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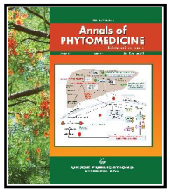

Review Article : Open Access

Ayurvedic approach towards the complication of dengue in India

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Abstract

Dengue fever is an illness instigated by Aedes mosquitoes (genus Flavivirus) belonging to the Flaviviridae family. It is predominant in most tropical and subtropical areas, primarily it is affecting Asia and Africa. Dengue virus spread with four different prevalent serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). WHO classified dengue fever as nonspecific fever, and dengue haemorrhagic fever (DHF). DHF extends from mild bruising on the skin to a clinical symptom of shock. In Ayurveda, Dandaka jwara can be correlated with dengue fever because they showed similar symptoms of dengue fever. Increased temperature, severe breaking pain in the joints, swelling and tenderness in joints, and flu-like symptoms are the common symptoms of dengue fever. Ayurveda has a variety of drugs that can act in viral conditions like *Andrographis paniculata, Acorus calamus, Azadirachta indica*, *etc*. They can help in dengue fever by improving immunity and controlling the hyperthermia. This study aimed to evaluate a deep understanding of dengue fever and admit a new approach for the management of its complications with an Ayurvedic perspective.

1. Introduction

Dengue virus is transmitted by Aedes mosquitoes. It is the most prevalent viral disease caused by the arthropods. Dengue fever is also known as breakbone fever due to the intense muscle spasms and pain in the joints. Although, most cases of dengue fever are very mild, severe cases can be life-threatening. Dengue virus is mainly found in tropical and subtropical regions.

Dengue fever has been on the rise for several years now, and dengue fever is considered an endemic disease in many parts of the world. People who are infected with one of the subspecies of the dengue viruses, may also develop hemorrhagic fever, if they are infected with another subspecies of the dengue virus (Schaefer *et al.,* 2022).

Dengue virus is transmitted by bites from infected Aedes mosquitoes. More than 50% of the world's population is infected with dengue, with annual infections ranging from 100 to 400 million people (Brady and Hay, 2020).

Dengue has been on the rise for the past half century due to several factors, such as climate change, urbanization, availability of vectors, and the vulnerability of populations (Messina *et al*., 2019).

Dengue infection is primarily transmitted through the bite of Aedes mosquitoes, which are composed of four primary vectors: *Aedes aegypti* (the most prominent), *Aedes alopictus* (a lesser-known species), *Aedes scutellaris* (a less well-known species), and *Aedes polynesiensis* (a species found in subtropical and tropical regions).

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Aedes aegypti originated in Africa and has since spread to the tropics and subtropics as a result of international trade. The other three species are found in the Southern Pacific region (Chen and Vasilakis, 2011).

1.1 Serotypes of dengue

The dengue virus is a member of the Flaviviridae family and is composed of four distinct serotypes; namely, DEN-1, DEN-2, DEN-3, and DEN-4 (Halstead, 1988). Serotype 2 is the most dangerous and fatal one.

1.2 Pathogenesis of dengue fever

The four dengue virus serotypes (DENV1-4) share 65-70% sequence homology. Primary infections are the initial, mild febrile illness, often asymptomatic. Secondary infections, involving a different serotype, can cause severe clinical symptoms like dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) (Weaver and Vasilakis, 2009).

Dengue pathogenesis is influenced by viral and host factors like NS1 viral antigen, DENV genome variation, ADE (antibody-dependent enhancement), memory T cells, anti-DENV NS1 antibodies, and autoimmunity, leading to severe human dengue (Mathew and Rothman, 2008).

The viral envelope, precursor membrane protein (pre-M), and non-structural protein 1 (NS1) are major targets for the host immune response. Infected monocytes produce interferon-α (IFN-α) and IFN-β, while DENV-specific $CD4^+$ and $CD8^+$ T lymphocytes attack infected cells and release IFN-γ, tumour necrosis factor-α (TNF-α), and lymphotoxin. Primary infection induces lifetime immunity to a specific serotype, but not to secondary infections (Guzman *et al.,* 2013; Simmons, 2010).

