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Plant polyphenols as broad-spectrum antivirals: Comprehensive potency profiling against major virus families

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ABSTRACT

Plant polyphenols are promising candidates for broad-spectrum antiviral development, but their comparative potency and selectivity across virus families remain poorly characterized. This study aims to systematically compare and profile the antiviral activity, potency, and selectivity of diverse plant polyphenol classes across major virus families relevant to human and animal health. A comprehensive literature search was conducted across five databases to identify studies reporting in vitro and *in vivo* antiviral activity of plant polyphenols, extracting quantitative IC_{50}/EC_{50} and selectivity index data. Potency matrices were constructed, and comparative visualizations, including heatmaps, violin plots, and radar charts, were generated to assess the spectrum and strength of antiviral effects. Analysis of 54 studies revealed that flavonoids, catechins, phlorotannins, and biflavonoids frequently exhibit sub- to low-micromolar IC_{50}/EC_{50} values against multiple virus families, particularly *Orthomyxoviridae*, *Flaviviridae*, and *Coronaviridae*. Certain scaffolds, such as dieckol and quercetin, demonstrated potent and broad activity (median IC_{50} <10 μM) with favorable selectivity indices. *In vivo* efficacy data, though limited, confirmed survival or viral load reductions in animal models. The findings highlight several polyphenol scaffolds with robust, multi-family antiviral activity and high selectivity, underscoring their potential for broad-spectrum antiviral drug discovery. Considering all, standardized evaluation and further translational research are warranted to optimize lead candidates.

INTRODUCTION

Viral diseases remain a significant threat to global health, agriculture, and economies, with frequent emergence and re-emergence of infectious agents highlighting the urgent need for new antiviral strategies. While vaccines and small-molecule antivirals have revolutionized the control of select viruses, the rapid mutation rates of many pathogens, coupled with the limited spectrum of current treatments, have driven the search for alternative or complementary approaches. Of particular interest are broad-spectrum antivirals capable of inhibiting diverse viruses across multiple families, given their potential utility in pandemic preparedness, treatment of co-infections, and management of emerging or drug-resistant viruses [1].

Plant-derived polyphenols have attracted growing attention as a promising source of broad-spectrum antiviral agents [2]. These secondary metabolites, found abundantly in various fruits, vegetables, herbs, and marine algae, exhibit a remarkable range of bioactivities, including antioxidant, anti-inflammatory, and antimicrobial properties [3–5]. Increasing evidence from in vitro, *in vivo*, and computational studies suggests that many polyphenols exert antiviral effects against both RNA and DNA viruses, often through diverse mechanisms such as inhibition of viral entry, replication, assembly, and modulation of host immune responses [6,7]. The relatively low toxicity and

established human consumption of many polyphenol-rich foods further support the rationale for exploring these compounds as potential antiviral leads [8].

Recent research has highlighted the antiviral activities of several polyphenol classes, including flavonoids, biflavonoids, tannins, phlorotannins, and chalcones, each demonstrating activity against viruses of public health concern. For instance, catechins from green tea have shown efficacy against influenza viruses, hepatitis C virus, and human immunodeficiency virus, while biflavonoids from marine algae and terrestrial plants display inhibitory activity against coronaviruses and enteroviruses [9,10]. Beyond individual compounds, extracts from polyphenol-rich sources such as *Cistus incanus* and traditional medicinal herbs have also demonstrated in vitro and *in vivo* antiviral efficacy, reinforcing the relevance of plant polyphenols in antiviral research [11,12].

Despite accumulating reports of antiviral activity, a comprehensive understanding of the spectrum and potency of plant polyphenols across major virus families remains limited. Most published studies focus on single compounds or extracts against specific viral targets, often with substantial heterogeneity in assay conditions, endpoints, and reporting standards. Systematic comparisons of polyphenol activity profiles, such as potency matrices, spectrum mapping, and structure-activity relationship analyses, are lacking. Such comparative analyses are critical for identifying not only potent antiviral candidates but also molecular scaffolds with inherent broad-spectrum activity [13].

The present study aims to address this knowledge gap by systematically profiling the antiviral potency and selectivity of plant polyphenols across a broad panel of virus families. Using curated data from published in vitro and *in vivo* studies, the antiviral activity landscape is visualized through comparative heatmaps, violin and forest plots, and radar charts, enabling quantitative comparisons of compound efficacy and breadth. Structure-activity relationship mapping further links major polyphenol classes to their observed antiviral profiles. This integrated analysis provides a foundation for rational selection and further development of plant polyphenols as candidates for broad-spectrum antiviral therapeutics.

MATERIALS AND METHODS

Literature search and study identification

A systematic literature search was conducted to assemble a dataset of plant polyphenol antiviral activities, guided by PRISMA recommendations. Five major databases—PubMed, Scopus, Web of Science, ScienceDirect, and MDPI—were searched in 2024 using combinations of terms such as "*polyphenol*," "*flavonoid*," "*antiviral*," "IC_{50}," "EC_{50}," "*potency*," and "*inhibition*." The full set of search strategies and database queries is summarized in Supplementary Table S1. The initial search retrieved 926 records, with an additional 34 studies identified through manual reference screening and database alerts. Duplicate records were removed, yielding 684 unique entries. All records were imported into EndNote X9 software, and deduplication was performed automatically and manually checked. Title and abstract screening were performed by two independent analysts. Exclusion criteria included studies lacking quantitative antiviral data, review articles without original results, works focused on synthetic analogs, in silico-only studies, and conference abstracts. After exclusion of 523 irrelevant or ineligible records, 161 full-text articles were evaluated for eligibility. Discrepancies between reviewers at any screening stage were resolved by consensus or by consulting a third reviewer. Ultimately, 72 studies met the inclusion criteria for qualitative

synthesis, of which 54 reported IC_{50} or EC_{50} data suitable for quantitative analyses, and 11 reported *in vivo* efficacy endpoints (Supplementary Table S3).

