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Review

Ayurvedic and Other Herbal Remedies for Dengue: An Update

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A B S T R A C T

Dengue fever is a flu-like ailment propagated by female mosquitos of the *Aedes aegypti* species. It is also known as *dandaka jwara* in Ayurveda. It is most common in the world's subtropical and tropical climate zones. Vomiting, severe headache, nausea, rashes, joint pain, pain behind the eyes, muscle pain, and swollen glands are all common dengue symptoms. If not handled promptly, these symptoms can lead to more severe issues such as exhaustion, blood in the vomit, continuous vomiting, bleeding gums, restlessness, severe abdominal pain, and rapid bleeding. Because there is no specific medication for dengue fever, the disease is treated by eliminating and managing the symptoms. Fortunately, there are a variety of ayurvedic remedies (like *Carica papaya* L., *Cissampelos pareira* L., *etc.*) that can help to tackle the same by strengthening the immune system and controlling hyperthermia. This review article provides a comprehensive overview of dengue virus infections, clinical symptoms, diagnosis, mitigation, and treatments, focusing on ayurvedic and herbal remedies.

1. Introduction

Dengue fever is among the world's most common neglected tropical diseases, and viruses (DENVs) have spread across the globe (Guzman et al., 2016; Gubler, 2002). The number of dengue patients has been increased by 30 times over the last 50 years. The population living in the tropical and subtropical zone have suffered the most. The dengue-endemic regions worldwide are the residence of around 2.5 million people (Southwood et al., 1972; Siler et al., 1926). Approximately, 50–100 million people get affected by dengue every year; among them 500,000 get hospitalized and 20,000 people end up dying (Hasan et al., 2016). However, many dengue infections remain undiagnosed and unreported, so it is assumed that the authentic yearly cases could be around 390 million (Bhatt et al., 2013; Chaturvedi et al., 2008).

1.1. Background

The term "dengue" is a Spanish word that means "affectation ", it came to use in 1828, after the first dengue outbreak in Cuba. *Aedes aegypti*, the yellow fever mosquito, also known as the Asian tiger mosquito, and the *Aedes albopictus* are the leading vector for dengue virus transmission with four different prevalent serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) (Halstead, 2008; Guzman et al., 2016a). The World Health Organization (WHO) classified dengue fever as non-specific fever, dengue fever (DF), and dengue hemorrhagic fever (DHF) in 1997 (Srikiatkhachorn et al., 2011). DHF was further classified as grades I–IV (Hadinegoro, 2012; Srikiatkhachorn et al., 2011).

Grade I: Minor bruising or a positive tourniquet test
Grade II: Random hemorrhage into the skin and elsewhere
Grade III: A clinical symptom of shock
Grade IV: Acute shock - a weak pulse rate and blood pressure that cannot be measured.

Here, grades III and IV comprise dengue shock syndrome (DSS). Dengue virus maintains a well-organized circle between the host and the mosquito, not only does the mosquito infect a person but it can also get infectious from an infected person (Fig. 1). The following aetiologies have been hypothesized for dengue virus infection: viral reproduction, especially in macrophages, direct virus skin infection, and immunological & chemical-mediated mechanisms triggered by the host–viral contact (Martín et al., 2010; X et al., 2017). The cycle includes 4 phases, 1) mosquito infection (by human), 2) extrinsic incubation (in the mosquito), 3) human infection (by mosquito), and 4) intrinsic incubation (in the human body)(Mithra et al., 2013).

If an *Aedes aegypti* feeds on an infected person in a viraemic phase of the disease, the mosquito turns into an infectious vector. Dengue virus first contaminates the gut cells of the mosquito in the extrinsic phase then distributes in the salivary gland and other tissues. As soon as it is infected, only one mosquito can infect several human hosts when it feeds or tries to feed on them (Murugesan et al., 2020). Approximately, 4–7 days after getting a mosquito bite, an infected host may start showing symptoms. An infected host (asymptomatic) can transfer the dengue virus to the mosquitos. Dengue virus transmits through the female *Aedes aegypti* mosquito is a member of the *Flavivirus* genus, belongs to the *Flaviviridae* family (Sabir et al., 2021). This is a virus

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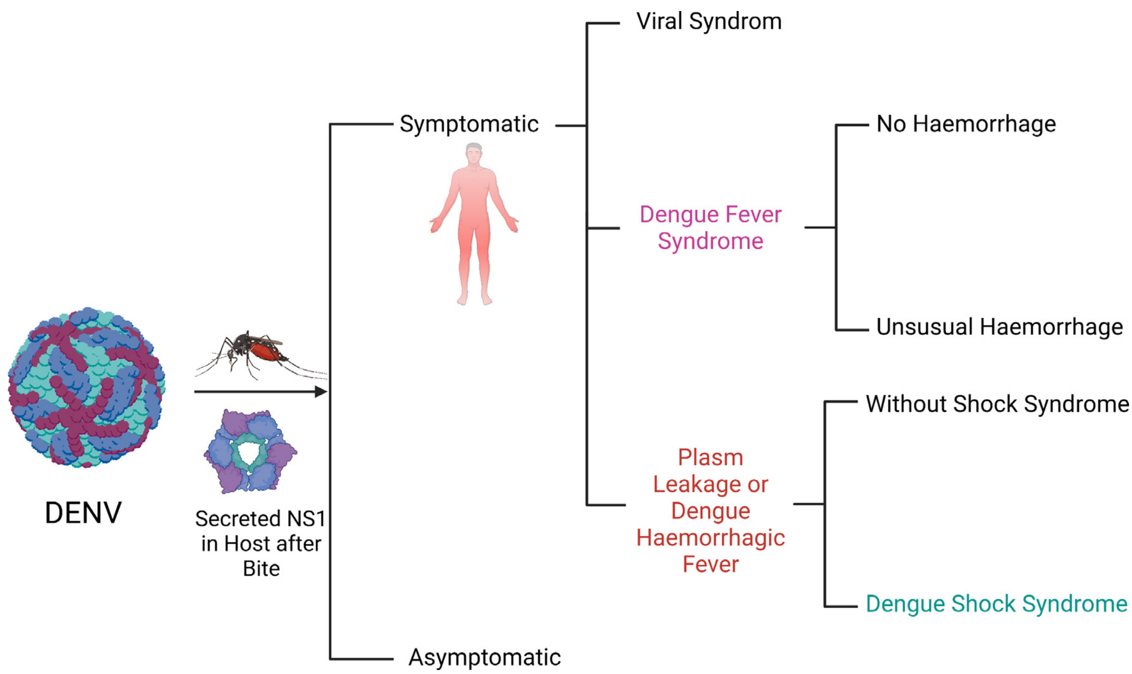

Fig. 1. Manifestations of dengue virus infection.

Table 1
Dengue virus proteins and their functions.

Protein Type	Protein Name	Function	References
Structural Protein	Viral Capsid Protein - C	Packaging of viral RNA	(Yong et al., 2021; Zhang et al., 2021)
	Viral Envelop Protein - E	Assist to envelope glycoprotein, binding to receptor and fusion	(Lo et al., 2016; Afreen et al., 2016)
	Viral pre membrane Protein-PrM	Prevent premature fusion	(Rey, 2003)
Non-Structural Protein	NS1	1) Signal transduction 2) Involved in the replication of viral RNA in its early stages. 3) It stimulates the innate immune system and is implicated in vascular leakage.	(Shriver-Lake et al., 2018)
	NS2A	4) Involved in RNA replication	(Xie et al., 2013; Xie et al., 2015)
	NS2B	5) Act as a co-factor for NS3 serine protease	(Lin et al., 2017)
	NS3	6) During RNA synthesis, it assists nucleoside triphosphatase and helicase in their roles.	(Katzenmeier, 2004)
	NS4A	7) Needed for the formation of replication vesicles	(Miller et al., 2007)
	NS4B	8) Inhibits interferon signal transduction 9) Suppresses IFNβ and IFNγ signaling	(Nemésio et al., 2012; Xie et al., 2015)
	NS5	10) Involved in the production of RNA 11) Involved in the IFN system blockage	(Sahili et al., 2019; Medin et al., 2005)

family with just a single positive-stranded RNA genome (5′ capped, not 3′poly (A) tail). This genomic make-up devises three structural proteins: capsid (C), pre-membrane (prM), and envelope (E) protein (Table 1). It also has seven non-structural (NS) proteins named NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Wang et al., 2020). A couple of impressions of capsid (C) protein encapsulates the RNA genome, which forms a viral nucleocapsid covered by a lipid bilayer, containing 180 specimens of anchored membrane and envelope proteins (E) (Sotcheff et al., 2020). PrM after modification converts into a membrane protein (M) and this PrM controls the virus synthesis, entrance of the virus, and envelope protein (E) folding. Membrane glycoprotein (M), is a build-up with three anatomical terrains, which are helpful in virion morphogenesis, membrane fusion, and receptor binding (Beeck et al., 2003). NS1 is responsible for viral infection confirmation. NS2A is a hydrophobic integral membrane protein that helps in RNA replication, where NS2B is a coenzyme of NS3 protease. NS3 controls the nucleoside triphosphate and helicase operating in viral RNA synthesis. NS4A helps in forming replication vesicles and NS4B suppresses the signaling of interferon beta and gamma (White et al., 2008). The largest and most conserved protein NS5 (105 kDa) is essential for RNA synthesis and efficiently blocks the interferon (IFN) system (Scott, 2009; Wang et al., 2020; Hasan et al., 2016; Guzman et al., 2016). The 2009 categorization replaced the previous 1997 WHO system, which addressed and highlighted the disease's two clinical phenomena: plasma leakage and defective hemostasis (Srikiatkhachorn et al., 2014). Under this classification, patients were considered as having either 1) dengue fever (a nonspecific febrile ailment that is the most prevalent DENV manifestation) or 2) dengue hemorrhagic fever and dengue shock syndrome (a combination of plasma leakage and coagulopathy, occasionally accompanied by hemorrhage, that can cause a fast drop in blood pressure, resulting in circulatory shock and organ dysfunction) (Rodrigo et al., 2021; Srikiatkhachorn et al., 2014; Guzman et al., 2016b).

1.2. Epidemiology

The origin of DENV is still unclear but epidemiological facts indicate that the severe outbreak of dengue was due to the slave trade and sailing ships throughout the world (Liu et al., 2021; Rijal et al., 2021). Post World War 2, Asia was affected by dengue because of the continued movement of soldiers, disturbing ecosphere, and swift urbanization (Shepard et al., 2016; Bravo et al., 2014). In India, the first affected region was Calcutta in 1963–1964. Apart from that, the other parts of India faced DHF in 1988 (Gupta et al., 2006). DENVs are sustained in densely populated tropical cities via a human–mosquito endemic–epidemic cycle (Lanciotti et al., 1994). Australia first reported dengue cases in 1873 and *Ae. Aegypti* single-handedly contaminated the whole continent as it is the only dengue-carrying vector present there (Guo et al., 2017; Mohd-Zaki et al., 2014). Africa has reported dengue infection for the first time at the beginning of the 19th century, but now DENV is isolated from Africa, and the occurrence of dengue fever is no longer reported in noticeable numbers. In 1920, Europe was free from dengue infection but a recent dengue outbreak between October 2012 and March 2013, leads to disease re-occurrence (Murray et al., 2013). *Ae. aegypti* and *Ae. albopictus* exist predominantly around the beaches of North America. Dengue is a common viral infection in North and South America as they were charged by DENV epidemics several times. According to a recent study, the yearly global economic burden of dengue fever is estimated to be around USD 8.9 billion (Shepard et al., 2016; Guzman et al., 2016; Hasan et al., 2016).

