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Therapeutic and Alternate Preventive Measures to Combat Dengue Epidemic in the Indian Subcontinent

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ABSTRACT

In this review we have explored the various alternatives that are being developed and explored for the effective control, prevention, and treatment of Dengue fever. Dengue fever affects approximately 2.5 billion people or half the world's population. Specifically, in the Tropics regions, it has acquired an endemic proportion. As a consequence, the search for alternative approaches for the prevention of dengue has assumed more urgency than in the past. Environmental measures for source reduction, use of vaccines, for mass immunization of population in endemic regions, and biological vector control measures are being extensively researched for advanced dengue prevention. Phytochemicals are also been explored in order to develop a bioactive molecule effective against vector-borne viral infections.

Keywords: Dengue, Vaccines, Phytochemicals, Biological control, Vector control

Abbreviations: DF: Dengue Fever, DENV: Dengue Virus, DHF: Dengue Hemorrhagic Fever, DSS: Dengue Shock Syndrome, WHO: World Health Organization, SEA: Southeast Asia, Bti: Bacillus thuringiensis israelensis, Ref: References.

INTRODUCTION

Dengue Fever (DF) is caused by the arthropod-borne flavivirus named Dengue Virus (DENV), transmitted by the *Aedes aegypti* mosquito [1]. Dengue is a vector-borne disease caused by the dengue virus (DENV, 1-4 serotypes). DENV virus is the most common arbovirus prevalent in tropical and subtropical regions [2]. Both *Aedes aegypti* and

Aedes albopictus are the main vectors for DENV in India [3]. Infection with DENV can elicits a wide spectrum of clinical symptoms ranging from being asymptomatic to the severe clinical state of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [2]. Mild symptoms of dengue can be confused with other illnesses that cause fever, aches and pains, or a rash. The most common symptom of dengue is fever with nausea, vomiting, rash, aches and pains (eye pain, joint pains).

Humans act as carriers and provide a favorable environment for multiplication of the virus, which subsequently gets transferred to uninfected vectors during bites [2].

No specific treatment for dengue fever exists, other than supportive measures for the management of fever. i.e., nursing care, fluid balance, electrolytes, and blood clotting parameters [4]. In the quest to find a solution and treatment option for DF and DHF various approaches have been explored.

Vaccine development [5-7] and various natural and artificial vector control measures [8] have been implemented in endemic regions. In this article, we review the approaches available to prevent and reduce incidences of Dengue epidemic in the Indian Subcontinent. This is a descriptive review. Articles related to the topic were located and selected from PubMed and Scopus database of peer-reviewed literature.

Impact of dengue fever on public health

Dengue is endemic in more than 100 countries and causes an estimated 50 million infections annually [9]. The World Health Organization (WHO) regions of Southeast Asia (SEA) and the western Pacific represent ~ 75% of the current global burden of dengue. In the Indian Subcontinent from the early 1990s, the incidence of DF and DHF is on the rise. In 1996, the first major epidemic of DHF and/or DSS occurred near Delhi and Lucknow in Uttar Pradesh and thereafter the virus started spreading across India [3].

Outbreaks of epidemic proportion have been reported from countries like India, Pakistan, Bangladesh, and Sri Lanka. In India from (2010-2014), 213 607 cases (incidence: 34.81 per million population) of dengue fever were observed [10]. This year Bangladesh reported over 75,000 cases of Dengue infection and declared it as the worst outbreak since records were maintained [11].

Available treatment options for dengue infection

Like most viral infections Dengue has no specific treatment. Fluid replenishment to avoid dehydration from vomiting and fever is generally recommended. Acetaminophen (paracetamol) can alleviate pain and reduce fever, however analgesics that increase bleeding complication such as aspirin, ibuprofen and naproxen sodium should be avoided. In severe cases of Dengue infection like DHF and DSS Supportive care in a hospital is recommended for platelet transfusion and Intravenous (IV) fluid and electrolyte replacement

Future perspectives

Finding alternative prevention and treatment option for DENV is the need of the hour. The rapid development in field of computational biology and multiomics has opened up a vast opportunity to screen large databases for potent drug molecules and vaccine candidates against DENV.

