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Research Article

# Amphotericin B from antifungal to antiviral therapy: promising modern therapeutic branch

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## Abstract

**Introduction:** Amphotericin B (AmB) which belongs to the polyene group has a wide spectrum *in vitro* and *in vivo* antimicrobial activity against fungi and parasites, but resistance to AmB is rare despite extensive use.

**Material and methods:** Atotal of 2530 articles were investigated in PubMed ($n$ = 1525), Medline ($n$ = 705), and Google Scholar ($n$ = 300). From 2530 articles, only 61 studies were included in this review. All the short and full articles were searched that were scheduled to be published until April 2020.

**Results:** After its discovery, AmB has been one of the most common first-line choices in treating systemic fungal infection for over seven decades from its discovery. Recently, some studies have focused on the potential antimicrobial action of AmB against some enveloped and non-enveloped viruses, such as human immunodeficiency virus, Japanese encephalitis virus, herpes simplex virus, and Rubella virus.

**Discussion:** Among the invading pathogens, viruses constitute the most common ones,Due to the continuous spreading of viral infections with the rise in death numbers, new therapeutics development is urgent, as in general, some lethal viruses have no specific antiviral drugs or vaccines. So, this review may serve as an impetus for researchers working in the field of medical microbiology, vaccination, and antiviral drug design by discussing the most recent information about the antiviral action of AmB, as well as trying to provide a deeper understanding of major properties, mechanisms of action, immune system responses, and antimicrobial efficiency of AmB.

**Conclusion:** 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, this review suggested that AmB as an effective anti-fungi drug may hold the promise of formulating a novel therapeutic option to treat many dangerous viruses, including those for treating which there are no active drugs or vaccines.

## Keywords

Amphotericin B, antifungal drug, viral infection, antimicrobial agents, antiviral therapy.

## Introduction

Formulations of Amphotericin B (AmB) remain the first-choice agents for the management of pulmonary and systemic fungal diseases (Felton et al. 2014). AmB is an ancient agent used over many decades in treating various fungal infections clinically in the human (AL-Khikani and AL-Janabi 2019). Its low fungal resistance and

broad-spectrum antifungal activities are the most valuable pharmaceutical properties that encourage continuous usage of AmB (Lanternier and Lortholary 2008).

The ancient formula of AmB that contains deoxycholateAmB (D-AmB) was approved for clinical use by the FDA in the 1950s; then lipid formulas of AmB were developed in 1990, which provided more safety than liposomal Amphotericin B (L-AmB) (Torrado et al. 2008). Amphotericin B destroys fungi and single-cell protozoa like *Leishmaniaspp* by preferentially binding to ergosterol than cholesterol because of its high affinity to ergosterol. Another mechanism is by the production of free radicals inside fungi, which causes oxygen depletion (Sangalli-Leite et al. 2011). Because AmB has immunomodulatory effects, it is capable of inducing pro-inflammatory mediators (Mesa-Arango et al. 2012).

TLR2 and CD14 have demanded AMB-dependent inflammatory stimulation of innate immune responses, TLR4 may provide stimulation as well (Sau et al. 2003). AmB produces a transcription of inflammatory cytokines, such as IL-6, TNF-α, IL-1β, chemokines (IL-8, MCP-1, MIP-1β), nitric oxide, prostaglandins, and intercellular adhesion molecule-1 (ICAM-1) from murine and human innate immune cells *in vitro* (Arning et al. 1995).

Besides AmB utilization as an antimicrobial agent to treat fungi and parasites, and the use of AmB and its derivatives against viral infection, enhancing the phenomena of antiviral activity of AmB towards numerous viruses by different mechanisms of actions, some studies investigated the efficacy of AmB to treat human immunodeficiency virus (Konopka et al. 1999), Japanese encephalitis virus (Kim et al. 2004), herpes simplex virus (Shiota et al. 1976), and Rubella virus (Kim et al. 2004).

