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Review on: Emerging Therapy for Dengue

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ABSTRACT

Dengue fever is an acute febrile disease. It's caused by one of the for closely related virus serotypes of genusareflavivirus, family flaviviridae.It is mainly spread by Aedes mosquito the virus group consist of four serotypes that manifest with similar symptoms. Dengue causes a spectrum of disease, ranging from a mild febrile illness to a life threatening hemorrhagic fever. Anti-dengue drugs such as host modulators, antivirus and RNAi therapeutics used in treatment of disease.

Keywords: Dengue viruses, Aedes mosquito treatment, flaviridae, anti-dengue drugs.

INTRODUCTION

Dengue fever is the fastest growing arboviral infection spore. Dengue has the most important arboviral infection world with infection more than 30 million [1]. It is cost by when Aedes mosquito carrying the virus bites a healthy person. This disease is mainly found in the tropical and subtropical regions of the world. According to WHO, an estimated 5, 00,000 people require hospitalization each year. Most cases occur in tropical areas of the world, America most susceptible to the disease as per data released by directorate of National vector Borne disease control programme (NUBDCP). [3] Currently there are no antiviral developed to treat dengue infection, and treatment remains supportive. Although a DENV vaccine has recently been used in some countries, It'sindications is limited due to risk of severe dengue in certain populations. This has led to calls for intensified research efforts for development of novel vaccine, therapeutics and vector control strategies against dengue virus [1, 3].

HISTORY

In the 18th century dengue has caused repeated epidemics worldwide H.Graham in 1903 implicated Aedesaegypti as the vector for the disease and the virus was isolated in 1944 by Albert Sabin et al. Dengue haemorrhagic fever gained nosologic status in 1954 and subsequently its became a pendemic in many areas of tropical Asia [1]. The first record of a case of probable dengue fever is in Chinese medical encyclopedia from Jin Dynasty which referred to flying insects. The primary vector A.aegyptispraed out of America in 15 to 19th centuries due to in part of increased globalization secondary to slave trade [3]

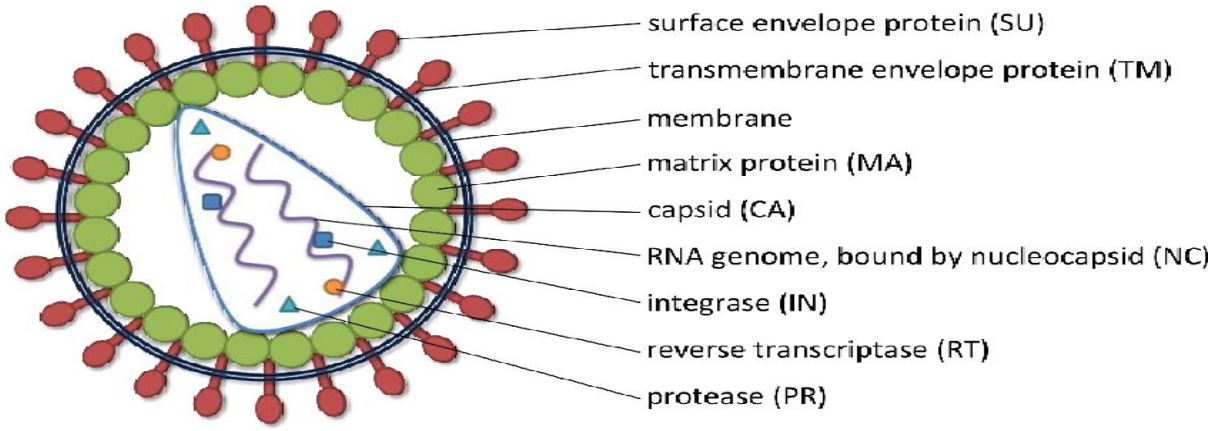


Figure 1 Structure of dengue virus

DENGUE FEVER [1]

Dengue fever (DF) and its severe forms dengue hemorrhagic fevers (DHF) and dengue shock syndromes (DSS) have become major international public health concerns. Dengue is most prevalent arthropod-borne viral illness in humans [1]. Dengue fever is also non as break bone fever is mosquito borne tropical disease its caused by dengue viruses. The dengue has transmitted by several species of mosquito the genus is Aedes those who become infected with virus a second time are at significantly greater risk of developing severe disease [3].

Causes

Dengue is caused due to for viruses namely has got four different types (I,II,III,IV) common name of disease break bone fever [1]. The virus enters a mosquito when it bites and already infected person. Once a person recovered he is immune to specific virus and not the other three types. the probability of developing severe dengue fever known as dengue haemorrhagic fever [3].

