Favipiravir as a treatment for COVID-19

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Favipiravir, developed by Japanese researchers as a treatment for influenza and other RNA viral infections, in 2020–2022, has become extensively used in Russia, China, India, Turkey, and many other countries as a treatment for a novel coronavirus infection. To date, a vast array of information has been accumulated in the scientific literature on various aspects of favipiravir pharmacology, i.e. production methods, mechanisms of antiviral action, *in vitro* and *in vivo* potency, clinical efficacy, and safety. This review provides key information on these aspects, with a focus on the use of the drug for the treatment of COVID-19. A brief comparative analysis of favipiravir with other direct antiviral agents for the treatment of COVID-19 is presented. Drawing on extensive literature, the review authors demonstrate the significant and multifaceted potential of this largely unique molecule.

Introduction

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a broad-spectrum antiviral drug active against RNA viruses. Favipiravir oral tablet dosage form was originally developed by Toyama Chemical (Fujifilm Group) in 1998. Favipiravir has been studied extensively in clinical trials around the world since the early 2010s as a treatment for severe infections caused by various RNA viruses [1]. After successful clinical trials of its use as a drug for the treatment of seasonal influenza conducted in Japan and the United States, in 2014, favipiravir under the trade name of Avigan, was approved in Japan as a drug for the treatment of new influenza viruses. Favipiravir was also used successfully for post-exposure prevention and treatment of patients with Ebola virus infection during the 2014 epidemic of this deadly virus in West Africa [2].

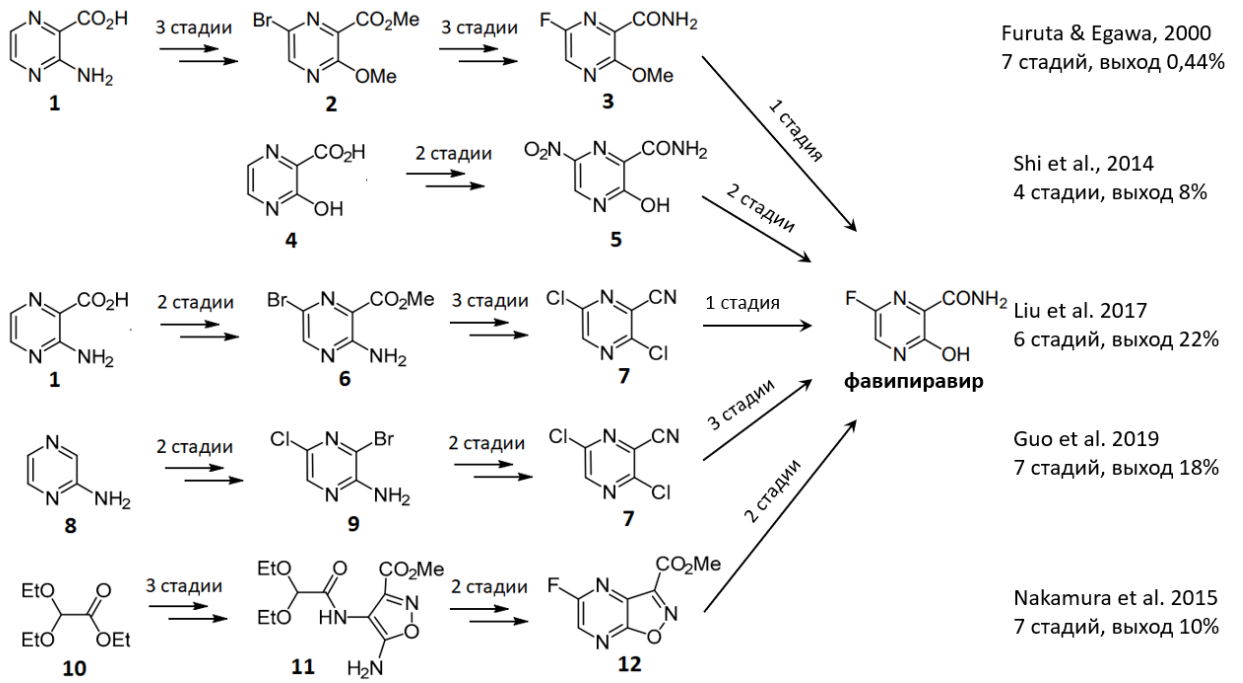
Soon after the start of the global coronavirus pandemic, favipiravir was used for the treatment of a new coronavirus infection, and by mid-2020 the drug was approved for the treatment of COVID-19 in a number of countries, including the Russian Federation, China, and India. Like most other specific drugs inhibiting the SARS-CoV-2 coronavirus that are currently approved for use or are in the clinical development phases, favipiravir mechanism of action disrupts the normal operation of coronavirus RNA-dependent RNA polymerase (RdRp) [3, 4]. To date, only a few drugs of this type have been approved in the world. The closest analogues of favipiravir in terms of the mechanism of action approved for the treatment of COVID-19 in a number of countries are remdesivir and molnupiravir. Another drug with a different mechanism associated with the inhibition of 3CL viral protease is paxloid (nirmatrelvir/ritonavir combination).

Despite extensive research in this direction, the question of creating effective and safe drugs for the therapy of COVID-19 currently remains open. In this situation, it is natural that the scientific community and healthcare systems are interested in favipiravir, which features a well-studied profile of antiviral activity, clinical efficacy and safety. A vast array of information on the drug has been accumulated in the scientific literature; for example, the PubMed bibliographic system has indexed nearly 900 scientific publications in peer-reviewed journals covering favipiravir research. Moreover, interest in the drug has grown dramatically since the onset of the COVID-19 pandemic: for example, in the PubMed system in 2020–2022, more than 1,000 publications related to its research have appeared.

The purpose of this review is to summarize the key aspects of favipiravir pharmacology as it is presented in peer-reviewed scientific literature. Drug production methods, key aspects of its mechanism of action, as well as preclinical and clinical pharmacology are discussed in separate sections. The review presents the status of the studies as of early December 2022.

1. Production methods

Several methods for the synthesis of favipiravir are described in the literature (Diagram 1).



3 стадии	3 stages
2 стадии	2 stages
1 стадия	1 stage
фавипиравир	favipiravir
Furuta & Egawa, 2000 7 стадий, выход 0,44%	Furuta & Egawa, 2000, 7 stages, 0.44% yield
Shi etal., 2014 4 стадии, выход 8%	Shi et al., 2014, 4 stages, 8% yield
Liu et al. 2017 6 стадий, выход 22%	Liu et al., 2017, 6 stages, 22% yield
Guo et al. 2019 7 стадий, выход 18%	Guo et al., 2019, 7 stages, 18% yield
Nakamura et al. 2015 7 стадий, выход 10%	Nakamura et al., 2015, 7 stages, 10% yield

Diagram 1. Favipiravir synthesis methods are described in the scientific and patent literature. The starting reagents and key intermediates are shown.

The first published method was developed by Toyama Chemical Co., Ltd in 2000 [5]. 3-aminopyrazine-2-carboxylic acid **1** was used as a starting reagent. The amination reaction of the intermediate 3-methoxy-6-bromopyrazine-2-carboxylate**2** was catalyzed by the expensive (S)-(−)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((S)-BINAP) in the presence of a palladium complex, and to obtain another key intermediate, 6-fluorine derivative**3**, fluorination was required using the highly aggressive Olach reagent. The overall yield of the final product as a result of this 7-step synthesis was less than 0.5% and, therefore, the method was unsuitable for industrial use.

By the time favipiravir received approval for clinical use (2014), a number of alternative synthesis methods more suitable for large-scale production were introduced. Specifically, in 2014, a synthesis, which included only 4 stages, was described [6]. First, the commercially available 3-hydroxypyrazine-2-carboxylic acid**4** was esterified and amidated, and then the pyrazine ring was nitrated to form an intermediate**5**. The latter was reduced in the presence of a nickel catalyst, and the resulting amino group was replaced by a fluorine atom at the last stage. The overall yield of the target product was 8%.

The most effective synthesis method to date was published in 2017 by Chinese researchers [7]. The starting 3-aminopyrazine-2-carboxylic acid**1** was first esterified and brominated to obtain the key intermediate**6**. The latter was subjected to diazotization, ammonolysis, and reaction with phosphoryl chloride under severe conditions, which led to formation of 3,6-dichloropyrazine-2-carbonitrile**7**. This intermediate was transformed into the final product as a result of a one-pot procedure, including successive reactions of chlorine atom substitution for fluorine, hydrolysis and aminolysis of the nitrile group.

A further modification, published in 2019 by Chinese developers, is associated with obtaining of favipiravir from pyrazine-2-amine**8**[8]. The first key intermediate**9** was obtained from**8** by sequential regioselective chlorination of the pyrazine ring, followed by bromination. Palladium-catalyzed

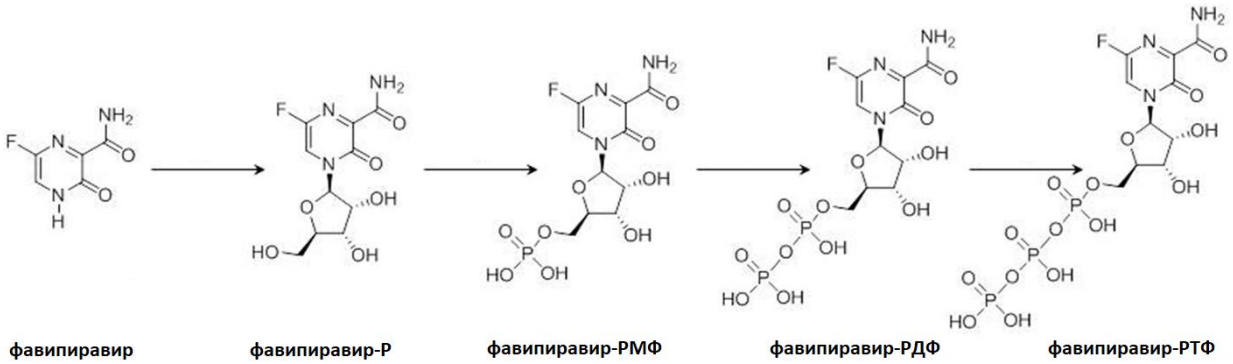
replacement of the bromine atom by the cyano group, followed by diazotization and chlorination according to Sandmeier, produced the second key intermediate**7**. Further nucleophilic fluorination, nitrile hydrolysis, and replacement of the fluorine atom by the hydroxy group led to the target favipiravir with a total yield of 12-18%, depending on the reaction conditions at the first stage of the synthesis. This method compares favorably with the previous one by the absence of a stage with the participation of phosphoryl chloride, which improves the safety and environmental friendliness of production.

