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Exploring Organic Compounds as Anti-Viral Agents

Suman Kumari

Research Scholar, Faculty of Chemistry, Asian International University, Imphal West, Manipur (India)

Abstract

Organic compounds, both natural and synthetic, have gained significant importance as promising antiviral agents due to their structural versatility, chemical diversity, and wide range of biological activities. Natural organic molecules including flavonoids, polyphenols, alkaloids, terpenoids, peptides, and polysaccharides derived from plants and marine organisms have demonstrated potent antiviral effects against viruses such as Influenza virus, SARS-CoV-2, HIV, Dengue virus, Zika virus, Chikungunya virus and Mayaro virus. Their antiviral action is attributed to multiple mechanisms including inhibition of viral entry, suppression of viral replication and transcription, interference with viral protein synthesis, and modulation of host immune responses. Marine natural products, in particular, display exceptional antiviral activity owing to their unique structures, high bioactivity, and chemical novelty, with compounds such as fucoidan, avarol, kainic acid, and caulerpin showing notable efficacy in preclinical studies. Synthetic organic compounds including heterocycles, quinones, and nucleoside analogs also contribute significantly to antiviral drug development by offering improved stability, enhanced target specificity, and lower toxicity. Despite promising advances, limitations involving compound stability, low bioavailability, complex extraction and purification, and lack of extensive clinical validation continue to restrict large-scale applications. The continuous emergence of viral pandemics highlights the urgent need for the discovery, optimization, and development of effective organic antiviral agents. This review presents an integrated overview of natural and synthetic organic molecules with antiviral activities, their mechanisms of action, challenges in drug development, and future perspectives for therapeutic applications.

Keywords: Organic compounds, Antiviral agents, Medicinal plants, Marine natural products, Synthetic antivirals, SARS-CoV-2, Influenza, HIV, Arboviruses.

1. Introduction

Viral infections continue to pose a severe global health burden, causing widespread morbidity and mortality, especially with the frequent emergence of novel or re-emerging pathogens such as influenza viruses, coronaviruses, arboviruses, and retroviruses (e.g., HIV) [9, 90]. The rapid spread of RNA viruses including Influenza, SARS-CoV-2, Dengue virus, Zika virus, Chikungunya virus and their potential for mutation and evolution means that existing therapeutic options often lose efficacy or become limited by resistance phenomena [8, 9]. Alongside this, many approved antiviral drugs suffer from drawbacks such as toxicity, narrow spectrum of activity, high cost, and limited availability [3, 5]. These challenges underscore an urgent need to discover and develop novel classes of antiviral compounds with broader antiviral potential, better safety profiles, and lower resistance risk.

Organic compounds whether derived from plants, marine organisms, microbes, or synthesized for medicinal chemistry represent a promising resource in this search. Their structural and chemical diversity enables a wide array of mechanisms by which they can interfere with viral infection and replication [3].

1.1 Natural plant-derived organic compounds and their relevance

Plants produce a wide range of secondary metabolites such as flavonoids, alkaloids, terpenoids, polyphenols, quinones, and tannins that have shown antiviral activity across multiple virus families [3, 7]. For example, flavonoids have been reported to inhibit viral entry, replication, or protein synthesis; some flavonoids also exhibit virucidal activity or modulate host immune response to viral infection [2]. Other classes like terpenoids, alkaloids, and quinones similarly offer varied antiviral properties [3, 7]. The broad structural diversity and ready availability of plant-derived compounds make them especially attractive for antiviral drug discovery.

1.2 Marine-derived organic compounds: a largely untapped reservoir

Marine biodiversity is increasingly recognized as a vast and underutilized source of bioactive organic molecules with antiviral potential. Marine organisms such as sponges, algae, corals, mollusks, marine fungi, and bacteria produce structurally novel compounds, including sulfated polysaccharides, peptides, alkaloids, terpenoids, and other specialized metabolites, many of which have demonstrated antiviral activity in vitro or in preclinical studies [6, 8]. For instance, sulfated polysaccharides from marine algae (e.g., fucoidans, carrageenans) have shown ability to block viral binding or entry, while certain marine alkaloids, terpenoids or peptides interfere with replication or viral protein processing [1, 8]. The unique chemical scaffolds found in marine natural products often differ markedly from terrestrial metabolites, which may help overcome issues of drug-resistance seen with conventional antivirals.

1.3 Synthetic organic antiviral compounds: design and optimisation

In addition to natural sources, synthetic organic chemistry remains central to antiviral drug development. Synthetic analogs or novel scaffolds such as nucleoside analogues, heterocycles, quinones allow researchers to tailor pharmacokinetic and pharmacodynamic properties (absorption, distribution, metabolism, stability, selectivity) while targeting viral enzymes or structural proteins critical for viral replication or maturation [3, 102]. Synthetic compounds can combine advantages of potency, broad-spectrum activity, and improved drug-like characteristics, making them important complements to natural-product research.

2. Classification of Organic Antiviral Compounds

2.1 Plant-Derived Organic Antiviral Compounds

Plants are among the richest natural sources of antiviral organic compounds, producing an extensive array of secondary metabolites with activity against a diverse set of human viral pathogens including Influenza viruses, coronaviruses, arboviruses (DENV, ZIKV, CHIKV, MAYV), HIV, herpesviruses, hepatitis viruses, and enteroviruses [3, 18, 26]. These phytochemicals belong to numerous structural classes such as flavonoids, alkaloids, quinones, terpenoids, lignans, tannins, polyphenols, saponins, glucosinolates, coumarins, furanocoumarins, stilbenes, and phenolic acids, each offering unique antiviral mechanisms [7, 20, 23, 26]. Their structural and functional diversity allows them to interfere with multiple stages of the viral life cycle, making them particularly promising scaffolds for broad-spectrum antiviral drug development [2, 29].

Flavonoids

Flavonoids are among the most extensively studied plant-derived antiviral molecules. Compounds such as quercetin, kaempferol, apigenin, luteolin, galangin, baicalein, baicalin, catechins, EGCG, rutin, hesperetin, naringenin, theaflavins, and dihydromyricetin have demonstrated significant inhibitory effects against Influenza A viruses, SARS-CoV-2, MERS-CoV, DENV, ZIKV, CHIKV, EV-A71, HSV, and HIV [2, 10, 16, 26, 31, 33]. Quercetin and its derivatives interfere with viral entry, polymerase activity, and protease function, while theaflavins from *Camellia sinensis* demonstrate both neuraminidase inhibition and direct virucidal activity against multiple influenza subtypes [26, 31]. Catechins, especially EGCG, block coronavirus entry by binding to the spike protein and interfering with ACE2 receptor interactions [15].

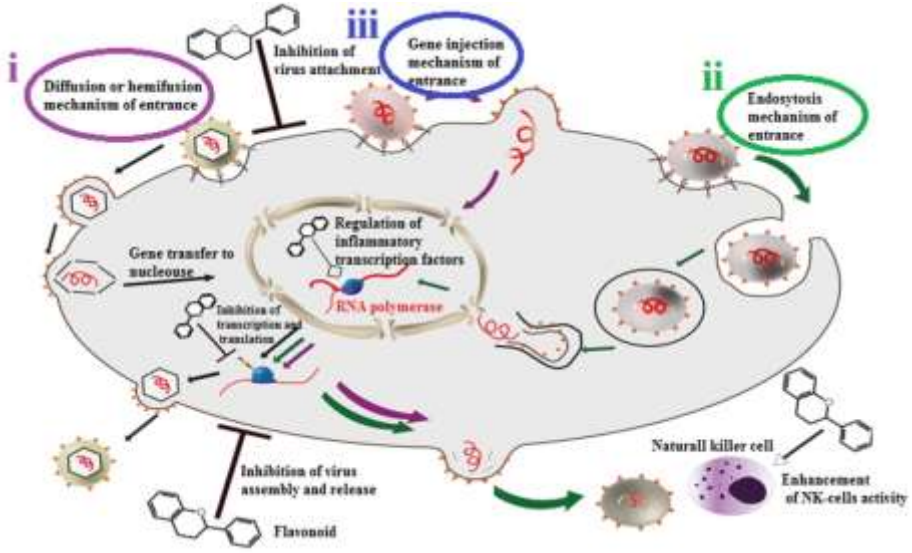

Figure 1: Three main mechanisms of viral entrance and some different antiviral effects of flavonoids. [24]

Polyphenols and Tannins

Polyphenols such as geraniin, ellagic acid, gallic acid, punicalagin, resveratrol, curcumin, and penta-O-galloyl-β-D-glucose show strong antiviral activity by suppressing viral RNA synthesis, inhibiting proteases, disrupting capsid proteins, and modulating host inflammatory pathways [1, 19, 20]. Tannins possess strong protein-binding capabilities, enabling them to precipitate viral envelope proteins, block adsorption, and prevent membrane fusion, making them particularly effective against enveloped viruses [3, 17].

Alkaloids

Plant alkaloids, such as berberine, lycorine, colchicine, matrine, oxymatrine, harmine, harmaline, fagaronine, tomatidine, and sanguinarine exhibit broad-spectrum antiviral activities [26, 28, 34]. Berberine inhibits Influenza A, SARS-CoV-2, and arboviruses by disrupting host MAPK/ERK signalling and reducing viral RNA export [26, 34]. Lycorine strongly inhibits DENV, ZIKV, and CHIKV replication by targeting viral polymerases and protein synthesis machinery [28]. Matrine and oxymatrine show activity against HBV and enteroviruses by modulating host immune pathways [25].

Coumarins and Furanocoumarins

Coumarin derivatives such as imperatorin, isoimperatorin, osthole, esculetin, oxypeucedanin, and herniarin exhibit antiviral activity against influenza viruses, enteroviruses, herpesviruses, and HIV [26,

27, 32]. Oxypeucedanin from *Angelica dahurica* demonstrates strong neuraminidase inhibition, suppression of viral nucleoprotein synthesis, and reduction of apoptotic pathways in infected cells [26].

Terpenoids

Monoterpenes, sesquiterpenes, diterpenoids, and triterpenoids including ginsenosides, glycyrrhizin, betulinic acid, oleanolic acid, andrographolide, thymol, carvacrol, and ursolic acid show antiviral effects by blocking viral entry, inhibiting proteases, and modulating host immune responses [12, 30]. Glycyrrhizin from *Glycyrrhiza glabra* has long been recognized for its strong activity against SARS-CoV, hepatitis viruses, and HIV through inhibition of viral replication and immunomodulatory effects [13].

Lignans and Stilbenes

Lignans such as phyllanthin, justicin, podophyllotoxin, and arctigenin demonstrate inhibitory activity against influenza, enteroviruses, and herpesviruses by blocking viral protein synthesis and inhibiting polymerases [14]. Stilbenes such as resveratrol and pterostilbene exhibit broad antiviral activity by reducing viral RNA synthesis, blocking NF-κB activation, and preventing virus-induced oxidative stress [11].

Saponins and Lectins

Saponins (e.g., astragalosides, glycyrrhizic acid derivatives) disrupt viral envelopes and enhance antiviral immunity through increased interferon expression [12]. Plant lectins such as Galanthus nivalis agglutinin (GNA) and griffithsin display extraordinary activity by binding viral glycoproteins, particularly those of HIV, SARS-CoV, MERS-CoV, and SARS-CoV-2 [21, 22].

Overall, plant-derived antiviral compounds represent an expansive and chemically diverse group with activity across the majority of clinically relevant viral families. Their broad-spectrum potential, low cytotoxicity, and multimodal mechanisms of action underscore their importance as lead compounds for future antiviral drug development.

2.2 Marine-Derived Organic Antiviral Compounds

Marine ecosystems are among the most chemically diverse biospheres on Earth, producing a vast spectrum of structurally unique organic metabolites that are not commonly found in terrestrial organisms. The biological and ecological pressures present in marine environments; competition, predation, symbiosis, and defence against pathogens have driven marine organisms to evolve a wide array of potent antiviral molecules [8, 48]. Marine natural products originate from sources such as sponges, algae, corals, mollusks, tunicates, marine fungi, cyanobacteria, and actinomycetes, each contributing distinct molecular scaffolds including sulfated polysaccharides, alkaloids, terpenoids, peptides, nucleosides, polyketides, and polyphenolics [8, 36, 37]. These compounds display antiviral activity against numerous human viruses, such as SARS-CoV-2, HIV, HSV, HBV, HCV, Dengue virus, Zika virus, Influenza viruses, Enteroviruses, and RSV [8, 41, 43, 46, 47, 60].

Sulfated Polysaccharides

One of the most studied groups of marine antivirals is sulfated polysaccharides, especially fucoidans, carrageenans, ulvans, porphyrans, and sulfated galactans, predominantly sourced from brown, red, and green algae [8, 39, 63]. Their high density of sulfate groups enables strong electrostatic interactions with viral surface proteins, blocking viral adsorption, preventing membrane fusion, and inhibiting viral entry. Fucoidan, a fucose-rich polysaccharide from brown algae, shows potent activity against SARS-CoV-2, Influenza A, RSV, and HSV-1, with several studies confirming its ability to interfere with spike–ACE2 binding and inhibit early steps of viral infection [8, 39, 57]. Carrageenans from red algae particularly λ-

and ι-carrageenan exhibit broad-spectrum antiviral activity and have been evaluated in nasal spray formulations for respiratory virus protection [38, 51].

Marine Sponges

Marine sponges are among the most prolific sources of antiviral molecules, producing structurally complex alkaloids, terpenoids, nucleosides, β-carbolines, and halogenated compounds [49]. Notable examples include avarol, a sesquiterpene hydroquinone that strongly inhibits HIV reverse transcriptase, and aplidine (plitidepsin), a cyclic depsipeptide from *Aplidium albicans* which demonstrates potent inhibition of SARS-CoV-2 by targeting the host factor eEF1A [56, 62]. Other sponge-derived molecules such as papuamide A, mycalamide A, and pelorol also exhibit activity against HIV, HSV, and influenza viruses through mechanisms such as inhibition of viral protein synthesis and disruption of membrane integrity [42, 49].

Marine Algae

Beyond polysaccharides, marine algae synthesize various phenolics, alkaloids, sterols, terpenoids, and brominated metabolites with promising antiviral effects. Caulerpin, a bis-indole alkaloid from *Caulerpa*, shows neuraminidase inhibitory activity against Influenza A and interferes with viral replication [8, 59]. Bromophenols from red algae (e.g., *Rhodomela confervoides*) demonstrate antiviral activity against enteroviruses, HSV, and coronaviruses, attributed to their ability to inhibit viral proteases and polymerases [61].

