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Literature Analysis of the Efficacy of Arbidol in Virus Infectious Diseases

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Abstract: Arbidol (ARB) is a broad-spectrum antiviral drug. However, its effects on virus infectious diseases remain unclear. We aimed to evaluate the efficacy of ARB in infectious virus diseases. We searched up to March 2020 in MEDLINE (Ovid SP), EMBASE (Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), for studies investigating ARB in virus infectious diseases. Descriptive analysis was made on the main results of the eligible articles that meet the inclusion criteria. Fifty-two studies were included finally, which involving influenza virus, respiratory syncytial virus (RSV), severe acute respiratory syndrome-coronaviruses (SARS-CoV), middle east respiratory syndrome-coronaviruses (MERS-CoV), hepatitis c virus (HCV), herpes simplex virus (HSV), severe acute respiratory syndromes-coronaviruses-2 (SARS-CoV-2), chikungunya virus (CHIKV), hantaan virus (HTNV), zika virus (ZIKV), coxsackievirus, lassa virus(LASV), Ebola virus (EBOV) and adenovirus (ADV). ARB is effective in the above viruses. Two studies showed that ARB was effective in SARS-CoV-2. *In vivo* and *in vitro* studies showed ARB had the capability of inhibiting SARS-CoV, MERS-CoV, HCV, HSV, ZIKV, CV, HTNV, ZIKV, CHIKV, LASV, EBOV, and ADV. Conclusion Clinical studies are still needed to confirm the efficacy of ARB in novel coronavirus pneumonia (COVID-19).

Keywords: COVID-19; Arbidol; Virus infectious; Systematic Literature Review.

1. Introduction

Viruses infectious diseases are disorders caused by viruses, such as human immunodeficiency virus (HIV), severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV), Ebola virus (EBOV) and so on. Viruses are very tiny germs; they are made of genetic material inside of the coating protein. The clinical symptoms of viral infection mainly manifested as a common cold, flu, warts, and even severe diseases, such as SARS MERS and Ebola.

Novel coronavirus pneumonia (COVID-19), a new type of coronavirus, was first reported from Wuhan, China, on 31 December 2019. Person-to-person transmission of COVID-19 has been confirmed [1]. There has been infected 331’636, with a rising death over 20’963 worldwide up to now. The World Health Organization (WHO) has recently declared the COVID-19 a public health emergency of international concern (PHEIC).

Recently, some antiviral drugs have been recommended for treating the novel coronavirus in China according to the sixth edition of COVID-19 Diagnosis Guidelines released by China's National Health Commission, such as interferon, lopinavir/ritonavir, chloroquine phosphate, ribavirin and arbidol (ARB) [2,3]. ARB that is made in Russian is a

potent broad-spectrum antiviral drug. ARB not only can inhibit the Influenza A and B viruses but also can inhibit the hepatitis C virus (HCV). The objective of this study was to conduct a systematic literature review (SLR) to evaluate the relative efficacy and safety of ARB in infectious virus diseases.

2. Materials and Methods

2.1. Literature search.

We searched MEDLINE (Ovid SP), EMBASE (Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), for articles published up to March 2020, using the keywords: 'arbidol', 'umifenovir'. Additionally, ClinicalTrials.gov was also searched for unpublished data. The reference lists of included studies and relevant review articles investigating the use of ARB in infectious virus diseases are screened for potentially eligible studies.

2.2. Study selection.

Studies were included if they met the following criteria: (1) using ARB as the tested agent; (2) involving test subjects with infectious virus diseases, the test subjects may be the patients, the animal models or the cell models; (3) whether or not be the comparative studies.

Studies were excluded if they met the following criteria: (1) if they did not meet the included criteria; (2) review studies; (3) pharmacokinetic studies; (4) pharmacoeconomics studies; (5) surveys studies.

2.3. Data extraction.

Two authors (YL, NS) reviewed all searched studies independently. Relevant data were extracted for a pre-defined pilot-tested data extraction form. The following data were extracted: the research design, the first author, year of publication, interventions, duration of follow-up, characteristics of participants, diseases, mechanisms. The main results of the available articles are described.

