

## Review Article

### Betasatellite: a hijacker of plant innate immunity

#### Abstract

Betasatellites associated with begomoviruses significantly exacerbate viral infections in economically important crops, prompting the evolution of various plant defense mechanisms, including RNA interference, phytohormone signalling and cellular modifications using autophagy and ubiquitination. Approximately 13.5-kDa  $\beta$ C1 protein plays a dual role by enhancing viral proliferation while simultaneously suppressing plant defenses, including signal transduction pathways and RNA silencing, thereby increasing host susceptibility to infection. Additionally,  $\beta$ C1 impairs chloroplast function, complicating the plant's defense strategies. In contrast, the  $\beta$ V1 protein, though less understood, appears to facilitate viral replication and interacts with the helper virus RE<sub>n</sub>, leading to altered localization within the cell. As only 40% of betasatellites encode the  $\beta$ V1 protein, further investigation into its molecular interactions and functions could provide crucial insights for developing effective antiviral strategies against geminivirus infections. This review highlights the complex interplay between betasatellites and host defenses, offering avenues for future research in crop protection.

**Keywords:** Betasatellite, Begomovirus, Phytohormone signalling and RNA interference

#### Introduction

Viruses are intracellular parasites that hijack the host cell's machinery to facilitate their establishment. A prime example of this dependency is noticed in the Geminiviridae family, where the reliance on host proteins is evident at every stage of their infection cycle, including of their replication [1]. Geminiviruses cause substantial crop losses globally, infecting important monocots and dicots [2]. These viruses are small, non-enveloped and have circular single stranded DNA genomes. They can be either monopartite or bipartite. According to International Committee on Taxonomy of Viruses, Geminiviridae family is classified into

nine different genera, namely; Begomovirus, Mastrevirus, Capulavirus, Becurtovirus, Curtovirus, Eragrovirus, Grablovirus, Turncurtovirus and Topocuvirus[3]

The genus Begomovirus includes approximately 350 species, distributed globally and spread by the *Bemisiatabaci*. A single genome (DNA-A), ranging from 2.5 to 3.2 kb, is contained by monopartite begomoviruses; while bipartite begomoviruses have two genomes, DNA-A and DNA-B. The DNA-A genome encodes proteins such as the coat protein (CP/AV1), replication-associated protein (Rep/AC1), transcriptional activator protein (TrAP/AC2), pre-coat protein (AV2), replication enhancer protein (REn/AC3) and C4 protein (AC4). In contrast, the DNA-B genome encodes movement protein (MP, BC1) and nuclear shuttle protein (NSP, BV1) [3,4].

Research in recent years has provided valuable insights into the association of begomoviruses with various satellite molecules, including betasatellites, alphasatellites, and deltasatellites [5,6]. Alphasatellites and betasatellites are circular, single-stranded DNA molecules, each approximately 1,350 nucleotides in length [7]. Alphasatellites have been shown to alleviate symptoms and reduce viral accumulation [8]. Recently, it was reported that replication-associated proteins from different alphasatellites interfere with RNA interference, resulting in increased viral load in *Nicotiana benthamiana* [9]. Deltasatellites, which are non-coding satellite molecules, were first discovered in bipartite begomoviruses and are frequently associated with infections caused by New World viruses [10]. While deltasatellites rely on helper viruses for replication, their role in disease progression remains unclear. Betasatellites, also circular single-stranded DNA molecules (1.3 kb), are linked with begomoviruses, playing a significant role in disease development. They depend on the helper virus for replication, encapsidation, and both local and systemic movement. Although they are usually associated with monopartite begomoviruses, betasatellites have also been detected alongside other geminiviruses, including bipartite begomoviruses [11].

Specific interactions between viruses and host proteins are essential for both the virus's virulence and the plant's antiviral defenses [12]. However, deciphering the plant's innate immune responses—such as R-gene mediated defense, RNA silencing, ubiquitin-mediated proteasomal degradation, and hormone signaling—remains challenging due to the complexity of these interactions. In recent years, there has been a notable increase in research focused on understanding the role of betasatellites in the ongoing evolutionary battle between plants and

viruses, as well as exploring the functions of the proteins they encode. This review aims to present a comprehensive and up-to-date analysis of viral strategies that counteract plant antiviral defenses.

