DENV Infection: a comprehensive review and framework for experimentation to assess new therapeutics

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The Dengue virus (DENV) infects millions of people worldwide, particularly in countries with high populations of mosquitoes. It belongs to the *Flavivirus* family and causes severe, sometimes fatal symptoms. When a person first becomes infected, they may experience mild symptoms such as a fever and a skin rash (maculopapular) around the body. If not treated, the patient may experience hemorrhagic fever, which is potentially caused by a low platelet count. The symptoms of hemorrhagic fever include internal bleeding of vital organs such as the intestines and the liver. If not treated, the patient will go into shock due to significant loss of blood. This could eventually result in the death of the patient. Currently, there is no widely available vaccine/medicine to prevent or treat DENV infection, nor is there any pharmaceutical option to mitigate the symptoms. We are surveying scientific literature to identify and assess possible molecular compounds that can inhibit infection by DENV. Many studies have been conducted in cell culture, which gives us quantitative information about the kinetics of the binding of the DENV proteins to cells. We can use this information to gauge how well certain compounds can prevent DENV attachment that will eventually cause infections in humans. We will not only survey the literature but also propose ideas for how scientific experiments could be performed to improve our understanding of possible pharmaceutical interventions.

Dengue, a viral infection, is a global health crisis, according to the European Centre for Disease Prevention and Control. Since the beginning of 2024, there have been over 13 million cases of Dengue and 8500 associated deaths [1]. However, there is no antiviral treatment available: individual or cocktail. According to the National Institutes of Health, a virus is an infectious microbe consisting of a nucleic acid segment, either DNA (DeoxyriboNucleaic Acid) or RNA (Ribonucleic Acid) [2]. Some viruses, also called enveloped viruses, comprise a protective protein coating, while others, called non-enveloped viruses, have no protective coating. Regardless of the structure of a virus, it needs entry into a host cell, where it takes advantage of the resources and energy of the cell to replicate and spread. By studying viruses at a molecular level, we will be able to understand how they interact with host cells, which in turn will enable us to find ways to fight them. The reason I want to focus my study on the DENV is because it affects millions of people worldwide, especially in tropical countries, and can potentially cause hemorrhagic death.

There are four serotypes of the virus: DEN-1, DEN-2, DEN-3, and DEN-4; unfortunately, infection by one serotype does not guarantee immunity from others. In fact, subsequent infection from other serotypes can lead to life-threatening outcomes [3]. Dengue is spread by mosquitoes, specifically those of the Aedes species, which contain a double-stranded RNA-binding protein called *Loqs2*. *Loqs2* helps control the population of DENV inside the body of the mosquito thus preventing the virus from infecting the mosquito, but still retaining the capability of the mosquito's role as a vector [4]. We can eliminate populations of these mosquitos by using

substances that contain DEET. However, we cannot eliminate all the mosquitos as it would break the logistic curve of its population growth. Instead, we should develop medical drugs that can disrupt the virus' infection cycle. Some mechanisms that would disrupt viral infections include inhibiting viral replication, preventing viral DNA integration into the host genome, and primarily preventing viruses from penetrating the host cells. Papaya leaf extract has been considered as a possible treatment option with promising results from initial studies [5]. Rich in vitamin C, vitamin A, and phytosterols, the consumption of this extract will potentially increase the H+ (positively charged hydrogen ion) concentration and decrease the pH of the cell environment, thus making it acidic. The increased acidity of the cell environment will possibly act as a barrier for the DENV and prevent it from attaching itself to the host cell. If the DENV cannot make copies of itself, then it will be unable to cause an infection.

DENV is part of the *Flavivirus* family. Since the first virus of this type discovered was the Yellow Fever virus, which causes jaundice - the yellowing of the skin and eyes of the patient, researchers named this family of viruses *Flavivirus,* with *flavus* meaning *yellow* in Latin [6]. Flaviviruses are single-stranded RNA viruses that are transmitted by arthropods: mosquitoes and ticks. DENV is transmitted by the female Aedes Aegypti mosquito species. DENV is prevalent in the tropical regions of the world where the Aedes Aegypti mosquito can thrive in warm and humid conditions. The other species of Flaviviruses that cause diseases include West Nile, Zika, Japanese Encephalitis, etc. Unfortunately, there is no treatment currently available for any of these diseases, leading to high probabilities of complications arising from their infections in humans.

