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COULD FAVIPIRAVIR BE AN EFFECTIVE AND SAFE OPTION FOR THE MANAGEMENT OF COVID-19?

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ABSTRACT
Through the ongoing world war against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) plague, a definite rational anti-viral treatment for corona virus disease 2019 (COVID-19) is still absent. Favipiravir (FPV), as an antiviral agent, demonstrates effectiveness towards Oseltamivir (OTV)-resistant influenza, and numerous RNA viruses. The aim of this work was to review both the FPV safety and effectiveness in managing SARS-CoV-2. A thorough search for relevant articles in the databases on the Egyptian Knowledge Bank limited to the period 12/4/2015 - 12/7/2020 was performed. Preference was given to articles concerning the therapeutic options for treating COVID-19 including FPV principally. Twenty six articles were selected. Six cited articles have reported FPV effectiveness towards several RNA viruses, while, 5 articles reported FPV potential activity towards SARS-CoV-2. Sixty-five% of the articles stated current investigations testing the effectiveness of FPV with other combinations in treating SARS-CoV-2. Only 1 article studied the adverse reaction of FPV. Although it is too early to give a final recommendation of using any medication for the exponentially spreading COVID-19, 20 of the articles revealed FPV activity against various RNA viruses particularly, resistant types. Japan has approved FPV for the treatment of pandemic influenza and China encouraged the use of it for SARS-CoV-2 treatment. Therefore, FPV could be a promising antiviral treatment as it is relatively safe in comparison to other treatment options for COVID-19.

KEYWORDS: COVID-19, coronavirus, SARS-CoV-2, pandemic, favipiravir, coronavirus treatment.

KEYPOINTS
FPV has been utilized in the treatment of coronaviruses infections so it is regarded as a promising antiviral agent against SARS-CoV-2. FPV has anti-viral activities towards different RNA viruses like bunyaviruses, filoviruses, and arenaviruses, all of which are identified to develop fatal hemorrhagic fever.

Some clinical trials (CTs) showed the superiority of FPV efficacy and/or safety over different treatment options for COVID-19.

Evidence from CTs to date demonstrated that FPV has been well tolerated in phases I, II and III. More than two thousand individuals without diseases were recruited in phase I trials. Phase II or III trials included patients suffering from influenza.

1 INTRODUCTION
At present, unpredicted outbreaks of infections due to evolving and/or re-evolving viral agents become very prevalent. Changes in the environment may play a role in the development of these plaques. For instance, the coronavirus that is called severe acute respiratory syndrome coronavirus (SARS-CoV) was blowout through 2002 then 2003. Several cases suffered sudden progressive respiratory symptoms allover Guangdong, China.[1-3] SARS-CoV disseminated quickly in about more than 27 nations. It infected more than 8000 subjects and led to death in approximately 800 cases. Also in 2012, additional coronavirus, called Middle East respiratory syndrome coronavirus (MERS-CoV),[1-3] disseminated similarly through many countries, leading to about 35% case fatality rate. In addition to that the recent (2014 - 2016) Ebola virus disease (EVD), West Africa plaque, infected about 28 646 individuals with fatality rate of almost 50%. Moreover, through 2015, Zika virus (ZIKV) has led to a pandemic in Brazil that distributed rapidly through tens of nations all over the world. ZIKV has the ability to affect the reproductive system of males as well as humanoid nervous system. It could develop microcephaly in fetuses of ZIKV-infected pregnant women.[1,4]

Lately, 2019 novel coronavirus (2019-nCoV, called SARS-CoV-2) has emerged and caused a new global epidemic. In Chinese researches, this new viral agent was strictly linked to corona viruses found in bats. Additionally, ninety percent of the SARS-CoV-2 genetic material was detected in Malayan pangolins.[5,6] SARS-CoV-2 relates to the RNA Coronaviridae family which has an obvious genetic variability and high recombination rate that make them simply disseminated among people all over the world.[6-8] The new pandemic viral disease was given its name by The World Health Organization (WHO) as COVID-19.[9] Tens of countries outside China had several definite confirmed cases,[3-7,9-26] the source of this outbreak.[3-6,9-11,14-27] On 31 December 2019, several case-patients of pneumonia of unspecified reason recognized in a Chinese city called Wuhan. Consequently, the WHO Chinese Country Office was informed.[28] This unknown illness has been initiated from the Seafood Market in this Chinese city that got closed on the first day of January 2020.[5] By January 2020, a total of 44 cases were reported to WHO by China. As of 20 January 2020, four nations from Southeast Asia have detected 282 confirmed case-patients.[28] Then, COVID-19 was confirmed authoritatively by WHO, on 30 January 2020, as a global public health crisis.[3] On 12 February 2020, the total number of patients have been exponentially increased to 45,171 confirmed case-patients in 25 countries including China (44,730 cases and 1,114 deaths) while outside of China it was only 441 cases and 1 death).[29] As of 12 April 2020, the total numbers have been continued rising to 1,696,588 confirmed case-patients and 105,952 deaths have been reported all over the world with approximately a mortality rate of 6.2 %.[30] Regarding COVID-19, vital organs are highly affected like human lung, kidney and heart because the viral agent targets angiotensin converting enzyme 2 receptor found in abundance in these organs additionally, result in multi organ damage.[15]

Coronaviruses can be considered of the frequent viral agents that have the ability to develop upper as well as lower respiratory disorders.[2] A previous overview from China involved 72,314 confirmed, suspected, and asymptomatic cases has demonstrated numerous significant epidemiological characteristics as well as symptoms of this pandemic disease.

Usually, most of the diagnosed patients with COVID-19 have the age that ranges between thirty to seventy nine years-old (86.6%).[7] The average incubation period of this viral infection is 5.2 days.[17] Hyperthermia (83–98%), cough (59–82%), dyspnea (19–55%), and muscle pain (11–44%) are the most frequent symptoms associated with the infection.[5, 7,17] Some cases could suffer from headache, turbulence, sore throat and runny nose, several hours before the onset of hyperthermia. Accordingly, fever could be a cardinal complain, but was not the only initial one in case of COVID-19. Few cases had hemoptysis, and some patients were found relatively without symptoms[7,17] by 1.2%.[5] 204 confirmed COVID-19 cases were enrolled in a study that reported gastrointestinal (GI) symptoms in 48.5% of the cases. These GI complains involved anorexia (83.8%), abdominal pain (0.4%), diarrhea (29.3%) and vomiting (0.8%). Only GI symptoms with neither upper nor lower respiratory symptoms were found in 7 cases from the total 204. 17 to 29% of patients may progress acute respiratory distress syndrome (ARDS). Other complications of COVID-19 consist of septic shock, ventilator-associated pneumonia, and acute kidney injury and/or cardiac injury.[17] Regarding arrhythmias, it was reported that nearly 7% of patients suffered from nonspecific palpitations and 16% of the hospitalized patients suffered from arrhythmias. Whether these arrhythmias are a direct manifestation of COVID 19 on heart or are happening because of hypoxic injuries, metabolic disturbances or neurohormonal imbalance is still indistinct. Furthermore, patients may be at raised risk of venous thromboembolism.[18] High levels of C-reactive protein with normal or decreased white blood cell counts, lymphopenia, or thrombocytopenia were detected in confirmed cases.[7] Virus particles induce cytokine storm which is related to disease severity.[5] Clinical diagnosis of COVID-19 is mainly based on epidemiological history, clinical manifestations and some auxiliary examinations.[6,17]

The symptoms of COVID-19 are more severe in geriatric population with comorbidities, while allergic illnesses, asthma, and chronic obstructive pulmonary disease are also considered as risk factors.[2,17,18,31] It was found that cardiac, diabetic patients and patients suffer from cerebrovascular disease are at high risk for infection. For example hypertensive patients represent 17% while other cardiovascular diseases represent 16.5% who are in need of ICU.[18] Pediatrics,[2] particularly newborn infants, are at high risk.[17] It is essential to notice that cases fatality rate (CFR) is reliant on the age of patient and related comorbidities. CFR is <1% for those < 50 years of age, 1.3% for age 50-59 years, 3.6% for patients 60-69 years, 8% for those between 70-79 years and > 14% for those > 80 years.[7,18] The mortality rate was high and extended to 49% among cases that were categorized as critical case-patients.[7]

Disposition depends on symptoms of patients, hemodynamic status, and patient capability to self-quarantine. Patients with mild symptoms and no substantial comorbidities without concern for worsening of clinical condition may be suitable for discharge, self-quarantine for 2 weeks, and home monitoring. Social distancing is an essential component for decreasing the spread of the virus. It consists of limiting events, mass gatherings, and even small group meeting. Individuals should remain two meters aside from other individuals.[17]

At this time, there is no definite safe and effective anti-viral therapy for COVID-19. Although most of the

COVID-19 case-patients have mild or moderate illness, up to 5-10% can suffer severe; potentially life-threatening manifestations that necessitate a crucial requirement for effective treatment options. Rational supportive treatment is regarded as the backbone of SARS-CoV-2 therapy.[7,32] In spite of the critical requirement to get an effective and safe antiviral treatment for COVID-19 through randomized controlled trials (RCTs), some treatment options are being used all over the world based on either *in vitro* or inferred evidence or observational studies. The most commonly used treatment options all over the world include FPV, chloroquine (CQ), hydroxychloroquine (HCQ), lopinavir/ritonavir (LPV/RTV), and Remdesivir (RDV).[32]

FPV (T-705) is a 6-fluoro-3-hydroxy-2-pyrazinecarboxamide as shown in Figure 1. It was developed by Fujifilm Toyama Chemical Co. Ltd, (division of Fujifilm, Japan) as an inhibitor of RNA-dependent RNA polymerase. Through competitive inhibition, the efficacy of viral replication can be greatly decreased.[7,10-12,23,32,33]

