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Current Advances in Zika Virus Transmission: Urgency for Effective Therapeutics and Prevention

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Abstract: Global emergence of Zika Virus (ZIKV) with prevalent outbreaks has been reported in numerous countries of South America, Central America and the Caribbean region. According to recent World Health Organization (WHO)-ZIKV situation report, 84 countries/territories/subnational areas represented with established mosquito-borne transmission of ZIKV. As of 10 August 2017, cumulative Zika cases and congenital syndrome associated with Zika virus reported by countries and territories in the Americas, 2015 – 2017 includes 217,471 confirmed cases with the Case Fatality Rate (CFR) of 0.01% and 78.08 incidence rate. ZIKV has undoubtedly become a major threat in countries endemic for other Flavivirus infection. Factors such as urbanization, global trade and travel, tropical/sub-tropical climate, prevalence of *Aedes* vector and poor waste management altogether are responsible for ZIKV infection in Southeast Asian countries. The occurrence of co-infection by other Flavivirus (Dengue) and ZIKV have been reported in tropical/sub-tropical region, implying the role of sero-cross reactivity and initiating antibody dependent enhancement of ZIKV infection. The trans-placental transmission of ZIKV in pregnant women makes the fetus more susceptible to ZIKV infection. In order to control ZIKV infection, development of robust vaccine and effective antivirals are required urgently. This review majorly discusses about ZIKV epidemiology, modes of transmission, antibody dependent enhancement and prevention and control strategies.

Keywords: Zika Virus, Antibody Dependent Enhancement, Vaccines, Antiviral Drugs, Complementary and Alternative Medicines

Introduction

Global emergence of Zika Virus (ZIKV) with prevalent outbreaks has been reported in numerous countries of South America, Central America and the Caribbean region (ECDPC, 2016). According to ZIKV situation report-March 2017, World Health Organization (WHO), 84 countries/territories/ subnational areas represented with established mosquito-borne transmission of ZIKV (WHO, 2017a). Estimates are suggesting the ZIKV infections in 2015-2017, ranged from at least 500,000 to 1.5 million. As of 10 August 2017 cumulative Zika cases and congenital syndrome associated with Zika virus reported by countries and territories in the Americas, 2015- 2017 includes 217,471 confirmed cases with the Case Fatality Rate (CFR) of 0.01% and incidence rate of 78.08 (PAHO/WHO, 2017). ZIKV was first identified in Uganda in 1947 (Dick *et al*., 1952) and there was a major outbreak reported in Yap (Federated States of Micronesia) in 2007 (Lanciotti *et al*., 2008). Towards the end of 2015, 14 Brazilian states were majorly affected with an estimation of 440,000-1,300,000 suspected cases (Hennessey *et al*., 2016). Thereafter, it was transmitted to the rest of the 29 countries of America (Chitti *et al*., 2016). In recent years, ZIKV has become a major threat in some Southeast Asian countries like India, China, Indonesia, Thailand, Maldives and Pakistan due to urbanization, global trade and travel, tropical/sub-tropical climate, prevalence of vectors and poor waste management (Messina *et al*., 2016) which might be responsible for the recent outbreaks of ZIKV in these countries. It is concluded that people living in two million square kilometers of tropical and sub-tropical region are at the highest risk for ZIKV transmission (Doss *et al*., 2017) because of co-circulation of other Flaviviruses primarily Dengue Virus (DENV) and ZIKV in this region commences probability of co-infection (Pessôa *et al*., 2016).

