



Exploring the Role of Heavy Metals and Their Derivatives on the Pathophysiology of COVID-19

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Received: 3 May 2021 / Accepted: 17 August 2021 / Published online: 27 August 2021
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Abstract

Many aspects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its disease, COVID-19, have been studied to determine its properties, transmission mechanisms, and pathology. These efforts are aimed at identifying potential approaches to control or treat the disease. Early treatment of novel SARS-CoV-2 infection to minimize symptom progression has minimal evidence; however, many researchers and firms are working on vaccines, and only a few vaccines exist. COVID-19 is affected by several heavy metals and their nanoparticles. We investigated the effects of heavy metals and heavy metal nanoparticles on SARS-CoV-2 and their roles in COVID-19 pathogenesis. AgNPs, AuNPs, gold-silver hybrid NPs, copper nanoparticles, zinc oxide, vanadium, gallium, bismuth, titanium, palladium, silver grafted graphene oxide, and some quantum dots were tested to see if they could minimize the severity or duration of symptoms in patients with SARS-CoV-2 infection when compared to standard therapy.

Keywords Heavy metals · COVID-19

Introduction

Since December 2019, the coronavirus infection disease 2019 (COVID-19), caused by a new form of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread around the world, killing thousands of people. Due to the rapid spread and ability of genetic mutations, and mortality from them, they have always been a major challenge for healthcare systems [1]. SARS-CoV-2 has 40 different strains and has created a worrying situation in the world [2]. This virus belongs to the family of SSRNA viruses and has four genera: alpha, beta,

gamma, and delta. Alpha and beta genus usually infect mammals, including humans [3], Unlike delta and gamma, which mainly infect birds [4]. In all of them, there are four types of proteins called spike (S), envelope (E), membrane (M), and nucleocapsid (N) [5]. Only protein S can bind to the receptors [6, 7] Although reports indicate that SARS-CoV-2 is more than 80% similar to the SARS genome and 50% similar to MERS, unfortunately, the SARS-CoV-2 transmission rate is much higher, but the resulting mortality rate is lower. Also, unlike SARS-CoV and MERS-CoV, which are more common in the hospital environment, SARS-CoV-2 is more prevalent in the community. The main SARS-CoV and SARS-CoV-2 receptors are both, ACE2, but the SARS-CoV-2 connection to the receptors is significantly faster (10 times). The main site of SARS-CoV-2 proliferation is the lungs, and after targeting the lungs, it damages the epithelium and causes inflammation. Cytokine secretion causes respiratory distress syndrome and multiple organ failure. Lymphopenia occurs in 81% of patients. There is also a decrease in platelets and albumin levels and an increase in aminotransferases, lactic dehydrogenase, keratin kinase, and CRP levels in COVID-19 patients. Acute respiratory distress syndrome occurs in 32.8% of patients, and acute heart damage occurs in 13%, which is a dangerous statistic

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[3]. The disease primarily causes damage to the upper respiratory tract and gastrointestinal tract [8]. Symptoms can vary depending on the degree of infection. These symptoms include respiratory problems, fever, cough, diarrhea, shortness of breath, and kidney failure [9]. Although COVID-19 threatens everyone, there is a higher risk for people with chronic obstructive pulmonary disease, obesity, cancer, smoking, immunodeficiency [10], hypertension, diabetes, respiratory disorders, and heart disease and they are more sensitive, so they need more health care. According to reports [11, 12], COVID-19 patients have a median age of 51.2 years, with males accounting for 55.9% of cases. The incubation period of the disease is 3 to 7 days. Diagnosis of coronavirus is by samples such as nasal swabs, nasopharyngeal or tracheal extract, sputum or lung tissue, and blood or feces of patients [13]. The laboratory diagnostic method is applied by the detection of nucleic acid by the reverse transcription–quantitative polymerase chain reaction. Despite many efforts, there is no definitive cure for this disease [3]. To provide treatment to patients, we need to use the currently approved drugs. But these available antiviral drugs are only a temporary solution, and definitely it will take some time for targeted therapies for the virus to be tested and reach the point of mass use by the general public. Vaccination is the only treatment that both strengthens the immune system and increases the number of antibodies [14].