Multiomics and computational biology: A recent study by Amemiya et al. [12] has identified various drug candidates for DHF using computational drug repositioning method to perform an integrated multiple omics analysis based on transcriptomic, proteomic, and interactomic data.

The study identified 389 proteins, 3,892 significant genes and 221 human proteins. Proteins like ACTG1, CALR, ERC1, HSPA5, SYNE2 were identified that can be used for drug repositioning to treat DHF. This approach can be used for the exploration of novel drug candidates [12].

Vaccine development

There is no specific dengue therapeutics available. A dengue vaccine is, therefore, representing a major advance in the control of the disease [13].

Development of Dengue vaccine has been found to be a cost-effective intervention to reduce morbidity and mortality across the endemic regions [5]. However, the current dengue vaccine candidates aim to protect against the 4 dengue serotypes, but the recent discovery of a fifth serotype could complicate vaccine development. Infection with one serotype does not provide immunity against the other serotypes [7]. As a result development of a vaccine for dengue is difficult.

A possible strategy in the treatment of dengue is to use chimeric tetravalent vaccines that show high neutralizing antibody against all dengue serotypes [5,7].

Dengvaxia®: Is a live attenuated tetravalent vaccine that is currently under evaluation in phase 3 clinical trials in Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam) and Latin America (Brazil, Colombia, Honduras, Mexic, and Puerto Rico). CYD-TDV uses prM/E of dengue virus 1-4 on YF-17D backbone [7]. Various trial results have shown the protective efficacy of Dengvaxia (R) between different age groups and serotypes to range between 50.2% and 76.6% [14].

FDA has approved the use of the vaccine only in individuals aged 9 to 16 living in parts of the United States where the DENV is endemic. Furthermore, the vaccine can only be given to children and teens that have had one previous laboratory-confirmed case of dengue [15]. European Commission approved the vaccine for use in dengue-endemic parts of Europe, mainly offshore territories, such as the Caribbean islands of Martinique and Guadeloupe [7]. The vaccine has not been approved by the Ministry of Health and Family Welfare, Government of India [7].

TDV (formerly DENVax): is also a live recombinant vaccine, which contains a whole attenuated dengue virus 2 PDK53 and chimeric dengue virus 1, 3, 4 on the dengue virus 2 PDK53 backbones [16,17].

TDEN-LAV (WRAIR/GSK): is a live-attenuated dengue virus vaccine prepared from re-derived PDK vaccine strains. Each strain undergoes three additional passages in fetal rhesus lung cells (FRhL) [16,18].

TDEN-PIV vaccine-WRAIR/GSK/FIOCRUZ: Is a monovalent and tetravalent inactivated dengue virus vaccine. Studies carried out in mice and Non-Human Primate (NHP) showed TDEN-PIV induced strong neutralizing antibodies with T cell responses thus conferring protection [16,19].

DNA Vaccines: The plasmid DNA vaccine uses plasmids, as a vector for expressing antigens of dengue virus *in vivo*. The various DNA vaccine candidates like pcTPANS1, αDEC-NS1, DENV3 prM/E, DENV4 prM/E, DENV1-4 E, DEN EDIII-CH3, DENV2 EDIIII scaffold/DNA are in the preclinical stages of development. The DNA Vaccine D1ME100/ TVDV (Monovalent)-NMRC is undergoing Phase 1 trials [16,20].

The various DNA vaccine candidates like MV-DENV1-4 EDIII, DENV1-4 E85-VEE, DENV2 DIII-S, hybrid DIII-S, MV-DENV1-4 EDIII (Tetravalent), rMVA/Sg-E, DENV2 E85-RRV, and DENV2 NS5-RRV (Tetravalent) are in the preclinical stages of development [16].

