

Use of Pharmaceutical Nanotechnology in Treatment of Covid-19: A Systematic Review Study

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Abstract

Background: The pathogenesis of SARS-CoV-2 is not fully understood, and currently there is currently no definitive drug or treatment against it. So, the drugs used to treat SARS-CoV-2 are mainly based on their effectiveness on previous species of coronaviruses. This review aimed to evaluate the studies performed on the use of the available drugs in the treatment of Covid-19 since the onset of this disease.

Method: Comprehensive search strategy was conducted in the following databases: PubMed, Web of Science (ISI) and Scopus, Psycinfo, Google Scholar, and national databases, including Scientific Information Database (SID) and MagIran from inception of Covid-19 to June 2022. Studies that reported the effect of different drugs in treatment of Covid-19 patients were included.

Results: 38 studies (114,552 participants) were included in this systematic review study on used drug treatment of patients with Covid-19 including Remdesivir, HCQ & Chloroquine, Favipiravir, Molnupiravir, Arbidol, Kaletra, Oseltamivir, IVIG & Interferon.

Conclusions: Remdesivir, HCQ & Chloroquine, Favipiravir, Molnupiravir, Arbidol, Kaletra, Oseltamivir, IVIG & Interferon are the most commonly used drugs in treatment of Covid-19. Although these drugs may be effective in improving the condition of Covid-19 patients in the inflammatory phase, the confirmation of their use requires more extensive clinical research.

Keywords: Pharmaceutical, Nanotechnology, Treatment, Covid-19.

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INTRODUCTION

Human coronavirus infection, first appeared in Wuhan, China in December 2019 and spread rapidly on a pandemic scale worldwide [1, 2]. This disease was named Covid-19 by the World Health Organization (WHO) on February 11, 2020 [3]. The growing prevalence of this disease has challenged the public health of the world and led to a morbid fear of contracting it in individuals [4, 5]. Corona virus is a packet-type virus with a single-stranded RNA of animal origin belonging to the family Coronaviridae and Nidovirales. They based of their genotype and serology, divided into three group including alpha, beta, gamma and delta. Human coronaviruses are caused by the alpha and beta type [6]. The causative agent of Covid-19 disease is a RNA virus [7], that primarily targets the human respiratory system [8]. Since the pathogenesis of SARS-CoV-2 is not fully understood, there is currently no definitive drug or treatment against it. So, the drugs used to treat this disease are mainly based on their effectiveness on previous species of coronaviruses such as MERS-CoV and SARS-CoV [9]. Pharmaceutical nanotechnology is a technology used in a wide range of products, especially medical and drug. At the

moment, there are 8879 nanotechnology products registered in the Nanotechnology Products Database, of which 2467 companies are responsible for the production, spread in 62 countries worldwide [10, 11]. One of the major problems to reduce SARS-CoV-2 damage is the absence, until now, of effectively and safely treated with few unwanted side effects. The best approach to introduce rapid therapy is to test drugs that are already available on the market, as these drugs have safety profiles as reported in the previously widely studied [12-14]. This systematic review aimed to evaluate the studies performed on used drug used in treatment of Covid-19 since the onset of this disease.

METHOD

Data Sources and Searches

In this article, the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines was followed for conducting this systematic review [15]. The searches were performed the following electronic databases: Pubmed, EMBASE, Web of Science (ISI), Scopus, psycinfo, Google scholar and Persian databases, including Scientific Information Database (SID), Irandoc and MagIran. The following example shows

how the terms were used as text words and key words in these databases: (Covi-19* OR treatment OR drug *) AND (Pharmaceutical OR nanotechnology) from the onset of Covid-19 epidemic on December 2019. These four databases were screened for consideration of the reference lists of articles at the full-text stage and review articles on the topic of covid-19, treatment, pharmaceutical and nanotechnology.

