J Herbmed Pharmacol. 2025; 14(3): 292-301.

http://www.herbmedpharmacol.com doi: 10.34172/jhp.2025.53076

Journal of Herbmed Pharmacology

Plant-derived tannins as anti-herpes simplex agents: A systematic review of *in vitro* evidence, molecular mechanisms, and therapeutic potential

Alizamen Salehifard Jouneghani[1], Dhiya Altememy[2], Majid Asadi-Samani[3*], Mohammad-Taghi Moradi[4*]

[1]Department of Pediatrics, College of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Department of Pharmaceutics, College of Pharmacy, Al-Zahraa University for Women, Karbala, Iraq
[3]Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran
[4]Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

ARTICLE INFO

Article Type:
Review

Article History:
Received: 20 Dec. 2024
Revised: 20 Mar. 2025
Accepted: 31 Mar. 2025
epublished: 1 Jul. 2025

Keywords:
Biological products
Tannins
Herpes simplex virus
Viral replication inhibitors

ABSTRACT

Introduction: The herpes simplex virus (HSV), a double-stranded DNA virus, establishes persistent infections and frequently reactivates. While acyclovir and its derivatives remain first-line therapies, the emergence of drug-resistant HSV strains highlights an urgent need for alternative antiviral agents. Tannins, plant-derived polyphenolic compounds, have demonstrated potent in vitro antiviral activity against HSV. This review synthesizes current evidence on the anti-HSV properties of tannins, with emphasis on their mechanisms of actions.

Methods: We systematically searched PubMed, ScienceDirect, Scopus, Chemical Abstracts, Google Scholar, and the Cochrane Library (1985–December 2024) using the keywords "Herpes simplex virus," "HSV," "antiviral," and "tannin."

Results: Thirty-seven tannins from diverse botanical sources were identified in vitro for anti-HSV activity, with efficacy assessed via selectivity index (SI). Thirty-five compounds inhibited HSV-1, among which pentagalloylglucose, tannic acid, and castalagin exhibited the strongest effects. Eight tannins showed anti-HSV-2 activity, with chebulagic acid and chebulinic acid being most potent. Four compounds were tested against acyclovir-resistant strains, and pentagalloylglucose emerged as the most effective. Mechanistic studies revealed that tannins disrupt viral attachment, penetration, and membrane fusion, while also targeting key viral enzymes and structural proteins essential for replication and assembly.

Conclusion: Tannins represent promising candidates for novel antivirals, particularly against acyclovir-resistant HSV. Further research is warranted to elucidate their mechanisms and translate these findings into clinical applications.

Implication for health policy/practice/research/medical education:
This systematic review highlights the therapeutic potential of tannin-rich herbal extracts as complementary or alternative treatments for herpes simplex virus (HSV) infections in clinical settings. Given their ability to inhibit viral replication and alleviate cytopathic effects, tannins may serve as natural antiviral agents to reduce lesion severity, recurrence frequency, and drug resistance in patients. The study supports future development of standardized, plant-based topical or oral formulations that could be integrated into HSV management protocols, especially for individuals with acyclovir-resistant strains or seeking phytotherapeutic options.

Please cite this paper as: Salehifard Jouneghani AZ, Altememy D, Asadi-Samani M, Moradi MT. Plant-derived tannins as anti-herpes simplex agents: A systematic review of in vitro evidence, molecular mechanisms, and therapeutic potential. J Herbmed Pharmacol. 2025;14(3):292-301. doi: 10.34172/jhp.2025.53076.

Introduction

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are the members of the Herpesviridae family, Alphaherpesvirinae subfamily, and *Simplexvirus* genus (1). HSV-1 and HSV-2 are highly prevalent among humans, infecting approximately 70% and 10% of the global

***Corresponding authors**: Majid Asadi-Samani, Email: asadi.m@skums.ac.ir; Mohammad-Taghi Moradi, Email: mtmoradi65@gmail.com

population, respectively (2,3). HSV-1 is mainly associated with infections of the oral cavity, pharynx, face, eyes, and central nervous system (CNS), whereas HSV-2 primarily causes genital infections. However, both serotypes are capable of infecting multiple anatomical regions (4). Genital herpes caused by HSV-2 is a significant sexually transmitted disease that often results in recurrent, painful lesions and can have serious psychosocial implications, including anxiety, depression, and social stigma. Moreover, HSV-2 infection has been identified as a co-factor increasing susceptibility to HIV and the risk of invasive cervical carcinoma (5). HSV has also been implicated in various ocular diseases such as stromal keratitis, endotheliitis, and neurotrophic keratopathy (6).