Finally, another interesting method proposed by Japanese researchers and based on an alternative strategy associated with the assembly of the pyrazine ring with a given substitution profile is worth mentioning [9]. Diethoxyacetate**10** is used as the starting reagent, which is subsequently converted first into the isoxazolamide derivative**11**, and then into the fluorinated isoxazolo[4,5-b]pyrazine derivative**12**. Subsequent cleavage of the isoxazole ring results in the final product. This method ensures a fairly effective production of the target favipiravir with a total yield of 10%.

The synthetic approaches developed to date enable the large-scale and cost-effective production of favipiravir, making it one of the most affordable COVID-19 therapies in the world.

2. Mechanism of action

Favipiravir is a prodrug which, when entering the cell, undergoes transformations leading to the active form – ribosyl triphosphate (RTF) [10, 11] (Diagram 2). At the first stage, favipiravir is phosphoribosylated by hypoxanthine-guanine-phosphoribosyltransferase, leading to favipiravir ribosyl monophosphate [12]. The mechanisms of subsequent transformations into the final ribosyl triphosphate are still poorly understood, and the observed experimental effects still await interpretation [13].



фавипиравир	favipiravir
фавипиравир-Р	favipiravir-R
фавипиравир-РМФ	favipiravir-RMF
фавипиравир-РДФ	favipiravir-RDF
фавипиравир-РТФ	favipiravir-RTF

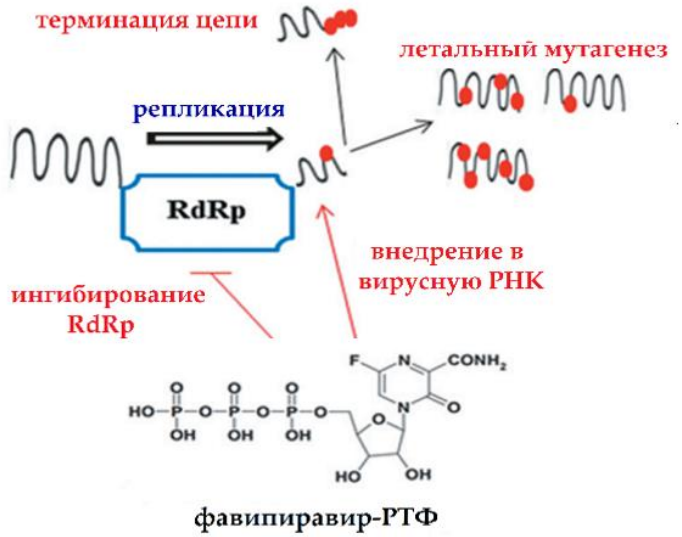
Diagram 2. Intracellular enzymatic transformations of favipiravir leading to the active ribosyl triphosphate (RTF) metabolite.

It should be noted that the diagram of favipiravir biochemical activation is unique among all antiviral drugs since it includes the pseudonucleic base ribosylation stage. All other antiviral compounds of this type are already assembled nucleoside analogs containing natural or modified fragments of ribose and nucleic acid base. This circumstance imposes certain features on the pharmacological profile of favipiravir, which are discussed in Section 3 of this review, devoted to the results of preclinical studies. The metabolites listed in Diagram 2 are not the only ones. In the liver, favipiravir is transformed into 5-hydroxyfavipiravir, which is further glucuronidated [10]. However, these metabolites no longer possess antiviral properties.

The biotarget of the active RTF metabolite of favipiravir is viral RNA-dependent RNA polymerase (Fig. 1). The favipiravir action mechanism is remarkable for a number of interesting and unique features that distinguish this drug from the other drugs also interacting with RdRp [3, 4].

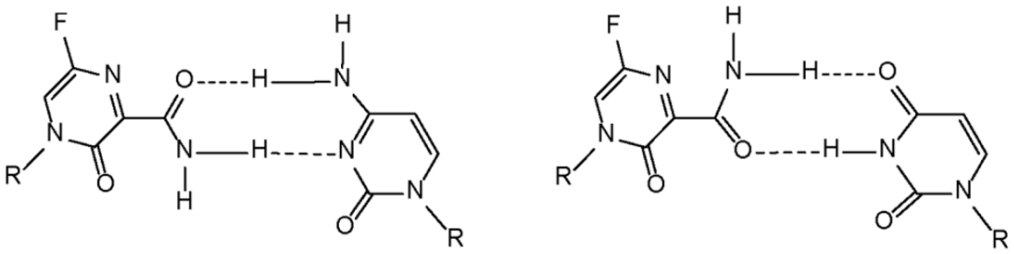
Favipiravir is able to integrate into the viral RNA replication products, mimicking both adenine and guanine nucleotides. As a result of this insertion, favipiravir inhibits viral replication, mainly through the formation of lethal mutations in RNA replicas. The reason for this mechanism is the unusual way of the favipiravir fragment binding to the SARS-CoV-2 replication polymerase complex in its precatalytic state [3]. The resulting complex ensures specific

dynamics of the enzymatic activity of the coronavirus polymerase, with a unique base conjugation scheme between favipiravir and pyrimidine residues, which explains the ability of favipiravir to mimic both adenine and guanine nucleotides (Fig. 2). It is especially important that the subtle structural features of this complex do not allow the viral RNA-polymerase complex to implement its specific exonuclease function, which makes it possible to "cut off" incorrectly inserted nucleotide units, thereby ensuring the replication proofreading.



терминация цени	chain termination
репликация	replication
ингибирование RdRp	RdRp inhibition
летальный мутагенез	lethal mutagenesis
внедрение в вирусную РНК	insertion into viral RNA
фавипиравир-РТФ	favipiravir-RTF

Fig. 1. Diagram of the mechanism of action of the active RTF metabolite, favipiravir.



фавипиравир-РТФ	favipiravir-RTF
фавипиравир (имитация гуанина)	favipiravir (guanine simulation)
цитидин	cytidine
фавипиравир (имитация аденина)	favipiravir (adenine simulation)
уридин	uridine

Fig. 2. Favipiravir is an RdRp substrate and is incorporated into the growing RNA strand, mimicking the type of complementary interaction characteristic of purine nucleobases–, both guanine and adenine.

Favipiravir is also capable of terminating the elongation of the growing chain, especially in cases when two or more residues of it are inserted into the RNA replica [3, 4]. Furthermore, the antiviral effect is due to the competitive inhibition of viral RNA polymerase as a result of non-covalent binding to its active site, which leads to a concentration-dependent slowdown in viral RNA replication [14]. In this regard, it is interesting to study the calculation of the binding energy of the active triphosphate metabolites

of favipiravir, remdesivir and molnupiravir with the active center of RdRp of the Norwalk virus, which features a high structural similarity to the RdRp of the SARS-CoV-2 coronavirus [15]. Optimization calculations were performed using the Prime MM-GBSA protocol, which ensures complete conformational flexibility of triphosphate ligands. The difference in binding energies ($\Delta\Delta G_{bind}$) was calculated by subtracting the binding energy (ΔG_{bind}) of the natural triphosphate (which is expected to be displaced from the active site) from the binding energy (ΔG_{bind}) of the corresponding triphosphate analogue of the nucleoside. The lower the $\Delta\Delta G_{bind}$, the higher the affinity for the active site and the probability of natural triphosphate substitution. The results of these calculations are presented in Table 1. The data obtained indicate that the active triphosphate metabolites of all three drugs are able of displacing effectively the corresponding natural substrate from the active site of RdRp, with the triphosphates of molnupiravir, remdesivir, and favipiravir in the form that mimic ATP exhibiting the highest affinity for the active site.

Table 1. Calculated binding energy parameters of the active triphosphate metabolites of the anti-SARS-CoV-2 nucleoside analogs with the RdRp active site [15].