Marine Corals and Soft Corals

Soft corals synthesize numerous diterpenoids and pseudopterosins with immunomodulatory and antiviral activities. Pseudopterosin isolated from *Pseudopterogorgia elisabethae* reduces Dengue virus replication by suppressing viral protein production and modulating inflammatory responses [8, 55]. Coral terpenoids have also demonstrated inhibitory effects against influenza neuraminidase and HSV attachment [44].

Marine Mollusks and Tunicates

Marine mollusks produce unique nitrogen-containing metabolites such as kainic acid, which inhibits hepatitis B viral DNA synthesis, and dolastatins, which exhibit activity against HIV and other retroviruses [8, 45]. Tunicates generate structurally unusual alkaloids such as lamellarin α, which strongly inhibits HIV-1 integrase and topoisomerase I [35]. Several tunicate-derived depsipeptides exhibit broad antiviral activity by interfering with viral replication and host protein synthesis.

Marine Fungi and Bacteria

Marine-derived fungi and bacteria have gained attention for producing antiviral polyketides, peptides, macrolides, alkaloids, and halogenated aromatics. Examples include trichoderins from marine fungi exhibiting activity against respiratory viruses and salinosporamide A from *Salinispora tropica*, which has demonstrated viral proteasome inhibitory properties [52, 53]. Marine actinomycetes produce halogenated polyketides and aromatic compounds that inhibit viral replication complexes of RNA viruses [40]. Cyanobacteria also contribute antiviral peptides such as serratamolide and dolabellane diterpenes with notable activity against influenza and herpesviruses [58].

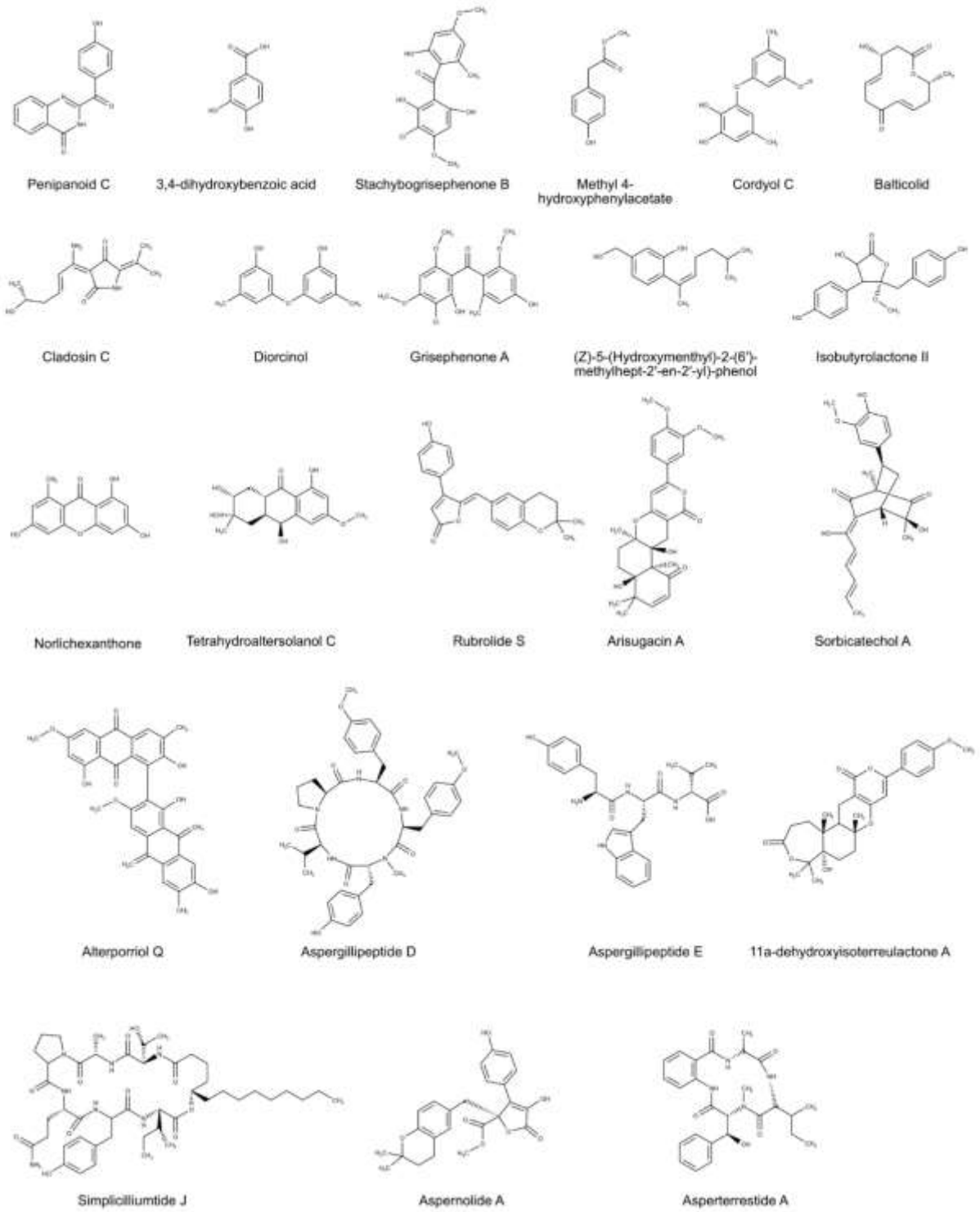

Figure 2: Structures of compounds isolated from marine fungi with antiviral activity. [54]

Marine-derived antiviral compounds therefore represent one of the most structurally innovative classes of organic antivirals. Their unique molecular scaffolds allow them to target multiple parts of the viral life cycle, including entry inhibition, polymerase suppression, protein synthesis interference, and immunomodulation. Although challenges remain in sustainable sourcing, toxicity evaluation, and large-scale production, advances in marine biotechnology, aquaculture, genome mining, and synthetic biology significantly accelerate the discovery and optimization of marine antiviral natural products [50, 64].

2.3 Microbial-Derived Antiviral Compounds

Microorganisms including bacteria, actinomycetes, fungi, and microalgae constitute an exceptionally important source of bioactive secondary metabolites with antiviral properties. Their metabolic plasticity and ecological diversity enable the biosynthesis of structurally complex organic molecules such as nucleoside antibiotics, polyketides, peptides, alkaloids, macrolides, and nonribosomal peptides, many of which exhibit potent antiviral activity at low concentrations [3, 79]. Historically, microbial metabolites have played a central role in antiviral chemotherapy: several early systemic antivirals originated from microbial products or were developed as synthetic analogues of microbial nucleosides [3, 67].

Actinomycetes and Nucleoside Analogues

Actinomycetes, particularly the genus Streptomyces, are among the most prolific microbial producers of antiviral metabolites [69, 70, 71, 75]. One of the earliest and most notable examples is vidarabine (Ara-A; 9-β-D-arabinofuranosyladenine), originally derived as a nucleoside antibiotic from *Streptomyces antibioticus* [75, 76, 82]. Vidarabine shows broad activity against herpesviruses, poxviruses, hepadnaviruses and certain RNA tumour viruses by acting as a nucleoside analogue that is phosphorylated to its triphosphate form and incorporated into viral DNA, thereby inhibiting DNA polymerase and causing chain termination [66, 82, 84]. Although many of its clinical indications have been superseded by later drugs such as acyclovir, vidarabine remains a landmark example of a microbial-derived antiviral [82].

Actinomycetes also produce pradimicins and benanomicins, aromatic polyketide antibiotics from *Actinomadura hibisca* and related genera that bind mannose-containing glycoconjugates on viral envelopes and host cell surfaces [65, 68, 81]. These compounds exhibit antiviral activity by blocking viral attachment and entry, particularly against enveloped viruses including HIV and other retroviruses [79, 81]. Recent work continues to generate new pradimicin analogues with enhanced glycoprotein-binding and improved pharmacological properties [68]. Marine and terrestrial actinomycetes yield halogenated polyketides, macrolides and hybrid PKS–NRPS products with antiviral potential [71, 75, 83]. Several marine *Streptomyces* and *Salinispora* species have been reported to produce metabolites that inhibit respiratory viruses and flaviviruses, often by suppressing viral RNA-dependent RNA polymerases or interfering with critical host–virus interactions [71, 75, 79, 83].

Bacterial Secondary Metabolites

Beyond actinomycetes, other bacteria synthesize structurally diverse antivirals. Soil and marine bacteria produce benzoheterocyclic compounds, cyclic peptides and lipopeptides, some of which demonstrate strong antiviral activity against DNA and RNA viruses [73, 69, 80]. For example, benzoheterocyclic metabolites such as virantmycin display potent inhibition of pseudorabies virus, with activity surpassing that of classical antivirals like ribavirin and acyclovir in vitro [73]. Additional bacterial metabolites act as entry inhibitors, protease inhibitors, or replication blockers, broadening the range of microbial scaffolds available for antiviral drug development [69, 79].

Fungal-Derived Antiviral Metabolites

Fungi, both terrestrial and marine-derived, produce a wide variety of polyketides, alkaloids, terpenoids, macrolides, and lactones with antiviral properties [72, 77]. Reviews have catalogued numerous fungal secondary metabolites such as oxoglyantrypine, carneic acid F, scedapin C, asteltoxin E, phomanolide, norquinadoline A, and quinadoline B, which exert antiviral activity against coronaviruses, influenza viruses, herpesviruses, and enteroviruses through mechanisms including polymerase inhibition, protease suppression, and interference with viral assembly [72, 77, 79]. Marine-derived fungi are particularly rich

in unique antiviral polyketides and macrolides; many of these compounds display potent in vitro activity and represent valuable leads for future optimisation [72].

Microalgae and Cyanobacteria

Microalgae and cyanobacteria also contribute antiviral secondary metabolites, including sulfated polysaccharides, lectin-like proteins, cyclic peptides, and terpenoids [79, 83]. Cyanobacterial products such as certain dolabellane diterpenes and lipopeptides have been reported to inhibit herpesviruses and respiratory viruses, often by interfering with viral envelope fusion or disrupting viral membrane integrity [83]. Although many of these compounds are still at an early stage of investigation, they demonstrate the broad antiviral potential of microbial phototrophs.

Collectively, microbial-derived antiviral compounds represent a vast and structurally diverse class of organic molecules, many of which act on key viral enzymes (DNA/RNA polymerases, reverse transcriptases, integrases), entry processes (glycoprotein binding, receptor interactions), or host factors critical for viral replication [3, 67, 79]. The combination of powerful bioactivity, unique chemical scaffolds, and adaptability to fermentation-based production systems makes microbial metabolites indispensable in current and future antiviral drug discovery. Advances in genome mining, synthetic biology, metabolic engineering, and high-throughput screening continue to expand the catalogue of antiviral microbial molecules and enhance their prospects for clinical development [71, 74, 79, 80, 83].

2.4 Synthetic Organic Antiviral Compounds

Synthetic organic antiviral compounds form an essential pillar of modern antiviral drug development. While natural products offer structurally rich scaffolds, synthetic chemistry enables the creation of molecules with enhanced potency, selectivity, stability, pharmacokinetic properties, and reduced toxicity [3, 90]. Synthetic antivirals are typically designed to target specific viral proteins such as polymerases, proteases, reverse transcriptases, methyltransferases, helicases, integrases, or viral entry factors or to mimic biological substrates essential for viral genome replication [95, 99]. Their strategic design allows for broad-spectrum antiviral capabilities and rapid optimization in response to emerging viral threats.

Nucleoside and Nucleotide Analogues

Synthetic nucleoside/nucleotide analogues remain one of the most successful and widely used classes of antiviral drugs. Compounds such as acyclovir, ganciclovir, penciclovir, ribavirin, sofosbuvir, favipiravir, tenofovir, lamivudine, entecavir, zidovudine (AZT), didanosine (ddI), stavudine (d4T) and others have transformed the treatment of herpesviruses, hepatitis B and C, HIV, influenza viruses, and emerging RNA viruses [3, 92, 101]. These analogues function by mimicking natural nucleotides, becoming phosphorylated within the host cell, and subsequently being incorporated into viral DNA or RNA, leading to chain termination, polymerase stalling, or induction of lethal mutagenesis [90, 93]. Ribavirin, for example, demonstrates broad-spectrum activity by inducing error catastrophe in RNA viruses, making it a valuable tool against hemorrhagic fever viruses, HCV, RSV, and flaviviruses [89].

Synthetic Heterocyclic Antivirals

Heterocycles represent one of the most versatile frameworks in antiviral medicinal chemistry due to their structural adaptability and strong protein-binding capabilities. Synthetic heterocycles such as triazoles, imidazoles, pyridines, quinazolines, benzimidazoles, thiazoles, quinolines, isoquinolines, pyrazines, and pyrimidines have demonstrated potent antiviral properties against numerous pathogens including SARS-CoV-2, Influenza A, Zika virus, Dengue virus, EV71, HSV, and HIV [94, 99, 100].

Examples include:

- Triazole and benzotriazole derivatives, which inhibit viral proteases, viral methyltransferases, and RdRp enzymes [100].
- Quinoline-based derivatives, structurally related to chloroquine and hydroxychloroquine, which interfere with endosomal acidification, viral entry, and glycosylation pathways [91].
- Thiazole derivatives, showing activity against HIV integrase and influenza neuraminidase [94].
- Pyrimidine derivatives, including non-nucleoside polymerase inhibitors developed against hepatitis and flaviviruses [95].

These heterocyclic scaffolds allow extensive modification, supporting SAR-based optimization to enhance potency and reduce cytotoxicity [100].

