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REVIEW

Emerging Potential of Metallodrugs to Target Coronavirus: Efficacy, Toxicity and their Mechanism of Action

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On eleventh March 2020, the contagion of the novel COVID-19 was announced by the WHO. Right now, there are no new enlisted medications that can viably cure the COVID-19 contagion. Some recently utilized drugs and combinations with their harmfulness profiles have been contemplated. The frequently announced poisonous impacts of these medicines, for example, hepatotoxicity, retinal harm, nephrotoxicity and cardiotoxicity. One of the most broadly examined drugs is favipiravir. The surface collaboration of favipiravir with organometallic composites came about by doping of transition metals of first row of the periodic table was analyzed to choose the most reasonable metallofullerenes for COVID-19 treatment. Some acknowledged pharmacophore edifices of bioactive constituents can be valuable in the explanation of against SARS-CoV-2 particulars. The advantage of utilizing arrangements encompassing phytochemicals is their sky-scraping wellbeing for ill persons and no negative reaction. Iron oxide nanoparticles (IONPs) were recently affirmed by the USFDA for anaemia therapy and variations have additionally exhibited its effectiveness against viruses *in vitro* for COVID-19. The adequacy of the Zn^{2+} salt enhancement could likewise be improved with *Nigella sativa* as its major bioactive segment would fill in as ionophore to permit Zn^{2+} to enter pneumocytes-the objective cell for the coronavirus (COVID-19). This review article depicts the utilization of medications, their usefulness and their harmful impacts for COVID-19 patients.

Keywords: SARS-CoV-2, Iron oxide nanoparticles, Metallofullerenes, *Nigella sativa*, Phytochemicals.

INTRODUCTION

The event of lung-fever of obscure morphology was enrolled in Wuhan, China on December 2019 [1,2]. The infection brought about by the infection was named COVID-19 by the WHO [3]. Twelve European medical clinics enrolled ill peoples with COVID-19 out of an examination pointed toward affirming the manifestation of neurological disorder. The most widely recognized manifestations in ill persons were cold, muscle torment, loss of hunger, facial pain and nasal congest. Neurological abnormal functioning manifestation was more normal in ladies [4]. Nervousness, panic attacks and tension were normal in ill persons suffering from coronavirus, potentially because of sleep disorders [5]. Ill persons suffering from gastrointestinal side effects had a higher frequency of temperature, cerebral pain, weakness, and shortness of breath [6]. Patients from Wuhan area experienced complexities, *e.g.*, RNAaemia, intense cardiovascular breakdown and secondary dysfunctions [7].

The broad spectrum of Coronavirus disease created by SARS-CoV-2 that started in December 2019, is one of those universal difficulties that rises above regional, political, philosophical, social and certainly scholastic borders [8]. Right now, there are no enlisted prescriptions that can successfully cure SARS-CoV-2 contamination [9]. Be that as it may, a few clinical preliminaries have been enlisted with the intend to analyze the viability of the generally enrolled drugs utilized for the prescription of further infection associated illness and circumstances [10]. No settled clinical adequacy of antiviral substrate for SARS-CoV-2 has been found at this point, while especial medicines, including favipiravir, remdesivir and arbidol are as of now under thorough examination for the remedy of SARS-CoV-2 [11,12]. Favipiravir is an affirmed antiviral medication in Japan for epidemic [13]. Contrasting the adequacy of favipi-

ravir and arbidol recommend that favipiravir might be a possible candidate to treat SARS-CoV-2 [11]. As indicated by the after effects, it very well may be speculated that favipiravir could be an appropriate medication for the remedy of SARS-CoV-2 dependent on upgrading medical recuperation rate on 7th day and diminishing irritation in throat, and ARDS [11].

Just a while ago, it has been discovered that favipiravir as a prodrug, amazingly forestalls the SARS-CoV-2 disease in Vero E6 cells [14,15]. Moreover, different examinations show that favipiravir is a powerful medication in keeping mice against the Ebola infection test [16]. Along these lines, clinical explores are promptly needed to evaluate the usefulness and security of this antiviral nucleoside against the COVID-19 treatment. The methodology of the old medications repositioning permits quicker arrival of the prescriptions available since numerous clinical preliminary steps become terminated, particularly in stages Ist and IInd. Furthermore, the current stockpile sequences for such medications are now existing in the medicinal industries. The chance of consolidating numerous enlisted drugs present available in the market, to expand the adequacy of the treatment, is one more preferred benefit of the methodology [17]. Notwithstanding, these new combinations of drugs surely display a danger, since the vast majority of these medicines can possibly cause various negative reactions when utilized in therapy of single compound and their combined uses can deliver novel or further articulated poisonous impacts as it is the situation with chemicals [18,19]. In addition, the wellbeing status of ill persons with SARS-CoV-2 sickness is regularly confounded by coinciding diseases, so specific consideration should be paid to the unfriendly/harmful impacts of the medications and their combinations utilized in expected restorative techniques. Fig. 1 shows the action of various combinations of drugs on the patient suffering from SARS-CoV-2.

Different nanostructures were set up broad utilizations in medicine transport systems attributable to high density proportion that is observably better analyzed than that of the customary microstructures [20,21]. Amid several nanostructures, CNTs, graphene and fullerenes are common due to their clear strategy for functioning and area enhancement, so they have been measured widely as medicine transporters [22,23]. Subsidiaries of fullerene have been utilized as expected transporters towards antitumor drugs attributable to have extraordinary highlights, for example, high stacking ability and protecting impacts on the heart and liver *versus* long-lasting noxiousness came about because of chemotherapeutics [24]. Furthermore, it was discovered that fullerene can pass the microorganisms film to show up at the cancerous cells, moving in the nucleus, lysosomes, and cytoplasm [25]. Among fullerenes, the C_{20} is the smallest structure that has a dodecahedral confine structure. The C_{20} was integrated unexpectedly by Prinzbach *et al.* [26] through the gas-phase production strategy. Further, this sort of fullerene was incorporated through ion-beam radiation and laser-ablation techniques [27].

The principle restricting component of fullerene family for biotic utilizations is their characteristic hydrophobicity. Towards conquering this complication, various examinations have been completed, meaning to discover reasonable methodologies for the creation of water-dissolvable fullerene. These strategies contain, development of host-guest centers that are water-soluble, expansion of surfactant, alcoholization and chemical modifications [28]. Among these methods, chemical modifications by embeddings polluted particles to fullerene indicated promising outcomes [29,30].