Eligibility criteria

As inclusion criteria in this review, the authors considered observational studies (Cohort studies, cross sectional), and clinical trial studies published as original used a validated method or instrument to assess efficacy and safety of drug in treatment of Covid-19 infection. Exclusion criteria included: Studies that did not report enough data to determine the efficacy and safety of drug, all type of review article, letters, editorial and interventional studies.

Data collection

According to the selection criteria, the results of the search were screened for relevant titles and abstracts. The relevant abstracts were chosen for full-text review to extract data. Also, references of relevant articles were screened for

relevance. Duplicates were removed. Then, for extracting the following information from included studies, a standardized data collection form was used: first author, study design, country of origin, year of publication, sample size, and conclusion of the studies.

Study quality

For each included article, author investigated all extracted data during the quality assessment process. The Newcastle-Ottawa Scale (NOS) was used for assessing the methodological quality of studies. First, the keywords were searched in the desired databases based on the determined time range. The articles that were in harmony with the keywords of the research include Pharmaceutical, nanotechnology, and Covid-19 was selected.

RESULTS & DISCUSSION

In this study, all published studies analyzing the pharmaceutical nanotechnology in treatment of Covid-19 were systematically reviewed based on the PRISMA guidelines Fig.1.

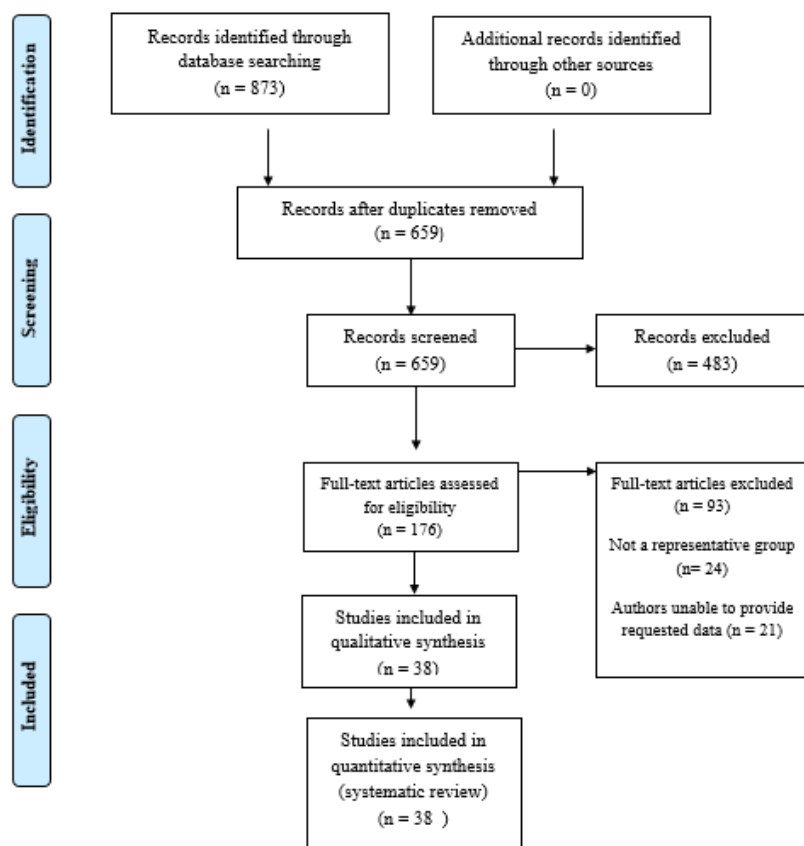


Fig.1: Four-phase PRISMA flow diagram showing the number of studies identified, screened, eligible, and included in the systematic review.

