Review Article

Tamoxifen from Chemotherapy to Antiviral Drug: Possible Activity against COVID-19

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Abstract

Tamoxifen (TAM) is the oldest and the most-prescribed selective estrogen receptor modulator (SERM). It is a member of the triphenylethylene group. TAM has been used to treat breast cancer that spreads to other parts of the human body; it is also utilized to decreasing the chances of breast cancer developing in high-risk patients. Recently, some studies focused on the potential antimicrobial action of TAM. 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 in shape. Coronavirus disease 2019 (COVID-19) is regarding the new genera of coronaviredia that appeared for the first time in Wuhan, China, in early December 2019. Due to the continuous spread 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-nCoV. Hence, this review will discuss the most recent information about the antiviral action of TAM against COVID-19 infection by trying to give a deep understanding of major properties, mechanisms of action, immune system responses, and antimicrobial efficiency of TAM that is regarding the promising way to treat COVID-19 novel infection. The current review may serve as an impetus for researchers working in the field of medical microbiology, vaccination, and antiviral drug design. The review also rationally reports and critically analyzes the available knowledge by focusing and mentioning future steps and strategies trying to find appropriate solutions regarding challenges in COVID-19 management by TAM utilization.

Keywords: Antimicrobial agents, antiviral drugs, chemotherapy, coronavirus, COVID-19, tamoxifen

Introduction

Tamoxifen (TAM) is a nonsteroidal selective estrogen receptor modulator (SERM) of the triphenylethylene family and was structurally derived from diethylstilbestrol-like estrogens and anti-estrogens.[1] It was primarily discovered in 1962, by Dora Richardson (scientist in chemistry).[2] TAM is listed on the World Health Organization's List of Essential Medicines.[3]

Coronavirus is a positive polarity RNA with envelope; it is 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 emerged causing the severe pulmonary outbreak. It is recorded as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).[4] Most common infected persons with COVID-19 were men with chronic pulmonary or cardiovascular disorders, hypertension, and diabetes. Infected individuals have a fever, coughing with sputum, headache, and diarrhea. Renal failure may be one of the viral complications.[5]

At present, there is no specific antiviral agent available to treat this COVID-19 infection; organ support in seriously ill individuals and symptomatic management are the fundamental steps in clinical treatment;[6] however, some drugs such as chloroquine and hydroxychloroquine are recently used to

Access this article online

Quick Response Code:

Website: www.bmbtrj.org

DOI: 10.4103/bbrj.bbrj_53_20

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How to cite this article: 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;4:108-16.

Submitted: 05-Apr-2020; **Accepted:** 07-Apr-2020; **Published:** 17-Jun-2020.

treat some cases of COVID-19 infections with many adverse side effects.[7]

TAM inhibits mitochondrial complex that leads to the inhibition of oxygen consumption; consequently, an increase in the AMP/ATP ratio and activation of the AMPK signaling pathway are increased both *in vitro* and *in vivo*.[8]

Tamoxifen, an anti-estrogen that competes for the estrogen receptor, modulates natural killer cell activity *in vivo*. It has been demonstrated that tamoxifen can enhance murine NK activity *in vivo* and can enhance human NK activity *in vitro* .[9] Another study demonstrated that cytotoxic T lymphocyte-mediated, NK cell-mediated and lymphokine-activated killer cell-mediated target-cell lyses were amplified by tamoxifen.[10]

TAM is mainly utilized to manage breast cancer in both females and males; it is also used to diminish the chances of breast cancer occurrence in high-risk people.[11] Beside the effectiveness of TAM on cancer cells, it also has other effects on numerous microbes including parasite, fungi, bacteria, and some viruses such as Ebola virus[12] and human immunodeficiency virus (HIV).[13]

High concentrations of TAM are deposited in the lung tissue in animals and humans;[14] this finding may be important in utilizing TAM in treating pulmonary disorders such as COVID-19 with low doses that may reduce the adverse effects of the drug.

This review focuses on understanding problems in COVID-19 infection treatment by providing a rational and critical discussion on the available knowledge to get a clear future vision regarding this novel virus management by revealing the possible promising role of TAM in this therapeutic branch.

