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The recent allopathic and herbal approaches for Zika Virus

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Abstract

The World Health Organization declared on February 1, 2016, the cluster of microcephaly cases and other neurological disorders. The geographical distribution of Zika virus has been expanded so tremendously since 2007. Its threat is real due to constant increase in the volume of international travel, difficulties in controlling Aedes populations, invasion of Aedes species to more temperate countries and global climate change. This may increases the geographical extents which are favourable to the breeding of mosquitoes. Zika virus (ZIKV) initially discovered in east Africa about 70 years ago. It came into the limelight in 2007 in Micronesia. It widely spread in Pacific islands then to Brazil in 2015. During ZIKV it was observed an increase of almost 20 times the number of reported cases of microcephaly in new born babies in Brazil. There is not any vaccine or approved drug available for the treatment and prevention of infections by this virus. EGCG, a polyphenol presenting green tea has been shown to have an antiviral activity for many viruses. The effect of EGCG on ZIKV entry in Vero E6 cells were assessed for the development of a drug against a Brazilians train of ZIKV. The drug was capable of inhibiting the virus entry by at least 1-log (>90%) at higher concentrations (4100 μM). The pre-treatment of cells with EGCG did not show any effect on virus attachment. This was the first study to demonstrate the effect of EGCG on ZIKV indicating the drug might be possible to use for prevention of Zika virus infections. Although, few studies demonstrated that there was an increased evidence of causal relationship of Zika virus (ZIKAV) infection and microcephaly, birth abnormalities and neurological disorders such as Guillain–Barr´e syndrome. ZIKAV transmission occurs mainly by the bite of infected mosquitos (Aedes species), but some reports reveals that infections may occur via placenta, breast milk, saliva, blood transfusion and sex.

Key words: Zika Virus, treatment approaches

Introduction

Zika virus also known as ZIKAV, its an mosquito borne from flavivirus which was first identified in Uganda in the year1947. later found in humans with increasing outbreaks in Uganda, Yap Island, French Polynesia in 1952, 2007, 2013, respectively, and New Caledonia, Easter Islands and Cook Islands in 2014 [1–4].The past decades have seen some hitherto exotic arboviruses and other arthropod-borne infections emerging from oblivion into epidemic diseases of global concern. The burden of dengue has been rising for five decades [5]. The 2004-2005 outbreak of chikungunya in East Africa and Indian Ocean was followed by worldwide spread in both the Old and New Worlds in the ensuing decade [6].

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The expanding geographical distribution of these arboviral diseases is further fuelled by climate changes and importation of invasive arthropod species (most notably various Aedes mosquitoes such as Ae. albopictus, Ae. japonicus, Ae. aegypti, and Ae. koreicus) into temperate countries of Europe and North America [7, 8].

During the out break in Brazil it was observed an increase of almost 20 times the number of cases of microcephaly in reported new born babies. Health officials believe there may be a link between the virus and this clinical condition. So far, no other Flavi-virus was shown to have teratogenic capacity [9].Despite the efforts of many researchers, upto this date there is no vaccine available for the treatment and prevention of infections caused by this virus. Besides, no drug with antiviral activity against this virus has been authorized. Such measures could greatly reduce cases of neurological damage in fetuses. The (-) epigallocatechin gallate (EGCG) (Fig. 1), a polyphenol present in large quantities in green tea has been shown

to have an intense anti viral activity for many viruses, including the human immunodeficiency virus (HIV), herpes simplex virus (HSV), influenza virus (FLU) and hepatitis C virus (HCV) [10-12]. These studies demonstrated that EGCG mainly acts by inhibiting the entry of the virus into the host cell. Furthermore, it has been shown that the administration of this drug is safe for healthy in- dividuals (Chow et al., 2003). Considering the fact that EGCG has an antiviral activity against different viruses including HCV, a virus belonging to the same family of ZIKV, and taking in account the need for the development of a drug against ZIKV, we assessed the effect of EGCG on ZIKV entry in Vero E6 cells [13].