A virus is a submicroscopic infectious agent, replicating only within an organism's living cells. Viruses can infect all life forms, including bacteria and archaea, from animals and plants to micro-organisms (Koonin et al. 2006). Nearly 5,000 species of viruses have been identified in detail of the millions of virus types in the world (Lawrence et al. 2009). Viruses, considered the most numerous type of biological entities, are found in almost every ecosystem on the Earth (Breitbart and Rohwer 2005). There are difficulties in treating viral infections, and some viruses have no specific therapy (AL-Khikani 2020a, b).

This review focuses on understanding problems and challenges in the viral 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 viral infection management by revealing the possible promising role of AmB in this therapeutic branch.

## General features of AmB

Amphotericin B is naturally produced by soil actinomyces, *Streptomyces nodosus* (Hamill 2013). The common features of AmB are the yellowish color and the aggregation nature with low solubility in water and many organic solvents, but solubility can be increased at pH under 2 or over 11 (Torrado et al. 2008). For over about five decades, due to its unique structure, AmB has been preferred to be used with high clinical effectiveness to treat numerous fungal diseases in the human body (Baginski and Czub 2009; Volmeret al. 2010) (Figs 1, 2).

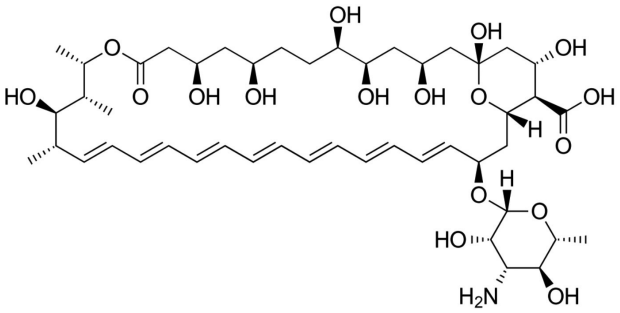


**Figure 1.** Structure of AmB.

The high rate of resistance of AmB has been observed in recent years against most common antibiotics (AL-Khikani 2019, 2020a, b), while AmB revealed low fungal resistance and broad-spectrum antifungal activities that are considered the most valuable pharmaceutical properties that encourage continuous usage of AmB (Volmer et al. 2010). In spite of the wide clinical use of AmB for more than five decades, its fungal resistance has been rarely recorded until now, compared with other antifungal agents (Ghannoum and Rice 1999; Cannon et al. 2007; Gray et al. 2012).

Some side effects associated with AmB are like those from other common antibiotics; these adverse effects are represented by nephrotoxicity caused by high dosees of AmB, which may reach 35 mg per day (Ghannoum and Rice 1999; Laniado-Laborín and Cabrales-Vargas 2009). It is excreted by both feces and urine without change, about forty percent of it is detected in feces, and another twenty percent is detected in urine; its molecular weight is 924 Da (Bellmannand Smuszkiewicz 2017).

More than 95% of AmB is protein-bound, mainly to albumin and low-density lipoprotein (Bekersky et al. 2002), administration of 1mg as a test dose before the therapeutic dose is required to detect intolerant patients, to eradicate high resistant mycoses; a dose of up to 1.5 mg per kg might be considered, but in these cases, long infusion of more than six hours is considered important (Bellmann and Smuszkiewicz 2017).

For several years, developing a novel oral Amphotericin B formula has been under way, which is considered effective in treating systemic mycoses infections in different animal models (Wasan 2020).

## Formula of AmB development

AmB was isolated from the soil of the Orinoco River region of Venezuela in the 1950s. DeoxycholateAmB