In this paper, I will review the molecular mechanisms of the DENV infection and the current therapeutics that are available to treat it. I propose that papaya leaf extract should be further considered as a natural therapeutic because of its potential to fight DENV.

Structure of DENV

The DENV is a roughly spherical virus with a diameter of 50 nanometers (nm). To put this into scale, a monocyte, one of the immune cells that DENV targets, measures 20 micrometers (μm) in diameter, which is 400x larger than a DENV. The protective coating on the DENV is called a capsid, a 20-faced protein shell. Ten types of proteins are present on the capsid, seven of which play a vital role in viral replication and assembly. These proteins include NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The innermost part of the virus is the nucleocapsid, a structure comprising of the viral genome and C (Capsid) proteins. Surrounding the nucleocapsid is a viral envelope made of a lipid bilayer. Embedded in the viral envelope are structural proteins E (Envelope) and M (Membrane) that form an icosahedron, a 20-sided polyhedron coating across the top of the lipid bilayer. This coating forms a protective outer layer and controls the entry of the virus into human cells [7].

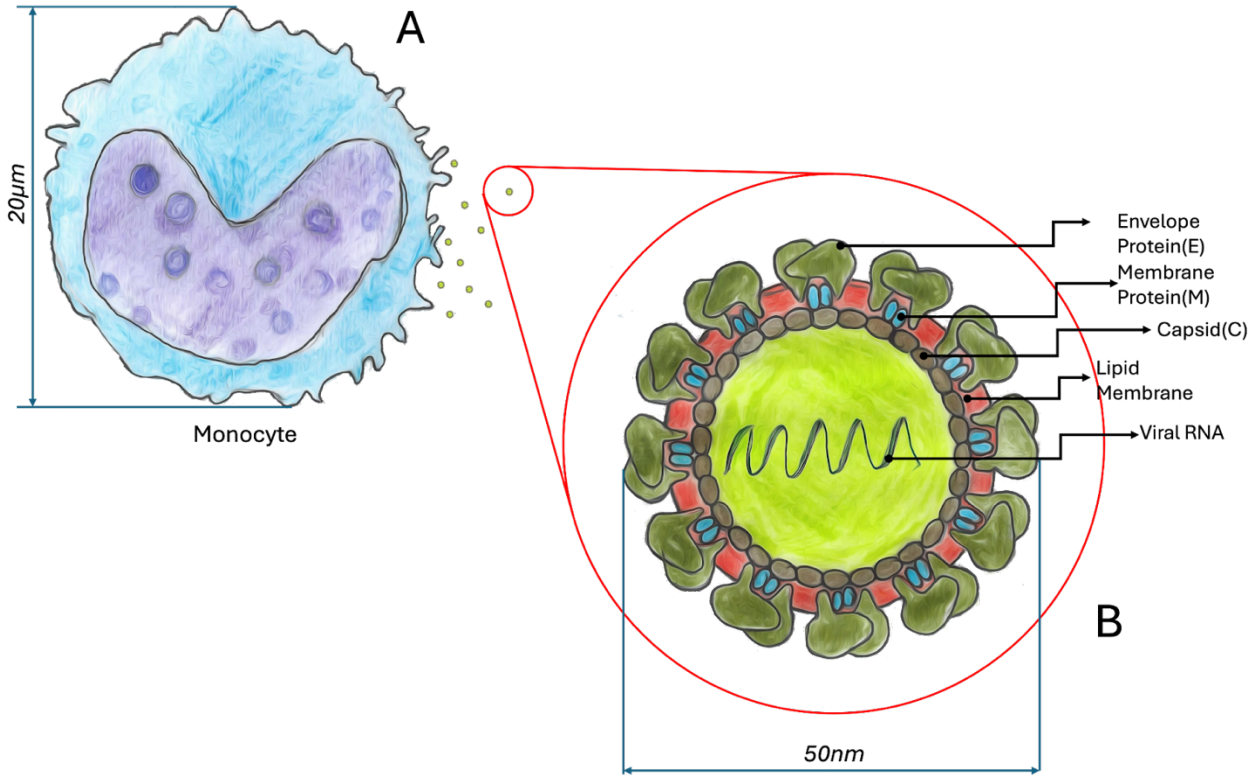

Figure 1: A. monocyte, one of the biggest cells that DENV attacks. Monocytes are 400x bigger than the DENV. Therefore, potentially, 611,464 DENVs can cover a monocyte all at once!
B. Cross-section of a DENV showing viral RNA protected by the Capsid, Lipid membrane, Membrane protein, and Envelope protein.

Human cells targeted by DENV

When an infected Aedes Aegypti mosquito bites a human, DENV enters the skin of the victim. DENV infects the nearby skin cells called keratinocytes. Specialized immune cells called Langerhans cells also get infected. The infected Langerhans cells travel through the lymphatic system to the lymph nodes to alert the immune system of the virus attack. In response, white blood cells called macrophages and monocytes are alerted to attack and destroy the virus.