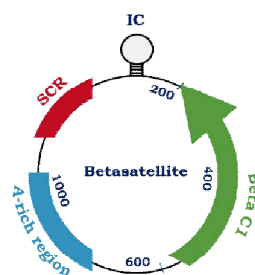
### Structural complexity and diversity of betasatellite

Sequence analysis of various betasatellites has identified three common structural features: (i) an A-rich region, (ii) a satellite conserved region (SCR) of 150–200 nucleotides (**Fig. 1**), which contains a potential hairpin loop structure with the nucleotide sequence TAATATTAC, and (iii) a single open reading frame (ORF) on the complementary strand that encodes the multifunctional  $\beta$ C1 protein (13-14 kDa). Nearly all of the 119 known betasatellite species encode the  $\beta$ C1 protein, which plays a crucial role in symptom manifestation and disease progression [13, 14]. Phylogenetic analysis has shown that  $\beta$ C1 proteins from betasatellites are categorized into three subgroups: I, IIA, and IIB, with most falling into subgroups IIA and IIB [15]. A recently characterized betasatellite protein,  $\beta$ V1, is important for geminivirus-betasatellite infections, although its specific function remains unknown [16].

**Figure 1: Intricate Structural**

A total of sixty-six distinct identified in association with wide range of hosts in

the "Old World," including regions such as Asia, Africa, and Europe. The majority of these betasatellites have been found in Asia, with 32 unique types specifically reported from the Indian subcontinent (Bangladesh, India, Nepal, Pakistan, and Sri Lanka). China also exhibits significant genetic diversity among its betasatellites. In Africa, the Cotton leaf curl Gezira betasatellite (CLCuGeB) and Ageratum leaf curl Cameroon betasatellite are the most common in the West and Central regions, while tomato leaf curl-associated betasatellites are



### Organization of Betasatellite

betasatellites have been various viral complexes across a approximately 20 countries in

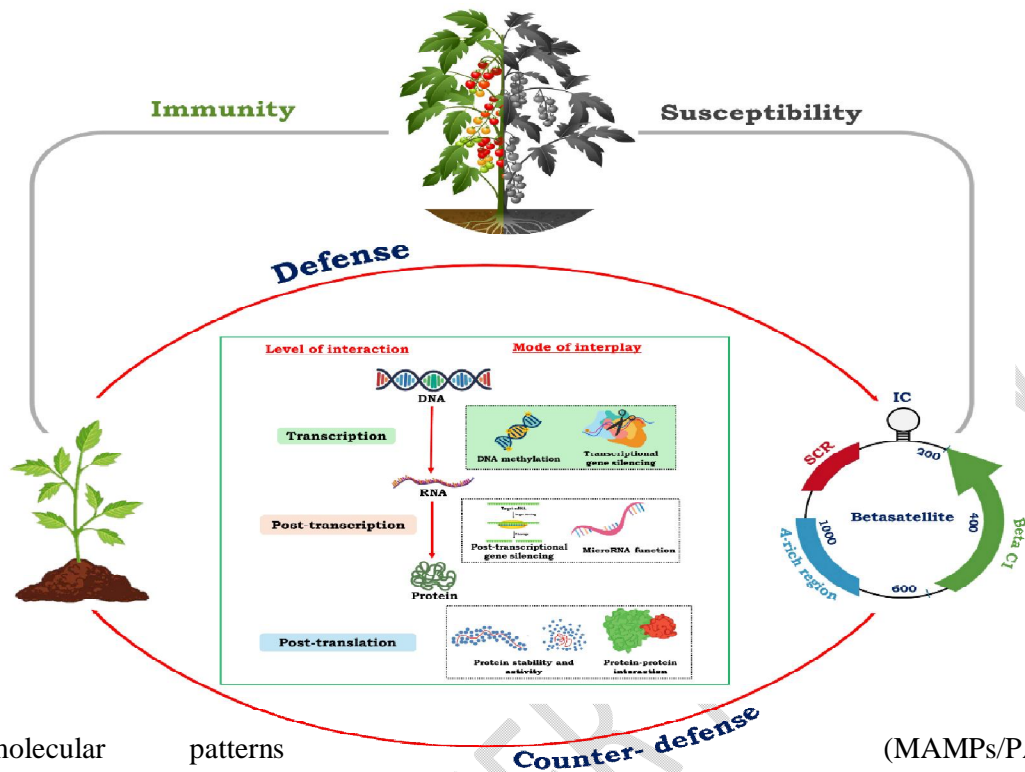
frequently found in Oman [17,18].

