Project Report

Exploring the natural compounds against dengue fever: a review

A project submitted in partial fulfilment of the prerequisites for the Bachelor of Pharmacy degree

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Approval

This project titled "A Review on **Exploring the natural compounds against dengue fever**'' submitted by Shamima Nasrin Mim ID:201-29-363, Daffodil International University's Department of Pharmacy has been acknowledged as satisfactory for partial fulfillment of the criteria for the degree of Bachelor of pharmacy (B. Pharm) and its style and contents have been authorized.

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Declaration

I hereby declare that this thesis report is done by me under the supervision of" Dr. Mohammed Shafikur Rahman, Associate Professor", Department of Pharmacy, Faculty of Health and Life Sciences, Daffodil International University, impartial fulfillment of the requirement for the degree of Bachelor of Pharmacy (B. Pharm). I am declaring that this project is my original work. I am also declaring that neither this thesis nor any part thereof has been submitted elsewhere for the award of Masters or any degree.

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Shamima Nasrin Mim

Author

Dedicated

To my beloved parents, my teachers, my supervisor.

Abstract

Aedes mosquitoes are primary vectors of the reemergent (DENV) and chikungunya virus (CHIKV). As a result, several recent investigations have been conducted to find antiviral compounds that might be used to treat DENV and CHIKV illnesses. In this study, we describe the advancements made in evaluating natural chemicals that specifically target the enzymes involved in viral replication. Dengue (DENV) is the most prevalent virus carried by mosquitoes worldwide. First, we evaluated the antiviral effectiveness of both natural and synthesized β-carbolines in preventing DENV-2 reproduction in cell cultures. It is determined that both the naturally occurring β carboline harmol and its synthetic equivalent, 9N-methylamine, suppress the development of DENV-2 while showing no virucidal properties. All DENV serotypes were shown to be inhibited by the active compounds, with DENV-2 being more susceptible to their antiviral actions. The mechanism of action of 9N-methylamine against DENV-2 was further studied. We found that the derivative did not affect the processes of adsorption-internalization or viral RNA synthesis.

Keywords: *Dengue, Antiviral, Mosquito, Larvicidal, Mosquitocidal and Mosquito repellents.*

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Chapter One
Introduction

1.1.General Introduction

Mosquitoes are vectors for the deadly dengue virus. An arbovirus, or dengue virus, causes the disease. Many emerging tropical nations now face a severe threat to public health from dengue fever, which is spread by mosquitoes. Over the last half-century, dengue fever has expanded across tropical areas [1]. Among tropical regions, this illness is most often seen in Southeast Asia. Death from dengue fever, especially the hemorrhagic form, is the leading infectious killer of indigenous people in Southeast Asia.[97] The majority of dengue cases occur in Southeast Asia, specifically in Vietnam and Thailand, according to Francisco Pinheiro, a former researcher from the Pan American Health Organization's Special Program for Vaccines and Immunization. Consequently, several groups are engaging in research and development related to dengue infections. According to the study, kids are more likely to suffer from this ailment in busy places [2]. China and East Asia, not part of tropical Asia, have also recorded dengue fever instances [3]. Luo et al. contend that circumstances in adjacent nations, particularly in Southeast Asia, are strongly linked to dengue fever outbreaks.

Since dengue outbreaks sometimes originate from the immigration of dengue patients from endemic locations, this raises the chance of viral importation from these nations [4]. Dengue fever has also recently emerged in Australia, and it is well known that this disease is very hazardous and requires meticulous treatment [5]. North Queensland's dengue outbreak has caused the local CDC to be somewhat worried [6].

1.2.Pathogenesis, clinical manifestation of dengue

Thinking about the mechanism, natural history, and clinical signs of dengue is crucial before diagnosing and starting therapy. As previously stated, the dengue virus, an arbovirus, is the causative agent of dengue fever. The world is home to four different serotypes of dengue virus. Aedes spp. is the mosquito species responsible for disseminating the dengue virus arbovirus. The primary vector, Aedes aegyptus, is thought to be responsible for more than two-thirds of the dengue cases worldwide. Local mosquitoes could spread the dengue virus even further if brought to a new environment. The most significant bio-ecological factors that may contribute to dengue's global spread are the sort of Ae. aegypti-to-human transmission, mosquito susceptibility, and transmission mode, according to epidemiology [7].

Since it's a virus, lymphotropic abnormalities, such as lymphocytosis, which abnormally activates lymphocytes, may manifest. An important pathogenic step in dengue infection is the breakdown of hemostasis. Illness symptoms include bleeding and thrombocytopenia in extreme instances, as well as vascular leakage and platelet destruction [8]. An immune-related mechanism is thought to be responsible for the thrombocytopenia seen in dengue [9]. On the other hand, immune-mimicking processes involving dengue virus and platelets are considered accountable for auto-destructive platelets in dengue hemorrhagic fever [10]. Platelet loss during an acute disease may be self-limiting, according to the natural history of dengue [11].

