MINI REVIEW

Potential metal-related strategies for prevention and treatment of COVID-19

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Received: 22 April 2021 / Revised: 28 September 2021 / Accepted: 10 October 2021 / Published online: 17 January 2022
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Abstract The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed severe threats to human health, public safety, and the global economy. Metal nutrient elements can directly or indirectly take part in human immune responses, and metal-related drugs have served as antiviral drugs and/or enzyme inhibitors for many years, providing potential solutions to the prevention and treatment of COVID-19. Metal-based drugs are currently under a variety of chemical structures and exhibit wide-range bioactivities, demonstrating irreplaceable advantages in pharmacology. This review is an intention to summarize recent progress in the prevention and treatment strategies against COVID-19 from the perspective of metal pharmacology. The current and potential utilization of metal-based drugs is briefly introduced. Specifically, metallohydrogels that have been shown to present superior antiviral activities are stressed in the paper as potential drugs for the treatment of COVID-19.

Keywords COVID-19; SARS-CoV-2; Metal-related drugs; Metal nutrient elements; Metallohydrogel

1 Introduction

In December 2019, an outbreak of pneumonia caused by a new strain of coronavirus named “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” was firstly reported [1]. Later on, cases of SARS-CoV-2 were found all over the world [1], arising a long-lasting worldwide health crisis. Systemic diseases such as viral pneumonia caused by this virus were named “coronavirus disease 2019 (COVID-19)” [2]. Till September 27, 2021, about 0.23 billion people worldwide had been infected by SARS-CoV-2 and its variants, and the cumulative death toll is about 4.7 million [3]. During the COVID-19 pandemic, prompt and firm contributions from worldwide researchers have resulted in many effective treatments. To date, a variety of antiviral drugs (such as nucleoside analogs, Type I interferons, protease inhibitors) [4], anti-inflammatory drugs (such as interferon alfa-2b, tocilizumab) [5], antibodies, corticosteroids, and convalescent plasmas [6] have been recommended toward the treatment of COVID-19, whereas genuinely effective drugs are still under screening [4, 7]. Mounting evidence indicates that the development of effective vaccines is the most promising route to stop the pandemic [7, 8]. Until the end of May 2021, the six-month vaccination worldwide has resulted in strongly curbed spreading of SARS-CoV-2 [9]. However, due to the unevenly distributed vaccine resources [10, 11] and the long-term side effects posed by COVID-19 [12–14], there is still an urgent need for drugs to combat this disease in an effective, safe, stable, and reliable way. As potential
solutions, metals and metal compounds have attracted widespread attention due to their unique pharmacological advantage in efficiency, safety, and stability.

Some metal elements, such as selenium, iron, and copper, are known to interrupt the infectious interaction between the virus and the host, preventing the virus from entering the host and/or alleviating the symptoms [15–18]. Trace metal elements such as zinc, selenium, and magnesium are known to play an important role in regulating the human immune system, and their deficiencies are related to the severity of the symptoms in COVID-19 patients [19–25]. In addition, metal compounds have various chemical structures and exhibit wide-range bioactivities [26]. Metallodrugs are known to play an important role in direct antiviral or inhibiting critical enzymes in the process of virus replication for the SARS-CoV-2 infection [27, 28]. Metallodrugs can also be used as adjuvant drugs to enhance the efficacy of antiviral drugs (such as zinc plus hydroxychloroquine) [29–31] or used as vaccine adjuvants [32, 33]. It has been illustrated that many metal nanoparticles and metal complexes exhibit excellent anti-inflammatory and antiviral activities [27, 28]. Some metal–organic complexes can also inhibit the replication of SARS-CoV-2 virus through targets such as 3-chymotrypsin-like protease (3CLpro), major protease (Mpro), and papain-like protease (PLpro) [34–36]. To date, many antiviral small molecule drugs have already been proved to be in the treatment of severe COVID-19 patients. For instance, dexamethasone was found to reduce deaths from SARS-CoV-2 [37], and remdesivir was demonstrated to shorten the length of hospital stay of COVID-19 patients [38]. More interestingly, dexamethasone sodium phosphate can self-assemble into a hydrogel through hydrogen bonding and metal coordination [39, 40]; and theoretically, this kind of metallohydrogel may exhibit synergetic effects in treating COVID-19 patients.