Today, nanoparticles have entered the field of corona control as an important issue [15], especially since the virus has a diameter of 60 to 140 nm, which is only slightly larger than nanoparticles, and this similarity in diameter is very beneficial [6]. The small size of the nanoparticles helps them to enter [1]. Nanoparticles are a new therapeutic approach and have attractive properties such as small size, specific shape, adjustable surface charge, paramagnetic cloud, photon conversion, bioavailability, biocompatibility, tolerance, and biodegradability and adaptability [16–18]. In addition, these nanoparticles can cross the blood–brain barrier and the blood–air barrier. Stable and targeted controlled secretion is also possible with them. Nanomedicine is involved in all areas of medicine. In gene delivery, artificial implants, immunoassays, biosensors, cancer treatment or diagnosis, imaging, nanotherapy, vaccine and biological material production, and targeted drug delivery are used. Nanoparticles have antimicrobial effects. Although their antiviral effects have not been conclusively proven, hopes are still high, and scientists are studying it. Nanoparticles consisting of titanium, silver, gold, and zinc have previously been shown effective against HIV, influenza, herpes simplex, RSV, and smallpox, and zikavirus [1, 12, 19–22].

Elemental heavy metals and their salts or complexes also have many effects on the body and disease. Inhibition of viral RNA synthesis, prevention of virus binding to cells and its entry [1, 6, 23], improving the inflammatory responses

[22, 24], inhibiting the viral replication [25, 26], stimulating and activating T cells [27], and inhibiting helix unwinding and ATPase activity of SARS-CoV-2 nsp13 [27] are some of the effects of heavy metals and their salts or nanoparticles on COVID-19. This study was aimed to review recent SARS-CoV-2 research to outline heavy metals and their derivative on the pathophysiology of COVID-19.

Method

The bibliographic search was performed on PubMed, Scopus, and Web of Science databases on February 4, 2021. Search keywords including “Arsenic” OR “Bismuth” OR “Cadmium” OR “Chromium” OR “Gallium” OR “Mercury” OR “Nickel” OR “Palladium” OR “Pb” OR “Silver” OR “Thallium” OR “Tin” OR “Titanium” OR “Vanadium” OR “Gold” OR “Metals” AND “coronavirus 2019” OR “COVID-19” OR “SARSCoV-2” in all fields. Any languages or date restrictions were not applied. Identified studies were screened by title, abstract, and full text. The reference list of identified studies was also evaluated to increment the sensitivity and choice of most literature, which we could not identify in the database. Initiate with most excellent sensitivity search found the number of 167 articles on external databases, and collected by a researcher using Endnote software. Then unifying the articles from all the cited databases and bringing out duplicate articles, the two researchers separately investigated all the articles and excluded the articles that were not related to the topic and the inclusion index criteria. Afterward, several articles after reviewing titles and abstracts were excluded. The extant articles were cautiously evaluated, and the relevant study was selected. The data for the studies, based on the title, examined method, sample size, etc., were evaluated. Finally, after obtaining related articles and limitations of search strategy, 100 articles were analyzed. During the reviewed articles in 2021, if we identified a new article, we would include it in our study.

Results

Selenium Nanoparticles and Ebselen

In the previous study [28], we discussed the level of selenium and its involvement in COVID-19. There is relativity between selenium level and COVID-19 cure rate. Patients with a higher level of selenium in their hair samples had a higher cure rate than patients with a lower amount of selenium. And it has been observed that patients who survived from COVID-19 had a higher level of selenium in their serum [29–34]. So we hypothesized that a higher intake of Se can lead to a higher cure rate in COVID-19. Selenium can

boost the immune system by enhancing the role of natural killer cells and T lymphocytes. Also, it has shown some antiviral activities [35]. The main consideration of selenium is its toxicity in high doses. Selenium has different forms but nano-selenium has lower toxicity and higher bioavailability and efficiency in preventing oxidative damage [36–39]. Also, selenium nanoparticles can be used in detection kits for SARS-CoV-2 [40]. Ebselen is an organic species of selenium. It has benefits in curing COVID-19; it can inhibit the COVID-19 virus through binding to the M^{pro} virion in the cell membranes [41]. Ebselen is a safe form of selenium and does not have toxicity which is observed in other forms of selenium and has the most efficacy at the concentration of 10 μ M against COVID-19. Also, hepatic damages that have been observed in patients infected with COVID-19 can be inhibited by ebselen [42–46].