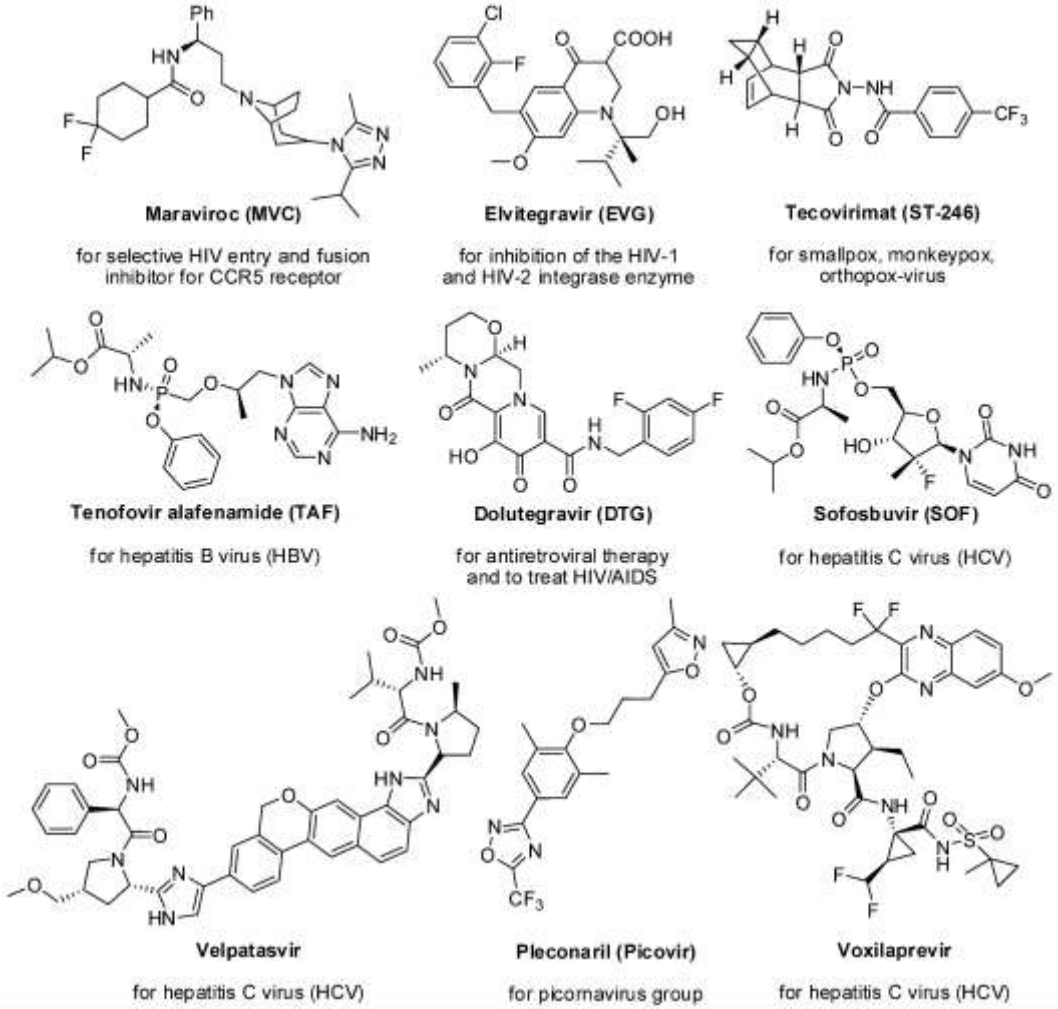

Figure 3: Some of the FDA-approved N-heterocyclic antiviral drugs. [85]

Synthetic Quinones, Flavonoid Analogues, and Phenolic Derivatives

Quinone-based structures such as naphthoquinones, anthraquinones, and benzoquinones exhibit strong antiviral properties by generating reactive oxygen species, inhibiting viral proteases, or disrupting viral protein folding [87, 88]. Synthetic modifications to natural phenolics (e.g., chalcones, xanthones, aurones, α, β-unsaturated ketones) significantly enhance antiviral activity against SARS-CoV-2, influenza viruses, and several arboviruses [2, 86]. Synthetic chalcone derivatives are particularly

noteworthy for inhibiting SARS-CoV-2 main protease (3CLpro), RNA polymerase, and viral entry pathways [4, 86].

Peptidomimetics and Protease Inhibitors

Synthetic peptidomimetics molecules that mimic essential peptide motifs form a key class of antiviral agents targeting viral proteases. Notable examples include:

- HIV-1 protease inhibitors such as ritonavir, lopinavir, indinavir, nelfinavir, darunavir [89].
- HCV protease inhibitors including boceprevir, telaprevir, simeprevir [96].
- SARS-CoV-2 protease inhibitors, such as nirmatrelvir (in Paxlovid), designed to inhibit 3CLpro [97].

These inhibitors block viral polyprotein cleavage, preventing maturation of essential viral enzymes and structural proteins.

Small Molecule Entry Inhibitors

Synthetic small molecules have been developed to interfere with viral entry by:

- Blocking receptor-binding domains
- Preventing membrane fusion
- Disrupting viral attachment factors
- Interfering with glycoprotein–host receptor interactions

Examples include umifenovir (arbidol), which inhibits membrane fusion in influenza and coronaviruses [98], and imidazole-based SARS-CoV entry blockers [94].

Modern Medicinal Chemistry Strategies

Advances in synthetic organic chemistry such as click chemistry, bioisosteric replacement, fragment-based design, pharmacophore modelling, machine learning-assisted lead optimization, and structure-guided ligand design have accelerated the development of novel antiviral candidates with improved:

- Affinity
- Selectivity
- Solubility
- Metabolic stability
- Oral bioavailability
- Resistance profiles

Emerging synthetic compounds continue to target viral polymerases, proteases, helicases, methyltransferases, endonucleases, and host–virus interaction complexes [97, 99]. Synthetic organic antiviral compounds therefore provide a broad, highly customizable platform for developing therapeutics with optimized pharmacological properties. Their structural versatility, rapid modifiability, and mechanistic specificity make them essential in addressing both established viral infections and newly emerging viral threats.

3. Mechanisms of Antiviral Action

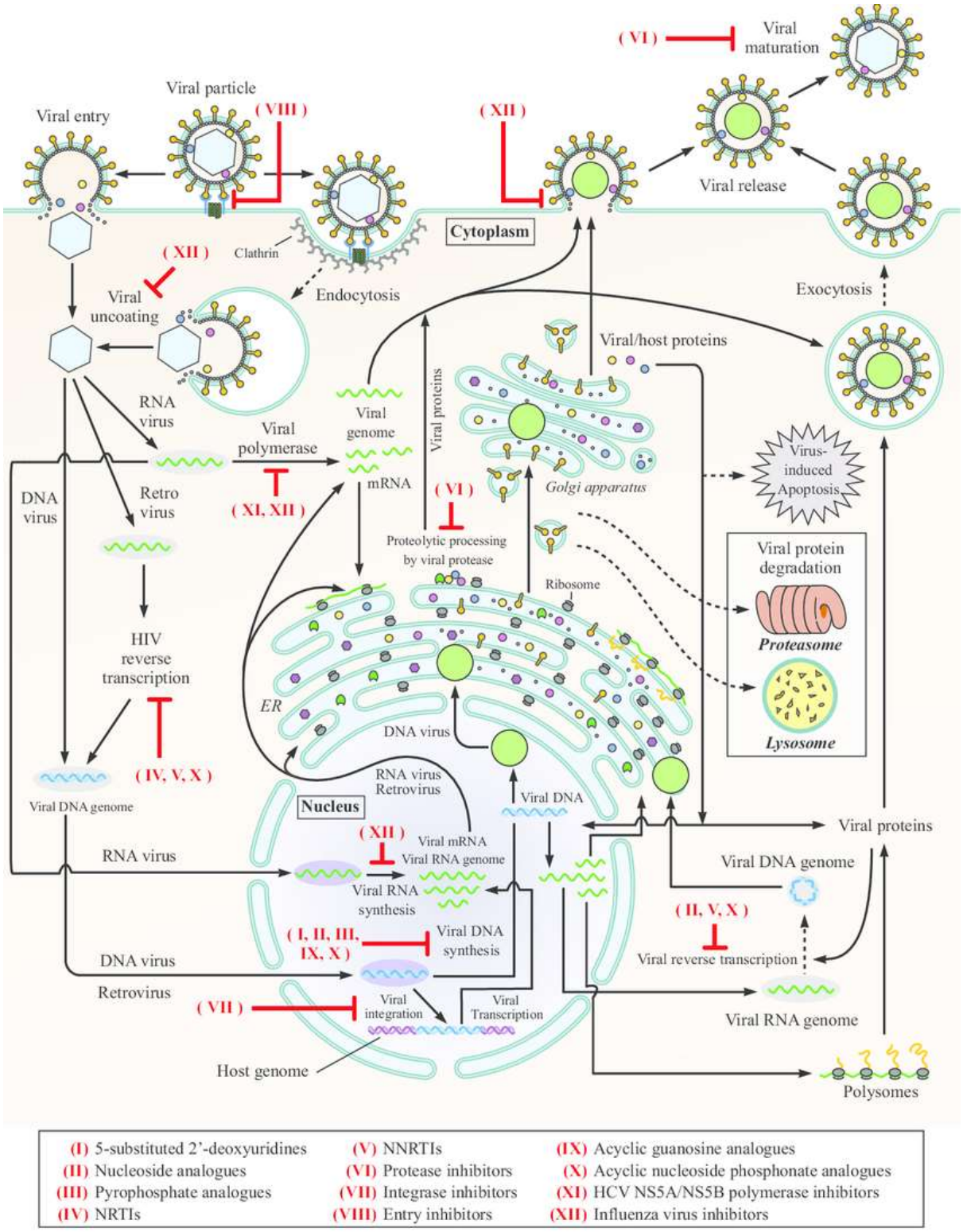

Figure 4: Mechanisms of drug actions during the viral life cycle. [102]

3.1 Inhibition of Viral Entry

Inhibition of viral entry represents one of the most effective and widely studied mechanisms through which organic antiviral compounds prevent infection. Viral entry typically involves a sequence of coordinated steps attachment to host receptors, membrane fusion or endocytosis, and uncoating all of

which can be disrupted by structurally diverse natural and synthetic molecules [3, 26, 29]. Because entry is the earliest stage of viral infection, compounds targeting this step often function as broad-spectrum antivirals capable of preventing infection before viral replication begins.

Blocking Viral Attachment

Many organic compounds interfere directly with viral surface proteins or host cell receptors required for viral docking. Plant-derived flavonoids such as quercetin, kaempferol, luteolin, apigenin, rutin, epigallocatechin gallate (EGCG) and polyphenols like resveratrol and ellagic acid have been shown to block viral attachment by binding to viral envelope proteins such as hemagglutinin (HA), E protein (flaviviruses), gp120 (HIV), and spike proteins of coronaviruses [2, 15, 26, 33]. These interactions disrupt the initial virus–host contacts and prevent high-affinity binding necessary for productive infection. Sulfated polysaccharides including fucoidan, carrageenans, ulvans, and porphyrans exhibit strong inhibitory effects against SARS-CoV-2, Influenza A, HSV-1, RSV, and Dengue virus by forming electrostatic interactions with positively charged regions of viral envelope glycoproteins, thereby preventing their attachment to cellular receptors [8, 103, 108]. Carrageenan-based nasal sprays have demonstrated clinical efficacy in reducing viral loads of respiratory viruses by blocking their early-stage attachment [105].

Inhibition of Host Receptor Recognition

Some organic compounds act by targeting host cell receptors or modulating their availability, thereby reducing the capacity of viruses to bind and enter cells. For example, terpenoids such as glycyrrhizin, saponins such as astragalosides, and alkaloids including berberine can interfere with receptor-mediated viral recognition by altering membrane charge, modulating cytokine-mediated receptor expression, or stabilizing receptor conformations that are incompatible with viral engagement [34, 106, 109]. Lectins from plants such as griffithsin and Galanthus nivalis agglutinin (GNA) bind multivalently to high-mannose glycans on viral envelope glycoproteins, effectively masking key recognition motifs and preventing viruses such as HIV, SARS-CoV, MERS-CoV, and SARS-CoV-2 from engaging host receptors [21, 22].

Inhibition of Membrane Fusion

Fusion inhibition is a crucial strategy against enveloped viruses. Organic molecules can prevent conformational rearrangements of viral fusion proteins or modulate membrane characteristics that block fusion events. Marine-derived compounds such as pseudopterosins, cyclic peptides, diterpenes, and bromophenolics have demonstrated inhibition of membrane fusion steps in Dengue virus, herpesviruses, and coronaviruses by preventing fusion peptide exposure or destabilizing lipid microdomains at the host–virus interface [8, 107]. Synthetic antivirals such as umifenovir (arbidol) also inhibit membrane fusion by stabilizing viral envelope proteins in a pre-fusion state and altering membrane curvature, thereby blocking entry of influenza viruses and coronaviruses [98].

Prevention of Endocytosis and Viral Internalization

Many viruses particularly influenza, enteroviruses, and flaviviruses enter cells via clathrin- or caveolin-mediated endocytosis. Several organic molecules exert antiviral effects by inhibiting these pathways. Flavonoids and polyphenols can interfere with endosomal acidification, a requirement for viral uncoating and membrane fusion within endosomes. Compounds such as quercetin, baicalein, and luteolin have been shown to increase endosomal pH or inhibit host ATPases essential for viral internalization [2, 104]. Certain marine polysaccharides also prevent viral internalization by forming

physical barriers around cell surfaces, reducing viral uptake and preventing the conformational transitions required for productive endocytosis [103, 108].

Overall, inhibition of viral entry is one of the most promising antiviral strategies because it acts before replication begins, reducing viral load at the earliest stage and limiting the establishment of infection. The diversity of organic compounds that target viral entry ranging from plant flavonoids and tannins to marine polysaccharides and synthetic entry inhibitors highlights the broad structural and mechanistic landscape of this antiviral approach. Their ability to block multiple entry-related processes (attachment, receptor recognition, fusion, and internalization) positions them as attractive candidates for both prophylactic and therapeutic antiviral applications.

3.2 Inhibition of Viral Replication and Transcription

Inhibition of viral replication and transcription is one of the most widely exploited antiviral strategies, as these processes are essential for the production of viral genomes and viral proteins required for assembly of progeny virions. Organic antiviral compounds both natural and synthetic are capable of interfering with replication by targeting viral polymerases, helicases, methyltransferases, nucleoproteins, replication complexes, and essential host cofactors [3, 116]. Because replication is central to viral proliferation, compounds acting at this stage often demonstrate strong antiviral potency, broad-spectrum activity, and reduced susceptibility to resistance when acting through multi-target mechanisms.

Inhibition of Viral Polymerases

Many organic compounds exert antiviral activity by inhibiting RNA-dependent RNA polymerases (RdRp), DNA polymerases, or reverse transcriptases (RTs), thereby blocking viral genome synthesis. Plant-derived flavonoids such as baicalein, quercetin, luteolin, apigenin, and myricetin display inhibitory effects on polymerases of SARS-CoV-2, influenza viruses, HIV, and flaviviruses by binding to catalytic residues or allosteric pockets within RdRp [2, 29, 26, 33, 114]. Polyphenols such as penta-O-galloyl-β-D-glucose, ellagic acid, and curcumin also inhibit transcription of viral RNA by interfering with polymerase–RNA interactions and essential phosphorylation steps [11, 19, 26].