In vivo and mechanistic study

For *in vivo* studies, effect size metrics such as survival rates, viral load reductions, and symptom improvement were summarized and linked to specific compound-virus-model combinations in Supplementary Table S3. Mechanistic evidence, including enzyme and viral target inhibition data, was extracted and catalogued in Supplementary Table S2 for contextual interpretation.

Data extraction and standardization

From each eligible study, the following data were extracted: polyphenol name, chemical class, virus species and virus family, assay format (*in vitro* or *in vivo*), reported IC_{50}/EC_{50} values, selectivity index (SI), cytotoxicity, animal model and species, dose, administration route, and efficacy endpoint (e.g., viral load, survival, symptom reduction). Data extraction was performed in duplicate by two independent reviewers using a pre-defined extraction form to ensure consistency and minimize transcription errors. When more than one IC_{50} or EC_{50} value was reported for a given polyphenol-virus pair, values were converted to a standard unit (μM) using molecular weights, and the median value was retained for analysis. For studies that only reported concentrations in μg/ml, conversion to μM was performed using published molecular weights from PubChem or ChemSpider. For studies reporting SI, the median SI per polyphenol-family combination was also calculated. All data entries were independently checked by two reviewers for accuracy. Key studies underpinning the dataset and providing methodological precedent include Besednova et al. [1], Droebner et al. [11], Song et al. [9], and Ryu et al. [10]. In cases of unclear or ambiguous results, attempts were made to contact the original authors for clarification.

Potency matrix construction

A comprehensive potency matrix was constructed. Rows correspond to unique plant polyphenols, columns to virus families represented in the dataset, including *Orthomyxoviridae, Flaviviridae, Herpesviridae, Picornaviridae, Togaviridae, Coronaviridae, Caliciviridae, Hepadnaviridae, Retroviridae, Circoviridae, Rhabdoviridae,* and *Astroviridae*. For polyphenol-family pairs with multiple available datapoints, the median IC_{50} or EC_{50} (μM) was used. Cells lacking data were left blank or neutral. Polyphenols were grouped by chemical class to facilitate comparisons of scaffold-activity relationships.

Data visualization

Antiviral spectrum and potency were visualized using a series of publication-ready figures. The primary heatmap depicted the lowest IC_{50} or EC_{50} value for each polyphenol-virus family pairing, using a blue-to-red color gradient to indicate potency, with annotated values where appropriate. Distribution of $\log_{10}(IC_{50}/EC_{50})$ values across virus families was visualized by violin plots overlaid with mean ± standard error markers. A comparative heatmap of median IC_{50}/EC_{50} values per polyphenol-virus family combination, with high-potency cells highlighted for IC_{50} <10 μM was also presented. Breadth, potency, and selectivity for major polyphenols were profiled via

radar charts, displaying normalized values for virus family coverage, -$\log_{10}$ median IC_{50}, and median SI. All visualizations were generated using Python (v3.9) and R (v4.2) with Seaborn, Matplotlib, and ggplot2 packages, ensuring accessibility and publication-quality resolution. A forest plot summarizes *in vivo* effect sizes (e.g., percent survival, viral load reduction) for each polyphenol-virus-animal model combination. All plots were generated using Python (v3.9) with Seaborn and Matplotlib libraries, and R (v4.2) with ggplot2, ensuring scripts and datasets are available from the corresponding author upon request for reproducibility.

Reproducibility statement

All data sources, extraction protocols, and analysis scripts are available from the corresponding author upon reasonable request to support full reproducibility.

Ethical considerations

This study did not use any new animal or human experiments. All *in vivo* efficacy data were extracted exclusively from previously published studies that had obtained their own institutional ethical approvals. The authors performed no new experiments, and no animals were handled, housed, or subjected to research as part of the present work. No laboratory chemicals, reagents, or experimental equipment were used in this study. All data analyzed were obtained from published sources, and the study did not involve new experimental procedures requiring laboratory materials or instrumentation.

Statistical analysis

Descriptive statistics (median, mean, interquartile range, standard error) were computed for IC_{50}/EC_{50} values within each virus family and polyphenol class.

RESULTS

Overview of included studies and data characteristics

A total of 54 primary studies, published between 1990 and 2024, met eligibility for quantitative synthesis (Supplementary Table S1). These included 48 reports providing direct IC_{50} or EC_{50} values and 11 studies contributing *in vivo* efficacy outcomes. Virus family coverage was broad, with the highest representation for *Coronaviridae* (12 studies), *Orthomyxoviridae* (10), *Flaviviridae* (9), and *Herpesviridae* (7); smaller datasets addressed *Picornaviridae*, *Retroviridae*, *Togaviridae*, *Caliciviridae*, and *Rhabdoviridae*. The most investigated polyphenol classes included flavonoids, catechins, phlorotannins, biflavonoids, and several mixed plant extracts (Table 1).

Altogether, 72 unique plant polyphenols were mapped against 91 virus species from 9 virus families. Most studies use in vitro assays, with a subset reporting *in vivo* animal model data (Supplementary Table S3). Potency values were standardized as IC_{50} or EC_{50} in micromolar units, and selectivity indices (SI) were available for approximately 40% of compound-virus pairs, enabling assessment of potential therapeutic window.

