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A Mathematical Model on the Effect of Papaya Leaves Extracts as a Dengue Fever Treatment

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Abstract
Dengue Fever is a mosquito-borne viral illness and a severe public health issue on a global scale. With approximately 100 million instances of infection recorded each year, the Dengue virus is a worry for people worldwide and controlling Dengue Fever. It is challenging due to complicated medical care environments. As a result, such illnesses should be identified and treated with swift-acting control measures. Mathematical models may show the intricated behaviour of the disease inside the human body-these models aids in improving our comprehension of the dynamics of the virus. In this article, we present a system of differential equations to qualitatively describe the immunological response to Dengue caused by antibodies. When extract of Papaya leaves treatment is administered, we propose investigating the dynamics of the within-host epidemic model of Dengue disease with platelet production rate, combining both the innate immune response and the adaptive immunological response. It was discovered that the actual threshold of antibody recruitment rate is what makes different steady states possible and stable. Also, we suggest undertaking a stability and sensitivity study to better understand this model's dynamics using the dynamical system technique. Finally, the findings indicated that immunostimulatory therapies that accelerate the removal of infected monocytes are superior to antiviral therapy that decreases the virus replication rate in infected cells. In the future, the results reported here can be used in new lines of inquiry to assess the effectiveness of Dengue vaccinations in controlling Dengue Fever.

Keywords: Dengue Fever, Within-host epidemic model, Papaya Leaves treatment, Stability Analysis, Equilibrium point.

1 Introduction

Dengue Fever (DF) is one of the deadly vector-borne illnesses brought on by the Dengue Virus(DV). It is a single positive-stranded R.N.A. virus of the Flaviviridae family spread via Mosquitoes. Over two billion individuals are infected with DV, and 50–100 million DF cases are registered worldwide yearly [1]. Aedes is a genus of mosquitoes, with Aedes- aegypti being the most common species. It was first discovered in tropical and subtropical climates, and individuals who live in these areas are at risk of contracting the DV that passes from one human host to another. There are four different serotypes of DV (DV1-DV4), and cross-reactive antibody cells have a role in the severity of the illness after heterodoxy transmissions [2].

Usually, initial infections cause undetectable or moderate DF illness and a lifelong antibody to that serotype when the virus is cleared from the body. However, Dengue Hemorrhagic Fever (D.H.F.) clears communicable diseases with various infections or causes severe illness [3]. An intense headache, rash, and high fever are all signs of DF; severe joint and muscle pain, nausea, vomiting, and eye pain are other symptoms [4]. Although DF seldom results in death, the sickness can be extremely painful and incapacitating and may spread like wildfire in a community with the emergence of a new variant.

Therefore, it is unknown if infections involving two serotypes lead to lifetime protection or whether tertiary and quaternary diseases are possible. In addition, uncertainty surrounds the factors that cause subsequent dengue infections to be severe. According to the proposal, an "antibody-dependent enhancement" process causes cross-reactive antibodies to contribute to the infection's growth (A.D.E.). A patient's first dengue strain infection results in the production of specific antibodies unique to that strain [5].

Long-lived plasma cells that produce antibodies against the original viral strain remain in the body even after treating the underlying infection [6]. Antibodies from the initial infection bind to the secondary infection but do not neutralize it when a disease with a second dengue serotype develops. However, phagocytic cells enlisted to dislodge viral protein immune complexes absorb non-neutralized viruses and get sick. Immunization is challenging because of the antibody-dependent enhancement because if the population isn't protected against all strains, they risk developing more severe diseases. Therefore, conducting a vaccination study that aims to immunize against all four serotypes is challenging [7].

Typically, DF is a self-controllable infection that needs proper care. Patients experiencing symptoms of fever may be treated with acetaminophen. Antibiotics, corticosteroids, nonsteroidal anti-inflammatory medicines, Aspirin, and Brufen, should all be avoided since they have no beneficial effects and can lead to gastritis and bleeding. The platelet count should be performed on patients with DF, whether confirmed or hypothesized, and hemoglobin levels routinely tested beginning on the third day of symptoms and continuing for 1-2 days after defervescence [8, 9]. Unfortunately, the prevention of dengue infection is not possible with vaccination. Therefore, tetravalent vaccinations have been developed and are presently undergoing clinical studies [10].

Various mathematical investigations of DF have been undertaken. However, only a few of those [11]-[16] discuss the within-host dynamics. Furthermore, each assumes that the creation of target cells (monocytes) is constant. This presumption is true for healthy, non-infected people, although monocyte production can vary greatly, especially during an illness [17]-[19]. Generally, the charge of regulates manufacturing is restricted by Macrophage Colony Stimulating Factor, a cytokine released by monocytes. Therefore, in contrast to past studies that explicitly included the involvement of cytokines and antibodies, our model also considers the platelet count during the interaction with the virus. This innovation results in a model that may show both increased and decreased monocyte and platelet counts during dengue illness, as we can observe in [17]-[19]. Therefore, we suggest examining the dynamics of the within-host epidemic model of Dengue illness with platelet production rate, incorporating both the innate immune response and the adaptive immunological response, when extract of Papaya leaves therapy is delivered.

The article is built up as follows. In Section 2, we created a within-host Mathematical model for immune response and papaya therapy for DF, examined the model in more detail, and explained the strategy. We investigate the stability of the model's equilibria in Section 3 and demonstrate positivity and boundedness in Section 4. Next, the Results and Discussion are carried out in Section 5. Finally, Section 6 provides the Conclusion.

2 The Mathematical model for DF of with-in-host

The model presented here encompasses the host's immunological response and DV within the host when Papaya leaves extract is given to the patients. The model consists of seven sets of first-order nonlinear ODEs that describe the Source term of Susceptible Monocytes Cells(SMC) (usually referred to as White Blood Cell), A(t), Infected Monocytes Cells(IMC), B(t), Healthy Platelets, P(t), Infected Platelets, Q(t), T immune reactivity, S(t), Dengue pathogens, V(t), Papaya leaves therapy(Treatment), T(t).

According to biology, when DV attack the human immune system, they are initially repelled by susceptible cells that are weak to infection before infecting immune cells across the body and spreading illness to humans. The production of SMC (η_A) is thought to occur continuously. Therefore

it is considered by logical growth rate. The success rate of the virus's penetration into healthy SMC, measured as β_1 per unit of time, determines whether it will get infected. The circulatory release of free virions, or the parameter N, is measured in the bloodstream. α indicates how quickly therapy-induced increases in immune production occur, and the remaining parameter descriptions involved in equations(1)-(7) are given in detail along with their values in Table 1.