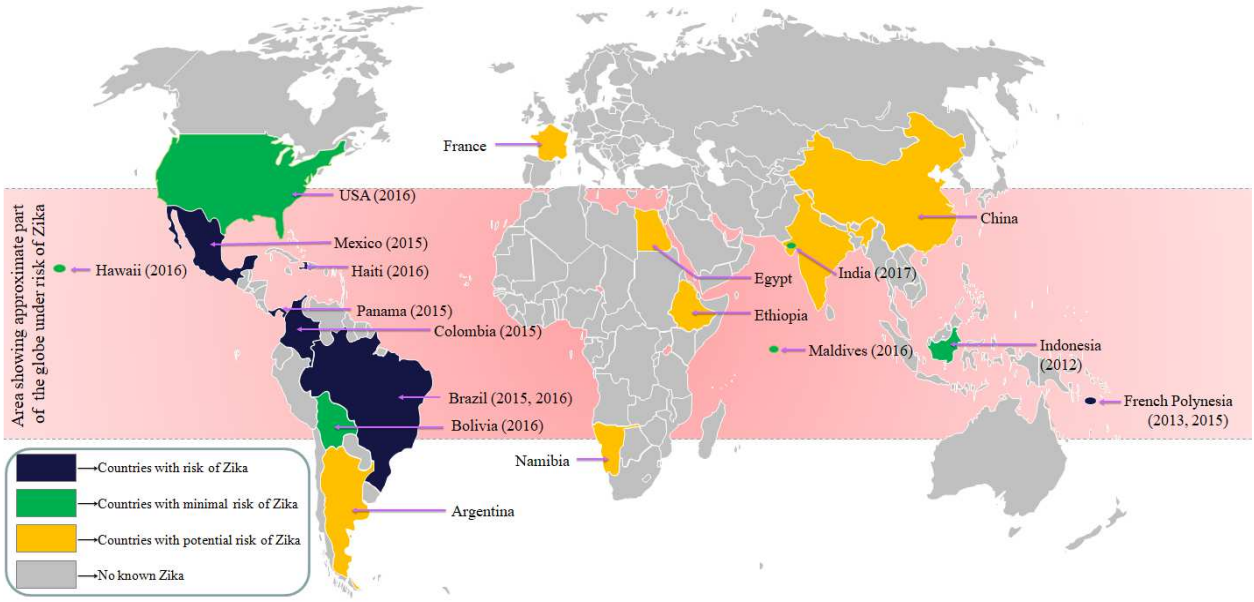

Fig. 1. Recent outbreaks of ZIKV global distribution of ZIKV infected countries during 2012-2017 [Source: WHO, 2017b]. Countries marked with orange color are at potential risk of getting infected by ZIKV especially the South East Asian countries

According to the current report of WHO and European Centre for Disease Prevention and Control (ECDC), countries at risk, potential risk and minimal risk of ZIKV infection were shown in Fig. 1. The first official epidemic was reported on the islands of Mac, Micronesia and Tahiti followed by French Polynesia (Musso *et al*., 2014) where 28,000 (10% of the overall population) people represented with confirmed cases of ZIKV infection. The foremost outbreak of ZIKV infection has been reported in Brazil in year 2015 where more than 200,000 people were infected and about 2,366 people were reported with microcephaly and various birth defects. In June 2015, near about 45 countries in America were infected with local ZIKV infection (Faria *et al*., 2017). Very recently three cases of ZIKV infection were reported to WHO from India where 34 year old mother, a 64 year old man and a 22 year old pregnant women were confirmed for ZIKV infection (http://www.who.int/csr/don/26-may-2017-zika-ind/en/). Endemic area for DENV is suggesting the highest risk for ZIKV outbreak. Detection of antibodies against the ZIKV due to sero cross-reactivity with other Flaviviruses such as dengue (Mourya *et al*., 2016) clearly implicated that India might be at higher risk for ZIKV infection (Vinodkumar *et al*., 2013).

ZIKV Genome

ZIKV is a mosquito born ssRNA (+) virus which belongs to genus *Flavivirus* and family *Flaviviridae* and comprises of ~11kb long genome with 3' and 5' Untranslated Regions (UTR). The 3400 amino acid long polyprotein encoded by ZIKV is co and post-translationally processed by host and virus proteases that give rise to three structural proteins namely as Capsid (C), pre-Membrane (prM) and Envelope (E) and seven non-structural proteins including NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 (Rodenhuis-Zybert *et al*., 2010). Similar to other Flavivirus, ZIKV follows the same replication cycle. ZIKV internalize by endocytosis through interaction of envelope protein with cell surface receptors, such as DC-SIGN (Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) and several members of phosphatidylserine receptor family. The acidic environment of the endosome promotes fusion of viral envelope with endosomal membrane; hence it allows the release of viral RNA into the cytoplasm for the initiation of translation. Later, translated viral proteins assists in the replication of viral RNA at the surface of endoplasmic reticulum where the assembly of viral RNA and viral proteins form immature virions within endoplasmic reticulum. The virus matures in the trans-Golgi network upon the furin-mediated cleavage of prM to M protein following egression into the surroundings via exocytosis (Hamel *et al*., 2015).

Modes of Transmission

ZIKV is predominantly transmitted to humans by an infected mosquito bite mainly by *Aedes aegypti* and *Aedes albopictus*. Through enzootic life cycle, the ZIKV is maintained between mosquitoes and primates.

