Chapter 17

Larvicidal and Insecticidal Activity of *Essential Oils* of Lemon Balm against *Aedes aegypti*

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ABSTRACT

As the most significant category of insects for public health, mosquitoes are capable of spreading zoonosis as well as serious human illnesses as Japanese encephalitis, Dengue fever, Malaria, Filariasis, and Yellow fever. Millions of people have died and become ill as a result of the diseases that these insects spread. There are not any commercially available drugs or vaccines for treating dengue fever at the moment. The single strategy implemented to lower the frequency of dengue is to manage *Aedes aegypti*, the vector that also serves as the main source of Zika, Yellow fever, and Chikungunya viruses. Nonetheless, synthetic substances that mostly comprise DEET (N, N-diethyl-3-methylbenzamide) in their formulations are the most widely used repellents. DEET has certain drawbacks even if it works well as an insect repellent for a range of insects. The main one is that it can act as a solvent for paints, varnishes, and some synthetic and plastic materials. Because of their potential insecticidal efficacy, rapid disintegration, affordability, and lack of persistence and bioaccumulation in the environment, natural product components such as lemon balm essential oil are suggested as synthetic insecticide substitutes when it comes to mosquito control. Lemon balm essential oil is derived from the leaves of the *Melissa officinalis* plant and is highly prized for its lovely citrus aroma as well as a number of potential health benefits. As this chapter has shown, one of its supposed applications is as a natural insect repellent, especially against mosquitoes.

KEYWORDS
Larvicidal, Insecticidal, Lemon Balm, Aedes aegypti

Received: 20-May-2024
Revised: 13-July-2024
Accepted: 08-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Wazir N, Sari AB, Farooqi SH, Ashraf M, Khan MA, Akhtar T, Aziz S and Naeem MI, 2024. Larvicidal and insecticidal activity of *Essential oils* of lemon balm against *Aedes aegypti*. In: Zafar MA, Abbas RZ, Imran M, Tahir S and Qamar W (eds), Complementary and Alternative Medicine: Essential oils. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 143-152. https://doi.org/10.47278/book.CAM/2024.238

INTRODUCTION

Ae. aegypti is indigenous to Africa, where ancestral populations are still present, reproducing in forests and ecotones, where adults prefer wild animals for blood feasts and larvae hide in tree holes (Lounibos, 1981; McBride et al., 2014). African villages and cities were popular mosquito breeding sites during extended dry seasons because people there started keeping water in containers when they first settled there. The African Aedes mosquito that took advantage of this new niche was *Ae. aegypti*. As females fled from huts in villages, they developed a taste for blood feasts from the most accessible source: people. Currently found in tropical and subtropical human settings across six continents, *Ae. aegypti* is known for having been "domesticated" (Powell and Tabachnick, 2013; Gloria-Soria et al., 2016)

The Reason Mosquitoes Find You Appealing

One of the most vital senses of mosquitoes is their ability to smell, or olfaction (Potter, 2014) that they depend on to keep their lives going. For instance, they locate oviposition sites for egg laying, nectar sources for feeding, and human hosts using their smell cues (Carey and Carlson, 2011). It has been established that a variety of human secretions (Figure 1),

such as carbon dioxide from breath, lactic acid from skin and exhaled air, and 1-octen-3-ol from perspiration and breath, are mosquito attractants (Dekker et al., 2005).

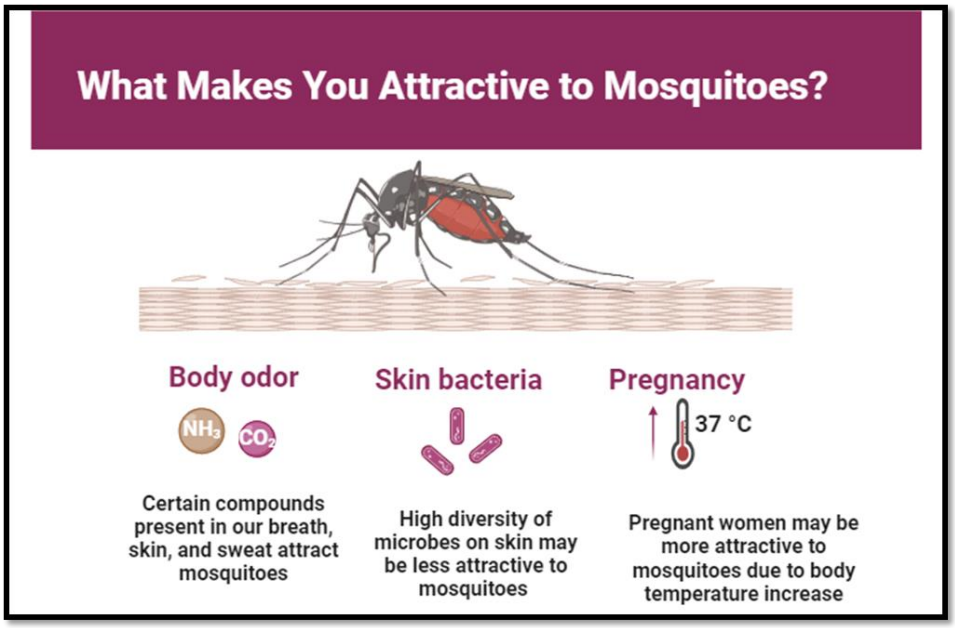

Fig. 1: Why mosquitoes are attracted to you?

