Review Article

# An Overview of Herbal Antiviral Compounds Against Dengue Virus (Ae. aygepti)"

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## Abstract

Dengue is the current prevalent disease caused by vector *A. aegypti* having four serotypes DENV 1,2,3,4. Natural biological systems are disrupted by the repeated use of synthetic repellents and often results in the development of resistance against dengue virus. These problems have emphasized the need for the development of new strategies for the selective control of mosquito larvae. Therefore antiviral active compounds are extracted from natural herbs to treat dengue virus. The aim of this paper is to review some opportunities in the development of anti-dengue drugs from celery, black seed, *ponneem, Cucurbitaceae U. tomentosa, Gastrodiaelata Bl, L. alba* and *L. citriodora, Vitextrifolia* and citrus plants like lemon, orange which might be helpful to control the epidemic.

**Keywords** : Dengue, A. aegypti, Antiviral, Drugs , Black seed, Ponneem.

## Introduction

Transmission of malaria, dengue fever, yellow fever, filariasis, schistosomiasis, and Japanese encephalitis are caused by major vector mosquitoes (James 1992; Gubler 1998). Among these dengue is the current prevalent disease. According to World Health Organization (WHO 2003), around 50 million dengue virus cases per year are estimated (Valdéz *et al*. 2009). Aedes mosquitoes, humans and lower primates are three natural hosts for dengue virus.

## Characteristics of Dengue Virus

Dengue virus is associated with the Flaviviridae family and has four serotypes DENV: 1, 2, 3, and 4. Dengue haemorrhagic fever and dengue shock syndrome are two severe forms of dengue fever (Hendarto and Hadinegoro 1992, Pancharoen *et al*. 2002). Virion consists of single-stranded RNA molecule of approximately 11 kb in length. The viral genome of dengue virus consist of three structural proteins, capsid (C), pre-membrane (prM), envelope (E) and seven non-structural proteins (NS1, **A**
2009; Talarico *et al*. 2007). The role of E protein is to interact within the virus (Rice 2007). Aedes aegypti mosquito is a vector for the transmission of DENV. Less effective transmitters are *Ae. albopictus and Ae. polynesiensis* (Ooi *et al*. 2009).

## Control of Vectors Through Insecticides

Applications of organophosphates and insect growth regulators are more frequently used to control the mosquito larvae (Yang *et al*. 2002). Insecticides and many synthetic agents have been developed for the control of mosquito-borne diseases. The disadvantage of using insecticides is that they are non-selective and are harmful to other organisms also. Natural biological systems are disrupted by the repeated use of synthetic repellents and often results in the development of resistance (Rozendaal 1997), provoke undesirable effects including toxicity to non-target organisms (Lee *et al*. 2001), this lead to the need for novel insecticides (Macedo *et al*. 1997).

## The Need to Screen Antiviral Compounds from Natural Herbs

These problems have emphasized the need for the development of new strategies for the selective control of mosquito larvae. Till now there is no antiviral drug for the treatment of Flavivirus and no vaccine is yet available. Therefore the development of antiviral drugs is required to prevent dengue mortalities. Traditional medicinal plants and herbs consist of active compounds that have antiviral activity (Jassim & Naji 2003). From various herb species oils are extracted that can directly inactivate the virus. These antiviral compounds possess unique biological activity and can act aslarvicides, insect growth regulators, repellents, and have restrictive activities (Mathivanan *et al*. 2010; Niraimathi *et al*. 2010; Samidurai *et al*. 2009).

There are many natural herbs which show antiviral activity against dengue virus. Drugs can be designed by using these natural herbs, potency of some of them are discussed here.

## Antiviral Activity of Para-Benzoquinones

Unsubstituted para-benzoquinone (with no alkyl group). Greater the methyl groups attached to the ring, greater will be the potency of para-benzoquinone (table 1). By appropriate structural modification of para-benzoquinones, it may be possible to develop novel insecticidal compounds potentially suitable to control the dengue mosquito (Damiao *et al*. 2010).

## Antiviral Activity of Cucurbitaceae Plants

Solvent extracts of five species of *Cucurbitaceae* plants show great larvicidal activity (figure 1). The petroleum ether extracts of *C. colocynthis*, methanol extracts of *C. indica*, *C. sativus*, *M. charantia,* and acetone extract of *T. anguina* are effective against dengue virus (Rahman *et al*. 2008)

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Table 1 Larvicidal activities ($LC_{50}$) and 95% CI of evaluated compounds 1–6 on third-instar larvae of *A. aegypti*

| Compound | $LC_{50}$ ppm (CI) |
|---|---|
| 1 | 90 (70 to 107) |
| 2 | 61 (50 to 76) |
| 3 | 33 (25 to 44) |
| 4 | 42 (34 to 51) |
| 5 | 57 (44 to 72) |
| 6 | 48 (40 to 56) |
| Temephos | 0.042 (0.035 to 0.05) |

## The antiviral and immune modulating effects of u. Tomentosa

*U. tomentosa* pentacyclicoxindole alkaloids displayed the antiviral and immune-modulating *in vitro* effects. Due to this nature novel properties are explored for the therapy of Dengue Fever (Sonia *et al*. 2008).