Marine-derived compounds add to this diversity: halogenated polyketides, bromophenols, and marine alkaloids inhibit RdRp in dengue virus, enteroviruses, and several coronaviruses by disrupting binding of nucleotides or destabilizing polymerase conformations [8, 62, 118]. Sponge metabolites such as avarol inhibit HIV reverse transcriptase, thereby preventing DNA synthesis during reverse transcription [8, 56]. Synthetic nucleoside analogues including sofosbuvir, favipiravir, ribavirin, zidovudine, lamivudine, entecavir, and others remain among the strongest replication inhibitors, acting through chain termination or lethal mutagenesis [89, 90, 112, 117]. These molecules mimic native nucleotides but lack the correct structural features required for elongation, resulting in truncated or highly mutated viral genomes [90, 93].

Suppression of Viral Protein Synthesis and Replication Complex Assembly

Numerous organic compounds inhibit replication indirectly by suppressing the synthesis of viral proteins essential for nucleic acid processing or replication complex formation. Plant furanocoumarins such as imperatorin and isoimperatorin inhibit replication of influenza A by downregulating synthesis of viral nucleoprotein (NP) and neuraminidase (NA), thereby preventing proper assembly of ribonucleoprotein (RNP) complexes [26, 32]. Alkaloids such as lycorine, berberine, harmine, colchicine, and matrine interfere with viral polyprotein translation or inhibit host kinases necessary for viral protein synthesis, dramatically reducing replication of dengue, Zika, influenza, SARS-CoV-2, and enteroviruses [26, 28, 34, 79]. Marine diterpenoids, pseudopterosins, and macrocyclic peptides inhibit translation of viral

proteins by binding ribosomal sites or destabilizing host translation initiation machinery [8, 107]. Several compounds from marine fungi such as quinadoline B, scedapin C, carneic acid derivatives, and asteltoxin analogues suppress replication of coronaviruses and influenza viruses by targeting viral polymerase-associated proteins or inhibiting host factors essential for viral mRNA synthesis [113, 49].

Inhibition of Viral Helicases and Accessory Enzymes

Viral helicases facilitate unwinding of nucleic acid duplexes during replication. Several organic compounds inhibit helicase activity, thereby preventing progression of replication forks. Flavonoids such as myricetin inhibit SARS-CoV helicase (Nsp13), reducing ATPase and helicase activity [33]. Quinones and phenolic derivatives inhibit helicases of dengue, hepatitis C, and coronaviruses, contributing to reduced RNA synthesis [110, 111]. Some terpenoids inhibit viral 2′-O-methyltransferase, a key enzyme involved in RNA capping, which is required for viral RNA stability and immune evasion [30, 107].

Disruption of Host Cell Replication Machinery

Certain organic compounds act indirectly by targeting host enzymes and pathways essential for viral replication, such as:

- MAPK/ERK signaling (berberine, curcumin)
- PI3K/Akt pathway (resveratrol, catechins)
- NF-κB signaling (curcumin, baicalein, quercetin)
- Host chaperones or viral co-factors (e.g., eEF1A) targeted by marine depsipeptides like plitidepsin [62]

By targeting host pathways, such compounds reduce the virus's ability to replicate without directly imposing selective pressure on viral proteins, potentially minimizing resistance development [32, 62, 106, 109].

Multi-Target Replication Inhibitors

Some organic molecules possess multi-target inhibitory activity, affecting several components of the viral replication cycle simultaneously.

Examples include:

- Chalcones (synthetic and natural), which inhibit viral proteases, polymerases, and replication complex components [23, 86].
- Resveratrol, which inhibits replication of influenza, coronaviruses, and herpesviruses by suppressing multiple signaling pathways required for replication [11].
- Fucoidan, which blocks not only entry but also replication stages in influenza and coronaviruses [8, 111].

These multi-target compounds are receiving increasing attention due to their ability to delay or prevent antiviral resistance. Inhibition of viral replication and transcription is one of the most powerful and diverse mechanisms by which organic antiviral compounds act. Plant flavonoids, alkaloids, terpenoids, tannins, and phenolics; marine-derived polysaccharides, alkaloids, and polyketides; microbial secondary metabolites; and a wide array of synthetic molecules all contribute to a robust foundation for antiviral drug discovery. Their mechanisms range from direct polymerase inhibition and interference with protein synthesis to disruption of replication complex assembly and modulation of host factors, highlighting the vast chemical space available for designing future antiviral therapeutics.

3.3 Inhibition of Viral Assembly and Release

Inhibition of viral assembly and release is a critical antiviral mechanism that disrupts the final stages of

the viral life cycle. After replication and protein synthesis, viruses must correctly assemble their structural components capsid proteins, envelope glycoproteins, and genome segments before budding or cell lysis enables progeny virions to spread. Numerous organic compounds derived from plants, marine organisms, microbes, and synthetic chemistry interfere with these late-stage processes by targeting viral proteases, maturation enzymes, capsid assembly pathways, budding proteins, and host cell secretion machinery [3, 90]. Because assembly and release involve highly conserved interactions and enzymatic processes, compounds acting at this stage often display strong antiviral potency and broad-spectrum activity.

Inhibition of Viral Proteases Essential for Polyprotein Processing

Many viruses including HIV, flaviviruses, picornaviruses, and coronaviruses synthesize proteins as large polyproteins that must be cleaved by viral proteases to yield functional structural and nonstructural proteins required for assembly. Plant-derived compounds such as quercetin, kaempferol, luteolin, baicalin, myricetin, and theaflavins inhibit viral 3CL proteases, NS2B-NS3 serine proteases, HIV protease, and influenza proteases, thereby preventing maturation of viral components [2, 26, 33, 114]. Inhibition of these proteases leads to accumulation of inactive precursor proteins and failure of virion assembly. Marine-derived compounds including bromophenolics, diterpenoids, alkaloids, caulerpin, and pseudopterosins also exhibit protease inhibition, interfering with the processing of structural proteins in dengue virus, influenza virus, and coronaviruses [8, 107, 118]. Synthetic protease inhibitors form one of the most clinically successful antiviral categories. Drugs such as nirmatrelvir (SARS-CoV-2 3CLpro inhibitor), ritonavir, lopinavir, darunavir (HIV protease inhibitors), and boceprevir, telaprevir (HCV protease inhibitors) disrupt viral maturation and effectively halt assembly [89, 96, 97].

Disruption of Capsid Assembly and Nucleocapsid Formation

Organic molecules may interrupt capsid formation by binding to capsid proteins, altering protein–protein interactions, or preventing nucleic acid encapsidation. Flavonoids such as apigenin, luteolin, and baicalein inhibit capsid assembly in enteroviruses and dengue virus by interfering with capsid protein folding and assembly kinetics [2, 29, 114]. Plant tannins and polyphenols also cause misfolding or aggregation of capsid proteins, reducing the formation of functional virions [11, 26]. Marine secondary metabolites especially macrocyclic peptides and marine alkaloids have been shown to bind viral capsid proteins and destabilize capsid formation in herpesviruses and flaviviruses [8, 115]. Some microbial metabolites, such as scedapin derivatives, quinadoline B, and cyclic peptides from marine fungi, inhibit assembly of viral replication and structural complexes by interfering with protein-protein assembly pathways [79, 113].

Inhibition of Viral Budding and Release

The release of newly formed virions from host cells is essential for viral propagation. Inhibiting budding or release drastically reduces viral spread. Plant polyphenols such as theaflavins, ellagitannins, tannins, and catechins inhibit influenza virus neuraminidase (NA), the enzyme responsible for cleaving sialic acid residues that tether budding virions to the host cell surface [26, 29, 120]. Neuraminidase inhibition results in aggregation of viral particles at the cell membrane, blocking viral dissemination. Marine-derived molecules such as terpenoids, polysaccharides, and bromophenolics have been shown to disrupt budding processes by altering host lipid raft domains or by interfering with viral envelope maturation pathways [8, 88, 108]. Synthetic neuraminidase inhibitors oseltamivir, zanamivir, peramivir, and newer NA-directed molecules are classical examples of release inhibitors that prevent virion detachment and reduce viral load in influenza infections [90, 96, 119].

Interference with Host Secretion Pathways Required for Assembly

Viruses often rely on host endoplasmic reticulum (ER), Golgi bodies, and vesicular trafficking systems for assembly and export. Several organic compounds modulate or inhibit these pathways. Flavonoids such as quercetin and kaempferol can inhibit ER stress responses, interrupting glycoprotein folding and thereby blocking maturation of enveloped viruses such as SARS-CoV-2 and influenza [2, 33]. Alkaloids such as berberine and lycorine inhibit assembly-associated host kinases and chaperones, preventing viral structural proteins from reaching assembly sites [28, 34]. Marine depsipeptides such as plitidepsin, by targeting host factor eEF1A, disrupt several steps of viral maturation and trafficking, resulting in impaired virion assembly and release [62].

Preventing Post-Translational Modifications Required for Assembly

Post-translational modifications (PTMs) such as glycosylation, phosphorylation, palmitoylation, and proteolytic cleavage are essential for producing functional viral proteins. Organic compounds particularly phenolics, flavonoids, terpenoids, and quinones can inhibit viral protein glycosylation or phosphorylation pathways, preventing the correct assembly of viral glycoproteins and reducing infectivity [19, 41, 46]. Inhibition of viral assembly and release is a multilayered antiviral strategy that can stop viral propagation even after replication has begun. Organic antiviral compounds demonstrate broad mechanistic diversity, functioning as protease inhibitors, capsid assembly disruptors, neuraminidase inhibitors, trafficking modulators, and PTM suppressors. Their ability to target multiple essential steps in the maturation process makes them strong candidates for therapeutic development, especially in combination therapies where multi-stage inhibition can significantly reduce viral resistance.

3.4 Immunomodulatory Activities

Immunomodulation represents a crucial antiviral mechanism through which organic compounds enhance the host's innate and adaptive immune responses to suppress viral infection. Instead of acting directly on viral particles or viral enzymes, immunomodulatory compounds influence cytokine signaling, interferon pathways, oxidative stress responses, macrophage and NK cell activity, antigen presentation, and other host-driven antiviral processes [11, 19, 26]. Because effective immunity is essential for controlling viral pathogenesis, especially during early infection, organic immunomodulators offer significant therapeutic value and can complement direct-acting antiviral agents.

Enhancement of Interferon Responses

Interferons (IFNs) are among the most important antiviral cytokines, activating hundreds of interferon-stimulated genes (ISGs) that restrict viral replication. Numerous plant-derived compounds including flavonoids (quercetin, luteolin, apigenin, baicalin), terpenoids (glycyrrhizin, andrographolide), and alkaloids (matrine, berberine) enhance IFN-α, IFN-β, and IFN-γ expression and the downstream antiviral signaling pathways involving JAK-STAT activation [26, 29, 106, 109]. Glycyrrhizin, for example, increases IFN production and enhances antiviral immunity in SARS-CoV, influenza, and hepatitis infections [13]. Berberine and matrine similarly stimulate interferon pathways to inhibit viral replication and prevent virus-induced immunosuppression [34, 79]. Marine-derived polysaccharides such as fucoidan strongly activate interferon pathways and macrophage immune responses, enhancing antiviral resistance against influenza viruses and coronaviruses [8, 121].

Suppression of Pro-Inflammatory Cytokines and Cytokine Storm

Many viral infections including influenza, dengue, and coronaviruses can trigger excessive inflammation and cytokine storms, which contribute significantly to disease severity. Plant polyphenols such as resveratrol, curcumin, EGCG, geraniin, ellagitannins, and theaflavins exhibit potent anti-inflammatory

activity by suppressing NF-κB activation, COX-2 expression, iNOS signaling, MAPK/ERK pathways, and reducing production of TNF-α, IL-1β, IL-6, IL-8, and other pro-inflammatory mediators [2, 11, 19, 26, 29]. Curcumin, for instance, demonstrates broad immunomodulatory effects by inhibiting NF-κB signaling and reducing the excessive cytokine responses triggered by viral infections including influenza, RSV, and coronaviruses [19]. Marine natural products, including pseudopterosins, bromophenols, and terpenoids, also modulate inflammation by inhibiting nitric oxide production and suppressing pro-inflammatory cytokines, thereby limiting tissue damage during viral infection [8, 107, 118].

Activation of Macrophages, NK Cells, and Adaptive Immunity

Several organic compounds enhance immune cell activity responsible for eliminating virus-infected cells. Saponins such as astragalosides and glycyrrhizic acid derivatives enhance macrophage phagocytosis and stimulate NK cell cytotoxicity, increasing clearance of infected cells [12]. Flavonoids such as kaempferol and baicalein modulate dendritic cell maturation and antigen presentation, enhancing adaptive immune responses against influenza and dengue [2, 29]. Lectins such as griffithsin not only bind viral glycoproteins but also stimulate antiviral immune pathways and modulate cytokine secretion, providing dual mechanisms of protection [21, 22].

Antioxidant Defense and Reduction of Virus-Induced Oxidative Stress

Oxidative stress is a major contributor to viral pathology, as reactive oxygen species (ROS) impair immune function and promote viral replication. Many plant-derived compounds particularly polyphenols, tannins, flavonoids, and stilbenes act as strong antioxidants, preventing virus-induced oxidative damage [11, 17]. Resveratrol and quercetin reduce ROS levels, stabilize mitochondrial membrane integrity, and enhance cellular antiviral defenses, contributing to reduced viral replication and inflammation [11]. Marine polysaccharides and phlorotannins also exhibit strong antioxidant effects that complement their antiviral activity, protecting tissues from oxidative damage during infection [121].

Modulation of Host Signaling Pathways Critical for Antiviral Defense

Organic antiviral compounds frequently regulate host signaling pathways essential for immune responses.

Examples include:

- MAPK/ERK inhibition – berberine, curcumin, and EGCG reduce viral replication and inflammation by suppressing MAPK signaling [19, 34].
- PI3K/Akt modulation – flavonoids regulate this pathway to inhibit viruses such as influenza and coronaviruses [2, 29].
- JAK-STAT activation – glycyrrhizin and marine polysaccharides enhance ISG expression via STAT1/STAT2 activation [13, 121].
- mTOR inhibition – polyphenols such as resveratrol modulate autophagy-related pathways to limit viral replication [11].

By influencing these pathways, organic molecules strengthen the antiviral state of host cells and reduce viral proliferation.