### **Subverting Plant defences: Betasatellites, loyal allies for helper viruses**

The intense evolutionary arms race between plants and viruses imposes strong selective pressures, driving viruses to develop mechanisms that help them evade plant immune responses. Geminiviruses are a prime example of how viruses have carefully crafted strategies to counteract plant defenses and establish successful infections. Over the past few decades, research has demonstrated that the  $\beta$ C1 protein is the main pathogenicity factor in begomovirus infections [19]. The multifunctional  $\beta$ C1 protein suppresses several host defense mechanisms, including post-transcriptional gene silencing (PTGS), transcriptional gene silencing (TGS), the ubiquitin-proteasome system, and plant defense hormone pathways (Fig. 2) [19, 20, 21 and 22] Additionally,  $\beta$ C1 contributes to disease and symptom development by promoting both intracellular and systemic virus movement and facilitating interactions between the virus, its vector, and the host.

### **Impact of betasatellites on; i) MAPK kinase pathway**

Pattern recognition receptors (PRRs) in plants identify microbe- or pathogen-associated



molecular patterns (MAMPs/PAMPs), triggering the first layer of the plant immune response through a signaling cascade that results in rapid and transient pattern-triggered immunity (PTI) [23]. In contrast, effector-triggered immunity (ETI) is more robust and long-lasting, initiated by pathogen effectors to counteract PTI. Both PTI and ETI activate the MAPK pathway, which plays a crucial role in regulating the expression of defense-related genes [24]. The MAPK cascade involves a series of kinase reactions featuring MEKK (MAPK kinase kinase), MKK (MAPK kinase), and MAPK, culminating in two primary combinations: MEKK1-MKK1/MKK2-MPK4 and MEKKs-MKK4/MKK5-MPK3/MPK6 [25]. Although the mechanisms through which viral PAMPs interact with their respective PRRs during the early stages of infection are still not well understood, a significant study found that TYLCCNB- $\beta$ C1 interacts with the kinase domains of two components in the MAPK cascade, MKK2 and MKK4. This interaction inhibits their kinase activity, thereby increasing the plant's susceptibility to TYLCCNV infection [26].

## **Figure 2: The Complex Network of Betasatellite-Host Interactions**

### **ii) RNA silencing**

RNA silencing is an evolutionarily conserved gene regulation mechanism that plays a vital role in the antiviral defense of plants [27]. Geminivirus infections induce alterations in the regulation of various defense-related microRNAs and small interfering RNAs (Fig. 2). Many of these changes are influenced by betasatellites, which affect different defense pathways and ultimately facilitate viral infection [28].

### **Suppression of transcriptional gene silencing**

In plants, transcriptional gene silencing (TGS) is an epigenetic phenomenon marked by repressive histone modifications and RNA-directed DNA methylation (RdDM) (Fig. 2). RdDM not only regulates the expression of endogenous genes but also effectively silences genes associated with DNA viruses. Because geminiviruses do not possess their own polymerase, they depend on the host's cellular machinery for both replication and transcription. Within the nucleus of an infected plant cell, the single-stranded genomic DNA of the geminivirus is converted into double-stranded DNA and binds to histones, forming minichromosomes that act as templates for replication and transcription. These minichromosomes become targets for the plant's TGS machinery. TGS and post-transcriptional gene silencing (PTGS) work together to bolster antiviral defenses by

specifically inactivating viral RNAs, which leads to reduced viral replication, hypermethylation of viral genomes, and the eventual alleviation of symptoms [29].

