NATURE’S RETORT TO THE DENGUE CRISIS
DENGUE

• Dengue or ‘breakbone fever’: A debilitating mosquito borne viral illness of the tropics

• It is caused by a flavivirus with four distinct serotypes: DV-1, DV-2, DV-3, and DV-4

• Spreads between humans by mosquito vectors of the Aedes genus, ie, Aedes aegypti and Aedes albopictus.
EPIDEMIOLOGY

• The World Health Organization estimates that 2.5 billion people worldwide live in dengue endemic areas, and 96 million new infections occur annually!!!
  - 70% cases in Asia (34% India alone)
Indian dengue scenario?

- India has 33 million apparent dengue cases and 100 million asymptomatic infections every year, more than any other country, reported a recent Oxford University study.
Rise In Dengue Cases In India, 2001-13
States With Most Dengue Cases In 2015

- Punjab
- Delhi
- Arunachal Pradesh
- Gujarat
- Maharashtra
- Telangana
- Andhra Pradesh
- Karnataka
- Tamil Nadu
- Kerala
- Punjab
- Delhi
- Arunachal Pradesh
- Gujarat
- Maharashtra
- Telangana
- Andhra Pradesh
- Karnataka
- Tamil Nadu
- Kerala
Why has natural product screening been neglected in antiviral research?

- Many plant extracts are cytotoxic.
- Low potential for chemical modification into a useful and unique pharmacophore.
- Advent of combinatorial and parallel chemistry coupled with high-throughput screening techniques has led to a decreased emphasis on plants as a compound source.
Challenges associated with natural products in antiviral research

- **Difficulty to deal with natural extracts** - how to prepare an extract suitable to specific needs

- **Variability of the source**: Re-collection of the same plant may not give the same chemical composition of an extract.

- **Resupply problem**, particularly in large quantities.
DRUG TARGETS for DENGUE

- Structural proteins: virus entry
- Non structural (NS) Proteins: viral replication
# Proteins encoded by Dengue virus

<table>
<thead>
<tr>
<th>Non structural Proteins</th>
<th>Function</th>
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<tbody>
<tr>
<td>NS1</td>
<td>Essential for viral growth; contributes to endothelial dysfunction</td>
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<tr>
<td>NS2A</td>
<td>Down-regulation of IFN-β stimulated gene expression</td>
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<tr>
<td>NS2B</td>
<td>Cofactor for NS3</td>
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<tr>
<td>NS3</td>
<td>Helps in unwinding of double stranded RNA</td>
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<tr>
<td>NS4</td>
<td>Determines dengue replication</td>
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<tr>
<td>NS5</td>
<td>Polymerase and methyltransferase activity</td>
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<th>Structural Proteins</th>
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<tr>
<td>Capsid</td>
<td>Necessary for packaging and release of viral particles</td>
</tr>
<tr>
<td>prM</td>
<td>Protects envelope from premature fusion</td>
</tr>
<tr>
<td>Envelope</td>
<td>Fusion &amp; entry of virus into host cell &amp; cell attachment</td>
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Antivirals

Anti mosquito

Natural remedies against Dengue

Mosquito repellants

Others
CONCLUSION

• **More research** on the active compounds of the studied plants is needed

• Determine new methods to **target the various stages** to prevent further spread

  Focusing on each phase in the **life cycle of the virus**

  (1) Infection of host cells

  (2) Viral maturation process

  (3) Synthesis of viral RNA

  (4) Spread of viral particles
TAKE HOME MESSAGE

• A need of **extensive networking** among academic research groups, clinicians and industries throughout the globe so that the **ethnobotanical knowledge** can be circulated and finally converted into an effective drug against Dengue.
IF THEY BREED
YOU WILL BLEED
Anti-Virals

Japanese orchid

Chinese ginger

Small egg plant
Anti-Virals

- **Iris moss**
- **Black Galingale**
- **Mazu phal**
Anti mosquitoes

Turmeric
- Turmerone obtained from volatile oil of *Curcuma longa*: 100% mosquitocidal

Pipli
- *Piper longum* fruit-isolated pipernonaline: Larvicidal

Kari patah
- acetone and petroleum ether extracts of *Murraya koenigii* leaves: Larvicidal
Mosquito Repellants:

**Kaatu/Dentate clausena**
Essential oil obtained by steam distillation of its leaves increases the mean protection time against the bites of *Aedes aegypti* without irritation to human skin.