General Properties of Tamoxifen

TAM is a nonsteroidal SERM. Its chemical formula is $C_{26}H_{29}NO$, and it has 371.524 g/mol molecular weight. It is a white odorless crystalline powder that is soluble in ethanol, acetone methanol, or methanol; is slightly soluble in water; is hygroscopic with high moisture rate, and is sensitive to ultraviolet light.[15] TAM is used for treating breast cancer in postmenopausal women and is used in postsurgery neoadjuvant therapy in endoplasmic reticulum (ER)-positive breast cancers. It has been mentioned that 5%–10% of the ER-negative breast cancers have also shown sensitivity to TAM treatment[15,16] [Figures 1 and 2].

TAM is available in two forms: a liquid form or a pill taken once a day; it is rapidly absorbed from the digestive tract with oral administration. Its oral bioavailability is high at approximately 100%, which is suggestive of minimal first-pass metabolism in the intestines and liver. Following intake, peak levels of TAM occur after 3–7 h. A majority of it is bound to albumin protein. It is excreted in bile and is eliminated in feces, while small amounts are excreted by the kidneys via urine. It has a long elimination half-life of typically 5–7 days, with a range of 4–11 days.[14]

Apart from this, some side effects are associated with long-term therapy by TAM (which should be carefully monitored in patients). However, it is associated with several physiological benefits such as the maintenance of bone density in postmenopausal women and a decrease in cardiovascular disease also with its tumoristatic action.[17] TAM and its derivatives show other therapeutic activities besides treating and preventing breast cancer.[18] It has an inhibiting effect (an anti-estrogen) in the mammary tissue and as a stimulating agent (an estrogen) in cholesterol metabolism. TAM binds to estrogen receptors (ER), inducing a conformational change in the receptor, and then leads to blockage or change in the expression of estrogen-dependent genes.[15]

Characteristics of Novel Coronavirus Disease 19

Coronaviruses are enveloped unsegmented (+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. The diseases of coronaviruses range from enteritis in cows and pigs and chickens with respiratory disease to life-threatening human lung infections.[19]

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. The disease spread rapidly, locally, to other parts of China, and internationally to several nations across six continents. On January 3, 2020, a novel species of enveloped RNA coronavirus was detected from a patient in Wuhan in bronchoalveolar lavage fluid samples and subsequently confirmed as the cause of this disease by the Chinese Center for Disease Control and Prevention. On January 7, 2020, it was named the 2019 novel coronavirus (i.e., 2019-nCoV) by the WHO. The WHO identified the 2019-nCoV-related illness as the 2019 coronavirus disease (COVID-19) on February 11, 2020.[20]

The newly emerging severe acute respiratory syndrome coronavirus (SARS-CoV-2) along with SARS coronavirus and Middle East respiratory syndrome (MERS) coronavirus seems to be the third highly pathogenic human coronavirus which has already emerged in the last two decades. Transmission of these viruses is known in both hospital and family settings.[21]

SARS-CoV-2 appears to be optimized to bind human receptor angiotensin-converting enzyme, 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]