2. Signs and symptoms of dengue fever

In the 2009 WHO classification, dengue infection was classified into three subcategories:

- Dengue without warning signs.
- Dengue with warning signs.
- Severe dengue (includes the involvement of the central nervous system (CNS) as a symptom of severe dengue).

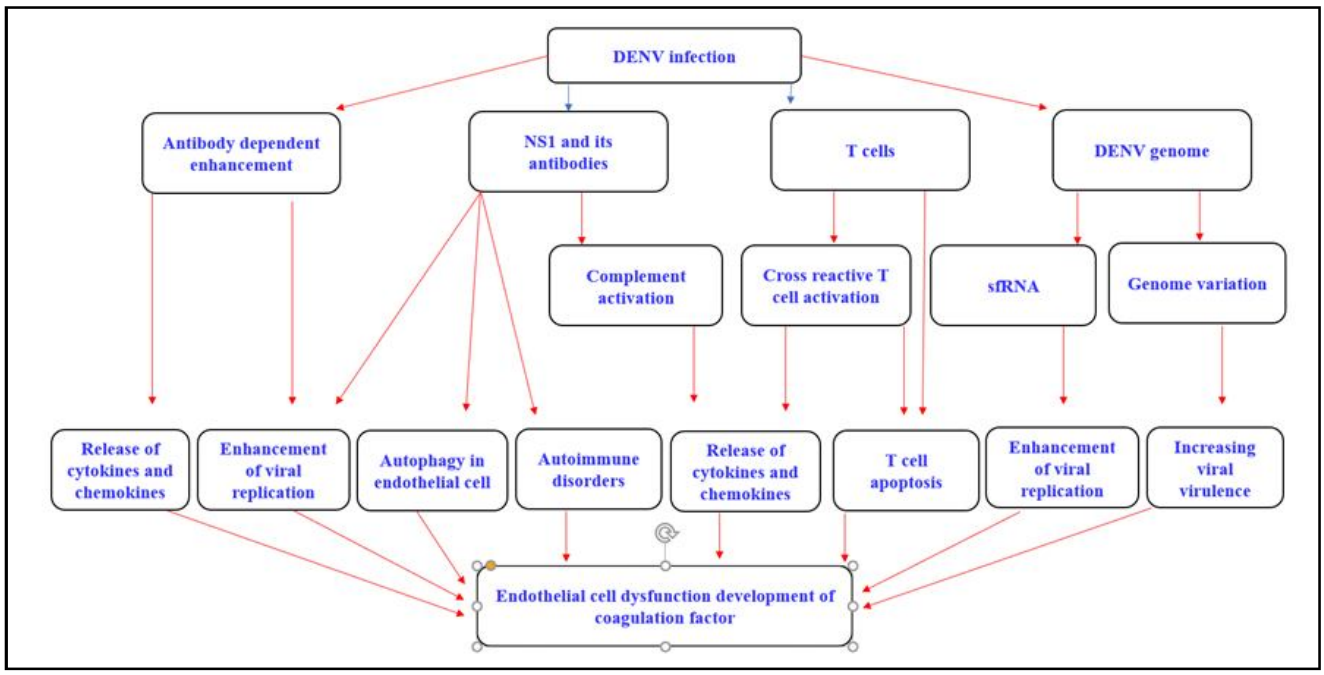

Figure 1: Pathogenesis of dengue.

2.1 Dengue without warning signs

- Nausea
- Vomiting
- Headache
- Eye pain
- Muscle aches
- Joint pain
- Rash
- Positive tourniquet test