Table 1. *In vitro* antiviral potency and selectivity of plant polyphenols (IC_{50}/EC_{50}, SI, virus family, chemical class).

Polyphenol name	Polyphenol class	Virus family	Virus species	Assay type	Study count
Acacetin	Flavonoid	*Orthomyxoviridae*	Influenza virus	In vitro plaque reduction	1
Amentoflavone	Biflavonoid	*Orthomyxoviridae*	Influenza B virus	In vitro CPE inhibition	1
Amentoflavone	Biflavonoid	*Orthomyxoviridae*	Influenza A virus	In vitro CPE inhibition	1
Amentoflavone	Biflavonoid	*Herpesviridae*	HSV-1	In vitro CPE inhibition	1
Amentoflavone	Biflavonoid	*Herpesviridae*	HSV-2	In vitro CPE inhibition	1
Amentoflavone	Biflavonoid	*Coronaviridae*	SARS-CoV	Enzymatic (3CLpro)	1
Apigenin	Flavonoid	*Togaviridae*	CHIKV	In vitro replication	1
Apigenin	Flavonoid	*Picornaviridae*	Enterovirus 71	In vitro CPE inhibition	1
Baicalein	Flavonoid	*Flaviviridae*	Japanese encephalitis virus	In vitro plaque reduction	1
Baicalein	Flavonoid	*Togaviridae*	CHIKV	In vitro CPE inhibition	1
Baicalein	Flavonoid	*Herpesviridae*	Human cytomegalovirus	In vitro plaque reduction	2
Baicalein	Flavonoid	*Orthomyxoviridae*	Influenza virus	In vitro CPE inhibition	1
Bavachinin	Flavonoid	*Coronaviridae*	SARS-CoV	Enzymatic (PLpro)	1
Chrysin	Flavonoid	*Picornaviridae*	Enterovirus 71	In vitro plaque reduction	1
Daidzein	Isoflavone	*Caliciviridae*	Feline calicivirus	In vitro titer reduction	1
Daidzein	Isoflavone	*Caliciviridae*	Murine norovirus	In vitro titer reduction	1
Epigallocatechin gallate	Catechin	*Orthomyxoviridae*	Influenza virus	In vitro plaque reduction	2
Epigallocatechin gallate	Catechin	*Picornaviridae*	Enterovirus 71	In vitro CPE inhibition	1
Epigallocatechin gallate	Catechin	*Circoviridae*	PCV2	In vitro plaque reduction	1
Epigallocatechin gallate	Catechin	*Retroviridae*	HIV-1, HIV-2	In vitro enzyme inhibition	2
Galangin	Flavonol	*Herpesviridae*	HSV-1	In vitro plaque reduction	1
C-Geranylated Flavonoids	Flavanone	*Coronaviridae*	SARS-CoV	Enzymatic (PLpro)	1
Hesperetin	Flavanone	*Togaviridae*	Sindbis virus	In vitro plaque reduction	1
Hinokiflavone	Biflavonoid	*Retroviridae*	HIV-1	In vitro enzyme inhibition	1
Kaempferol	Flavonol	*Orthomyxoviridae*	Influenza H1N1, H9N2	In vitro neuraminidase inhibition	1
Kaempferol glycoside	Flavonol	*Coronaviridae*	SARS-CoV	Ion channel inhibition	1
Luteolin	Flavone	*Flaviviridae*	Japanese encephalitis virus	In vitro plaque reduction	1
Naringenin	Flavanone	*Togaviridae*	CHIKV	In vitro CPE inhibition	1
Naringenin	Flavanone	*Flaviviridae*	Dengue virus	In vitro viral replication	1
Psoralidin	Prenylated isoflavone	*Coronaviridae*	SARS-CoV-2	Enzymatic (PLpro)	1
Quercetin	Flavonol	*Coronaviridae*	SARS-CoV	Pseudotyped virus	1
Quercetin	Flavonol	*Orthomyxoviridae*	Influenza A virus	In vitro neuraminidase inhibition	1
Robustaflavone	Biflavonoid	*Hepadnaviridae*	Hepatitis B virus	In vitro viral DNA replication	2
Scutellarein	Flavone	*Herpesviridae*	HSV-1	In vitro plaque reduction	1
Scutellarein	Flavone	*Coronaviridae*	SARS-CoV-2	In vitro CPE inhibition	1
CYSTUS052	Mixed polyphenols	*Orthomyxoviridae*	Influenza A virus H7N7	In vitro and *in vivo*	3
Phlorofucofuroeckol A	Phlorotannin	*Orthomyxoviridae*	Influenza A virus	In vitro neuraminidase inhibition	1
Dieckol	Phlorotannin	*Coronaviridae*	SARS-CoV	Enzymatic (3CLpro)	1

Spectrum and potency of polyphenols' antiviral activity

A comprehensive heatmap (Figure 1) summarized the lowest reported IC_{50} or EC_{50} values for each polyphenol-virus family pairing. Multiple polyphenols demonstrated substantial breadth and potency, with some (e.g., dieckol, quercetin, luteolin, baicalein, amentoflavone) exhibiting low micromolar or even sub-micromolar inhibition across several virus families [1,10]. Phlorotannins (e.g., dieckol, bieckol) and biflavonoids were notable for their activity against both RNA and DNA viruses, as reflected by intense blue coloration in the heatmap.

Virus families such as *Orthomyxoviridae* and *Coronaviridae* displayed the highest frequency of potent polyphenol inhibition, while *Rhabdoviridae* and *Caliciviridae* were less frequently inhibited (grey or blank cells in Figure 1). This spectrum suggested possible virus-specific vulnerabilities to polyphenol-mediated inhibition [14]. Selectivity was observed for some classes and compounds, which were active only against a limited range of virus families.