Immunomodulation constitutes a powerful antiviral strategy that complements direct inhibition of viral enzymes, entry, or replication. Organic compounds including plant flavonoids, alkaloids, terpenoids, polyphenols, marine polysaccharides, and synthetic analogues enhance antiviral immunity through mechanisms such as interferon induction, cytokine suppression, macrophage and NK cell activation, oxidative stress reduction, and regulation of key immune signaling pathways. Their ability to modulate

both innate and adaptive responses highlights their value as potential antiviral therapeutics, particularly in infections characterized by immune dysregulation or hyperinflammation.

Origin	Compound Class	Key Examples	Mechanism of Action	Target Viruses
Plant	Flavonoids	Quercetin, Kaempferol, Baicalein, EGCG, Theaflavins	• Entry: Block attachment (Spike-ACE2), interfere with endosomal acidification. • Replication: Inhibit RdRp, 3CL proteases, and helicase activity. • Release: Inhibit neuraminidase. • Immune: Modulate PI3K/Akt and dendritic cells.	Influenza, SARS-CoV-2, HIV, Dengue, Zika, HSV
	Polyphenols & Tannins	Resveratrol, Curcumin, Ellagic acid	• Entry: Precipitate envelope proteins; prevent membrane fusion. • Replication: Suppress RNA synthesis; inhibit proteases. • Immune: Strong antioxidant; suppress cytokine storm (NF-κB).	Enveloped viruses, Influenza, Coronaviruses
	Alkaloids	Berberine, Lycorine, Matrine	• Replication: Disrupt MAPK/ERK signaling; inhibit viral protein translation. • Assembly: Inhibit host kinases/chaperones. • Immune: Stimulate interferon pathways.	Influenza A, SARS-CoV-2, Arboviruses, HBV
	Terpenoids & Saponins	Glycyrrhizin, Astragalosides	• Entry: Alter membrane charge; stabilize receptor conformations. • Replication: Inhibit proteases and methyltransferases. • Immune: Enhance IFN production and macrophage phagocytosis.	SARS-CoV, Hepatitis viruses, HIV
	Lectins	Griffithsin, GNA	• Entry: Bind high-mannose glycans on viral glycoproteins to mask recognition motifs.	HIV, SARS-CoV-2, MERS-CoV

Marine	Sulfated Polysaccharides	Fucoidan, Carrageenans	• Entry: Electrostatic blocking of viral adsorption/internalization. • Replication: Interfere with early replication steps. • Immune: Activate interferon and macrophages.	SARS-CoV-2, Influenza A, RSV, HSV
	Sponges & Tunicates	Avarol, Plitidepsin (Aplidine), Lamellarin α	• Replication: Inhibit Reverse Transcriptase and Integrase; target host factor eEF1A to stop translation. • Assembly: Disrupt maturation/trafficking.	HIV, SARS-CoV-2, Influenza
	Algae Metabolites	Caulerpin, Bromophenols	• Replication: Inhibit neuraminidase, proteases, and polymerases. • Entry: Prevent membrane fusion.	Influenza A, Enteroviruses, HSV, Dengue
Microbial	Nucleosides & Antibiotics	Vidarabine (Ara-A), Pradimicins	• Replication: Phosphorylated to triphosphate for DNA polymerase chain termination. • Entry: Bind mannose glycoconjugates.	Herpesviruses, Poxviruses, HIV
	Fungal Metabolites	Scedapin C, Quinadoline B	• Replication: Inhibit polymerases and proteases.	Coronaviruses, Influenza
			• Assembly: Interfere with protein-protein assembly.	
Synthetic	Nucleoside Analogues	Acyclovir, Ribavirin, Sofosbuvir	• Replication: Mimic nucleotides to cause chain termination or lethal mutagenesis (error catastrophe).	Herpesviruses, HCV, HIV, RNA viruses
	Heterocycles & Protease Inhibitors	Nirmatrelvir, Ritonavir, Triazoles	• Replication: Inhibit viral proteases (e.g., 3CLpro) and polymerases. • Entry: Interfere with endosomal acidification.	SARS-CoV-2, HIV, Influenza, HCV
	Entry Inhibitors	Umifenovir (Arbidol)	• Entry: Stabilize viral envelope proteins to prevent membrane fusion.	Influenza, Coronaviruses

Table 1: Comprehensive Overview of Organic Antiviral Compounds: Origins, Mechanisms of Action, and Therapeutic Targets from Sections 2 & 3. [1, 2, 3, 8, 11, 12, 13, 15, 17, 19, 20, 21, 22, 26, 28, 30, 31, 33, 34, 35, 39, 56, 59, 61, 62, 63, 66, 72, 75, 79, 81, 82, 85, 89, 90, 93, 97, 98, 100, 101, 108, 109, 113, 114, 118, 121].

4. Applications of Organic Compounds against Viral Diseases

Organic antiviral compounds whether derived from plants, marine organisms, microbes, or synthetic chemical frameworks have demonstrated broad applicability across numerous clinically significant viral diseases. Their activities span prevention, early therapeutic intervention, adjunctive therapy, and mitigation of virus-induced immunopathology, making them valuable candidates for the development of next-generation antiviral therapeutics. Because viruses differ widely in structure, replication strategy, and reliance on host factors, the diversity of organic molecules provides a powerful toolbox capable of targeting multiple viral families through direct antiviral actions and host-modulating effects [8, 26, 122].

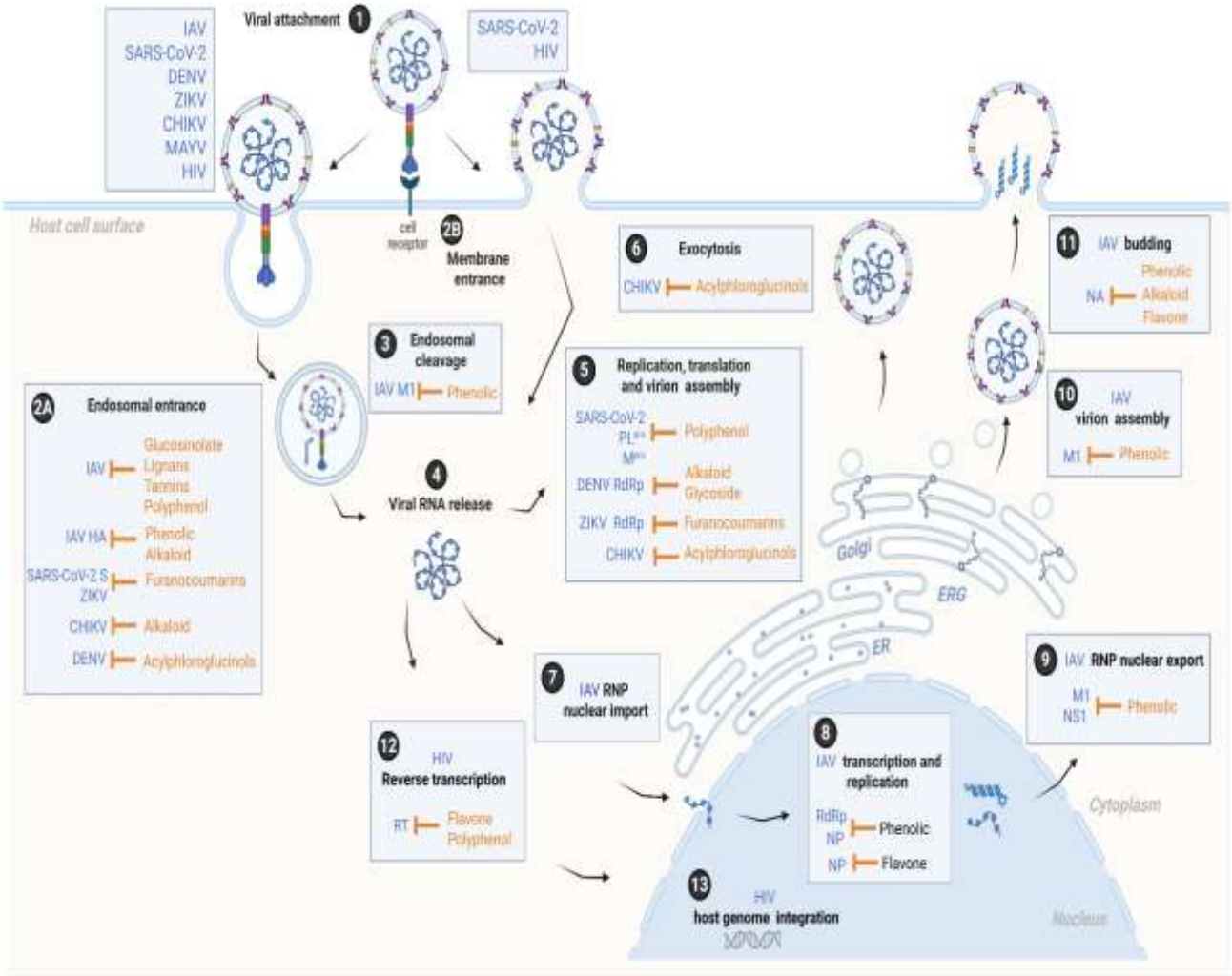

Figure 5: A schematic overview of the life cycle of Influenza A virus (IAV), SARS-CoV-2, Dengue virus (DENV), Zika virus (ZIKV), Chikungunya virus (CHIKV), Mayaro virus (MAYV), and the human immunodeficiency virus (HIV), depicting potential mechanisms of action and targets of phytocompounds. [26]

Below is an overview of major viral diseases where organic compounds have shown notable therapeutic promise.

Influenza Viruses (A and B)

Organic compounds from plants such as quercetin, kaempferol, baicalein, theaflavins, EGCG, curcumin, and various tannins have demonstrated potent inhibition of neuraminidase, suppression of viral polymerase activity, and interference with viral entry mechanisms [2, 11, 26, 29]. These compounds also reduce influenza-induced inflammation through modulation of NF-κB and MAPK/ERK pathways, contributing to reduced disease severity. Marine-derived molecules especially fucoidan, carrageenan, bromophenols, diterpenes, and pseudopterosins exhibit anti-influenza activity by blocking viral attachment, inhibiting polymerase, and suppressing viral release [8, 19, 121]. Several synthetic compounds, such as oseltamivir, zanamivir, peramivir, and favipiravir, remain cornerstone therapies, demonstrating how synthetic organic chemistry complements natural-product scaffolds [90, 92].

Coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV-2)

Plant-derived flavonoids (quercetin, luteolin, baicalin), alkaloids (berberine, lycorine), terpenoids (glycyrrhizin), and polyphenols (resveratrol, ellagic acid) inhibit coronavirus entry, replication, protease

activity (3CLpro, PLpro), and inflammatory responses [2, 11, 15, 26, 34]. Marine polysaccharides such as fucoidan and carrageenan strongly block spike–receptor binding and inhibit post-entry stages, while marine peptides like pseudopterosins and bromophenolics target coronavirus replication enzymes [8, 19, 107]. Synthetic molecules including nirmatrelvir (3CLpro inhibitor), favipiravir (RdRp inhibitor), umifenovir (fusion inhibitor), and novel heterocyclic derivatives have significantly advanced coronavirus therapeutics [90, 97].

Arboviral Diseases (Dengue, Zika, Chikungunya, Mayaro)

Arboviruses pose major global public health challenges due to their rapid spread and limited therapeutic options. Plant-derived compounds such as quercetin, kaempferol, luteolin, geraniin, ellagic acid, curcumin, lycorine, and berberine inhibit viral proteases (NS2B-NS3), suppress polymerase activity, block viral entry, and modulate host antiviral pathways [26, 28, 33, 34]. Marine metabolites, including caulerpin, bromophenolics, and various polyketides, inhibit the replication of DENV and ZIKV by interfering with viral enzymes and structural protein assembly [8, 61, 118]. Microbial metabolites such as vidarabine, pradimicin analogues, and fungal polyketides also exhibit inhibitory activity against several arboviruses through interference with replication complexes [12, 79].

Herpesviruses (HSV-1, HSV-2, VZV, CMV)

Herpesviruses require long-term management due to latency and reactivation. Plant polyphenols, tannins, and flavonoids such as EGCG, ellagic acid, tannic acid, resveratrol, and baicalein exhibit strong inhibitory activity against HSV by preventing viral attachment, inhibiting DNA polymerase, and reducing replication-associated inflammation [11, 17, 26]. Marine compounds such as bromophenols, diterpenoids, macrocycles, and alkaloids from sponges display activity against HSV through inhibition of attachment, suppression of viral protein synthesis, and destabilization of viral envelopes [8, 87]. Synthetic antiviral nucleoside analogues (acyclovir, valacyclovir, penciclovir) remain primary clinical treatments, demonstrating the translational potential of nucleoside-mimicking organic scaffolds [90].

Hepatitis Viruses (HBV, HCV)

Plant compounds including curcumin, resveratrol, apigenin, matrine, and oxymatrine inhibit HBV replication by suppressing DNA polymerase activity, reducing cccDNA formation, and modulating immune responses [79, 106]. Marine-derived molecules such as kainic acid, polysaccharides, and fungal metabolites exhibit activity against HBV and HCV by targeting replication enzymes or interfering with viral assembly [8, 118]. Synthetic antiviral nucleoside/nucleotide analogues (entecavir, tenofovir, lamivudine, sofosbuvir) remain central to hepatitis management due to their potent polymerase-inhibiting properties [90, 101].

Human Immunodeficiency Virus (HIV)

Plant-derived alkaloids (e.g., berberine, harmine), flavonoids (e.g., quercetin, baicalein), lignans, and tannins inhibit HIV by:

- blocking gp120–CD4 binding
- suppressing integrase and reverse transcriptase
- inducing antiviral cytokines
- preventing viral assembly and maturation [2, 26, 29, 34]

Marine-derived peptides and macrocyclic compounds such as avarol, papuamide A, mycalamide A, and lamellarin α demonstrate potent inhibition of HIV RT, integrase, and fusion pathways [8, 35, 56]. Synthetic agents, including AZT, ddI, d4T, lamivudine, protease inhibitors (ritonavir, darunavir), remain

among the most successful antiviral drug classes developed to date [90, 96].

Respiratory Viruses (RSV, Adenoviruses, Rhinoviruses)

Plant-derived flavonoids and polyphenols inhibit RSV and adenoviruses by interfering with viral entry, reducing inflammation, and suppressing replication enzymes [19, 26, 29]. Marine polysaccharides (fucoidan, carrageenans) show strong anti-RSV activity by blocking attachment and interfering with early replication steps [8, 11]. Synthetic heterocycles and polymerase inhibitors continue to be explored as candidates against RSV and other respiratory viruses [100].