1.3. Diagnosis

The very first set of symptoms that a patient reports for dengue, are high fever with aches, nausea, and muscle pains. These are also associated with other febrile illness (OFI) that makes dengue confirmation complex as a part of early diagnosis (Heilman et al., 2014). To solve the problem, the World Health Organization (WHO) has issued a guideline for dengue infection, where symptoms are classified according to their severity (Hadinegoro, 2012). For example, if a person traveled to any dengue-endemic areas, had fever with any two signs (nausea, vomiting, flush, pain, aches, and leukopenia), and diagnosed positive for a Tourniquet test confirm DENV infection. Secondly, some warning indications of dengue infection include stomach pain, tenderness, prolonged vomiting, clinical fluid accumulation, mucosal hemorrhage, fatigue, restlessness, and liver enlargement > 2 cm. Laboratory test findings such as an increase in hematocrit with a rapid reduction in platelet count are considered as the early sign of the dengue infection (Tang and Ooi, 2012). Severe dengue is the last and most critical stage of dengue with symptoms like plasma linkage, severe hemorrhage, and severe organ impairment (central nervous system, heart, liver, eye) (Tang and Ooi, 2012). In laboratory diagnosis, different blood tests are done for dengue patients such as virus isolation, NS1 antigen capture test, nucleic acid amplification tests (NAATs), RT-PCR test, serological tests (Haemagglutination-inhibition test, IgA, IgM or IgG detection, MAC-ELISA, *etc.*), and some combined approaches are also taken to confirm dengue infection (Peeling et al., 2010). With early diagnosis and proper care, dengue patients can fully recover within 1–2 weeks (Wong et al., 2020). To reduce false-positive results, incorporate NS1 antigen acquisition with IgM and IgG serology. The integration of methods for detecting NS1 and/or IgM and/or IgG has shown a significant improvement in diagnosing dengue (Shu et al., 2004). There are as of now some commercial kits available that use this strategy. The sensitivity of identification is close to 100 percent when using this hybrid method (Wang and Sekaran, 2010).

2. Pathophysiology of the Dengue Viral Infection

The infection cycle of DENV commences with the virus adhering to the cell surface receptors, *i.e.* the cognate receptor (engaged in chronic infection) and Fc receptor (participates in antibody-dependent enhancement) of the host cell via receptor-mediated endocytosis (Fig. 2). Scientists have claimed that endocytosis happens with two mechanisms; one is clathrin-mediated and another is non-classical clathrin-independent endocytosis (Martina et al., 2009). Once the virus internalizes into endosomes, the proton pump lowers the pH causing conformational alterations in E glycoprotein, resulting in viral spike protein formation. The ends of the spike proteins are hydrophobic, which helps in the penetration of endosomes and the release of capsids in the cytoplasm. The capsid proteins break into fragments releasing the viral RNA, which gets associated inside the rough endoplasmic reticulum (Guzman et al., 2016).

The viral RNA act as messenger RNA, and is translated into a single polypeptide with the assistance of host cellular machinery, translation initiation proteins, and ribosomes of the host (Rampersad et al., 2018; Chavda et al., 2021e, 2021f, 2021c) During this stage, non-structural proteins contort the endoplasmic reticulum membrane and help in the formation of membrane-bound multi proteins assembly called a replication complex (Martina et al., 2009). This is the place where the genome is duplicated and new viral RNA replicas incorporate into nascent viral particles. Apart from cleaving the polypeptide into polyproteins and remodeling the endoplasmic reticulum membrane, non-structural proteins also secure inefficient RNA synthesis, processing, and capping of viral proteins (Bhatt et al., 2021). Because of the crucial role of specific non-structural proteins (NS2B, NS3, and NS5 along with NS4B) in the DENV replication cycle, they are the niche targets to develop new DENV inhibitors (Norazharuddin et al., 2018). As the newly formed virus particle penetrates the endoplasmic reticulum, its pre-membrane protein wraps the tips of the envelope proteins and prevents its premature fusion into the cell. The virus buds and passes via the golgi apparatus, where a cellular protease (furin), cleaves prM in an acidic milieu, allowing virus particles to fully mature and get released via exocytosis (Dandeniya-Arachchi et al., 2019; Bhatt et al., 2021; Martina et al., 2009). The DENV is transferred to the female mosquito when it sucks blood from the human body during the viremic phase of illness. Inside the mosquito, the virus travels to the midgut cells and replicates to numerous virions, and finally, salivary glands are infected. When the mosquito's salivary gland becomes infected, it remains infective for a lifetime (Sim et al., 2012). Antibody-dependent enhancement (ADE) is believed to be linked with the severe stage of the disease (Fig. 3) that is linked to a secondary heterotypic infection, which may lead to enhanced severity (Morens, 1994). This process helps DENV to get a higher viral load. Ultimately, secondary heterotypic DENVs illness via ADE is regarded as a significant risk factor that contributes to disease intensity. This mechanism should be taken into account when developing an efficient dengue vaccine. Dengue life cycle comprises three phases namely the febrile phase, critical phase, and recovery phase (Fig. 2). The febrile phase may last up to 7 days with significant symptoms like high fever and chills which persist for 3–7 days, retro-orbital pain, conjunctival or pharyngeal infection, *etc.* (Kalayanarooj, 2011; Halsey et al., 2014). A patient needs rest, hydration, fever reducers, and medical observation. The critical phase occurs between the 3rd and 7th day. This phase begins with fever drops. Rest and hydration must continue. During this phase, warning signs of dengue may appear. This warning sign includes vomiting, edema, vascular leak syndrome, eye impairment, and drowsiness. One warning sign is enough to immediately seek health care services. If no warning sign appears then the recovery phase resumes between the 7th and 10th day. In this phase, patients improve overall and may be able to return to day-to-day life activities little by little. Identifying the dengue phase and warning signs in a timely way may save a life.

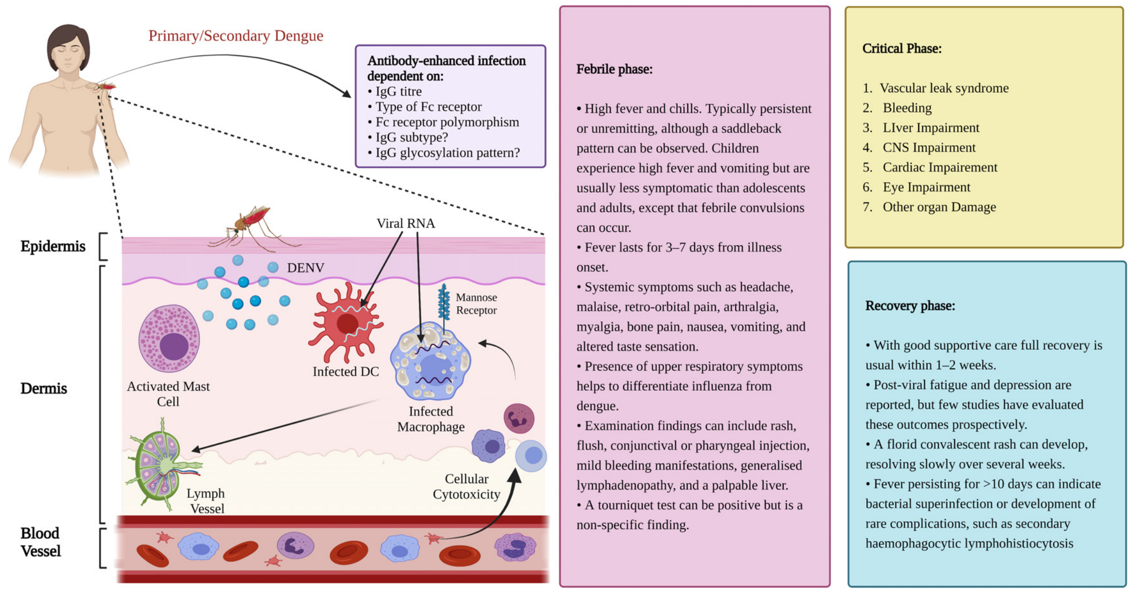

Fig. 2. Stages of dengue life cycle and subsequent symptoms of disease with different phases emphasize the entire pathophysiology of dengue.

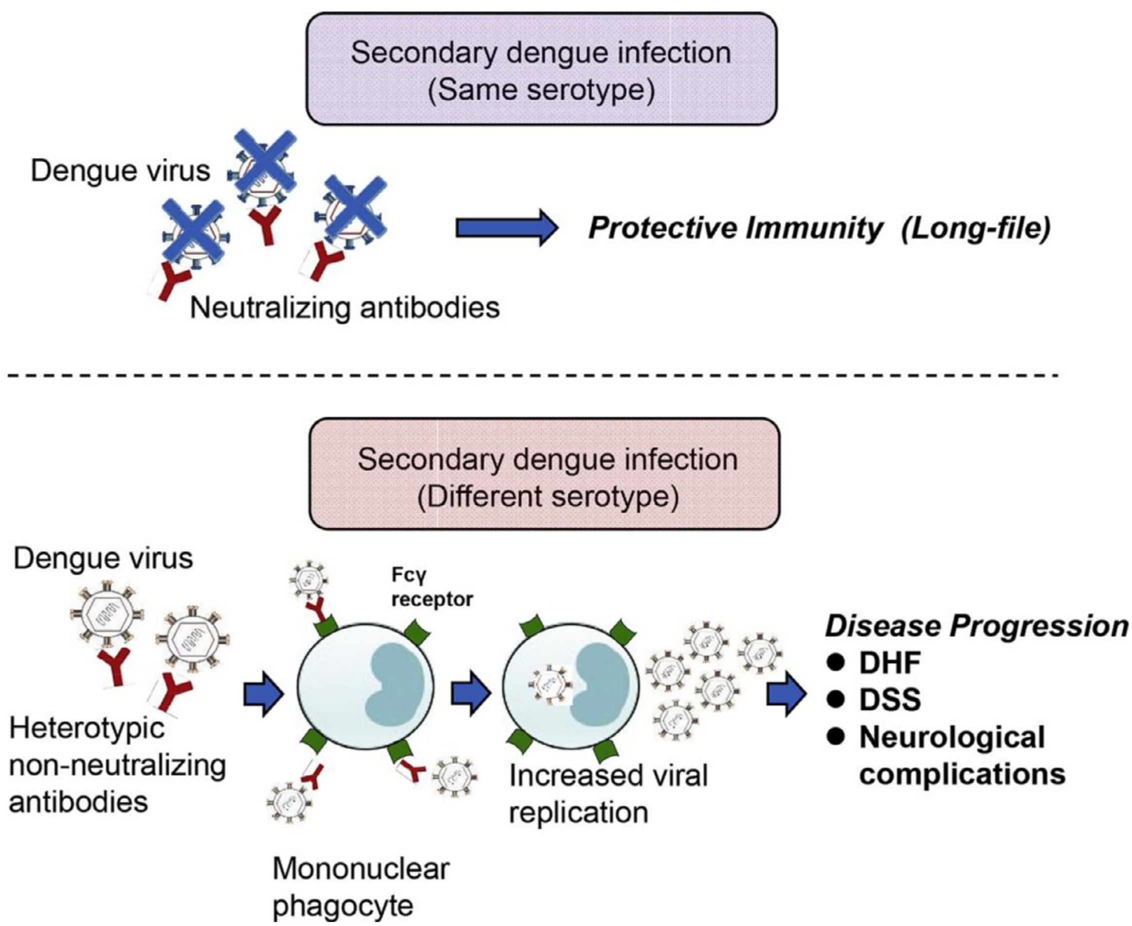

Fig. 3. The mechanism of antibody-dependent enhancement of dengue virus infection. Primary DENVs infection induces long-life protective antibody which can neutralize the same serotype of DNEVs (upper). In secondary heterotypic DENVs infection, the previous anti-DENVs antibodies cross-react with the heterotypic DENVs and form immune-complex. The virus-antibody immune complex interacts with Fcγ receptors, which are mainly expressed on macrophages or phagocytes. The heterotypic DENVs propagate inside the Fcγ-expressing immune cells and further enhance the viral infectivity (lower). (Adopted from (Wang et al., 2020) under CC BY-NC–ND 4.0).

Cytokine dysregulation progressed with TNFα and IFNγ leading to plasma leakage that is linked with amplified activation of complements in DHF (Wijeratne et al., 2018). Different functionalities of immune mediators are detected in DHF like anti-inflammatory (IL1RA), chemotactic (IP-10), growth factor (HGF), soluble receptor (sTNFRp75), adhesion (VCAM1), and enzymatic (MMP2) activities that can be used as prognostic markers (Wijeratne et al., 2018; Wang et al., 2020). Cytokine dysregulation also impacts the lipid profile of the host. The increase of triglycerides (TG), very-low-density lipoproteins (VLDL) and HDL, and the decrease of total cholesterol (TC) and LDL have been observed in DHF (Durán et al., 2015).