Iron Oxide Nanoparticles

As we discussed in our last article in detail [28], the iron level of the body affects the COVID-19, so that abundant iron can increase viral infections. We observed that iron chelators may be beneficial because they reduce the iron level and it causes prevention in SARS-CoV-2 replication [47]. Now we will talk about the iron oxide nanoparticles. These nanoparticles are well biocompatible. Since they are presently used to treat anemia and are Food and Drug Administration (FDA) approved, they can be effectively produced on a large scale. In any case, for their antiviral effects, more tests ought to be done to get more exact data and make their use more secure and more useful [48]. The antiviral action of these nanoparticles is due to their binding to virus surface proteins. As a result, they interfere with the virus entering the cells. We know that SARS-CoV-2 must bind to the ACE2 receptor to enter the cells, which the spike protein in the virus is exceptionally vital in this process. Iron oxide nanoparticles attach to the coronavirus spike protein [2, 48]. The S1 subunit has the receptor-binding domain (RBD) that makes the virus highly desirable to the receptor. The result of this attaching to spike protein is the inhibition of virus binding to the host receptors and thus the inhibition of the virus. These changes within the structure of the virus may be irreversible and the viral infection is reduced. Iron oxide nanoparticles can also be used within the generation of robes, masks, gloves, hospital fabrics, etc., to anticipate the spread of infection [48]. The docking study studied by Abozeid et al. found that interaction of iron oxide nanoparticles (IONPs) with S1-RBD results in the creation of the most stable complex, which is thought to be linked to viral protein conformational changes and hence impede virus entry into host cells. A clinical trial for FDA-approved IONPs for COVID-19 treatment has been authorized, as this binding

could trigger virus elimination through the formation of reactive oxygen species [48].

Silver Nanoparticles (AgNP)

Many different inorganic nanomaterials have been studied to fight the coronavirus; the most effective are AGNPs, which act as potential antiviral agents as well as drug carriers [49]. They have biological activities and antibacterial, antifungal, and anti-cancer effects [50–52] and catalytic properties [16, 17]; non-toxic nature and high quantum efficiency [18, 53]; disinfectant capacity [54, 55]; stability [56]; water purification properties [57]. Silver-based nanomaterials have antimicrobial and antiseptic effects by producing reactive oxygen species (ROS) and are currently used to treat COVID-19 patients [6].

Although these nanoparticles have not yet been definitively considered for the treatment of SARS-CoV-2, given their previous therapeutic effect against some viruses such as HIV, influenza, hepatitis B, and RSV and neuro-viruses, hopes for its use against SARS kept alive [58]. AGNPs are synthesized by physical, chemical, and biological methods, but the biological method is more environmentally friendly and safer [59]. So far, four types of AgNP have been reported as treatment candidates:

1. Glutathione-capped silver sulfide nanoclusters (GSH-Ag₂S NCs)
2. PVP-coated silver nanomaterials (PVP-AgNMs), which include silver nanowires (AgNWs) and silver nanoparticles (AgNPs)
3. Silver nanoparticle–anchored graphene oxide nanoparticles (GO-AgNPs)
4. PDDA-coated PVP-functionalized graphene oxide-silver nanocomposites (PDDA-PVP-GO-AgNCs) [60]

Their main mechanism is not yet known for sure, but AGNPs inhibit the entry of viruses and also prevent the formation of free radicals in the interaction with biological molecules. They also damage cellular DNA and RNA. A small number of AGNPs have antiviral properties against beta coronavirus [61]. Ag⁺ ion reduces oxidative stress, induces antibody response and cytokine production, and inhibits viral RNA synthesis. It also binds to the gp-120 subunit glycoprotein of the virus and inactivates the virus before binding to the host [1, 6, 23].

Continuous Ag⁺ production is important for therapeutic effect [62]. The pseudovirus entry assay test showed that AGNPs interfered with the entry of the virus. AGNPs bind to proteins on the surface of the virus that is rich in sulfhydryl groups. AGNPs cause the breakdown in disulfide bonds, and the proteins become unstable. As a result, they are effective against virus infection because disulfide bonding is very

important in binding the SARS-CoV-2 virus protein spike to the ACE2 receptor. AGNPs can also be useful in killing intracellular viruses by interacting with viral nucleic acids [58]. They have almost no specific toxicity and can be safely used in studies [63]. The existing hypothesis attributes AGNP toxicity to the direct binding of metal to the surface of a viral protein [60]. ROS production can also be effective in toxicity. Toxicity is concentration dependent (usually seen at concentrations above 20 ppm), and a series of surface changes can prevent metal surfaces from attaching directly to cells to reduce toxicity. Toxicity also depends on the type of cell and the type of AGNPs and their size. So the smaller particles cause more contact surface with the protein and create more toxicity (AGNPs with a size of 2 nm are toxic even at a concentration of 2 ppm). If AGNPs be improperly disposed of, they can have detrimental effects on the destruction of the ecosystem. So we have to have a proper protocol for disposal. The greatest effect of AGNPs is seen in the diameter range of 2 to 15 nm. Coated or capped AGNPs are better than simple AGNPs because they are both more stable and less agglomerated and their cytotoxicity is reduced [58].

The therapeutic effect of oral inhalation of AGNPs: Inhalation of colloidal silver solution fights respiratory infections, which is very important for oral inhalation of colloidal nanoparticles to determine the level of minimum inhibitory concentration (MIC) [6, 64, 65].

