NATURE'S RETORT TO THE DENGUE CRISIS

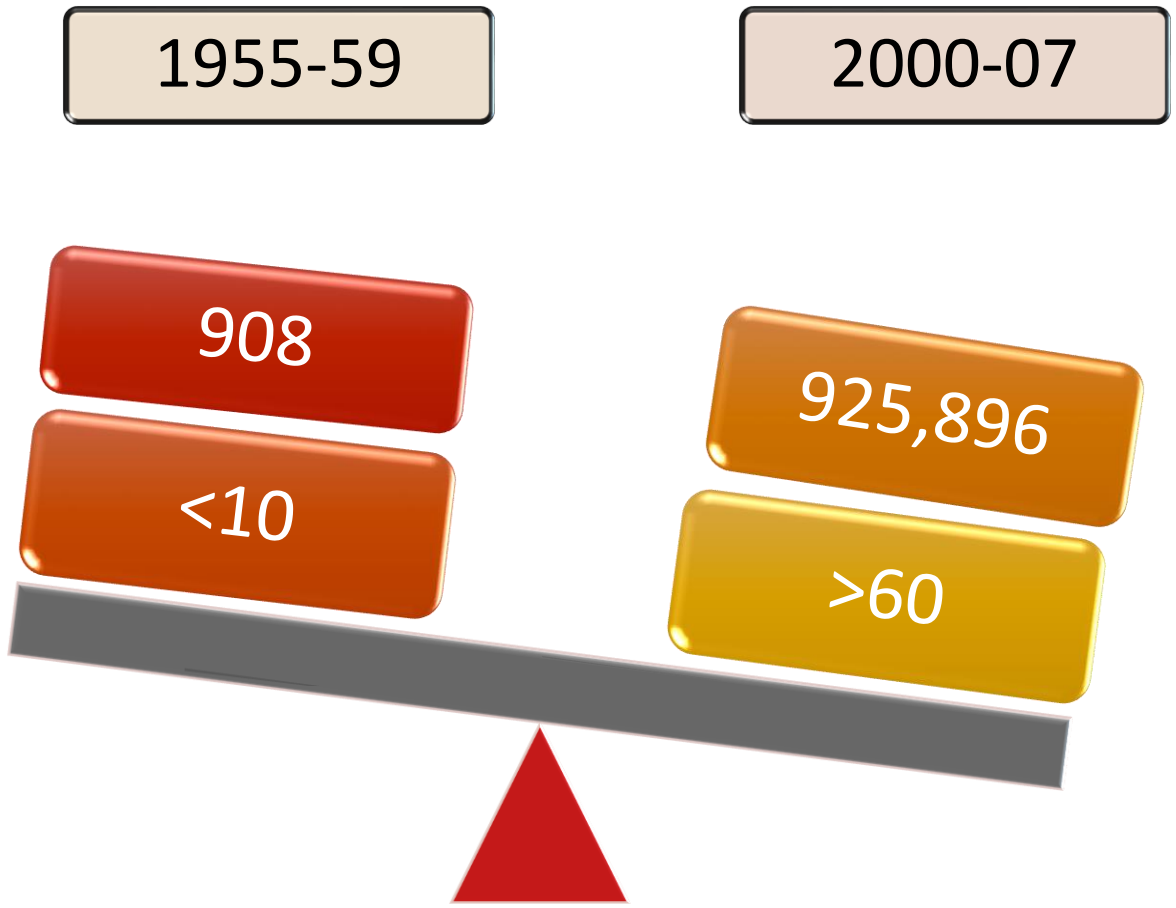
DENGUE

- Dengue or ‘ breakbone fever’ : A debilitating mosquito borne viral illness of the tropics
- It is a 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!!!