A Mathematical model of a DF with Papaya leaves therapy is described as follows,

$$\frac{dA}{dt} = s_1 + \eta_A A\left(1 - \frac{A}{A^{max}}\right) - \beta_1 VA - \mu_A A + \xi_1 TA \quad (1)$$

$$\frac{dB}{dt} = \beta_1 AV - \mu_B B \quad (2)$$

$$\frac{dP}{dt} = s_2 + \eta_P P\left(1 - \frac{P}{P^{max}}\right) - \beta_2 VP - \mu_P P + \xi_2 TP \quad (3)$$

$$\frac{dQ}{dt} = \beta_2 PV - \mu_Q Q \quad (4)$$

$$\frac{dS}{dt} = \gamma P - \mu_S S - \beta_3 SV \quad (5)$$

$$\frac{dV}{dt} = N\mu_B B - \beta_1 VA - \beta_2 VP - \beta_4 VS - \beta_5 VT - \mu_V V \quad (6)$$

$$\frac{dT}{dt} = \alpha\delta - \mu_T T \quad (7)$$

3 The positive and bounded solution of the system

The following propositions demonstrate that systems (1)-(7) solutions are positive and bounded [20]. Further, it is subsequently utilized to support the analytical finding.

Proposition: Positivity

Let $a_i > 0, i = 1, 2, ..., 7$ the closed set

$$\Omega = \left\{ (A, B, P, Q, S, V, T) \in \Re^7 \geq 0 : 0 \leq A \leq a_1, 0 \leq B \leq a_2, 0 \leq P \leq a_3, 0 \leq Q \leq a_4, 0 \leq S \leq a_5, 0 \leq V \leq a_6, 0 \leq T \leq a_7 \right\}$$

is the specific region with all solutions being within the positive.

Proof

Let $A(t), B(t), P(t), Q(t), S(t), V(t), T(t)$ be the solution of the system of equations (1)-(7) with the initial conditions

$$A(t) \geq 0, B(t) \geq 0, P(t) \geq 0, Q(t) \geq 0, S(t) \geq 0, V(t) \geq 0, T(t) \geq 0 \quad (8)$$

when $t = 0$,

$$\left(\frac{dA}{dt}\right)_{A=0} = s_1 > 0$$

$$\left(\frac{dB}{dt}\right)_{B=0} = \beta_1 AV \geq 0, \quad for\ A,V \geq 0$$

$$\left(\frac{dP}{dt}\right)_{P=0} = s_2 > 0$$

$$\left(\frac{dQ}{dt}\right)_{Q=0} = \beta_2 PV \geq 0, \quad for\ V,P \geq 0$$

$$\left(\frac{dS}{dt}\right)_{S=0} = \gamma P > 0, \quad for\ P \geq 0$$

$$\left(\frac{dV}{dt}\right)_{V=0} = N\mu_B B \geq 0, \quad for\ B \geq 0$$

$$\left(\frac{dT}{dt}\right)_{T=0} = \alpha\delta > 0$$

Hence all the solutions of the systems (1)-(7) with initial conditions and the values in Table 1 are non-negative.

Proposition: Bounded solution of the system

For any $t \geq 0$, $i(t)$, where $i = A,B,P,Q,S,V,T$ be the solution of the system of equations (1)-(7) according to the initial conditions (8) such that $i(t) \leq Sup\{i(0), M_j\}$, $j = 1,2,3,...,7$ is bounded on $[0, a_k), k = 1,2,...7.$ for some $a_k > 0$

Proof

Case: 1

All of the variables in the model are positive, according to Proposition 3.1. Let $k_1 = \eta_A - \mu_A + \frac{\xi_1 \alpha f}{\mu_A}$

then (1) becomes,

$$\frac{dA}{dt} = s_1 + k_1 A - \beta_1 A^2 = -\beta_1 [A - X][A - Y] \quad (9)$$

where $X = \frac{\frac{k_1}{\beta_1} + \sqrt{\left(\frac{k_1}{\beta_1}\right)^2 + 4\frac{s_1}{\beta_1}}}{2}$ and $Y = \frac{\frac{k_1}{\beta_1} - \sqrt{\left(\frac{k_1}{\beta_1}\right)^2 + 4\frac{s_1}{\beta_1}}}{2}$

The solution of (9) is given by $A(t) = \frac{X - YCe^{-\beta_1(X-Y)t}}{1 - Ce^{-\beta_1(X-Y)t}}$ (10)

where $C = \frac{A_0 - X}{A_0 - Y}$. Since $X > 0, Y < 0$ *and* $A(t) \leq \frac{X - YCe^{-\beta_1(X-Y)t}}{1 - Ce^{-\beta_1(X-Y)t}} = M_1$

Therefore,

$$A(t) \leq Sup\{A(0), M_1\} \quad for\ \ t \in [0, a_1) \quad (11)$$

which implies $A(t)$ is bounded.

Case:2

Let $D(t) = A(t) + B(t)$ then

$$\frac{d}{dt}D(t) = s_1 + \eta_A A\left(1 - \frac{A}{A_{max}}\right) - \mu_A A - \mu_B B + \xi_1 TA$$
$$\leq s_1 + \eta_A M_1\left(1 - \frac{M_1}{A_{max}}\right) - \mu D(t) + \xi_1 TM_1$$

$$\Rightarrow \frac{dD(t)}{dt} + \mu D(t) = s \quad (12)$$

The solution of (12) is given by

$$D(t) = \frac{s}{\mu}\left[1 - e^{-\mu t}\right] + D(0)e^{-\mu t}$$

Therefore,

$$D(t) \leq Sup\left\{D(0), \frac{s}{\mu}\right\} \quad (13)$$

which implies $D(t)$ is bounded.

From (11) and (13), there exist $M_2 > 0$ such that $B(t) < M_2 \quad for \quad t \in [0, a_2)$ (14)

which implies $B(t)$ is bounded.

