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Therapeutic activity of medicinal plants and their derivatives in controlling mosquito vector-borne diseases in north-east India

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Abstract
North-east India is one of the highly affected region by mosquito-borne diseases. MBDs cause major hindrance in the lives as well as survivability of people here. The most reported mosquito vector-borne diseases here are Malaria, Dengue, Japanese encaphalities, Lymphatic filariasis and Chikungunya to name a few. While the hot and humid climate is one of the factor for widespread distribution of mosquito species in North-eastern states, it is also bestowed with abundant medicinal plants which can be used for the treatment of MBDs. The long-standing innate connection between the ethnic groups and the environment, particularly with plants, has given contemporary civilization access to a wide range of herbal treatments. This study mainly focuses on the present scenario of MBD in north-eastern states of India and the therapeutic uses of plants endemic to this region which have medicinal properties to cure or prevent such diseases.

Keywords: Mosquito, vector-borne, medicinal plants, north-east India

Introduction
Vector-borne diseases (VBDs) have been a matter of concern since time immemorial. However, it has become a critical health concern in recent years as they account for 17% of all illnesses and impairments worldwide [63]. Annually, more than a billion people contract VBDs, and more than a million of these infections result in death [1]. The term "vector" refers to an organism that can spread disease from one human to another or from an animal to a human. The Southeast Asian region is home to a wide variety of vector-borne diseases, including those spread by sand flies (kala-azar), mosquitoes (malaria, dengue, Japanese encephalitis, lymphatic filariasis), and snail mediated diseases (schistosomiasis). Mosquito-borne infectious illnesses (MBIDs) account for the majority of reported cases, death, and years of life with a disability among all recognised VBDs [64]. Malaria, dengue, chikungunya, and Japanese encephalitis are the most widespread mosquito-borne diseases. Each year, malaria causes 400,000 deaths and 219 million new cases worldwide. Dengue/DHF affects more than 3.9 billion people in 129 countries and results in 40,000 fatalities each year [4]. In the past 30 years, dengue has multiplied 30 times in occurrence around the globe. Africa, Asia, and the Indian Subcontinent are the main regions where Chikungunya is mostly reported. In contrast, America was impacted by a significant outbreak in 2015. The lack of access to adequate health care, inadequate housing, sanitation, and water supply are some of the socioeconomic factors that affect the majority of VBDs [7].

Mosquito vector-borne diseases in north-east India
The eight states that make up North-east India are Assam, Arunachal Pradesh, Meghalaya, Mizoram, Manipur, Tripura, Nagaland and Sikkim. The region's total geographic area is 262185 km^2, or 7.9% of India's total land area [39]. Out of four, one of India's Biodiversity Hot Spots is situated here. According to research, the abundance of possible mosquito vectors that could transmit the pathogens of various mosquito-borne diseases among rural communities is influenced by paddy agriculture in the area, habitational settings with nearby bodies of water, high temperatures, and humidity.

Additionally, a lack of awareness of the illness, communication breakdowns, and weaknesses in the government's delivery systems have led to the spread of these diseases [10]. Due to extraordinary population growth brought on by human migration, urbanisation, and environmental degradation, North-East India, in particular Assam, is currently experiencing rapid ecological changes. This opens up potential for vector proliferation and higher susceptibility. Hence, recent outbreaks of mosquito-borne diseases like Malaria, Japanese Encephalitis, Dengue, Lymphatic Filariasis as well as Chikungunya to some extent has been witnessed in this region.

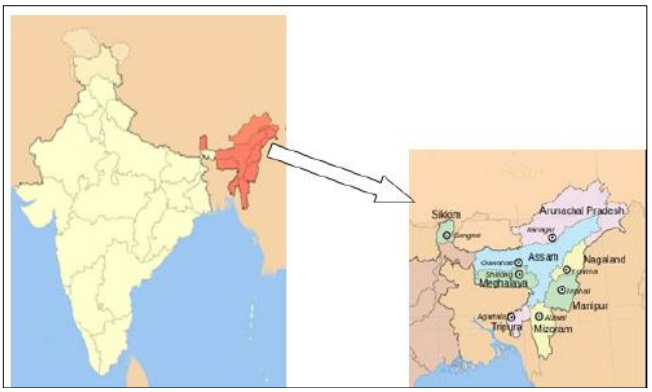


Fig 1: Map of India showing the North-eastern states, the study area. (Image source: Google)