3. Results and Discussion

3.1 Literature search.

Our study selection process is illustrated in Fig. 1. A total of 271 articles were identified. After screening the titles and abstracts, 52 potentially eligible articles underwent full-text reviewing. A total of 30 were excluded for the following considerations: (1) review (n=12); (2) pharmacokinetic (n = 13); (3) drug interactions (n = 1); (4)duplicate(n=4).

3.2.Study characteristics.

The virus spectrum characteristics of the included studies are shown in table 1. Based on the analysis of the publication time, it can be seen that the articles mainly focused after 2009 (n=129, 72.07%). The earliest published time was 1991, a total of 17 articles (9.50 %) were published in 2009, which was the most published year—[See Fig. 2 for the bibliometric diagram]. Among the included studies, *in vivo*, and *in vitro* studies were 9, animal studies were 6, cell studies were 23, clinical studies were 14. 21 studies were carried out in Russia (40%),

25 studies were in China(48%), 3 studies were in The United States(6%), 2 studies were in France(4%), 1 study was in Italy(2%).

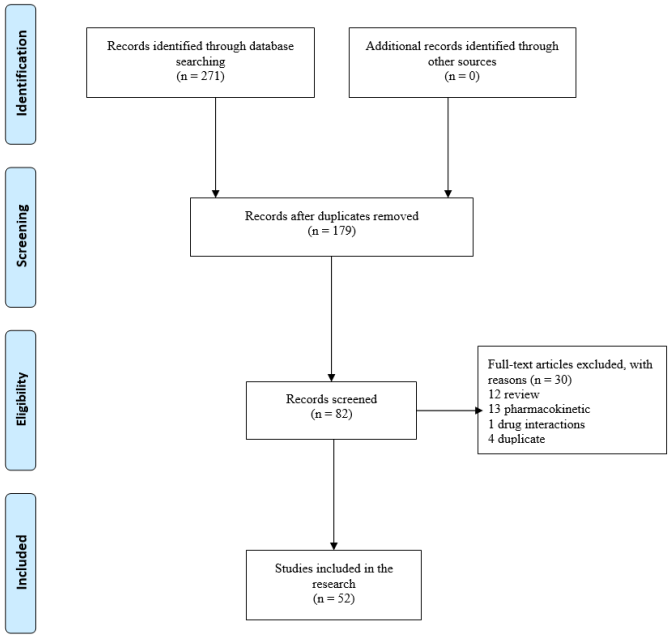

Figure 1. Flow diagram of the current study.

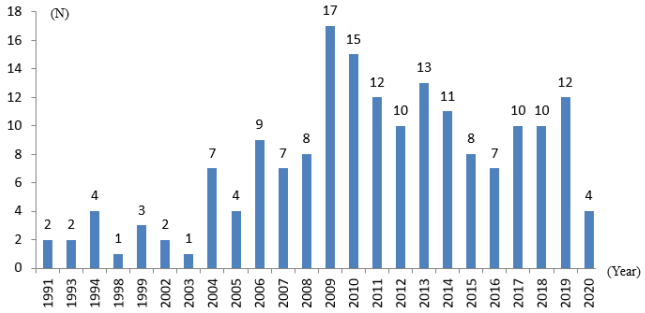

Figure 2. The publication time of arbidol in infectious diseases.

3.3 The effectiveness.

3.3.1. Influenza.

Thirty studies reported ARB for influenza viruses. Influenza viruses can be divided into three types: A, B, and C. Influenza A virus often occurs antigenic variation, infectious, rapid spread, easy to occur a wide range of epidemics. Influenza A is highly pathogenic to humans. The Influenza A virus that can infect humans is as following: (H1N1), H5N1, H7N1, H7N2, H7N3, H7N7, H7N9, H9N2, and H10N8. Among the subtypes of Influenza A virus, H1, H5, and H7 are highly pathogenic, while H1N1, H5N1, and H7N9 merit our attention.

3.3.1.1. Influenza virus (unclassified).

There are 15 studies on the common influenza virus (unclassified). According to Diagnosis and Treatment Plan for Influenza issued by China in 2019, it recommended ARB for antiviral treatment within 48 hours, 200 mg each time, 3 times a day, a course of treatment for 5 days [4].

