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Review

Pathogenesis of COVID19 and the applications of US FDA-approved repurposed antiviral drugs to combat SARS-CoV-2 in Saudi Arabia: A recent update by review of literature

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ABSTRACT

Still, there is no cure for the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused coronavirus disease 2019 (COVID19). The COVID19 pandemic caused health emergencies which resulted in enormous medical and financial consequences worldwide including Saudi Arabia. Saudi Arabia is the largest Arab country of the Middle East. The urban setting of Saudi Arabia makes it vulnerable towards SARS-CoV-2 (SCV-2). Religious areas of this country are visited by millions of pilgrims every year for the Umrah and Hajj pilgrimage, which contributes to the potential COVID19 epidemic risk. COVID19 throws various challenges to healthcare professionals to choose the right drugs or therapy in clinical settings because of the lack of availability of newer drugs. Current drug development and discovery is an expensive, complex, and long process, which involves a high failure rate in clinical trials. While repurposing of United States Food and Drug Administration (US FDA)-approved antiviral drugs offers numerous benefits including complete pharmacokinetic and safety profiles, which significantly shorten drug development cycles and reduce costs. A range of repurposed US FDA-approved antiviral drugs including ribavirin, lopinavir/ritonavir combination, oseltamivir, darunavir, remdesivir, nirmatrelvir/ritonavir combination, and molnupiravir showed encouraging results in clinical trials in COVID19 treatment. In this article, several COVID19-related discussions have been provided including emerging variants of concern of, COVID19 pathogenesis, COVID19 pandemic scenario in Saudi Arabia, drug repurposing strategies against SCV-2, as well as repurposing of US FDA-approved antiviral drugs that might be considered to combat SCV-2 in Saudi Arabia. Moreover, drug repurposing in the context of COVID19 management along with its limitations and future perspectives have been summarized.

1. Introduction

In late 2019, an infectious disease coronavirus disease 2019 (COVID19) caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in Wuhan, China (Tobaiqy et al., 2020). Later on, scientists performed next-generation sequencing to detect this unknown virus and identified the newly emerged Beta variant of the coronavirus (β-CoV) strain (Guan et al., 2020; Wu et al., 2020). In addition to this, it was also detected that this beta variant is hereditarily similar to the existing SARS-CoV-1 virus (79.5 % identity), Middle East respiratory syndrome coronavirus (MERS-CoV) (50 % identity), and two SARS-CoVs originated in bat. Since the new variant was genetically similar to preceding CoV strains, therefore the newly emerged β-CoV strain was announced as a novel strain of SCV-2 (Hillary and Ceasar, 2023). The COVID19 pandemic caused health emergencies which further led to lockdowns, curfews, and quarantine. Moreover, this pandemic caused an overall breakdown of society, families, and individuals along with huge medical and financial consequences. Indeed, this pandemic rapidly spread across the world, which also caused severe health emergencies in Saudi Arabia (Salam et al., 2022).

The Kingdom of Saudi Arabia is a large country with regard to geographic region, which includes 118 governorates, 13 administrative regions, and 5 planning regions. Saudi Arabia has a population of 35.3 million and its floating population is mainly accountable for the SCV-2 transmission (Anil and Alagha, 2021). Population size is positively linked with the proportion of individuals with COVID19 in the population, nevertheless Saudi Arabia took decisive strategic and mitigation measures including hospital preparedness and community action including quarantine, social distancing and hand hygiene to curb the

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SCV-2 transmission (Al-Otaibi, 2020). However, Saudi Arabia faced multiple public health challenges including implementation of travel regulations, regulation of religious mass gatherings, knowledge gaps, vaccine hesitancy, and adverse psychological effects associated with COVID19. Some of these challenges faced in Saudi Arabia were similar to other countries, however there are some unique challenges in Saudi Arabia owing to the cultural and religious context (Sheerah et al., 2023).

Drug repurposing involves the identification of the newer indications of existing drugs, which is regarded as an economical and effective approach (Huang et al., 2020). It has been estimated that around 75 % of known drugs have the potential to be repositioned for a range of diseases (Huang et al., 2020). The potential of drug repurposing has already been evaluated against various epidemic viruses, among them the transmission of herpes simplex virus (HSV) and hepatitis B virus (HBV) could be decreased by using a several antivirals. For instance, telbivudine, adefovir, lamivudine, tenofovir, entecavir were found to be effective in HBV patients; whereas valacyclovir, famciclovir, and acyclovir can decrease the viral intensity in the case of HSV infection. On the other hand, healthcare professionals face unique challenges and significant demands in choosing the right drugs or therapy in clinical settings because of the lack of availability of newer drugs. Still, there is a deficiency of specific effective drugs or novel antiviral medication for COVID19 treatment. Therefore, screening for efficient medications to treat COVID19 is urgent and vital. Indeed, drug discovery and licensing involve a very long development period. The new drug discovery involves the cost of over a billion dollars, which can take between 10 and 15 years along with a disappointing 2.01 % success rate (Yeu et al., 2015). This enormous cost and long period delay the pharmaceutical research output in new drug discovery, which can further result in a continuous gap between the available drugs and therapeutic needs. Thus, repurposing of US FDA-approved antiviral drugs against SARS-CoV2 can be beneficial and cost-effective. Repurposing of approved drugs has a growing demand to treat several diseases, since it uses safe compounds with known pharmacodynamic, pharmacokinetic, and preclinical profiles that can be directly enrolled in clinical studies to fasten the cost-effective drug discovery process (Pushpakom et al., 2018). Moreover, World Health Organization (WHO) and other health organizations also endorse the benefits of repurposing of experimental and approved drugs to treat emerging diseases (Singh et al., 2020). Indeed, a range of medications have already been successfully repurposed to treat COVID19, such as including oseltamivir, ribavirin, darunavir, remdesivir, lopinavir/ritonavir combination nirmatrelvir/ritonavir combination (paxlovid), molnupiravir.

In this review, several COVID19-associated discussions have been provided including emerging variants of concern (VOCs) of SCV-2, COVID19 pathogenesis, COVID19 pandemic scenario in Saudi Arabia, drug repurposing strategies against SCV-2, and repurposing of US FDA-approved antiviral drugs that might be used to fight against SCV-2 in Saudi Arabia. Moreover, drug repurposing in the context of COVID19 management along with its limitations and future perspectives have been presented.