The adsorption property of favipiravir drug onto diverse metallofullerenes came about by substitution doping of fullerene C_{20} by first row of transition metals in the periodic table. The

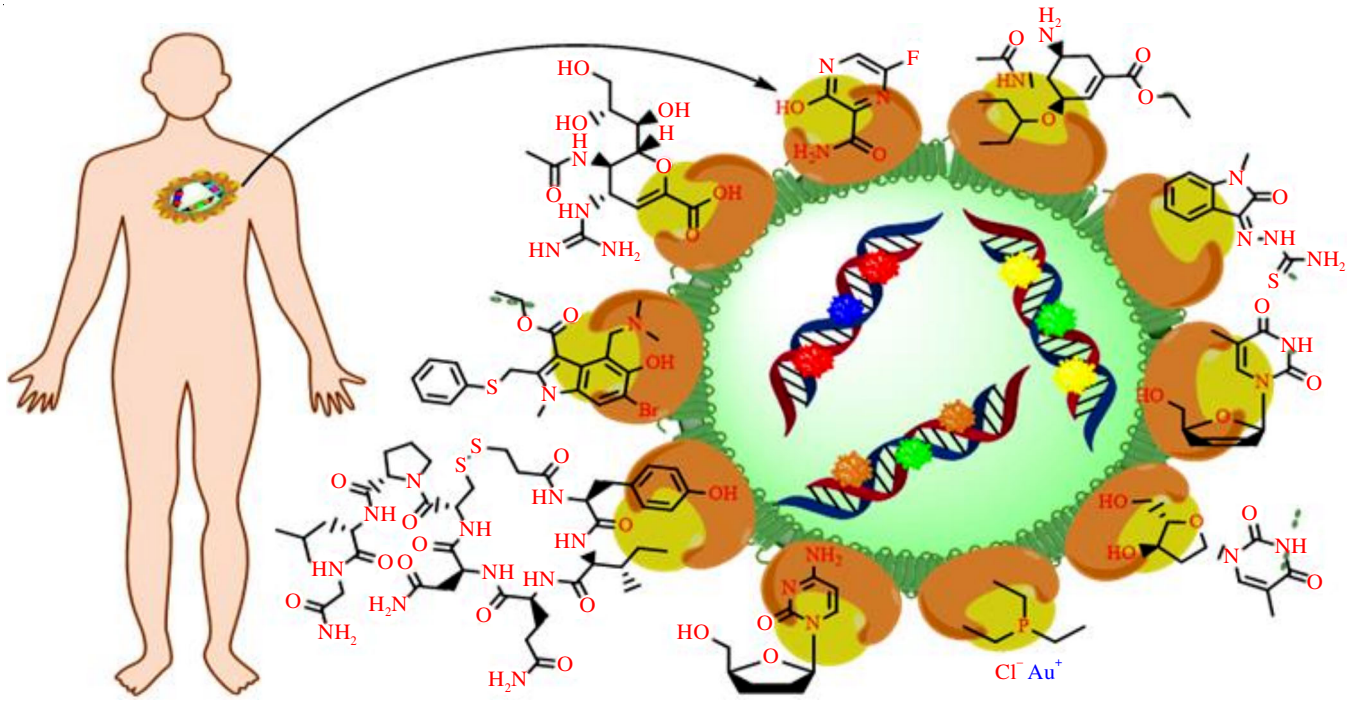


Fig. 1. Mechanism of action of some combination of drugs on patient suffering from SARS-CoV-2

purpose behind selecting the expressed transition metals for doping on C_{20} depends on the natural inclination of these atoms to design centers with carbon-based composites. It has been uncovered that DFT gives incredible data on the sub-atomic frameworks and their associations [31].

Essential hindering compounds like betulinic acid, indigo, aloeemodine, luteolin and quinomethyl triterpenoids, quercitin or gallates can be successful as antiviral arrangements [32]. These substances demonstration through the mechanism of protein hindrance. The investigations were directed on early SARS-CoV $3CL^{pro}$. Phytochemicals were separated from restorative plants, diterpenoids, biflavonoids with SARS-CoV $3CL^{pro}$ inhibitory action by acquiring removal of ethanol. Naturally occurring biologically active molecules (quercetin, epigallocatechin gallate and galusatechin gallate) demonstrated great restraint properties by binding to $3CL^{pro}$ active site and the 3-OH galloyl gathering, which was needed for infection inhibitory action [32].

To battle the COVID-19 pandemic, a few methodologies, for example, antibody and antiviral turn of events, just as community control trials to restrict diseases are in progress to ensure HCPs and limit contamination blow out in the society. Since immunization and new antiviral improvement can take long run of time [33]. The WHO embraced the methodology of repurposing drugs of realized safety profile to be immediately functional for SARS-CoV-2 prescription conventions [34]. Abo-Zeid *et al*. [35] applied nanoparticles for the treatment of viral infection(s) with promising outcomes. Accordingly, we chose to explore the repurposing of metal oxide nanoparticles (MONPs) for the treatment of COVID-19 and control of SARS-CoV-2 contaminations just as nosocomial clinic diseases. The antimicrobial action of MONPs was first reported by Abo-Zeid & Williams [36]. The MONPs antimicrobial effectiveness probably results from a few systems of activity, however the standard component includes the creation of receptive oxygen species (ROS), which are strongly antimicrobial. Microorganisms don't promptly create protection from ROS creation since ROS oxidizes various destinations and biomolecules in the microorganism, bringing about cell demise [37].

The use of MONPs as antiviral specialists has additionally been as of late explored by Abo-Zeid & Williams [36,38] because of the way that numerous virus anxiety developed impervious to the present medication methods. The antiviral action of IONPs has recently been examined against dengue infection [39], flu infection (H1N1) [40] and rotavirus [41]. Iron oxide nanopar-ticles (IONPs) are biocompatible and have been affirmed by the FDA for prescription of anaemia [42]. In light of these studies, we speculate that IONPs antiviral action is by means of association with the viral surface proteins and impedance with infection connection as well as passage into the host cell, brin-ging about balance. In this manner, IONPs could be an auspicious and benign possi-bility for fast utilization in the therapeutics of SARS-CoV-2 ill persons.

The pneumonic condition in SARS-CoV-2 is serious and related with its high death rate [43]. The basic difficulties to deal with the current COVID-19 pandemic are because of an absence of a preventive antibody just as a viable medication against the SARS-CoV-2. Besides, there is an extraordinary pace of spread of the infection and high death rate on a worldwide scale. Globally, the scientists and clinicians are contending to locate a powerful treatment for SARS-CoV-2. The capability of utilizing *Nigella sativa* (normally known as dark seed) and Zn^{2+} salt as an enhancement is smarter to treat COVID-19 in human being. Consequently, the point of this investigation was to assess the well-being of medications or medication combinations, at present alluded in the examinations as probable impressive treatment alternatives for the therapeutics of SARS-CoV-2. In this review article, the literary information on the poisonousness of specific medications just as the accessible medical information regarding the conceivable toxic impacts of the elected mixture of drugs is discussed.

Structural features of SARS-CoV-2: COVID-19 has a critical likeness with other coronaviruses with the rate similarity to the genome being 79% and half, separately [44]. There are likewise examines indicating that SARS-CoV and SARS-CoV-2 have nucleotide comparability of 89.1% and nucleic acids personality of 80% [45,46]. COVID-19 infections are wrapped positive sense RNA infections with coiled proportioned nucleocapsid. SARS-CoV-2 is described by their particular highlights of having club-formed spike prognoses on their exteriors. The infection has four fundamental primary proteins, called spike protein (S), an envelope protein (E), layer protein (M) and nucleocapsid protein (N), alongside other non-underlying proteins (Nsps) [47]. Spike (S) protein is a class I combination protein which is actuated by human proteases and severed at S1/S2 containing RBD and at S20 fraction liable for infection combination with cell membrane [47]. The E protein likewise has two spheres, a water repellent part and a charged cytoplasmic tail [48]. It is known to be practical in epidemiologic gathering by the arrangement of ion networks which support in planning with other epidemiological proteins [48]. The M protein (25-30 kDa) gives the infection its profile and can adjust for 2 unique adaptations permitting it to elevate membrane curve to tie the nucleocapsid. The E protein (8-12 kDa) is a transmembrane protein and it was discovered that infections without E protein have no toxic activity. The N protein is the protein shaping nucleocapsid with great proclivity for virus-related RNA and plays a part in the bundling of encapsulated genome to infectious constituent part [49,50]. This protein has three spaces, known as N-arm, C-tail and the essential linker locale. It likewise accomplishes the tasks like restraint of host cell protein interpretation, adjustment of host cell uptake, and cell apoptosis [50,51].