Similarly, we can prove $P(t)$ and $Q(t)$ are bounded by applying the procedure of Cases 1 and 2. Therefore we get,

$$P(t) < M_3 \quad for \quad t \in [0, a_3)$$
$$Q(t) < M_4 \quad for \quad t \in [0, a_4) \quad (16)$$

Case: 3

The solution of (7) is $T(t) = \frac{\alpha f}{\mu}\left[1 - e^{-\mu t}\right] + T(0)e^{-\mu t}$

Therefore, $T(t) \leq Sup\left\{T(0), \frac{\alpha\delta}{\mu}\right\} \quad for\ t \in [0, a_7)$ (17)

There exist $M_5 = \frac{\alpha f}{\mu} > 0$ such that $T(t) < M_5 \quad for \quad t \in [0, a_7)$ (18)

which implies $T(t)$ is bounded.

Consequently, we can prove $S(t)$ and $V(t)$ are bounded by applying the procedure of Case 3. Therefore we get,

$$S(t) < M_6 \quad for \quad t \in [0, a_5)$$
$$V(t) < M_7 \quad for \quad t \in [0, a_6) \quad (20)$$

Hence, the evidence that systems (1)–(7) given to the initial conditions (8) have bounded solutions on $[0, a_k)$ for some $a_k > 0$ is drawn from the equations (11), (14), and (20).

Proposition: Positivity and Bounded

For any $t > 0$, the solution of systems (1) – (7) under the initial conditions (8) is positive and bounded.

Proof

We demonstrated in Propositions 3.1 and 3.2 that, given to initial conditions (8), the solutions of the systems are positive for every $t \in [0, a_k)$.

Moreover, the solutions on $[0, a_k)$ are uniformly bounded with a_k approaches to infinity.

Symbol	Values	Abbreviations
s_1	10	Source term of SMC[22]

s_2	100	Source term of Platelets[10]
A_{max}	3 x 104	Maximum quantities of SMC[10]
P_{max}	45 x 104	Maximum quantities of Platelets[10]
η_A	0.1	Replacement of SMC[24]
η_P	0.1	Replacement of platelets[10]
N	500	Number of viruses produced by IMC [8]
β_1	0.0013	Lysing rate of Monocyte[8]
β_2	0.5	Lysing rate of Platelets [22]
β_3	0.9	Lysing rate of DV[22]
β_4	0.007	The rate at which antibodies destroy viral particles[23]
β_5	0.87	The rate at which Papaya leaves destroy viral particles[18]
ξ_1	0.05	Transformation rate of Healthy SMC to more stronger[23]
ξ_2	0.5	Transformation rate of Platelets cells to more stronger[22]
μ_A	0.14	The natural death rate of SMC[21]
μ_B	0.14	Death rate of IMC[24]
μ_P	0.11	The natural death rate of Platelets[21]
μ_Q	0.01	The death rate of infected Platelets[12]
μ_V	3.48	The death rate of viral particles[8]
μ_S	0.009	The death rate of Immunity cells[23]
μ_T	0.07	The death rate of Papaya leaves[12]
α	2	The rate at which the production of immunity by therapy[10]
δ	25	Quantity of Papaya leaves per day[10]

Table 1: List of symbols and abbreviations.

4 Stability Analysis

A sensitivity analysis was carried out to determine DF's effect in different cases of immune cells through the equilibrium points. When a Dengue infection is minimal, the DV interacts with immune cells but does not significantly affect the immune system. Hence, the stability of equilibria in all possible cases should thus be discussed [21]. The Jacobian matrix of the system of equations (1)-(7) is often represented by ΔJ_{E_n}, and the associated Eigenvalues are $\lambda_k^{(j)}$, where k stands for the number of Eigenvalues and j for the number of equilibrium points, then it is given by

$$\Delta J_{E_n} = \begin{pmatrix} a_{11} & 0 & 0 & 0 & 0 & -\beta_1 A & \xi_1 A \\ \beta_1 V & -\mu_B & 0 & 0 & 0 & \beta_1 A & 0 \\ 0 & 0 & a_{33} & 0 & 0 & -\beta_2 P & \xi_2 P \\ 0 & 0 & \beta_2 V & -\mu_Q & 0 & \beta_2 P & 0 \\ 0 & 0 & \gamma & 0 & -\mu_S - \beta_3 V & -\beta_3 S & 0 \\ -\beta_1 V & N\mu_B & -\beta_2 V & 0 & -\beta_4 V & a_{66} & -\beta_5 V \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_T \end{pmatrix}$$

Where, $a_{11} = \eta_A - \frac{2A\eta_A}{A_{max}} - \mu_A + \xi_1 T$, $a_{33} = \eta_P - \frac{2P\eta_P}{P_{max}} - \mu_P + \xi_2 T$, $a_{66} = -\beta_1 A - \beta_2 P - \beta_4 S - \beta_5 T - \mu_V$.

Proposition: Trivial Equilibrium

We start by investigating the local stability for a trivial equilibrium point $E_0(0,0,0,0,0,0,0)$. Then, the corresponding Jacobian matrix is expressed as

$$\Delta J_{E_0} = \begin{pmatrix} \eta_A - \mu_A & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_B & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \eta_P - \mu_P & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_Q & 0 & 0 & 0 \\ 0 & 0 & \gamma & 0 & -\mu_S & 0 & 0 \\ 0 & N\mu_B & 0 & 0 & 0 & -\mu_V & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_T \end{pmatrix}$$

The Eigenvalues of the matrix ΔJ_{E_0} is given by,

$$\left.\begin{aligned} \lambda_1^{(0)} &= \eta_A - \mu_A < 0, \lambda_2^{(0)} = -\mu_B < 0, \lambda_3^{(0)} = \eta_P - \mu_P > 0, \lambda_4^{(0)} = -\mu_Q < 0, \\ \lambda_5^{(0)} &= -\mu_S < 0, \lambda_6^{(0)} = -\mu_T < 0, \lambda_7^{(0)} = -\mu_V < 0. \end{aligned}\right\} \quad (21)$$

The advantage of the Eigenvalue sign is used to determine the system's stability. The ODE system is locally asymptotically stable if all Eigenvalues are precisely negative. Conversely, instability exists if any one of the Eigenvalues is positive. If all Eigenvalues are negative and one is zero, then the system is stable but not asymptotically stable.

According to (21), the system is unstable since all Eigenvalues except for $\lambda_3^{(0)}$ are negative (From Table 1). Therefore, we conclude that no viral infection is spreading in Proposition (4.1). The equilibrium point E_0 is thus not possible.

