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PHARMACOLOGICAL ACTIVITY OF METAL-BASED ORGANIC COMPLEXES AGAINST DIFFERENT VIRAL DISEASES

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ABSTRACT

The necessity of the development of compounds with effectiveness in therapy against infective diseases has increased in the last 3 years in connection with the spread of COVID-19. The current study aimed to summarize the pharmacological activities of metal-based organic compounds against different viral diseases, including COVID-19. A systematic literature review was carried out by using data sources in Medline, Pub Med, SCOPUS, and Science Direct. The used methods were collecting data, summarizing, and analyzing information. Antiviral properties exert metal complexes with ligands, such as: hydrazones; thiosemi-carbazones: Pt(II), Pd(II); Ga(III); Pd(II); Co(III), Ni(II), Cu(II)); fluoroquinolones, quinoline: Pd(II); phenylquinoline, phenylpyridine; tetrahydropyrimidines: Ag(I); phenanthroline: Cu(II); Valacyclovir: Cu(II)). Complexes of Zn(II). Co(II), Cu(II), Ni(II), Mg(II), Mn(II), and Zn(II) exert antiviral effects against the DNA Herpes simplex viruses HSV-1, HSV-2. Co(II), effective towards the HIV are complexes of the following metals: Au(II), Co(II), Cu(II), Fe(III), La(III), Mg(II). Ni(II), Pd(II), Pt(II), Ru(II). Against the HIV have been described to be active complexes of the following metals: Au(II), Co(II), Cu(II), Fe(III), La(III), Mg(II), Ni(II), Pd(II), Pt(II), and Ru(II). In connection with the continued spread of the severe acute respiratory syndrome – Coronavirus 2 (SARS-CoV-2), today's very actual strategy is the development of effective COVID therapeutics. The perspective trend in the creation and investigation of potential agents for the effective application towards SARS-CoV-2, are Auranofin and Cu(II), Ni(II), Mn(II), and Zn(II) complexes of Coumarin.

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Introduction

Metal-Based Organic Complexes as Potential Antiviral Agents

Viral diseases are caused by viruses, which by *attachment of their* capsid proteins *to the* receptors of the surface of living cells can penetrate cells through receptor-mediated endocytosis. Virus replication is accomplished through the synthesis of viral messenger RNA (mRNA) and proteins, which multiply the genome. Replication of DNA viruses occurs within the cellular nucleus, whereas RNA virus replication occurs in the cytoplasm.

It has been reported that viruses such as Herpes, Coxsackie B, Influenza A can influence the induction of autoimmune diseases [1].

Different types of viruses affecting humans are classified as follows:

1. DNA viruses: Herpes simplex (HSV-1 and HSV-2), Hepatitis B, Epstein-Barr, Human papillomavirus and Human cytomegalovirus
2. RNA viruses: Coxsackie virus B3, Chikungunya, Dengue, Ebola viruses, Enterovirus 71, Hepatitis C, Human immunodeficiency virus, Human norovirus, Human T-lymphocyte virus, Influenza A, Japanese encephalitis virus, Parainfluenza 3, Respiratory syncytial virus, Rift Valley fever virus, Vesicular stomatitis virus, Zika virus [1].

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The Baltimore classification of viruses is predicated on the various mRNA production mechanisms. Single-stranded ssRNA or ssDNA, double-stranded dsRNA or dsDNA, and reverse transcriptase (RT) or non-RT-dependent dsRNA or dsDNA are utilized to separate viral genomes. The Baltimore classification includes the following seven categories of viruses:

1. dsDNA viruses: Adenoviruses, Herpesviruses, Poxviruses;
2. ssDNA viruses: Parvoviruses;
3. dsRNA viruses: Reoviruses
4. (+) ssRNA viruses: Coronaviruses, Picornaviruses, Togaviruses;
5. (−) ssRNA viruses: Orthomyxoviruses, Rhabdoviruses;
6. dsDNA-RT viruses - DNA with RNA intermediate in life-cycle: Hepadnaviruses;
7. ssRNA-RT viruses - RNA with DNA intermediate in life-cycle: Retroviruses.

Viral diseases caused by viruses are summarized in **Table 1** [1]:

Table 1. Viral diseases are caused by different virus types.

Viral diseases	Virus types
AIDS (acquired immunodeficiency syndrome)	HIV (Human immunodeficiency virus) [2]
Chikungunya fever	Chikungunya virus (Alphavirus) (*Togaviridae*) [3]
Coronavirus disease 2019 (COVID-19)	Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) [4]
Dengue fever	Dengue viruses (DEN-1, DEN-2, DEN-3 and DEN-4) – Flavi viruses [3, 5]
Ebola hemorrhagic fever (Ebola virus disease)	Ebola virus (EBOV) [6]
Hepatitis A, B, C, D, E diseases	Hepatitis A, B, C, D, E viruses [7]
Herpes simplex diseases	Herpes simplex virus 1 and 2 (HSV-1 and HSV-2) [8]
Human papillomavirus infection	Human papillomavirus (HPV), *Papillomaviridae* [9]
Human parainfluenza virus infection	Human parainfluenza viruses (HPIV) [10]
Influenza A/Victoria 3/75, influenza A/Jena 48/78, influenza A/fowl plague, influenza B/Johannesburg)	*Orthomyxoviridae* species [11]
Newcastle disease	Avian paramyxovirus serotype-1 (APMV-1), *Paramyxoviridae* [12]
Vaccinia	Orthopoxvirus (*Poxviridae*) [13]
Zika fever	Zika virus [3]

Organic metal complexes possess potential activity against different viral diseases [14, 15]. Metal complexes of Curcumin [16], flavonoids [17], chalcones [18] and organic complexes with the following different metals: Ag(I) [19], Co(II) [20], Cu(II), Fe(III), Ni(II), Zn(II), Ti(IV) [21], Co(II), Cu(II), Ni(II), Zn(II) [22], Pd(II) [23] have been reported as antiviral agents.
Antiviral properties exert metal complexes with ligands, such as:

1. hydrazones [24]; 1-adamantoylhydrazones: Pd(II) and Pt(II) [25];
2. thiosemicarbazones: Pt(II), Pd(II) [26]; Ga(III)) [22]; Pd(II) [27]; Co(III), Ni(II), Cu(II)) [28];
3. bis(thiosemicarbazones): Pd(II) [29];
4. fluoroquinolones: Cu(II) [30];
5. quinoline: Pd(II) [31];
6. phenyl quinoline, phenylpyridine [32];
7. tetrahydropyrimidines (Ag(I)) [19];
8. phenanthroline: Cu(II) [21];
9. Acyclovir: Zn(II), Cu(II)) [33].

Complexes of Au, Co, Cu, Fe, Mn, Ni, Pd, Ru, Zn, and V have been described to exhibit potential antiviral properties against different types of viruses [34]. Cytomegalovirus can be blocked by metal complexes of 6-arylthio-3-hydroxypyrimidine-2,4-diones [35]. It has been observed the increased aggregation of Papillomavirus *in vitro* as a result of the action of Cu(II)-anthracenyl terpyridine complex [36]. It has been shown that ruthenium-*p*-cymene complexes [37], Pd(II) and Pt(II) complexes with 2-(diphenylphosphino) benzaldehyde 1-adamantoylhydrazone [25]. exert antiviral activity towards poliovirus type 1 [37].