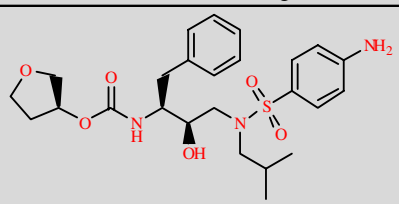
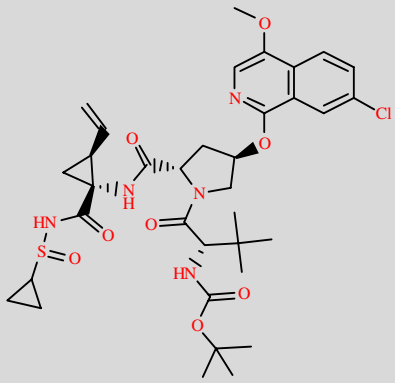
Hemagglutinin esterase (HE) ties to sialic acid and displays esterase action to encourage virus-related S protein cell section and epidemiological blowout [52]. The COVID-19 infection is recognized to taint the host cell through authoritative to the ACE2 with the assistance of its S proteins [46]. The S1 subunit is known to bind to the receptor on the cell for example ACE2 with the assistance of its RBD [53]. The S2 subunit is associated with the membrane fusion of the infection and host cell. COVID-19 is a non-divided positive sense ssRNA 30kb in size. The spike proteins which are available in the present epidemic are not the same as those of the previous ones [54,55].

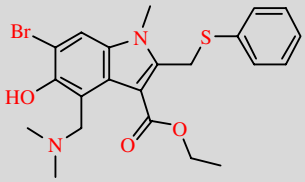
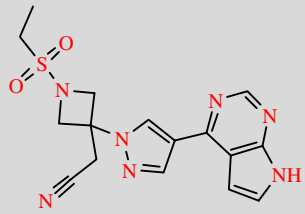
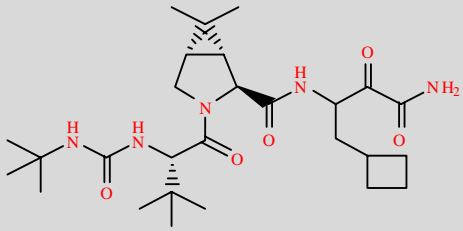
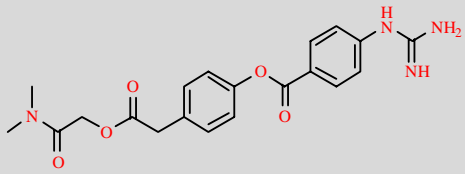
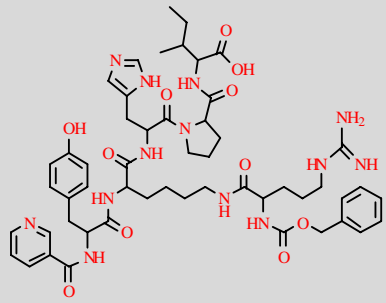
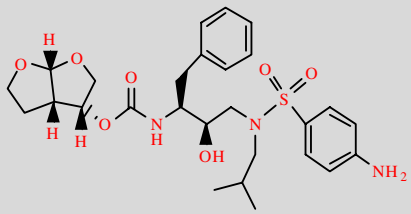
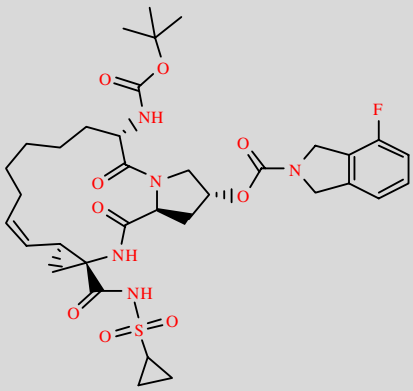
SARS-COV-2 and some repurposing medicines: The causative specialist for novel coronavirus is SARS-CoV-2. Other comparative specialists recently known are Middle East respiratory syndrome virus and SARS-CoV [56,57]. They assault patient's lower respiratory framework by attacking the pulmonary epithelial cells, conveying their nucleocapsid and seizing the cell apparatus to duplicate in the cytoplasm. The novel coronavirus has a place with Coronaviridae group of encompassed single-stranded, positive-strand RNA structure. The skeleton of SARS-CoV-2 is almost similar to that of other reported coronaviruses. Critically, the constraining remains of this family cooperate with the ACE-2 straight forwardly [58,59]. Since the easy spread of SARS-CoV2 can be calamitous for the whole ecosphere, the medical services specialists have proposed certain protective strategies. Isolating the tainted ill persons, forceful testing and fast analysis of supposed casualties, utilization of suitable face-masks, regular cleaning of hands will assist with countering and control the movement of this extreme infection [60]. At present, no medication or immunization is accessible for adapting this illness. Additionally, SARS-CoV-2 is much more infectious contrasted with other seasonal infections as one pre-suggestive or asymptomatic individual is competent to infect >2 healthy people. Analysts are currently directing on the repurpose system of prevailing medications. A few prescriptions were accounted for to have been utilized to treat persons suffering from SARS-CoV-2.

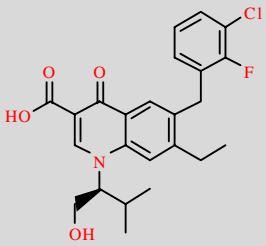
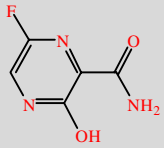
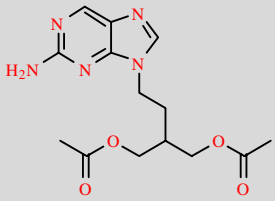
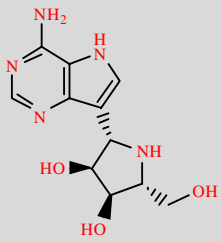
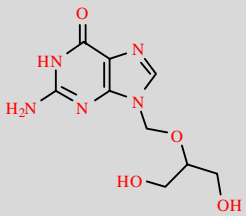
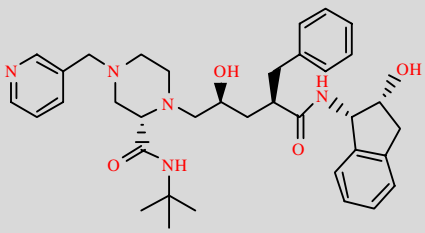
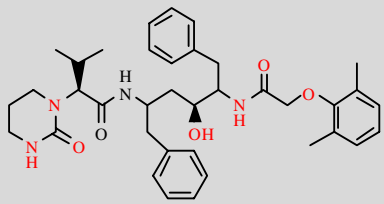
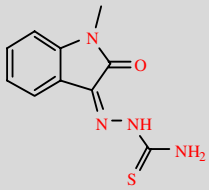
A recent research [61] reported that more than 30 specialists viewed antivirals as possibly powerful in the medications of SARS-CoV-2. Some of these prescriptions are at present going through clinical preliminaries for request in COVID-19 action. Another article [62] furthermore records some more medications indinavir, fosamprenavir, tipranavir, presatovir, abacavir, elvitegravir, deoxyrhapontin, disulfiram, carmofur, chalcone, *etc*. as compounds which may have antiviral action against SARS-CoV-2, just as a few Chinese natural herbs. A couple of antiviral drugs have been utilized, among which were lopinavir/ritonavir, umifenovir and an antimalarial medication chloroquine [63]. Nonetheless, in view of developing information some new effectively enrolled prescriptions warrant consideration have been remembered for clinical preliminaries strategies [64]. The organization of anti-toxins, for example, azithromycin with hydroxychloroquine were discovered helpful in the prescription of bacterial super-diseases in COVID-19 positive ill persons [65]. Another examination announced the adequacy of chloroquine and remdesivir to restrain COVID-19 disease *in vitro*. Up until now, the restorative techniques of the combinations of prescriptions in the SARS-CoV-2 infection depended predominantly on the involvement with the therapy of other coronavirus diseases [66]. A portion of these combination incorporate interferons, suggesting that interferons might be valuable in the SARS-CoV-2 prescription [67].

