Review Article

Amphotericin B as antiviral drug: Possible efficacy against COVID-19

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Submission: 13-04-2020
Accepted: 21-04-2020
Published: 18-06-2020

Abstract:

Since its discovery, amphotericin B (AmB) is still one of the most common first-line choices in treatment pulmonary mycoses for over seventh decades from discovery. AmB which is belonged to the polyene group has a wide spectrum *in vitro* and *in vivo* antimicrobial activity against fungi and parasites, resistance to AmB is rare despite extensive use. Recently, some studies focused on the potential antimicrobial action of AmB against some enveloped viruses such as human immunodeficiency virus, Japanese encephalitis virus, and rubella virus. Coronaviruses are enveloped positive-sense RNA nucleic acid viruses that have club-like spikes, characterized by a distinctive replication strategy; they are round and sometimes pleomorphic shapes. COVID-19 is regarding the new genera of coronaviridae that appear the first time in Wuhan, China, in early December 2019. Due to the continuous spreading of the novel COVID-19 with the exponential rise in death numbers, new therapeutic development is urgent, in general, there are no specific antiviral drugs or vaccines for 2019-novel coronavirus. Hence, this review may serve as an impetus for researchers working in the field of medical microbiology, vaccination, and antiviral drug design by discussion the most recent information about the antiviral action of AmB against COVID-19 infection as well as trying to a deep understanding of major properties, mechanisms of action, immune system responses, and antimicrobial efficiency of AmB. Since AmB is expected to alter the structure of the viral envelope, membrane integrity of cells, and internal cellular organelles, besides its other unique properties such as host immunomodulatory effects, so this review suggested that AmB as an effective anti-fungi drug thus may hold the promise of formulating a novel therapeutic option to treat COVID-19.

Keywords:

Amphotericin B, antimicrobial agents, antiviral drugs, coronavirus, COVID-19

Amphotericin B (AmB) is an ancient agent used over many decades in treating various fungal infections clinically in the human.[1] Low fungal resistance and broad-spectrum antifungal activities are the most valuable pharmaceutical characters that encourage continuous usage of AmB.[2]

Coronavirus is positive polarity RNA with envelope, it related with the zoonotic infection that belongs to coronaviridae, there are four known genera of coronavirus, but on January 10, 2020, a modern coronavirus in Wuhan in China have been emerged causing the severe pulmonary outbreak, it is recorded as COVID-19 by the World Health Organization. At present, no specific antiviral to treat this novel virus, organ support in seriously ill individuals and symptomatic management are fundamental steps in clinical treatment, however, some marketed drugs are used to prevent acute respiratory distress syndrome (ARDS) besides nutrient supplements.[3] Chloroquine and hydroxychloroquine recently used to treat some cases of COVID-19 infections with many side adverse.[4]

AmB destroys fungi and single-cell protozoa like *Leishmania* spp. by preferentially binding to ergosterol than cholesterol because it is high affinity to ergosterol. Another mechanism is by the production of free radicals inside fungi that causes oxygen

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.ATM_147_20

How to cite this article: AL-Khikani FH. Amphotericin B as antiviral drug: Possible efficacy against COVID-19. Ann Thorac Med 2020;15:118-24.

depletion.[5] Because AmB is had immunomodulatory effects, it capable of inducing pro-inflammatory mediators.[6]

Toll-like receptor 2 (TLR2) and CD14 have demanded AmBdependent inflmmatory stimulation of innate immune responses as well as TLR4 may also provide stimulation.[7] AmB produces a transcription of inflammatory cytokines such as interleukin (IL)6, tumor necrosis factoralpha (TNF-α), IL-1 β, besides chemokines such as IL8, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), nitric oxide, prostaglandins, and intercellular adhesion molecule1 from murine and human innate immune cells *in vitro*.[8] Besides AmB utilization as an antimicrobial agent to treat fungi and parasites, AmB and its derivatives against viral infection have been evaluated enhancing the phenomena of antiviral activity of AmB towards numerous viruses by different mechanisms of actions, some searches studied the efficacy of AmB to treat human immunodeficiency virus (HIV).[9] Japanese Encephalitis Virus (JEV),[10] herpes simplex virus (HSV),[11] and the Rubella virus.[10] This review focuses on understanding problems and challenges in COVID-19 infection treatment in the light by providing a rational and critical discussion on the available knowledge to get a clear future vision, appropriate solutions, and effective strategies regarding this novel virus management by revealing the possible promising role of AmB in this therapeutic branch.