Linnaeus species *Ae. aegypti* is known to carry important and dangerous illnesses, including Dengue, Chikungunya, Yellow Fever, and Zika Fever. This mosquito is native to Africa, although it is also found in tropical and subtropical areas, as well as tranquil places across the world (Benelli and Duggan, 2018). A little bit detail of these *Aedes* borne infections is given here.

Dengue Infection

Currently, dengue is one of the most significant tropical diseases that go unreported in the globe (Guzman and Harris, 2015) and in the past few decades, its occurrence has more than tripled along with the spread of dengue viruses and *Ae. aegypti* mosquitoes across new geographic areas (DENVs) (Organization et al., 2009). Dengue fever is considered the most dangerous illness in terms of epidemiology because to its high rates of morbidity and fatality. It is believed that the virus affects 60 million individuals worldwide each year, killing roughly 10,000 of them (Bhatt et al., 2013; Stanaway et al., 2016).

Dengue Virus Life Cycle

Mature viral particles bind to their hosts' cells and enter by endocytosis. When the viral and endosomal membranes merge within the cell, the viral genome is liberated (Figure 2). Viral RNA is translated into proteins, which initiates replication. Proteins from the Dengue Virus (DENV) can attach to lipids in cells and be released. After reaching maturity in the endoplasmic reticulum (ER), the virus leaves the host. Certain discharged particulates are still immature and not contagious (Guzman and Harris, 2015).

Transmission of Dengue Virus

If *Ae. aegypti* mosquito feeds on an infected person during the viremic phase of the illness, the mosquito can then carry the virus. Dengue viruses enter mosquito midgut cells and other tissues during the extrinsic phase of the cycle, then proceed to the salivary glands. A mosquito carrying the dengue virus can infect multiple individuals once it feeds or tries to feed (Figure 3). Dengue fever symptoms typically take four to six days to manifest, and an infected person can spread the virus to a new mosquito during this time. People who are symptomatic or not can infect mosquitoes with the dengue virus (Guzman et al., 2016).

Clinical Symptoms

The acute febrile stage is when fever happens. Diarrhea and mild stomach discomfort are possible. Adults typically exhibit a "flu-like syndrome" that includes body aches, headaches, and malaise, with digestive symptoms predominating over respiratory symptoms (Guzman et al., 2016).

Chikungunya Virus (CHIKV) Infection

Aedes mosquitoes carry the Chikungunya virus (CHIKV), an arthropod-borne virus that mostly causes acute and persistent articular symptoms (Simon et al., 2008). It was first discovered in Asia in 1954 after being first reported in Africa (Tanzania) in 1954. It produced widespread epidemics on both continents from the 1960s to the 1980s, and then there was a relatively peaceful period for the next 20 years (Pastorino et al., 2004). Recently, CHIKV has

resurfaced, infecting millions of people in nations surrounding the Indian Ocean that have climates conducive to high vector densities (Caglioti et al., 2013).

