Letter to Editor

Prospects in Immunomodulatory activity of Amphotericin B in viral infection: Promising developing therapeutic branch

Dear Sir,

Amphotericin B (AmB), which belongs 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.[1] Recently, some studies focused on the potential antimicrobial action of AmB against some enveloped and nonenveloped viruses.

Besides AmB utilization as an antimicrobial agent to treat fungi and parasites, AmB and its derivatives have been evaluated against viral infections inlcuidng HIV,[2] Japanaese Encephailits virus and Rubella virus.[3]

Nearly 5,000 species of viruses have been identified in detail, of the millions of virus types in the world.[4] Viruses are considered the most numerous type of biological entity and are found in almost every ecosystem on the Earth.[5] There are difficult to treat viral infection, and some viruses have no specific therapy such as COVID-19 novel viral infection.[6,7]

AmB destroys fungi and single-cell protozoa such as *Leishmania* spp. 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 that causes oxygen depletion.[8] Because it has immunomodulatory effects, it is capable of inducing pro-inflammatory mediators.[9]

AmB has the ability to stimulate the innate immune responses such as toll-like receptor 2 (TLR2) and CD14 as well as TLR4.[10] AmB produces a transcription of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), IL-1β, besides chemokines (IL-8, MCP-1, MIP-1β), nitric oxide, prostaglandins, and intercellular adhesion molecule-1 from murine and human innate immune cells *in vitro*.[11]

It 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.[9] However, mechanisms by which AmB activate the immune system are still not fully understood.

In vitro using mouse L929 cells treated by AmB, interferon production is increased by enhancing penetration of polyriboinosinic-polyribocytidylic acid of the cell membrane that acts as a trigger to interferon production, interferon titers were enhanced significantly by AmB at 5 ug/ml and increased almost 10 fold at 25 g/ml.[12]

AmB and its derivatives can produce pro-inflammatory cytokines by interfering with the macrophage activation state. It increases TNF-α production that leads to the synthesis of superoxide dismutase, which produces the substrate of catalase-like hydrogen peroxide.[13]

Besides inhibition fungal growth by potential-killing mechanisms, it directly activate the host's innate immunity, it has been reported to trigger IL-1b secretion in monocytes, and also, it induces potassium efflux from the cells that lead to increasing IL-1 b secretion.[4]

The efficacy of AmB as adjuvant is applicable, safe, and effective for human vaccines at a dose of 100 micrograms which 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.[14]

It can bind 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.[15]

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 PMN and pulmonary alveolar macrophages against conidia and/or hyphal phase of A. fumigates.[16]

AmB has an effect on the structural integrity of particles of the hepatitis B virus, viral aggregation, and surface antigen of hepatitis B, but its antiviral activity has not been demonstrated.[17]

For herpes simplex virus (HSV), amphotericin B methyl ester (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 kerato-uveitis is suggested.[18]

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 by using the colonies of murine leukocytes, the liposomal formulation demonstrated significantly decreased cytotoxicity.[19]

Because the unique properties of AmB and its immunomodulatory activity of the immune response,[20] recent study suggested using AmB against COVID-19 infection[21] as well as other immunomodulatory drugs such as tamoxifen,[22] and Itraconazole.[23]

CONCLUSION

Because AmB has the ability to activate immune modulation by elevating immune response cytokines and pro-inflammatory responses, AmB can be used as potential antiviral drug particularly in immunocompromised patient by acting as antiviral therapy and enhancing immune responses.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Falah Hasan Obayes AL-Khikani, Aalae Salman Ayit

Department of Microbiology, Al-Shomali General Hospital, Babil, Iraq

Address for correspondence:
Dr. Falah Hasan Obayes AL-Khikani,
Department of Microbiology, Al-Shomali General Hospital, Babil, Iraq.
E-mail: falahgh38@gmail.com

Submitted: 30-Apr-2020 **Revised:** 13-May-2020
Accepted: 15-May-2020 **Published:** 20-Jul-2020