Proposition: Virus presence, immunity absence without Papaya Therapy

Now let's consider the local stability of the equilibrium point $E_1\left(A^*, B^*, P^*, Q^*, 0, V^*, 0\right)$ for the absence of immunological response. Then, the associated Jacobian matrix is therefore written as follows

$$\Delta J_{E_1} = \begin{pmatrix} a & 0 & 0 & 0 & 0 & b & c \\ f & -\mu_B & 0 & 0 & 0 & k & 0 \\ 0 & 0 & l & 0 & 0 & 0 & 0 \\ 0 & 0 & m & -\mu_Q & 0 & 0 & 0 \\ 0 & 0 & \gamma & 0 & -n & 0 & 0 \\ -p & u & -q & 0 & r & s & v \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_T \end{pmatrix}$$

Where, $a = \eta_A - \frac{2A\eta_A}{A_{max}} - \mu_A + \xi_1 T, b = -\beta_1 A, c = \xi_1 A, f = \beta_1 V, k = \beta_1 A, l = \eta_P - \frac{2P\eta_P}{P_{max}} - \mu_P + \xi_2 T,$

$m = \beta_2 V, n = \beta_3 V - \mu_3, p = -\beta_1 V, u = N\mu_B, q = \beta_2 V, r = -\beta_4 V, s = -\beta_1 A - \mu_V, v = -\beta_5 V.$

The Eigenvalues of the matrix ΔJ_{E_1} is given by,

$$\left.\begin{aligned} \lambda_1^{(1)} &= -\mu_T < 0, \ \lambda_2^{(1)} = -\mu_Q < 0, \ \lambda_3^{(1)} = -n < 0, \ \lambda_4^{(1)} = l > 0, \\ \lambda_5^{(1)} &= \frac{1}{6}\left[R_1 + 12\sqrt{R_2}\right]^{1/3} - 6R_3 / \left[R_1 + 12\sqrt{R_2}\right]^{1/3} + \frac{a + s - \mu_B}{3} < 0, \\ \lambda_6^{(1)} &= \frac{1}{12}\left[R_1 + 12\sqrt{R_2}\right]^{1/3} + 3R_3 / \left[R_1 + 12\sqrt{R_2}\right]^{1/3} + \frac{a + s - \mu_B}{3} < 0, \\ \lambda_7^{(1)} &= \frac{1}{12}\left[R_1 + 12\sqrt{R_2}\right]^{1/3} + 3R_3 / \left[R_1 + 12\sqrt{R_2}\right]^{1/3} + \frac{a + s - \mu_B}{3} \\ &- \frac{\sqrt{3}}{6}\left[I\sqrt{3}R_1 + 12\sqrt{R2}\right]^{1/3} + 6R_3 / \left[R_1 + 12\sqrt{R_2}\right]^{1/3} < 0 \end{aligned}\right\} \quad (22)$$

Since all Eigenvalues are negative except $\lambda^{(1)}{}_4$, we conclude that in Proposition 4.2, the system becomes unstable if the viral infection spreads without immunity.

Proposition: Virus and immunity present with papaya therapy

Next, let's examine the local stability of the equilibrium point $E_3\left(A^*, B^*, P^*, Q^*, S^*, V^*, T^*\right)$ for the presence of immunological response. Therefore, the resulting Jacobian matrix is mentioned as follows.

$$\Delta J_{E_3} = \begin{pmatrix} C_{11} & 0 & 0 & 0 & 0 & -\beta_1 A & \xi_1 A \\ 0 & -\mu_B & 0 & 0 & 0 & \beta_1 A & 0 \\ 0 & 0 & C_{33} & 0 & 0 & -\beta_2 P & \xi_2 P \\ 0 & 0 & 0 & -\mu_Q & 0 & \beta_2 P & 0 \\ 0 & 0 & \gamma & 0 & -\mu_S & -\beta_3 S & 0 \\ 0 & N\mu_B & 0 & 0 & 0 & C_{66} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_T \end{pmatrix}$$

Where, $C_{11} = \eta_A - \frac{2A\eta_A}{A_{max}} - \beta_1 V - \mu_A + \xi_1 T, C_{33} = \eta_P - \frac{2P\eta_P}{P_{max}} - \beta_2 V - \mu_P + \xi_2 T, C_{66} = -\beta_1 A - \beta_2 P - \beta_4 S - \beta_5 T - \mu_V$.

The Eigenvalues of the matrix ΔJ_{E_3} is given by,

$$\left.\begin{array}{l} \lambda_1^{(3)} = -\mu_T < 0,\ \lambda_2^{(3)} = -\mu_S < 0,\ \lambda_3^{(3)} = -\mu_Q < 0,\ \lambda_4^{(3)} = C_{33} < 0, \\ \lambda_5^{(3)} = C_{11} < 0,\ \lambda_6^{(3)} = M_1 - M_2 + M_3 < 0,\ \lambda_7^{(3)} = M_1 - M_2 - M_3 < 0. \end{array}\right\} \quad (23)$$

Where, $M_1 = -\frac{C_{66}}{2}, M_2 = -\frac{\mu_B}{2}, M_3 = \frac{\sqrt{4N\mu_B\beta_1 A + C_{66}^2 + 2C_{66}\mu_B + \mu_B^2}}{2}$.

Since all Eigenvalues are negative, we conclude that in Proposition 4.3, the system becomes stable if DV exists with papaya therapy.

Proposition: Virus clearance due to immunity present with Papaya therapy

Finally, let us deliberate in detail about virus clearance due to immunity present with papaya therapy through the local stability of the endemic equilibrium point $E_4\left(A_*, 0, P_*, 0, S_*, 0, T_*\right)$. Following that, the

equivalent Jacobian matrix is written as

$$\Delta J_{E4} = \begin{pmatrix} a_{11} & 0 & 0 & 0 & 0 & -\beta_1 A & \xi_1 A \\ 0 & -\mu_B & 0 & 0 & 0 & \beta_1 A & 0 \\ 0 & 0 & a_{33} & 0 & 0 & -\beta_2 P & \xi_2 P \\ 0 & 0 & 0 & -\mu_Q & 0 & \beta_2 P & 0 \\ 0 & 0 & \gamma & 0 & -\mu_S & -\beta_3 S & 0 \\ 0 & N\mu_B & 0 & 0 & 0 & a_{66} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_T \end{pmatrix}$$

Where, $a_{11} = \eta_A - \frac{2A\eta_A}{A_{max}} - \mu_A + \xi_1 T, a_{33} = \eta_P - \frac{2P\eta_P}{P_{max}} - \mu_P + \xi_2 T, a_{66} = -\beta_1 A - \beta_2 P - \beta_4 S - \beta_5 T - \mu_V$.