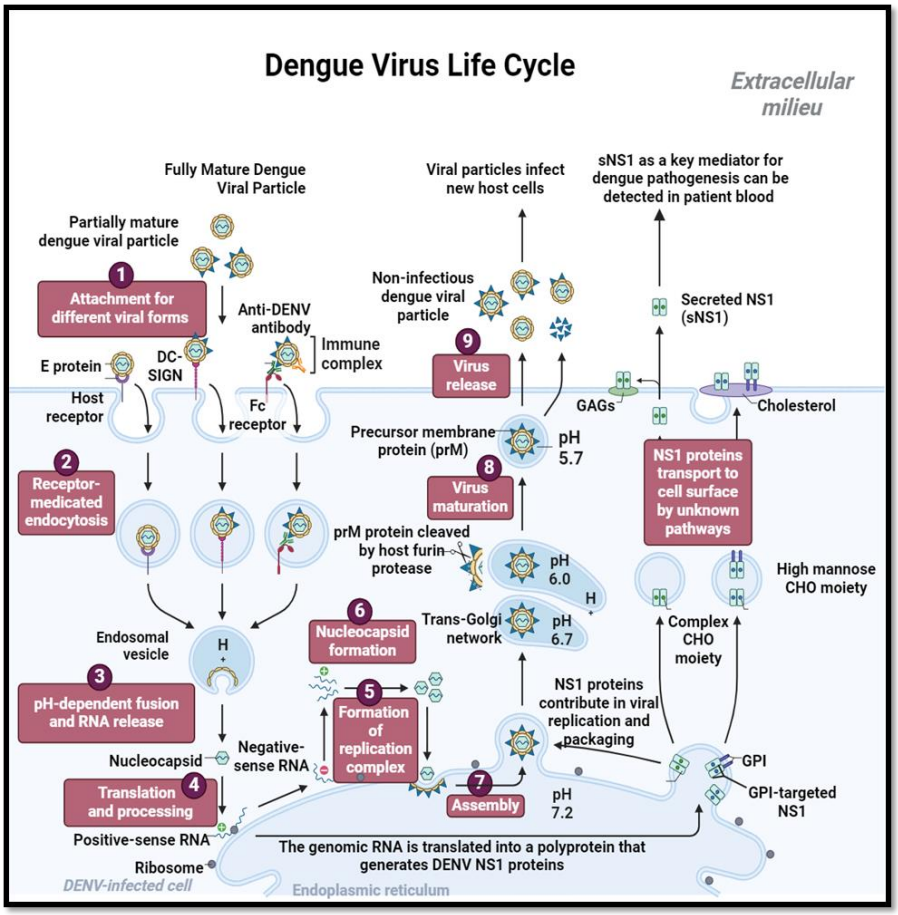

Fig. 2: Life-Cycle of Dengue Virus.

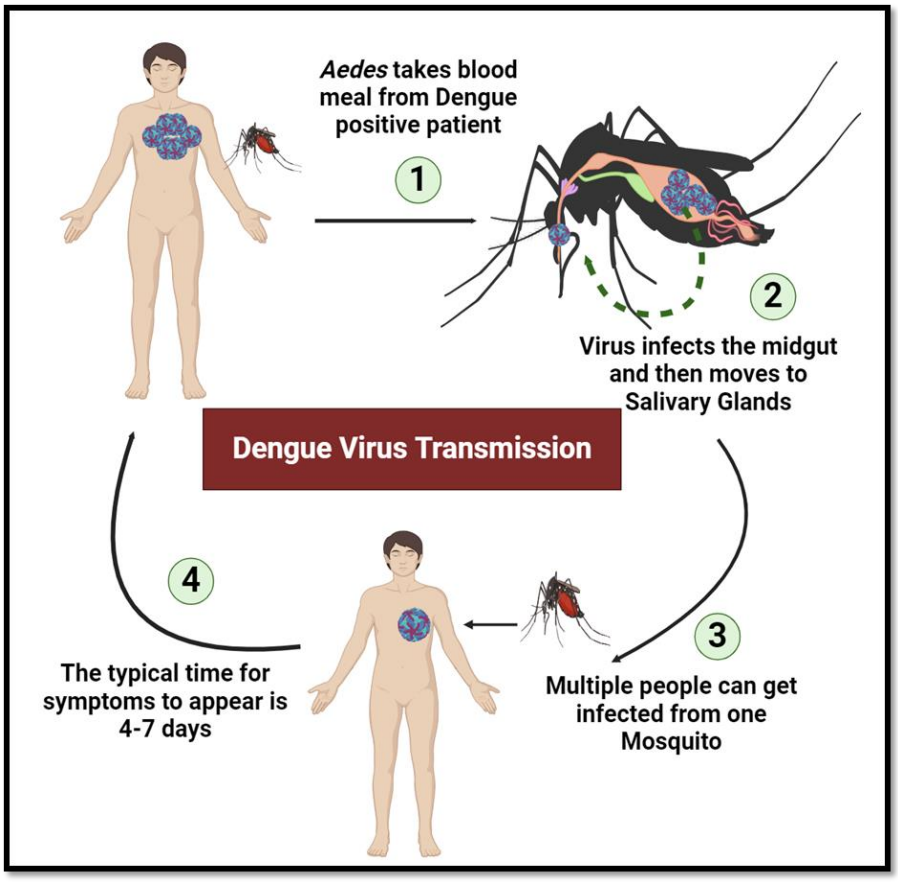

Fig. 3: Transmission of Dengue Virus.

Life Cycle of Chikungunya Virus

Replication cycle of Chikungunya virus (alphavirus) in susceptible cells (Figure 4) occurs in following steps:

1) Envelope protein-2 (E2) attaches itself to the surface of cells through an unidentified receptor and maybe glycosaminoglycans acting as attachment factors.

2) By means of clathrin-mediated endocytosis, CHIKV gains entry into the cell. The fusion peptide in Envelope protein-1 (E1) is inserted into the endosomal membrane as a result of endosome acidification.

3) The nucleocapsid is released into the cytoplasm upon the fusion of the viral envelope and endosomal membrane.

4) Positive-sense genomic RNA is released during nucleocapsid disintegration, and nonstructural protein (nsP) translation takes place.

5) The plasma membrane (PM) is modified by the assembly of four nsPs, genomic RNA, and maybe host proteins to create viral replication compartments (spherules) that hold viral dsRNA. To produce genomic, antigenomic, and subgenomic vRNAs, nsP1-4 localizes to the spherule neck and perform the role of a replicase.

6) Multiple spherules are housed in enormous cytopathic vacuoles (CPV-1) that are formed during spherule internalization. The spherules in CPV-I or at the PM are operational.

7) Following translation of subgenomic RNA into a structural polyprotein, capsid autoproteolysis releases the free capsid into the cytoplasm. After posttranslational modification, E2/E1 travel via the secretory route and arrive at the PM.

8) Capsid-genomic RNA interaction results in the formation of isosahedral nucleocapsids.

9) At the PM, nucleocapsids assemble with E2/E1, causing mature progeny virions to emerge.