2. Structural properties of SARS-CoV-2

SCV-2 belongs to the *Coronaviridae* family and morphologically these viruses are enveloped, single-stranded RNA viruses. It has already been identified that SCV-2 is enclosed by an Envelope (E) protein and this virus forms helical capsids composed of nucleocapsid (N) protein. In addition to this, the membrane (M) and E proteins facilitate SCV-2 assembly, while the spike (S) protein facilitates the virus for the entry into the hosts. The S protein looks like a crown (Fig. 1) and its size is much larger (180–200 kDa) than the other proteins for example M, S, and E proteins (Ren et al., 2006). Along with the structural proteins (including N, E, M, and S proteins), there are also a range of non-structural proteins (nsps) (including nsps 1 to 16) present in SCV-2 that play several roles. For example, Nsp1 mediates the viral RNA processing and replication, whereas the host cell's survival signalling pathways are regulated by Nsp2. On the other hand, nsp3 breaks the translated proteins, while ER membranes are modified by transmembrane domain 2 containing nsp4. Nsp5 significantly contributes in the polyprotein replication, and nsp6 plays a role as a transmembrane. The arrangement of template-primer RNA and nsp12 is markedly ameliorated by nsp7 and nsp8. Although the complete mechanism of nsp9 is still not clear, it is believed that nsp9 plays role as a single-stranded RNA binding protein. Nsp10 protein associates methylation of the viral mRNA cap, while nsp11 serves as an intrinsically disordered protein. An important component for the replication and transcription of SCV-2 is RNA-dependent RNA polymerase (RdRp), which is provided by nsp12. Proofreading during viral RNA synthesis is mediated by the exoribonuclease nsp14, while nsp15 has a Manganese (Mn^{+2})-dependent endoribonuclease function. Finally, the nsp16 protein interacts with the mRNA recognition domains of U1 and U2 small nuclear RNAs to prevent mRNA splicing in the course of SCV-2 infection (Hillary and Ceasar, 2023).Fig. 2..

3. Emerging variants of concern of SARS-CoV-2

3.1. Alpha variant (B.1.1.7)

In December 2020, B.1.1.7 or alpha variant of SCV-2 was first reported in the UK following complete whole genome sequencing (Volz et al., 2021). In comparison with the original strain of SCV-2, 23 different mutations are present in the viral genome of B.1.1.7 lineage (Davies et al., 2021; Wu et al., 2021). Among these 23 mutations, 8 of them were found in the spike (S) protein including, Δ144 deletion, Δ69-

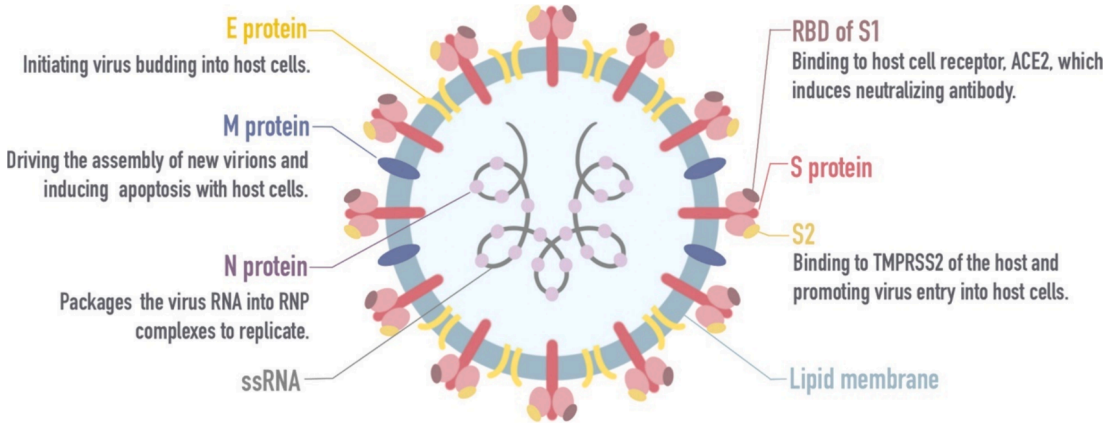

Fig. 1. Structural and functional properties of SARS-CoV-2.).
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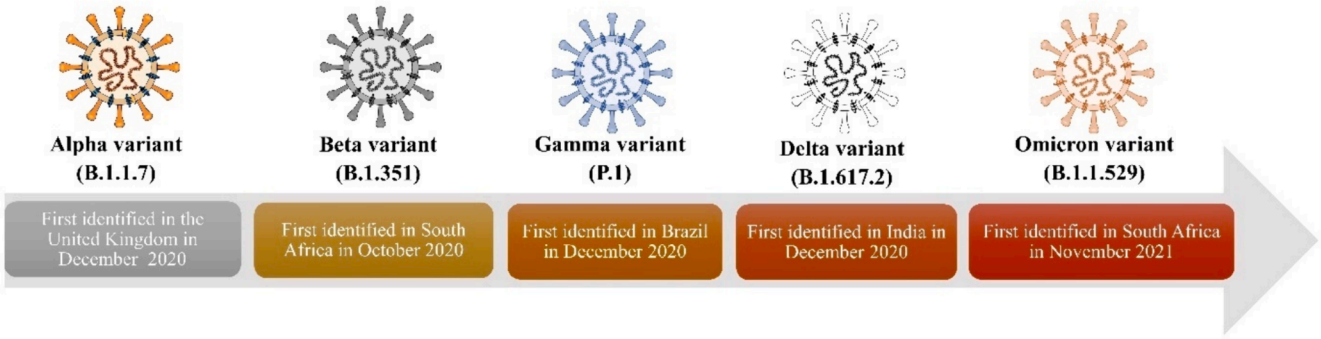

Fig. 2. Timeline showing the emergence of SARS-CoV-2 variants of concern.

70 deletion, T7161I, D1118H, S092A, A570D, P681H, and N501Y have been identified along with S982A. In the B.1.1.7 variant, the N501Y mutation causes conversion of asparagine to tyrosine in the S protein's angiotensin-converting enzyme 2 (ACE2) receptors at position 501, which facilitates the SCV-2 for its entry into the host cells. In South Africa, the N501Y mutation has been designated as 501YV2 variant. Rest of the S protein mutations help SCV-2 to rapidly spread in hosts. WHO announced the B.1.1.7 variant as a VOC as the mortality rate of individuals infected with this alpha variant was 2.26-fold higher than the original strain of SCV-2 (Challen et al., 2021).

3.2. Beta variant (B.1.351)

The B.1.351 or beta variant of SCV-2 was first detected in October 2020 in South Africa. This beta variant contains 9 different spike mutations (Table 1) including L18F, D614G, L18F, A701V, E484K, K417 N, R2461, D215G, and D80A (Tegally et al., 2020). Three of these mutations including N501Y, K417, and E484K are present in the S protein receptor-binding domain (RBD), which helps the entry of SCV-2 into the host cells (Wibmer et al., 2021).

3.3. Gamma variant (P.1)

In December 2020, the gamma variant (P.1) of SCV-2 was first reported in Brazil (Faria et al., 2021). In contrast to the original SCV-2 strain, there are 17 different mutations present in the viral genome of P.1 variant. Among them, the S mutations involves 10 mutations such as N501Y, D138Y, K417T, E484K, T20 N, T10207I V11176, H655Y, R190S, P26S, and L18F (Faria et al., 2021). Three out of these 10 mutations including L184, K417 N, and E484K are present in ACE receptors, which mediates of SCV-2 entry in the host cells [32].

Table 1
The list of variants of concerns of SARS-CoV-2 and their spike mutations. (Hillary and Ceasar, 2023).