3. Allopathic Remedies for Dengue

Dengue can be asymptomatic or symptomatic, with approximately 20% of cases being symptomatic. In a broad sense, DF is a self-febrile disease that manifests 3–10 days after being bitten by an infected mosquito. The beginning phase of dengue disease may manifest as a mild "flu-like" ailment with symptoms related to malaria, influenza, chikungunya, and Zika (Teixeira and Barreto, 2009; Wang et al., 2020). There is no dedicated antiviral drug for the DENV, symptomatic treatment is the only way to treat the disease (Wang et al., 2020). Apart from that, there is no licensed vaccine for treatment and prophylactics against DENVs infection. The only medication for reducing body temperature and pain is Acetaminophen (paracetamol) and proper hydration of the body (Shen et al., 2021). Nonsteroidal anti-inflammatory medicines (NSAIDs) should not be used to treat pain associated with dengue infection since they can increase bleeding. In most cases, patients recover within 2 weeks. In some cases, a patient can face some severe problems that need urgent consultation of doctors for treatment. As hydration is the primary remedy for dengue fever so the doctor needs to follow some guidelines regarding rehydration or water replacement therapy prepared and approved by the WHO (Fig. 4) (Nasir et al., 2017; Lum et al., 2014). If the patient has convenient access to a nearby health care facility, he or she can be recommended for the treatment with simply full blood counts every day. The case of, excessive vomiting, diarrhea, severe prostration, or early bleeding is the sign that one should be admitted to the hospital and monitored closely. Platelet transfusions are routinely administered to patients with severe hemorrhagic symptoms or extremely low platelet counts, while the precise platelet count at which platelets should be administered has yet to be determined. In individuals with shock syndrome, platelets are only alive for a brief time after being transfused (Kansay et al., 2018). Some of the recommendations to manage dengue include, bed rest, antipyretics or sponging to control the fever, analgesics or mild sedatives to help with the pain, and fluid or electrolyte therapy to help with hydration (Wang et al., 2020).

4. Herbal and Ayurvedic Remedies for Dengue

In the Ayurveda, various upchar or remedies are defined for the management of dengue fever includes *langhana* (Fasting), *deepana* (stimulating one's appetite), *panchana* (Digestive), and *mrudu swedana* (Sweating) (Singh et al., 2017). Many ayurvedic herbs are used that are used as immune-boosting agents, treat hyperthermia (jwara), and prevent mosquito bites. Fever (*Jwara*) can affect all the *dhatus* (plasma, blood, muscle, fat, bone, bone marrow, and reproductive fluid) and *doshas* ("fault" or "defect"; *Vata, Pitta* and *Kapha*). 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 2. Dengue is *sannipataja* disease (disturbance in all the three dosha) caused due to *pitta* (fire and water*)* dominance (Fever and aggravation of *Rakta Dhatu*) however; *Vatta* (space and air) and *Kapha* (earth and water) are also seen. *Panchkarmas* therapy is not recommended for treatment (Shepherd and Hinfey, 2015). To strengthen your immune system, boil tulsi in water and drink it throughout the day. To enhance the body's defense mechanism, chew 10–15 basil leaves twice a day. According to 35 research that reported the traditional usage of 25 plants from 20 families, *Carica papaya* L. and *Euphorbia hirta* (L.) Millsp. were the most extensively utilized across different geographical locations for treating DENV infection (Saleh and Kamisah, 2021).

4.1. Methodology

This review article tried to thoroughly evaluate recent statistics on the effectiveness of herbal/ayurvedic medicines for the management of dengue fever. The methodology used for this review work is summarized in Fig. 5. The study was according to the PRISMA guidelines to conduct a systemic literature review. We have started searching through significant databases such as Web of Science, PubMed, Scopus, Elsevier, Springer, and Google Scholar with keywords like "Herbs for dengue"' "Phytochemicals for dengue", "Ayurvedic remedies for dengue fever," and then we started with a specific search (1990–2021). Two independent reviewers evaluated the level of data quality from the selected pieces of literature.

From the identified components, first, we have omitted the components for which no strong literature support is available. From the remaining components, we have considered the compounds based on the *in vivo* data evaluation and searched for specific research around dengue. Later on, from the highly researched components against dengue, the clinical trial database is evaluated. Here we have also considered the current use of such components in outpatient management as well as for hospitalized patients. We have also not incorporated the research studies with negative results reported.

4.2. Medicinal plants used in the dengue treatment

4.2.1. Vacha

A hermaphrodite *Acorus calamus* L. (Family: Acoracea), commonly known as a sweet flag (English), Vacha and Safed bach (Hindi), is a perennial herb having a height of about 1–4 feet found in wet, boggy climates in the moist and damp soil of Asia, Europe, and America (Tiwari et al., 2012). Leaves are narrow and flattened like irises Glycosides, phenolic compounds, alkaloids, flavonoids, saponin, and triterpenoids are some significant phytochemical groups present in *Acorus calamus* L. It has a long history of medicinal use for endurance, hepatitis, digestive disorders, bronchitis, sinusitis, and appetite-related issues (Hemalika et al., 2020; Rosmalena et al., 2019). In America and India, it is used as a powerful rejuvenator herb for the brain. Various chemical constituents like β-Asarone, ascorbic acid (Vitamin C), and calamusin D are found in this plant. Its roots have been used for the treatment of cholera and neurodegeneration disease for a long time. Tatanan A found in the ethanolic extract of big thick rhizome shows a promising anti-dengue effect (Yao et al., 2018; Lim et al., 2021). Researchers have conducted a study on the root of the *Acorus calamus* L. and found that Tatanan A can inhibit the early stage of viral RNA replication (confirmed with RNA replication assay), which can ultimately inhibit the mRNA and levels of proteins in the dengue virus (Yao et al., 2018). However, Tatanan A was used as an antihyperglycemic drug due to its nature to activate glucokinase. Similarly, the methanolic extracts of *A. calamus* showed prospective anti-dengue activities both *in vitro* (96.5% at a dose of 20 μg/mL) and *in silico* (Rosmalena et al., 2019). In summary, Tatanan A was discovered to be a unique natural DENV drug and a possible therapeutic candidate for DENV infection.

4.2.2. Alligator weed

Alternanthera Philoxeroides (Mart.) Griseb. (Family: Amaranthaceae) are commonly known as Alligator weed and Pigweed (English), Danta (Bengali), Mosalehonagone (Kannada), and Panikhutara (Assamese). It is an aquatic, perennial, broad leaves herbaceous plant mainly found in Europe and tropical land. It grows in a variety of habitats. However, it is usually found in water (Pulipati and Babu, 2020; Kanna, 2019).

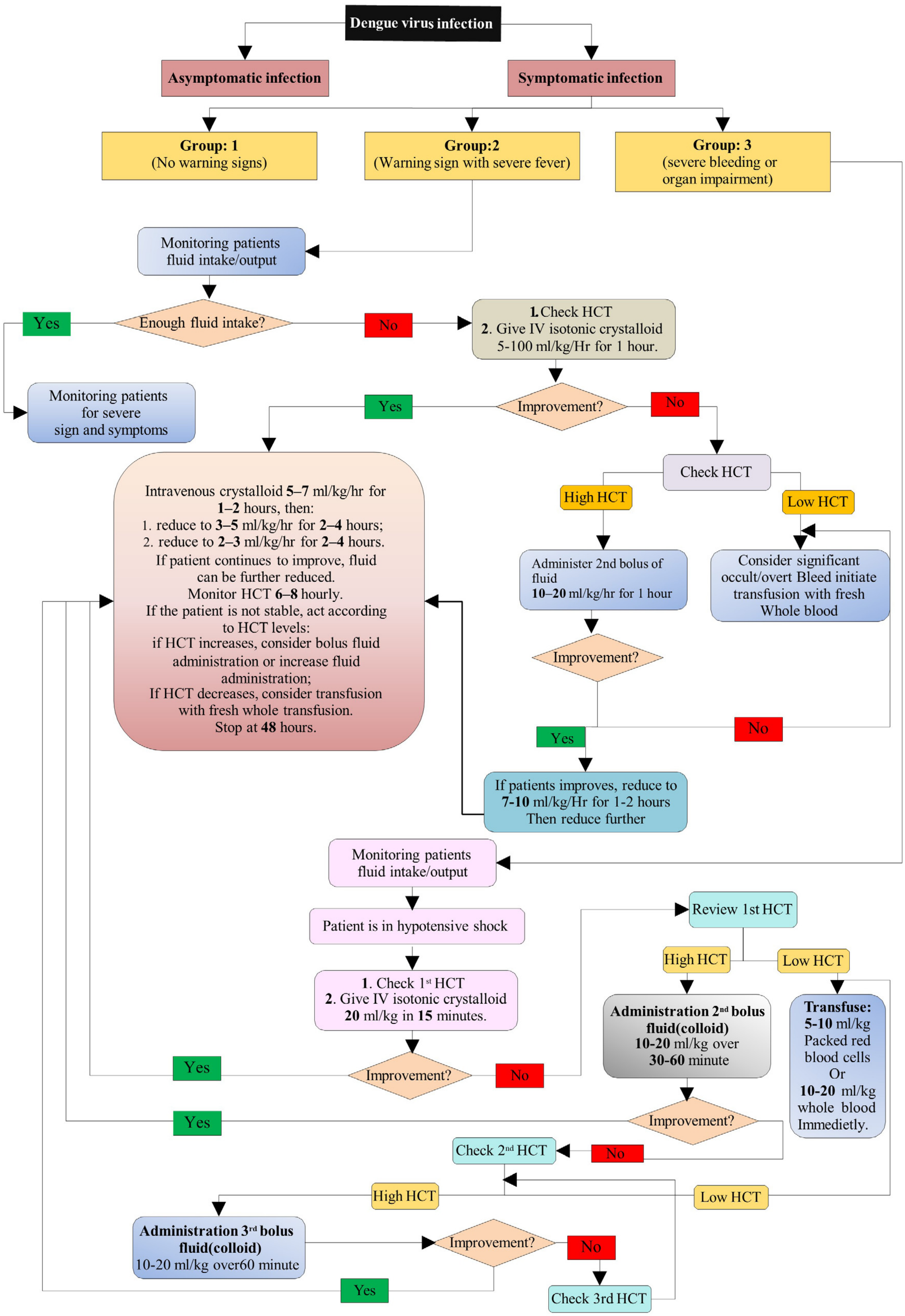

Fig. 4. Dengue infection management guide by WHO.

Table 2
Herbal or Ayurvedic remedies for dengue management.