10) Nucleocapsids are studded within the hexagonal E2/E1 lattices of CPV-IIs, which develop later in infection.

11) Most likely, CPV-IIs are used as transport vehicles.

12) Structural protein assembly locations.

13) permitting the development of mature virions.

14) Egress (Kujala et al., 2001; Frolova et al., 2010; Spuul et al., 2010).

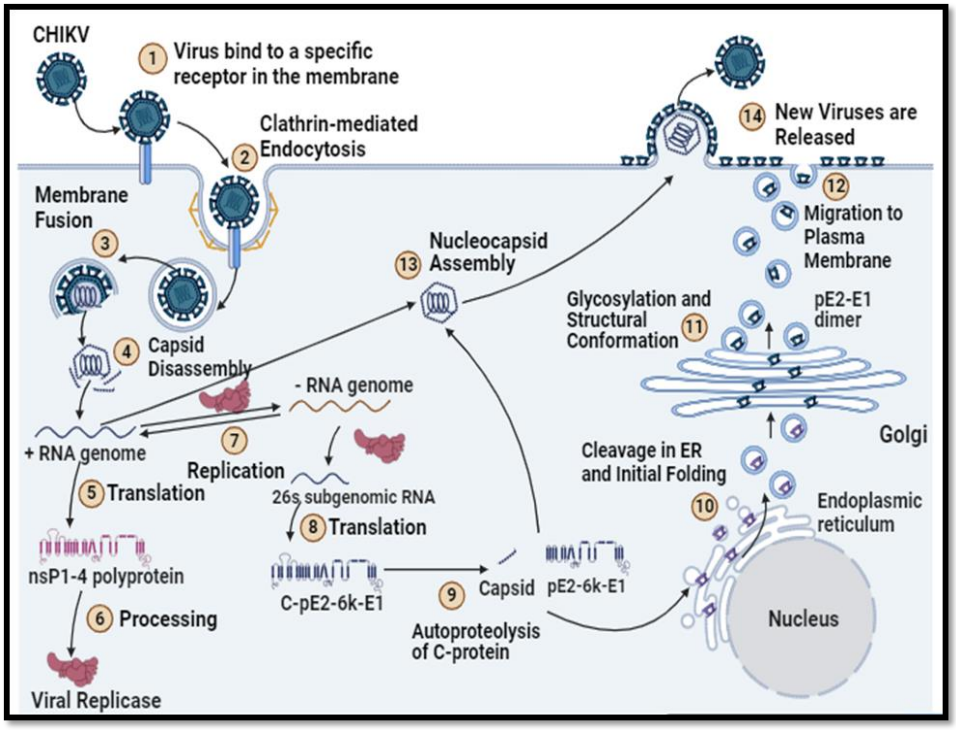

Fig. 4: Replication cycle of Chikungunya virus (alphavirus) in susceptible cells

Two Stages to the Chikungunya Infection

Acute Stage

Most people infected with CHIKV show acute symptoms two to six days after being bitten by the infectious mosquito (Josseran et al., 2006). The initial symptoms appear suddenly and persist for almost a week before clearing up on their own (Figure 5). The ten days following the commencement of the sickness are referred to as the acute stage (Simon et al., 2007). The most common symptoms include headache, arthralgias, back discomfort, and high temperature (Organization, 2008). Intense exhaustion, anorexia, myalgias, nausea, vomiting, and even momentary forgetfulness in older individuals are all linked to illness (Simon et al., 2011).

Chronic Stage

A newly infected patient may experience early aggravation, inflammatory relapses, chronic rheumatism, and a significant decline in quality of life following the brief recovery following the acute stage of the virus (Simon et al., 2007). This decline is more common in those over 40 and/or those with underlying medical disorders, especially rheumatic or traumatic diseases (Sissoko et al., 2009). The persistence of symptoms during the acute phase (Figure 5) is also linked to high CHIKV virus loads (Hoarau et al., 2010). A few weeks after the condition starts, further ocular abnormalities such as optic neuritis, retinitis, anterior uveitis, and episcleritis may appear and might occasionally result in blindness (Mahendradas et al., 2008).

After CHIKV infection, the most typical symptom is polyarthritis similar to Rheumatoid Arthritis (RA). The 1987 American College of Rheumatology criteria state that RA is characterized as follows: anti-CHIKV IgM and IgG antibodies are present; persistent arthritic symptoms from the start of CHIKV infection until the diagnosis of RA is made; and there is no other definitive diagnosis of arthritis (Bouquillard and Combe, 2009).

