Review

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Posted Date: 1 June 2026

doi: 10.20944/preprints202606.0012.v1

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 doi:10.20944/preprints202606.0012.v1

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Cross-Family Mechanistic Analysis of Plant Alkaloids Against Neglected Arboviruses and Related RNA Viruses

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Abstract

Neglected arboviruses dengue (DENV), Zika (ZIKV), yellow fever (YFV), Japanese encephalitis (JEV), and chikungunya collectively affect hundreds of millions of people annually, yet no specific antiviral drug has been approved for any of them. Alkaloids, nitrogen-containing specialized metabolites produced by diverse plant families, have emerged as a promising source of broad-spectrum antiviral scaffolds. This review compiles and critically analyzes ~100 alkaloid antiviral activities across several RNA virus families, providing a comparative mechanistic analysis. Lycorine, narciclasine, emetine, and berbamine, among others, exhibit potent activity against phylogenetically distant viruses, with the most potent interactions reported against flaviviruses (narciclasine: EC_{50} 0.02 µM against DENV, ZIKV, YFV, and JEV; pancratistatine: 0.0063 µM against ZIKV). Structure-activity analysis of multiple alkaloid classes identifies key pharmacophoric features, including the phenanthridone nucleus (lycorine derivatives) and the bis-benzylisoquinoline scaffold (tetrandrine, berbamine), as determinants of antiviral potency, selectivity, and broad-spectrum activity. Genetic resistance data and replicon experiments challenge the widely accepted model of lycorine as a nucleoside inhibitor of flaviviruses, instead indicating that the membrane-associated NS4A-2K-NS4B replication complex is the actual functional target. Converging structural, biochemical, and transcriptomic evidence suggests that ribosome-mediated translational stress may represent an additional host-directed mechanism for isoquinoline-type alkaloids, though this hypothesis requires formal validation. The present analysis highlights that *in vivo* validation remains limited to a few compound-virus combinations. Unbiased target deconvolution and formal testing of the ribosome/integrated stress response hypothesis stand out as essential research priorities.

Keywords: neglected tropical diseases; flavivirus; mechanism of action; ribosome; structure-activity relationships; integrated stress response; broad-spectrum antivirals

1. Alkaloids to Fight Neglected Arboviral Diseases

Neglected tropical arboviruses, including dengue (DENV), Zika (ZIKV), yellow fever (YFV), Japanese encephalitis (JEV), and chikungunya (CHIKV), together threaten over half the world's population, primarily in low- and middle-income countries [1]. Dengue alone accounts for an estimated 390 million infections per year, with 14.6 million cases notified to the WHO in 2024 and a population at risk projected to increase by 40% by 2035. While most patients recover within two weeks, all serotypes can induce symptoms ranging from high fever (40°C/104°F), severe headache, retro-orbital pain, muscle and joint pain, nausea, vomiting, swollen glands, and a skin rash, as well as life-threatening complications such as dengue hemorrhagic fever and dengue shock syndrome [2,3]. Reinfection significantly increases the risk of severe clinical manifestations, including

 doi:10.20944/preprints202606.0012.v1

abdominal pain, persistent vomiting, and mucosal bleeding. ZIKV is associated with congenital microcephaly. While most infections remain asymptomatic, clinical manifestations typically appear 3 to 14 days post-exposure, including rash, fever, conjunctivitis, and arthralgia, which may last up to a week. However, outbreaks over the last decade have highlighted severe neurological complications, such as Guillain-Barré syndrome in adults and microcephaly in newborns of infected pregnant women. YFV remains endemic in Africa and South America despite an effective vaccine, and JEV is the leading cause of viral encephalitis in Asia. CHIKV causes an acute febrile illness with severe polyarthralgia that can persist for months to years in 30-60% of patients, representing a significant long-term morbidity burden [4]. Major outbreaks since 2004 have spread the virus from East Africa to the Americas, the Caribbean, and Southeast Asia [5]. As with DENV and ZIKV, clinical management is limited to symptomatic support [2,6,7]. JNJ-1802 (mosnodenvir), a first-in-class pan-serotype DENV inhibitor, is currently in phase 2 clinical trials, marking the most advanced antiviral candidate for any neglected arbovirus to date [8,9]. Fortunately, there have been significant advances in vaccines, with Qdenga (TAK-003) now approved in over 40 countries for DENV [10], and Ixchiq (VLA1553) for CHIKV receiving FDA approval in 2023, although recent safety concerns have led to restricted use [11].

Dengue and chikungunya are formally recognized by the WHO as neglected tropical diseases (NTDs), while ZIKV, YFV, and JEV are managed under the same Global Arbovirus Initiative framework. The co-circulation of DENV, ZIKV, and CHIKV through shared *Aedes* mosquitoes creates a compounding public health challenge in endemic regions, where differential diagnosis is often unavailable at the point of care. These RNA viruses, despite their phylogenetic diversity, share a common replication logic. Infection proceeds through sequential steps, including receptor binding and endosomal entry, translation of the viral genome by host ribosomes in the cytoplasm, proteolytic processing of the polyprotein, assembly of membrane-associated replication organelles, RNA synthesis, and virion assembly and release (Figures 1-2). Each of these steps constitutes a potential therapeutic target. For some related viruses, this logic has been successfully exploited, i.e. DAAs targeting the hepatitis C virus (HCV) NS5B polymerase or NS3 protease have transformed patient outcomes [12], and nirmatrelvir inhibits the SARS-CoV-2 main protease. However, for the neglected arboviruses, no drug targeting any of these steps has yet reached final approval.

Alkaloids, nitrogen-containing specialized metabolites produced across the three kingdoms of life, have long been recognized for their pharmacological properties. They are particularly abundant in medicinal plants, where they exhibit the greatest structural diversity (Table 1) [13,14]. In their natural hosts, they play a role in defense against predators and pathogens [15,16] and are distributed throughout various tissues, where they may accumulate at concentrations ranging from 1 to 15% of plant dry weight [17,18]. Over 27,600 alkaloids have been characterized across major structural classes. In medicinal chemistry, these molecules are classified based on their underlying chemical scaffolds, which dictate both their biosynthetic origins and their spatial interactions with biological targets. These primary classes include indole and monoterpene indole scaffolds, isoquinolines (IQ), benzylisoquinolines (BIQ), bis-benzylisoquinolines (bis-BIQ), phenanthridines, tropanes, piperidines, iminosugars, and steroidal frameworks [19–23]. Several have become cornerstones of modern medicine, such as morphine (analgesic), quinine (antimalarial), emetine (antiamoebic), vincristine (antineoplastic), and galanthamine (anti-cholinesterase), demonstrating their potential as clinically viable drugs. Despite the extensive antiviral activity documented *in vitro*, no alkaloid or alkaloid-derived compound has been approved as an antiviral drug for any indication. The only candidate to reach clinical trials for a neglected arbovirus, celgosivir, a castanospermine prodrug targeting host α-glucosidases, failed to demonstrate efficacy in phase II despite a favorable safety profile [24], underscoring the need for a deeper mechanistic understanding before advancing further candidates.

 doi:10.20944/preprints202606.0012.v1

Table 1. Medicinal plant families producing antiviral alkaloids.