Herpes Simplex

Acylhydrazone-based ligands and their transition metal complexes have been studied as antiviral molecules. Complexes of N'-(2-hydroxy-3-methoxybenzylidene)-2-hydroxybenzoyl hydrazone with Co(II), Cu(II), Ni(II), Mg(II), Mn(II) and Zn(II) possess activity against the DNA Herpes simplex viruses HSV-1, HSV-2 [24].
Pd(II) complexes of pyridine-2-carbaldehyde thiosemicarbazone are active toward HSV-1 [26]. Pd(II) complexes of benzylbis(thiosemicarbazone) and 3,5-diacyl-1,2,4-triazole bis (4-methylthiosemicarbazone) exert effect against the replication of Acyclovir-resistant Herpes simplex virus type 1 and type 2. Throughout the inhibition of the expression of HSV-1 protein gG protein gD, and protein gD, metal complexes suppress the process of the transactivation of the virus genome. The

mechanism of action of complexes also is connected with the decreasing of the process of transfer of infection from one the another cell [29].
It has been demonstrated, that cyclometalated iridium(III) complexes, containing chelating ligands, such as fluorinated phenylpyridine, phenylquinoline, or pyridine-2-carboxylate, can interact hydrophobically with the double helix of HSV-1 and HSV-2 viruses, on which mechanism of action is based their antiviral properties towards these viruses [32].
Bovine lactoferrin metal complexes with manganese, ferric, or zinc ions inhibit HSV-1 and HSV-2 replication in vitro [38]. Cobalt complexes with biguanide derivatives exhibit antiviral activity against Herpes virus type 2 [39]. Herpes simplex has been influenced by ruthenium-p-cymene complexes [37, 40] and by bis-cyclopentadienyl metallocene dichlorides of titanium and molybdenum [41]. Mononuclear Cu(II), Fe(III), Ru(III), and Zn(II) complexes of Acyclovir have been investigated towards the BHV-1 (Bovine herpes virus type-1) [42].
Antiviral properties against Herpes simplex virus include Curcumin-Cu(II) complex [43], Caffeic acid, Rosmarinic acid, and Chicoric acid [44]. The Caffeic acid chelates are effective towards HSV-1 and HSV-2. It has been reported that the antiviral activity of the Caffeic acid Fe(III) complex increases 100-fold in comparison with the activity of Caffeic acid [44].

Orthomyxoviruses
The four influenza genera are part of the seven genera in the family *Orthomyxoviridae*:
Influenza A virus (IAV), genus *Alphainfluenzavirus*
Influenza B virus (IBV), genus *Betainfluenzavirus*
Influenza C virus (ICV), genus *Gammainfluenzavirus*
Influenza D virus (IDV), genus *Deltainfluenzavirus*

Complexes of Au, Co, Cu, Fe, Mn, Ni, Pd, Ru, Zn, and V have been investigated to exhibit potential antiviral properties towards Influenza viruses by suppression of the process of replication of viral RNA [34]. It has been described that bis-cyclopentadienyl titanium dichloride exert antiviral effect against Orthomyxoviruses (Influenza A/Victoria 3/75, Influenza A/Jena 48/78, Influenza A/fowl plague, Influenza B/Johannesburg), Orthopoxvirus (Vaccinia), Paramyxovirus (Newcastle disease), and Rhabdovirus (Vesicular stomatitis) [41].
Copper complexes exhibit antiviral activity towards S31N M2 mutation of Influenza A virus [45]. It has been observed that Co(III) biguanide derivatives are active against the California influenza virus [39]. Caffeic acid chelates are effective towards Vaccinia virus [44]. Selenium-ruthenium complex is reported to exert activity towards Influenza virus [46].

Chikungunya Virus
As a result of the Chikungunya virus (Alphavirus of the family Togaviridae), chikungunya fever develops. This arthropod-borne virus is transmitted through the bite of a female Aedes sp. mosquito. Aedes aegypti and Aedes albopictus mosquitoes are the primary vectors. The disease is known to begin in 1950 in Africa, followed by 1955 in Tanzania, 1960 in Bangkok, and 1963 - 1973 in India. In 2004 the disease occurred in Kenya and the emergency for faster spread in the world increased. The beginning in Europe is dated from 2007 when the infection was found in Italy [47].
It has been investigated that an antiviral activity against the Chikungunya virus possesses:
1. Ag(I) complexes of antibacterial drug Mafenide [48];
2. Co(III) pyridine-thiosemicarbazone [49];
3. ruthenium p-cymene complex [50];
4. metal complexes of alpha-phellandrene, which is a natural compound [50].

It has been described that triphenylphosphine Au(I) derivatives can effectively inactivate the Chikungunya virus [51]. It has been reported that N-heterocyclic carbene metal derivative: Cu(I)-1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene complex inhibits **6**0 % of the virus replication [52].
It has been observed that the cobalt (III)-thiosemicarbazone complex can play an important role as a potential suppressor of the Chikungunya virus by causing up to 80 % inhibition on virus replication [53]. It has been reported that the platinum (II)-Rimantadine metallodrug can be a promising anti-virus agent. The mechanism of protection from the infection is based on the blockage by the complex of viral entry in human cells [54].

Dengue Virus
Dengue virus is a pathogen which worldwide causes infectious mosquito-borne diseases worldwide. For the first time, it occurred in Jakarta in 1968. The virus is distributed in tropical and subtropical areas. Dengue virus contains 4 serotypes as follows: DENV-1–DENV-4. These viruses belong to the family Flaviviridae and originated from the genus Flavivirus. The process of transmission of the virus to humans is caused by *Aedes agypty* and *Aedes albopictus*. Till now Dengue vaccine has not been approved. Therefore to decrease the emergency of the infection, is required the development of effective agents, which can reduce the fast spread of viruses. The Dengue virus NS5 protein is found to be an important target for antiviral agents investigation. Cobalt(II)-Morin (2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one) complex has been investigated to exert antiviral effect, due to suppression of the process of replication of Denga serotype 2 virus [55]. Anti-

Dengue serotype 2 virus activity is also proven to possess also Zn(II) complex of the same ligand (2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one) [56].

The following compounds are anti-Dengue virus agents:

1. 1 4,4′-diaminobenzanilide schiff base metal complexes [57];
2. Cu(2,4,5-triphenyl-1H-imidazole) [58].
3. Zn(II)-2, 4, 5-triphenyl-1H-imidazole Complex [59]
4. cobalt-protoporphyrin IX and tinprotoporphyrin IX [60]

It has been reported that cobalt-protoporphyrin IX and tinprotoporphyrin IX can inactivate the Dengue and Yellow Fever viruses [60].