CTs from healthy Japanese volunteers revealed that the highest serum concentration of FPV (C_{max}) occurred after 2 h of oral administration, and declined rapidly with a short half-life of 2-5.5 h. The plasma protein binding of FPV was 54% in human. The FPV human serum albumin and α1-acid glycoprotein were 65.0% and 6.5%, respectively. FPV undergoes liver metabolism mainly by aldehyde oxidase, and partially by xanthine oxidase, producing an inactive oxidative metabolite T-705M1 which is excreted by the kidney. After multiple dosing of intravenous (i.v.) FPV in cynomolgus macaques indicates obvious nonlinear pharmacokinetics over time and over a range of doses. While after a continuous administration in the non-human primates a continuous decline in plasma concentration, after 7 days, was also revealed.[10]

In March 2020, FPV was approved by the National Medical Products Administration of China as the first antiviral for managing COVID-19 in China, as the clinical studies had revealed efficacy with marginal side effects.[7] In an open-label, CT of 80 cases with COVID-19, 35 cases were given oral FPV plus interferon (IFN)-α (by aerosol inhalation) were compared to 45 cases were given LPV/RTV plus IFN- α. A less viral clearance time with obvious improvement in chest imaging was demonstrated in case of the FPV arm versus the control arm.[10,11,32] Evidence from CTs to date demonstrated that FPV has been well tolerated in > 2000 healthy individuals in phase I trials or patients with influenza virus infections in phase II or III trials.[34] In spite of the overall good tolerance revealed by CTs, FPV has been associated with teratogenic risks. In embryo-fetal developmental studies, FPV teratogenicity was detected in all the animal species investigated (mice, rats, rabbits, and monkeys). The FPV exposure leading to teratogenicity in animals was comparable to that in humans treated with FPV. FPV treatment in females who are pregnant or may probably be pregnant should consequently be contraindicated as a rule. In case of women of childbearing potential, the proper contraception period following the end of the treatment is considered to be one week in which the serum FPV level will decline to less than the limit of detection, even when individual difference in the pharmacokinetics is considered.[33, 34]

It was demonstrated that FPV has anti-viral activities towards different RNA viruses like bunyaviruses, filoviruses, and arenaviruses, all of which are identified to develop fatal hemorrhagic fever. So that FPV could be a promising medication for definitely incurable RNA viral pandemic diseases.[33] Consequently, the aim of this article was to review the efficacy and safety of FPV as a promising antiviral treatment option for managing COVID-19.

2 METHODS

2.1 Study Eligibility

The articles included in this study are reviews, opinions and recommendations, RCTs, prospective or retrospective observational studies that showed FPV well-known efficacy against various RNA viruses, its role in managing COVID-19, and its safety profile.

2.2 Search strategy

An electronic search of Elsevier, Sage, Springer/Nature, Thomson Reuters and Wiley databases as part of the great digital library, Egyptian Knowledge Bank (EKB), was restricted to the period from 12/4/2015 to 12/7/2020. The search was performed using the subsequent search string: COVID-19 OR Coronavirus OR Corona Virus OR SARS-CoV-2 OR Corona Virus disease OR disease 2019 OR Disease OR infection OR pandemic OR virus OR acute OR challenges OR critical OR respiratory OR influenza respiratory syndrome OR severe OR severe acute OR spread OR syndrome OR syndrome coronavirus OR viral OR viral infection disease AND (favipiravir OR treatment OR drug OR review). All search terms were limited to peer reviewed, full text, English journals and the specified dates.

Exclusion criteria include books, non-English language, or being irreverent to the objectives. Preference was given particularly to clinical/non clinical articles of FPV that were concerned with the treatment of COVID-19, activity against RNA viruses, or safety of this drug as demonstrated in Figure 2.

2.3 Data extraction

Data extraction was conducted by 3 researchers (MGM, MSM and ZA) who separately evaluated all selected articles to extract the ones relevance to this review. Discrepancy was resolved through compromise. The inclusion process was performed by only one researcher (MGM), but when there was any uncertainty about any

article to be involved or not, a second researcher, MAR, was referred to.

3 RESULTS

3.1 Search Results

Thirty articles was selected according to the inclusion and exclusion method of relevant articles. After reviewing the abstracts of these articles for relevance, 26 articles were included as shown in Figure 2. Table 1 is a summary of the selected articles with their authors, COVID-19 treatment options, type of each study, objectives, recommendation, and outcomes. The twenty-six articles illustrated FPV activity against numerous RNA viruses, its promising activity against SARS-CoV-2, ongoing studies testing the efficacy of FPV and its combinations in treating COVID-19 like Baloxavir marboxil (BXM), CQ, HCQ, interferon-α, ribavirin (RBV), tocilizumab (TCZ), traditional Chinese medicines and Umifenovir (UMV). In addition, these articles investigated drug related problems associated with FPV treatment in comparison to other available treatment options for COVID-19 like convalescent plasma COVID-19 (CCP), corticosteroids (CS), CQ, emetine (EMT), FPV, HCQ, LPV/RTV, RDV, RBV and TCZ.

3.2 FPV probable antiviral activity against various RNA viruses

Table 1 also shows that 12 cited articles of the 26 discussed FPV activities against numerous RNA viruses that suggests a potential ability of it as a promising antiviral agent to inhibit Coronaviruses particularly, SARS-CoV-2 (keeping in mind that any article can refer to more than one activity). FPV approval for treatment of severe influenza in Japan reported in 4 articles.

FPV *in vitro* activity towards OTV-resistant influenza A, B, and C viruses reported in 9 articles. FPV approval for treatment of novel influenza in China reported in 7.7% of the articles. The utilization of FPV in the treatment of SARS and MERS cases reported only in one article. FPV inhibits the replication of Ebola virus in Vero E6 cells and guards type I interferon receptor-deficient mice from Ebola virus infection reported in 3 articles. FPV blocking of the reproduction of alpha-, flavi-, bunya-, noro-, filo-, arena-, Lassa fever and rabies RNA viruses discussed in 4 articles. Only one article studied FPV indication for severe fever with thrombocytopenia syndrome (SFTS) according to CTs.

Figure 3 demonstrates the percentages of cited articles that reported FPV activities towards various RNA viruses suggesting a probable ability of it as a hopeful antiviral agent to inhibit coronaviruses principally, SARS-CoV-2.

3.3 FPV probable antiviral property against SARS-CoV-2 infection

Figure 4 shows the percentages of cited articles that demonstrating FPV activity against SARS-CoV-2. Nine cited articles from the twenty-six demonstrated FPV hopeful activity against COVID-19. This activity was reported as a Chinese clinical open-label study with other showing FPV superiority as an antiviral agent over LPV/RTV), while seven articles, as well as an RCT (ChiCTR200030254) demonstrated the superiority of FPV over UMV. In addition, a Japanese case report showed the 1st case of meningitis related to SARS-CoV-2 in a 24-year-old man whose viral infection was managed by FPV. The official permit as a COVID-19 treatment in China is reported in one article.

3.4 Ongoing CTs evaluating the efficacy of FPV

Figure 5 represents the percentages of cited articles of *ongoing CT* testing the efficacy of FPV as a monotherapy or in combinations in treating COVID-19. Eight of the undergoing CTs were conducted in China, and 2 CTs in Japan (reported in 3 articles), as well as a current RCT in Thailand on a combination of FPV with CQ (reported in 9 articles). Traditional Chinese medicines and inhaled interferons are being investigated in combinations reported in two articles. A study published by the University of Hong Kong was reported by 3 articles. In addition to, the CTs, NCT04336904, NCT04346628 and NCT04349241 were conducted in Italy, USA and Egypt, respectively, were mentioned in 2 articles. A current Iranian 2 CTs, NCT04359615 and NCT04376814, examine the efficacy of FPV and HCQ combination, mentioned in 2 articles.

3.5 FPV safety profile

Table 2 shows the different COVID-19 treatment options with their reported adverse drug reactions (ADRs) while Table 3 demonstrates the cited article(s) that reported each ADR linked to each SARS-Cov-2 treatment option. Regarding FPV safety, an article is reporting FPV ADRs like diarrhea, liver injury and poor diet. While ADR as teratogenicity is noticed in either FPV or RBV treatment of COVID-19. Treatment with CCP is associated with various ADRs like secondary infections. The same ADR was observed in either CS or TCZ (which was its only ADR). In the other hand, using CS for COVID-19 management is also associated with increased mortality, bone marrow problems and joint pain, diabetes, avascular necrosis, psychosis; delayed viral clearance, and prevention of immune response. While patients treated with CQ or HCQ were suffered from QTc. Prolongation. Although treatment with HCQ is also associated with retinopathy and G6PD deficiency (contraindication), CQ is associated with kidney injury, liver injury, seizures, and psoriasis. Treatment of COVID-19 with EMT resulted in hazardous ADR, cardiotoxicity, listed in one article. LPV/RTV treatment combination is associated with numerous ARs like diarrhea, nausea, vomiting, rash, liver injury, chest tightness and palpitations, asthenia. RDV treatment was linked to obvious ARs effects like nausea, vomiting, rectal hemorrhage, and hepatic toxicity, transaminitis, and remedesivir resistance was mentioned for this drug. RBV also showed hematological AR.

In the same context, different COVID-19 treatment options were reported to be associated with drug-drug interactions (DDI) as listed in Table 4. CQ or HCQ DDI with anti-depressants, anti-psychotics, moxifloxacin, ondansetron, LPV/RTV and remdisivir is leading to exaggerated QTc prolongation. Also their interaction with LPV/RTV trigger hypoglycemia. CQ interaction with either azithromycin or OTV with high doses of any the combinations could lead to high mortality rates and cardiac ADRs. LPV/RTV interactions with statins could lead to myopathy because of the increased levels of statins. It should be mentioned that there was no reporting DDI for CCP, CS, EMT, FPV, RDV, RBV or TCZ with other used drugs in COVID-19 patients or others.