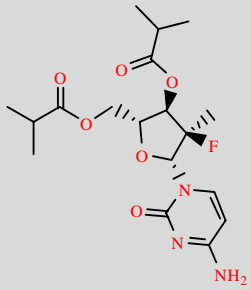
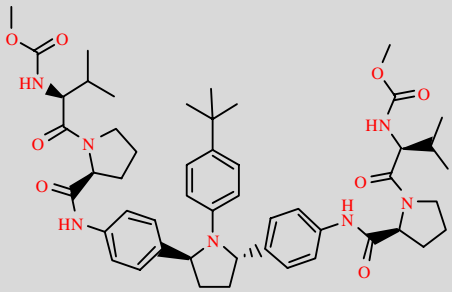
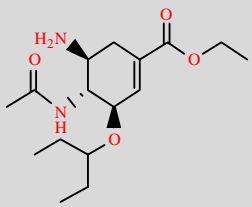
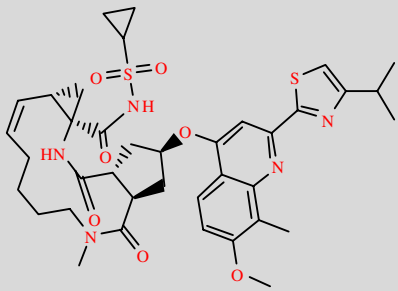
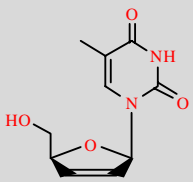
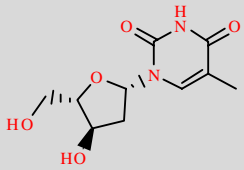
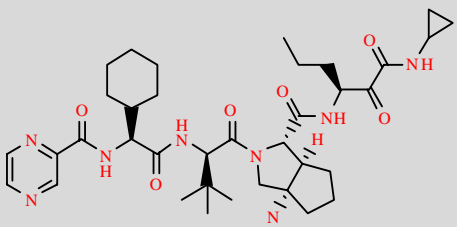
An overview of these combinations of medications is given in Table-1. Thinking about all accessible information, this review is centered around the accompanying meds/blends of medications. The utilization of different medications in coronavirus treatment has likewise been proposed, for example, Rho kinase inhibitors. It was proposed that these medications, for example fasudil, could counter events, for example, aggravation, resistant cell relocation, apoptosis and other significant occasions prompting lung harm. Albeit such prescriptions don't focus on the infection itself, they can possibly forestall certain outcomes of COVID-19 contamination, without a doubt to the advantage of patients [68]. Remembering that an enormous number of drugs is being examined, we have focused on the prescriptions either directing on the infection itself or medications, which have at first been explored or accessible to the health experts in the underlying infection flare-up regions. Until any exact medication system is accessible for SARS-CoV-2, the utilization of subsidiaries of recently realized antiviral medications is a

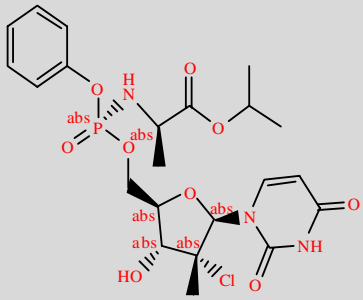
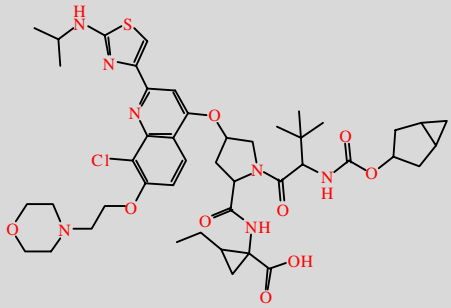
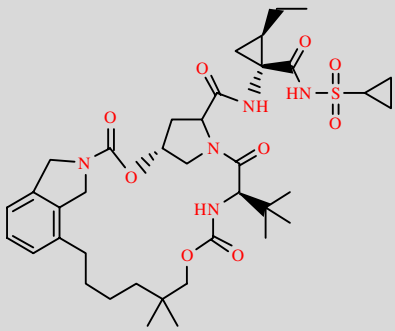
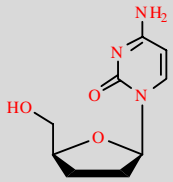
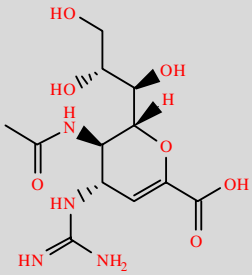
TABLE-1
SOME MEDICINES USED TO TREAT COVID-19, THEIR STRUCTURES AND MECHANISMS OF ACTION

Name of the drugs	Structure of the drugs	Active against	Mechanism of action
Amprenavir		HIV	Protease inhibitor
Asunaprevir		Hepatitis C	Protease inhibitor

Arbidol (Umifenovir)		Influenza	Inhibits membrane fusion
Baricitinib		Rheumatoid arthritis	Inhibits Janus kinase
Boceprevir		Hepatitis C	NS3/4A protease inhibitor
Camostate		Pancreatitis	Inhibits serine protease
CGP42112A		Vasolidation and blood pressure reduction	Angiotensin AT2 receptor agonist
Darunavir		HIV	Inhibits HIV protease enzyme
Danoprevir		Hepatitis C	NS3/4A protease inhibitor

Elvitegravir		HIV	Integrase inhibitor
Favipiravir		Influenza	Inhibits viral RNA-dependent RNA polymerase (RdRp)
Famciclovir		Hepatitis B	Inhibits viral DNA polymerase
Galidesivir		Ebola	RNA polymerase inhibitor
Ganciclovir		Cytomegalovirus	Inhibits viral DNA polymerase
Indinavir		HIV	Protease inhibitor
Lopinavir		HIV	Protease inhibitor
Marboran/ Methisazone		Small pox virus	Inhibits rRNA and protein synthesis

Mericitabine		Hepatitis C	Inhibitor of RdRp
Ombitasvir		Hepatitis C	NS5A inhibitor
Oseltamivir		Influenza viruses A	Inhibits the neuraminidase enzyme
Simeprevir		Hepatitis C	Hepatitis C virus protease inhibitor
Stavudine		HIV	Inhibits HIV reverse transcriptase enzyme
Telbivudine		Hepatitis B	Reverse transcriptase inhibitor
Telaprevir		Hepatitis C	NS3/4a protease inhibitor

Uprifosbuvir		Hepatitis C	NS5B polymerase inhibitor
Vedroprevir		Hepatitis C	Inhibitor of the Hepatitis C virus (HCV) NS3
Vaniprevir		Hepatitis C	NS3/4A protease inhibitor
Zalcitabine		HIV	Nucleoside reverse transcriptase inhibitor
Zanamivir		Influenza viruses	Neuraminidase inhibitor

helpful technique. There is a list of antivirals utilized against COVID-19 is shown in Table-1 [69].