It is common for almost all afflicted individuals to have a fever and positive results from tourniquet tests [12]. Fever often lasts four to seven days since the virus causes it. Most

patients have a complete recovery with no problems, even if they may experience various odd clinical presentations [13]. In addition to symptoms in the respiratory and gastrointestinal systems, these unusual diseases might manifest without fever or other significant symptoms [14]. A high-severity case of dengue fever would be defined as overt bleeding dengue hemorrhagic fever or dengue shock syndrome, highlighting the seriousness of the disease. In the most common dengue fever, the sole indicator of infection is a petechial that develops during the tourniquet test [15]. Significant rates of morbidity and death are anticipated in the absence of appropriate treatment for serious illnesses. Controlling dengue requires vigilant monitoring for severe illness manifestations. From mild dengue to dengue shock syndrome, the hematocrit rises, and the platelet count falls, perhaps due to increased haemoglobin concentration [16].

1.3.Mosquito Control

There are several ways to deal with mosquitoes, which may be found in all phases of their life cycle (egg, larva, and pupa) [17]. For a long time, mosquito populations were controlled by using toxic synthetic pesticides such as carbamates, pyrethroids, and organophosphates, which primarily target insect larvae [18]. Newer pesticides, such as oxadiazines and neonicotinoids, have less environmental persistence and toxicity [19]. These chemicals are used extensively even though they are bad for the environment and all life forms. The use of pyrethroids, foggers, and synthetic pesticides used aerially against adults only worsens the issue of insect resistance [20]. Methods such as the Sterile Insect Technique (SIT), the Incompatible Insect Technique (IIT), and the Release of Insects Carrying a Dominant Lethal gene (RIDL) involve chemically irradiating insects and

genetically altering male mosquitoes to become sterile. Because of their host-specificity, flexibility, and infectiousness, entomopathogenic fungi, including those from the families Entomophthorales, Hypocreales, and Pezizales, are another tactic utilized against the adult stage [21]. To manage Aedes aegypti in different regions, the Globe Mosquito Program now employs unique strains of Wolbachia bacteria. This approach involves feeding bacteria to lab mosquitoes, which are then released into the local Ae. aegypti population to reproduce. The risk of arbovirus transmission to humans is decreased when mosquitoes carry bacteria [22]. Applications of Bacillus thuringiensis to larval habitats and things like pheromones that hinder development, reproduction, and oviposition are examples of biological control strategies that work against the immature stages. The fish of the Gambusia and Poecilia genera (Poeciliidae family) [23], the "elephant mosquito" of the Toxorhynchites genus [24], and the copepods, which include a large number of Mesocyclops species, are among the natural predators. Finally, plant-based insecticides (pesticides, larvicides, and ovicides) [25] need extra attention because of the incredible variety of species on Earth. It is estimated that there are 400,000 terrestrial species. Herbal insecticides may include secondary metabolites, essential oils, or plant extracts [20].

1.4.Natural Products to Control dengue fever

According to published studies, the hunt for natural compounds derived from plants that may reduce Aedes aegypti has been ongoing since the 1980s [26]. Chemical pesticides are still the most used even though they pose a significant threat to non-target animals. Here are some potential outcomes that may arise from these substances: (i) poisoning and death; (ii) cancer, either by cytotoxic or non-genotoxic mechanisms; (iii) adverse effects on the reproductive, neurological, renal, and respiratory systems [27]. Worryingly, mosquitoes are becoming more resistant to chemical pesticides and more harmful as vectors. The knockdown resistance (kdr) mutation, which affects the Ae—aegypti nervous system's sodium channel, is responsible for the insect's resistance to pyrethroid pesticides [28]. The use of pyrethroids to treat Aedes aegypti in Brazil was, however, discontinued in 2011 due to a technical notification [29]. How much, how often, and for how long pesticides are used determines the extent of resistance [30]. Modifications to the insecticide target site, which is usually caused by genetic mutations [31], alterations to the insect metabolism involving biotransformation enzymes [32], and changes to the insect cuticle that reduce pesticide absorption [33], are some theories regarding mosquito resistance mechanisms.