4 DISCUSSION

4.1 FPV activity against numerous RNA viruses

FPV has been approved in 2014 for treating severe pandemic influenza infection in Japan.[2,26,27,35] It is well-known by its *in vitro* activity towards OTV-resistant influenza A, B, and C viruses after its conversion to an active phosphoribosylated derivative (FPV-RTP) in cells. China has approved FPV for treatment of novel influenza on 15/2/2020.[11,36] FPV has been utilized in treating SARS and MERS cases.[24] The progresses in research and development of small viral inhibitors molecule against re-emerging and emerging viruses were reviewed. It illustrated that FPV as a broad-spectrum inhibitor of RNA polymerase, inhibits the reproduction of Ebola virus in Vero E6 cells and guards' type I interferon receptor-deficient mice from Ebola virus infection. In addition to FPV activity as anti-influenza virus, it is able to block the reproduction of alpha-, flavi-, bunya-, noro-, filo-, arena-, Lassa fever, rabies and other RNA viruses.[2,11,36,37] FPV has been launched for further indications for severe fever with thrombocytopenia syndrome (SFTS) depending on CTs.[37] Also it is being investigated for more RNA viruses.[35] This suggests a possible promising ability of FPV as an antiviral agent to inhibit Coronaviruses as well.[2]

4.2 FPV activity towards COVID-19

LPV/RTV combination has been utilized in SARS or MERS cases.[3,11,16,21,24] They lessened the titers of coronavirus with no or little coronavirus titers were detected in the additional study but the investigation involved only a 54-year old male who is the third case suffered SARS-CoV-2 in Korea.[3,36] Another group has reported that 10 SARS-CoV-2 cases have showed good clinical consequences after receiving sustained LPV/RTV. In a different study of 17 cases given oral LPV/RTV alone, 52.9% of the cases demonstrated clearance of viraemia on day fourteen. Unfortunately, an open labeled CT of one hundred and ninety nine SARS-CoV-2 cases did not reveal any significant reduction in time to clinical improvement, death or viral load after adding LPV/RTV.[27] Therefore, for investigating FPV efficacy in the treatment of COVID-19 in comparison to LPV/RTV, the Third People's Hospital of Shenzhen and the Clinical Medical Research Center of the National Infectious Diseases has conducted a clinical open-label study that involved a total of 80 patients. FPV efficacy was tested in 35 cases and compared to LPV/RTV efficacy in 45 cases after treatment with interferon-α in Chinese cases with mild COVID-19. These patients were not suffering hypoxemia or respiratory distress and finally clearance of the virus was early shown in the cases who were on FPV. Moreover, chest radiology illustrated more improvement in FPV group than LPV/RTV group at day 14. So that initial outcomes showed that FPV had more powerful antiviral activity than that of LPV/RTV.[11,20,22,24,25,27,38] LPV/RTV was evaluated in an open-label, RCT, where cases with SARS-CoV-2 were given either LPV/RTV two times every day plus standard of care, or standard of care only. No advantage was detected with LPV/RTV over standard care.[19,22,36] It was stated that LPV/RTV combination has not influenced patient survival.[17] The routine usage of LPV/RTV in critically ill patients is possibly not necessary. The outcomes of current trials will help rise the accuracy of assessments and the certainty in the current guidelines.[21] A RCT (ChiCTR200030254) has revealed the efficacy of FPV in comparison to UMV (Arbidol).[27, 36]

UMV is developed in Russia in 1988 and has since been officially approved in China and Russia for the prophylaxis and treatment linked to influenza A and B and other arbovirus. UMV exhibited *in vitro* antiviral efficiency against broadly spreading virus strains such as hepatitis C virus (HCV), the Ebola virus, human herpes virus 8 (HHV-8), and Tacaribe arenavirus. *In vitro* efficacy of UMV towards SARS-CoV-1 and SARS - CoV -2 was reported. In comparison to treatment with only LPV/RTV, the blend of LPV/RTV and UMV has revealed enhanced negative conversion rate of COVID-19 and improved chest CT scans.[36] The RCT (ChiCTR200030254) demonstrated that SARS-CoV-2 cases managed by FPV have higher recovery rate (71.43%) than that managed by UMV alone (55.86%), and the time of relief from cough and fever are obviously less in FPV arm than in UMV arm.[27,36]

In late February 2020, a case report from Japan illustrated the first case of meningitis associated with SARS-CoV-2 in a twenty four-year-old man treated with FPV. The case has reported in depth that on day one, the patient felt fever, generalized lassitude and headache. On day two, he visited the clinic; the doctor prescribed antipyretic agents and Laninamivir according to his symptoms. On day 9 his family found him lying on the floor in his vomit and unconscious. He was rushed to the hospital but during transportation, he had temporary generalized seizures that continued approximately a minute. He had apparent stiffness in his neck. The specific SARS-CoV-2 RNA wasn't identified in the nasopharyngeal swab but was identified in his cerebrospinal fluid. Varicella-zoster and anti- HSV 1 IgM antibodies weren't identified in serum samples. A

brain magnetic resonance imaging exhibited hyperintensity beside the wall of right lateral ventricle and hyperintense signal changes in the hippocampus and right mesial temporal lobe, suggesting the probability of SARS-CoV-2 meningitis. In the emergency room, mechanical ventilation after the endotracheal intubation was essential due to recurrent seizures. The patient was diagnosed with meningitis and viral pneumonia therefore, was admitted to the ICU. Intravenous acyclovir, vancomycin, ceftriaxone, levetiracetam and CS were initiated. FPV was recommended to be received by nasogastric tube for 10 days since day two. This treatment option against SARS-CoV-2 managed the viral infection. On day 15, the patient was still in the ICU due to the affected consciousness as a result of encephalitis, only the therapy for impaired consciousness in addition to bacterial pneumonia was continued.[14] Consequently, FPV deemed to have promising potency in treating COV-19 outbreak particularly, after its positive results on the Chinese patients. FPV has gained official permit as a COVID-19 treatment in China by March, 2020.[22] Since then, CTs investigating FPV towards SARS-CoV-2 have been conducted robustly in many nations including China and Japan. Till mid-April 2020, there were 8 undergoing CTs in China and 2 in Japan investigating the antiCOVID-19 efficacy of FPV. These studies include non-R and RCT investigating the safety and efficacy of FPV alone ChiCTR2000030113, JPRN-jRCTs031190226, JPRNjRCTs041190120) or in conjunction with interferon-α (ChiCTR2000029600), BXM (ChiCTR2000029544, ChiCTR2000029548), TCZ (ChiCTR2000030894, NCT04310228), or CQ phosphate (ChiCTR2000030987, NCT04319900).[22,25,36]

In Thailand an ongoing RCT on a combination of FPV and CQ for managing COVID-19 has been initiated on 21st of March 2020. Researches have showed that CQ is an established anti-malarial medication and has the ability to inhibit the reproduction of numerous intracellular micro-organisms containing coronaviruses *in vitro.* CQ could have a diverse mechanism of action that could vary according to the pathogen studied. The anti-viral and anti-inflammatory properties of CQ could provide benefits in managing SARS-CoV-2.[3,11,15,16,21,23,25,27,36] A single study of over one hundred patients of COVID-19 found CQ was superior to control pneumonia exacerbation, enhancing imaging findings and virus-negative transformation, and decreasing the progression of the disease.[17]

An article observed the decreased load of SARS-CoV-2 in the nasopharynx of patients of COVID-19, particularly when HCQ combined with azithromycin; and reported the superior efficacy of HCQ over CQ in preventing SARS-CoV-2 *in vitro.*[38] CQ and HCQ didn't display any anti SARS-COV-2 effect during *in vivo* investigations. As the pathogenesis of COVID-19 is still unknown, therefore, the immune effect motivated by CQ or HCQ administration in COVID-19 patients is unpredicted.[23] Regarding surviving sepsis campaign that depended on the opinion of a board of 36 professionals from 12 countries, it was reported that there is inadequate evidence to issue a recommendation on the usage of CQ or HCQ in critically ill COVID-19 adults.[21] In 15th of June 2020, the U.S. Food and Drug Administration (FDA) found that CQ and HCQ were doubtful to be effective in managing SARS-CoV-2 infections consequently, their emergency use authorization was revoked.[36,39]

4.3 CTs testing the efficacy of FPV

FPV clinical investigations have been used alone as a monotherapy but still under CTs.[3,5,6,15,17,18,20,21,35] FPV as well as UMV, RBV, traditional Chinese drugs and inhaled interferons are being investigated alone or in combinations in different countries.[18,21] Most of the medications against SARS-CoV-2 undergoing CTs rely on their capability of impeding main constituents of the coronavirus infection lifecycle involving block the entry of the virus into the cell of the host by CQ, UMV or interferon, inhibit the replication of virus by ASC09, LPV/RTV or /cobicistat/darunavir, which impede the 3C-like protease and inhibit the synthesis of RNA virus by FPV, RDV, or RBV).[8] According to the University of Hong Kong research team, FPV has failed to inhibit viral replication at concentrations below 100 μM in Vero E6 cells (*in vitro*) but was active at concentrations exceeding 100 μM. The nucleoside analogues require cellular activation before being able to function. This happens as a result of host cellular nucleoside kinases action which may be different between cell types, and this may play a role in the needed doses to inhibit viral replication.[4,19,36] The initial findings of this promising antiviral agent FPV are predicted to be obtainable soon like: NCT04336904, NCT04346628 and NCT04349241 conducted in Italy, USA and Egypt, respectively, as well as the two studies, NCT04359615 and NCT04376814 conducted in Iran to investigate the efficacy of the combination FPV and HCQ.[15, 25]

