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Recent Status of Dengue Cases, Death and Evolving Curative Herbal Remedies - A Systemic Review of Scientific Evidence

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ABSTRACT

Dengue, a rejuvenating viral disease is a mosquito borne tropical disease caused by dengue virus. It is disseminated by Aedes mosquito, particularly Aedes aegypti. Symptoms typically begin three or fourteen days after infection, which include a high fever, headache, vomiting, muscle and joint pain and a characteristics skin rash. If it is a severe dengue also known as dengue haemorrhagic fever resulting in bleeding, low level of blood platelets, blood plasma leakage or into dengue shock syndrome where dangerously low blood pressure occurs. Countries like India, a land of traditional medicines are focusing mainly on the herbal medicines as a trusted approach, since there are no effective treatment available for dengue if properly treated mortality can be reduced. Out of 22 plants, only 4 species were studied scientifically- *Azadirachta indica, Carica papaya, Hippophae rhamnoides and Cissampelos pareira.* This article aims on the review of recent status of dengue and curative herbal remedies.

Keywords: Basal metabolic panel, Dengue, Flavivirus, Herbal medicines.

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INTRODUCTION

Dengue, a delibilating viral disease is caused by RNA virus named Dengue fever virus[1], belonging to the family *Flaviviridae*, of genus Flavivirus. The yellow virus, Zika virus are the intimacy of the same genus. The first record case of dengue fever is in a Chinese medical encyclopedia, which demonstrated the disease as "Water poison" associated with flying insects. Benjamin Rush, who coined the term as "BREAK BONE FEVER" [due to the symptom of athralgia and myalgia] in 1789, which was the first confirmed case report. By 19th century, the disease was termed and acknowledged. It is estimated that only 9 countries had experienced the dengue epidemics. Contemporarily, the disease is endemic in more than 100 countries according to WHO. Flavivirus , the core reason for the disease is found to have its origin in Asia or Africa.

Transmission

Dengue virus is disseminated by *Aedes mosquito*, particularly *Aedes aegypti*[i][2]. Other species including *A.albopictus, A.polynesiensis, A. scutellaris* which causes many other manifestation. A female mosquito, when bites a tainted individual, during the initial 2-10 days febrile period, becomes infected by virus in the cells lining the gut. After 8-10days, the virus dispatches to the other tissues including salivary glands. In an interesting condition, the mosquito does not have any influence on virus.