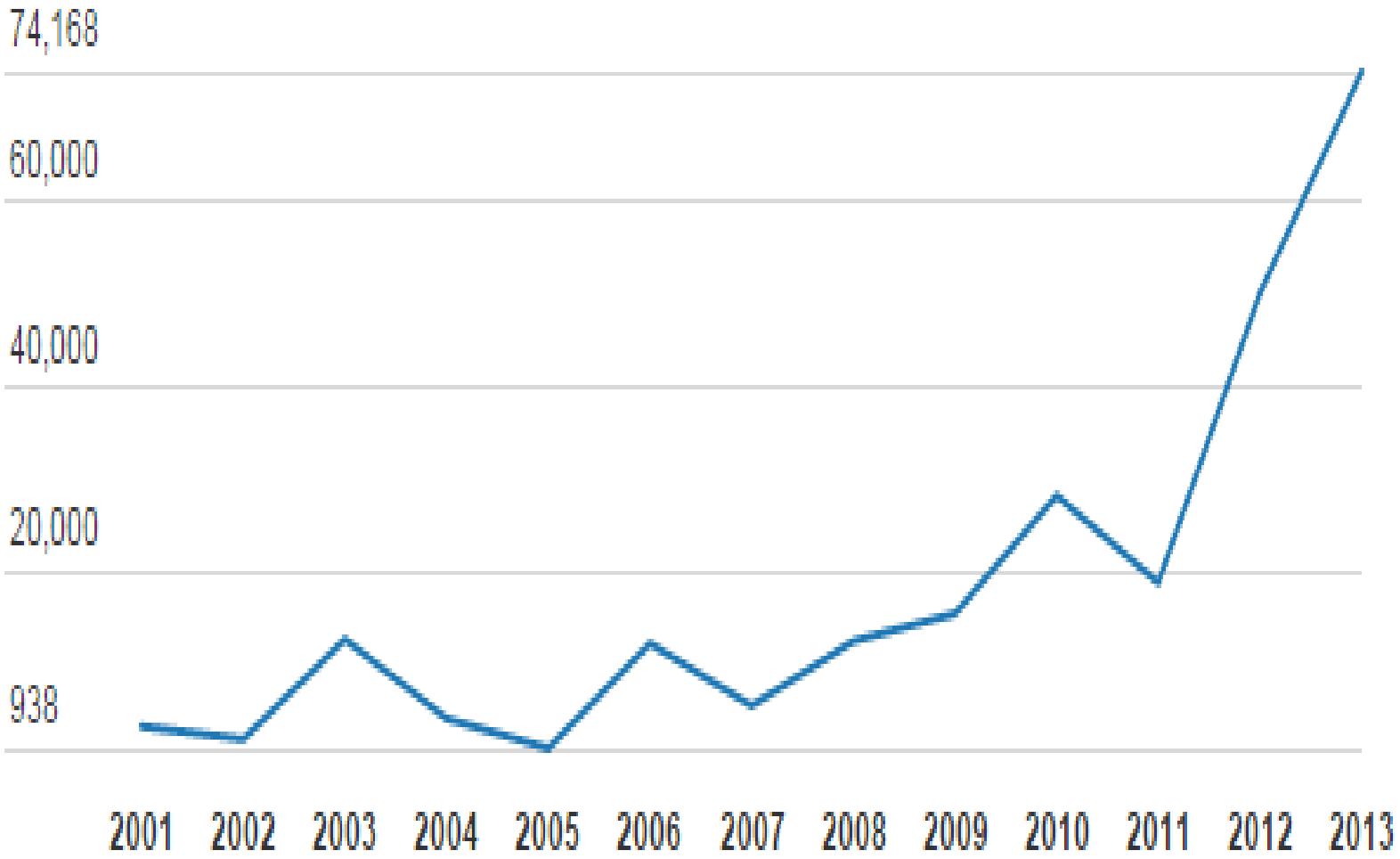
  - 70% cases in asia (34% india alone)