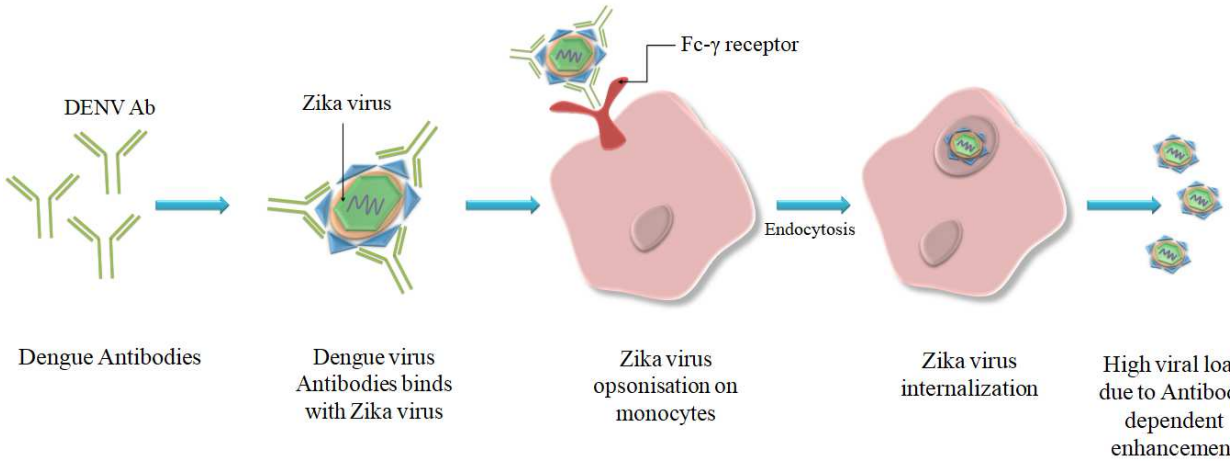

Fig. 2. Antibody Dependent Enhancement (ADE) of ZIKV preexisting antibodies against DENV are insufficient to neutralize ZIKV internalization rather the ZIKV opsonized via Fc receptor expressing monocytes which are the major site for the DENV replication

Six thousand primates and ten thousand mosquitoes are enough to maintain ZIKV transmission cycle (Althouse *et al*., 2016). *A. aegypti* and *A. albopictus* are found in the tropical and subtropical regions hence, these areas are more prone to ZIKV transmission. Till date, ZIKV has been isolated from 17 different *Aedes* mosquito species whereas four belongs to genera *Anopheles* including *Culex perfuscus, Mansonia uniformis, Anopheles coustani* and *Anopheles gambiae* (Slavov *et al*., 2016). This wide range of mosquitoes is clearly suggesting the complexity of transmission dynamics of ZIKV. During the French Polynesian outbreak ZIKV transmission was associated with blood transfusion, where 3% of asymptomatic blood donors were confirmed for ZIKV (Basarab *et al*., 2016) thus making blood transfusion a novel mode of ZIKV transmission. In recent times, several cases of male-to-female ZIKV transmission have been reported thus raising the concern of ZIKV transmission in the human semen (Imperato, 2016). Maternal to fetus transmission of ZIKV has also been reported where infection during pregnancy leads to microcephaly in infants and Guillain- Barré syndrome (Besnard *et al*., 2014).

Clinical Manifestation

Like other Flavivirus infections, up to 80% of human ZIKV infections are asymptomatic (Marano *et al*., 2016). Clinical manifestations appear after an incubation period of 3 to 12 days and are reported to be characterized by body rashes, fever (37.5°C to 38.5°C), headache, giddiness, gastrointestinal disturbances, muscle pain and conjunctivitis (Basarab *et al*., 2016). Recent studies suggested that flaviviral infections target the eyes and brain with few cases associated with bilateral macular and perimacular lesions (Mlakar *et al*., 2016). In 2015, it was reported that there was an astonishing 20-fold increase in parental microcephaly cases as compare to 2014 (Fauci and Morens, 2016). Although the relationship between ZIKV and microcephaly is not clearly understood but it is possible that virus attacks the stem cells during early brain development causing the destruction of some brain tissues.