4.4 Safety of FPV in comparison to SARS-CoV-2 treatment options

4.4.1 FPV vs CCP

Previous clinical practices from Ebola virus, MERS-CoV, SARS-CoV-1, H5N1 avian influenza, and H1N1 influenza infections have shown that passive immunotherapy might be a possible treatment option for these cases. Consequently, passive immunotherapy might be helpful in SARSCoV-2.[5,15,21-23,25,36,38] It is thought that CCP injection might develop antibody-mediated cellular cytotoxicity and phagocytosis.[25,36] According to the pandemic SARS and influenza (H1N1) virus, the treatment of severe infection with CCP was related to reduction of respiratory viral load, serum cytokine.[23, 36] A study depended on both meta-analysis of twenty seven studies of treatment of SARS-CoV patients and uncontrolled case series of 5 SARS-CoV-2 patients reported that immunotherapy might decrease death in severe acute respiratory infections because of influenza and SARS-CoV; related to lessening in the load of the

virus and enhancement in fever, oxygenation, and chest imaging in a case series. This outcome was restricted by the small sample size, multiple potential confounders, and lack of controls.[21,38] Limited findings on SARS-CoV-2 cases from China showed clinical advantages. Pilot study revealed clinical improvement in the form of dyspnea, cough, chest pain and fever while no severe adverse reactions were listed.[36]

Regarding surviving sepsis campaign, a panel of 36 experts from 12 countries voted against the routine usage of CCP in critically sick COVID-19 adults.[21] CCP increases the risk of other viral infections due to the phenomenon of neutralizing antibodies-dependent enhancement (ADE) of virus infection. A major drawback of using CCP option is the lack of donor. Fortunately, by increasing the total of recovered people, this drawback would be resolved.[25] FPV is not linked to this CCP drawback.[1-6,8,11,14-27,35-38]

4.4.2 FPV vs. CS

It is believed by researchers in Medical field that CS, methylprednisolone (MPS) in particular, may enhance dysregulated immunity responses flaring up as a consequent to sepsis and improve reduced blood pressure.

By examining a cohort study which was established retrospectively, 201 from the confirmed patients as a COVID-19 case and developed ARDS showed improvement using MPS (1-2 mg/kg/day i.v. for 5-7 days) putting a prospect that MPS may be favorable for patients who develop ARDS in reducing the risk of death. In another study, 46 severe COVID-19 patients suffered from acute respiratory failure, utilize MPS. They found enhancement in clinical symptoms such as fever, hypoxia. The course of infection also, if compared to patients who did not receive the medicament, appeared to be alleviated. The maximum dose of MPS that can be used was applied clinically in China and is typically 40-80 mg i.v. daily for 3-6 successive days. Dexamethasone (DMS) has established efficacy on ARDS as it showed capability to reduce ventilator days and mortality in COVID-19 patients.[36]

The usage of CS for treating the modified-SARS pandemic is divisive because of their consequent implications on anti-viral responses that our immunity carries on. CS could increase the mortality in severe COVID-19 patients with systemic hyperinflammation. The significant factors such as patient selection, half-life, formulation, and dosage of the CS define the clinical outcome. In this regard, a preprinted study showed that early, short-term and little dose of corticosteroid (MPS) enhanced clinical manifestation in severe ill patients of COVID-19 who suffer from ARDS.[25]

A board of 36 professionals from 12 countries recommended the usage of systemic CS in mechanically ventilated COVID-19 adults suffering from ARDS but recommended against their usage in similar critically ill patients but not suffer from ARDS.[21,36]

CS, the most commonly used anti-inflammatory medicament, is still frequently ordered in treating COVID-19 patients (72.2% in the ICU setting).[15,38] Chinese guidelines of COVID-19, indicate the caution of using steroid because of its unclear ramifications in the setting of viral respiratory attack. Numerous studies came out to the find that CS usage to treat SARS has low clinical outcomes. Another concern of CS is their adverse effects that are either occurring shortly after use or are delayed. Roughly, most of SARS patients treated with CS suffered from bone marrow problems and joint pain.[15] A retrospectively conducted study with 84 patients having ARDS as a resultant of COVID-19 found minor mortality in those treated with MPS, but the results are limited by the study observational design, limited size of the sample, and possible confounders. Because the modified-SARS pandemic might be associated with a cytokine storm similar to that seen with other viral infections, compromising immunity has been proposed as a beneficial approach for patients with signs of hyperinflammation, such as hyperferritinemia. Though immunity-compromisers' benefits are still unverified and the role of CS in the modified-SARS pandemic remains imprecise, a systematic review of observational studies of CS for SARS found no influence on mortality but possible problems, diabetes, avascular necrosis, psychosis, and delayed viral clearance. Likewise, an observational study found that CS for MERS didn't affect mortality, nevertheless did delay clearance of the virus. The outcome suggested that CS might raise mortality and secondary infections in influenza. The suitable dose (low dose versus high dose), priority in treatment (early versus late), and role for CS (cytokine storm or comorbidity management) require extra transparency and more researches. There is some concern that the usage of CS may produce harmful sequels (i.e., prevention of immunity responds and pathogen clearance) in COVID-19 patients. Also, the Infectious Diseases Society of American recommends, CS not to be routinely used in COVID-19, but with ARDS in the setting of a CT. Eventually, the clinical use of CS still necessitate more study to be established and better be considered on a case by case basis.[36] FPV is not associated with the preceding ADRs linked to CS.[1-6, 8,11,14-27,35-38]

4.4.3 FPV vs. CQ and HCQ

Although, CQ and HCQ emergency use authorization was revoked,[36,39] CQ is used for treating patients suffering from SARS-CoV-2 infection.[16] A study conducted in vitro found that CQ impedes viral infection. Besides, results from the above single study of 100 patients with COVID-19 found that CQ showed superior controlling capability in pneumonia exacerbation, normalizing imaging findings and virus-negative conversion, and lessening disease course.[6,17] Initial findings from clinical investigations of CQ are predicted to be obtainable soon.[15] CQ and its derivative, HCQ are used now in the treatment of COVID-19 patients.[16]

HCQ did not provide upper negative conversion rates, but had decreased symptoms through the anti-inflammatory effect and lymphopenia recovery.[36] HCQ use could decrease the time to clinical recovery in COVID-19 patients due to the significant viral load reduction/disappearance.[25] CQ is regarded as a safe treatment option in pregnancy,[4] but CQ and its derivative, HCQ must be used cautiously because they have the probability of QTc interval prolongation. Therefore, electrocardiography is important before starting these medications. These drugs should not be used in patients receiving drugs that cause the QTc. interval prolongation such as anti-depressants, anti-arrhythmic, antihistaminic, anti-psychotics, teneligliptin, moxifloxacin and ondansetron.[16]

It was found that elevated doses of CQ (0.6 g two times daily over 10 days or cumulative dose of 12 g) could be linked with obvious cardiac ADRs and should not be used for SARS-Cov-2 treatment.[36] An elevated doses of CQ diphosphate and azithromycin led to great mortality rates and cardiac ADRs.[25] Administering CQ or HCQ with LPV/RTV and RDV increases the risk of QTc prolongation.[16] Increasing the doses of OTV and CQ diphosphate combination led to great mortality rates and cardiac ADRs.[25] Consequently, CQ and HCQ are not suitable for some cardiac patients due to their significant ADRs of QT interval prolongation.[36,38] FDA has reported that regarding current cardiac ADRs and other severe ADRs, the known and probable benefits of CQ and HCQ no longer compensate the known and possible risks for the authorized use.[39]

Fortunately, the probability of FPV to prolong QT interval was not reported.[1-6,8,11,14-27,35-38]

CQ administration is prohibited in case of known hypersensitivity, severe kidney or liver diseases, a history of epilepsy, and psoriasis.[4] All these precautions were not reported about FPV.[1-6,8,11,14-27,35-38]

Lately, HCQ has substituted CQ due to its superior potency and lower DDI probability.[22] Also HCQ, in India, has gained approval as a 3rd or 4th line drug in the treatment of type 2 diabetes since 2014, so it would be meaningful to detect its impact in patients with diabetes, infected with COVID-19.[16] Hypoglycemia as an adverse event due to the DDI between CQ or HCQ and LPV/RTV was observed in diabetic patients.[16] Side effects still limiting the use of HCQ which is contraindicated in case of retinopathy, G6PD. deficiency, QTc interval prolongation or history of allergy to HCQ.[22] All these ADRs were not linked to FPV.[1-6,8,11,14-27,35-38]

4.4.4 FPV vs. EMT

EMT was tested as a treatment option against SARS-CoV-2 infection. It inhibits protein synthesis, used as anti-protozoan and approved for treatment of amebiasis. EMT is effective against malaria by targeting the ribosomal E site of Plasmodium Falciparum. *In vitro* studies showed that EMT is effective in inhibiting SARS-CoV-2., however, its cardio-toxic effect is limiting its use,[19] which is not associated with FPV.[1-6,8,11,14-27,35-38]

4.4.5 FPV vs. LPV/RTV

The early findings of the Chinese CT in 80 COVID-19 cases indicated that FPV is more potent antiviral than LPV/RTV, demonstrated that no significant ADRs were noted in the FPV treatment group. It was found that LPV/RTV use was associated with some GIT manifestations including diarrhea, nausea, and vomiting.[22,38] The whole number of side effects in the FPV arm of the study was 4, which was significantly <25 ADRs (55.56%) in the other arm. Diarrhea appeared in 2 patients, 1 suffered a liver injury and 1 had a poor diet in the FPV arm. Meanwhile, diarrhea affected 5 patients, vomiting appeared in 5, 6 suffered nausea, 4 were affected by rash, 3 by liver injury, and 2 with chest tightness and palpitations in the LPV/RTV arm.[24] In the same context, it was reported that LPV/RTV was associated with asthenia and GIT symptoms like diarrhea and nausea in an open-label RCT, where cases with SARS-CoV-2 were given either LPV/RTV two times daily plus standard of care, or standard of care only.[36] Besides, hypercholesterolemic patients who receive statins therapy, have the probability to interact with the combination of LPV/RTV and these DDI can lead to defects in muscles because of increased level of statin when administered together.[18]

Similar DDIs between FPV and statins were not reported.[1-6,8,11,14-27,35-38]