Carboxylesterases and cholinesterases are the enzymes that mainly cause resistance to develop. Both quantitative (enzyme overproduction) and qualitative (mutations that change the enzymatic characteristics) mechanisms contribute to carboxylesterases' organophosphate resistance, as is well documented [34]. The majority of cases of cholesterase resistance are caused by altered genes. Carbage and organophosphate pesticides are the most effective against acetylcholinesterase because they bind to its

specific location [35]. The impacts of temephos and its breakdown products have been previously recorded in aquatic habitats [36], and there are other instances, such as malathion and its metabolites in non-target species like Daphnia magna (Cladocera: Daphniidae) [37]. Since they decompose naturally in the field and water with little residue, insecticides derived from plant-based natural materials provide a promising alternative to traditional pesticides that are safer for the environment and effective against mosquitoes [38]. Because most of the secondary metabolites generated by insects serve as defences against organic predators, researchers have focused heavily on insecticides of a natural origin, particularly those derived from plants and microorganisms [39]. At least a few of the hundreds of plant metabolites thought to exist have insecticidal properties [40]. Botanical insecticides are usually a good idea because they break down naturally and don't harm non-target species like homeothermic animals.[98] The synergistic combination of therapeutic components in extracts reduces pest resistance and derives multiple action mechanisms [41].

1.4.1.Essential Oils

During the extraction process, essential oils show notable activity and yield between 0.5 and 2.0% because of the synergistic interaction of their constituent parts. They need special consideration as a result.[99] With few exceptions, their very low or nonexistent animal toxicity is a significant advantage (Figure 1). Manufactured goods are often low- or non-toxic to fish, birds, and mammals (LD50 for rats surpassing 5000 mg/kg). Nevertheless, some of the pure chemical components of essential oils have a moderate level of danger (LD50 in rats of 800–3000 mg/kg) [46].

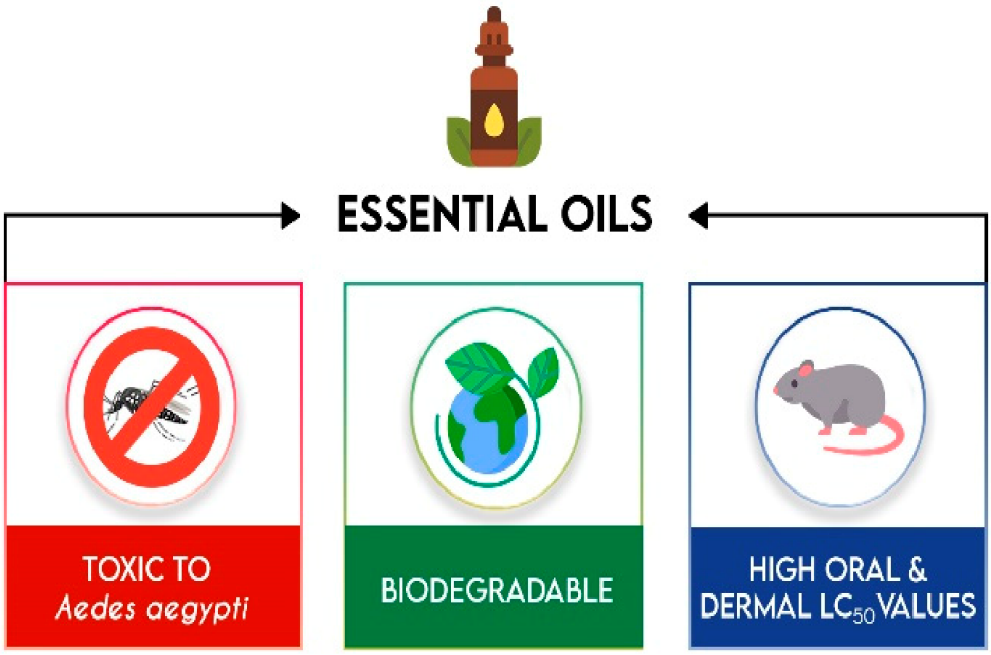


Figure 1. An environmentally friendly alternative for repelling Ae. aegypti mosquitoes: essential oils.

