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Research Article

Metal Complexes and Their Potential Therapeutic Role Against COVID-19: Recent Developments in Drug Designing

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Abstract

COVID-19 is a global pandemic caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Being associated with high mortality rates, this pandemic has forced several countries worldwide to impose complete lockdowns to limit the spread of infection. Despite the development of various vaccines, there is still an urgent need to design novel treatments backed with safety data for fighting SARS-CoV-2 and its various mutants. Currently, scientists are putting their strenuous efforts into finding the best treatment option for COVID-19. In this regard, metal complexes being active antiviral agents and immunity enhancers have great potential against SARS-CoV-2. Herein, metal complexes' therapeutic role and significance against treating SARS-CoV-2 or any of its target proteins are discussed.

Keywords: COVID-19, SARS-CoV-2, pandemic, metal complexes

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1. Introduction

In December 2019, a novel virus called severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was identified as a causative agent of COVID-19. Unfortunately, the swift spread of this virus resulted in loads of mortality and morbidity across the globe [1]. On March 11, 2020, the World Health Organization (WHO) declared this health emergency a pandemic and issued various safety measures to prevent the spread of infection. During the pandemic, almost all sorts of academic, social, cultural, and political activities were canceled, and a complete lockdown was observed worldwide to limit the spread of infection. Throughout 2020, scientists were engaged in discovering, investigating, and analyzing various drugs to determine the cure of this lethal disease [2–4].

2. Overview

Currently, many compounds are under clinical evaluation; however, the best treatment option is still not known. Providentially, after strenuous efforts of scientists in collaboration with academia and pharmaceutical industries, many effective vaccines had been developed in 2020. These vaccines provide a prophylactic defense to healthy people but may be less useful in the emergence of virus variants and patients with a compromised immune system. Therefore, it is necessary to seek additional novel cures for COVID-19 [5].

In an attempt to find new treatments, researchers are also focusing on preparing and screening drug metal complexes. Apart from being a potential candidate to treat COVID-19, drug metal complexes could be a source of multifold benefits, for example, the human body needs metal ions to perform vital functions such as an iron-containing protein (hemoglobin) that carries oxygen to all tissues of the body. Similarly, zinc fingers play a role in DNA recognition and the regulation of gene functions [6, 7].Moreover, trace elements including zinc and copper are essential for growth and play a role in the development and boosting of the immune system. In this aspect, different approaches can be considered to utilize drug metal complexes as effective therapeutic agents against COVID-19 [8].

Initially, drug repurposing strategy can be considered to assess previously established metallodrugs, such as a gold drug called auranofin seems a potential candidate, yet few other approved metal complexes are also creditable. Secondly, chemically diverse libraries of inorganic compounds can be monitored to identify molecules with efficient activity against COVID-19. This approach is the pathway-guided discovery which is based on basic knowledge of the mechanism of action and exploration of the chemical entities that effectively inhibit viral proteins responsible for COVID-19 pathogenesis [9].

Many computational tools are available that are frequently used in research to gauge the activity of chemical compounds based on an understanding of the drug and its target structure. In this respect, vanadium complexes were screened and found to be effective against COVID-19 [10]. Recently, copper complexes of two ligands, including chloroquine and hydroxychloroquine, were prepared, characterized by various techniques such as X-ray diffraction, spectroscopy, and thermal analysis, and screened via *in silico* method. The study outcomes verified that polar and non-polar groups in metal complexes were balanced compared to the parent drug. This balance in structure facilitates metallodrug binding to the active site of the viral ADP-ribose-1 monophosphatase enzyme. As a result, the activity of this enzyme is inhibited, which is the desired effect to prevent

COVID-19 infection [11]. Another in silico study reported the synthesis of Cu (II) and Co (II) thiazole-based ligand complexes and described their role as facilitators for interacting with COVID-19 proteins via molecular docking studies [12]. Moreover, Refat *et al.* confirmed the synthesis of binuclear Schiff base complexes (Zn[II], Cu[II], Co[II], and Ni[II]) through elemental, electronic, and spectral analysis. The synthesized drug metal complexes were further screened for biological evaluations through molecular docking. The results of molecular docking studies revealed that Ni(II) complex displayed better binding efficiency for COVID-19 protease (6LU7) [13]. Furthermore, Rad *et al.* proposed a new strategy for COVID-19 treatment via simulation studies that involved transition metal (Fe, Cr, and Ni) doped fullerenes–favipiravir complexes [14].

Transition metals have a significant place in the field of inorganic chemistry. In the past few years, a lot of investigation was done on the therapeutic activities of the transition metals, and these could be proved beneficial for the COVID-19 treatment. For example, in the latest research, various transition metals, including Co(II), Cd(II), Mn(II), Cr(III), Ni(II), Hg(II), Zn(II), and Cr(III) were tested with gibberellic acid (HGA) which is a plant hormone to produce complexes. These novel complexes were screened by computational methods to evaluate their possible interaction with the COVID-19 active site called 6LU7. The study results showed that Mn(II) exhibited higher binding energy with the active site and acted as a potential inhibitor of 6LU7. Hence, it could be a beneficial therapeutic agent to cure COVID-19 infection [15].

Similarly, Omar *et al.* reported synthesis and characterization of tridentate Schiff base metal complexes of Zn(II), Cu(II), Mn(II), Ni(II), Fe(III), Cd(II), and Cr(III). They performed molecular docking studies via MOE2008 software for screening the potential drug for COVID-19. They explore the possible binding modes of all synthesized metal complexes against COVID-19 main protease (SARS-CoV-2) in a complex with inhibitor UAW247 (PDB ID: 6XBH). It was concluded from the data of interaction energies that the desired hit to lead (H_2L) compound was Cr(III) complex. Cr(III) complex had lesser binding energy and stable interaction, suggesting the probability of intense antiviral activity against COVID-19 [16].

Zn(II) is also a viral inhibitor (RNA-dependent RNA polymerase inhibitor) as well as an immunity enhancer. Various studies have reported effects of intracellular Zn(II) levels on DNA and RNA viruses, particularly those affecting the respiratory tract, such as influenza, picornaviruses, and respiratory syncytial virus. One of the mechanisms for the success of chloroquine and hydroxychloroquine therapy for COVID-19 treatment involves their roles as an ionophore of Zn(II), that is, bringing more Zn(II) into the cells. Thus, among transition metals, Zn(II) is one of the promising and potential candidates

responsible for direct inhibitory effect against the SARS-CoV-2 replicative cycle [17]. The work of Poupaert *et al.* also seconds the eminence grise of Zn(II) for COVID-19 treatment. The authors provided evidence regarding Zn^{++}interactions at molecular levels via quantum mechanics molecular simulations. They propose first- and second-generation macrolides such as azithromycin (Zn^{++}-antibiotic complex) as a potential candidate for COVID-19 treatment [18].

3. Conclusion

To date, there is no specific treatment available for the COVID-19, and in this regard, exploration of the metal complexes can be proved fruitful. The majority of the research was conducted by using in silico approach. It is suggested that the activity of the metal complexes should be appraised by using appropriate in vitro and in vivo models. Further, issues of possible toxicity should be addressed to avoid any unwanted effects.

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Ethical Considerations

Not applicable.

Conflicts of Interest

The authors declare that they have no conflict of interest regarding this paper.

Availability of Data and Material

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