4.4.6 FPV vs. RDV

The anti-Ebola virus RDV, targets, inhibits the RdRp and block viral RNA synthesis.[5,6,18,23,26,27,36] RDV, a nucleoside analog, has wide showed capability against RNA viruses.[3,5,11,23,25,27] RDV has prevented virus from infecting a human liver cancer Huh-7 cells, sensitive to COVID-19.[23] It was effective in vitro and in vivo models, and lately it was tested as i.v. doses in human volunteers by Washington health department. They declared that it could be effective against SARS-CoV-2.[3,6,21,23,25,36,38] RDV exerted therapeutic efficacy in the first COVID-19 case in USA, and 2 phase III trials have been started to assess RDV in COVID-19.[3,5,20] Also it is reported that RDV has an established activity against animal and *in vitro* forms of SARS-CoV and MERS-CoV.[11,17,21,25,36,38] Initial findings from clinical investigations of RDV [NCT04252664, NCT04257656] are predicted to be obtainable soon.[15,21] Considering its clinical use, good improvement among severe COVID-19 patients was reported (68%, n= 53). Moreover, promising findings were shown in the treatment of SARS-CoV-2 in the USA.[11,25-27] Although RDV has showed noticeable potency against COVID-19, it has an ADRs profile that include nausea, vomiting, rectal hemorrhage, and hepatic toxicity.[22] The most relevant

side effects associated with RDV usage are transient GI tract symptoms and transaminitis.[27] Furthermore, remedesivir resistance was reported by 2 mutations F476L and V553L in the RdRP nsp12 of a murine-CoV. These 2 residues were detected in case of SARS-CoV-2 virus at F480 and V557.[19] Neither the previous ADRs profile nor the resistance was reported with FPV.[1-6,8,11,14-27,35-38] Moreover, the paramount property of FPV as an antiviral medication is the evident lack of generation of FPV-resistant viruses. This great character of FPV among antiviral agents is anticipated to play a crucial role in the management of serious RNA viral infectious diseases for which typical safe and effective treatment options are unattainable.[37]

4.4.7 FPV vs. RBV

RBV is a guanosine analogue antiviral agent which displayed an obvious efficacy in managing various viral infectious diseases,[1,2,5,6,11,18,19,22,35,37] such as respiratory syncytial virus (RSV), some viral hemorrhagic fevers, and hepatitis C virus. According to previous *in vitro* studies, RBV is an effective treatment for SARS-CoV.[2,5,6,19,22,35] A research group has observed that some of the compounds now undergoing CT including RBV as well as OTV and baloxavir exhibit no obvious antiviral effect against the *in vitro* form of SARS-CoV-2 virus when their concentration fails below 100 μM[19]. Another group has reported that RBV has been utilized in SARS or MERS patients.[22,24] However, RBV implications on hemoglobin level that may harm a patient with respiratory distress syndrome, makes it unfavorable choice.[2,22] During the past outbreak of SARS, however, RBV was widely used, but consequently found to be useless and sometimes was unsafe.[38] Another article reported that the *in vivo* studies in SARSCoV-1 and *in vitro* studies in SARS-CoV-2 have showed no promising results. Moreover, common clinical dosing is linked to hematological ADRs.[27] An additional investigation has declared that the main problem with RBV was the occurrence of hemolysis.[23] In addition, to the anemia ADR, RBV clinical use in RSV infection treatment is associated with the risk of teratogenicity.[2] Anemia was not connected to FPV as an ADR.[1-6,8,11,14-27,35-38]

4.4.8 FPV vs. TCZ

TCZ, a specific monoclonal antibody that antagonize interleukin-6 receptor (IL-6R), has displayed initial positive effects in reducing cytokine release syndrome.[5,15,16,18,22,25,38] It is developed by Roche and Chugai Pharmaceutical for controlling rheumatoid arthritis and systemic juvenile idiopathic arthritis cases. A study surfaced in April 2020 showed that 21 case with severe or critical COVID-19 in China were treated with TCZ, at time of publication, 20 of them recovered and 1 was on the way to be recovered (but still in ICU). Consequently, a great multicenter clinical study was initiated (ChiCTR2000029765) and had about 500 cases managed by TCZ already enrolled[25,36] after its approval in China for this indication[20,21] Regarding surviving sepsis campaign, a panel of 36 experts from 12 countries reported that there is inadequate proof to issue a recommendation on the usage of TCZ in critically sick COVID-19 adults.[21]

Secondary infection is considered a common side effect in case of using immunomodulation agents such as TCZ.

Critically ill COVID-19 patients are vulnerable to secondary infection and may have a raised tendency to acquire comorbid chronic infections, such as tuberculosis and hepatitis B. It is uncertain to what degree TCZ may cause secondary infection. Hence, the goal of the treatment should be to inhibit or reduce inflammatory responses that threaten people's lives while reducing the potential of secondary infection. For this cause, prophylactic antibiotics may be used. Therefore, TCZ should be used with cautious.[15]

The previous ADR associated with TCZ was not reported to FPV.[1-6,8,11,14-27,35-38]

4.5 Current status of FPV

In the 26th of May 2020, the Japanese government has decided to prolong the timeline for the official approval of FPV as a treatment for SARS-CoV-2 till June or far along.[40] In 7th of June 2020, it was reported that FPV manufacturing company will continue CTs of FPV, as a treatment option for COVID-19, different from the primarily planned end in June because of the the reduction in the numbers of confirmed COVID-19 cases that led to difficulty in reaching the enrolling target of 96 COVID-19 cases.[41]

Initial CTs of FPV in Russia have provided encouraging finding in the treatment of COVID-19 cases, so in 14th of May 2020, Russia began to tout FPV as a helpful treatment option for SARS-CoV-2 infections.[42] FPV based medication was officially approved in Russia and it was registered in Russia as Avifavir, for managing COVID-19 cases. It was reported that this promising medication would be available for clinics beginning from the 11th of June 2020.[43]

4.6 Strengths and Limitations

Regarding the data collections for this review, the Egyptian Knowledge Bank (EKB), the world's leading digital library providing indefinite resources absolutely for Egyptians, was relied upon. This work has limited to the published CTs and ongoing researches in different countries all over the world but the significant limitation of this article is the lack of multicentered radamised CTs with suitable patients sample size.

4.7 Future research

Depending on our review, further investigations particularly, multicentered RCTs are needed in order to prove that FPV could be regarded as a safe and effective treatment option for COVID-19. Besides, these prospective RCTs could provide the rational treatment guidelines for SARS-CoV-2 infections.

Figure 1: The chemical structure of favipiravir (FPV).

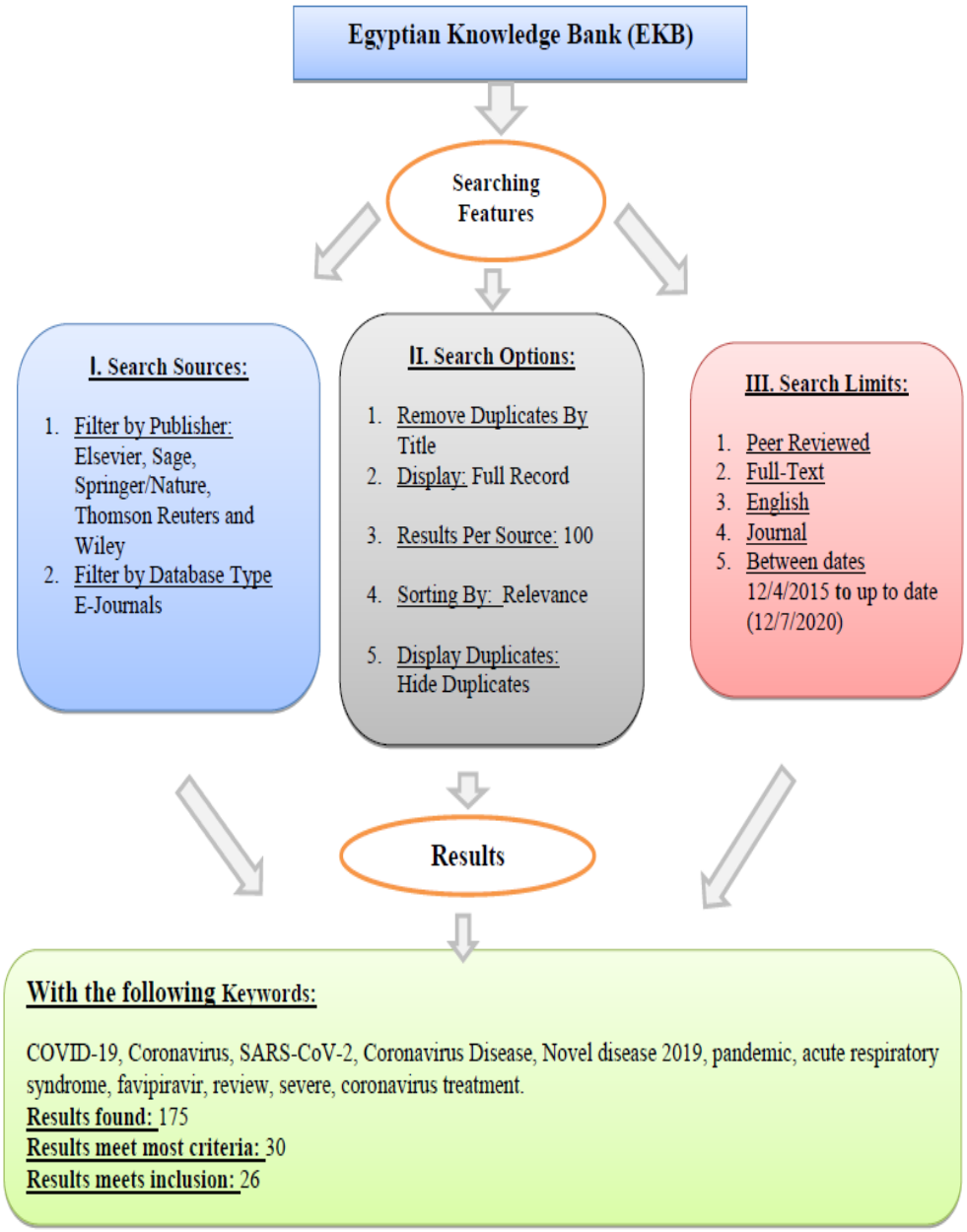


Figure 2: Diagram of the included and excluded articles.

