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## Short Review

## Evolving herbal formulations in management of dengue fever



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## ABSTRACT

Dengue is endemic in more than 100 countries and it is estimated that annually above 390 million infections occur globally. During the period between 1996–2015, a massive increase of more than 500 per cent has been recorded in number of dengue cases reported in India. Till date, there are no specific globally accepted treatments for dengue fever in any system of medicine. Dengue does not cause very high mortality if properly handled and is currently being managed by clinicians through various adjuvant and alternative therapeutic options. Various plant based preparations have been used in different parts of India for combating dengue and are simultaneously also being scientifically validated by researchers. However, number of such scientific validation studies on phytomedicines are very less in India. Out of twenty-two plants reported against dengue, only four have been studied scientifically. *Azadirachta indica*, *Carica papaya*, *Hippophae rhamnoides* and *Cissampelos pareira* extracts were found effective and demonstrated improvement in clinical symptoms and direct inhibitory effect on dengue virus. *C. papaya* clinical trial showed increase in platelet count and faster recovery. These plants may be explored further as probable candidates for drug discovery against dengue. There is a need to search more such herbal formulations, which are being practiced at local level, document properly and validate them scientifically to confirm efficacy, mechanistic action and safety, before use. The herbal formulations being used by communities are the low hanging fruits which may provide alternative or adjuvant therapy if proper validation, value addition and product development steps are followed. This paper aims to review the recent status of dengue cases, deaths and evolving curative herbal solutions adapted and reported from India to combat the disease.

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## 1. Introduction

The incidence of dengue, a viral infection, has rapidly risen in humans through extensive transmission by the bites of infected female *Aedes aegypti* mosquitoes. Dengue Haemorrhagic Fever (DHF) or severe dengue was initially documented during the dengue epidemics in Thailand and Philippines in 1950s; it is now becoming the leading cause of sickness and mortality in several Asian and Latin American countries, including India. Four different types of closely linked virus serotypes responsible for dengue are DENV-1, DENV-2, DENV-3 and DENV-4. These viruses are predominantly transmitted when infected female mosquito *A. aegypti* bites healthy individuals. Once infected, humans act as carriers and provide favorable environment for multiplication of the virus,

which subsequently gets transferred to uninfected vectors during bites [1]. Patients suffer with eminently high fever along with some associated symptoms such as moderate to severe headache, pain in joints and behind eyes, vomiting, rashes and inflamed glands. If not handled well, dengue becomes complicated and patient suffers due to respiratory distress, fluid accumulation, severe bleeding, organ damage etc. which becomes fatal in critical cases [1].

Presently, dengue is endemic in more than 100 countries across the globe including India; prior to 1970, only nine countries were reported to have epidemics of severe dengue [1]. Bhatt et al. (2013) analyzed under-reporting of the actual number of dengue cases and estimated that annually about 390 million infections occur throughout the globe [2]. In India, dengue virus was first isolated in the year 1944 in Kolkata from the serum samples of infected US soldiers [3]. In 1996, the first major epidemics of Dengue Haemorrhagic Fever (DHF) and/or Dengue Shock Syndrome (DSS) occurred near Delhi and Lucknow in Uttar Pradesh and thereafter the virus started spreading across India [4–6].

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Currently, the Indian population is infected by dengue viruses and sizable numbers of mortalities are recorded every year. India has a rich biodiversity and tradition of using plant-based medicines for preventive and curative healthcare. Traditionally large numbers of plants are reported for their use against contagious diseases, including infection caused by viruses. During recent years, there are many online and offline published contents which demonstrate and portray use of plants and their formulations for their therapeutic effects against dengue. This paper aims to review the recent status of dengue cases, deaths and evolving curative herbal solutions adapted and reported from India to combat the disease. Data on utilization of various herbal and traditional medications popular among clinicians, patients and common public for contending dengue are also compiled.