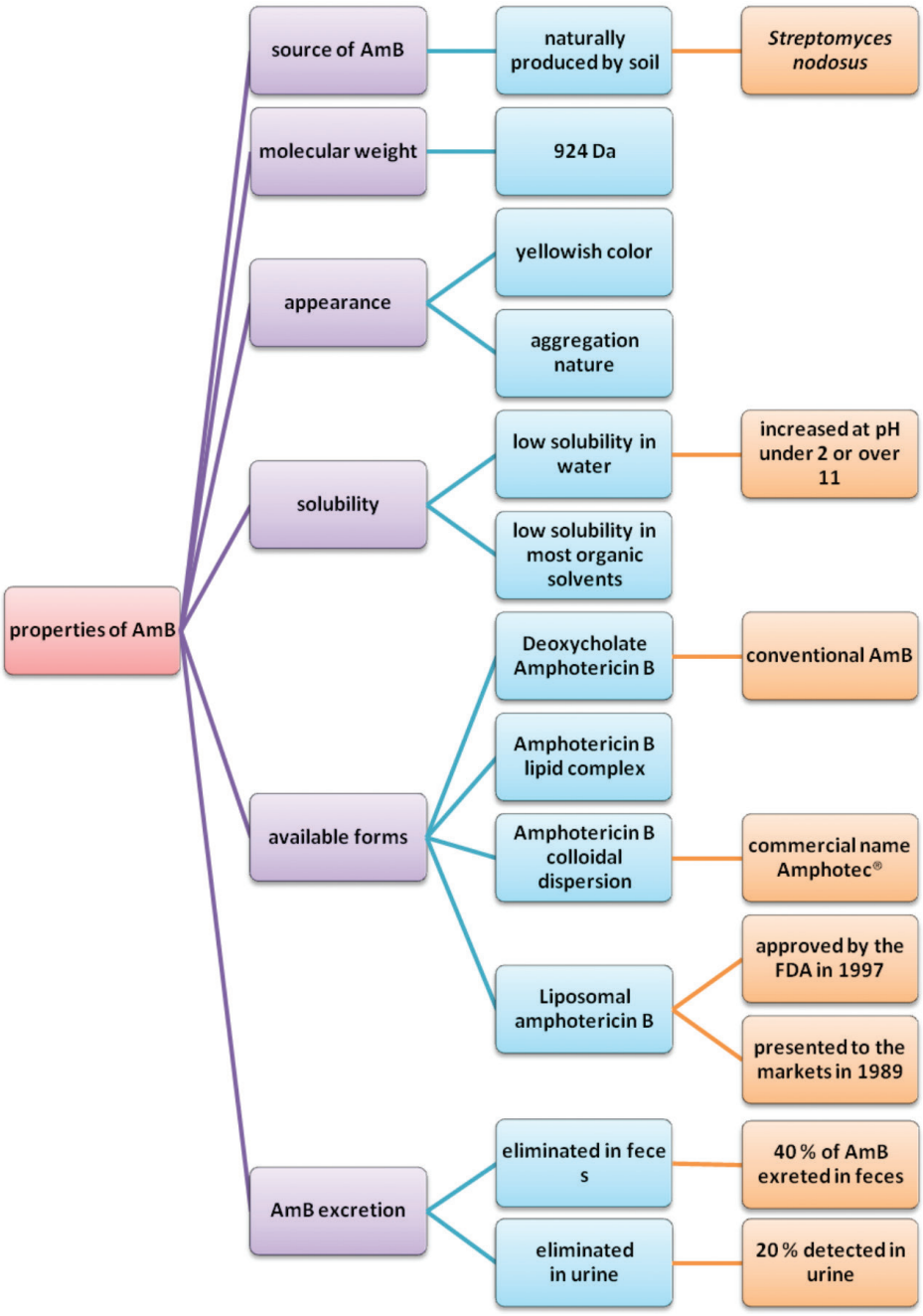


**Figure 2.** Some properties of AmB.

(D-AmB) is the first form of AmB developed in 1955 to be used against systemic fungal infections (Stone et al. 2016). It was soon approved of for clinical use by the FDA in 1958, though its structure was not known yet due to its broad-spectrum of antifungal activities (Volmer et al. 2010). Fungizone-Squibb is the first intravenous formula of D-AmB introduced to the markets in 1958 (Mesa-Arango et al. 2012).

