Cell Communication and Signaling

REVIEW

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Immunomodulation in dengue: towards deciphering dengue severity markers

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Abstract

Background Dengue is a vector-borne debilitating disease that is manifested as mild dengue fever, dengue with warning signs, and severe dengue. Dengue infection provokes a collective immune response; in particular, the innate immune response plays a key role in primary infection and adaptive immunity during secondary infection. In this review, we comprehensively walk through the various markers of immune response against dengue pathogenesis and outcome.

Main body Innate immune response against dengue involves a collective response through the expression of proinflammatory cytokines, such as tumor necrosis factors (TNFs), interferons (IFNs), and interleukins (ILs), in addition to anti-inflammatory cytokines and toll-like receptors (TLRs) in modulating viral pathogenesis. Monocytes, dendritic cells (DCs), and mast cells are the primary innate immune cells initially infected by DENV. Such immune cells modulate the expression of various markers, which can influence disease severity by aiding virus entry and proinflammatory responses. Adaptive immune response is mainly aided by B and T lymphocytes, which stimulate the formation of germinal centers for plasmablast development and antibody production. Such antibodies are serotype-dependent and can aid in virus entry during secondary infection, mediated through a different serotype, such as in antibody-dependent enhancement (ADE), leading to DENV severity. The entire immunological repertoire is exhibited differently depending on the immune status of the individual.

Short conclusion Dengue fever through severe dengue proceeds along with the modulated expression of several immune markers. In particular, TLR2, TNF-α, IFN-I, IL-6, IL-8, IL-17 and IL-10, in addition to intermediate monocytes (CD14+CD16+) and Th17 (CD4+IL-17+) cells are highly expressed during severe dengue. Such markers could assist greatly in severity assessment, prompt diagnosis, and treatment.

Keywords Dengue, *Aedes* mosquitoes, Innate immunity, Adaptive immunity, Immunomodulator

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Background

Dengue virus (DENV) infection, known as "break-bone fever" is a vector borne disease transmitted by *Aedes* mosquitoes [1]. Global health concerns of dengue has reached a critical magnitude, with approximately 100–400 million cases being reported annually, with a mortality risk of 1% [2]. Dengue is rapidly spreading across the world and has been reported in over 100 countries [3]. Pediatric DENV infection is on the rise in India, with significant morbidity and mortality [4]. In addition, children with DENV infection present more complications in comparison to adults owing to a developing immune system [4–6]. The lack of effective vaccines and drugs has rendered dengue a significant tropical health concern [7]. The most advanced dengue vaccine is a combination of genes from four DENV serotypes and the yellow fever vaccine. This vaccine underwent placebo-controlled clinical studies in 35,000 children, aged 2–16 years in ten dengue-endemic countries to assess its effectiveness and safety. However, the efficacy of the vaccine was not conclusive [8]. Dengvaxia is one such promising vaccine; however, with low efficacy of around 61%, because of cross-neutralizing antibodies against different serotypes [8, 9]. Therefore, early detection, severity analysis, and prompt treatment are a few important strategies to manage dengue outcome.

DENV infection is characterized by a wide range of clinical manifestations. Although 60% of DENV cases are asymptomatic, infection with any of the four DENV serotypes could lead to dengue fever (DF) [10, 11]. As per WHO (2009), dengue is classified into DF, dengue with warning signs (DWS) (PCV or hematocrit > 20% from baseline, CRP < 30 mg/ml [10] AST ~ 84.5 IU/L, ALT ~ 59.9 ± 31.3 IU/L [11]) and severe dengue (SD) (hematocrit > 20% from baseline, AST ~ 507 ± 106.8 IU/L, ALT ~ 234 ± 30.6 IU/L [11] LDH > 1000 IU [12], CRP > 30 mg/ml [10]). Dengue manifests initially in the form of mild fever in approximately 90% of cases, with characteristics including rapid onset of fever, vomiting, stomach discomfort, flushing, skin erythema, myalgia, arthralgia, headache, and leukopenia [13]. A subset of patients could develop DWS with more aggravated clinical symptoms, such as mucosal bleeding, hepatomegaly, increased hematocrit levels, and a rapid decline in platelet count. Some patients could progress to SD that is marked by severe plasma leakage (evidenced by shock or fluid accumulation with respiratory difficulty), severe bleeding, and/or severe organ impairment (such as hepatitis, encephalitis, or myocarditis) [14].

DENV induces both innate and adaptive immune response in pediatric and adult populations. DENV triggers the activation of dendritic cells (DCs) and macrophages, followed by monocyte proliferation and maturation. Furthermore, the adaptive immune response involving B and T lymphocytes is more pronounced in secondary infection [15]. However, it is important to address all the aspects of dengue pathogenesis to comprehend the role of the immune system in modulating disease severity. While DENV can infect endothelial cells in laboratory settings [16, 17], investigations have not detected widespread endothelial cell infection in SD cases [17]. Additionally, DENV has not been found in skin lesions located beyond the site of virus infection in humans [15]. Such findings suggest that vascular pathologies are probably predominantly mediated by the immune system [15]

Innate immune response in dengue pathogenesis and severity

Human immune system plays a crucial role in DENV infection. Importantly, the innate immune response is the major player in primary DENV infection [18]. Initial DENV infection results in the recruitment and maturation of DCs, which is marked by elevated expression of major histocompatibility complex (MHC)-II and several costimulatory molecules, including CD40, CD83, CD80, and CD86 [19, 20]. Myeloid DCs (mDCs) (Lin^- $HLA\text{-}DR^+$, $CD11c^+$ $CD123^{lo}$) are involved in antigen capture, processing, and presentation of DENV to T cells [21]. Plasmacytoid DCs (pDCs) (Lin^- $HLA\text{-}DR^+$, $CD11c^-$, $CD123^+$) are primarily involved in the production of type-I interferon and limiting viral replication [22]. Lertjuthaporn et al. (2018) reported that the relative population of mDCs in SD was significantly lower than that in DF and healthy individuals [19]. This reduced mDC count could be correlated with DC migration to peripheral tissues and apoptosis [21]. Studies have suggested that mDCs residing in epithelial tissues synthesize tumor necrosis factor-alpha (TNF-α), interferon alpha (IFN-α), and interleukin (IL-6), which promote DC migration from the blood to the site of inflammation during DENV infection [19, 23, 24].

pDCs, a distinctive subset of immune cells, act as primary sensors of DENV infected cells, orchestrating immune responses [25]. They detect virus via toll-like receptors, TLR7-sensing single-stranded ribonucleic acid (ss-RNA) and TLR9-sensing unmethylated CpG-containing DNA, leading to type I interferon (IFN-I) and cytokine secretion mediated by the interferon regulatory factor (IRF)-7 and nuclear factor kappa B (NF-κB) pathways [26–31]. DENV infection induces the cytosolic release of mitochondrial DNA (mtDNA) through mechanisms involving reactive oxygen species (ROS) generation and protein kinase (PK) activation, disrupting transcription factor A mitochondria (TFAM)-mtDNA association. TLR9 detects this mtDNA, initiating signaling cascades, involving mitogen-activated protein kinases (MAPKs) p38 and NF-κB, resulting in proinflammatory

and antiviral cytokine production [30]. Notably, patients with SD manifestations exhibit lower IFN-α expression in response to TLR9 ligand stimulation compared with those with milder symptoms. This suggests that a deficiency in TLR9 signaling contributes to the severity of the disease [32].