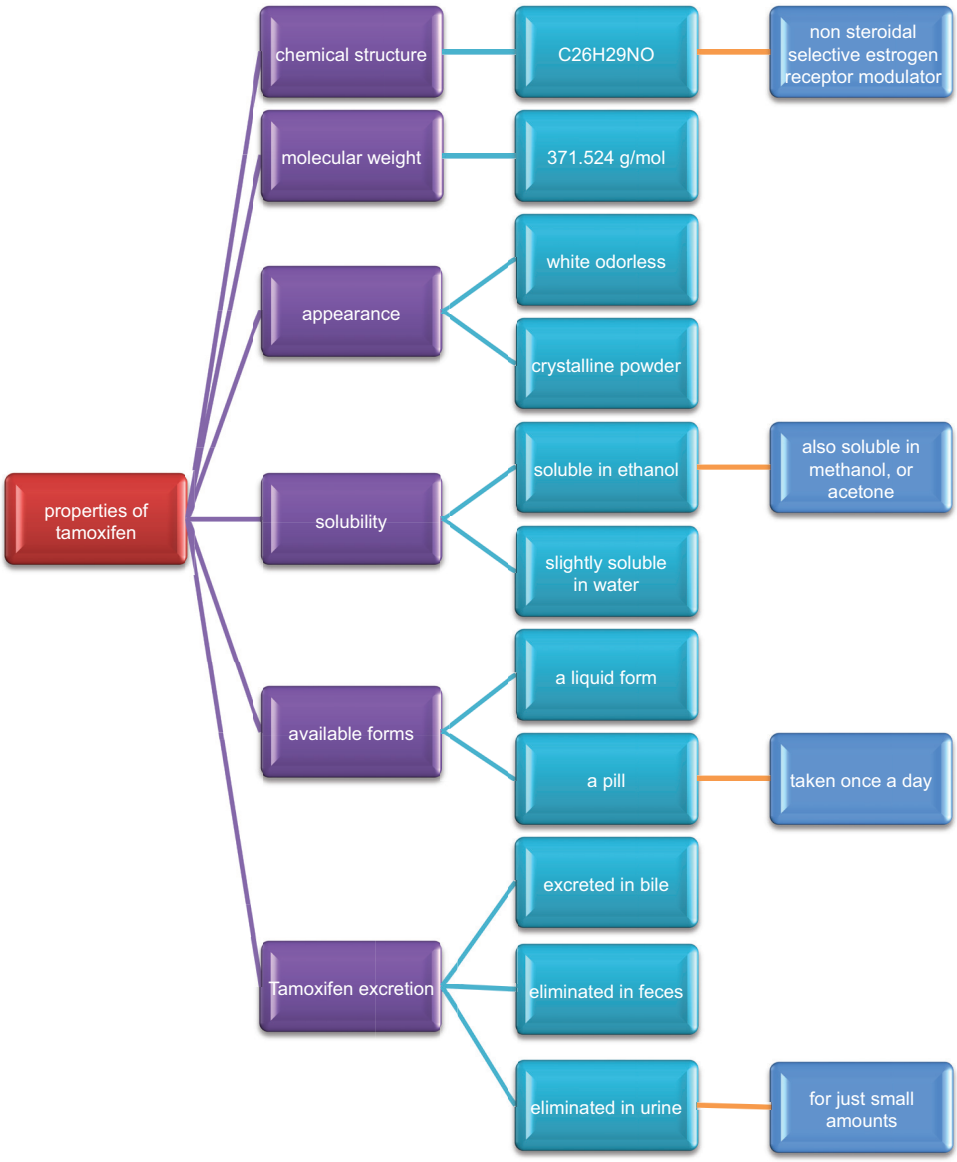

Figure 1: Some properties of tamoxifen

Coronaviral transmission from contaminated dry places was suggested through the self-inoculation of mucous membranes in the nose, eye, or mouth, highlighting the importance of a thorough understanding of coronavirus survival in inanimate surfaces. Various types of biocidal agents are used globally for disinfection, particularly in health-care environments such as peroxides, alcohols, sodium hypochlorite, or benzalkonium chloride.[23]

Therapeutic Options of Coronavirus Disease 19

At present, the number of cases due to the novel COVID-19 is still increasing with time, so effective treatment methods and more effective strategies should be developed to prevent the terrifying pandemic spreading among many countries worldwide.[24,25] Until this moment, there is 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 drug for treating novel COVID-19, it may take a long time for an evaluation. However, some marketed drugs are good to prevent ARDS, which boost immune responses with safe use such as metformin, firates, and atorvastin, besides nutrient supplements.[6]

Lopinavir is a protease inhibitor used to treat HIV infection which acts as a booster when combined with ritonavir.[26] In the management of SARS, compared with patients treated with ribavirin alone, patients treated with lopinavir/ritonavir and ribavirin had a lower risk of ARDS or death.[27] The prescribed dosage of lopinavir/ritonavir for COVID-19 infection is greater than that for HIV-infected individuals. Hence, according to the modern study, if lopinavir/ritonaviris is used for the management of COVID-19 infection, a doubled dosage for HIV infection is demanded.[28]

Zinc and other metal-containing formulations show anti-viral effectiveness, cheap, safe, and readily available properties.

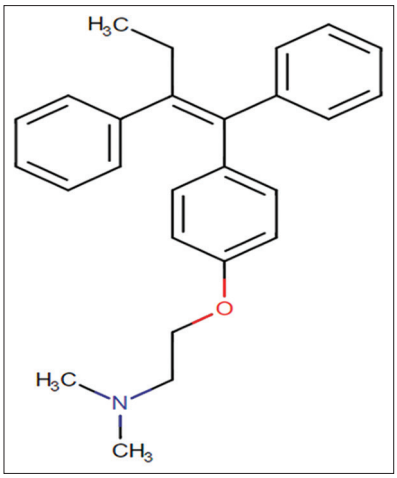

Figure 2: Structure of tamoxifen[15]