In addition to the old formula of Deoxycholate Amphotericin B (D-AmB), three lipid formulas were developed: Liposomal Amphotericin B, Amphotericin B colloidal dispersion, and Amphotericin B lipid complex to limit the adverse effects of conventional AmB (D-AmB) in the human body and increase its therapeutic activity.

Liposomal Amphotericin B (L-AmB) is a developed form of the first AmB formula (D-AmB) to reduce the adverse effect (Stone et al. 2016). L-AmB was presented to the markets in 1989 as the first drug to manage leishmaniasis and then approved by the FDA in 1997 (Torrado et al. 2008). When L-AmB is used alone, it reduces nephrotoxicity (Moen et al. 2009). Using L-AmB is restricted by its high prices; also patents need monitoring nine days after the treatment begins (Kato et al. 2018).

Amphotericin B lipid complex (ABLC) is commercially called Abelcet, which has a ribbon-like structure and 1:1 molar ratio with tow phospholipids layers (Torrado et al. 2008). It was approved by the FDA in 1995. The risks to kidneys and lungs are very low compared with those

when using other formulas of AmB (Torrado et al. 2008), which may be due to a large size of the ABLC formula, making it easy for macrophages to uptake them,with a high rate of clearance from plasma; a safe dose required for ABLC is 5 mg/kg/day (Hamill 2013).

Amphotericin B colloidal dispersion (ABCD) is another formula of AmB, which has a commercial name of Amphotec, with an equal concentration of cholesterol phosphate (Torrado et al. 2008). The diverse effect of ABCD utilization resembles that of D-AmB, but it differs by a more rapid clearance from plasma through macrophage engulfment (Hamill 2013).

## Mechanisms of action of AmB

There is no clear vision of the mechanism of action to explain the antifungal effect of AmB, though it has been used for many decades. The most accepted one is that AmB binds to ergosterol of the fungal cell membrane causing its dysfunction by forming pore ion channels (Hartsel et al. 1993; Shimizu et al. 2010). Pore formation may lead to inhibition of fungal glycolysis and quick efflux of $K^+$ and $Mg^+$ ions inside fungal cells, which increasesthe acidity followed by fungal cell death (Hamill 2013) (Fig. 3).

The mechanisms of L-AmB begin to operate when the liposomal vesicle becomes attached to fungal cells in the infection site, then AmB is released from binding vesicle to adhere to ergosterol of fungal cell membrane and damage it (Gray et al. 2012).

Another mechanism of Amphotericin B involves the production of free radicals inside fungi (Sangalli-Leite et al. 2011; Mesa-Arango et al. 2012), which consequently leads to form oxygen depletion and superoxide anion, which in turn affects the cellular pathways of fungi (Haido and Barreto-Bergter 1989). Moreover, AmB has immunomodulatory properties that induce a pro-inflammatory response, which gives protection to the immunocompromised persons (Mesa-Arango et al. 2012).

## Immunomodulatory features of AmB

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 (Mesa-Arango et al. 2012). However, mechanisms by which AmB activates the immune system is still not fully understood.

Amphotericin B increases interferon production in mouse L929 cells, enhancing penetration of polyriboinosinic-polyribocytidylic acid of the cell membrane that acts as a trigger to interferon production; interferon titers were enhanced significantly by Amphotericin B at a dose of 5 ug/ml and increased almost 10-fold at 25 ug/ml (Borden and Leonhardt 1976).

Amphotericin B and its derivatives can produce pro-inflammatory cytokines by interfering with the macrophage activation state. AmB increases tumor necrosis factor-alpha production, which leads to the synthesis of superoxide dismutase which in turn produces the substrate of catalase like hydrogen peroxide (Clayette et al. 2000).