Spared

The Dengue virus is present in the blood of the patient. Suffering from dengue fever whenever an aedes mosquitoes bites a patient of dengue fever it sucks blood and dengue viruses enters into its body [1]. The virus undergo further development in the body of mosquito for a few days. The virus enters into the body and he/she becomes infected and develop symptoms [3].

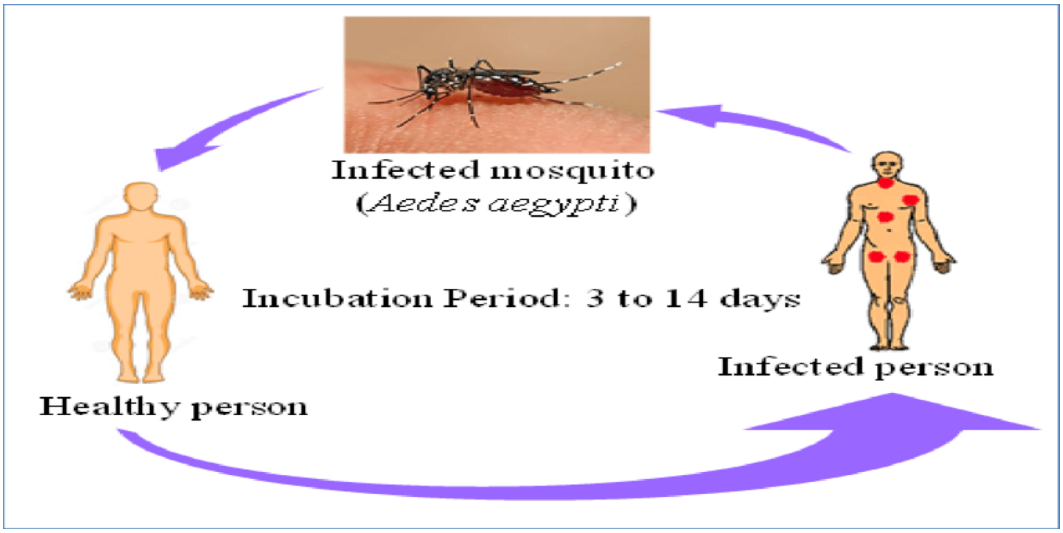


Fig.2: Transmission

Life cycle

Until a few hundred years ago dengue virus was transmitted in sylvatic cycles in the Asia and Africa between mosquitoes of the genus aedes and non-human primates with rate emergences into the human population [1]. The global spread of dengue virus as followed its emergence from sylvatic and the primary life cycle now exclusively involves transmission between human and aedes mosquitoes [3].

Symptoms

- Mild symptoms of dengue can be confused with other

  Illness that cause fever and pains or rash

- Severe headaches, pain in muscles and joints

- Pain behind eyeballs especially on pressing eyes on or

  Moving eyeballs

- Mild pain in throat

- Loss of appetite, feeling of nausea

- Change in test sensations in mouth [4]

Methods of bio-analysis for anti-dengue activity [1, 3]

Pre-clincal

Dengue is very hazardous to human kind. Dengue it is positive strand RNA virus with an 11kb genome encoding of polyprotein precursor to generate at least 10 proteins including three structural proteins and 7 non structural

proteins. In man, the intial target of dengue is thought to be dendritic cells, followed by lymphatic spread and then distribution to macrophages and monocytes.

Clinical

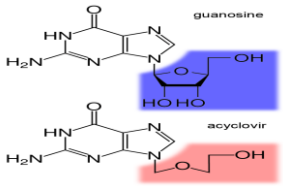
Clinical methods of evaluation of anti-dengue effects are development. A major hurdle facing DENV clinical trials is need for establishment of accurate diagnostics testing for case identification. The current diagnostics for DENV available in us are other hi resource countries (Igm and IgG, ELISA, PCR) current point of care (POC) diagnostics test for DENV best on lateral flow detection of secreted Igm and DENV NSI protein in plasma IgA.

Treatment

Agents in development for anti-dengue activity

Nucleoside analogues

Balapiravir (RG1626) is prodrug of a nucleoside analogue. Which is must triphosphorylated for conversion into active form. Balapiravir represents the first direct antiviral agent that has been tested in patients.Balapiravir clinical development of compound for treatment of chronic HCV was halted because of an unacceptable benefit to risk ratio. Since the RDRP of DENV shows similarities with HCV it was anticipated that drug would also be affecting DENV[1,5].