## Anti-Dengue Virus Bioactivities of Gastrodiaelata Bl Plant

Two alpha-D-glucans WGEW and AGEW from Gastrodiaelata Bl show anti-dengue virus bioactivities. There structures were explained by using gas chromatography (GC), gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR). The deduced structures are alpha-D-(1--> 4)-glucan with an alpha (1-- >4) linked branch attached to O-6 branch points with dissimilar branch degrees. Distinct degrees of substitution (DS) were prepared by adding sulphate derivatives. Strong anti-dengue virus bioactivities are showed by all sulfated derivatives.

## Antiviral property of L. Alba and L. Citriodora oil

*L. alba* and *L. citriodora* oil has inhibitory effect on all four DENV serotypes. The essential oil penetrates within the skin and produce inhibitory effect to block viral replication (Carson *et al*. 2001). Plaque reduction assay is performed to examine antiviral activities of the selected essential oils. Against all examined viruses 50% inhibition of plaque formation was observed (figure 2, 3).

## Antiviral Activity of Citrus Plants against Dengue Virus

Citrus seeds and peel of citrus plants have been tested against insects and proved to be effective. The extracts of *Citrus grandis* (Chakutra), *Citrus paradisi* (Grape Fruit), *Citrus jambhiri* (rouph lemon) and *Citrus reticulata* (Kinnow) are more effective against dengue virus infections (Waseem *et al*. 2010).

## Antviral Activity of Vitextrifolia Leaves against Ae. Agypti

From the methanol extract of *Vitextrifolia* leaves, a crystalline compound methyl-*p*-hydroxybenzoate is isolated and structure is elucidated by NMR and single crystal X-ray diffractometer (Figure 4). This compound

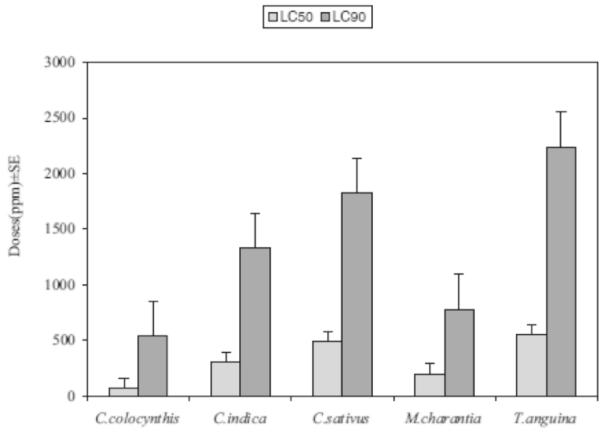


**Fig. 1**. Antiviral activity of five species of cucurbitaceae plant

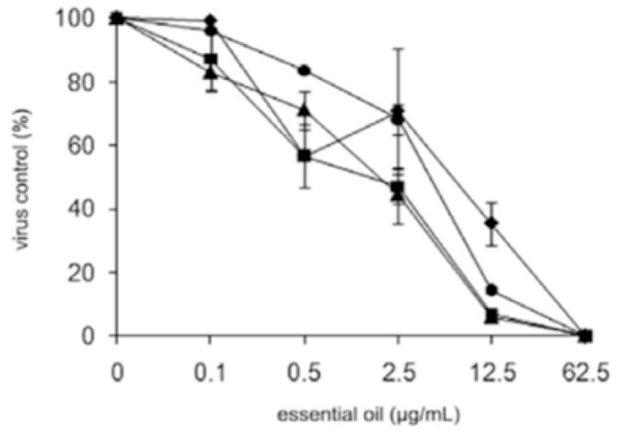


**Fig 2.** Lippia alba essential oil effects on plaque formation of DENV, DENV2, DENV3, DENV

possesses 100% larval mortality of *Ae. aygepti* (Kannathasan *et al*. 2011).

## Ponneem A Herbal Formulation against Dengue Virus

Oils of neem (*Azadirachtaindica*) and karanj (*Pongamiaglabra*) forms a novel herbal formulation known as PONNEEM. Active compounds of *A.indicaareazadirachtin, salanin, nimbidin, nimbin, nimbolide, mahmoodin and geduninandin P. glabra, karanjin are* oleic acid, linoleic acid, linolenic acid, palmitic acid and stearic acid (Maheswaran *et al*. 2011).