Malaria

According to World Malaria Report 2022 published by World Health Organisation, 247 million cases were reported worldwide while the death toll was 619,000 worldwide in the year 2021. India is responsible for 2% of all malaria cases and 2% of all malaria deaths worldwide [65]. In the WHO South-East Asia Region, the nation accounted for 82.4% of all malaria-related deaths in 2021. India's diverse geography and ecosystems contribute to the complexity of the disease's epidemiology.

Plasmodium falciparum and *Plasmodium vivax* are the two main malaria parasites that cause the disease in India (though cases of *P. ovale* and *P. malariae* have also been reported from some parts of the country). Nine species of *Anopheles*, of which six are main vectors for the disease, are involved in its transmission [21].

North-east is highly endemic to Malaria which is mostly caused by *Plasmodium falciparum* here. The primary malaria vectors in NE India are thought to be the *Anopheles dirus* and *Anopheles minimus* complex mosquitoes, which each have their own ecological niches [46]. The primary vectors of malaria in North-east India are *Anopheles minimus* and *Anopheles baimaii*. Apart from them, other vactors like *A. annularis, A. phillipinensis/nivipes* and *A. culicifacies* are considered to be secondary vectors in the region [9].

In July 2022, Assam reported around 86 cases of malaria, the highest being in Kokrajhar district.