To circumvent plant defenses, plant viruses produce proteins that act as suppressors of transcriptional gene silencing (TGS). The  $\beta$ C1 protein has been demonstrated to inhibit methylation-mediated RNA silencing (Fig. 2). It acts as a TGS suppressor by targeting the enzyme S-adenosyl homocysteine hydrolase (SAHH), thereby blocking the production of S-adenosyl-methionine, which serves as a methyl group donor for DNA methylation [30].

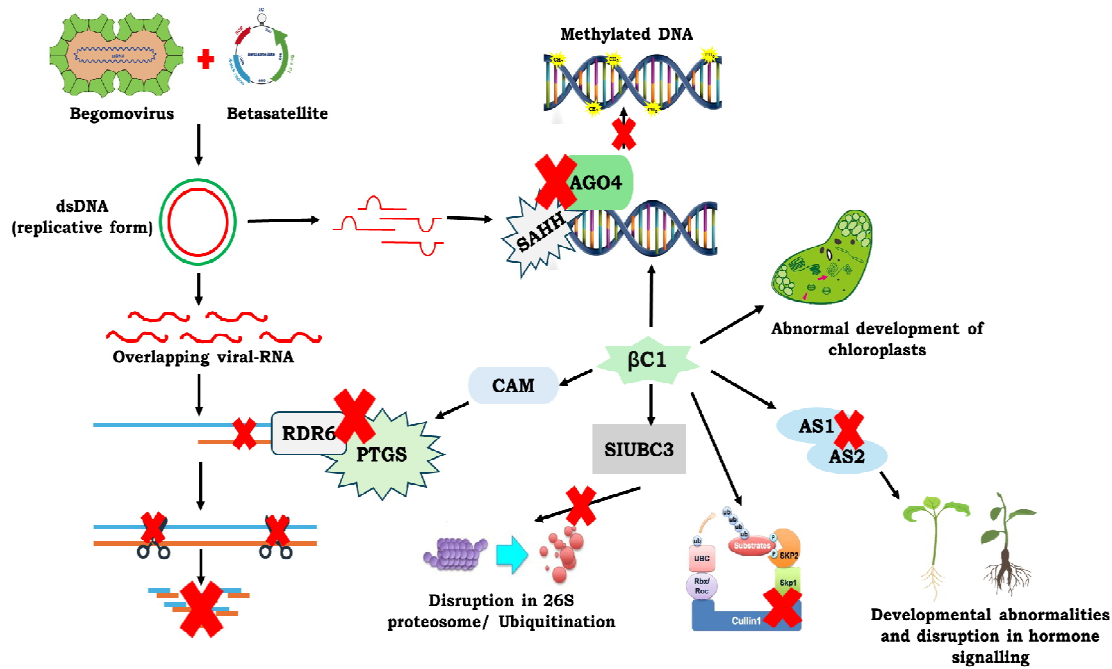
### **Suppression of post-transcriptional gene silencing**

The post-transcriptional gene silencing (PTGS) machinery is a powerful and conserved mechanism that plants use to degrade double-stranded foreign RNA (Fig. 2), aiding them in defending against pathogenic viruses. In response, plant viruses produce silencing suppressor proteins that impede this gene silencing process. Research has shown that the interaction between calmodulin-like protein (NbCaM) and suppressor of gene silencing 3 (SGS3) leads to the degradation of SGS3, which is mediated by the phosphatidylinositol 3-kinase complex. This class III phosphatidylinositol 3-kinase is involved in initiating autophagy, and the subsequent degradation of SGS3 facilitates geminivirus infection[31].

### **iii) Ubiquitin-proteasome machinery**

The ubiquitin-proteasome system is essential for degrading redundant or misfolded cellular proteins, as well as regulatory proteins that have short lifespans. The process of ubiquitination involves the sequential actions of three types of enzymes: E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme), and E3 (ubiquitin ligase). Plants have developed defense mechanisms that leverage their proteasomal degradation system to target and eliminate both viral and cellular proteins that help regulate viral infections [32](Fig. 3). Many plant viruses exploit the host's ubiquitin system as a strategy to hijack the host's cellular machinery. The SCF complex, an E3 ubiquitin ligase found in host plants, consists of S-phase kinase-associated protein (SKP1), Cullin protein (CUL1), and F-BOX. The CLCuMuB- $\beta$ C1 protein interacts with SKP1, disrupting the SKP1-CUL1 interaction and thus preventing the formation of the SCF-E3 ubiquitin ligase complex in plants [21]. Consequently, the interaction between  $\beta$ C1 and components of the plant's ubiquitin-

proteasome system is a crucial factor in the pathogenicity of the betasatellite.