[5,14]

Fig.3.structure of Nucleoside analogues

RNA dependent RNA Polymerase (NS5) inhibitors

N-sulfonylanthranillic acid derivatives were identified as DENV RdRp inhibitors through screeing of one million compound. The identified hit was found to bind DENV NS5 at site of entrance to RNA tunnel [1].

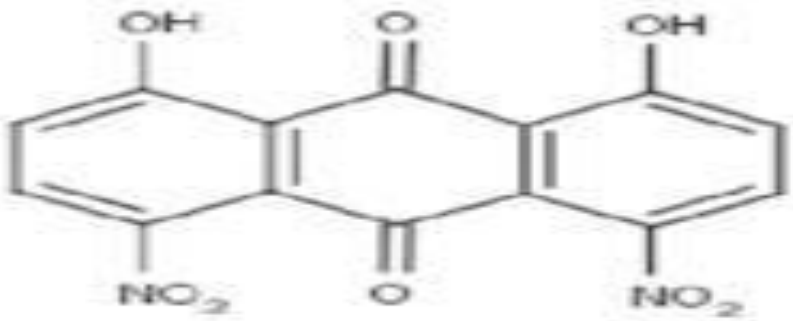
BP13944

A screen of 60,000 compounds in a DENV serotype 2 luciferase harbouring replication. It is developed by high throughput screening with dengue virus Replicon cells select for resistance in viral NS2B/NS3 protease [1, 6].

Protease (NS2b-NS3) inhibitors

Recombinant retrocyclin 1. Rothan et al. Produced recombinant NS2b-NS3 protease in E.coli. NS2B-NS3 protease at the luminal side by host cell peptidase. Dengue virus NS2b/NS3 protease is a serine proteases that belongs in

chymotrypsin family with classic ser-HiS-ASP catalyst [1, 6.

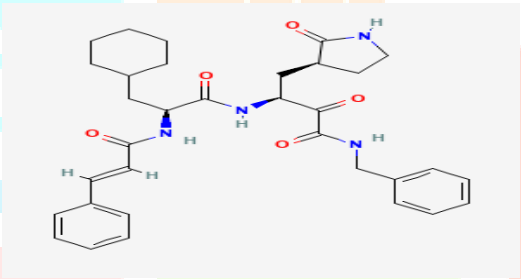


[6,15]

Fig.4 Structure of Protease inhibitor

α-ketoamides

Electrophilic trap for serine component of DENV NS2b – NS3 protease and have identified a-ketoamides [1].

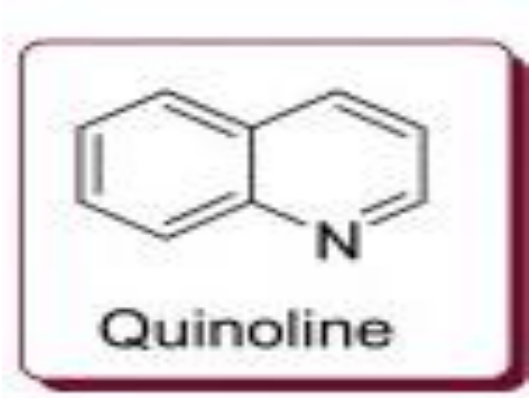


[16]

Fig.5 Structure of α- ketoamides

Quinoline containing compounds

Using virtual screening for DENV protease inhibitors followed by scaffold hopping, to expand chemical diversity [1].

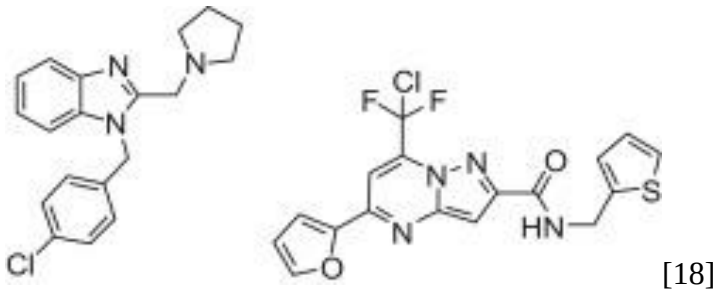


[17]

Fig. 6 Structure of quinoline

NS4b inhibitor

Van cleef et al. Recently screened the NIH clinical collection of drug like small molecule for anti-DENV activity in hela cells. NS4b is multi transmembrane protein residing in the endoplasmic reticulum membrane as part of DENV replication complex.