Remdesivir

Remdesivir (GS-5734) is a monophosphoramidate product of adenosine analog that has a wide range of antivirals, including Paramyxoviruses, Filoviruses, Pneumoviruses and Coronaviruses [16]. In vitro, Remdesivir inhibits many human and animal viruses tested, including SARS-CoV-2 [16, 17], and has shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS [18]. Remdesivir is also a potent inhibitor of SARS-CoV-2 proliferation in human nasal and bronchial airway epithelial cells [19]. It has been used in treatment of Covid-19 patients over the past two years in some countries [20], and recent studies have shown the benefits of this drug in treatment of

patients with Covid-19 [20-23]. Two clinical studies also report the use of Remdesivir in severe [23], or mild [24] respiratory infections caused by SARS-CoV-2. Different studies showed different result of remdesivir in treatment of Covid-19 patients; Recovery in 68% of patients made by Remdesivir [20], remdesivir reduced need for mechanical ventilation [25], risk of hospitalization and death [26], mortality, time of recovery, and increased clearance virus [27], shorter time of recovery [28], remdesivir didn't show any benefit in severe patients [29], and isn't associated with improving clinical sign of Covid-19 patients [27]. Performed studies on remdesivir summarized in **Table 1**.

Table 1: Characteristics of performed studies on Remdesivir in treatment of Covid-19 patients.

First Author	Year	Study Design	Sample Size	Place	Conclusion
Grein [20]	2020	Clinical report	53	Multi center	Recovery in 68% of patients made by Remdesivir.
Wang [27]	2020	RCT	237	Chine	Remdesivir reduced mortality, time of recovery, and increased clearance virus of Covid-19 patients.
Ali Karim [25]	2022	RCT	1282	Canada	Remdesivir had significant effect on outcomes and need for mechanical ventilation.
Florence Ader [30]	2022	RCT	857	Europe	There was no clinical benefit in use of remdesivir
Yeming Wang [27]	2020	RCT	237	Chine	Remdesivir wasn't associated with improving clinical sign of Covid-19 patients
Beigel [28]	2020	RCT	1062	USA	Remdesivir shortened time of recovery in Covid-19 patients
Jason D [29]	2020	RCT	397	USA	In severe Covid-19 patients remdesivir didn't show any benefit
R.L. Gottlieb [26]	2021	RCT	562	Finland	Remdesivir reduced risk of hospitalization and death.

Hydroxychloroquine (HCQ) & Chloroquine

Hydroxychloroquine is an analogue of Chloroquine with a lower risk of drug interactions, that both of them have a long history in treating malaria [31]. Their antiviral effects against the HIV are discussed, which is done by inhibiting the virus from entering the host cells. Another mechanism of antiviral effect of these drugs is related to post-translational modification of newly synthesized proteins by inhibition of glycosylation [32]. Short-term use of Chloroquine and HCQ as adjunctive therapy in Covid-19 infection, especially in the early stages to prevent virus replication, has performed in some countries; Chen et al. reported that HCQ improves patients' clinical symptoms despite low side effects [33], Huang et al. stated that Chloroquine is benefit in treatment of Covid-19 patient without any toxicities [34], Gao et al. stated that HCQ reduced the pneumonia due to Covid-19 virus (41). Another studies reported that HCQ isn't effective in patients with SARSCoV-2-positive hypoxic pneumonia

[35], HCQ reduce 30% mortality [36], HCQ did not show significant reduction in mortality or need for mechanical ventilation [37], HCQ don't reduce the Covid-19 mortality [38], HCQ doesn't reduce mortality or need for mechanical ventilation [39], doesn't improve clinical status at 15 days [40], and HCQ does not prevent severe outcomes or improve clinical scores [41]. Two other studies also reported no benefit in treatment of HCQ [42, 43]. Performed studies on HCQ & Chloroquine summarized in **Table 2**.

Table 2: Characteristics of performed studies on HCQ & Chloroquine in treatment of Covid-19 patients.