Gold Nanoparticles (AuNP)

AuNP is used to identify DNA sequences, proteins, bacteria, and viruses and usually has antiviral and antibacterial effects in cancer studies. AuNP activates GNR-50PPP-SSRNA immunity through nanocomplexes, which reduces the replication of viruses, including influenza H1N1 virus, by regulating the expression of IFN- β and other IFN stimulated genes (ISGs) [66]. AuNP hyaluronic acid and IFN complex are used for the targeted treatment of hepatitis C infection [67]. Highly nanodispersed quasispherical AuNP inhibits HSV and is very safe, does not induce resistance, and also has good antiviral properties [68]. AuNP suppresses HIV, influenza, and HSV [69, 70]. AuNP improves the inflammatory response by reducing the expression of interleukin IL1, IL6, TNF- α , INF- γ , and nitric oxide synthetase [22, 24].

AuNPs have good biocompatibility and, if used in vaccine production, stimulate the immune system well and are easily distributed through lymph nodes in the body and activate CD8+ (T killer cell mediated). They are also used for intranasal distribution [24]. They also have the potential to detect viruses as well as antiviral effects, and because of their stable nature, further studies are not useless [71]. Even though there is no authoritative remedy for COVID-19, controlling excessive inflammation or cytokine storms can help treat patients. IL-6, in specific, plays a critical part

in causing extreme side effects and harm, so neutralizing and reducing its level decreases the cytokine storm [72, 73]. Cytokine storm, which is accompanied by excessive inflammation, can put an individual with COVID-19 in a critical circumstance. In truth, this storm of cytokines disturbs the functioning of the immune system. Looking at patients conceded to the ICU who involved serious side effects of the infection, we discover that the level of IL-2, IL-7, IL-10, TNF- α , and granulocyte-colony-stimulating factor is higher than ordinary. There is also an increment within the systemic level of IP-10, monocyte chemoattractant protein-1 (MCP-1), and macrophage incendiary protein-1A (MIP-1A) in COVID-19 patients [74, 75]. So we can say that cytokine storms can increment the risk of death [75]. Finally, we can say AuNPs may affect COVID-19 due to their reducer effect on the expression of cytokines like IL1, IL6, TNF- α , and INF- γ and inhibiting the cytokine storm.

Gold-Silver Hybrid NP

Combined gold and silver nanoparticles could be a therapeutic strategy to prevent coronavirus. They are a type of core-shell heterostructure nanocrystals used today in various fields such as decomposition, optical devices, electrical devices, and acoustic imaging. Continuous Ag+ release is very important in the therapeutic response. As the number of viruses increases, more reactive oxygen species (ROS) are produced, causing the silver shell to oxidize at the Au/AgNP level. As a result, it releases Ag+, which enhances its antiviral activity, and these results encourage us to treat coronavirus [62].

Copper Nanoparticles

Copper is an essential trace element in the body and the need for protecting DNA from oxidative stress. The role of copper in the pathophysiology of the coronavirus was discussed in our previous work in detail [47]. Briefly, with oxide iodide and sulfide forms, it has antiviral activity against herpes simplex, influenza H1N1, and human neuro virus [76]. The controlled release of copper ions, which is possible by the nanosystem, is the main cause of the antimicrobial and antiviral effects. With the controlled release of copper ions, the production of ROS species is also regulated [77]. Copper has activity against SARS-CoV-2 by three mechanisms: (1) damaging virus membrane and destruction of DNA and RNA, (2) generating reactive oxygen species (ROS) that kills virus, and (3) interfering with important and functional proteins [78–87]. It is hypothesized that an increase in copper levels is related to the body's physiological response to inflammation [88]. Copper may raise ceruloplasmin levels, improving the human body's response to inflammation. Ceruloplasmin has been proven to help the host defend itself by balancing

the excessive levels of ferritin [89]. Andreou et al. in their study proposed combining the five medicines including remdesivir (RDV), copper, N-acetylcysteine (NAC), NO, and colchicine as a possible antiviral therapy for SARS-CoV-2. NAC may prevent the host cells from excess toxicity of copper, but NAC reduces the absorption of copper. However, a combination of copper with NAC could be used to decrease the RNA levels of the virus in the early stage of infection. Also, combination therapy of copper, NAC, RDV (as antiviral agents), NO (as pulmonary vasodilation), and colchicine (as cytokine storm inhibitor [90]) could decrease or even stop the infection [91]. So it may be suggested that copper nanoparticles may also affect the pathophysiology of COVID-19 due to their impression on ROS production.

Quantum Dots

Nanocrystals are semiconductor materials with a size of 2 to 10 nm. Used in cell labeling and image recognition and tracking and includes carbon, silver, gold, CdSeS/ZnS, etc. [92]. In combination with fluorescent samples, it is also used for continuous fluorescence detection and imaging in a series of cellular processes [93]. Unfortunately, their antiviral use is limited. GSH (glutathione)-coated telluride cadmium (Cd) TeQDs alter PRV surface proteins, preventing the virus from entering the host cell [94].