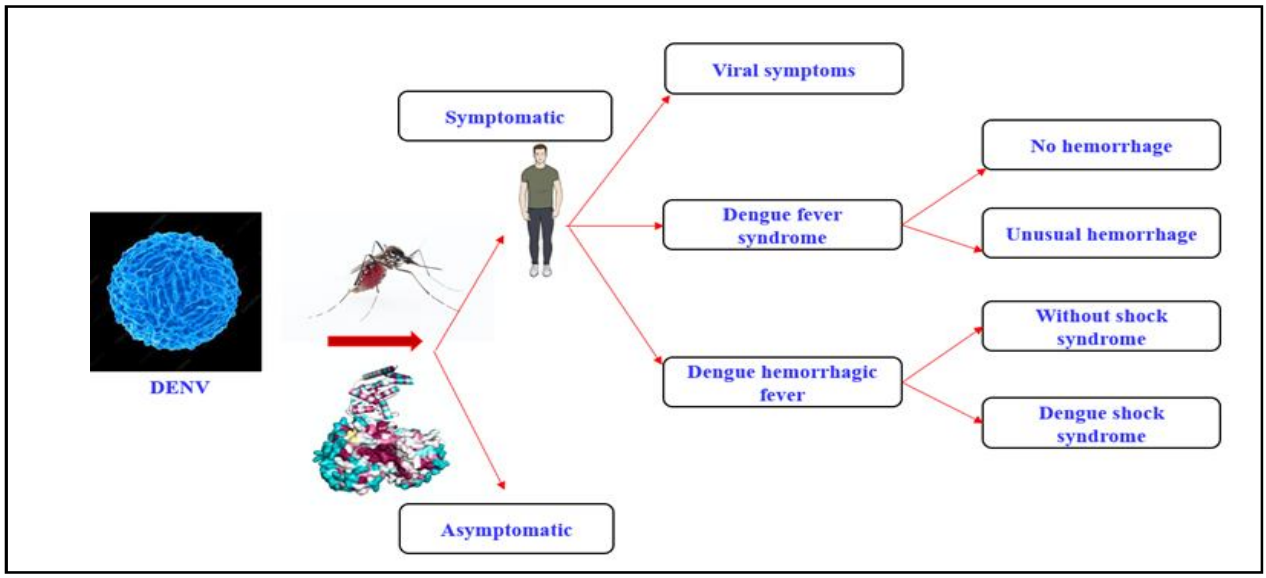

Figure 2: Classification of dengue infection.

2.2 Dengue with warning signs

- Abdominal pain
- Vomiting
- Ascites
- Mucosal bleeding
- Lethargy
- Hepatomegaly (>2cm)
- Increased haematocrit
- Rapid decrease in platelet count (< 1.5 lakhs are symptoms of a severe infection).

2.3 Severe dengue

- Severe plasma leakage leading to shock
- Fluid accumulation with respiratory distress
- Severe bleeding
- Severe organ involvement
- Aspartate aminotransferase or alanine aminotransferase (e"1000 units/l)
- Impaired consciousness
- Organ failure

2.4 Complications of dengue

- Difficulty in breathing
- Internal bleeding and organ damage
- Dengue shock syndrome (death due to low blood pressure).

3. Investigation for dengue

NS1 antigen test is a glycoprotein produced by all flavivirus strains and excreted by infected mammalian cells at the acute stage of infection. The majority of NS1 antigen assays are consistent with moderately high sensitivity and highly specific for dengue infection, NS1 antigen detection sensitivity is higher in primary infection than in secondary infection (Solanke *et al.,* 2015).

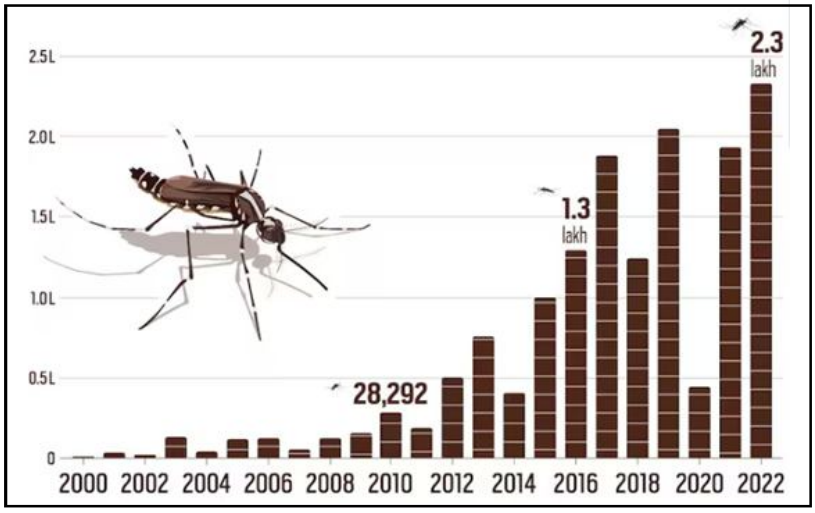

Figure 3: Prevalence of dengue in India.