Ebola Virus

Ebola virus disease is a viral hemorrhagic fever [61]. First cases of the disease were found in 1976, in Sudan and in Congo near the Ebola river, from which is originated the name of the disease [62]. Complexes of Au, Co, Cu, Fe, Mn, Ni, Pd, Ru, Zn, and V have been shown to exert antiviral effects against Ebola virus by inhibiting virus entry into the cells and by blocking replication of RNA [34]. Ebola pseudotyped virus can be inhibited by Caffeic acid metal complexes [44].

Zika Virus

Zika virus is included in the *Flaviviridae* family and is spread by *Aedes* mosquitoes. The disease microcephaly, which occurs after infection with Zika virus is associated with the neural disorder. This disease is characterized by brain defects in newborns [63]. An autoimmune disease called Guillain–Barré syndrome also can be caused by Zika virus infection. Copper(II) or cobalt(III) thiosemicarbazones with an effect on Zika virus have been reported [64].

Organic metal complexes with potential antiviral activity against Herpes simplex, Chikungunya, Dengue, and Zika viruses are presented in **Table 2**.

Table 2. Metal complexes with potential antiviral activity against Herpes simplex, Chikungunya, Dengue, Zika viruses

Metal	Ligand
Ag(I)	2-mercapto-3,4,5,6-tetra-hydropyrimidine [19] Mafenide [48]
Co(III)	Acyclovir: Co(II) [33] pyridine-thiosemicarbazone [49] thiosemicarbazones [64]
Cu(II)	bis(diisopropylsalicylato) (1,10-phenanthroline) [21] fluoroquinolones [30] Curcumin [43] anthracenyl-terpyridine [36] (2,4,5-triphenyl-1H-imidazole) [58] thiosemicarbazones [64]
Ga(II)	α-(N)-heterocyclic thiosemicarbazones [22]
Ir(III)	pyridine-2-carboxylate [32]
Pd(II)	quinolylmethylphosphonate [31] pyridine-2-carbaldehyde thiosemicarbazone [26] bis(thiosemicarbazone [29] 3,5-diacyl-1,2,4-triazole bis(4-methylthiosemicarbazone [29]
Ru(II)	*p*-cymene [42, 50] alpha-phellandrene [50]

Organic complexes of different methals with equal ligands have been described to exert potential antiviral activity against Herpes simplex, Chikungunya, Dengue, and Zika viruses, and some of the methals and ligands are presented in **Table 3**.

Table 3. Complexes of different methals with equal ligands with potential antiviral activity against Herpes simplex, Chikungunya, Dengue, and Zika viruses

Metal	Ligand
Fe(III) ne Co(III), ne Cu(II), Ni(II)	thiosemicarbazone [28]
Cu(II), Ni(II), Zn(II)	chalcones [18]
Cu(II), Fe(III), Zn(II), Ru(III)	Acyclovir [42]
Co(II), Cu(II), Fe(III), Ni(II), Zn(II), Ti(IV)	3,5-disubstituted salicylates [21]

Co(II), Cu(II), Ni(II), Mg(II), Mn(II), Zn(II)	N'-(2-hydroxy-3-methoxybenzylidene)-2-hydroxybenzoyl hydrazone [24]

Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV) is a rotavirus. The disease is spread worldwide and millions of people are infected [65]. Reverse transcriptase is a potential target for therapeutics [66].

Complexes of Au, Co, Cu, Fe, Mn, Ni, Pd, Ru, Zn, and V have been described to exhibit potential antiviral properties against HIV, by the mechanism of suppression of the process of replication of RNA [34]. Metal complexes of a sulfonate-N-donor ligand have been investigated for anti-HIV activity [65].

Research has documented the activity of curcumin boron complex [16], polypyridyl ruthenium complexes [67] and complexes of the subsequent metals against HIV: Au(II) in Auranofin [68], Au(III) [69], Cu(II) [66], Co II, Cu(II), Ni(II), Pd(II) [70], Zn(II) [71], Pt(II), Ru(II) [72], vanadium [73], Fe(II), Fe(III), La (III) [74], Mg(II), Zn(II) (Lactoferrin) [75]. Antiviral activity towards HIV has been shown for metal complexes with ligands, such as imidazole [66], bisthiosemicarbazone [69], bicyclams, porphyrins [70], benzofuran [74]. thiosemicarbazones [76]. Platinum(II) and ruthenium(II) complexes [77], triazolyl Ru(II), Os(II), and Ir(III) complexes [78], and thiouracil metal complexes exert potential anti-HIV effect [79] **(Table 4)**.

Table 4. Organic metal complexes with potential anti-HIVactivity

Metal	Ligand
Au(III)	bis(thiosemicarbazone) [69]
Cu(II)	imidazole [66] (pyridoxalthiosemisemicarbazone) [76]
Ni(II)	[bis(citronellathiosemisemicarbazone) [76]
Ru(II), Os(II), and Ir(III) Pd(II)	triazole [78]
Fe(III), (Ni)	porphyrins [70]

Complexes of different methals with equal ligands have been described to exert potential antiviral activity against HIV **(Table 5)**.

Table 5. Complexes of different metals with equal ligands with anti-HIVactivity.

Metal	Ligand
Co(II), Cu(II), Ni(II), Zn(II), Pt(II)	bicyclam [70]
Cu(II), Fe(III), La(III), Zn(II)	(5-(1H-benzo[d]imidazol-2-yl)-1H-pyrrol-3-yl)(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)methanone [74]
Co(II), Cu(II), Fe(II), La(III)	3-(6-hydroxy-4,7-dimethoxybenzofuran-5-carbonyl)-6H-pyrimido [1,6-a]pyrimidine-6,8(7H)-dione [74]

The FDA-approved gold-containing drug Auranofin for the treatment of rheumatoid arthritis has been investigated for therapeutic application towards cancer, neurodegenerative disorders, and HIV [67, 68]. The potent antiviral effect of bovine lactoferrin, saturated with ferric, manganese, or zinc ions is a result of its mechanism of action, which includes inhibition of the replication of DNA of HIV [57].

The metal bicyclam complexes (JM3100, JM3462, JM3469, JM3461, and JM3158), containing Cu, Co, Ni, Zn, and Pd, respectively, represent a new class of highly effective HIV inhibitors. The important characteristic of these compounds is their selectivity against HIV. The most active is JM3100: 1,1'-[1,4-phenylenebis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride dehydrate. Metalloporphyrins with Fe and Ni have been reported to suppress the process of replication of HIV [70].