**Figure 3: The Molecular Mechanisms of Betasatellite's Immune Evasion**

#### iv) Phytohormones

Phytohormones play a crucial role in plant biology, regulating various physiological processes and defending against biotic and abiotic stresses [33]. Plant viruses can disrupt phytohormonal signaling both directly and indirectly [34] (Fig. 3). Salicylic acid, gibberellic acid, and jasmonic acid are particularly important in geminiviral infections [35]. Recent studies have shown that the  $\beta$ 1 protein encoded by betasatellites targets hormonal pathways and organelles involved in their biosynthesis. The chloroplast is vital for plant defense due to its role in phytohormone synthesis. Immunoelectron microscopy has identified TYLCCNB- $\beta$ 1 in both the nucleus and chloroplasts of *Nicotiana benthamiana* [36]. The radish leaf curl betasatellite-encoded  $\beta$ 1 (RaLCB- $\beta$ 1) disrupts photosynthesis by altering the structure of chloroplasts, creating favorable conditions for viral infection [37]. Furthermore, RaLCB- $\beta$ 1 interacts with PsbP (oxygen-evolving enhancer protein 2) in *N. benthamiana*, undermining its protective role against geminiviral DNA [37]. The *Synedrella* yellow vein clearing virus (SyYVCV) and its  $\beta$ 1 protein (SyYVCB- $\beta$ 1) disrupt chloroplast functions by inhibiting NtRecA1 and inducing the expression of the DPD1 nuclease, which damages the plastid genome and reduces photosynthetic efficiency. This degradation also increases inorganic phosphate levels in the cytoplasm, potentially facilitating viral replication.

Geminiviral infections also elevate jasmonic acid (JA) levels, a key regulator of plant defense. The  $\beta$ C1 protein inhibits JA biosynthesis by interacting with AS1 and targets JA signaling by disrupting the SCFCOII complex through SKP1 interactions. Additionally, TYLCCNB- $\beta$ C1 hinders the dimerization of MYC, a transcription factor in the JA pathway, while CLCuMuB- $\beta$ C1 inhibits gibberellic acid (GA) signaling by interacting with GAI, a negative regulator of GA signaling.

### **Movement within and outside:**

When plants become infected with viruses, their spread within the host occurs through three primary pathways: (1) inter- and intracellular movement via plasmodesmata, (2) transport through phloem or xylem to nearby tissues, and (3) transfer to other plants through mechanical means or vectors. Bipartite begomoviruses depend on nuclear shuttle proteins (NSP) and movement proteins (MP) for their movement, although the specific mechanisms are still being studied.

Several studies suggest that the NSP-MP complex is involved in intracellular movement [38, 39]. Currently, two main models explain the intercellular movement of bipartite geminiviruses. In the first model, NSP moves independently from the nucleus to the cytoplasm, where it is replaced by MP, similar to a relay race. In the second model, MP transports a viral complex that includes NSP, often referred to as "couple skating" [40-43]. Recent evidence supports the "couple skating" model, indicating that NSP interacts with a syntaxin-domain-containing protein (NISIP) and may be part of a viral DNA complex that moves intracellularly via endosomes [44]. CLCuMuB and the Ageratum yellow vein betasatellite (AYVB) have been shown to enhance the function of the movement protein (MP) in the tomato leaf curl New Delhi virus (ToLCNDV) and the Sri Lanka cassava mosaic virus (SLCMV). Additionally, AYVB facilitates successful infection when co-inoculated with various strains of cassava mosaic virus, effectively acting as a substitute for DNA B [45]. Furthermore, the  $\beta$ C1 protein encoded by the bhendi yellow vein mosaic betasatellite (BYVMB) possesses a nuclear export signal (NES) and interacts with the host importin-like protein karyopherin  $\alpha$  through the viral coat protein, likely aiding in viral transport [46]. CLCuMuB- $\beta$ C1 also interacts with calmodulin-like protein 11 (GhCML11) in a calcium-dependent manner, promoting its expression to facilitate viral movement and transmission [47].