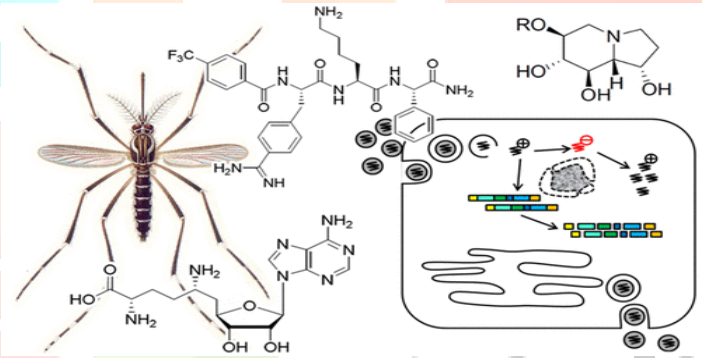


[18]

Fig.7 NS4B inhibitor

Translation inhibitors

A high throughout screen for reduction of elimination of DENV CPE and identified benzomorphan compounds through suspension of RNA translation.

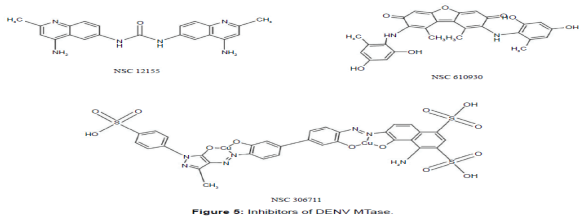


[19]

Fig.8 Structure of translation inhibitors

Methyl Transferase (NS5) inhibitors

Using a fragament-based drug discovery approach, recently screened 500 drugs like fragments by thermal sift assay for binding to DENV NS3 helicase.

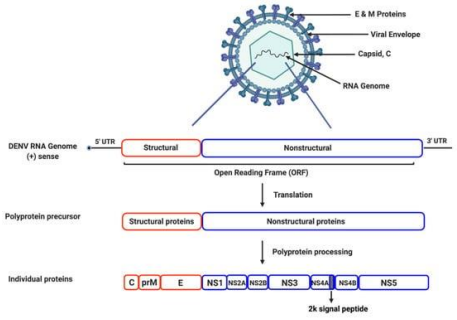


[20]

Fig.9Structure of Methyl transferase Inhibitors

Capsid inhibitor

A high throughout small molecule screen with readout of DENV induced CPE was performed on over 2,00,000 copmounds.



[21

]Fig.10 Structure of Capsid inhibitors

Peptide inhibitor of various DENV protiens

Several groupshave recently proposed the use of peptide inhibitors to block DENV infection.

Host modulators

This property in attempts to inhibit viral replication through deprivation of these required host factors or dependency factors [6].

Ribavirin

Ribavirin is a broad acting inhibitor of DNA and RNA viruses this helps to attempts inhibits inosine monophosphate dehydrogenase. Deprivation of these required host factors of dependency factors.

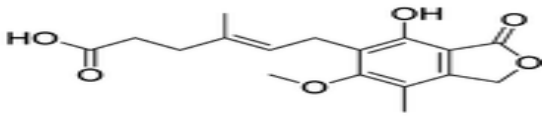
[22]

Fig.11 structure of Ribavirin

Mycophenolic acid

The immunosuppressive agent mycophenolic acid and a nonnucleoside inhibitor of IMP dehydrogenase as also been shown to inhibit dengue cell culture mycophenolic acid inhibits

dengue virus infections by preventing replication of viral RNA [6].



[22]

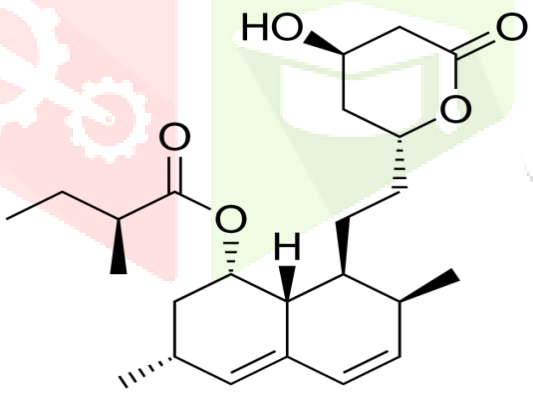
Fig.12 Structure of Mycophenolic Acid

Agents that target host mediated post translation modifications

A glycosidase inhibitors

Lovastatin

Lovastatin to be safe and good in treatment of dengue fever. Clinical statins are inhibitors of 3–hydroxy–3 methylglutaryl coenzyme A (HMG-COA) reductase used for lipid lowering and mortality reduction in cardiovascular disease [6].

