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Original Article

Molnupiravir, favipiravir and other antiviral drugs with proposed potentials for management of COVID-19: a concern on antioxidant aspect

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Abstract: COVID-19 is an important global public health problem that causes millions of infections worldwide. The specific antiviral drug for this new infection is still under research. Some new antiviral drugs, including molnupiravir and favipiravir, are proposed for usefulness in management of COVID-19. Additionally, some classic antiviral drugs used for other viral infections are also reproposed for the potentials for management of COVID-19. In the management of COVID-19, there are several pharmacological actions. An important consideration in antiviral therapy is the management of oxidative stress, which plays important roles in viral infections including to COVID-19. The analysis of antioxidative properties of alternative drugs for management of COVID-19 is interesting and can give basic data for further new antiviral drug researching. Here, the authors perform a molecular analysis on molnupiravir, favipiravir and other antiviral drugs with proposed potentials for management of COVID-19 to determine their antioxidative properties. Data from electron acceptor and donor calculation for each drug is used for further estimating overall antioxidative characteristic. Based on the present study, all studied drugs have overall antioxidative properties. Hence, the advantage of molnupiravir, favipiravir and other antiviral drugs with proposed potentials for the management of COVID-19 is their direct action on viral molecule via binding-blocking process as well as antixodiative process. For management of COVID-19 antioxidative stress, other non-antiviral drugs that are proposed for clinical advantage might also be useful.

Keywords: Molnupiravir, favipiravir, antiviral drug, COVID-19, antioxidant

Introduction

In late 2019, a new coronavirus infection started problem in Asia then expanded worldwide [1]. A pandemic occurs and already results in many million cases of COVID-19 around the world. Until 2021, there is still no effective specific antiviral drug for the management of COVID-19 [2]. COVID-19 is typically treated using different medications that have been repurposed based on pharmacological mechanisms that may be effective in the management of the new infection [2].

Recently, some new antiviral drugs are reported for possible usefulness in management of COVID-19. Molnupiravir and favipiravir are new hopes for management of COVID-19. With specific action on viral RNA, the two drugs are expected for effective management of COVID-19 [3, 4]. Additionally, some classical well-known antiviral drugs, such as antiretroviral drug for HIV infection control and antiviral hepatitis drugs, are also reproposed for applicability in management of COVID-19 [5, 6]. Pharmacologically, several drug targets are focused and tested for management of COVID-19 [5, 6]. There are several pharmacological actions that might be useful in infection management [5, 6].

Of several mechanisms, an important consideration in general antiviral treatment is the management of oxidative stress. Oxidative stress is a pathobiological process that is observed in many viral infections including COVID-19 [7, 8]. Regarding COVID-19, oxidative stress is associated with hyperinflammation clinical problems [8, 9]. Management of oxidative stress in COVID-19 is an interesting issue in molecular pharmacology. The study on antioxidative prop-

Table 1. Overall antioxidatve characteristic of studied antiviral drugs

Antiviral drugs	Data on molecular redox capacity		Overall antioxidative characteristic (unit)
	Molecular electron donor (unit)	Molecular electron acceptor (unit)	
Molnupiravir	4.5	0.4	4.1
Favipiravir	4.5	0.4	4.1
Lopinavir	4.4	0.4	4.0
Remdesivir	4.4	0.4	4.0
Tenofovir	4.1	0.4	3.7
Galidesivir	4.4	0.3	4.1
Ribavirin	5.0	0.4	4.6

erties of alternative drugs for management of COVID-19 can provide basic data for further new antiviral drug researching.

Materials and methods

The present study is a molecular pharmacology study. Here, the authors perform a molecular analysis on molnupiravir, favipiravir and other antiviral drugs (lopinavir, remdesivir, tenofovir, galidesivir and ribavirin) proposed potentials for COVID-19 treatment aiming at assessment on their antioxidative properties. Available primary data from molecular electron acceptor and donor calculation is used for further antioxidative property analysis. In the quoted primary study [9], a quantum molecular calculation based on density functional theory is done [10]. The electro-donating (ω-) and electro-accepting (ω+) powers, which representing molecular redox capacity, molecular electron donor and acceptor, are calculated. An estimation for overall antioxidative characteristic of each drug is done. For calculation, overall antioxidative characteristic is equal to "molecular electron donor property-molecular electron acceptor property".

Results

Based on data on molecular electron donor property and molecular electron acceptor property of each drug, molecular calculation for antioxidative characteristic of each drug is done. Estimated antioxidative characteristic of each drug is presented in **Table 1**. According to estimation, all studied drugs have a positive antioxidative characteristic, which means acting as an electro donor reducing agent. Of all studied antiviral drugs, ribavirin has the best overall antioxidative characteristic following by three drugs which has an equal antioxidative characteristic; galidersivir, molnupiravir and favipiravir.

Discussion

As a new emerging disease, searching for new effective drug for the management of COVID-19 is necessary. During COVID-19 pandemic, both repurposing of classical drugs and development of new drugs are performed aiming at containment of COVID-19 [2, 3]. Antiviral, antibiotic, and antiparasitic drugs have all been repurposed for use in COVID-19 therapy [2, 3]. Based on several pharmacological mechanisms, drugs are repurposed for possible role in managing COVID-19. Regarding antiviral drug, attacking on viral molecule, such as blocking RNA replication related enzyme, is the main molecular action for COVID-19 therapy [2, 3].

