Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Cyclin dependent kinase inhibitors as a new potential therapeutic option in management of COVID-19

Dear Editor

Cyclin dependent kinases (CDKs) play a crucial role in regulation and progression of cell division cycle [1]. In general, viruses modify CDKs signalling pathway and regulate cell division cycle in a way that leads to enhancement of viral replication [1]. A recent evidence showed that the novel coronavirus (SARS-CoV-2) increases phosphorylation of CDK2 which affects its activities and subsequently leads to cell cycle arrest [2]. The same effect was observed with coronavirus infectious bronchitis virus and other RNA viruses [2]. Host Cell division cycle arrest provides supply of essential nucleotide and DNA repair and replication proteins which are essential for viral replication [2]. It has been noticed that CDKs are required for replication of DNA and RNA viruses [3]. Experiments showed that cyclin dependent kinase inhibitors (CDKIs) decrease replication of DNA viruses such as cytomegalovirus, herpes virus and varicella-zoster virus [1]. Furthermore, CYC202 and flavopiridol (CDKIs) block viral replication of RNA viruses, such as HIV-1 virus [4]. In fact, CDKIs inhibit viral replication by targeting host cellular proteins rather than viral proteins [5]. Therefore, CDKIs have a broad antiviral effect compared with conventional antivirals because of lack of specificity [3]. The other advantage of CDKIs in comparison with antivirals is less risk of development of viral resistance as CDKIs do not target viral proteins [3]. CDKIs inhibit strains of HIV-1 and herpes simplex virus-1 which are resistant to conventional antivirals [5]. Despite the high resistance rate of influenza A virus to most of Food and Drug administration (FDA) approved antivirals, Treatment of human A549 cells with CDKIs such as dinaciclib and flavorpiridol exhibited a strong antiviral effect against different strains of influenza A viruses. [6]. Interestingly, when CDKIs are used in combination with conventional antiviral drugs, they show additive antiviral effect [3]. Based on these observations, CDKIs can be considered as a potential novel therapeutic route in management of novel coronavirus disease 2019 “COVID-19” as they have a different mechanism of action which provides more advantages over the use of conventional antivirals.

There is limited evidence for the possible beneficial effect of CDKIs in management of COVID-19. It is argued that CGP-604747 drug, a CDKI, might have a role in management of lung injury induced by COVID-19 [7]. RNA sequencing of human lung tissues from two COVID-19 patients showed that CGP-604747 decreased expression of markers genes for lung injury [7]. Moreover, dinaciclib showed a strong antiviral activity against SARS-CoV-2 in two cell lines [2]. Although these findings are considered as promising results, the therapeutic effect of this drug class cannot be confirmed without randomised control trials (RCTs) to prove the efficacy of CDKIs. As CDKIs interfere with cell cycle regulation, there is a concern that this drug class might have a cytotoxic effect. Low molecular weight CDKIs such as flavopiridol and roscovitine showed no toxicity in human clinical trials against cancer [3]. However, CDK 4/6 inhibitors such as palbociclib, ribociclib and abemaciclib, had few significant adverse events during the management of breast cancer, which include neutropenia, prolongation of QTc interval and hepatotoxicity [8]. Therefore, RCTs are required to test the safety of using CDKIs to manage patients with COVID-19 on short-term basis.

In conclusion, CDKIs can be considered as a new treatment option in COVID-19 based on their proven experimental antiviral effect, broad spectrum antiviral activity, less risk of development of viral resistance and relative safety profile according to the results from cancer clinical trials. Therefore, a randomised clinical trial should be conducted in patients with COVID-19 to test the efficacy and safety of this drug class in management of this viral disease.

Authors contribution

Gargouri, M: designed the main ideas of the study and revised the manuscript for important intellectual content. Alzwi, A: revised the manuscript for important intellectual content. Abobaker, A: drafted the initial manuscript

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Declaration of Competing Interest

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