Normally, these white blood cells can attack and ingest the viruses that enter the body. However, DENV has the ability to bind itself to specific receptors found on these cells to gain entry into them and replicate. The infected monocytes and macrophages become carriers of the DENV, spreading the virus throughout the body as they travel through the lymphatic system. Apart from the skin cells and the white blood cells, DENV also infects bone marrow cells and macrophages found in both the liver and spleen [8]. Therefore, it is important to target the entry of the Dengue virus into host cells to control the infection.

The journey of the DENV's entry into the cell begins with the attachment of its spike protein to the host cell-surface receptors and ends with the DENV delivering its

genome to the host cell cytoplasm - the entire process orchestrated by Clathrin-Mediated Endocytosis (CME) [9]. CME is an important mechanism that allows mammalian cells to absorb essential molecules like nutrients, hormones, and other cargo through the cell surface - a process essential to the cell's survival. Viruses take advantage of this host cell mechanism to enter the cell and infect it. Because of the complexity of the DENV's entry mechanism, we are presented with a challenge in coming up with a drug to combat DENV.

I posit that the solutions require a deep understanding of the biochemistry of DENV infection.

Biochemistry of Dengue virus infection - details about the interactions that take place between the DENV and the host cell at the nanoscale

The E protein found on the spike protein of DENV is made up of three parts: Domain I, Domain II, and Domain III. Domain I is a hinge connecting Domain II and III and contributes to the change of the spike protein structure under low pH conditions inside the endosomes of the host cell. Domain II consists of residues of a hydrophobic amino acid, which contribute to the fusion of the virus membrane with the host cell membrane, leading to viral entry into the host cell. Domain III interacts with the host receptor molecules directly. This region of a mature DENV is glycosylated; in other words, it is attached to one or more oligosaccharides at its end, with which it can bind with the carbohydrate-detecting host cell receptors, thus entering the cell (Refer to Figure 2.)