Some selected medicines in Covid-19 therapy and their toxic effects

Ritonavir: The utilization of ritonavir, an individual from an assembly of the fresher protease inhibitors was endorsed in 2000 by FDA [70,71]. Hepatotoxicity was evaluated by observing the action of AST and ALT. The trademark places where the flow of blood happened were the little joints of the hands just as the soft tissue of the palms [72]. Supervision of medications from the protease inhibitor group prompts appropriation of endoplasmic reticulum-inferred record aspect that are associated with lipogenesis and to lack of adiponectin [70]. The restraint of proteasomal corruption of apolipoprotein B is additional mechanism that is related with the beginning of dyslipidemia in ill persons who get this assembly of medications [71,73].

Lopinavir: Lopinavir is antiretroviral of the protease inhibitor class, utilized in blend with other antiviral medications for HIV-1 contamination prescription and perceived as expected medication for COVID-19 sickness [65]. In the examination

achieved on 120 HIV-positive ill-persons, the low rate of serious liver damage inferable from lopinavir blood levels was noticed [74]. Lopinavir is generally used as the coformulation with ritonavir to keep up beneficial medication concentration, making it the second line of antiretroviral treatment. Subsequently, there are restricted instances of unfavourable or harmful impacts of single lopinavir medications.

Remdesivir: Remdesivir is expansive range antiviral prodrug that goes about as adenosine nucleotide analogue, utilized for RNA infection diseases medications [15]. A new report by Grein *et al*. [75] uncovered that the height of hepatic chemicals, hypotension, renal hindrance and the diarrhoea were the most well-known unfriendly impacts related with remdesivir organization in SARS-CoV-2 ill persons. Genuine antagonistic impacts, for example, intense kidney damage, hypotension, poisoned stun and numerous tissue disorder syndrome were accounted for in 12% of topics. Another investigation on ebola patients detailed AST and ALT rise also, in ill persons who got intravenous remdesivir [76]. Reversible ALT and AST increment was noticed, be that as it may, no variations from the norm in absolute bilirubin, alkaline phosphatase or egg whites occured. In these preliminaries, remdesivir showed no harmful impact on kidneys either [77].

Umifenovir: Umifenovir is RNA polymerase inhibitor affirmed for flu medication just in Russia and China. Because of mechanism of activity, the medication has been perceived as expected treatment for new COVID-19 contamination [11]. Umifenovir was demonstrated to be protected, in any event, for use in pregnant ladies and indicated no teratogenic impacts [78]. Umifenovir has a broad therapeutic index and expected that it is also well tolerated. Intake of 200 mg to volunteers showed brilliant acceptability. The utilization more than a few days to one month was additionally all around endured. An examination indicated no poisonous impact event during chronic administration of this medication [79]. Certain antagonistic impacts were accounted for, conspicuously gastrointestinal intimidating impacts and expanded transaminase levels [80]. In an investigation of umifenovir and paracetamol combinations harmfulness in trial creatures, oral no observed adverse effect level (NOAEL) was resolved at 200 mg/kg every day [81].

Therapeutics for SARS-CoV-2 with selected combinations of medicines and their adverse effects

Lopinavir/ritonavir: Because of the low dosage of ritonavir utilized in combination with lopinavir, there are not many cases in which ritonavir poisonousness has been accounted [82]. A few reports have referenced harmful impacts on retinal damage [83]. A few researchers express that the reason for the poisonous impacts of ritonavir is the current liver dysfunction. Liver dysfunction prompts the aggregation of ritonavir in blood plasma, where it is generally 99% protein-bound [84]. Certain suggestions direct staying away from the utilization with respect to this combination of medicines, if conceivable. At the point when these medications are utilized in combination, it is encouraged to screen side effects, for example, queasiness, diarrhoea, vomiting, raised transaminase and lactate levels, icterus and dyslipidemia [85].

Lopinavir/ritonavir along with umifenovir: This combination prompted liver harm in about half of diagnosed ill persons together with the expansion of serum aminotransferase enzymes and jaundice. In the retrospective investigation, specialists announced that this combination of medications were more compelling than lopinavir/ritonavir combination, however prompted comparative unfavourable impacts: higher bilirubin levels, mild diarrhoea and queasiness [86].

Chloroquine along with azithromycin: The outcomes acquired in this examination proposed a synergistic impact of the two medications. Chloroquine-azithromycin combination of medications has been utilized formerly. In a medical preliminary led in Africa, the combination verified to be benign in malaria fever treatment, where just a single ill person had a genuine symptom of vomiting. Most opposite results were mild or exceptionally minor [87].

Molecular targets for an effective SARS-CoV-2 therapeutics: Likewise, the global academic network is striving to discover new substances equipped for battling the SARS-CoV-2 infection. To this regard, the information on the infection at the atomic level is quickly growing and the conceivable druggable targets are being recognized and characterized [88]. Quiet, SARS-CoV-2 has a spike protein answerable for infection authoritative to the host cell surface receptor, *e.g*. the angiotensin-converting enzyme 2 (ACE2). Additionally, SARS-CoV-2 contains an RNA-subordinate RNA polymerase (RdRp), answerable for repeating the RNA genome. All the previously mentioned proteins are accepted to essential druggable focuses to differentiate SARS-CoV-2 development and replication, and explicit endeavours are being done to discover atoms proficient for hitting these objectives specifically [89,90].

Some metal-based drugs (Probable anti-covid agents): Some metals and metal-based molecules like gold, bismuth, antimony and mercury-based metal molecules are generally used to treat an assortment of sicknesses, for the most part irresistible, including tuberculosis and syphilis and various parasitic infections [91]. Indeed, even arsenicals were to a great extent utilized in the clinical centers around then. Later on, these inorganic metal-based molecules were steadily abandoned in light of developing concerns with respect to their fundamental poisonousness and the emergence of novel organic medications frequently indicating better pharmacological exhibitions and a lower toxic effect. However, some inorganic medications are as yet being used in today clinical practice for a couple of explicit applications where they assume important and indispensable roles, forming a noteworthy viability with an adequate noxiousness [92]. The most striking model is offered by the expansive utilization of cisplatin and its analogs in malignant growth chemotherapy; despite their noteworthy foundational harmfulness, it tends to be assessed that platinum drugs are available in about half of current chemotherapeutic conventions for disease treatment [93]. Taking into account these contentions, we firmly energize the worldwide academic community to investigate methodically and quick possibilities of metal-based molecules in medication disclosure programs for COVID-19 therapeutics. Two fundamental systems to find powerful metal-based medications for COVID-19 treatment are discussed in the following segments:

Approaches to regulate active metallodrugs for COVID-19 infection:

(i) **Regulation of some medications through repurposing of clinically recognised metal-based treatments:** As expressed over, a direct way to deal with the discovery of successful metallodrugs for COVID-19 virus is given by the repurposing of metal-based medications, clinically endorsed for other remedial signs, against the COVID-19 illness. There are various endorsed metal-based medications with promising highlights and a satisfactory harmfulness profile that may be considered for repurposing. Especially appealing appear to be those metallodrugs bearing a delicate metal community equipped for binding firmly to free thiol groups of target proteins [94]. To this conclusion, we are supporting a quick assessment of a clinically recognized gold(I) drug, for example auranofin [95]. Significantly, auranofin is more powerful than hydroxychloroquine against HIV diseases; also, its improved action is related with a more positive pharmacokinetic profile [96,97].