Virus-vectored dengue vaccines: The virus-vectored vaccine uses viruses as a vector for expressing antigens of dengue virus *in vivo*. Some of the viruses used as vector are Adenovirus [21], Alphavirus [22], and Vaccinia virus [23]. A vaccine candidate expressing a single tetravalent dengue virus antigen was designed. This vaccine contains the EDIII of dengue virus 1-4 as well as M protein ectodomain (ectoM) of dengue virus 1 [16].

Recombinant vaccines: Various researchers studied the vaccine potential of *E. coli* expressed recombinant dengue virus proteins [24]. These are vaccines developed against capsid, pre membrane and envelope genes of DENV-1, -2 and -3 inserted into a copy of a DNA infectious clone of DENV-2 are being developed and are currently undergoing clinical trials [25].

In a novel approach, a Multi-Walled carbon Nanotube (MWNT) conjugated with Dengue Virus 3 E proteins (MWNT-DENV3E) was developed. The immunogenicity of MWNT-DENV3E was evaluated in BALB/c mice and generated higher titers of neutralizing antibodies [16].

TRAIL protein: Tumor necrosis factor-related Apoptosis-Inducing Ligand (TRAIL) [26]. DENV induces TRAIL expression in immune cells and HUVECs at the mRNA and protein levels.

A substantial rise in accumulation of DENV RNA was noted in monocytes, B cells and HUVECs treated with antiTRAIL antibody and a reduction in DV RNA was observed in monocytes treated with TRAIL [26]. Furthermore, recombinant TRAIL inhibited DV titers in DV-infected DCs by an apoptosis-independent mechanism [26]. These data suggest that TRAIL plays an important role in the type I IFN-mediated antiviral response to DV infection and is a candidate for antiviral interventions against DV [27]. Activation of the TRAIL signaling pathway might, therefore, be used as antiviral therapy in the future.

Alternative treatment options for dengue

Phytochemicals: The exploration of phytochemicals in the search of new bioactive molecules has gained momentum in the last decade [28]. To date, 31 different species have been found to have the potential to treat dengue, some of these have not yet been investigated scientifically [29]. Some of our most common fruits and vegetable extracts have been found to be very effective against Dengue infection.

Carica papaya: Commonly known as *Papaya* (English) and *Pepe*/*Papeeta* (Bengali/ Hindi). The fruit and leaves are effective against dengue fever by increasing the platelet count, white blood cells and neutrophils in blood [30]. Fruits are directly eaten raw.

Leaves are boiled in water with or without guava leaves and the water is taken orally. A team of chemical engineers in the Malaysian University's Food and Pharmaceutical Engineering Group is tackling the challenge of extracting the bioactive compound carpaine (Figure 1) [31].

Carpaine (alkaloid) has the potential to become an effective drug molecule against Dengue infection. Carpaine was proved to have antioxidant [32,33], immunomodulating [34] and membrane stabilizing activity (Figure 2). The aqueous leaf extracts of *Carica papaya* when orally administered for 5 days to a 45-year-old patient bitten by carrier mosquitoes, increased the platelet and neutrophil count, After oral administration of 25 mL aqueous extract of *C. papaya* leaves to the patient twice daily, the PLT count increased from 55 × 103/μL to 168 × 103/μL, WBC from 3.7 × 103/μL to 7.7103/μL and NEUT from 46.0 to 78.3 % (Tables 1a-1c) [30-46].