1.5.Natural Products as a Source of Pharmaceuticals

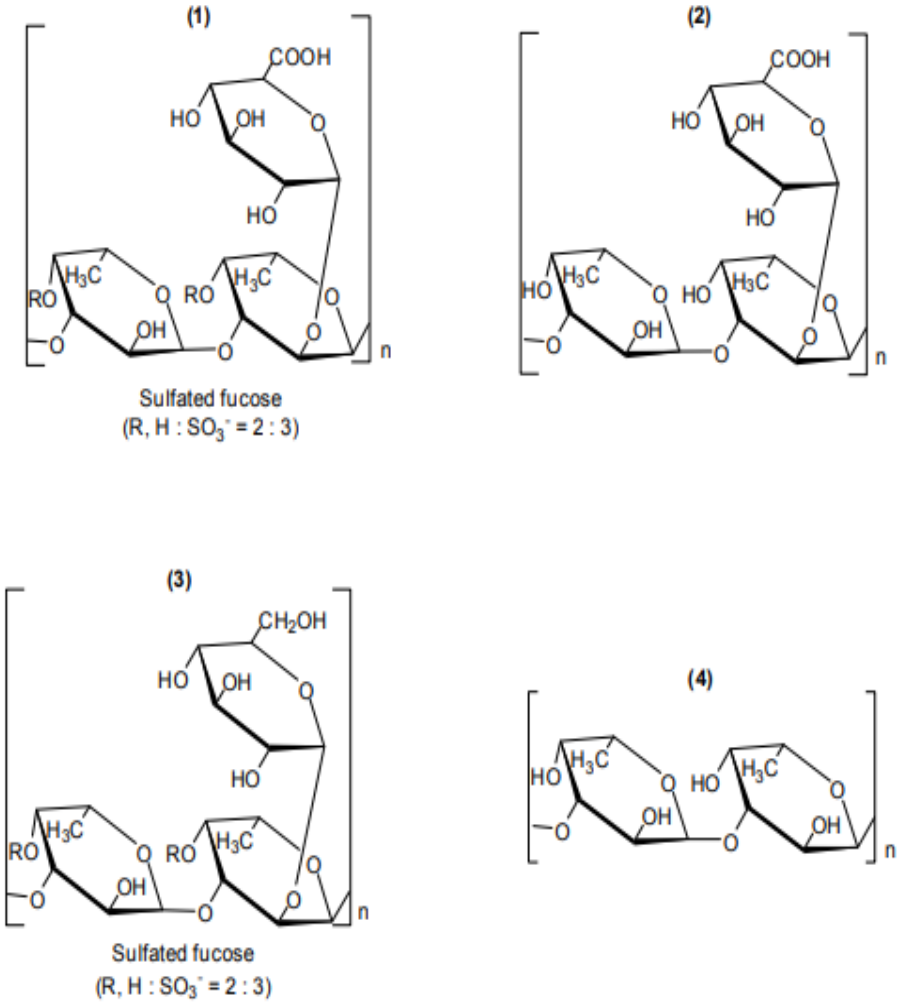
Using naturally occurring compounds in the hunt for novel pharmaceuticals is an old method of drug discovery [42]. Researchers have looked at chemical components found in nature as a potential source of new medicines since the dawn of pharmaceutical development. According to statistics, natural products or their analogues make up over half of all newly synthesized chemical entities [43]. There are a lot of plants that have anti-DENV and anti-CHIKV properties. As a result of geographical and economic limitations, 80% of the people in several African and Asian nations get their primary care from traditional medicine practitioners, according to a World Health Organization brief [44]. Herbal remedies and medicinal plants are booming in popularity worldwide due to the low

incidence of side effects, if any. Isolation (identification and assessment) and analysis of compounds from these plants need further publication of the study [45]. The progress in evaluating natural compounds that target the enzymes responsible for DENV and CHIKV replication is detailed here. The majority of the chemicals listed here are derived from plants.

1.5.1.Polysaccharides

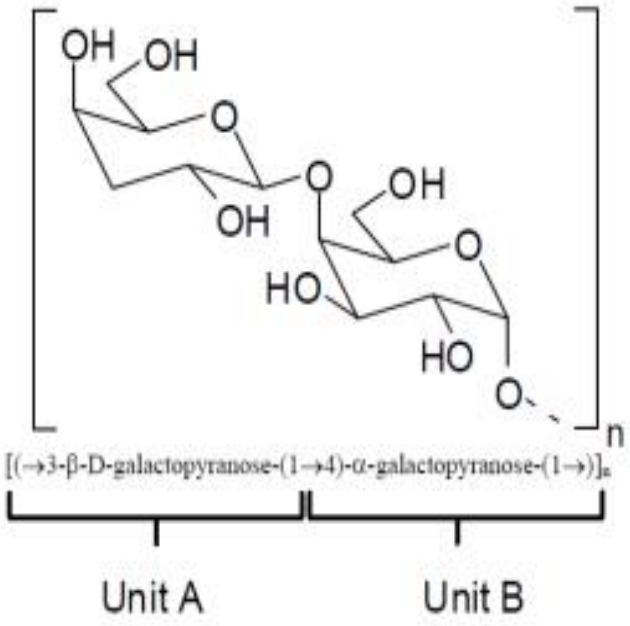
Fucoidans are polysaccharides that contain abundant L-fucose and sulfate ester groups. Several bioactivities, including antiviral characteristics, have been shown for these chemicals, most of which are sourced from brown seaweed [46]. A fucoidan polysaccharide was isolated from the brown seaweed marine alga Cladosiphon okamuranus (1, Figure 1). Its molecular makeup includes glucuronic acid residues in repeating units and sulfated fucose. This polysaccharide protects against dengue virus type 2 (DENV-2) infection, according to studies on Cladosiphon fucoidan (1) [47]. Fucoidan derivatives (2-4) (Figure 1) were also tested for their effect on dengue virus serotype two infection of BHK-21 cells. Decreased fucoidan (1) yielded derivative 3, whereas sulfated group removal from fucoidan (1) yielded derivative 2. A fucose polymer is what is known as fucan (4).