Variants of concerns		Spike mutations
Alpha		D1118H, S982A, P681H, D614G, A570D, N501Y, Del 144, Del 69–70, T716I
Beta		N501Y, A701V, D614G, K417 N, D215G, L18F, D80A
Gamma		N501Y, P26S, T1027I, L18F, V1176F, K417 N/T, D138Y, H655Y, E484K, D614G, T20 N
Delta		L452R, D950 N, P681R, D614G, Del 156, T478K, T19R, R158G, Del 157
Omicron	BA.1	G496S, S371L, S477 N, T547K, N501Y, Q493R, N969K, Q498R, N764K, D796Y, H655Y, K417 N, D614G, Y505H, N856K, S373P, G446S, N679K, N440K, NL211-212I ins214EPE, G339D, Del 69–70, S375F, T95I, A67V, GVYY142-145D, Q954H, E484A, P681H, L981F, T478K
	BA.2	S371F, T478K, Q498R, P681H, Q954H, N764K, Y505H, H655Y, N969K, E484A, N679K, N501Y, S375F, G339D, K417 N, T376A, D796Y, D614G, G142D, R408S, Q493R, T19I, D405 N, S477 N, V213G, N440K, S373P, LPPA24-27S

3.4. Delta variant (B.1.617.2)

In December 2020, B.1.617.2 or the delta variant was first identified in India. Because of the highly infectious nature of this variant, both the WHO and Centers for Disease Control and Prevention (CDC) designated this variant as a VOC, which is over 2 times more infectious than the earlier variants. The emergence of B.1.617.2 also resulted in the second wave of the COVID19 pandemic in multiple countries, especially in India (Zhang et al., 2021). There are ten different mutations found in the S protein of this variant including G142D, D950 N, L452R, R158G, P781R, T614G, L452R, Δ156-157deletion, and T19R (Zhang et al., 2021).

3.5. Omicron variant (B.1.1.529)

In November 2021, B.1.1.529 or the Omicron variant of SCV-2 was first discovered in South Africa (Saxena et al., 2022). Around 18,621 mutations have been reported in this variant. Among them, over 17,703 (97 %) mutations found in the coding area, whereas the rest of the 558 (3 %) mutations are present in the extra-genic area. Both CDC and WHO designated this variant as a VOC owing to the different genome construction of this variant as compared to the current variants. Over 30 mutations including S375F, Q954H, L981F, N969K, D796Y, G339D, S373P, S371L, N440K, K417 N, T478K, S477 N, Y505H, E484A, N501Y, G496S, A67V, H69del, G142D, T95I, Y143del, Y145del, A63T, Q19E, G204R, P13L, R203K, S33del, E31del, and T91 were identified primarily in the RBD of S proteins (Daria et al., 2022). Several other concerning mutations including T478K, D641G, K417 N, and N501Y have also been recently noticed in this B.1.1.529 variant, which are rapidly spreading worldwide (Hillary and Ceasar, 2023).

3.6. XD, XE, and XF variant

In January 2022, the recombination of Omicron BA.1 and BA.2 variants led to a new Xe variant, which was first reported in the UK. There are 3 mutations present in this variant including NSP12–C14599T, V1069I, and NSP3–C324IT. The WHO declared this Xe variant as a VOC. On the other hand, XF and XD subvariants share genetic materials from former Delta AY.4 and Omicron BA.1 variants. On the other hand, the XD subvariant was first identified in France, Denmark, and Belgium; whereas XF sub-variant was first identified in January 2022 in the UK (Hillary and Ceasar, 2023).

4. Pathogenesis of COVID19

Individuals with COVID19 are likely to be affected by acute cardiac

injury and ground-glass opacities. An increased blood level of chemokines and cytokines is also present in individuals with COVID19. The binding of S proteins of SCV-2 results in the downregulation of ACE2 expression in host cells. Therefore, lower level of ACE2 remains available to be converted from angiotensin II to angiotensin-(1–7), which can further result in severe lung injury and increased hypertension (Zhang et al., 2020a, 2020b). SCV-2′s S protein has the capacity to detect and bind with the glucose-regulated protein 78 (GRP78) substrate-binding domain β (SBDβ), which can mediate the viral entry during cellular stress responses. It has been observed that the virus shows enhanced infectivity in cells in the occurrence of transmembrane protease serine 2. The S protein contains a furin protease cleavage site (Ibrahim et al., 2019). Furin increases SCV-2 infectivity, since it is expressed well in human airway cells (P et al., 2022). SCV-2 most commonly results in mild upper respiratory tract symptoms and infrequent gastrointestinal symptoms. Fig. 3 illustrates the COVID19-associated clinical manifestations.

An increased level of proinflammatory neutrophils and macrophages is also seen in the bronchoalveolar lavage fluid of individuals with COVID19, which further leads to severe symptoms (Fig. 4) than the individuals presenting mild symptoms (Liao et al., 2020). Following the entry into the cells, both endosomal toll-like receptors and cytosolic innate immune sensors detect the SCV-2 that signals downstream to generate proinflammatory mediators and type-I/III interferons. The increased level of inflammatory chemokines/cytokines enhances the detrimental tissue injury through vasodilation and endothelial dysfunction, which mediate the enrolment of various immune cells including neutrophils and macrophages. Indeed, the weakened barrier function and vascular leakage cause lung edema and endotheliitis that can limit gas exchange and subsequently mediate a hypoxic environment, which can eventually result in respiratory failure. It has been observed that hyperinflammation in the lung can mediate the transcriptional alterations in neutrophils and macrophages to cause tissue injury, which eventually results in irreversible lung injury.

5. Overview of COVID19 pandemic in Saudi Arabia

Saudi Arabia is the largest Arab country of the Middle East. Both the population and area of Saudi Arabia are 0.4 % of the world (Abdulhaq et al., 2022). In regards to the world's COVID19 cases, Saudi Arabia's COVID19 cases rapidly increased from 0.2 % on March 21, 2020 to 1.5 % by June 20, 2020, however this rapid increase was decreased to 0.01 % by February 28, 2021 and thereafter even less than that, owing to several interventions over that period (Salam et al., 2022). Increased number of COVID19 cases are reported in the administrative areas of Saudi Arabia including major residential, educational, developmental, and commercial zones. Increased COVID19 cases were observed in Riyadh between May 2020 and July 2020, however the number of cases dropped since August 2020, however there was a slight increase after January 2021. Along with Riyadh, Mecca and the Eastern Region were also heavily affected (1,496 and 1,586, 23,647 cases per 100,000 population, correspondingly) as compared to other administrative areas (Salam et al., 2022).