First Author	Year	Study	Sample	Place	Conclusion
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	Year	Design	Size	Place	Conclusion
Chen [33]	2020	RCT	62	Chine	HCQ improves patients' clinical

					symptoms despite low side effects
Huang [34]	2020	RCT	233	Chine	Chloroquine is benefit in treatment of Covid-19 patient without any toxicities
Gao [44]	2020	RCT	100	Chine	Chloroquine reduced the pneumonia due to Covid-19 virus
Matthieu Mahévas [35]	2020	RCT	181	France	HCQ isn't effective in patients with SARSCoV-2-positive hypoxic pneumonia
Castelnuovo[36]	2020	observation	3451	Italy	HCQ reduce 30% mortality
Magagnoli [37]	2020	observation	807	USA	HCQ did not show significant reduction in mortality or need for mechanical ventilation
Rosenberg [38]	2020	Cohort	1438	USA	HCQ don't reduce the Covid-19 mortality
Geleris [39]	2020	observation	1446	USA	HCQ doesn't reduce mortality or need for mechanical ventilation
Cavalcanti [40]	2020	RCT	667	Brazil	HCQ did not improve clinical status at 15 days
RCG¹ [45]	2020	RCT	1561	United kingdom	HCQ isn't associated with lower incidence of death at 28 days
Robert [41]	2020	RCT	128	USA	HCQ does not prevent severe outcomes or improve clinical scores
David [42]	2020	RCT	821	USA Canada	There is no benefit in treatment of HCQ in Covid-19 patients.
Mehra [43]	2020	RCT	96032	Multi center	HCQ has no benefit for Covid-19 patients

Favipiravir

Favipiravir (T-705) is a RNA-dependent RNA polymerase (RdRp) inhibitor that was used in patients infected by Ebola virus [46], and as a new antiviral compound is undergoing clinical trials for the treatment of human influenza [47]. It has a unique function among other anti-influenza drugs, in that it directly inhibits viral RNA polymerase [48], and in

vitro and some clinical trials studies has shown an inhibitory effect on pathogenic RNA viruses [49]. The use of this drug in treatment of Covid-19 patients has been studied in some studies; Cai et al. reported that Favipiravir has a positive effect on viral clearance and disease recovery [50], Chen et al. said Favipiravir has a slow recovery rate & few side effects [51], and improves clinical sign in mild-to-moderate COVID-19 patients [52]. Performed studies on Favipiravir summarized in **Table 3**.

Molnupiravir

Molnupiravir, the prodrug of the ribonucleoside analog β -D-N4-hydroxycytidine (NHC), is rapidly converted in plasma to NHC and then to the active 5'-triphosphate form by host kinases [53]. The active 5'-triphosphate serves as a competitive substrate for virally-encoded RNA-dependent RNA polymerase (RdRp), and once incorporated into nascent viral RNA, induces an antiviral effect via accumulation of mutations that increase with each viral replication cycle [53, 54]. Different studies have reported different results of Molnupiravir in the treatment of Covid-19 patients; Molnupiravir is effective at reducing nasopharyngeal SARS-CoV-2 infectious virus [55], didn't demonstrate clinical benefit [56], and reduce the risk of hospitalization or death [57].

Performed studies on Molnupiravir summarized in **table 3**.

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Table 3: Characteristics of performed studies on Favipiravir & Molnupiravir in treatment of Covid-19 patients.

First Author	Year	Study Design	Sample Size	Place	Conclusion
Cai [50]	2020	RCT	80	Chine	Favipiravir has a positive effect on viral clearance and disease recovery
Chen [51]	2020	RCT	240	Chine	Favipiravir has a slow recovery rate & few side effects in treatment of Covid-19 patients.
Fischer [55]	2021	RCT	202	USA	Molnupiravir is effective at reducing nasopharyngeal SARS-CoV-2 infectious virus.
Jose [56]	2022	RCT	304	Multi center	Molnupiravir didn't demonstrate clinical benefit
Udwadia [52]	2021	RCT	150	India	Favipiravir improves clinical sign in mild-to-moderate COVID-19 patients
Jayk Bernal [57]	2022	RCT	1433	USA	Early treatment with Molnupiravir reduced the risk of hospitalization or death