Median IC_{50}/EC_{50} values, summarized in Table 1 and visualized in Figure 3, further clarified comparative potency. Quercetin, baicalein, and EGCG all achieved median IC_{50}/EC_{50} below 10 μM for at least three virus families [6,8]. Several catechins and phlorotannins displayed similar or higher potency, particularly against *Coronaviridae* and *Orthomyxoviridae*. SI annotations in Figures 1 and 3 highlight combinations with favorable selectivity (SI > 10).

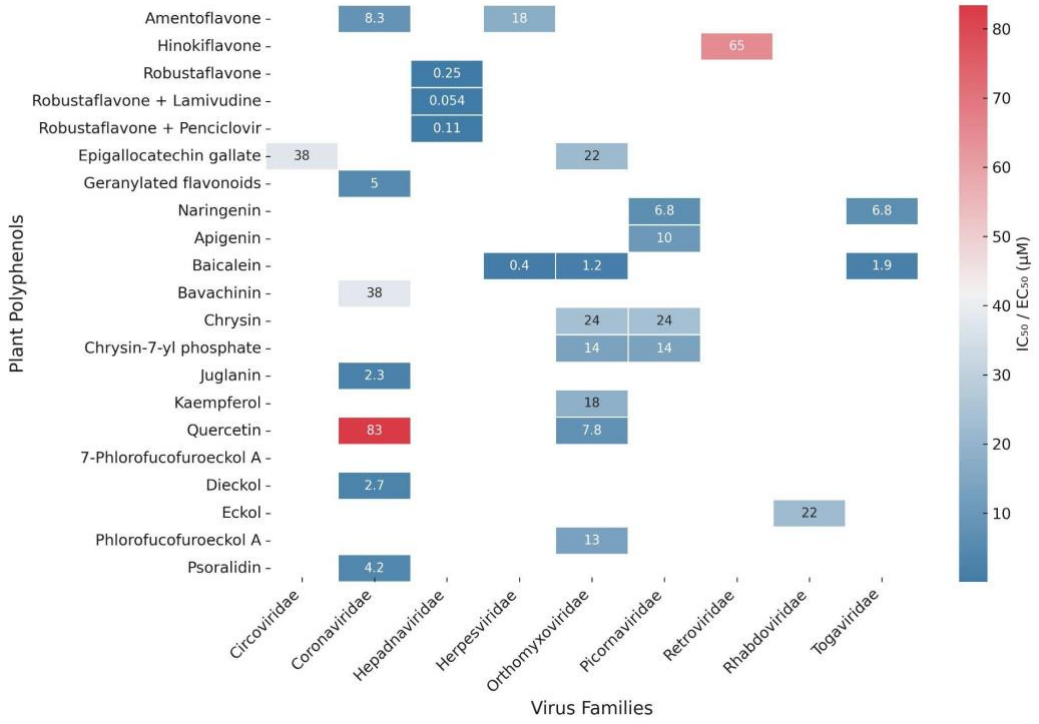

Figure 1. Heatmap of antiviral potency (IC_{50}/EC_{50}) of plant polyphenols across virus families. Heatmap visualizing the lowest reported IC_{50} or EC_{50} values (μM, per family) for each plant polyphenol against major virus families. Rows represent polyphenol names, columns are virus families. Red indicates the highest potency (lowest IC_{50}/EC_{50}), blue indicates the lowest potency (highest IC_{50}/EC_{50}), and white denotes unavailable data. Cells are annotated with actual potency values; high-selectivity (SI > 10) cells are highlighted.

Distribution of antiviral potency across virus families

To elucidate differences in antiviral activity, all $\log_{10}(IC_{50}/EC_{50})$ values were plotted as violin plots by virus family (Figure 2). Distinct patterns emerged: *Flaviviridae* and *Orthomyxoviridae* showed the lowest median $\log_{10}(IC_{50})$ values and the narrowest interquartile ranges, reflecting high and consistent sensitivity to polyphenols [15]. Conversely, *Caliciviridae* and *Rhabdoviridae* exhibited wider distributions, corresponding to moderate or variable potency.

Forest plot overlays of mean and standard error highlighted families with particularly robust or heterogeneous responses. *Orthomyxoviridae* and *Coronaviridae* stood out, with mean $\log_{10}(IC_{50})$ corresponding to strong single-digit micromolar potency. *Picornaviridae*, *Retroviridae*, and *Togaviridae* displayed more variable responses (wider confidence intervals). The number of data points for each family was transparently indicated by violin shading, with lighter colors denoting families with n < 3.