Methods

To conduct a review article of the potential effects of AmB in treating viral infection and possible activity on COVID-19, the databases of Scopus, EMBASE, PubMed, and Google were searched with keywords of AmB, antiviral agents, and therapeutic option of COVID-19. We searched all the short and full articles that were scheduled to publish until April 2020.

General features of amphotericin B

AmB is naturally produced by soil actinomyces, *Streptomyces nodosus*.[12] It has yellowish color and aggregation nature with low solubility in water and many organic solvents, but solubility can be increased at pH under 2 or more than 11.[13] Over about five decades, the unique structure of AmB is staying prefers to use with high effectiveness clinically to treatment numerous fungal diseases in the human body[14,15] [Figures 1 and 2]. Low fungal resistance and broad-spectrum antifungal activities are the most valuable pharmaceutical characters encourage continuous usage of AmB.[16]

Deoxycholate AmB (D-AmB) is the first form of AmB developed in 1955 to use against systemic fungal infections.[17] In addition to the old formula of D-AmB, three lipid formulas were developed Liposomal AmB, AmB colloidal dispersion, and AmB lipid complex (ABLC) to limit the adverse effects of conventional AmB D-AmB in the human body and increase its therapeutic activity.

There is no clear vision about the mechanism of action to explain the antifungal effect of AmB although it has been used for many decades. The most accepted one is the activity of AmB adheres to the ergosterol of the fungal cell membrane causing dysfunction by forming pore ion channels.[17-20] Pore formation may lead to inhibition of fungal glycolysis and quick efflux of K+ and Mg+ ions inside fungal cells which increase the acidity consequently fungal cell death occurs[12] [Figure 3].

Characteristics and therapeutic options of coronavirus disease-19

Coronaviruses are enveloped un-segmented (+RNA) viruses, distinguished by club-like spikes extending from their top, an extraordinarily large genome of RNA, and a special strategy for replication. These are circular and rarely pleomorphic with a diameter of 80–120 nm.[21] In early December 2019, multiple cases of unknown origin pneumonia occurred in Wuhan, Hubei Province, China. Most of these patients have recorded entry to the Huanan Seafood Wholesale Market, which has sold lots of live animals. Severe acute respiratory syndrome coronavirus (SARS-CoV-2) appears to be optimized to bind human receptors ACE2, and the spike protein SARS-CoV-2 acts at S1–S2 by inserting 12 nucleotides at the functional polybasic (furin) cleavage site, which also leads to a predicted collection of three O-lined glycans around the site.[22]

At present, the number of cases due to the novel COVID-19 is still increased with time, so effective treatment methods and more effective strategies should be developed to prevent terrifying pandemic spreading among many countries worldwide.[23,24] Until this moment, no specific drug to treat this new virus, organ support in seriously ill individuals and symptomatic treatment are major steps in clinical management. To develop specific antiviral for treating novel COVID19, It may take a long time for an evaluation. However, some marketed drugs are good to prevent ARDS and boost immune responses with safety use such as metformin, firates, atorvastin, besides nutrient supplements.[3] Lopinavir is a protease inhibitor used to treat HIV infection that combined with ritonavir as a booster.[25]

Recently, studies demonstrated the clinical and virologic benefits of chloroquine and hydroxychloroquine in patients with COVID-19 compared to controls.[4,26] Both