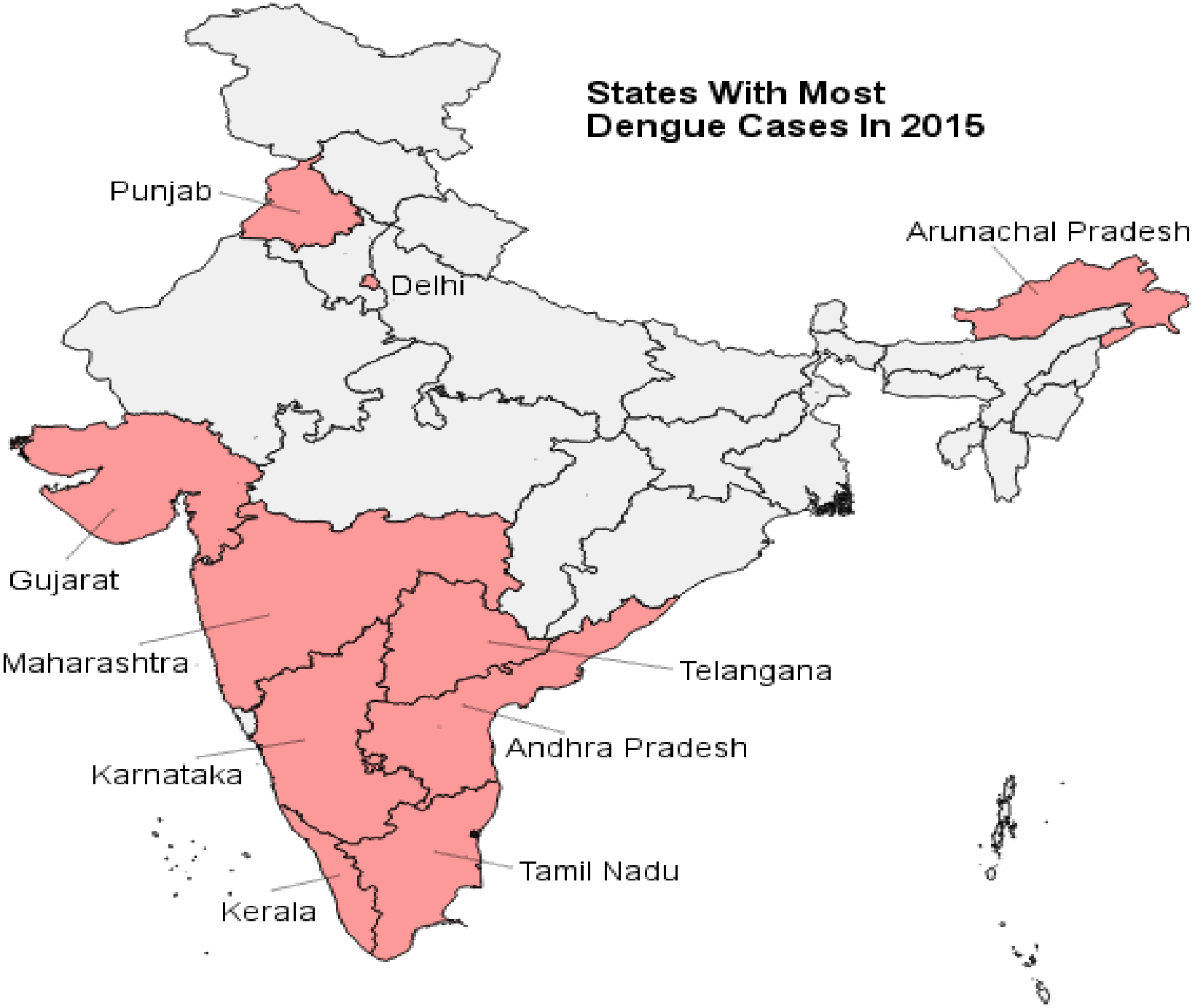


Indian dengue scenario ?

- 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

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

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


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

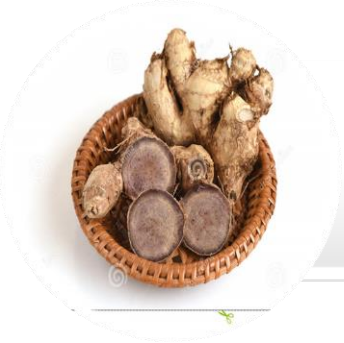
Japanese orchid

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

Pippli

- **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.