Plant family	Antiviral alkaloid	Geographical distribution	Domains of application	Ref.
Solanaceae (Tropane)	Atropine	Cosmopolitan, especially tropical America	Food, Medicinal, Ornamental	[15]
Rutaceae (Isoquinoline / Benzo[c]phenanthridine)	Octopamine, 5,6-Dihydro-6-methoxynitidine	Tropical and subtropical zones	Food, Medicinal Cosmetics, Ornamental	[25]
Rubiaceae (Isoquinoline / Ipecac and Monoterpene indole)	Emetine, hirsutine	Tropical and subtropical zones	Medicinal (antiviral)	[26, 27]
Piperaceae (Piperidine)	Piperine	Tropical zones, Latin America	Medicinal (antiviral)	[15]
Moraceae (Polyhydroxyalkaloid / Iminosugar)	Homonojirimycin	Tropical and subtropical zones	Food, Ecological, Medicinal, Ornamental	[28]
Menispermaceae (Bis-benzylisoquinoline / bis-BIQ)	Cepharanthine, fangchinoline, tetrandrine	Warm temperate to tropical zones	Industrial, Medicinal (antiviral)	[27]
Liliaceae (Steroidal)	Cyclopamine	Cosmopolitan	Food, Medicinal, Ornamental	[22]
Fabaceae (Indolizidine / Quinolizidine)	Castanospermine, oxysophoridine	Cosmopolitan	Food, Medicinal, Ornamental	[19]
Cephalotaxaceae (Cephalotaxine / Cephalotaxane)	Homoharringtonine	Asia, North America	Medicinal (antiviral)	[29]
Berberidaceae (Isoquinoline: protoberberine & bis-BIQ)	Berberine, Berbamine	Subtropical zones	Food, Medicinal (Antiviral, antimycobacterial, anti-inflammatory), Homeopathy	[30]
Apocynaceae(Monoterpene indole / Phenanthroindolizidine	Ajmalicine, vocangine, 18-	Tropical, subtropical zone	Medicinal, Ornamental	[26]

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	Methoxycoronaridine, tylophorine			
Amaryllidaceae (Amaryllidoideae: Lycorine, Crinine, Haemanthamine, Narciclasine, Cherylline types)	Cherylline, crinamine, haemanthamine, haemanthidine, lycorine, Narciclasine, pancracine, pancratistatine	Tropical, subtropical, temperate zones	Medicinal (antitumoral, antiviral, etc.), Ornamental	[16, 31–34]

Ref.: Reference.

Antiviral activity of plant-derived alkaloids has been documented since the early 1990s [35], and multiple recent reviews have cataloged their activity [15,36,37]. While these reviews provide valuable compilations of antiviral alkaloids organized by virus or alkaloid class, the present work takes a complementary approach by discussing the presented evidence by molecular target, enabling cross-family comparisons and a critical assessment of the strength of each mechanistic claim.

Plant alkaloids are distributed across a broad evolutionary range of families (Table 1), notably within large families such as *Solanaceae*, *Fabaceae*, and *Rubiaceae*. Tropical lineages, including *Rutaceae*, *Apocynaceae*, and *Piperaceae*, are also identified as significant sources of structural diversity. These botanical families often exhibit highly specialized biosynthetic pathways that yield distinct structural scaffolds. For instance, the *Menispermaceae* comprise numerous species known for bis-benzylisoquinoline alkaloids, and the *Amaryllidoideae* (a subfamily of *Amaryllidaceae*), are an exceptionally prolific group; approximately 20% of their species produce specialized alkaloids belonging to unique isoquinoline-derived structural types (such as lycorine, crinine, haemanthamine, and narciclasine cores) [31]. Notably, these alkaloid-producing families are largely endemic to tropical and subtropical regions where arboviral transmission is most intense (Table 1), suggesting that traditional medicinal plant use in these communities may yield leads for antiviral drug discovery.

The present review consolidates ~100 alkaloid-virus combinations reported across multiple RNA virus families to facilitate cross-family analysis. The predominance of *Amaryllidaceae* in this survey partly reflects the research focus of the contributing groups and the abundance of literature on this plant family. Information on alkaloids active against DNA viruses was excluded and is summarized elsewhere [36,37]. Mechanistic knowledge accumulated for well-resourced pathogens (HCV, SARS-CoV-2, influenza) was used as a comparative framework to interpret and extrapolate the antiviral potential of alkaloids against neglected arboviruses, for which target identification remains critically underdeveloped. The analysis is discussed by molecular target, encompassing viral entry, polymerase activity, protease-dependent processing, ribosome binding, and host innate immune modulation. The strengths of the evidence for target claims are discussed, and the most promising research opportunities are highlighted.

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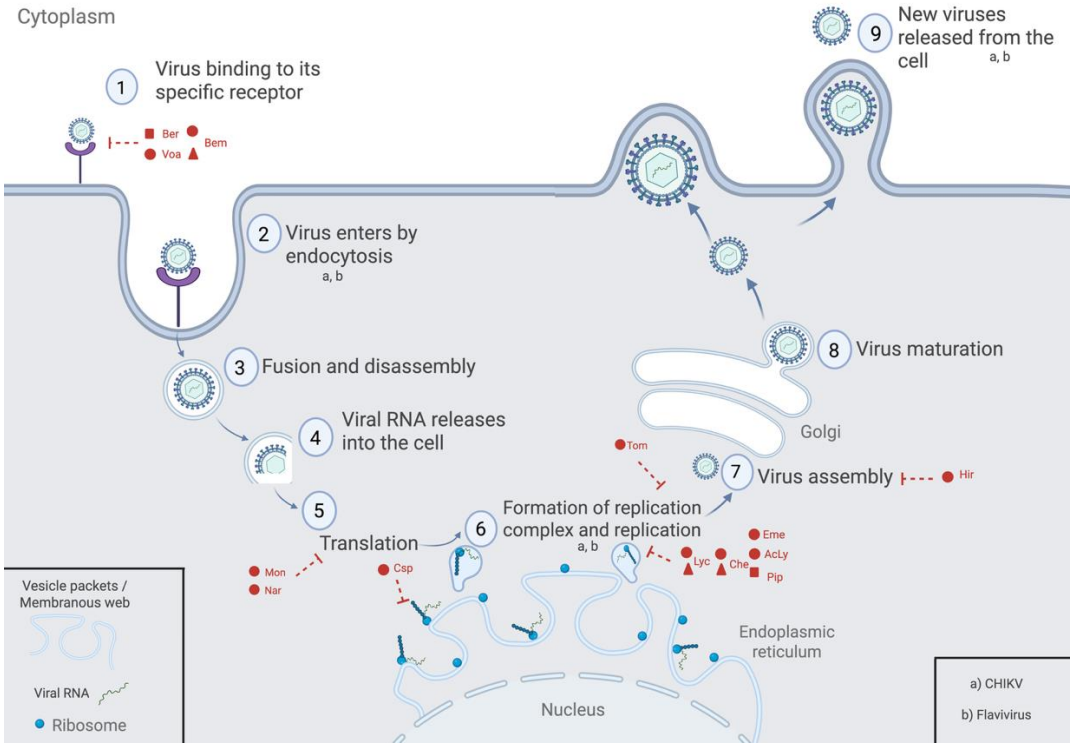