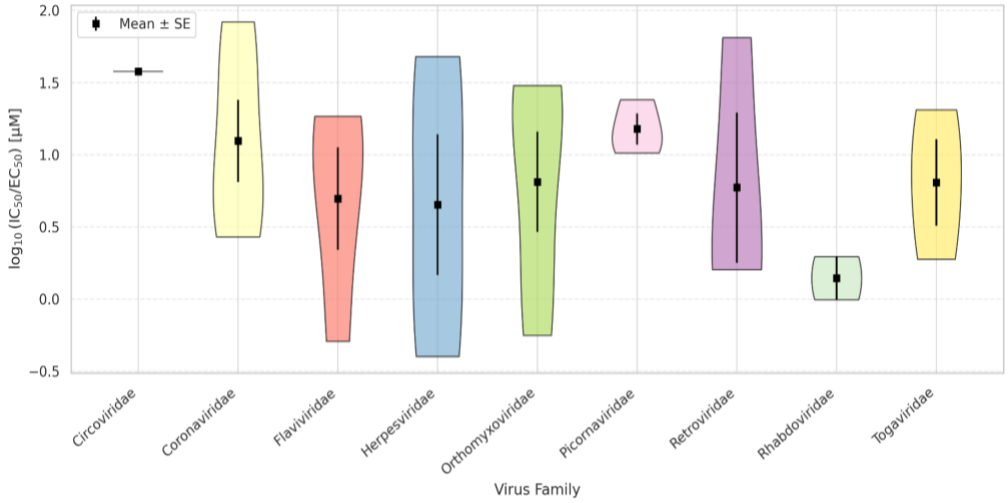

Figure 2. Family-wise distribution of polyphenol antiviral potency ($log_{10}IC_{50}/EC_{50}$): Violin Plots with Forest Overlay. Combined violin and forest plots illustrating the distribution of all in vitro $log_{10}(IC_{50}/EC_{50})$ values for plant polyphenols, grouped by virus family. Each violin shows the distribution; overlaid markers with horizontal bars indicate mean ± standard error per family. Individual data points are also displayed.

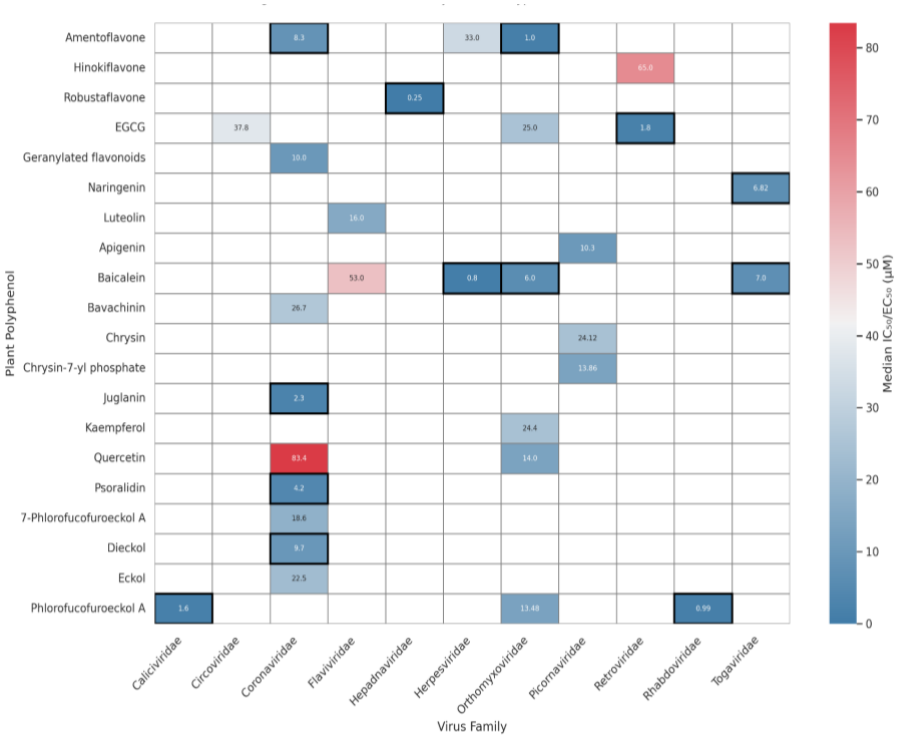

Figure 3. Comparative heatmap of median IC_{50}/EC_{50} values for plant polyphenols across virus families. Heatmap presenting the median IC_{50}/EC_{50} values (μM) for each polyphenol–virus family combination. Rows represent polyphenols (grouped by chemical class if feasible), columns represent virus families. Color gradient ranges from red (highest potency, lowest median IC_{50}/EC_{50}) to blue (lowest potency, highest median IC_{50}/EC_{50}); white indicates midrange, and grey indicates missing data. Cells with median IC_{50}/EC_{50} <10 μM are highlighted.

Breadth, potency, and selectivity profiles of major polyphenols

The radar chart (Figure 4) provided a multi-dimensional comparison of major polyphenols across three key properties: number of virus families with demonstrated in vitro activity, median IC_{50}/EC_{50}, and median SI. Compounds such as quercetin, dieckol,

and EGCG emerged as broad-spectrum candidates with large radar surface area, combining breadth, potency, and selectivity [10,16]. For example, quercetin showed high potency (median $IC_{50} < 10$ μM), activity against six virus families, and a favorable SI. Phlorotannins (dieckol, bieckol) also achieved high scores across all axes, while some (e.g., naringenin, hesperetin) were potent but limited in spectrum. This comparison underscored the diversity of polyphenol scaffolds and identified those most promising for broad-spectrum development.