The Eigenvalues of the matrix ΔJ_{E_4} are,

$$\left.\begin{array}{l} \lambda_1^{(4)} = -\mu_T < 0, \lambda_2^{(4)} = -\mu_S < 0, \lambda_3^{(4)} = -\mu_Q < 0, \lambda_4^{(4)} = -L_1 < 0, \\ \lambda_5^{(4)} = -L_2 < 0, \lambda_6^{(4)} = L_3 + \sqrt{L_4} < 0, \lambda_7^{(4)} = L_3 - \sqrt{L_4} < 0. \end{array}\right\} \quad (24)$$

Where, $L_1 = \frac{-TP_{max}\xi_2 + 2P\eta_P - P_{max}\eta_P + P_{max}\mu_P}{P_{max}}, L_2 = \frac{-TA_{max}\xi_1 + 2A\eta_A - A_{max}\eta_A + A_{max}\mu_A}{A_{max}},$

$L_3 = \frac{-A\beta_1 - P\beta_2 - S\beta_4 - T\beta_5 - \mu_B - \mu_V}{2},$

$$L_4 = \frac{1}{2}\{A\beta_{21}^2 + 4AN\beta\mu_B + 2AP\beta\beta_{12} + 2AS\beta\beta_{14} + 2AT\beta\beta_{15} + P^2\beta_2 + 2PS\beta\beta_{24} + 2PT\beta\beta_{25} + S^2\beta_4 + 2ST\beta\beta_{45} + T^2\beta_5^2 - 2A\beta\mu_{1B} + 2A\beta\mu_{1V} - 2P\beta\mu_{2B} + 2P\beta\mu_{2V} - 2S\beta\mu_{4B} + 2S\beta\mu_{4V} - 2T\beta\mu_{5B} + 2T\beta\mu_{5V} + \mu_B^2 - 2\mu_B\mu_V + \mu_V^2\}$$

All Eigenvalues are negative when Table 1's values are applied in (24). Its stability supports our Novelty model for DF through the endemic equilibrium point $E_4(A_*0, P_*0, S_*0, T_*)$. The justification for proposition 4.4 is that we proved that when papaya leaf extract is used as a therapy, platelet production increases, and DV is cleaned. There are no infected susceptibility cells and infected platelets.

5 Result and Discussion

We created a mathematical model of the immune system's reaction to DV and applied it to assess the severity of the disease's effects following papaya therapy. Table 1 provides the biological values for each variable in the numerical simulation. From Figure 1, the targeted cell rate has grown gradually for getting an infection from the initial point until stabilizing after 20 days.

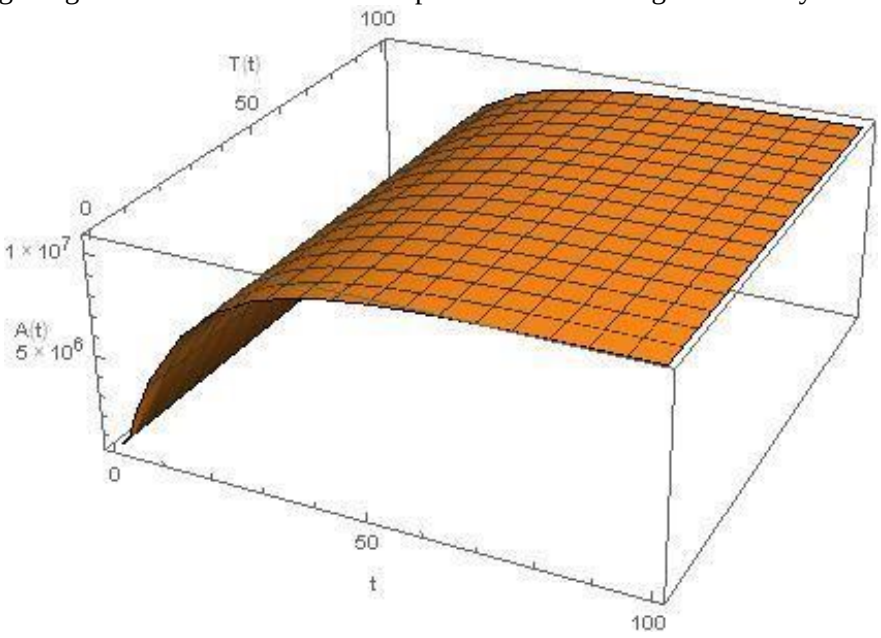

Figure 1: Impact of Susceptible Monocytes Cells

In Figure 2, After 14 days, the rate of infected targeted cells steadily decreased. After 40 days, it reached a plateau and did not increase significantly. In Figure 3, the bone marrow is suppressed by Dengue, and it does manufacture platelets. Therefore, starting on the fourth day, the rate of platelets losing their count increased and stabilized after 20 days.

From Figure 4, it can be shown that healthy individuals' platelet counts decrease when they become infected with the DV and can even go below 40000 platelets per litre. Typically, this occurs after three to four days of fever, during the peak time of the infection. Moreover, it takes 20 days to achieve a stable state.