In this review, we first briefly introduce the pathogenic mechanism of COVID-19: SRAS-CoV-2 enters cells, replicates in large quantities, and then destroys the immune system, leading to the onset of various symptoms. Then, the key roles of metal drugs and metal elements in the viral infection and immune response process are summarized. Finally, in order to combine the advantages of metal-related antiviral therapies and immune modulating therapies to combat COVID-19, the formation of a special type of metallohydrogels composed of cross-linked antiviral small molecule drugs and metal ions, and their potential applications in the treatment of COVID-19 patients are described and discussed. Although there is a lack of clinical evaluation regarding the performance of metallic drugs in preventing or treating COVID-19, the unique role of metals is worthy of further understanding and exploration. We expect that this review can provide an innovative view of metallic drugs, especially metallohydrogels, and consequently open up a new application area for metal-based drugs.

2 Overview of COVID-19 and SARS-CoV-2

2.1 Epidemiology of COVID-19

SARS-CoV-2, the coronavirus that causes COVID-19, has been proven to be highly contagious to all age groups, whereas most patients who showed symptoms are aged 40–69 (66.68%) [41]. Usually, patients older than 50 years old have a higher mortality rate after being infected [41]. No matter if the infected person is symptomatic or asymptomatic, the person is contagious, making the primary source of the infection be virus-infected people [42, 43]. It has been reported that SARS-CoV-2 has multiple routes of transmission, such as respiratory droplets caused by coughing and close contact [44, 45], fecal transmission, and aerosol transmission [46].

COVID-19 has a common incubation period of 1–14 days [45, 47]. And COVID-19 patients are often accompanied by some common symptoms, such as fever, cough, myalgia, fatigue, and dyspnea [48]. In severe cases, complications including pneumonia, acute respiratory distress syndrome (ARDS), acute organ damage (including liver, heart, kidney), liver dysfunction, and neurological symptoms can be shown [49–52]. Notably, ARDS, which can lead to respiratory failure, is the main cause of death in COVID-19 patients [53].

The COVID-19 caused at least 0.22 billion infection cases and 4.5 million deaths until the start of September, 2021 [3]. Strict regulations intended to limit social contact have been imposed by most countries. And along with the vaccination campaigns, the spreading speed of SARS-CoV-2 has been strongly curbed. However, developing countries such as South American countries and African countries are still at high risk. New variants that are even more contagious and fatal are still pressuring the whole world. And the long-term post-infection symptoms are severely lowering the patients’ living qualities. Therefore, there is still an urgent requirement to accelerate the research on the diagnosis, vaccine, and treatment of SRAS-CoV-2.

2.2 Pathogenic characteristics of SARS-CoV-2

SARS-CoV-2 belongs to the β-coronavirus genus, which is an enveloped positive-stranded single-stranded RNA virus with a total genome length of approximately 30 kb. These virus particles have a round or oval shape, with a diameter ranging from 60 to 140 nm [54]. The structural proteins
encoded by the genome include four types: spike (S) glycoprotein, envelope (viral envelope E) protein, matrix (M) glycoprotein, and helical nucleocapsid (N) protein (Fig. 1). It should be pointed out that S protein is the protein that binds to human host cell receptors. S protein causes virus-cell membrane fusion, which is a key step of virus invasion [55]. In addition, S proteins are highly affiliated to the angiotensin-converting enzyme (ACE2) receptors, which are highly expressed in human epithelial cells [56]. Although there is no strong evidence to prove the animal reservoir of SARS-CoV-2, a large amount of scientific evidence proves the origin of zoonotic diseases [57].

2.3 Infection process of SARS-CoV-2

The main mechanism of SARS-CoV-2 entry into cells is recognition by angiotensin-converting enzyme 2 (ACE2) receptor and cleavage of transmembrane serine proteinase 2 (TMPRSS2) [58, 59].