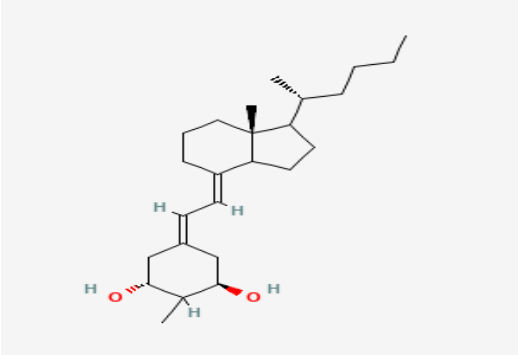


[23]

Fig.13 Structure of Lovastatin

Vitamin D

Vitamin D has a well characterized role in calcium and phosphorus homeostatis, but additionally has a role in the immune response to bacterial and viral pathogens [7].



[24]

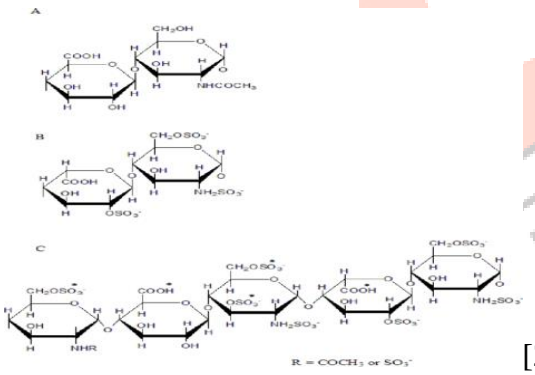
Fig.14 Vitamin D structure

Host kinase inhibitors

Using aimmunofluroscence image based assay suitable identification of small molecule.

Heparin and heparansulfate

Heparin sulphate (HS) has been characterized as a DV receptor in multiple model system, how ever the physiological relevance of this findings has been questioned by observations that flaviviruses can under go cell culture adaptation resulting increased binding to HS. Viral sensor (RIG-I and TIR3) agonist DENV SN1 antigen detection is often used to diagnose dengue in patient and have role in dengue pathogenesis [8].



[25]

Fig.15 Structure of Heparin and Heparan Sulfatate

Interferon

The type 1 IFNS, its including in the IFN alpha used interferon alpha and Ribavirin (RBV) as combination therapy against DENV infected and Huh-7 cells were exposed to RBV and/or IFN, and the viral burden was quantified over time by plaque assay, drug interaction for antivial effect were determined by fitting a mathematical model to the data. We then assed clinically relavant exposure of IFN plus RBV using hollow fiber infection model (HFIN) system [9].

IEG activation will circumvent viral subversion of IFN signaling

In general IFN alpha can successfully inhibit the DENV if given preinfection but not post-infection and due to DENV mediated suppression of early members of the IFN signalling pathway thorough some antiviral effect was observed in post-infection administration of PEGRLIFN-alpha 2a. The preliminary studies, to identified 120 host antiviral candidates.