## 2. Status of dengue infections and deaths in India

Reported infected cases and mortality due to dengue in Indian states were thoroughly evaluated for last 20 years using licensed version of [www.indiastat.com](http://www.indiastat.com). The data in Fig. 1(A&B) illustrate dengue cases and related deaths during 1996–2015 and also depict its status in different states and union territories of India. An increase of more than 500 per cent has been observed in the number of dengue cases during the period between 1996 (16,517 cases) to 2015 (99,849 cases). Data indicate that in India dengue viruses are getting all the required support systems for their rapid transmission and multiplication, i.e. favorable climatic conditions, abundantly available vectors, and human population for infection. In spite of increasing number of cases, a gradual decrease of about 40 per cent in mortality has been recorded from the year 1996 (545 deaths) to 2015 (220 deaths). Improvements in the Indian health-care systems, easy accessibility to medical practitioners, awareness

among stakeholders, early reporting and precise diagnosis, and availability of timely and better treatment options for patients may be some of the reasons for reduced mortality due to dengue infections. However, still there is a need to develop a drug which can target the dengue virus and also immunize individuals against primary as well as secondary infections. In 2015, Delhi (15,867) had the highest number of reported cases of dengue, followed by Punjab (14,128), Haryana (9921) and West Bengal (8516). Maximum number of deaths due to dengue was recorded in Delhi (60) followed by Kerala (25), Maharashtra (23) and Punjab (18) (Fig. 1A&B). There is no positive correlation between the number of cases reported and deaths occurred in various states of India. This may be due to various levels of preventive and curative therapies and also depends upon the immune responses of the patients during the treatment phase. Negligence by the patients and other stakeholders may be the key cause of increased death after infection.

## 3. Evolving herbal treatment options for dengue

Till date, there are no specific globally accepted treatments for dengue fever in any system of medicine. Dengue does not cause very high mortality and is currently being managed by clinicians through various adjuvant and alternative therapeutic options; however the patient suffers a lot during the treatment. Due to non-availability of specific drugs similar to other infectious diseases, patients often panic once detected with dengue. Preparations and formulations based on plants have also been tried and used by traditional healers and simultaneously being scientifically validated and documented by modern researchers. In this article we have reviewed various plants and their preparations which have been reported for dengue and are summarized in Table 1. Google, Google Scholar and Pubmed were searched using the following key

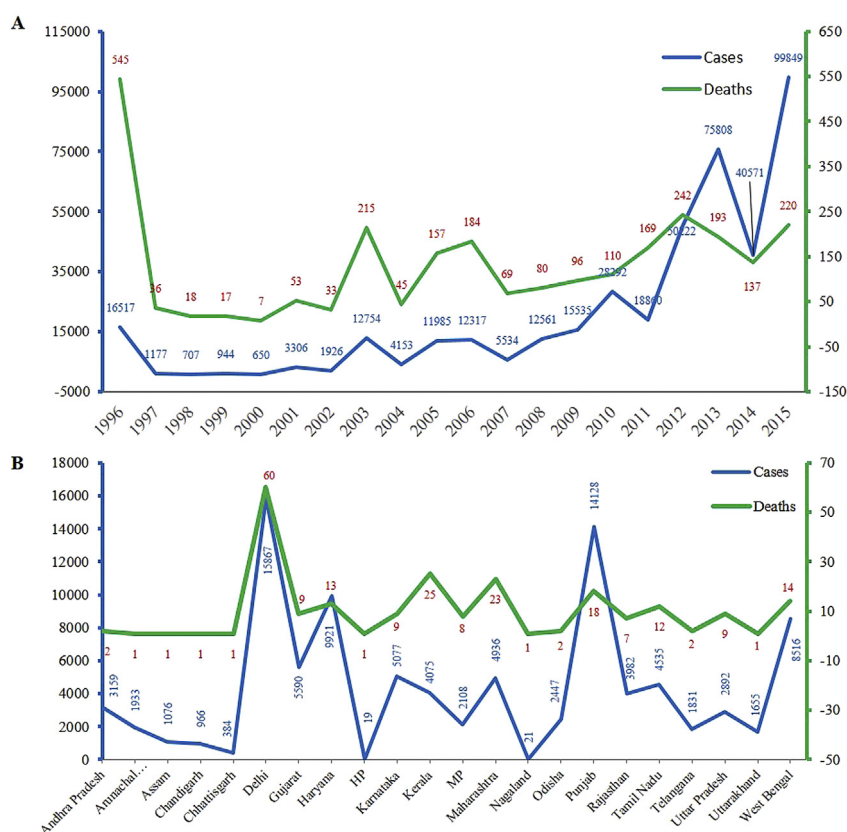


Fig. 1. A – Status of cases reported and deaths in India during 1996–2015. B – State wise infection and deaths due to dengue in India.