They could be used as adjuncts to monotherapy or as combinational drugs.[29]

Recently, studies demonstrated the clinical and virologic benefits of chloroquine and hydroxychloroquine in patients with COVID-19 compared to controls.[7,30] Both drugs have known safety profiles; side effects are suspected in most common antibiotics,[31,32] also TAM has adverse effects such as cardiotoxicity (prolonged QT syndrome) after prolonged use in patients with hepatic or renal impairment and those who are immunosuppressed. However, both drugs were reportedly well tolerated in COVID-19 patients. At present, hydroxychloroquine is under evaluation in clinical trials for pre-exposure or post-exposure prophylaxis of COVID-19 and management of infected persons with mild-to-severe infection.[33] Anyway, the activity and clinical safety of this drug in patients with COVID-19 remain unclear and must be confirmed by more clinical studies.

In general, there are no specific antiviral drugs or vaccines for COVID-19 infection. All of the drug options come from experience treating SARS, MERS, or some other new influenza virus previously. Active symptomatic support remains key to treatment. These drugs mentioned above would be helpful and the efficacy needs to be further confirmed.

Mechanisms of Actions of Tamoxifen

SERMs are nonsteroidal compounds that bind to estrogen receptors and exert either estrogenic or anti-estrogenic effects on target tissues. These steroid hormones bind with globulin or albumin in the plasma and diffuse across the cell membrane by binding 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.[34]

In hepatitis C virus (HCV) infection found that treatment with TAM can suppressed virus genome replication The authors explain that part of erythrocyte sedimentation rate (ESR) resided on the ER membranes interacted with HCV RNA polymerase NS5B. They suggested that ESR_ promoted NS5B association with the replication complex RC and that TAM abrogated NS5B-–RC association. Thus, ESR_ regulated the presence of NS5B in the RC and stimulated HCV replication of endogenous ESR-reduced HCV replication.[13]

In Ebola virus (EBOV), the TAM also played 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.[12]

The antiviral activity of TAM on the HIV, HCV, herpes simplex virus type 1 (HSV-1), and vesicular stomatitis virus (VSV) is occurred by suppression of viral RNA replications.[35]

Tamoxifen and Immune System

Scientists demonstrated two decades ago that a deficiency of NK cells in patients infected with the SARS coronavirus was associated with the more severe disease. Since NK cells are still best appreciated for their non-redundant roles in defence against some viruses. Thus, NK cell therapy may be deployable, rapidly scalable approaches to treating COVID-19. Moreover, it is well established that immunotherapy can enhance vaccine-induced immunity.[36]

NK cells are a type of innate immune cell, which respond immediately to new pathogens. It is the host's first line of defense against tumors and viral infection. NK cells kill cancerous or virally infected cells by recognizing molecules, which are called stress antigens.[37] In human lungs, NK cells are located in the parenchyma and are not detected outside the parenchyma, accounting for about 10%–20% of the lymphocytes.[38]

TAM, an anti-estrogen that competes for the estrogen receptor, modulates NK cell activity *in vivo*. It has been demonstrated that TAM can enhance murine NK activity *in vivo* and can enhance human NK activity *in vitro*.[39,40] Another study demonstrated that cytotoxic T lymphocyte-mediated, NK cell-mediated, and lymphokine-activated killer cell-mediated target-cell lyses were amplified by TAM.[41,42]

Numerous studies are describing the effects of female sex hormones (steroid hormones estrogen) on NK cell activity. It is well established that sustained estrogen (b-estradiol) treatment of mice leads to a reduction *in vivo* NK cell activity.[43,44] However, as TAM does not reduce estrogen levels in postmenopausal patients,[45,46] the enhancement of NK by TAM could not be ascribed to the reduction in serum estrogens.

A variety of DNA and RNA viruses have been shown to stimulate prostaglandin E2 (PGE2) production through cyclooxygenase-2 expression,[47-50] resulting in negative feedback in the regulation of macrophages and NK cells through inhibitory effects on interleukin (IL)-12 production and the expression of IL-12 receptors,[51] inhibiting interferon (IFN)-γ.[52] In NK cells,

PGE2 functions by suppressing the responsiveness of IL-12[53] and IL-15,[54] which suppresses the cytolytic effects of NK cells.[55] PGE2 abrogates the NK cell "helper" function by inhibiting the ability of NK cells to produce IFN-γ.[56] Indeed, this documented ability of TAM to reduce PGE production may be the mechanism that resulted in the positive modulation of NK activity in both *in vivo* and *in vitro* settings.[57]

Furthermore, PGE2 can play a role in viral infection directly by increasing the production and release of virions and stimulating viral gene expression.[58] As TAM decreased the PGE2 production,[59] targeted PGE2 may reduce viral replication and enhance antiviral immunity [Figure 3].