Saudi Arabia has witnessed both highs and lows in terms of economic sectors, infrastructure in place, urban growth, and population size (Hershan, 2023). The rapid transmission of SCV-2 was also observed in

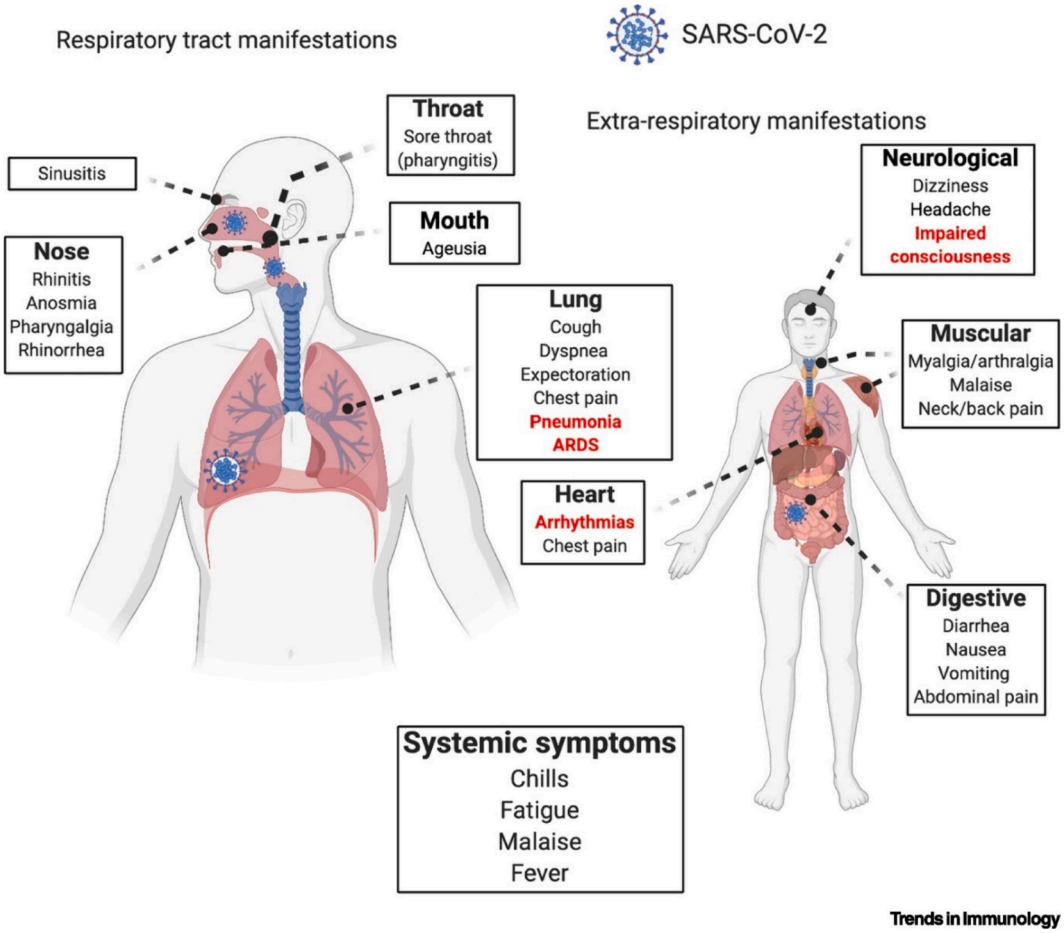

Fig. 3. Clinical manifestations associated with Coronavirus Infectious Disease 2019 (COVID19).).
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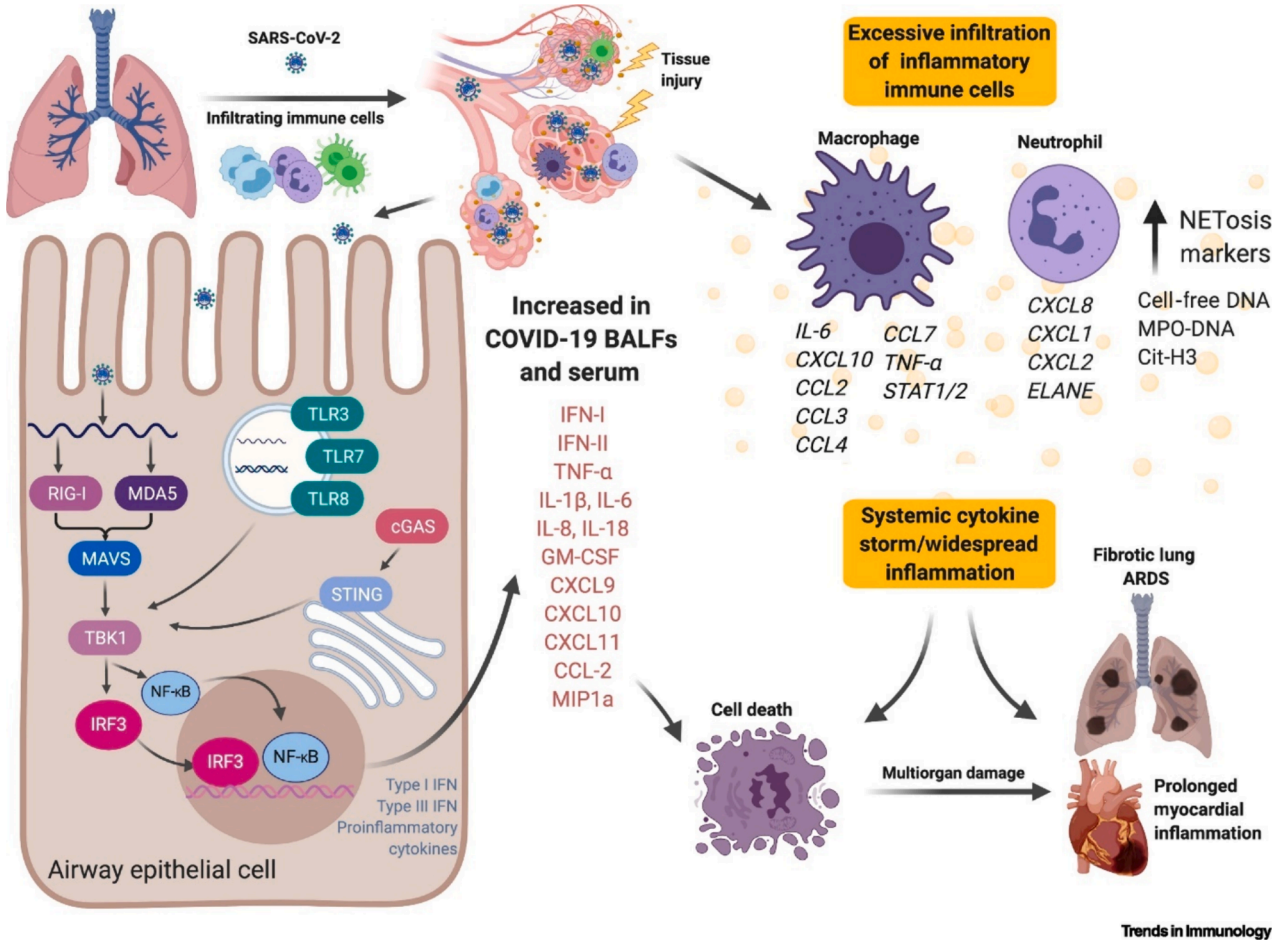

Fig. 4. Pathological features of coronavirus infectious disease 2019 (COVID19)-related lung infection.).
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the Eastern Region, Mecca, and Riyadh, which corresponds to the aforesaid factors. Nonetheless, fewer COVID19 cases were reported in Jazan, Al-Qassim, Aseer, and Medina, which are the second group of administrative regions of Saudi Arabia. Despite implementing several control measures, the variations in the number of reported cases in the administrative areas could be due to the variations across livelihoods, commercial activities, religious and social festivities, and urbanization (Hershan, 2021; Jokhdar et al., 2021). Overall, the urban setting of the Kingdom of Saudi Arabia makes it vulnerable towards respiratory pathogen-caused outbreaks. Moreover, this country's religious areas are visited by millions of foreign pilgrims every year for the Umrah and Hajj pilgrimage, which further contributes to the potential risk of epidemics (Sheerah et al., 2023).

