

Cross-Talk Between JAK/STAT, NF- κ B, and Interferon Signalling Pathways in Dengue Virus Infection: Immunomodulatory and Antiviral Implications of Selenium Supplementation.

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ABSTRACT

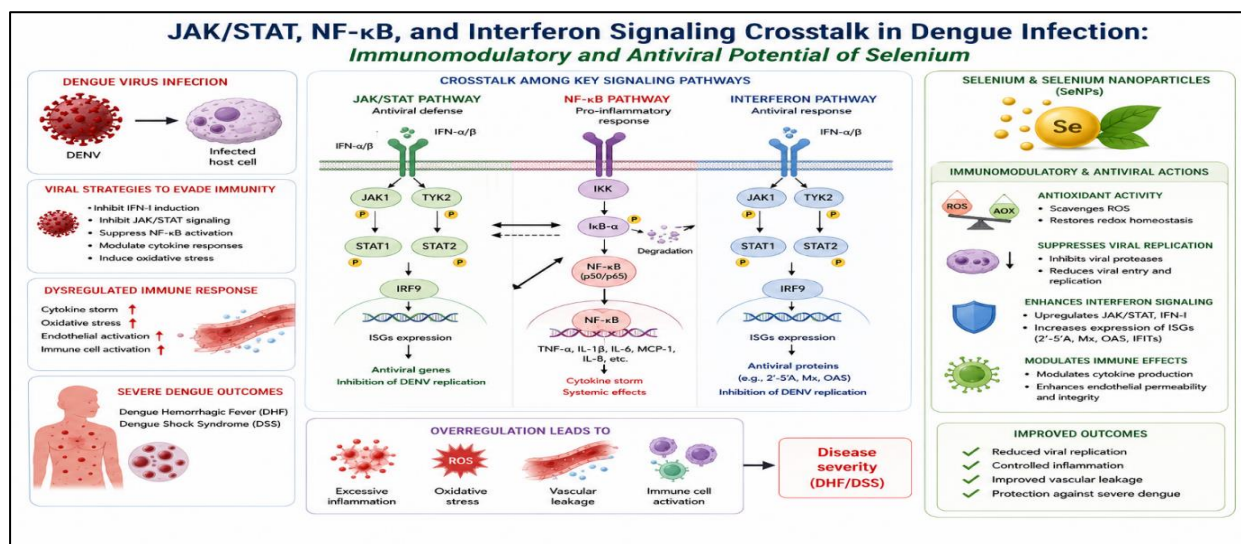
Dengue Virus (DENV) infection has always been a prominent public healthcare challenge all over the world, specifically in tropical & subtropical zones of the globe. Its progression from mild fever to severe dengue induced haemorrhagic fever and dengue shock syndrome is intensely associated with dysregulated immune responses (DIR) and excessive inflammation. Amid the major intracellular signalling pathways playing important roles in dengue pathogenesis, the Janus kinase/signal transducer & activator of transcription (JAK/STAT) pathway, and nuclear factor-kappa B (NF- κ B) pathway, along with interferon (IFN) signalling pathway play pivotal roles in coordinating antiviral defence and inflammatory responses. DENV modulates these pathways to evade host immunity, improve viral replication, and promote cytokine storm creation. Cross-talk among these signalling cascades determines severity of disease by regulating cytokine elaboration, oxidative stress, endothelial permeability, and immunological activation. Selenium, an essential trace element with powerful antioxidant and immunomodulatory properties, has emerged as a promising adjunct active therapeutic molecule in viral infections. Selenium and selenium nanoparticles (SeNPs) regulate redox homeostasis, suppress NF- κ B-mediated inflammation, and enhance interferon-mediated antiviral responses. Recent researches have not only supported but also have signified the antiviral, antioxidative, anti-inflammatory, and immunoprotective effects of selenium formulations for all types of infections including DENV. This review discusses the molecular interactions and correlations among the JAK/STAT pathway, the NF- κ B pathway, and the interferon pathway during dengue infection. It also consists of the discussion on potential immunomodulatory and antiviral implications of selenium supplementation as a host-directed therapeutic strategy.

Keywords: JAK/STAT pathway, NF- κ B, interferon signalling, selenium, selenium nanoparticles, cytokine storm, oxidative stress, antiviral immunity

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INTRODUCTION

Dengue fever falls under the category of most significant viral diseases disseminated through arthropod vectors which affect human being and represents for major concern on public health globally, particularly in the zones of tropical & subtropical climatic conditions (Khan et al., 2023). Dengue Virus popularly denoted as DENV, the main causative agent is a positive-sense single-stranded RNA virus which belongs to the genus *Flavivirus* within the family *Flaviviridae*. There exist four serotypes which can be distinguished antigenically, are DENV-1, DENV-2, DENV-3, and DENV-4. *Aedes aegypti* and *Aedes albopictus* mosquitoes serve as arthropod vectors for spread of these serotype varieties of DENV. (Zerfu et al., 2023) According to global epidemiological estimates, dengue infection affects hundreds of millions of individuals annually, with increasing incidences attributed to urbanization, climate change, globalization, and vector expansion. (Ebi & Nealon, 2016) (Rahman et al., 2024) The scale of this burden continues to grow, as global surveillances have recorded approximately fourteen million dengue cases including more than 9,000 casualties in 2024 alone, the highest annual totals ever documented, underscoring the urgency of understanding the host signalling mechanisms that determine clinical outcome. (Haider et al., 2025) Clinical manifestations of dengue infection encompass quite broad spectrum of diseases which include a wide range starting from asymptomatic infection and self-limiting Dengue fever to the severe levels of dengue related haemorrhagic fever (DHF) and the dengue shock syndrome (DSS). (Nanaware et al., 2021) Life-threatening dengue is characterized by thrombocytopenia, Coagulation disorder, plasma leakage, endothelial dysfunction, hemorrhage, and Multiorgan damage. Although viral disease burden contributes to disease progression, accumulating evidence indicates that Immune-mediated mechanisms and dysregulated host inflammatory responses are the principal determinants severity of disease. (Nasir et al., 2024)

Following entry into host cells, DENV infects monocytes, macrophages, dendritic cells, endothelial cells, and hepatocytes through receptor-mediated endocytosis. (Rouse & Sehwat, 2010) Viral replication induces rapid activation of innate immune signalling pathways through recognition of pathogen associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), including Toll like receptors (TLRs), retinoic acid inducible gene-I (RIG-I), and melanoma differentiation associated protein (MDA5). In turn, activation of above-mentioned receptors induces downstream signalling cascades involving interferon regulatory factors (IRFs), nuclear factor-kappa B (NF-κB), and Janus kinase/signal transducer & activator of transcription

(JAK/STAT) pathways, which co-ordinately control antiviral immunity and inflammatory responses. (Kularatne & Dalugama, 2022) The interferon (IFN) signalling pathway builds the first line of host antiviral defense against dengue infection. Type I interferons (IFN-α and IFN-β) activate interferon-stimulated genes (ISGs) through JAK/STAT-mediated signalling, consequently leading to suppression of viral replication and augmentation of innate and adaptive immune responses. (Chen et al., 2025)

IFNα/β → JAK1/TYK2 → STAT1/STAT2 → ISGs

Though, DENV has evolved advanced immune evasion mechanisms mediated by viral non-structural proteins, namely NS2A, NS4A, NS4B, and NS5, Which impair interferon production and disrupt STAT phosphorylation, thereby impairing antiviral signalling and promoting viral persistence. (Lee et al., 2022a) Concurrently, activation of the NF-κB signalling pathway initiates transcription of numerous pro-inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1). Although controlled NF-κB activation contributes to antiviral defense, excessive or sustained activation promotes Excessive inflammation, endothelial permeability, and cytokine storm Creation, which are hallmarks pathogenesis of severe dengue. (Vendramini-Costa & Carvalho, 2012)