Kaletra (Lopinavir/Ritonavir)

Kaletra is a Lopinavir / Ritonavir combination product marketed under the Kaletra brand, and, as a protease inhibitor, prevents the detachment of Gag-Pol polyprotein precursors, resulting in the formation of immature and non-infectious viral particles. In fact, the main antiviral effect of Kaletra is due to the presence of Lopinavir in this compound, and the Ritonavir used in it inhibits Lopinavir by inhibiting the metabolized cytochrome P450 and increasing its serum concentration [58]. It has been used in combination with other antiviral drug to treat HIV infection [59]. Some reports indicate the positive effect of Kaletra in the treatment of patients with Covid-19 [60, 61]. While in some other studies, no signs of clinical improvement were found in these patients [59, 62]. Some studies also reported that Kaletra had no signs of clinical improvement [59], effective in Covid-19 treatment [63], and shorts the

clearance period of Covid-19 virus [64]. Performed studies on Kaletra were summarized in **Table 4**.

Arbidol

Arbidol, also known as Umifenovir, has been used in Russia and China to treat influenza virus infections. This drug has no significant side effects and also been used to treat SARS-CoV-1. The antiviral mechanism of Arbidol against influenza B and A is inhibiting viral mixing with the target cell membrane, which prevents the virus from entering it [65]. Result of performed studies on Arbidol showed that this drug has positive effect in less than 7 days treatment of Covid-19 patients [66], effective in delaying the onset of lung damage, reducing the possibility of transmitting the virus to the lower respiratory tract [67], and is capable of greatly reducing mortality in Covid-19 patients [62]. Performed studies on Arbidol were summarized in **Table 4**.

Table 4: Characteristics of performed studies on Arbidol & Kaletra in treatment of Covid-19 patients.

First Author	Year	Study Design	Sample Size	Place	Conclusion
Chen [66]	2020	RCT	240	Chine	Arbidol had positive effect in less than 7 days treatment of Covid-19
Deng [67]	2020	Cohort	33	Chine	Arbidol is effective in delaying the onset of lung damage, reducing the possibility of transmitting the virus to the lower respiratory tract.
Liu [62]	2020	observation	504	Chine	Arbidol is capable of greatly reducing mortality in Covid-19 patients.
Nojomi [68]	2020	RCT	100	Chine	Arbidol, compared to Kaletra more improves clinical sign.
Hung [64]	2020	RCT	127	Chine	Kaletra shorts the clearance period of Covid-19 virus.
Xu [63]	2020	observation	50	Chine	Kaletra effective in Covid-19 treatment.
Cao [59]	2020	RCT	199	Chine	No signs of clinical improvement found in treatment of Kaletra.

Oseltamivir

Oseltamivir is a viral neuraminidase inhibitors drug [69] that has been approved for treatment of patient infected by influenza A and B. This drug inhibits the spread of host cells viral particles and reduces the spread of the virus in the respiratory airway [70]. Use of this drug in Covid-19 epidemic has been reported with or without antibiotics and corticosteroids (51); Li et al reported that combined use of

Arbidol and Oseltamivir can be effective in reducing the mortality of Covid-19 patients [62]. QiTan et al. in their study in Vitro stated that Oseltamivir isn't suitable for the treatment of COVID-19 [71], and Chiba said that Oseltamivir can reduce the duration of clinical sign [72]. Performed studies on Oseltamivir summarized in **Table 5**.