Drug product	Active metabolite	Active site binding type	$\Delta\Delta G_{bind}$
favipiravir	favipiravir-RTF	simulated ATP (see Fig. 2)	-12.7
		GTP simulation (see Fig. 2)	-1.0
remdesivir	remdesivir-TF	ATP analog	-13.6
molnupiravir	N^4-hydroxycytidine-TF	enamine tautomer	-21.8
		oxime tautomer	-10.1

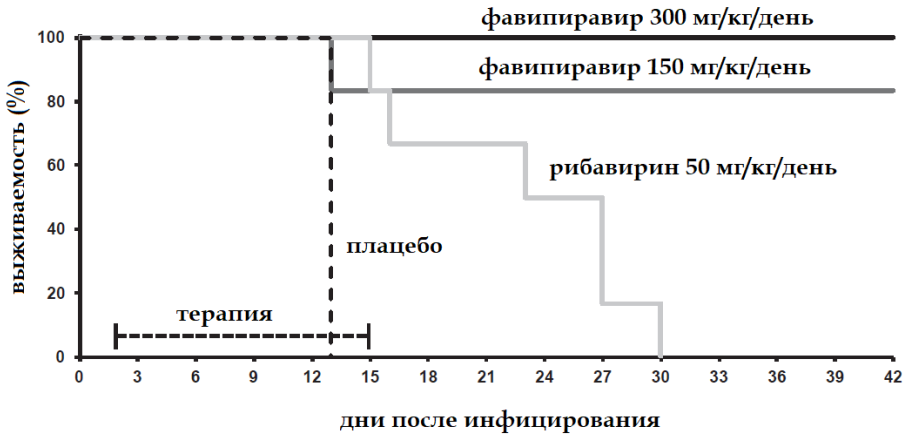
It should be noted that the transformation into active triphosphate metabolites, which then act on highly conserved replication systems of RNA viruses, is a characteristic feature of all antiviral drug substances, structural nucleoside analogues, including remdesivir and molnupiravir [4, 16–18]. At the same time, the favipiravir mechanism of action does not allow the formation of resistant viable viral strains, which has been shown both in preclinical and clinical studies [20–24, 28]. Nucleoside analogs with a pseudonucleoside part are more susceptible to the emergence of resistant strains, which is illustrated, for example, by the identification of the clinical strain SARS-CoV-2 resistant to remdesivir [25]. Additional comparative information on the COVID-19 therapies action mechanisms, as well as on the resistance development, is presented in Section 5 of this review.

3. Antiviral activity *in vitro* and *in vivo*

***In vitro* studies**. Unlike RNA viruses, human cells do not have RdRp, but have DNA-dependent RNA polymerase (DdRp) and DNA polymerase (DdDp). Favipiravir-RTF obtained by chemical synthesis was tested for inhibition of these polymerases [29]. Favipiravir-RTF inhibited the RdRp of the influenza virus (IC_{50} 0.341 μmol/L), but did not inhibit DNA polymerase of human cells at doses up to 1000 μmol/L. These results are consistent with the data that favipiravir does not inhibit the synthesis of DNA and RNA at a concentration of 637 μmol/L in MDCK cells [10], and is inactive against DNA viruses [30]. These facts explain the high selectivity of favipiravir and its cellular metabolites in relation to RNA viruses and its safety for human use.

Favipiravir has a pronounced effect against a wide range of RNA viruses such as influenza, Ebola, yellow fever, chikungunya fever, norovirus, enterovirus, and others [28, 31]. Chinese researchers studying the effect of favipiravir *in vitro* using the Vero E6 cell line infected with SARS-CoV-2 found that favipiravir inhibits viral replication: half-maximum effective concentration (EC_{50}) = 61.88 μM, semi-cytotoxic concentration (CC_{50}) > 400 μM, selectivity index (SI) > 6.46) [32]. In another paper, a Franco-German team of scientists found that favipiravir inhibits the cytopathic effect induced by the SARS-CoV-2 virus in Vero E6 cells (EC_{50} = 118 μM) [4].

***In vivo* studies**. Systematic studies in preclinical *in vivo* models have demonstrated the high protective efficacy of favipiravir against a wide range of RNA viruses [28]. As an illustration, Fig. 3 shows the results of treatment of lethal Lassa virus infection in guinea pigs with favipiravir (according to Safronetz D et al. [34]). Treatment was started 48 hours after infection. Groups of nine guinea pigs were infected with a lethal dose of Lassa virus (GPA-LASV), after which they were treated with subcutaneous injection once a day for two weeks, favipiravir (150 or 300 mg/kg/day), ribavirin (50 mg/kg/day) or placebo. Moreover, favipiravir ensured 100% survival of animals in this model, even in cases where treatment began 5 or 7 days after infection, and if therapy was started on the 9th day after infection, only one animal died during the 42-day experiment. This example demonstrates the very high protective effect of favipiravir.



выживаемость (%)	survival rate (%)
фавипиравир 300 мг/кг/день	favipiravir 300 mg/kg/day
фавипиравир 150 мг/кг/день	favipiravir 150 mg/kg/day
рибавирин 50 мг/кг/день	ribavirin 50 mg/kg/day
плацебо	placebo
терапия	therapy
дни после инфицирования	days after infection

Fig. 3. Results of lethal Lassa virus infection treatment in guinea pigs with favipiravir (according to Safronetz D et al. [34]).

It might sound self-contradictory, but *in vivo* studies on animal models infected with the SARS-CoV-2 virus are still rarer than clinical trials of drugs against the same pathogen. This paradox is due to the fact that in the context of the coronavirus pandemic, the world's research resources were in an emergency mode mainly concentrated on accelerated clinical trials of repositionable drugs that could quickly lead to specific COVID-19 therapies.

In studies on Syrian hamsters infected with the SARS-CoV-2 virus, favipiravir in a therapeutic regimen at the doses of 600 and 1000 mg/kg twice daily for 4 days significantly, up to 4 $\log_{10}$ units, reduced the titers of the infectious virus in the lungs and markedly improved their histopathology [35]. Moreover, the high dose of favipiravir (1,000 mg/kg per day) almost completely blocked viral infection in hamsters that came into direct contact with infected individuals, while hydroxychloroquine was ineffective for preventive purposes. In another study, it was shown that a high dose of favipiravir (1,400 mg/kg per day), administered 1 day before intranasal infection with the SARS-CoV-2 virus, led to a complete suppression of viral replication of the virus in the lungs of hamsters [36]. Thus, to date, it has been reliably established that favipiravir in non-toxic doses exhibits a pronounced protective effect against the SARS-CoV-2 virus in a small animal model.

In general, the information available to date on the preclinical efficacy of favipiravir in *in vitro* and *in vivo* models indicates its significant pharmacological effect against the SARS-CoV-2 virus, albeit in rather high doses.

Peculiarities of the biochemical activation intracellular cycle. As noted in the section on the favipiravir action mechanism, the scheme of its biochemical activation is unique among all antiviral drugs, since it includes the stage of favipiravir phosphoribosylation by hypoxanthine-guanine-phosphoribosyltransferase, leading to ribosyl monophosphate of favipiravir [12]. All other antiviral compounds of this type are already assembled nucleoside analogs containing natural or modified fragments of ribose and nucleic acid base. This circumstance determines certain peculiarities of the favipiravir pharmacological profile.

The multistage cycle of favipiravir biochemical activation with the participation of intracellular enzymes leads to a deterioration in the dose and concentration-dependent efficacy parameters. It was shown that the phosphoribosylation reaction is ineffective: for example, when favipiravir was incubated with an extract of MDCK cells, its maximum conversion to favipiravir-RMF after 25 hours did not exceed 35% [12, 13]. An interesting experimental fact is that the very low stability of aqueous solutions of ribonucleoside favipiravir under mild conditions close to physiological [37]: for example, the half-life of this compound in a 5 mM ammonium bicarbonate solution (pH 8) is only 112 min. It was shown, in particular, that under such conditions there is a rapid replacement of the fluorine atom by the hydroxyl group, which leads to

production of inactive metabolites. The authors of this paper suggested that the rapid degradation of favipiravir ribonucleoside can contribute to the overall low efficiency of its transformation into active ribosyl triphosphate.

The mechanisms and efficacy of the further phosphorylation of favipiravir-RMF, leading to active ribosyl triphosphate, are still poorly understood. In any case, it is obvious that the total yield of the active metabolite is quite low, calculated on the basis of the initial favipiravir, which is reflected in the high concentrations of favipiravir, which are required to achieve significant effects of suppressing the replication of RNA viruses at all levels – cellular *in vitro*, preclinical *in vivo*, and clinical.

On the other hand, certain advantages arising from the peculiarities of the biochemical activation cycle of favipiravir with the participation of intracellular enzymes should be noted. It can be assumed that this cycle provides increased control by the cell over the level of the active metabolite through feedback mechanisms, which potentially prevents side reactions and associated toxic effects. This conclusion is indirectly confirmed, firstly, by the 1000-fold lower mutagenic activity of favipiravir compared to molnupiravir [33], and secondly, by the inability of favipiravir to inhibit DNA polymerases of human cells at concentrations up to 1000 μM/L [29]. These experimental facts explain the high selectivity of favipiravir in relation to RNA viruses and safety for humans. Additional comments on this issue are presented in section 5 of this overview.

Another consequence of the unique non-nucleoside nature of favipiravir is the complete structural similarity of the completed ribosyl triphosphate part of the active metabolite of favipiravir to natural ribonucleoside triphosphates. In contrast, in many antiviral nucleoside analogs (for example, remdesivir, halidesivir, gemcitabine, and others), this part of the structure is modified, which potentially entails a narrowed action spectrum and an increased likelihood of the resistant strain formation. An indirect confirmation of this conclusion is the recent identification of the clinical strain of SARS-CoV-2, resistant to remdesivir [25], while the significantly longer experience of research and practical use of favipiravir made it possible to identify only a number of non-viable or evolutionarily unstable resistant strains, but did not lead to detection of clinical resistant mutations [38].

From the process point of view, the absence of the stage of the ribosyl part addition to the pseudonucleic pyrazine base means a significant simplification of the synthesis technology and a decrease in the drug manufacturing cost. It should be noted that the synthetic ribosyl derivative of favipiravir (favipiravir-R, Diagram 2) did not show any improvement in pharmacological parameters compared to favipiravir [38].