Figure 2: Fucoidan (1) and derivatives 2-4



Therefore, the glucuronic acid residue and the sulfate groups are necessary for fucoidan (1) to inhibit DENV-2 [48]. The sulfated fucose residues of Cladosiphon fucoidan and glutaric acid have been shown to affect DENV-2's ability to bind to cellular receptors dramatically; however, the exact chemical mechanism by which this substance exerts its inhibitory effects is still unclear. Isolated galactanes, a polysaccharide, have been discovered in red seaweeds [49].

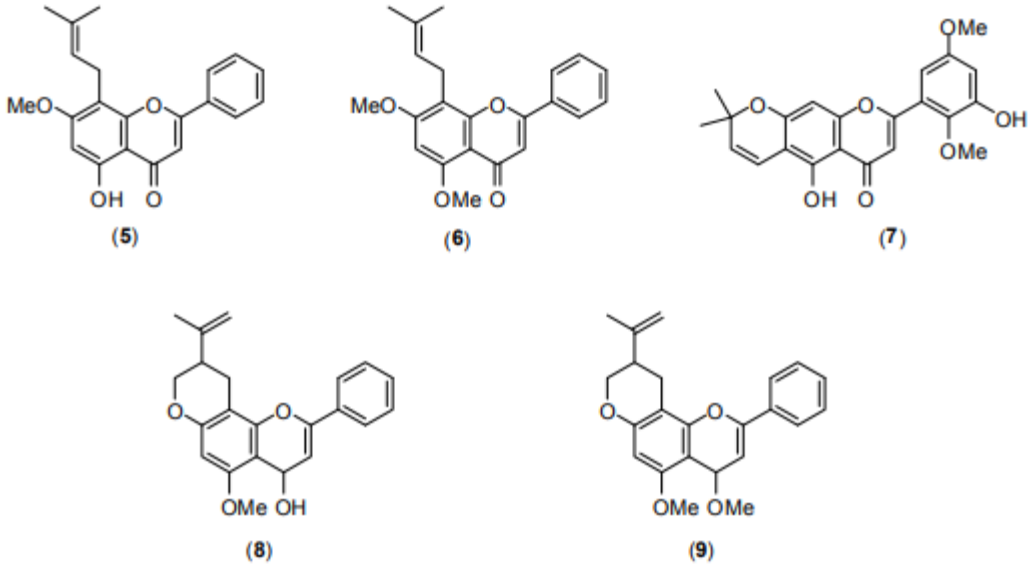
Figure 3: Repeating basic structure of galactans



1.5.2.Flavonoids

Plaque testing assessed the antiviral activity of DENV-2 serotype and LLC-MK2 cells in vitro. Of the five evaluated flavonoids, only glabranine (5) and 7-O-methylglabranine (6) had substantial inhibitory effects.[100] At 25 μmol/L, these two flavonoids reduced viral infection by 70%. The values of the IC50 were withheld. The little antiviral impact was seen with the additional flavonoids 7-9. Two compounds with a prenyl side-chain at C-8, glabranine (5) and 7-O-methylglabranine (6), were shown to block replication [50] effectively. This suggests that the antiviral effect of the flavonoids under study is related to their structure.

Figure 4. Structures of flanovoids from Mexican Tephrosia species



Houttuynia cordata is a typical side dish in western and northern Thailand, and its aqueous extract was tested against DENV-2 [51]. Used in the experiments were concentrations of ten and one hundred μg/mL. When administered at higher doses, DENV-2 could halt intracellular viral RNA synthesis (treatment mode), protect HepG2 cells from infection (protection mode), and be directly blocked from infecting cells. The inhibitory impact of the defensive mode was the greatest.[101] In experiments on LLC-MK2 cells, the aqueous extract exhibited a protective effect against virion release in the concentration range of 10-40 μg/mL

1.6.Antivirals

1.6.1.Irish moss/carrageen moss

Chondrus crispus, a member of the Gigartinaceae family and often referred to as Irish moss or red seaweeds, is one commercial source of carrageenan. Carrageenans are a member of the natural polysaccharide class. Red seaweeds known to be carrageenophytes generate kappa, iota, and lambda carrageenans, which have been shown to have potent antiviral effects [52].