Besides AmB is capable of inhibition of fungal growth by direct killing mechanisms, so it is considered to directly

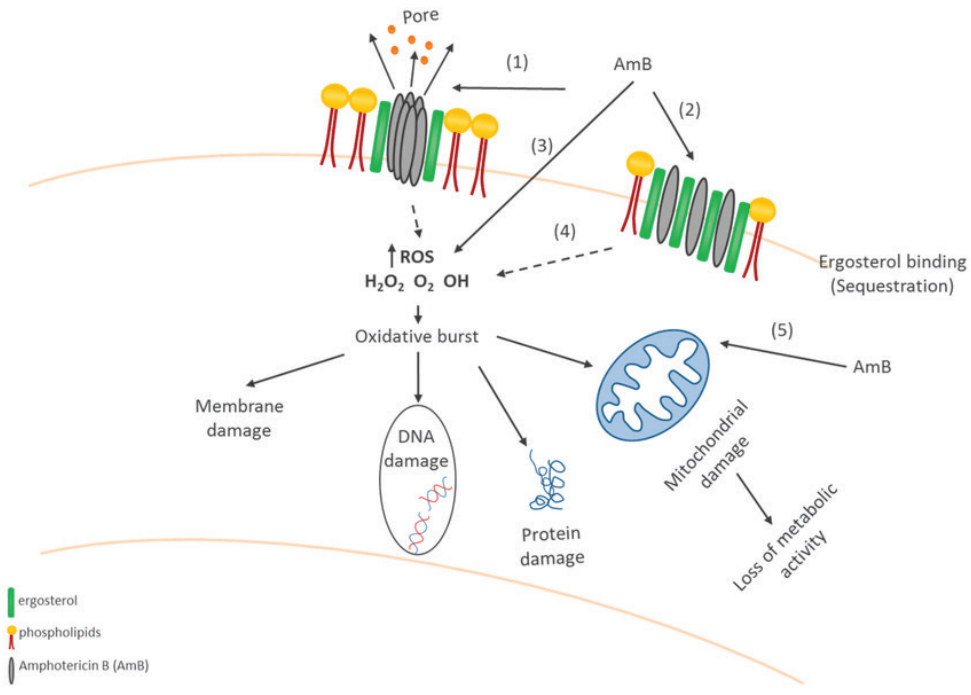


**Figure 3.** AmB mechanism of action (Lass-Flörl 2018).

activate the host's innate immunity; it has been reported to trigger interleukin-1 b (IL-1 b) secretion in monocytes, and it also induces potassium efflux from the cells, which leads to increasing IL-1 b secretion (Darisipudi et al. 2011).

The adjuvantic efficacy of AmB is applicable as a safe and effective adjuvant for human vaccines at a dose of 100 micrograms, acting 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 (Salyer et al. 2016).

It can bind toll-like receptors (TLR), which results in the release of cytokine and chemokine. The release of pro-inflammatory cytokines has been associated with binding to TLR2 and TLR4 and produces anti-inflammatory mediators respectively (Bellocchio et al. 2005).

The defensive effects during infection were correlated with the immunomodulatory properties and the pro-inflammatory activity caused by AmB; it enhances the antifungal activity of polymorphonuclear cell (PMN) and pulmonary alveolar macrophages against conidia and/or hyphal phase of *A. fumigates* (Roilides et al. 2002).

## AmB as antimicrobial drug

Despite numerous alternative therapies, such as azole and echinocandins, AmB is still commonly used because it is typically inexpensive, fast fungicidal, with the widest range of antimicrobial activity,which rarely induces resistance.

Systemic mycoses, including those which are caused by opportunistic fungi, such as *Aspergillus* spp., *Candida* spp., and zygomycetes and those caused by primary pathogenic fungi, such as *Histoplasma capsulatum*, *Blastomyces* spp., *Coccidioidesimmitis*, *Cryptococcus* spp. and *Paracoccidioides* spp. are mostly treated by AmB (Dupont 2002; Adler-Moore and Proffitt 2008; Peçanha et al. 2016).

Invasive systemic fungal infections have been recently considered the major cause of morbidity and mortality in immunocompromised individuals, who have an immunodeficiency condition, such as those with AIDS, transplant recipients or tumor patients receiving immunosuppressive chemotherapy (Torrado et al. 2008).