ZIKAV is primarily transmitted by the bite of infected mosquitoes, and the virus has been isolated from a number of Aedes mosquito species, notably Aedes aegypti (Ae. aegypti). The Ae. aegypti mosquito species are predominantly found in tropical and sub-tropical areas. Another potential transmitter, Aedes albopictus (Ae. albopictus), is entomologically well recognized in several parts of Europe, particularly in Mediterranean countries. Aedes polynesiensis is also incriminated as a possible contributor to ZIKAV transmission in the outbreak of French Polynesia. However there are several unknown facts and knowledge gaps about the pathogenesis, transmission, complications and treatment of ZIKAV infection. The family Flaviviridae contains some of the most clinically important arboviruses. The prototype agent, yellow fever virus, is indeed the first human virus discovered and found to be transmitted by an arthropod vector, [14-16].

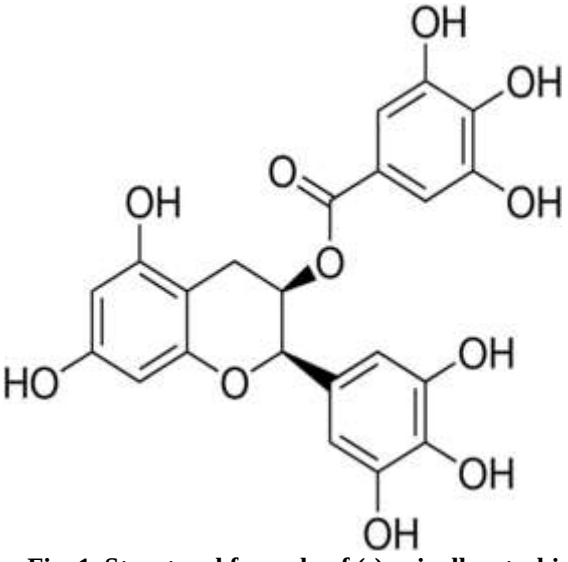

Fig. 1. Structural formula of (-) epigallocatechin gallate (EGCG) [94].

There are currently four genera in Flaviviridae, Flavivirus (53 species), Hepacivirus (one species, the hepatitis C virus), Pegivirus (two species), and Pestivirus (four species) [17]. With the exception of the hepatitis C virus, most of the clinically relevant pathogens belong to the genus Flavivirus. Epidemiologically, the arthropod-borne flaviviruses can be divided into mosquito-borne and tick-borne viruses. Flaviviruses with no known vectors are also found in animals. Clinically, the most prominent syndromes caused by flaviviruses are undifferentiated febrile illnesses (often presenting as a fever with rash syndrome), central nervous system infection (especially encephalitis), visceral involvement, and haemorrhagic fever. Flaviviruses are enveloped, single-stranded, positive sense RNA viruses measuring about 50 nm in size. The viral genome is about 10.5 to 11 kbp in size [18, 19]. The viral genome produces a polyprotein with more than 3000 amino acids; this polyproptein is then cleaved into three structural and seven non-structural proteins [20].

Virus preparation:-

It was used a strain of Zika virus (ZIKVBR) isolated from a febrile case in the state of Paraíba (Fariaetal.,2016), north eastern Brazil, courtesy of Dr. Pedro Vasconcelos, Instituto Evandro Chagas, Brazil. A sample of this virus was inoculated in Aedes albopictus cells clone C6/36 and incubated for10–12 days until onset of cytopathic effects. Subsequently a freeze-thaw cycle was done, the supernatant was clarified, aliquoted and stored at -80 °C until it was again necessary. The virus was received at its second passage after sample collection and all experiments were done with a third passage virus. An African Strain (MR766) was used to confirm the results obtained with the Brazilian strain. The virus sample was gently donated by Dr. Amilcar Tanuri, Universidade Federaldo Rio de Janeiro, Brazil. Upon the receipt of the sample it was inoculated on Vero E6 cells and it was performed the same procedure used for the other strain [21].

Methods of ZIKAV transmission:-

Human to human transmission of ZIKAV predominantly occur from the bite of an infected mosquito of the Aedes species [1, 22]. ZIKAV RNA has been isolated in blood, semen, urine, saliva, amniotic fluid, breast milk and cerebrospinal fluid [23–30]. Transmission of ZIKAV has been suggested via other non-vector means such as sex, maternal-foetal transmission and blood transfusions [31–42]. However, no study described transmission of ZIKAV person to person casually or by non-sexual close contact. There

has been one reported case of laboratory-acquired ZIKAV disease in the US [43].