Figure 1. Replication cycle of the *Flaviviridae* family, with alkaloid targets indicated. (1-2) Attachment to specific receptors (e.g., DC-SIGN receptor (CD209) for DENV, AXL receptor for ZIKV; CD81/claudin-1 for HCV) and entry via endocytosis. (3-4) Endosomal fusion and release of the (+) RNA genome. (5-6) Translation of the polyprotein and assembly of the non-structural (NS) protein complex within specialized ER-derived organelles (vesicle packets or membranous web), where genomic replication and production of RNAs occur. (7-8) Viral assembly and maturation through the Golgi apparatus via cleavage by the host peptidase furin. (9) Egress of mature virions. Specific symbols in red are used to denote the antiviral activity and molecular targets of the discussed alkaloids. ● DENV, ▲ ZIKV, and ■ HCV. Berberine (Ber ■), Berbamine (Bem ●▲) and Voacangine (Voa ●) target the early stages of infection, specifically viral entry and endosomal trafficking. Montanine (Mon ●), Narciclasine (Nar ●) and tomatidine (Tom ●) are proposed to interfere with translation and polyprotein processing. Lycorine (Lyc ●▲), acetyllycorine (AcLyc ●), cherylline (Che●▲), piperine (Pip ■) and emetine (Eme ●), target the replication phase in most studies. Hirsutine (Hir●) has been identified as an inhibitor of viral assembly. Castanospermine (Csp●) targets the final maturation of viral particles by inhibiting the proper folding and processing of viral proteins, specifically the prM-E complex, as they pass through the Golgi apparatus. References are available in Tables 2, 3, and 4. Although CHIKV(a) belongs to the Togaviridae (genus Alphavirus), its replication cycle shares key features with flaviviruses (b), including receptor-mediated endocytosis, cytoplasmic replication within membrane-associated complexes, and budding of enveloped particles; CHIKV alkaloid data are therefore compiled alongside flaviviruses in Table 3. Created with Biorender.

2. Viral Target of Alkaloids: Cross-Family Analysis

RNA viruses are a major contributor to the emergence of new infectious diseases [38]. Their rapid evolution and mutation rate make them challenging pathogens to eradicate, requiring specific vaccination and antiviral strategies [39]. The viruses covered in this review span a broad spectrum of replication strategies, tissue tropisms, and clinical impacts. Members of the *Flaviviridae* include neglected arboviruses transmitted by *Aedes* mosquitoes (DENV, ZIKV, YFV, JEV) and the blood-borne HCV (Figure 1). *Coronaviridae* range from endemic seasonal pathogens (e.g., Human coronavirus (HCoV)-OC43) to epidemic and pandemic viruses (e.g., severe acute respiratory syndrome (SARS)-CoV, Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2) (Figure 2). *Orthomyxoviridae* (e.g., influenza virus) cause recurrent seasonal epidemics with pandemic potential. Additional viruses (CHIKV, Ebola virus (EBOV), human immunodeficiency virus (HIV-1),

 doi:10.20944/preprints202606.0012.v1

respiratory syncytial virus (RSV), hepatitis B virus (HBV), parainfluenza virus (HPIV)-3) are included where alkaloid data are available.

Despite their diversity, these viruses share common vulnerabilities that alkaloids may exploit, including dependence on host translational machinery, membrane-associated replication complexes, and the encoding of conserved enzymes, such as polymerases and viral proteases (Figures 1 and 2). Antiviral alkaloids target several distinct molecular targets. Tables 2-7 compile the antiviral activities of alkaloids reported against DENV and ZIKV (Table 2), other flaviviruses and CHIKV (Table 3), HCV (Table 4), coronaviruses (Table 5), influenza virus, HIV-1, and other relevant viruses (Table 6).

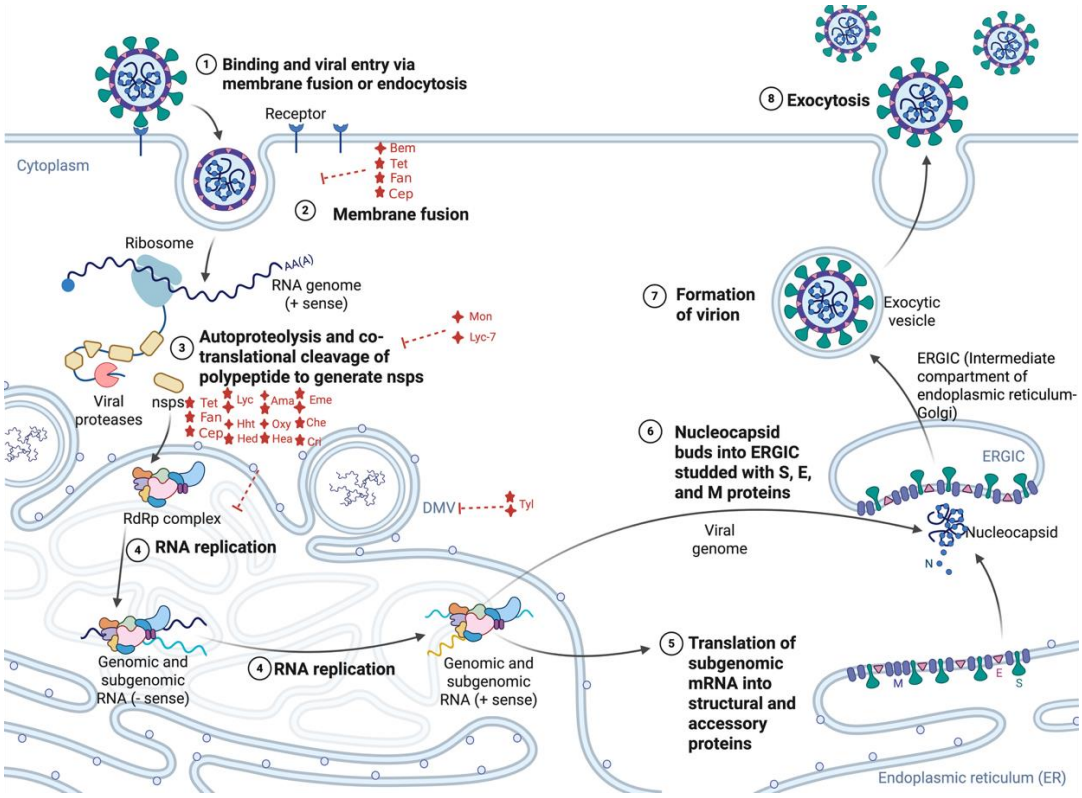

Figure 2. Replication cycle of the Coronaviridae family. (1) Attachment to host receptors, such as angiotensin-converting enzyme 2 (ACE2) for SARS-CoV-2 or 9-O-acetylated sialic acids for HCoV-OC43, which involves the hemagglutinin-esterase (HE) protein. (2) Entry and release of the genomic RNA by endocytosis. (3) Polyprotein translation (pp1a/pp1ab) and autocleavage into Nsps. (4) Replication-transcription complex (RTC) assembly and RNA replication/transcription within double-membrane vesicles (DMVs). (5) Translation of subgenomic mRNAs into structural and accessory proteins. (6-7) Viral assembly in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) and maturation. (8) Release via exocytosis, where the HE protein facilitates HCoV-OC43 detachment Specific symbols in red are used to denote the antiviral activity and molecular targets of the discussed alkaloids. ★ HCoV-OC43 and ✦ SARS-CoV-2. Bis-benzylisoquinolines such as tetrandrine (Tet ★), fangchinoline (Fan ★), and cepharanthine (Cep ★) primarily block the early infection process. In the host cytosol, translational elongation is modulated at the ribosomal PTC by montanine (Mon ✦) to trigger ribosome collisions, while Lycorine derivative compound 7 (Lyc-7 ✦) stabilizes host ZAP-S to disrupt essential -1 programmed ribosomal frameshifting (-1PRF). Emetine (Eme ★ ✦) and lycorine (Lyc ★) are shown to inhibit replication or protease-dependent steps. A diverse group of Amaryllidaceae alkaloids, including amarbellisine (Ama ★ ✦), haemanthamine (Hea ★), and crinamine (Cri ★), interfere with post-entry mechanisms within 4 to 8 hours post-infection. Adapted from BioRender.com. Detailed EC_{50} values and mechanistic evidence for each compound are provided in Table 5.