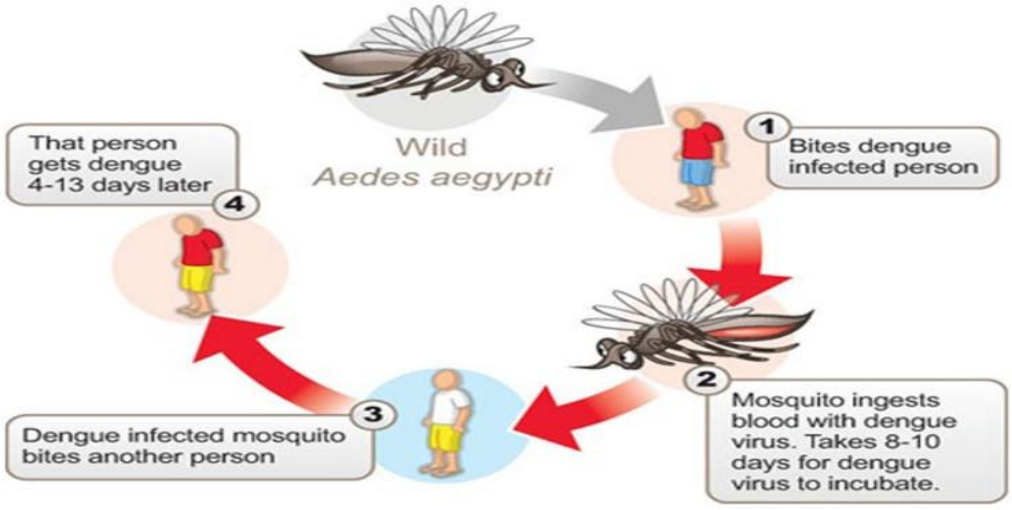


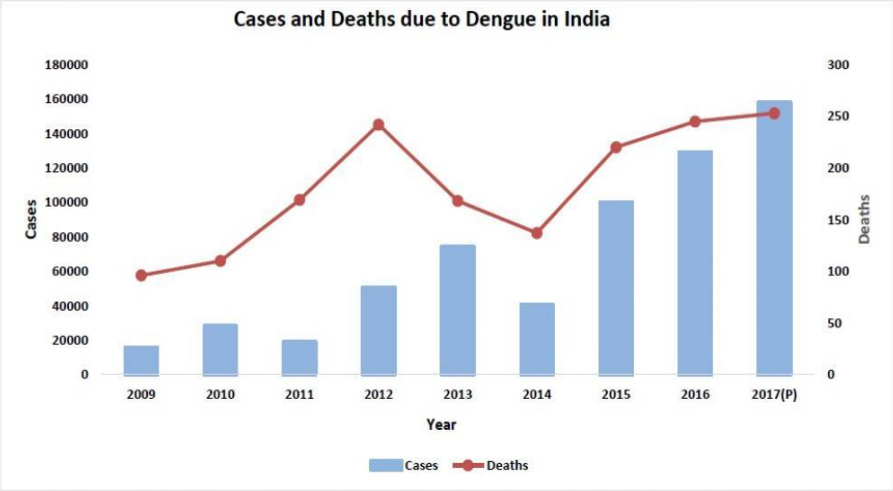
Figure 1: Transmission of dengue virus

DENGUE CASES AND DEATHS: 5 WORST AFFECTED STATES IN 2017

	2014		2015		2016		2017	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Kerala	2575	11	4075	25	7439	13	18,727	35
Karnataka	3358	2	5077	9	6083	8	13,016	5
Tamil Nadu	2804	3	4535	12	2531	5	11,552	18*
West Bengal	3934	4	8516	14	22,865	45	5389	13
Delhi	995	3	15,867	60	4431	10	4545	1

*Data available with the National Vector Borne Disease Control Programme (NVBDCP) till 8 October, 2017. However, the Tamil Nadu state health department has confirmed that 80 have died since January.

Figure 2: Dengue cases and deaths:5 worst affected states in 2017 (3)



Source: Directorate of National Vector Borne Disease Control Programme, Dte.GHS, Ministry of Health & Family Welfare

Figure 3: Cases and Deaths due to dengue in India (4)

Mechanism

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signaling proteins, such as cytokines and interferons , which are responsible for many of the symptoms, such as the fever, the flu-like symptoms, and the severe pains. In severe infection, the virus production inside the body is greatly increased and many more organs (such as the liver and the bone marrow) can be affected. Fluid from the blood stream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs, furthermore, dysfunction of the bone marrow due to the infection of the stromal cells leads to reduced number of

platelets, which are necessary for effective blood clotting, tis increases the risk of bleeding, the other major complication of dengue fever

A.aegyptia is likely to bite during the early hour of morning and in the evening, mainly in the ropic and the subtropic region[3]. When an infected female mosquito bites a healthy individual , the saliva along with the virus enters the conglomeration of WBC and fascimilates inside the cells and unfurls throughout the system and has impact on liver and bone marrow[4]. Fluids from blood stream leaks out through blood vessels due to capillary permeability which result in low blood circulation proceeding with low blood pressure, to supply sufficient blood to vital organs. Making the matter worse, the bone marrow dysfunction due to the septicaemia of stromal cells leads to thrombocytopenia

Replication of Virus

Albopictus is found to be more sensitive being getting infected than A. aegyptia but the latter is found to disseminate the virus DENV readily to all organs producing a high degree of potency of the organism. [5]

Flavivirus of which the DENV belongs is of positive strained enveloped RNA virus. The virion is found to have 3 structural proteins:

- Capsid protein
- Membrane protein
- Envelope protein

Capsid protein forms viral nucleocapsid. E and M are attached to the lipid bilayer which is surrounding the nucleocapsid. E is present in the form of homodimer ,DENV is icosahedral and spherical nucleocapsid in nature. Monomer of E is effective in infectious stage of dengue virus.