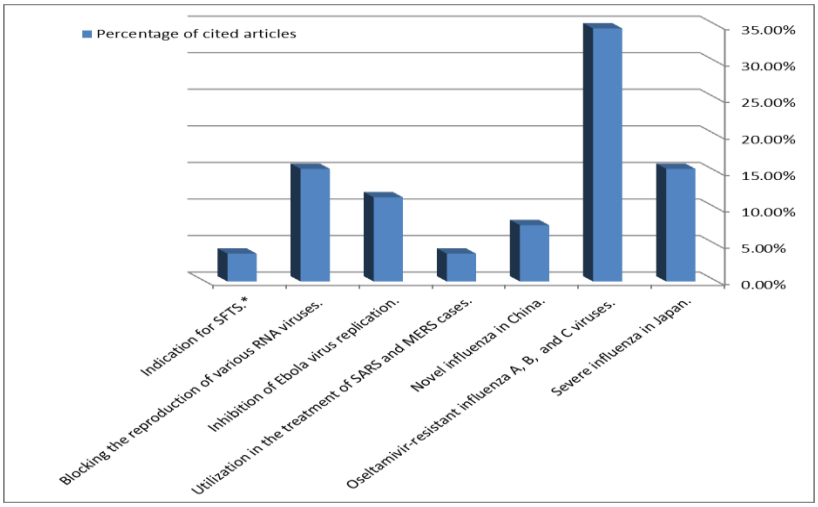


Figure 3: The percentages of cited articles that illustrated FPV activity against numerous RNA viruses suggesting a possible ability of it as a promising antiviral agent to inhibit coronaviruses particularly, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).
(SFTS): Severe fever with thrombocytopenia syndrome.

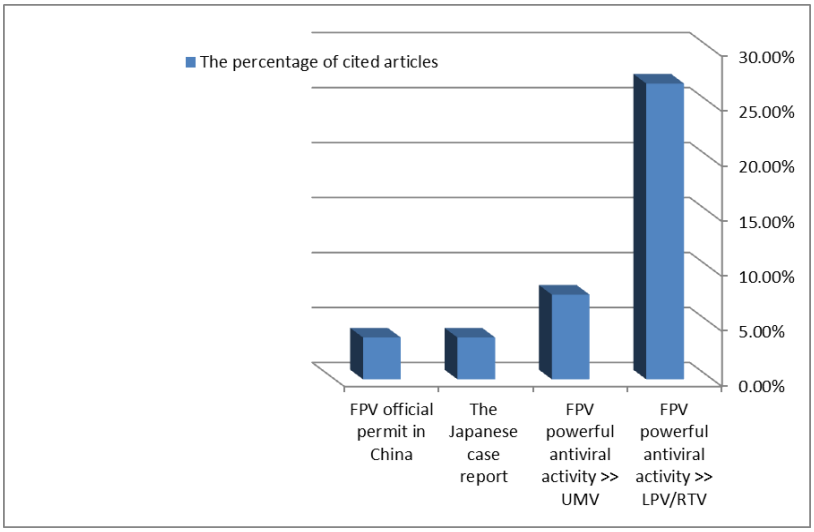


Figure 4: The percentages of cited articles that demonstrate favipiravir activity against SARS-CoV-2.
(FPV): Favipiravir, (LPV/RTV): Lopinavir/ritonavir, (UMV): Umifenovir.

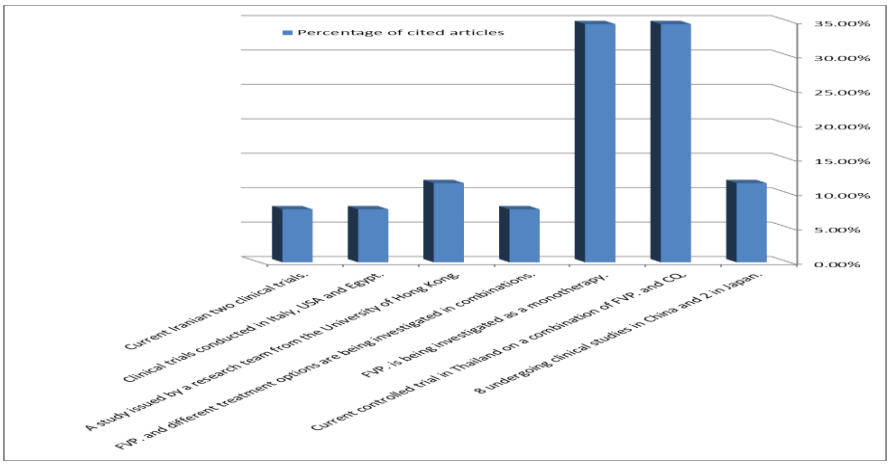


Figure 5: The percentages of cited articles that illustrate ongoing studies testing the efficacy of FPV and its mentioned combinations in treating COVID-19.
(CQ): Chloroquine, (FPV): Favipiravir.

Table 1: A summary of the selected 26 references with their objectives, outcomes, study type and the mentioned SARS-CoV-2 treatment option(s):

S	Author(s)	Mentioned COVID-19 Treatment Option(s)	Type of Study	Objective(s)	Comment(s)/Recommendation(s) Outcome(s)
1.	Alhazzani, W., et al., 2020.[21]	FPV LPV/RTV Remdesivir Ribavirin CLQ HCQ Convalescent plasma Umifenovir Tocilizumab	Editorial	To illustrate how the physicians could manage critically ill patients with COVID-19 in the intensive care unit.	• Aerosol generating procedures, be done in a negative pressure room while the healthcare workers are wearing fitted respirator masks. • Endotracheal intubation, be performed by the most experienced member. • In acute resuscitation, avoid using hydroxyethyl starch. • If norepinephrine is not available, dopamine is not to be used. • Oxygen supply is to be used if SpO2 is < 90% and the target, be no more than 96%. • Patients are to use invasive oxygen supplying method with low tidal volume if non-invasive procedures associated with worsening. • In ARDS patients on mechanical ventilator, plateau pressure of < 30 cm H_2O is to be targeted and use higher PEEP strategy.
2.	Cai, Q., et al., 2020.[24]	FPV LPV/RTV Ribavirin IFN-α	An open-label control study	To demonstrate the safety and efficacy of FPV against LPV/RTV	• FPV is more powerful than Lopinavir/Ritonanir with less side effects. ($P<0.05$)
3.	Chavez, S., et al., 2020.[17]	FPV LPV/RTV Remdesivir CQ Tocilizumab	Review article	To offer` an emergency doctors with an outline of the most current understanding of COVID-19 and recommendations on the assessment and management of patients with supposed COVID-19.	• Emergency-care providers should obtain a full travel history from all patients • Consider every patient with acute respiratory symptoms a COVID-19 patient. • Early detection and isolation of a patient with COVID-19 in the ED may help curb the rapid spread of the disease. • Research should focus on developing evident knowledge of the disease and the best treatment
4.	Choy, K.-T., et al., 2020.[19]	FPV LPV/RTV Remdesivir Ribavirin Emetine Oseltamivir Baloxavir marboxil Tocilizumab IFN-α	Review article	To illustrates the efficiency of antiviral agents that may be effective in the treatment of SARS-COV-2.	• Antiviral effect of remdesivir, lopinavir, homorringtonine, and emetine were effective *in vitro* against SARS-CoV-2 at concentrations <100 µM. • FPV and ribavirin were effective at concentrations > 100 µM. • Some combinations showed synergistic efficacy (as remdesivir and emetine) and this suggest possible increase in the above drugs' efficacy when placed in suitable combination.
5.	Das, U.N., 2020.[8]	FPV LPV/RTV Remdesivir Ribavirin CLQ Umifenovir	Editorial	To show that lipids (arachidonic acid) may be useful in treating coronavirus.	• Unsaturated fatty acids such as (AA, EPA and DHA) and their metabolites could, with the appropriate use, deactivate enveloped viruses and reduce the inflammatory response consequent to an infection.

		Oseltamivir Baloxavir marboxil IFN			
6.	Dong, L., et al., 2020.[11]	FPV LPV/RTV Remdesivir Ribavirin CQ IFN-α	Review article	To describe the mode of action of FPV as an antiviral that can be used for COVID-19 treatment.	• There are about 30 agents that thought to have potential efficacy against COVID-19 pandemic. • Remdesivir and FPV preliminary studies results showed promising results. • A further research to approve their efficacy and safety is needed.
7.	Guo, D., 2020.[4]	FPV CLQ	Review article	To show the potential efficacy of antiviral drugs against COVID-19.	• Only two compounds, CLQ and RDV were detected to potently block COVID-19 *in vitro* at low-micromolar concentration and showed high selectivity index. • Both drugs need more studies to approve their clinical efficacy.
8.	Guo, Y.-R., et al., 2020.[3]	FPV LPV/RTV Remdesivir Ribavirin CLQ Convalescent plasma Oseltamivir	Review article	To review the mechanism of action of FPV that may be a promising treatment for COVID-19.	• COVID-19 induced pneumonia is of higher infectivity but lower virulence when compared to SARS and MERS. • Elderly and people with certain underlying medical conditions require special care using supporting measures, combined with potent antiviral drugs, such as remdesivir, CLQ, or FPV • These drugs require more studying to be approved for COVID-19.
9.	Gupta, M.D., et al., 2020.[18]	FPV LPV/RTV Remdesivir Ribavirin CLQ HCQ Tocilizumab	Editorial	To Show the link between SAR-2 infection and cardiac manifestations To demonstrate the proper treatment options in case of cardiac patients. To recommend precautionary measurement in cardiac patients.	• Cardiac patients should follow physical distancing measures and the general protection guideline's recommendation for cardiac patients. • Cardiac care professionals should follow the protective guidelines to decrease the risk of acquiring COVID-19. • All guidelines and interventions need to be assessed periodically for validity.
10.	Hamed, M.A., 2020.[23]	FPV LPV/IRT Remdesivir Ribavirin CQ HCQ Convalescent plasma Interferon I	Review article	To Show the potential treatments for COVID-19.	• With non-approved drug or vaccine till now against COVID-19 therefore, each country should • Apply the precautionary measures according to WHO's. • Approve national medical care programs to decrease the risk of exposure to any future viral outbreaks specifically to patients which have other medical conditions
11.	Hossein-khannazer, N., et al., 2020.[25]	FPV LPV/RTV CLQ HCQ Emetine Ribavirin Remdesivir, Convalescent Plasma IFN—α Tocilizumab	Review article	To Review some available treatment options that are used to manage SARS-CoV-2 infectious disease.	• Though antiviral medications look effective in managing COVID-19 and its clinical complications, till now, specific pharmacotherapy for this new viral infection is absent. • Managing both the immune response and inflammation are vital steps. • New treatments involving mesenchymal stromal cell therapy and immune cell therapy have hopeful outcomes. • More researches on immunopathogenesis