 doi:10.20944/preprints202606.0012.v1

2.1. Viral Entry Inhibition

Entry inhibition is a pharmacologically diverse mechanism reported for antiviral alkaloids, spanning at least three distinct molecular steps. Bis-BIQ alkaloids are well-characterized entry inhibitors. Tetrandrine, fangchinoline, and cepharanthine inhibit HCoV-OC43 infection of human lung cells, likely by disrupting endolysosomes (Table 5) [40]. Berbamine acts at a different step, binding to the post-fusion core of the SARS-CoV-2 Spike S2 subunit and blocking membrane fusion [41]. Since acidification is also required for pH-triggered fusion of flaviviruses in late endosomes, recent studies have confirmed that all five bis-BIQ tested (berbamine, tetrandrine, iso-tetrandrine, fangchinoline, and cepharanthine) inhibit ZIKV, DENV (Table 2), and JEV (Table 3) infection by blocking both entry and replication [42]. The entry-inhibition mechanism involves blockade of Transient Receptor Potential-Mucolipin (TRPML) channels, lysosomal pH alkalization, and reduced expression of the ZIKV receptor, NCAM1 [43,44]. Bis-BIQ scaffold thus represents a validated cross-family entry inhibitor class active against both *Coronaviridae* and *Flaviviridae,* targeting multiple entry steps depending on the specific compound and virus. HIV-1 enters cells via fusion rather than endocytosis, yet this step can also be blocked by some alkaloids, such as aloperine, a quinolizidine-type alkaloid (Table 7) [45].

The IQ alkaloid berberine displays a less conserved antiviral mechanism. Against HCV, Hung et al. [46] demonstrated that berberine binds the E2 glycoprotein, blocking entry with a classical receptor-level mechanism (Table 4). However, during DENV and ZIKV infections, berberine does not affect entry (Table 2) [47]. Likewise, emetine exhibits a virus-dependent pattern, inhibiting MERS-CoV (Table 5) and EBOV (Table 6) entry [48], but targeting later steps of ZIKV replication (Table 2) [49]. This underscores that mechanistic data from one virus cannot directly be extrapolated to another. A dual-mechanism profile, entry blockade for one virus, replication inhibition for another, is potentially advantageous for a broad-spectrum antiviral, as it reduces the likelihood that resistance at a single target will abolish efficacy across viral families.

Voacangine monoterpenoid indole alkaloid (MIA) and its derivatives could inhibit the entry of some DENV serotypes (Table 2) [50]. Interestingly, to date, several *Amaryllidaceae* alkaloids tested in time-of-addition or entry-specific assays, including lycorine against influenza H5N1 (Table 6) [51], DENV (Table 2) [52], and CHIKV (Table 3); and seven alkaloids against HCoV-OC43 (Table 5)[53], have shown post-entry activity. While this does not exclude the possibility that untested compounds or virus-alkaloid combinations may involve entry inhibition, the consistency of these findings across multiple viral families and diverse alkaloid scaffolds supports a shared post-entry activity for this alkaloid class.

2.2. RNA-Dependent RNA Polymerase Inhibition

Most RNA virus replication requires the expression of an RNA-dependent RNA polymerase (RdRp) that can replicate its genome (Figure 1 and Figure 2). Retroviruses, such as HIV-1, use a reverse transcriptase that allows their genome to transition to a DNA provirus. As specifically encoded by the virus, these polymerases are a frequently reported target for antiviral alkaloids, but the strength of evidence varies dramatically across viral families and compounds. For lycorine (Table 5), the most compelling enzymatic evidence comes from the coronavirus field. Jin et al. [54] demonstrated that lycorine directly inhibits MERS-CoV RdRp activity with an IC_{50} of 1.4 μM in a cell-based reporter assay, a value concordant with its cellular EC_{50} and more potent than remdesivir (IC_{50} 6.3 μM) in the same system.

Lycorine maintains submicromolar activity against all tested flaviviruses and has demonstrated significant *in vivo* efficacy, with an 83% improvement in survival in ZIKV-infected mice [55]. However, it's possible activity as a direct NS5 RdRp inhibitor is considerably weaker than widely assumed. Using subgenomic replicons, our results demonstrated that lycorine and cherylline inhibit DENV RNA replication (Table 2) [52]. In addition, Agrawal et al. (2024) confirmed that lycorine reduces total and negative-strand RNA synthesis across all four DENV serotypes and CHIKV [56]. Molecular docking placed lycorine near the catalytic sites of both DENV and CHIKV RdRps (Tables

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2 and 3) [56], but these remain computational predictions. Indeed, while biochemical assays in the literature suggest an IC_{50} for the purified ZIKV NS5 protein in the high micromolar range, we recently confirmed that lycorine and its derivatives exhibit only weak DENV RdRp IC_{50} values (>100 μM), despite their potent antiviral EC_{50} (<1 μM) (manuscript under revision). This discrepancy represents an inhibitory concentration approximately 250 times higher than the cellular EC_{50} [55]. In contrast, for emetine, Yang et al. [49] clearly demonstrated direct inhibition of ZIKV NS5 RdRp with an IC_{50} of 0.121 μM, a concentration well within the pharmacologically relevant range, while cardiotoxicity was observed only at concentrations 400-600-fold higher [48].

Although numerous compounds are listed as replication inhibitors in Tables 2-6, this does not imply that they act at the level of the RdRp. Direct and convincing enzymatic evidence exists only for lycorine against MERS-CoV and for emetine against ZIKV. For the remainder, the inhibition of replication reflects the outcome of time-of-addition or replicon experiments and does not distinguish among RdRp inhibition, interference with replication complex assembly, or translational effects on viral protein production.

Table 2. Reported antiviral activity and mechanism of action of diverse alkaloid families against Dengue and Zika viruses.

	Alkaloid	**EC_{50} (μM)**	**CC_{50} (μM)**	**SI**	**Target**	**Ref**
			DENV			
Amaryllidaceae	Acetyllycorine	0.4	> 300	> 750	Replication	[3]
	Lycorine	0.48-0.59	> 10	> 16.9	Replication; RNA synthesis	[52,56]
	1-O-acetyl-2-oxolycorine	1.8	> 300	> 166.6	n.e.	[57]
	2-Oxolycorin	0.5	> 300	> 600	n.e.	[3]
	Lycoricidine monoacetate	5.15	> 143	> 27	n.e.	[35]
	Lycoricidine triacetate	> 17.17	> 114	> 6.6		
	(+) -*trans*-dihydronarciclasine	0.51	> 159	> 311		
	7-Deoxyisonarciclasine	28.99	> 181	> 6.2		
	7-Deoxy-*trans*-dihydronarciclasine	1.17	> 170	> 145		
	cis-hydronarciclasine	7.11	> 159	> 22		
	7-Deoxypancratistatin	2.15	> 170	> 79		
	Pseudolycorine	1.35	25.26	18.7	n.e.	[35]
	Pancracine	0.36	25.93	72.02	n.e.	[58]
	Haemanthamine	0.34	2.19	65.26		
	Haemanthidine	0.48	16.80	35		
	Pretazettine	0.8	11.45	14.3		
	Pancratistatin	0.19	1.71	9.0		
	Vittatine	15.53	n.d.	n.d.		
	11-Hydroxyvittatine	3.92	113.06	28.84		
	Cherylline	8.8	> 100	> 11.3	Replication	[52,59]
	Narciclasine	0.02	0.09	4.5	n.e.	[60]