6. Drug repurposing strategies against SARS-CoV-2

Current drug development and discovery is an expensive, complex, lengthy, and uncertain process, which involves a higher level of failure rate in clinical trials (CTs) (Cusinato et al., 2021). There is a growing interest regarding the potential to repurpose US FDA approved drugs for uses that are outside their typical medical indications. Drug repurposing could be enhanced through multiple screening methods including computational, cell-based, or biochemical screening (Table 2). Indeed, the major benefits of drug repurposing are the accessibility to complete pharmacokinetic profiles, *in vitro/in vivo* screening data, formulation development data, bulk manufacturing facility, toxicity studies, and medication safety information of US FDA-approved drugs; which shortens drug development cycles, reduces costs and allows rapid access to required CTs and regulatory reviews (Pillaiyar et al., 2020). Repurposed drugs were previously discovered largely based on serendipitous observations. Along with this serendipity, various methods can be used in drug repurposing including computational methods, phenotypic screening, and binding assay methods (Parvathaneni et al., 2019). However, recent methods of drug repurposing do not depend on producing empirical data associated with the mechanism of action or binding characteristics (Parvathaneni and Gupta, 2020). Phenotypic methods include *in vitro/in vivo* screening, however there are some challenges of this method including target deconvolution and hit validation (Parvathaneni et al., 2019).

Drug repurposing has significant contribution in the identification of rapidly available drugs against SCV-2. Nevertheless, initially most of the drug repurposing studies were reliant on computational methods and did not involve *in vitro/in vivo* experimental validations or in-depth analysis of useful translational effects (Zhou et al., 2020). Interestingly, the outcomes of these computational drug repurposing methods resulted in mixed and diverse results that were unsuccessful in bringing together the therapeutics in a single group of drugs (Singh et al., 2020). For example, initially 3-Chymotrypsin-like protease (3CLpro) showed excellent X-ray crystallography structures, nonetheless the use of repurposed inhibitors of 3CLpro including the lopinavir/ritonavir combination in clinical settings did not result in anticipated outcomes (Sisay, 2020). Therefore, more host or viral targets were analysed and a range of compounds were repurposed afterwards including investigational molecules and natural compounds that were efficient at least in phase I CTs, however are not approved yet. Antiviral drugs were also extensively analysed through several methods, which demonstrated the

Table 2
A summary of the approaches used in drug repurposing.

Drug repurposing approach	Uses	References
Genetic association	Identifies potential genes that are closely linked with a disease which might serve as a potential drug target	(Pushpakom et al., 2018)
Signature matching	Compares signatures of a drug including its structural, transcriptomic, or adverse effect profile with another disease phenotype or drug	(Pushpakom et al., 2018)
Retrospective clinical analysis	Exploration of postmarketing surveillance data, clinical trial data and electronic health records, which might aid drug repurposing	(Pushpakom et al., 2018)
Pathway or network mapping	Identification of Repurposing targets through developing disease or drug networks based on protein interactions, gene expression patterns, and disease pathology	(Pushpakom et al., 2018)
Molecular docking	Uses structure-based computational approach to evaluate the predict binding of a ligand and a therapeutic target	(Parvathaneni and Gupta, 2020)
Binding assays to identify relevant target interactions	Identification of novel targets of known drugs byexploring binding interactions of ligands to assay components	(Parvathaneni and Gupta, 2020)
Phenotypic screening	Involves potential clinical evaluation of various compounds by using high-throughput phenotypic screening by utilizing *in vitro* or *in vivo* disease models	(Parvathaneni and Gupta, 2020)

potential of targeting RdRp in the discovery of antiviral drugs against COVID19 (Dragoni et al., 2020). CTs revealed more potential of this target, therefore European Medicines Agency (EMA) as well as US FDA approved remdesivir as the first SCV-2-specific antiviral drug.

Chloroquine is extensively utilized in the treatment of malaria, which was found to effectively treat COVID19 in initial studies and was regarded as an effective drug candidate against COVID19. Researchers in a study evaluated and reported the *in vitro* anti-viral activity of ivermectin (an anti-parasitic drug) (Caly et al., 2020). Some studies confirmed the potential of a range of other drugs including niclosamide (an antihelminthic drug), arbidol (an antiviral drug), lopinavir/ritonavir (a combination of antiretroviral drug utilized to prevent and treat HIV or human immunodeficiency virus), interferon-alpha, and angiotensin receptor blockers (drugs that are utilized to treat heart failure and high blood pressure). Along with these investigations several other drugs including favipinavir, teicoplanin, and remdesivir exhibited promising effects against influenza, MERS, and SARS-CoV (Li et al., 2019; Xu et al., 2020); therefore safety as well as efficacy these drugs are being evaluated against COVID19. Potential of a range of other drugs including azithromycin, hydroxychloroquine, and oseltamivir alone or in combinations is also being evaluated against SCV-2.

7. Repurposed US FDA-approved antiviral drugs that have the potential to combat SARS-CoV-2 in Saudi Arabia

7.1. Ribavirin

Ribavirin is an antiviral drug (belongs to class of nucleoside analogues) that was US FDA-approved as a part of a combination therapy in chronic hepatitis C treatment (Table 3) (Singh et al., 2020). The effects of ribavirin have already been evaluated in the treatment of both MERS and SARS. This drug showed a selectivity index of over 3.65 and a high level of EC_{50} (109.50 μM) in Vero cells. The monophosphate form of

Table 3
A summary of repurposed US FDA-approved antiviral drugs that might be utilized in COVID19 treatment in Saudi Arabia.

US FDA-approved antiviral drug	Mode of action against SARS-CoV-2	Originally developed to treat	References
Ribavirin	Inhibits the inosine monophosphate dehydrogenase enzyme	Hepatitis C	(Singh et al., 2020)
Remdesivir	Suppresses the RNA-dependent RNA polymerase (RdRp)	Hepatitis C	(Beigel et al., 2020)
Lopinavir/ ritonavir combination	Suppresses chymotrypsin-like protease	Human immunodeficiency virus (HIV)	(Ortega et al., 2020)
Oseltamivir	Neuraminidase inhibitor	Influenza	(Indari et al., 2021)
Darunavir	Suppresses chymotrypsin-like protease	HIV	(Singh et al., 2020; Triant and Siedner, 2020)
Nirmatrelvir/ Ritonavir combination (Paxlovid)	Inhibits 3-chymo-trypsin-like cysteine protease (3CLpro)	Coronavirus disease 2019 (COVID19)	(Singh et al., 2022)
Molnupiravir	Inhibits RdRp	Influenza	(Sheahan et al., 2020)