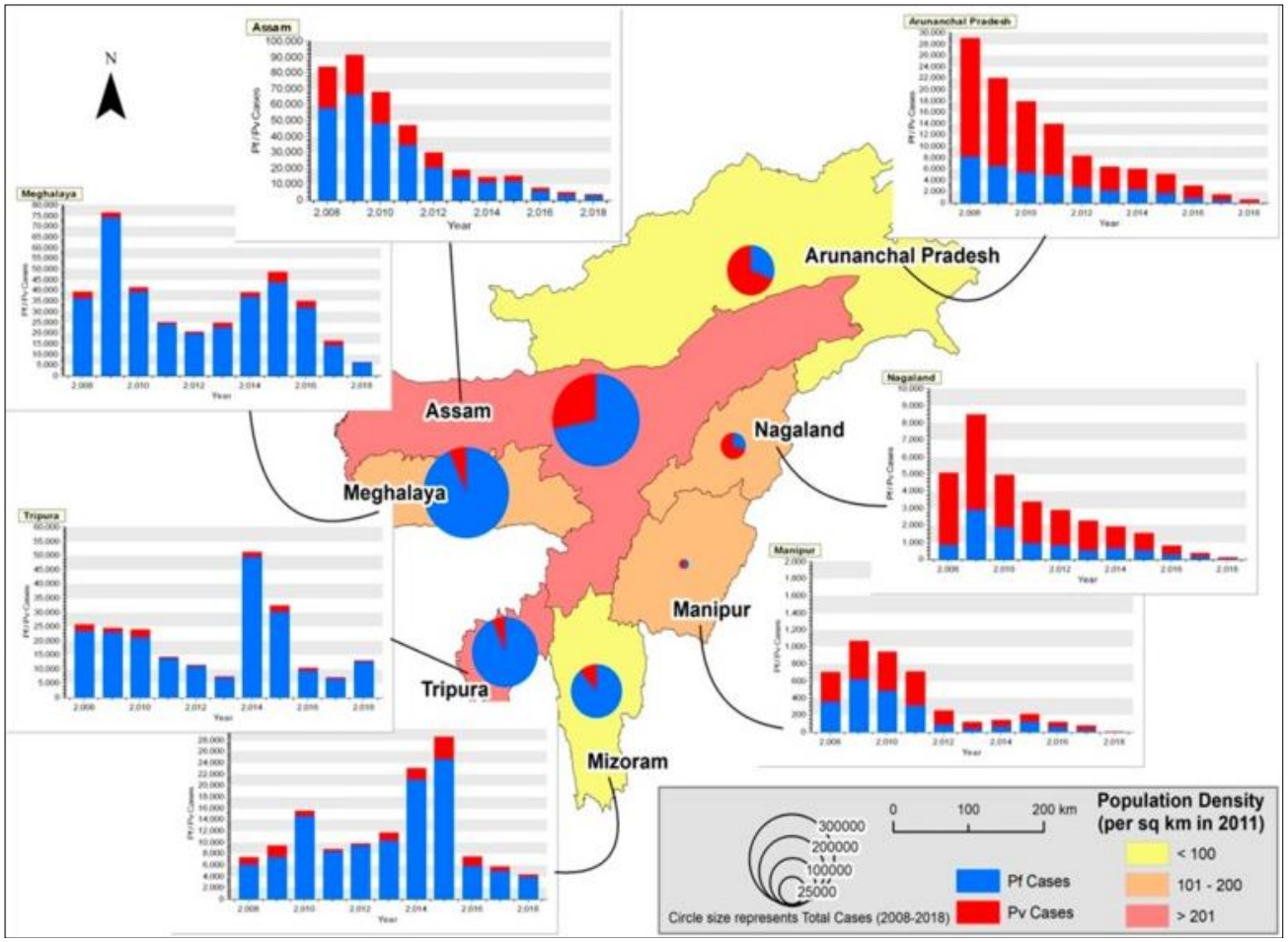


Fig 2: Distribution of *Plasmodium falciparun* (Pf) and *Plasmodium vivax* (Pv) cases over time and space in NE India between 2008 and 2018. The hue of the background represents each state's population density (as per 2011 census). The proportional pie chart displays all Pf and PV instances recorded in the states from 2008 to 2018 [52].

Dengue

Dengue is an arboviral illness spread by mosquitoes that is brought on by the Dengue virus (DENV), which comes in four different strains: DENV1, 2, 3, and 4. *Aedes aegypti* and *Aedes albopictus* female mosquitoes are the primary carriers of the dengue virus. The primary dengue vector, *Aedes aegypti*, is highly adaptable to both natural and artificial conditions [42]. Nearly 70% of the dengue epidemic's global impact is borne by Asia alone. 237 dengue cases were recorded for the first time in 2010, followed by 1058 and 4526 cases in 2012 and 2013, respectively [59]. During the post-monsoon months of September to December, the Guwahati metropolitan area saw the majority of dengue cases (>70%). Patients from all sexes and across the age spectrum made up this group, but adult males between the ages of 26 and 60 had the highest number of instances. Currently, dengue is spreading to semi-urban areas and neighbouring states and districts in north-east India. Till October 2022, states like Arunachal Pradesh reported 163 dengue cases, Manipur- 313, Mizoram- 437, Meghalaya- 15, Sikkim- 209, Tripura- 44 and Nagaland- 68 [13].

The recent outbreak of dengue in Assam particularly in Karbi Anglong Autonomous Council in the year 2022 has been a matter of concern for the state administration.

The 2022 dengue outbreak in Assam as well as neighbouring states were so extreme that it led the state administration to shut down educational institutions in affected areas. The reports provided by National Health Mission (NHM) Assam stated that there were 551 dengue cases since November of which 478 cases were from Karbi Anglong Autonomous Council particularly from the district headquarters of Diphu. Three deaths were also reported. Manipur and Mizoram have witnessed five deaths in the same year.

Lymphatic filariasis

In India, filariasis has been a serious public health issue. 41% of global lymphatic filariasis cases are contributed by India.The renowned Indian physician Susruta first wrote about the illness in his book "Susruta Samhita" in the sixth century B.C [6]. *Wuchereria bancrofti*, which is spread by the common vector *Culex quinquefasciatus*, has been the most prevalent illness in mainland India and is responsible for 99.4% of the problem there. The disease is widespread both in urban and rural settings. The prevalence of *Brugia malayi* infection is primarily confined to rural areas as a result of the vector's unusual nesting habits linked to floating plants. The primary vector is *Mansonia (Mansonioides) annulifera*, and the secondary vector is *M(M) uniformis*. Due of its low density, *M(M) Indiana's* vectorial role is extremely constrained. In mainland India, infections with *W. bancrofti* and *B. malayi* both display nocturnal periodicity of microfilaraemia [2].