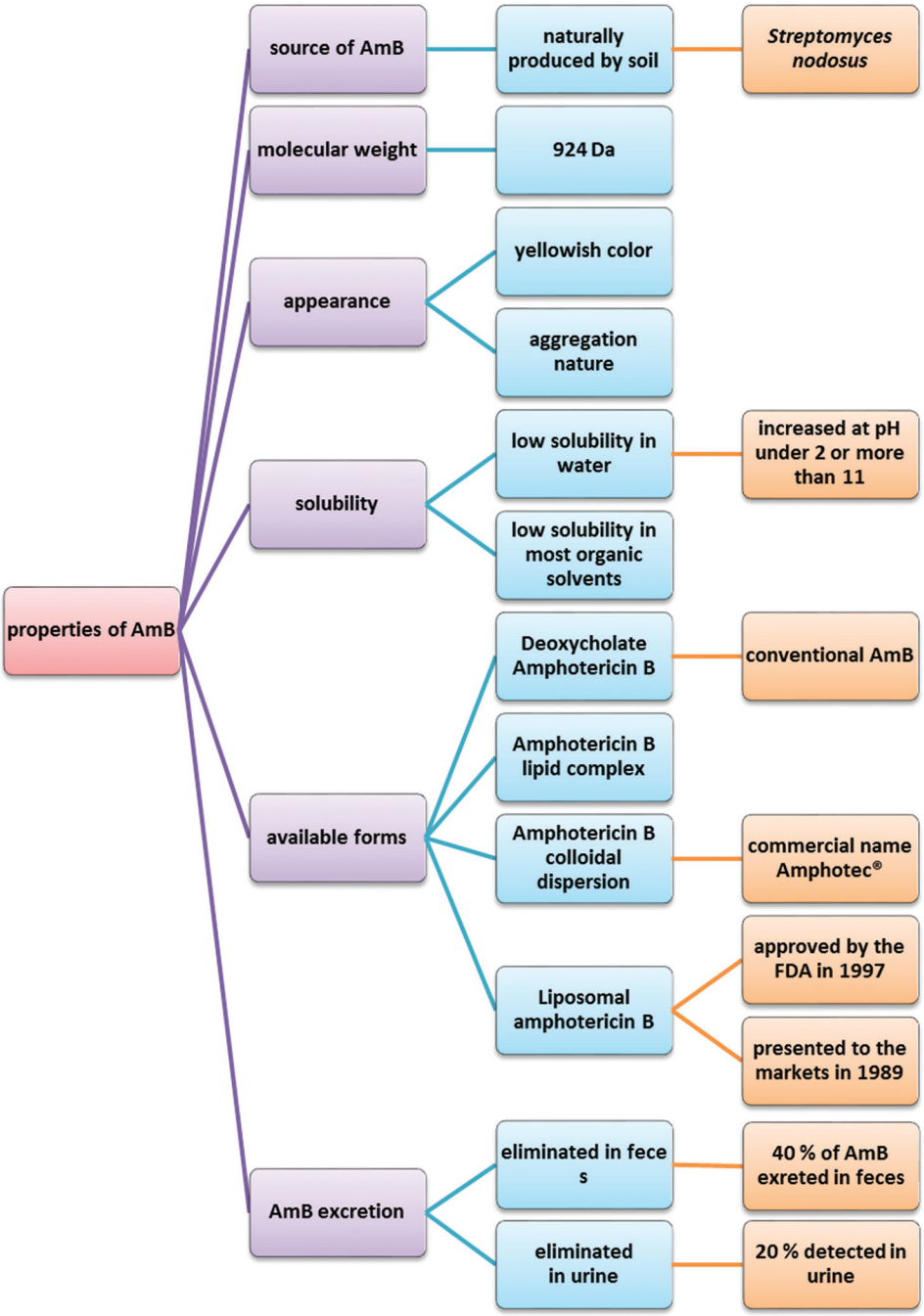

Figure 1: Some properties of amphotericin B

drugs have known safety profiles; the main side effect is cardiotoxicity (prolonged QT syndrome) after prolonged use in patients with hepatic or renal impairment and those who are immunosuppressed. Anyway, the activity and clinical safety of this drug in patients with COVID-19 remain unclear and must be confirmed by more clinical studies.

Amphotericin B and immune system modulation

AmB has potent immunomodulatory properties on the host cells *in vitro* and *in vivo* enhancing the immune response of the host. This effect of AmB is not only in the presence of the pathogen, but also when the causative agent is absent by stimulating the production of multiple mediators of the immune system.[6] However, mechanisms by which AmB activates the immune system still not fully understand. AmB and its derivatives can produce pro-inflammatory cytokines by interfering with the macrophage activation state. AmB increases TNF-α production that leads to the synthesis of superoxide dismutase, which produces the substrate of catalase like hydrogen peroxide.[27]