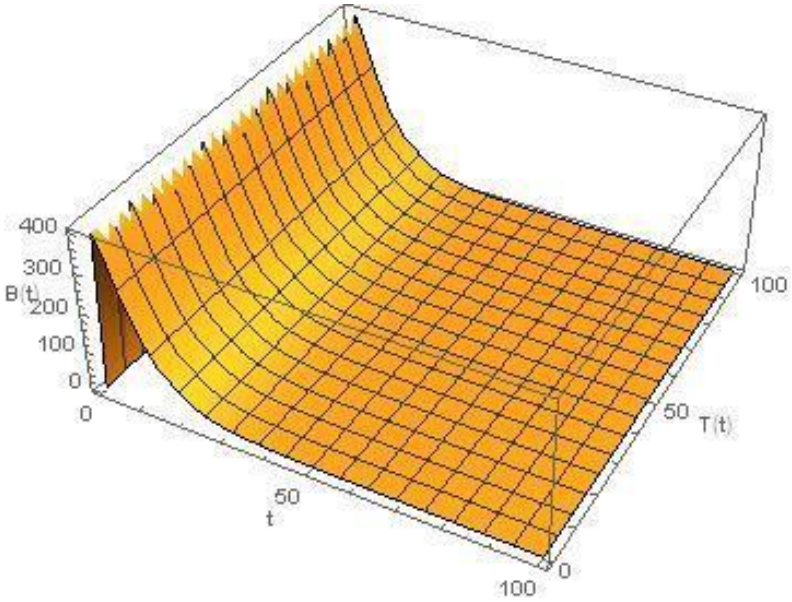

Figure 2: Appearance and behaviour of Infected Monocytes Cells

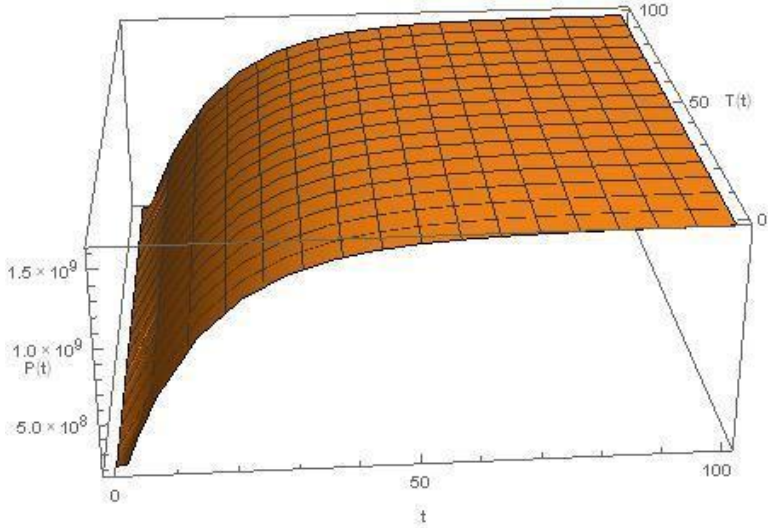

Figure 3: Influence of Healthy Platelets

Figure 5 clearly shows that there is no strength in the immune cells to combat them after contracting the DV at the initial stage. However, the immune cell count increased after only five days and reached its usual level twenty days later.

As patients progressed against their condition, the viral load eventually reduced after 5-6 days. According to dengue viral load characteristics in patients, the most significant viral load was typically $2/10^8$ copies/ml within the first day of symptoms. But on the fourth day, it is increased to $3/10^8$ copies/ml. The virus load then progressively dropped during the next few days. Finally, on the 7^{th} day after the fever, the infection rate dropped to zero copies/ml, as shown in Figure 6.

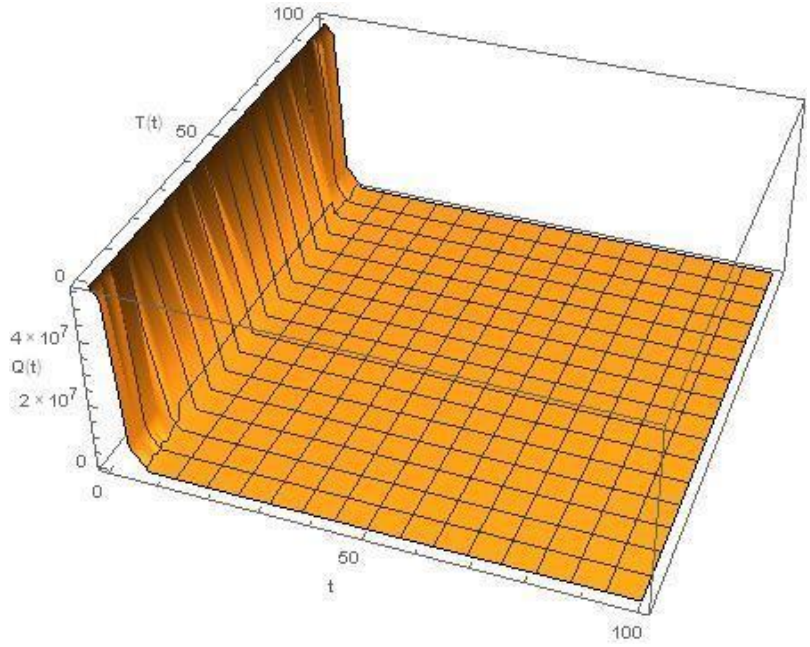

Figure 4: Effect and behaviour performances of Infected Platelets

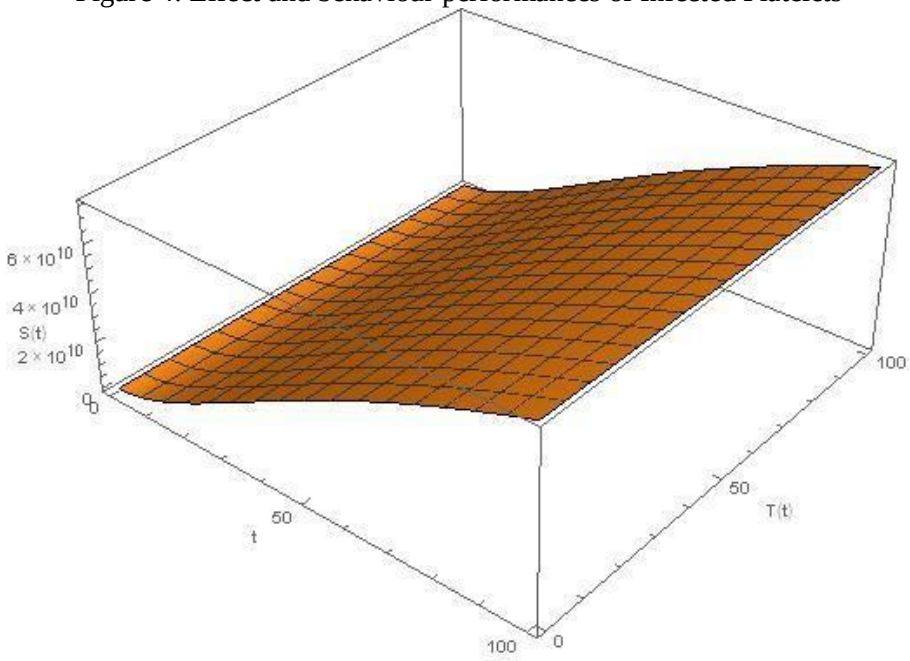

Figure 5: Impact of Immunity Response

The effectiveness of papaya therapy for DV is shown in Figure 7. Patients' immune systems receive a boost from day one when administered after papaya leaf therapy. Additionally, it stabilizes after 20 days.