Wang Mengzhao *et al*. conducted the randomized controlled, double-blind trial to verify the clinical efficacy, safety, and tolerability of ARB in the treatment of Influenza among 232 patients [5]. Qualified subjects were randomly assigned to ARB hydrochloride or placebo treatment. The two groups were treated with 200 mg/time, 3 times/day in 5 days. The experimental results showed that the oral administration of ARB hydrochloride capsules 200mg 3 times /d within 36h of onset was effective in the treatment of Influenza. The median duration of disease in the experimental group and the control group was 72.0 and 96.0 h, respectively. The severity of the disease was also significantly reduced, with a median decrease of 780.0 and 684.0 in total symptom scores, respectively.

Russian scholars Kiselev, O. I *et al*. conducted a randomized controlled, double-blind study on the clinical efficacy and safety of ARB in the treatment of adult influenza [6]. The study included a total of 293 adults from 18 to 65 years old who were diagnosed with Influenza or an acute respiratory infection within 36 hours. There are two treatment groups: oral ARB 200 mg 4 times a day for 5 days or placebo 4 times a day for 5 days. The result shows that the efficacy of ARB was assessed in 119 (40.6%) influenza patients, of whom 45 were laboratory-confirmed, and 74 were diagnosed based on clinical and epidemiological data. As for the laboratory-confirmed patients, 23.8% who took ARB experienced remission of all symptoms within 60 hours of starting the treatment. This figure was better than that of the placebo group (4.2%) ($P < 0.05$). Compared with the placebo, ARB reduced the severity of the condition, symptoms of nasal mucositis, and so on, with the most significant reduction observed in the first 2-3 days after starting treatment. At the same time, the proportion of patients shedding the Influenza virus on day 4 in the ARB group was significantly lower than that in the placebo group (25 vs. 53%; $P < 0.05$). The result shows that the effects of ARB treatment for Influenza were most efficient in adults during the acute phase of the illness.

A study had evaluated the efficacy of ARB against Influenza in established mice and ferret disease models [7]. It was found that the survival rates of 25 mg/ml and 45 mg/ml ARB mice were 40% and 50%. Compared with the control group, both 25 mg/ml and 45 mg/ml ARB reduced the expansion of lung index in mice. In the ferret model, antiretroviral treated ferrets developed a fever at 2 dpi and gradually decreased at 3 dpi, while relatively high temperatures were observed in the virus group up to 4 dpi. The study showed that ARB could reduce lung injury caused by the Influenza virus. ARB can inhibit virus proliferation and regulate the expression of inflammatory cytokines *in vivo* and *in vitro* and can be used as an effective drug for the treatment of influenza virus infection.

3.3.1.2. H1N1.

Seven studies reported ARB for H1N1. H1N1 was originally described as a human infection with swine flu. On 30 April 2009, the World Health Organization, the Food and Agriculture Organization of the United Nations, and the World Organization for Animal Health announced that they had agreed to use the H1N1 flu as a reference. H1N1 refers to the glycoproteins on the surface of the virus. H stands for erythromycin with a total of 1-16 types; N stands for neuraminidase, with a total of 1-9 types. Both H and N of this virus are type 1, and there it is called H1N1. The H1N1 virus is an Influenza A virus, belonging to the orthomyxoviridae family. Influenza A virus genus, its genetic material is RNA. The typical virion is globular, with a diameter of 80 nm - 120 nm and a capsule membrane. There are many protruding glycoproteins radially arranged on the capsule membrane, which are hemagglutinin

HA, neuraminidase NA, and M2 protein. The nucleocapsid inside the virus particle is helical and symmetrical, with a diameter of 10nm.

LIU Q *et al*. adopted MTT method to determine *in vitro* cytotoxicity and antiviral activity of ARB after MDCK cells were infected with A/FM/1/47 seasonal influenza (H1N1) and A/Hubei/71/2009 pandemic influenza (H1N1) [8]. Mice were infected with A/FM/1/47 seasonal (H1N1). After 4 hours, ARB (45, 90, 180 mg·kg-1·d-1) or the neuraminidase inhibitor oseltamivir (22.5 mg·kg-1·d-1) was administered orally, one time per day, for 5 days. After that, the body weight, median survival time, virus titer, and lung index of the mice were assessed. The result showed that H1N1 viruses were equally sensitive to ARB *in vitro* tests. In mice, ARB (90 and 180 mg·kg-1·d-1) significantly reduced mortality, reduced viral titer, and inhibited levels of il-1β in bronchoalveolar lavage and lung tissue, il-6, il-12, and TNF-α, and increased levels of il-10. However, ARB did not significantly affect the levels of IFN-α and IFN-γ. It is believed that ARB can effectively inhibit H1N1 staining, reduce virus replication, and regulating the expression of inflammatory cytokines.