Figure 1. Anti-Dengue Viral infection activity of bioactive compound carpaine (Citatons: *[33], **[32],+[35], #(Nottingham.2018))

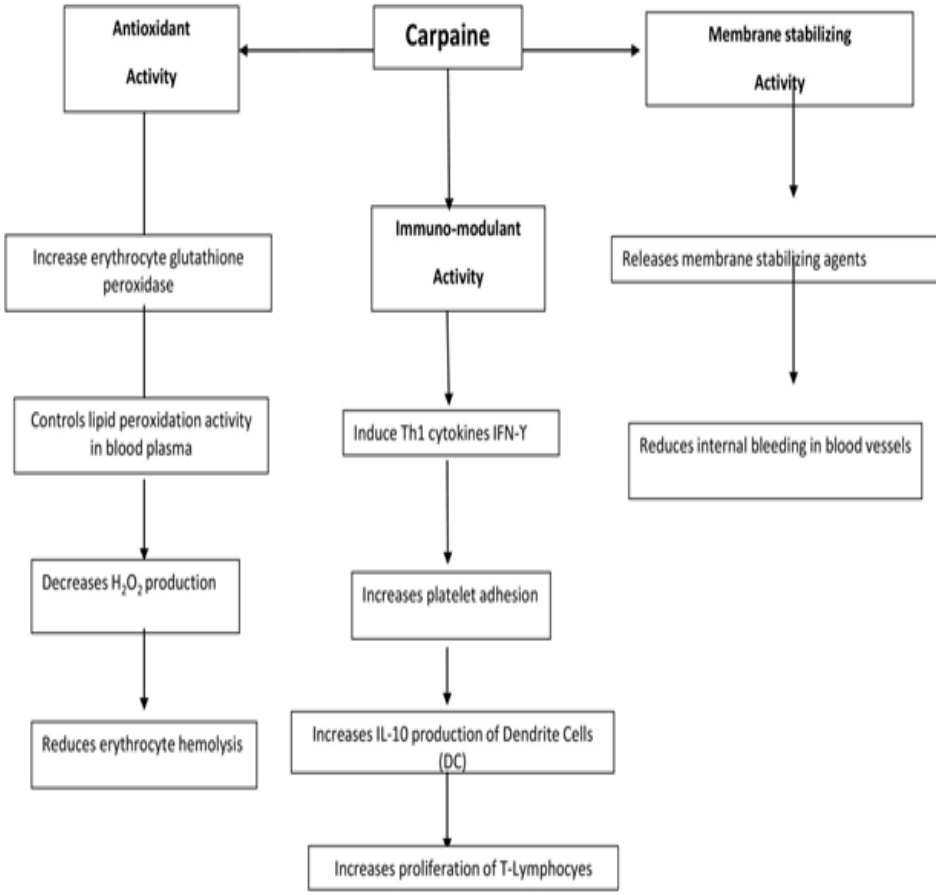

Table 1a. Species of medicinal plants from various families that have been used in traditional medicine in the Indian sub-continent and simultaneously being scientifically validated and documented by modern researchers

Family	Plant	Common Name	Source	Bioactive compound (Figure 2b)	Mechanism of Action	Ref.
Chordariaceae	*Cladosiphon okamuranus*	Mozuku (Japanese), Brown Seaweed (English)	Whole Plant	Fucoidan	Fucoidan interacts directly with envelope glycoprotein (EGP) on DEN2 and inhibits the virus.	[46]
Elaeagnaceae	*Hippophae rhamnoides*	*Sea Berry* (English)	Leaf	Unknown	Effective against DENV-2	[1,47]
Verbena	*Lippia alba*	*bushy mat grass, Pitionia* (English)& *Motmotia*	Leaf	Essential Oil	Effective against DENV-2	[1,48]

		(Bengali)				
	Lippia citriodora	Lemon verbena and Lemon beebrush (English)	Leaf	Essential oil	Effective against DENV-1, 2 and 3	[48]
Cucurbitaceae	*Momordica charantia*	*Bitter Gourd* (English) and *Korola/Karela* (Bengali and Hindi)	Fruit	Phytosterols	Inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects	[37,49]
Lamiaceae	*Ocimum sanctum*	"*Holy Basi"* (English) and "Tulsi" (Bengali and Hindi)	Leaf	orientin, luteolin (Figure 2b) and vicenin (Figure 2c)	Acts as a preventive medicament against DF. Also the leaf extract is effective against DENV-1	[37]

Table 1b. Species of medicinal plants from various families that have been used in traditional medicine in the Indian sub-continent and simultaneously being scientifically validated and documented by modern researchers.