4. COVID-19 therapy. Clinical data

Pharmacokinetics and metabolism. Favipiravir is remarkable for a convenient oral formulation and a favorable pharmacokinetic profile [39, 40]. Studies conducted on healthy Japanese volunteers have shown that it has a high oral bioavailability (~ 94%) and a low volume of distribution (10-20 L). The maximum concentration of favipiravir in the blood plasma occurs 2 hours after oral administration, and then rapidly decreases with a half-life of 2-5.5 hours. Both T_{max} and elimination half-life increase after multiple doses. The rate of favipiravir binding to human blood plasma proteins is 54% [41].

The drug undergoes oxidative metabolism in the liver, mainly under the influence of aldehyde oxidase (AO) and partially xanthine oxidase with the formation of an inactive 5-hydroxyl metabolite, which is excreted by the kidneys [39]. *In vitro* studies have shown that favipiravir can inhibit AO activity in a concentration- and time-dependent manner, which explains the self-inhibition of favipiravir inactivation metabolism and an increase in the plasma favipiravir/5-hydroxyfavipiravir ratio after repeated administration [39]. Given the fact that a number of drugs (e.g., citalopram [42], zaleplon [43], famciclovir [44], and sulindac [45]) are metabolized by aldehyde oxidase, the potential for drug-drug interactions has been noted in the literature, and it must be monitored carefully [40].

Safety profile. Favipiravir has a favorable and well-studied safety profile. The most complete systematic information on this matter is presented in the review paper of a group of researchers from the UK [46]. The authors conducted queries in the EMBASE and MEDLINE databases, supplemented with relevant information from the ClinicalTrials.gov website. All studies evaluating the use of favipiravir in humans prior to March 27, 2020 were analyzed. Twenty-nine studies have been identified as potential sources of evidence for the clinical safety of favipiravir. Oseltamivir, umifenovir, lopinavir/ritonavir, or placebo were used as comparators. The study showed that favipiravir demonstrates a lower share of grade 1-4 and gastrointestinal adverse events, as well as an overall safety profile comparable to the comparators (in the overwhelming majority of cases when compared with placebo). The only significant side effect observed in most clinical trials was an increase in uric acid levels, with a statistically significant difference between

favipiravir and the comparators (5.8% versus 1.3% of cases, $P < 0.0001$). This effect is not associated with clinical manifestations and is transient, however, longer periods of post-therapeutic follow-up are required to fully assess its potential long-term consequences. The possible drug influence on prolongation of the QT interval has also been reported, but the question remains unclear: early pharmacodynamic studies indicate a potential positive relationship [47], but a subsequent Japanese study did not confirm this risk [48].

The results of a nationwide observational cohort study of Japanese patients who received favipiravir as part of clinical care between February 2020 and December 2021 have been published recently. In total, there were 17,508 hospitalized patients receiving favipiravir from 884 hospitals. It was also concluded that favipiravir was well tolerated by patients with COVID-19 [87].

A similar conclusion about the good tolerability of favipiravir is characteristic of the vast majority of clinical trials published to date. Based on the available data, taking favipiravir is not contraindicated even in patients with impaired renal function. Thus, based on the results of a retrospective analysis of 921 clinical cases, it was concluded that the drug was generally well tolerated by patients, including those with severe renal impairment [50]. Another study investigated favipiravir therapy in patients under 18 years old with a confirmed diagnosis of COVID-19 and multisystem inflammatory syndrome in children (MIS-C) with kidney impairment [51]. It was concluded that favipiravir is a suitable treatment option in patients with COVID-19 with renal impairment, without the need for dose adjustments.

The most serious data in the context of mass use are that favipiravir has teratogenic potential and embryotoxicity, which were shown in animal models [47]. For this reason, the Japanese Bureau of Medicines Safety recommends that women of child-bearing potential should not use favipiravir. Recently, it has also been shown that exposure to favipiravir in pregnant white Wistar rats can impair the metabolism and stages of bone formation, as well as delay the development of embryos [88].

However, it should be noted that at present there is no information in the literature about any adverse effects of favipiravir for pregnant women or the fetus. Moreover, according to a recent study based on a sample of 29 pregnant women, favipiravir did not affect the weight, length, or head circumference of the newborns [89]. It was concluded that favipiravir is not teratogenic in humans. Another group of researchers who studied individual cases of the drug use by pregnant women agreed with the colleagues [90]. Experimental evidence that taking favipiravir does not affect spermatogenesis and serum androgen levels in male patients in the long term perspective has also been obtained [49]. However, according to current clinical guidelines, pregnancy should be ruled out before favipiravir is prescribed to women of childbearing potential, and men taking favipiravir should use effective contraception during therapy and for 7 days after its termination.

Clinical efficacy of COVID-19 therapy. Favipiravir has been studied extensively in clinical trials around the world since the early 2010s as a treatment option for severe infections caused by various RNA viruses [1]. After successful clinical trials of its use as a drug for the treatment of seasonal influenza conducted in Japan and the United States, in 2014, favipiravir was approved in Japan as a drug for the treatment of new influenza viruses. Favipiravir was also used successfully for post-exposure prevention and treatment of patients with Ebola virus infection during the 2014 epidemic of this deadly virus in West Africa [2].

In response to the coronavirus pandemic, since the beginning of 2020 though the present, dozens of clinical trials of favipiravir as a therapy for COVID-19 have been initiated. The start has been made by Chinese researchers, who yet in March 2020 presented the first encouraging data on the clinical efficacy of the drug for the treatment of COVID-19 in a cohort of 80 patients [52]. Favipiravir has shown significantly improved efficacy in COVID-19 treatment than the lopinavir/ritonavir combination in terms of disease progression and viral clearance.

Since then, dozens of different clinical trials have been conducted with favipiravir or its combinations. The results of the most significant papers, according to the authors of this review, are presented in Tables 2 and 3.

Table 2. Clinical trials demonstrating the effectiveness of favipiravir in the treatment of COVID-19.

No.	Main result	Source
1	The first data on the clinical efficacy of the drug for the treatment of COVID-19 in a cohort of 80 patients, published in March 2020. F. has shown significantly improved efficacy in COVID-19 treatment than the lopinavir/ritonavir combination in terms of disease progression and viral clearance.	[52]

2	In May 2020, a multicenter randomized Phase II/III clinical trial of F. (Avifavir) in patients with moderate COVID-19 disease (Clinical Trials Registration NCT04434248) was conducted in Russia. The drug ensured effective clearance of the SARS-CoV-2 virus in 62.5% of patients within 4 days, was safe and well tolerated.	[53]
3	A randomized, open-label, parallel, multicenter Phase III trial of adult patients (18-75 years old) with confirmed COVID-19 with mild to moderate symptoms was conducted in India. 150 patients were randomized into F. (n = 75) and control (n = 75) groups. The median time to cessation of virus secretion was 5 days versus 7 days (P = 0.129), and the median time to clinical cure was 3 days versus 5 days (P = 0.030), for F. and controls.	[54]
4	In Japan, a randomized, blind, placebo-controlled phase III trial was conducted to assess the efficacy and safety of F. in 156 COVID-19 patients with moderate pneumonia. The primary endpoint was the combined result defined as time to improvement in temperature, oxygen saturation (SpO_2), chest imaging results, and recovery to complete clearance of SARS-CoV-2. The median time to reach the primary endpoint was 11.9 days in the F group and 14.7 days in the placebo group, with a significant difference (p = 0.0136).	[55]
5	The successful treatment of patients with early COVID-19 F., providing a quick and effective clearance of the nasal secretions from the SARS-CoV-2 virus, regardless of whether it was started relatively early or late during the first week of infection was described.	[56]
6	In a prospective, randomized, open, multicenter trial of F. for the treatment of 89 patients with COVID-19 in 25 hospitals in Japan, F. was shown to shorten the time to recovery. Neither disease progression nor death occurred within 28 days.	[57]
7	The study included 107 critically ill COVID-19 patients admitted to the intensive care unit (ICU). The median ICU stay was 6.6 days in the F. group and 9 days in the lopinavir/ritonavir group, with a statistically significant difference (p = 0.010).	[58]
8	204 patients with COVID-19 pneumonia were studied. F. appeared more effective than LPV/RTV in reducing mortality among hospitalized patients with COVID-19.	[59]
9	A multicenter randomized controlled trial including 96 patients with COVID-19 investigated chloroquine and F. None of the patients in the F group required artificial ventilation (p = 0.129). F. reduced the length of hospital stay and the need for mechanical ventilation.	[60]
10	Two difficult cases of successful cure of patients with a severe course of COVID-19 using F. therapy in combination with a corticosteroid and extracorporeal membrane oxygenation are described.	[61]
11	Forty patients with COVID-19 who developed severe pneumonia were studied. After the treatment with F, 30 patients (82.5%) were discharged from the hospital with full recovery, 6 patients (15%) died, and 1 patient (2.5%) was still in the intensive care unit at the time of the article writing. Conclusions: F was associated with significant clinical and laboratory improvement in the majority of patients, it demonstrated good safety profile with no serious adverse effects, and its further research is justified.	[62]
12	The use of F was investigated in 180 patients with severe COVID-19 pneumonia. The initiation of F within the first 72 hours after the onset of the disease symptoms reduced mortality in patients with COVID-19.	[63]
13	The study included 168 patients with mild to moderate severity of COVID-19, of whom 112 received favipiravir and 56 received standard treatment. The median time to clinical improvement was 6.0 days in the favipiravir group and 10.0 days in the standard therapy group; the difference was 4 days (P = 0.007). The level of virus elimination on day 5 in the favipiravir group was significantly higher than in the standard therapy group: 81.2% vs. 67.9% (P = 0.022). The frequency of clinical improvement on day 7 in the favipiravir group was 1.5 times higher than in the standard therapy group: 52.7% versus 35.8% (P = 0.020).	[64]
14	237 health care workers diagnosed with mild to moderate COVID-19 between March 11,	[91]