3.3.1.3. H3N2.

Three studies reported ARB for H3N2. H3N2, a subtype of Influenza a virus, has minor changes compared to H1N1, with no major changes in transmission pattern, infectivity, or lethality.

Loginova S *et al*. compared the efficacy of ARB, ribavirin, oseltamivir, and amantadine in the treatment of Influenza a virus (H3N2) [9]. It was found that the efficacy of ARB was lower than that of ribavirin, which was comparable to amantadine and lower than oseltamivir.

3.3.1.4. H5N1.

Five studies reported ARB for H5N1. H5N1 virus, namely A (H5N1) or H5N1, also known as H5N1 virus, H5N1 avian Influenza, is a highly pathogenic subtype of Influenza A virus, with hemagglutinin type 5, neuraminidase type 1. It is originated in poultry and wild birds and can be transmitted to humans. Unlike the human flu virus, it does not spread easily from person to person.

Some Russian researchers studied the therapeutic activity of ARB, oseltamivir, rimantadine, and ribavirin in albino mice infected with Influenza a virus (H5N1) through respiratory tract [10]. The result showed that the protective and therapeutic effect of ARB (11.7±1.7%) was weaker than that of ribavirin (36.7±1.7%), and the protective treatment effect of ribavirin was similar to that of oseltamivir (50.0±0.0%) and amantadine (38.3±1.7%).

3.3.2. Respiratory Syncytial Virus (RSV).

Two studies reported ARB for RSV. RSV is an RNA virus belonging to the paramyxoviridae family. Under the electron microscope, it was similar to the parainfluenza virus, with a particle size of about 150nm, which was slightly smaller than the parainfluenza virus. The virus can be transmitted by airborne droplets and close contact. It is more common in newborns and infants within 6 months. The symptom of an infant is heavier, can have high fever, rhinitis, pharyngitis, and laryngitis, show later for bronchitis and pneumonia. After infection in adults and older children, the main manifestation is upper respiratory tract infection.

He Jing *et al*. studied the antiviral activity and mechanism of ARB hydrochloride against RSV [11]. The anti-RSV effect of ARB was observed by cytopathic effect (CPE) and thiazole blue (MTT) colorimetry. The result showed that half of the toxicity concentration (TD50) of ARB was 85.39 mg/L. When the drug concentration was 25 mg/L, the inhibition rates of the virus were 81.61%, 79.57%, 40.39%, and 78.60%, respectively. In the antiviral biosynthesis group, the direct killing virus group and the drug anti-adsorption were 4h groups. The effective concentrations of half of the corresponding drugs (ED50) in the 4 groups were 11.52, 8.74, 25.36, and 10.40mg/L. It was found that ARB could significantly inhibit the cytopathic effect (CPE) of RSV infected cells and increase the inhibition rate of the virus in a dose-dependent manner.

3.3.3. Severe Acute Respiratory Syndrome coronavirus (SARS-CoV).

Only one study reported ARB for SARS-Cov. SARS-CoV belongs to the coronavirus family [12]. It is the largest RNA virus known. The diameter of the virus is 80-120 nm. In this study, ARB was used as a positive control drug to observe the inhibitory effect of ARB on SARS-CoV by MTT and cytopathic methods. The result showed that the maximum non-toxic concentration of ARB was 10ug/ml by MIT method, and the treatment index TI of SARS-Cov was 1.77. The IC50 of the positive control drug ribavirin was 66.1ug/ml, and the treatment index TI was > 6.1. The results showed that ARB inhibited SARS-CoV *in vitro*.