		Umifenovir Oseltamivir			and immune response during the COVID-19 are required.
12.	Shio-Shin J., et al., 2020.[22]	FPV LPV/RTV Remdesivir Ribavirin CLQ HCQ Convalescent plasma Baloxavir marboxil Tocilizumab Oseltamivir IFN-α	Review article	To demonstrate the roles of some medications like antiviral drugs, antibiotics and anti-inflammatory treatment options in managing COVID-19.	• Regarding the treatment options of COVID-19: • Remdesivir is the most promising option. • FPV and HCQ combined with azithromycin appear to be acceptable alternatives. • ACE inhibitors and ARBs need to be prescribed with caution. • Acetaminophen is safer than NSAIDs for treating fever. • In case of refractory shock, low-dose steroid might be considered.
13.	Jordan, P.C., et al., 2018[2]	FPV Ribavirin Oseltamivir	Review article	To prove that FPV as nucleoside analogs is a broad spectrum antivirus against various RNA viruses.	• Nucleoside analogs to face respiratory viruses remains relatively new and needs further exploration to understand. • Successful future development of nucleoside analogs should include developing lung-targeting formulations.
14.	Kumar, R. et al., 2020[27]	FPV LPV/RTV, CLQ HCQ, ribavirin remdesivir Interferon Tocilizumab Umifenovir	Review article	To review the in vivo and in vitro effectiveness of some suggested treatments on COVID-19 as well as their well-known efficacy on SARS-CoV-1 and MERS. To assess the probability for re-purposing them in managing SARS-CoV-2 infectious disease.	• SARS-CoV-2 treatment options are growing continuously. • Until now, the available data on such medications come from clinical studies so; well-informed and rational use is the necessity at this time.
15.	Li, X., et al., 2020.[6]	FPV Remdesivir Ribavirin CLQ	Review article	To describe the diagnosis and the potential treatment of COVID-19.	• The nature of the virus and the individual's immune system defines the interaction between them and the incidence and development of the virus. • Possibility of getting infection, the duration and severity of the disease, and the reinfection depend on the nature of the virus and the human immune system. • Developing accurate diagnostic procedures is imperative in order to face this pandemic and confine its spread.
16.	Liu, B., et al., 2020[15].	FPV Remdesivir CLQ HCQ Convalescent plasma Tocilizumab	Review article	To investigate the pathogenesis of COVID-19, especially cytokine release syndrome (CRS) and to demonstrate the probability of interleukin-6 (IL-6) receptor blocking in managing CRS.	• Using biologicals like tocilizumab to manage COVID-19 induced CRS is a novel area.
17.	Misra, D.P., et al.,	FPV LPV/RTV	Review article	To elucidate the rheumatic	• Rheumatologists, during the current pandemic, should fulfill their role by

	2020.[20]	Remdesivir CLQ HCQ Tocilizumab		manifestations related to COVID-19, and the particular concerns for these patients' population. To discusses the probable therapeutic targets for managing COVID-19, some of which are frequently recommended in rheumatology practice settings.	giving great attention to details, raising people's awareness and seek possible strategies to minimize the number of severe cases. • In case of injury induced by immune hyperactivity, rheumatologists shall be called to decide a suitable immunomodulator according to each case until developing a permanent strategy to control COVID-19 induced hyper-immune activity.
18.	Moriguchi, T., et al., 2020.[14]	FPV	Case report	To demonstrate the ability of COVID-19 to develop CNS symptoms.	• Though the SARSCoV-2 RNA was not identified in the nasopharyngeal swab, it was observed in the cerebrospinal fluid (CSF). • FPV had been recommended to be received via nasogastric tube for ten days from day two. • FPV deemed to have a hopeful effectiveness in treating COVID-19.
19.	Phua, J., et al., 2020.[39]	FPV Remdesivir Ribavirin CLQ LPV/RTV HCQ Convalescent plasma Tocilizumab Oseltamivir	Review article	To compare the safety of FPV with other drugs used to treat COVID-19.	• Decision makers must work with ICU specialists to prepare for a substantial increase in critical care bed capacity. • They should protect them against physical, psychological and nosocomial diseases that increased with the long work schedules and ethical decisions. • Researchers also, have a long road of dedicated work to assure the efficacy and safety of the preliminary used drugs as Remdesivir and FPV
20.	Shiraki, K. and T. Daikoku, 2020.[38]	FPV Ribavirin Oseltamivir Baloxavir marboxil	Review article	To describe the mode of action of FPV as an antiviral and its contraindications.	• FPV has gained approval to use as anti-influenza virus in case of lethal infections and has showed efficacy against wide range of RNA viruses in animal models. • Its use has not been linked to the emergence of resistant strains. • The only problem is the negative implications it produces against embryos. • Thus, FPV as a prophylaxis and treatment can be considered in the future strategies against influenza outbreaks and other RNA virus-induced pandemics.
21.	Singh, A.K., et al., 2020.[16]	FPV CLQ HCQ Umifenovir Tocilizumab Oseltamivir Ribavirin LPV/r Baloxivir marboxil	Review article	To demonstrate the uses of CLQ in the treatment of SARS-COV-2, side effects and interactions with other drugs.	• CLQ and HCQ are considered acceptable options in the absence of other options. • Their low cost makes them suitable for all countries. • The currently conducted studies regarding their safety and efficacy, in presence and absence of diabetes, are essential and should await their preliminary results.
22.	Tan, K.S., et al., 2017.[36]	FPV Ribavirin Oseltamivir	Review article	To show the probability of using current antiviral	• Viruses were found to be the main cause of Rhinosinusitis (RS) and its exacerbation. • More detailed study could improve our

				agents against respiratory viruses to prevent acute (ARS) and chronic (CRS) rhinosinusitis exacerbation.	knowledge of RS virology, enhance our treatment methodology and reduce the misuse of antibiotics.
23.	Wang, X., et al., 2017.[1]	FPV CLQ Ribavirin	Review article	To demonstrates the newest progress in the improvement of small-molecule viral inhibitors against re-emerging and emerging viruses.	• Small molecule viral inhibitors although pose lower potency and shorter half-life when compared to antibodies, their development is relatively inexpensive and they are convenient for oral administration. • The possible strategy to overcome future emergence and re-emergence of viral diseases is to develop wide-spread antivirals.
24.	Watanabe, M., 2020.[26]	FPV LPV/RTV Remdesivir	Review article	To report the detected surgical and clinical outcomes of SARS-CoV-2 To highlighting the infection status in the Japanese islands and other nations.	• It reports that abundant of the pathology of SARS-CoV-2 infection is still mysterious. • Novel epidemiological information and clinical results are evolving continuously every day, so health care practitioners should refer to the up-to-date findings.
25.	Wu, R., et al., 2020.[37]	FPV LPV/RTV Remdesivir Ribavirin CLQ HCQ Convalescent plasma Tocilizumab Oseltamivir IFN-α Umifenovir	Review article	To illustrates hopeful and utmost updated treatment options for the prophylaxis and cure of SARS-CoV-2 cases till the official approval of definite medications and vaccines for COVID-19	• The article reports that the SARS-CoV-2 outbreak is the utmost worldwide public health disaster in the previous one hundred years.
26.	Zhou, G., et al., 2020.[5]	FPV LPV/r Remdesivir Ribavirin CLQ Convalescent plasma Oseltamivir Tocilizumab	Editorial	To investigate the symptoms and the potential treatment of COVID-19.	• Scientists from all over the world should collaborate to combat the novel pandemic. • People have to adhere to restricted public health measures and new drugs (such as FPV) should undergo further investigations under the supervision of suitable committees to reach the most suitable treatment.

(BXM): Baloxavir marboxil, (CCP): Convalescent plasma COVID-19, (CQ): Chloroquine, (EMT): Emetine, (FPV): Favipiravir, (HCQ): Hydroxychloroquine, (IFN-α): Interferon-alpha, (LPV/RTV): Lopinavir/ritonavir, (OTV): Oseltamivir, (RDV): Remdesivir, (RBV): Ribavirin, (TCZ): Tocilizumab, (UMV): Umifenovir

Table 2: Illustrates the various mentioned SARS-Cov-2 treatment options with their reported adverse drug reactions.