COVID-19

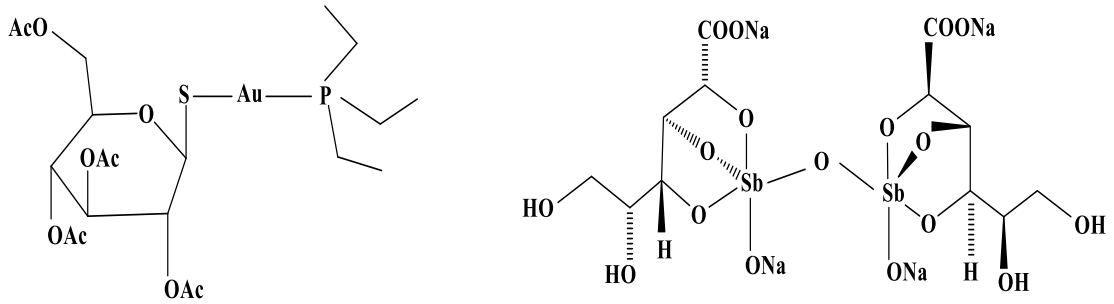
The severe acute respiratory syndrome – Coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the worldwide pandemic COVID-19, which has had an impact on millions of individuals across the globe [80]. The World Health Organization formally declared the outbreak on March 11, 2020 [81]. ACE 2 receptors of alveolar cells are targets of the virus [82]. The disease is characterized by cytokine storm syndrome [83, 84]. SARS-CoV-2 replication, transcription, and infectivity depend on polyproteins, which depend on both processes of replication and transcription of SARS-CoV-2 virus [81, 82]. The inhibition of the RNA polymerase complex can effectively lead to the suppression of the replication process in viruses [80]. Therefore the inhibition of the RNA polymerase complex is an important target for the mechanism of action and potential antiviral agents.

In accordance with the continued spread of SARS-CoV-2 and increasing deaths [85]. the development of transition metal complexes for antiviral applications is an important trend as the alternative treatment against SARS-CoV-2 [86].

Metal complexes with potential antiviral application against SARS-CoV-2 as therapeutics [41, 85, 87] are:

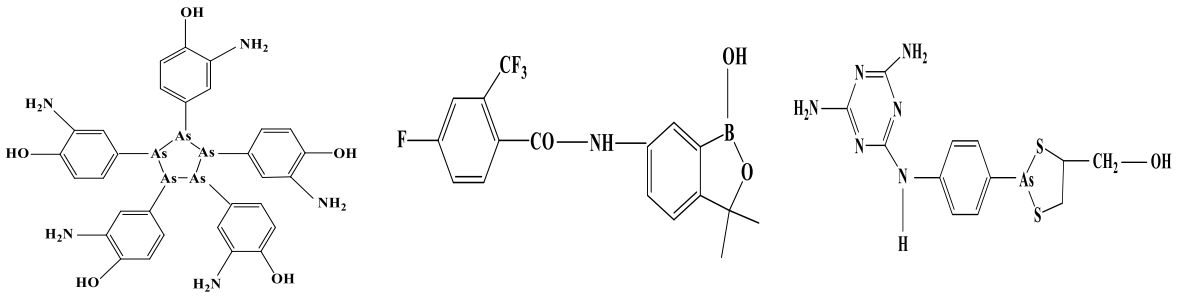
1. Auranofin [88], an important agent for therapeutic application in patients suffering with COVID-19 [89], due to exhibit properties to suppress the replication of SARS-COV-2 [88] and to decrease the inflammation in cells after Covid infection [90];
2. The FDA-approved antimalarial drug Ferroquine as the potential inhibitor of spike glycoprotein found in the SARS-CoV-2 [91];
3. Fe-porphyrins complexes as the potential inhibitors of RNA-dependant RNA polymerase [91];
4. Fe(III) complexes of 4-methoxy-salicylaldehyde condensation product with S-methylthiosemicarbazone derivatives of 1,1,1-trifluoroacetylacetone [92];
5. Ni(II) complexes of 4-methoxy-salicylaldehyde condensation product with S-methylthiosemicarbazone derivatives of methylacetoacetate [92];
6. Cu(II), Ni(II), Mn(II), Zn(II) complexes of 3-acetyl-7-hydroxy coumarin [93];
7. rhodium pentamethylcyclopentadienyl complexes, with direct virucidal activity towards SARS-CoV-2 [85];
8. metal-containing polymers [94].

Auranofin was approved by the FDA in 1985 as an antirheumatic drug. Injectable antiarthritic gold drugs are Disodium aurothiomalate, Aurothioglucose, and Sodium aurothiopropanol sulfonate. Auranofin possesses a potent antimicrobial effect against multidrug-resistant pathogens like *Staphylococcus aureus* and *Enterococcus faecalis.* Auranofin exerts antiparasitic action towards the parasite *Leishmania infantumq* [95, 96]. In comparison Sodium stibogluconate (Pentostam) **(Figure 1)** is intravenosal anti-Leishmanial drug. In comparison, other Au agents as Chloroquinoline complexes of Au(I) are active against malaria. Other approved metal complexes as antiinfective drugs were introduced in 1910 Salvarsan is the first anti-syphilis arsenium drug, and Benzoxaborole (SCYX-7158) and Melarsoprol, which has been developed for oral treatment of human African trypanosomiasis **(Figure 2)**.



a) b)

Figure 1. Structures of Auranofin and Sodium stibogluconate. a) Auranofin. b) Sodium stibogluconate



a) **b)** **c)**

Figure 2. Structures of Salvarsan, Benzoxaborole and Melarsoprol. a) Salvarsan. b) Benzoxaborole. c) Melarsoprol

Auranofin has been proven as a metal-based compound with potential for antiviral application [95]. Auranofin possesses anti-Covid 19 therapeutic activity, based on the ability to inhibit SARS-COV-2 replication by the following mechanisms [90]:

1. inhibition of redox enzyme thioredoxin reductase, leading to oxidative stress;
2. suppression of papain-like protease, leading to oxidative stress [81];
3. induction of endoplasmic reticulum stress;
4. activation of the unfolded protein response in cells [81];
5. reduction of RNA of SARS-CoV-2 RNA [81];
6. stimulation of the production of reactive oxygen species [88];
7. dysregulation of intracellular redox homeostasis [88];
8. attenuation of inflammation in human cells by [90]:
    a. blocking of interleukin-6 signalling by inhibition of phosphorylation of JAK1 [96];
    b. suppression of overproduction of pro-inflammatory cytokines;

c. blocking of cyclooxygenase expression;
d. inhibition of the formation of PGE2 in macrophages [96];
e. reduction of the expression of SARS-induced cytokines in human cells [96].