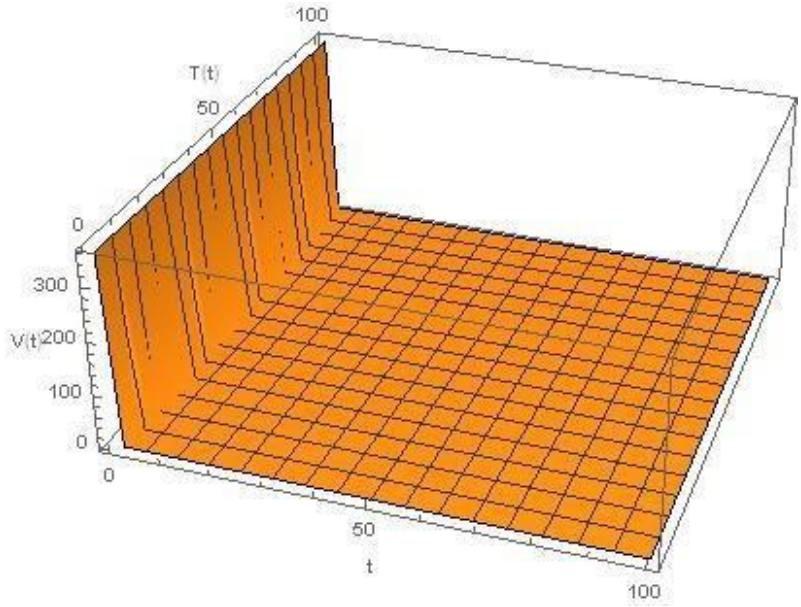

Figure 6: Effect of Dengue Viral Load

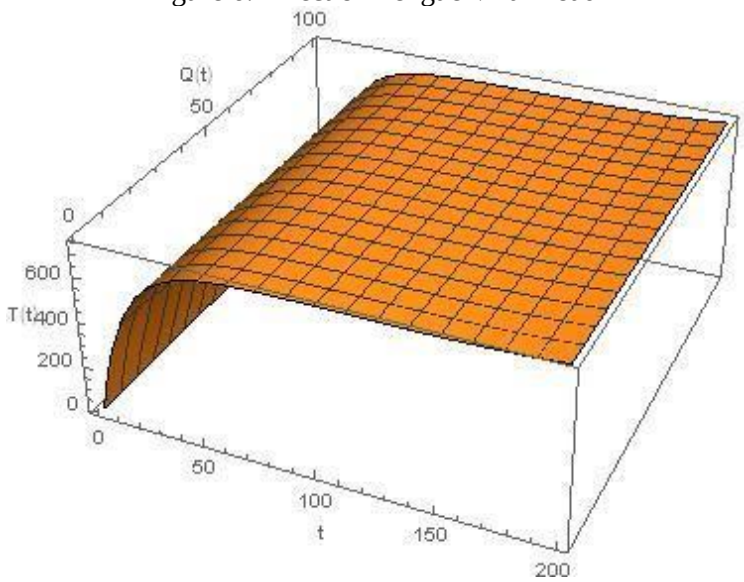

Figure 7: Therapeutic effects of papaya leaves

The infection is prolonged even when the treatment effectively decreases viral and infected cell loads. It nonetheless sounds like a worthwhile strategy. As shown in Figure 8, we may now contrast this situation with the death rate at which infected monocyte was previously reported. We reduced the quantity β_1 by 50% and 75% before plotting the outcomes after the case without treatment and keeping other parameter values, as shown in Table 1. Figure 9 illustrates the following circumstance. Let us compare it to the previously reported death rate for infected platelets. As shown in Table 1, we maintained other parameter values while reducing β_2 by 50% and 75% before showing the results next to the case without treatment.

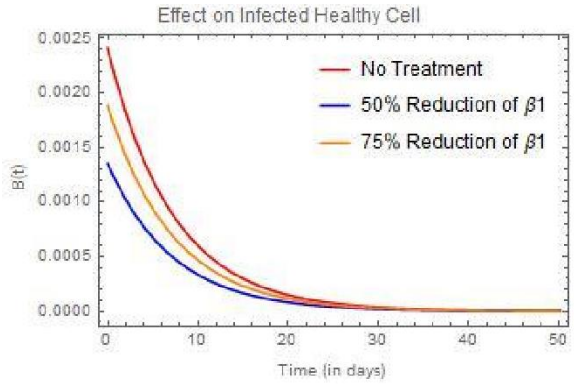

Figure 8: Dynamic behaviour of the Infected Monocyte cells for different valuesof β1(0.0013, 0.00065, 0.000975)

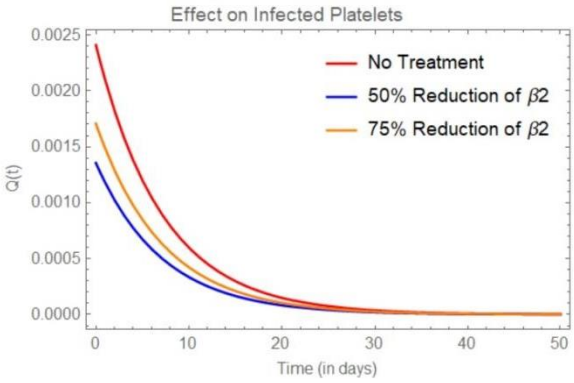

Figure 9: Dynamic behaviour of the Infected Platelets for different values ofβ2(0.5, 0.25, 0.375)

Figure 10, the influence of viral load also decreases when monocyte death rates drop by 50% and 75%. But in Figure 11, the death rate of Platelets count was reduced to 50%, and the viral load did not decrease as well. However, when it was reduced to 75%, the viral load decreased and became stable after 7 days.

