Introduction

At the end of 2019, novel coronavirus pneumonia (NCP) emerged in Wuhan and had spread rapidly. The pathogen was confirmed as novel coronavirus, which was officially named coronavirus disease-19 (COVID-19) by the World Health Organization (WHO) [1]. The clinical characteristics of COVID-19 include fever, respiratory symptoms, dyspnea, cough and pneumonia [2–5]. Currently, there is no specific antiviral treatment for COVID-19, using the agents which approved or in development for other viral infections is one of the potentially quickest ways to find treatment for this new viral infection. Favipiravir is an effective agent that acts as a nucleotide analog that selectively inhibits the viral RNA dependent RNA polymerase or causes lethal mutagenesis upon incorporation into the virus RNA. In view of recent studies and discussion on favipiravir, in this mini review we aimed to summarize the clinical trials studying the efficacy and safety of favipiravir in patients with COVID-19.
February 14, a clinical trial on favipiravir for the treatment of COVID-19 initiated by the Clinical Medical Research Center of the National Infectious Diseases and the Third People’s Hospital of Shenzhen achieved promising results. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir. No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group [7].

Studies of Favipiravir Conducted In Vitro

Nucleoside analogues in the form of adenine or guanine derivatives target the RNA-dependent RNA polymerase and block viral RNA synthesis in a broad spectrum of RNA viruses, including human coronaviruses. Favipiravir (T-705), a guanine analogue approved for influenza treatment, can effectively inhibit the RNA-dependent RNA polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus [16], and a recent study reported its activity against 2019-novel corona virus. Chinese researchers who studied the effect of favipiravir in vitro (using Vero E6 cell line infected by SARS-CoV-2) found favipiravir to be effective in reducing viral replication (half-maximal effective concentration (EC50) = 61.88 μM, half-cytotoxic concentration (CC50) > 400 μM, selectivity index (SI) > 6.46) [21].

Clinical Trials

At least 18 different clinical trials for SARS-CoV-2 already registered in the Chinese Clinical Trial Registry (ChiCTR) and the International Clinical Trials Registry Platform (WHO ICTRP) propose to use favipiravir in the treatment of COVID-19 (▶Table 1). For example, patients with 2019-nCoV are being recruited in randomized trials to evaluate the efficacy of favipiravir plus interferon-α (ChiCTR2000029600), favipiravir plus baloxavir marboxil (an approved influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544) and favipiravir plus Chloroquine Phosphate (ChiCTR2000030987). In a recent publication, Cai and colleagues found that favipiravir showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance indicate. They investigated the effect of favipiravir versus Lopinavir/Ritonavir on the treatment of COVID-19. They reported that favipiravir was independently associated with faster viral clearance and a higher improvement rate in chest imaging. Their findings suggested that favipiravir has significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance, as compared with Lopinavir/Ritonavir [7]. In the recent study Chen and colleagues compare the efficacy and safety of favipiravir and arbidol to treat COVID-19 patients on clinical recovery rate of day
Table 1  Characteristics of clinical trials studying the efficacy and safety of favipiravir in patients with new coronavirus pneumonia (COVID-19).