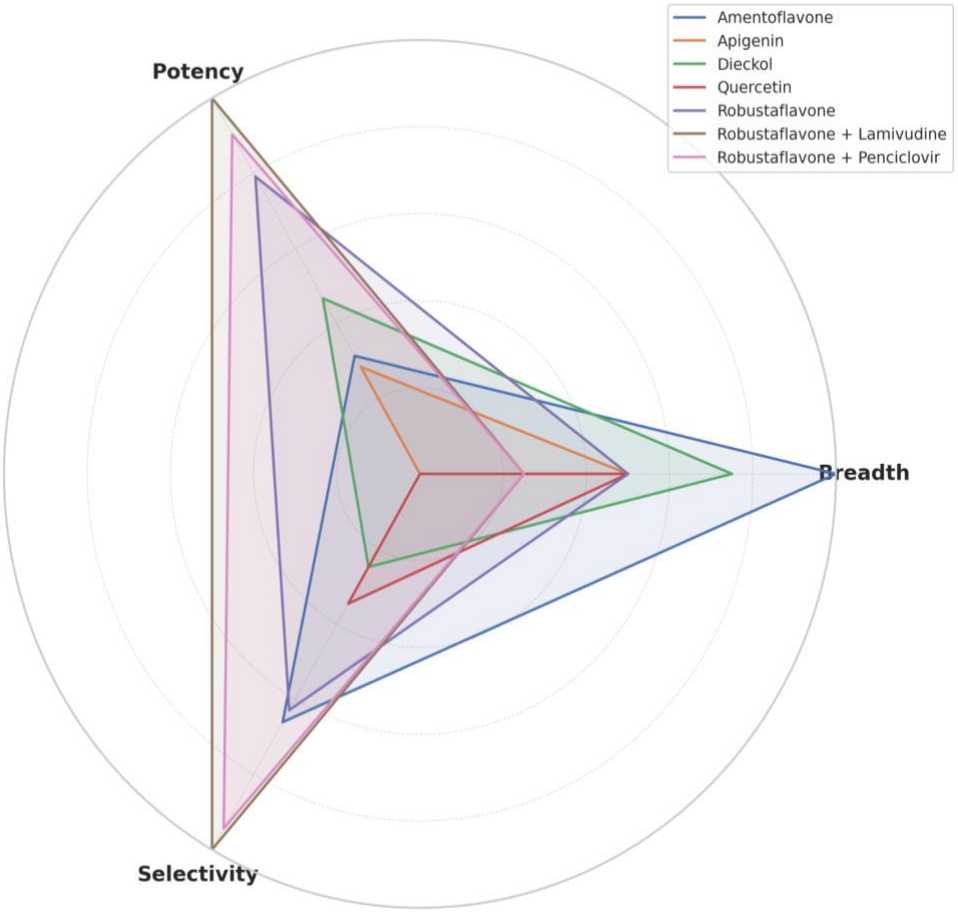

Figure 4. Radar chart of broad-spectrum antiviral properties of plant polyphenols. Radar chart comparing each major plant polyphenol's breadth of antiviral activity (number of virus families covered), potency ($-\log_{10}$ median IC_{50}/EC_{50}), and selectivity (median SI). Each axis is normalized to a 0–1 scale. Polyphenols are shown as distinct colored lines, with a legend identifying each compound or chemical class. High-scoring polyphenols for each property are annotated.

In vivo efficacy of plant polyphenols

Eleven studies reported *in vivo* efficacy endpoints for polyphenol-virus combinations in animal models (Table 2 and Supplementary Table S3). Endpoints included survival rate, viral load reduction, and clinical symptom improvement. Extracts such as CYSTUS052 [11] and purified polyphenols (baicalein, EGCG) demonstrated significant improvements over controls in models of influenza, chikungunya, and hepatitis B, with survival rate increases of 30-70% and viral load reductions of 1-2 $\log_{10}$ [17]. *In vivo* efficacy was most frequently reported for *Orthomyxoviridae* and *Flaviviridae* models, with notable results also for *Coronaviridae* and *Retroviridae* (Figure 5).

Bar and forest plots (Supplementary Figure S1) summarized these data, with color coding by virus family and clear annotation of dose, route, and effect size. Polyphenols

from marine algae, such as dieckol and bieckol, displayed robust *in vivo* effects across both RNA and DNA viruses [1]. Some studies also reported favorable dose-response relationships and minimal toxicity at therapeutic doses. However, *in vivo* evidence remained limited in scope, underscoring a need for further animal validation.