Previous studies have shown that DENV evades the innate immune response by inhibiting IFN-I production and signaling [27, 28]. The viral proteins nonstructural (NS)2A and NS3 degrade signaling molecules and inhibit RIG-like receptor (RLR)- mitochondrial antiviral-signaling protein (MAVS) interaction to prevent IFN-I production [27]. Additionally, NS2A, NS4A, NS4B, and NS5 block signal transducer and activator of transcription (STAT)1 and STAT2 phosphorylation, with NS5 further degrading STAT2 via the proteasome [27], thereby inhibiting TANK-binding kinase 1 (TBK1) and IRF-3 phosphorylation and IFN-α/βR signaling, which are crucial for the IFN-I-mediated immune response [28]. However, recent studies indicate that these inhibitory mechanisms are not effective in DCs during DENV infection because the sensing of RNA products precedes the activity of newly produced viral proteins that block RLR signaling [31]. pDCs facilitate IFN-II induction via IRF-7, modulating the interplay between IFN-I and IFN-II responses (Fig. 1) [30]. Evidence suggests that DCs can comprehend pathogen-inherent signals and play a crucial role in polarizing T helper (Th) cell development [33]. Pathogen-associated molecular patterns (PAMPs) recognized by TLRs and RLRs present on DCs can induce various cytokine responses and antigen-presenting cell functions [33]. DENV infection of DCs triggers the activation of RLRs such as RIG-1 and melanoma differentiation-associated protein (MDA5) [34]. The activation of RLRs typically leads to the production of IFN-I via enhancement of the transcription factor IRF3. IFN-I activates IFN-α/β receptors on DCs, which leads to the phosphorylation of STAT1 [29]. STAT1 plays an important role in the production of IL-27, a vital signal for differentiating CD4+ T cells into follicular T helper (Tfh) cells [31]. Tfh cells promote the proliferation and differentiation of B cells in the germinal center and synthesize IL-21, which stimulates B cells to produce antibodies [31]. Previous studies have shown that the silencing of RIG-1 and MDA5 leads to a reduction in the production of IFN-I, which retards DC maturation and Th-1 polarization [29, 35]. This leads to a reduction in cytokines, such as IL-6, TNF, and IFN-γ, and chemokines, mainly chemokine (C-C motif) ligand 2 (CCL-2), CCL-3, and CCL-4, which are associated with disease severity [29].

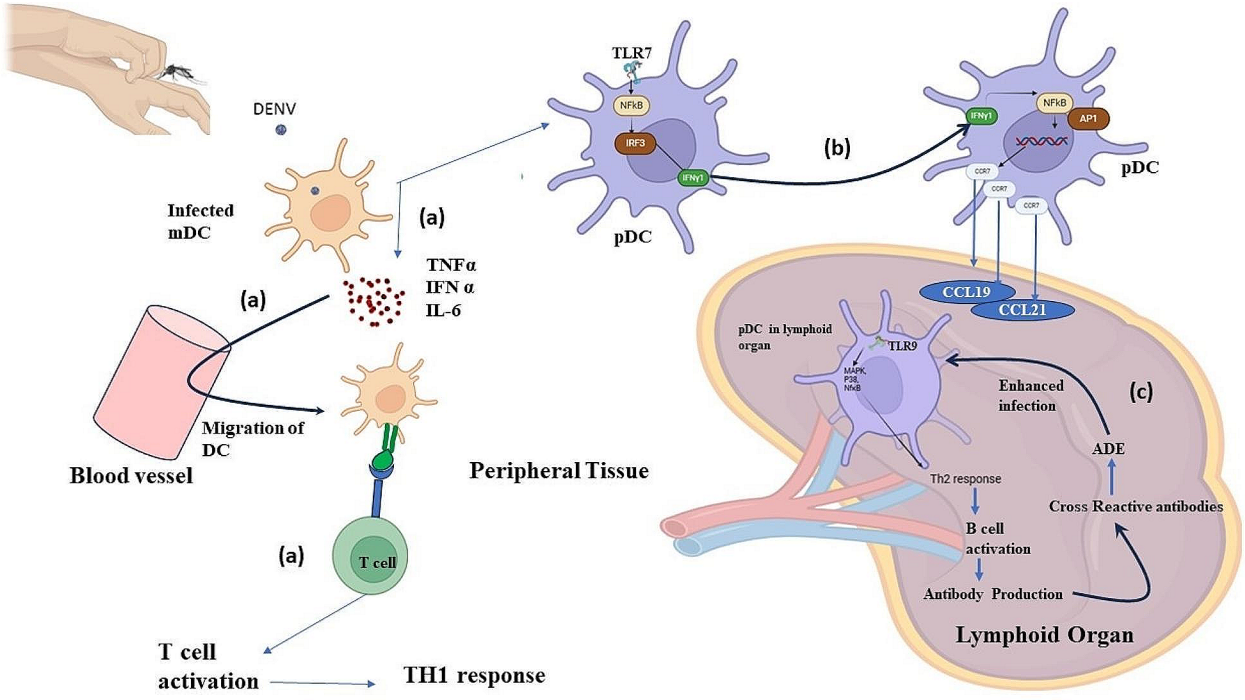

Fig. 1 Innate immune response involving myeloid dendritic cells (mDCs). (**a**) Infected mDCs initiate the production of proinflammatory cytokines like TNF-α, IFN α, and IL-6 that are responsible for migration of mDCs to the site of infection (peripheral tissue), where the mDCs further activate the T lymphocytes and induce Th1 response. (**b**) Mitochondrial DNA (mtDNA) detected by TLR7 induces the expression of IFN-λ in other pDCs along with production of CCR-7. CCR-7 further acts as a receptor for CCL-19 and CCL-21 and assists in the migration of pDCs to lymphoid organs. (**c**) TLR9 detects mtDNA in pDCs that initiates signaling cascades involving MAPK p38 and NF-κB, thereby inducing Th2 response against DENV

DENV infection also activates DCs through the TLR2/myeloid differentiation primary response protein (MyD88) pathway, stimulating the production of MAPKs, such as c-Jun N-terminal Kinase (JNK), extracellular signal-regulated kinase (ERK) 1/2 and p38, leading to IL-6 and TNF-α production [36]. This pathway also enhances DC maturation by upregulating costimulatory and MHC molecules that are crucial for T-cell antigen presentation. Furthermore, it promotes primary DENV replication in DCs and fosters Th2-biased immune responses, potentially exacerbating SD through antibody-dependent enhancement (ADE) [36–38].