It has been reported that cyclometallated gold(III) complexes [97] and silver N-heterocyclic carbene complexes [98] are potential compounds towards viruses

Conclusion

Organometal complexes are potential antiviral agents against different types of viral diseases in humans as 1) DNA viruses: herpes simplex (HSV-1 and HSV-2), human papillomavirus and human cytomegalovirus; 2) RNA viruses: influenza A, parainfluenza 3, coxsackievirus B3, Chikungunya, Dengue, Ebola, Zika, human immunodeficiency virus. Metal complexes with ligands, such as: hydrazones; thiosemicarbazones: Pt(II), Pd(II); Ga(III); Pd(II); Co(III), Ni(II), Cu(II)); fluoroquinolones, quinoline: Pd(II); phenylquinoline, phenylpyridine; tetrahydropyrimidines: Ag(I); phenanthroline: Cu(II); Valacyclovir: Cu(II)) exhibit antiviral activity. Complexes of Zn(II). Co(II), Cu(II), Ni(II), Mg(II), Mn(II) and Zn(II) possess activity against the DNA Herpes simplex viruses HSV-1, HSV-2. Co(II), An antiviral potential against, Chikungunya, Dengue, Zika viruses possess Cu(II), Ni(II), Mg(II), Mn(II), Zn(II) oranic complexes. Against the HIV have been described to be active complexes of the following metals: Au(II), Co(II), Cu(II), Fe(III), La(III), and Mg(II). Ni(II), Pd(II), Pt(II), Ru(II). In connection with the continued spread of the severe acute respiratory syndrome – Coronavirus 2 (SARS-CoV-2), today's very actual strategy is the development of effective COVID therapeutics. The perspective trend in the creation and investigation of potential agents for the effective application towards SARS-CoV-2, are Auranofin and of Cu(II), Ni(II), Mn(II), Zn(II) complexes of Coumarin, lthiosemicarbazone complexes.

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References

1. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and autoimmunity: A review on the potential interaction and molecular mechanisms. Viruses. 2019;11(8):762. doi:10.3390/v11080762
2. Bonney EY, Lamptey H, Kyei GB. HIV cure: An acceptability scientific agenda. Curr Opin HIV AIDS. 2023;18(1):12-7. doi:10.1097/COH.0000000000000771
3. Ryan SJ, Carlson CJ, Mordecai EA, Johnson LR. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. PLOS Neglect Trop Dis. 2019;13(3):e0007213. doi:10.1371/journal. pntd.0007213
4. Oran P, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 Infection: A narrative review. Annal Intern Med. 2020;173(5):362-7. doi:10.7326/M20-3012
5. Sobhia ME, Ghosh K, Singh A, Sul K, Singh M, Kumar R, et al. A multi-perspective review on Dengue research. Curr Drug Targets. 2019;20(15):1550-62. doi:10.2174/1389450120666190724145937
6. Nicastri E, Kobinger G, Vairo F, Montaldo C, Leonard E, Mboera G, et al. Ebola virus disease: Epidemiology, clinical features, management, and prevention. Infect Dis Clin North Am. 2019;33(4):953-76. doi:10.1016/j.idc.2019.08.005
7. Nguyen MH, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B virus: Advances in prevention, diagnosis, and therapy. Clin Microbiol Rev. 2020;33(2):10-1128. doi:10.1128/CMR.00046-19
8. Zhu Sh, Viejo-Borbolla A. Pathogenesis and virulence of Herpes simplex virus. Virulence. 2021;12.1:2670-702. doi:10.1080/21505594.2021.1982373
9. Kombe AJK, Li B, Zahid A, Mengist HM, Bounda GA, Zhou Y, et al. Epidemiology and burden of human Papillomavirus and related diseases, molecular pathogenesis, and vaccine evaluation. Front Public Health. 2020;8:552028. doi:10.3389/fpubh.2020.552028
10. Farahmand M, Malekshahi SS, Jabbari MR, Shayestehpour S. The landscape of extrapulmonary manifestations of human Parainfluenza viruses: A systematic narrative review. Microbiol Immunol. 2021;65(1):1-9. doi:10.1111/1348-0421.12865
11. Yu JS, Li F, Wang D. The first decade of research advances in Influenza D virus. J Gen Virol. 2021;102(1):jgv001529. doi:10.1099/jgv.0.001529
12. Mansour SMG, El-Bakrey RM, Mohamed FF, Hamouda EE, Abdallah MS, Elbestawy AR et al. Avian paramyxovirus type 1 in Egypt: Epidemiology, evolutionary perspective, and vaccine approach. Front Vet Sci. 2021;8:647462. doi:10.3389/fvets.2021.647462