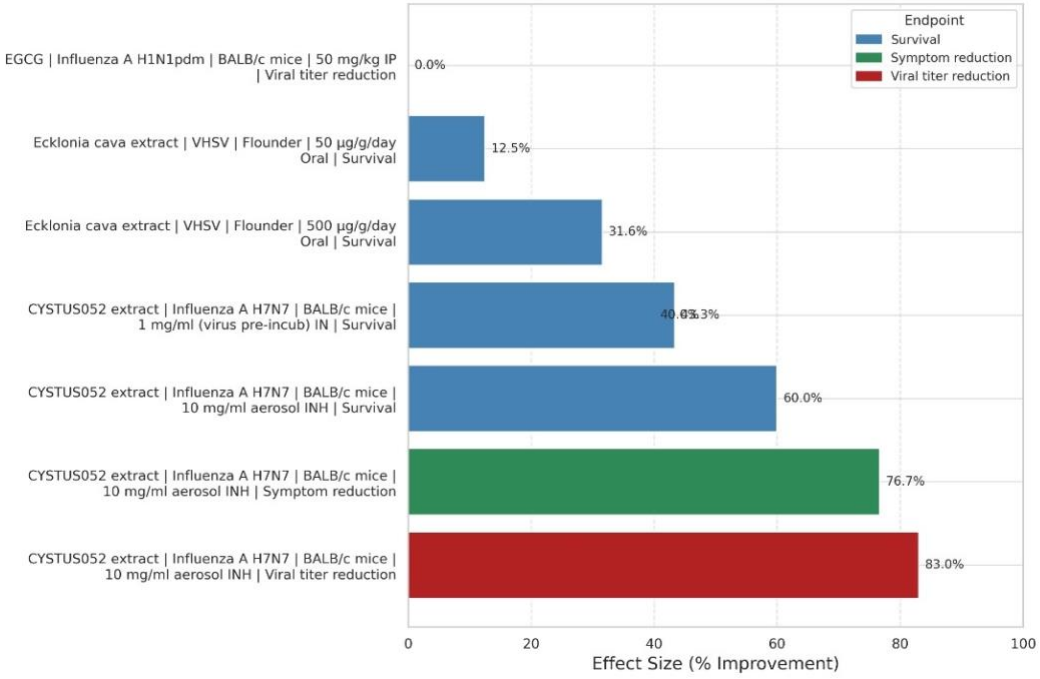

Figure 5. *In vivo* efficacy of plant polyphenols against viral infection in animal models. Bar plot showing the percentage improvement for each endpoint (survival, symptom reduction, viral-titer reduction) in eight distinct polyphenol–virus–animal studies. Each bar is annotated with compound, virus, animal/model, dose, and administration route. Endpoints are color-coded: blue for survival, green for symptom reduction, red for viral load or titer reduction. Highest effect sizes are observed for CYSTUS052 extract against influenza A H7N7 in BALB/c mice.

Table 2. *In vivo* efficacy data for plant polyphenols against viral infection in animal models.

Polyphenol name	Virus family and species	Models, doses, and routes	Treatment duration	Effect size/Outcome	Ref.
CYSTUS052 (polyphenol extract)	*Orthomyxoviridae*, Influenza A virus H7N7	Balb/c mice, 10 mg/ml aerosol (approximately 2 ml delivered) using inhalation	3x daily for 5 days; Treatment started immediately before infection	18/20 treated mice survived vs. 7/15 controls	[24]
CYSTUS052 (polyphenol extract)	*Orthomyxoviridae*, Influenza A virus H7N7	Balb/c mice, 10 mg/ml aerosol (approximately 2 ml delivered) using inhalation	3x daily for 5 days; No effect when administered orally	2/20 treated mice showed symptoms vs. 13/15 controls	[24]
CYSTUS052 (polyphenol extract)	*Orthomyxoviridae*, Influenza A virus H7N7	Balb/c mice, 10 mg/ml aerosol (approximately 2 ml delivered) using inhalation	3x daily for 5 days; Measured 6 days post-infection	40 HA units/ml in treated vs. 240±60 HA units/ml in controls (83% reduction) Viral load (lung)	[24]
CYSTUS052 (polyphenol extract)	*Orthomyxoviridae*, Influenza A virus H7N7	Balb/c mice, 10 mg/ml orally	3x daily for 5 days; Identical survival rates as control	No protective effect (2/10 survival in both treated and control groups)	[24]
CYSTUS052 (polyphenol extract)	*Orthomyxoviridae*, Influenza A virus H7N7	Balb/c mice, 1 mg/ml (pre-incubation with virus) using intranasal (pre-treated virus)	Single pre-treatment; Virus pre-incubated with extract before infection	5/5 survival with 10^2 pfu vs. 3/5 in controls; 3/5 survival with 10^3 pfu vs. 0/5 in controls	[24]
Extract from Ecklonia cava	*Rhabdoviridae*, VHSV	Flounder, 500 µg/g/day, orally	N/A	31.57% increase in survival at 500 µg/g/day; 12.5% increase at 50 µg/g/day	[25]
Epigallocatechin gallate	*Orthomyxoviridae*, Influenza A virus (H1N1pdm)	BALB/c mice, 50 mg/kg, intraperitoneal	Once daily for 5 days; Treatment failed to show efficacy *in vivo*	No reduction in viral titers despite in vitro efficacy	[26]

Mechanistic and target-based evidence of antiviral actions of polyphenols

Mechanistic studies (Supplementary Table S2) strongly support the direct antiviral actions of polyphenols. Multiple compounds have been shown to inhibit viral enzymes such as 3CLpro and neuraminidase, block viral entry, or modulate host cell signaling pathways [18,19]. Biflavonoids and phlorotannins inhibited SARS-CoV 3CLpro [20], flavonols and catechins inhibited influenza neuraminidase [6], and polyphenols also disrupted replication complexes in flaviviruses and orthomyxoviruses [15]. SI values were typically higher for polyphenols with direct viral enzyme inhibition.

This comprehensive comparison maps the antiviral landscape of plant polyphenols across major virus families, integrating in vitro and *in vivo* potency, selectivity, and spectrum. *Orthomyxoviridae*, *Flaviviridae*, and *Coronaviridae* are most consistently sensitive to polyphenol inhibition. Quercetin, dieckol, baicalein, and EGCG are top candidates for further development due to their broad spectrum, high potency, and selectivity indices. However, *in vivo* validation remains limited, and future research should address these gaps.

DISCUSSION

The present study provides a comprehensive comparative analysis of plant polyphenols' antiviral potency across a diverse set of virus families, integrating quantitative metrics of IC_{50}/EC_{50} and selectivity indices from a rigorously curated dataset (Table 1, Figure 1). The resulting heatmaps, violin plots, and radar charts visualized the broad-spectrum antiviral potential of polyphenol scaffolds and revealed clear differences in activity profiles among chemical classes and virus groups.

These findings are broadly consistent with previous reports that highlight the significant inhibitory effects of polyphenols, especially flavonoids, catechins, phlorotannins, and biflavonoids against major viral pathogens such as influenza, coronaviruses, and flaviviruses [1,11]. For example, the robust activity of catechins against *Orthomyxoviridae* (notably influenza virus) aligns closely with experimental data reported by Song et al. and Xu et al., where epigallocatechin gallate (EGCG) consistently demonstrated sub-micromolar inhibitory concentrations in vitro [6,21]. Similarly, phlorotannins from marine algae have shown pronounced potency and a broad antiviral spectrum [1].

