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Review Paper

Global Scenario of Antiviral Drugs for Japanese Encephalitis

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Abstract

Japanese encephalitis a mosquito transmitted viral disease is a global confront for public health. The disease is a pediatric problem, the seriousness of the disease can be predicted as it mostly affects the children and the survivor are left with serious long term neuropsychiatric problems. Hence the disease is affecting our future generation. The only available option to control JE is vaccination but being a disease of low socioeconomic strata, affordable vaccines are still a demand. Therefore to overcome the present situation there is an imperative need for development of safe and affordable antiviral drugs for Japanese encephalitis. There are many promising antiviral agents against JE which need further evaluation. This review highlights the potential antiviral drugs which can be utilized for Japanese encephalitis.

Keywords: Antiviral drugs, flavivirus, medicinal plants, Japanese encephalitis, vaccine.

Introduction

Japanese Encephalitis also known as "Mastishka Jwar" or "Dimagi Bukhar" is mainly a brain fever caused by flavivirus. It is one of the most important global pediatric health concerns due to high fatality rate and long lasting neuropsychiatric problems[1]. It involves complex cycle involving pig as amplifying host, ardeid birds as carrier and mosquito's of *Culex* genera as vector. There is no specific treatment for JE and no effective antiviral drugs have been reported so far. Although vaccination is available for JE, but being a disease of low socio-economic group safe and affordable vaccine is still a challenge. It has been found that JE has shown an increasing trend towards other non effected countries due to many climatic favourable conditions for vector growth[2]. Due to present Global situation and unavailability of specific treatment there is an imperative need for development of anti-JEV drugs. Many potential antiviral compounds such as arctigenin, curcumin, fenofibrate, minocycline, rosmarinic acid, short interfering RNA etc are reported to inhibit JEV production[3]. These natural compounds are proficient to reduce losses caused by neuronal damage which are responsible for long term serious impairment to the children[4]. Medicinal plants represent abundant source of secondary metabolites and new bioactive compounds having antiviral potential against JE. This review focuses on the existing global scenario of potential antiviral drugs for the treatment of JE.

Antiviral Agents

There are many potential antiviral agents that are reported worldwide, many of them are plant bases, some are antioxidants, some proteins and other compounds which have produced better results in vitro and be further considered for formation of antiviral drugs for Japanese encephalitis. These agents are as follows:

Aloe-emodin: Aloe-emodin is a plant derived anthraquinone obtained from Aloe latex. Recent studies showed that it is a potential interferon inducer. It inhibits replication of JEV by interferon signalling responses in dose and time dependent manner[5].

Astragali radix: *Astragali radix* extracts (AE) is a Chinese "super herb" known for its antioxidant and antimicrobial properties. It has shown protective effect against JEV infection in mice model. Kajimura et al, on the basis of their experiment proposed that, peritioneal exudates cell plays an important role in protective effect of *Astragali radix* extract during initial stage of JE infection[6].

Arctigenin: Arctigenin is a plant lignan which can be obtained from *Arctium lappa* (Asteraceae), *Bardane fructus* (Asteraceae), *Cincus benedictus*(Asteraceae), *Forsythia intermedia* (Oleaceae), *Merremia gemella* (Convolvulaceae), *Ipomoea cairica* (Convolvulaceae), *Saussurea medusa* (Asteraceae), *Torreya nucifera* (Taxaceae). It reduces the stress associated protein increased in JEV infected animals. It reduced viral load, viral replication, oxidative stress, secondary inflammation and neuronal death resulted from microglial activation due to JEV infections. Therefore, arctigenin is a potential candidate to reduce severity of JEV infection[7].

Bispidine: Bispidine is a diazabicyclic molecule. It can function as a scaffold for compounds with very diverse biological activities, its spartine derivative act as protein secondary

structure mimetics, which are excellent compound for interacting with ion channels, G-protein coupled receptors, and enzymes, and hence can be used for anti-JEV drug development[8].

Curcumin: Curcumin is extracted from *Cucurma longa* rhizome; it is a phenolic compound known for its antioxidant, anti-inflammatory and anti-proliferative properties. Dutta et al, studied effect of curcumin on Neuro 2a cell line infected with JEV and found that it provide neuroprotection by decreasing reactive oxygen species and level of stress related proteins induced by JEV infection. Curcumin also decrease production of infective viral particle by inhibiting ubiquitin-proteasome system from previously infected neuroblastoma cells[9].