Comparably to tocilizumab, auranofin is prepared for the meddling and hindering interleukin-6 signaling pathways through phosphorylation of JAK1 and STAT3 [98]. Moreover, auranofin shows an intense inhibitory activity toward indicated proteases emerging from its capacity to organize firmly to proteins bearing free cysteine residues [99]. On the ground of these inspirations, a fast off-label assessment of auranofin as an antiviral specialist for the treatment of COVID-19 patients is energetically suggested. This proposition is currently reinforced by later *in vitro* evidences showed up during the composition that auranofin represses powerfully SARS-CoV-2 replication while constricting aggravation in human cells. Kumar *et al.* [100] first tainted Huh7 cells with SARS-CoV-2 infection; next, cells were treated with 4 μM of auranofin and, just as supernatants, inspected at expanding time spans (24 and 48 h). Infection RNA duplicates were estimated by applying RTPCR.

Auranofin (Fig. 2) treatment essentially decreased the viral RNA in the supernatant (70%) after 24 h. Remarkably, at the 48 h time point, this rate was significantly higher (85%). Intracellular viral RNA diminished by 85% following 24 h, while a 95% decrease was identified following 48 h. Additionally, auranofin was all around targeted by Huh7 cells at the established concentrations. Results featured that auranofin repressed the replication of SARS-CoV-2 in the contaminated cells with

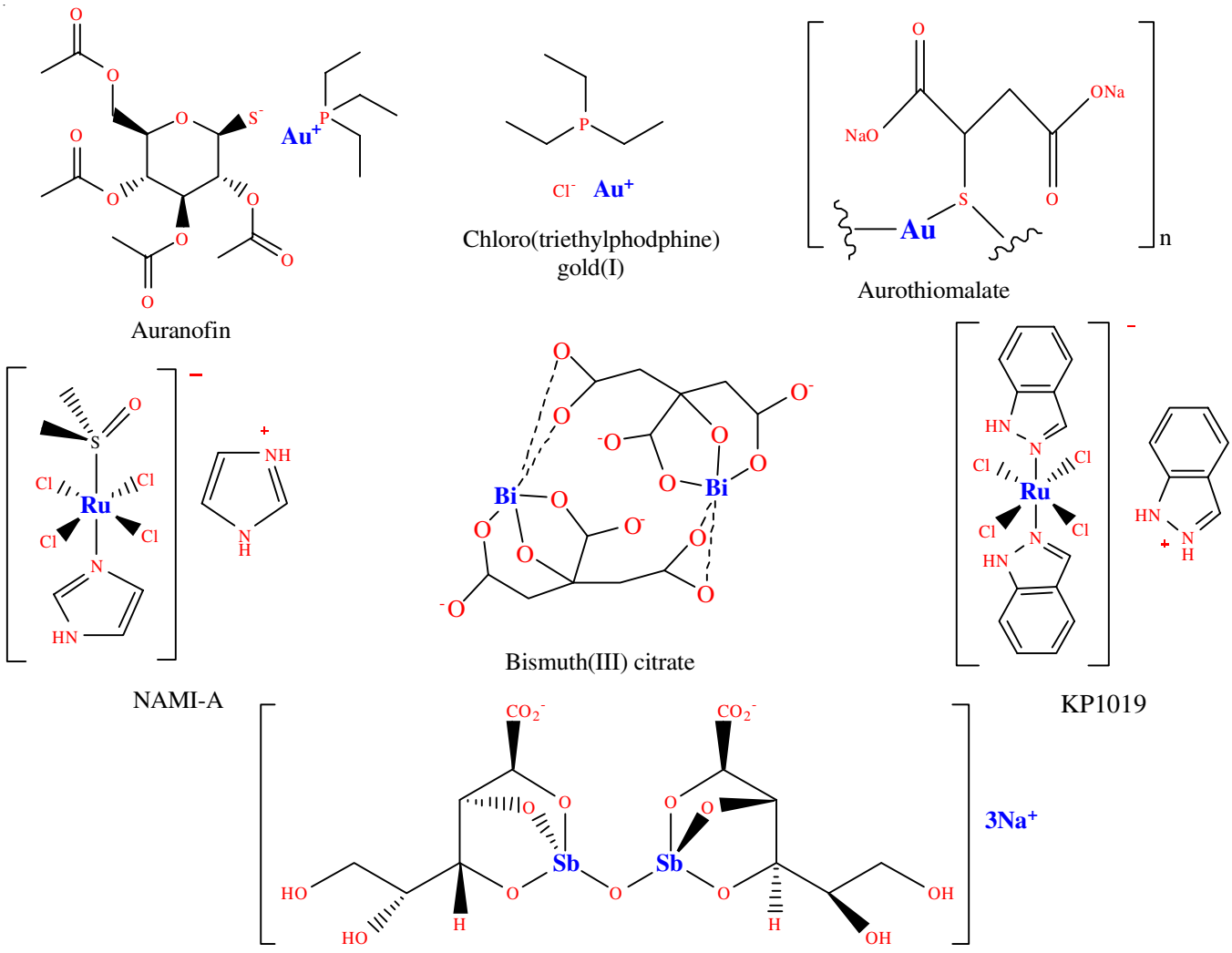


Fig. 2. Some repurposed metal-based medications useful in treating COVID-19 infection

an EC_{50} of about 1.5 μM [100]. Similar creators showed that auranofin is fit for diminishing the outflow of SARS-CoV-2-prompted cytokines in Huh7 cells. SARS-CoV-2 disease activate a high increment of mRNA articulation of IL-6 which may bring about serious lung irritation phenomena; at change just a 2-fold increment in articulation of IL6 was found in the cells treated with auranofin [100]. By and large these outcomes firmly uphold the reasonableness of auranofin for COVID-19 treatment. Such medication repurposing procedure proposed for auranofin could be all around reached out to some other clinically recognized gold medications for rheumatoid arthritis, for example, aurothiomalate (Fig. 2) and aurothioglucose. The auranofin analogue, chloro(triethylphosphine)gold(I), where thio-sugar moiety is supplanted by a simple chloride ligand (Fig. 2) is another promising applicant. Chloro(triethylphosphine)gold(I) industrially accessible and has been clinically tried in comparison with auranofin for the treatment of arthritis [100]. Outstandingly auranofin-Cl, through the pharmacologically dynamic cation $[Et_3PAu]^+$, can bind the chemically important His133 residue of cyclophilin models [101]. This last component is quite compelling thinking about that as some molecules associating with cyclophilin A have been chosen as promising medication applicants against COVID-19 [102]. Likewise, a couple of clinically endorsed bismuth and antimony based molecules (Fig. 2) indicating the unconventional reactivity properties and an unequivocally thiophilic character along with an adequate poisonousness profile, should be remembered for this sort of assessment.

Yang *et al*. [103] found that a progression of bi-based building blocks bearing N, O-containing polydentate ligands including porphyrin complexes are highlighted by powerful restraint exercises against helicase ATPase. Recently, the inhibitory power of some bismuth salts in clinical use, specifically bismuth potassium citrate, ranitidine bismuth citrate and bismuth citrate was accounted for toward the NTPase and RNA helicase exercises of non-underlying SARSCoV-2 nsp13 protein, that assumes a significant part in SARS-CoV-2 infection replication. This discovery focuses to nsp13 as an extra druggable objective for new antiviral specialists [104]. Beyond bismuth, likewise the experimental anticancer ruthenium compounds NAMI A and KP1339 may be acceptable candidates for hostile to COVID 19 testing; NAMI A and KP1339 were recently admitted to clinical preliminaries for disease therapy and were demonstrated to be very protected at moderately high concentrations [105]. Later on, NAMI A was released from clinical preliminaries because of limited anticancer adequacy in the selected malignant growth model. Presently, studies are in progress to survey the viability of these ruthenium based molecules in repressing SARS-CoV-2 replication *in vitro*.