IFN-λ produced in DCs in response to initial DENV infection plays dual roles by regulating the immune response and exacerbating pathophysiology. Elevated IFN-λ1 levels has been observed in DENV-infected individuals compared with healthy controls [39, 40]. IFN-λ1 also inhibits DENV2 replication in epithelial cells [40]. Dengue infection and viral NS1 were implicated in IFN-λ1 production in DCs, which is regulated by TLR3, IRF3 and NF-κB [40]. IFN-λR1 deficiency hinders DENV-induced DC migration towards CCL-19/CCL-21 (Fig. 1), possibly through a reduction in chemokine receptor (CCR)-7 levels, whereas IFN-λ1 promotes CCR-7 expression via autocrine signaling by influencing DC migration [39]. DC migration from the periphery to the lymphoid organs is a crucial step in DENV infection, facilitating viral spread and initiating immune responses by priming adaptive B- and T- cell interactions [39].

An important type of innate immune cell, monocytes, which are categorized into classical monocytes (CMs), intermediate monocytes (IMs), and nonclassical monocytes (NCMs) based on CD14 and CD16 expression, have been implicated in DENV-related endothelial damage [41–44]. Studies have revealed a significant increase in IMs during DENV infection, which is correlated with disease severity, whereas CM remains stable and NCM levels are reduced [45]. In particular, increased IM has been associated with severe manifestations, whereas NCM may confer protective effects in dengue [41, 45]. The CM and IM subsets exhibit increased expression of genes associated with chemotaxis, endothelial dysfunction, and vascular permeability, including vascular endothelial growth factor (VEGF) A, CCL-2, CXCL-8, CXCL-2, CXCL-3, and IL-6ST [41]. The IM subset additionally expresses plasminogen activator urokinase (PLAU), preventing clot formation [41, 46], and modulates T-cell function through the production of cytokines, such as TNF receptor family (TNFSF)-9, IL-27, IL-23, IL-18, and IL-12 [47, 48]. The NCM subset primarily expresses IL-15, which acts as a pro-survival factor for adaptive immune cells and also aids in the activation of T and NK cells [41]. Coculture of DENV2 with IM subsets and B cells led to increased differentiation of B lymphocytes into IgM-producing plasmablasts, which was mediated by B-cell activating factor and proliferation-inducing ligand (APRIL) and IL-10, thereby potentially exacerbating DENV infection through ADE [45].

In febrile dengue, monocytes, particularly those in the IM and CM subsets, presented increased TLR2 and TLR4 expression. TLR4, known for its role in bacterial responses, also contributes to dengue pathogenesis [49–51]. TLR2 activation triggers the NF-κB pathway by inducing the expression of proinflammatory cytokines, such as IL-1β and TNF-α, during DENV infection [49–51]. Studies have shown that elevated TLR2 expression in the CM and IM subsets correlates with disease severity, whereas low TLR expression in the NCM correlates with milder forms of dengue, indicating endothelial protection [52–54]. High TLR2 expression in CM during SD suggests reduced internalization, influencing inflammatory responses. TLR2 axis activation, which is dependent on clathrin-mediated endocytosis, balances inflammatory and antiviral responses during DENV infection [40, 55].

Natural killer (NK) cells, important players in innate immunity play pivotal roles in DENV infection. Initially, they eliminate virus-infected cells, contributing to early antiviral response [15]. Recently, NK cells have matured and continue to modulate immune responses, potentially developing into memory cells that confer protection against future infections [55]. NK cells produce antiviral cytokines, release cytotoxic granules such as granzyme B, and trigger the FAS/TRAIL pathway to induce the apoptosis of infected cells [56]. NK cell subsets express various activation and differentiation markers, including CD57, which is considered a marker of memory NK cells that can rapidly expand in response to viral antigens. During DENV infection, activated NK cells express CD69, CD107b and tissue-migrating receptors, suggesting their role in the immune response [57]. Both $CD56^{dim}$ and $CD56^{bright}$ NK cells are similarly activated during DENV infection, with the $CD56^{dim}$ subset displaying potent cytotoxic and cytokine-producing abilities [58]. Reduced NK cell cytotoxicity may lead to uncontrolled macrophage expansion, prolonged proinflammatory cytokine release, and tissue damage, which are associated with macrophage activation syndrome (MAS) as observed in SD cases [59]. In SD, decrease in HLA class I molecules on target T cells signals distress, triggering NK cell activation with peak activation coinciding with critical illness [60]. The HLA B57-restricted NS1 peptide influences killer cell immunoglobulin-like receptor (KIR)$3DL1^{+}$ NK cell function during this phase, suggesting the interplay between HLA class I and NK cell [61]. Viral peptides modulate KIR-MHC interactions, hampering inhibitory KIR-MHC binding and thereby preventing NK cell activation (Fig. 2). The viral peptide repertoire, its binding affinity, and NK cell KIR expression dictate the