TLR activation → NF-κB → Pro-inflammatory mediators (Proinflammatory cytokines)

Significantly, these signalling pathways do not function autonomously but instead exhibit extensive molecular cross-talk that determines the balance between protective antiviral immunity and Disease-associated inflammation. The interaction between JAK/STAT, NF-κB, and interferon pathways regulates cytokine production, oxidative stress responses, apoptosis, autophagy, and endothelial integrity during dengue infection. Deregulation of this unified signalling network is associated with significantly to viral immune evasion, immune exhaustion, vascular leakage, and advancement toward Life-threatening disease manifestations. (Mahjoor et al., 2023) Oxidative stress has emerged as a critical pathogenic factor in dengue infection. Overproduction of reactive oxygen species (ROS) during viral replication activates redox-sensitive transcription factors like NF-κB and further amplifies inflammatory responses. Elevated oxidative stress also harms endothelial cells, disrupts vascular homeostasis, and contributes to plasma leakage and thrombocytopenia. As a consequence, modulation of

oxidative stress and inflammatory signalling pathways has gained considerable attention as a potential therapeutic strategy related to Dengue disease management. (Zhang et al., 2019)

Selenium (Se), an essential trace element incorporated into Bioactive selenoproteins, plays a fundamental role in Antioxidant defense system, redox regulation, Immune response modulation, and antiviral protection. Selenium-dependent enzymes, involve glutathione peroxidases (GPx), thioredoxin reductases (TrxR), & selenoprotein P, protect cells against oxidative damage by neutralizing reactive oxygen species and maintaining intracellular redox equilibrium. Selenium Inadequacy has been associated with impaired immune function, enhanced oxidative stress, increased viral pathogenicity, and dysregulated inflammatory responses. (Avery & Hoffmann, 2018) Recent advances in nanotechnology have further highlighted the Therapeutic significance of selenium nanoparticles (SeNPs), which possess Increased bioavailability, enhanced biological activity, and reduced toxic effects compared with inorganic selenium-based compounds. Researchers have demonstrated that SeNPs exhibit powerful antioxidant, anti-inflammatory, antiviral, antimicrobial, and immunomodulatory properties. Moreover, selenium nanoparticles have demonstrated modulate NF- κ B & JAK/STAT signalling pathways, suppress ROS-mediated inflammation, and enhance interferon-mediated antiviral responses, suggesting their potential utility as host-directed therapeutic agents against viral infections. (Ikram et al., 2021)

Emerging evidence also indicates that selenium supplementation may attenuate cytokine storm formation, reduce endothelial dysfunction, and restore immune homeostasis during viral infections. Despite increasing interest in selenium biology, the precise molecular mechanisms through which selenium modulates immune signalling cross-talk during DENV infection remain insufficiently understood. (Huang et al., 2012) Therefore, this review aims to comprehensively discuss the molecular interactions among JAK/STAT, NF- κ B, and interferon signalling pathways during DENV infection and critically evaluate the immunomodulatory and antiviral implications of selenium supplementation, with particular emphasis on selenium nanoparticles as emerging therapeutic candidates for dengue-associated inflammatory and oxidative stress-mediated complications.

2. DENV and Host Immune Responses

2.1 DENV Structure and Genome

DF is caused by DENV an enveloped positive-sense single-stranded RNA virus belonging to the genus *Flavivirus* of the *Flaviviridae* family. The virion is approximately 50 nm in diameter and contains a ~10.7 kb RNA genome flanked by untranslated regions essential for viral replication and translation.

The viral genome encodes a single polyprotein that is cleaved into: (Iheukwumere et al., 2025) 1. Three structural proteins: Capsid (C), premembrane/membrane (prM/M), and envelope (E), 2. Seven non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5

The envelope (E) glycoprotein mediates host-cell attachment and membrane fusion, while non-structural proteins regulate viral replication and immune evasion. NS5 functions as an RNA-dependent RNA polymerase and suppresses interferon-mediated antiviral signalling through STAT2 degradation. (Roy et al., 2024)

2.2 Viral Entry and Replication

DENV infects monocytes, macrophages, dendritic cells, endothelial cells, and hepatocytes through receptor-mediated endocytosis involving receptors such as DC-SIGN, mannose receptor, and heparan sulfate proteoglycans. (Begum et al., 2019)

DENV attachment → endocytosis → endosomal fusion → RNA release

Following endosomal acidification, conformational rearrangement of the E protein promotes membrane fusion and release of viral RNA into the cytoplasm. The positive-sense RNA genome is translated into a polyprotein at the rough endoplasmic reticulum and processed into mature viral proteins.

(+ssRNA) → polyprotein translation → replication complex formation → progeny RNA synthesis

Replication occurs within ER-derived membranous replication complexes formed by NS proteins. Newly synthesized virions mature through the Golgi apparatus and are released by exocytosis. Viral replication induces oxidative stress, ER stress, mitochondrial dysfunction, and inflammatory signalling activation. (Kim et al., 2017) (Reyes-del Valle et al., 2014)

2.3 Innate Immune Recognition

First line immune defence responses recognize DENV derived pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), including Toll-like receptors (TLR3, TLR7), Retinoic acid-inducible gene-I (RIG-I) and Melanoma differentiation-associated protein 5 (MDA5) Recognition of viral RNA activates adaptor proteins such as MAVS (Mitochondrial Antiviral Signalling Protein) and MyD88 (Myeloid Differentiation Primary Response 88) and TRIF (TIR-DOMAIN-CONTAINING ADAPTOR-INDUCING INTERFERON-B), leading to activation of interferon regulatory factors (IRF3/IRF7) & NF- κ B signalling pathways. (Kao et al., 2018a)

DENV RNA → TLRs/RIG-I/MDA5 → IRF3/IRF7 and NF- κ B activation

IRF3 and IRF7 stimulate production of type I interferons (IFN- α/β), that activate the pathway of JAK/STAT and stimulating interferon-genes (ISGs) with against viral activity. (Muhammad et al., 2025)

IFN- α/β $\rightarrow$ JAK/STAT $\rightarrow$ ISGs

$\rightarrow$ antiviral response

Simultaneously, NF- κ B activation induces advance inflammatory, cytokines including TNF- α , IL-6, and IL-1 β . overactivation of these pathways contributes to cytokine storm formation, endothelial dysfunction, thrombocytopenia, and vascular leakage associated with severe dengue infection.(Shrivastava et al., 2020)

3. JAK/STAT Signalling Pathway in Dengue Infection

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a major antiviral signalling cascade activated during DF infection. Type I interferons (IFN- α/β) produced following viral recognition bind to interferon receptors (IFNAR1/IFNAR2), leading to activation of JAK1 and TYK2 kinases.(Schiefer & Hale, 2024)

IFN- α/β $\rightarrow$ IFNAR $\rightarrow$

JAK1/TYK2 $\rightarrow$ STAT1/STAT2

Activated JAK kinases phosphorylate STAT1 and STAT2 proteins, that associate with IRF9 to form the ISGF3 transcription complex. ISGF3

translocates to the nucleus and induces transcription of interferon-stimulated genes (ISGs) that establish an antiviral state within infected and neighboring cells. (Fig. 01. Mechanism of Activation)

STAT1 + STAT2 + IRF9 $\rightarrow$ ISGF3 $\rightarrow$ ISGs

Interferon-stimulated genes including PKR, OAS, Mx proteins, and IFIT proteins inhibit viral RNA replication, suppress viral protein synthesis, degrade viral genomes, and enhance innate immune defense. In addition, JAK/STAT signalling regulates natural killer cell activation, antigen presentation, cytokine production, and adaptive immune responses.(Weber, 2020)