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	Narciclasin-4-O-β-D-xylopyranoside	7.9	39.3	5.0		
	Montanine	0.06-0.26	2.67	10.3-44.5	Translation	[61]#
Apocynaceae	Voacangine	171.4 ±26	4.3 ± 1.3	39.8	Entry	[50]
	Voacangine-7-hydroxyindolenine	145.5 ± 20.4	9.0 ± 1.4	16.1		
	Rupicoline	259 ± 1.8	8.8 ± 0.8	29.4		
	3-Oxo-voacangine	> 261.5	n.d.	n.d.		
Berberidaceae	Berbamine	0.5422	76.35	140.8	Entry and replication (host TRPML channels and endosomal trafficking)	[42]
	Berberine	0.7	205.1	293	infectious particle formation ; host p38 MAPK	[47]
Fabaceae	Castanospermine	1	> 5000	> 5000	Incorporation of viral protein (prM-E) and C.	[62]
Rubiaceae	Emetine	0.12	> 10	> 83.3	Replication	[63]
Rubiaceae	Hirsutine	0.57	> 50	> 87.7	Assembly	[64]
Solanaceae	Tomatidine	0.82	80.2	97.7	Synthesis of viral protein E	[65]
			ZIKV			
Amaryllidaceae	Cherylline	20.30	> 100	> 4.9	Replication	[52]
	Lycorine	0.41	> 10	> 24.4		
	Narciclasine	0.02	0.12	6.0	n.e.	[60]
	Narciclasine-4-O-β-D-xylopyranoside	7.90	51.58	6.5		
	Pretazettine	1.90	> 100	> 52.6		
	(+) *-trans-*dihydronarciclasine	0.031	0.18	5.8	n.e.	[32]
	Pancratistatin	0.0063	> 150	> 23809	n.e.	[35]
Berberidaceae	Berbamine	1.90	76.35	40.19	Entry (host TRPML channels and endosomal trafficking) and replication	[42]

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	Berberine	0.2	15.3	205	Infectious particle formation, host p38 MAPK	[47]
Menisp ermace ae	Cepharanthine	0.37	18.60	50.26	Replication (host cells)	[42]
	Fangchinoline	4.77	9.50	1.99		
	Tetrandrine	1.29	12.31	9.54		
	Iso-tetrandrine	2.11	51.83	24.57		
Rubiace ae	Emetine	^IC_{50} 0.121	n.d.	n.d.	NS5 RdRp	[49]

[#] This study is a preprint. Ref.: Reference. EC_{50}: concentration of 50% inhibition of infection, CC_{50}: concentration of 50% cytotoxicity. ^: represents biochemical IC50, measured through a cell-free assay directly evaluating an enzyme inhibition. SI: selectivity index (CC_{50}/EC_{50} or IC_{50}).). > indicates that the maximum nontoxic concentration tested did not reach the 50% cytotoxicity threshold, the corresponding SI values represent minimal calculated selectivity. ± standard deviation of the mean. n.d: Not determined. n.e.: not elucidated. TRPML: Transient Receptor Potential Mucolipin. MAPK: Mitogen-Activated Protein Kinase. RdRp: RNA-dependent RNA polymerase.

2.3. Viral Protease Inhibition and Protease-Dependent Processing

Arbovirus genomes are translated into a single polyprotein that requires processing by host and viral proteases (Figure 1). Some evidence supports direct protease inhibition by alkaloids. Li et al. [66] described lycorine as a main protease (M^{pro}) inhibitor of SARS-CoV, using cytopathic effect-based screening, and the target was later confirmed experimentally for SARS-CoV-2 by Narayanan et al. [67] in a cell-based protease assay. To our knowledge, no equivalent data exist for flaviviral proteases (NS2B-NS3). Lycorine, like cherylline, did not inhibit a replication-deficient DENV replicon (NS5 catalytic mutant), which measures only cap-dependent translation of the input RNA [52]. This result demonstrates that lycorine's anti-DENV activity requires active viral RNA replication and excludes a primary translational mechanism for this virus.

Zou et al. (2009) reported resistance data that provide a solid link between lycorine and protease-dependent processing in flaviviruses [57]. The V9M resistance mutation in the WNV viral genome, arising from continuous lycorine treatment, maps to the 2K peptide, a 23-amino-acid transmembrane segment between NS4A and NS4B. Critically, the cleavage at the NS4A-2K junction is performed by the viral NS2B-NS3 protease, and this cleavage is a prerequisite for the subsequent host signal peptidase (signalase) cleavage at the 2K-NS4B junction [68]. This sequential, protease-dependent processing of NS4A-2K-NS4B is essential for the membrane rearrangements that form the scaffold of the viral replication complex. The V9M mutation enhances viral RNA replication ~100-fold in the presence of lycorine (but only 2-4-fold in its absence), possibly by altering 2K-mediated membrane reorganization or the efficiency of NS2B-NS3 cleavage at the NS4A-2K site.

This resistance data suggests that the functional target of lycorine in flaviviruses is more likely the membrane-associated NS4A-2K-NS4B replication complex than the NS5 polymerase itself. This interpretation is consistent with the weak direct enzymatic inhibition of NS5. Interestingly, Fikatas et al. [27] identified a novel series of indole alkaloid derivatives, structurally related to the ervatamine-silicine family, with a piperidine ring, that interfere with the replication complex, through targeting NS4B (genetically validated resistance mutation). Together with the specific targeting of the most clinically advanced DENV antiviral JNJ-1802, which blocks the NS3-NS4B protein-protein interaction [69], the lines of evidence converge on the central role of NS4B and its interactions with NS3 in flavivirus replication. These findings position the NS4B-NS3 axis and the membrane-associated replication complex as a privileged therapeutic target in flaviviruses.

 doi:10.20944/preprints202606.0012.v1

Table 3. Reported antiviral activity and mechanism of action of diverse alkaloid families against various flaviviruses and CHIKV.

Virus	Alkaloid	EC_{50} (μM)	CC_{50} (μM)	SI	Target	Ref
JEV	*cis*-dihydronarciclasine	41.06	202.09	4.9	n.e.	[35]
	Lycorine	1.04	9.40	8.2		
	Narciclasine	*IC_{50} 0.026	0.101	3.88		
	7-Deoxypancratistatin	1.55	9.05	5.9		
	Cepharanthine	0.5063	18.60	36.73	Replication (host cells)	[42]
	Fangchinoline	3.870	9.50	2.45		
	Tetrandrine	5.172	12.31	2.38		
	Iso-tetrandrine	5.751	51.83	9.01		
YFV	*cis*-dihydronarciclasine	31.04	206.94	6.6	n.e.	[35]
	Lycorine	0.79	7.10	7.3		
	Narciclasine	*IC_{50} 0.0195	120	6.1		
	7-Deoxypancratistatin	1.29	8.41	6.52		
	Berbamine	2.541	76.35	30.05	Entry and replication (host TRPML channels and endosomal trafficking)	[42]
AHFV	Lycorine	1.7	16.2	9	n.e.	[35]
WNV	Lycorine	0.23	24	104.3	Replication complex (peptide 2K)	[57]
CHIKV	Berberine	1.8 ± 0.5	> 100	> 55.6	Protein synthesis	[70]
	Harringtonine	0.24	n.d.	n.d.	n.e.	[29]
	Lycorine	~1	n.d.	n.d.	Translation	[56,71]
		*IC_{50} 0.319	>50	>156	Post-entry and RNA synthesis	