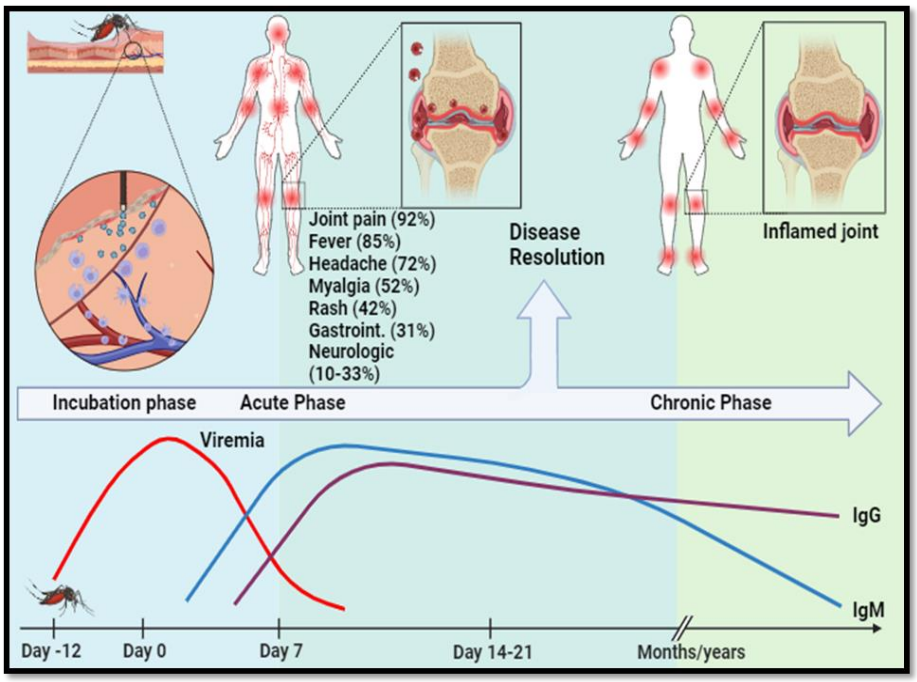

Fig. 5: Chikungunya disease progression with typical viremia and antibody immune response.

Zika Virus (ZIKV) Infection

In 1947, the Zika virus was discovered by a monitoring monkey in Uganda's Zika woodland. It is a member of the Flavivirus genus and family Flaviviridae. Subsequent epidemiological studies revealed that the Zika virus had extensively dispersed across Southeast Asia and sub-Saharan Africa. In Nigeria in 1954, there was the first recorded case of human infection; however, the virus's identity was later called into doubt, and Spondweni was assumed to be the culprit. In Uganda, reports of the earliest known human infection date back to 1962–1963 (Wikan and Smith, 2016).

Life Cycle of ZIKV

ZIKV adheres to a host cell's surface before entering through a procedure known as endocytosis (Figure 6). The virus enters the cytoplasm after combining with the endosomal membrane deep within the cell. The virus's genome is released by the viral particle. Translating a single polypeptide from viral RNA into 10 different proteins, the virus duplicates its genome. On the surface of the endoplasmic reticulum, viruses clump together. The trans-Golgi network carries the immature virus particles until they reach adulthood and are infectious. Once they leave the cell, the evolved viruses may infect other cells (Acosta-Ampudia et al., 2018).

Clinical Manifestations of ZIKV Infection

In most cases, a ZIKV infection is asymptomatic. When it manifests, symptoms include conjunctivitis, a wide pruritic maculopapular rash, arthralgia, and myalgia. The illness normally goes away after 3 to 12 days of incubation (Figure 7). Many injuries to the central and peripheral nervous systems, including meningoencephalitis, GBS, TM, ophthalmological symptoms, and other neurological problems, have been connected to ZIKV (Acosta-Ampudia et al., 2018).

Yellow Fever Infection

Mosquitoes carry the flavivirus that causes yellow fever, which is common in tropical parts of Africa and South America. Travelers and inhabitants of endemic places are still at danger for this disease, despite the fact that there has been a trustworthy vaccination for roughly 70 years. The disease has historic significance (Monath and Vasconcelos, 2015).