ribavirin can cause inosine monophosphate dehydrogenase enzyme suppression that regulates guanosine triphosphate pools. It has been observed that the depletion of the intracellular GTP pool can cause indirect suppression of the viral RdRp enzyme. Ribavirin also has the capacity to interfere with mRNA capping. Intravenous administration of ribavirin 2 to 3 times per day at a dose of 500 mg for over 10 days in combination with interferon-α or lopinavir/ritonavir provided more resistance to COVID19 individuals against respiratory distress syndrome and even death. Ribavirin has an oral bioavailability of 52 % owing to its hepatic first-pass metabolism. This drug contains a half-life of 3.7 h. A common adverse effect of ribavirin is hemolytic anemia, which requires a reduction of its dose. Creatinine clearance of the patients receiving ribavirin treatment should be closely monitored because of the associated risk of renal impairment. Other risk factors during ribavirin therapy include low body weight, female gender, reduced renal function, and older age (Singh et al., 2020). Unfortunately, ribavirin exhibited teratogenic effects in animal studies, thus usage of this drug ought to be avoided during pregnancy. Other treatment-associated common adverse effects include inhalation, pulmonary edema, and bronchospasm. Depression, anorexia, skin rashes, thrombocytopenia, and neutropenia are the other ribavirin treatment associated with minor adverse effects. A CT involving various combinations in treating individuals with mild to moderate COVID19 including interferon-alpha + lopinavir/ritonavir + ribavirin, interferon-alpha + ribavirin, and interferon-alpha + lopinavir/ritonavir revealed that lopinavir/ritonavir + ribavirin exhibited substantial gastrointestinal adverse effects.

7.2. Remdesivir

Remdesivir, a nucleotide analogue prodrug, is the first antiviral drug that has been US FDA-approved to treat both pediatric (aged 12 years or more) and adult patients with COVID19. EMA also approved this drug to treat hospitalized pediatric patients (aged 12 years or more) and adult patients suffering from severe COVID19 while there are no available therapeutic alternatives. This antiviral drug already demonstrated its efficacy against multiple viruses including MERS-CoV, SARS-CoV, and Ebola. Remdesivir was originally developed to treat hepatitis C. In CTs, this drug was further studied to evaluate its efficacy against Ebola, however the development of this drug was discontinued because of the lack of considerable efficacy (Pardo et al., 2020). Cellular enzymes

convert the masked monophosphate form of remdesivir into the bioactive triphosphate form, which then becomes able to compete and mimic adenosine for inclusion of chain within the catalytic region of viral polymerases. This drug plays the role as a nonobligate chain terminator. In addition, it has a good pharmacokinetic profile and an extended half-life that makes this drug appropriate for systemic administration. Remdesivir has been considered as an auspicious drug candidate since the beginning of the COVID19 pandemic. The repurposing of remdesivir against SCV-2 mediated the registration of phase III CTs with this drug in early 2020. Remdesivir has been extensively studied in numerous CTs to evaluate its potential to treat COVID19 (Burki, 2020). Unfortunately, the findings of these CTs were sometimes debatable and controversial in terms of the effects on overall mortality. Moreover, several mild to moderate adverse effects were observed in the CTs associated with remdesivir use including constipation, respiratory failure, hypotension, kidney injury, anemia, nausea, and hepatocellular toxicity. However, recent findings suggest that remdesivir can be safely administered in hospitalized individuals with COVID19 (Y. Wang et al., 2020). The Solidarity CT with remdesivir concluded its lack of efficacy, however it was also summarized that remdesivir can shorten the recovery time by 4–6 days.

7.3. Lopinavir/ritonavir combination

Both ritonavir and lopinavir act as antiretroviral protease inhibitors and their combination was originally US FDA-approved in 2000 in the treatment of HIV patients. In the human body, the host proteases rapidly degrade lopinavir, therefore it is given at a lower dose with ritonavir. This combination ensures the long active time of lopinavir via suppressing the cytochrome P450 enzymes. The major proteases of HIV are aspartic proteases, whereas cysteine proteases are the major proteases of coronavirus. Protease inhibitors that are used in HIV therapy for nonspecific inhibition of proteases also demonstrated their efficacy in COVID19 treatment (Ortega et al., 2020). Lopinavir shows comparable binding energies against the proteases of both HIV-1 and SCV-2. Treatment with the lopinavir/ritonavir combination resulted in substantial virus clearance in individuals with COVID19. Interestingly, it was demonstrated that the condition of a 47-year-old COVID19 patient rapidly improved following treatment with the lopinavir/ritonavir combination, who previously failed to respond to other therapies including interferon and methylprednisolone therapies (Han et al., 2020). In Zhejiang province of China, the lopinavir/ritonavir combination was administered with interferon α in 14 patients, where the average hospital stay was 2 weeks and all participants with COVID19 were cured (Qiu et al., 2020).

Nonetheless, lopinavir/ritonavir treatment did not ameliorate the mortality rate in another CT involving 199 participants with severe COVID19 (Cao et al., 2020), some COVID19 patients even experienced adverse drug effects including gastrointestinal disturbances. A different trial was carried out with 4 individuals with COVID19, where patients were orally administered with arbidol (3 times per day, 0.2 g), lopinavir (400 mg)/ritonavir (twice a day, 100–400 mg), and Shufeng Jiedu capsule (a Chinese traditional medicine, 2.08 g was administered three times per day) as a combined therapy for 6–15 days (Z. Wang et al., 2020). In this trial, it was reported that 3 patients exhibited marked amelioration in symptoms of pneumonia and substantial amelioration in severe pneumonia was observed in the remaining COVID19 patient (Z. Wang et al., 2020). Poor bioavailability is a common problem observed with most of the HIV protease inhibitors owing to the extensive metabolism via microsomal CYP3A4 enzymes. In addition, any other agents that suppress or induce these metabolizing enzymes can also affect the effectiveness of these HIV protease inhibitors. Treatment with protease inhibitors can result in several side effects including hypercholesterolemia, hypertriglyceridemia, diabetes, vomiting, and diarrhea. Severe hepatic injury can also occur associated with the treatment. Thus, more experimental and clinical studies are essential to demonstrate their benefits in COVID19 treatment. Gastrointestinal disturbance and diarrhea are most commonly observed with the lopinavir/ritonavir treatment. Other minor side effects include headache, asthenia, skin rashes, dyslipidemia, as well as increased levels of liver enzymes. Furthermore, treatment with lopinavir/ritonavir can increase the level of alanine aminotransferase, which can result in mild hepatotoxicity. Single-use of ritonavir at an increased dose of 600 mg twice daily might elevate the risk of severe hepatotoxicity. Retinal pigment epitheliopathy can rarely occur with the ritonavir treatment at a high dose (Singh et al., 2020).