Name of the Plant	Family	Parts Used	Chemical Constituents	References
Acorus calamus L. (Sweet flag)	Acoraceae	Root	Tatanan A	(Khwairakpam et al., 2018; Mukherjee et al., 2007; Rosmalena et al., 2019)
Alternanthera Philoxeroides (Mart.) Griseb. *(Alligator weed)*	Amaranthaceae	Whole plant	Phaeophytin a, pheophytin a', oleanolic acid, beta-sitosterol, 3-beta-hydroxystigmast-5-en-7-one, alpha-spinasterol, 24-methylene cycloartanol, cycloeucalenol, and phytol	(Rattanathongkom et al., 2009; Jiang et al., 2005)
Andrographis paniculata Nees (Kalmegha)	Acanthaceae	Aerial part, and Leaf	Andrographalide	(Edwin et al., 2016; Ali-Seyed and Vijayaraghavan, 2020; Ramalingam et al., 2018)
Azadirachta indica A.Juss. (Neem)	Meliaceae	Leaf	Azadirachtin	(Dwivedi et al., 2020; Rao et al., 2020)
Boesenbergia rotunda (L.) Mansf. (Finger root and Chinese ginger)	Zingiberaceae	Whole plant	4-Hydroxyanduratin, and Panduratin A	(Kaushik et al., 2021a; Eng-Chong et al., 2012)
Carica papaya L. (Papaya, Papita)	Caricacae	Leaf	Quercetin, Papain, and Chymopapain	(Sharma et al., 2019; Sarker et al., 2021; Alara et al., 2020)
Cissampelos pareira L. (Abuta, Ice vine, and False pareira)	Menispermaceace	Aerial part	Cissampeloflavone	(Leite et al., 2016)
Citrus limon (L.) Burm.f. (Lemon)	Rutaceae	Pulp	Limonene, and Beta-pinene	(Tang et al., 2012.)
Cladogynos orientalis Zipp. ex Span. (Chettaphangkhee)	Euphorbiaceae	Whole plant	Dichloromethane	(Akram et al., 2021)
Cryptonemia crenulate (J. Agardh) J Agardh (Red seawood)	Halymeniaceae	Whole plants	Galacton	(Rodrigues et al., 2017)
Curcuma longa L. (Turmeric, Haldi)	Zingiberaceae	Rhizome	Curcumin	(Ichsyani et al., 2017; Balasubramanian et al., 2019)
Cymbopogon citratus Stapf (Lemon grass)	Poaceae	Whole plant	Citral, and Geranyl acetate	(Chiamenti et al., 2019; K et al., 2015; Rosmalena et al., 2019)
Distictella elongata (Vahl) L. G. Lohmann (White Trumoet Vine, White Bignonia)	Biognoniaceae	Leaf, Stems, and Fruits	Pectolinarin	(LR et al., 2011)
Euphorbia hirta (L.) Millsp. (Spurge, tawa–Tawa, gatas–gatas)	Euphorbiaceae	Leaf	Alkaloids, Diterpenoids, and Stigmasterone	(Perera et al., 2018; TAYONE et al., 2013)
Flagellaria indica L. (Sabah)	Flagellariaceae	Whole plant	Flavonoids, Anthraquinones, and Tannins	(Saleh et al., 2021)
Hippophae rhamnoides L. (Sea buckthom)	Elaeagnaceae	Leaf	Carotenoids, and Tocopherols	(Agrawal et al., 2016; MJ et al., 2008)
Lippia alba (Mill.) N.E. Br. ex Britton & P. Wilson (Pronto Alivio)	Verbanaceae	Whole plant	Beta-elemene,(E) Caryophyllene	(Ocazionez et al., 2010; Quispe-Bravo et al., 2020)
Momordica charantia L. (Bitter Melon, Karela)	Cucurbitaceae	Fruit	Cucurbitane, Momordicin, and Momordenol	(Chandrasekaran, 2019; Pongthanapisith et al., 2013)
Psidium guajava L. L. (Guava, Jambu Batu (Malaysia)	Myrtaceae	Leaf	Ethylacetate	(Dewi et al., 2020)
Rhizophora apiculate Blume (Bakau)	Rhizophoraceae	Whole plant	Ethanol, and Benzophenone	(Thangam and Kathiresan, 1993)
Sambucus nigra L. (Elder berry, Black elder, European elder)	Adoxaceae	Fruits	Cyanidin-3- glucoside, and Cyanidin-3 sambubioside	(Bartak et al., 2020; Castillo-Maldonado et al., 2017)
Scutellaria baicalensis Georgi (Baikal skullcap, Chinese Skull cap)	Lamiaceae	Roots	Biacalein	(Zandi et al., 2013)
Uncaria tomentosa (Willd. ex Schult.) *DC.* (Cats claw)	Rubiaceae	Stem barks	Oxindole alkaloids	(Yepes-Perez et al., 2021)
Cladosiphon okamuranus	Chordariaceae	Whole plant	Fucoidans, laminarans	
Cinnamomum osmophloeum (Indian Bay Leaf)	Lauraceae	Leaf and buds	Cinnamaldehyde	(Hidari et al., 2008)
Eucalyptus citriodara (Lemon-scented gum)	Myrtaceae	Whole plant	Beta- citronellal	(Meisyara et al., 2021)

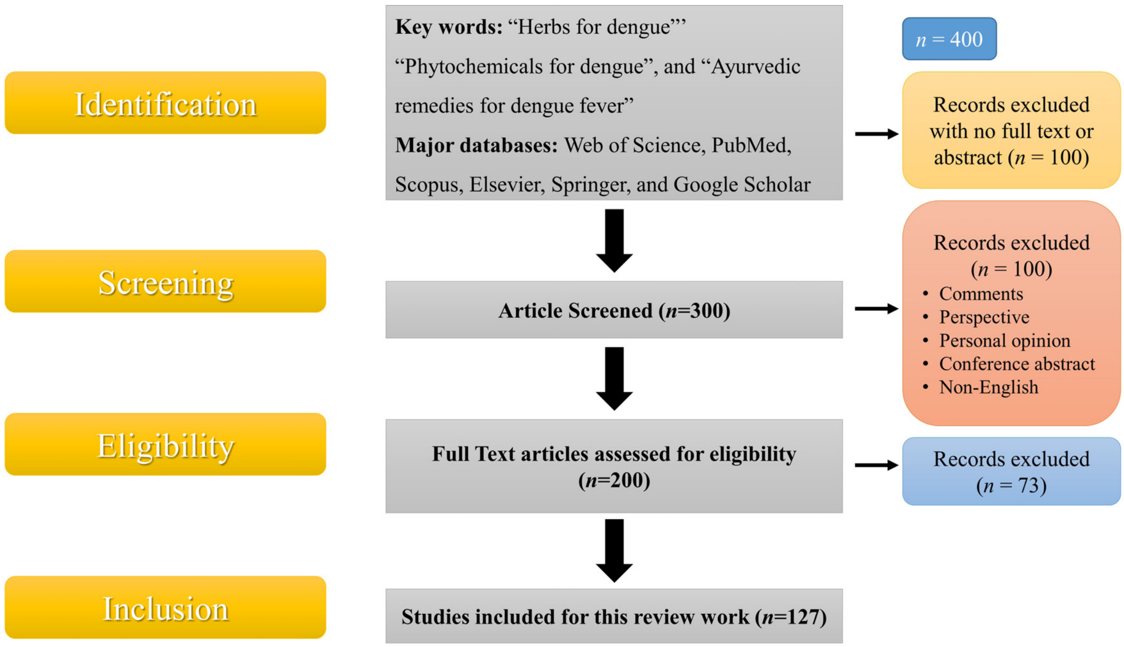

Fig. 5. The flowchart of the criteria and selection guidelines for included literature in this systemic review.

It has smooth, hollow stems that trail down the ground or across the water. It can sometimes create vast mats along the banks of deep rivers or shorelines. Leaves of Alligator weed are elliptic with smooth margins that grow on the stem. The whitish flowers grow in clusters on a 2 inches long stalk. It has a wide range of applications in a variety of countries as a panacea for viral infection, infectious disease, inflammation, and many more. Scientists checked its antiviral properties in various extract types (ethyl acetate, coumane of *A.philoxeroides*, petroleum ether, ethyl acetate, and aqueous extract). They found that its aqueous extract can inhibit human immunodeficiency virus (HIV), and its petroleum ether extract is highly effective against the DENV virus *in vitro* with ED_{50} of 47.43 (Sarangi and Manoj, 2014; Saleh and Kamisah, 2021).

4.2.3. Kalmegh

Andrographis paniculata Nees (Family: Acanthaceae), commonly known as the king of bitters in English, kalmegha in Sanskrit, Andrografis in Spanish, and Nilavembu in Tamil. It is a bitter taste herb cultivated in India, China, Thailand, and tropical areas of America. Kalmegh is the storehouse of phytochemicals like alkaloids, tannins, flavonoids, quinones, terpenoids, *etc*. Andrographolide found in the plant shows antidiabetic, hepatoprotective activity, hypolipidemic activity, hypnotic activity, gastroprotective activity, and many more potential pharmacological effects (Nugroho et al., 2012). The demand for *Andrographis paniculata* Nees is significantly increased in the past few years due to its overwhelming therapeutic potential. It is advantageous for its immunological potential in cancer and viral diseases. It blocks the DENV viral entry and viral replication, which will ultimately block the viral protein synthesis (Adiguna et al., 2021). Andrographolide also blocks the protease activity (Ramalingam et al., 2018). Scientists have tested the anti-dengue effect of both aqueous extract and ethanolic extract of *Andrographis paniculata* Nees. They found that *A.paniculata* Nees can inhibit 75% of dengue viral load and ethanolic extract of *A.paniculata* Nees is highly effective against dengue viruses (Neelawala et al., 2019; Walia et al., 2021). A similar *in vitro* study concluded the optimum nontoxic concentration of isolated andrographolide on the C6/36 cell line to be 15.62 g/mL (the MTT assay) (Kaushik et al., 2021b). In C6/36 cell lines, andrographolide demonstrated 97.23 percent anti-dengue activity against the DENV-2. The results of molecular docking revealed that the interaction between andrographolide and dengue protein NS5 had the highest binding energy of -7.35 kcal/mol. Andrographolide's anti-DENV activity against serotype 2 was tested in two cell lines (HepG2 and HeLa), while DENV-4 action was tested in HepG2. Andrographolide showed substantial anti-DENV activity in both cell lines, reducing both cellular infection and virus output, with 50 percent effective concentrations (EC_{50}) for DENV 2 of 21.304 M and 22.739 M for HepG2 and HeLa, respectively (Panraksa et al., 2017). An antiviral assay based on cytopathic effects (CPE) denoted by the degree of inhibition when DENV1-infected Vero E6 cells were treated with MNTD of six medicinal plants revealed that *A. paniculata* Nees has the most antiviral inhibitory effects (Tang et al., 2012). These findings were confirmed by an *in vitro* inhibition assay using MTT, which revealed that 113.0 percent and 98.0 percent of cell viability were recorded, compared to 44.6 percent in DENV-1 infected cells. The methanolic extract from *A. paniculata* Nees inhibited DENV in the Vero E6 cell line with an IC_{50} value of 20 µg/mL. Its leaves have been used for anti-dengue properties, sore throat, flu, respiratory infection, anticancer, anti-inflammatory, and anti-diabetic activity (Hossain et al., 2021).

4.2.4. Neem

Azadirachta indica A.Juss. (Family: Meliaceae), commonly known as 'neem' in India, is a fast-growing tree mainly cultivated in the Indian subcontinents. Neem is used as anti-inflammatory, antifungal, antitumor, and antibacterial agents (Alzohairy, 2016). Neem contains quercetin, sitosterol, and polyphenolic flavanoids, they have antibacterial and antifungal properties. The results of molecular docking revealed that nimbin, desacetyl nimbin, and desacetyl salannin have a high binding affinity for DENV NS2B-NS3 pro, whereas azadirachtin and salannin had no interaction with the target protein. The DENV NS2B-NS3 pro binding 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). According to a study published in the Journal of Ethnopharmacology in 2002, neem leaf extract inhibits the growth of DENV-2, a viral hemorrhagic illness associated with the Ebola virus (Parida et al., 2002). In this study, the maximum nontoxic concentration of water extract from neem trees was assessed in cloned cells of larvae of *Aedes albopictus* cells. *In vivo* tests revealed that it prevented virus growth, while *in-vivo* tests on mice revealed that the neem extract inhibited virus growth, as evidenced by the absence of symptoms

(Parida et al., 2002). At various doses, kaempferol 3-O-rutinoside and epicatechin were tested for treated cells (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay) and *in vitro* antiviral activity (focus forming unit assay) against DENV-2 strain (Dwivedi et al., 2021). The antiviral assay revealed that kaempferol 3-O-rutinoside and epicatechin inhibited DENV-2 infectivity in a dose-dependent manner, with maximum viral inhibition of 77.7 percent and 66.2 percent recorded for 100 M kaempferol 3-O-rutinoside and 1000 M epicatechin, respectively, without significant cell toxicity. These findings suggested that bioflavonoids derived from *Azadirachta indica* A.Juss. could be used to develop an effective anti-dengue drug (Dwivedi et al., 2021). Rasool and colleagues have prepared silver nanoparticles of aqueous extracts of (i) *Azadirachta indica* A.Juss. leaves and reported a concentration-dependent larvicidal potential of AgNPs with an LC_{50} value of 1.25 mg/L (Rasool et al., 2020). The results obtained by Rao and colleagues, in terms of newer potential ligands (Gedunin and Pongamol) against dengue are significant as this provides a basis for experimentally verifying and extending the same to develop a cure (Rao et al., 2020).