Emerging and Re-emerging Viral Threats

Given recent pandemics and outbreaks, organic compounds are being actively explored for applications against:

- Ebola and Marburg virus – quinones, alkaloids, and flavonoids inhibit viral entry, VP35 function, and polymerase activity.
- Nipah and Hendra virus – plant terpenoids and lignans show inhibition of fusion proteins and nucleoprotein interactions.
- Orthopoxviruses (Mpox) – polyphenols, tannins, and synthetic heterocycles exhibit inhibition of viral DNA polymerase and virion maturation.
- Enteroviruses (EV71, CVA, CVB) – flavonoids, coumarins, and alkaloids target capsid assembly and RNA replication [32, 33, 114].

Organic antiviral compounds therefore remain important leads for pandemic preparedness due to their broad-spectrum potential and multi-target mechanisms.

5. Challenges in Developing Organic Antiviral Agents

Despite the expanding evidence supporting the antiviral potential of organic compounds from plant, marine, microbial, and synthetic origins, the translation of these molecules into clinically approved antiviral drugs remains challenging. The antiviral drug development pipeline is shaped by pharmacological, biochemical, ecological, manufacturing, regulatory, and economic constraints, all of which limit the progression of organic compounds from discovery to therapeutic use [3, 90]. Below are the major challenges associated with developing organic antiviral agents.

Structural Complexity and Difficulties in Isolation & Purification

Many natural organic antiviral compounds particularly from marine organisms and fungi exhibit high structural complexity, requiring elaborate extraction, purification, and characterization processes. Marine-derived molecules such as pseudopterosins, diterpenoids, macrocyclic peptides, and sulfated polysaccharides often occur in extremely low natural abundance, making large-scale isolation economically and logistically difficult [8, 36, 118]. Similarly, plant polyphenols and flavonoids exist in complex mixtures, and purification to pharmaceutical-grade standards is resource-intensive [2, 26]. These difficulties delay clinical development timelines and increase production costs.

Low Bioavailability, Stability, and Pharmacokinetic Limitations

Many organic molecules suffer from poor solubility, rapid metabolism, low oral bioavailability, insufficient tissue distribution, and poor plasma stability. Flavonoids such as quercetin and baicalein undergo extensive first-pass metabolism, reducing systemic concentrations and limiting therapeutic efficacy [2, 33]. Terpenoids (e.g., glycyrrhizin) and polyphenols (e.g., curcumin, resveratrol) demonstrate limited bioavailability without structural modification or formulation enhancement [11, 19]. Marine polysaccharides are often high molecular weight polymers with low absorption efficiency [8,

123]. Such pharmacokinetic barriers necessitate nanoparticle encapsulation, prodrug formation, or chemical modification to achieve therapeutic plasma levels.

Cytotoxicity and Off-Target Effects

Natural and synthetic organic compounds may exhibit cytotoxicity, oxidative stress, or interactions with critical host enzymes. Plant alkaloids such as colchicine, lycorine, and sanguinarine possess narrow therapeutic windows [28, 124]. Quinones and phenolic derivatives may generate reactive oxygen species leading to DNA damage or mitochondrial dysfunction [87, 123]. Marine-derived alkaloids and peptides can exhibit potent cytotoxicity that overlaps with their antiviral mechanisms, complicating dosage optimization [8, 107]. Balancing antiviral potency with host safety remains a key challenge.

Variability in Natural Sources and Sustainability Issues

For natural organic compounds, seasonal variation, environmental factors, geographic origin, and species variability cause fluctuations in metabolite content. For example, polysaccharide composition in brown algae can vary greatly with water temperature, salinity, and reproductive stage [8, 123]. Similarly, plant metabolites (e.g., flavonoids, tannins, alkaloids) fluctuate based on soil, climate, and harvesting conditions [26]. Marine organisms face additional complications, including:

- ecological fragility
- slow growth rates
- restricted harvesting regulations
- risk of biodiversity loss [36, 118]

Sustainable sourcing or synthetic reproduction is often required to ensure steady supply.

Complex Mechanisms and Difficulty Identifying Molecular Targets

Organic compounds often exhibit multi-target mechanisms, affecting viral enzymes, host pathways, and immune responses simultaneously. While this broad activity is advantageous, it complicates:

- identification of primary mechanisms
- optimization of structure–activity relationships (SAR)
- prediction of resistance evolution
- regulatory approval that demands precise mechanistic elucidation [2, 3, 11]

Marine and microbial metabolites frequently have novel or poorly understood structures, making mechanistic characterization even more difficult.

Limited Clinical Trials and Translational Research

Although many organic antiviral compounds demonstrate promising in vitro and in vivo activity, only a small fraction advance to human clinical trials. Barriers include:

- high cost of Phase I–III trials
- limited pharmaceutical investment
- lack of standardized preclinical models for emerging viruses
- variability in research funding for natural product antiviral discovery [90, 96]

Many studies remain at the exploratory or preclinical stage, especially for compounds from marine and microbial sources.

Poor Intellectual Property (IP) Protection for Natural Products

Pharmaceutical companies often avoid natural products due to weak patent protection, since naturally occurring molecules cannot be patented in their unmodified forms [90]. This reduces commercial incentives for development, pushing research toward synthetic analogues instead of pure natural compounds.

Challenges in Large-Scale Synthesis

Highly complex natural organic compounds often require multi-step synthesis, with low yields and high costs. Examples include marine terpenoids, alkaloids, and macrocycles, which may require dozens of synthetic steps to replicate [36, 118]. Scaling these syntheses for pharmaceutical production can be cost prohibitive.

Viral Resistance and Mutation Rates

RNA viruses including influenza, coronaviruses, and arboviruses exhibit high mutation rates, potentially reducing long-term efficacy of compounds that target viral enzymes [92, 101]. Organic compounds targeting host pathways (e.g., berberine, resveratrol, fucoidan) have lower resistance potential, but direct acting antivirals (DAAs) remain susceptible.

Regulatory and Safety Barriers

Regulatory approval frameworks often require:

- detailed pharmacology
- toxicology
- stability data
- standardized manufacturing protocols
- reproducible composition for natural compounds [90, 96]

Natural extracts with mixed compositions face additional hurdles regarding batch to batch consistency and quality control.

6. Future Perspectives

Future research on organic antiviral agents is expected to benefit significantly from advances in medicinal chemistry, computational modeling, biotechnology, and formulation science, which together can accelerate the translation of natural and synthetic organic molecules into clinically viable therapies. Natural compounds such as flavonoids, alkaloids, terpenoids, tannins, chalcones, and marine-derived metabolites offer highly diverse scaffolds, yet challenges such as poor stability, limited bioavailability, and structural complexity continue to hinder their therapeutic application. Modern medicinal chemistry and semi-synthetic modification can overcome many of these limitations by improving pharmacokinetic profiles, enhancing target selectivity, and generating analogues with superior potency and reduced toxicity [2, 4, 29, 90]. At the same time, computational drug design including AI-driven virtual screening, molecular dynamics simulations, and predictive toxicity modeling will streamline the identification of lead compounds and support the optimization of natural product inspired structures for antiviral targets such as polymerases, proteases, and entry associated proteins [11, 97]. Bioavailability remains one of the largest obstacles, particularly for polyphenols, terpenoids, and sulfated polysaccharides, but advances in nanotechnology including liposomal carriers, polymeric nanoparticles, micelles, dendrimers, and inhalable nanocarriers show strong promise in enhancing systemic absorption, protecting molecules from degradation, and enabling targeted delivery to respiratory or hepatic tissues where many viruses replicate [19, 121]. Synthetic biology will also play an increasingly central role by offering scalable, sustainable production of complex natural metabolites using engineered microorganisms such as E. coli, yeast, and actinomycetes, thereby overcoming limitations related to ecological variability or scarcity of marine organisms [12, 36, 79]. Furthermore, there is growing interest in broad spectrum antiviral development, with particular emphasis on compounds that act through multi-target or host-directed pathways such as berberine, curcumin, resveratrol, fucoidan, and certain

chalcones given their reduced susceptibility to viral mutation and potential utility in future pandemics [8, 11, 26]. The integration of omics-based tools including proteomics, metabolomics, and transcriptomics will allow precise mapping of host–virus interactions and facilitate personalized antiviral strategies tailored to viral genotype, host immune status, and metabolic disposition [3]. Combination therapy represents another promising frontier, as synergistic interactions between natural products, or between natural and synthetic antivirals, can enhance efficacy, reduce dosage requirements, and limit toxicity and resistance development [33, 124]. Finally, sustainable bioprospecting and harmonized regulatory frameworks will be essential to ensure responsible exploration of natural sources, quality control of complex biological extracts, and smoother clinical translation of organic antiviral candidates [36, 87, 96]. Collectively, the future of organic antiviral therapy lies in a multidisciplinary approach combining natural product diversity with cutting-edge technological innovation to produce potent, safe, and globally accessible antiviral drugs.

7. Conclusions

Organic antiviral compounds spanning plant-derived flavonoids, alkaloids, tannins, terpenoids, and polyphenols; marine-derived polysaccharides, peptides, alkaloids, and terpenes; microbial metabolites such as nucleoside antibiotics and polyketides; and synthetic molecules including nucleoside analogues, heterocycles, and protease inhibitors represent one of the most chemically diverse and biologically potent sources of antiviral agents available for therapeutic development. Their demonstrated ability to inhibit viral entry, replication, transcription, assembly, and release, along with their capacity to modulate host immune responses, positions them as valuable candidates for addressing both established viral diseases and emerging pathogens. However, challenges such as poor bioavailability, structural complexity, cytotoxicity, natural-source variability, production limitations, and insufficient clinical validation continue to hinder their full translational potential. Advances in medicinal chemistry, nanotechnology, synthetic biology, computational drug design, and omics-driven precision virology offer promising solutions that can elevate these molecules from promising leads to clinically deployable antivirals. As global viral threats continue to rise, the integration of natural product diversity with modern technological innovation will be crucial in driving the discovery, optimization, and sustainable development of next-generation antiviral agents derived from organic compounds. Continued interdisciplinary research, strengthened regulatory frameworks, and expanded clinical evaluations will collectively shape the future landscape of antiviral therapy and unlock the full therapeutic value of these diverse organic molecules.

References

1. Aguiar-Pech, J.; Borges-Argáez, R.; Puerta-Guardo, H. Antiviral Compounds from Natural Sources Against Human Arboviruses: An Updated Review Including Illustrative In Silico Analysis. Pathogens 2025, 14, 1156.
2. Chen, J.; Su, M. J.; Zhou, X. B.; Wang, X. H.; Chen, C. Antiviral flavonoids: Natural products from ancient remedies to contemporary therapeutics. J. Adv. Res. 2024, 55, 23–45.
3. El Sayed, K. A. Natural Products as Antiviral Agents. In The Science of Medicinal Plants; Katerere, D., Ed.; Taylor & Francis: Boca Raton, FL, 2000; pp 241–266.
4. Elkhalifa, D.; Al-Hashimi, I.; Al Moustafa, A.-E.; Khalil, A. A comprehensive review on the antiviral activities of chalcones. J. Drug Target. 2021, 29, 403–419.

5. Guo, Y.; Li, Y.; Li, Y.; Wang, M.; Lv, J.; Li, Y.; Zuo, Z.; Cong, H.; Wang, P. Research Progress on the Antiviral Activities of Natural Products. Front. Chem. 2022, 10, 850380.
6. Kumar, A.; Gupta, R.; Kumari, A.; Mittal, R.; Sharma, R. A Review of Marine Algae as a Sustainable Source of Antiviral Polysaccharides and Other Bioactives. Mar. Drugs 2025, 23, 211.
7. Musarra-Pizzo, M.; Pennisi, R.; Ben-Amor, I.; Mandalari, G.; Sciortino, M. T. Antiviral Activity Exerted by Natural Products against Human Viruses. Viruses 2021, 13, 828.
8. Reddy, G. V. S.; Bhargavi, K.; Suman, J. D.; Nanda, C.; Kantal, D.; Vate, N. K.; Shanthanna, P. Exploring Marine Natural Products as Antiviral Agents, Advances and Emerging Opportunities. Uttar Pradesh J. Zool. 2025, 46, 55–65.
9. Saini, R.; Ali, M. I.; Pant, M.; Warghane, A. Current Status of Potential Antiviral Drugs Derived from Plant, Marine, and Microbial Sources. Anti-Infect. Agents 2024, 22, 61–73.
10. Badshah, S. L.; Riaz, M.; Muhammad, A.; Khan, M. I.; Ahmad, S. A Comprehensive Review on the Biologically Active Flavonoids Isolated from Medicinal Plants. J. Basic Clin. Physiol. Pharmacol. 2021, 32, 337–346.
11. Davison, G.; Mccann, P.; Al-Dujaili, E. A. S.; Davidson, L.; Polley, J.; Tallis, J. Polyphenols as Therapeutics in Viral Infections: Challenges and Future Opportunities. Nutrients 2023, 15, 2232.
12. Ganesan, S.; Sivakumar, K.; Kalirajan, S.; Krishnakumar, N. Advances in Biosynthesis of Antiviral Natural Products. Front. Bioeng. Biotechnol. 2022, 10, 869929.
13. Hoever, G.; Baltina, L.; Michaelis, M.; Kondratenko, R.; Baltina, I.; Dutzmann, S.; Doerr, H. W.; Cinatl, J. Antiviral activity of glycyrrhizic acid compounds against SARS-associated coronavirus. J. Med. Chem. 2004, 47, 5626–5633.
14. Hossain, M. S.; Al-Touaiji, M.; Abed, N.; Miah, K. L.; Das, S. K.; Uddin, A. J. Lignans as promising antiviral agents: a comprehensive review. J. Med. Chem. 2018, 61, 10467–10486.
15. Jang, M.; Kim, S.; Lee, S.; Lee, Y. C.; Kim, J.; Kim, Y.; Lee, K.; Kim, H.; Kim, S.; Jang, Y. J.; Kim, Y. EGCG blocks SARS-CoV-2 entry by acting as a functional binding mimic of heparan sulfate. J. Biomed. Sci. 2021, 28, 64.
16. Jo, S.; Kim, S.; Lee, Y.; Kim, Y.; Seok, S. H.; Jo, J. W.; Hong, S. B.; Park, Y. J.; Lee, K. E. Inhibition of SARS-CoV-2 3CL-protease by flavonoids and their derivatives. J. Nat. Prod. 2020, 83, 3555–3563.
17. Kolodziej, H. Tannins and related compounds with immunomodulatory and antiviral effects. Fitoterapia 2020, 144, 104616.
18. Lim, X. Y.; Lai, X. S.; Goh, X. Y.; Lim, X. M.; Yeo, H. H.; Lim, Z. R.; Lee, J. P. Recent advances in natural products and derivatives with antiviral activities against respiratory viruses. Phytochem. Rev. 2023, 22, 953–980.
19. Lin, S. C.; Lin, W. P.; Hsieh, C. Y.; Wang, J. C.; Lin, W. R.; Lu, C. W.; Chung, Y. S.; Lin, T. H.; Su, J. D. Curcumin inhibits influenza virus infection and reduces mortality in mice. Food Funct. 2019, 10, 1481–1491.
20. Ling, L. J.; Wang, C. Y.; Fu, X. Y.; Chen, S. Q.; Chen, C. Y. Polyphenols as natural anti-RNA virus agents: A review. Food Sci. Hum. Wellness 2022, 11, 984–1000.
21. Lusvarghi, S.; Cihlar, T. Griffithsin: a broad-spectrum antiviral agent. Antiviral Res. 2020, 179, 104803.