Clinical presentation of ZIKAV disease:-

Before 2013, ZIKAV infection had been described as a mild, self-limiting illness associated with fever, rash, joint pain and conjunctivitis [44]. Other clinical presentations have been described in association with ZIKAV infection during the current outbreak. The incubation period for ZIKAV is unknown but the ymptoms may appear within 3–12 days after the infected mosquito bite and may resolve within 7 days [45]. The illness is usually mild and 80% of cases of ZIKAV infection may be asymptomatic [1]. The Symptoms and signs of ZIKAV may include "low-grade fever, maculopapular rash, arthralgia, conjunctivitis, malaise, myalgia, retro-orbital pain and asthenia" [46-48]. Rarely, other features such as nausea, diarrhoea, abdominal pain, mucus membrane ulceration and pruritus may occur [49]. Thrombocytopenia has been noted in case reports [50, 51]. The symptoms of ZIKAV infection usually resolve within 7 days. Severe disease is uncommon, hospitalization is not usually required and the case fatality rate is low [52, 53].

Zika diagnosis and treatment:-

In many advanced laboratories, diagnostic testing for ZIKAV is performed primarily on serum. Other specimen types such as urine, saliva, amniotic fluid, and tissue has also been evaluated. However, ZIKAV is routinely diagnosed using RT-PCR for Zika viral RNA or ZIKAV serology [54-56]. A definitive diagnosis of ZIKAV infection is made by the recognition of viral nucleic acid in serum while viremia is often brief and diagnosis by RT-PCR will be productive if undertaken in the first week after the commencement of clinical symptoms [57, 58]. RT-PCR is positive for a short window period after clinical infection and during viremia [57].

Additionally, it may be difficult to isolate nucleic acid from clinical samples in the low level viremia generally observed in ZIKAV infection [58]. For these reasons, negative results of RT-PCR testing cannot be used to exclude ZIKAV infection. Experience from the study of similar arbo-flaviviruses indicates that as the presence of active virus in the blood diminishes the ZIKAV, IgM antibodies will occur and will remain detectable for several months [59]. ZIKAV IgM and neutralizing antibodies classically develop towards the end of the first week of clinical presentation [60]. ZIKAV-specific IgM antibodies detected by IgM-capture enzyme-linked immunosorbent assay or immunofluorescence assays in serum may be used for the diagnosis of ZIKAV infection six or more days after the onset of clinical symptoms [55].

A major challenge in the interpretation of serological test results is cross-reacting antibodies against related arbo-viruses (e.g. dengue, chikungunya and yellow fever viruses). The plaque reduction neutralization test can be used to differentiate antibodies of closely related antibodies and aid in the verification of results [61]. There is limited data that ZIKAV RNA can be detected by RT-PCR in urine [62-65] and saliva [66].

Antenatal diagnostic procedures and techniques for the diagnosis of ZIKAV infection have not yet been reliably established. ZIKAV has been identified by RT-PCR in the amniotic fluid ofcongenital ZIKAV infected cases [67-71].Immunohistochemistry and RT-PCR have also identified ZIKAV infection in the tissues of foetal losses and infant demise shortly after birth [72]. Ultrasonography may detect microcephaly and congenital malformations associated with ZIKAV infection including brain atrophy, hydranencephaly, abnormal gyration, cerebral calcifications, absent corpus callosum, ventricular dilatation, hydrops fetalis, anhydramnios and intrauterine growth retardation [73-76]. These findings were noted as early as 18–20 weeks of gestation although they are often detected later [73, 77, 78].Challenges exist with respect to clinical and technical factors associated with the use of ultrasonography to detect microcephaly and the sensitivity of detecting microcephaly using ultrasonography [79, 80].