3.3.4. Middle East Respiratory Syndrome coronavirus (MERS-CoV).

Only one study reported ARB for MERS-CoV [13]. MERS-CoV and SARS-CoV are coronaviruses, but they are genetically distinct and infect people through different receptors. This study evaluated the *in vivo* and *in vitro* efficacy of ARB combined with the Lianhua Qingwen capsule to inhibit MERS-CoV replication. In this study, the model was MERS-CoV infected Vero cells. In the mice model of MERS-CoV infection, the mice were randomly divided into 3 groups, 6 in each group, namely the virus group, the ARB group (90mg/ (kg. d)), and the Lianhua Qingwen group (1300mg/ (kg. d)). The titer of mouse pneumonovirus was detected by plaque test on the 3rd and 5th day after drug treatment. The result showed that the TC50 of ARB and Lianhua Qingwen capsules in Vero cells were 36.78ug/ml and 4023.27ug/ml, respectively, the minimum concentrations of *in vitro* inhibition of MERS-CoV replication were 4ug/ml and 900ug/ml respectively. The therapeutic indexes were 2.19 and 0.47. There was no statistically significant difference in virus titer between the two drugs after MERS-CoV infection in mice and the control group ($P > 0.05$). Therefore, the study considered that ARB could inhibit MERS-CoV replication *in vitro.*

3.3.5. Hepatitis c virus (HCV).

Two studies reported ARB for HCV. HCV is a spherical and single-stranded plus-strand RNA virus. Russian researchers studied the effect of ARB on the expression of HCV RNA and protein [14]. The effect of ARB on HCV was not mediated by the type 1 IFN signaling pathway. The effect of ARB on virus interaction occurs at the membrane level. The experiment observed that under a strictly controlled pH of 5.0, ARB completely blocked the fusion of HCV liposome sheath from multiple genotypes with liposome membranes. It is unlikely that other weak bases, such as chloroquine, can inhibit viral replication by increasing the pH in the body.

3.3.6. Herpes Simplex Virus (HSV).

Four studies reported ARB for HSV. HSV is a typical representative of the herpes virus. According to the difference of antigenicity, HSV can be divided into two serotypes: HSV-1 and HSV-2. The DNA of the two viruses has 50% homology, and they have the common antigen and the type-specific antigen [15]. HSV-2 is a highly contagious virus that causes severe genital diseases and skin diseases that persist for life.

Nian Ma *et al*. studied the antiviral effect of ARB on HCE cells and HSV-2 in BALB/c mice and its possible potential mechanism [16]. The result showed that in HCE cells and BALB/c mice, ARB effectively inhibited HSV-2 replication in a dose-dependent manner, mainly by acting on virus entry and early infection. *In vivo* experiments showed that ARB could improve the survival rate of infected HSV-2 mice, prolong the survival time, reduce genital tract damage, and reduce the level of viral proteins in target tissues. Qiuling Du *et al*. .also studied the effect and mechanism of ARB on HSV-2 *in vivo* and *in vitro* [17]. The result showed that ARB had certain anti-HSV-2 activity *in vitro* in a dose-dependent manner.

Some studies tested the antiviral effect of ARB on HSV-1 *in vitro* and *in vivo* [18]. The experimental results showed that ARB significantly inhibited the formation of HSV-1 plaque and progeny virus when the EC50 value (50% effective concentration) was 5.39 ug/ml and 2.26 ug/ml. ARB has also been shown to be effective in reducing the severity and duration of lesions in guinea pig models of skin infection with HSV-1.

3.3.7. Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2).

Two studies reported ARB for SARS-CoV-2. SARS-COV-2 is the pathogenic virus of novel coronavirus pneumonia (COVID-19). Currently, it is believed that the first step into the human body is the binding of human angiotensin-converting enzyme 2 (ACE2) by S protein. The affinity between the SARS-CoV-2 S protein and ACE2 is 10 to 20 times higher than that of SARS-CoV, which may be one of the reasons why theSARS-CoV-2 protein is more infectious [19]. Considering that SARS-CoV-2, SARS-CoV, and MERS-CoV are both coronaviruses, the treatment of ARB may be effective.