ADR / Treatment Option	Avascular necrosis	Anaemia	Asthenia	Bone marrow problems	Cardiotoxicity	Chest tightness	Delayed viral clearance	Diabetes	Diarrhea	G6PD. Deficiency	Immune response inhibition	Joint pain	Kidney injury	Liver injury	Mortality	Nausea	Palpitations	Poor diet	Psoriasis	Psychosis	QTc. prolongation	Rash	Rectal hemorrhage	Resistance	Retinopathy	Secondary infection	Seizures	Teratogenicity	Transaminitis	Vomiting
CCP																										■				
CS	■			■			■	■			■	■			■					■						■				
CQ													■	■					■		■						■			
EMT					■																									
FPV									■					■				■										■		
HCQ										■											■				■					
LPV/RTV			■			■			■					■		■	■					■								■
RDV														■		■							■	■					■	■
RBV		■																										■		
TCZ																										■				

(ADR.)*: Adverse Drug Reaction, (CCP): Convalescent plasma COVID-19, (CS): Corticosteroids, (CQ): Chloroquine, (EMT): Emetine, (FPV): Favipiravir, (HCQ): Hydroxychloroquine, (LPV/RTV): Lopinavir/ritonavir, (RDV): Remdesivir, (RBV): Ribavirin, (TCZ): Tocilizumab

■ : Associated with, □ : Not Associated with

Table 3: Shows the cited article(s) that reported each adverse reaction(s) linked to each COVID-19 treatment option.

Treatment Option	Adverse Drug Reaction(s)	Reported by:	Percentages of cited articles
CCP	Secondary Infection	Hossein-khannazer, N., et al., 2020.[25]	Only one article (3.8%)
CS	Increased mortality	Hossein-khannazer, N., et al., 2020,[25] Phua, J., et al., 2020.[39]	Two articles (7.7%)
	Bone marrow problems and joint pain	Liu, B., et al., 2020.[15]	Only one article (3.8%)
	Diabetes, avascular necrosis, psychosis, and secondary infections	Phua, J., et al., 2020.[39]	Only one article (3.8%)

	Delayed viral clearance	Phua, J., et al., 2020,[39] Wu, R., et al., 2020.[37]	Two articles (7.7%)
	Prevention of immune response	Hossein-khannazer, N., et al., 2020.[25] Wu, R., et al., 2020.[37]	Two articles (7.7%)
CQ	QTc. prolongation	Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
	Kidney injury, liver injury, seizures and psoriasis	Guo, D., 2020.[4]	Only one article (3.8%)
EMT	Cardiotoxicity	Choy, K.-T., et al., 2020. [19]	Only one article (3.8%)
FPV	Diarrhea, liver injury and poor diet	Cai, Q., et al., 2020.[24]	Only one article (3.8%)
	Teratogenicity	Shiraki, K. and T. Daikoku, 2020.[38]	Only one article (3.8%)
HCQ	Retinopathy, G6PD. deficiency(contraindication)	Jean, S.-S., P.-I. Lee, and P.-R. Hsueh, 2020.[22]	Only one article (3.8%)
	QTc. prolongation	Jean, S.-S., P.-I. Lee, and P.-R. Hsueh, 2020.[22] Singh, A.K., et al., 2020.[16]	Two articles (7.7%)
LPV/RTV	Diarrhea, nausea	Cai, Q., et al., 2020.[24] Jean, S.-S., P.-I. Lee, and P.-R. Hsueh, 2020.[22] Phua, J., et al., 2020.,[39] Wu, R., et al., 2020.[37]	Four articles (15.4%)
	Vomiting	Cai, Q., et al., 2020.[24] Jean, S.-S., P.-I. Lee, and P.-R. Hsueh, 2020.[22], Phua, J., et al., 2020.[39]	Three articles (11.5%)
	Rash, with liver injury, chest tightness and palpitations	Cai, Q., et al., 2020.[24]	Only one article (3.8%)
	Asthenia	Wu, R., et al., 2020.[37]	Only one article (3.8%)
RDV	Nausea, vomiting, rectal hemorrhage, and hepatic toxicity	Jean, S.-S., P.-I. Lee, and P.-R. Hsueh, 2020.[22]	Only one article (3.8%)
	Transaminitis	Kumar, R., et al., 2020.[27]	Only one article (3.8%)
	Remedesivir resistance	Choy, K.-T., et al., 2020.[19]	Only one article (3.8%)
RBV	Haematological adverse reactions	Jean, S.-S., P.-I. Lee, and P.-R. Hsueh, 2020.[22] Jordan, P.C., S.K. Stevens, and J. Deval, 2018.[2] Kumar, R., et al., 2020.[27]	Three articles (11.5%)
	Teratogenicity	Jordan, P.C., S.K. Stevens, and J. Deval, 2018.[2]	Only one article (3.8%)
TCZ	Secondary Infection	Liu, B., et al., 2020.[15]	Only one article (3.8%)

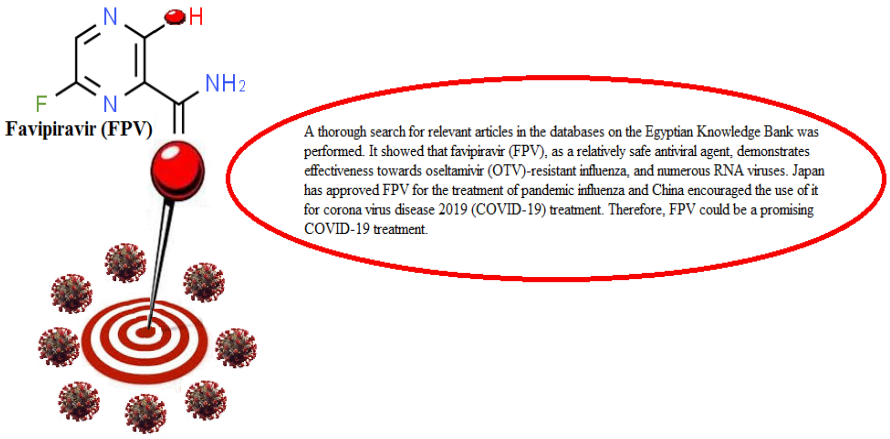
(CCP): Convalescent plasma COVID-19, (CS): Corticosteroids, (CQ): Chloroquine, (EMT): Emetine, (FPV): Favipiravir, (HCQ): Hydroxychloroquine, (LPV/RTV): Lopinavir/ritonavir, (RDV): Remdesivir, (RBV): Ribavirin, (TCZ): Tocilizumab

Table 4: shows the cited article(s) that reported each drug interaction(s) of the mentioned COVID-19 treatment options.

Treatment Option	Interacting Drug(s)	Consequences	Comments	Reported by:	Percentages of cited articles
CCP	————	————	————	————	————
CS	————	————	————	————	————
CQ	QTc. interval prolonging medications	Exaggerated QTc. prolongation	————	Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
	LPV/RTV and RDV	QTc. prolongation	————	Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
	LPV/RTV	Hypoglycemia	————	Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
	Azithromycin	High mortality rates	elevated doses of	Hossein-	Only one article (3.8%)

		and cardiac adverse reactions	the combination	khannazer, N., et al., 2020. [25]	
	OTV	High mortality rates and cardiac adverse reactions	elevated doses of the combination	Hossein-khannazer, N., et al., 2020. [25]	Only one article (3.8%)
EMT	————	————	————	————	————
FPV	————	————	————	————	————
HCQ	QTc. interval prolonging medications	Severe QTc. prolongation	————	Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
	LPV/RTV and RDV	QTc. prolongation		Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
	LPV/RTV	hypoglycemia		Singh, A.K., et al., 2020. [16]	Only one article (3.8%)
LPV/RTV	Statins	myopathy because of the increased levels of statins	————	Gupta, M.D., et al., 2020. [18]	Only one article (3.8%)
RDV	————	————	————	————	————
RBV	————	————	————	————	————
TCZ	————	————	————	————	————

(CCP): Convalescent plasma COVID-19, (CS): Corticosteroids, (CQ): Chloroquine, (EMT): Emetine, (FPV): Favipiravir, (HCQ): Hydroxychloroquine, (LPV/RTV): Lopinavir/ritonavir, (RDV): Remdesivir, (RBV): Ribavirin, (TCZ): Tocilizumab



5 CONCLUSIONS

The RdRp. inhibitor, FPV could be considered as a promising antiviral agent for treating COVID-19 due to its approval for managing pandemic influenza in Japan and China. Likewise, FPV could be a hopeful antivirus against SARS-CoV-2 due to its familiar effectiveness against OTV-resistant influenza A, B, and C viruses, Ebola and copious RNA viruses. As well, the recent Chinese open-label CT has proven FPV activity towards SARS-CoV-2 in comparison to the combinaton LPV/RTV. Accordingly; China has given FPV an official permit as a COVID-19 treatment. Furthermore, regarding this antiviral agent safety profile in comparison to the other mentioned treatment options, it could be generally considered safe but should only be avoided in a special population - pregnant women- due to its teratogenecity. The other treatment options are associated with many serious ADRs listed above. Consequently, FPV could be regarded as a relatively safe treatment option. Further studies on this promising RdRp inhibitor, FPV, are ongoing and required beside the results that are anticipated to be available soon from the various CTs of this antiviral agent alone or in combinations with different treatment options in different countries all over the world in order to verify the safety and the effectiveness of FPV and its combinations against COVID-19. It is a hope that this work could help in the mangement of SARS-CoV-2 and encourage more countries to utilize this antiviral agent-FPV as a promiusing COVID-19 treatment alone or in combination.

6 Declarations

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6.2 Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest with this work.

6.3 Ethics approval
Not applicable
6.4 Consent to participate
Not applicable
6.5 Consent for publication
Not applicable
6.6 Availability of data and material
It is confirmed by the authors that all relevant data are included within the article.
6.7 Authors' contributions
Data extraction was conducted by 3 researchers (MGM, MSM and ZA) who separately evaluated all selected articles to extract the ones relevance to this review. Discrepancy was resolved through compromise. The inclusion process was performed by only one researcher (MGM), but when there was any uncertainty about any article to be involved or not, a second researcher, MAR, was referred to. MAR was also responsible for the final review of the article.

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