Tamoxifen as an Anticancer Drug

Breast cancer is one of the hormone-dependent cancers; it is the most frequent cancer type in females stimulated, usually by estrogen hormone.[11] "In 1977, The USA Food and Drug Administration approved the usage of TAM for the treatment of postmenopausal women suffering from advanced breast cancer," also as postsurgery adjuvant treatment for eliminating micro-metastasis from primary breast cancer.[60]

A dose of 20 mg twice daily of TAM is more effective to manage advanced, recurrent, or metastatic breast carcinoma.[61] TAM can be used for long period ranging from (5 to 10) years.[62] At low concentration (microgram), TAM plays an inhibitory role in cell growth and cytotoxic action by effects on protein kinase C (PKC) of tumor cells.[63] The TAM antitumor activity perhaps includes its ability to induce the oxidation reaction of the breast cancer cells by increasing Nrf2 expression.[64] The growth of tumor can be reduced by TAM through its inhibitory effects on mitochondrial complex l, causing inhibition in oxygen consumption as indicated by the increase of AMP/ATP ration, and then activation of AMPK signaling pathway.[65] TAM can regulate the action of inhibitor tumor cell growth factors such as transforming growth factor-beta (TGF-β) and the factor that stimulate cell growth such as insulin like growth factor 1 (IGF 1).[15] The prolonged binding of TAM to the nuclear chromatin can lead to reducing DNA polymerase activity, followed by impaired thymidine utilization, blockade of estradiol uptake, and decreased estrogen response. TAM binding sites and its metabolites are located with DNA duplex, these bindings site (drug–DNA) are through both hydrophobic and hydrophilic contacts.[15,66]

Antimicrobial Effect of Tamoxifen

In addition to the effect of TAM 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 antitumor or adjunctive treatment or synergistic with another treatment to increase its effectiveness or reduce its toxicity.

It has also been attempted to treat leishmaniasis according to the mechanism of action for the activity of TAM, which is hypothesized to include the induction of altered membrane physiology for the parasite, and suggested that it is suitable for the synthesis of less toxic anti-leishmanial derivatives and more effective.[67] An interesting study administered TAM and curcumin (which is a natural phenolic compound with a broad