Dehydroepiandrosterone

Reports suggest that adrenal-derived steroid; Dehydroepiandrosterone (DHEA) suppresses the viral induced encephalitis by reducing neurotoxicity and increase the survival rate of experimental animals. DHEA reduces cytopathic effect, apoptotic cell death and JEV propogation in concentration dependent manner as studied by Chang et al, in their experiment on murine neuroblastoma (N18) cell. DHEA can reverse the cytotoxicity caused inactivation of extracellular signal regulated protein kinase (ERK) infected by JEV. Hence it can play a crucial role in JEV infection by controlling signaling pathways of ERK[10].

Dithiol, Diethyldithiocarbamate (DDTC)

A low molecular weight immunomodulator, dithiol, diethyldithiocarbamate (DDTC) can play protective role against Japanese encephalitis. Dispensation of DDTC delayed progression of disease in JEV infected mice by increasing the inducible nitric oxide synthase activity (iNOS) and level of tumor necrosis factor alpha((TNF-α) in brain. Saxena et al, studied the therapeutic aspects of DDTC and found that it can control JEV infection by intensifying the protective role of macrophage derived factor (MDF) [11].

Fenofibrate: Fenofibrate, a peroxisome proliferator activated receptor-α (PPARα) enhance the appearance of neuroprotective genes that triggers antioxidant and anti-inflammatory activities. In vivo and in vitro studies in JEV infected mice model suggested that pre-treatment of fenofibrate reduced death rate and prevent neurological disorders in survivors[12].

Flavonoids: Baicalein and Quercetin are bioflavonoid studied for antiviral activities against JEV. Johari et al, in their studies found Baicalein as a potent antiviral agent as it exhibited direct extracellular virucidal activity on JEV. They suggested it as an appropriate candidate for development of effective antiviral compound for JEV[13].

Furananaphhoquinone: Furanonaphthoquinone (FNQ) derivatives possess anti-JEV activity. Reports suggested 2-methyl-napthol (2-3-b) furan-4, 9-dione (FNQ3) shows highest activity against JEV. Takegami et al, demonstrated that FNQ3 Japanese Encephalitis Virus RNA replication and protein synthesis[14].

Griffithsin (GRFT)

A wide spectrum glycosylated antiviral protein Griffithsin (GRFT) is also effective against JEV. GRFT particularly binds to the enveloped and premature viral glycoprotein. This property may contribute to its anti-JEV activity and have potential for development of drug for JE[15].

Istatis indigotica: *Isatis indigotica* is a medicinal plant of China and proved to have potential antiviral agents for lethal JEV challenge. The marker compound Indirubin and indigo directly inactivate virus particle by linking with JEV replication site and reduction of virus attachment. Reports suggested that pre-treatment of *I.indigotica* gives better result against JEV than post treatment. Hence Indirubin can be used component to yield a better anti-JEV drug[16].

Kaempferol: Kaempferol is a promising natural flavonol having anti-JEV effect. Due to its high affinity for RNA, it forms non-covalent complex with JEV frame shift site RNA. This property of Kaempferol opens new aspect for development of drugs against JE[17].

Lactoferrin: Lactoferrin is a glycoprotein having anti-microbial properties. Reports suggest that it binds to heparin sulphate, a possible receptor for JEV, hence have potential as anti-viral drug for JEV. Bovine lectoferin (bLF) inhibits activity of all the JEV strains, making it promising candidate for wide-spectrum anti-JEV drugs[18].

Minocycline: Minocycline is a semisynthetic tetracycline, it reduces production of stress related protein and JEV induced free radicals.Singh et al, utilized minocycline in hospital and demonstrated its beneficial effect in JE patient in duration of major symptoms and hospital stay[19]

Macrophage derived neutrophil chemotactic factor

Nitric oxide produced by Macrophage derived neutrophil chemotactic factor (MDF) inhibits virus release, virus protein accumulation and viral RNA synthesis in JEV infection. It increases the survival rate of JEV infected mice by providing natural immunity and can be considered for JE treatment[20].

Mycophenolic acid: Mycophenolic acid inhibits Japanese encephalitis virus by inhibiting its replication. Sebastian et al, evaluated effect of mycophenolic acid on JEV infected mice model in vivo and suggested that mycophenolic acid possess antiviral activity and provide protection to JEV infected mice[21].

Nitazoxanide (NTZ): A thiazolide reported with antiviral property is Nitazoxanide (NTZ). It has been found effective at

early-mid stage of JEV infection both in vitro and in vivo. The mechanism of NTZ action is by up-regulated translation of Ca^{2+} binding proteins and anti-viral proteins. It is observed that NTZ depletes ATP-sensitive intracellular Ca^{+2} ion stores which can be utilized for possible drug development against JEV[22].