Take alveolar cells as an example. There are two possible ways for the viral genome to enter the host cell: (1) endocytosis; (2) fusion (Fig. 2) [59–61]. During endocytosis, the S protein, which is located on the surface of SARS-CoV-2, recognizes and specifically binds to the ACE2 receptor on the cell membrane of lung epithelial cells. Then endocytosis occurs, allowing the virus to enter the host cell. The possible fusion process is that after the S protein recognizes the ACE2 receptor, TMPRSS2 activates the S protein and cleaves the binding site. Then the S protein fuses with the host cell membrane, and the virus core enters the cell. The lysosome of the host cell digests helical N protein, and the viral genome is released. After the viral genome entering, the viral RNA replicates in the host cell. The new viral protein is synthesized and then forms progeny viral particles with RNA. The newly synthesized virus particles are transported out of the cell via exocytosis, and a new round of infection begins. Eventually, the virus infects alveolar cells [62]. As metal-related drugs may block the virus entry process and/or directly inhibit viral replication, destroy viral structure, or inhibit the activity of key enzymes [16, 17, 63], they can be applied to the prevention and treatment of COVID-19.

2.4 Immune response of COVID-19 patient

Immune imbalance and excessive inflammation activation are closely related to the disease progression and poor prognosis of COVID-19 patients [54, 64]. The host’s innate and adaptive response, the balance between the virus’s toxicity and the ability to evade the host’s immune response, together determine the outcome of the disease [65].

2.4.1 Body’s innate immune response

Once the SARS-CoV-2 virus invades host cells, the body initiates innate immune defense. Cells at the infected site are stimulated by the virus, which produces cytokines. Then macrophages and monocytes are activated and release a large number of cytokines, such as interferon I/III (IFN), pro-inflammatory tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 1α (MIP1α). Furthermore, the activated macrophages induce NK cells activation. NK cells then kill and destroy infected cells [65]. If the body’s immune regulation function is expected, the infection will be controlled. On the contrary, the concentration of multiple cytokines will increase abnormally. High concentrations of cytokines will trigger the hyper-inflammatory response and the cytokine storm.

The NK cells decreased significantly in patients with severe COVID-19 symptoms, and the immune function was inhibited by the up-regulation of the natural killer group 2 member A (NKG2A) expression on the surface of NK cells. The ability of NK cells to secrete CD107α, IFN-γ, IL-2, and TNF-α is thus down-regulated. This down-regulation will lead to a decline in anti-infection ability, weakened immune regulation, and worsening of the disease [66].

2.4.2 Body’s adaptive immune response

When the innate immune system is unable to resist SARS-CoV-2, further attacks by the virus will activate the adaptive immune response. Dendritic cells (DC) become mature after receiving antigen stimulation and then activate T cells. CD4 + T cells in T cells can promote and activate CD8 + T cells to directly attack and kill infected cells.
Moreover, this cell will also differentiate into Th1 cells to activate B cells. The B cells can differentiate into plasma cells responsible for secreting antibodies and memory cells with a specific ability to recognize antigens. Plasma cells produce a large number of virus-specific neutralizing antibodies, such as IgM, IgG, and IgA [64, 65, 67].

As is known to all, some trace metal elements benefit from regulating the body's immune response and enhancing resistance [27, 29–33, 35, 36]. Therefore, metal nutrients will play an essential and beneficial role in alleviating excessive inflammation and producing neutralizing antibodies.

3 Metal-related prevention and treatment strategies

Metallodrugs such as metal nutrients and metal compounds can play an important role in the prevention and treatment of COVID-19. At present, two methods are used to discover potential metal-based drugs for COVID-19: repurposing existing medications and developing new drugs [27, 28]. These metallodrugs might directly inhibit virus replication [68, 69], prevent viruses from entering cells [63], or inhibit the activity of critical enzymes in the process of virus replication [34–36, 70, 71]. Furthermore, the combination of antiviral drugs and metals can be more effective.

There are several reasons for metal-based drugs to prevent and treat COVID-19: (1) The effect on the body attacked by the virus: participate in the immune system; inhibit the virus from entering cells; and inhibit virus replication. (2) Metal-related drugs play a synergistic effect: enhance the efficacy of antiviral drugs; vaccine adjuvants; and topical antiviral materials. (3) A metal antiviral hydrogel is proposed as a promising method to combat COVID-19 [29–31].

3.1 Metal nutrient elements participate in immune response

People with metal deficiency are susceptible to COVID-19 [16, 18, 19, 23, 72], which may be due to being out of balance in immune regulation. Supplementing metal nutrients in the early stages of infection can help support optimal immune function and be used as a preventive strategy for high-risk groups [73]. Therefore, metal nutrients could be beneficial to reduce the infection of COVID-19 and even the rate of severe illness and mortality (Fig. 3).