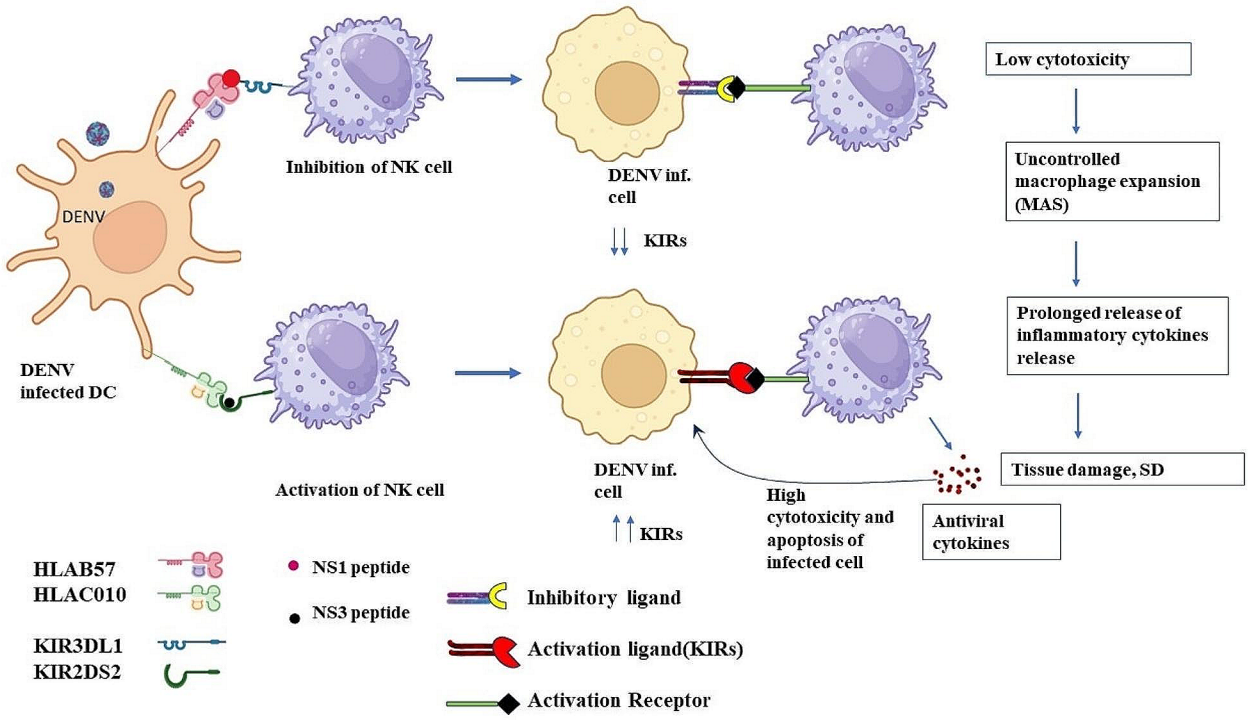

Fig. 2 Dengue virus non-structural protein 1(NS1) inhibits natural killer (NK) cell cytotoxic effects. Dengue NS1 restricts the KIR3DL1 receptor on NK cell and prevents KIR-MHC binding, which further inhibits NK cell function resulting in reduced cytotoxicity. Reduced cytotoxicity causes macrophage hyperactivation and proinflammatory cytokine production leading to tissue damage and clinical severity. On the contrary, NS3 binds with KIR3DL2 receptor and leads to the activation of NK cells, leading to high cytotoxicity and rapid clearance of DENV-infected cells

modulation of NK cell recognition during DENV infection, highlighting the complexity of HLA class I expression, viral peptide presentation, and NK cell activation in dengue illness [61]. The NKp30 receptor and IL-15 levels are significantly elevated in DF patients, facilitating DC-NK cell crosstalk, which is essential for the expression of adaptive immune response. However, NKp30 expression was comparable between healthy controls and SD patients, whereas IL-15 levels remained unaltered [58]. Therefore, the efficient activation of NK cells may be required for mitigating SD manifestations.

Adaptive immune responses in dengue pathogenesis and severity

The adaptive immune response typically develops after one week after the initial DENV infection. Rapid activation of T cells is mediated primarily by DCs and monocytes [62]. However, recent studies have shown that DENV can directly interact with and infect T cells. Specifically, primary naive CD4+ and CD8+ T cells are susceptible to DENV infection [63]. Both cell types support viral replication and secrete viable virus particles during the severe phase of infection [63]. DENV infects and replicates in CD4+ and CD8+ T cells through interactions with the heparan sulfate moiety on the surface of T cells. Interestingly, DENV infection does not induce apoptosis in these T cells, a process generally crucial for viral clearance. This suggests a potential viral escape mechanism that may contribute to disease severity [56, 63, 64]. T cells are the pioneers in the response to viral diseases; however, studies have revealed a paradoxical role, with both protective and pathogenic effects of T cells during DENV infection [65]. The specificity of cross-reactive T cells during primary infection becomes predominant in secondary infection, leading to ineffective viral clearance and promoting excessive production of proinflammatory cytokines, leading to SD [15, 66–68]. In contrast, several studies have suggested the protective role of T cells in DENV infection [69–71]. T cells play a crucial role in defending against DENV infection, with cytotoxic effects and proinflammatory cytokine production being the key mechanisms [72]. The activation of $CD8^+$ T cells in peripheral tissues, particularly in the skin—the primary site of dengue infection—leads to the upregulation of chemokine markers such as CCR-5, CCXR-3, and CXCR-6 [69] (Fig. 3). Additionally, $CD8^+$ T cells induce the expression of CLA, facilitating their infiltration into the dermal region and providing rapid protection during SD [69, 73]. Upon recognition, antigen-specific activated $CD8^+$ T cells differentiate into cytotoxic effector T cells in secondary lymphoid organs, effectively eliminating infected cells [74]. The "original antigenic sin"

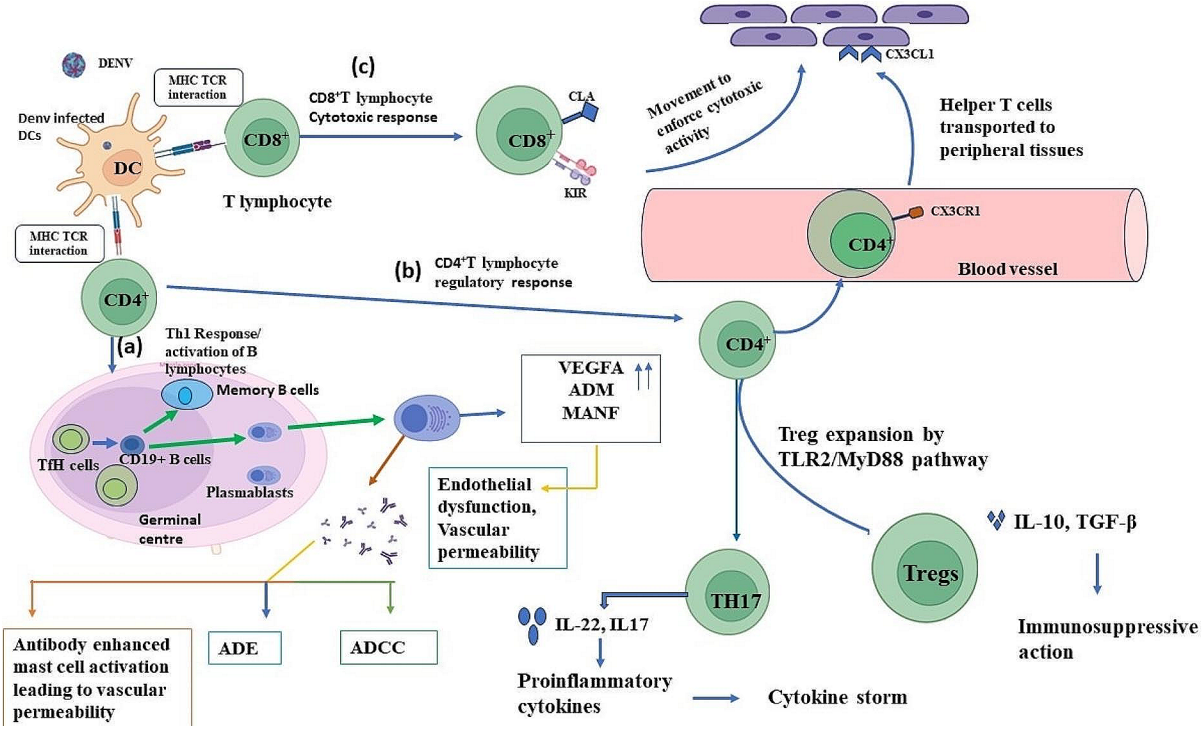

Fig. 3 Adaptive T-cell response to dengue virus (DENV) infection. (**a**) Dendritic cell (DC) presentation of the DENV antigen activates $CD4^+$T cells that develop into T follicular helper (TfH) cells. TfH cell further migrates to the periphery of the B cell follicle in the lymph nodes, where they take part in the germinal center reaction that fosters the growth of DENV-specific plasma cells and memory B cells. These plasma cells enhance the production of antibodies that aid in mast cell activation and activate antibody-dependent cellular cytotoxicity (ADCC) and antibody dependent enhancement (ADE) during secondary DENV infection. (**b**) Activated $CD4^+$T cells also lead to the development of T regulatory (T_{regs}) and T helper 17 (Th17) cells. Th17 cells are then transported to peripheral tissues. (**c**) CD8 + T cells after activation move directly to the peripheral tissues leading to cytotoxic activity

hypothesis in dengue suggests that during secondary infection, cross-reactive memory T cells from the primary infection dominate [70, 75], leading to cytokine storm and SD manifestations. While homologous DENV infections enhance protection, heterologous infections activate both naive and memory T cells, leading to a potentially harmful immune response [71, 76, 77].