| ID                  | Public title                                                                 | Country  | Recruiting Status | Type           | Registration time |
|---------------------|------------------------------------------------------------------------------|----------|-------------------|----------------|------------------|
| ChiCTR2000029544    | A randomized controlled trial for the efficacy and safety of Baloxavir Marboxi, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy | China    | Pending           | Interventional  | 2020/02/03       |
| ChiCTR2000029548    | Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxi, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients | China    | Pending           | Interventional  | 2020/02/04       |
| ChiCTR2000029600    | Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) | China    | Recruiting        | Interventional  | 2020/02/06       |
| ChiCTR2000030113    | Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir | China    | Recruiting        | Interventional  | 2020/02/23       |
| ChiCTR2000030254    | the Efficacy and Safety of Favipiravir for novel coronavirus–infected pneumonia: A multicenter, randomized, open, positive, parallel-controlled clinical study | China    | Completed         | Interventional  | 2020/02/26       |
| ChiCTR2000030894    | Favipiravir Combined with Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial | China    | Recruiting        | Interventional  | 2020/03/16       |
| ChiCTR2000030987    | A Randomized Controlled Trial for Favipiravir Tablets Combine with Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia (COVID-19) | China    | Recruiting        | Interventional  | 2020/03/20       |
| ChiCTR2000033491    | Oral Favipiravir for Patients with Delayed SARS-Cov-2 viral RNA Clearance | China    | Completed         | Interventional  | 2020/06/02       |
| EUCTR2020-001528-32-IT | Adaptive randomized trial for therapy of Coronavirus disease 2019 at home with oral antivirals | Italy    | Recruiting        | Interventional  | 24/06/2020       |
| NCT04464408        | Favipiravir Therapy in Adults with Mild COVID-19 | Saudi Arabia | Not yet recruiting | Interventional  | 28/06/2020       |
| JPNN-jRCTs0412000025 | Phase II trial of combination therapy with favipiravir and corticosteroids for COVID-19 | Japan    | Recruiting        | Interventional  | 01/07/2020       |
| EUCTR2020-002106-68-GB | FLARE: Favipiravir ± Lopinavir: A RCT of Early antivirals | United Kingdom | ongoing | interventional | 07/07/2020       |
| IRTCT20150107020592N30 | Prophylactic Favipiravir for Healthcare Workers in COVID-19 Pandemic | Iran     | Recruiting        | Interventional  | 10/07/2020       |
| NCT04471662        | Nelfinavir and Favipiravir Combination in Newly Diagnosed COVID19 Egyptian Patients | Egypt    | Not yet recruiting | Interventional  | 13/07/2020       |
| NCT04474457        | Efficacy and Safety of Favipiravir in the Treatment of COVID-19 Patients Over 15 Years of Age | Turkey   | Recruiting        | Observational   | 15/07/2020       |
| NCT04475991        | Safety and Efficacy of Maraviroc and/or Favipiravir vs Currently Used Therapy in Severe COVID-19 Adults | Mexico   | Not yet recruiting | Interventional  | 15/07/2020       |
| NCT04478448        | Bioequivalence Study of Favipiravir From Flupirava 200 mg Tablet (European Egyptian Pharmaceutical Industries, Egypt) Versus Avigan 200 mg Tablets (Man. by Toyama Chemical Co., Ltd Japan) | Egypt    | Recruiting        | Interventional  | 16/07/2020       |
| NCT04501783        | Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients with Mild to Moderate COVID-19 | Russian Federation | Active, not recruiting | Interventional | 05/08/2020       |
Favipiravir is known to be teratogenic; therefore, administration of alanine aminotransferase (ALT) and total bilirubin, and increased aspartate aminotransferase (AST), alkaline phosphatase (ALP), effects on hematopoietic tissues such as decreased red blood cell findings after administration of oral favipiravir included: adverse dose toxicity studies involving dogs, rats, and monkeys, notable the adverse reactions of this drug should be kept in mind. In repeat-value of this antiviral agent for COVID-19 treatment. Furthermore, to wait for more clinically valid evidence to confirm the positive reduction viral replication, with half-maximal effective concentrations (EC50) 61.88 μM [21]. Furthermore favipiravir, has been tested in clinical trials with Covid-19 patients in China. According to an open-label, non-randomized trial the results showed shorter viral clearance time than the control group that received lopinavir/ritonavir [7]. In addition another multicenter, open-labelled clinical trial reported that in moderate COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment because of the higher clinical recovery rate of day 7 and more effectively reduced incidence of fever, cough besides some manageable antiviral-associated adverse effects [23]. However, data of the above studies indicate the efficacy of favipiravir, we need to wait for more clinically valid evidence to confirm the positive value of this antiviral agent for COVID-19 treatment. Furthermore, the adverse reactions of this drug should be kept in mind. In repeat-dose toxicity studies involving dogs, rats, and monkeys, notable findings after administration of oral favipiravir included: adverse effects on hematopoietic tissues such as decreased red blood cell (RBC) production, and increases in liver function parameters such as aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and total bilirubin, and increased vacuolization in hepatocytes. Testis toxicity was also noted [28]. Favipiravir is known to be teratogenic; therefore, administration of favipiravir should be avoided in women if pregnancy is confirmed or suspected [25] and toxicity information regarding favipiravir in humans is not readily available so the Ministry of Health, Labor and Welfare granted conditional marketing approval with strict regulations for its production and clinical use [29].

Conclusion
Favipiravir might be crucial for ensuring an efficient treatment, decrease mortality and allow early discharge in relation to Covid-19. However more clinical studies are urgently needed to evaluate the efficacy and safety of this antiviral nucleoside for COVID-19 treatment.

Author Contributions
M Ghasemnejad-Berenji; literature review and writing the manuscript writing the original draft of the review article. S. Pashapour: literature review and revising the review article.

Conflict of Interest
The authors declare that they have no conflict of interest.

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