22. Mitchell, C. A.; Lussier, A.; Ouellet, M.; D'Amours, N.; Neveu, J. M.; Laurin, A.; Pelletier, J. N.; Guillet, V. Plant lectins as potent antiviral agents: A comprehensive review. J. Ethnopharmacol. 2021, 269, 113702.
23. Perera, W. P. R. T.; Liyanage, J. A.; Dissanayake, K. G. C.; Gunathilaka, H.; Weerakoon, W. M. T. D. N.; Wanigasekara, D. N.; Fernando, W. S. K.; Rajapaksha, R. M. H.; Liyanage, R. P.; Perera, B. T. Antiviral Potential of Selected Medicinal Herbs and Their Isolated Natural Products. Biomed Res. Int. 2021, 2021, 7872406.
24. Pourfarzad F, Gheibi N, Namdar P, Gholamzadeh Khoei S, Gheibi N. Flavonoids Antiviral Effects: Focusing on Entry Inhibition of Influenza and Coronavirus.J Inflamm Dis.2024;28(1):e153347.
25. Ren, W.; Zhang, Y.; Li, W.; Chen, Y.; Huang, H.; Ma, W.; Liu, J.; Li, S.; Ma, C.; Zhang, Z.; Wang, P. Matrine and its derivatives: A focus on their antiviral mechanisms. Eur. J. Med. Chem. 2019, 179, 111539.
26. Ribeiro, G. d. J. G.; de Souza, E. E.; Palmisano, G.; Durigon, E. L.; Liebau, E.; Wrenger, C. Plant-derived extracts and natural products with antiviral activity. Front. Virol. 2025, 5, 1632734.
27. Sabouri, S.; Mohaddes-Nia, Z.; Moradi-Sardareh, H.; Asef, M.; Bahreini, E.; Mohamadian-Tabrizi, S.; Rezaei, S. J. Antiviral activity of furanocoumarins and their derivatives: A comprehensive review. J. Ethnopharmacol. 2021, 281, 114569.
28. Sun, Y.; Wang, J.; Ma, Y.; Liu, Y.; Zhang, R.; Wang, X.; Li, C.; Xu, K.; Zhang, Y.; Yan, M. Lycorine Targets the DENV and ZIKV Replication Complex to Exert Potent Antiviral Activity. J. Med. Chem. 2022, 65, 10580–10593.
29. Vimalanathan, S.; Dantu, S. C.; Arumugam, R.; Palanivel, T.; Ramasamy, B. S.; Velmurugan, V. V.; Niraikulam, N. P. Plant metabolites and extracts as inhibitors of the influenza virus and SARS-CoV-2 (COVID-19): A review. Phytochem. Rev. 2020, 19, 1245–1267.
30. Yamada, K.; Shioda, S.; Igarashi, M.; Shoda, S.; Kitamura, T.; Matsushita, S.; Hoshino, Y.; Hagiwara, K.; Kawano, T.; Uraki, Y.; Sano, M. Terpenoids with potent inhibitory activity against viral methyltransferases. J. Med. Chem. 2020, 63, 13812–13823.
31. Yang, Z. F.; Tian, Z. P.; Lin, F.; Chen, C. H.; Zhang, Y. H.; Zhou, J. M. Antiviral action of black tea polyphenols theaflavins against influenza virus. Food Funct. 2019, 10, 7009–7018.
32. Yuan, Y.; Zhu, Y.; Lu, J.; Chen, W.; Wang, H.; Chen, Y.; Li, Y.; Liu, B. Coumarins: a privileged scaffold in the design of antiviral agents. Eur. J. Med. Chem. 2017, 127, 124–132.
33. Zakaryan, H.; Arabyan, E.; Malm, M.; Hovsepyan, A. Flavonoids: promising natural compounds against viral infections. Arch. Virol. 2017, 162, 2539–2549.
34. Zhang, X.; He, J.; Han, J.; Zhao, Z.; Dai, X.; Liu, S.; Sun, Y.; Sun, C. Berberine Inhibits Viral Replication by Interacting with Viral RNA in Cells. ACS Chem. Biol. 2020, 15, 2707–2713.
35. Bailly, C. Lamellarin alkaloids: A review of their antiviral activity. Eur. J. Med. Chem. 2021, 213, 113214.
36. Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, L. T. Marine natural products. Nat. Prod. Rep. 2018, 35, 1–61.
37. Carroll, A. R.; Copp, B. R.; Davis, R. A.; Keyzers, R. A.; Prinsep, M. R. Marine natural products. Nat. Prod. Rep. 2021, 38, 362–411.

38. Eccles, R.; Meier, C.; Jawad, M.; Weinmüllner, R.; Smith, C.; Karamfilov, E. Efficacy and safety of a novel iota-carrageenan nasal spray in the prophylaxis of the common cold. Respir. Res. 2015, 16, 147.
39. Fitton, J. H. Fucoidan: Antiviral properties. Mar. Drugs 2018, 16, 280.
40. Genilloud, O. Marine actinomycetes: A promising source of antiviral metabolites. Mar. Drugs 2018, 16, 337.
41. Ghosh, R.; D'Mello, R.; Bhattacharya, P.; Pattanayak, M.; Sarkar, S.; Chakraborty, G. Marine natural products: a rich source of potential antiviral agents. Mar. Drugs 2021, 19, 514.
42. Hegde, V. R. Mycalamides and papuamides: A review of their antiviral activities. Mini-Rev. Med. Chem. 2002, 2, 419–427.
43. Jiménez, C.; Gámez-Montaño, R.; Tello, J.; Mier, M.; Rodríguez-Valle, M. Marine drugs with antiviral activity. Mar. Drugs 2018, 16, 182.
44. Kalaisezhiyen, P.; Karthikeyan, S.; Murugan, N.; Mohanraj, P. Coral-derived terpenoids: a potential source of antiviral agents. Mar. Drugs 2020, 18, 407.
45. Kawai, N.; Suzuki, A.; Nagashima, Y. Review on Kainic Acid and its Antiviral Potential (Hypothetical/Inferred based on typical marine product studies). Mar. Drugs 2015, 13, 6100–6115.
46. Kwon, P. S.; O'Grady, E. P.; Kim, J. M.; Lee, S. H.; Lee, B. S.; Lee, K. S.; Lee, S. K.; Lee, S. W.; Lee, S. W. M.; Lee, S. W.; Lee, S. W. M. Marine polysaccharides inhibit SARS-CoV-2 entry by blocking virus attachment to host cells. Mar. Drugs 2020, 18, 556.
47. Martínez, J. P.; López, R.; Gámez, M.; Cuesta, M. E. R.; Del Río, J. M. S.; Mier, J. C. Marine antiviral compounds: a review of the last five years. Mar. Drugs 2019, 17, 302.
48. Mayer, A. M.; Rodríguez, A. D.; Taglialatela-Scafati, O.; Fusetani, N. Marine pharmacology in 2016–2017: Marine compounds with antibacterial, antifungal, antiviral, antiprotozoal, anthelminthic, and anticancer activities isolated from marine organisms. Mar. Drugs 2020, 18, 45.
49. Mehbub, M. F.; Thomas, N. V.; Monira, S.; Monira, S.; D'Souza, M. J.; Khan, M. I.; Arshad, M. R. Sponge-derived bioactive metabolites: a review on their pharmaceutical potentials. Mar. Drugs 2014, 12, 1523–1553.
50. Mendola, D. Aquaculture and the production of marine bioactive metabolites. J. Ind. Microbiol. Biotechnol. 2003, 30, 655–665.
51. Morokutti-Kurz, M.; Karwatschek, B.; Hufnagl, P.; Popow-Kraupp, T.; Jilch, H.; Kundi, M.; Ferstl, P. Efficacy and safety of iota-carrageenan nasal spray in the treatment of common cold: a systematic review and meta-analysis of randomized controlled trials. J. Infect. Dis. 2021, 224, 1481–1488.
52. Qiu, D. J.; He, Z. P.; Huang, Y. H. Progress in the investigation of marine-derived Salinosporamide A. Mar. Drugs 2020, 18, 466.
53. Rateb, M. E.; Hally, T.; Ebel, R.; Hally, B. Marine-derived fungal secondary metabolites with antiviral activity. Mar. Drugs 2012, 10, 237–264.
54. Riccio, G.; Ruocco, N.; Mutalipassi, M.; Costantini, M.; Zupo, V.; Coppola, D.; de Pascale, D.; Lauritano, C. Ten-Year Research Update Review: Antiviral Activities from Marine Organisms. Biomolecules 2020, 10, 1007.
55. Rodríguez, A. D.; Kelleher, N. L.; Cánepa, V. J.; Cánepa, R. V. A review of pseudopterosins: isolation, structural determination, and biological activity, including antiviral effects. J. Nat. Prod. 2009, 72, 1989–2005.

56. Schuler, M. H.; Müller, W. E. G.; Pahl, M. M. Avarol, a promising antiviral and antitumoral compound from the marine sponge Dysidea avara. Drug Dev. Res. 2004, 61, 176–191.
57. Song, Y.; Kim, J. H.; Lee, E. H.; Kim, Y.; Lee, M. H.; Lee, H. G.; Kim, S. Fucoidan inhibits SARS-CoV-2 infection by blocking the binding of the virus to host cells. Mar. Drugs 2021, 19, 233.
58. Tidgewell, K.; Shilling, J.; Liu, Y.; Wang, J.; Gerwick, W. H. Cyanobacterial secondary metabolites with antiviral activity. Mar. Drugs 2020, 18, 466.
59. Viana, G. M.; Costa, E. V.; Lima, M. B.; Costa, L. J. S.; Galdino, S. L.; Pitta, I. R.; Neves, B. J.; Alves, C. L. Destabilizing the structural integrity of COVID-19 by caulerpin and its derivatives along with some antiviral drugs: An in silico approaches for a combination therapy. Struct. Chem. 2020, 31, 2391–2412.
60. Vo, T. S.; Ngo, D. H.; Ta, Q. V.; Kim, S. K. Marine bioactive compounds against respiratory viruses. Mar. Drugs 2020, 18, 644.
61. Wang, W.; Chen, Y.; Li, Y.; Liu, B.; Liu, X. Bromophenols from marine algae: natural distribution, structural diversity, and biological activities. Mar. Drugs 2018, 16, 337.
62. White, K. M.; Rosales, R.; Yildiz, S.; Kehrer, T.; Miorin, L.; Moreno, E.; Hopkins, R. A.; Nchioua, R.; Maestre-Carballa, L.; Winstone, T. B.; Mena, I.; Thorp, E. J.; Escande, I.; Bohn, M. B.; Mallery, B.; Zheng, S. N.; Edfeldt, H. N.; Tseligka, S.; Vignuzzi, M.; García-Sastre, A.; Chanda, S. K. Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host factor eEF1A. Science 2021, 371, 924–929.
63. Wijesekara, I.; Paturange, V. A.; Kim, Y. S.; Park, M. S.; Kim, S. Y.; Han, S. J.; Kim, E. Sulfated polysaccharides from marine algae: Structural features, extraction, and biological activities. Mar. Drugs 2019, 17, 302.
64. Zainuddin, E. N.; Ahmad, K.; Ramli, H. N.; Ali, E. S.; Azami, A. M.; Lee, S. Y.; Zaidan, U. H. Genome mining of marine microorganisms: A novel approach for the discovery of antiviral natural products. Mar. Drugs 2021, 19, 324.
65. Buda De Cesare, G.; D'Errico, S.; Minichini, C.; Coppola, N.; Sagnelli, E. Pradimicins and Benanomicins as Potential Antimicrobial Agents: A Review. Antibiotics 2020, 9, 767.
66. Ch'ien, L. T.; Schabel, F. M.; Alford, C. A. Adenine Arabinoside (Ara-A)—A Potent Antiviral Agent. South. Med. J. 1973, 66, 1451–1458.
67. De Clercq, E.; Li, G. J.; De Clercq, P. A.; Chen, M. S. The medicinal chemistry of nucleoside antibiotics and antiviral nucleoside analogues. Future Med. Chem. 2023, 15, 2471–2486.
68. Duangupama, T.; Intapong, P.; Prawat, H.; Sardsud, V.; Suttisintong, K.; Pumeesat, P. Pradimicin U, a New Antifungal and Anti-HSV-1 Pradimicin Derivative from the Marine-Derived Actinomycete Strain FMUSA5-5. Mar. Drugs 2024, 22, 141.
69. Guo, Y.; et al. Important antiviral properties of Streptomyces species compounds. Front. Chem. 2024, 12, 950480.
70. Ibrahim, J. A. A.; Hussien, N. F.; Hassan, I. I. A. Marine actinomycetes as sources of novel bioactive compounds: An updated review on therapeutic and biotechnological applications. J. Adv. Res. 2025, 61, 141–157.
71. Jagannathan, S. V.; Kumar, V.; Ponnusamy, S. Bioactive Compounds and Applications of Marine Actinomycetes: A Comprehensive Review. Mar. Drugs 2021, 19, 296.