Dengue-specific $CD8^+$ T cells include $CD45RA^-CCR\text{-}7^-$ effector memory (T_{em}) and $CD45RA^+CCR\text{-}7^-$ effector memory re-expressing CD45RA (T_{emra}) cells, each exhibiting distinct transcriptomic profiles related to costimulatory and effector functions [78]. Importantly, compared with DENV-specific T_{emra} cells, DENV-specific T_{em} cells presented consistent upregulation of KIR genes, particularly *KIR2DL3* [78]. In dengue patients, a significant increase in $HLA\text{-}DR^+$ $CD38^+$ and $HLA\text{-}DR^-$ $CD38^+$ $CD8^+$ T cells, particularly the $HLA\text{-}DR^+$ $CD38^+$ subset, has been reported, indicating a robust antigen response with proliferation, cytotoxic effects, and tissue surveillance [65]. The genes upregulated in $CD38^+$ $HLA\text{-}DR^+$ $CD8^+$ T cells include *perforin (PRF1), granzyme A, granzyme B, marker of proliferation (MK)I67, TOP2A, checkpoint kinase (CHEK)-1, CXCR-6, CCR-1, CCR-5, CX3CR-1* and *XCL-1*, which are involved in cytotoxic effector activities, tissue homing, and cell proliferation [65, 79]. These findings underscore the crucial role of activated CD8 T cells in tissue surveillance and cytotoxic effector functions [80]. The majority of antigen-specific CD4 T cells, following viral infections develop into Th1 and Tfh cells, which aid CD8 T cells and B cells in the development of germinal centers, where the differentiation of memory B cells and plasmablasts occurs [65]. These DENV-specific CD4 T cells are involved in the production of IFN-γ, TNF-α, and IL-2 postinfection, which are presumed to be involved in the Th1 response [65]. IFN-I induces an immune response in $CD45RA^+CCR\text{-}7^-$ effector-memory expressing T cells (T_{emra}) by stimulating CX3CR-1 cytotoxic $CD4^+$ T cells, which play a protective role in dengue infection [72]. The ligand for CX3CR-1, CX3CL-1/fractalkine is a chemokine produced as a membrane protein in endothelial cells [81]. CX3CR-1 expression promotes migration from the bloodstream to peripheral tissues [82].

Studies that examined the role of T_{regs} in dengue infection reported an increase in $FoxP3^+$ cells compared with those in healthy individuals; however, such enhancement was not associated with disease severity or the viral response [83–85]. TGF-β is important for generating T_{regs} in the peripheral tissue [86], and certain suppressive functions of T_{regs} are mediated by cytokines, such

as IL-10 and TGF-β. However, IL-10 and TGF-β levels do not correlate with the levels of FoxP3+ cells [85]. TGF-β levels initially decrease during dengue infection possibly because of thrombocytopenia, and platelets are the primary machinery involved in the production of TGF-β [87]. Despite lower platelet counts in patients with SD than in those with DF, the plasma TGF-β levels of the patients with SD were higher because of the increased activation of platelets [88]. Most FoxP3$^+$ cells in SD are naive T_{regs} with limited suppressive capacity, whereas only a small fraction exhibit strong suppression [85]. T_{regs} express CTLA-4 and Fas in SD; however, their effectiveness in suppressing DENV-specific T-cells in vivo remains unclear. Additionally, the levels of immunosuppressive cytokines, such as IL-10 and TGF-β, do not correlate with FoxP3$^+$ cell expression, suggesting a predominance of naive, spontaneous T_{regs} [85]. In a recent study, the TLR2/MyD88 pathway was reported to be involved in the T_{regs} proliferation and suppressive capacities, suggesting that DENV is sensed by TLR2, which further influences disease severity [84]. TLR2-mediated T_{regs} proliferation leads to milder dengue manifestations via increased IL-10 production, whereas the activation of macrophages and DCs by TLR2 promotes proinflammatory cytokine production, contributing to SD [84]. Some studies have explored the use of rapamycin and prednisolone as immunomodulators to enhance the suppressive activity of T_{regs}. These findings could guide the development of therapeutic strategies for SD [89].

Recent research has revealed several IL-17-producing cells in DENV-infected patients, particularly in SD patients [90, 91]. Elevated blood levels of IL-17A are associated with SD, along with a positive correlation between serum IL-17A and IL-23, enhancing IL-17-based immune responses [90]. Th17 cells derived from naive CD4$^+$ T cells in response to TGF-β, IL-1β, IL-6, and IL-21 during secondary infection produce IL-17, potentially contributing to the cytokine storm observed in SD patients, suggesting a crucial role of Th17 and IL-17-producing cells in dengue immunopathogenesis [84]. However, Th17 cells also produce another cytokine, IL-22 under the influence of IL23, which induces the innate immune response in secondary infection as a protective response [92]. Therefore, modulating Th17 cells to produce IL-22 could be an important therapeutic strategy for reducing the severity of secondary dengue infection. Therefore, increased levels of IL-17 and IL-10 are indicators of SD [93, 94].

Elevated CD19$^+$ cell levels and altered subgroup distributions were observed in dengue patients, with plasmablasts and plasma cells constituting up to 50% of circulating B cells during acute infection [95]. B cells expressing FcγRIIB receptors, particularly the leukocyte immunoglobulin-like receptor (LIL) RB1, are implicated in ADE, potentially increasing viral susceptibility [96]. The increased proliferation of B cells in dengue is associated with increased Ki67 expression in naive B cells and the role of B-cell activating factor (BAFF) synthesized by IMs [95, 96]. The B-cell response during DENV infection produces antibodies that play a dual role: neutralizing antibodies offer protection, whereas subneutralizing antibodies may facilitate viral entry via Fc receptors, leading to ADE [97, 98]. In severe cases, plasmablasts exhibit increased expression of cytokines such as VEGF-A, which is implicated in vascular permeability, along with adrenomedullin (ADM), ADM-2, and mesencephalic astrocyte-derived neurotrophic factor (MANF), which are known to exacerbate endothelial dysfunction [99]. Elevated levels of bone morphogenetic protein (BMP-6), associated with vascular hyperpermeability, and TNFSF10, with effects similar to those of VEGF, further underscore the complex immune responses in dengue, and could be indicators of SD [99–102].