Anti-Flaviviral Antibody Dependent Enhancement (ADE) of ZIKV

People living in Flavivirus endemic countries are at potential risk for ZIKV infection; this might be due to common *Aedes* vectors, significant sequence similarity among Flaviviruses and generation of sero-complex and sero-cross reactivity that leads to Antibody Dependent Enhancement (ADE) of ZIKV infection. Dengue and ZIKV are closely related (Dejnirattisai *et al*., 2016) as they both have similar antigenic domains (41-46% in amino acid sequence of envelope protein) which results in substantial sero-cross reactivity. Pre-existing antibodies of DENV helps in opsonization of ZIKV for internalization via Fc receptor present on monocytes and macrophages which are principle site for virus replication (Fig. 2). These non-neutralizing cross reactive antibodies increases the infectivity in the host cells (Lauren *et al*., 2016). This leads to ADE of ZIKV infection that eventually causes higher viremia in ZIKV-infected patients in areas endemic for Flaviviruses. Our recent studies have shown novel Flavivirus-specific B cell epitopes which might be responsible for ADE during ZIKV infection (Saxena SK *et al*., Pers. Comm.).

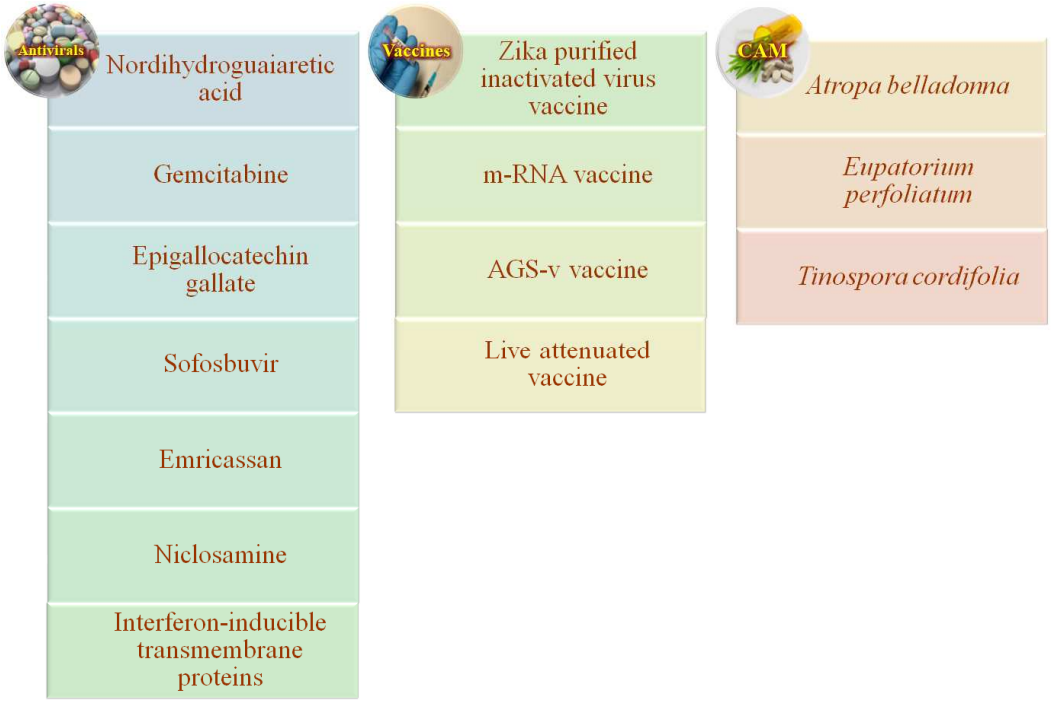

Fig. 3. Therapeutics for Zika virus potential antiviral drugs, vaccines, complementary and alternative medicines for the treatment of Zika virus infection

Diagnosis

The diagnosis of the ZIKV infection depends on the time interval between infection and clinical presentation. Most people infected with ZIKV represents very mild symptoms and do not present for clinical evaluation. Therefore, diagnosis often depends upon the measurement of IgM antibodies against ZIKV infection using ELISA (Nugent *et al*., 2016). Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) detects ZIKV in blood but within 3-5 days of the onset of symptoms. Virus can also be identified in urine, seminal fluid, saliva and amniotic fluid (Bingham *et al*., 2016).

Prevention and Control Strategies

Currently there is no Food and Drug Administration (FDA) approved vaccine or antiviral for ZIKV infection. There are several vaccines and antiviral drugs for ZIKV which are under research and clinical trials (Fig. 3).

Investigational Vaccines

Zika Purified Inactivated Virus Vaccine

Zika Purified Inactivated Virus (ZPIV) vaccine might prove to be efficient against ZIKV infection as in preclinical development it was found that the vaccine induced antibodies neutralizes the virus and protects it from ZIKV infection. It contains whole inactivated ZIKV particles whose protein shell remains intact so it can invoke an immune response when there is ZIKV infection. It is based on the similar approach that is used to develop vaccine for Japanese encephalitis (Abbink *et al*., 2016).