**Table 1**  
Medicinal plants reported from India for their activity against dengue virus.

SN	Plant	Part/extract used	Details of study/report
1	<i>Azadirachta indica</i>	Leaves extract	<i>In vitro</i> and <i>in vivo</i> study done against dengue virus type-2 showed positive effect in reduction of virus [7]
2	<i>Hippophae rhamnoides</i>	Leaves extract Leaves extract	Used by tribal and traditional healers in various districts of Bihar [8] <i>In vitro</i> assay against dengue virus type-2, extract has a significant anti-dengue activity [9]
3	<i>Carica papaya</i>	Leaves extract Leaves extract Leaves extract Leaves extract Leaves extract Leaves extract	Increase in platelet count in dengue patients and management of disease [10] Relevant uses in Ayurveda [11] Used by local people of North Eastern plain zone of India [12] Used by traditional healers and local people of Goa [13] Used by traditional healers and local people of Madhya Pradesh [14] Used by traditional healers and local people of Uttar Pradesh [15] Clinical trials on patients indicate increase of platelets due to administration of extract [27]
4	<i>Solanum virginianum</i>	Leaves extract Leaves decoction along with pepper and ginger	Used by traditional healers and local people of Odisha [28] Used by Santhal community in West Bengal [16]
5	<i>Tinospora cordifolia</i>	Stem decoction Stem decoction Stem and leaves	Used by Gujar community in Trikuta hills, Jammu and Kashmir [17] Used by tribal and local people of Bijnor in UP [18] Used by tribal and local people of Chhattisgarh [19]
6	<i>Ocimum sanctum</i>	Leaves Leaves	Reported for its use as leave decoction [20] Reported for its use as leave decoction [21]
7	<i>Andrographis paniculata</i>	Whole plant	Used by traditional healers in various districts of Bihar [8]
8	<i>Alternanthera sessilis</i>	Whole plant	Used by traditional healers in various districts of Bihar [8]
9	<i>Achyranthus aspera</i>	Whole plant	Used by traditional healers in various districts of Bihar [8]
10	<i>Calotropis procera</i>	Leaf and bark	Used by traditional healers in various districts of Bihar [8]
11	<i>Solanum xanthocarpum</i>	Whole plant	Used by traditional healers in various districts of Bihar [8]
12	<i>Plectranthus vettiveroides</i>	Whole plant	Used by traditional healers in South India and in formulations [22]
13	<i>Brassica juncea</i>	Whole plant	Used by traditional healers of Nimari communities of Madhya Pradesh [23]
14	<i>Adhatoda vasica</i>	Leaves extract	Reported for its use in formulation [24]
15	<i>Euphorbia hirta</i>	Whole plant	Used by traditional healers and communities of Uttar Pradesh [15]
16	<i>Cassia fistula</i>	Root	Reported for its use as tonic [25]
17	<i>Swertia chirata</i>	Whole plant	Reported for its use as decoction [25]
18	<i>Datura metel</i>	Leaves	Reported for its use as decoction [25]
19	<i>Coriandrum sativum</i>	Leaves	Reported for its use as decoction [25]
20	<i>Peganum harmala</i>	Powdered seed	Reported for its use as decoction [25]
21	<i>Abutilon indicum</i>	Whole plant	Reported for its use as decoction or infusion [25]
22	<i>Cissampelos pareira</i>	Whole plant	Extract tested in <i>in vitro</i> and <i>in vivo</i> conditions and found effective against all four serotypes [26]

words – dengue, herbal, plant, traditional, India for the articles published during 2008–2016.

Very limited number of plants have been studied scientifically for their efficacy against dengue virus. In one of such study, crude aqueous extract of neem leaves and compound Azadirachtin were evaluated against replication of dengue virus type-2. Extract from neem leaves showed significant inhibitory activity against dengue virus, while pure Azadirachtin didn't depict any inhibitory effect in both *in vitro* and *in vivo* experiments. Maximum non-toxic concentrations of neem leaves extract in *in vitro* virus inhibition assay (on C6/36 cells) and *in vivo* virus inhibition studies (on suckling mice) were found to be 1.897 mg/ml and 120–30 mg/ml respectively. Different concentrations of neem extract were mixed with 100 LD<sub>50</sub> dose of virus in equal proportions and incubated for 1 h. 20 µl of this mixture was inoculated intracerebrally in each mice pup. Clinical signs of dengue such as; weight loss, slow gait, inability to suck mother's milk and flaccid paralysis followed by death were observed for 5 days. Absence of clinical symptoms and virus specific amplicon was observed in the mice pups inoculated with test extract [7]. The above study validates the efficacy of neem leaves in combating dengue and also supports the fact that single phytomolecule based medications are always not superiorly effective than the extracts. Hence, in addition to making efforts to identify pure molecules, researchers should also consider the original herbal extracts and preparations while doing validation and drug discovery.