4. Ayurvedic and herbal remedies for dengue

In the Ayurveda, various remedies are defined for the management of dengue fever includes langhana (fasting), deepana (stimulating one's appetite), pachana (digestive), and mrudu swedana (sweating) (Singh and Rawat, 2017). Many Ayurvedic herbs are used that are used as immune-boosting agents, treat hyperthermia (jwara) and prevent mosquito bites. Medicines that are used in the management of dengue include padmakadi taila, lakshagodanti churna, vasavaleha, sudarshan churna, sootshekhara, sanjivani vati, vasantsukumar, *etc*., while the herbs used to prepare the same are summarized in Table 1.

4.1 *Acorus calamus*

Acorus calamus also known as the sweet flag in English, Vacha in Hindi. It is a perennial herb with a height of approximately 1-4 feet. It is native to wet, marshy areas in Asia, Europe, and the United States. Tatanan A, a chemical compound is isolated from ethanal extract of *Acorus calamus* root. Tatanan A showed the best anti DENV effect, has been demonstrated to be capable of inhibiting the initial replication of viral RNA, as demonstrated by an RNA replication assay. This inhibition of RNA replication is effective in inhibiting the mRNA and protein levels of the dengue virus (Khwairakpam *et al*., 2018).

4.2 *Andrographis paniculata*

Andrographis paniculata known as the King of Bitters in English, Kalmegha in Sanskrit, Nilavembu in Tamil, is an herb with a bitter taste that is cultivated in India and China, *etc*. Aerial part and leaf having the most important phytochemicals like alkaloids, tannins, flavonoids, quinones, terpenoids, *etc.,* are available in the drug Kalmegha. A chemical compound andrographolide shows antidiabetic, hepatoprotective, hypolipidemic, gastroprotective, and numerous further implicit pharmacological properties including viral conditions. It blocks the DENV viral entry and viral replication, which will eventually block the viral protein conflation (Khwairakpam *et al.,* 2018; Ali and Vijayaraghavan, 2020).

Table 1: List of herbal drugs used dengue fever

S.No.	Local of drug	Latin name	Part used
1.	Vacha	*Acorus calamus*	Root
2.	Kalmegh	*Andrographis paniclata*	Whole plant
3.	Neem	*Azadirachta indica*	Leaf
4.	Haridra	*Curcuma longa*	Rhizome
5.	Patha	*Cissampelos pareira*	Aerial part
6.	Erand karkati	*Carica papaya*	Leaf
7.	Chinese ginger	*Boesenbergia rotunda*	Whole plant
8.	Lemon grass	*Cymbopogon citratus*	Whole plant
9.	Dugdhika	*Euphorbia hirta*	Leaf
10.	Bakau	*Rhizophora apiculate*	Whole plant
11.	Baikal skullcap	*Scutellaria baicalensis*	Roots
12.	Native cassia bark tree	*Cinnamomum osmophloeum*	Leaf and buds
13.	Elderberry	*Sambucus nigra*	Fruits

4.3 *Azadirachta indica*

Azadirachta indica commonly known as Neem has been widely used in tropical and subtropical areas in many countries. Former studies have specified that stem bark of *Azadirachta indica* contains quercetin, sitosterol, and polyphenolic flavonoids; they have antimicrobial, antifungal, and anticancerous properties and also parades with strong anti-inflammatory, antipyretic activity (Murthy *et al.,* 1978; Parida *et al.,* 2002). Nimbin, desacetyl salannin, and desacetyl nimbin have a high binding affinity for DENV NS2B-NS3 pro, whereas azadirachtin and salannin had no interface with the target protein. The DENV NS2B-NS3 probinding energy for nimbin, desacetyl nimbin, and desacetyl salannin was found to be – 5.56, – 5.24, and – 3.43 kcal/mol, respectively (Dwivedi *et al.,* 2016). Neem leaf extract (azadirachtin, nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin) inhibits the growth of DENV-2, a viral haemorrhagic illness by preventing (Parida *et al.,* 2002).