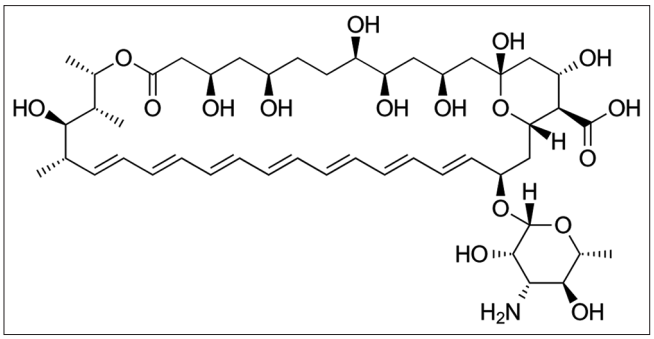

Figure 2: Structure of amphotericin B

The adjuvantic efficacy of AmB is applicable as a safe and effective adjuvant for human vaccines at a dose of 100 micrograms, act as TLR2 and TLR4-agonists; the immune stimulatory molecules would increase the repertoire of tools available for interrogating innate immune memory mechanisms, and produce further venues for vaccine adjuvant development.[28]

Antiviral activity of amphotericin B

Because AmB can affect cholesterol structure in viral envelopes and cellular membranes as well as intracellular organelles, it might have an antiviral effect. Indeed, its antiviral effect has been demonstrated in several enveloped viruses such as HIV, rubella viruses, JEV, and vesicular stomatitis virus (VSV) [Figure 4].

AmB inhibits the replication of the JEV at the postinfection step by interfering with viral replication or inhibiting the synthesis of viral proteins. JEV is a single-stranded RNA of 11 kb and 370 kDa with an envelope. The treatment of infected cells with 5 μg/ml of AmB, reduces 200-fold of infectious virus titer as well as the accumulated level of JEV envelope protein dramatically decreased in the infected cells. AmB might interfere with the synthesis and/or maturation of viral glycoproteins (envelope, prM, NS1) within the endoplasmic reticulum (ER) lumen by impairing the function of ER since the binding of AmB to the cholesterol in ER membrane would make it more susceptible to damage on viral infection.[10] Alternatively, AmB might change the microenvironment on ER that regarding the JEV replication site,[29] thus resulting in the inhibition of viral RNA replicase complex formation on ER.

The antiviral activity of AmB was exerted for HIV by binding to cholesterol in the lipid bilayer membrane of the HIV particles. AmB was also proposed to be effective in blocking early steps in HIV entry.[9,30] In another study, the antiviral activity of MS8209, a derivative of AmB, was observed in CD41 cells transfected with a lacZ gene caused by Type 1 infection with HIV. It has been shown that MS8209 prevents viral entry after receptor binding and possibly before viral-cell membrane fusion,

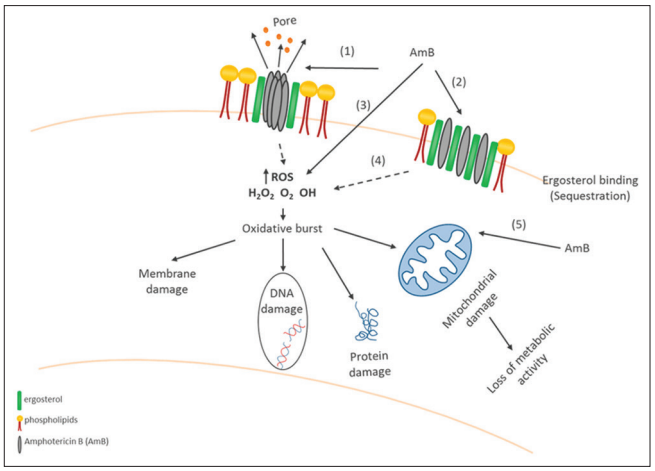

Figure 3: Mechanism action of amphotericin B

as both processes are mediated by HIV-1 proteins and CD4 envelopes.[30]

The binding of amphotericin B methyl ester (AME) changes the viral membrane properties. AME binding may directly block Vpu's ion channel activity or can indirectly alter Vpu's role through cholesterol/membrane binding, thereby disrupting the development of HIV1 particles. Vpu plays an important function in the pathogenesis of lentiviral *in vivo*.[31]

Using a liposomal encapsulated preparation of AmB (a polyene macrolide antibiotic) for the *in vitro* inhibition of HIV was evaluated. There was no clear difference in inhibiting HIV growth between the effective doses of the free form of AmB compared with the liposomal encapsulated formulation. Virus replication at a concentration of 5–10 μg/ml of the medications was blocked using colonies of murine leukocytes, the liposomal formulation demonstrated significantly decreased cytotoxicity.[32]