Although Bancroftian filariasis (*Wuchereria bancrofti*) is common in Assam, only the following districts have reported cases of the disease: Darrang, Udalguri, Dhemaji, Dhubri, Dibrugarh, Kamrup/Kamrup (Metro), and Nalbari, Baksa and Sivasagar [59]. This reporting is based on native transmission, which is supported by clinical cases and community-based microfilariae carriers. Surveys conducted on the prevalence of filariasis in these districts have revealed a significantly higher microfilaria rate (4.7-10.3%) in tea garden tribes (descended from migrated tribes from West Bengal, Bihar, Madhya Pradesh, Odisha, and Uttar Pradesh), as opposed to the indigenous populations living in close proximity to a tea garden, which could be attributed to variation in sociocultural living conditions and host-parasite response [28, 60].

The National Filaria Control Programme (NFCP) was established in India in 1955 to implement control measures in endemic areas.

To end lymphatic filariasis, significant efforts have been made by mass drug administration (MDA) of diethylcarbamazine and albendazole [27].

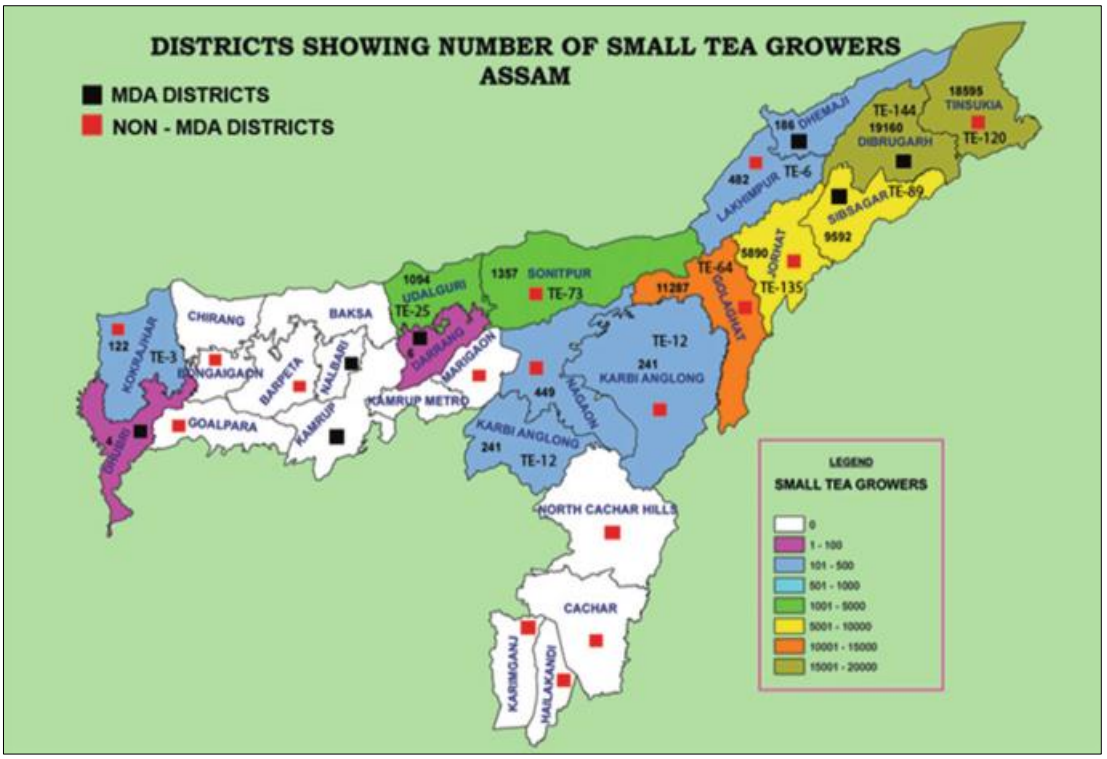
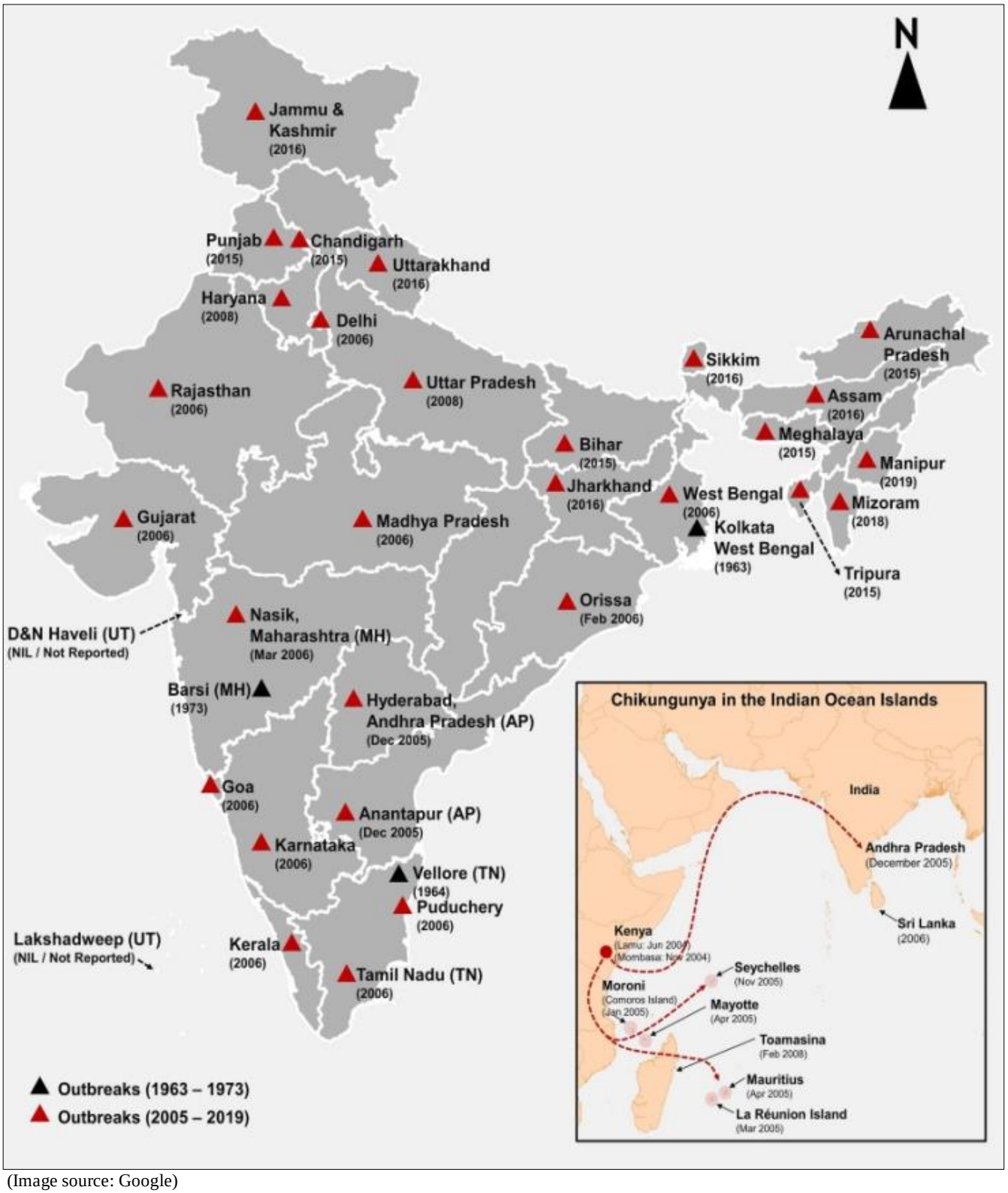


Fig 3: MDA and Non-MDA districts of Assam [28]

Chikungunya

The arthropod-borne viral illness Chikungunya (CHIK) is significant for public health. The Chikungunya virus (CHIKV), which is the pathogen, is a member of the Togaviridae family, *Alphavirus* genus of viruses [62]. Mosquito species *Aedes aegypti* and *Aedes albopictus* are the main carriers of CHIK in humans [58]. Fever, joint discomfort, muscle pain, headache, nausea, exhaustion, and rash are some of the clinical signs of CHIK.