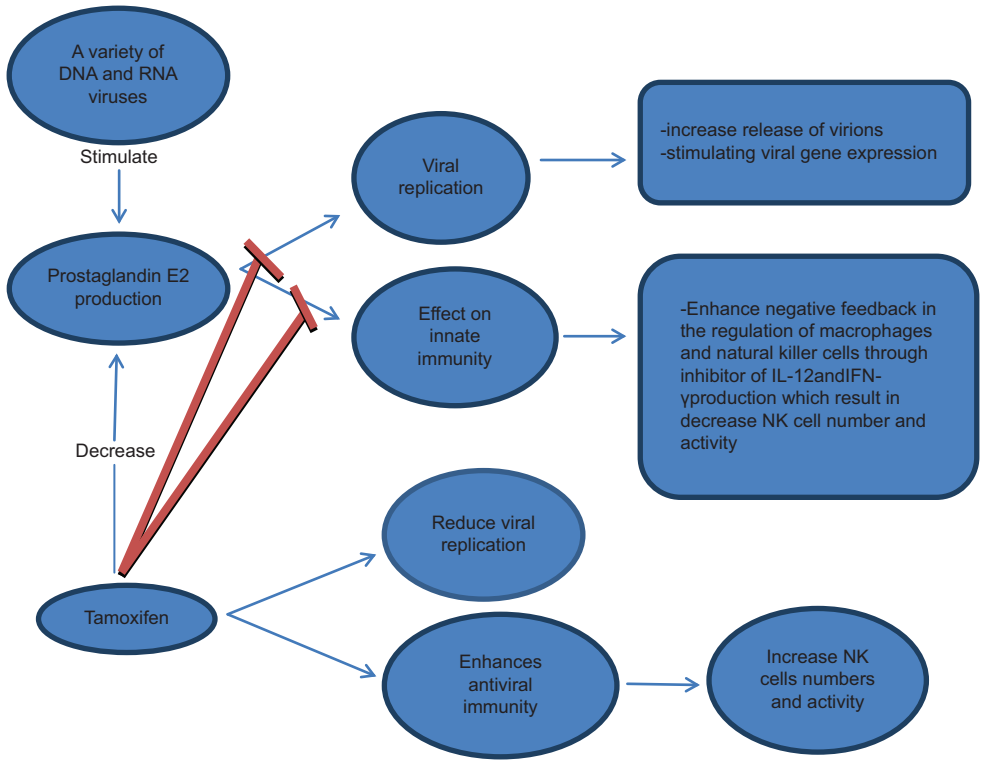

Figure 3: Tamoxifen enhances the immune response

spectrum of biological activity, for example, anti-inflammatory, antimicrobial, antifungal, antiviral, and chemopreventive) and demonstrated that when two drugs are administered together, the competition between them for the binding site on albumin can lead to decrease in bound fraction and an increase in the concentration of free biologically active fraction of drug.[68] Drug reposition could be defined as an alternative technique to find current clinically approved drugs for other indications, to find a cost-effective approach against several infections.[69,70]

TAM is a nonsteroidal anti-estrogen that is widely used for treating and preventing breast cancer.[15] 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.[71] These additional therapeutical functions of known drugs are always required for discovering other utilization over time, which is called drug repositioning (drug repurposing or drug reprofiling).[72]

Several studies have experimented TAM as an antifungal, parasite, bacteria, and virus, that we are dealing with now and have attracted the world's attention due to the propagation of the novel COVID-19. The idea of using it as a fungal drug was based on the binding of TAM to calmodulin and calmodulin-like protein (which is a key in intracellular signaling and in controlling the response of fungi to stress, such as that encountered following phagocytosis by macrophages) and preventing the activation of calcineurin. Since TAM targets calmodulin as part of its mechanism of action, indicating that calmodulin inhibition can be used to guide a systematic optimization of the anti-cryptococcal activity of the triphenylethylene scaffold.[73,74] There is a recent review of the full effects of TAM on fungi.[75]

Tamoxifen as a Antiviral Drug

Besides TAM's utilization in chemotherapy,TAM and its derivatives against viral infection have been evaluated; some searches studied its efficacy to treat HIV, HCV, HSV-1, and EBOV [Figure 4].

HIV in 1990, TAM was identified as a disruptor of HIV replication during chronic infection by the effect on the PKC activator phorbolmyristate acetate, which used to up-regulate viral replication (4B-phorbol-12-myristate-13-acetate-mediated model), Where it is known the inhibition of PKC function in intact human cells by TAM and that may have related to its antitumor action.[76] Further, TAM was used as a disruptor of HIV-associated trans-activation in cells of monocytic and T-cell lineages at half-maximal inhibitory concentrations of _10 < M.[13] TAM also suppressed HIV replication in nonstimulated, HIV-infected lymphocytes via pathways independent of its antiestrogen activity.[77]

TAM suppressed HCV genome replication through their effect on ESR function. Part of ESRα resided on the ER membranes, thus reacted with HCV RNA polymerase NS5B then prevents viral genome replication.[78] Another study performed many experiments in multiple steps in the life cycle of HCV. i.e. attachment, entry, replication, and postreplication events and indicated that TAM and other SERM may have beneficial antiviral enhancement properties for HCV-infected postmenopausal women and show promise for new antiviral treatments for both women