DENV-2 was more effectively suppressed by the carrageenan extracts from Meristiella gelidium (Tengusa and Makusa). Because the dengue virus first interacts with the glycosaminoglycan heparan sulfate (HS) to attach to the host cell, it may hinder the early phases of the viral entry [53].

1.6.2.Chinese ginger

The common name for Boesenbergia rotunda is Chinese ginger. A membrane-associated protein called NS2B stabilises and controls the replication complex throughout the viral life cycle. Digesting polyprotein required for viral replication requires the serine protease NS2B-NS3 [54]. Investigated how different flavanone groups and their chalcones affected the DENV-2 protease. Boesenbergia rotunda (L.), sometimes called Chinese ginger or finger root, is the source of several bioactive chemicals. According to their findings, DENV-2 NS3 protease was effectively and competitively inhibited in vitro by the cyclohexenyl chalcone derivatives 4-hydroxypandurantin A and pandurantin A.

1.6.3. Black galingale

Black galingale is the general name for Kaempferia parviflora. However, Chandramul is the local name. Boron is a chemical component. According to recent research, a bioactive component in K. parviflora directly inactivates DEN-2 particles. There is a dosage dependence on the plant extract activity [55]. Additionally, using the plant extract as a mosquito repellent works well [56].

1.6.4.Mazu phal

Quercus lusitanica and Quercus infectoria contain gallic and ellagic acids (Mazu Phal). It has been shown that plant extracts may dose-dependently inhibit viral proliferation [57]. The glycoprotein known as NS1 is present in all flaviviruses and is believed to be essential to the virus's survival. The effect of Q. In conclusion, Q. lusitanica extract efficiently prevents the multiplication of dengue virus type 2 in conventional cell culture and proteomics techniques [58].

1.7.Anti-mosquitoes

1.7.1.Pippli

Often called Pippli or Papal, Piper longum Piperaceae. The plant is used root, and stem. The following sequence of these species' effectiveness was demonstrated: Piper ribesoides > Piper sarmentosum > Piper longum [59]. Concerning Stegomyia aegypti, the dengue and dengue hemorrhagic fever vector, ethanolic extract showed adulticidal activity. When applied to Aedes aegypti larvae in their fourth stage, piper longum fruit-isolated pipernonaline demonstrated potent larvicidal effects [60].

1.7.2.Kari patah

The whole Rutaceae family Murraya koenigii is known as Kari patah or Kariapat. In one experiment, whole plant crude extracts in hexane, diethyl ether, dichloromethane, and ethyl acetate were given to mosquitoes at the pupal and adult stages, where they were permitted to develop and fed typically. It thus results in anomalies in the creation of adults. Therefore, it is a larvicidal agent [61]. Murraya koenigii leaf extracts in acetone and petroleum ether at concentrations between 250 and 900 ppm have shown larvicidal efficacy against Aedes aegypti larvae [62].

1.7.3.Mentigi

A genus of marine plants in the Lythraceae family is called Pemphis acidula, sometimes known as Mentigi. The repellant attributes of crude leaf portions from Pemphis acidula are shown against Aedes aegypti. In this investigation, P. acidula was shown to have repellent properties against Aedes aegypti adult mosquitoes [63].

1.7.4.Anisuan

Anisuan is another name for Pimpinella anisum. The Apiaceae family is where it belongs. The main ingredients are: 9–13% moisture, 18% protein, 8–23% of the oil is fatty, 2-7% essential, 5% starch, 22-28% N-free extract, and 12–25% crude fibre. Anethole accounts for 80–90% of the 2-3% essential oil typically obtained after distillation [64]. Trans-anethole has mutagenic properties. This plant's essential oil is poisonous to Aedes aegypti larvae [65]. Anetholes are insecticidal against Aedes aegypti larvae [66]. When anethole is used as a fumigant rather than a contact agent, its insecticidal effects are more potent [67].

Chapter Two
Literature review

2. Literature review

Mosquitoes spread various viruses, the most common of which is dengue fever (DENV). We started by checking whether β-carbolines, both synthetic and natural, might halt DENV-2 replication in cell cultures that use antiviral activity. According to the findings, a manufactured version of natural βcarboline harmol, 9N-methylamine, and the growing DENV-2 virus are suppressed without exhibiting any virucidal effects. It was shown that the active chemicals inhibited all serotypes of DENV, with DENV-2 being more vulnerable to their antiviral effects. Additional research was conducted to determine how 9N-methylamine inhibits the growth of DENV-2. We discovered that the derivative unaffected viral RNA production and adsorption-internalization pathways. Based on measurements of infectious virus particles and the genomes of both intracellular and extracellular viruses, 9N-methylamine would inhibit the release and maturation of viral particles into the extracellular media, impacting the infection's ability to propagate. According to other findings, the antiviral action of 9N-methylamine is unconnected to its capacity to inhibit p38 MAPK phosphorylation.