In India, Chikungunya was first reported in West Bengal in the year 1963 [53]. Subsequently, it spreaded to several other states. Among the north-eastern states, Assam reported first hospitalized case of Chikungunya in 2008 [19]. Thereafter, Meghalaya was affected by this disease in 2010 where it still remains as one of the major health concern [29]. The possibility of CHIKV circulation and dissemination to more recent locations exists in this region of the country due to the prevalence of the vector mosquito [17].



(Image source: Google)

Fig 4: Chikungunya outbreaks in different parts of India

Japanese encephalitis

A significant public health issue in Southeast Asia is the Japanese encephalitis (JE). The Japanese encephalitis virus (JEV) is a flavivirus spread by mosquitoes that is in the same genus as the West Nile, dengue, and yellow fever viruses. The virus infects the brain and is disseminated by mosquito bites. When mosquitoes bite infected animals, the virus, which is also present in pigs and birds, is transmitted to the mosquitoes. Humans contract Japanese encephalitis from infected *Culex* mosquito species through their bites (mainly *Culex tritaeniorhynchus*). Inflamed brain tissue leads to lower degrees of consciousness, seizures, headaches, photophobia, vomiting, and in rare circumstances, death.

Since 1960s, the disease has placed a heavy cost on the Indian subcontinent [22]. The state reported the first incidence of Japanese encephalitis in 1978, and since then, cases and deaths have been reported in each successive year. The Northeast of India has had a long relationship with mosquito-borne diseases. With confirmed cases and a high case-fatality rate affecting people of all ages, the disease, which was formerly endemic to the state's eastern region, is rapidly spreading. The state is prone to the spread of JE due to climatic factors, an abundance of potential mosquito vectors, amplifying hosts, agricultural activities, and human sociocultural behaviour. The disease is most prevalent from June through August, which are the wet summer months [45]. In 2022, Assam reported over 434 cases of JE causing the death of 93 people since July. The number of cases, deaths, and illnesses has doubled as a result of the protracted flooding that made stagnant water a favourable breeding habitat for mosquitoes in Assam, this monsoon. The *Culex vishnui* mosquito, which is primarily found in Assam, thrives in stagnant water because it provides a favourable environment for reproducing. After that, the virus is spread to the hosts when it bites wild birds and pigs. The virus spreads when an additional *Culex vishnui* bite afflicted pigs, birds, and eventually people [26].

The state of Arunachal Pradesh sprang into action with fogging and focused pesticide spray during the 2019 JE epidemic to stop the disease from spreading further. East Siang, Upper Subansiri, and the Papum Pare districts, where the disease has been identified, are the focus of a nationwide campaign for the early detection and treatment of Japanese encephalitis.

Two deaths were reported in the western regions of the Garo Hills in Meghalaya that same year, which prompted an emergency. The health department began awareness campaigns in unsafe and inaccessible areas in Tripura as well [10].

Medicinal plants found in north-east India against mosquito vector-borne diseases