## Nematocidal activity of celery against ae. Aegypti

Bioactive compounds of *Apiumgraveolens* (Celery) possess nematocidal activity against *Ae. Aegypti* (Rafikali *et al*. 2000; Rafikali and Muraleednaran 2001).

## Black Seed a Valuable Remedy of Dengue Infection

Black seed, *Nigella sativa* belongs to Ranunculaseae family. It has active compounds like Quinones, thymoquinones, dithymoquinones (Daba and Abdel-

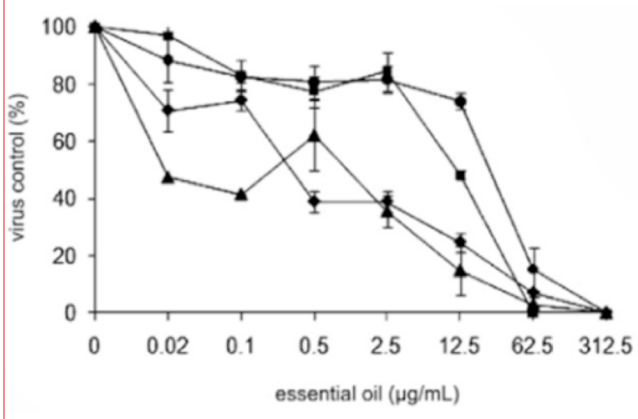


**Fig. 3.** Lippiacitriodoraessential oil effects on plaque formation of DENV 1, DENV2, DENV3, DENV4

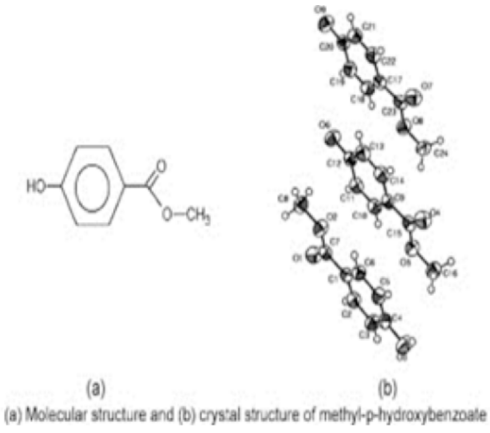


**Fig.4.** Molecular and crystal structure of methyl-p-hydroxy benzoate.

Rehman, 1998, Naji *et al* 1999). Thymoquinones carries antiviral activity against *Ae. agypti* by enhancing the immune response of vertebrates (Ahmed *et al*. 2008)

Novel anti-dengue compounds *from Rhizophoraapiculata Blume*, *Piper retrofractum Vahl*, *Flagellariaindica Linn*, *Cladogynosorientalis Zipp* and *Houttuyniacordata Thunb* have not yet been identified. In future there will be a need to focus on the purification, exact mechanism of their antiviral action, and characterization of their active compounds.

It is concluded from the present review that the, natural herbs possess lead compounds for the development of larvicidal activity. These compounds could be investigated in detail with the objective of isolation and characterization of biologically active molecules which could be used as lead compounds in drug discovery.

## REFERENCES

1. Abdul Rahuman A and Venkatesan P 2008. Larvicidal efficacy of five cucurbitaceous plant leaf extracts against mosquito species. Parasitology Research, 103:133–139.
2. Cheng S, Huang C, Chen W, Kuo Y, Cheng S 2008. Larvicidal activity of tectoquinone isolated from red heartwood-type Cryptomeria japonica against two mosquito species. Bioresource Technology, 99:3617–3622.
3. Gubler DJ. 1998. Resurgent vector borne diseases as a global health problem. Emergence of Infectious Diseases, 4:442–450.
4. Hendarto SK and Hadinegoro SR. 1992. Dengue encephalopathy. Acta Paediatrica Japonica, 34:350-357.
5. James AA. 1992. Mosquito molecular genetics: the hands that feed bite back. Science, 257:37–38.
6. Jassim S and Naji M. 2003. Novel antiviral agents: a medicinal plant perspective. Journal of Applied Microbiology, 95: 317-412.
7. Lee SE, Kim JE and Lee HS. 2001. Insecticide resistance in increasing interest. Agricultural Chemistry & Biotechnology, 44:105–112.
8. Lindenbach B, Rice C. 2007. Flaviviridae: the viruses and their replication. In D Knipe D, P Howley, *Fields virology*, Willians& Wilkins, Philadelphia, pp. 991-1041.
9. Macedo ME, Consoli RAGB, Grandi TSM, Anjos AMG, Oliveira AB, Mendes NM, Queiroz RO and Zani CL. 1997. Screening of Asteraceae (Compositae) plant extracts for larvicidal activity against *Aedesfluviatilis* (Diptera: Culicidae). Memórias do Instituto Oswaldo Cruz, 92:565–570.
10. Ooi EE and Gubler DJ 2009. Dengue in Southeast Asia: epidemiological characteristics and strategic challenges in disease prevention. Cadernos de Saúde Pública, 25:115-24.
11. Pancharoen C, Kulwichit W, Tantawichien T, Thisyakorn U and Thisyakorn C. 2002. Dengue infection: a global concern. Journal of Medical Association of Thiland, 85:25-33.
12. Rothwell C, Lebreton A and Chuan Young Ng, *et al* 2009. Cholesterol biosynthesis modulation regulates dengue viral replication. Virology, 389:8-19.
13. Rozendaal JA 1997. Mosquitoes and other biting Diptera. In: Vector control. World Health Organization, Geneva, Switzerland, pp. 5–177.
14. Sánchez-Valdéz E, Delgado AM, Torres-Martínez JA, Torres-Benítez JM 2009. Clinical response in patients with dengue fever to oral calcium plus vitamin D administration: study of 5 cases. Proceedings of the Western Pharmacology Society, 52:14–17.
15. Talarico LB and Damonte EB 2007. Interference in dengue virus adsorption and uncoating by carageenans. Virology, 363:473-85.
16. Yang YC, Lee SG, Lee HK, Kim MK, Lee SH and Lee HS. 2002. A piperidine amide extracted from *Piper longum L.* fruit shows activity against *Aedesaegypti* mosquito larvae. Journal of Agricultural and Food Chemistry, 50:3765–3767.