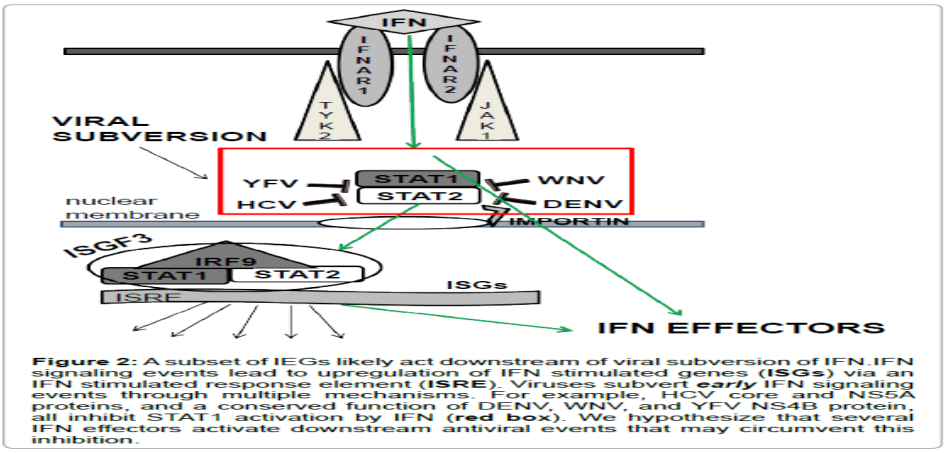


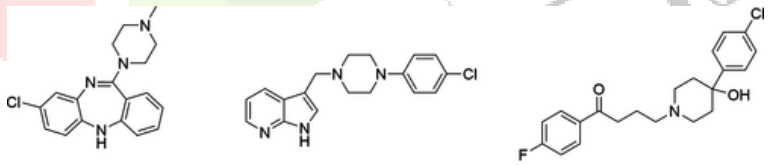
Figure 2: A subset of IEGs likely act downstream of viral subversion of IFN.IFN signaling events lead to upregulation of IFN stimulated genes (**ISGs**) via an IFN stimulated response element (**ISRE**). Viruses subvert ***early*** IFN signaling events through multiple mechanisms. For example, HCV core and NS5A proteins, and a conserved function of DENV, WNV, and YFV NS4B protein, all inhibit STAT1 activation by IFN (**red box**). We hypothesize that several IFN effectors activate downstream antiviral events that may circumvent this inhibition.

Fig.3: IEG activation will circumvent viral subversion of IFN signalling

D4 dopamine receptor antagonists

D4 dopamine receptor (DRD4) in DENV infection, antagonism of DRD4 and subsequent downstream phosphorylation of epidermal growth factor receptor (EGPR) related kinase (ERK) were found to impact DENV infection negatively

blockade of signalling through this network was confirmed as mechanism of anti-DENV activity[10].



2, clozapine
D_4 K_i = 10 nM
D_2/D_4 = 7.4
D_3/D_4 = 20

3, L-745,870
D_4 K_i = 0.43 nM
D_2/D_4 = 2,233
D_3/D_4 = 5,349
D_1/D_4 >10,000
D_1/D_5 >10,000

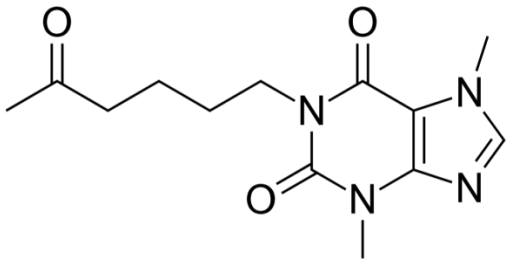
4, haloperidol
D_4 K_i = 2.3 nM
D_2/D_4 = 0.6
D_3/D_4 = 0.9

[26]

Fig.16 Structure of D4 Dopamine antagonist

Pentoxifylline

The drug petoxifylline has been shown to blunt the proinflammatory actions of tumor necrosis factor a key mediator of dengue hemorrhagic fever [11].

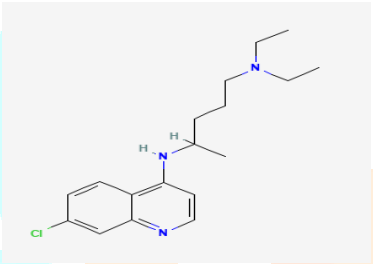


[27]

Fig.17 Structure of Pentoxifylline

Chloroquine

Chloroquine and antimalarial agent has shown some anti-viral effects this study evaluated its effects in patients with dengue iysosomotropic 4-amino quinoline derivative well known as anti-malarial drug [12].



[28]

Fig.18 Structure of chloroquine

RNAi

RNA interference is an important and effective gene silencing process which degrades targeted RNA by a sequence specific process. Several studies have been conducted during last decade to evaluate efficiency of siRNA in inhibiting dengue virus replication RNAi used against several human pathogens including human immunodeficiency virus.

Other compounds

Other agents that has been suggested to display anti dengue activity including genetic in an amino glycoside antibiotic which has been found to have unique property among amino glycoside.

Medicinal plant derivatives

There is a significant amount of research dedicated to a hypothesis driven and practice based identification of naturally occurring compound. Different scientific databases were used to source for literature on plants used against this infections. Extensive studies on potential of medicinal plants needed to confirm their efficacy. This reveals capabilities of medicinal plants an their phytochemical inhibiting DENV [13].

Conclusion

Dengue spread increased across the world. Due to the enhancement in spreading the public health priority in many countries was triggered. Government and health care pharmaceutical industries should have taken initiative to develop new strategies to improve diagnosis and treatment against disease. Each person should transfer awareness against disease. Globalize awareness and precautionary measures should need to control incidence. Combined effect need to tackle the prevalence of dengue.

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