3.1.1 Zinc

Zinc (Zn) ion is a critical element of the body’s immune balance, and especially it is urgently needed by hosts and pathogens. It is essential for regulating the growth and function of immune cells, and Zn homeostasis can regulate cell signal transduction [74, 75]. More importantly, long-term hypozincemia may be a factor related to the risk of COVID-19 [22]. Patients with poor clinical outcomes have significantly lower serum zinc levels than those with good clinical outcomes [19]. The lack of Zn will cause more complications in COVID-19 patients, associated with more extended hospital stay and increased patient mortality [20].

Zn has many functions: (1) enhance the ability of innate immunity and adaptive immunity in the process of virus infection [76]; (2) help improve the response of the virus to Type I interferon (IFN-1); (3) enhance the production of IFN-α to counteract the antagonistic effect of SARA-CoV-
2 virus protein on IFN [77]; (4) promote the proliferation and differentiation of T and B lymphocytes, thereby improving immune function [78]. Low levels of Zn can affect the function of NK cells and are related to the up-regulation of interleukin-6 (IL-6) [76]. In addition, Zn supplementation may facilitate COVID-19 treatment and patient recovery. Finzi [79] reported that four COVID-19 cases treated with high-dose oral Zn salts showed improvement in symptoms within 24 h. Moreover, Finzi [80] analyzed the situation of 28 COVID-19 patients treated with Zn and found that patients’ symptoms began to improve on average 1.6 days after Zn treatment, and all patients improved after seven days.

3.1.2 Selenium

Selenium (Se) is one of the indispensable trace elements in the human body, and it has effective anti-inflammatory, antioxidant, and immune regulation functions [81]. The lack of Se will enhance the RNA viruses’ mutation, reproduction, and virulence [15]. An observational study found that the Se level in serum samples of surviving patients with COVID-19 was significantly higher than that of non-surviving patients [23]. In some areas of China, the cure rate of COVID-19 patients is significantly positively correlated with the local Se level [82]. The serum Se level of patients in southern India was significantly lower than that of apparently healthy individuals [83].

Selenium is the active ingredient of many antioxidant enzymes. The selenium-dependent enzyme, glutathione peroxidase 1 (GPX1), is an antioxidant [84]. GPX1 can scavenge reactive oxygen species (ROS) and free radicals in host cells, thereby avoiding the increase of oxidative stress and the mutation of the viral genome [84]. Zhang et al. [85] found that increasing Se intake can promote the production of redox-active selenium, which may inhibit SARS-CoV-2 protease. Se plays an essential role in the maintenance, maturation, and function of T cells, as well as in the production of T cell replacement antibodies [86]. The inhibition of NK-κB signaling by Se can avoid excessive immune and inflammatory responses, downregulate the release of pro-inflammatory cytokines and chemokines, and prevent the occurrence of cytokine storms [87]. Therefore, it could be considered that Se supplementation is beneficial to the cure of COVID-19 patients and can also prevent SARS-CoV-2 infection.

3.1.3 Magnesium

Magnesium (Mg) is the principal cation in human cells and an essential element necessary to maintain the normal physiological functions of cells. Mg has a lot of functions, such as anti-inflammatory, antioxidant, vasodilator, and neuroprotective effects [24]. The insufficiency of Mg can cause adverse symptoms such as a decrease in the number of T cells, a copious production of inflammatory cytokines in the plasma, and impaired retinal function [72]. These symptoms may lead to critical illness and complications of COVID-19. Mg reduces the production of inflammatory cytokines. Sugimoto et al. [88] discovered that Mg reduced the generation of cytokines TNF-α and IL-6 in the maternal, term, and premature infants. They also found that magnesium could increase basal IκBα levels, and it was linked to decreased activation and nuclear localization of NF-κB under TLR stimulation. Therefore, Mg supplementation might have a potential impact on avoiding...
cytokine storms. An observational survey of patients with COVID-19 showed that there was a significant reduction in patients aged ≥ 50 years who received oral vitamin D3 (1000 IU), Mg (150 mg), and vitamin B12 (500 μg) supplements every day for 14 days [89]. Furthermore, supplementing phosphate, Mg, and vitamin D is beneficial to the regeneration of ATP consumed by cytokine storms. This preventive strategy for high-risk groups helps prevent complications [25].