Family	**Plant**	**Common Name**	**Source**	**Bioactive compound (Figure 2a)**	**Mechanism of Action**	**Ref.**
Amaranthaceae	*Andrographis paniculata*	Creat" (English) and "Kalomegh" (Bengali)	Leaf	Andrographolide	The presence of primary flavonoid compounds like terpenes and polyphenols. However, diterpenes such as andrographolide, 14 deoxyandrographolide, and 14-deoxy-11,12-didehydroandrographolide (Figure 2a) present in methanolic extract of A. paniculata have proven antiviral activity against DENV-1	[36-38]
		Neem (English) and		Azadirachtin		

Meliaceae	*Azadirachta indica*	*Neem* (Bengali/ Hindi).	Leaf	(Figure 2a), nimbin, nimbidin, and nimbolides (Figure 2b),	Larvicidal activity of Neem oil has also been reported	[39-42]
Poaceae	*Cymbopogon citratus*	*Lemon Grass* (English) and *Gandhabena* (Bengali)	Leaf Essential Oil	luteolin, apigenin, homoorintine flavonoides.	Anti-dengue agent, particularly against DENV-1 serotype, with <50% inhibition. 1) Interfere with viral adsorption 2) Inhibit viral replication.	[37,43]
Euphorbiaceae	*Euphorbia hirta*	*Asthma plants* (English), *Barokarni* (Bengali)	Leaf	Unknown	Increases the platelet and total leukocyte counts after 24 hours, in the patients of 30-55 age group, no significant increase observed in the 14-25 age groups.	[44,45]

Table 1c. Species of medicinal plants from various families that have been used in traditional medicine in the Indian sub-continent and simultaneously being scientifically validated and documented by modern researchers.

Family	**Plant**	**Common Name**	**Source**	**Bioactive compound (Figure 2b)**	**Mechanism of Action**	**Ref.**
Phyllanthaceae	*Phyllanthus amarus, Phyllanthus nirui, Phyllanthus urinaria, Phyllanthus watsonii*	"Gooseberry" (English) and "Bhui Amloki" (Bengali and Hindi)	Whole plant samples (minus roots)	Gallic acid, geraniin (Figure 2b), syringing (Figure 2c), and corilagen	*Phyllanthus* showed strongest inhibitory activity against DENV2 with more than 90% of virus reduction in simultaneous treatment.	[47,50]
Asteraceae	*Tagetes erecta*	Marigold (English) and Gada/Gendha Phool (Bengali/Hindi)	Essential oil	piperitone (45.72%), d-limonene (9.67%) piperitenone (5.89%)	Larvicidal effect on the 3rd instars of *Aedes aegypti*	[51,52]
Fabaceae	*Tephrosia crassifolia Tephrosia madrensis Tephrosia viridiflora*	Wild Indigo (English) Sarphanka (Hindi)	Leaf Flowers	Glabranine (*T. madrensis*) 7-O-methyl-glabranine	Exert strong inhibitory effects on dengue virus replication in LLC-MK2 cells.	[53]

Potential bioactive molecules

Baicalein and baicalin: In an *in-silico* study by Hassandarvish et al. [54] on baicalein and baicalin (Figure 2a) as inhibitors of DENV replication. The results showed that both compounds can act as ligands, and can bind with chosen viral proteins. Baicalein and baicalin also act as receptors, through hydrogen bonding and other interactions such as pi-pi interactions, pi-sigma interactions and pi-cation interactions. The data showed a significant affinity between the tested compounds and the NS2B-NS3 protease of DENV. Baicalin, a flavone glycoside (Figure 2a) derived from *Scutellaria baicalensis* [55]. It is the main metabolite of baicalein released following administration in different animal models and human [56].