ISGs $\rightarrow$ inhibition of DENV replication and antiviral immunity

Despite its antiviral role, DENV efficiently suppresses JAK/STAT signalling through multiple immune evasion mechanisms mediated by viral non-structural proteins. NS5 induces proteasomal degradation of STAT2, thereby preventing formation of the ISGF3 complex and reducing antiviral gene expression.(Lee et al., 2022b)(Fig. 02. Antiviral Functions)

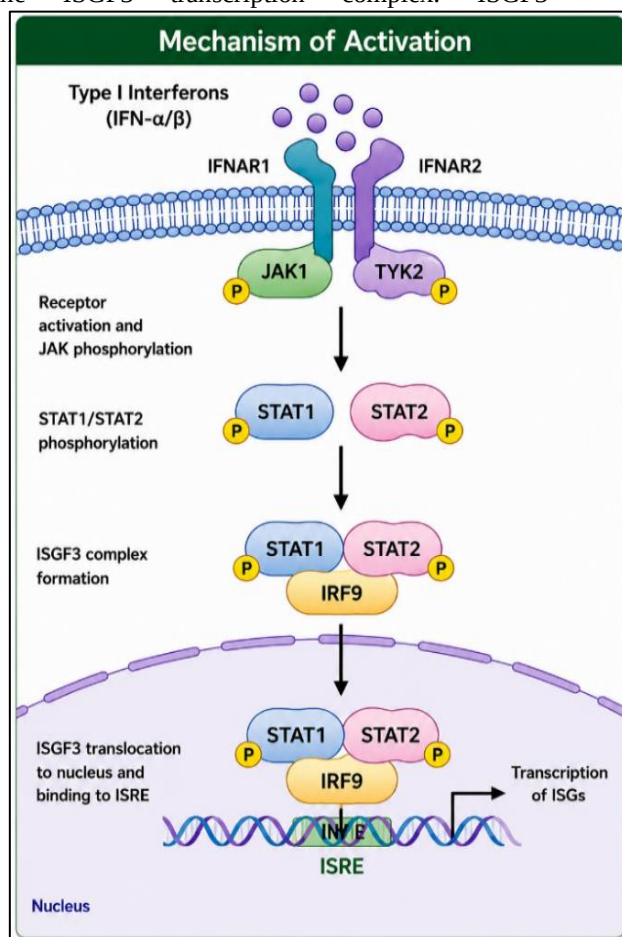


Fig. 01. Mechanism of Activation

DENV NS5 $\rightarrow$ STAT2 degradation $\rightarrow$ impaired antiviral signalling

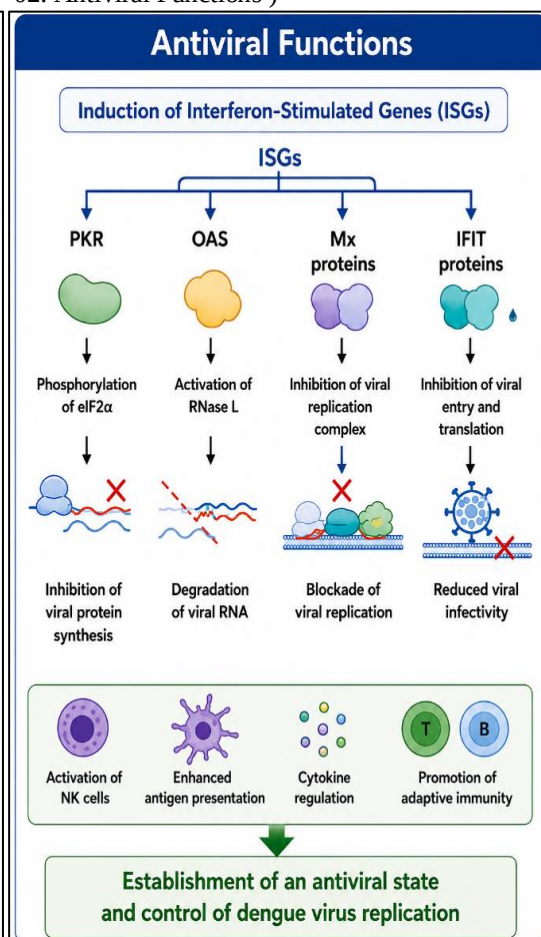


Fig. 02. Antiviral Functions

NS4B inhibits STAT1 phosphorylation, while NS2A and NS4A interfere with upstream interferon production by suppressing IRF3 activation. These mechanisms impair interferon-mediated antiviral

responses, enhance viral replication, and contribute to immune dysregulation and severe dengue pathogenesis.(Dodantenna, 2026) (Fig. 03. Viral Evasion Mechanisms)

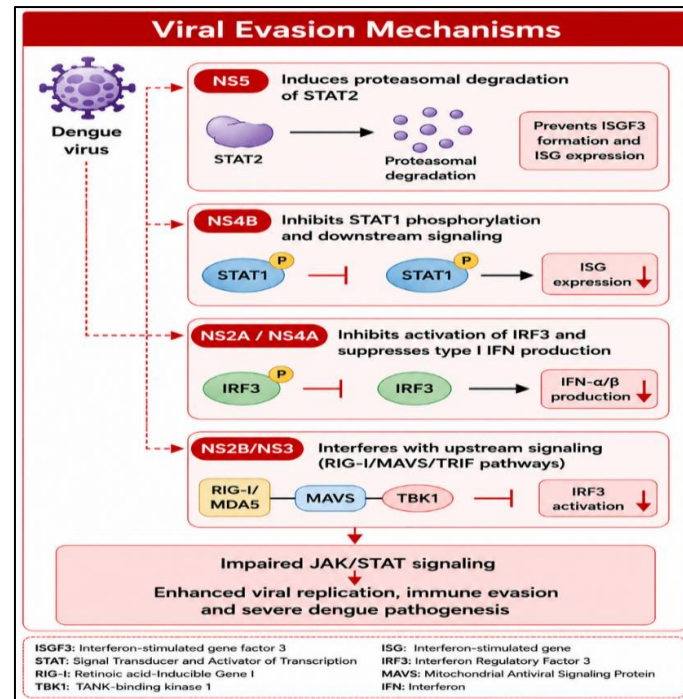


Fig. 03. Viral Evasion Mechanisms

4. NF-κB Signalling Pathway in Dengue Infection

The main signalling pathway nuclear factor-kappa B (NF-κB) is a central coordinator of inflammatory and first line immune response during DF infection. Activation of NF-κB occurs rapidly following recognition of dengue viral RNA by pattern recognition receptors and contributes to transcription of advance inflammatory cytokines, chemokines, adhesion molecules, and immune mediators. Although controlled NF-κB activation participates in antiviral defense, excessive and sustained activation contributes significantly to immunopathogenesis, vascular leakage, and severe dengue manifestations. (Chermahini et al., 2025)

4.1 Activation of NF-Kb

DENV infection activates NF-κB signalling through engagement of Toll-like receptors (TLRs), RIG-I-like receptors, and other pathogen recognition receptors expressed on immune and endothelial cells. Viral RNA recognition activates adaptor proteins including MyD88, MAVS, and TRIF (TIR-DOMAIN-CONTAINING ADAPTOR-INDUCING INTERFERON-B), leading to activation of the IκB kinase (IKK) complex. (Valdés-López et al., 2025a)

DENV RNA → TLR3/TLR7/RIG-I → MyD88/TRIF (TIR-DOMAIN-CONTAINING ADAPTOR-INDUCING INTERFERON-B)/MAVS → IKK activation

Activated IKK phosphorylates inhibitor of κB (IκBα), targeting it for ubiquitination and proteasomal degradation. Degradation of IκBα releases NF-κB dimers, primarily p65/p50, which translocate into the nucleus and initiate transcription of inflammatory genes.

IKK → IκBα phosphorylation → NF-κB nuclear translocation

In addition to PRR-mediated activation, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress induced during dengue replication further amplify NF-κB activation.