Intravenous Immunoglobulin (IVIG)

IVIG is a blood product derived from the healthy donor plasma and is rich of bacterial antibodies and viral IgG. Its continuous injection can improve serum IgG levels and effectively neutralize pathogens in patients' airways, leading to improvement and shortening of diseases course. IVIG can also improve the body's defenses, block receptors associated with the target cell, and prevent further pathogen damage to the target cell [73]. Patients with a severe clinical course of SARS-CoV-2 infections have higher levels of anti-inflammatory cytokines [74]. On the other hand, it has been shown that IVIG is effective in treating inflammatory disorders due to its protective effects against pathogens entering the body [75]. So, IVIG is considered as a suitable treatment option in Covid-19 patients with severe inflammation [76]; Xie et al stated that IVIG can reduce need for mechanical ventilation, and time of recovery [77], Zhou et al said short time use of IVIG is effective in recovery of sever Covid-19 patients [78], and Tabarsi et al. demonstrated that IVIG doesn't have positive effect in treatment of severe COVID-19 patients [79]. Performed studies on IVIG summarized in **Table 5**.

Interferons (IFNs)

Interferons are proteins that bind to cell surface receptors and inhibit the proliferation of some viruses, such as hepatitis C and B viruses, by acting on JAK-STAT signaling cascades and regulating the transcription of interferon-controlled genes. Interferon beta has two classes, 1 and 2, which control a wide range of regulatory processes in immune cells. For example, the function of antigen-presenting cells, enhancing the capacity of B lymphocytes to deliver antigens, stimulating T lymphocytes, and the production of inflammatory cytokines are largely controlled by these interferon's [69]. The results show that interferon beta can improve pulmonary function [16]. It has also been reported to prevent the replication of SARS-CoV-2 and MERS-CoV with this group of proteins [80]. The results of studies on the effect of this drug in treatment of patients with Covid-19 showed that Interferon shorts the hospitalization period, and virus clearance period of mild to moderate Covid-19 patients [64], and early treatment with interferon can eliminate the virus from the upper respiratory tract [81]. Performed studies on IFNs summarized in **Table 5**.

Table 5: Characteristics of performed studies on Oseltamivir, IVIG & Interferon in treatment of Covid-19 patients

First Author	Year	Study Design	Sample Size	Place	Conclusion
Liu [62]	2020	Observation	504	Chine	Oseltamivir is effective in reducing mortality of Covid-19 patients.
QiTan [71]	2020	Observation	-	In Vitro	Oseltamivir isn't suitable for the treatment of COVID-19
Chiba [72]	2021	RCT	16	Japan	Oseltamivir can reduce the duration of clinical sign
Xie [77]	2020	Observation	58	Chine	IVIG can reduce need for mechanical ventilation, and time of recovery
Zhou [78]	2020	Clinical report	10	Chine	Short time use of IVIG is effective in recovery of sever Covid-19 patients
Tabarsi [79]	2021	RCT	84	Iran	IVIG doesn't have positive effect in treatment of severe COVID-19 patients
Mohtadi [82]	2020	Case series	5	Iran	Treatment with IVIG can improve the clinical condition of COVID-19 patients.
Hung [64]	2020	RCT	127	Chine	Interferon shorts the hospitalization period, and virus clearance period of mild to moderate Covid-19 patients.
Zhou Q [81]	2020	RCT	77	Chine	Early treatment with interferon can eliminate the virus from the upper respiratory tract..

CONCLUSION

In the final review of the studies, the results showed that Chloroquine and HCQ had little effect on the recovery of patients with Covid-19. The study of Kaletra had weak results that can be an important factor in changing the attitude of therapists in using these drugs alone or in combination with other drugs. Remdesivir has been implicated in the treatment and improvement of symptoms in patients with Covid-19, but definitive results require more comprehensive studies. The effective therapeutic role of

Arbidol has been confirmed in all reviewed studies. Favipiravir and Molnupiravir are the drugs that have effective therapeutic effects and fewer side effects, but their therapeutic effects are less than other drugs. Oseltamivir and Interferon can be used as part of the treatment of patients with Covid-19 if used in combination with another antiviral drug. The results of using IVIG as a therapeutic factor in patients with Covid-19 showed that although these drugs may be effective in improving the condition of patients in the inflammatory phase, but confirmation of their use requires more extensive clinical research.

CONFLICTS OF INTEREST

The author declare no conflict of interest.

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