Moghaddam et.al [56] through their *in-vitro* antiviral experiments showed that baicalin inhibited virus replication at IC50=13.5 ± 0.08 μg/ml with SI=21.5 following virus internalization by Vero cells. Against DENV-2 Baicalin exhibited virucidal activity at IC50=8.74 ± 0.08 μg/ml and showed anti-adsorption effect with IC50=18.07 ± 0.2 μg/ml.

Honokiol: It is a lignan biphenol (Figure 2b) derived from *Magnolia grandiflora* (Magnolia Tree) [57]. CY Fang et al. detected the antiviral activity of Homokiol against serotype 2 (DENV-2). Honokiol inhibits DENV-2 replication. Studies have exhibited Honokiol mediated suppression of DENV-2 in Baby Hamster Kidney (BHK) and human hepato-carcinoma Huh7 cells. Honokiol was found to inhibit the replication, viral gene expression, and endocytotic process of DENV-2, making it a promising agent for chemotherapy of DENV infection [57].

Quercetin: It is a plant polyphenolic flavanoid (Figure 2c) derived from *E. perfoiliatum* [58]. Quercetin has been found to possess potent antiviral property against DENV [59]. Molecular docking analysis studies conducted by Mir et al. [60] that flavanone like quercetin can interrupt the fusion process of the virus by inhibiting the hinge region movement and by blocking the conformational rearrangement in envelope protein. Another study found that quercetin down-regulates IL-1β in quercetin treated virus challenged HepG2 cells [61].

Peridinin is an apocarotenoid pigment (Figure 2c) that some organisms use in photosynthesis [62]. Peridinin absorbs blue-green light in the 470-550 nm range. Peridinin was found to have potential anti-DENV activity [63]. Perdinin was found to have an EC50 (μM) (half-maximal effective concentration) of 7.62 ± 0.17 against DENV-1, 4.50 ± 0.46 against DENV-2,5.84 ± 0.19 against DENV-3 and 6.51 ± 0.30 against DENV-4 [64].

Catechin belongs to the group of flavan-3-ols (or simply flavanols) (Figure 2a). It is a type of phenolic compounds very abundant in green tea [65], cocoa [66], red wine [67], beer [68] and fruits (such as apples, blueberries, gooseberries, grape seeds, kiwi and strawberries) [69].

The antioxidant action of catechin is well-established by various *in vitro*, *in vivo* studies [70,71]. Green Tea Catechins (GTCs) are polyphenolic compounds from the leaves of *Camellia sinensis* [65].

Epigallocatechin-3-gallate (EGCG), a GCT has antiviral effects against a number of viruses. Molecular docking studies show that GTCs possess potential NS4B DENV1, DENV2, DENV3 and DENV4 inhibitory binding sites [72]. The drug-likeness score of catechin is 0.92, the score indicates that all the compound is non-toxic and can be used as drugs [72].