4.2 Role in Inflammation

NF-κB regulates expression of numerous inflammatory mediators that contribute to antiviral defense and immune cell recruitment. Activated NF-κB induces transcription of: TNF-α, IL-6, IL-1β, IL-8, MCP-1, ICAM-1 and VCAM-1

NF-κB → TNF-α,

IL-6, IL-1β, MCP-1

These mediators promote: Leukocyte recruitment, Endothelial activation, Vascular permeability, Fever and systemic inflammation. NF-κB signalling also interacts with MAPK and JAK/STAT pathways to coordinate innate and adaptive immune responses. Controlled activation assists in viral clearance by enhancing cytokine-mediated antiviral defense and immune surveillance. However, persistent activation results in excessive inflammatory responses and tissue injury. Increased NF-κB activity has been strongly associated with endothelial dysfunction, thrombocytopenia, plasma leakage, and disease severity in dengue patients. (Uno & Ross, 2018a) (Pan et al., 2022)

4.3 NF-κB and Cytokine Storm

Hyperactivation of NF-κB is a major contributor to cytokine storm formation during severe dengue infection. Excessive production of pro-inflammatory cytokines and chemokines results in systemic hyperinflammation and vascular pathology.

Excessive NF- κ B activation $\rightarrow$ cytokine storm $\rightarrow$ vascular leakage

Elevated levels of TNF- α , IL-6, IL-1 β , IFN- γ , and other inflammatory mediators increase endothelial permeability through disruption of tight junction proteins and glycocalyx integrity. This leads to plasma leakage, hypotension, hemorrhage, and progression toward dengue hemorrhagic fever and dengue shock syndrome. (Valdés-López et al., 2025b)

Reactive oxygen species (ROS) generated during infection further amplify NF- κ B activation, establishing a positive feedback loop between

oxidative stress and inflammation. (Batista et al., 2025)

ROS $\rightarrow$ NF- κ B activation $\rightarrow$ inflammatory amplification

Moreover, dengue viral proteins such as NS1 contribute to endothelial activation and cytokine dysregulation through NF- κ B-dependent mechanisms. Persistent inflammatory signalling may also induce apoptosis, mitochondrial injury, and immune exhaustion, thereby aggravating disease severity. (Tarasuk et al., 2022) (Fig. 04. NF- κ B Signalling Pathway in Dengue Infection)

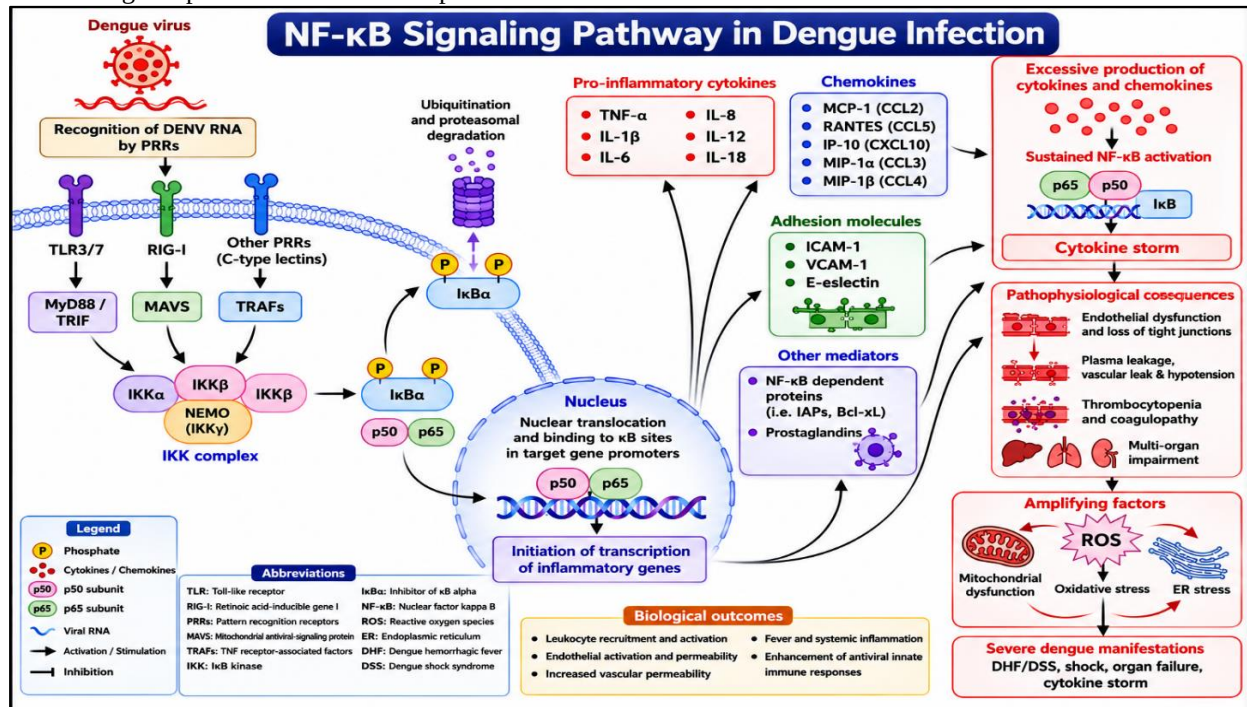


Fig. 04. NF- κ B Signalling Pathway in Dengue Infection

Consequently, modulation of NF- κ B signalling has emerged as a promising therapeutic strategy to reduce hyperinflammation and prevent severe dengue-associated complications. (Rama Ravo & Yap, 2025)

5. Interferon Signalling Pathway in Dengue

Interferon (IFN) signalling represents the primary antiviral defense mechanism against DF infection. Recognition of dengue viral RNA by pattern recognition receptors including TLR3, TLR7, RIG-I, and MDA5 activates interferon regulatory factors IRF3 and IRF7, leading to production of type I interferons (IFN- α/β). (Kao et al., 2018b)