Plant name	Common name	Family	Disease against used	Parts used	References
Acorus calamus L.	Sweet flag	Araceae	Malaria	Rhizome (Taken with quinine, stops remittent fever)	[55]
Adhatoda zeylanica	Malabar Nut	Acanthaceae	Malaria	Leaf (used during bath or as paste to cure malaria)	[31]
Andrographis paniculata	Green chiretta	Acanthaceae	Malaria, Dengue, Lymphatic filariasis	Leaf (anti-malarial, anti-dengue agent especially against DENV-1 serotype, Also anti-filarial against *B. malayi*)	[11], [67], [37]
Azidarachta indica	Neem	Meliaceae	Malaria, Dengue, Lymphatic filariasis, Chikungunya	Leaf extract	[43], [15]
Cinchona officinalis	Peruvian Bark Tree	Rubiaceae	Malaria	Bark	[23, 30]
Cinnamonum bejolghota (Buch.-Ham)	Tezpta (Mizo language)	Lauraceae	Malaria	Bark and leaf (bark and leaves are boiled with the leaves of *Anacolosa crassipes*)	[31]
Coptis teeta Wall	Golden thread herb	Rananculaceae	Malaria	Root, rhizome (administered orally)	[47, 56, 66]
Croton tiglium L.	True Croton	Euphorbiaceae	Malaria	Leaf, flower (powdered and consumed with water)	[11]
Carica papaya L.	Papaya tree	Caricaceae	Malaria, Dengue	Leaf	[3, 55]
Datura metel L.	Thorn Apple	Solanaceae	Malaria	Seed, leaf, root (taken during fever with catarrhal and cerebral complication	[34]
Dichroa febrifuga Lour.	Chinese quinine	Saxifragaceae	Malaria	Roots and leafy tops are used in malarial fever. Therapeutic activity is due to quinazoline derivatives	[34]
Halenia elliptica D. Don	Spurred Gentian	Gentianaceae	Malaria	Plant (taken orally during malarial fever)	[47]
Hedyotis scandens Roxb.	Climbing Diamond Flower	Rubiaceae	Malaria	Root and leaf	[31]
Hydrangea macrophylla (Thunb.) Ser	Big leaf hydrangea	Saxifragaceae	Malaria	Leaf and root (considered more potent than quinine)	[57]
Melodinus monogynus Roxb.		Apocynaceae	Malaria	Leaf, wood and root (used as anti-malarial drug)	[34]
Ocimum sanctum L.	Holy Basil	Lamiaceae	Malaria	Root (decoction is given as diaphoretic)	[48, 12]
Picrasma javanica Bl.		Simaroubaceae	Malaria	Bark (taken orally in lieu of quinine)	[31]
Piper mullesua Buch.	Hill Pepper	Piperaceae	Malaria	Leaf, fruit (Dried and consumed during malaria	[11]

Ham.				and fever)	
Stephania japonica miers.	Snake vine	Menispermaceae	Malaria	Tuber	[11]
Vitex peduncularis Wall		Verbenaceae	Malaria	Bark, leaf, stem (useful in malaria and black water fever)	[31, 48, 56]
Boerhavia diffusia L.	Hog Weed	Nyctaginaceae	Dengue	Plant (mixed with *Tinospora cardifolia* creates anti-dengue effect)	[5]
Alternanthera philoxeroides (Mart.) Griseb	Alligator Weed	Amaranthaceae	Dengue	Leaf	[24]
Cissampelos pareira	Velvet leaf	Menispermaceae	Dengue	Stem (anti-inflammatory activity)	[8]
Euphorbia hirta		Euphorbiaceae	Dengue	Leaf, roots (decoction increases platelet count)	[44]
Houttuynia cordata	Fishwort, Chameleon plant	Saururaceae	Dengue	Leaf extract (inhibits DENV-2)	[32]
Lippia citriodora	Lemon beebrush	Verbenaceae	Dengue	Leaf	[40]
Alstonia scolaris	Scholar tree	Apocynceae	Filariasis, Elephantiasis	Latex, leaf	[15]
Aegle marmelos Corr	Wood Apple	Rutaceae	Lymphatic filariasis	Leaf (methanolic extract)	[25]
Butea monosperma L.	Bastard Teak	Fabaceae	Lymphatic filariasis	Roots and leaves	[50]
Caesalpinia bonducella L.	Gray Nicker	Caesalpiniaceae	Lymphatic filariasis	Leaf juice and seed powder	[20]
Vitex negundo Linn.	Horseshoe vitex	Verbenaceae	Lymphatic filariasis	Root extract	[51]
Trachyspermum ammi	Thymol seed	Apiaceae	Japanese Encephalitis, Lymphatic filariasis	Seed oil	[49]

Conclusion

The Government of India has left no stone unturned to combat mosquito vector borne diseases in the country. Several initiative and schemes have been launched in favour of the same. Alongside it, the north-eastern part of the country's rich flora has proved to be a boon for it. Traditional knowledge and practices have proved to be life saviours in remote areas where medical help cannot reach on time. The need for an alternative drug for MBDs were realized by the local communities here which led them to use the indigenous resources and draw benefit from them. Today, when the world is fighting the menace of biodiversity loss, it is of utmost importance for us as responsible humans to protect and safeguard our flora and fauna without which survival will not be possible.

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