For rubella viruses, AmB at a late stage of virus replication revealed an antiviral impact against the rubella virus, while no antiviral activity was found against measles and mumps viruses that belong to paramyxoviridae.[33] These results suggest that AmB specifically prevents the replication of a certain enveloped virus while rubella, measles, and mumps viruses are all enveloped single-stranded RNA viruses composed of a membranous membrane, making them the main target of AmB.[10] The drug interacts with the viral envelope and at the early stage of virus infection, respectively, Fungizone acted in the late stage in the case of the rubella virus. E1 and E2 undergo modifications such as the addition and removal of oligosaccharides and fatty acids during posttranslational processing.[33]

AmB has an effect on the structural integrity of particles of the hepatitis B virus, viral aggregation, and surface

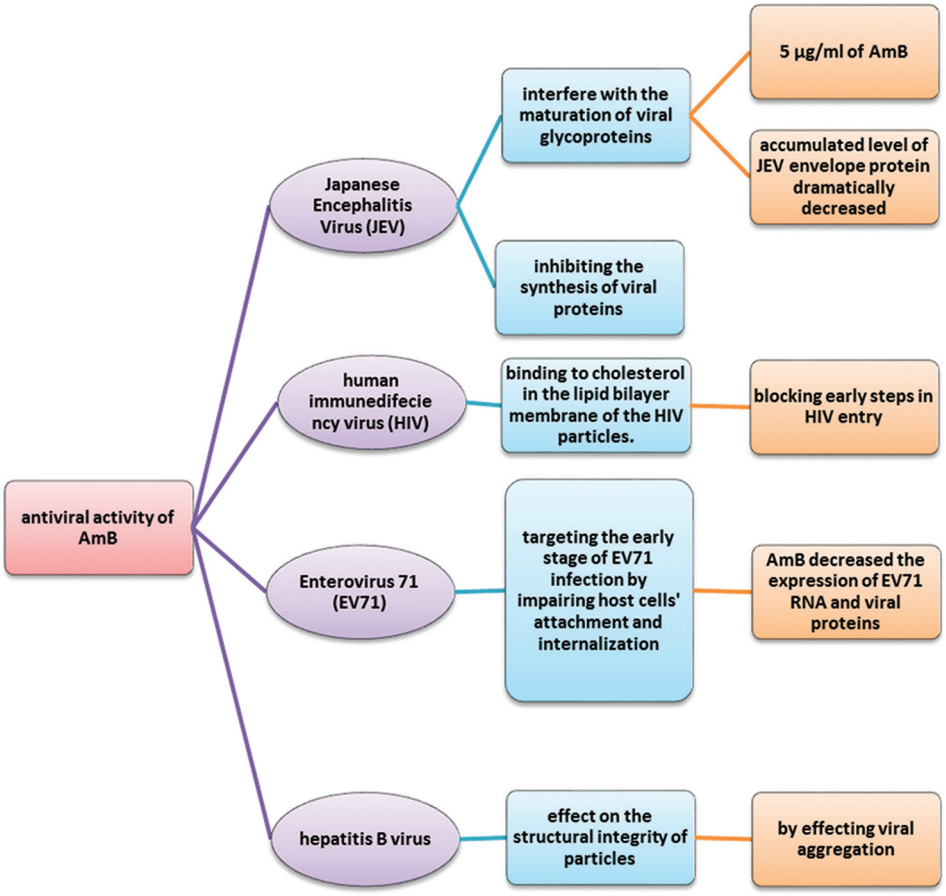

Figure 4: Mechanisms of actions of amphotericin B against some viral infections

antigen of hepatitis B but its antiviral activity has not been demonstrated.[34]

AmB demonstrated antiviral activity against virus replication of pseudorabies, potentiating the antiviral action of acyclovir. The optimum polyene antibiotic concentrations expressing the potentiating effect were lower than needed for the induction of K+ leakage from the cells. There was no evident AmB induces stimulation of thymidine incorporation into infected BHK-21 cells. The model presented may be useful to study the potentiation phenomenon of polyene macrolide antibiotics.[35]