3.1.4 Iron

Iron (Fe) is a recognized regulator of normal immune system function. COVID-19 infection and pathogenesis are related to abnormal iron metabolism in the body [16]. Multiple pieces of evidence indicate that low serum Fe levels are related to the severity and fatality rate of COVID-19 [90, 91]. The increase in ferritin concentration is correlated with the severity of the disease. Because of the excessive release of cytokines, COVID-19 is considered part of the symptoms of ferritin syndrome, and Fe depletion therapy has been proposed [92]. In the control and treatment of COVID-19 infection and its complications, Fe chelating agents have potential immunomodulatory, Fe chelation, and antioxidant effects [93]. Fe chelating agents can be used as an auxiliary drug to reduce ARDS and help to control the infection of the SARS-CoV-2 virus to human organs by reducing NF-κB and inhibiting IL-6 synthesis [93]. Deferoxamine can reduce the level of IL-6 and inflammatory response in the endothelium in vitro through its chelation and immunomodulatory effects, thereby reducing the severity of SARS-CoV-2 infection and improving the therapeutic effect [94]. From binding to the receptors of the coronavirus, the Fe chelator lactoferrin (Lf) can prevent the virus from entering the host cells [17]. Therefore, it is a potential application to Fe chelator for the treatment of COVID-19.

3.1.5 Other metal nutrient elements

Copper (Cu) is involved in the functions of critical immune cells, and the lack of copper is associated with the increase in infection rates [95]. Lithium (Li) seems to inhibit NF-κB and may play a role in inflammation caused by SARS-CoV-2 infection [96].

The supplementation of trace metal nutrients helps the recovery of physiological immunity and reduces inflammation and oxidative stress. It is necessary to build a robust immune system and resist the epidemic of COVID-19. Therefore, metal nutrients are of great importance.

3.2 Metallo drugs inhibiting virus from entering cells

Metal nanomaterials are common metal-based drugs that can prevent SARS-CoV-2 from entering cells. Silver and silver nanomaterials (AgNPs) have been widely explored in pharmaceutical preparations due to their remarkable antiviral and antibacterial effects [97]. Jeremiah et al. [98] observed that AgNPs with diameters ranging 2–15 nm have efficacious inhibition of the SARS-CoV-2 virus around the cell at concentrations between 1 × 10⁻⁶ and 10 × 10⁻⁶. And they also found that AgNPs effectively inhibit the entry of viruses into cells by destroying the integrity of the viruses. It must be noted that AgNPs show cytotoxic effects at concentrations of 20 × 10⁻⁶ and above. A molecular dynamics (MD) simulation showed that gold nanoparticles functionalized by novel peptides (AuNP-Pep) had a more stable binding ability to receptor binding domains (RBD) than ACE2. This novel peptide was designed based on the 15 amino acids of ACE2 (Fig. 4a–c) [63]. Therefore, this composite nanostructure could potentially block the RBD of SARS-CoV-2. Experiments also suggested that these AuNP-pep could prevent SARS-CoV-2 from entering host cells by interfering host cells from recognizing the viral S protein. Iron oxide nanoparticles (IONPs) are a drug approved by the FDA for the treatment of anemia, and it has been proven to have in vitro antiviral activity and have the ability to limit virus replication and further infection. Abo-Zeid et al. [99] revealed that IONPs (Fe₂O₃ and Fe₃O₄) are related to SARS-CoV-2 virus protein conformation changes and virus inactivation through molecular docking studies (Fig. 4d, e). Fe₃O₄ could bind to S1-RBD to form a stable structure. And the combination of IONPs with S1-RBD could generate ROS, resulting in the destruction of the virus structure. Therefore, IONPs can restrict virus entry into cells and further infection.

Metal complexes have a wide range of structural changes and diverse stereochemistries due to their multiple specific ligand combinations. They are drugs with strong adaptability. Chuong et al. [100] proved that the two pentamethylcyclopentadienyl (Cp*) rhodium piano stool complexes (Fig. 5) showed direct virucidal activity against SARS-CoV-2 and speculated that the complexes might act on the S protein on the surface of the virus.