Currently, treatment for COVID-19 is still a challenge. Antiviral drug therapy is the hope. At an early phase of the COVID-19 outbreak, there was no antiviral drug. Some available drugs, including antibiotics and antiviral drugs, were proposed as possible alternative drugs for treatment of COVID-19 [11-16]. At the same time, several research attempts started. At present, there are many ongoing antiviral drug researches aiming at searching for a new effective antiviral drug against COVID-19 [17, 18]. Based on current data, some antiviral drugs might be useful for COVID-19 therapy. Examples of antiviral drugs that are reported for possible role in COVID-19 therapy are molnupiravir and favipiravir. Molnupiravir is a new oral antiviral drug that is expected to be effective against SARS CoV2 [19]. Available data showed that molnupiravir might help reduce hospitalization or death in COVID-19 [19]. Regarding favipiravir, it is an effective agent that inhibits the viral RNA. This drug is repurposed for management of COVID-19 and it is currently used in many countries [20].

For antiviral drug therapy, there are many molecular pharmacological mechanisms that are possible useful for management of infection [17, 18]. Antioxidative mechanism is also a

mechanism that might be useful [9, 17, 18]. The pathogenesis of COVID-19 is very and involve in pathological suppression of innate immune response and induction of oxidative stress, which further result in hyperinflammation [21]. Hence, application of an antioxidant might have possible role in COVID-19 treatment. In this article, the authors focus interest on oxidative stress management. During COVID-19 illness, oxidative stress might develop and result in tissue pathology [7, 8]. Hyperinflammation caused by an aberrant host response can cause severe COVID-19 disease, and a cytokine surge is linked to cellular oxidative damage [7, 8]. As a result, antioxidative treatment management has been postulated as a possible method for COVID-19 therapy [9]. Hence, a management by antioxidative therapy is also a proposed candidate mechanism that might be useful for COVID-19 therapy [9]. Antioxidant characteristic of currently available alternative drugs for management of COVID-19 is interesting. Basically, a drug molecule can be either electron donor or acceptor properties. This indicates that the drug may operate as a reducing or antioxidative agent, which is beneficial in the management of sickness, or as an oxidative agent, which may exacerbate illness [9].

Hence, assessment of overall drug antioxidative characteristic is interesting. Here, the authors performed an additional study to estimate antioxidative characteristic of molnupiravir, favipiravir and other alternative antiviral drugs. All studied drugs are antiviral drug that can have direct interaction on viral molecules. For example, target of molnupiravir and favipiravir is on viral RNA biological process. Adding to direct attack or binding-blocking process, a drug can also have an antioxidative characteristic that might be useful in management of oxidative stress occurring during infection. A drug with high overall antioxidative characteristic should have advantage in management of oxidative stress, which is an important problem causing poor outcome in COVID-19. Hence, a drug with high overall oxidative characteristic, such as molnupiravir, favipiravir and ribavirin in this study, should be benefit in reduction of poor clinical outcomes. There are some clinical evidences that those drugs, molnupiravir, favipiravir and ribavirin, are useful for limiting severe COVID-19 [19, 20, 22]. If the drugs with high overall antioxidative characteristic also have good direct binding-blocking property, those drugs will be a favorable drug for treatment of COVID-19. Examples of drugs with both high antioxidative characteristic and good direct binding-blocking process property are molnupiravir and favipiravir.

All of the antiviral medicines included in this study had positive antioxidative properties, according to the findings. As a result, these medications are expected to behave as antioxidants. However, this suggests that these medications can be used as an antioxidant or to treat COVID-19. Because each medicine still has its own direct molecular contact with the viral component, as previously described, a combination action is obtained. Indeed, some alternative classical drugs that are proposed for management of COVI-19 also have high antioxidative characteristics, but there is no direct molecular interaction with the pathogen. Good examples are chloroquine and hydroxychloroquine [23]. Although the medicine does not have a direct molecular interaction, it does have antioxidative properties that can assist regulate hyperinflammatory process-related oxidative stress at least.

Nevertheless, an important limitation of the present work is the lack of a control drug showing the normal overall antioxidative characteristic. In fact, a drug with low antioxidative characteristic might be useful if it has other molecular mechanism that counteracts the pathogen. As already mentioned, antioxidative characteristic is only one factor contributing to usefulness in the management of severe clinical problem in COVID-19. Other molecular factors, such as molecular binding property, are still important factors determining effectiveness of a drug against SARS CoV2.

Conclusion

All studied drugs have positive overall antioxidative properties. Therefore, advantage of molnupiravir, favipiravir and other antiviral drugs in COVID-19 therapy is based on both antioxidative characteristic and their direct actions on viral molecule. The pharmacological process of the drugs is via both binding-blocking process and antioxidative pathway. For the management of COVID-19 antioxidative stress, other non-antiviral drug that is reproposed for clinical usefulness might also have a role and should be further studied.

Disclosure of conflict of interest

None.

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