CD24^{hi} CD27^{hi} and CD24^{hi}CD38^{hi} B cells are known as regulatory B cells (B_{regs}) and produce IL-10 and/or TGF-β to reduce inflammation and suppress proinflammatory Th1/Th17 responses [103]. Tfh cells, a CD4$^+$ T-cell subset found in GCs, influence GC formation and guide humoral responses [104]. Recent studies reported an association between plasmablasts and Tfh cells in SD patients, suggesting that cTfh cells facilitate naive B-cell differentiation into plasmablasts [105]. Additionally, a correlation between CD27$^+$CD38$^+$ plasmablasts and CXCR5$^+$PD-1$^+$ or CXCR5$^+$ICOS$^+$PD-1$^+$ subsets of cTfhs was observed, indicating that regulatory signals promote naive B-cell differentiation during acute DENV2 infection [105]. Patients with kidney and liver damage during acute dengue manifestations also had similar observations, with increased levels of cTfhs. Elevated Tfh levels cause naive B cells to develop into memory B cells and plasmablasts, leading to increased antibody production [105]. Antibodies can form complexes with antigens and deposit them in the glomerular basement membrane, causing kidney damage [105]. B_{regs} are affected by the sCD40L concentration in the blood [106] because sCD40L levels are low in SD patients [107], as they are produced primarily by platelets [106]. Patients with thrombocytopenia generally have a low number of B_{regs} [96], which provides evidence for the above correlation. Naive B cells and plasmablasts were also found to be unresponsive to TLR stimulation in vitro and exhibited decreased production of anti-inflammatory cytokines, such as IL-10 and TNF-α, suggesting ineffective management of cytokine storm during SD [107].

Cytokine modulates immune responses in dengue severity

Cytokines play a crucial role in the pathophysiology of DF, DWS, and SD. Studies have shown that the inflammatory response associated with dysregulated cytokine production assists in the progression to SD [108]. Recent studies have highlighted the complex interplay between proinflammatory and anti-inflammatory cytokines [109, 110] in dengue severity (Fig. 4).

Increased levels of various cytokines, such as TNF-α, IL-1β, IFN-γ, IL-4, IL-6, IL-13, IL-7, GM-CSF, IL-8, IL-10, IL-12p70, IL-17A and MIF are reportedly associated with SD manifestations, such as increased inflammation, endothelial damage, and plasma leakage [109, 111]. IL-6 and IL-8 serve as predictors of dengue severity and are particularly elevated in SD compared with DF [112]. IL-6, which is induced by TNF-α and IL-1, upregulates CRP and sPLA2, potentially impacting endovascular permeability. Compared with those in mild cases, increased IL-6 levels are consistently observed in SD patients [113, 114]. Cytokines such as IL-10 have been identified as potential diagnostic markers for DF [94]. IL-10 is a cytokine with pleiotropic effects on immunoregulation and inflammation, including the inhibition of immune mediator responses such as the activity of Th1-derived IFN-γ and activity of NK cells [115–117], antigen presentation, and phagocytosis [110]. The expression of the immunosuppressive cytokine IL-10 decreases during SD; in contrast, the expression of inflammatory cytokines, such as TNF-α and IL-1β tends to increase during