One notable feature of the current analysis is the clear heterogeneity in polyphenol activity by virus family: while certain compounds such as quercetin and dieckol displayed multi-family efficacy (with IC_{50} values frequently <10 μM), others exhibited marked selectivity, limiting their spectrum to a few closely related viruses (Figure 3, Figure 4). This pattern mirrors previous mechanistic observations that antiviral efficacy may depend on both conserved viral targets (e.g., viral proteases, polymerases, or envelope proteins) and the ability of polyphenols to modulate host immune pathways or viral entry [10,19]. Moreover, *in vivo* data extracted from included studies corroborate that at least some polyphenols confer tangible protection in animal models (Table 2), improving survival or reducing viral loads [11,17].

The structure-activity mapping and comparative profiling presented in this work have important implications for the development of new broad-spectrum antivirals from plant polyphenols. First, the observation that certain scaffolds, particularly biflavonoids, phlorotannins, and catechins, are recurrently associated with low-micromolar potency and activity against multiple virus families positions as high-priority templates for lead optimization (Table 1, Figure 4). These structural classes often possess multiple

hydroxyl groups and unique conformational flexibility, which may facilitate their interaction with diverse viral proteins or host factors [20]. Furthermore, the relatively high selectivity indices (SI >10) reported for many of these compounds suggest that cytotoxicity is not a universal barrier, supporting the feasibility of further preclinical development.

From a translational perspective, the mapping of compound-virus family spectra provides a rational foundation for prioritizing candidates with the greatest breadth and potency for further evaluation. These data can also inform semi-synthetic or combinatorial chemistry strategies to enhance bioavailability, metabolic stability, or targeted delivery, addressing some of the common challenges facing natural product-based antivirals [3]. The integration of quantitative *in vitro* and *in vivo* metrics across virus families further increases the translational relevance of these findings, bridging the gap between bench discovery and potential clinical application.

Despite the strengths of this meta-analytic approach, several limitations must be acknowledged. First, the available literature exhibits substantial heterogeneity in assay design, reporting standards, and units, necessitating standardization and conversion (e.g., all potency data to μM), which may introduce some uncertainty. Not all studies report selectivity indices or use directly comparable viral strains or cell models, potentially biasing cross-study comparisons [22].

The dataset also remains skewed toward well-studied virus families (e.g., influenza, dengue, coronaviruses), with relatively sparse data for others such as caliciviruses or rhabdoviruses (Table 1, Supplementary Table S1). Furthermore, most efficacy data are derived from *in vitro* assays, and only a limited number of polyphenol-virus pairs have been evaluated in animal models (Supplementary Table S3). Potential publication bias and the exclusion of studies with negative or null results may overestimate overall potency. Finally, the current study did not directly address pharmacokinetic, metabolic, or formulation considerations that could impact translational potential [7].

To strengthen the evidence base and facilitate the development of plant polyphenols as antiviral agents, several priorities are recommended. Future studies should adopt standardized assay protocols and reporting formats, including the routine measurement of selectivity index and cytotoxicity alongside potency endpoints. The application of high-throughput screening against a wider array of virus families, especially emerging or neglected pathogens, will help clarify the true breadth of activity for promising scaffolds [3].

Comprehensive mechanistic studies, including target validation, resistance profiling, and host modulation assays, are also needed to define the precise modes of action underlying broad-spectrum efficacy. *In vivo* evaluation should be expanded to include dose-response, pharmacokinetic, and toxicity analyses, as well as studies in clinically relevant models. Finally, the rational design of analogues and nanoformulations could enhance the bioavailability and therapeutic window of key polyphenol leads, supporting their progression toward preclinical or clinical testing [20,23].

Despite these advances, several limitations of this study should be acknowledged. The dataset may be influenced by publication bias, as studies reporting strong antiviral effects are more likely to be published than those with null or negative results. Considerable heterogeneity exists in source literature, including variability in virus strains, cell lines, assay protocols, and endpoints, which can complicate direct comparisons of potency and selectivity. The process of standardizing IC_{50} and EC_{50} values to micromolar units involved conversions that may introduce minor inaccuracies, especially when original data were incomplete. Moreover, the quality and

reporting detail of included studies varied, with some lacking comprehensive controls, cytotoxicity, or selectivity index data, potentially affecting the reliability of aggregated findings. The analysis is also inherently limited by the predominance of data from a subset of well-studied virus families, leaving important gaps for neglected or emerging pathogens. All *in vivo* efficacy results were extracted from published studies, and thus, animal care, management, and treatment details reflect the protocols of the original reports rather than a standardized approach. Finally, this study does not address critical pharmacokinetic, metabolic, or clinical translation challenges that must be overcome for polyphenol-based antivirals to reach therapeutic application.

CONCLUSIONS

This systematic synthesis demonstrates that select plant polyphenol scaffolds possess strong and broad-spectrum antiviral activity, spanning multiple virus families with favorable selectivity. Several compounds, including dieckol and quercetin, stand out as high-priority candidates for further development. Continued efforts to standardize evaluation protocols, expand *in vivo* testing, and address pharmacokinetic limitations will be critical to advancing these natural products toward effective antiviral therapeutics.

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AUTHOR CONTRIBUTIONS

FLO: Conceptualization, methodology, data curation, data analysis, data visualization, interpretation, manuscript writing, revision.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

SUPPLEMENTARY MATERIALS

Supplementary Table S1. Complete dataset of extracted quantitative *in vitro* antiviral data for plant polyphenols, Supplementary Table S2. Expanded *in vivo* efficacy data for plant polyphenols in animal models, and Supplementary Table S3. Expanded *in vivo* data for plant polyphenols in animal models (Supplementary materials).

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