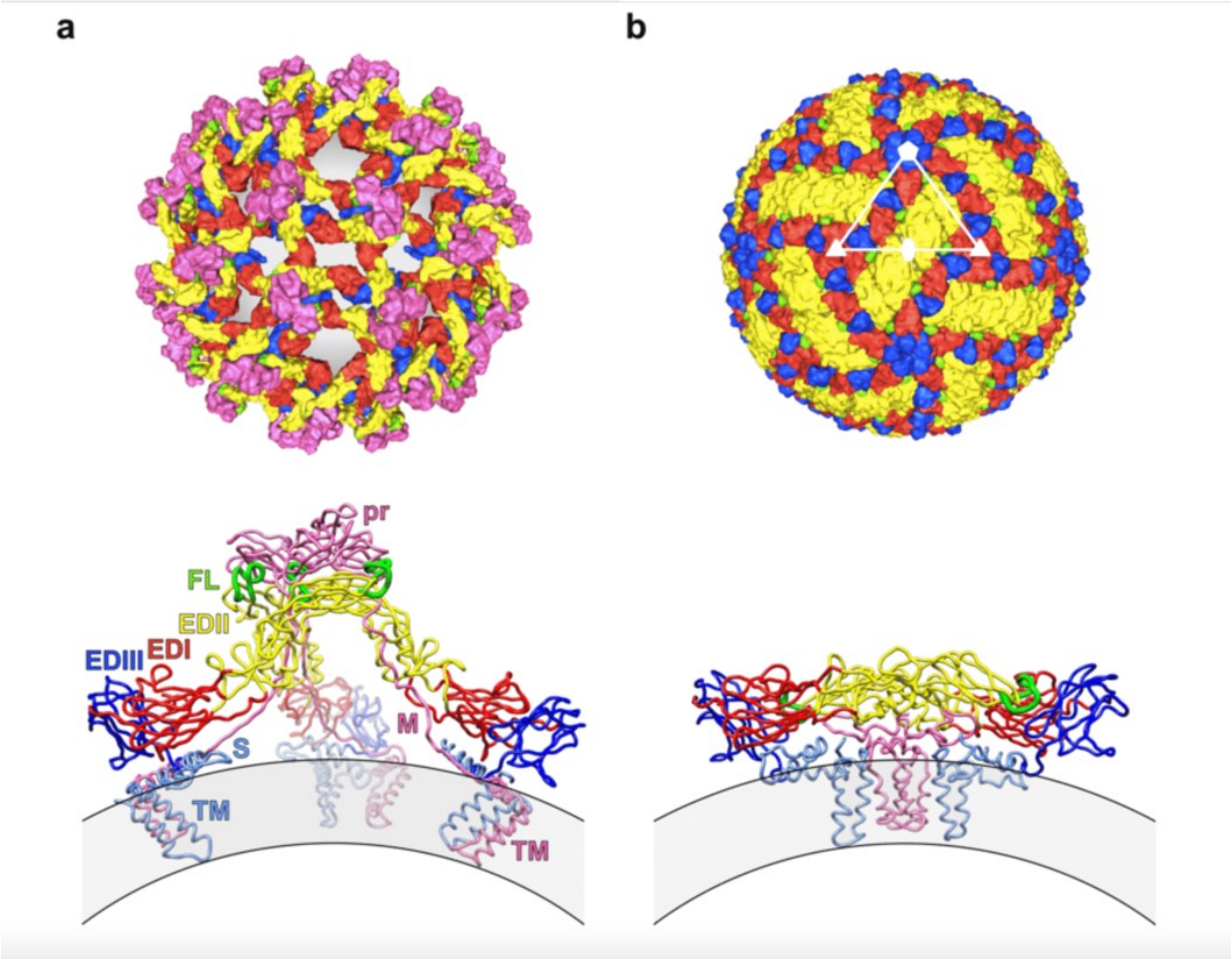

Fig 2: These images are taken from [10]. (a) Upper panel: Cryo-electron microscopy (cryo-EM) structure of the immature DENV particle. Lower panel: Side view of a single trimeric prM–E spike in ribbon form. (b) Upper panel: Cryo-EM structure of the mature DENV particle. The mature infective DENV is formed in the Golgi apparatus of the host cell. The acidic environment at the end of the Golgi apparatus is conducive to bringing about changes in the structure of a DENV to make it infectious. Lower panel: Side view of a single E protein dimer and the underlying M proteins in ribbon form. The host-derived lipid bilayer is depicted in gray. E protein domain I (EDI); E protein domain II (EDII); E protein domain III (EDIII); fusion loop (FL); stem region (S); transmembrane anchor (TM); precursor peptide (pr); membrane protein (M).

When a DENV attaches itself to the host cell receptors through its spike protein, the host cell's Adapter Proteins AP-2 attach themselves to the receptors. Molecules of a structural protein called Clathrin arrive at the site and attach themselves to AP-2. The cell membrane at the occupied receptors then begins to curve inwards. This process marks the beginning of the formation of a vesicle, an important step in the endocytosis process. Eventually, after the membrane curves inwards far enough so that the entire DENV gets enclosed by the host's cell membrane, the formed vesicle is pinched off at the outer cellular area. This matured Clathrin-coated vesicle protects the DENV and its RNA. Clathrin uncoating then follows. The membrane of the DENV then fuses with the vesicle's membrane, leading to the release of the nucleocapsid

into the cytoplasm. The protein of the capsid is removed, freeing the single-stranded RNA for replication [11]. Once inside the cytoplasm, the RNA is replicated using the host cell's resources. The newly transcribed RNA is packed inside a nucleocapsid. The structural proteins are then synthesized around the nucleocapsid, which is eventually glycosylated to form a mature DENV. The newly synthesized mature DENV is released from the host cell through exocytosis, a process complementary to endocytosis, allowing it to infect neighboring cells.