4.2.5. Kulanjan

Boesenbergia rotunda (L.) Mansf. (Family Zingiberaceae), usually referred to as "Chinese keys" or finger root in English, Kulanjan in Hindi, Temu kunci in Malay, and Krachai-Dang in Thailand, is one type of ginger that is found in India, Southeast Asia, Sri Lanka, and Southern China (Saah et al., 2021; Eng-Chong et al., 2012). It is a medicinal herb commonly used as an ingredient of food in curry and soup due to its aromatic flavor, which stimulates appetite and in various ethnomedicinal preparation. It is also used to treat fever, inflammation, flatulence, gout, stomachache, and dyspepsia (Ongwisespaiboon et al., 2017). Pinostrobin, pinocembrin, alpinetin, cardamonin, panduratin A, and 4-hydroxypanduratin A are some components of bosenbergia, which produce anti-DENV activities in high to low spectrum (Liew et al., 2020). Pandurate A and 4-hydroxypanduratin A inhibit DENV-2 NS2B/3 protease cleavage, predominantly by 65% at 80 ppm of concentration (Abduraman et al., 2018). Pinocembrin and cardomonin impart a lower suppressive effect in every concentration but, when mixed, exhibit a synergistic effect on DENV-2 protease. Pinostrobin and cardomonin inhibit NS3 protease in a non-competitive manner, whereas panduratin A and 4-hydroxypanduratin A inhibit competitively (Lim et al., 2021).

4.2.6. Papita

Carica papaya L. is called Papita in Hindi, belongs to the Family *Canicaceae*. It is a little tree with few branches. It is native to Mexico and Northern South America, and throughout the Caribbean islands (Nafiu et al., 2019). India produces nearly six million tonnes of *C. papaya* every year. The whole plant of *C. papaya* has medicinal properties; traditionally, papita (Papaya) leaves are used to treat malaria. It is also used as an abortifacient, purgative, or smoked to relieve asthma. It is also helpful in the treatment of dengue, jaundice, obesity, whooping cough, dyspepsia, bronchitis, syphilis, *etc.* The most crucial ancient use of *papita* is for the increment of white blood cells and platelets; normalizing clotting and restoring the good health of the liver (Dharmarathna et al., 2013). Papaya leaf juice has been used in Siddha medicine, a traditional form of medicine in India, to increase platelet counts. In ancient Ayurvedic texts in India, papaya leaf was reported to increase blood volume (Nandini et al., 2021). Papita leaves have three types: green, yellow, and brown, where green leaves have more nutritional value than others (Saleh and Kamisah, 2021). Through LCMS analysis, it is indicated that *Carica papaya* L. leaves extract contains 21 constituents like tocopherol (Vitamin E), ascorbic acid (Vitamin C), carpaine, deoxy kaempferol, kaempferol (Robigenin), deoxy quercetin, quercetin, dicoumarol, coumaroyl quinic acid, coumarin, folic acid, cystine, homocysteine, cysteine sulfoxide, L-glutamic acid, P-coumaroyl alcohol, dimethoxy phenol, umbelliferone, phenylalanine, caffeoyl alcohol, and methyl nonyl ketone (Canini et al., 2007). There are also some pharmacologically active phyto-compounds like phenolics, alkaloids, flavonoids, and amino acids. If a patient is given two spoons of papaya leaf juice thrice a day with an interval of 6 h, the platelet count of the patient increases, it can even control dengue at both transmission and host levels (Sarala et al., 2014). Although some studies indicated that, in some cases, the patient's platelet increment was not significant after several updates of papaya leaf juice and some studies claim that dengue infection inhibitory action of papaya is related to patients' symptoms only. According to Chinnappan et al., *Carica papaya* L. leaf extract has dengue-specific neutralizing actions on plasma infected by dengue, suggesting platelet protective action of *Carica papaya* L. (Lim et al., 2021). In an *in vitro* study, upon direct addition of C. papaya leaf extract, both dengue platelet-rich plasma (PRP) and control PRP showed a significant reduction in platelet aggregation. Within the dengue group, PRP from severe and nonsevere cases showed a significant decrease in aggregation without any difference between them (Chinnappan et al., 2016). An open-labeled randomized controlled trial was carried out on 228 patients with DF and dengue hemorrhagic fever (DHF) demonstrated that *Carica papaya* L. leaves juice significantly accelerates the rate of increase in platelet count (Subenthiran et al., 2013). Comparison of mean platelet count between intervention and control group showed that mean platelet count in the intervention group was significantly higher than the control group after 40 and 48 h of admission. A randomized open-labeled clinical trial (CTRI-REF/2017/02/013,314) in 51 laboratory-confirmed adult dengue patients with platelet counts ≤ 30,000/μL confirmed the possible immunomodulatory and antiviral activity of Carica papaya L. leaf extract (Sathyapalan et al., 2020). Senaka Rajapakse and colleagues have conducted a systemic review on Carica papaya L extract in dengue with 86 studies out of which they have identified nine studies for qualitative analysis (Rajapakse et al., 2019). According to them, “there is a need for further well designed clinical trials examining the effect of CP on platelet counts, plasma leakage, other severe manifestations of dengue, and mortality, with clearly defined outcome measures.”

4.2.7. Laghu patha

Cissampelos pareira L. is a flowering plant that belongs to the family Menispermaceae (Singh et al., 2017). In Hindi, it is called laghu patha, also known as velvetleaf. It is found in India, Sri Lanka, and the rainforest of amazon. *C. pareira* L. is primarily used in Ayurveda; it is traditionally used as a blood purifier and curing inflammation in India. Alkaloids, phenols, saponins, glycosides are primary phytochemicals present in the laghu patha. The root part of this plant is helpful in wound healing, also known for antinociceptive and antiarthritic actions. *C. pareira* L. has shown substantial antiviral effects against all four serotypes of the dengue virus (Sood et al., 2015). *C. pareira* L. extracted with alcohol can stop the replication of dengue in living cells. The aerial section of *C. pareira* L. has shown antiviral activity against DENV- 3 (Lim et al., 2021; Saleh and Kamisah, 2021). A patent is also approved for the anti-dengue activity of the *Cissampelos pareira* L. extracts (WO2010084477A1). Pareirarine, cissamine, and magnoflorine from *Cissampelos pareira* L. exhibited 40–80% inhibition DENV-2 infection model (Haider et al., 2021).

4.2.8. Chettaphangki

Cladogynos orientalis Zipp. ex Span. is a shrubs belonging to the family euphorbiaceae with a common name chettaphangki (Sithisarn et al., 2015). It is found primarily in Southeast Asian countries such as Thailand, Vietnam, Cambodia, Malaysia, Indonesia, Philippines, and Southern China. Its root, stem, and leaves have phenolic and flavonoid contents, which impart antioxidant and antibacterial activities (Kanchanapoom, 2007). A thin layer of chromatographic data shows that leaves extract of *Cladogynos orientalis* Zipp. ex Span. contains rutin while the root and stem have scopoletin and chettaphanin (Sithisarn et al., 2015). Rutin is responsible for its antioxidant actions and chettaphanin has antibacterial effects. Chettaphagki is also known for its anti-dengue activities to defeat DENV-2 (Pong et al., 2020). The dichloromethane extract derived from *C. Orientalis* was evaluated for anti-dengue activity and the outcome shows that 12.5 μg/mL ethanol extract imparts 34.85% inhibitory effect on dengue virus (Kadir et al., 2013).

4.2.9. Cryptonemia crenulata

Cryptonemia crenulata (J. Agardh) J Agardh are the marine plants belonging to the family halymeniaceae. It is a rarely found marine species of microalgae and grows very slowly. *Cryptonemia crenulata* (J. Agardh) J Agardh is a red seaweed found in Brazil and some places in Florida of America. Its main chemical constituents are galatians, polysaccharides, and phytochemical test indicated presence of phytochemicals like glycosides (35.33 mg), anthroquinones (10.43 mg), sterols (20.17 mg), phenols (25.50 mg), flavonoids (10.17 mg), saponins (22.50 mg), fatty acids (0.545 mg), alkaloids (12.56 mg), triterpenoids (55.33 mg), *etc*. (Schneider et al., 2018). Its sulfated galactan crude extract has antiviral properties. When examined for DENV infection, it showed antiviral effects against DENV-2, slightly effective for DENV-3 and DENV-4 with no effect on DENV-1. It significantly inhibits the entry of the DENV into host cells (Lim et al., 2021).

4.2.10. Haldi

Curcuma longa L. is a flowering plant (Haldi in Hindi) belonging to the family Zingiberaceae. Turmeric is the common name for *Curcuma longa* L. and is found in Southeast Asian countries. India alone grows 40 to 45 varieties of turmeric (Prasad et al., 2011). The rhizomes of turmeric are collected, dried, and marketed in powder form. *C. Longa* L. has some medicinal values like anticancer, anti-inflammatory, antidiabetic, and antioxidant (Sharifi-Rad et al., 2020). Ichsyani et al. has examined its antiviral activity properties through *in vivo* and *in vitro* techniques using human liver cells and mice cells derived intraperitoneally. Both the tests show *C. Longa* L. extract has DENV killing activity (Lim et al., 2021). Curcumin binding causes the characteristic -hairpin of the C-terminal NS2B to unfold/displace, negatively impacting the protease's closed (active) conformation, according to molecular docking. This research discovered a cavity that is most likely conserved in all flaviviral NS2B-NS3 proteases and could thus be used as a therapeutic target for the discovery/design of small-molecule allosteric inhibitors (Lim et al., 2020). Furthermore, because curcumin has been used as a food additive for thousands of years in many countries, it can be used directly to combat flaviviral infections and as a good starting point for developing potent allosteric inhibitors. Curcumin is a weak inhibitor of the viral protease, according to a recent study. However, the analogs inhibited DENV infectivity more potently in plaque assays, indicating that these compounds target the cellular pathway(s) required for viral replication and/or assembly (Balasubramanian et al., 2019).

4.2.11. Gandhatrina

Cymbopogon citratus Stapf belongs to the family Poaceae (Borges et al., 2021), commonly known as lemon-grass in English, Gandhatrina in Hindi, and Aavartaki in Sanskrit. It is found in India, Sri Lanka, and some other Asian countries. It possesses antifungal, anti-inflammatory, and antiprotozoal properties (Avoseh et al., 2015). Lemon grass contains appreciable amounts of phytochemicals such as alkaloids, glucosides, phenols, flavonoids, saponins, terpenoids, *etc*. It is vastly used as a mosquito repellant in the chemical industry where the separated oil, which is further processed to nanoemulsion, reliably repels mosquitoes (Mapossa et al., 2021). It has shown 98.9% inhibition of DENV-2 in an *in-vitro* experiment using methanol extract from its roots. It also inhibits DENV-1 affected Vero E6 cells depending on their cytopathic activities. Methanolic extract of *C. citratus* suppresses DENV-1 mildly. The assay done by the MTT method shows an anti-dengue effect (Kadir et al., 2013). Gold nanoparticles (AuN) using the leaf extract of *Cymbopogon citratus* Stapf, which acted as a reducing and capping agent in low doses (18.80 ppm to 41.52 ppm) proved to control larval populations in copepod-based control programs (Murugan et al., 2015). The methanolic extracts of *C. citratus* showed inhibition of DENV-2 at a dose of 20 µg/mL to 98.9% (Rosmalena et al., 2019).

4.2.12. White bignonia

Distictella elongata (Vahl) L. G. Lohmann, commonly known as white bignonia in English, is a shrub mainly found in Central America, Amazonia, and Brazil belongs to the family Bignoniaceae (Kataoka and Lohmann, 2021). It is marked by flavonoids, terpenoids, quinones, aromatic compounds like lignin, and mainly naphthoquinones (LR et al., 2011). Napthoquinones show various biological activities like anticancer, antimalarial, antimicrobial, and antifungal. This family is highly renowned for its antiviral effect and rich antioxidant activity. It was found that pectolinarin and acacetin-7-*O*-rutinoside, (the two major chemical component that is found in leave and fruits of *Distictella elongata* (Vahl) L. G. Lohmann shows anti-DNV-2 activity (EC_{50} 11.1 ± 1.6 μg/mL; SI > 45) (Simões et al., 2011; Saleh and Kamisah, 2021).