7.4. Favipiravir

In 2014, favipiravir (an antiviral drug), a synthetic prodrug, which was developed and approved in Japan to treat influenza. Favipiravir has the ability to effectively inhibit RdRp, which showed a selectivity index of over 6.46 and an EC_{50} value of 61.88 μM in the case of COVID19 treatment (M. Wang et al., 2020). Despite high EC_{50}, favipiravir can be further tested in animal studies owing to its effectiveness against the Ebola virus. in a mice model, favipiravir showed 100 % efficacy against the Ebola virus even though this antiviral drug had increased EC_{50} in Vero cells. Various combinations of this drug including baloxavir + favipiravir, interferon-α + favipiravir have been evaluated in several randomized trials. In China, favipiravir was approved on February 15, 2020 in the treatment of patients with COVID19, as this drug markedly decreased the sickness of individuals with COVID19 (Dong et al., 2020). Favipiravir is currently unapproved in the UK and USA. However, because of the broad-spectrum antiviral therapy of favipiravir, the US FDA has granted its use as an investigational new drug. Favipiravir suppresses a wide range of strains of influenza virus by acting as a nucleoside precursor. This drug exerts its antiviral effect through its nucleotide triphosphate form by directly suppressing the activities of RDRP in the transcription and replication of influenza A virus and causing fatal mutations within the viral genome. However, more studies are required to identify its precise and detailed mode of action and the interaction of favipiravir with the viral polymerase and nucleotide.

Favipiravir has an elimination half life of 2 to 5.5 h, while its oral bioavailability is around 100 %. Favipiravir's plasma protein binding in humans is 54 % and it goes through hepatic metabolism primarily via aldehyde oxidase and partway via xanthine oxidase and kidneys excrete its inactive oxidative metabolite (T-705 M1). In a study, it was observed that the time to maximum drug concentration, elimination, and kinetics of absorption of favipiravir are altered when used against the Pichindé arenavirus. Moreover, an elevated level of T-705 was observed in infected animals (Gowen et al., 2015). The drugs that go through metabolism via aldehyde oxidase including famciclovir, sulindac, citalopram, zaleplon, amitriptyline, propafenone, verapamil, amlodipine, felodipine, cimetidine, estradiol, tamoxifen, and raloxifene might increase the concentration of favipiravir. An elevated area under curve of acetaminophen has been reported when it is co-administered with acetaminophen perhaps because of the favipiravir-mediated sulfate transferase suppression (Du and Chen, 2020). in guinea pigs, oral administration of favipiravir did not result in any toxicity when administered 500 mg/kg per day for 10 days (Mendenhall et al., 2011). Indeed, the equivalent human dose of this drug is 108 mg/kg/day, which is much higher as compared to the recommended dose for COVID19 on first day (53 mg/kg/day). Nonetheless, the usage of favipiravir might be approved following the availability of more CT data (Singh et al., 2020).

7.5. Oseltamivir

Oseltamivir is a neuraminidase inhibitor and the US FDA approved this drug to treat seasonal flu. This antiviral drug is effective against multiple influenza virus strains. In an in vitro study, an IC_{50} value of 0.1–4.9 nM was observed with oseltamivir against H5N1 influenza. Nonetheless, in an in vivo study, a higher dose and longer duration of

treatment were required against H5N1 influenza. There is a deficiency of in vitro studies with oseltamivir against COVID19. Multiple CTs have been carried out with oseltamivir as part of a combination therapy. However, in a study, oseltamivir did not exert a positive impact on COVID19 treatment. Indeed, 20 CTs with this drug have been registered as a possible treatment against COVID19 (Indari et al., 2021).

7.6. Darunavir

Darunavir (an antiviral drug) was originally US FDA-approved for the HIV treatment. This antiviral suppresses non-peptide protease, which ameliorates the binding affinity and decreases the dissociation rate. These properties make this drug more potent than its counterparts. Darunavir was identified by using computational methods, which showed this drug's incredible hit for suppression of SCV-2′s chymotrypsin-like protease. However, the findings of a structural analysis did not observe any binding between SCV-2 protease and darunavir. In Shanghai, a drug screening based on enzymatic activity assay and *in silico* experiment showed 30 potential agents with antiviral properties against SCV-2 including darunavir. Furthermore, darunavir's therapeutic doses of darunavir are too low to exert cytotoxic actions, which provides a wide margin of safety. This drug also suppressed the *in vitro* replication of SARS-CoV2 at 300 μM concentration by 280 folds in comparison with the untreated group (Khan et al., 2021). In Italy, along with other supportive therapy and anti-viral drugs, darunavir was administered 600 mg twice daily for clinical management of individuals with COVID19, which increased the modified early warning score from below 3 to over 4 (Nicastri et al., 2020). Following oral administration, darunavir is absorbed rapidly and possesses a 15 h terminal elimination half-life. Around 95 % of darunavir remains bound with plasma proteins and CYP3A4 mediates its metabolism. Thus, the bioavailability of darunavir can be increased because of the simultaneous administration of small doses of ritonavir, as ritonavir inhibits CYP3A4. A caution should be taken while giving darunavir with other CYP3A4 inhibitors, since there might be some contraindications. In a study, it was observed that there is a potential risk of myocardial infarction along with darunavir use in patients with HIV, which suggests an increased risk of cardiovascular disease with darunavir use. Thus, the prescription of darunavir needs to be carefully considered in individuals with existing cardiovascular diseases (Singh et al., 2020; Triant and Siedner, 2020). Further studies are essential to explore the pharmacological profile of darunavir during the treatment of COVID19.

7.7. Nirmatrelvir/ritonavir combination

The Nirmatrelvir/ritonavir combination (Paxlovid) shows antiviral activity and has been US US FDA-approved in treating patients with mild to moderate COVID19. Nirmatrelvir is a 3C-protease inhibitor of SCV-2 and ritonavir plays a role as a boosting agent to improve the efficacy of nirmatrelvir (Singh et al., 2022). Paxlovid is a partially repurposed drug in which nirmatrelvir was specifically developed for COVID19 treatment by Pfizer. However, nirmatrelvir was discovered by utilizing the drug repurposing methods, where existing drugs were analysed for potential effects to counter the activities of SCV-2′s major protease. Preliminary studies exploring the effects of nirmatrelvir/ritonavir against SARS-CoV-1 exhibited good outcomes, therefore Pfizer evaluated its effect on SCV-2 to evaluate its effectiveness. Research data suggests encouraging initial results, where treatment with this combination resulted in an 88 % decrease in the rates of hospitalization and death in individuals unvaccinated against COVID19. It has been exhibited that paxlovid is also highly effective against the SCV-2′s Omicron variant. Vaccinated people were selected for the second trial of Paxlovid who had increased risks for COVID19. However, the trial findings were unsatisfactory, which failed to show any effectiveness in accelerating the recovery of individuals from SCV-2 infections. Nevertheless, Pfizer on June 30, 2022 applied for the US FDA's full authorization by including these two preliminary study findings (Singh et al., 2022). Paxlovid was further analysed by an Israeli study. In this study, Paxlovid was administered to 3902 patients. Among them, Paxlovid decreased hospitalization by 73 % in individuals who are over 65 years old, while Paxlovid failed to decrease the viral infection in participants aged 40 to 64 (Singh et al., 2022). Based on the study findings, WHO and the National Institutes of Health fervently endorsed the usage of Paxlovid in treating older COVID19 patients with an increased risk of hospitalization. Thus, Paxlovid was US FDA-approved in December 2021 for individuals aged over 65 with COVID19 (Hillary and Ceasar, 2023).