(ii) **Regulation of some drugs through the transmission of libraries of metal-based compounds:** Extensive *in vitro* testing of huge and delegate libraries of metal-based specialists of restorative interest against SARS-CoV-2 replication is exceptionally justified. Investigational boards ought to predominantly incorporate groups of therapeutically reasonable metal based specialists demonstrating an adequate harmfulness profile. Inferable from their moderately protected harmfulness profiles, bismuth, ruthenium and antimony compounds may be ideal applicants [106]. Nonetheless, a cautious examination of their harmfulness profile should be preventively performed. The possible interest on this last class of metallodrugs has now been affirmed by Ott *et al*. [107]. Two recently synthesized gold organometallics was tried to evaluate the capacity of these gold compounds to impede the viral section measure through the restraint of the cooperation between the SARS-CoV-2 spike and ACE2 receptor. The gold organometallic compounds are attempted to be intense inhibitors of the infection replication measure [107].

In all, moderately large groups of metallic molecules should be considered for screening including arrangement of primarily related metal building blocks. The different metal based molecules could be positioned by their antiviral power and valuable structure activity connections may be drawn. This sort of screening may be additionally helped by the investigation of the inhibitory properties of the panel building blocks toward chosen viral focuses on that appear to be critical for infection endurance and replication, for example, the two primary proteases and the RNA polymerase. This kind of data may prompt a type of pathway driven or target driven disclosure approach. Specifically, a solid restraint of viral cysteine proteases by metal based molecules containing exceptionally delicate and thiophilic metal centers, for example, gold(I), antimony(III) and bismuth(III) likely could be anticipated dependent on HSAB contemplations. Then again, ruthenium-based molecules are anticipated to bind specially to dissolvable uncovered imidazole molecules and subsequently block practically pertinent histidine residues [108,109]. Likewise, the possibility that metal-based molecules may cause applicable changes in the host cell, *e.g*. induction of oxidative stress, hindering infection attack and replication should be mulled over as a sensible antiviral system.

Some other targets, SARS-COV-2 and active binding sites: The major binding sites being investigated in COVID-19 are discussed in the following section:

1. **Chymotrypsin-like protease ($3CL^{pro}$):** $3CL^{pro}$ otherwise called primary protease (Mpro) or Nsp5 is a significant protein found in SARS-CoV which is answerable for the proteolytic capacity in the development phase of the infection [110] Subsequently, $3CL^{pro}$ is the main objective for drugs against coronaviruses [111].

2. **RNA dependant RNA polymerases (RdRp):** RdRp (Nsp12) is the essential compound which has a significant part in the duplication and record of the infection. With the assistance of its other co-factors Nsp7 and Nsp8, the cooperation among Nsp12 and the RNA is reinforced, in this way upgrading the RdRp movement [112].

3. **Papain like protease (PL^{pro}):** Because of its significant capacity in the virus-related repetition cycle, PL^{pro} is alternative significant druggable objective for COVID-19 [113].

4. **22-O-methyltransferase (22-O-MTase):** 22-O-MTase becomes enacted on binding with the Nsp10. Henceforth, Nsp10-Nsp16 complex is a druggable objective attributable to its essential part in virus-related repetition [114].

5. **Helicase:** Nsp13 is another significant objective to build up a treatment strategy against covids [115].

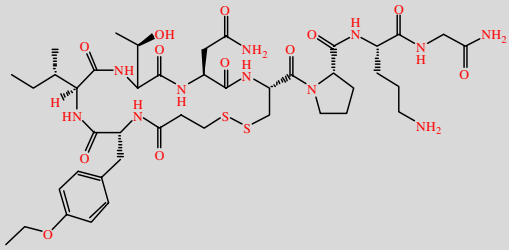
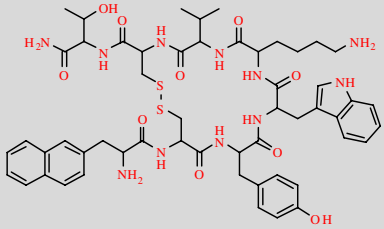
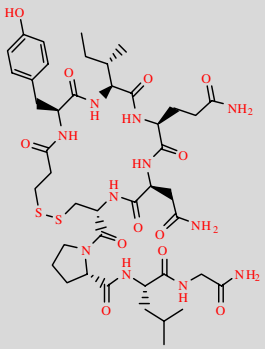
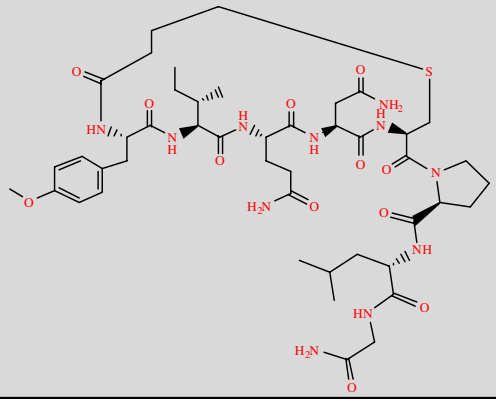
6. **ACE2 receptor:** The affection of novel coronavirus S-protein to the ACE2 receptor is advanced than that of previous coronaviruses [116].

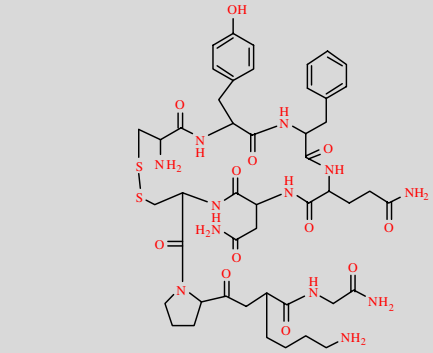
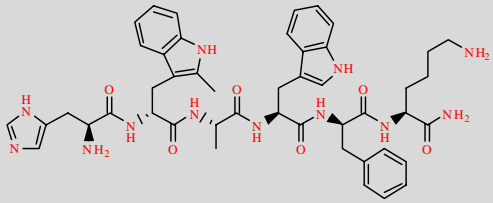
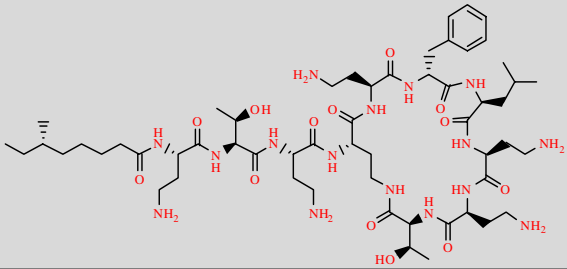
7. **Glucose-regulated proteins (GRP78, PDB ID: 3LDL):** GRP78 is overexpressed under cell stress and translocate from the endoplasmic reticulum to the plasma film, where it tends to be perceived as a receptor to intercede viral disease with the assistance Pep42 protein of the infection cell [117].

Table-2 demonstrates some FDA approved drugs, their structures, interacting residues and their uses in the previous treatments which can be repurposed for treatment of COVID-19 patients.