By developing molecules that can disrupt at least one stage of the virus infection cycle, we can successfully prevent the virus from causing dengue fever and eventually prevent complications and death.

Studies have shown that host cell receptors like nLc4Cer (found on epithelial cells), DC-SIGN (adhesion molecule on Dendritic cells), L-SIGN (found on endothelial cells of liver and lymph nodes), and Mannose receptor (found on dendritic cells and macrophages), are the main sites where all four serotypes of DENV can dock themselves to (See Table 1). DENV serotype 2, being the most widespread, is known to dock onto Heparin Sulphate Receptors (HSR) [12, 13, 14], a receptor found on all cell types in the human body. This binding typically occurs through electrostatic interactions between the highly negative charges of HSR and the basic amino acid portions of DENV2 spike proteins with a net positive charge. Several molecules have been found to prevent the adhesion of DENV2 onto the HSR. Heparin, a drug on the World Health Organization's essentials list, has been widely used as an anticoagulating agent. Later, it was found to prevent virus attachment to heparan-sulfate receptors on host cells [15]. Experiments using heparin to inhibit DENV attachment to Heparan-sulfate receptors have indicated success [14]. However, the anti-coagulating nature of Heparin makes it a non-candidate as a therapeutic for DENV since the reduction in platelet count and internal bleeding is the problematic outcome of this disease. However, in the initial stages of the infection, there is a drop in the platelet count, which might make it possible for us to use Heparin for treatment and potentially prevent platelet counts from dropping further and leading to Dengue Hemorrhagic Fever. Specifically, the decision to administer Heparin should be based on the circulating NS1 (antigen) values, the serotype of the virus, the severity of the disease (Dengue Fever or Dengue Hemorrhagic Fever), and immunological status (primary or secondary infection) [16] (See Figure 3 for structures and electrostatic nature of Heparin, Heparan-Sulphate, and the E protein of DENV).

Molecule	Type	Cell type	Serotype
DC-SIGN	C-type lectin	Monocyte-derived dendritic cells	DENV 1, 2, 3, and 4
Heparan sulfate	Glycosaminoglycans	Vero CHO K1	DENV 2
nLc4Cer	Glycosphingolipid	K562 BHK-21 LLC-MK2	DENV 2
Mannose receptor	Protein	NIH3T3 Monocytes Macrophages	DENV 1, 2, 3, and 4
High-affinity laminin receptor	Protein	HepG2 PS clone D	DENV 1, 2 and 3
CLEC5A	C-type lectin	Macrophages	DENV 1, 2, 3, and 4
L-3	Glycosphingolipid	AP-61	DENV 2
40- and 45-kDa glycoproteins	Glycoprotein	C6/36 cells	DENV 4

Table 1 [17]: Carbohydrate receptors on host cells targeted by the four serotypes of DENV. DC-SIGN, Mannose receptor, High-affinity laminin receptor, and CLEC5A receptors are mostly found on immune cells such as macrophages, monocytes, neutrophils, and dendritic cells. These are the receptors to which all serotypes of DENV can bind themselves, which is evidenced by widespread damage done to the immune system by DENV.