Ref.: Reference. EC_{50}: concentration of 50% inhibition of infection. *: represents IC50 values determined using a cell-based phenotypic assay. CC_{50}: concentration of 50% cytotoxicity. SI: selectivity index (CC_{50}/EC_{50} or IC_{50}). > indicates that the maximum nontoxic concentration tested did not reach the 50% cytotoxicity threshold, the corresponding SI values represent minimal calculated selectivity. ± standard deviation of the mean. n.d: Not determined. n.e.: Not elucidated. TRPML: Transient Receptor Potential Mucolipin. JEV: Japanese Encephalitis Virus. YFV: Yellow Fever Virus. AHFV: Alkhurma Hemorrhagic Fever Virus. WNV: West Nile Virus. CHIKV: Chikungunya Virus. TRPML: Transient Receptor Potential Mucolipin.

 doi:10.20944/preprints202606.0012.v1

2.4. Other Viral Targets

Tylophorine and its derivatives exhibit nanomolar antiviral activity against coronaviruses by binding viral genomic/subgenomic RNAs and nucleocapsid proteins [72], but have not been tested against flaviviruses to our knowledge.

Overall, the most robust viral target assignments are currently that lycorine targets MERS-CoV RdRp but NS4A-2K-NS4B membrane complex for WNV; emetine against ZIKV RdRp; and ervatamine-silicine-type indole derivatives target NS4B for DENV/ZIKV (resistance mutation). Strikingly, the two genetically validated targets in flaviviruses both implicate the NS4A-NS4B axis rather than NS5.

Table 4. Reported antiviral activity and mechanism of action of diverse alkaloid families against Hepatitis C virus.

	Alkaloid	**EC_{50} (μM)**	**CC_{50} (μM)**	**SI**	**Target**	**Ref**
Amaryllidaceae	Lycorine	1.03 ± 0.12	9.9 ± 0.72	9.6	HSP70 (host-target mechanism)	[73]
Berberidaceae	Berberine	7.87 ± 1.10	82.75 ± 0.27	10.51	Entry (E2 glycoprotein binding)	[47]
Piperaceae	Piperine	*IC_{50} 52.18 ± 3.21	n.d.	n.d.	NS5B polymerase	[74]

Ref.: Reference. EC_{50}: concentration of 50% inhibition of infection. *: represents IC50 values determined using a cell-based phenotypic assay. CC_{50}: concentration of 50% cytotoxicity, SI: selectivity index (CC_{50}/EC_{50} or IC_{50}). ± standard deviation of the mean. n.d: Not determined.

3. Host Factors as Targets Across Virus Families

As obligate intracellular pathogens, viruses rely on the host cell machinery to successfully complete their replication cycle and proliferate. While endogenous, these factors can be temporarily targeted to prevent viral replication and protect the host.

3.1. Ribosome Binding and Translational Stress: Old Evidence for An Emerging Antiviral Mechanism

The interaction of *Amaryllidaceae* alkaloids with the ribosome has been characterized at increasing resolution over five decades. Jimenez et al. (1976) demonstrated dose-dependent inhibition of protein synthesis by lycorine in mammalian cells [75]. Kukhanova et al. (1983) localized the target to the donor site of the peptidyltransferase center (PTC) of wheat-germ ribosomes [76]. Garreau de Loubresse et al. (2014) confirmed lycorine and narciclasine binding near the tRNA/mRNA interface by crystallography [77], and Pellegrino et al. (2018) solved the 3.1 Å structure of haemanthamine at the 80S ribosomal PTC A-site [78]. Consistent with a translational target, Li et al. (2021) used two independent CHIKV replicon systems to demonstrate that lycorine inhibits primarily viral translation [71]. Time-of-drug addition and SARS-CoV-2 replicon assays also suggest a post-entry step consistent with translation as the target of AAs [53].

Nonetheless, the ribosome/translation target does not apply universally across viral families. For DENV, cherylline and lycorine failed to inhibit a translation-only replicon (NS5-deficient), demonstrating that active RNA replication is required for its antiviral effect [52]. This virus-specific variation suggests that the translational target identified for CHIKV [71] and the replication complex target for DENV/WNV represent distinct, family-dependent mechanisms. Such mechanistic versatility is analogous to that observed for berberine (Table 3). This also underscores that distinguishing translational from replicative effects remains technically challenging for compounds that may affect both processes [56].

Narciclasine EC_{50} of 0.02 μM is remarkably consistent across all four neglected flaviviruses tested, DENV, ZIKV, YFV, and JEV (Table 2 and 3) [35,60], a uniformity that suggests a host-directed

 doi:10.20944/preprints202606.0012.v1

mechanism. Indeed, this compound binds the eukaryotic ribosome near the tRNA/mRNA interface [77]. Determining whether narciclasine inhibits a DENV translation-only replicon will help directly assess whether its anti-flaviviral activity operates through the ribosomal mechanism suggested by its structural data, or through a distinct pathway. If narciclasine does inhibit the translation-only replicon, this would confirm that a structurally distinct Amaryllidaceae alkaloids can target different steps of the viral cycle even within the same virus. Intriguingly, narciclasine has not been tested against influenza or CHIKV, leaving its cross-family breadth undefined. Compounds of the narciclasine-type scaffold (notably pancratistatine) were reported as cytotoxic and devoid of anti-SARS-CoV-2 activity in Vero-E6 cells [79], but as discussed in [59], cell-line-dependent results for structurally related compounds urge caution in generalizing these findings. Indeed, a synthetic derivative, 7-hydroxyl-dihydronarciclasine, displayed strong antiviral activity against SARS-CoV-2 (Table 5) [80].

Table 5. Reported antiviral activity and mechanism of action of diverse alkaloid families against HCoV-OC43, SARS-CoV-2, and various coronaviruses.

	Alkaloid	**EC_{50}(μM)**	**CC_{50} (μM)**	**SI**	**Target**	**Ref**
			HCoV-OC43			
Amaryllidaceae	Lycorine	1.6 ± 0.4	34.9 ± 5.2	22	Replication or	[53]
	Haemanthamine	1.6 ± 0.7	49.2 ± 4.8	32	translation	
	Haemanthidine	1.7 ± 0.6	36.7 ± 1.8	22		
	Crinamine	0.5 ± 0.1	25.2 ± 1.2	51		
	Amarbellisine	0.2 ± 0.1	12.1 ± 2.4	60		
	Cherylline	8.0 ± 1	> 100	> 13		
	Pancracine	2.6 ± 1.3	81.4 ± 11.8	31		
	Ungeremine	1.6 ± 0.3	6.6 ± 2.4	4		
	Clivimine	18.7 ± 9.9	> 100	> 5		
	Tazettine	21.6 ± 3.6	> 100	> 5		
	Obliquine	23.0 ± 0.6	> 100	> 4		
	11-hydroxyvittatine	23.3 ± 0.8	> 100	> 4		
Apocynaceae	Tylophorine	16 ± 5	> 10,000	> 610	Replication	[81]
Menispermaceae	Tetrandrine	8.29	14.51	> 40	Entry;	[40]
	Fangchinoline	0.92	12.40	13	Replication	
	Cepharanthine	0.73	10.54	11		
Rubiaceae	Emetine	0.30	2.69	8.96	Replication	[82]
			SARS-CoV-2			
Amaryllidaceae	Montanine	*IC_{50} 1.71	165	> 96.49	Translation	[61]
Amaryllidaceae (semi-synth.)	Lycorine derivative compound 7	0.73	79.81	109	Translation (-1PRF)	[83]
Apocynaceae	Tylophorine	0.013	> 10	> 769	Replication: Transcription	[81]
Berberidaceae	Berbamine	IC_{50} 43.4	nd	nd	Entry; Postfusion core	[41]
Cephalotaxaceae	Homoharringtonine	2.55	59.75	23.43	Replication	[48]
Fabaceae	Oxysophoridine	0.18	> 40	> 222	Replication	[84]