**Laung/clove**
Essential oil of this plant is used as insect repellents including *Aedes aegypti*.

**Citronella grass**
Active constituent of this plant is essential oil, *citronella oil*. This oil is used in candles and lanterns that can be burned to repel mosquitoes, so it is used as a fumigant.

**Peacock flower**
Crude benzene and ethyl acetate extracts of its leaves are used as repellent for *Aedes aegypti*.
Anti Dengue

Others

Papaya extract

Tawa tawa

Psidium guava

Andrographis paniculata

Cryptocarya chartacea

Neem

Black bean

Alligator weed
Japanese Orchid

• *Gastrodia elata*

• Active principle: **WSS45** (sulfate derivative of an alpha D-glycan)
  
  - interferes with the adsorption of the DENV to the host cell.
  
  - therefore inhibit **viral entry**
Chinese ginger

• *Boesenbergia rotunda*

• Active principle: *cyclohexenyl chalcone derivatives* (4 hydroxypandurantin A and pandurantin A)
  - potent and competitive inhibitors of DENV-2 *NS3 protease* in vitro
  - therefore inhibit *viral replication.*
Small egg plant

• *Oldenlandia affinis*

• It is a perennial herb with a woody root. It is distributed widely in the tropical zone of Africa.

• Active principle: **CYCLOTIDES**

  ➢ these are low molecular weight proteins which are resistant to proteases

  ➢ inhibit NS2B - NS3 protease.
Iris Moss

- *Chondrus crispus* (Red seaweeds)

- Active principle: Carrageenans - linear sulfate polysaccharides.

- Since DENV interacts with heparan sulfate (HS) for its initial binding to the host cell, these polysulfates may interfere with the early events leading to virus entry.
Black galingale

- *Kaempferia parviflora*

- DEN-2 particles are directly inactivated by some bioactive compound in *K. parviflora*.

- The plant extract is also effectively used as a mosquito repellent.
Muzu phal

- *Quercus lusitanica*

- Active principle: gallic acid and ellagic acid

  - down regulation of NS1 protein Expression
  - hence inhibitory effect on viral replication
Carica papaya

- Membrane stabilizing properties
- Prevent platelet lysis due to the presence of other phenolic compounds
- Inhibits heat-induced and hypotonicity-induced hemolysis of erythrocytes
- Larvicidal properties
Euphorbia hirta,

- Also called tawa tawa in Philippines
- A pantropical weed, possibly native to India
- Tawa tawa tea increases platelet counts
Psidium guava

- Evergreen shrub or small tree
- Native to the Caribbean, Central America and South America
- Water decoction contains quercetin which inhibits the formation of enzyme mRNA in the virus
Andrographis paniculata

- An annual herbaceous plant
- Family Acanthaceae
- Native to India and Sri Lanka.

Mode of antiviral action:
1) Interfere with viral adsorption
2) Inhibit viral replication
Cryptocarya chartacea

- Active principle: chartaceones A-F, pinocembrin
  - NS5 inhibitor/ Anti-RdRp (RNA dependent RNA polymerase) activity
Neem

- *Azadirachta indica*
- aqueous leaf extract
- invitro assay results showed inhibition of DENV2 replication
Alligator weed

- *Alternanthera philoxeroides*
- perennial aquatic plant
- Invitro anti-dengue activity - petroleum ether extract
Black bean

- *Catanospermum australae*

- Active principle: *Catanospermine*
  - natural alkaloid
  - Alpha-glucosidase inhibitor – therefore *Virus assembly inhibitor*
  - Effective against all dengue serotypes in vitro and in vivo (mice)