Synergism with other antifungal agents could also improve AmB activity against pathogenic fungi, for examplethe mixture with flucytosine against melanized fungi of Chaetothyriales order that triggers primary cerebral infections (Deng et al. 2016).

A combination of both systemic and topical utilizations of AmB was used in a 6-month-old infant with chemotherapy used to treat bilineal leukemia, with a soft-tissue fungal infection due to Rhizopus spp. The successful result was obtained by systemic administration of liposomal Amphotericin B (10 mg/kg/d) and local administration of 0.1% Deoxycholate-AmB formula in D5W (0.1 g/100 mL). He completed the course after 8 weeks of the treatment with clear resolution (Di Pentima et al. 2014).

Leishmaniasis is another infection that can be also treated by AmB, in which 85% of cutaneous leishmaniasis and 77% of old-world mucosal leishmaniasis cases due to *Leishmaniainfantum* were cured after treatment with AmB (Mosimann et al. 2018).

AmB has been used over many decades in management of different fungal infections in the human, such as pulmonary mycosis. All of the known available formulas of AmB are administrated via intravenous injection to treat severe systemic fungal infections, while the development of the topical formula of AmB is still under preliminary development, including topical pulmonary AmB (AL-Khikani 2020c). An opportunistic systemic fungal infection is considered the most common type of fungal infection, mainly treated by AmB (AL-Khikani and AL-Janabi 2019).

Intravenous injection (I.V) of 3.39 mg/kg/day of ABLC in 23 patients with paracoccidioidomycosis revealed a 100% cure rate (Peçanha et al. 2016).

Bronchial installation is another type of tropical use of AmB. A person with lung chromomycosis due to *Scedosporiumprolificans* that appeared after lung transplantation failed to be treated by systemic itraconazole, while the improvement of bronchial obstruction was noticed after 3 instillations of AmB, which was carried out once every 3 months for 2 years (Mitomo et al. 2018).

Another study involved 12 patients with aspergilloma treated with intracavitary antifungal agents from 1988 through 1992 by an endobronchial or percutaneous approach. The Amphotericin B management was performed in 7 patients by dissolving AmB in 10 to 20 ml of 5% dextrose. The patients with effective topical treatment had a shorter mean period of the disease course (3.6 months) than the less effective group (44.4 months). That study suggested that the old mycetoma was not effective to antifungal agents, so early diagnosis and therapy were demanded to achieve a better treatment effect (Yamada et al. 1993).

Thirty-six high-risk patients with symptoms of deep mycosis were detected after 7–9 days of primary fluconazole prophylactic therapy; the laboratory diagnoses showed invasive aspergillosis in 29 patients, and deep invasive Candida infection in 7. L-AmB was given at 1–2.2 mg/kg/day via intravenous injection for 10 days. The fungal infection was eradicated in all 36 patients. Negative cultures were obtained after 5 or 6 days of the antifungal therapy. There were no adverse reactions observed to L-AmB. No mycotic relapses or relapse were detected during the follow-up (Lequaglie 2002).

From the previous studies, it can be concluded that AmB plays a critical role in pulmonary mycosis treatment with different formulas. Systemic and topical utilization of AmB have been used to treat fungal infections in the multiple systemic organs with good toleration.

## AmB as antiviral therapy

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 human immunodeficiency virus, rubella viruses, Japanese encephalitis virus, and vesicular stomatitis virus.

Viruses defined as obligate intracellular microorganisms that depend on the host cell to get resources that are demanded to replicate the viral genome; viruses have evolved various mechanisms to manipulate the environment of infected cells to replicate more efficiently. Viral genomes can be single- or double-stranded DNA or single- or double-stranded RNA. While many viruses replicate their genomes by directly generating an exact DNA or RNA copy of the genome, other viruses, such as retroviruses, use reverse transcription to generate intermediates that are needed for replication (Nascimento et al. 2012).