 doi:10.20944/preprints202606.0012.v1

Menispermaceae	Tylophorine	0.0140	5.10	364	Replication; transcription	[81]
Rubiaceae	Emetine	0.46	56.46	122.7	Replication	[48,85]
		Other coronavirus				
Virus	**Alkaloid**	**EC_{50} (μM)**	**CC_{50} (μM)**	**SI**	**Target**	**Ref**
Amaryllidaceae	Lycorine	0.016 ± 0.001	14.98 ± 0,91	> 936	Replication (SARS-CoV)	[66]
		*IC_{50} 1.021 ± 0.025	> 50	48.97	Replication (RdRp) (SARS-CoV)	[54]
		^IC_{50} 1.406 ± 0.260	> 50	35.56	Replication (RdRp) (MERS-CoV)	[54]
Berberidaceae	Berbamine	29.2 ± 7	n.d.	n.d.	Entry (MERS-CoV)	[86]
Menispermaceae	Tetrandrine	7.0 ± 0.8	n.d.			
	Fangchinoline	1.7 ± 0.2	n.d.			
Rubiaceae	Emetine	1.43	3.63	2.54	Replication (HCoV-NL63)	[82]

Ref.: Reference. EC_{50}: concentration of 50% inhibition of infection. *: represents IC50 values determined using a cell-based phenotypic assay. ^: represents biochemical IC50, measured through a cell-free assay directly evaluating an enzyme inhibition. CC_{50}: concentration of 50% cytotoxicity, SI: selectivity index (CC_{50}/EC_{50} or IC_{50}). > indicates that the maximum nontoxic concentration tested did not reach the 50% cytotoxicity threshold, the corresponding SI values represent minimal calculated selectivity. ± standard deviation of the mean. -1PRF: -1 Programmed Ribosomal Frameshifting. RdRp: RNA-dependent RNA polymerase. n.d.: Not determined. HCoV-OC43: **Human Coronavirus OC43.** SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2. MERS-CoV: Middle East Respiratory Syndrome Coronavirus. HCoV-NL63: Human Coronavirus NL63.

3.2. The Integrated Stress Response Following Ribosome Stalling

In addition to impairing protein synthesis, ribosomal inhibition triggers an integrated stress response (ISR) and may modulate the immune response. Independent antiviral observations converge on the hypothesis that translational stress may contribute to antiviral activity, though they do not establish a causal chain. McNulty et al. (2023) reported ISR activation (PERK/eIF2α) by a truncated ring-A isocarbostyril [80] in HSV-1-infected brain organoids. PERK kinase upregulation leads to eIF2α phosphorylation and ATF4 induction, the canonical ISR effector axis. Although ISR activation has been reported to intersect with innate antiviral signaling in some contexts, the pathway linking eIF2α phosphorylation to type I interferon production remains mechanistically undefined and distinct from the canonical IRF3/IRF7-dependent induction routes. We also detected upregulation of ATF4 transcription, early after antiviral *Amaryllidaceae* alkaloids treatment in the context of HCoV-OC43 infection, as well as an increase in *IFN-β* transcript (Table 5) [53]. A preprint [61]suggests that narciclasine and montanine (Table 2 and 5) bind to ribosomal PTC, yielding ribosome collision and the ISR axis. This positions ISR activation as a potential bridge between the translational perturbation and the induction of an antiviral innate immune response. Although the alkaloid-dependent ribosome-mediated ISR effect on viral translation has yet to be formally established, this hypothesis is intriguing.

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3.3. Host Innate Immune Signaling

Convergent lines of evidence suggest that alkaloids may modulate host innate immune signaling pathways. Cepharanthine was recently shown to reduce IL-6 production following DENV infection (Table 2) [44]. Giannoni et al demonstrated that berberine inhibits ZIKV-induced activation of both ERK1/2 and p38 MAPK in infected cells, and that the p38 inhibitor SB202190 phenocopied berberine's antiviral effect [47] (Table 2). Since p38 MAPK regulates inflammatory cytokines and modulates cap-dependent translation via MAPKAPK2-mediated phosphorylation of eIF4E, a pathway parallel to the eIF2α-centered ISR, berberine may engage the same translational-immune interface through a distinct upstream kinase. Berberine also impaired the formation of intracellular and extracellular infectious DENV particles (Table 2), thus involving late-stage assembly and host signaling. In a complementary observation, Huang et al. (2026) showed that lycorine restores the type I IFN response suppressed during infection with infectious bronchitis virus in chicken cells by upregulating MDA5 expression through the RIG-I-like receptor pathway rather than the ISR [87]. This suggests that some alkaloids may enhance innate antiviral immunity through multiple independent mechanisms, likely depending on the compound, virus, and cell type.

Of note, none of these observations demonstrates that immune modulation is the primary antiviral mechanism rather than a bystander effect. Translational inhibition alone, by reducing the burst of viral protein synthesis that positive-strand RNA viruses require, could account for much of the antiviral activity without requiring ISR signaling. Disentangling these possibilities will require experiments in which ISR or MAPK signaling is specifically blocked while monitoring viral replication in alkaloid-treated cells.

3.4. Additional Host-Targeting Mechanisms

At least three other host-directed antiviral pathways have been experimentally established for alkaloids. Lycorine derivatives downregulate the host chaperone Hsc70, destabilizing the HCV replication complex (Table 4) [73]. This represents a validated host-targeting pathway with potential transferability to DENV, where Hsc70 is also required for replication [88,89], though this has not been tested. Lycorine inhibits the synthesis of the nucleoporin Nup93, blocking nuclear export of influenza nucleoprotein [90], but there is no equivalent in flaviviruses (which replicate in the cytoplasm). Du et al. (2026) identified a novel mechanism for lycorine derivative compound 7, stabilization of ZAP-S (zinc-finger antiviral protein, short isoform), which disrupts -1PRF, validated by *in vivo* data in hamster models (Table 5) [83]. This mechanism is conserved across SARS-CoV, SARS-CoV-2, and MERS-CoV.

Castanospermine and other iminosugars inhibit DENV infection at the level of secretion and viral infectivity by targeting host α-glucosidases, disrupting *N*-glycan processing and viral glycoprotein folding [62], a mechanism active against DENV, HCV, HIV, and influenza that has progressed furthest toward clinical application. For most alkaloid-arbovirus pairs, including the most potent (narciclasine, pancratistatine, amarbellisine), the molecular target remains unconfirmed. Resolving this deficit is an important challenge facing this field.