	2020 and January 1, 2021, who received hydroxychloroquine (n = 114) or F (n = 123), were studied. Both drugs were similar in terms of improving clinical symptoms, but F was significantly more effective in reducing viral load and hospitalization rate. Besides that, F caused significantly fewer adverse effects than hydroxychloroquine.	
15	A double-blind, randomized, controlled trial was conducted in 57 hospitalized patients with early-stage COVID-19. Of these, 29 patients received F, and the remaining 28 patients received placebo in accordance with the standard of care. F has demonstrated a significant improvement in the clinical condition and recovery of patients with COVID-19 at the early stages of infection.	[92]
16	The efficacy of F in mild cases of COVID-19 without pneumonia and its effect on the virus elimination, the clinical condition, and the risk of developing COVID-19 pneumonia were investigated. The average time to sustained clinical improvement was 2 and 14 days for F and the control group, respectively. The F group also had a significantly higher chance of clinical improvement within 14 days after enrolment (79% versus 32%, respectively, P <0.001).	[93]
17	The mortality rate from COVID-19 in the intensive care unit (ICU) and the total hospital mortality rate in patients who received F and lopinavir-ritonavir were compared. A total of 100 patients were examined. F was used as a treatment for 85% of patients, and the rest received lopinavir-ritonavir. The mortality rate among patients treated with F was lower than that among patients treated with lopinavir-ritonavir.	[94]
18	In Russia, two groups of patients with moderate COVID-19 pneumonia confirmed by a PCR test were studied: the first group (n = 100) received F, and the second (n = 100) a standard of care (SC). The group treated with F showed significant improvements in most of the primary and secondary endpoints compared to the SC group: 27% and 15% of patients with an improvement in clinical status on day 10 of therapy, respectively, P = 0.0372; median time (days) to the onset of clinical improvement – 8 and 12, P < 0.0001; of patients (%) with complete elimination of the virus on day 10 according to the results of PCR – 98% and 79%; median time (days) until the end of the fever – 4 and 5 days, P = 0.052; the share of patients with improvement in the lung condition according to CT by the end of the therapy period – 60% and 40%, P = 0.1953; % of patients without clinical signs of the disease on day 10 after the start of therapy – 44 and 10; % of patients whose body temperature dropped below 37.2°C on day 3 after the start of therapy – 60 and 37 (all values are given for groups F and SC, respectively).	[95]

Table 3. Retrospective studies demonstrating the efficacy of favipiravir in the treatment of COVID-19.

No.	Main result	Source
1	115 patients with severe COVID-19 were retrospectively studied. A significant reduction in the viral load of SARS-CoV-2 in the nasopharynx was achieved in COVID-19 patients who received a phosphate-containing therapy regimen. A significant decrease in the viral load in the nasopharynx was observed three days after the start of therapy with F (P = 0.001).	[65]
2	A retrospective study of F therapy in patients with COVID-19, which was conducted in two public/specialized hospitals in Saudi Arabia, was described. Results: the median time to discharge was 10 days in the group receiving F, compared to 15 days in the group receiving maintenance therapy. The benefit of fast discharge has been observed across the full range of COVID-19 severity conditions.	[66]
3	A retrospective observational cohort study was conducted involving adult patients with COVID-19 at a single center in Turkey. It was found that early initiation of F therapy reduces the viral load and disease progression, as well as the level of C-reactive protein. To improve clinical results, F treatment should be started immediately.	[67]
4	In a retrospective study, favipiravir and hydroxychloroquine showed comparable efficacy in terms of reducing mortality and oxygen demand in patients with COVID-19, but favipiravir has a more favorable safety profile with respect to cardiotoxicity.	[68]

5	The association between F therapy and the frequency of hospitalizations to intensive care units (ICU) in Istanbul in connection with COVID-19 was investigated. Results: The share of patients requiring intensive care unit hospitalization decreased from 24% to 12%, and the percentage of intubated patients decreased from 77% to 66%. These differences were statistically significant. The inclusion of F in the national treatment protocol for COVID-19 in Turkey may explain the decrease in the frequency of hospitalization in the intensive care unit and intubation.	[69]
6	A review of the experience in the treatment of pneumonia caused by COVID-19 with F was carried out in order to identify predictors of response to treatment. It was found that patients with non-severe pneumonia on admission, whose fever released within two days of treatment, were more likely to be cured by F.	[96]
7	International and Chinese databases were searched for randomized controlled clinical trials evaluating F for the treatment of COVID-19. A meta-analysis was performed and the published literature was summarized to evaluate the relevant therapeutic effects. It was found that F significantly contributes to the elimination of the virus and reduces the duration of hospitalization in patients with mild to moderate severity, which can reduce the risk of severe disease outcomes in patients. However, the results did not show the benefits of F for patients in severe condition.	[97]
8	A multicenter retrospective study of 360 patients conducted at four centers in India to assess the efficacy and safety of F was described. F was found to ensure a clinical cure for more than 90% of patients with mild to moderate COVID-19, thus indicating the benefits of using F for the treatment of COVID-19. F is well tolerated and causes only minimal and transient adverse effects.	[98]
9	The comparative clinical data of patients with COVID-19 who received F. at an early stage (within 3 days after admission), and patients who received treatment three days after admission were studied. It turned out that early treatment with F can decrease the length of hospital stay and improve the clinical performance of patients with COVID-19.	[99]
10	The objective of an observational retrospective study conducted in the intensive care unit of the King Saud Medical City from June to August 2020 was to evaluate the efficacy and safety of F in severe COVID-19 infection. F demonstrated a good therapeutic response in patients with severe COVID-19 infection in terms of the average length of stay in the intensive care unit, although it did not demonstrate a decrease in mortality.	[100]
11	This study retrospectively collected demographic and clinical information on patients with COVID-19 who received F during hospitalization from April 27, 2021, to July 2, 2021. Low hospitalization and mortality rates were observed in patients with mild to moderate COVID-19 who received F Caution may be required in elderly patients, in patients with dyspnea or loss of taste, and in patients receiving a 10-day course of F or additional corticosteroids.	[101]

Many of the clinical trials of favipiravir as a therapy for COVID-19 are currently in the active phase. The current status of completed studies has been analyzed in a number of research and review publications (e.g. [70, 71]) as well as meta-studies. A meta-analysis of 9 completed clinical trials showed significant clinical improvement in the favipiravir group compared to the control group within seven days after hospitalization [72]. The favipiravir group had a higher viral clearance rate, a lower need for oxygen therapy, and a 30% lower mortality rate than the control group, although these results were not statistically significant. The authors of the review suggested that the lack of statistical significance of these results is due to the fact that most of the studies involved patients with developed symptoms of the disease, while for the maximum effect, it is desirable to use favipiravir before the patient develops severe symptoms of COVID-19.

Another systematic meta-analysis of 11 clinical trials showed that favipiravir effectively clears the SARS-CoV-2 virus by day 7 and promotes clinical improvement within 14 days [73]. The drug is effective for the treatment of COVID-19, especially in patients with mild to moderate disease severity. The share of patients with clinical improvement on days 7 and 14 in the F group was 54.33% and 84.63%, respectively, compared to 34.40% and 65.77%, respectively, in the control group.

The potential of using combinations of favipiravir with other drug products should be also taken into account. Several clinical studies on this topic have already been carried out (Table 4) and indicate good prospects of this approach.

Table 4. Clinical trials of favipiravir combinations with other drugs.

No.	Description	Source
	Participants with mild COVID-19 pneumonia were enrolled in a prospective, single-center study. Patients received combinations of intravenous (IV) Aprotinin and HCQ (cohort 1), inhalation treatment with Aprotinin and HCQ (cohort 2), or IV Aprotinin and F. (cohort 3). All cohorts showed 100% efficacy in preventing the transfer of patients (n = 30) to the intensive care unit. The effect in cohort 3 with F was the most pronounced, and the median time to elimination of SARS-CoV-2 was 3.5 days, the normalization of the CRP concentration took 3.5 days, the normalization of D-dimer concentration took 5 days; body temperature was normalized within 1 day, improvement of the clinical condition or discharge from the hospital took 5 days, and the decrease in lung damage in patients on day 14 was 100%.	[74]
	Eleven clinical cases of treating patients with severe COVID-19 who received combined treatment with nafamostat mesylate and favipiravir are described. All 11 patients were monitored in a clinical setting for at least 33 days, one patient died.	[75]
	The treatment of 26 patients with COVID-19 is described: 14 were randomized to the combination group, 7 to the favipiravir group and 5 to the tocilizumab group. The cumulative rate of remission of the lung lesion on day 14 was the highest in the combination group. The combination therapy significantly alleviated clinical symptoms and helped to normalize blood counts.	[76]
	Combined oral therapy with favipiravir, camostat and ciclesonide can shorten hospital stay without safety concerns in patients with moderate COVID-19 pneumonia.	[102]

It should also be noted that there are good prospects for enhancing the clinical efficacy of favipiravir through the development of more optimal forms of use. For example, delivery of favipiravir via a soft mist inhaler has been shown to ensure a higher local lung concentration in rats compared to plasma, without any lung damage, cardiac or hepatorenal dysfunction [103]. In another paper, *in vitro* aerodynamic profiles of the inhaled form of favipiravir were investigated [104]. The results obtained also suggested that the favipiravir solution for inhalation can be considered as a promising form of drug delivery to the lungs for the treatment of patients with COVID-19.