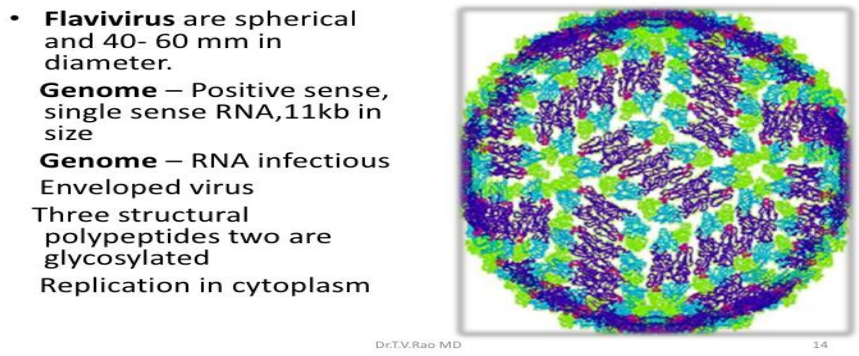


Figure 4: Dengue Virus-A Flavivirus

Structure of DENV

The dengue virus genome accommodates about 11,000 nucleotide bases which codes for 3 varieties of protein molecules- C, prM and E which forms the virus particle including 7 other structural protein molecules [NS1,NS2a,NS2b,NS3,NS4a,NS5a] accountable for viral replication. Dengue is provoked from four serotypes-DENV-1, DENV-2, DENV-3 ans DENV-4.

Signs and symptoms:

Since dengue was given the name of BREAK BONE FEVER ,major symptoms include myalgia and athralgia [6]. severe flu like illness beginning with sudden onset of fever, painful headache and even eye pain, skin rash. severity is increased when haemmorhage like symptoms are seen. Dengue haemmorhagic fever gets developed to Dengue shock syndrome when indications such as cold clammy skin, restlessness followed by rapid, narrow and weak pulse rate.

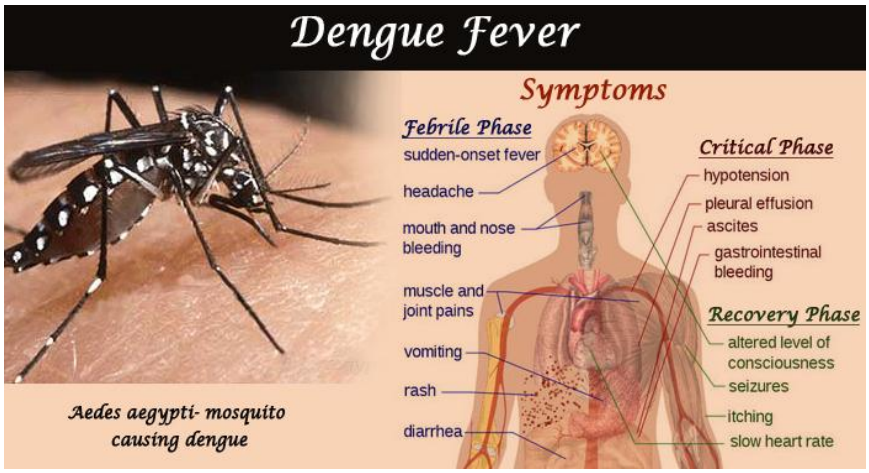


Figure 5 Signs and Symptoms of dengue fever(6)

Laboratory Diagnosis

Dengue fever is usually recognized via combination of blood test because body's immune retaliation to virus is complex as well as dynamic. At present, significant diagnostic test include the ANTIBODY TEST Ig M and IgG for the detection of antibodies produced by immune system within 4 days of DENV viral exposure. Similarly the MOLECULAR TEST FOR DENGUE VIRUS to detect the DEN virus and its serotype causing infections which can be diagnosed upto 7 days after the onset of symptoms. For the detection of decreased platelet count, haemoglobin , RBC and haematocrit , test named COMPLETE BLOOD COUNT is carried out in severe stage of the disease. To look for the evidence for dehydration which occur with several associated illness, BASIC METABOLIC PANEL is carried out.

Virus Isolation

Here the causative organism, flavivirus is collected onset maximum of 5days, from either blood, plasma, serum or other tissues. The samples for its active efficiency must be stored atn 4º-8ºc, if to be used for several times then ideal temperature of 70ºc should be maintained. By several screening methods, the pathogenic virus can be determined.