DENV RNA $\rightarrow$ IRF3/IRF7

$\rightarrow$ IFN- α/β

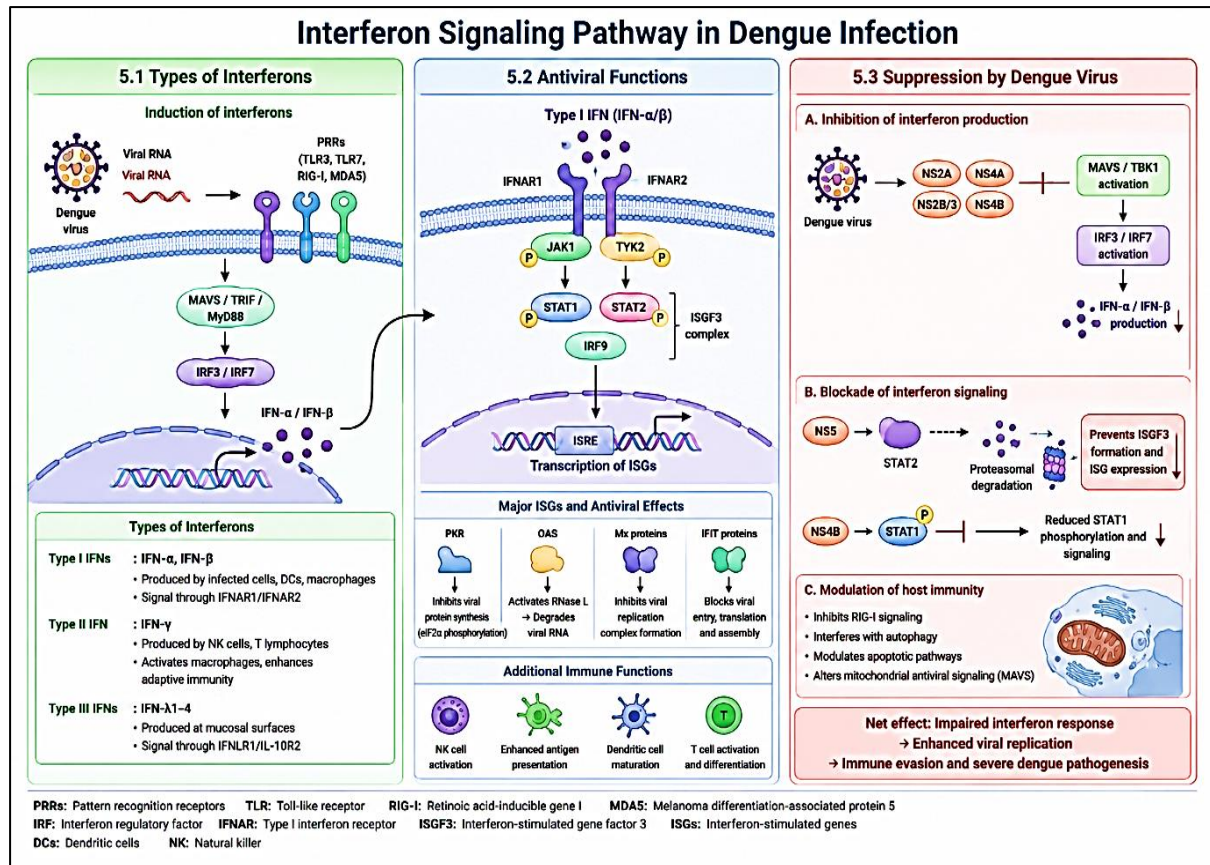
Type I interferons bind to IFNAR receptors and activate the JAK/STAT signalling cascade, resulting in formation of the ISGF3 transcription complex and induction of interferon-stimulated genes (ISGs). (Rahbari et al., 2017)

IFNAR $\rightarrow$ JAK1/TYK2 $\rightarrow$ STAT1/STAT2 $\rightarrow$ ISGF3 $\rightarrow$ ISGs

Interferon-stimulated proteins including PKR, OAS, Mx, and IFIT suppress dengue viral replication through inhibition of viral RNA synthesis, degradation of viral genomes, and blockade of viral protein translation.

PKR/OAS/Mx/IFIT $\rightarrow$ inhibition of DENV replication

In addition to direct antiviral effects, interferons enhance natural killer cell activation, antigen presentation, dendritic cell maturation, and adaptive immune responses. Dengue virus efficiently suppresses interferon signalling through multiple immune evasion mechanisms mediated by non-structural proteins. NS5 induces proteasomal degradation of STAT2, while NS4B inhibits STAT1 phosphorylation and downstream antiviral signalling. (Diamond, 2009; A. Ghosh et al., 2025; Guo et al., 2018a)



DENV NS5 → STAT2 degradation → impaired IFN signalling

Furthermore, NS2A, NS4A, and NS2B/3 inhibit IRF3 and TBK1 activation, reducing type I interferon production and weakening antiviral immunity.

NS2A/NS4A/NS2B3 → IRF3/TBK1 inhibition → reduced IFN production

Suppression of interferon signalling facilitates viral replication, immune evasion, cytokine dysregulation, and progression toward severe dengue pathogenesis. (A. Ghosh et al., 2025)

6. Cross-Talk Between JAK/STAT, NF-κB, and Interferon Pathways

The JAK/STAT, NF-κB, and interferon pathways form an interconnected immune signalling network during DF infection. Recognition of dengue viral RNA by TLRs, RIG-I, and MDA5 activates both NF-κB and interferon regulatory factors (IRF3/IRF7), leading to production of pro-inflammatory cytokines and type I interferons. (Macha et al., 2024)

DENV RNA → IRF3/IRF7 + NF-κB activation

Type I interferons activate the JAK/STAT pathway through IFNAR-mediated phosphorylation of STAT1 and STAT2, resulting in induction of interferon-stimulated genes (ISGs) with antiviral activity. (Uno & Ross, 2018b)

IFN-α/β → **JAK/STAT → ISGs**
 NF-κB signalling regulates inflammatory cytokines

including TNF-α, IL-6, IL-1β, and IFN-β, thereby coordinating antiviral immunity and inflammatory responses.

NF-κB → TNF-α, IL-6, IL-1β

During severe dengue infection, excessive NF-κB activation and suppression of interferon/JAK/STAT signalling by viral non-structural proteins lead to cytokine storm, oxidative stress, endothelial dysfunction, and enhanced viral replication.

NS5 → STAT2 degradation → impaired antiviral signalling

Thus, balanced cross-talk among these pathways is essential for effective antiviral defense, whereas dysregulation contributes to severe dengue pathogenesis. (Badia et al., 2022; Guo et al., 2018b; Shil et al., n.d.; Zhong et al., 2025)

Systems-level mathematical modelling of this network lends quantitative support to the qualitative picture above: coupled positive-feedback (autocrine IFN-β stabilising nuclear IRF3 and NF-κB within the first responding cells) and positive-feedforward (paracrine IFN-β sensitising neighbouring cells through up-regulation of RIG-I, PKR, and OAS1A) circuits convert graded viral signals into switch-like, near-binary cell-fate decisions between an antiviral state and apoptosis, in contrast to the more graded, pulsatile responses evoked by bacterial ligands. (Czerkies et al., 2018) Extending this framework to dengue infection, NS5-mediated

STAT2 degradation and NS2A/NS4A-mediated suppression of IRF3 activation (Section 3) can be understood not merely as isolated lesions in single pathways but as interventions that destabilise the entire feedback architecture linking IRF3, NF-κB,

and JAK/STAT. The practical consequence is that infected and bystander cells may fail to commit cleanly to a protective antiviral programme, instead drifting toward the mixed, hyperinflammatory phenotype that characterises severe dengue.

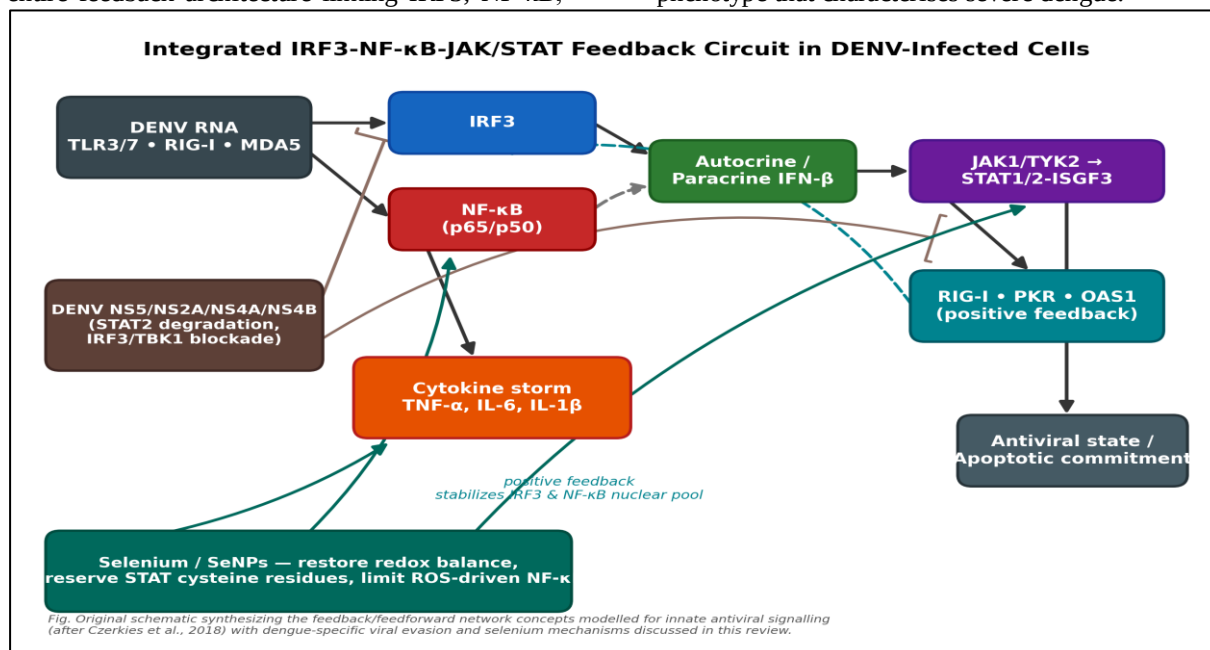


Fig. 06. Integrated IRF3-NF-κB-JAK/STAT Feedback Circuit Linking Viral Evasion Mechanisms and Candidate Selenium Intervention Points (original schematic).