Wang Z *et al*. presented the clinical characteristics and treatment of 4 cases of mild or severe COVID-19 in the Shanghai Public Health Clinical Center [20]. All patients received antiviral treatment, including lopinavir/ritonavir, ARB, and other necessary support care. After treatment, pneumonia-related symptoms improved significantly in 3 patients, 2 of whom were diagnosed as COVID-19 and discharged from the hospital, and 1 of whom was tested negative for the virus for the first time. By the data collection deadline, the remaining patients with severe pneumonia had shown signs of improvement. The result may provide clues for the treatment of COVID-19. However, the trial also indicated that the efficacy of antiretroviral drugs such as lopinavir/ritonavir, ARB, and Shufeng detoxification should be further verified.

Qu Xiangkun *et al*. analyzed 70 cases of COVID-19 diagnosed and treated from 31 January 2020 to 11 February 2020 [21]. According to the different treatment methods, they were divided into the combined drug group (40 cases) and the ARB group (30 cases). Both groups were given routine oral administration of ARB, and on this basis, the combined drug group was given oral administration of Shufeng Jiedu capsule for a course of 10 days. The fevers and symptoms of dry cough, nasal obstruction, runny nose, sore throat, fatigue, and diarrhea were compared between the two groups. The result showed that the antifebrile time and the disappearance time of dry cough, nasal obstruction, runny nose, sore throat, fatigue,

and diarrhea in the combined treatment group were significantly shorter than those in the ARB group (P<0.05). The pharyngeal swabs were re-examined on the 10th day, and 12 cases in the combined drug group were negative once, and 7 cases in the ARB group were negative once. The negative conversion time of SARS-CoV-2 in the combined treatment group was significantly shorter than that in the ARB group (P<0.05). Therefore, it was concluded that the combination of Shufeng Jiedu capsule and ARB in the treatment of COVID-19 was superior to ARB alone, and could significantly shorten the time for the improvement of clinical symptoms and the time for the transformation of SARS-CoV-2 into negative.

3.3.8. Chikungunya Virus (CHIKV).

One study reported ARB for CHIKV. CHIKV belongs to the Semliki Forest (SF) antigen complex group of the family capriviridae and genus alphavirus. The virus is about 70nm in diameter, has an envelope, and contains 3 structural proteins and 4 non-structural proteins. Its genome is a segment-free plus stranded RNA. Humans and non-human primates are the main hosts of CHIKV. Chikungunya fever is an acute infectious disease caused by CHIKV and transmitted by Aedes mosquitoes, characterized by fever, rash, and joint pain [22].

Ilenia Delogu *et al*. from France studied the *in vitro* antiviral activity of ARB against CHIKV [23]. It was found that ARB had an effective inhibitory activity against the virus on Vero cells or primary human fibroblasts (mrc-5 lung cells) (IC50 < 10ug/ml). The activity concentration of ARB was significantly lower than its cytotoxic concentration (CC50 ≥ 200ug/ml) and was similar to that of the Influenza A virus.

3.3.9. Hantaan virus (HTNV).

Four studies reported ARB for HTNV. HTNV belongs to the Bunyaviridae family and is a negative-stranded RNA virus with enveloped segments. There are two types of hantavirus: hantavirus pulmonary syndrome (HPS) and hantavirus hemorrhagic fever with renal syndrome (HFRS).

Deng Haiying *et al*. reported the *in vivo* and *in vitro* experimental study of ARB against HTNV [24]. Suckled BALB/c mice with the uninfected virus were given 5, 10, or 20 mg·kg-1·d-1 once per day for 10 days. Histopathological changes and viral antigens were detected on days 12 and 28 after infection. The viral load of the target organs and serum TNF- levels were measured at 4, 8, 12, and 16 days after infection. *In vitro* test results showed that ARB had strong *in vitro* inhibition of HTNV activity before and after virus infection, with 50% inhibition concentration (IC50) of 0.9-1.2ug/ml. The half lethal dose (LD50) of ARB to Suckling mice was 78.42 mg·kg-1·d-1.: oral administration of ARB improves survival and mean time to death (MTD). ARB treatment reduces histopathological changes, reduces viral load and viral antigen levels, and regulates serum TNF-levels. It is believed that ARB has the ability to induce protective antiviral activity *in vivo* and *in vitro*.