4.2.13. Dugdhika

Euphorbia hirta (L.) Millsp. belongs to the family Euphorbiaceae. It is called Dugdhika in Hindi and is commonly known as an asthma plant or dove milk. *Euphorbia hirta* (L.) Millsp. is found in Java, Sumatra, Peninsular, Malaysia, India, Philippines, and Vietnam as garden beds, wasteland, and garden paths (Kumar et al., 2010). It's reported that Dugdhika contains triterpenes, phytosterols, polyphenols, flavonoids, *etc*. as biologically active ingredients. It is a valuable ayurvedic herb in treating asthma, bronchitis, diarrhea, dysentery, conjunctivitis, worm infestation, ringworm, and boils. Water decoction of *E. hirta* leaves is used as a medicine for dengue fever in the Philippines; it cures dengue fever in 24 h along with internal hemorrhage (Guzman et al., 2016; Perera et al., 2018). Increment in blood platelet ability is under investigation, and its anti-dengue mechanism of action is yet to be revealed.

4.2.14. Harcharal

Harcharal (*Flagellaria indica* L.) is a climbing plant that belongs to the family Flagellariaaceae. It is commonly known as whip vine or bush cane. *F.indica is* generally grown in tropical and subtropical zones like India, Southeast Asia, Polynesia, and Australia. Its activity is evaluated in Vero cells, 45.52% suppression of DENV-2 was detected in the *in-vitro* experiment, and the 12.5 µg/mL of the ethanolic extract showed by antiviral activity that is confirmed by MTT assay. The CC_{50} of ethanol essence is found 312 µg/mL (Ali et al., 2021).

4.2.15. Charma/Dhurchuk

Hippophae rhamnoides L. that is frequently referred to as Sea-buckthorn in English (Charma/ Dhurchuk in the Indian region) is a nitrogen fixation shrub belonging to the family Elaeagnaceae. It is commonly found in hilly places and notably colder regions. It is vastly found in Himalaya, Ladakh, Himachal Pradesh, Arunachal Pradesh, Uttarakhand, and Sikkim (Li et al., 1996; Bernáth et al., 1992). It contains alkaloids, flavonoids, quercitin, isorhamnetin, but flavonoids and quercitin are found in higher amounts. Quercitin is the main chemical that prevents dengue virus multiplication by targeting the virus's intracellular wall. It also shows therapeutic action like anti-inflammatory, antiulcer, and antioxidant. The alcoholic extract of leaves of *Hippophae rhamnoides* L. was evaluated for anti-dengue effect against DENV 2 in infected blood-derived human macrophages, and it was found effective (Ali et al., 2021; Saleh and Kamisah, 2021; Kadir et al., 2013; Lim et al., 2021). The extract was able to maintain the cell viability of Dengue-infected cells at par with Ribavirin along with the decrease and increase in TNFα and IFNγ respectively. The anti-dengue activity of SBT extract was further determined by the traditional plaque assay. Because of its more significant regulatory requirements, an aqueous extract of the stem of *C. hirsutus* (AQCH) was chosen. In fingerprinting assessment, five chemical indicators were recognized: Sinococuline, 20-Hydroxyecdysone, Makisterone-A, Magnoflorine, and Coniferyl alcohol. In a test of primary dengue infection in the AG129 mouse model, AQCH extract at 25 mg/kg body weight provided protection when given four and three times per day. At the dose of 25 mg/kg, AQCH was also protective in the secondary DENV-infected AG129 mouse model when administered four and three times a day. Furthermore, the AQCH extract decreased serum viremia as well as small intestinal pathologies such as viral load, pro-inflammatory cytokines, and vascular leakage (Shukla et al., 2021).

4.2.16. Basula

Lippia alba (Mill.) N.E. Br. ex Britton&P. Wilson, commonly known as Basula in Hindi, Bushy mat grass, Bushy lippie, and Pitiona in English, is a bushy perennial flowering shrub grown in southern Texas Mexico, the Caribbean Islands, Central, and South America belong to the family Verbenaceae. It is a multibranch shrub reaching a height of about five to six feet (Hennebelle et al., 2008). It prefers a position in complete sun to partial shade. The essential oil derived from L. *alba* has essential biological, pharmacological, and aromatic properties. Linoleum and Limonene are found in abundant in plants which inhibits dengue virus serotype replication on Vero cells (Teixeira et al., 2014). L. *alba* predominantly inhibits DENV-2, while the effect on other serotypes is not much considerable (Ali et al., 2021; Saleh and Kamisah, 2021; Kadir et al., 2013; Lim et al., 2021). An *in vitro* study on the inhibitory effect of L. *alba* essential oils against dengue virus serotypes replication reveals that virus plaque reduction for all four dengue serotypes was observed by treatment of the virus before adsorption on the cell. The IC_{50} values for L. alba oil were between 0.4–32.6 μg/mL (Ocazionez et al., 2010). The inhibitory effect of the essential oil seems to cause direct virus inactivation before adsorption on the host cell. Molecular docking confirmed the antiviral activity of β-caryophyllene showing interactions with amino acid residues from the target sites of NS2B-NS3 and in more significant numbers with NS5 (Nogueira Sobrinho et al., 2021).

4.2.17. Karela/Kugua

Momordica charantia L., often known as bitter melon or bitter gourd in English and karela or kugua in Hindi, is a herbaceous, and climber plant mainly cultivated in subtropical and hot arid regions belonging to the family *Cucurbitaceae* (Jia et al., 2017). It has phytochemicals like flavonoids, essential oil, glycosides, triterpenes, alkaloids, *etc*. It is having pharmacological properties like antidiabetic, antiviral, antitumor, antibacterial, antioxidant, and antiulcer. Its bitterness is believed to have a cooling and strengthening effect. Compounds like Phenols, isoflavones, anthraquinones, flavonoids, terpenes, quinines, and cucurbitacin make it bitter (Tungmunnithum et al., 2018). It is used as a therapeutic medication for a laxative, purgative, and antimalarial. It is also used to treat gout, jaundice, kidney stones, and eczema. Researchers evaluated the larvicidal activity of *M. charantia* by macerating the fruits and flowers in the methanol, hexane, and methyl acetate. The results showed that hexane had little toxicity, whereas methanol extract had effective anti-DENV 1 activity (Mituiassu et al., 2021; Jia et al., 2017).

4.2.18. Amrood

Psidium guajava L. belongs to the family Myrtaceae, also known as common guava in English, Amrood in Hindi, and Peyara in Bengali. Generally, these plants are found in tropical and subtropical areas worldwide. The leaves extract of *Psidium guajava* L. shows significant immune-boosting results against viral infections result by increasing the platelet count in the human body (Kumar et al., 2021). Research shows that water boiled with guava leaves can increase platelet count to 100.000/mm^3 in between 16 h (Factor et al., 2014; Kadir et al., 2013). Researchers found five chemical components from the root, leaves, and bark of *Psidium guajava* L. Galic acid, Naringin, Quercetin, Catechin, and Hesperidin, amongst those five compounds, Catechin shows the most effective viral inhibitor with more than 90% in two different strategies. Four compounds (except Hesperidin) are proven effective at a concentration lower than 100 μg/mL. Catechin has the highest cytotoxic concentration, 50% (CC_{50}) value of 833.3 μg/mL, and Hesperidin has the lowest value of 41.38 μg/mL; on the other hand, it has the highest effective concentration (CE_{50}) value of 225.8 μg/mL. Quercetin has the highest selectivity index (SI) value of 34.3, making it more selective than other compounds (Trujillo-Correa et al., 2019). Troninol's thrombopoietin-stimulating feature can be regarded as an alternative cure for thrombocytopenia-related instances such as dengue fever (Berlian et al., 2017). Trombinol significantly increased the expression of thrombopoietin at the level of mRNA and protein secretion in HepG2 cell lines. Additionally, combining *in vitro* and *in silico* evaluations allowed Andrea Isabel Trujillo-Correa and colleagues to identify gallic acid, quercetin, and catechin from the ethanolic extract of *Psidium guajava* L. with promising antiviral activity against DENV (Trujillo-Correa et al., 2019).

4.2.19. Bakau

Rhizophora apiculate Blume *which is* commonly known as Bakau, a marine mangrove plant has a practical medicinal effect belonging to the family Rhizophoraceae. Its leaf, root, and stem extract exhibits potent antibacterial, antiviral and antifungal effects (Abeysinghe, 2010). The study was conducted to test the anti-dengue effect of *Rhizophora apiculata*, and it was found that ethanolic extract having a concentration of 12.5 μg/mL can inhibit the activity of DENV-2 by 56.14% (Trujillo-Correa et al., 2019). In contrast, a higher concentration of 100 μg/mL of the ethanolic extract can inactivate the activity of viral particles by 41.5%. Larvicidal efficacies of an ethanolic fraction of *Rhizophora apiculate* Blume against the late IV instar larvae of the dengue vector, Aedes aegypti showed a maximum percentage of protection (Ali et al., 2014).

4.2.20. Baikal

Scutellaria baicalensis Georgi belongs to the family *Lamiaceae,* usually known as Chinese skullcap in English and Baikal in Hindi, mainly found in the Indian region, also in several East Asian and North American countries (Zhao et al., 2016). The presence of baicalein (flavonoid) inhibits four types of dengue virus replication. Research shows that the IC_{50} values for the Vero cells of DENV ranged from 86.9 to 95.19 μg/mL, and when these cells were treated with *Scutellaria biacalensis* root extract, the IC_{50} value decreased to 56.02 to 77.41 μg/mL, which poses a virucidal activity against dengue virus (Sucipto et al., 2018; Zandi et al., 2013).

4.2.21. Eldar sharaab

Sambucus nigra L. belongs to the family Adoxaceae, also known as Elderberry in English, and Eldar sharaab in Hindi is generally found in Europe and North American countries (Młynarczyk et al., 2018). This plant is highly rich in catechin, flavonoids, and phenolic acid compounds, and it also contains a higher portion of flavonoids. It especially riches in glycosides, various kinds of glycosides such as cyandin-3-glycoside and cyanidin-3-sambubioside. Two other (minor) anthocyanins are cyanidin-3,5-diglucoside and cyanidin-3-sambubioside-5-glucoside. It has extensive uses in traditional herbal medicine as an antiviral drug for influenza A and B, HIV, and Herpes simplex-1(Mukhtar et al., 2008). The flowering parts and leaves of *Sambucus nigra* L. show anti-DENV-2 activity at 400 μg/mL (Mahboubi, 2020). It is also shown that a mixture of both flowers and leaves extract is more effective rather than the only flower or only leaves extract.

4.2.22. Ulat-kanta

Uncaria tomentosa (Willd. ex Schult.) DC. belongs to the family Rubiaceae, commonly known as Cats claw in English, and Ulat-Kanta in the Indian region. It is generally found in the tropical jungle of South and Central America. Cats claw is rich in phytochemicals like indole alkaloids, oxindole, glycosides, organic acids, triterpenes, *etc*. An experiment shows that both methanolic extract and alkaloid fraction of *Uncaria tomentosa* (Willd. ex Schult.) DC. decreases DENV-Ag+ cell rates in experimented monocytes of the human body (SR et al., 2008). *Uncaria tomentosa* (Willd. ex Schult.) DC. contains oxindole and indole alkaloids, triterpenoid glycosides, sterols, and flavonoids, where alkaloid fraction contributes more as increasing antiviral properties by inhibiting pro-inflammatory cytokine activities. TNFα, IL10, and IFNα levels are significantly decreased by the alkaloid fraction, which is also strong immunomodulation thus poses an anti-dengue solid effect. The hydro methanolic extract decreases the DENV-Ag detection at 10 μg/mL. On the other hand, the alkaloidal fraction works significantly at 1 μg/mL, and the non-alkaloid fraction shows no effect on DENV-Ag monocytes (Reis et al., 2008).