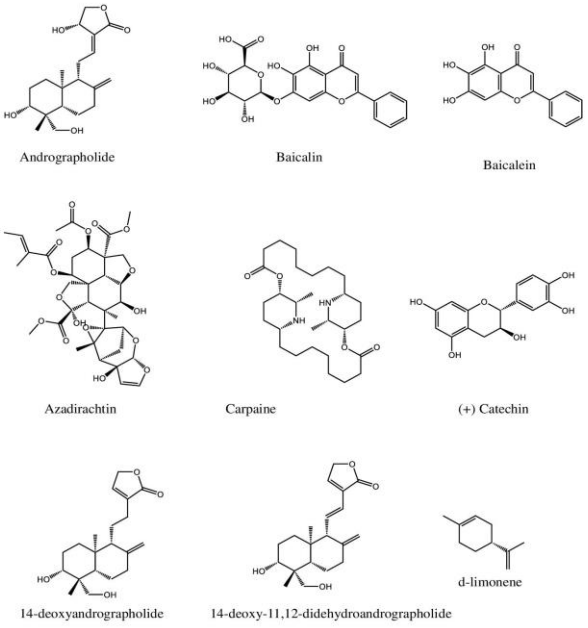

Figure 2a. Bioactive compounds effective against Dengue Infection

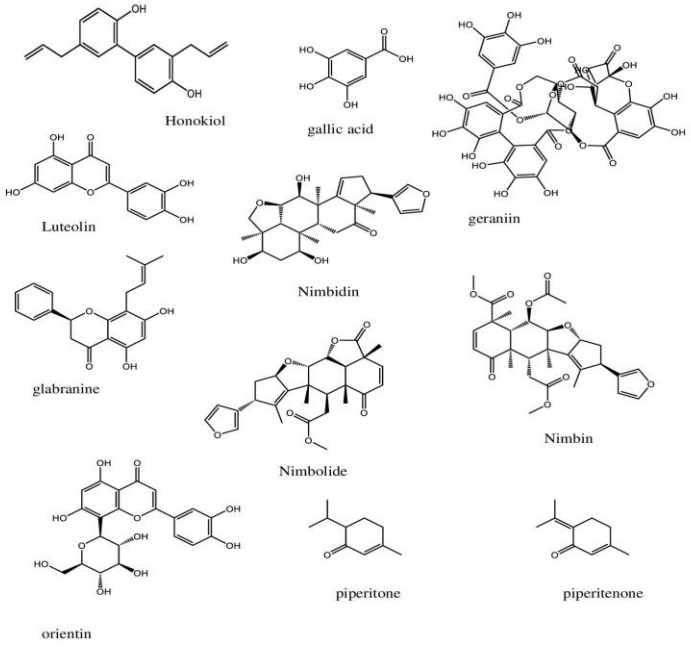

Figure 2b. Bioactive compounds effective against Dengue Infection

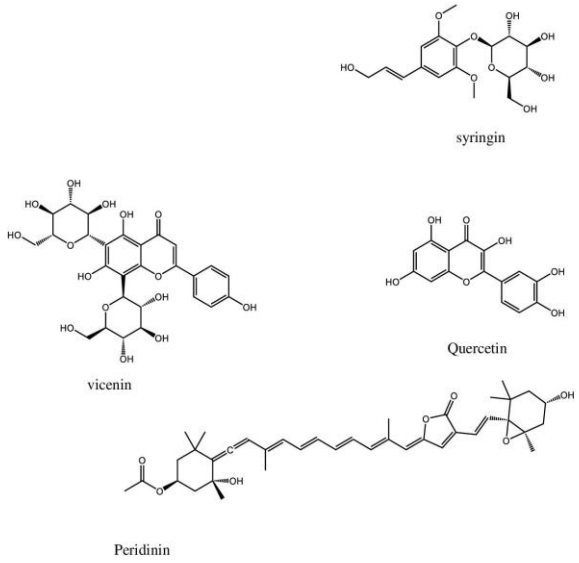

Figure 2c. Bioactive compounds effective against dengue infection

Environmental management of dengue mosquito populations

The spread of DF and DHF in the subcontinent has been a direct impact of changes in environmental factors, urbanization, inadequate sanitation and hygiene, population immunological factors, host-pathogen interactions, and inadequate vector control measures [73].

Source reduction

Environmental management [74] initiatives can include major changes in a community, such as installing water systems with direct connections to residences and replacing wells and other open water-storage containers, which can be mosquito-breeding habitats. The strategy is to eliminate unnecessary accumulation of container in the vicinity, that collect water (such as plastic jars, bottles, cans, tires, and buckets) in which *Aedes aegypti* can lay their eggs. Community-based approaches must go hand in hand with educational initiatives that teach people about mosquito vectors and the risks of having mosquito-breeding habitats near their homes.