13. Lima MT, Oliveira GP, Afonso JAB, Souto RJC, de Mendonça CL, Dantas AFM, et al. An update on the known host range of the Brazilian vaccinia virus: An outbreak in buffalo calves. Front Microbiol. 2019;9:3327. doi:10.3389/fmicb.2018.03327
14. Anthony EJ, Bolitho EM, Bridgewater HE, Carter OWL, Donnelly JM, Imberti C, et al. Metallodrugs are unique: Opportunities and challenges of discovery and development. Chem. Sci. 2020;11(48):12888-917. doi:10.1039/d0sc04082g
15. Munnangi SR, Youssef AAA, Narala N, Lakkala P, Narala S, Vemula SK et al. Drug complexes: Perspective from academic research and pharmaceutical market. Pharmaceut Res. 2023;40(6):1519-40. doi:10.1007/s11095-023-03517-w
16. Ardebili A, Pouriayevali MH, Aleshikh S, Zahani M, Ajorloo M, Izanloo A, et al. Antiviral therapeutic potential of Curcumin: An update. Molecules. 2021;26(22):699423. doi:10.3390/molecules26226994
17. Kowalczyk M, Golonko A, Świsłocka R, Kalinowska M, Parcheta M, Swiergiel A, et al. Drug design strategies for the treatment of viral disease. Plant phenolic compounds and their derivatives. Front Pharmacol. 2021;12:709104. doi:10.3389/fphar.2021.709104
18. Elkhalifa D, Al-Hashimi I, Al Moustafa AE, Khalil A. A comprehensive review on the antiviral activities of chalcones. J Drug Targeting. 2021;29(4):403-19. doi:10.1080/1061186X.2020.1853759
19. Zachariadis PC, Hadjikakou SK, Hadjiliadis N, Skoulika S, Michaelides A, Balzarini J, et al. Synthesis, characterization and in vitro study of the cytostatic and antiviral activity of new polymeric silver(I) complexes with ribbon structures derived from the conjugated heterocyclic thioamide 2-mercapto-3,4,5,6-tetra-hydropyrimidine. Eur J Inorg Chem. 2004;2004(7):1420-6. doi:10.1002/ejic.200300672
20. Fernandes LP, Silva JMB, Martins DOS, Santiago MB, Martins CHG, Jardim ACG, et al. Fragmentation study, dual anti-bactericidal and anti-viral effects and molecular docking of cobalt(III) complexes. Int J Mol Sci. 2020;21(21): 8355. doi:10.3390/ijms21218355
21. Gil-Moles M, Ott I. Transition metal-based antiviral agents against SARS-CoV-2 and other pathogenic viruses. In: Targeted Metallo-Drugs. CRC Press; 2023:105-38.
22. Refat MS, Gaber A, Alsanie WF, Kobeasy MI, Zakaria R, Alam K. Utilization and simulation of innovative new binuclear Co(II), Cu(II), and Zn(II) diimine Schiff base complexes in sterilization and coronavirus resistance (Covid-19). De Gruyter 2021;19(1):772-84. doi:10.1515/chem-2021-0068
23. Abate C, Carnamucio F, Giuffrè O, Foti C. Metal-based compounds in antiviral therapy. Biomolecules. 2022;12(7):933. doi:10.3390/biom12070933
24. Rogolino D, Carcelli M, Bacchi A, Compari C, Contardi L, Fisicaro E, et al. A versatile salicyl hydrazonic ligand and it's metal complexes as antiviral agents. J Inorg Biochem. 2015;150(1):9-17. doi:10.1016/j.jinorgbio.2015.05.013
25. Simic V, Kolarevic S, Brceski I, Jeremic-Jera D, Vukovic-Gacic B. Cytotoxicity and antiviral activity of palladium(II) and platinum(II) complexes with 2-(diphenylphosphino) benzaldehyde 1-adamantoylhydrazone. Turk J Biol. 2016;40(3):661-9. doi:10.3906/biy-1503-23
26. Varadinova T, Kovala-Demertzis D, Rupelieva M, Demertzis M, Genova P. Antiviral activity of platinum(II) and palladium(II) complexes of pyridine-2-carbaldehyde thiosemicarbazone. Acta Virol. 2001;45(2):87-94.
27. Karaküçük-İyidoğan A, Taşdemir D, Oruç-Emre EE, Balzarini J. Novel platinum(II) and palladium(II) complexes of thiosemicarbazones derived from 5-substituted thiophene-2-carboxaldehydes and their antiviral and cytotoxic activities. Eur J Med Chem. 2011;46(11):5616-24. doi:10.1016/j.ejmech.2011.09.031
28. Arslan BA, Kaya B, Şahin O, Baday S, Saylan CC, Ülküseven B. The iron(III) and nickel(II) complexes with tetradentate thiosemicarbazones. Synthesis, experimental, theoretical characterization, and antiviral effect against SARS-CoV-2. J Mol Struct. 2021;1246:131166. doi:10.1016/j.molstruc.2021.131166
29. Genova P, Varadinova T, Matesanz AI, Marinova D, Souza, P. Toxic effects of bis(thiosemicarbazone) compounds and its palladium(II) complexes on Herpes simplex virus growth. Toxicol Appl Pharmacol. 2004;197(2):107912. doi:10.1016/j.taap.2004.02.006
30. Dorotíková S, Kožíšková J, Malček M, Jomová K, Herich P, Plevová K, et al. Copper(II) complexes with new fluoroquinolones: Synthesis, structure, spectroscopic and theoretical study, DNA damage, cytotoxicity and antiviral activity. J Inorg Biochem. 2015;150:160-73. doi:10.1016/j.jinorgbio.2015.06.017
31. Tusek-Bozic L, Cmrecki V, Balzarini J, De Clercq E. Cytotoxicity and antiviral activity of palladium(II) quinolylmethylphosphonate complexes. Synthesis of acetate complexes. Lett Drug Design Discov. 2006;3(8):528-33. doi:10.2174/157018006778194772
32. Bai D, Tian Y, Chen K, Zhang X, Wang F, Cheng Y, et al. Novel 6F-iridium(III) complexes as potent theranostic agents: Hypoxia probing, radiosensitization and antiviral functionalities. Dyes Pigments. 2020;182:108635. doi:10.1016/j.dyepig.2020.108635
33. Muratov BA, Turaev KK, Umbarov IA, Kasimov SA, Nomozov AK. Studying of complexes of Zn(II) and Co(II) with Acyclovir (2-amino-9-((2-hydroxyethoxy)methyl)-1,9-dihydro-6H-purine-6-OH). Int J Engineer Trends Technol. 2024;72(1):202-8. doi:10.14445/22315381/IJETT-V72I1P120

34. Yousuf I, Bashir M, Arjmand F, Tabassum S. Advancement of metal compounds as therapeutic and diagnostic metallodrugs: Current frontiers and future perspectives. Coord Chem Rev. 2021;445:214104. doi:10.1016/j.ccr.2021.214104
35. Wang L, Edwards TC, Sahani RL, Xie J, Aihara H, Geraghty RJ, et al. Metal binding 6-arylthio-3-hydroxypyrimidine-2,4-diones inhibited human cytomegalovirus by targeting the pUL89 endonuclease of the terminase complex. Eur J Med Chem. 2021;222:113640. doi:10.1016/j.ejmech.2021.113640
36. Kumar A, Kuhn LT, Balbach J. A Cu2+ complex induces the aggregation of human papillomavirus oncoprotein E6 and stabilizes p53. FEBS J. 2018;285(16):3013-25. doi:10.1111/febs.14591
37. D'Amato A, Mariconda A, Iacopetta D, Ceramella J, Catalano A, Sinicropi MS, et al. Complexes of ruthenium(II) as promising dual-active agents against cancer and viral infections. Pharmaceuticals (Basel). 2023;16(12):729. doi:10.3390/ph16121729
38. Marchetti M, Pisani S, Antonini G, Valenti P, Seganti L, Orsi N. Metal complexes of bovine lactoferrin inhibit in vitro replication of Herpes simplex virus type 1 and 2. Biometals. 1998;11(2):89-94. doi:10.1023/a:1009217709851
39. Kirin VP, Demkin AG, Sukhikh TS, Ilyicheva TN, Maksakov VA. Cobalt complexes with biguanide derivatives – synthesis, structure and antiviral activity. J Mol Struct. 2022;1250(2):131486. doi:10.1016/j.molstruc.2021.131486
40. Maldonado N, Amo-Ochoa P. The role of coordination compounds in virus research. Different approaches and trends. Dalton Trans. 2021;50(7):2310-23. doi:10.1039/D0DT04066e
41. Cirri D, Pratesi A, Marzo T, Messori L. Metallo therapeutics for COVID-19. Exploiting metal-based compounds for the discovery of new antiviral drugs. Expert Opin Drug Discov. 2021;16(1):39-46. doi:10.1080/17460441.2020.1819236
42. Avcioglu MV, Golcu A. Synthesis of Acyclovir metal complexes: Spectral, electrochemical, thermal, and DNA binding studies. Synth React Inorg Metal-Org Nano-Metal Chem. 2015;45(4):581-90. doi:10.1080/15533174.2013.831877
43. Zandi K, Ramedani E, Mohammadi K, Tajbakhsh S, Deilami I, Rastian Z, et al. Evaluation of antiviral activities of curcumin derivatives against HSV-1 in Vero cell line. Nat Prod Commun. 2010;5(12):1935-8. doi:1934578X1000501220
44. Langland J, Jacobs B, Wagner CE, Ruiz G, Cahill TM. Antiviral activity of metal chelates of caffeic acid and similar compounds towards herpes simplex, VSV-Ebola pseudotyped and vaccinia viruses. Antivir Res. 2018;160(1):143-50. doi:10.1016/j.antiviral.2018.10.021
45. McGuire KL, Hogge J, Hintze A, Liddle N, Nelson N, Pollock J, et al. Copper complexes as Influenza antivirals: Reduced zebrafish toxicity, Engineered Nanomaterials Health Safety. IntechOpen. 2019. doi:10.5772/intechopen.88786
46. Li Y, Chen D, Su J, Chen M, Chen T, Jia W, et al. Selenium-ruthenium complex blocks H1N1 influenza virus-induced cell damage by activating GPx1/TrxR1. Theranostics. 2023;13:1843-59. doi:10.7150/thno.83522
47. Staples JE, Breiman RF, Powers AM. Chikungunya fever: An epidemiological review of a re-emerging infectious disease. Clin Infect Dis. 2009;49(6):942-8. doi:10.1086/605496
48. Esquezaro PG, Manzano CM, Nakahata DH, Santos IA, Ruiz UEA, Santiago MB, et al. Synthesis, spectroscopic characterization and in vitro antibacterial and antiviral activities of novel silver(I) complexes with Mafenide and ethyl-Mafenide. J Mol Struct. 2021;1246:131261. doi:10.1016/j.molstruc.2021.131261
49. de Fernandes LP, Silva JMB, Martins DOS, Santiago MB, Martins CHG, Jardim ACG, et al. Fragmentation study, dual anti-bactericidal and anti-viral effects and molecular docking of cobalt(III) complexes. Int J Mol Sci. 2020;21(21):8355. doi:10.3390/ijms21218355
50. de Oliveira DM, de Santos IA, Martins DOS, Gonçalves YG, Cardoso-Sousa L, Sabino-Silva R, et al. Organometallic complex strongly impairs Chikungunya virus entry to the host cells. Front Microbiol. 2020;11:608924. doi:10.3389/fmicb.2020.608924
51. Aires RL, Santos IA, Fontes JV, Bergamini FR, Jardim ACG, Abbehausen C. Triphenylphosphine gold(I) derivatives promote antiviral effects against the Chikungunya virus. Metallomics. 2022;14(8):mfac056. doi:10.1093/mtomcs/mfac056
52. Fontes JV, Santos IA, Rosa LB, Lima RL, Jardim AC, Miguel DC, et al. Antileishmanial and anti-Chikungunya activity of Cu(I)-N-heterocyclic carbenes. Chem Select. 2022;7(31):e202201560. doi:10.1002/slct.202201560
53. Martins DOS, Souza RAC, Freire MCLC, de Moraes NCRM, Santos IA, de Oliveira DM, et al. (2023). Insights into the role of the cobalt(III)-thiosemicarbazone complex as a potential inhibitor of the Chikungunya virus nsP4. J Biol Inorg Chem. 2023;28(1):101-15. doi:10.1007/s00775-022-01974-z
54. Santos IA, dos Santos Pereira AK, Guevara-Vega M, de Paiva REF, Sabino-Silva R, Bergamini FR, et al. Repurposing potential of Rimantadine hydrochloride and development of a promising platinum(II)-rimantadine metallodrug for the treatment of Chikungunya virus infection. Acta Trop. 2022;227:106300. doi:10.1016/j.actatropica.2021.106300
55. Sucipto TH, Churrotin S, Setyawati H, Mulyatno KC, Amarullah IH, Ueda S, et al. Inhibitory activity of cobalt (II)-morin complex against the replication of dengue virus type 2. Indones J Trop Infect Dis. 2017;6(6):141-4. doi:10.20473/ijtid.v6i6.6126
56. Sucipto TH, Setyawati H, Churotin S, Amarullah IH, Sumarsih S, Wardhani P, et al. Anti-Dengue type 2 virus activities of Zinc(II) complex compounds with (2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one) ligands in Vero cells. Indones J Trop Infect Dis. 2019;7(5):108-9. doi:10.20473/ijtid.v7i5.10851