4.4 *Curcuma longa*

Curcuma longa is commonly known as turmeric, a family of Zingiberaceae. It is found in Southeast Asian countries. There are around 45 varieties of turmeric available in India (Prasad and Aggarwal, 2011). The phytochemical studies observed that medicinal properties like anticancer, anti-inflammatory, antidiabetic, and antioxidant activities are available in *Curcuma longa* (Shafiri *et al.,* 2020). Antiviral properties of Curcumin derived from *Curcuma longa*, studies conducted *in vitro* techniques using human liver cells and mice cells derived intraperitoneally. Curcumin has DENV-killing activity, by involved in preventing RNA synthesis and RNA replication characteristics according to molecular docking (Lim *et al.,* 2021).

4.5 *Cissampelos pareira*

Cissampelos pareira is commonly known as Patha, a family of Menispermaceae. It is seen in India, Srilanka, *etc. Cissampelos pareira* is traditionally used for the purification of blood and cures inflammation in the body. Primary phytochemicals existing in the *Cissampelos pareira* are alkaloids, phenols, saponins, and glycosides. The root is the useful part in wound healing, also used for antinociceptive and antiarthritic actions. *Cissampelos pareira* has revealed significant antiviral effects against all four serotypes of dengue fever (Sood *et al*., 2015).

4.6 *Carica papaya*

Carica papaya is commonly known as Erand Karkati in Sanskrit, it belongs to the family Caricaceae. *Carica papaya* owns various medicinal possessions making it unique among other 22 species of caricaceae. The *Carica papaya* plant is renowned for its medicinal properties, with papaya leaves being used in traditional medicine to treat malaria. It has also been used as a purification agent, and as a smoking cessation aid for asthma. In addition, papaya has been used to treat dengue fever, hepatitis, obesity, dyspepsia, and bronchitis. The most important ancient application of *Carica papaya* is to increase white blood cells and platelets, which helps to normalize clotting and restore liver health (Nafiu *et al.,* 2019). Papaya has three types of leaves: green, yellow, and brown, green leaves have more nutritional value than others (Saleh and Kamisah, 2021). *Carica papaya* leaves extract encompasses 21 constituents like tocopherol, ascorbic acid, carpaine, deoxy kaempferol, kaempferol, deoxy quercetin, quercetin, dicoumarol, coumaroyl quinin acid, coumarin, folic acid, cystine, homocysteine, cysteine sulfoxide, L-glutamic acid, P-coumaroyl alcohol, dimethoxy phenol, umbelliferon, phenylalanine, caffeoyl alcohol, and methyl nonyl ketone (Canini *et al.,* 2007). Phyto-active compounds present in papaya leaf juice, including phenolic, alkaloid, flavonoid, and amino acid compounds. If, a patient consumes 2 spoons of papaya leaf juice three times a day at intervals of 6 h, it can lead to an increase in the patient's platelet count and reduce the platelet aggregation and may even be effective in controlling dengue infection at both the transmission and host levels (Sarala and Paknikar, 2014). The administration of *Carica papaya* extracts to dengue patients with thrombocytopenia for 7 days resulted in a significant increase in platelet count (Gadhwal *et al.,* 2016). The results of this study

indicated that *Carica papaya* extract modulated DENV infection induced lower pro-inflammatory cytokines levels of TNF-α, interferon-gamma (IFN-β), interleukin 6 (IL-6), interleukin 4 (IL-4) and increased levels of helper T cells (Th2) cytokine IL-4 in CPLE group correlated with an increase in platelet count (Sathyapalan *et al.,* 2020).