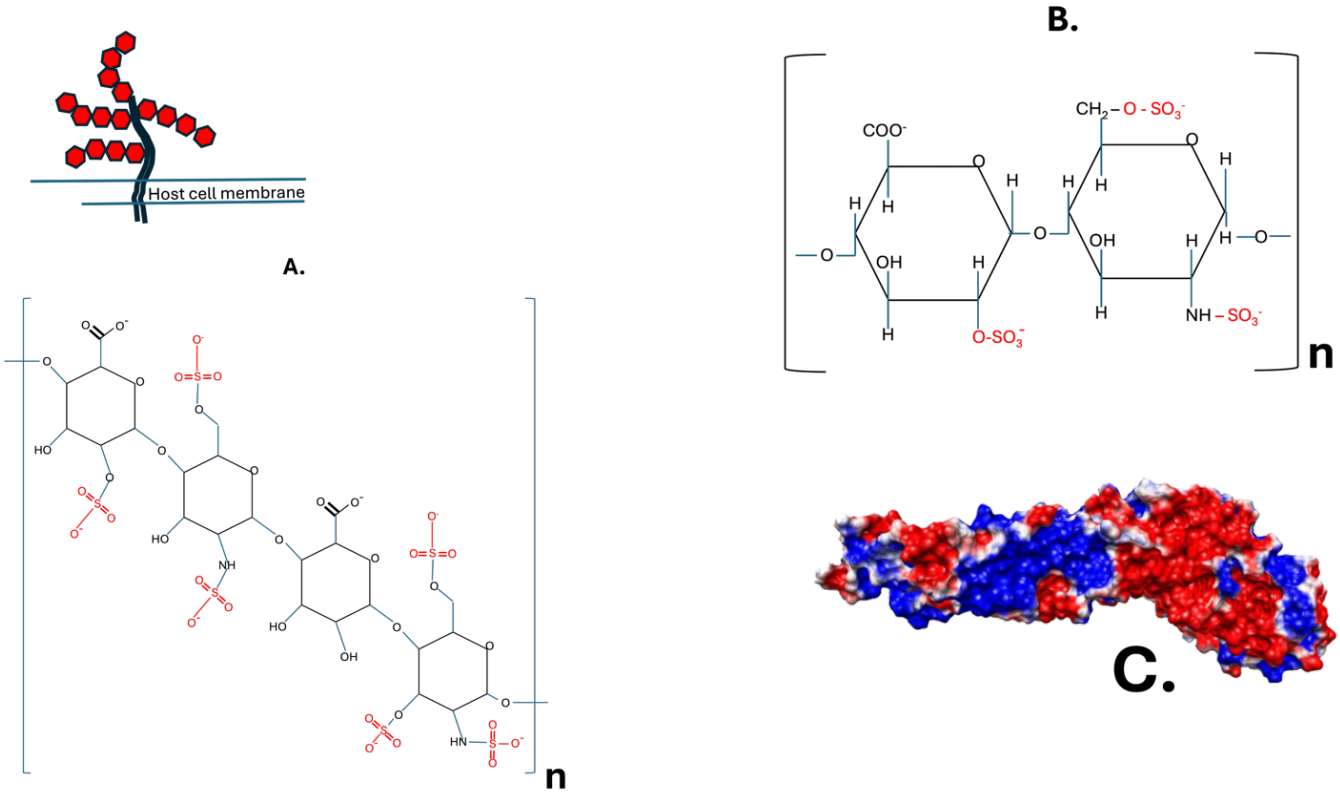

Figure 3: A. The molecular structure of Heparan-sulfate (HS) and the host cell surface receptor containing chains of HS molecules. These receptors are predominately on epithelial or skin cells. Epithelial cells are the cells that DENV attacks first when an infected mosquito bites a human. Only serotype DENV2 can attach itself to HS receptors but since DENV2 is the most common type of DENV, it is important to understand how DENV2 will interact with HS host cell receptors. B. The molecular structure of Heparin, a drug that has a structure like HS, with highly negative sulfate molecules. C. [18] Electrostatic potential mapping of the E protein monomer. The red regions have a net negative charge, and the blue regions have a net positive charge. Heparin will compete with HS sites on the host cell receptors for binding with the positive sites of the E protein, the site of Domain III, neutralizing it.