Monopartite begomoviruses use different strategies for movement, relying on proteins such as V1, V2, C4, and  $\beta$ C1. The  $\beta$ C1 protein, located in both the nucleus and cytoplasm, interacts with host proteins to facilitate viral transport. These viruses typically move through the phloem, with vectors like Bemisia tabaci assisting in their transfer. Notably,  $\beta$ C1 manipulates plant defenses to enhance vector performance while reducing the fitness of non-vectors. Recent research suggests an evolutionarily conserved interaction between viruses and their vectors, particularly concerning a conserved site in  $\beta$ C1 that regulates terpenoid biosynthesis, affecting vector efficiency. Researchers have identified a highly conserved site (S33) in  $\beta$ C1, where phosphorylation inhibits terpenoid biosynthesis by disrupting MYC dimerization, indirectly improving vector performance. This conserved site is present in 105 out of 119 analyzed  $\beta$ C1 proteins, primarily from the recently evolved phylogenetic subgroups IIA and IIB [15]. Studies have highlighted the evolutionarily conserved nature of tripartite interactions, demonstrating how viruses have developed strategies to manipulate plant defenses, thereby enhancing their rapid transmission.

### **A Ray of Hope: The Potential of Betasatellites in Disease Management**

Among various strategies for disease management, RNA interference (RNAi) stands out as a promising method for developing transgenic plants that can target multiple viral proteins, disrupting the viral life cycle. In silico analysis has shown that several open reading frames (ORFs) of ToLCV could be targeted by different microRNAs [48]. Similarly, strategies are being developed to confer resistance to  $\beta$ C1. An exciting study utilized this approach to construct amplicons targeting  $\beta$ C1, providing resistance against cotton leaf curl disease (CLCuD). A transgenic *Nicotiana benthamiana* plant containing an RNAi construct targeting the betasatellites of the cotton leaf curl Khokran virus (CLCuKV) and the cotton leaf curl Multan virus (CLCuMuV) exhibited a significantly reduced viral load during infection [128]. A recent investigation revealed that barley HvMPK3 and the small brown planthopper's LsERK (Laodelphax striatellus extracellular signal-regulated kinase) directly phosphorylate the nucleoprotein of barley yellow striate mosaic virus (BYSMV, a rhabdovirus) at serine 290, triggering an antiviral immune response [49]. Identifying similar targets for  $\beta$ C1 could aid in developing transgenic whiteflies incapable of transmitting begomoviruses, akin to strategies used to create genetically modified mosquitoes that cannot spread malaria [50]. Given the mixed opinions regarding transgenic crops in various regions, focusing on these targets could pave the way for alternative strategies.

## **Conclusion**

Betasatellites linked to begomoviruses exacerbate viral infections in numerous economically significant crops. In response, host plants have developed various defense mechanisms against these viruses, including RNA silencing, hormonal responses, and host proteome regulation through ubiquitination, phosphorylation, and autophagy. The approximately 13.5-kDa  $\beta$ C1 protein plays a pivotal role in this process by promoting viral replication while simultaneously suppressing host defenses. It disrupts signal transduction pathways, interacts with MAPK proteins, and inhibits RNA silencing, thereby increasing the host's susceptibility to infection. Additionally,  $\beta$ C1 impairs chloroplast function. The less-studied  $\beta$ V1 protein also contributes to viral proliferation and interacts with the RE<sub>n</sub> of the helper virus, altering its localization. However, the specifics of these interactions remain poorly understood. Given that only 40% of betasatellites encode  $\beta$ V1, further research into its role could lead to improved antiviral strategies against begomovirus infections.

## **Declaration of generative AI and AI-assisted technologies in the writing process**

During the preparation of this work, ChatGPT has been only used to rephrase the sentences. However, any of the AI tools has not been used to generate the results. Authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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