7. Oxidative Stress in Dengue Pathogenesis

Oxidative stress is now recognized as a central feature of dengue pathogenesis. As the virus replicates within host cells, it disrupts mitochondrial function, induces endoplasmic reticulum stress, and activates inflammatory immune pathways collectively driving excessive reactive oxygen species production.

DENV replication → ROS generation → oxidative stress

Elevated ROS activates NF-κB and inflammatory signalling pathways, leading to increased formation of TNF-α, IL-6, IL-1β, and additional pro-inflammatory mediators. (Olagner et al., 2014)

ROS → NF-κB activation → inflammatory cytokines

Oxidative stress also contributes to endothelial dysfunction, lipid peroxidation, mitochondrial injury, apoptosis, vascular permeability, plasma leakage, thrombocytopenia, and severe dengue manifestations. (Fernandes-Santos & de Azeredo, 2022)

7.1 Sources and Amplifiers of Oxidative Stress in DENV Infection

Beyond pattern-recognition-receptor signalling, DENV disrupts the host's endogenous antioxidant defence system at its transcriptional root. The nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) axis normally coordinates the antioxidant gene network responsible for glutathione and thioredoxin

biosynthesis. During DENV infection, the viral NS2B3 protease complex targets Nrf2 for proteolysis-independent, lysosome-dependent degradation, silencing this protective network and permitting progressive ROS accumulation between 24- and 48-hours post-infection. (Bedford et al., 2020)

DENV NS2B3 → Nrf2 degradation → antioxidant gene suppression → ROS accumulation

Loss of Nrf2 activity not only removes antioxidant buffering but also disinhibits NF-κB-dependent inflammatory transcription and interferon signalling, since Nrf2 normally exerts feedback restraint over both pathways; its depletion therefore represents a convergence point at which oxidative, inflammatory, and antiviral signalling become mutually reinforcing. (Ferrari et al., 2020) Individuals with glucose-6-phosphate dehydrogenase (G6PD) Inadequacy, which restricts NADPH regeneration essential for glutathione recycling, show heightened susceptibility to DENV replication, underscoring the dependence of antiviral redox defence on unimpaired pentose phosphate pathway activity. (Ferrari et al., 2020)

7.2 Cellular oxidative stress biological markers and Correlation with Disease Severity

Clinical investigations Repeatedly show that circulating markers of lipid and protein oxidation rise in parallel with clinical severity of dengue,

while enzymatic antioxidant defence decline. (Gil et al. 2004) reported elevated peroxidation potential and malondialdehyde plus 4-hydroxyalkenal concentrations, together with altered superoxide dismutase and reduced glutathione peroxidase activity, in adult dengue patients relative to healthy controls. (Lim et al., n.d.) similarly documented measurable oxidative damage, evidenced by elevated protein carbonyl and malondialdehyde levels, early in the course of DF, and subsequent work indicates that oxidative stress is maximally

increased in dengue shock syndrome, intermediate in dengue haemorrhagic fever, and lowest in uncomplicated DF, indicating a severity-dependent gradient (Ferrari et al., 2020; Lim et al., n.d.) extended these observations by linking oxidative modification of plasma proteins and lipid peroxidation, assessed around defervescence, to pro-inflammatory cytokine concentrations and to subsequent progression toward severe dengue, proposing oxidative biomarkers as early predictors of clinical deterioration.

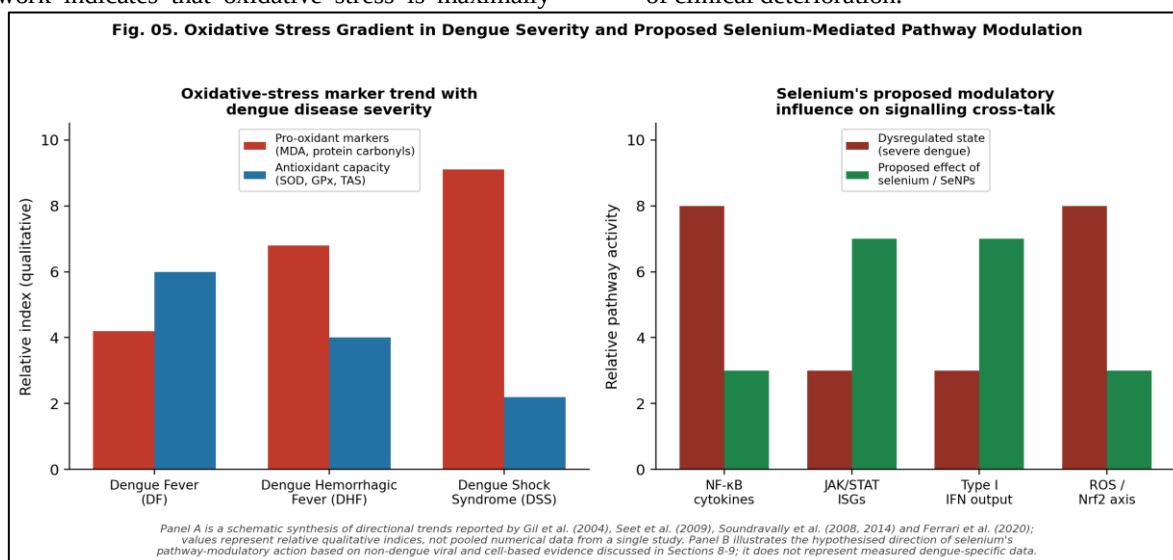


Fig. 05. Oxidative-Stress Gradient Across Dengue Severity and Proposed Selenium-Mediated Pathway Modulation (schematic synthesis of literature trends)

7.3 Pathophysiological Consequences of Oxidative Injury

Sustained ROS exposure damages endothelial tight-junction proteins and the glycocalyx layer, promoting the vascular permeability that underlies plasma leakage in dengue haemorrhagic fever and dengue shock syndrome. Concomitant mitochondrial injury and lipid peroxidation activate intrinsic apoptotic pathways in endothelial and immune cells, while oxidative modification of platelet membranes has been implicated in thrombocytopenia. (Perera et al., 2025)

Oxidative injury → endothelial/glycocalyx damage → plasma leakage + thrombocytopenia

Because Nrf2 depletion, NF-κB hyperactivation, and impaired interferon signalling converge on a common redox-sensitive node, therapeutic strategies capable of restoring antioxidant capacity, such as the selenium-dependent enzyme systems discussed in the following sections, are of particular mechanistic interest for interrupting this self-amplifying cycle. (Ke Yee et al., 2026)

8. Selenium and Immune Regulation

Selenium is an essential trace element involved in antioxidant defense, redox regulation, and immune homeostasis. Selenium is incorporated into biologically active selenoproteins including glutathione peroxidase (GPx), thioredoxin reductase

(TrxR), and selenoprotein P. (Zoidis et al., 2018)

8.1 Biological Functions

Selenium-dependent enzymes regulate intracellular redox balance by neutralizing reactive oxygen species and protecting cellular structures from oxidative damage.