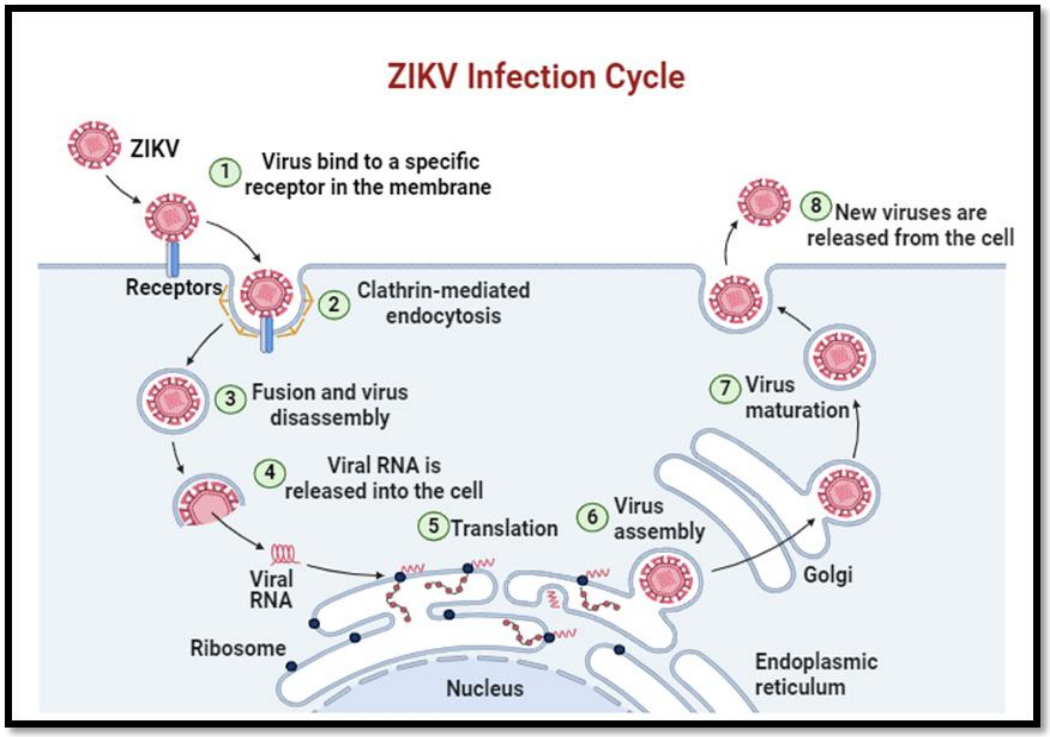

Fig. 6: Infection Cycle of ZIKV

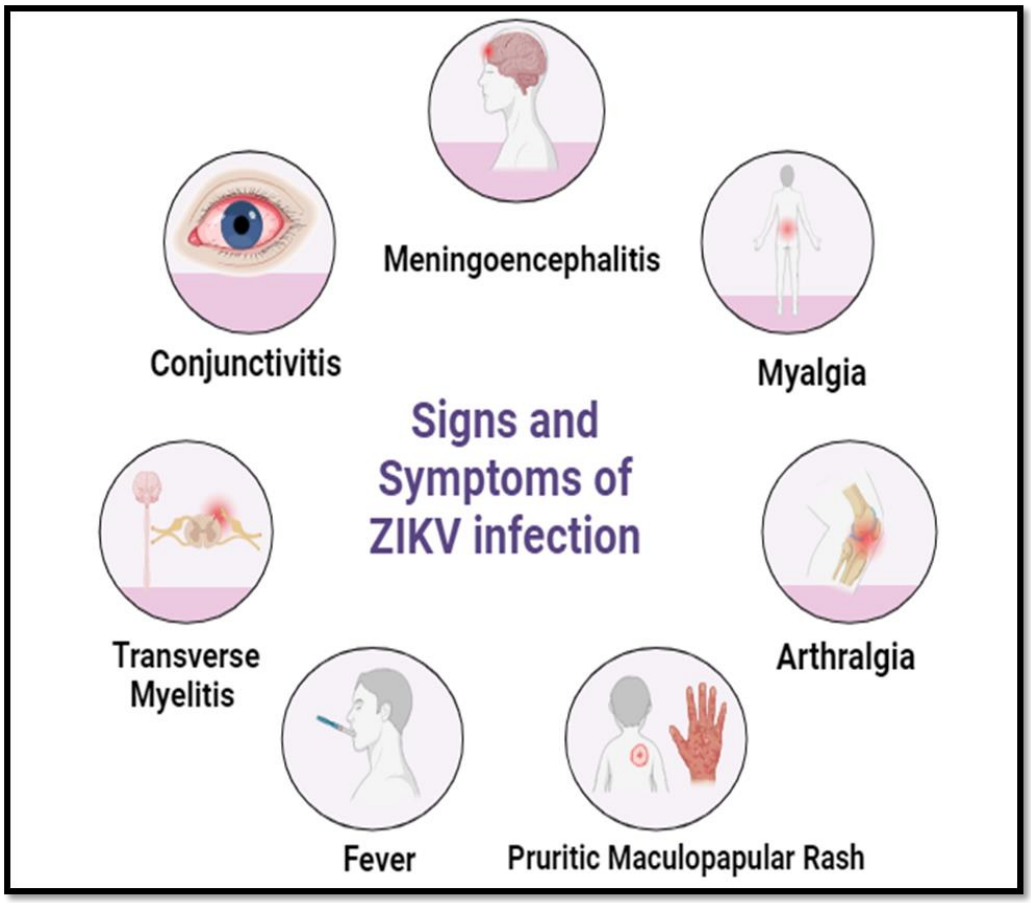

Fig. 7: Signs and Symptoms of ZIKV infection.

Replication Cycle of Yellow Fever Infection

The yellow fever virus (YFV) binds to host cell receptors and then enters the host through receptor-mediated endocytosis to start its reproduction cycle. In order to promote translation and replication in the cytoplasm of the host cell, the released viral RNA genome is used by the RNA-dependent RNA polymerase (RdRp) (Figure 8). RNA genomes and freshly produced viral proteins then come together to form new virus particles, which develop by taking on an envelope made of host cell membranes. Ultimately, the replication cycle is continued by the release of mature virus particles through budding, which infect nearby cells (Gubler, 2007).