Curcumin-stabilized cationic carbon dots (CCM-CDots) alter the structure of the virus's surface proteins, thus suppressing the synthesis of the negative strand of an RNA virus and preventing the virus entry through ROS generation. As a result, they stimulate the production of ISGs as well as pro-inflammatory cytokines [22, 95].

Zirconium QDs are also more sensitive to corona detection than the ELISA method. QDs can be very effective, and on the other hand, one strategy is to cover the therapeutic molecules on the QDs and introduce this product into the body. The benefit of this is that the drug can slowly release the active ingredient in the body [96].

Metal-Grafted Graphene Oxide (GO)

It is a carbon atom with a thickness of one atom located in a hexagonal lattice in two dimensions [97] and is used as an agent against bacteria and anti-cancer effect [98]. Metal-grafted graphene oxide has an antimicrobial effect and is used with metals such as silver, iron, zinc, and copper or with photocatalysts such as MnS₂, CdS, and TiO₂[77]. GO nanocomposites with AGNP provide better antiviral activity than GO alone or even AG alone [99]. Antiviral activity of silver graphene (GO-Ag) oxide nanocomposites against enveloped and non-enveloped viruses has been reported [1].

Zinc Oxide

It has significant antimicrobial activity. The role of zinc in the pathophysiology of coronavirus only and combination with agents such as hydroxychloroquine was discussed in our previous work [47]. Zinc-containing compounds have recently been observed to have antiviral activity against SARS-CoV-2. These compounds act on the virus by binding to the virus and destroying the viral coat, as well as inhibiting viral protease and polymerase. In particular, hesperidin-mediated zinc nanoparticles bind well to the main protease of SARS-CoV-2 and act on the site of action on the ACE2 receptor and inhibit virus entry. Zinc oxide nanoparticles are well absorbed and inexpensive. They are also low in toxicity and safe [100]. Zinc has an antiviral effect through a series of processes such as the effect on binding, penetration, infection, uncoating, and replication of the virus [101]. Since zinc is a membrane stabilizer, it can directly inhibit virus entry into the host cell [102]. Zinc salts can have an antiviral effect on SARS-CoV-2 by inhibiting virus entry and polyprotein processing or inhibiting RNA-dependent RNA polymerase (RdRP) activity [25, 103]. Zinc stimulates metallothioneins (metal-binding proteins that can regulate zinc homeostasis and reduce heavy metal toxicity [104]) to release zinc into the cytoplasm, decreases oxidative stress caused by RSV and influenza, and maintains a state of cellular redox [105]. The entry of the virus into the cell activates the NF- κ B, which can cause a cytokine storm in the patient and increase the ARD [106, 107]. Zinc can suppress kappa kinase activity, thus inhibiting NF- κ B signaling and producing fewer pro-inflammatory cytokines [103, 108, 109]. Inhibition of NF- κ B also increases the antiviral effect of IFN. Also, this dietary intervention with zinc in appropriate concentrations can increase enterocyte stores and improve gastrointestinal symptoms caused by the SARS-CoV-2 virus [103]. Zinc is involved in the production of IL-12 and IFN and also increases IL-12 production by stimulating macrophages, and IL-12 can activate natural killers and T cytotoxic cell. Although zinc has many benefits, high doses of zinc over 6 weeks can disrupt activity and neutrophils, thereby suppressing immunity, and there is a concern about long-term use of zinc. Zinc has good antioxidant, anti-inflammatory, and immune regulatory activity, thus protecting the body against the virus. Given all this, zinc can be considered a good option to deal with SARS-CoV-2 [104]. Briefly, negatively charged zinc oxide ZnO-MNSs trap viruses and prevent them from entering corneal fibroblasts that are the target of HSV1 infection. It can also prevent the virus from spreading [110]. Zinc combined with pyrithione interferes with SARS-CoV-2 RNA replication in cell culture, thus preventing it from replicating [25, 26]. Also in silico studies were done to obtain the best target for treatment. According to Mohamed Hamdi's study in 2021, Zn oxide NPs with

