nano-sized tailored recombinant spike protein for vaccine load [259]. Virus-like particles are nano sized but mimic the associated molecular pattern, they can be easily customized for specific peptide load delivery and can be modulated as effective adjuvant action to increase immunization efficacy. Previously it efficiently served as a vehicle for drug/vaccine in immunotherapies and cancer [260]. Therefore, these nanotechnologies guided peptide delivery mechanism may be potentiated more efficiently and rapid remedial.

8.4. Strategy III: live attenuated, inactivated vaccines and viral vectors

Live attenuated vaccine groups contain specific viable viruses with mechanically attenuated virulence [261]. Therefore, they become harmless but can trigger a sustained and accurate immunity against the respective pathogen. Live attenuated vaccines are developed in a classical way through passaging in cell culture until it loses its pathogenic properties and restricted to mild infection after administration [262]. A few vaccine candidates from Serum Institute of India-Codagenix, Griffith University-Indian Immunologicals Ltd. and Mehmet Ali Aydinalar University-AcibademLabmed Health Services A.S. are presently in the pre-clinical stage and they are using codon deoptimized live attenuated SARS-CoV-2 virus for vaccine development [263]. This procedure is risky for treating novel pathogens because it can retransfer to pathogenic form, reactivation of immune systems [264]. Evolved sophisticated technologies like nano-engineering, genetic code expansions and nano-platform-based synthetic genomic engineering are now used to design genetically stable and highly progenitive live attenuated vaccines that can induce a sustained immunity with lesser side-effects.

Inactivated Vaccines are a classical method of vaccine designing. This method played an indispensably crucial impact on designing a vaccine for epidemic viral diseases like polio, hepatitis A, rabies, tick-borne encephalitis and influenza [265]. This group of vaccines is chiefly made up of heat-killed or chemically inactivated specific viruses or their derivative fractions [266]. Due to their non-amplifying feature, they are safer than live attenuated vaccine but the effectivity of triggering immunogenicity is lesser than the live attenuated vaccine. Therefore a second booster dose is required to enhance its optimal efficacy. Presently a few vaccine candidates developed from Sinovac, Wuhan Institute of Biological Products-Sinopharm and Beijing Institute of Biological Products-Sinopharm are currently in Stage III clinical trial [267].

Repurposed several mammalian viruses through genetic engineering or nanotechnology-based viral vectors like adenoviruses are used in vaccine development due to their inherent adjuvant properties, specificity, scalability and tissue targeted facility [268]. Presently some of the highly awaited and esteemed candidates are using this method in their vaccine development. AZD1222 is made up of ChAdOx1-S is a non-replicating viral vector based vaccine candidate from the University of Oxford and AstraZeneca and it is presently continuing in Phase III clinical trial. It is a weakened version of a common cold adenovirus of chimpanzees and that has been genetically manipulated to attenuate replication property within the human body [269]. Another candidate from CanSino Biological Inc./Beijing Institute of Biotechnology is using Adenovirus Type 5, non-replicating viral vector in vaccine development. These nanoengineered viral vector based vaccines presently in Phase III clinical trial [270]. Gamaleya Research Institute designed a vaccine with rAD26 + rAD5-S nonreplicating viral vector. This adenovirus-based vector presently in Stage III clinical trial [271]. Ad26COVS1 is a prominent non-replicating viral vector from Janssen Pharmaceutical Companies. They are using recombinant JNJ-78436735 candidate of Ad26COVS1 in SARS-CoV-2 vaccine development and study depicted successfully preventing subsequent infection [272]. A recent study said high dose of intranasal SARS-CoV-2 infection in hamsters results severe clinical symptoms, comprising a high rate of virus replication in tissue followed by pneumonia, weight loss and subsequent mortality. Results demonstrated the efficacy of this vaccine in protection against clinical SARS-CoV-2 disease. Presently it is continuing Stage III clinical trial.

9. Conclusion and future perspectives

The Covid-19 pandemic is still in tremendous global massacre state. The situation is being more and more catastrophic day by day. Daily rate of newly affected patients as well as in mortality rate is increased horrifyingly. Still, there is no solution for this unprecedented challenge.

In this scenario, tools of nanotechnology are significantly demonstrated progressive impact not only in Covid-19 and Covid-19 associated disease treatment like Hypercytokinaemia, ARDs, *etc.* but also in diagnosis, coding sophisticated vaccine, its large scale manufacture as well as supports distribution chain and in development in non-hazardous administration methods. Besides developing specific anti-viral therapeutics against multifaceted molecular interplays induced by Covid-19 infection, it is equally important to develop a sophisticated nano-carrier. This article summarizes and envisions various ways of therapeutic development and immunization strategies as well as the effectiveness of repurposed medicines by using nanotechnology. Comparing with previous successful nanomedicines, which are established high efficacy against coronavirus epidemics like SARS-CoV and MARS, this article summarizes and envisions eminent therapeutic possibilities for futuristic and non-hazardous management against Covid-19 which is urgently needed to restrict the present pandemic. Palpable ideas and hypothetical possibilities mentioned in this review may only give a light in developing treatment procedure against distorted immuno-system related organ damage by Covid-19 infection as well assist us in developing standard vaccine by using nanotechnology-based platform. Therefore, constant progress in nanotechnology-based approaches may be accelerating the development of novel diagnostic and therapeutic ways that fabricate treatment against Covid-19 more efficiently.

Vocabulary

Covid-19 abbreviated name for corona virus disease 2019
SARS-CoV-2 severe acute respiratory syndrome coronavirus 2
IGTV International Committee on Taxonomy of Virus
ACE2 a receptor named angiotensin converting enzyme 2, through which virion enter into host cell

RBD	receptor binding domain
NPs	nano particles
LNP	lipid nanoparticle
CGA-JK3	cyclohexylamide
GN	graphite nano particle
AuNPs	gold nanoparticles
GNO	graphene oxide nano particle
ZO-NPs	zinc oxide nano particles
SiO_2-Fe	silica coated nano iron

CRediT authorship contribution statement

S.C. and S.M. designed, illustrated and wrote the main manuscript text. K.D.C. participated in concept development and manuscript preparation. S.C., S.M. and K.D.C. contributed equally. C.K.G. and K.D.S. supervised overall project as well as participated in idea development and editing of manuscript.

Declaration of competing interest

The authors declare no competing financial interest.

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