RT-PCR

For the detection of viral nucleic acid, real time –PCR is the effective technique. It consist of four primers for 4senotype detection. RT-PCR isn of 2types- single plex and multiplex, of which detection of all types of virus is possible through multiples RT-PCR of virus is possible through multiplex RT-PCR.

Serological Test

ELISA test IgM is done for the serum IgM detection.

Haemo glutuination inhibition test

For the determination of coagulation of antibodies by the viral entry.

Prevention and Control

Since there is no effective treatment against dengue or any other mosquito causing disease such as yellow fever, malaria, zika virus, it is necessary to prevent ourselves from these agents. A. aegyptia, prefers biting in the early hours of day and in the evening. Hence use of mosquito repellant such as DEET(N,N Dimethyl toluamide) an EPA registered insert repellent. Also the use of picardin(KBR3023) is effective. Use of mosquito nets, permethrin treated clothing can be preferred. Natural remedies such as use of cider oil or citronella oil;, which favours mosquitocidal activity. Stagnant pools must be cleared things holding water must be bleached every week, which helps the larvicidal activity.

Herbal medicines

India, a land of traditional medicines, due to the change in the life style and the influence of working population. The valve of herbal medicines had been reduced for the past decade, but there are some forces driving people to focus on their wellness, and to afford a curative treatment in terms of time as well as money[7]. Now-a-days countries like India are focusing mainly on the herbal medicines as a trusted approach for its no side effects. Numerous nutraceutical as well as herbal medicines combination are upcoming formulation in market, proving their efficiency in providing curative treatment[8]. There herbal medicines do not possess any" ***MAGIC BULLET SYSTEM***", it is such a field of medicines which provides a long life, empowerment and it is the treatment with no side effect. Till date, variety of plant extract have been demonstrated and published which possess

mosquito cidal activity including the insecticidal activity of Vernonia anthelminthica Linn of the family *Asteracea* and anti dengue activity of Valeriana jatamansi belonging to the family *Valerianacea*.

The present status of treating dengue by herbal extract is done by 31 species having potent activity[9]. Anti dengue activity of Euphorbia hirta is done in philipiness It is found to reverse the viral fever and have the ability of preventing the development of disease in to critical stages. Secondly the use of Seabuckthorn leaf extract possessing anti dengue activity[10]. Extract of S. villosum against mosquito vector[11][12]. Leaf extract of Acalypha alnifolia against dengue fever. Quercetin, an active compound of Guava leaves, is found to inhibit the formation of enzyme mRNA in the virus(13).

Mimosa scabrella

Figure 6: Flowers and seeds of *MIMOSA SCABRELLA*(14)

Also known as Bracatinga, belonging to the family Fabaceae. It is prepared from the seeds by ethanolic extract of *Mimosa.scabrella* by cytopathic effect. In vitro with DENV-1 in C6/36 cell culture assay produced a 100 fold decrease in virus title of DENV-1Effective in concentration of 347mgL-1 which showed protection against death in 87.7% of YFV infected mice [in vivo]. Galactomannans is the active constituent which aims on the serotype of DENV-1 and YFV [invivo and invitro].

Momordica charantia

Figure 7: Fruit of *Momordica charanti*(15)

Also known as Bitter melon or peria found in tropical and subtropical region of Asia, Africa and Carribean belonging to the family Cucurbitaceae. The MNTD of the methanolic extract of *Momordica charantia* against Vero E6 cells was investigated in vitro. *M. charantia* recorded a maximal dose that was not toxic to cells of 0.20 mg mL^{-1}. The methanolic extract of *M. charantia* showed inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects.

Carica papaya

Figure 8: Fruit of *Carica papay*[16]

Known as papaya, in hindi it is called as papitha found in central American region. Papain, Chymopapain, Chystatin, L- Tocopherol, Ascorbic acid, Flavanoids, Cyanogenic glucosides and Glucosinolates . Infected individual by carrying mosquito was administered with 25ml aqueous extract of papaya leaves to the patient twice in a day Potential increase in the platelets was observed from 55g103/IL to 168g103/IL, WBC from3-7g103/IL to 7.7g103/IL and Neutrophils from 46.0 to 78.3% . Effective in disease causing destabilization of biological membrane[17]

Solanum virgianium

Figure 9: Leaves and Flowers of *Solanum virgianium*[18]

Commonly called as Surattense or yellow fruit night shade (kantakari) belonging to the family Solanaceae. It is found that it consist of mainly of diosgenin, beta cytosterol, triterpenes like Tupeol,

coumarin, scopolin through column chromatography. Flavonoids are also found to be present along with tolerable level of metals like Cu, Fe, Pb, Zn,Cd. Crude extract of Solanum virgianium leaves showed effective larvicidal activity of mosquito along with ginger and pepper which is effectively used by Santhal community of West Bengal. Root decoction is effective in treating Hernia and constipation.