The mosquitoes that transmit dengue fever to people are Aedes aegypti and Aedes albopictus. The life cycle of the holometabolous mosquito, Aedes aegypti, consists of many stages, including larva, adult, and egg [91].

By acting as a reservoir and source of additional viruses produced during viral replication in the host, humans may transmit the illness to unaffected mosquitoes [92].

Chapter Three
Purpose of the study

3. Purpose of the study

The purpose of this research is to gather the most positive data on the investigation of natural substances as a means of combating dengue fever.

- To understand the dengue fever's pathogenesis.
- To compile the most promising information about dengue fever treatment using natural chemicals.
- To get knowledge about dengue fever immunotherapy.
- To gain knowledge about using antivirals and anti-mosquito chemicals in dengue disease cases.
- Collect information about the usage of natural substances to treat dengue fever.
- To find out more about dengue fever therapy utilizing polysaccharides.
- Gather information on using natural substances to treat dengue illness.
- Gather information to do further research.

Chapter Four
Methodology

4. Methodology

4.1.Method of searching

PubMed, SciFinder, Elsevier, Springer, Scopus, Science Direct, Google Scholar, and Web of Science were among the conventional books and databases on natural chemicals against dengue fever published between 2000 and 2023 that were examined.

4.2.Criteria

- The pathophysiology of Dengue fever.
- The mechanism of dengue immunotherapy.
- Current prospects for antiviral compounds against dengue fever.
- Dengue fever are treated with natural compounds and Essential Oils, Polysaccharides and Flavonoids.
- No treatment exists that can completely cure dengue fever.

4.3.Data analysis

An exploratory reading of the various articles was conducted to develop and analyze the items while the work's title and abstract were assessed. Once the experiment is complete, read the study on how natural chemicals may be used to prevent dengue illness. Create a central file before drafting the final review paper, use Grammarly, and practice paraphrasing sentences.

Chapter Five
Result & Discussion

5. Result & Discussion

5.1.Plants derived mosquitocidal agents

Research on mosquitocidal chemicals derived from plants is growing in the natural product literature. Insecticides find larval mosquitoes to be significant targets since they make controlling them in this environment easier, as they grow in water. The recently discovered critical larvicidal insect growth regulators are endotoxins produced by Bacillus thuringiensis israelensis and B. sphaericus, methoprene, pyriproxyfen, and diflubenzuron. As an antifeedant plant, Azardichita India is extensively recognized in several countries [68]. Several essential oils, such as citronella, calamus, thymus, and eucalyptus, have shown potential in eliminating mosquito larvae [69]. Since natural substances generated by plants kill mosquitoes, this section has focused on them and has separated them into several subcategories under the subsequent subheadings. Chemical classifications have been used to organize the review to highlight possible mechanism-based activity.

5.2.Alkanes, alkenes, alkynes, and simple aromatics

Octacosane (1), a hydrocarbon that was isolated from Moschosma polystachyum, has a significant larvicidal effect on the Culex quinquefasciatus mosquito, with an LC50 value of 7.2 ± 1.7 mg/L [70]. Strong anti-Culex pipiens larval activity is shown by the acetylenic compounds falcarinol (2) and falcarinol (3), which were isolated from Cryptotaenia Canadensis [71]. Compound 2, which is more lipophilic, is more hazardous than polar acetylene 3, with LC50 values of 3.5 and 2.9 ppm in 24 and 48 hours, respectively [72]. Volatile aromatics that may be isolated from vanilla scent include vanillin (6), 4-hydroxy-

2-methoxycinnamaldehyde (7), 3-ethoxymethylphenol (4), 4-butoxymethylphenol (5), and 3,4-dihydroxyphenylacetic acid (8). These compounds are very toxic to mosquito larvae. Compound 8 shows 17% larval mortality at 1.0 mg/mL, while compounds 4-5 show 100% larval death at 0.5, 0.4, 2.0, and 1.0 mg/mL dosages, respectively [73].

