Mechanisms Action of Tamoxifen in Viral Infections: Promising Expected Therapeutic Branch

Dear Editor,

Tamoxifen is a nonsteroidal selective estrogen receptor modulator (SERM), structurally derived from diethylstilbestrol-like estrogens and anti-estrogens.[1] It has been used to treat breast cancer that spread to other parts of the human body; it is also utilized to decreasing the chances of breast cancer developing in high-risk patients.[2]

Besides tamoxifen utilization as chemotherapy, tamoxifen, and its derivatives against viral infection have been evaluated, some searches studied the efficacy of it to treat human immunodeficiency virus (HIV), hepatitis C virus (HCV), herpes simplex virus type 1 (HSV-1), and Ebola Virus. Some side effects associated with tamoxifen (TAM) as the most common drugs.[3-7]

Nearly 5000 species of viruses have been identified in detail, of the millions of virus types in the world that considered the most numerous type of biological entity, and are found in almost every ecosystem on Earth.[8] There are difficult to treat viral infection and some viruses have no specific therapy such as COVID-19 novel viral infection.[9-11]

The triphenylethylene represents the backbone of TAM and other TAM-related estrogen receptor antagonists, it is a SERM which has shown activity against a wide range of medically important human pathogens, including bacteria, parasites, fungi, and viruses.[12] These additional therapeutically functions of known drugs are always required for discovering other utilization over time which is called drug repositioning (drug repurposing or drug reprofiling).[13]

Tamoxifen inhibits mitochondrial complex one that leads to the inhibition of oxygen consumption, consequently, an increase in the adenosine monophosphate/adenosine triphosphate ratio and activation of the activated protein kinase signaling pathway are increased in both *vitro* and *vivo*.[8]

SERMs are nonsteroidal compounds that bind to estrogen receptors and exert either estrogenic or anti-estrogenic effects on target tissues. These steroid hormones binding globulin or albumin in the plasma and diffuse across the cell membrane by bind with a high affinity to specific nuclear receptor proteins. This activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate many physiologic functions that may elicit the synthesis of different RNA species in diverse target tissues.[14]

In HCV found that tamoxifen suppressed genome replication. The endoplasmic reticulum (ER) membranes interacted with HCV RNA polymerase NS5B suggested that ESR promoted NS5B association with the replication complex (RC) and that tamoxifen abrogated NS5B RC association. Thus, ESR regulated the presence of NS5B in the RC and stimulated HCV replication of endogenous ESR reduced HCV replication.[15]

HIV in 1990, TAM was identified as a disruptor of viral replication during chronic infection based on the protein kinase C (PKC) activator phorbol myristate acetate was used to up-regulate viral replication (4B-phorbol-12-myristate-13-acetate-mediated model) and as a disruptor of HIV-associated transactivation in cells of monocytic and T-cell lineages at half-maximal inhibitory concentrations (IC50) of 10 < M.[15] Where it is known the inhibition of PKC function in intact human cells by TAM and that may have related to its antitumor action.[16] TAM also suppressed HIV replication in nonstimulated, HIV-infected lymphocytes through pathways independent of its antiestrogen activity.[17]

In the Ebola virus, the tamoxifen also plays a role in inhibitors of the ER α-glycosidase and a variety of compounds that have been found to inhibit EBOV infection by blocking viral entry.[18]

The antiviral activity of TAM on viral infection is by different ways such as inhibition viral replication in HIV, HCV, and (HSV-1) *in vitro*. Furthermore, the effect of TAM on infection with vesicular stomatitis virus by suppressed RNA replication [Figure 1].[19]

Furthermore, a recent study suggested using TAM to treat COVID 19 viral infection due its unique properties as well as its immunomodulatory effect on immune responses by different mechanisms that may help body to fiht viral diseases.[2] Besides other drugs such as AmB[20] and ITZ.[21-25]

In conclusion, tamoxifen is ready for use and accessible. We noticed that the most common viruses that tamoxifen targeted have envelopes and spikes, be its nucleic acid or nucleic acid, but all may be similar in complexity and contain specific virus proteins that can be targeted by the medication protocol. This particularly important to evaluate the potential activity of TAM on other viruses especially those do not have specific treatment or vaccine.

In addition to the effect of tamoxifen on cancer cells, it was found to have other effects on many microbes, as it possesses mechanisms that made it ready for repurposing as an anti-tumor or adjunctive treatment or synergistic with another treatment to increase its effectiveness or reduce its toxicity.

Major mechanisms of TAM in viral infections are suppressed HCV genome replication, disruption of viral replication during chronic infection, suppressed viral RNA synthesis, expression