The results of a number of ongoing clinical trials can be expected to clarify key aspects of the clinical use of favipiravir as a treatment for COVID-19 and other hazardous RNA viral infections.

Analysis of critical publications. As evidenced by the data from Tables 3 and 4, in most studies of the clinical efficacy of favipiravir for the treatment of COVID-19, convincing results have been achieved, indicating the undoubted clinical efficacy of the drug. However, a number of recent studies, including randomized clinical trials, have shown the limited efficacy of favipiravir for the treatment of patients with COVID-19 (Table 5).

Table 5. Studies showing a limited clinical efficacy of favipiravir.

No.	Description	Source
1	Patients with COVID-19 confirmed by PCR and symptoms for 5 days or less were randomized in a 1 : 1 ratio to receive F or corresponding placebo for 14 days. F did not improve virological cure times or clinical outcomes, and did not show antiviral effect during the treatment of early symptomatic COVID-19 infection.	[105]
2	The objective of the pilot study was to compare three groups: F, hydroxychloroquine, and standard therapy in symptomatic patients infected with SARS-CoV-2, in an open-label, randomized clinical trial. The endpoints were comparable between F, hydroxychloroquine and standard therapy for mild to moderate COVID-19 disease. At the same time, F therapy seemed safe with a tendency to increased virus clearance.	[106]
3	In a multicenter, double-blind, placebo-controlled clinical trial, adults with early COVID-19 of mild to moderate severity were randomized in a 1 : 1 ratio to receive F or placebo. The time to	[107]

	sustained clinical recovery (TT-SCR), COVID-19 progression, and cessation of virus secretion was assessed. F was well tolerated, but was not effective for the specified endpoints.	
4	The study was aimed at assessing the impact of F on the clinical parameters of hospitalized patients with moderate and severe COVID-19. 598 patients with moderate and severe COVID-19 were studied, of which 156 (26%) received F therapy was ineffective in terms of reducing the length of hospital stay and in-hospital mortality among patients with moderate to severe COVID-19.	[108]
5	An open-label, randomized clinical trial was conducted in 14 public hospitals in Malaysia (February-July 2021) among 500 symptomatic COVID-19 patients ≥50 years old with comorbidities. For this category of patients with COVID-19 in a group of a high risk of disease progression, oral F did not prevent disease progression.	[109]
6	A retrospective cohort study of COVID-19 patients admitted to the intensive care unit was conducted at five hospitals in the Kingdom of Saudi Arabia. It was found that F. is not superior to the other antiviral drugs in terms of eliminating the disease symptoms, preventing complications, and controlling the cytokine storm. F also did not affect the length of hospital stay in comparison with the control group, as well as the overall mortality.	[110]

Given the availability of such data, it is required to analyze both objective and possible subjective factors that can affect the clinical efficacy of favipiravir.

First of all, it is required to emphasize the desirability of starting the administration of favipiravir as early as possible. Optimal treatment results are achievable if treatment is started within the first 3-5 days. This conclusion follows both from the available extensive clinical experience [72], and from the well-known fact based on the results of viral dynamic modeling that favipiravir, like any other drug affecting viral replication, will have only a limited effect on viremia if the treatment is started after its peak, regardless of the antiviral drug efficacy [78]. This conclusion is critically important for the treatment of COVID-19 with favipiravir and other direct antiviral drugs, since it has been shown experimentally that the maximum viral load in the upper respiratory tract with SARS-CoV-2 infection is achieved approximately on day 4 after infection [79] in the case of mild and moderate forms of the disease, and subsequently, the pathogenesis of the disease develops mainly due to immunoinflammatory processes that are not directly related to the influence of the virus. A wide range of the other factors also affect the effectiveness of therapy, including the severity of the disease, sex and age of the patients, the presence of comorbidities, genetic differences between the studied populations, and much more.

In this regard, it is characteristic that at least half of these studies, which showed the limited clinical efficacy of favipiravir (Table 5), covered patients with moderate and severe pneumonia who started treatment after a rather long time following the infection, or about elderly patients with severe concomitant diseases at risk.

Another factor is associated with the pharmacokinetics of favipiravir. Thus, a recent prospective observational study analyzed the pharmacokinetic characteristics of favipiravir in adult patients hospitalized with mild to moderate COVID-19 [111]. It has been found that the concentration of favipiravir in the blood of patients shows significant variability during treatment with COVID-19, and therapeutic monitoring of the drug may be required to maintain target concentrations. It is obvious that this feature introduces additional variability in the results of clinical trials of favipiravir.

Such a specific factor as the patient's adherence to (compliance with) the therapy also has a significant impact. In the literature, it has been argued repeatedly that the most vulnerable in relation to unsatisfactory adherence to the treatment are patients with diseases that are low-symptomatic or asymptomatic and require a long course of treatment [80]. Both global experience and observations of Russian clinicians (unpublished data) indicate that high doses of favipiravir (1600 mg on the first day and up to 800 mg on subsequent days) and a relatively long course (up to 14 days) result to the patients' poor compliance. So far, no systematic research of the factor of compliance with favipiravir therapy have been noted, however, in some publications it is noted that it should be taken into account as a criterion for the recruitment of patients for a clinical trial (e.g., [81]). The problem of patient's compliance with continuous favipiravir therapy was repeatedly reported on Indian websites, which resulted with that some manufacturing companies have developed special dosage forms containing increased doses of the drug or suspensions (e.g., [112]).

If the researchers fail to take these factors into account, this may distort the conclusions. Unfortunately, many critical works are characterized by certain drawbacks and/or limitations of the clinical trial design. As an example, we can consider the paper [77], which concluded that the addition of favipiravir to the standard of care does not bring significant benefits. In particular, in the favipiravir group, compared with the control group, the percentage of viral-negative patients after 14 days from the start of therapy was lower (77% versus 100%, respectively), and the median time from the start of the drug administration until the clinical improvement improved only slightly (14 days versus 15 days, respectively).

However, there are a number of critical counterarguments to be made about these findings. First, a very small sample of patients who participated in this study: 9 and 10 people in the favipiravir and control groups, respectively, should be noted; that is, all results obtained were statistically insignificant. Secondly, the treatment regimens and duration before the start of the study were different among the patients, and therefore the condition of the patients in the groups at the beginning of the study differed significantly, which was not taken into account during the analysis of endpoints; thus, the average level of C-reactive protein in the favipiravir group was significantly higher (27.3 mg/L versus 2.1 mg/L in the control group), which indicates more developed inflammatory processes. Third, patients in the favipiravir group were significantly older (58.0 ± 8.1 versus 46.6 ± 14.1 in the control group). Fourthly, both groups featured a significant imbalance in terms of the median time from the onset of the disease symptoms to the start of treatment: it was 8.5 days in the favipiravir group, and 13.6 days in the control group; therefore, it is not surprising that both virus clearance and the time to achieve clinical improvement since the start of administration did not show significant improvements in the favipiravir group (in fact, patients in the favipiravir group showed an average of 5-6 days faster recovery, if we count not since the therapy initiation, but since the onset of symptoms). Fifth, it should be taken into account that 8.5 days from the onset of symptoms is too late to start therapy with favipiravir for the reasons discussed above. Most of these limitations were noted by the authors of this paper, therefore, it serves not as an example of unfair interpretations, but rather as an illustration of the fact that both accounting and analysis of all the numerous factors affecting the results of such studies is a quite challenging and not always feasible task in real-life conditions.

A more detailed analysis of critical works is beyond the scope of this study. According to the authors of this study, such studies are, undoubtedly, useful since an objective critical analysis of the factors leading to a decrease in the efficacy of favipiravir therapy contributes to the development of optimal and most effective clinical strategies.

5. Comparison with competing drugs for COVID-19 therapy

To determine the most effective clinical-therapeutic or pharmaco-economic strategy in the fight against such a dangerous disease as COVID-19, the most important question is the choice of the preferred pharmacotherapeutic drug. In this regard, it is required to compare favipiravir with other specific treatments for COVID-19. Currently, these include remdesivir, molnupiravir and paxlovid (nirmatrelvir/ritonavir combination).

Comparative studies of these drugs are rarely found in the literature. Perhaps the only systematic review of this kind is the recent work of Russian and American researchers, which presents a comprehensive comparative analysis of the similarities and differences between three oral therapies for COVID-19 – favipiravir, molnupiravir and nirmatrelvir [113]. This review can be recommended as a relevant and objective study on the topic under consideration. In this paper, we provide some additional information and comments that may be useful when choosing the optimal therapy. The following is a comparative analysis of these drugs with a focus on efficacy, safety, and resistance formation.

Mechanism of Action Transformation into active triphosphate metabolites is a characteristic feature of most antiviral compounds, structural analogues of nucleosides, including favipiravir, remdesivir, and molnupiravir. Remdesivir predominantly terminates the elongation of the growing RNA strand, while molnupiravir causes lethal mutations in RNA transcripts [16]. In comparison with these drugs, favipiravir seems to implement a more complete set of mechanisms – termination of RNA elongation, lethal mutagenesis, and competitive inhibition of RdRp. The implementation of these three mechanisms leads to an effective inhibition of the RNA-viral genome replication processes by favipiravir and a pronounced virucidal action.