Selenium → GPx/TrxR activation → ROS detoxification

Selenium additionally enhances innate and adaptive immunity, regulates cytokine production, maintains endothelial integrity, and modulates inflammatory signalling pathways. (Dong, Li, Wang, Meng, Chang, et al., n.d.; Szliszka et al., 2009)

8.2 Selenium Nanoparticles

SeNPs (Selenium nanoparticles) exhibit enhanced bioavailability, improved biological activity, and low toxic effect compared with inorganic selenium compounds. (Lubos et al., 2011)

SeNPs (Selenium Nanoparticles) → Improved antioxidant and antiviral activity

SeNPs (Selenium nanoparticles) Preferentially scavenge ROS, suppress inflammatory signalling, and Shield cells from damage against oxidative injury. (Hawkes & Alkan, 2010;)

8.3 Selenium Deficiency and Enhanced Viral Virulence: Mechanistic Evidence

Evidence-based findings for selenium's role in restraining RNA virus pathogenicity comes from

classic studies in selenium-deficient murine models. (Beck et al. 1995) revealed that an ordinarily benign strain of coxsackievirus B3 acquired stable, virulence-conferring point mutations in its genome after replicating in selenium-deficient mice, converting it into a myocarditis-inducing pathogen; the mutant strain retained its virulence. When thereafter passaged into selenium-replete animals, affirming that the change resided in the viral genome instead of the host. (Beck, n.d.)

Selenium inadequacy → impaired glutathione peroxidase-1 activity → RNA virus genome mutation → Enhanced virulence

Documented comparable findings across several RNA virus families, Such as influenza and poliovirus, concluding that host Selenium inadequacy below about 1 µmol Se/L blood promotes oxidative-stress-driven viral genome Unstable state and impairs immunocompetence, with selenium repletion reducing mutation frequency and re-establishing immune function. The available evidence derives principally from coxsackievirus and influenza models rather than DENV directly; it establishes a plausible mechanistic rationale for evaluating selenium status as a determinant of flavivirus behaviour in a Selenium-inadequate host, a hypothesis That persists to be tested specifically in dengue (Harthill (2011))

8.4 Selenium Status in Viral and Critically Ill Populations

Observational evidence from other acute viral and severe illness settings reinforces the association between low circulating selenium and unfavourable clinical trajectories. In patients with critical illness, serum selenium concentrations below about 70 µg/L have been associated with higher illness-severity scores and elevated inflammatory markers, while selenium supplementation has been linked to favourable changes in procalcitonin, C-reactive protein, and inflammatory cytokine concentrations. (Mahmoodpoor et al., 2022)

Comparable severity-dependent decreases in serum selenium have also been reported in SARS-CoV-2 infection, with patients with worsening disease exhibiting lower selenium concentrations than those with mild disease. Dengue-specific selenium status data remain limited, but these cross-viral observations support the biological plausibility of selenium depletion as a contributor to, rather than merely a consequence of, life-threatening viral infection.

9. Immunomodulatory Effects of Selenium in Dengue

Selenium exerts potent immunomodulatory and

antiviral effects through regulation of oxidative stress and immune signalling pathways including NF-κB, JAK/STAT, and interferon signalling.

9.1 Selenium and NF-κB Suppression

Selenium suppresses ROS-mediated NF-κB activation and reduces production of pro-inflammatory cytokines. (Cheng et al., 2024)

Selenium → reduced ROS → NF-κB suppression

This leads to decreased expression of TNF-α, IL-6, IL-1β, and MCP-1.

9.2 Selenium and JAK/STAT Regulation

Selenium enhances interferon-mediated JAK/STAT signalling and promotes expression of interferon-stimulated genes involved in antiviral defense. (Tolomeo et al., 2022)

Selenium → enhanced JAK/STAT signalling → ISGs

9.3 Selenium and Interferon Responses

Selenium supports interferon production and enhances innate antiviral immunity through modulation of redox-sensitive signalling pathways. (Dong, Li, Wang, Meng, Cui, et al., n.d.)

Selenium → enhanced IFN-α/β responses

9.4 Antiviral Potential

Selenium and selenium nanoparticles exhibit broad antiviral activity through antioxidant, anti-inflammatory, and immune-regulatory mechanisms.

SeNPs → antiviral immunity + reduced inflammation

Experimental studies demonstrated that SeNPs reduce oxidative stress, enhance immune responses, suppress inflammatory cytokines, and improve cellular antioxidant capacity. (J. Ghosh & Chattopadhyay, 2026; Jakopovic et al., 2021)

Direct, dengue-specific in vitro evidence for selenium's antiviral activity does in fact exist, partially closing the translational gap noted elsewhere in this review: biosynthesised selenium nanoparticles produced by actinobacteria demonstrably suppressed the growth of DENV serotype 1 in cell culture, alongside concurrent antioxidant and anti-biofilm activity, providing a proof-of-concept that SeNPs can act directly on a dengue serotype rather than only through host-directed antioxidant mechanisms. More broadly, recent medicinal-chemistry surveys classify organoselenium antivirals into several structural families, including ebselen derivatives, N-heterocyclic selenium compounds, and selenium nanoparticles, each acting through overlapping redox-modulatory and enzyme-inhibitory mechanisms, reinforcing the rationale for evaluating these agents as host-directed adjuncts across RNA virus infections, dengue included. (Jain & Priyadarsini, 2026)

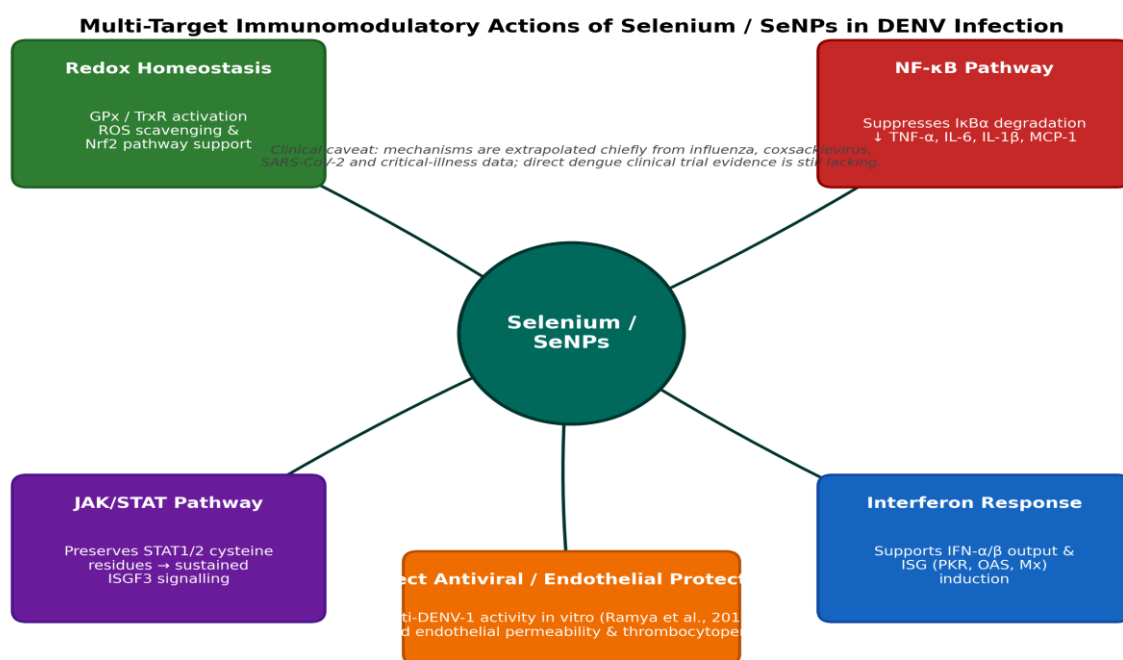


Fig. 07. Multi-Target Immunomodulatory Actions of Selenium and Selenium Nanoparticles Across the JAK/STAT, NF-κB, and Interferon Pathways (original schematic).