Sodium selenite can oxidize the thiol group in the viral protein disulfide isomerase [101]. Therefore, Kieliszek and Lipinski [102] hypothesized that selenite could inhibit viruses entering healthy cells and eliminate their infectivity.
3.3 Metallodrugs inhibiting virus replication

Some metal nanoparticles have shown antiviral properties, which can be effective in treating COVID-19 patients [27, 28]. Auranofin is an FDA-approved nano-gold drug that exhibits antiviral properties. Rothan et al. [68] reported that low micromolar concentrations of auranofin could inhibit replication of SARS-CoV-2 in human cells and result in a reduction in SARS-CoV-2-induced cytokines by its antiviral and anti-inflammatory properties. The removal of SARS-CoV-2 RNA in cells treated with auranofin was quite significant, showing a 95% reduction at 48 h after infection. Some metal compounds may inhibit the virus replication process and reduce the symptoms of virus infection. Some bismuth salts have shown efficacy against the SARS-CoV-2 virus in vitro [70, 71]. As a dose-dependent agent, bismuth potassium citrate (BPC) can significantly inhibit the nucleoside triphosphate hydrolase (NTPase) and RNA helicase activities of SARS-CoV-2 non-structural protein 13 (nsp13) [70]. Ranitidine bismuth citrate (RBC) not only effectively inhibits NTPase and RNA helicase activities, but also shows an inhibitory effect on the ATPase (half maximal inhibitory concentration of IC50 = 0.69 μmol·L⁻¹) and DNA-unwinding (IC50 = 0.70 μmol·L⁻¹) activity of SARS-CoV-2 helicase [71]. Re(I) tricarbonyl complexes can reduce the activity of the 3-chymotrypsin-like protease (3CLpro, IC50 = 7.5–24.1 μmol·L⁻¹), which is the SARS-CoV-2 main cysteine protease [34]. Karges et al. [34] synthesized and characterized a range of Re(I) tricarbonyl complexes capped by chloride and water ligands and investigated their activity in vitro. The aqua compounds show significant inhibition activity of the 3CLpro, possibly via reacting with the Cys145 active site residue (Fig. 6). Scior et al. [35] conducted computer simulations and reported that some vanadium complexes could combine with the major protease (M pro) of SARS-CoV-2 to inhibit virus replication. Gold metallodrugs are efficient inhibitors of SARS-CoV-2’s papain-like protease (PL pro), which plays a key role in virus replication [36]. Haribabu et al. [103] synthesized three Pd(II) complexes. These complexes have a higher affinity for the M pro of SARS-CoV-2 than that with chloroquine and hydroxychloroquine. Pectol et al. [104] proved that...
dinitroso-iron complexes (DNICs) could be used as inhibitors of SARS-CoV-2 Mpro through computer prediction and external studies. In addition, Bernstein and Zhang [69] used gallium maltolate (GaM) to treat SARS-CoV-2-infected Vero E6 cells to evaluate the antiviral ability. Its ability to prevent virus replication has been proven, and its efficacy is related to dosage. The concentration for 50% of maximal effect (EC50) of GaM was about 14 μmol·L−1, and cytotoxicity was not observed at a concentration of at least 200 μmol·L−1.

3.4 Improving efficacy of antiviral drugs

The use of antiviral drugs in combination with metal drugs can enhance efficacy and reduce side effects. Morad et al. [105] wrapped hydroxychloroquine on Ag, Au, and Pt nanoparticles and then conducted first-principles simulations of these particles. The results show that as a drug delivery system, precious metal nanoparticles (NPs) with antiviral and antibacterial properties can reduce side effects. Chloroquine/hydroxychloroquine combined with zinc or zinc complexes may enhance their clinical efficacy [30, 31]. Quinoline-based Cu(II) complexes are designed and synthesized as potential drugs against COVID-19 [106].

3.5 Metallodrugs as vaccine adjuvants to prevent COVID-19

Metal nanoparticles and metal salts can be used as SARS-CoV-2 vaccine adjuvants [107–109]. PiCoVacc, a purified vaccine candidate using an alum adjuvant, can protect rhesus monkeys challenged by SARS-CoV-2 [32]. Gold nanoparticles (AuNPs) functionalized with SH-PEG-NH2 have the potential to become a vaccine adjuvant [33].