A more detailed evaluation of the foetal intracranial anatomy by means of serial foetal ultrasonography or foetal brain MRI might be recommended. Treatment of ZIKAV infection is non-specific. Treatment is generally supportive and is based on relieving symptoms mainly based on pain relief, fever reduction, and anti-histamines for pruritic rash including preventing dehydration with oral fluids. Treatment with acetylsalicylic acid and non-steroidal anti-inflammatory drugs is discouraged because of a potential increased risk of haemorrhagic syndrome. Pregnant women should be treated with acetaminophen for alleviation of fever [76].

The immunological response of the human host following ZIKAV infection is subject for future studies. The experience and lessons learnt from other human infection and immunological reaction from dengue infection in humans may be used as a reference point until further immunological observation is known. The potential role of antibody dependent enhancement of ZIKAV infection and disease has not been examined [81]. Immunological analysis as illustrated by two case reports, demonstrated that

recovery from ZIKAV infection is associated with restoration of normal numbers of immune cells in the periphery as well as with normal function of antigen-presenting cell [50].

EGCG: A effect of herbal molecule on ZIKA virus:-

Virucidal effect of EGCG:-

In order to determine the anti-ZIKV effect of EGCG, Vero E6 cells were used for evaluation. Briefly, Vero E6 cells (1.5-105) were seeded in each well of a12-well plate and incubated at 37°C with 5% CO2 for 24h prior to infection. Approximately 106 focus forming units of ZIKVBR or MR766 were mixed to different concentrations of pure EGCG (Sigma Aldrich, 495% purity) and incubated for 1h at room temperature to assess the virucidal activity of this compound. Following, the drug-treated viral supernatant were serially diluted in Dulbecco modified essential medium (DMEM) and added to the plates. After incubation for 1h at 37°C for viral adsorption, 1mL of DMEM supplemented with 2% fetal bovine serum (FBS) (Cultilab) and 1% carboxymethylcellulose sodium salt (Sigma-aldrich) were added to the wells and plate was incubated for 96h. After four days media was removed, cells were fixed with 10% formaldehyde and stained with 1% crystal violet (Sigma-aldrich) diluted in 20% ethanol. Foci were counted and compared to control (diluent only).

Cytotoxicity of EGCG on Vero E6 cells:-

In order to confirm that the inhibitory effect observed was not a result of a change in cellular conditions, we assessed the cytotoxicity of EGCG in Vero E6 cells. For this assay, 5-103 Vero E6 cells were added to each well of a 96-well plate and incubated for 24h at 37°C. Media was removed and replaced with DMEM containing different concentrations of EGCG (0–200 mM). The effects of the EGCG on the cells were determined at 1, 24, 48 and 72h post addition of the drug to culture media. The supernatants were removed, and a solution of 3-(4,5-dimethylthiazol-2-yl)–2,5-diphenyl tetrazolium bromide (MTT -1 mg/mL) was added to each well and the plate was incubated for 30min at 37°C. Subsequently to incubation, the MTT crystals were solubilized with 100 mL of Dimethyl sulfoxide (DMSO) and the absorbance was measured at 570nm.

Pre-treatment of Vero E6 cells with EGCG:-

We also tested a pre-treatment of cells with EGCG before performing the infection. For this, 24h before the assay Vero E6 cells were added in a 12-well plate and incubated at 37°C. In the following day, the culture growth medium was replaced with DMEM containing 50 μM EGCG and incubation proceeded for1h at 37°C. After this period, the medium containing the drug was removed and the cell mono layer was washed 3 times with PBS to eliminate any trace of EGCG. Then the virus was inoculated on the treated cells and the remainder of the procedure was similar to that used in the test of virucidal activity [94].

Zika-associated neurological syndromes:-

A rise in Guillain–Barr´e syndrome (GBS) has been reported in several countries in the Americas and the Pacific in association with the current ZIKAV outbreak [82-86]. GBS is a serious, immune-mediated illness exhibiting as progressive paralysis over 1–3 weeks, with a 5% death rate and up to 20% of patients left with a significant disability. Based on the study methods and case ascertainment, the annual incidence of GBS could be estimated in the range of 0.4–4.0 cases per 100000 population per year. Furthermore, earlier studies have also found that GBS is more common in adults, with risk increasing with age and men more likely to be affected than women [87]. During the outbreak of ZIKAV in French Polynesia, in the 4 months

between November 2013 and February 2014, 42 patients were diagnosed with GBS among 28000 persons presenting for medical care [82], representing a marked increase from the approximately 5 cases detected annually in the previous 4 years [83].