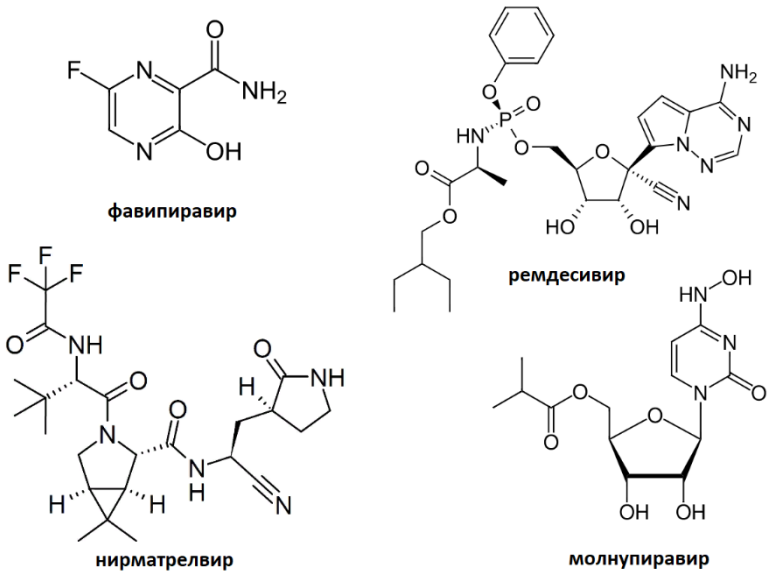


Fig. 4. Structures of direct antiviral agents for the treatment of COVID-19. Nirmatrelvir is the active ingredient of paxlovid.

Paxlovid has a different mechanism of action. Its main active ingredient, nirmatrelvir, is an inhibitor of the coronavirus 3CL protease, while the second component, ritonavir slows down the metabolism of nirmatrelvir by hepatic cytochromes to maintain higher concentrations of the main active ingredient in the systemic circulation [114].

Efficacy in preclinical studies. As shown in section 3 of this review, favipiravir and its cellular metabolites are highly selective for RNA viruses. Moreover, they are active against a wide range of RNA viruses, such as influenza, Ebola, yellow fever, chikungunya fever, norovirus, enterovirus and others, which has been demonstrated in both *in vitro* and *in vivo* models, as well as in clinical trials [28, 31]. Among the competing drugs, only molnupiravir can be compared with favipiravir in terms of the range of action against various RNA viruses, while paxloid and especially remdesivir have a narrower range of action.

The concentration parameters of favipiravir efficacy in *in vitro* and *in vivo* models, as a rule, are inferior to those for remdesivir and molnupiravir. Thus, the activity of remdesivir in an *in vitro* cell model (EC_{50} = 0.77 μM, CC_{50} > 100 μM, SI > 129.87) was significantly higher than that of favipiravir (EC_{50} = 61.88 μM, CC_{50} > 400 μM, SI > 6.46) [32]. Similarly, in a direct comparison with favipiravir, the anti-SARS-CoV-2 activity of molnupiravir in another cell model was more than 100 times higher [33]. These differences in *in vitro* activity correlate well with the significantly higher doses of favipiravir required for comparable efficacy in *in vivo* models and in the clinic. An explanation for these experimental facts should be sought in the features of metabolic intracellular transformations of favipiravir in comparison with remdesivir and molnupiravir (see Section 3 of this review).

Safety As shown in section 4 above, the totality of preclinical and clinical data indicates a high safety of the favipiravir use. The clinical side effect profile of favipiravir in the treatment of COVID-19 is mainly associated with hyperuricemia, elevated liver enzymes, diarrhea and nausea, all of which are transient. The most problematic aspect caused by the mechanism of action and associated with potential embryotoxicity is fully reflected in the instructions for clinical use, according to which the drug is contraindicated to pregnant and lactating mothers.

The side and toxic effects of the other three drugs under consideration are at least equally serious and deserve close attention when choosing a therapy.

Specifically, the pronounced mutagenic potential of molnupiravir revealed in the course of preclinical studies should be noted. A direct comparison of the impact of molnupiravir and favipiravir on mammalian cells was carried out in a recent paper by a group of researchers from the United States [33]. In this study, it was shown that molnupiravir has a potent mutagenic influence on mammalian CHO-K1 cells starting from a concentration of 0.3 μM, equal to its EC_{50} on the same cell line infected with SARS-CoV-2, and at a concentration of 3 μM the mutagenic effect of molnupiravir is comparable to the effect of direct influence of UV radiation on cells. It is assumed that the mutagenicity of molnupiravir is due to the fact that its nucleoside form, N4-hydroxycytisine (rNHC), which enters the cell in the assembled form, without

the participation of cellular enzyme systems, is convertible into the corresponding 2'-deoxyribonucleoside under the influence of cellular phosphatases and ribonucleotide reductase (dNHC), which is a substrate of cellular DNA polymerase and can cause mutations therein. The probability of implementation of a long chain of enzymatic reactions required for the conversion of favipiravir to a corresponding 2'-deoxyribonucleoside seems to be minimal, which is indirectly confirmed by its 1000-fold lower mutagenic activity compared to molnupiravir [33]. These positive differences between favipiravir and molnupiravir are apparently associated with the features of the biochemical activation cycle of favipiravir with the participation of intracellular enzymes noted in Section 3 of this overview. It can be assumed that this cycle provides increased control by the cell over the level of the active metabolite through feedback mechanisms, which potentially prevents side reactions and associated toxic effects.

In line with the specified mutagenic potential, molnupiravir has a pronounced embryo-fetal toxicity. Furthermore, an increase in liver weight was observed in a 28-day rodent study of molnupiravir; an increase in the level of liver enzymes was also observed in clinical trials of the drug. High toxicity to bone and cartilage was identified as another specific risk; in animal studies, this risk was associated with a very low dose-associated safety limit (0.7 to 3.3 times in male and female rats, respectively), which necessitates a reduction in the drug dose. In view of these results, the use of molnupiravir is contraindicated in persons under 18 years old, as well as in pregnant and lactating mothers, and the mode of administration is associated with strict control of the dosage and duration of the course of therapy [115]. Clinical use of molnupiravir usually causes adverse effects on the side of central nervous system such as dizziness and headache, as well as gastrointestinal adverse effects such as diarrhea and nausea [115].

Although the hepatotoxic effects caused by nirmatrelvir are reversible and are not accompanied by histopathological changes, it is still unknown whether the potentiation of hepatotoxicity occurs when nirmatrelvir and ritonavir are taken in combination. Animal studies of ritonavir have identified the liver as one of the target organs, the impact on which leads to hepatocellular, biliary, and phagocytic changes, accompanied by an increase in the level of hepatic enzymes [116]. In line with the specified toxic effects, the patient information leaflet for ritonavir requires monitoring of the liver function [117].

With regard to the risks to reproduction, paxlovid as a drug combination was not evaluated in the framework of the standard reproductive toxicity program. Nirmatrelvir is tolerated well in standard fertility studies and embryofetal animal studies at doses up to 1000 mg/kg [118]. Ritonavir also lacks a clinically significant risk for reproduction, but it exhibits embryo-development toxicity in doses associated with toxicity to the mother, hepatotoxicity, increased levels of total cholesterol and triglycerides, as well as diabetes mellitus [119]. Given the limitations described, paxlovid is currently approved for use in the United States for patients 12+ years old weighing at least 40 kg. However, safety in the younger population has not been confirmed by any preclinical or clinical data.

Common adverse effects of the clinical use of paxloid include gastrointestinal disorders such as nausea, diarrhea (including severe electrolyte imbalance), vomiting, dyspepsia, oral and peripheral paresthesia. CNS adverse effects include headache, dizziness, peripheral neuropathy, seizures, fainting, etc. There is also a decrease in hematological parameters, an increase in hepatic enzymes and renal function parameters.

Clinical efficacy First of all, it should be noted that, so far, the research literature has not reported the appearance of clinical trials aimed at a direct comparison of the effectiveness of these drugs. This determines the need to compare mediated data obtained in more or less different clinical settings.

Section 4 of this overview provides data on the clinical use of favipiravir, which, in general, in our opinion, indicate its undoubted benefit for overcoming COVID-19. Most of the clinical trials published in the research literature in 2020-2022 have provided evidence of favipiravir efficacy in the treatment of COVID-19. When the treatment is started at an early stage, the drug significantly increases the survival rate of patients, reduces the viral load, the need for artificial lung ventilation and the duration of hospital stay. Several clinical trials have shown limited efficacy of the drug, which may be due to both objective factors and shortcomings in the clinical trial design.

Remdesivir was approved by the US Food and Drug Administration for the treatment of coronavirus disease 2019 (COVID-19) based primarily on the results of one double-blind, randomized control trial [120], which demonstrated a faster mean recovery time in patients who received the drug (10 days), compared to the placebo group (15 days). However, further clinical trials have questioned the drug efficacy. Thus, double-blind clinical trial showed no statistical difference in terms of the clinical improvement between patients receiving remdesivir and placebo [121]; the results of a larger clinical trial by WHO did not reveal a significant difference in mortality between patients receiving remdesivir and

standard care either [122], which prompted the organization to recommend not using the drug for COVID-19 [123].

The prospects for the clinical use of molnupiravir are quite obscure. Given the ambiguous preclinical and clinical safety profile (see above), as well as strict restrictions on the doses used and the duration of therapy, the clinical efficacy of the drug has been questioned in a number of studies. In particular, there is an evidence of the futility of using molnupiravir in moderate (SpO_2 90-93% indoors) and severe COVID-19 [124]. It is worth noting that since the absolute risks were reduced from 14.1% to 7.3% in the placebo group, the number needed to treat (NNT) to prevent one hospitalization or death is 14.7. This means that an average of 15 patients would have to be treated with molnupiravir instead of placebo so that one additional patient avoids hospitalization or death. With such limited efficacy, the drug should be absolutely safe and affordable for wide use, which is not entirely true [125].