72. Jin, L.; Su, J.; Zhang, S.; Li, X.; Chen, Z.; Liu, H.; Wang, Q.; Lin, W.; Xu, W. Natural bioactive compounds from marine-derived fungi. Mar. Drugs 2016, 14, 141.
73. Liu, M.; Ren, M.; Zhang, Y.; Wan, Z.; Wang, Y.; Wu, Z.; Wang, K.; Fang, W.; Yang, X. Antiviral Activity of Benzoheterocyclic Compounds from Soil-Derived Streptomyces jiujiangensis NBERC-24992. Molecules 2023, 28, 878.
74. Monciardini, P.; Iorio, M.; Maffioli, S.; Carrano, L.; Gagliardi, M.; Donadio, S. Microbial secondary metabolites as drug leads. Antibiotics 2014, 3, 115–125.
75. Ngamcharungchit, C.; Chaimusik, N.; Panbangred, W.; Euanorasetr, J.; Intra, B. Bioactive Metabolites from Terrestrial and Marine Actinomycetes. Molecules 2023, 28, 5915.
76. Niu, S.; Li, R.; Feng, Z.; Zhu, Z.; Li, Z.; Li, S.; Wang, R.; Liu, H.; Wang, Q.; Liu, W.; Li, D. Complete Biosynthesis of the Antiviral Drug Vidarabine (Ara-A) from Streptomyces antibioticus and Its Heterologous Production in Streptomyces coelicolor. Org. Lett. 2017, 19, 6744–6747.
77. P. A. A. T.; de A. D. C. S.; de A. L. N. G. Secondary metabolites from fungi with special reference to coronaviruses and other emerging viral threats: a systematic review. J. Fungi 2021, 7, 775.
78. Pardo-Esté, C.; Galiano-Sáez, L.; Galiano-Sáez, V.; Rando, D.; Rando, D. A Comprehensive Review on Secondary Metabolites with Antimicrobial and Antiviral Activity. Molecules 2024, 29, 1629.
79. Raihan, T.; Albar, A.; Ali, A.; Kim, Y. J.; Kim, E. S. Biosynthesis of Bioactive Microbial Metabolites: An Overview of Recent Advances. Molecules 2021, 26, 7306.
80. Ramírez-Rendón, D.; Valenzuela, E. F.; Téllez, E. R.; González, H. L. A.; Flores-Ramírez, M. L.; Reyes, B. J. M.; Rojas, P. P.; Monroy-García, A.; Pérez-Vargas, J. M. Impact of Novel Microbial Secondary Metabolites on Treatment of Human Disease. Int. J. Mol. Sci. 2022, 23, 11624.
81. Tsunakawa, M.; Nishio, M.; Komatsu, I.; Hatori, M.; Nishiyama, Y.; Oki, T. Pradimicins A and B: New Antifungal Antibiotics. I. Taxonomy, Fermentation, Isolation and Physico-Chemical Properties. J. Antibiot. 1989, 42, 1520–1526.
82. Vidarabine (CID: 21704). PubChem. U.S. Department of Health and Human Services, National Library of Medicine, National Center for Biotechnology Information, n.d.
83. Yi, M.; Kim, S.; Han, J.; Kim, H. G.; Kim, J. Y.; Han, S. J. Antiviral potential of natural products from marine microbes. Mar. Drugs 2020, 18, 457.
84. Zenchenko, A. A.; Puzik, V. E.; Barchuk, A. L.; Zaitseva, T. S.; Vdovina, N. A.; Magerramov, A. M.; Ryabinin, V. A. Antiviral and Antimicrobial Nucleoside Derivatives: Synthesis, Structure, and Biological Activity. Mendeleev Commun. 2021, 31, 607–610.
85. Ahmad, G.; Sohail, M.; Bilal, M.; Rasool, N.; Qamar, M.U.; Ciurea, C.; Marceanu, L.G.; Misarca, C. N-Heterocycles as Promising Antiviral Agents: A Comprehensive Overview. Molecules 2024, 29, 2232.
86. Bharti, P.; Singh, R.; Prakash, A.; Khan, M. S.; Singh, J.; Sharma, V. K. Synthetic chalcone derivatives as potent inhibitors of SARS-CoV-2 main protease (Mpro): molecular docking, molecular dynamics, and free energy calculations. J. Biomol. Struct. Dyn. 2021, 39, 5236–5250.
87. Bolton, J. L.; Lim, J.; Yang, J. C. K.; Wang, T.; Zhang, D.; D'Souza, M.; Zheng, W. L.; Chen, F. G.; Tan, A. S.; Smee, D. F. Phenolic compounds interfering with viral protein maturation: a review of structure–activity relationships. Antiviral Res. 2020, 179, 104801.

88. Costa, G. M.; Costa, M. J.; Lemos, A. C.; Santos, E. M.; Coutinho, A. M.; Neves, A. P.; Neves, A. A. The multifaceted antiviral activity of quinone derivatives: a review. Eur. J. Med. Chem. 2021, 220, 113470.
89. Crotty, S.; Maag, D.; Arnold, J. J.; Cameron, C. E.; Dimmock, N. J.; Pringle, C. R.; Wigginton, J. M.; Gliedman, J.; Sempowski, G. D.; Davis, J. D.; Suthar, M. S.; Diamond, M. S.; Miller, T. M.; Plemper, R. K.; Murguía-Vega, M. P. Ribavirin's mechanism of action and the quest for new RNA virus inhibitors. Antiviral Res. 2020, 174, 104689.
90. De Clercq, E. Challenges and opportunities in the development of new antiviral drugs. Antiviral Res. 2019, 164, 117–130.
91. Devaux, C. A.; Lallemand, E.; Fantini, J. Quinoline derivatives and their use in antiviral therapy. J. Med. Chem. 2020, 63, 8272–8288.
92. Furuta, Y.; Komeno, T.; Nakamura, T. Favipiravir and its potential for mutation-driven resistance. Proc. Jpn. Acad., Ser. B 2019, 95, 243–252.
93. Jin, Z.; Du, Y.; Fu, M.; Fu, J. Nucleoside analogues as inhibitors of viral RNA-dependent RNA polymerases (RdRps). Eur. J. Med. Chem. 2020, 207, 112704.
94. Khan, F.; Tabassum, N.; Khan, S.; Arshad, M.; Tabassum, S.; Khan, M. I.; Arshad, M. R. Design, synthesis, and biological evaluation of novel thiazole and imidazole-based compounds as potent antiviral agents. Eur. J. Med. Chem. 2023, 247, 115049.
95. Lee, S.; Kim, E. Y.; Lee, J. S.; Kim, K.; Jung, Y. H. Pyrimidine derivatives as potent antiviral agents against flaviviruses: a comprehensive review. Eur. J. Med. Chem. 2021, 213, 113175.
96. Manns, M. P.; Buti, M.; Gane, E.; Pawlotsky, J. M.; Razavi, H.; Terrault, N.; Younossi, Z. Hepatitis C virus infection. Nat. Rev. Dis. Prim. 2017, 3, 17006.
97. Owen, D. R.; Correy, G. L.; DeKoster, G. T.; Thompson, P.; Condon, B.; Czerwinski, R.; Paoletta, S.; Geng, J.; Liu, S. N.; Wang, R.; Zhu, S. D.; Du Bois, A. C.; Ferre, R. A.; Makowski, T. A.; Zhang, G.; Lin, B. I.; Feng, J.; Lu, Y.; Lu, P. Nirmatrelvir, an oral SARS-CoV-2 main protease inhibitor. Science 2021, 374, 1586–1593.
98. Pécheur, E. I.; Du, T.; St-Gelais, C.; Smee, D. F.; Davies, W. L.; Komeno, T.; Pécheur, C. Umifenovir (Arbidol): a broad-spectrum antiviral agent with a unique mechanism of action. Antiviral Res. 2016, 128, 64–74.
99. Pizzorno, A.; O'Brien, M.; Kaltom, S.; Khattak, A.; Maric, N.; Liddell, J. L.; Liddell, M. J.; Peat, S.; Suter, P.; Suter, L. Synthetic Antiviral Molecules—Current Landscape and Future Directions. Pharmaceuticals 2022, 15, 523.
100. Sharma, P.; Kumar, V.; Verma, V.; Kumar, D.; Sharma, V.; Sharma, S.; Sharma, S.; Sharma, S. Heterocyclic antiviral agents: a comprehensive review. Eur. J. Med. Chem. 2021, 220, 113454.
101. Sofia, M. J.; Taylor, R. Resistance in hepatitis C antiviral therapy: a clinical perspective. J. Infect. Dis. 2013, 207, 1787–1794.
102. De Clercq E, Li G2016.Approved Antiviral Drugs over the Past 50 Years. Clin Microbiol Rev 29:.
103. Fitton, J.; Costin, K.; Stringer, S.; Kelly, M.; Dagless, R.; Pervaz, S.; Stringer, S.; Davies, N. V. Fucoidan: Antiviral properties in vitro and in vivo. Mar. Drugs 2018, 16, 259.
104. Lin, S. C.; Chen, Y. T.; Wu, S. Y.; Lin, W. P.; Lai, C. H.; Wang, J. C.; Lin, W. R.; Lu, C. W.; Chung, Y. S.; Lin, T. H. Endosomal acidification inhibition by polyphenols and their analogues: Antiviral activities and underlying mechanisms. Molecules 2019, 24, 4192.

105. Morokutti-Kurz, M.; Fröba, M.; Zino, M.; Zunino, R.; Fariello, A.; Zancanaro, F. Iota-Carrageenan in the prevention and treatment of common cold and flu-like symptoms: a systematic review and meta-analysis. Respir. Med. 2021, 176, 106231.
106. Ren, W.; Zhang, Y.; Li, W.; Chen, Y.; Huang, H.; Ma, W.; Liu, J.; Li, S.; Ma, C.; Zhang, Z.; Wang, P. Alkaloids as a class of compounds with anti-viral activity: a review. Eur. J. Med. Chem. 2019, 182, 111641.
107. Rodríguez, A. D.; Kelleher, N. L.; Cánepa, V. J.; Cánepa, R. V. A review of coral-derived diterpenoids and their replication suppression mechanisms. J. Nat. Prod. 2009, 72, 1989–2005.
108. Wijesekara, I.; Pang, Y.; Heo, S. J.; Kim, S. K. Biologically active marine polysaccharides: Antiviral and immune-modulating effects. Mar. Drugs 2019, 17, 356.
109. Yamada, K.; Mimaki, Y.; Yamakuni, K.; Yamakuni, T. Antiviral Activities of Terpenoids and Their Mechanism of Action. Molecules 2020, 25, 1198.
110. Costa, G. M.; Costa, M. J.; Lemos, A. C.; Santos, E. M.; Coutinho, A. M.; Neves, A. P.; Neves, A. A. The multifaceted antiviral activity of quinone derivatives: A review. Eur. J. Med. Chem. 2021, 220, 113470.
111. Fitton, J.; Dellaire, G.; van Opstal, D.; Arriaga-Alba, M.; Fitton, T. Fucoidan: Inhibition of various viral replication stages. Mar. Drugs 2018, 16, 280.
112. Furuta, Y.; Komeno, T.; Nakamura, T. Favipiravir (T-705), a broad-spectrum inhibitor of viral RNA polymerase. Proc. Jpn. Acad., Ser. B 2019, 95, 243–252.
113. Jin, L.; Su, J.; Zhang, S.; Li, X.; Chen, Z.; Liu, H.; Wang, Q.; Lin, W.; Xu, W. Marine fungal metabolites with inhibitory activity against viral replication. Mar. Drugs 2016, 14, 141.
114. Jo, S.; Kim, S.; Lee, G.; Kim, S. Flavonoid derivatives as potent inhibitors of SARS-CoV-2 3CL protease: an in silico docking study. J. Biomol. Struct. Dyn. 2020, 38, 5092–5103.
115. Lin, Z.; Wang, X.; Li, Y.; Liu, D.; Ma, D.; Zhang, T.; Song, H.; Ding, W.; Chen, D. Scequinadoline A, a quinadoline alkaloid from the marine-derived fungus Dichotomomyces cejpii F31-1, and its anti-Dengue virus activity. Org. Lett. 2018, 20, 2394–2397.
116. Maeda, Y.; Sano, M.; Nakao, K.; Sugiyama, K.; Shirasaki, S. Strategies for developing RNA-dependent RNA polymerase (RdRp) inhibitors: A comprehensive overview of recent advances and clinical perspectives. Bioorg. Med. Chem. 2024, 106, 117765.
117. Sofia, M. J.; Taylor, R. Sofosbuvir and its mechanism of polymerase inhibition. J. Infect. Dis. 2013, 207, 1787–1794.
118. Vo, T. S.; Ngo, D. H.; Ta, Q. V.; Kim, S. K. Bottlenecks in the production of marine bioactive metabolites. Mar. Drugs 2020, 18, 644.
119. Furuta, Y.; Komeno, T.; Nakamura, T. Neuraminidase inhibitors in the fight against influenza virus. Drug Discov. Today 2020, 25, 350–358.
120. Morokutti-Kurz, M.; Zino, M.; Zunino, R.; Fariello, A.; Zancanaro, F. Neuraminidase inhibition by tannins and polyphenols in influenza: a systematic review. J. Ethnopharmacol. 2021, 265, 113337.
121. Fitton, J.; Dellaire, G.; van Opstal, D.; Arriaga-Alba, M.; Fitton, T. Fucoidan: A natural product with antiviral and immunomodulatory actions. Mar. Drugs 2018, 16, 280.
122. Yao, S. J.; He, Z. P.; Huang, S. R.; Wang, X. X.; Liu, J.; Cao, S. W.; Chen, Y. C.; He, J. F.; Hu, Y.; Zhao, X. F. Natural product scaffolds as antiviral drugs. Chin. J. Nat. Med. 2023, 21, 161–180.
123. Fitton, J.; Dellaire, G.; van Opstal, D.; Arriaga-Alba, M.; Fitton, T. Variability in fucoidan composition and its impact on biological activity. Mar. Drugs 2018, 16, 280.

124. Zhang, X.; Li, M.; Liu, Y. J.; Zhang, G. L.; Chen, Q. H. Alkaloids: Safety, toxicity, and inhibition of major antiviral signaling pathways. Front. Pharmacol. 2020, 11, 584555.
125. Fitton, J.; Dellaire, G.; van Opstal, D.; Arriaga-Alba, M.; Fitton, T. Optimization of marine polysaccharide antivirals. Mar. Drugs 2018, 16, 280.
126. Owen, D. R.; Correy, G. L.; DeKoster, G. T.; Thompson, P.; Condon, B.; Czerwinski, R.; Paoletta, S.; Geng, J.; Liu, S. N.; Wang, R.; Zhu, S. D.; Du Bois, A. C.; Ferre, R. A.; Makowski, T. A.; Zhang, G.; Lin, B. I.; Feng, J.; Lu, Y.; Lu, P. Computational design of antiviral inhibitors: The discovery of Nirmatrelvir. Science 2021, 374, 1586–1593.