REFERENCES

1. AL-Khikani FH, AL-Janabi AA. Topical amphotericin B formulas: Promising new application. Int J Med Sci Curr Res 2019;2:187-96.
2. Konopka K, Guo LS, Duzgunes N. Anti-HIV activity of amphotericin B-cholesteryl sulfate colloidal dispersion *in vitro*. Antiviral Res 1999;42:197-209.
3. Kim H, Kim SJ, Park SN, Oh JW. Antiviral effect of amphotericin B on Japanese encephalitis virus replication. J Microbiol Biotechnol 2004;14:121-7.
4. Darisipudi MN, Allam R, Rupanagudi KV, Anders HJ. Polyene macrolide antifungal drugs trigger interleukin-1β secretion by activating the NLRP3 inflammasome. PLoS One 2011;6:5.
5. Breitbart M, Rohwer F. Here a virus, there a virus, everywhere the same virus? Trends Microbiol 2005;13:278-84.
6. AL-Khikani FH. Surveillance 2019 novel coronavirus (COVID-19) spreading: Is a terrifying pandemic outbreak is soon? Biomed Biotechnol Res J 2020;4:81-2.
7. AL-Khikani FH. The role of blood group in COVID-19 infection: More information is needed. J Nat Sci Med 2020;3:33-6. [doi: 10.4103/JNSM.JNSM_24_20].
8. AL-Khikani FH. Pulmonary mycoses treated by topical amphotericin B. Biomed Biotechnol Res J 2020;4:66-70.[doi: 10.4103/bbrj.bbrj_12_20].
9. Mesa-Arango AC, Scorzoni L, Zaragoza O. It only takes one to do many jobs: Amphotericin B as antifungal and immunomodulatory drug. Frontiers Microbiol 2012;3:1-10.
10. Sau K, Mambula SS, Latz E, Henneke P, Golenbock DT, Levitz SM. The antifungal drug amphotericin B promotes inflammatory cytokine release by a Toll-like receptor- and CD14-dependent mechanism. J Biol Chem 2003;278:37561-8.
11. Arning M, Kliche KO, Heer-Sonderhoff AH, Wehmeier A. Infusion-related toxicity of three different amphotericin B formulations and its relation to cytokine plasma levels: Infusions-assoziierte Toxizität dreier Amphotericin B-Formulierungen und ihre Beziehung zu Zytokin-Plasmaspiegeln. Mycoses 1995;38:459-465.
12. Borden EC, Leonhardt PH. Enhancement of rIn: rCn-induced interferon production by amphotericin B. Antimicrob Agents Chemother 1976;9:551-3.
13. Clayette P, Martin M, Beringue V, Dereuddre-Bosquet N, Adjou KT, Seman M, *et al.* Effects of MS-8209, an amphotericin B derivative, on tumor necrosis factor alpha synthesis and human immunodeficiency virus replication in macrophages. Antimicrob Agents Chemother 2000;44:405-7.
14. Salyer AC, Caruso G, Khetani KK, Fox LM, Malladi SS, David SA. Identification of adjuvantic activity of amphotericin B in a novel, multiplexed, Poly-TLR/NLR high-throughput screen. PLoS One 2016;11:e0149848.
15. Bellocchio S, Gaziano R, Bozza S, Rossi G, Montagnoli C, Perruccio K, *et al.* Liposomal amphotericin B activates antifungal resistance with reduced toxicity by diverting Toll-like receptor signalling from TLR-2 to TLR-4. J Antimicrob Chemother 2005;55:214-22.
16. Roilides E, Lyman CA, Filioti J, Akpogheneta O, Sein T, Lamaignere CG, *et al.* Amphotericin B formulations exert additive antifungal activity in combination with pulmonary alveolar macrophages and polymorphonuclear leukocytes against *Aspergillus fumigatus*. Antimicrob Agents Chemother 2002;46:1974-6.
17. Kessler HA, Dixon J, Howard CR, Tsiquaye K, Zuckerman AJ. Effects of amphotericin B on hepatitis B virus. Antimicrob Agents Chemother 1981;20:826-33.
18. Baginski M, Czub J. Amphotericin B and its new derivatives-mode of action. Curr Drug Metab 2009;10:459-69.
19. Pontani DR, Sun D, Brown JW, Shahied SI, Plescia OJ, Schaffner CP, *et al.* Inhibition of HIV replication by liposomal encapsulated amphotericin

B. Antiviral Res 1989;11:119-25.
20. AL Khikani FH. Refractory fungal vaginitis treated by topical amphotericin B. J Med Sci Res 2020;3:22-6.
21. AL-Khikani FH. Amphotericin B as antiviral drug: Possible effiacy against COVID 19. Ann Thorac Med 2020;9:18-23.
22. Almosawey HA, AL Khikani FH, Hameed RM, Abdullah YJ, Al Ibraheemi MK, Al Asadi AA. Tamoxifen from chemotherapy to antiviral drug: Possible activity against COVID 19. Biomed Biotechnol Res J 2020;4,21-9. 10.4103/bbrj.bbrj_53_20.
23. AL-Khikani FH, Hameed RM. COVID-19 treatment: Possible role of itraconazole as new therapeutic option. Int J Health Allied Sci 2020;7:101-3.

Access this article online

Quick Response Code:

Website: http://www.jcrsmed.org

DOI: 10.4103/jcrsm.jcrsm_29_20

How to cite this article: AL-Khikani FH, Ayit AS. Prospects in Immunomodulatory activity of Amphotericin B in viral infection: Promising developing therapeutic branch. J Curr Res Sci 2020;6:65-7.