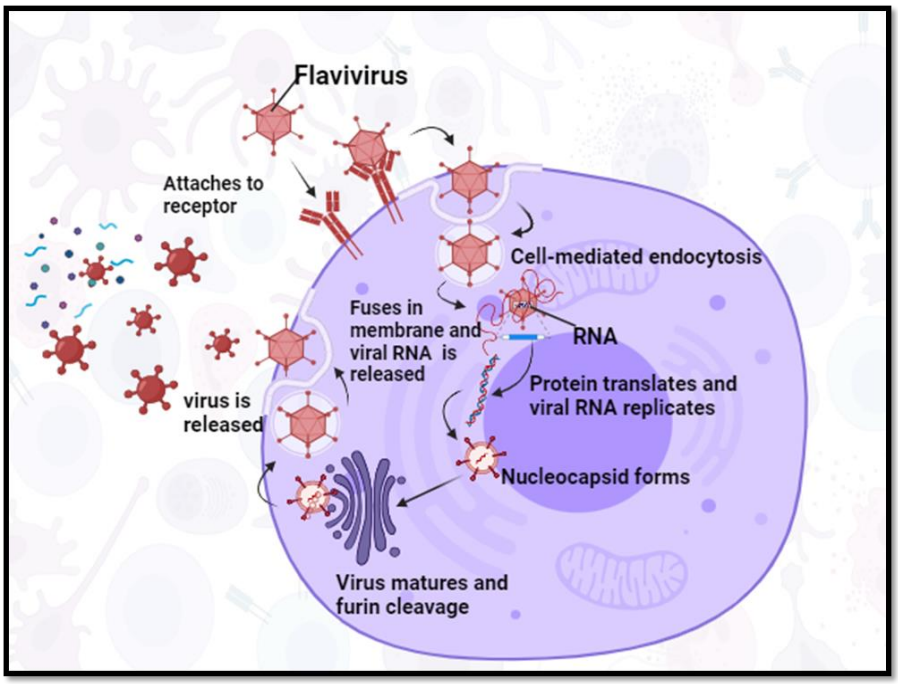

Fig. 8: Replication Cycle of Yellow Fever Infection.

Transmission of Yellow Fever Virus

The virus can only infect a comparatively small number of hosts before becoming productively infected. The primary vectors of transmission in the wild are blood-feeding mosquitoes, primarily from the genera *Haemagogus* and *Aedes* in South America and Africa, respectively, as well as transovarial transmission via these vectors. The disease known as "Jungle Yellow Fever" is occasionally transmitted to humans by sylvatic mosquitoes that bite them after feeding on a viremic monkey. But *Aedes aegypti*, a species that breeds in water-filled receptacles inside or close to houses, can also serve as the viremic host for the spread of the disease between humans (Monath and Vasconcelos, 2015).

Vector control: A strategy to prevent Human Life-Threatening Diseases

As was previously said, one mosquito serves as the main vector for a number of serious human diseases. As such, controlling the one mosquito species is more effective than combating each disease as it emerges.

In order to protect humans against vector mosquitoes, chemicals can irritate, repel, or kill them (Grieco et al., 2007). Several research work has focused on artificial substances (Pothikasikorn et al., 2007; Polsomboon et al., 2014) designed to lessen disease transmission and mosquito populations (Noosidum et al., 2008). However, due to the issue of toxicity, non-biodegradable material effects, vector resistance to synthetic insecticides, and detrimental effects on non-target organisms, new strategies utilizing natural products are required to control harmful insects and disease vectors (Jantan et al., 2005).

Research has indicated that insect repellents function in a comparable way. Each repellent exerts its deterrent effects by binding to and interacting with particular insect gustatory and odorant receptors, which changes their activity (Xu et al., 2014). With 200 million users globally, N,N-Diethyl-meta-Toluamide (DEET) is the repellant that has been most frequently used for nearly 50 years (Syed and Leal, 2008) because of how well it protects troops (Das et al., 1999). However, research has demonstrated that using DEET can have a number of dangerous negative effects, such as skin irritation and dermal infection (Das et al., 1999; Patel et al., 2012). Therefore, research is being done to determine whether botanicals may effectively repel mosquito vectors and serve as a viable substitute for industrial insecticides (Warikoo and Kumar, 2015). Mosquito breeding places have increased as a result of insufficient waste management systems and water supplies. Due to them, the number of mosquito-borne illnesses that now affect over 700,000,000 people worldwide has increased dramatically (Jantan et al., 2005). Because natural product components break down quickly, are inexpensive, do not persist in the environment, and do not bio-accumulate, it has been suggested that they could take the role of synthetic pesticides in the control of mosquitoes (Ajaegbu et al., 2022).

Melissa officinalis:* A Medicinal Herb to Control *Ae. aegypti

M. officinalis, or lemon balm, is one of the most significant herbs among the autochthonous therapeutic plants of the genus *Melissa*. In Central and Southern Europe as well as Asia, *M.officinalis* is a common plant. In sandy and shady places, lemon balm grows spontaneously (Schnitzler et al., 2008) although it has also been observed to grow at altitudes from sea level to the mountains on moist wasteland. This plant is classified according to the following taxonomy; Plantae is the kingdom; Tracheophyta is the division; Speramtophyta is the subdivision; Magnoliopsida is the class; Asteranae is the superorder; Lamiales is the order; *Melissa* is the genus; *officinalis* is the species (Miraj et al., 2017).

The insecticidal characteristics of *M. officinalis* essential oil are covered in this chapter, along with how it works as a repellent and larvicidal against *Ae. aegypti*, the critically ill species that causes dengue fever.