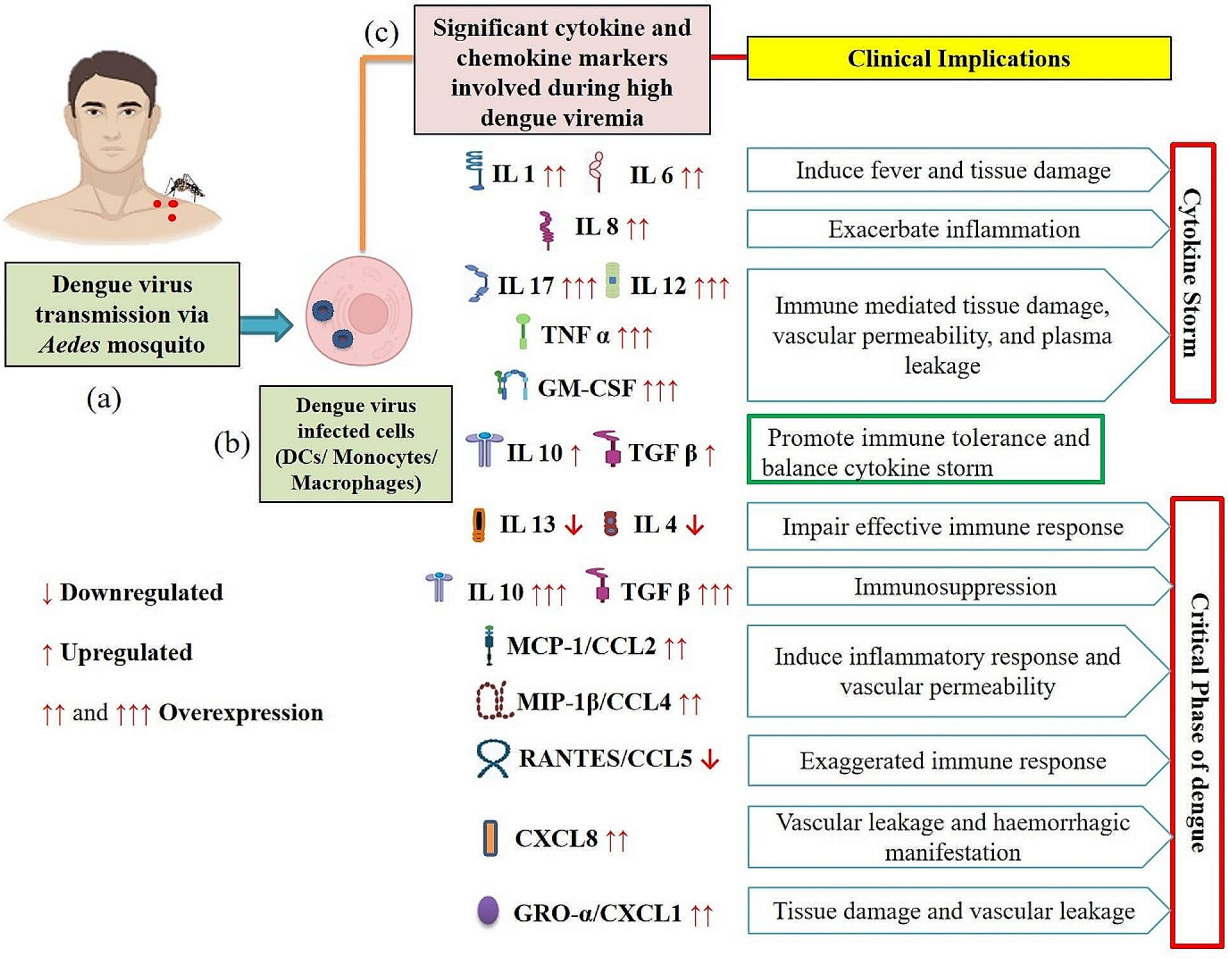

Fig. 4 Mechanistic effects of complex interplay between pro-inflammatory and anti-inflammatory cytokines and chemokines during dengue virus (DENV) infection. (**a**) Infection of DENV to host via *Aedes* mosquito during blood meal. (**b**) DENV infects target cells including dendritic cells, macrophages, and monocytes, initiating host immune response. (**c**) Infected cells release pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-17, IL-12, TNF-α, and GM-CSF and chemokines such as MCP-1/CCL-2, MIP-1β/CCL-4, CXCL-8, and GRO-α/CXCL-1. Proinflammatory cytokines activate other immune cells and promote the release of anti-inflammatory cytokines, such as IL-10 and TGF-β that limits the extent of immune responses. During high dengue viremia, excessive release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-17, IL-12, TNF-α, and GM-CSF) and chemokines (MCP-1/CCL-2, MIP-1β/CCL-4, CXCL-8, and GRO-α/CXCL-1), upregulation of anti-inflammatory cytokines (IL-10 and TGF-β), and downregulation of chemokine RANTES/CCL-5 lead to exaggerated immune response. This surge in immune response results in cytokine storm and contribute to SD manifestations

SD [109]. These complex interactions of several cytokines with negative and positive feedback mechanisms regulate dengue pathogenesis and severity [109].

Cytokine activation is crucial for controlling viral replication; however, excess cytokine activation leads lead to increased inflammation and disease progression [118]. Compared with healthy controls, patients with DF and DWS exhibit increased levels of proinflammatory cytokines TNF-α and CXCL-10 [114]. TNF-α enhancement is associated with increased vascular permeability and platelet phagocytosis, contributing to thrombocytopenia in dengue patients [119]. The regulatory cytokines IL-10 and TGF-β downregulate TNF-α synthesis, whereas IFN-γ induces its synthesis, indicating complex cytokine interactions in dengue pathogenesis [120]. Some studies have reported that neutralizing TNF-α antibodies can effectively reduce dengue encephalitis and mortality [121]. Additionally, phenolic compounds, such as quercetin and fisetin, have been shown to reduce TNF-α levels in DENV-infected mice, suggesting their potential role in managing dengue infection [120].

IFN-γ is a key cytokine in the Th1 response; however, it plays complex roles during dengue infection. High levels of IFN-γ have been found in dengue patients infected with different serotypes, indicating that it is an important cytokine in dengue infection [122]. Activated T lymphocytes and NK cells secrete IFN-γ and exhibit antiviral activity by both directly inducing the expression of effector molecules such as nitric oxide and indirectly by increasing antigen presentation and triggering apoptosis [123]. In addition to these cells, histopathological studies of SD patients have revealed the accumulation of macrophages and mononuclear phagocytes at the site of inflammation, which results in high IFN-γ levels, suggesting the possible role of mononuclear cells in the production of IFN-γ [124]. Serum metabolomics analysis of DF and SD patients identified IFN-γ as a potential early prognostic marker for assessing dengue severity [125]. The Th2 response is typically associated with humoral immunity and is characterized by the production of cytokines, such as IL-4, IL-5, and IL-13, which are less involved in the direct antiviral response and more focused on B-cell activation and antibody production [126]. IL-17 is a cytokine associated with the Th17 response [93]. SD patients exhibit an increased number of T cells expressing IL-17 in renal tissue, which contributes to intense acute inflammation and tissue injury [127]. This, in turn, can lead to an increase in vascular permeability, a characteristic feature of SD [93, 127].

Potential therapeutic strategies against DENV infection

Several strategies involving antioxidants and immunomodulatory molecules could be used for combating dengue disease outcomes. A recent study investigating the effects of quercetin and fisetin flavonoids on dengue cytokine responses revealed that both molecules exhibited antiviral activity against DENV 2 and DENV 3, suggesting potential therapeutic options for dengue management [120]. Flavons (fisetin) and flavonols (quercetin) may function through several mechanisms, including direct interactions with E, NS1, NS3, and NS5 [128–131] or may be involved in modulating signaling pathways involved in innate responses, such as reactivating the JAK-STAT pathways involved in the antiviral response by inducing IFN-I expression [40, 132–134]. Studies have also revealed that quercetin and fisetin have the potential to modulate cytokine responses during dengue infection because of their anti-inflammatory and immunomodulatory properties (Fig. 5) [120]. Both flavonoids inhibit the secretion of TNF-α, which prevents the activation of NF-κB pathways and consequently disrupts the production of other proinflammatory cytokines. Moreover, quercetin and fisetin significantly reduce the production of CCL-2, a chemokine that regulates macrophage and monocyte movement during the inflammatory response, by inhibiting key proinflammatory signaling pathways such as the NF-κB and MAPK pathways [135]. Quercetin also inhibits CXCL8, which induces neutrophil chemoattraction and recruitment. Although quercetin has the potential to alter the kinetics of IL-10 and IFN-γ, it does not influence the regulatory role of IL-10 or the antiviral effects of IFN-γ [120].

Carica papaya L. leaf, a traditional remedy for dengue, has garnered increasing attention for its potential immunomodulatory effects (Fig. 5). A recent study on mice with symptomatic dengue reported an increase in total white blood cell and neutrophil counts posttreatment, alongside a reduction in proinflammatory cytokines in plasma, including GM-CSF, GRO-α, IL-1β, IL-6, MCP-1, and MIP-1β, which are thought to be mediators of SD [136]. This immunomodulatory action is attributed to flavonoids such as quercetin, kaempferol, and rutin [137–139], which are known for their ability to mitigate proinflammatory cytokine production [140, 141]. Additionally, *C. papaya* has been associated with increased platelet levels in patients, potentially through thrombocytosis activity mediated by the upregulation of genes such as *arachidonate 12-lipoxygenase (ALOX-12)* and *platelet-activating factor receptor (PTAFR)* [142]. By mitigating the effects of proinflammatory cytokines such as IL-6 and IL-1 β, which activate monocytes, platelets, and coagulation enzymes, *C. papaya* may prevent thrombocytopenia by reducing monocyte-platelet aggregation near endothelial cells [52, 143].