More recently, Carica Papaya (CP) leaf extract has been used successfully as a home remedy to improve the prognosis of Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF) [19] [20]. Various researchers have conducted experiments to confirm the effectiveness of the CP leaf extract in improving the outcome of DF and DHF. They found that the administration of CP leaf extract led to an increase in the platelet count of the patient. Since none of these studies have been conducted in a controlled manner, it is too early to establish the efficacy of the CP leaf extract. Moreover, researchers have not been able to establish a direct correlation between the administration of CP leaf extract and the increase in the platelet count. However, CP leaf extract contains beneficial compounds like flavonoids and vitamins with therapeutic properties. If we can find specific compounds in the CP leaf extract that can, for example, bind to the DENV envelope protein to neutralize it, preventing the virus from entering the host cell, then we might

be able to conduct controlled experiments to find out the dosage and efficacy of the CP leaf extract. In addition, with the knowledge of the structure of these compounds, we might be able to develop a synthetic antiviral drug that will be available to people worldwide in their fight against DENV.

Currently, the only beneficial effect of CP leaf extract known in humans is its ability to improve platelet count by increasing the production of megakaryocytes that eventually increase thrombocytes [20]. I have developed an experimental setup that will use statistical measures to test the hypothesis that CP leaf extract has the beneficial effects of neutralizing and/or killing DENV and of its ability to protect human cells from DENV attack.

Experimental setup to determine Carica Papaya leaf extract's efficacy in slowing down cell death

To test the hypothesis that Carica Papaya leaf extract will reduce the rate of cell death, I have proposed the following experimental setup. For this experiment we will need, epithelial cells from the mammalian cell line.

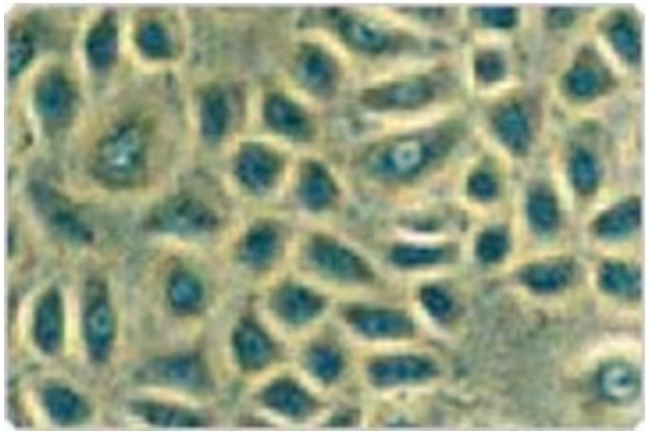

Figure 4: Epithelial cells from the human cell line [21]. I chose epithelial cells as opposed to other cells because DENV infects this cell first when the mosquito bites a human. Another reason for choosing this
type of cell is because they are flat, making it easier to observe DENV binding to the cell and infecting it.

I will now explain a theoretical framework for how an experiment could be done to test the efficacy of the papaya leaf extract. The control sample will have *X* number of epithelial cells with *Y* number of DENV virus particles. However, X will be a more accurate measurement because human cells are easier to count than virus particles. As seen in Figure 1, a white blood cell is 400 times larger than a DENV. Also, you can easily see moat human cells under a standard microscope, while for DENV, we will need an electron microscope. In the treatment dish, there will be the same number of epithelial cells and DENV, except that there will also be *V* milliliters

of Carica Papaya extract. I chose not to use specific numbers because the amounts of each material could be different depending on the experimentalist. For example, a Chemical/Biomedical Engineer would want to use large quantities of these materials because they are working on a large scale, while a biologist or chemist might use small quantities of these materials since they are working on a small scale. Currently, there are two methods to determine the amount of live virus and, potentially, the amount of cell death [22]: a 5-hour method, which just uses DENV antigens that were produced in a lab, and a 24-hour method, which uses live DENV collected from volunteers [23]. I suggest using the 24-hour method because it is a more realistic representation of what happens during a DENV infection. After 24 hours, I suggest counting the number of infected cells in the control and treatment groups. The null hypothesis proportion (p_0) will be the proportion of dead, infected cells in the control group, and the alternative hypothesis proportion (p_a) will be the proportion of dead cells in the treatment group. From there, I suggest using a One Sample Z test of proportions to determine whether Carica Papaya reduces DENV infection. I suggest testing the results at the 5% and 10% significance levels to reduce the probability of a Type II error. A Type II error in this scenario would show that CP leaf extract is not effective even though it is effective. If this occurs, then we will miss out on an opportunity to increase the survival rate of Dengue infection, which can have positive effects on the community. Even if Carica Papaya extract is not as effective as we thought, then we won't be harming people since the compounds in Carica Papaya leaf extract are natural and non-toxic, therefore not causing as many side effects as a pharmaceutical like Aspirin, which is known to cause severe internal bleeding. This experiment could be conducted on immune cells (T-cells) and hepatic cells as well to find out what effects CP leaf extract might have on the count of infected cells.