Educational initiatives and awareness programs

Educational initiatives and awareness about mosquito vectors and the risks of having mosquito-breeding habitats near homes can encourage people to take an active role in participating in vector reduction [75].

Personal measures to reduce contact with mosquitoes

Aedes aegypti bites people during the day, so covering extremities (e.g., hands and legs) can reduce mosquito bites when spending time outdoors. In addition, mosquito repellents can be used to lower the risk of mosquito bites. People can reduce the risk of mosquitoes entering their homes by using window and door screens or by keeping their doors and windows closed [74,75].

Chemical control of dengue mosquitoes

The Centers for Disease Control recommends mosquito repellents that contain DEET, picaridin, lemon eucalyptus oil, or IR3535 as the active ingredient [75]. The use of insecticides is recommended in emergency situations during dengue epidemics or when there is evidence that an epidemic is emerging. On a regular basis, however, sustainable, coordinated, community-based environmental approaches are favored over chemical methods for controlling mosquitoes [74,75].

Biological vector control measures

Biological management approaches are favored because mosquitoes can develop resistance to insecticides [76]. In addition, insecticides are expensive, and high doses can be toxic to humans and other species. Biological vector control measures can be implemented by improving biodiversity in urban sectors. Restoring safe habitats for fishes, frogs, and bats can drastically improve the predator-prey ratio and lead to an effecting natural vector control measure (Table 2) [76].

Table 2. Methods of biological vector control

Sl. No.	Animal	Species	Mechanism of vector control	Ref.
1	Bacteria	*Bacillus thuringiensis israelensis*	Numerous studies have been conducted to understand the efficacy of using Bti for vector control. A systematic review analyzed the effectiveness of Bti. The results of the systematic review indicated that Bti can be effective in reducing the number of immature *Aedes* in treated containers in the short term, there is very limited evidence that dengue morbidity can be reduced through the use of Bti alone. Further studies are warranted to examine the function of Bti in conjunction with other vector control methods.	[77-79]
2	Fish	*Clarias gariepinus*	*C. gariepinus* fed on the larvae of *An. arabiensis* and culicines	[80]
		Gambusia affinis	Called “Mosquito Fish”. The diet of this fish sometimes consists of large numbers of *mosquito* larvae, relative to body size	[76]
		Poecilia reticulate	Commonly known as “Rainbow fish or Guppy” have been used on a large scale to fight dengue and Zika epidemics	[81]
3	Frog	*Rana tigrina*	Commonly known as “Indian bullfrog” (English) or “Kola bang” (Bengali), Bufo melanostictus commonly known as Asian common toad (English) feed on insect larvae, including those of mosquitoes	[82]
4	Bat	*Myotis lucifugus Eptesicus fuscus*	Individuals of some bat species can capture up to 1,000 mosquitoes in a single hour. One of the most efficient and environmentally friendly ways of reducing the mosquito infestation could be to install a bat house. The DNA analysis of bat droppings from little brown bats (*Myotis lucifugus*) and big brown bats (*Eptesicus fuscus*) revealed that mosquito DNA at 100 percent of little brown bat roosting sites, and in 72 percent of individual samples from those sites.	[83,84]

CONCLUSION

In conclusion, Dengue, Chikungunya, and Zica all belong to Flaviviridae family of viruses and are spread by mosquitoes and all three diseases are very similar in symptoms. As such, preventive measures, like environmental management against dengue can also work against Chikungunya and Zica virus infections. Therefore despite the technical difficulties in creating a vaccine, and practical difficulties in conducting clinical trials on specific therapies, the role of the environment and public health and sanitation aspect of disease prevention should be the primary focus for developing effective therapeutic and preventive measures to prevent Dengue epidemic in the Indian subcontinent.

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