It is worth noting that DNA intercalation by isoquinoline alkaloids such as berberine and emetine is well characterized in the context of DNA viruses and protozoa [91,92]. For RNA viruses, however, the relevance of this mechanism is less clear. Pépin et al. (2017) demonstrated that DNA intercalating agents can activate cGAS-STING signaling through low-level host DNA damage, providing an alternative route to type I IFN induction [93]. Whether the alkaloids discussed here engage this pathway in addition to the ribosome-mediated ISR remains to be determined.

 doi:10.20944/preprints202606.0012.v1

Table 6. Reported antiviral activity and mechanism of action of diverse alkaloid families against diverse RNA and DNA viruses.

	Alkaloid	EC_{50} (μM)	CC_{50} (μM)	SI	Target	Ref
		Hepadnavirus (HBV)				
Fabaceae	Sophaline A-D	160 - 400	n.d.	n.d.	HBsAg and	[94]
	Sophaline F-H/ E, I	35 / 400	n.d.	n.d.	HBeAg	[95]
Rutaceae	5,6-Dihydro-6-methoxynitidine	200	n.d.	n.d.	secretion	[96]
	Skimmianine	200	n.d.	n.d.		[96]
	5-methoxydictamine	200	n.d.	n.d.		[94,96]
		Other RNA viruses (RSV/EBOV/HPIV-3)				
Liliaceae	Cyclopamine	*IC_{50} 0.46 to 0.82 *in vitro*	n.d.	n.d.	n.e.	[97]
Rubiaceae	Emetine	*IC_{50} 10.2	>100	>9.8	Entry	[49]
Solanaceae	Atropine	MNTC 5.53	n.d.	n.d.	n.e.	[98]
	Octopamine	MNTC 10.45	n.d	n.d.		
		Lentivirus (HIV-1)				
Amaryllidaceae	*Extract of *Crinum asiaticum* var. *japanicum*	ED_{50} 12.5μg/mL	CD_{50} 200μg/mL	16	Replication	[99]
Ancistrocladaceae	Michellamine D	3 (against HIV-RF)	n.d.	n.d.	n.e.	[100]
	Michellamine F	2 (against HIV-RF)	n.d.	n.d.		
Apocynaceae	18-Methoxycoronaridine	9.5 ± 3 - 12.8 ± 5	328	34.5 - 25.6	RT	[101]
Fabaceae	6-O-Butanoyl castanospermine (B-CAST)	*IC_{50} 0.19–0.58	n.d.	n.d.	Maturation	[102]
	Aloperine	1.75 ± 059	> 86.2	> 49.25	Entry	[45]
	Aloperine N-(1-butyl)-4-trifluoromethoxy-benzamide	0.69 ± 013	> 42.1	> 61.01		
Lauraceae	Hernandonine	^IC_{50} 16.3	n.d.	n.d.	n.e.	[103]
	Laurolitsine	^IC_{50} 7.7	n.d.	n.d.		
	7-oxohernangerine	^IC_{50} 18.2	n.d.	n.d.		
	Lindechurine A	^IC_{50} 21.1	n.d.	n.d.		
Menispermaceae	Fangchinoline	0.8 – 1.7	6.4-6.9	3.8-8.6	Maturation	[104]
Rubiaceae	Emetine	14,1	250	17.7	Entry; RT	[105]
Rutaceae	Buchapine	2.99	55.89	18.69	n.e.	[106]
	3-(3-methyl-2-butenyl)-4-[(3-methyl-2-butenyl) oxy]-2(1H)-quinolinone	3.8	71.17	18.72		
	4-(Isopentyloxy) quinolin-2-ol	3.9	114.67	29.47		

Ref.: Reference. EC_{50}: concentration of 50% inhibition of infection. *: represents IC50 values determined using a cell-based phenotypic assay. ^: represents biochemical IC50, measured through a cell-free assay directly

 doi:10.20944/preprints202606.0012.v1

evaluating an enzyme inhibition. CC_{50}: concentration of 50% cytotoxicity. ED_{50}: Effective Dose 50%. CD_{50}: Cytotoxic Dose 50 %. SI: selectivity index (CC_{50}/EC_{50} or IC_{50}) or (CD_{50}/ED_{50}). > indicates that the maximum nontoxic concentration tested did not reach the 50% cytotoxicity threshold, the corresponding SI values represent minimal calculated selectivity. ± standard deviation of the mean. n.d.: Not determined. n.e.: Not elucidated. MNTC: Maximum Non-Toxic Concentration, HBV: Hepatitis B Virus, HBsAg: Hepatitis B surface Antigen, HBeAg: Hepatitis B e Antigen, RSV: Respiratory Syncytial Virus, EBOV: Ebola Virus, HPIV-3: Human Parainfluenza Virus type 3, HIV-1: Human Immunodeficiency Virus type 1. RT: reverse transcriptase.

4. Conclusions

This review compiled over 100 alkaloid-virus combinations across RNA virus families and identified four chemical scaffolds, isoquinoline (emetine, berberine), benzylisoquinoline, bis-benzylisoquinoline (tetrandrine, berbamine), and isocarbostyril (lycorine, narciclasine), as displaying cross-family antiviral activity. The most potent interactions were concentrated against neglected arboviruses for which no approved therapeutics currently exist. This analysis reveals both strengths and weaknesses in the field. The most robust mechanistic assignments come from well-characterized viral systems and are supported by enzymatic, structural, or genetic validation. In contrast, the widely cited lycorine-NS5 interaction for flaviviruses lacks enzymatic confirmation at pharmacologically relevant concentrations, and over half of all alkaloid-virus mechanisms remain entirely uncharacterized. Converging structural, biochemical, and transcriptomic evidence spanning five decades suggests that ribosome-mediated translational stress may constitute an additional, unifying mechanism for isoquinoline-derived alkaloids, including the *Amaryllidaceae* subgroup, but this hypothesis requires formal validation. Addressing the mechanistic deficit through unbiased target deconvolution, formal testing of the ribosome/ISR hypothesis, expanded taxonomic coverage, and *in vivo* validation will determine which plant-derived alkaloids can be translated into therapeutics for the neglected arboviruses that continue to threaten global health.

Author Contributions: Conceptualization, M.R., M.S.M., H.G., N.M., and I.D-P.; methodology, , M.R., M.S.M., N.M., and I.D-P.; validation, H.G., N.M. and I.D-P.; formal analysis, M.R., M.S.M., and N.M., investigation, M.R., M.S.M., and N.M.; resources, H.G. and I.D-P.; data curation, M.R., M.S.M., and N.M.; writing—original draft preparation, M.R., and M.S.M.; writing—review and editing, M.R., M.S.M., N.M., H.G. and I.D-P.; supervision, N.M., H.G. and I.D-P..=; project administration, H.G. and I.D-P.; funding acquisition, I.D-P.. All authors have read and agreed to the published version of the manuscript

Funding: This research was funded by Canada Research Chair on plant specialized metabolism, grant number CRC-2023 00353 to I.D-P.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We thank all members of the laboratories of Professors Isabel Desgagné-Penix and Hugo Germain. We would like to express our gratitude to Serge Basile Nouemssi and Aracely Maribel Diaz Garza for their valuable advice during the initial stages of writing of this review. The authors acknowledge the use of Claude AI (Anthropic) for language revision. Following the use of this tool, the authors reviewed and edited the content as needed and take full responsibility for the publication's content. Warm thanks are extended to the Canadian taxpayers and the Canadian government for their support of the Canada Research Chairs Program.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Not applicable.

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 doi:10.20944/preprints202606.0012.v1

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