a high degree of purity and crystallinity were successfully produced. A putative interaction between ZnO NPs and the ACE2 receptor as a COVID-19 target has been predicted using *in silico* molecular docking. In CCD-19Lu human lung fibroblasts, a dose-dependent cellular absorption of ZnO NPs was achieved. The findings point to the disclosed ZnO NPs' potential for respiratory tract infection outbreaks, suggesting that they could be used alone or in combination with other pharmacologically effective horizons for further investigation and technological transfer [111]. Quercetin (a ubiquitous natural flavonoid) having anti-inflammatory, antiviral, anti-proliferative, anti-oxidative, anti-bacterial, and anti-cancerous activity is a zinc ionophore and prevents the virus from entering the cells. So the combination of zinc and quercetin could be against COVID-19 in two different ways: (a) quercetin inhibits entry of virus and (b) zinc inhibits viral transcription [112]. Also, hydroxychloroquine (HQ) is a zinc ionophore, increases the intracellular concentration of zinc, and so increases the effect of zinc on the RdRP of the virus [113]. The antiviral activity of HQ has been interested recently and HQ is a candidate for the treatment of COVID-19. However, HQ has not had any effects on some viruses including influenza in clinical studies. HQ also reduces the acidity of the endosomes so the release of viruses into the cytoplasm will be prevented. The combination of HQ and zinc might be beneficial in the treatment of COVID-19 [114].

TPNT1

TPNT1 is the name of the colloidal aqueous solution containing Au-NP (1 ppm), Ag-NP (5 ppm), ZnO-NP (60 ppm), and ClO₂ (42.5 ppm) with + 32.81 zeta potential. In plaque reduction assay, the number of plaques was significantly decreased with the 100-fold diluted TPNT1 containing 0.01 ppm Au-NP, 0.05 ppm Ag-NP, 0.6 ZnO-NP, and 0.425 ppm ClO₂. The IC₅₀ of TPNT1 was calculated 143 ± 15.5-fold dilution. It has been determined that 93.5–100% of plaque formations of widespread SARS-CoV-2 strains (NTU03, NTU14, and NTU16) could be inhibited by TPNT1. It has been observed that the viral replication and also viral nucleoprotein expression in H1975-ACE2 cells could be inhibited by TPNT1. Better inhibition of SARS-CoV-2 replication occurred when SARS-CoV-2 was pre-incubated by diluted TPNT1. According to results from ELISA assay using ACE2-Fc-biotin and spike protein, TPNT1 could inhibit the binding of SARS-CoV-2 spike protein to ACE2 receptors. After receptor binding, syncytium formation is an important step for entry of the virus. Results show that syncytium formation has an obvious reduction by using TPNT1. As we say above, TPNT1 may be a prophylactic option for SARS-CoV-2 and its side opportunistic

infection. More studies are needed for better knowledge about these metal nanoparticle compounds [115].

Vanadium

It is a versatile metal and in various combinations and can be effective in treating diseases such as diabetes and even cancers. Vanadium compounds, for example, affect the body's immune system by stimulating and activating T cells. Vanadium polyoxide clusters have a good antiviral effect. Also, due to their nuclear properties, they can be a suitable contrast agent that can be used in imaging and better detection of radiological images [116]. Vanadium-based drugs are considered today because they are both less toxic and can have biological activities such as anti-diabetic and anti-cancer properties [117]. Due to vanadium compounds stimulate and activate T cells, they may improve the immune system against coronavirus.

Gallium

An elderly woman with acute respiratory failure, who was diabetic, with COVID-19 infection has been evaluated. The gallium scintigraphy in this patient demonstrated a higher level of gallium uptake on the right mastoid with focal intense, which means she had right mastoiditis; however, low level of gallium uptake in lung tissue had been observed even though COVID-19-related pneumonia was getting worse. Although gallium scintigraphy is effective to identify lung infections, gallium is not effective to COVID-19-related lesions in the lung and there is no relation between Ga uptake in the lung and COVID-19-related lung disorders [118]. On the other hand, there is some evidence that gallium has shown both anti-inflammatory and antiviral activity due to its chemical similarity to Fe³⁺ and zinc. There are three hypotheses that show gallium maltolate GaM could have antiviral activity against COVID-19. One of them is that Ga could compete with zinc and as it is known that Zn is essential for COVID-19 entry to cells; another theory is that Ga could compete with iron ions, and it can cause iron deprivation; iron being vital for the replication of the virus means that Ga could be effective [119, 120]. And at last, it is observed that gallium has an anti-inflammatory effect which is effective against hyperinflammatory signs observed in harsh cases of COVID-19 patients which is similar to septic shock [121, 122]. GaM inhibited replication of virus dose dependently with a concentration of 14 μM, which replication inhibited by 50% [123].