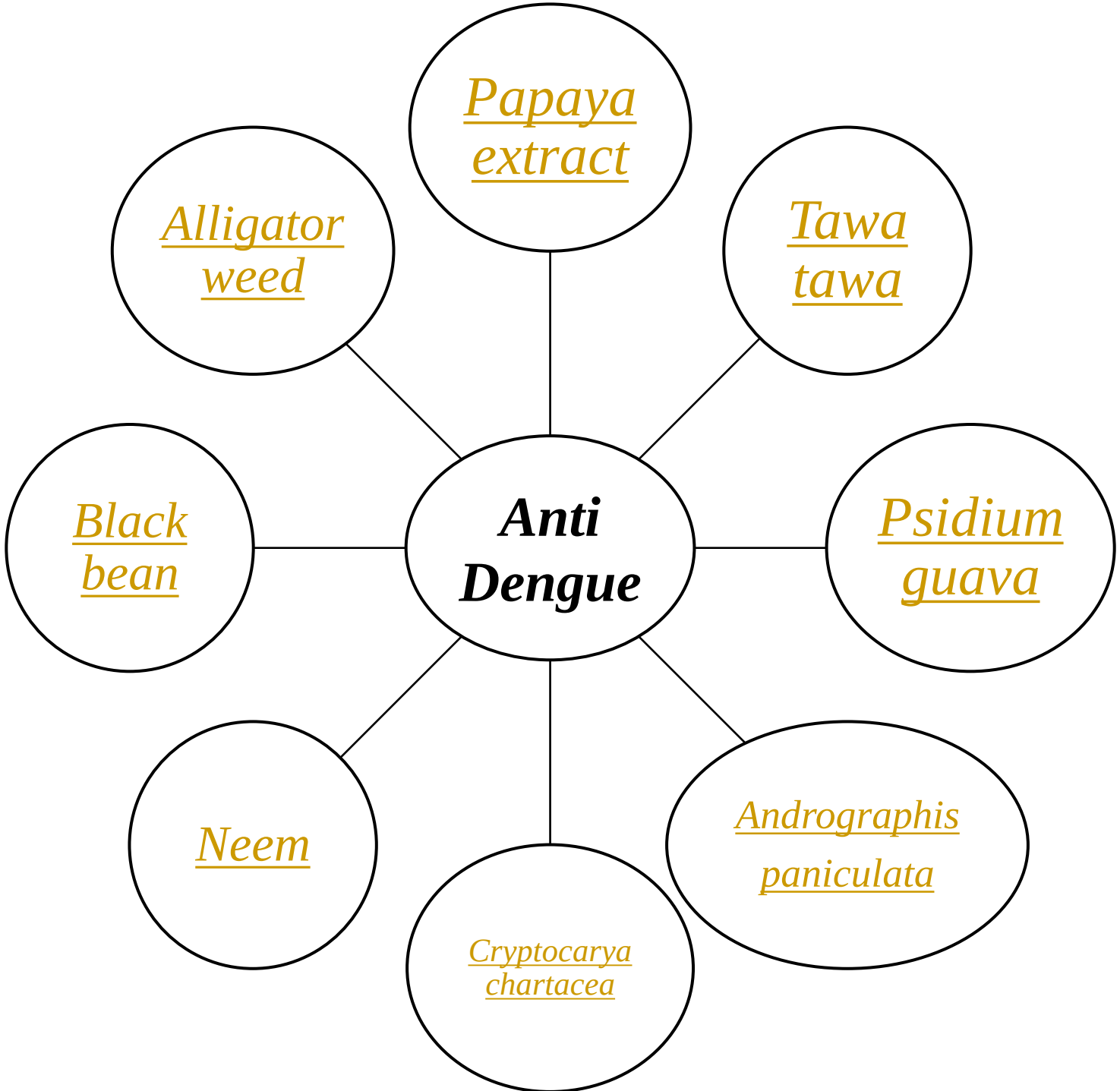
Peacock flower

Crude benzene and ethyl acetate

extracts of its leaves are used

as repellent for Aedes aegypti

Others


Papaya extract
Alligator weed
Tawa tawa
Black bean
Anti Dengue
Psidium guava
Neem
Andrographis paniculata
Cryptocarya chartacea

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 repellant.

Mazu 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)