4.7 *Boesenbergia rotunda*

Boesenbergia rotunda is commonly known as finger root, family of Zingiberaceae. It is a type of ginger available in India, Southeast Asia, Srilanka, and Southern China (Saah *et al.,* 2021). It is widely used as a therapeutic drug and also used as an ingredient of food due to its aromatic flavour, which stimulates appetite. It is also used to treat fever, inflammation, gout, stomach ache, and dyspepsia (Ongwisespaiboon and Jiraungkoorskul, 2017). Pinostrobin, pinocembrin, alpinetin, cardamonin, panduratin A, and 4-hydroxypanduratin A are some chemical components of *Boesenbergia rotunda*, which yield anti-DENV activities (Liew *et al.,* 2020). Pinocembrin and cardomonin show a synergistic effect on DENV-2 protease. Pinostrobin and cardomonin inhibit NS3 protease and panduratin A and 4-hydroxypanduratin A inhibit competitively (Lim *et al.,* 2021)

4.8 *Cymbopogon citratus*

Cymbopogon citratus is commonly known as Lemon grass in English, Avartaki in Sanskrit and it belongs to the family Poaceae . It is found in tropical countries, especially in Southeast Asia. Significant levels of phytochemicals such as alkaloids, glucosides, phenols, flavonoids, saponins, terpenoids, *etc*., are present in lemon grass. It is extensively used as a mosquito repellent because the separated oil, which is then turned into nanoemulsion, effectively prevents insects (Mapossa *et al.,* 2021). In an *in vitro* investigation, it demonstrated 98.9% suppression of DENV-2 using a methanol extract from its roots. In addition, it inhibits the cytopathic activities of Vero E6 cells that have been exposed to DENV-1. *Cymbopogon citratus* methanolic extract somewhat affects DENV-1. The MTT method's test demonstrates an anti-dengue effect (Kadir *et al.,* 2013).

4.9 *Euphorbia hirta*

Euphorbia hirta is commonly known as Dugdhika in Sanskrit, it belongs to the family Euphorbiaceae. It is found in tropical and subtropical countries, it is mainly seen in India, Malaysia, and Vietnam as garden beds (Kumar *et al.,* 2010). In an *in vitro* investigation utilizing a methanol extract from its roots, it demonstrated 98.9% suppression of DENV-2. Depending on their cytopathic actions, it also inhibits Vero E6 cells afflicted by DENV-1. Additional methanol according to reports, Dugdhika includes physiologically active substances such as triterpenes, phytosterols, polyphenols, and flavonoids. It is a useful ayurvedic plant for treating boils, worm infestation, conjunctivitis, diarrhea, dysentery, and asthma. In the Philippines, internal hemorrhage *Cymbopogon citratus* and water decoction of *Euphorbia hirta* leaves are used as treatments for dengue fever. Together, they cure the illness in 24 h. An antidengue effect can be shown in the MTT method's test (Guzman *et al.,* 2016).

4.10 *Rhizophora apiculata*

Rhizophora apiculata commonly known as Bakau, is a maritime mangrove plant that belongs to the family Rhizophoraceae. Various parts including leaf, root, and stem extracts have powerful antibacterial, antiviral, and antifungal properties (Abeysinghe, 2010). *Rhizophora apiculata* was tested for its ability to prevent dengue, and it was shown that an ethanolic extract with a concentration of 12.5 g/ml can reduce DENV-2 activity by 56.14%. A larger dose of the ethanolic extract, 100 g/ml, can, nevertheless, inactivate the activity of viral particles by 41.5%. An ethanolic fraction of *Rhizophora apiculata* larvicidal efficacy against late IV instar larvae of the dengue vector *Aedes aegypti* showed the greatest degree of protection (Trujillo *et al.,* 2019; Ali *et al.,* 2014).

4.11 *Scutellaria baicalensis*

Scutellaria baicalensis known as Baikal skullcap is a flowering plant that belongs to the family Lamiaceae. It is found in India and tropical countries. It has been presented many actions, one of the main activities is constrains dengue virus replication. Numerous phytochemicals have been isolated from the root; baicalein, baicalin, wogonin, norwogonin, oroxylin A, and β-sitosterol are the major ones (Yang *et al.,* 2002). Its flavonoid, baicalein, has an IC_{50} value of 86.9-95.19 µg/ml, and when treated with root extract, it reduces the IC_{50} to 56.02-77.41 µg/ml (Sucipto *et al.,* 2018).