Bismuth

According to biochemistry effects of SARS-COV-2 Nsp13, it has shown that Nsp13 has both nucleoside triphosphate

hydrolase (NTPase) and RNA helix unwinding activity. The presence of some divalent metal ions is vital for NTPase and also helix unwinding activity of SARS-CoV-2 nsp13. For example, some of these ions such as Mg^{2+} , Mn^{2+} , Zn^{2+} , and Ca^{2+} have a supportive effect on ATPase activity of nsp13; however, Mg^{2+} has the highest efficacy on ATPase activity. However, if Mg^{2+} concentration is more than 2 mmol/L, it has an inhibitory effect on ATPase activity. The effects of three bismuth salts on nsp13 activity have been evaluated. Three bismuth salts including bismuth potassium citrate (BPC), ranitidine bismuth citrate (RBC), and bismuth citrate (BC) which are used in gastrointestinal diseases. All RBC, BPC, and BC have strong dose-dependent Nsp13 inhibitory effects. However, BC had a less inhibitory effect. So it has been seen that these drugs could inhibit both helix unwinding and ATPase activity of SARS-CoV-2 nsp13 [27]. Nsp enzyme is essential for replication of SAR-CoV-2. This enzyme has zinc-binding domains on its structure and bismuth (III) has an inhibitory effect on this enzyme. Based on the previous analysis, SARS-CoV-2 helicase has three canonical zinc fingers [124]. Ranitidine bismuth citrate can bind to Nsp13 and separate zinc from zinc-binding domains of the enzyme [125]. Bismuth citrate has shown potent anti-SARS-Cov-2 activity both in vitro and in vivo, and the affinity to infected cells was high with an index of 975. RBC is not effective in replication of the virus at the pre-incubation level; however, viral load will be decreased by 2 logs when RBC adds in co-incubation and post-entry-level, which means this drug has a function in the viral entry level [125]. Bismuth alone is not as effective as RBC, and also RBC had much more affinity to bismuth. An 85-year-old man with Crohn's disease who has diarrhea problem in the last 10 days of his visit was evaluated. He also complained about his debilitating cough problems and 5-day regimen of azithromycin prescribed by his primary physician, which was not effective. So he was also suspicious of COVID-19, and while he was waiting for the results of his laboratory tests, he was prescribed with oral 525 mg 2–4 times a day bismuth subsalicylate (BSS), and in the first 6 h of therapy, diarrhea problems improved. Results of the laboratory tests demonstrated that he was COVID-19 positive. After 6 days of BSS therapy, he had improvements in cough and diarrhea. So BSS could have antiviral activity because it can potentially inhibit severe acute respiratory syndrome coronavirus helicase adenosine triphosphatase [126].

Titanium

Different effects of titanium complexes have been evaluated (antibacterial effects, antifungal effects, and its effect on SARS-CoV-2). Some Schiff base complexes of titanium (HNP-Hn-HNPH2 complex) in silico studies showed better affinity and anti-retroviral activity than standard

hydroxychloroquine. It has evaluated that the titanium complex had the most affinity to SARS-CoV-2 main protease (6LU7), and also this ligand is non-carcinogenic and it does not inhibit P-glycoprotein [127].

Palladium

The affinity of three different complexes of Pd to the main protease of SARS-CoV-2 has been evaluated, and the docking energy of these three complexes was significantly more than chloroquine and hydroxychloroquine, which means Pd complexes have a much better affinity [128].

The data are summarized in Table 1.

Discussion

In our previous study, we discuss the roles of trace elements and electrolytes in the pathophysiology of COVID-19. We discovered that changes in electrolytes or trace elements in the body affect the pathophysiology of COVID-19 [28]. Here the important findings were presented in Table 1. Abundant zinc has a good effect due to its antiviral property [129, 130], but increasing iron has a bad effect because it rolls in viral replication [131, 132]. COVID-19 patients showed both hypokalemia and hyponatremia, and we know that sodium and potassium are involved in many functions in the body, and their changes may cause some dysfunctions [133, 134]. Some other metals and nutrition were discussed in the previous study. Now we studied heavy metals and their salts or nanoparticles in this research. We demonstrated that Ag nanoparticles inhibit virus entry, reduce oxidative stress, and inhibit viral RNA synthesis [1, 6, 23]. Au nanoparticles reduce the expression of some cytokines like IL1, IL6, TNF- α , and INF- γ , so they might be useful in COVID-19 patients to prevent cytokine storm [22, 24, 75]. A combination of silver and gold nanoparticles (gold-silver hybrid NPs) provides a continuous release of Ag^+ and might have better effects compare to each one alone [62]. Copper nanoparticles have a regulatory effect on ROS production and so might influence the pathophysiology of COVID-19 [77]. Metallic quantum dots can be produced from some metals. GSH-coated telluride cadmium (Cd)TeQDs can prevent some viruses from entering [94]. Zirconium QDs are used for the detection of coronavirus, and they are more susceptible than ELISA [96]. Also, silver graphene (GO-Ag) oxide has shown antiviral effects against enveloped and non-enveloped viruses even more than Ag alone [1, 99]. Vanadium can stimulate the activation of T cells [116], and bismuth has an inhibitory effect on helix unwinding and ATPase activity of SARS-CoV-2 nsp13 [27], so these metals might be useful in the treatment of COVID-19. About gallium