Discussion

There is controversy around whether a virus is a living species or a non-living species. This is because bacteria can thrive outside of their host, while viruses need a host cell to attach themselves to be able to survive and replicate. Thus, viruses pose a threat to people without robust ways to stop viral entry. Viruses cause deadly diseases in humans hence, active research is needed to create vaccines and medications to prevent viruses from attacking the host cells and to help eliminate them if they do gain entry into the human body.

The DENV starts its journey inside a female Aedes Aegypti mosquito. The presence of the gene *Loqs2* makes them a vector of the virus. When an infected mosquito bites a human, DENV is introduced into the human body. From here, the virus attacks different kinds of cells, including the skin, liver, spleen, and immune cells, possibly leading to complications and death. It has been an intense area of study to find ways to eliminate the source of DENV. Through years of research, many technologies have been developed to check mosquito populations naturally. For example, using genetic engineering, scientists have been successful in changing the genome of mosquitoes so that they are sterile and eventually die out as a species. In another breakthrough, a group of scientists have used a bacteria named Wolbachia [24], typically absent in Aedes Aegypti mosquitos, to wipe out large populations of Aedes Aegypti

mosquitoes. Specifically, Wolbachia was injected into the eggs of the Aedes Aegypti species. Mosquitoes that hatched from the infected eggs carried this bacterium. Male mosquitos with Wolbachia, when released into the wild, mated with Wolbachia-free female mosquitos. The resulting eggs never hatched, thus reducing the propagation of this species. Even though this technology has no harmful effects on the environment or other living species, it is not 100% effective in catalyzing the decline of the mosquito population. This is because the population of mosquitos without Wolbachia will never reach zero according to the logistic model for population growth. This calls for the active development of effective vaccines and therapeutics to prevent the incidence of DENV and to treat infected people.

DENV can cause complications and death in humans. According to the CDC, there are two vaccines available to prevent Dengue Fever [25], but these vaccines can only prevent secondary infections, with only 80% efficacy. Since these vaccines were developed with live-attenuated DENV, they are not administered to senior citizens, whose weaker immune systems may not respond as effectively as a young person's immune system. Additionally, they do not have the capability to protect people from their first Dengue infections. Hence, in my opinion, research should be actively conducted to develop not only a suitable vaccine that prevents primary infection in people of all age groups but also an effective therapeutic for people who are currently susceptible to primary and secondary infections, with priority given to the latter.

Some recent studies show that Carica Papaya (CP) leaf extract consumption as a home remedy has led to increased platelet counts, improving the prognosis of Dengue Fever. However, these studies have not been conducted in a controlled manner, so it is not possible to establish whether CP leaf extract directly increases platelet count or if it helps prevent the virus from attaching itself to the host, which eventually prevents further infection and causes a natural increase in platelet count. To ascertain the role of CP leaf extract in preventing DENV from attaching itself to host cells, I am proposing a statistical experiment that will maximize the power of the quantitative data we will collect. For this experiment, I suggest we use skin cells from a mammalian cell line along with DENV-2, the commonly found serotype. For the procedure, I suggest we use a One Sample Z test for Differences in Proportions to determine whether Carica Papaya leaf extract decreases the percentage of skin cells that apoptose. To make my conclusion, I will test these results at the 5% and 10% levels to determine whether CP leaf extract prevents DENV from attaching itself to the host (skin) cells.

Acknowledgements:

I would like to extend my heartfelt gratitude to Dr. Aleena Laxmi Patel, a postdoctoral scholar at Stanford University, for her invaluable guidance and encouragement, without which this research work and publication would not have been possible.

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