Chemical Constituents in Essential Oil (EO) of *M. officinalis*

It has been shown that the EO sample of *M. officinalis* has around 24 components, the bulk of which are citronellal (22%), β-citronellol (14%), geraniol (17%), geranial (11%), and geranyl acetate (12%) (Baranitharan et al., 2016). Studies conducted on *M. officinalis* reveal that citral, a combination of geranial (α-citral) and neral (β-citral) isomers, is the main volatile constituent (Pinto et al., 2015). The study conducted by (Luz et al., 2014) shows variations in the chemical composition of the essential oil (EO) extracted from *M. officinalis* leaves collected in the summer and winter, both in terms of quantity and quality, indicating the influence of the seasons. As per the quantification by external pattern, the concentration of geranial and neral was higher in the summer season (47% geranial and 31% neral) compared to the winter period (16% geranial and 9% neral). From a phytochemical perspective, EOs and other natural plant extracts have been viewed as significant substitutes, especially given their wide range of chemical composition (Martins et al., 2021). Geographical and agronomic circumstances, including soil, plant genotypes, phytogeographic factors, microclimatic conditions, and plant genotypes can all influence the amount and range of EO present in plants of the same species grown in various places. But generally speaking, the essential elements stay the same; their levels of concentration simply change (Kumar et al., 2011).

Larvicidal activity of *M. officinalis* against *Ae. aegypti*

Larivicidal potential is categorized using Lethal Concentration (LC). When an EO's LC_{50} > 100 mg/L, it is deemed inactive; when it is less than 100 mg/L, it is considered active; and when it is less than 50 mg/L, it is considered highly active (Dias and Moraes, 2014). According to (Martins et al., 2021)the EO of *M. officinalis* showed highly effective larvicidal action by maintaining LC_{50} < 50 mg/L as LC_{50} is 40 mg/L. At different concentrations (125, 250, 500, and 1000 ppm), the larval mortality of *M. officinalis*' EO against *Ae. aegypti* is 0, 12, 12, and 20%, respectively (Onah et al., 2022). When *M. officinalis* is used as an EO against *Ae. aegypti*, the larval death rate is 72.5% (Sheng et al., 2020). The LC50 and LC90 values for essential oil's capacity to inhibit *Ae. aegypti* larvae are 61 and 88 mg/L respectively (Koliopoulos et al., 2010).

Table 1: The LC_{50} and LC_{90} Values of five compounds (Citronellal, β-Citronellol, Geraniol, Geranial and Geranyl acetate) of essential oil of *M. officinalis*

Major Compounds	LC50 (ppm)	95% CL (LCL–UCL)	LC90 (ppm)	95% CL (LCL-UCL)
Citronellal	85	(62–102)	159	(138–192)
β-Citronellol	109	(88–134)	185	(162–257)
Geraniol	98	(79–125)	172	(145–238)
Geranial	145	(129–169)	248	(228–287)
Geranyl acetate	126	(105–142)	213	(195–253)

The values are given as the average of five replications. LCL: Lower confidence limit; UCL: Upper confidence limit; LC50: Lethal concentration 50; LC90: Lethal concentration 90; CL: Confidence Limit (Baranitharan et al., 2016). In the literature, other compounds of EO of *M. officinalis* (citral, carvona and limonene) chemotypes showed effective larvicidal activity with LC50 = 7 mg/mL, LC50=29 mg/mL and LC50 = 31 mg/mL, respectively (Silva, 2019).

Repellent activity of *M. officinalis* against *Ae. aegypti*

Relative repellent effectiveness of 1% essential oil of Melissa against laboratory mosquitoes of *Ae. aegypti* on guinea-pigs and human hand skin is 92 and 60% respectively (Oshaghi et al., 2003). *M. officinalis* essential oil has notable mosquitocidal property. Repellent activity of different compounds of *M. officinalis* is up to 120 minutes against *Aedes* mosquitoes (Baranitharan et al., 2016). Essential oils of *M. officinalis* have a repellent effect on adult *Ae. aegypti* at "high" doses of 0.2 mg/ cm^2, "moderate" doses of 0.08 mg/ cm^2, and "low" doses of 0.04 mg/ cm^2, with an average of 0 and 5 landings. At both high and moderate dosages, this essential oil provides complete protection against mosquitoes (Giatropoulos et al., 2018).

Conclusion

The international concerns are human infections spread by insects, especially those carried by mosquitoes, such as viruses like Dengue, Zika, and Chikungunya that are carried by *Aedes* mosquitoes. In the last fifteen years, insecticide-based methods have been used to reduce mosquito vectors in order to contain viral epidemics. Alarming rates of pesticide resistance in insect populations, however, are already posing a danger to disease control and necessitating the development of new, targeted tactics that can lower vector-mediated transmission. An alternative and successful method of eliminating annoying insects has been shown by numerous studies to be the use of essential oil components and their derivatives. Because most essential oil ingredients are determined to be harmless to mammals, birds, and the aquatic ecology, essential oils are justified as green insecticides. *M. officinalis* is one of the crucial herbs having the insecticidal effects. Without endangering people or the environment, its essential oils can be utilized to create mosquito-repellent personal protection compositions that are both affordable and effective.

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