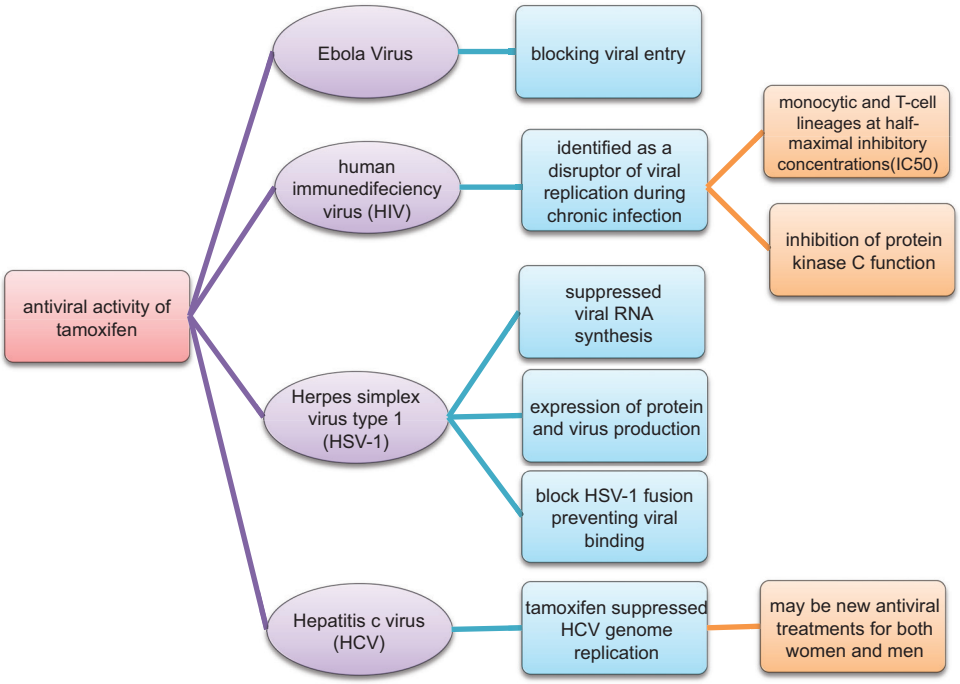

Figure 4: Mechanisms of actions of tamoxifen against some viral infections

and men, and TAM action increased when cells are exposed to the drug before infection.[79,80]

The activity of TAM toward HSV-1 has been evaluated by one study, which revealed that pretreatment or treatment with TAM and 5-nitro-2-(3-phenyl-propylamino) benzoic acid at various time points during HSV-1 infection, suppressed viral RNA synthesis, expression of protein, and virus production. A chloride channel-inhibitory activity of TAM is thought to block HSV-1 fusion preventing viral binding, penetration, and nuclear translocation.[81]

Further studies have shown that TAM and other SERMs (raloxifene [RLX], the CLMs stereoisomers enclomiphene and zuclomipheneare) also used as a therapeutic option against EBOV disease. Different strategies have been followed to target the virus and block viral entry.[12,82] Other studies indicated that the efficiency of some SERM (such as clomiphene and toremifene [TOR]) does not necessarily depend on the classical pathways represented by ER. Combination of TOR and CLM have been used to treat EBOV infection .[83,84] It will be interesting to see more effective therapies based on SERMs because some of these combinations have shown synergistic activity.

One study reviewed different therapeutic groups as ER antagonists, kinase signaling inhibitors, protein-processing inhibitors, inhibitors of lipid or sterol metabolism, and inhibitors of DNA synthesis or pair, and neurotransmitter inhibitors and suggested that TAM citrate and TOR citrate have antiviral effects on MERS-CoV at 10.11 μM and 12.91 μM, respectively, and 92.88 μM and 11.96 μM on SARS-CoV, respectively.[85]

High concentrations of TAM deposition have been found in the lung tissue in animals and humans, consequently low uptake dose of TAM is required to reach effective concentration in the pulmonary tissues, low concentrations accompanied with few side effects if any.[14] Thus, this feature may be important in utilizing TAM in the treatment of pulmonary disorders such as COVID-19.

Conclusions

COVID-19 is an emerging virus, which is considered 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 COVID-19 are required; more research is urgently needed to better understand the better treatment of the COVID-19 infection.

The potential ability of TAM to inhibit different types of pathogens including some viruses can introduce a new drug with another choice to treat COVID-19. Undeveloped specific antiviral agent against COVID-19, will not be a problem anymore after complete proving the successful antiviral application of TAM against COVID-19.

TAM is ready to use and it is accessible. We noticed that all viruses targeted by TAM 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.

TAM can be used as immunotherapy against COVID 19 since its ability to modulation of NK cells activity in both the *in vivo* and *in vitro* and reduce viral replication, through reducing PGE2 production. In addition, the efficacy of TAM on the various viral infection through their effect on viral RNA nucleic acid replication. Thus, using TAM instead of chloroquine and hydroxychloroquine in patients with COVID 19 may give reduced side effects and maybe a promising branch to be evaluated clinically. This finding demands more studies in laboratories and clinical trials.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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