In another study, alcoholic extract of *Hippophae rhamnoides* leaves was tested against dengue virus type-2 infected human macrophages. Human blood matured macrophages were isolated and infected with dengue virus at 1:100 dilution and cultured. Crude *H. rhamnoides* extract showed significant anti-viral activity as concluded from decrease in TNF- $\alpha$ , increased IFN- $\gamma$  production in dengue-infected cells and increased cell viability. These positive effects were comparable with the commercially available anti-viral drug, Ribavirin [9]. This plant may be further explored for its immunomodulatory effects, in addition to testing its anti-dengue efficacy in *in vivo* and clinical conditions, after accessing safe animal and human doses.

Another study by Sood et al. demonstrated significant anti-viral activity of the alcoholic extract of *C. pariera* Linn (Cipa) against all four dengue viruses (DENV-1, -2, -3, -4). Significant inhibitory effect at 100 µg/ml dose was observed on NS1 antigen secretion. Dose-dependent decline in the viral titre upto ~2 logs was observed. The extract showed significant anti-pyretic effect with no major changes in the platelet counts or erythrocyte count as compared to control. *In vivo* studies in AG129 mouse further demonstrated the efficacy of Cipa extract against dengue. Oral administration of Cipa extract (250 mg/kg b.w.), twice a day continuously for 5 days resulted in significant increase in median survival time of the challenged mice. It was also reported that production of TNF- $\alpha$  cytokine was down-regulated and there were no signs of toxicity at dose of 2000 mg/kg b.w. [26].

Evidence of efficacy of *C. papaya* in human against dengue infection has also been reported recently. In one study *C. papaya* leaf juice was extracted, filtered using traditional method and two table spoonfuls of juice was administered orally to 5 dengue patients three times per day after every 6 h interval. Platelet counts before and after the treatment were recorded. It was found that intake of *C. papaya* leaf juice resulted in significant increase in the platelet counts in the dengue virus infected patients within 24 h of treatment [10].

In order to evaluate the potential of *C. papaya* leaf extract (CPLE) in preventing the condition of thrombocytopenia associated with dengue fever, a double-blind, placebo-controlled, randomized trial was conducted on 300 patients across 5 centres. The intervention group was administered CPLE tablet (1100 mg), three times daily for five days while the control group was given placebo for the same frequency and duration as the intervention group. It was observed that the intervention group was able to recover faster with higher increase in platelet count from 2nd day onwards as compared to the control group. Additionally, significant increase in the WBC counts was also observed in the intervention group as compared to the control group. It was suggested that the effect may be due to increase in the expression of Arachidonate 12-lipoxygenase and Platelet-Activating Factor Receptor gene responsible for platelet production [27].

Many more scientific validation studies followed by clinical trials are needed for other reported plants in order to ascertain their safety, efficacy and mode of action. In validation studies, these plants may also be tried alone or in different combinations to understand their synergistic effects in terms of efficacy and safety.

#### 4. Conclusion

Non-availability of specific target drugs against dengue undoubtedly must be creating uncertainty in the minds of infected individuals. This situation not only creates panic in the patients but also puts pressure on clinicians who manage the disease. This also helped Indian society to find out alternative options for treatment and prevention of dengue. Various plants and their preparations have been used traditionally in different parts of India for combating dengue. Use of plants against dengue by herbal healers and local communities of North East plains, Goa, Madhya Pradesh, Bihar, West Bengal, Uttar Pradesh etc. have been documented in various literature. When we analyzed scientific validation studies of evolving herbal alternatives, all the three methods and models (*in vitro*, *in vivo* and clinical trial) of efficacy testing against dengue viruses have been adapted by the Indian researchers. However, number of such scientific validation for plants effective against dengue are very less in India, below double digits. About twenty-two plants from all over India were found in literature search which were recommended for their use against dengue. However, only two to three plants/extracts have been tested scientifically and also have shown evidences of efficacy. There is a need to search more such herbal formulations which are being practiced at local level, document them properly and validate them scientifically to confirm efficacy, understand mechanistic action and safety so that they can be exploited for their anti-dengue potential. The potential herbal formulations being used by the communities and healers are the low hanging fruits which may provide alternative or adjuvant therapy if proper validation, value addition and product development steps are followed.

#### Conflict of interest

None.

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