Table:1 [Compilation of essential plant extracts with proven mosquito-killing capabilities]

Plant species	Family	Plant parts	Mosquitoes species	Ref
Abuta grandifolia	Menispermaceae	Fruit	Aedes aegypti	[74]
Acacia ferruginea	Leguminosae	Leaf	Culex quinquefasciatus	[75]
Acacia nilotica	Fabaceae	Leaf	Anopheles gambiae	[76]
Acalypha indica	Euphorbiaceae	Leaf	Anopheles stephensi	[77]

5.3. Antiviral activity of other flavonoids

Research has shown that a neurovirulent strain of the Sindbis virus cannot replicate in vitro when flavanone naringenin is present [78]. Furthermore, viral yield experiments reduced the cytopathic effect induced by the Sindbis and Semliki Forest viruses [79]. This flavanone's rutinose moiety inhibits naringin's antiviral properties. It's noteworthy to note that naringin's glycoside form doesn't have any anti-Sindbis virus action. Long-term treatment lowers HCV by 1.4 logarithmic units; naringenin may also stop the assembly of HCV particles within cells [80]. The same experiment showed that hesperetin, a distinct flavanone prevalent in citrus fruits, had the highest anti-CHIKV action during the virus's

intracellular replication [81]. This suggests that hesperetin's anti-CHIKV action may be focused on these proteins. Fava beans and soybeans are two of the numerous plants that contain the isoflavonoid genistein. By preventing the phosphorylation of viral proteins, the tyrosine kinase inhibitor genistein suppressed the proliferation of the New World arenavirus Pichinde and bovine herpesvirus type 1 [82]. The combination of kinase inhibitors, such as genistein, exhibited broad-spectrum antiviral activity against both filoviruses and arenaviruses [83]. It has been shown that genistein inhibits HIV infection of dormant CD4 T cells and macrophages by interfering with HIV-mediated actin dynamics [84].

Furthermore, since it can block the viral Vpu protein, which is assumed to produce a cation-permeable ion channel in infected cells, it may act against the HIV ion channel [85]. As part of its antiviral action, genistein also hindered the transcription of HSV-1, HSV-2, and the viruses that cause avian leucosis virus subgroup J to reproduce [86]. The antiviral qualities of the other flavonoids are listed in Table 2.

5.4. Future perspectives

Even though flavonoids are widely distributed in human diets and provide many biological benefits. How effectively humans absorb and are bioavailable for flavonoids depends on several factors, including molecular sizes, esterification in the gastrointestinal tract [87]. Researchers have looked at several methods to improve a compound's solubility or alter its absorption site in the stomach. [102] Hesperetin-7-glucoside's structural alterations have successfully raised plasma levels of hesperetin in healthy individuals by moving the absorption location from the large to the small intestine [88]. The oral bioavailability of

flavonols extracted from sea buckthorn was enhanced by Wang et al. [89] Researchers have also looked at the bioavailability of flavonoids when they are added to synthetic nanoparticles and consumed orally. Chitosan nanoparticles with improved EGCG and catechin stability had higher intestinal absorption rates [90]. Thanks to polymeric micelles and poly (D, L-Lactide) (PLA) nanoparticles, the poorly absorbed apigenin and quercetin—which have limited bioavailability and considerable first-pass metabolism—were released in a more prolonged way [91].

Table 2 [Flavonoids with antiviral properties]

Flavonoids	Class	Source(s)	Antiviral activity	Other biological activities
Galangin	Flavonol	Propolis, leaves of lesser galangal (Alpinia officinarum) and rhizome of Alpina galanga	Coxsackie B virus type 1 [94]	Antibacterial and anticarcinogenic activity
Morin	Flavonol	Bark, leaves and stem of white mulberry (Morus alba), leaves and fruit of Osage orange (Maclura pomifera), guava (Psidium guajava), and leaves of old fustic (Maclura tinctoria)	Canine distemper virus [95], Moloney murine leukemia virus [96]	Antihypertensive, antiangiogenic, hepatoprotective, neuroprotectant and antiinflammatory activity

Chapter Six
Conclusion

6. Conclusion

In the last several decades, many chemicals that influence dengue virus serotypes have been made available via the natural product pool. Some intriguing actions have been associated with the substances mentioned. Yet, researchers have only scratched the surface of nature's enormous chemical reserve in the hunt for dengue-fighting antivirus software. Naturally occurring antiviral dengue drugs will be safe and efficacious for human use. In addition, the structures of natural compounds may be used as models in synthetic efforts to enhance these compounds in search of even more powerful dengue virus-attacking chemicals. An increasing number of cases of dengue fever are putting lives in danger. Without an approved vaccine or medicine, natural remedies that kill dengue larvae and mosquitoes, repel mosquitoes, and have antiviral properties may help control the disease. We recommend more research into the active components of the plants under investigation to create medications for the treatment of dengue fever. Creating dengue (DENV 1-4) treatment based on ethnobotanical knowledge requires worldwide networking of academic research groups, medical experts, and enterprises.

Chapter Seven
References

7. Reference

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