Tinospora cordifolia

Figure 10: leaves of *Tinospora cordifolia*[19]

It is locally named as heart leaved monseed, guduchi and glloy which is belonging to the family Menispermaceae. Indigeneous to tropical areas of India, Myanmar and Srilanka. Columbin, berberin, tinosporic acid are the constituents which are present in it. It is found to be consisting of analgesic, anti inflammatory, anti oxidant, anti bacterial and immunomodulatory. 40 ml of aqueous extract of Tinospora cordifolia stem for 15 days showed increase in the platelet count overall improvement in lowering the temperature in relieving macupapular rash, anti allergic and good appetizer with no side effect.

Curcuma longa

Figure 11: Leaves and Flowers of *Curcuma longa*[20]

Widely known as Turmeric obtained from the family Zingiberaceae. Ethanolic acetate extract of Curcuma longa rhizome gives 3 Curcuminoids which inhibits topoisomerase-I and topoisomerase-

II [plays in DNA replication][17]. Curcuminoids of which Curcumin-III is more effective. Tumerone obtained from volatile oil of C. longa gives 100% of mosquito cidal activity.

Ocimum tenuiflorum

Figure 12: Leaves of *Ocimum tenniflorum*(21)

Synonym is Ocimum sanctum commonly known as holy basil, an aromatic perennial plant belonging to the family Lamiaceae which is cultivated throughout Asian tropics. It consists of mainly Eugenol, beta element, beta caryophyllene , germacrene with trace amount of terpenes. Methanolic extract of Ocimum tenuiflorum containing about 88.6 ± 21.4% showed inhibitory anti viral effect against DENV-1 through the inhibition of CPE formation as well as viral replication. Other uses include for treating bronchitis, bronchial asthma, arthritis, eye disease, anti fertility, anti diabetic etc.

Azidarachta indica

Figure 13: Leaves of *Azidarachta indica*(22)

Popularly known as Neem, found in the regions of India and Pakistan mainly in tropical and subtropical regions, belonging to the family Meliaceae. It is followed by the cytotoxic studies and to determine MNTD [Maximal Non Toxic Dose] in a virus inhibition study against the serotype DENV-2. Aqueous extract of neem inhibited 100-10,000 TCID [Tissue Culture Infected Dose].

Concentration is 120-130mg/ml MNTD as indicated by the absence of 5 11-bp dengue group specific amplicons upon RT-PCR

Andropogan citratum

Figure 14: Leaves of *Andropogan citratum*[23]

Commonly known as Citronella grass belonging to the family Poaceae. Its mosquito repellant activity is due to the presence of the Citronella oil. C.Limon did not present cytopathic effect or cell death from DENV-1 AGAINST Vero E6 cells. Its is done by the process of Nanoemulsion by pressure homogenization that is conversion from large emulsion droplets (195-220nm) to smaller size droplets (150-160nm) for its higher release rate. The constituents which are responsible for possessing the activity includes geraniol,citronella and citronellol which are monoterpenes

Adathoda vasica

Figure 15: Leaves of *Adathoda vasica*[24]

Commonly known as Malabarnut of family Acanthaceae is indegeneous to Asia, as Siddha, Ayurveda, Homeopathy and Unani system of medicine. Methanolic extracts of fractions of Adathoda vasica leaf extract showed larvicidal activity against the Culex quinque fasciantus and the vector

Aedes aegypti where the mortality rates were high. Vasicine and Vasicinone are the major constituents present in it. Also to treat bronchitis, sedative expectorant, anti spasmodic and anti helminthic.