3.3.10. Coxsackie virus (CV).

Two studies reported ARB for CV. CV is a kind of intestinal virus, with a diameter of 28 nm. The nucleic acid is a single strand of RNA with CV to the high sensitivity of rats. According to their infected rats produced lesions, CV can be divided into two groups, A and B group. Humans infected with CV easily cause herpangina and change of paralytic polio etc.

Hilin Zhang *et al*. found that ARB could effectively inhibit CV B4 infection [25], while Qiong Zhong's *in vivo* and *in vitro* test proved that ARB could effectively inhibit CV B5 infection [26].

Table 1. Virus spectrum characteristics of included studies (n =52).

Diseases	Virus	Include studies (n)	
		Clinic	Non-Clinic
Influenza	Influenza A or B virus	11	4
	H1N1	1	6
	H3N2	-	3
	H5N1	-	5
Croup	Respiratory syncytial virus (RSV)	-	2
Severe Acute Respiratory Syndromes(SARS)	Severe Acute Respiratory Syndromes-Coronaviruses (SARS-CoV)	-	1
Middle East Respiratory Syndrome(MERS)	Middle East Respiratory Syndrome-Coronaviruses (MERS-CoV)	-	1
Hepatitis	Hepatitis C Virus (HCV)	-	2
Herpes	Herpes Simplex Virus (HSV)	-	4
Covid-19	Severe Acute Respiratory Syndromes-Coronaviruses-2 (SARS-CoV)-2	2	-
Chikungunya fever	*Chikungunya Virus* (CHIKV)	-	1
Fever, renal involvement	Hanta Virus (HTNV)	-	4
Aseptic meningitis	Coxsackie Virus (CV)	-	2
Zika	Zika Virus (ZIKV)	-	1
Hemorrhagic fever	Lassa Virus (LASV)	-	1
Ebola hemorrhagic fever	Ebola Virus (EBOV)	-	1
Upper respiratory infection	Adeno Virus (ADV)	-	1

3.3.11. Zika virus (ZIKV).

Only one study reported ARB for ZIKV. ZIKV belongs to the Flaviviridae family, a single-stranded plus stranded RNA virus with a diameter of 20 nm. It is an arbovirus transmitted by mosquitoes, and its host is not clear. The incubation period (from exposure to the onset of symptoms) of ZIKV disease is unknown and can be several days. Only about 20 percent of people infected with ZIKV will show mild symptoms. Typical symptoms include acute onset of low fever, maculopapular, joint pain (mainly involving the small joints of the hands and feet), and conjunctivitis. Other symptoms include myalgia, headache, orbital pain, and weakness.

One study proved the antiviral potential of ARB against ZIKV [27]. The experiment tested the antiviral activity of ARB in human lung epithelial cells, human liver cancer cells, and Vero cells infected with ZIKV. Before, during, and after the addition of ARB, infection confirmed the best time to fight infection. Experiments have proved that ARB can inhibit ZIKV by preventing the virus from entering. ARB had dose-dependent inhibitory effects on ZIKV isolates, and ARB could prevent ZIKV-induced cytopathic changes.

3.3.12. Lassa Virus and Ebola Virus (LASV and EBOV).

Only one study reported ARB for LASV and EBOV. LASV caused viral hemorrhagic fever of Lassa. LASV is a single-stranded RNA virus belonging to the family arenviridae. The virus particles are from round to polymorphic, with a capsule membrane and a ‘T’ shape protruded on the surface of the virus envelope. The length of LV the form of circular nucleocapsid, ranging in length from 400nm-1300nm.

EBOV belongs to the filoviridae family, with a length of 970 nm, long filamentous, single-stranded negative-stranded RNA virus. The virus particle diameter is about 80 nm. The virus with strong infectivity is generally about 665-805 nm long. It has branching, u-shaped, 6-shaped or ring-shaped, and branching is more common. The EBOV is a kind of can cause humans and other primates to have deadly infectious diseases of EBOV. Hemorrhagic fever virus, which causes Ebola hemorrhagic fever is the deadliest viral hemorrhagic fever in the modern world, infected virus symptoms with a fellow fiber of Marburg virus, including nausea, vomiting, diarrhea, skin color changes, the whole-body pain, bleeding, bleeding *in vitro, in vivo*, such as a fever.