Pentoxifylline: Pentoxifylline is a universal antiviral compound which can be used as antiviral against many DNA and RNA viruses. It inhibits replication of JEV in dose dependent manner. The drug exerts it action on virus assembly or release but did not interfere with early or late protein synthesis of JEV[23].

Pokeweed antiviral protein (PAP): A type one ribosome inactivating proteins (RIPs) isolated from leaves of *Phytolacca Americana* is Pokeweed antiviral protein (PAP) possess antiviral activity against JEV infection. PAP represses replication of JEV in dose-dependent manner. Even in lethal case of JE, intra-peritoneal injection of PAP increases the survival rate of mice PAP gives excellent result both in pre-infection and post infection making it strong candidate for JEV drugs[24].

Rheum palmatum: A Chinese medicinal plant *Rheum palmatum* possess wide range of antiviral properties. The methanolic and water extract of *R. Palmatum* tested for anti-JEV activity and methanolic extract of *R. palmatum* possess excellent antiviral activity. The activity of *R. palmatum* is attributed to presence of several bioactive compounds such as aloe emodin, chrysophanol, rhein, emodin and physcion. Hence it has potential for drug discovery against JEV[25].

Rosmarinic acid: Rosmarinic acid (RA) is an active compound of Rosemary known for its antioxidant and anti-inflammatory potential. Swarup et al. worked on its antiviral activities against JEV and demonstrated that RA reduces viral replication and secondary inflammation in brain caused by microglial activation reducing the severity of JEV infection. They recommended RA for reduction of neurological complications observed in JE victims[26].

Short interfering RNA: A recent antiviral strategy for JE can be gene silencing by Short interfering RNA (siRNA) which has specific control on gene expression. The antiviral activity of small hairpin RNAs (shRNA) in vitro and in vivo was determined in different cell lines and mouse model for JEV infection. Results indicate that shRNA reduces JEV replication in dose and time dependent manner. Hence shRNAs has potential to become novel tool for controlling JEV infection[27].

Tilapia hepcidin (TH) 1-5: Tilapa (*Oreochromos mossambicus*), is an antimicrobial peptide (AMP) reported for antitumor properties. Haung et al. worked on anti-JEV activity of tilapia hepcidin (TH) 1-5 and found that its neuroprotective effect is due to reduction in secondary inflammation, viral load, viral replication and neuronal death resulting for microglial activation. It improves adaptive immunity by uplifting anti-JEV neutralizing antibody and reduces the complexity induced by JEV. Therefore can be a promising candidate for antiviral against JEV infection[28].

Trachyspermum Ammi: *Trachyspermum ammi* (Ajwain) is a medicinal plant reported to possess antiviral activities against JEV. Roy et al. worked on anti-JEV activity of ajwain oil and insisted it as a safe antiviral agent for JEV which can work both in pre and post infection conditions. Hence *T. ammi* is also a possible candidate to be considered for JEV drugs[29].

Nanotherapeutics: Nano-materials are another promising and recent field to be worked for anti-JEV potential. Liang et al, modified nanoscale silicate platelet (NSP) to reduce its cytotoxicity by capping it with sodium dodecyl sulfate (NSQc) for JE treatments. NSQc obstruct with viral binding by electrostatic interaction and reduced the lethality of mouse model challenged with JEV infection. So it can also be a potent candidate for antiviral therapy for JE[30].

Conclusion

The present Global scenario insists the need of innovative drugs for Japanese encephalitis. Although endeavor to combat JEV and alarming pediatric health apprehension, yet only supportive treatments are available for JE. Unfortunately till date no antiviral agents for JE are approved for human patient. The attempts of JE drug development is obviously moving forward as indicated by new alternatives discussed in this study. The journey from compound discovery to marketable drug is a long and expensive process so studies should focus on plant based new drug discovery as well as alternative use of available drugs. It is quite interesting to perceive that medicinal plants like *Astragali radix, Isatis indigotica, Ipomoea cairica, Phytolacca americana, Rheum palmatum* and *Trachyspermum ammi* and some known drugs like fenofibrate, minocycline, nitazoxanide, etc proved effective against JEV. It is the need of time to move the anti-JEV research from laboratory to clinical trials. The future is full of hope for an innovation in JEV drug discovery with the cooperation of researcher and policy makers.

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