4.2.23. Samudree sivaar

Cladosiphon okamuranus is a marin algae that belongs to the family Chordariaceae. Marine algaes are divided into three types and *C. okamuranus* comes under class Phaeophyceae because of its drown color. In hindi it's called samudree sivaar (Nishitsuji et al., 2016). It is a form of edible seaweed which is naturally found in Okinawa, Japan. Marin seaweeds usually contains various diverse types of bioactive components such as flavonoids, terpenoids, saponin, cardiac glycosides, phenolic, and phlorotannin but *C. okamuranus* is exceptionally enriched in Polysaccharides which is highly abundant with fucoidans and laminarans (Peñalver et al., 2020). Fucoidan is well known for its antiviral activity where as glucoronic acid and sulfated fucose are two vital elements for its anti-dengue effect. One viral infection assay performed on fucoidan derived from marine algae *C. Okamuranus* illustrated that Cladosiphon fucoidan notably impeded DEN2 contamination to BHK-21 cells when used dose-dependently (Elizondo-Gonzalez et al., 2012). The anti-dengue effect of fucoidan is remarkably more on DENV - 2 than other types of DENV. Around 20% of DEN2 infected cells can be recovered by 10 microgram per milliliter of fucoidan comparing normal cells. On the other hand, fucoidan does not show any particular suppressor action on dengue type-1 virus infections, it is proposed that difference of EGP structures built on amino acid remnant can impact the interactivity of fucoidan with the virus. Among, all types of dengue virus, the DEN2 strain ThNH-7/93 was extremely susceptible to the cladosiphon fucoidan as it has 100–fold more significant anti-dengue activity on ThNH-7/93 than that on DEN3 and DEN4 (Andrew et al., 2021).

4.2.24. Tejpatta

Cinnamomum osmophloeum commonly known as Pseudocinnamomum, indigenous cinnamon, and Indian Bay leaf in English, Tejpatta (Hindi), Tejpat (Manipuri & Bengali), Talishappattiri (Tamil), Tamalapatram (Malayalam), Talisapatri (Telegu), Patrata (Kannada), Tamaal Patra (Gujarati) belongs to the family Lauraceae (Laurel family) (Yeh et al., 2014). It is a small to moderate size ever green tree having tough three veined leaves commonly found in Northern India, China, and Srilanka. It bears tiny greenish-yellow insignificant flowers. Its leaves and buds are used both for spices and perfumery. Cinnamaldehyde, an essential oil extracted from *C. osmopholoeum* has numerous commercial use (Lin et al., 2011). An experiment conducted to check the larvicidal activities of different chemotypes of leaf essential oil from eight provenances of indigenous cinnamon, cinnamaldehyde type, and cinnamyl acetate types showed an excellent larvicidal effect against the fourth instar larvae of Aedes aegypti. Among, all the effective constituents in leaf essential oils namely cinnamaldehyde, eugenol, anethole, and cinnamyl acetate, cinnamaldehyde had the best mosquito larvicidal activity with an LC_{50} of 29 ppm against *A. aegypti* (Cheng et al., 2004).

4.2.25. Safeda

Eucalyptus citriodora Hook. is also known as lemon-scented gum in English, safeda (Hindi), Talanoppi (Telegu), Neelgiri (Kannada), which is a long, woody tree that belongs to the family Myrtaceae. This plant is very familiar with North-eastern Australia and the tropical region's people. It consists of beta-citronellal, pulegol, citronella, terpinolene, beta-pinene, linalool (Castillo et al., 2017) where's beta-citronellal is the main chemical constituent (71.77%) (Maciel et al., 2010). It has significantly shown repellent and oviposition deterrent activity against *A. aegypti* (Castillo et al., 2017). In scientific findings, Manh et al. found mosquito larvicidal activity (LC_{50}) value of *E. citriodora* is 104.4 ppm (plant collected from Vietnam), on the other side Vera et al. found the value of 70 ppm (plant collected from Colombia) (Manh et al., 2020). It has also shown that *E. citriodora* oil has constituents like p-menthane-3, 8-diol which has almost the same efficacy as compared with DEET repellents (synthetic repellents) (Peter, 2016).

4.3. Phytochemicals used in dengue medication

Natural products have grabbed the attention of many people in recent years, particularly in developing countries. India has the oldest history of curing diseases using medicinal phytochemicals derived from natural resources, mainly from the extract and phytochemical constituents of the plants (Ahmad et al., 2021). Plants produce biochemical/phytochemical constituents by a primary or secondary process (Chavda et al., 2021; Shad et al., 2014). These phytochemicals can initiate a defense mechanism for invading infection or pathogens, also plays a vital role in growth. Phytochemicals mentioned below are helpful as a dengue fever treatment.

4.3.1. Polysaccharides

Polysaccharides containing sulfur into their structure are described to have several biological actions; antiviral activity is one of them (Álvarez-Viñas et al., 2021). Carrageenan, ivan, and fucan sulfated polysaccharides are some of the polysaccharides with potential anti-dengue activity (Hans et al., 2021). This type of polysaccharides blocks the virus from binding to the host cell, which adverts the possibility of the virus penetrating the cytoplasm of the host and eventually prevents the occurrence of dengue fever. The result of docking a study shows that the LYS/295 and Gly/59 of DENV E protein interact with the sulfate and carboxyl group of the sulfated polysaccharides and imparts antiviral activity (Ali et al., 2021; Saleh et al., 2021; Lim et al., 2021).

A **Carrageenans**: Carrageenans are one type of galactan polysaccharide; galactans are derived from red seaweeds. Carrageenans are sulfated polysaccharides of D-series or their 3,6 - anhydro derivatives with 4-linked-alpha-galactose residues (Bouhlal et al., 2011; Jiao et al., 2011). Among various compounds tested, sulfated polysaccharides were found effective for the anti-dengue effect (Baba et al., 1988). It shows structural similarities with heparin sulfate (HS), a residual part of cell membrane proteoglycans (Bernfield et al., 2003; Rostand et al., 1997; Biochimie, 2001). Heparin sulfate is involved in the early stage of the DENV replication cycle. Carrageenan, a sulfated polysaccharide can interfere in the life cycle of the DENV virus by interfering with nucleocapsid adsorption and uptake into the cytoplasm (Talarico et al., 2007; Chen et al., 1997; Carlucci et al., 1999).

B **Fucoidan**: Fucoidan, a sulfated polysaccharide obtained from marine brown seaweed, *Cladosiphon okamuranus* is composed of carbohydrate units including glucuronic acid a sulfated fucose residues (L et al., 2003; LB et al., 2005; Nagaoka et al., 1999). They have a large amount of L-glucose and sulfate ester groups in their composition and are known for their many bioactivities, antiviral activity is on among them (Duarte et al., 2001; B et al., 2008; Zhang et al., 2015). Study shows that viral infection by DENV–2 is inhibited when it is treated with fucoidan. It shows 80% inhibition activity against DENV-2 when treated with 10 μg/mL of fucoidan, where serotypes 3 and 4 of dengue virus are mildly affected by fucoidan. DENV-2 shows strong structural binding to fucoidan. Both the functional groups, sulfated group and glucuronic acid in fucoidan result in interaction and inhibition of viral infection by DENV–2 (Hidari et al., 2008b; HM et al., 2007, Hidari et al., 2008a; T et al., 2003). Fucoidan derivatives such as fucan, sulfate groups, glucuronic acid, and sulfated fucose residues of cladosiphon fucoidan can effectively inhibit serotype - 2 contacts with cellular receptors (KI et al., 2013; Fitton, 2011).

4.3.2. Terpenes and terpenoids

Terpenes are secondary metabolites derived from primary metabolites with the help of enzymatic enucleation (Ghosh et al., 2019; Yang et al., 2020; Saravanan et al., 2021). Typically, terpenes are a dense gathering of several isoprene units, and the altered forms of terpenes are known as terpenoids. Compared to various kinds of terpenes, triterpene has a compound shape and many leakage sites with some modification possibilities, so they are biologically specified (Aldred et al., 2009; Ghildiyal et al., 2020; Saravanan et al., 2021). The non-structural proteins (NS2B - NS3pro) of DENV forms H-bonds and hydrophobic bonds with triterpenoids, which trigger the antiviral action. Triterpenoids also have larvicidal activity because of the hydroxyl group present in them. Betulinic acid, bigelovin, lneupatorolide, lupeol, nimbin, and ursolic acid are the triterpenoid with anti-dengue activity (Ali et al., 2021; Saleh et al., 2021; Lim et al., 2021).

A **Betulinic acid**: It is a natural lupane structured pentacyclic terpenoids obtained from various species of plant such as *Betula pubescens* Ehrh. (Loe et al., 2020; Tricou et al., 2010). According to time-course studies, betulinic acid inhibits the post-entry stage of the dengue virus, which includes the viral replication cycle, viral RNA production, and viral protein synthesis (J et al., 2016; Peyrat et al., 2017; Teixeira et al., 2014). Betulinic acid also shows antiviral activity against other viruses such as the chikungunya virus, zika virus, and flavivirus (JK et al., 2019).

B **Nimbin:** Nimbin is a potent chemical derived from *Azadirachta indica A.Juss.* leaf extract. Traditionally the leaf extract had been used as the best cure for viral infection (Tiwari et al., 2010; MM et al., 2002). The envelope protein of the dengue virus has a huge role in the life cycle of dengue (Lavanya et al., 2015). It assists in the progression of viral entry into the host cell suggesting it as an effective antiviral target (Sayed, 2000). Silico analysis study of nimbin suggests it to be effective against the surface proteins of all four strains of dengue virus (R et al., 2005).

4.3.3. Fatty acids

Fatty acids are composed of carboxylic acid, saturated and unsaturated aliphatic chains. Fatty acids are categorized into several classes based on the number of carbons, which are as follows: a. Fatty acids with a medium-chain (C8-C14) b. Fatty acids with a long chain (> C16) c. Fatty acids with extremely long-chain (> C20/22)

Fatty acids are composed of long chains of carbon and hydrogen atoms. Some carbon atoms are connected by single bonds, whereas others are joined by double bonds. These bonds dictate the molecule's fatty acid type. Phenolic lipids resembling the structure of the β-OG molecule inhibits envelope fusion of DENV-2 protein by targeting KI loops present in the virus. It is reported that fatty acids have anti-dengue activity, but the larvicidal activity of fatty acids may alert because of geometric isomerism, length of the chain, and degree of saturation (Tongluan et al., 2017). Fatty acids like arachidic acid, linoleic acid, behenic acid, and palmitic acid impart potential mosquitocidal and antiviral activity (Ali et al., 2021; Saleh et al., 2021; Lim et al., 2021).

4.3.4. Glycosides

Glycosides are naturally occurring complex organic compounds made up of sugar (glycone) and non-sugar (aglycone) parts combined with glycosidic bonds. Glycosides are crystalline or amorphous and are soluble in a polar solvent (exception-resin glycoside) and insoluble in other organic solvents like ether (Bartnik et al., 2017). They are primarily bitter except for glycyrrhizin. Medicinally, glycosides act as antibacterial, antifungal, anti-inflammatory and are used to decrease blood glucose levels due to stimulation of insulin secretion. Currently, FDA approved lanatoside C as a compound with anti-dengue activity (Ginex et al., 2020; Cheung et al., 2014). Data reveals that lanatoside C has a tremendous IC_{50} value against dengue virus infection. It reduces the viral RNA and viral protein synthesis, thus inhibiting the early processes of the viral replication cycle of dengue (Cheung et al., 2014). Research finding suggests that lanatoside C carries broad-spectrum antiviral activity, hence effectively against various groups of the virus (Ali et al., 2021; Saleh et al., 2021; Lim et al., 2021).

A **Lanotoside C**: Lanotoside C is a cardiac glycoside with antiviral and antitumor activity (Chao et al., 2017; Cheung et al., 2014). It is extracted from *Digitalis lanata* Ehrh. A study conducted on lanotoside C reveals about reduction of DENV-2 virus titer when treatment with lanotoside C (JS et al., 2011). It targets the post-entry stage of the virus cycle and inhibits viral RNA synthesis (XG et al., 2009). Lanotoside C has shown inhibitory action on all four types of dengue virus (IA et al., 2010). It has potent antiviral activity against DENV that is also endorsed by U.S. FDA (Cheung et al., 2014; Ginex et al., 2020; Boldescu et al., 2017).