However, as in the case of favipiravir, critical assessments are interspersed with positive results. An example is the results of a phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of molnupiravir treatment initiated within 5 days of the onset of signs or symptoms. When used early, molnupiravir reduced the risk of hospitalization or death in non-hospitalized, unvaccinated adults with mild to moderate laboratory COVID-19 infection [126]. In another randomized controlled trial in patients with mild to moderate COVID-19, molnupiravir significantly accelerated the clearance of omicron-type SARS-CoV-2 in patients with COVID-19 [127].

Information on the clinical efficacy of paxlovid is still limited. The results of a phase 2-3, double-blind, randomized, controlled trial in which symptomatic, unvaccinated, non-hospitalized adults at high risk of developing severe COVID-19 received either 300 mg of nirmatrelvir plus 100 mg of ritonavir (paxloid) or placebo twice daily for 5 days have been reported [128]. COVID-19-related hospitalizations or death from any cause prior to day 28, viral load, and safety were assessed. For the study cohort, the risk of progression to severe COVID-19 was 89% lower in the paxlovid group compared to the placebo group, with no apparent safety concerns. However, it is too early to draw final conclusions on the effectiveness of paxlovid therapy, especially since a number of studies have noted its limited efficacy and serious adverse effects, as well as the possibility of COVID-19 relapses after paxlovid therapy [129, 130].

As a summary to this subsection, it should be noted that at present, none of the drugs under consideration is absolutely effective against COVID-19.

Resistance issues. It is known that the RNA virus replication systems are highly conservative [4, 17, 18]. In combination with the structural features of the active metabolite of favipiravir (in particular, the complete similarity of its ribosyl triphosphate part to natural nucleoside triphosphates), this ensures a very wide spectrum of antiviral activity, as well as high ruggedness to the resistance development. Mutations of RNA viruses leading to favipiravir-resistant variants are nonviable [19, 20] or evolutionarily unstable when developed in the absence of favipiravir (e.g., [21]). The lack of resistance to favipiravir, observed even with prolonged exposure to the drug on cells infected with the influenza virus [22, 23], was confirmed in clinical trials [24]. Apparently, similar patterns are observed for molnupiravir: there are arguments in favor of the fact that the SARS-CoV-2 virus does not generate the forms resistant to this drug [131]. Nucleoside analogs with a pseudonucleoside part, with certain advantages in the effectiveness of inhibiting the replication of specific RNA viruses, are more susceptible to the emergence of resistant strains. An illustration is the recent identification of a clinical strain of SARS-CoV-2 resistant to remdesivir [25].

Currently, there have also been reports of mutant forms of the SARS-CoV-2 virus resistant to paxlovid [132].

It should also be noted that at present, of the development of new biological agents (for example, antibodies, small interfering RNAs, etc.), capable of highly specific interactions with key molecular and supramolecular systems ensuring the "life cycle" of the virus, is actively developing. For example, specific neutralizing antibodies that can block the interaction of the S-protein of the coronavirus with specialized receptors on the surface of the target cell, thereby disrupting the process of virus penetration into the cell are being developed [26]. However, due to the host's or vaccine-induced immunity pressure, the viral envelope proteins are prone to antigenic drift, which leads to the evasion of immunity [27]. Apart from the cost of the cycle of the therapy, during the local periods of clinical use, antibodies and other highly specific biological agents are highly effective means of blocking viral infections, which allow achieving ideal specificity for a specific viral strain and minimizing adverse effects. However, for long-term therapeutic use, low molecular weight inhibitors targeting highly conservative targets, such as viral polymerase, are a more logical and effective solution, less dependent on the development of pathogen resistance. Moreover, these targets are better suited for the development of broad-spectrum antiviral drugs, which include favipiravir [28].

Cost efficiency of the therapy From a process point of view, favipiravir stands out from competitors by a relative simplicity of the synthesis technology and, accordingly, the lower costs of the drug product. Favipiravir is one of the most affordable specific therapy for COVID-19 (see, for example, [82]). Specifically, the cost of a 5-day cycle of COVID-19 therapy with favipiravir in the Russian Federation as of November 2021 is RUB 4.2–5.000 (USD 60–70). For comparison, the list price of remdesivir, which is also a low molecular weight inhibitor of viral RNA polymerase, was USD 2340 for a 5-day treatment cycle as of mid-2020 [83]. Remdesivir –is the first drug approved under the US FDA accelerated procedure for the treatment of COVID-19 in the UK, EU and US. Since the very beginning of its clinical use, the efficacy of remdesivir, especially in combination with its very high cost, raised serious doubts among specialists. The cost inefficiency of using remdesivir for the treatment of COVID-19 was noted, in particular, in a recent study [84].

The cost-effectiveness of using favipiravir for the treatment of COVID-19 in a mass pandemic setting is also obvious in comparison with biotechnological drugs. For example, the cost of a cycle of COVID-19 therapy with tocilizumab (Actemra) in the Russian Federation in 2021 amounted to RUB 78.800 [85].

Conclusion

The mechanism of action of favipiravir is disruption of the normal operation of the coronavirus RNA-dependent RNA polymerase (RdRp).

Favipiravir is a prodrug, the active cell metabolite of which, favipiravir ribosyl triphosphate, has a unique mechanism of action. The method of biochemical cellular activation of favipiravir is unique among all known antiviral drugs based on nucleosides or their analogues, since it includes the stage of the pseudonucleic pyrazine base phosphoribosylation. This aspect entails increased metabolic control of the cell, which allows reducing the adverse effects of therapy, minimizing the potential for the formation of resistant strains, and reducing the cost of manufacturing a drug substance; a negative consequence is a reduced total yield of the active metabolite based on the initial favipiravir and the need to use large doses of the drug.

Unlike most other inhibitors of viral RNA-dependent RNA polymerase, favipiravir not only terminates the replicating RNA chain, but also introduces lethal mutations into it. Due to the peculiarities of the spatial interaction of the favipiravir fragment with the RNA polymerase complex, the introduced mutations avoid the mechanism of viral control of the correct reading, which leads to RNA replicas incompatible with the continuation of the RNA virus life cycle. The third mechanism is competitive inhibition of the RdRp active site, which slows down the replication of the viral genome.

Due to its impact on the highly conserved replication mechanisms of RNA viruses, favipiravir has a very broad spectrum of action. It has been proven to be highly effective in suppressing influenza, Ebola, SARS-CoV-2 and many other viruses. Another positive feature of the impact on highly conservative replication systems is the high drug ruggedness to the resistance development, which is why it compares favorably with not only highly specific biological products (for example, antibodies, miRNA, etc.), but also with many other nucleoside analogues, to which clinical resistant strains appear. The problem of the rapid occurrence of mutations is especially characteristic of RNA viruses, since viral RNA polymerase is prone to a high frequency of errors during replication.

In a series of clinical trials conducted in 2020-2022, evidence of the efficacy of favipiravir for the treatment of COVID-19 was obtained. When the treatment is started at an early stage, the drug significantly increases the survival rate of patients, reduces the viral load, the need for artificial lung ventilation and the duration of hospital stay. There is good potential for the development of effective combined drugs with the other antiviral agents, as well as modified forms of delivery.

Favipiravir has a convenient oral formulation as well as a favorable pharmacokinetic profile. Favipiravir also has a good safety profile compared to the other antiviral agents. In a clinical setting, a number of adverse effects are observed, mainly hyperuricemia, which, however, are transient; as with most other drugs, favipiravir is not recommended during pregnancy. Despite a rather high dose load, no fatalities associated with the drug administration were observed during the long-term clinical use.

A number of effective approaches to the drug synthesis, suitable for industrial use, have been developed. Due to the low cost of the pharmaceutical substance, favipiravir has significant advantages for large-scale use not only over expensive biotechnological drugs, but also over most synthetic low-molecular-weight drugs (for example, remdesivir), which is especially important in the context of a large-scale pandemic.

There are some limitations associated with the use of favipiravir. Adverse effects such as teratogenicity and embryotoxicity have been shown

in animal models. Despite the emergence of clinical data indicating the absence of a teratogenic effect, current clinical guidelines prohibit the drug administration by women during pregnancy. Clinical trials have also showed the limited efficacy of the drug at the late stages of the COVID-19 disease, characterized by severe symptoms, as well as in patients at risk due to comorbidities or advanced age. These limitations impose the need for careful monitoring during the clinical use of the drug, as well as additional studies.

Comparative analysis with the other approved direct antiviral drugs indicates the presence of both certain advantages of favipiravir and individual disadvantages. The closest nucleoside analogues of favipiravir in terms of the mechanism of action approved for the treatment of COVID-19 in a number of countries are remdesivir and molnupiravir. Both of these drugs are not devoid of significant drawbacks significantly limiting their use. Specifically, remdesivir is remarkable for an inconvenient injectable form, low efficacy of the therapy, the eventual development of resistant pathogens, serious adverse effects, and high cost (for example, [83, 84]). Molnupiravir, an N-hydroxycytidine derivative, has a pronounced mutagenic impact on mammalian cells [33], while there is an evidence of its low efficacy in moderate to severe COVID-19 [86]. Both drugs received approval for clinical use under accelerated regulatory procedures, and therefore, until now, many key aspects of their efficacy and safety remain poorly understood. Another drug implementing an alternative mechanism of action, i.e. inhibition of viral protease, is paxlovid. Given the sometimes contradictory information, the clinical efficacy and safety of paxlovid are still debatable in the scientific and industrial community. The choice of a specific drug for therapy should be based on an analysis of a combination of pharmacological, clinical, and pharmacoeconomic factors.

In general, the theoretical and experimental data accumulated to date indicate that favipiravir is an effective tool in the arsenal of modern healthcare, capable of making a significant contribution to overcoming the COVID-19 pandemic. The research on this question is ongoing.

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