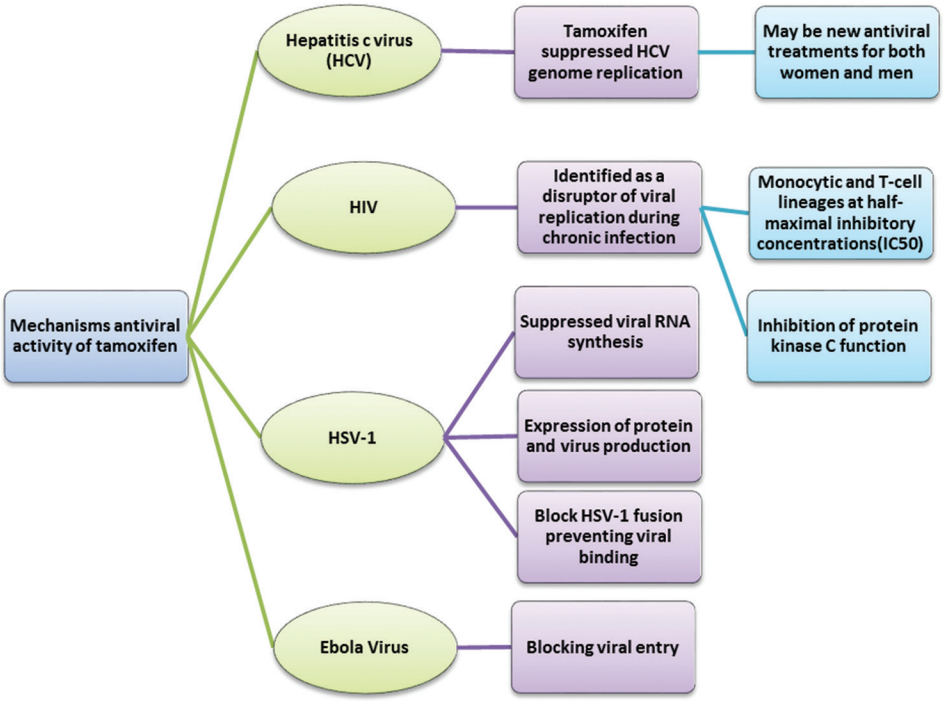

Figure 1: Mechanisms actions of tamoxifen for certain viral infections

of protein and virus production, block HSV-1 fusion preventing viral binding, blocking viral entry, and inhibition of PKC function.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Maximov PY, McDaniel RE, Jordan VC. Tamoxifen: Pioneering Medicine in Breast Cancer. Vol. 7. Germany: Springer Science & Business Media; 2013. p. 44-8.
2. 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;4:1-9.
3. AL-Khikani FH. Pulmonary mycoses treated by topical amphotericin B. Biomed Biotechnol Res J 2020.4:24-8.
4. AL-Khikani FH. Refractory fungal vaginitis treated by topical amphotericin B. J Med Sci Res 2020;3:13-6.
5. AL-Khikani FH, Abadi RM, Ayit AS. Emerging carbapenemase *Klebsiella oxytoca* with multidrug resistance implicated in urinary tract infection. Biomed Biotechnol Res J 2020;4:66-8.
6. AL-Khikani FH, The forgotten role of methenamine to prevent recurrent urinary tract infection: Urgency for reuse 100 years after discovery. Pharm Biomed Res 2020;6:13-6.
7. Obayes AL-Khikani FH, Kadim BJ, Ayit AS, Abidalali MH. Evaluation Cephalosporins Resistance in Pathogenic Bacteria Isolated Clinically. World News of Natural Sciences. 2020;31:110-9.
8. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes Infect 2020;22:74-9.
9. 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.
10. AL-Khikani FH. The role of blood group in COVID-19 infection: More information is needed. J Nat Sci Med 2020;3:17-20.
11. AL-Khikani FH. COVID19 and blood type: People with which group are more vulnerable? J Med Sci Res 2020; 3:68-70.
12. Montoya MC, Krysan DJ. Repurposing estrogen receptor antagonists for the treatment of infectious disease. mBio 2018;9:e02272-18.
13. Doan TL, Pollastri M, Walters MA, Georg GI. The future of drug repositioning: Old drugs, new opportunities. Annu Rep Med Chem 2011;46:385-401.
14. Whalen K, Finkel R, Panavelil T. Lippincott Illustrated Reviews: Pharmacology 6th. University of Florid, Collage of Pharmacy, Gainesville, Florida. 2015.p. 351.
15. Laurence J, Cooke H, Sikder SK. Effect of tamoxifen on regulation of viral replication and human immunodeficiency virus (HIV) long terminal repeat-directed transcription in cells chronically infected with HIV-1. Blood 1990;75:696-703.
16. Horgan K, Cooke E, Hallett MB, Mansel RE. Inhibition of protein kinase C mediated signal transduction by tamoxifen. Importance for antitumour activity. Biochem Pharmacol 1986;35:4463-5.
17. Mesange F, Delarue F, Puel J, Bayard F, Faye JC. Ligands of the antiestrogen-binding site are able to inhibit virion production of human immunodeficiency virus 1-infected lymphocytes. Mol Pharmacol 1996;50:75-9.
18. De Clercq E. Ebola virus (EBOV) infection: Therapeutic strategies. Biochem Pharmacol 2015;93:1-10.
19. Cham LB, Friedrich SK, Adomati T, Bhat H, Schiller M, Bergerhausen M, *et al*. Tamoxifen protects from vesicular stomatitis virus infection. Pharmaceuticals (Basel) 2019;12:44-9.
20. AL-Khikani FH. Amphotericin B as antiviral drug: Possible effiacy against COVID19. Ann Thorac Med 2020;12:1-6.

21. AlKhikani FH, Hameed RM. COVID19 treatment: Possible role of itraconazole as new therapeutic option. Int J Health Allied Sci 2020;9:74-7.
22. AL-Khikani FH. Potential antiviral properties of antifungal drugs. J Egypt Women's Dermatol Soc. 2020;12:141-143 DOI: 10.4103/JEWD.JEWD_40_20.
23. AL-Khikani FH. COVID-19 and blood type: People with which group are more vulnerable?. J Med Sci Res 2020;3:158-9.
24. AL-Khikani FH. COVID-19: Containment strategies and management options. Journal of Nature and Science of Medicine. 2020;3:221-3.
25. AL Khikani FH, Hameed RM, Almosawey HA. Immunological prospects of tamoxifen as modern antiviral therapy. J Mar Med Soc 2020;10:89-91.

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