Table 1 Data summary

Metals and NPs	Target	Action
AgNp	The virus itself and entry of the virus	AGNPs inhibit the entry of the virus and prevent the formation of free radicals and also have an antiviral effect on beta coronavirus [1]. Ag binds to the gp-120 subunit glycoprotein of the virus and inactivates the virus before binding to the host [2–4]
Silver grafted graphene oxide (GO)+	-	GO nanocomposites with AGNP provide better antiviral activity than GO alone or even AG alone [5]
AuNP	Cytokines and immune response of the body	AuNPs may affect COVID-19 due to their reducer effect on the expression of cytokines like IL1, IL6, TNF- α , and INF- γ and inhibiting the cytokines storm [6, 7]. They also activate CD8 + cells [6]
Vanadium	The immune response of the body	Vanadium compounds stimulate and activate T cells; they may improve the immune system against coronavirus [8]
Copper nanoparticles	Effect of the virus on the body	Copper nanoparticles affect the pathophysiology of COVID-19 due to their impression on ROS production [9]
Zinc oxide	Replication of virus	Zinc combined with pyrithione that interferes with SARS-CoV-2 RNA replication in cell culture, thus preventing it from replicating [10, 11]
Bismuth	Replication of virus	Bismuth compounds inhibit both helix unwinding and ATPase activity of SARS-CoV-2 nsp13 [12]. Bismuth citrate has shown potent anti-SARS-Cov-2 activity both in vitro and in vivo [13]
Gallium	1. Entry and replication of virus 3. Immune response of the body	There are three hypotheses: 1. Ga could compete with zinc and as it is known Zn is essential for COVID-19 entry to cells 2. Ga could compete with iron ions and it can cause iron deprivation since iron is vital for the replication of the virus [14, 15] 3. Gallium has an anti-inflammatory effect which is effective against hyperinflammatory signs [16, 17]
Zirconium quantum dots	Detection of virus	They are more sensitive to corona detection than the ELISA method [18]
Titanium	-	Titanium complex had the most affinity to SARS-CoV-2 main protease (6LU7) and also this ligand is non-carcinogenic and it does not inhibit P-glycoprotein [19]
Palladium	-	Three different complexes of Pd have an affinity to the main protease of SARS-CoV-2 [20]

there are two ideas, some studies believe that gallium has an anti-inflammatory and antiviral activity against SARS-CoV-2 and inhibits viral replication [119–123], but other studies believe that there is no relation between gallium uptake and COVID-19 related disorders [118]. Palladium and some Schiff base complexes of titanium have an affinity to the main protease of SARS-CoV-2, so they may be useful in vaccine production [127, 128]. There is no sufficient information about toxicity and the adverse effects of metal nanoparticles. The toxicity of nanoparticles depends on some factors including type, shape, size, purity, administration route, and the time of exposure to metal nanoparticles. It has known that spherical metal nanoparticles are non- or less toxic than other shapes. The data of studies about toxicity and adverse effects of metal nanoparticles are not enough or may be sometimes consistent. So more research is needed for sufficient and reliable information about toxicity of metal nanoparticles [115]. Considering the effects of heavy metals and their products like nanoparticles and quantum dots, preventing and treatment of

COVID-19 seems useful and might help us better control the disease.

Conclusion

In the present study, by reviewing the available articles, we inquire about the effects of heavy metals and their other forms, including nanoparticles, quantum dots, and salts, to see if they have roles in the pathophysiology of COVID-19 and which one is more effectual. We observed that some metals or their other forms have good effects on SARS-CoV-2 and its disease COVID-19 and can improve patients. More studies and clinical assessments need more information about the effects of metals on COVID-19 to decide on using them in prevention or treatment lines.

Author Contribution Conception and design of the study: F.N. and M.T.; acquisition of data, analysis, and interpretation of data: A.B.,

F.N., H.N., and F.N.; drafting the article: A.B. and F.N.; revising the article critically for important intellectual content: M.T., M.A., S.H., A.F and F.N.; final approval of the version to be submitted: M.T. and F.N.

Funding This work was support financially by Hamadan University of Medical Sciences, Hamadan, Iran.

Data Availability All data are available via the corresponding author.

Code Availability Not applicable.

Declarations

Ethics Approval This study has been approved by the Ethics Committee of Hamadan University of Medical Sciences. Hamadan, Iran (IR.UMSHA.REC.1400.379).

Conflict of Interest The authors declare no competing interests.

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