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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Plausible mechanisms of Niclosamide as an antiviral agent against COVID-19

Sai Kiran S.S. Pindiprolu[a], Sai Harshini Pindiprolu[b,*]

[a] School of Pharmaceutical Sciences and Technologies, JNTUK, Kakinada, India
[b] Sree Sai Dental College and Research Institute, Srikakulam 532001, Andhra Pradesh, India

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ABSTRACT

Corona virus disease 2019 (COVID-19) pandemic caused 18 440 deaths world wide as of 25 March 2020 and posing a serious threat to public health. There is a need, therefore, for effective therapeutic strategies to cure this disease. However, high attrition rates, substantial costs and slow pace are the major limitations of novel drug discovery. Drug repurposing, by employing 'old' drugs to treat 'new' diseases is an attractive approach in drug discovery. Niclosamide (NIC) is an approved anti-helminthic drug with diverse antiviral mechanisms. In this work we hypothesize, the potential antiviral mechanisms of NIC against COVID-19.

Introduction

Coronaviruses (CoV) are divided into four genera, α and β CoV infect mammals, while γ and δ CoV tend to infect birds. There are six human-susceptible CoVs are reported till date. α-CoVs, HCoV-229E and HCoV-NL63, and β-CoVs, HCoV-HKU1 and HCoV-OC43 causes mild respiratory symptoms similar to a common cold. The other two known β-CoVs, SARS-CoV and MERS-CoV are responsible for severe and potentially fatal respiratory tract infections [1–3].

Corona virus infectious disease 2019 (COVID-19), caused by novel corona virus, SARS-CoV-2 is an emerging infectious disease posing a serious threat to public health [4]. SARS-CoV-2 is a ß-corona virus, first identified in Wuhan, China. Recently world health organisation (WHO) declared COVID-19 as a pandemic. As of 25 March 2020, there were nearly 18 440 deaths occurred worldwide due to COVID-19. However, there are no clinically approved vaccines or therapeutic agents are available for treating COVID-19 [5,6]. Researchers, therefore, focused on discovery of novel anti-viral agents against this pandemic. However, high attrition rates, substantial costs and slow pace are the major limitations for discovery of new drugs against this emerging pandemic [7].

Drug repurposing/repositioning is a strategy of identifying newer therapeutic applications for existing clinically approved drugs [8]. This can be an effective approach to accelerate drug discovery process against emerging pandemics like COVID-19. Niclosamide (NIC) is an FDA approved anthelmintic drug. Recent drug repurpose screening identified NIC as an antimetabolite, antibacterial and anticancer agent [9,10] Compelling body of evidences also suggest NIC also possess broad spectrum antiviral properties including SARS-CoV (IC_{50} = 1.56 μM) [11,12]. Recently, it was also reported that, NIC exhibited *in vitro* antiviral activity against SARS-CoV-2 (IC_{50} = 0.28 μM) [13]. NIC, therefore, can therefore be a potential drug candidate for COVID-19. The plausible therapeutic mechanisms by which NIC acts as an antiviral agent against COVID-19 were presented in this work.

Plausible antiviral mechanisms of NIC against COVID-19

Spike (S) protein, 3C-like main protease, NTPase/helicase, RNA-dependent RNA polymerase (RNA replicase) and host receptors are the crucial drug targets of SARS-CoV-2 [1,14]. The following pharmacological mechanisms may contribute to the antiviral propensity of NIC against COVID-19.

i. NIC can block endocytosis of SARS-CoV-2

SARS-CoV-2 infects the permissive cells through the receptor of angiotensin converting enzyme-2 (ACE-2). Following receptor binding and induced conformational changes of S-protein, cathepsin L proteolysis occurs within endosomes for viral entry into host cells [15,16].

* Corresponding author.
E-mail address: drharshini93@gmail.com (S.H. Pindiprolu).

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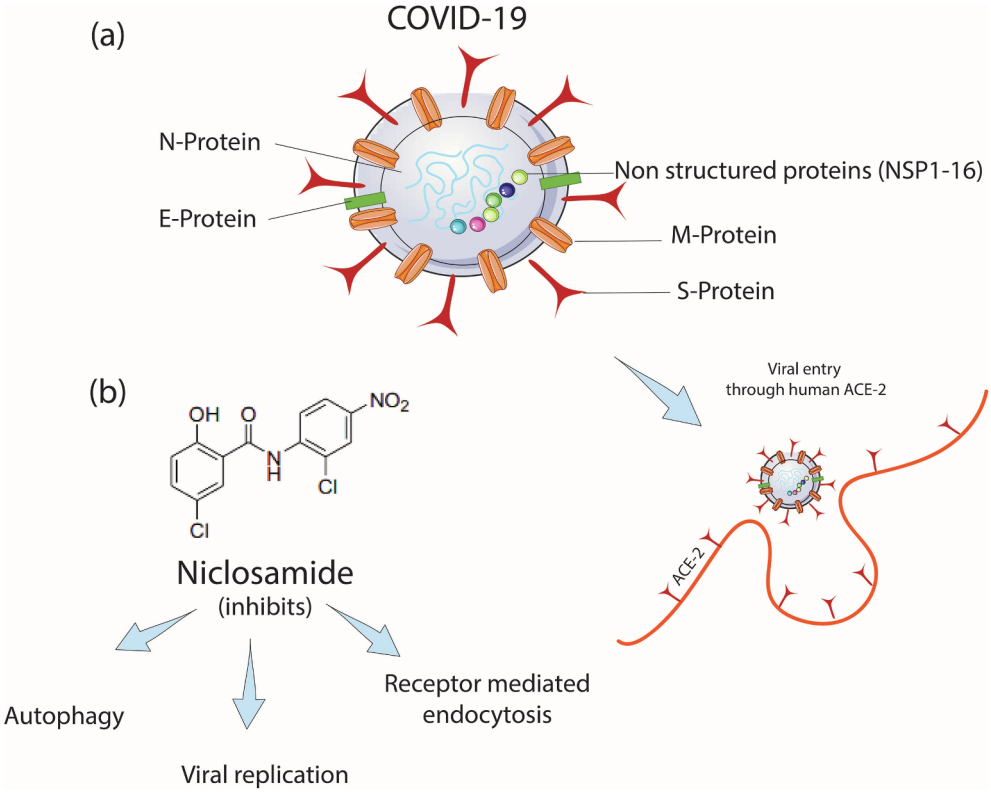

Fig. 1. (a) Structure of SARS-CoV-2; (b) plausible mechanisms of NIC to control viral replication of COVID-19.

NIC was reported to pH dependent endocytosis of human rhino virus (HRV) and influenza [17]. This mechanism may also contribute to the antiviral effects of NIC against SAR-CoV-2. The ACE-2 inhibitory activity of NIC, however, need to be confirmed.

ii. NIC can prevent autophagy of SARS-CoV-2 by inhibition of S-Phase kinase associated protein 2 (SKP2)

Recently it was reported that, NIC inhibited SKP2 and enhanced autophagy and reduced the replication of MERS-CoV replication [18]. This can be the potential antiviral mechanism of NIC against SARS-CoV-2 (Fig. 1).

Conclusion

Drug repurposing is an attractive approach for bringing new drugs quickly into market. Various drug repurposing screens identified NIC as a potential drug candidate against COVID-19. Prevention of viral entry by altering endosomal pH and prevention of viral replication by inhibition of autophagy are the plausible mechanisms of NIC against COVID-19. Clinical efficacy of NIC against COVID-19, therefore, need to be evaluated against COVID-19.

Competing interests

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109765.

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