A case-control study in French Polynesia also showed an odds ratio of > 34 between GBS and a history of ZIKAV infection. Overall, 7 countries in the Americas have reported an increase in cases of GBS with at least one case detected to have laboratory confirmed ZIKAV [1, 4].

Other neurological complications have been reported in association with ZIKAV including acute myelitis [84], meningoencephalitis [85] and brain ischemia [86]. In addition to bite avoidance measures, non-pregnant, sexually active women of reproductive age residing in endemic areas should consider the issues of family planning and contraception, taking into account various social and religious precepts [88]. At present, the only flaviviral vaccines available for human use are yellow fever (live attenuated), Japanese encephalitis (inactivated, live attenuated, and chimeric), tick-borne encephalitis (inactivated) vaccines, and the newly marketed dengue vaccine (live attenuated, recombinant, tetravalent; marketed since 2015). Claims were made by an Indian biotechnology company that two Zika virus vaccine candidates (recombinant and inactivated) can be tested soon; however, no details on the vaccine preparations are currently available in the scientific literature [89].

In any case, a normal vaccine development cycle usually requires years of preclinical and clinical studies

and a Zika virus vaccine for human use is unlikely to be available in the near future. In the absence of vaccines or chemoprophylaxis, the prevention of Zika virus infection follows the general rules for other vectorborne infections. Broadly speaking, this involves two major areas, personal protection through bite avoidance and vector control. Bite avoidance is equally important to both residents in and travellers to endemic areas. Personal protection includes general measures such as protective clothings, proper choice and use of insect repellents, and mosquito-proofing of houses. The use of insecticide-impregnated bednets has been one of the core elements in the prevention and control vectorborne diseases such as malaria in endemic countries. However, its role against the Aedes vectors of Zika virus depends on the behaviours of the vectors in specific geographical areas. In general, Ae. aegypti mosquitoes are endophilic (resting indoors), endophagous (biting indoors), anthropophagic (preferentially biting humans), and diurnal and crepuscular in their activities. Ae. albopictus mosquitoes are generally exophilic (resting outdoors), exophagous (biting indoors), and anthropophilic, and are aggressive daytime biters [90-92].

However, it is known that the endophilic/exophilic and endophagous/exophagous behaviours are not absolute and these can be variable in different geographical areas [93]. A thorough knowledge of the local mosquitoes and their behaviours are therefore crucial to the control of vectorborne disease and this underlines the importance of long-term local vector surveillance.

Conclusion

The rapid distribution and outbreak of ZIKAV becomes a global concern and threat. The spreading and transmission of the virus will continue to be detected in new geographic locations and populations. Many countries harbour the mosquito vectors, responsible for the transmission of ZIKAV. Other potential transmission patterns and ways may also contribute towards a long term circulation of the virus. In conclusion, as per one study that EGCG, a natural compound found in abundance in many foods, especially in green tea, inhibits in vitro the entry of ZIKV into the host cell. The mechanism by which this inhibition occurs is probably related to the direct interaction of the drug with lipid envelope, leading to a subsequent destruction of the virus particle. We also presented that the action of this drug is not related to blocking or reducing the expression of cell receptors used by the virus in their entry process. Studies demonstrated that EGCG is chemically unstable, having low permeability membrane as well as rapidly metabolized by the organism. The maximum plasma concentration reached by this drug is approximately 7 μM, almost 15 times smaller than the optimal concentration for the elimination of ZIKV. Moreever, some studies have been shown that the bioavailability of EGCG can be increased by chemical modifications such as per acetylation or by using nano encapsulation.

All in all, it's the first report demonstrating that EGCG is possibly used in therapy and prevention of infections caused by the Zika virus. Nevertheless, prior its effective implementation factors, such as their bioavailability and the safety evaluation should be improved. The unique challenge of Zika virus infection lies not only on the control of the disease but to find the potential squeal of congenital infections and severe neurological complications. Furthermore studies may provide lights to the pathogenic mechanisms, more sensitive predictors of congenital abnormalities and the possibilities of vaccination.

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