Lipid Nanoparticle Encapsulated Zika Virus m-RNA Vaccine

Messenger RNA has been developed as a highly efficient platform to deliver vaccine antigens and therapeutic proteins. Researchers found that a single low-dose of vaccine containing Zika virus m-RNA encapsulated in a lipid nanoparticle (m-RNA LNP) elicited an effective neutralizing antibody response in mice and non-human primates (Fernandez and Diamond, 2017).

AGS-v Vaccine: A Magic Bullet for Zika Virus Infection

A potential vaccine candidate AGS-v which has dual action mechanism that aims in prevention of human infection as well as controls mosquito population. During Phase 1 clinical trials it was reported that rather than targeting specific pathogens, AGS-v elicits an immune response to four proteins present in mosquito saliva. Pre-vaccinated individuals generate antibodies that attack the salivary glands of the mosquito upon mosquito bites carrying viruses which reduces the survival of mosquito (Unwin, 2017).

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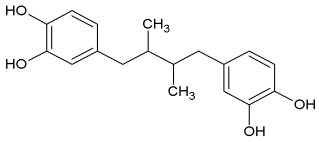
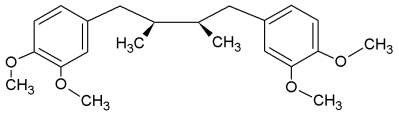
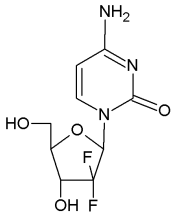
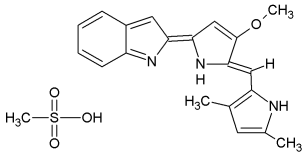
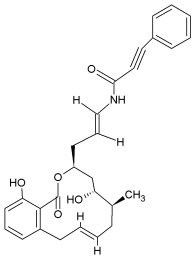
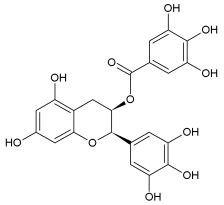
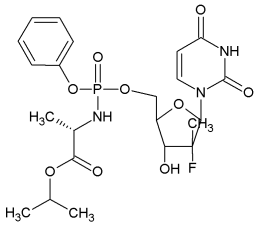
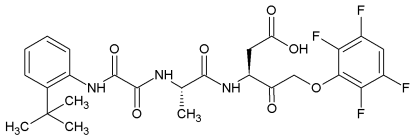
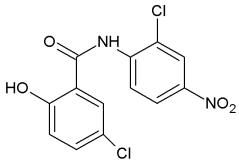
Table 1. Antiviral drugs against Zika virus infection

S. no.	Drug	Structure
1.	Nordihydroguaiaretic acid	
2.	Tetramethyl Nordihydroguaiaretic acid	
3.	Gemcitabine	
4.	Obatoclax	
5.	Saliphenylhalamide	
6.	Epigallocatechin Gallate	
7.	Sofosbuvir	
8.	Emricasan	
9.	Niclosamide	

Live-Attenuated ZIKV (Δ10) Vaccine

A live-attenuated vaccine is developed by deleting one segment of the viral genome so that it cannot cause a disease. In preclinical trials on type 1 interferon receptor-deficient mice, researchers reported that the vaccine is highly attenuated, protective and immunogenic against ZIKV infection as it contains the deleted 10-nucleotides present in the 3'untranslated region of the ZIKV genome (Shan *et al*., 2017).

ZIKV Antivirals

In present scenario there are no approved antiviral to prevent ZIKV infection. Recently FDA-approved some promising drugs for hepatitis C virus and Ebola virus that might also be effective for ZIKV infections. Here we briefly discuss the existing potential antiviral drugs for ZIKV infection (Table 1).

Nordihydroguaiaretic Acid ($C_{18}H_{22}O_4$) *and Tetramethyl Nordihydroguaiaretic Acid* (M_4N)

Nordihydroguaiaretic acid (NDGA) and M_4N (synthetic methylated derivative of NDGA) has earlier shown efficacy towards restriction of replication in hepatitis C and dengue virus. The antiviral effect of NDGA and M_4N disrupts the lipid metabolism by interfering the sterol regulatory element binding proteins (SREBP). NDGA and M_4N might prove to be potential candidates for antiviral development against ZIKV infection (Merino-Ramos *et al*., 2017).