57. Seethalakshmi M, Amaladhas TP. Application of 4,4-diaminobenzanilide Schiff base metal complexes as anti-tumor and anti-Dengue agents. J Environ Nanotechnol. 2020;9(1):11-20. doi:10.13074/jent.2020.03.201390
58. Sucipto TH, Martak F. Inhibition of Dengue virus serotype 2 in Vero cells with [Cu(2,4,5-triphenyl-1H-imidazole)2(H2O)2].Cl2. Infect Dis Rep. 2020;12(11):93-7. doi:10.4081/idr.2020.8744
59. Sucipto TH, Wibrianto A, Martak F, Churrotin S, Amarullah IH, Setyawati H, et al. Effect of Zinc(II)-2,4,5-triphenyl-1H-imidazole complex against replication DENV-2 in vero cell. Indones J Trop Infect Dis. 2020;8(3):183-8. doi:10.20473/ijtid.v8i3.11776
60. Assunção-Miranda I, Cruz-Oliveira C, Neris RLS, Figueiredo CM, Pereira LPS, Rodrigues D, et al. Inactivation of Dengue and Yellow Fever viruses by heme, cobalt-protoporphyrin IX and tinprotoporphyrin IX. J Appl Microbiol. 2016;120(3):790-804. doi:10.1111/jam.13038
61. Letafati A, Ardekani SO, Karami H, Soleimani M. Ebola virus disease: A narrative review. Microb Pathog. 2023;181:106213. doi:10.1016/j.micpath.2023.106213
62. Junaid A, Tang H, van Reeuwijk AJ, Abouleila Y, Wuelfroth P, van Duinen V, et al. Ebola hemorrhagic shock syndrome-on-a-chip. iScience. 2020;23(1):100765. doi:10.1016/j.isci.2019.100765
63. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. N Engl J Med. 2016;374(10):951-8. doi:10.1056/NEJMoa1600651
64. Dutta S, Celestine MJ, Khanal S, Huddleston A, Simms C, Arca JF, et al. Coordination of different ligands to copper(II) and cobalt(III) metal centers enhances Zika virus and dengue virus loads in both arthropod cells and human keratinocytes Biochim Biophys Acta. 2018;1862(1):40-50. doi:10.1016/j.bbagen.2017.10.004
65. Ghosn J, Taiwo B, Seedat S, Autran B, Katlama C. HIV. Lancet. 2018;392(10148):685-97. doi:10.1016/S0140-6736(18)31311-4
66. Sucipto TH, Martak F. Synthesis of metal-organic (complexes) compounds copper(II)-imidazole for antiviral HIV candidate. Indones J Trop Infect Dis. 2016;6(1):1-7. doi:10.20473/ijtid.v6i1.1204
67. Wang MF, Li Y, Bi XD, Guo YX, Liu M, Zhang H, et al. Polypyridyl ruthenium complexes as bifunctional TAR RNA binders and HIV-1 reverse transcriptase inhibitors. J Inorg Biochem. 2022;234:111880. doi:10.1016/j.jinorgbio.2022.111880
68. Diaz RS, Shytaj IL, Giron LB, Obermaier B, Della-Libera E, Galinskas J, et al. Potential impact of the antirheumatic agent auranofin on proviral HIV-1 DNA in individuals under intensified antiretroviral therapy: Results from a randomised clinical trial. Int J Antimicrob Agents. 2019;54(5):592-600. doi:10.1016/j.ijantimicag.2019.08.001
69. Fonseca CAM. Biological activity of gold compounds against viruses and parasitosis: A systematic review. Bio Chem. 2022;2(2):145-59. doi:10.3390/biochem2020010
70. De Clercq E. Antiviral metal complexes. Metal Based Drugs. 1997;4(3):173-92. doi:10.1155/MBD.1997.173
71. Boros E, Dyson PJ, Gasser G. Classification of metal-based drugs according to their mechanisms of action. Chem. 2020;6(1):41-60. doi:10.1016/j.chempr.2019.10.013
72. Yufanyi DM, Abbo HS, Titinchi SJJ, Neville T. Platinum(II) and ruthenium(II) complexes in medicine: Antimycobacterial and anti-HIV activities. Coordin Chem Rev. 2020;414:213-85. doi:10.1016/j.ccr.2020.213285
73. Nareetsile F, Matshwele JTP, Ndlovu S, Ngaski M. Transition metal complexes with HIV/AIDS inhibitory properties. Chem Rev Lett. 2022;3(3):140-60. doi:10.22034/CRL.2020.230856.1057
74. Galal SA, Abd AS, Hegab KH, Magd-El-Din AA, Youssef NS, El-Diwani HI. Novel antiviral benzofuran-transition metal complexes. Eur J Med Chem. 2010;45(7):3035-46. doi:10.1016/j.ejmech.2010.03.034
75. Zhou H, Zhu Y, Liu N, Zhang W, Han J. Effect of iron saturation of bovine lactoferrin on the inhibition of hepatitis B virus in vitro. Biochem Biophys Mol Biol. 2024;12:e17302. doi:10.7717/peerj.17302
76. Moharana AK, Dash RN, Subudhi BB. Thiosemicarbazides: Updates on antivirals strategy. Mini Rev Med Chem. 2020;20(20):2135-52. doi:10.2174/1389557520666200818212408
77. García-Gallego S, Rodríguez JS, Jiménez JL, Cangiotti M, Ottaviani MF, Muñoz-Fernández MA, et al. Polyanionic N-donor ligands as chelating agents in transition metal complexes: Synthesis, structural characterization and antiviral properties against HIV. Dalton Trans. 2012;41(21):6488-99. doi:10.1039/C2DT11793b
78. Putterill B, Rono C, Makhubela B, Meyer D, Gama N. Triazolyl Ru (II), Os (II), and Ir (III) complexes as potential HIV-1 inhibitors. Biometals. 2022;35(4):771-84. doi:10.1007/s10534-022-00400-w
79. Al-Masoudi NA, Saleh BA, Karim NA, Issa AY, Pannecouque C. Synthesis and anti-HIV activity of new 2-thiolumazine and 2-thiouracil metal complexes. Heteroat Chem. 2011;22(1):44-50. doi:10.1002/hc.20654
80. Pal M, Musib D, Roy M. Transition metal complexes as potential tools against SARS-CoV-2: An in silico approach. New J Chem. 2021;45(4):1924-33. doi:10.1039/D0NJ04578k
81. Karges J, Cohen SM. Metal complexes as antiviral agents for SARS-CoV-2. Chembiochem. 2021;22(16):2600-07. doi:10.1002/cbic.202100186
82. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109(1):102433. doi:10.1016/j.jaut.2020.102433
83. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. doi:10.1016/S0140-6736(20)30628-0

84. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, et al. COVID-19, cytokines and immunosuppression: What can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol. 2020;38(2):337-42. doi:10.55563/clinexprheumatol/xcdary
85. Chuong C, DuChane CM, Webb EM, Rai P, Marano JM, Bernier CM, et al. Noble metal organometallic complexes display antiviral activity against SARS-CoV-2. Viruses. 2021;13(6):980. doi:10.3390/v13060980
86. Ioannou K, Vlasiou MC. Metal based complexes against SARS-CoV-2. Biometals 2022;35(4):639-52. doi:10.1007/s10534-022-00386-5
87. Ghosh AK, Brindisi M, Shahabi D, Chapman ME, Mesecar AD. Drug development and medicinal chemistry efforts toward SARS - coronavirus and COVID-19 therapeutics. Chem Med Chem. 2020;15(11):907-32. doi:10.1002/cmdc.202000223
88. Marzo T, Messori L. A role for metal-based drugs in fighting COVID-19 infection? The case of Auranofin. ACS Med Chem Lett. 2020;11(6):1067-68. doi:10.1021/acsmedchemlett.0c00190
89. Sonzogni-Desautels K, Ndao M. Will Auranofin become a golden bew treatment against COVID-19? Fronti Immunol 2021;12:683694. doi:10.3389/fimmu.2021.683694
90. Rothan HA, Stone S, Natekar J, Kumari P, Arora K, Kumar M. The FDA-approved gold drug Auranofin inhibits novel coronavirus (SARS-COV-2) replication and attenuates inflammation in human cells. Virology. 2020;547:7-11. doi:10.1016/j.virol.2020.05.002
91. Pal M, Musib D, Zade AJ, Chowdhury N, Roy M. Computational studies of selected transition metal complexes as potential drug candidates against the SARS-CoV-2 Virus. Chem Select. 2021;6(29):7429-35. doi:10.1002/slct.202101852
92. Janković N, Milović E, Jovanović JĐ, Marković Z, Vraneš M, Stanojković T, et al. A new class of half-sandwich ruthenium complexes containing Biginelli hybrids: Anticancer and anti-SARS-CoV-2 activities. Chem Biol Interact. 2022;363:110025. doi:10.1016/j.cbi.2022.110025
93. El-Bindary AA, El-Desouky MG, El-Afify MAM. Thermal and spectroscopic studies of some prepared metal complexes and investigation of their potential anticancer and antiviral drug activity against SARSCoV-2 by molecular docking simulation. Biointerf Res Appl Chem. 2022;12(1):1053-75. doi:10.33263/BRIAC121.10531075
94. Akbari A, Bigham A, Rahimkhoei V, Sharifi S, Jabbari E. Antiviral polymers: A review. Polymers 2022;14(9):1634. doi:10.3390/polym14091634
95. Abd-El-Lateef HM, El-Dabea T, Khalaf MM, Abu-Dief AM. Development of metal complexes for treatment of coronaviruses. Int J Mol Sci. 2022;23(12):l6418. doi:10.3390/ijms23126418
96. Kim NH, Lee MY, Park SJ, Choi JS, Oh MK, Kim IS. Auranofin blocks interleukin-6 signalling by inhibiting phosphorylation of JAK1 and STAT3. Immunol. 2007;122(4):607-14. doi:10.1111/j.1365-2567.2007.02679.x
97. Balsera-Manzanero M, Soengas RG, Carretero-Ledesma M, Cordero E, Soto SM. Heteroleptic (S^C)-cyclometallated gold(III) complexes as novel antiviral agents. Heeliyon. 2024;10(6):E27601.
98. Gil-Moles M, O'Beirne C, Esarev IV, Lippmann P, Tacke M, Cinatl J, et al. Silver N-heterocyclic carbene complexes are potent uncompetitive inhibitors of the papain-like protease with antiviral activity against SARS-CoV-2. RSC Med Chem. 2023;14(7):1260-71. doi:10.1039/d3md00067b