Examples of most common human diseases caused by viruses include influenza, common cold, chickenpox, and cold sores. Numerous serious infections, such as rabies, Ebola virus disease, avian influenza, AIDS (HIV), and SARS are also caused by viruses. The ability of viruses to cause different diseases is called virulence (Wigington et al. 2016).

AmB inhibits the replication of the Japanese encephalitis virus (JEV) at the post-infection 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. Treatment of infected cells with 5 µg/ml of AmB reduces 200-fold the infectious virus titer; besides, the accumulated level of JEV envelope protein dramatically decreases 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 cholesterol in the ER membrane would make it more susceptible to damage upon viral infection (Kim et al. 2004). Alternatively, AmB might change the microenvironment on ER regarding the JEV replication site (Rice 1969), thus resulting in the inhibition of viral RNA replicase complex formation on ER.

The antiviral activity of AmB was exerted for human immunodeficiency virus (HIV) by binding to cholesterol in the lipid bilayer membrane of the HIV particles. AmB was also proposed to be effective in blocking the early steps in HIV entry (Pleskoff et al. 1995; Konopka et al. 1999). In another study, the antiviral activity of MS8209, a derivative of Amphotericin B, was observed in CD41 cells transfected with a lacZ gene caused by type 1 infection with human immunodeficiency virus. It was shown that MS8209 prevents viral entry after receptor binding and possibly before viral-cell membrane fusion, as both processes are mediated by HIV-1 proteins and CD4 envelopes (Pleskoff et al. 1995).

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 HIV-1 particles. (Waheed et al. 2008).Vpu plays an important function in the pathogenesis of lentiviral *in vivo* (Hill et al. 2008).

For Rubella viruses, AmB at a late stage of virus replication revealed an antiviral impact against Rubella virus, while no antiviral activity was found against measles and mumps viruses that belong to Paramyxoviridae (Umino and Tashiro 2001). 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, making them the main target of AmB (Kim et al. 2004).The drug interacts with the viral envelope and at the early stage of virus infection, respectively, whereas Fungizone acted at the late stage in the case of Rubella virus. E1 and E2 undergo modifications, such as the addition and removal of oligosaccharides and fatty acids during post-translational processing (Umino and Tashiro 2001).

AmB has an effect on the structural integrity of particles of hepatitis B virus (HBV), viral aggregation, and surface antigen of hepatitis B, but its antiviral activity has not been demonstrated (Kessler et al. 1981).

The water-soluble methyl ester of Amphotericin B inactivates vesicular stomatitis virus (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 ineffectiveness, depending upon the temperature at which the drug-virus interaction took place. Morphologically many damaged particles were seen after exposure to AME (Jordan et al. 1978).

For herpes simplex virus (HSV), AME has been analyzed for its anti-herpes simplex virus activity in the rabbit cornea, which was considered a semisynthetic derivative of Amphotericin B. 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 kerato-uveitis is suggested.

## Conclusion

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, which 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.

Among the host's different forms of pathogenic diseases, one of the most severe public health issues worldwide is viral infections. Because viruses reproduce essential metabolic processes within host cells, they are difficult

to eradicate without the use of drugs that typically induce toxic effects in the host cells.

The potential ability of AmB to inhibit different types of pathogens, including some viruses, can introduce a new drug with another choice to treatment untreatable viral infections that have no specific antiviral agent, which will not be a problem anymore after the definitive proof of the successful antiviral application of AmB.

AmB is ready for use and accessible. It was noticed that most viruses that AmB targeted had envelopes and RNA nucleic acid; however, these viruses may be similar in complexity and contain specific virus proteins that can be targeted by the medication protocol. While using AmB in modern branches, 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 a viral infection, the immune system plays a crucial role in viral elimination and body defending, so using an antibiotic that has the ability to enhance an immune response, activating innate immunity, stimulate pro-inflammatory responses, like AmB, may be very important to protect from various viral invasions. It has strong immunomodulatory characteristics due to 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.

As shown, AmB has unique properties to treat different viral infections thus, using it may be a promising branch to be evaluated clinically, but this finding demands more studies in medical laboratories and through clinical trials.

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