The water-soluble methyl ester of AmB inactivates VSV in association with morphological alterations of the envelope, one-fourth part of concentrated VSV and three-fourths part of AME at a final concentration of 100, ug/ml were prepared and incubated for 60 min at 4 and 37°C, respectively. Exposure of VSV to AME at a concentration of 100, mg/ml resulted in a 100-to 1,000-fold decrease in infectivity, depending on the temperature at which the drug-virus interaction took place. Morphologically, many damaged particles were seen after exposure to AME.[36]

For HSV, AME was analyzed for its anti-HSV activity in the rabbit cornea, which was considered a semisynthetic derivative of AmB. It was extremely active in the prevention of HSV lesions, and its antiviral activity was linearly correlated with AME's logarithmic dosage. At least, the antiviral function was similar to that of 5-iodo-2'-deoxyuridine (IDU). AME should be successful against IDU-resistant HSV and herpetic keratouveitis is suggested.[11]

Infections with Enterovirus 71 (EV71) lead to cardiopulmonary symptoms and mortality in young children, the strong inhibition of EV71 with polyene antibiotic AmB. AmB decreased the expression of EV71 RNA and viral proteins in RD cells and HEK293 cells. As a result, AmB inhibited the development of EV71 with an EC50 (50% effective concentration). In addition to EV71, AmB also strongly inhibited EV68. Results from mechanistic studies revealed that AmB was targeting the early stage of EV71 infection by impairing host cells' attachment and internalization of EV71. AmB, as an important anti-fungal drug, thus carries the possibility to treat EV71.[37]

AmB has a potential and promising branch in viral infection management including different enveloped

viruses. High concentrations of AmB formulations deposition as ABLC and L-AmB have been found in the lung tissue;[13] this means the low dose of AmB is required to reach demand concentration in the pulmonary tract. Low concentrations accompanied with few side effects if any as well as easily uptake by macrophage with a high rate of clearance from plasma and the safety of high dose (5 mg/kg/day). Thus, utilizing L-AmB or ABLC formulas as a novel therapeutic agent in the treatment of pulmonary disorders such as COVID-19 may be promising.

Conclusion

COVID19 is an emerging virus considered as a global public health emergency, which requires a collaborative higher level of responsive measures from all countries. Efficient communication, collaboration, and cooperation in implementing scientific evidence-based measures on the personal, national, and international levels are crucial. Urgent clinical trials on potential drugs for COVID19 are required; more research is urgently needed to better understand the better treatment of the COVID19 infection.

Although the viral envelope is derived from the host cell membrane, AMB appears to be relatively more toxic to the virion than to the host cell. Certain differences between the virion and the host cell may be responsible for this finding because the host cell may be able to repair AMB-induced membrane defects, as well as the viral envelope, is composed of a portion of the cell membrane that is altered from normal host cell composition and contains viral proteins, so the viral envelope might be an important strategy for the development of a novel antiviral drug.

The potential ability of AmB to inhibit different types of pathogens including some viruses can introduce a new drug with another choice to treatment COVID-19. No specific antiviral agent against COVID-19 will not be a problem anymore after complete proving the successful antiviral application of AmB against COVID-19.

AmB is ready for use and accessible. We noticed that most viruses that AmB targeted have envelopes and RNA nucleic acid; however, all may be similar in complexity and contain specific virus proteins that can be targeted by the medication protocol. Using AmB in modern branches and new applications is demanded because AmB is a potential antifungal agent with rare resistance, as well as its broad-spectrum activity toward many microbial infections.

As it is known, in viral infection immune system plays a crucial role in viral elimination and body defending, so using an antibiotic that has the ability to enhance immune response, activating innate immunity, stimulate pro-inflammatory responses; like AmB may be very important to protect from viral invasion such as COVID-19. It has strong immunomodulatory characteristics by triggering pro-inflammatory responses; this effect has been associated with protective effects. AmB acts during infection, not only on the pathogen but also on the host. This issue is of particular interest because patients affected by viral infections may be immunocompromised.

According to the previous findings regarding the efficacy of AmB to various viral infection with RNA nucleic acid besides unique properties of AmB to treat a viral infection, thus, using of AmB instead chloroquine and hydroxychloroquine in patients with COVID19 may give reduced side effects and may be promising branch to be evaluated clinically, this finding demands more studies in medical laboratories and clinical trials.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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