3.6 Metal antiviral materials blocking spread of SARS-CoV-2

Adding antivirus coatings to masks, protective clothing, or touch surfaces (such as door handles and railings) can effectively inhibit the spread of the virus. Hosseini et al. [110] described a copper oxide porous hydrophilic coating, which can effectively reduce the SARS-CoV-2 virus infection rate and has good stability. Nonwoven masks with shellac/copper nanoparticles (CuNPs) nanocoating hybrid will be self-sterilizing and reusable [111]. Copper@ZIF-8 core–shell nanowires can impart antimicrobial activity to a medical-grade mask by processing the mask’s filter media [112]. Aasi et al. [113] evaluated the adsorption of hydrogen peroxide on metal-decorated single-walled carbon nanotubes. The results show that Pt-, Rh-, Ru- and Cu-single-wall carbon nanotubes are the best candidates for designing antiviral surfaces.

Silver and copper, which are regarded as common antibacterial materials, may also be effective in antivirus. Bright et al. [114] proved that copper and silver have the effect of inactivating coronaviruses. Zeolite (sodium aluminosilicate) powders amended with silver and silver/copper could cause significant reductions of human
coronavirus 229E. Therefore, we believe that silver and copper have the potential as antiviral agents.

3.7 Metallohydrogels as a promising antiviral drug for combating COVID-19

Hydrogels are widely used in the medical field. Incorporating metal components into the gel matrix can result in a multifunctional gel material [115]. One of the advantages is that hydrogels can be used as carriers to slow antiviral components’ release. It has been reported that the metal nanoparticles (mNPs) containing hydrogel can be used in antibacterial and anticancer treatments [116, 117]. In addition, the use of hydrogel to load paracetamol is recommended for the antipyretic treatment of COVID-19 to achieve the purpose of controlled release [118]. Therefore, metal drugs with antiviral effects are encapsulated in hydrogels to develop metal antiviral hydrogels with sustained-release effects. For example, the metal nano-drug hybrid hydrogel can be used in antiviral therapy through slow-release metal nano-drugs.

Metal ions have been proved to be effective physical cross-linkers for small molecule drugs to form hydrogels [39]. For instance, calcium ions have been employed to cross-link dexamethasone sodium phosphate to form a supramolecular hydrogel, and the anti-inflammatory effect of dexamethasone has been preserved in the resulting gel [40]. Dexamethasone has now been proved to reduce the death toll caused by SARS-CoV-2 [37]. By cross-linking dexamethasone with metal ions (e.g., \( \text{Ca}^{2+}, \text{Zn}^{2+} \)) to form a hydrogel, a safe and effective formulation of dexamethasone can be introduced to the patients. And by varying the ratio of dexamethasone/ion, the release rate of dexamethasone can be controlled. Moreover, through local injection or aerosolization of the hydrogel and inhalation, hydrogel prepared by non-covalent bonding between small antivirus molecules and metal ions can be applied directly to the lesion, providing a more efficient cure to COVID-19 patients.

4 Summary and outlook

In summary, this review briefly introduces the pathogenesis of COVID-19 and outlines current strategies in the prevention and treatment of COVID-19 using metal-related drugs. These preventions and treatment programs are mainly based on two approaches: immune regulation and antiviral therapy. Trace metal nutrients can regulate the body’s immune system and intervene in the process of viral infection, while many metallodrugs have been used as antiviral drugs, enzyme inhibitors, auxiliary drugs, and vaccine adjuvants. Therefore, it is worth attempting to develop new metallodrugs and repurposing existing metallodrugs. Based on the various applications of metallohydrogels in the medical field, the development of metallohydrogels may open up a new era of metallodrugs. Nevertheless, there is still a lack of data and clinical trials to verify the efficacy and safety of metal-based drugs in curing COVID-19. Further researches and evaluations remain necessary.

Acknowledgements This work was financially supported by Hunan Provincial Key Laboratory of Micro & Nano Materials Interface Science, the National Natural Science Foundation of China (Nos. 21773311 and 21972169), Hunan Provincial Science and Technology Plan Project, China (No. 2019TP1001).

Declarations

Conflicts of interests The authors declare that they have no conflict of interest.

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