A new strategy for COVID-19 using transition metal doped fullerenes: It has been inferred that substituting a carbon particle of fullerene by a metal atom is an appropriate strategy to propel the medication conveyance property by expanding its adsorption potential [125]. Various geometries were examined and the most vigorously ideal ones were chosen for additional examinations. The FMO investigation was directed to perceive any conceivable hybridizing of the medication particle and each metallofullerene. The vibrational spectra comparing to the adsorption of favipiravir particle on metallofullerene was processed to consider the adjustment in the IR force and vibrational frequencies. Time-dependent DFT (TD-DFT)

TABLE-2
SOME FDA APPROVED DRUGS USED TO TREAT COVID-19 AND THEIR INTERACTING RESIDUES WHERE MECHANISM OF ACTION OF THESE DRUGS CAN BE FOLLOWED

FDA approved drugs	Structure	Interacting residues	Treatments	Ref.
Atosiban		ASP760, GLU811, SER814, TYR619, ASP833	Inhibitor of oxytocin and vasopressin	[118]
Lanreotide		ASP761, ASP760, ASN691, SER682	Analogue of somatostatin involved in suppressing growth hormones, glucagon and insulin	[119]
Demoxytocin		TRP617, TYR619, LYS621, SER682, ASP760, ASP761, GLU81	Oxytocin analogue	[120]
Carbetocin		ALA550, ARG553, THR556, ASP623, ASP760, TYR619, TRP617, TRP800	Synthetic analogue oxytocin, postpartum hemorrhage	[121]

Lypressin		ARG624, VAL557, ARG555, ARG553, ASP760, ASP761, ALA762, GLU811, TRP617, TYR619	Vasopressins (Lysine vasopressin), diabetes insipidus, anti-diuretic	[122]
Examorelin		GLU811, ASP760, SER814, GLN815, ARG555	Synthetic peptide increases the plasma level of growth hormone	[123]
Polymyxin B1		ARG555, ASN691, ASP618, ASP761, ASP760, CYS813	Antibiotic used against multi-drug-resistant gram-negative bacterial infection	[124]

technique was utilized for the investigation of progress in the UV-visible spectra and properties of excited states of every system upon adsorption of favipiravir molecule. The predominant calculation of various metallofullerene-Favipiravir complex was researched by some researchers. In view of the detailed outcomes, there are two dynamic situations on the metal piece of metallofullerenes for favipiravir adsorption.

For all $C_{19}M$ frameworks aside from $C_{19}Zn$, the transition metal particle made two new bonds with favipiravir atom while the perplexing arrangement of $C_{19}Zn$ with favipiravir molecule was a consequence of one bond formation. The metallofullerene accomplished by the central part of the first row of the periodic table were best contender for drug transporters dependent on the higher adsorption energies. The metallofullerenes demonstrated auspicious possessions to be utilized as a transporter of favipiravir drug. However, the kind of metal component is the basic theme. The doping of fullerene with the middle components of the first row transition metals, in particular Cr, Fe and Ni, would be the finest arrangement to adsorb favipiravir, as a probable medication for novel coronavirus treatment [126].

Role of iron oxide nanoparticles for treating COVID-19: Viral contaminations express to a significant general medical problem, with negative effects on medical services as well as various financial expenses. This is obviously confirmed by the novel coronavirus flare-up with its evolution being the greatest epidemic and general wellbeing emergency of the recent period. Despite the fact that there are numerous proficient antiviral specialists being used, they actually have limitations because of the advancement of virus-related obstruction and the gathering within off-target structures prompting antagonistic impacts. Accordingly, there is a popularity for disclosure of new techniques to recover the antiviral treatments to control or restrict the blowout of virus-related contaminations. Abo-Zeid *et al.* [127] explored the possible antiviral action of iron oxide nanoparticles (IONPs) on COVID-19 and HCV by molecular docking studies. Their models showed that both Fe_2O_3 and Fe_3O_4 joined proficiently with novel coronavirus (COVID-19) S1-RBD and HCV glycoproteins, E1 and E2. They also found that Fe_3O_4 shaped a more-stable complex with S1-RBD while for HCV E1 and E2, a more stable complex was framed with Fe_2O_3. It has been prescribed for FDA-affirmed IONPs to continue into clinical preliminaries for novel coronavirus. Moreover, because of their capacity to deliver ROS, IONPs are additionally prescribed for synthesis of antimicrobial textures to be utilized in the assembling of sterile garments. These utilizations are proposed to be a high-level measure to switch viral and nosocomial diseases in emergency clinics [127].

Combination of zinc and *Nigella sativa* for COVID-19 treatment: Thymoquinone and nigellimine, black seed may offer various advantages to treat COVID-19, for example, (i) obstructing the entry of the infection into pneumocytes and (ii) giving ionophore to upgraded take-up of Zn^{2+} can improve host immune response against SARS-CoV-2 just as repress its replication by hindering the viral RdRp. Notwithstanding, it is critical to distinguish the right doses for both black seed or its subsidiaries. It very well may be noticed that black seed oil has been utilized at portions of between 40-80 mg/kg/day as

adjunctive treatment with no harmful effects. Then again, Zn consumption over its suggested day by day allowance may be hurtful which shifts as indicated by age, sex and other ailments. People with health issues, for example, with liver and kidney ailments just as pregnant ladies should counsel the doctors prior to choose for any self-recommended Zn supplement. *Nigella sativa* (black seed) could be considered as a characteristic substitute which contains various bioactive parts, for example, thymoquinone, dithymoquinone, thymohydroquinone, and nigellimine. *Nigella sativa* in blend with Zn could be valuable as a supplement to COVID-19 treatment [128].

Conclusion

Metal based medications forms a generally little but exceptionally particular class of pharmacological substances that incorporates an enormous assortment of metal centers and structural motifs. Some inorganic medications are as yet in clinical use with significant roles because of the event of explicit pharmacological activities that can't be accomplished with the typical natural medications. Some other inorganic compounds have been rediscovered as powerful antiparasitic drugs. At the point when another serious disease appears for which there are no powerful clinical therapies as it is the situation of COVID-19 infection, all the conceivable remedial open doors should be investigated. We accept that consideration of a huge exhibit of metal-based specialists in the screening libraries and projects may altogether extend the chemical space and increment the possibility of finding successful medications. A first examination of the fundamental druggable targets of SARS-CoV-2 features the presence of a couple of catalysts, specifically two significant cysteine proteases and the helicase, which may be ideal targets for compounds bearing soft metal centers. Eminently, a couple of fundamental outcomes recommend that chose gold and bismuth-based metal complexes can create a robust restraint of those reactant exercises consequently differentiating viably infection replication. Accordingly, repurposing methodologies may be stretched out too many metal compounds that are as yet in clinical use or that were in clinical use previously. Testing might be well reached out to a couple of metal compounds which are going through clinical preliminaries like anticancer ruthenium compounds. This may maintain a strategic distance from those drawn out results that typically limit the clinical use of metallodrugs. Cautious cost/advantage examinations may encourage their utilization. Likewise, quick preliminary tests may be arranged in evaluating whether at a protected portion the considered metal compounds are remedially dynamic in COVID-19 patients. Essentially, there is at present a practically complete absence of these urgent information which may guarantee the protected utilization of metal based medications against SARS-CoV-2. Detailed work expressed that iron oxide nanoparticles showed positive outcomes for the patients suffering from COVID-19. Moreover, some naturally occurring phytochemicals which are valuable *e.g*. *Nigella sativa* in combination with zinc is useful for SARS-COV-2 patients. This review article summarizes the previously and recently used drugs with their positive and negative results for the COVID-19 patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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