The one study pointed out that because the overlap was geographically similar and the way it enters the cell was similar, a drug could be found to treat the infection of the two viruses [28]. The study directly compared eight drugs that had been approved or were in clinical trials to see if they had the ability to block the two viral glycoprotein-mediated entry. Later tests showed that ARB could inhibit a variety of enveloped viruses entering cells through the endocytic pathway. The study admits ARB or drugs containing ARB could be developed to treat LASV and EBOV.

3.3.13. Adeno Virus (ADV).

Only one study reported ARB for ADV [29]. ADV is a double-stranded DNA virus without an envelope, first discovered by Rowe in 1953. At present, at least 90 genotypes have been found, which are divided into 7 subgenera of a-g. ADV infection can cause pneumonia, bronchitis, cystitis, and encephalitis. The major ADV related to respiratory tract infection is subgenus B (hadv-3, 7, 11, etc.).

In this study, cell activity was detected by observing the cytopathic effect (CPE), thiazole blue (MTT) colorimetric assay, and viral titration. The experimental results showed that although ARB had no direct killing effect on ADV-7 and could not prevent the adsorption and penetration of the virus, it could significantly inhibit the biosynthesis of ADV-7, with the toxicity concentration of half cells (CC50) of 85.37mg/L, the effective concentration of half cells (IC50) of 15.39mg/L and the therapeutic index (TI) of 5.55. It is believed that ARB plays a role *in vitro* by inhibiting viral biosynthesis, but the specific mechanism still needs further study.

4. Conclusions

So far, there were six coronaviruses that may cause disease in humans: HCoV-OC43, HCoV-229E, HCoV-HKU1, HCoV-NL63, SARS-CoV, and MERS-CoV [30]. SARS-CoV-2 is identified to be a new beta coronavirus, which is similar to SARS-CoV. WHO, on 11 March 2020 declared COVID-19 a pandemic. Unfortunately, there have been no vaccine or treatment available yet for SARS-CoV-2. ARB, as a non-nucleoside broad-spectrum antiviral drug, had already been administered in the Union of Soviet Socialist Republics (USSR) in 1974. It had been used for the treatment and prevention of influenza A and B viral respiratory infections based on the drug label. So far, some studies had found the antiviral mechanism involves: (1) Binding to both lipids and protein residues. ARB had interfacial activity and can site in the shallow layer above the glycerol backbone of phospholipids [31]. ARB could disrupt the virus attaching to cytoplasm membrane; (2) Inhibiting the viral entry. ARB could interact with proteins and lipids, which may prevent viruses from slipping into cells [32]; (3) Inhibiting viral

fusion. This inhibitory process was by means of ARB interfering with the conformational changes of in virus and improving membrane rigidity [33]; (4) Inhibiting of viral replication, convergence, and budding. ARB was shown to inhibit RNA replication in replicon systems and created lipid-rich internal membrane surroundings beneficial for viral replication.

ARB had been recommended for treating COVID-19 in China according to Diagnosis Guidelines (the 6th edition). It showed that ARB was effective for many viruses based on the literature analysis: (1) ARB has been shown to display antiviral activity against influenza viruses, included H1N1, H3N2, H5N1; (2) ARB can inhibit the replication of MERS-CoV *in vitro;* (3) ARB has anti-SARS-CoV activity *in vitro*; (4) ARB can inhibit several aspects of the HCV lifecycle by acting on HCV entry, fusion, and replication; (5) ARB showed anti-HSV activity *in vitro* and played a role in inhibiting the late replication cycle of the virus; (6) ARB as one of the antiviral drugs was effective against COVID-19 and it was recommended by COVID-19 diagnosis guidelines; (7) For many other viruses, including CHIKV, HTNV, ZIKV and CV, the results showed ABR had antivirus effect *in vitro*.

Despite by far, there was no specific drug treatment for COVID-19 [34-35]. In conclusion, ABR had proven to be an effective broad-spectrum antiviral drug *in vitro* and *in vivo*. A few clinical studies confirmed the antiviral action for Influenza and COVID-19. So it is necessary to carry out multicenter randomized control trials about ABR in the future and providing references for its clinical application.

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Conflicts of Interest

The authors declare no conflict of interest.

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