Table 2: Dengue fever and its complications managed with single drugs in Ayurveda

S. No.	Important phytochemicals	Latin name	References
1.	Tatanan A	*A. calamus*	Khwairakpam *et al*., 2018
2.	Andrographalide	*A. paniclata*	Edwin *et al*., 2016
3.	Azadirachtin	*A. indica*	Dwivedi *et al*., 2016
4.	Curcumin	*C. longa*	Ichsyani *et al*., 2017
5.	Cissampeloflavone	*C. pareira*	Leite *et al*., 2016
6.	Quercetin, Papain		Sarker *et al.,* 2021
	and Chymopapain	*C. papaya*	Sharma *et al.,* 2019
7.	4-Hydroxyanduratin, and Panduratin A	*B. rotunda*	Kaushik *et al*., 2021
8.	Citral, and Geranyl acetate	*C. citratus*	Rosmalena *et al.,* 2019
9.	Alkaloids, Diterpenoids, and Stigmasterone	*E. hirta*	*Perera et al.,* 2018
10.	Ethanol, and Benzophenone	*R. apiculate*	Thangam and Kathiresan, 1993
11.	Biacalein	*S. baicalensis*	Zandi *et al.,* 2013
12.	Cinnamaldehyde	*C. osmophloeum*	Hidari *et al.,* 2008
13.	Cyanidin-3- glucoside, and Cyanidin-3 sambubioside	*S. nigra*	Bartak *et al.,* 2020

4.12 *Cinnamomum osmophloeum*

Cinnamomum osmophloeum is commonly named Indian Bay leaf in English, Talishappattiri in Tamil, it is used as a food flavour and traditional medicinal plant. It belongs to the family Lauraceae. The essential oils extracted from *Cinnamomum osmophloeum* leaves, identified through HPLC, include β-pinene, camphene, benzaldehyde, β-pinene, 3-pheayl pionaldehyde, cis-cinnamaldehyde, trans-cinnamaldehyde, isobornylacetate, eugenol, and cinnamil acetate (Wang *et al*., 2008). The study found that leaf essential oil from eight indigenous cinnamon sources, including cinnamaldehyde, exhibited excellent antiviral effects against *Aedes aegypti*, with cinnamaldehyde showing the most effective activity (Cheng *et al*., 2004).

4.13 *Sambucus nigra*

Sambucus nigra commonly known as Elderberry, is a flowering shrub belonging to the family Adoxaceae. It is mainly found in Europe and North America. This plant is rich in flavonoids, catechin, and phenolic acid compounds, with glycosides like cyandin-3-glycoside and cyanidin-3-sambubioside, and has extensive uses in traditional herbal medicine for antiviral drugs (Mukhtar *et al*., 2008). *Sambucus nigra* flowering parts and leaves exhibit anti-DENV-2 activity at 400 µg/ml, with a mixture of both extracts being more effective (Mahboubi, 2020).

Figure 4: ***A. calamus***

Figure 5: ***C. longa***

Figure 6: ***A. paniclata***

Figure 7: ***C. pareira***

Figure 8: **A.** ***indica***

Figure 9: ***C. papaya***

Figure 10: ***B. rotunda***

Figure 11: ***C. citratus***

Figure 12: ***E. hirta***

Figure 13: *R. apiculate*

Figure 14: *S. baicalensis*

Figure 15: *C. osmophloeum*

Figure 16: *S. nigra*

5. Conclusion

Dengue fever is a highly infectious viral infection transmitted by Aedes mosquitoes. Symptoms of dengue fever can range from mild to severe, with potentially life-threatening consequences such as hemorrhagic fever and shock, and a diagnosis must be made as soon as possible to prevent further complications. Although, typically self-limiting in nature, dengue fever has become a major public health issue in tropical and sub-tropical countries. In Ayurveda, various single drugs and many formulations are explained in the management of various types of fever in all aspects. Antiviral, anti-inflammatory and immunomodulatory effect of *Azadirachta indica*, antiviral effect of *Acorus calamus*, antimicrobial, antioxidant, anti-inflammatory effect of *Curcuma longa*, antiviral, antifungal, antibacterial effect of *Carica papaya*, *etc*., were used to control the dengue fever and its complications, to maintain the positive health.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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