4.3.5. Alkaloids

Alkaloids are compounds having basic N-atom in their structure. They are categorized into various types: true alkaloids, proto alkaloids, pseudo alkaloids, cyclopeptide alkaloids, and they can also be categorized based on the skeleton: pyrrolizidine derivatives, indole derivatives, imidazole derivatives, purine derivatives. Among various types of alkaloids, indole alkaloids have been found effective against dengue activity. Hirsutine, one of the significant examples of indole alkaloid, shows therapeutic activity like anti-hypertensive, cardioprotective, and anti-arrhythmic due to its properties to inhibit Ca^{+2} influx and release of intracellular Ca^{+2}. This calcium homeostasis is believed to have a vital role in the anti-dengue effect of Hirsutine (Quintana et al., 2020; Saravanan et al., 2021; Saravanan and Arjunan, 2021). Time of drug addition and time of drug elimination assay suggest that Hirsutine inhibits the viral entry and the assembly of viral particles, their budding, and release in the life cycle of the virus. Other alkaloids like Flinderole, isoborreverine, pungiolide, reserpic acid, and tubulosine have also been reported to inhibit the DENV viral replication at the early as well late-stage by interacting with the ribosome to inhibit viral protein synthesis (Nag et al., 2020; Fikatas et al., 2021; Ali et al., 2021; Saleh et al., 2021; Lim et al., 2021).

A **Hirsutine**: Hirsutine, found in *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. plant, was discovered to be a powerful anti-DENV component with low cytotoxic effects (Kato et al., 2014). Hirsutine was found to have antiviral properties against all DENV strains of the virus. In the DENV's entire life cycle, hirsutine suppresses the viral particle's pre-release stage (Powers and Setzer, 2016). As a result, it has been hypothesized that hirsutine did not target the stage of viral adhesion and entrance. In the DENV lifecycle, time-of-drug-addition and time-of-drug-elimination experiments revealed that hirsutine blocked not only the viral entrance and viral genome RNA replication steps, but also the viral particle assembly, budding, and release steps. In addition, the replicon assay revealed that hirsutine did not affect viral genome translation or replication (Hishiki et al., 2017). In the combination strategy, three of the four-indole alkaloids (VOAC, VOAC–OH, and rupicoline) inhibited the invasion induced by the DENV-2/NG and DENV-2/16,681 genotypes (Monsalve-Escudero et al., 2021).

4.3.6. Flavonoids

Flavonoids are phytoconstituent with a C-15 skeleton comprised of two phenyl rings and a heterocyclic ring categorized into distinct groups like isoflavones, flavones, neoflavones, flavonoids, and anthocyanins based on the attachment of ring B with ring C (Anusuya and Gromiha, 2019; Boniface and Ferreira, 2019). Various modes have been reported to combat viral infection like inhibiting replication of virus by inhibiting RNA polymerase and by forming a complex with viral

RNA which will ultimately mitigate virus replication (Sarwar et al., 2018; Anusuya, 2019). Flavonoids are the potential non-competitive inhibitors of NS2B-NS3 protease of the dengue virus. Flavanone, the subclass of flavonoids, inhibits the DENV virus by inhibiting targeting E protein, whereas isoflavones act against DENV4-NS4B protein revealed by molecular docking (Jayadevappa, 2020; Boniface and Research, 2019). A recent study by researchers revealed that luteolin could inhibit the proprotein of furin enzyme required for maturation of immature viral particles; also, it can target NS2B and NS3 protease activity. Some of the flavonoids with anti-dengue effects are glabranine, pongamol, catechin, quercetin, rutin, myricetin (Perumalsamy et al., 2015; Ninfali et al., 2020; Ali et al., 2021; Saleh and Kamisah, 2021; Lim et al., 2021).

4.3.7. Essential oils

The essential oil derived from turmeric is used as an insect repellent. Turmeric essential oil repels *An. dirus, Cx quinquefasciatus*, and *Aedes albopictus* for 4.5 to 8 h, and *Aedes aegypti* for 0.3 to 2.8 h. *C.longa* (Turmeric) imparts 94.7% spawning discouragement activity on mosquitos where DEET and IR3535 (chemical repellent) have no repugnance for the same. Some native plants of Southeast Asia like neem, galingale, clove, basil, citronella grass, and thyme have mosquito repellency abilities in their essential oils (Flechas et al., 2018; Chandrasekaran, 2019). Essential oils derived from *Citrus sinensis* (Balasubramani et al., 2018; Yaméogo et al., 2021; Huang et al., 2020), *Cymbopogon citratus* Stapf, *Eucalyptus citriodora, Ocimum basilicum*, and *Syzgium aromaticum* tested for their repellency on *Ae. aegypti, Culex quinquefasciatus*, and *Anopheles dirus* described that citratus oil is a potential invader of all the species of mosquitos. The properties of *Cinnamomum osmophloeum* can significantly control the spread of *Ae. aegypti*.

Neem oil mixed with polyoxyethylene ether, sorbitan dioleate, and epichlorohydrin can reduce Anopheles by 100%, Culex by 95.5%, and Aedes by 100%. Neem oil also controls *A.aegypti* efficiently. Essential oils like Geraniol collected from various aromatic plants impart insecticidal and repellent control on Anopheles, Culex, and Ades in their breeding sites. So, it can be helpful as an alternative to synthetic pesticides (Ali et al., 2021; Saleh et al., 2021; Lim et al., 2021).

4.3.8. Miscellaneous

A **Squalamine:** It is present in the white blood cells of sea lampreys and the tissues of dogfish sharks (squals acanthias). A plaque essay evaluated on human endothelium cells (HMEC-1) for dengue virus infection describes that squalamine has a potent inhibitory action on DENV sero types. It can reduce dengue by 60% when applied at a concentration of 40 μg/mL and compressors infection spreading at 100 μg/mL concentration (M et al., 2011; RR et al., 2014). Squalamine can nullify the negative electrostatic surface charges of intracellular membranes in such a way that makes the cell least active in facilitating viral replication.

B **Narasin**: Narasin is derived from fermented *Streptomyes aureofaciens* and is a polyester antibiotic that imparts antibacterial activity. Narasih can inhibit all the four serotypes of the dengue virus with a concentration of less than 1 μM but suspect for minimal cytotoxicity is there. In an experiment Huh-7 cells infected by DENV-2 were treated with Narasin, the result pointed at the inhibitory effect during the post-entry phases of viral replication of DENV infection (JS et al., 2011). Nursing's antiviral action is most likely linked to the inhibition of viral protein synthesis; it prevents viral protein synthesis while leaving viral RNA replication unaffected.

5. Dengue and Coronavirus Disease 2019 (COVID-19)

The monsoon season comes along with the risk of vector-borne diseases like dengue and malaria. The world is already battling epidemics of the coronavirus (Chavda et al., 2022, 2021, 2022; Basu et al., 2022; Chavda and Apostolopoulos, 2021; Chavda et al., 2021, 2021). Many symptoms of dengue and COVID-19 overlap can make the treatment complex. Currently, many different variants of SARS-CoV-2 are emerging and research on vaccines are underway with bosster dosing strategy (Chavda and Apostolopoulos, 2022c, 2022a, 2022b). With COVID-19 taking a toll on respiratory health and affecting other parts of the body,dengue can make it even harder to recover. Co-infection is a condition when a healthy person contracts with two or more diseases at the same time (Epelboin et al., 2020; M et al., 2020). During the pandemic, several cases of simultaneous infection of dengue and COVID-19 have occurred. The report says simultaneous treatment of and COVID-19 is complex and often gives no results (Tsheten et al., 2021; Lorenz et al., 2020; Nacher et al., 2020). Hence preventing simultaneous infection of COVID 19 and dengue becomes a priority issue (Verduyn et al., 2020). According to Yan and colleagues (Yan et al., 2020), "Failing to consider COVID-19 because of a positive dengue rapid test result has severe implications not only for the patient but also for public health." It is also very tough to distinguish between dengue fever and COVID 19 since all share similar symptoms (Malibari et al., 2020). Common symptoms include:

i High fever
ii Headache
iii Muscle and joint pain
iv Vomiting
v Nausea
vi Diarrhea
vii Skin rashes

Previously, there have been reports of misdiagnosis due to false COVID-19 positive results. Although additional symptoms like cough, loss of smell, taste, and/or sore throat may encourage further investigations for COVID-19 (Wu et al., 2020; Rojas et al., 2021). The diagnosis necessitates the use of a variety of tools, including direct virus detection tests and indirect immune response tests, as well as an accurate interpretation of the results based on the clinical and epidemiological characteristics of both infections (Agudelo Rojas et al., 2021). Various computational methodologies and Nano therapeutics approaches can also be explored to get the controlled drug action with minimal side effects (Chen et al., 2022; Chavda et al., 2021, 2019b, 2019a).

6. Conclusion

Dengue fever is a severe viral infection carried by Aedes mosquitos and caused by a Flaviviridae RNA virus. The symptoms might range from asymptomatic fever to life-threatening consequences including hemorrhagic fever and shock. It is critical to acquire a diagnosis as soon as possible to avoid death. Although dengue fever is usually self-limiting, it has become a public health crisis in tropical and subtropical nations. Dengue fever has grown into a global public health hazard, affecting more than 2.5 billion people in more than 100 nations. The doctor should be informed of the many clinical signs of this ailment so that therapy can begin as soon as possible. Future efforts to combat this horrible disease will focus on mosquito control, vaccine development, and antiviral therapy. Despite all these development in the therapeutic domain, there is still no special cure available to tackle dengue.

Ayurvedic or herbal remedies may be effective alternative treatments for dengue fever management (Singh et al., 2017). There are many herbal drugs that have proven *in vitro* and *in vivo* antidengue activity. Lanatocide C is an FDA-approved herbal component for dengue management. Around 8 clinical research were undertaken on DENV serotypes in 30 species from 25 families against different DENV serotypes (Table 3). The limitation here is the sample size that demands future clinical studies in a large diverse population for a better understanding of safety and efficacy. This review justifies investigating the potential mechanisms of action and laying the groundwork for future research. The field of phytochemical research has created an attractive niche for scientists to get a deeper insight into ayurvedic or herbal remedies for dengue cures. There

Table 3
Summary of clinical research undertaken on DENV serotypes.

Plant Name	Biological Source	Research Outcome	Reference
Dugdhika	*Euphorbia hirta* (L.) Millsp.	A randomized trial with 125 patients with confirmed dengue fever treated with herbal water of *Euphorbia hirta* (L.) Millsp. showed a moderate increase in their platelet count.	(Mir et al., 2012)
Abuta, Ice vine, and False pareira	*Cissampelos pareira* L.	The leaf extract was able to increase the platelet counts.	US20160243182A1
Dhurchuk	*Hippophae rhamnoides* L.	The leaf extract was able to maintain the cell viability of dengue-infected cells at par with Ribavirin along with the decrease and increase in TNF-α and IFN-γ respectively.	(Jain et al., 2008)
Papita	*Carica papaya* L.	25 mL of aqueous extract of *C. papaya* leaves was administered to a patient infected with Dengue fever twice daily. Results reported reveal improvement in platelets, and white blood cell counts.	(Ahmad et al., 2011)
		Leaves juice in an open-labeled randomized controlled trial was on 228 patients significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue hemorrhagic fever.	(Subenthiran et al., 2013)
		Carica papaya L. leaf extract capsule of 500 mg once daily and routine supportive dengue treatment for consecutive five days increases the platelet count in dengue fever without any side effect and prevents the complication of thrombocytopenia.	(Gadhwal et al., 2016)
		A Multi-centric, Double-blind, Placebo-controlled, Randomized trial with the administration of *Carica papaya* L. leaf extract in patients with dengue fever significantly increase the platelet count.	(Kasture et al., 2016)
		A placebo-controlled randomized trial in 51dengue patients (platelet counts ≤30,000/μL) with the administration of *Carica papaya* L. leaf extract demonstrated immunomodulatory and antiviral activity.	(Sathyapalan et al., 2020)
		C. papaya leaf liquid extract as adjunctive therapy for four patients receiving standard care treatment for chronic immune thrombocytopenic purpura demonstrate better antiviral activity against DENV.	(Hampilos et al., 2019)
		The patient was administered with *C. papaya* leaf liquid extract (1 tablespoon twice daily) with meals. Following, the patient's platelet counts rebounded from less than 10,000/μL to 113,000/μL.	(Koehler et al., 2022)

are many herbal targets identified however, their mechanisms are yet to be validated.

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Vivek P. Chavda: Conceptualization, Writing – original draft, Writing – review & editing. **Anup Kumar:** Writing – original draft. **Rittwika Banerjee:** Writing – original draft. **Nayan Das:** Writing – original draft.

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Supplementary Materials

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