7.8. Molnupiravir

Molnupiravir is an antiviral drug and the drug was repurposed for the treatment of COVID19. US FDA authorized the emergency of molnupiravir to treat individuals with mild to moderate COVID19. It was reported that the cytidine analogue β-d-N4-hydroxycytidine (NHC) exhibits its function via viral mutagenesis. In addition, it is incorporated into new strands of RNA and leads to the addition of numerous mutations during subsequent replication rounds (Sheahan et al., 2020). Molnupiravir is an NHC prodrug that does not terminate the chains, which might explain the process through which it exerts the proofreading activity of coronavirus exonucleases. It has been confirmed that molnupiravir primarily suppresses coronaviruses through viral mutagenesis. In host cells, NHC has been reported to be metabolized into deoxy-NHC to result in mutations of DNA. Indeed, molnupiravir at EC_{50} values lower than 1 μM exhibited broad-spectrum antiviral properties against Ebola, influenza, and coronaviruses. Molnupiravir decreases the SCV-2 load in primary human airway epithelial cells, hence decreases the disease severity as well as lung injury in the ferret, hamster, and mouse models of SCV-2. Furthermore, 2 first-in-human studies of pharmacokinetics were carried out in phase 1b/2a placebo-controlled study with dose-escalation and a phase 1 dose-finding study of a five-day treatment course of oral therapy in healthy individuals among adult outpatients with COVID19 within five days of appearance of symptoms (Khoo et al., 2021; Painter et al., 2021).

In a phase II CT, virological endpoints among patients receiving molnupiravir 200 mg, 400 mg or 800 mg orally every 12 h were compared to placebo in 176 non-hospitalized study participants with COVID19 exhibiting fever and/or symptoms of respiratory illnesses. Out of 74 individuals with positive cultures, 6 out of 25 (24 %) placebo participants versus 0 out of 49 pooled molnupiravir participants exhibited positive cultures at day 5. As per the findings of this trial, 800 mg of molnupiravir was considered for further investigation. In October 2020, 2 major phase II and III trials with both non-hospitalized and hospitalized patients with SCV-2 infections were initiated. After reviewing the data by the safety monitoring board, the study with the hospitalized patients was not continued owing to the lack of effectiveness of molnupiravir. Following the completion of the CT involving non-hospitalized participants, it was concluded that early molnupiravir treatment lowered the risk of death or hospitalization in unvaccinated COVID19 individuals. However, because of the mutagenic potential (Tao et al., 2021), molnupiravir has not been assessed in women trying to get pregnant or pregnant women.

8. Limitations of approved repurposed drugs against SARS-CoV-2

Indeed, it is vital to identify and address the limitations of repurposed drugs for their potential to tackle the possible resistance because of the evolving nature of SCV-2. Mutations are continuously being reported in the SCV-2 genome, therefore addition of innovative cell-based therapies including stem cell-based therapies might prove beneficial in reducing the limitations of repurposed drugs to overcome long-term effects including vessel and tissue damage. More studies are required to modify and optimize to obtain better therapeutic effects. Techniques

used in precision and personalized medicines require further evaluation that particularly addresses varying responses of patients with COVID19 in terms of their immune response, genetic profile, disease history, co-morbidities, and recovery rate (Murmu et al., 2024).

In spite of extensive research and efforts in the drug repurposing field, still there are obstacles in the further use of repurposed drugs, such as delivery efficiency, safety, and therapeutic dosage. Finding the right dosage of a repurposed drug within the approved therapeutic window and confirming the therapeutic roles of the dosage in CTs are the major concerns. Rarely, novel drug-target interactions are reported within the authorized therapeutic margin. Typically, a higher dose is needed for effectiveness against novel indications and the need to reassess the routes of administration substantially determines further development of repurposed drugs. Moreover, if the required dosage to exhibit potency goes beyond that margin, it is mandatory to carry out safety studies. Therefore, sometimes it is not possible to find clinical usage of novel drug-target interactions of repurposed molecules within well-established safety ranges to obtain clear therapeutic improvements (Oprea et al., 2011). In most cases, the required effective levels to achieve antiviral actions are much higher as compared to those clinically attainable with the approved regimens. On the other hand, a fewer number of CTs are needed for repurposed molecules, however it is essential to carry out clinical studies on effectiveness against novel uses. Therefore, the major difference between drug repurposing and de-novo drug discovery is lowered and lessening the drug repurposing benefits. Repurposed drugs sometimes need to be administered through different routes in order to show the desired action against novel indications. The stability problem of the repurposed drugs also needs to be solved by utilizing proper carrier systems (Czech et al., 2019; Newman, 2018).

9. Future perspectives

There is a growing interest in the usage of drug repurposing in drug discovery because of the time-consuming and expensive conventional drug discovery process that involves greater failure rates. Indeed, drug repurposing accelerates the cost-effective detection of novel uses of existing drugs within a short period of time with lower attrition rates, which in due course benefits both the healthcare system and patients. Discovery of therapeutics should match the speed of the growing number of emerging viruses. Although a range of therapeutic agents were found to show effectiveness against multiple respiratory viral infections including certain strains of influenza and coronaviruses. There is a major challenge of resistance towards the available antiviral drugs. In addition, emerging strains of SCV-2 are causing pandemics and making it difficult to provide treatment with the existing drugs. Repurposing US FDA-approved drugs has already been demonstrated to be efficient in leveraging drugs with known safety profiles to control the COVID19 pandemic. Nevertheless, a proper route of delivery and delivery system needs to be used for reducing the dose and delivering the repurposed drugs to the target regions. An integration of toxicology and pharmaceutical sciences is required to overcome problems associated with safety and dosing (Parvathaneni and Gupta, 2020). Owing to the continuously evolving nature of SARS-CoV-2 and potential mutations, a continuous monitoring and review of the effectiveness of medications mentioned in this article are required, particularly in the emergence of a new variant of the virus.

10. Conclusions

Still there is no cure for the COVID19 pandemic despite the availability of a range of drugs and vaccines. Nevertheless, a number of drugs approved as a therapy for other diseases were evaluated in CTs against SCV-2 were successful, such drugs are regarded as repurposed drugs. Among them, the use of antiviral drugs was found to be promising including remdesivir, ribavirin, lopinavir/ritonavir combination, oseltamivir, darunavir, nirmatrelvir/ritonavir combination, and molnupiravir. These drugs have been demonstrated their safety and efficacy in multiple CTs against COVID19. Therefore, this article may help researchers and healthcare professionals in Saudi Arabia to select the potential US FDA-approved antiviral drugs to tackle COVID19 and emerging variants of SCV-2.

Abbreviations

ACE2, angiotensin-converting enzyme 2; COVID19, coronavirus disease 2019; CTs, clinical trials; EMA, European medicines agency; GRP78, glucose-regulated protein 78; HBV, hepatitis B virus; HSV, herpes simplex virus; NHC, β-d-N4-hydroxycytidine; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCV-2, SARS-CoV-2; US FDA, United States Food and Drug Administration; VOCs, variants of concern; β-CoV, beta variant of the coronavirus.

CRediT authorship contribution statement

Almonther Abdullah Hershan: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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