Andrographis paniculata

Figure 16: Leaves of *Andrographis paniculata*[25]

Popularly termed as king of bitter, pertaining to the family Acanthaceae. Its use is generally beinga curative substance for flu, sore throat and upper respiratory problems. The efficiency of this plant is mainly due to presence of Andrographolide, an active constituent, done by the process of ”Antiviral assay” based on Cytopathic effect against Vero E6 cells [in vitro] inDENV-1.

Murraya koenigii

Figure 17: Leaves of *Murraya koenigi*[26]

Commonly known as Curry tree, found in a tropical and sub tropical region of Indian nativity belonging to the family Rutaceae. The constituents named goinimbine, murrayacine, murrayanine, murrayafoline-A, 3-methylcarbazole together with b-isosterol are effective for its mosquitoedal activity, the method is carried out by ethyl acetate crude extract of whole plant. Adult mosquitoes were grown and were fed, as a result of the experiment, the adult mosquitoes lost their biting ability and consciousness because of the knock-down ability of the plant

Piper longum

Figure 18: Leaves of *Piper longum*[27]

Locally called as pipal or pepper belonging to the family Piperaceae. The leaves of the plant is found to contain major constituent as Thymol (20.077%) and c-elements (10.42%). Ethanolic extract of 3 species of this families that is Piper longumL, P.ribesoides wall and P.sarmentosum Rox were prepared and their efficacy is in the order of P.longum> p.sarmentosum Roxb> P.ribesoides wall. The larvicidal activity against Aedes aegypti of P.longum after exposure to 3 hours was evaluated. It is found to reduce the activities of α and β carboxylesterases and superdioxide and its affected the mosquito gut cellular organelle[28].

Quereus lusitaniea

Figure 19: Leaves of *Quereus lusitaniea*[29]

Locally termed as Mazuphal also known as Quercus inferctoria, a small tree or shrub belonging to the family Fagaceae (Quercaceae). Invitro antoiviral activity against DENV-2 assessed in C-6/36 cells. The MNTD of 0.25mg/ml completely inhibits 10-1,000 TCID 50 of virus, 0.032 mg/ml,(low dose) showed 100% inhibition activity with 10TCID 50 Of virus, and only 50%, 25% inhibition with 100 and 1,000 TCIS 50 respectively. Secondly, down regulation of NSI, (a glycoprotein of flavivirus) of infected C-6/36 cells through Proteomia technique. The methanolic extract of the plant showed inhibition activity by conventional cell culture method too[30]

Psidium guajava

Figure 20: Fruits of *Psidium guajava*[31]

Well known as Jambu biji (guava leaves) belonging to the family Myrtaceae, Indigeneous to Mexico, Central and South America, the carribheam widely cultivated in tropical and subtropical regions. Guava leaves are found to contain biologically active substances such as Kaempferol and quercetin possessing anticancer activity. Aqueous extract of Guava leaves is found to prevent bleeding in dengue Haemmorhage fever and increase the platelet count within 16 hours to about 100.000/mm cube.

Direct sonication of guava leaves, was the technique chosen for its shortest extraction time, lesser impurity and high toxicity.

***Euphorbia hirta*[32]**

Figure 21: Leaves of *Euphorbia hirta*[33]

Commonly named as gotas-gatas or common weed in garden beds, Garden paths and wastelands, belonging to the family Euphorbiaceae used as a Forklorie medicine in Philipines.[34] Preliminary anti-dengue assay by plaque reduction neuteralization test is done. It is found that internal haemmorhaging will stop and cures dengue fever by the ethyl acetate extract; which afforded 6 known triterpene and 3 Flavanoid compounds

Calotropis procera

Figure 22: Flowers of *Calotropis procera*[35]

Locally named as Sodom apple, kings crown , belonging to the family Apocyanaceae. It is native to Western Asia, South Asia and Indochina. Methanolic extract of Calotropis procera was found to be effective and feasible larvicidal activity against dengue vectors. Methyl beta carboline-1-carboxylate, (+)dehydrovomifoliol pleurone, calotropagenin and calotoxin through NMR spectroscopic analysis. Decoction of the whole plant is taken as a tonic, purgative, emetic, also to cure diarrohea, dysentery, intestinal worms, elephantiasis and leprosy. Root powder mixed with Capsicum, pepper to treat rheumatism and arthritis.

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