In Figure 12, the viral load fell as well as the rate at which antibodies kill viral particles was slowed to 75%, and it took more than nine days for the viral load to stabilize. However, when it was decreased by half, the viral load dropped and stabilized after 7 days. Figure 13 shows that the rate at which the therapy destroys viral particles was increased to 50%, the viral load was lowered, and it took more than five days for the viral load to stabilize. But when it was raised to 75%, the viral load dropped and stabilized in four days.

Figure 14 shows a decrease in viral load when a 50% reduction in the death rate of infected monocyte cells. Also, it took more than ten days for the viral load to stabilize. However, the viral load declined and stabilized after six days, when it was reduced by 75%.

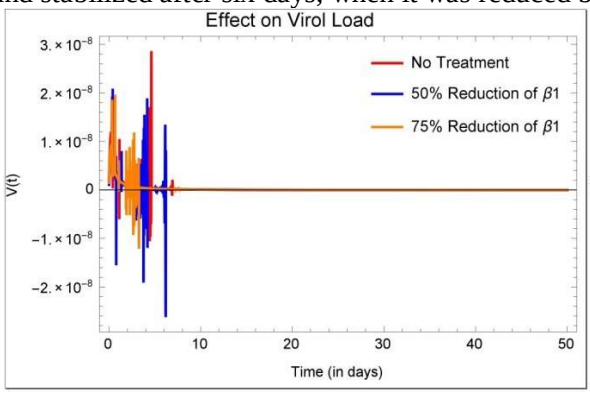

Figure 10: Dynamic behaviour of the Dengue pathogens for different values of β1(0.0013, 0.00065, 0.000975)

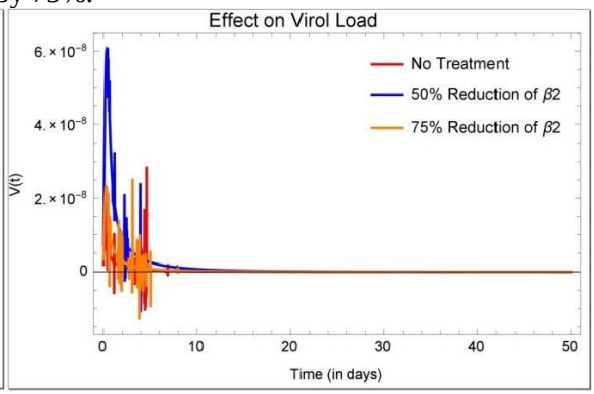

Figure 11: Dynamic behaviour of the Dengue pathogens for different values of β2(0.5, 0.25, 0.375)

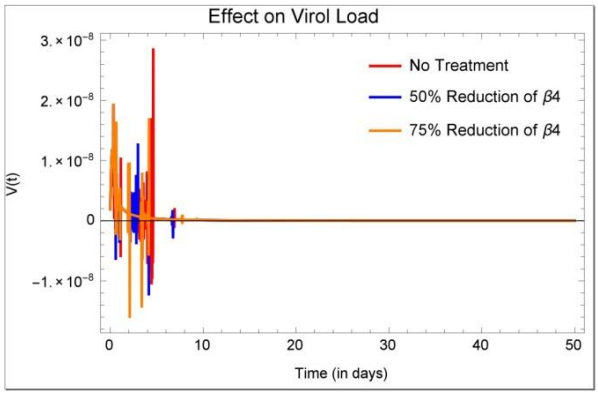

Figure 12: Dynamic behaviour of the Dengue pathogens for different values of β4(0.007, 0.0035, 0.00525)

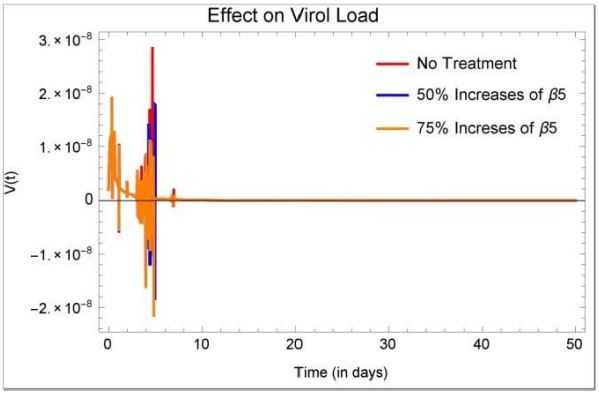

Figure 13: Dynamic behaviour of the Dengue pathogens for different values of β5(0.87, 1.78, 2.61)

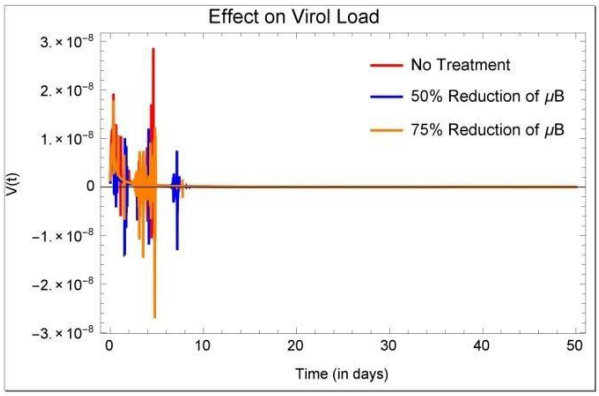

Figure 14: Dynamic behaviour of the Dengue pathogens for different values of μB(0.14, 0.07, 0.105)

We created and investigated a novelty within-host model of a system of differential equations to describe the immunological response to Dengue when extract of Papaya leaves treatment is administered. The novel strategy In contrast to earlier immune system models, the model of nonlinear dynamics includes the concept of platelet count. Furthermore, we mathematically investigated the stability of the model's equilibria and demonstrated positivity and boundedness through propositions. The rate of targeted cells, infected targeted cells, platelet count, infected platelet count, antibody immune system, viral load, and papaya therapy were all carefully investigated numerically. We have determined that the parameters $\beta_1, \beta_2, \beta_4, \beta_5,$ and μ_β are crucial.

Furthermore, we demonstrated how the parameter $\beta_1, \beta_2, \beta_4, \beta_5,$ and μ_β factors cause the system behaviour to shift from stable to periodic. If we raise this value β_5 even further, the virus is effectively eradicated, and the system enters a steady state free of sickness. Our research shows that using papaya therapy is crucial in developing an antiviral treatment strategy.In future work, we would like to model the effects of earlier and delayed treatment using delay differential equations.

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