Several studies investigated the effects of *C. papaya* on dengue patients [142, 144]. In a study involving 300 dengue patients across five health centers in Uttar Pradesh, India, the intervention group treated with papaya leaf

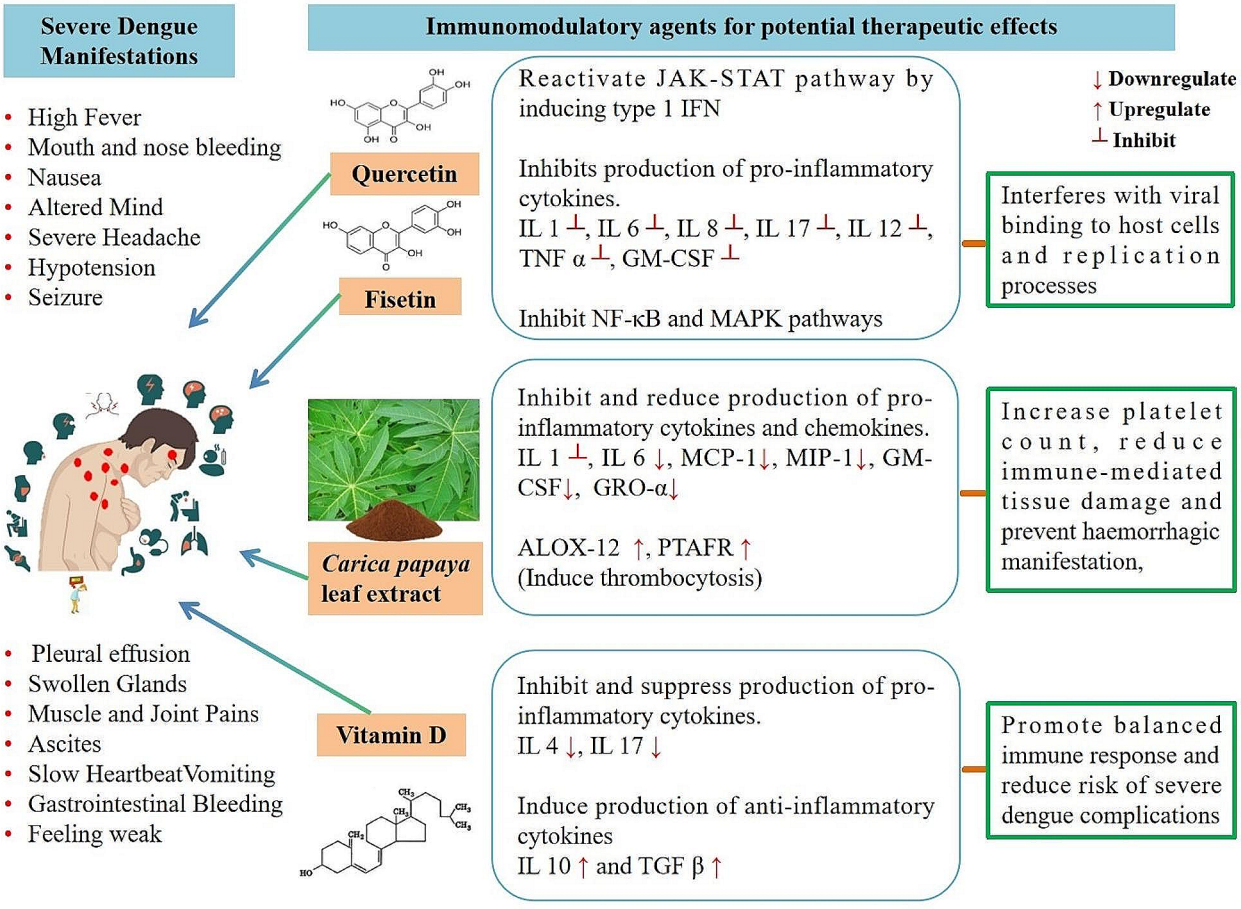

Fig. 5 Mechanistic figure showing potential therapeutic effects of antioxidants including quercetin, fisetin, *Carica papaya* leaf extract, and immunomodulatory agent vitamin D on the cytokine and chemokine responses in suppressing severe dengue manifestations

extract tablets three times a day presented a significant increase in the platelet count within five days of therapy [144]. Similarly, in another investigation conducted in Selangor, Malaysia in 228 patients with SD, half of the participants were included in a treatment group that received oral administration of papaya leaf juice for three days. Blood parameters were monitored every 8 h, and a significant increase in the platelet count was observed in the treated group [142]. There were no reported significant adverse effects following this treatment or toxicology studies, which ruled out any toxic effects even at higher doses [142, 145].

Norantea brasiliensis, another climbing shrub type that grows on the sandbanks of Rio de Janeiro, was found to have both antiviral and immunomodulatory activity; the crude extract as well as its subfractions influenced the production of several cytokines, such as TNF-α, IL-6, IL-10 and IFN-α [146].

The immunomodulator, vitamin D known for its immunomodulatory properties can influence the immune response in DENV infection during entry, recognition and cytokine responses [147] (Fig. 5). Vitamin D inhibits IL-4-mediated DC-SIGN expression, which promotes virus entry in DCs [148]. In the presence of $1,25(OH)_2D_3$, macrophage-derived monocytes (MDMs) exhibit reduced expression of TLR4 [149], which promotes the disruption of endothelial integrity via the production of proinflammatory cytokines [150]. A recent study reported that 1,25(OH)2D3 suppressed the synthesis of IL-17 and IL-4, while promoting the synthesis of IL-10 [151]. IL-10 levels were also increased in patients who received 4000 IU/day of vitamin D for 10 days [37, 149]. Vitamin D is also known to induce the expression of T_{reg} cells, which suppresses proinflammatory responses during DENV infection [152]. A recent clinical trial investigating the role of vitamin D in dengue patients revelaed that vitamin D supplementation suppressed the production of proinflammatory cytokines in MDMs, thereby ameliorating disease severity [153].

Conclusion

The intricate interplay between DENV and the immune system unveils a multifaceted scenario, wherein both innate and adaptive responses play pivotal roles. Specific immune cells, such as CD14+ CD16+ intermediate monocytes (IM) are classical innate markers of dengue severity. Dysregulation of the immune responses is the key strategy employed by DENV for the survival and induction of severe manifestations within the host. Pro-inflammatory cytokines IFN-I, IFN-γ, TNF-α, IL-1β, IL-4, IL-6 and IL-8 are released as a result of this dysregulated state, seriously harming vascular and endothelial tissues. In addition, the expression of specific cellular markers, including TLR2, TLR4, and TGF-β are associated with disease severity. However, certain markers such as IL-10, IL-15, CCR-5, CCR-7, and CD16 are also linked to milder manifestations. Understanding the balance between immune activation, dysregulation, and modulation is of paramount importance in devising effective therapeutic strategies. Future studies could focus on the development of specific immune diagnostic panels, including the targeted innate and adaptive immune markers for dengue severity analysis and early prediction. Docking studies involving antioxidants and plant based products, such as flavonoids and terpenes with DENV proteins could be performed for assessing their interaction with DENV, which can ameliorate disease severity.

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Author contributions
M.K.D. and B.D. did conceptualization, investigation, methodology, project administration, supervision, writing-original draft, writing-review and editing. M.K.D., S.S., and S.R. contributed in formal analysis, figure designing, writing-review & editing. C.K.B and B.D. did review & editing, project administration; M.C.S. and B.D contributed in writing- review & editing, data curation, project administration, supervision.

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Data availability

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Declarations

Ethics approval and consent to participate
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