Gemcitabine (Nucleoside Analogue), Obatoclax and Saliphenylhalamide

Gemcitabine ($C_9H_{11}F_2N_3O_4$), Obatoclax ($C_{21}H_{23}N_3O_4S$) and Saliphenylhalamide ($C_{28}H_{29}NO_5$) interferes with de novo pyrimidine biosynthesis which inhibits ZIKV replication by interfering with the transcription, translation and post translation modifications of viral RNA (Kuivanen *et al*., 2017).

Epigallocatechin gallate ($C_{22}H_{18}O_{11}$)

Epigallocatechin gallate (EGCG) is a polyphenol compound present in green tea. EGCG directly interacts with lipid envelope which leads to subsequent disruption of the viral particles followed by inhibition of ZIKV entry into the host cell (Carneiro *et al*., 2016).

Sofosbuvir ($C_{22}H_{29}FN_3O_9P$)

Sofosbuvir is an RdRp (RNA dependent RNA polymerase) inhibitor that has been approved by FDA for the treatment of hepatitis C virus infection (Onorati *et al*., 2016). It could be a probable antiviral candidate for ZIKV as reduces viral NS1 staining in human neuroepithelial stem cells.

Emricasan ($C_{26}H_{27}F_4N_3O_7$)

Emricassan might be effective in the treatment of ZIKV infection as it is a caspase-3 inhibitor that protects neural progenitor cells from dying after being infected with Zika virus, both in two and three dimensional cell layers (organoids) that mimic important structures in developmental process.

Niclosamide ($C_{13}H_8C_{l2}N_2O_4$)

Niclosamide is an anthelmintic drug that is approved by FDA for the treatment of tapeworm infection. It is considered safe during pregnancy. This feature of niclosamide could enable its use in pregnant women with the Zika virus infection (Cheng *et al*., 2016). Combination of emricasan and niclosamide might be very effective against ZIKV infection.

Interferon-Inducible Transmembrane Proteins (IFITMs)

IFITMs inhibit the multiplication of flaviviruses such as West Nile and Dengue viruses. IFITM restricts the virus from entering the cell by preventing it from crossing the lipid bilayer. IFITM3 is more potent in restricting ZIKV at the site of attachment as well as in inhibiting the host factors responsible during endocytosis, membrane fusion and vesicular trafficking (Bailey *et al*., 2014).

Complementary and Alternative Medicines (CAM)

CAM has been very efficient in treating some contagion diseases like dengue, yellow fever and chikungunya. *Eupatorium perfoliatum* and *Atropa belladonna* (Paul and Datta, 2011) can be used for ZIKV treatment as they have bioactive compounds like scopolamine and hyoscyammine which are native to Western Asia and North Africa (Saxena *et al*., 2016). *Tinospora cordifolia* is naturally occurring herbal medicine and proved to be very helpful in the treatment of several viral infections and considered as a potential immunomodulator as it reinforce the immune system and combat infection. It helps in enhancing the phagocytic system especially in the macrophages. *Tinospora cordifolia* has been efficacious in case of other diseases like dengue, chickungunya, influenza and hence they might play a decisive role in the treatment of ZIKV (Mittal *et al*., 2014).

Future Perspectives and Conclusions

According to WHO, Zika has been declared as a public health emergency of international concern, therefore, it is utmost necessary to restrict the escalating number of incidences of ZIKV infection. The countries at potential risk of ZIKV infection are mostly the developing countries with high population

density, humid climate suitable for breeding mosquitoes, improper health-care system and poor waste management. The leading health organizations should establish a proper surveillance system especially in areas endemic for other Flaviviruses, to monitor and authenticate the number of cases of Zika. A robust molecular diagnostic tool is required for the definite identification of ZIKV due to high similarity and sero-cross reactivity among the genome of Flaviviruses. Identification of ZIKV specific antigenic marker, UTR sequences and RNA secondary structures may lead us to the prognosis for ZIKV infected individuals. Mosquito control programs and public awareness regarding the Zika symptoms, precautions for pregnant women should also be augmented. In order to control the prevalence rate of ZIKV, a strong vaccine and effective antivirals are the most promising.

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Author's Contributions

Yash Raj, Swatantra Kumar and Amrita Haikerwal: Coordinated the data-analysis and contributed to the preparation of the manuscript.

Madhu M. Goel and Madan LB Bhatt: Contributed reagents/materials/analysis tool.

Shailendra K. Saxena: Conceived and designed the manuscript, contributed reagents/materials/analysis tool including analysis of the data and preparation of the manuscript.

Competing Interests

The authors declare that they have no competing interests.

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