9.5 Mechanistic Extensions Across Selenium-Modulated Pathways

In H1N1 influenza models, selenium nanoparticles administered to selenium-deficient mice restored tissue selenium content and attenuated virus-induced elevations in NF-κB, TNF-α, IL-1β, and IL-6, together with reduced apoptotic lung injury, illustrating a direct in vivo link between selenium repletion and dampened NF-κB-driven inflammation during RNA virus infection. (Liu et al., 2023) Selenoprotein-dependent maintenance of intracellular redox balance preserves the cysteine residues required for JAK/STAT kinase activity and DNA binding, providing a biochemical rationale for selenium's capacity to sustain interferon-driven STAT1/STAT2 phosphorylation under oxidative challenge, an effect that would be expected to oppose the JAK/STAT suppression exerted by dengue non-structural proteins described in Section 3.

Mechanistically, selenium nanoparticles exert dual redox control by inducing localised ROS generation sufficient to damage viral nucleic acids and envelope proteins, while simultaneously limiting the excessive systemic ROS accumulation that would otherwise injure host cells; ribavirin-conjugated selenium nanoparticles have additionally been shown to suppress caspase-3-dependent apoptotic signalling and neuraminidase activity in influenza models, illustrating the structural versatility of selenium-based antiviral strategies. (Jain & Priyadarsini, 2026)

9.6 Translational Considerations and Evidence Gaps

It is important to note that most of the mechanistic evidence summarised above is derived from coxsackievirus, influenza, SARS-CoV-2, and general critical-illness models rather than from dengue-infected human subjects. A notable exception is the in vitro demonstration that biosynthesised selenium nanoparticles suppress DENV serotype 1 growth in culture (Ramya et al., 2015), which provides encouraging, if preliminary, proof-of-concept for direct antiviral activity against a dengue serotype. However, to date no published clinical trial has evaluated selenium or selenium nanoparticle supplementation in DF patients, and serum selenium status has not been systematically characterised across dengue severity grades. The scientific rationale presented in this review is hence hypothesis-generating: it extrapolates from redox and cytokine biology shared across RNA virus infections to propose selenium as a plausible, testable adjunct in DENV, rather than as an established therapy. Dedicated observational studies correlating selenium status with dengue severity, followed by controlled supplementation trials, are required before selenium-based interventions can be considered for medical use in dengue virus management. (Dhesi & Aarons, n.d.)

10. Therapeutic Perspectives

Targeted therapeutic approach of oxidative stress and immune dysregulation represents a promising strategy for DENV Fever management therapy. Modulation of JAK/STAT, NF-κB, and interferon signalling pathways may reduce viral replication, cytokine storm formation, endothelial dysfunction, and Exaggerated inflammatory responses.

Selenium(SeNPs) supplementation increase antioxidant defense through activation of selenoproteins including glutathione peroxidase and thioredoxin reductase.

Selenium (SeNPs) → antioxidant defense → reduced Reactive oxygen species (ROS)

By suppressing Reactive oxygen species (ROS)-mediated NF-κB activation, selenium(SeNPs) may reduce production of pro inflammatory cytokines and attenuate pro-inflammation.

Reduced Reactive oxygen species (ROS) → NF-κB suppression → reduced inflammation

Selenium nanoparticles (SeNPs) exhibit increases bioavailability, low toxic effects, and powerful antioxidant, antiviral, and immunomodulatory activities.

Selenium (SeNPs) → improve antiviral and immunomodulatory effects

Potential pharmacotherapeutic approaches include: Selenium SeNPs supplementation, Selenium nanoparticles, NF-κB inhibitors, JAK/STAT modulators, Interferon-based therapies. These strategies may increase antiviral immunity and reduce severe dengue-associated complications.

11. Future Directions

Future research should focus on:

- Clinical trials investigating selenium (SeNPs) supplementation in DENV patients.
- Molecular investigations on pathway cross-talk
- Nanoparticles-selenium drug delivery systems
- Biomarker-based personalized therapies
- Host-directed antiviral strategies

12. Conclusion

The Janus kinase/signal transducer and activator of transcription, nuclear factor kappa-light-chain-

enhancer of activated B cells (JAK/STAT, NF-κB), and interferon signalling pathways play central roles in the pathogenesis of DENV infection. Their dynamic cross-talk regulates antiviral immunity, inflammation, oxidative stress, and cytokine production. Dysregulation of these pathways contributes to severe DENV manifestations Such as cytokine storm, vascular leakage, and immune dysfunction. Selenium SeNPs supplementation, particularly in nanoparticle form, exhibits promising immunomodulatory, antioxidant, and antiviral properties by regulating these signalling pathways and restoring immune homeostasis. Further mechanistic investigations and clinical studies are required to establish selenium SeNPs as a potential adjunct therapeutic strategy in DENV management.

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Author Contributions

Dr. Kaushal Kumar(*Corresponding Author*): Prof Shobhna Singh, (*Author*) Prof. Alok Srivastava (*Author*) Conceptualization, supervision, and revision of the manuscript. Mr. Abushan Khan(*Author*): Review of literature, data curation, manuscript preparation, and visualization. Both authors read and approved the final manuscript.

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Data Availability

No data was used for the research described in the article.

List of Abbreviations

Abbreviation	Full Form
C	Capsid protein
DC-SIGN	Dendritic Cell-Specific ICAM-3-Grabbing Non-integrin
DENV	Dengue virus
DF	DF
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
E	Envelope protein
ER	Endoplasmic Reticulum
GPx	Glutathione Peroxidase
ICAM-1	Intercellular Adhesion Molecule-1
IFIT	Interferon-Induced Protein with Tetratricopeptide repeats
IFN	Interferon
IFN-α/β	Interferon-alpha/beta
IFN-γ	Interferon-gamma
IFNAR	Interferon-alpha/beta Receptor
IKK	IκB Kinase
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6

IL-8	Interleukin-8
IRF	Interferon Regulatory Factor
IRF3/IRF7/IRF9	Interferon Regulatory Factor 3/7/9
IκBα	Inhibitor of Kappa B alpha
ISGF3	Interferon-Stimulated Gene Factor 3
ISGs	Interferon-Stimulated Genes
JAK/STAT	Janus Kinase/Signal Transducer and Activator of Transcription
JAK1	Janus Kinase 1
MAPK	Mitogen-Activated Protein Kinase
MAVS	Mitochondrial Antiviral Signalling protein
MCP-1	Monocyte Chemoattractant Protein-1
MDA5	Melanoma Differentiation-Associated protein 5
Mx	Myxovirus resistance protein
MyD88	Myeloid Differentiation primary response 88
NF-κB	Nuclear Factor-kappa B
NS1–NS5	Non-Structural proteins 1 to 5 (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5)
OAS	2'-5'-Oligoadenylate Synthetase
PAMPs	Pathogen-Associated Molecular Patterns
PKR	Protein Kinase R
prM/M	Premembrane/Membrane protein
PRRs	Pattern Recognition Receptors
RIG-I	Retinoic Acid-Inducible Gene-I
ROS	Reactive Oxygen Species
Se	Selenium
SeNPs	Selenium Nanoparticles
STAT1/STAT2	Signal Transducer and Activator of Transcription 1/2
TBK1	TANK-Binding Kinase 1
TLRs	Toll-Like Receptors
TNF-α	Tumor Necrosis Factor-alpha
TRIF	TIR-Domain-containing Adaptor-Inducing Interferon-β
TrxR	Thioredoxin Reductase
TYK2	Tyrosine Kinase 2
VCAM-1	Vascular Cell Adhesion Molecule-1

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