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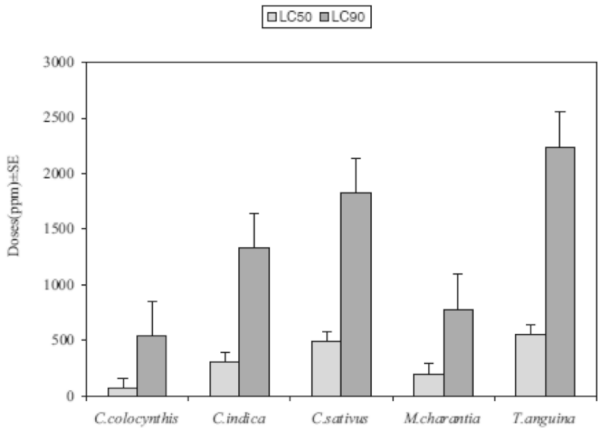


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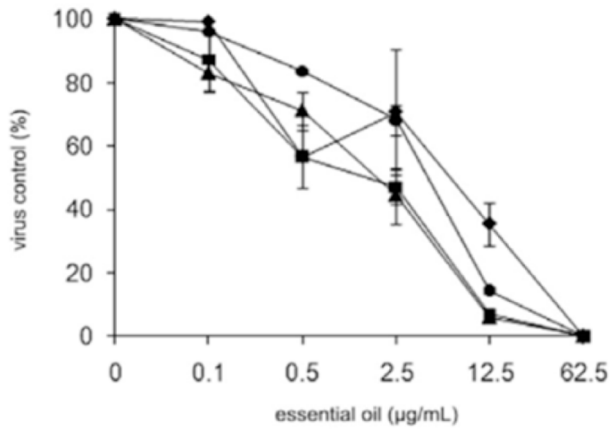


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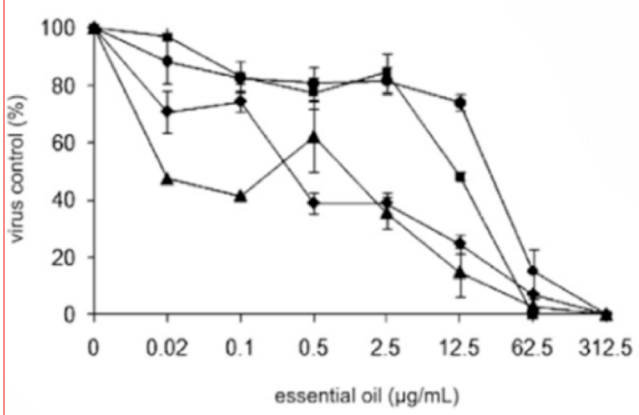


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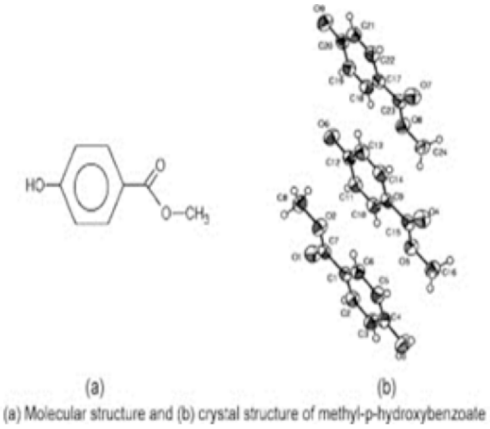


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