The current standard treatment of HSV infections primarily involves acyclovir (ACV) and its analogs. Despite their efficacy, prolonged use has led to the emergence of drug-resistant HSV strains and undesirable side effects (7,8). Consequently, there is an urgent need to identify novel antiviral agents with alternative mechanisms of action to overcome drug resistance. Natural compounds, particularly those derived from medicinal plants, have attracted increasing attention due to their chemical diversity and bioactivity (9).

Medicinal plants are rich sources of secondary metabolites such as flavonoids, polyphenols, saponins, alkaloids, and glycosides, many of which have demonstrated promising anti-HSV properties (10). Among these, tannins, a major group of polyphenols, have gained particular interest due to their structural complexity and biological potency. Tannins are high-molecular-weight compounds capable of forming stable complexes with proteins and carbohydrates through multiple hydroxyl groups, which distinguishes them from other polyphenols (11). Traditionally, tannins are classified into hydrolyzable tannins and condensed tannins (proanthocyanidins), with further subcategories including gallotannins, ellagitannins, complex tannins, and phlorotannins (12). In plants, tannins serve as defensive compounds against pathogens, herbivores, and environmental stressors. Their broad spectrum of biological activities has led to their exploration in medical, pharmaceutical, and veterinary contexts (13). Several in vitro studies have demonstrated that tannins possess antiviral activity against a range of viruses, including enteroviruses, caliciviruses, rotaviruses, influenza virus, rhabdoviruses, paramyxoviruses, HIV, adenoviruses, and notably, HSV. Although the exact antiviral mechanisms of tannins remain to be fully elucidated, proposed modes of action include inhibition of viral adsorption, prevention of viral entry into host cells, and suppression of viral replication enzymes such as reverse transcriptase (14).

This review aims to compile and analyze the current body of evidence regarding the anti-HSV effects of tannins derived from natural sources, with a particular focus on their mechanisms of action. By shedding light on these phytochemicals, we seek to support the development of novel, plant-based antiviral therapies, especially for treating ACV-resistant HSV strains.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews guidelines to ensure methodological transparency and reproducibility. A comprehensive literature search was performed to identify in vitro studies evaluating the antiviral effects of tannins against HSV.

We systematically searched the following electronic databases: PubMed, ScienceDirect, Scopus, Chemical Abstracts Service, Google Scholar, and the Cochrane Library, covering all articles published up to December 2024. The search strategy involved combinations of the following keywords: "Herpes simplex virus", "HSV", "antiviral", and "tannin". Boolean operators (AND, OR) were used to optimize the retrieval of relevant literature.

To ensure the inclusion of high-quality and comparable studies, we applied the following eligibility criteria:

- Inclusion criteria
  - Studies published in English.
  - In vitro experimental studies investigating the antiviral activity of tannins against HSV-1 and/or HSV-2.
  - Articles reporting relevant antiviral efficacy parameters, such as 50% cytotoxic concentration (CC_{50}) and 50% inhibitory/effective concentration (IC_{50} or EC_{50}).
- Exclusion criteria
  - Review articles, editorials, and conference abstracts without original data.
  - Studies lacking sufficient experimental detail or missing quantitative antiviral efficacy data (e.g., lacking CC_{50} or IC_{50}/EC_{50} values).
  - Non-English publications.

Additionally, the reference lists of the selected articles were manually screened to identify any relevant studies not retrieved during the initial database search. Duplicate articles were removed using reference management software, and remaining records were screened by title and abstract, followed by full-text evaluation (Figure 1).

Two independent reviewers conducted the screening and data extraction processes. Discrepancies were resolved through discussion or consultation with a third reviewer.

Results

A total of 905 titles were collected on academic databases. After applying the selection criteria, 58 full-text articles were screened for eligibility; 38 articles were retained for a final review. Figure 1 shows a PRISMA flow diagram depicting the screening procedures and search results.

The anti-HSV activities of various tannins were evaluated in vitro, focusing on their efficacy and selectivity index

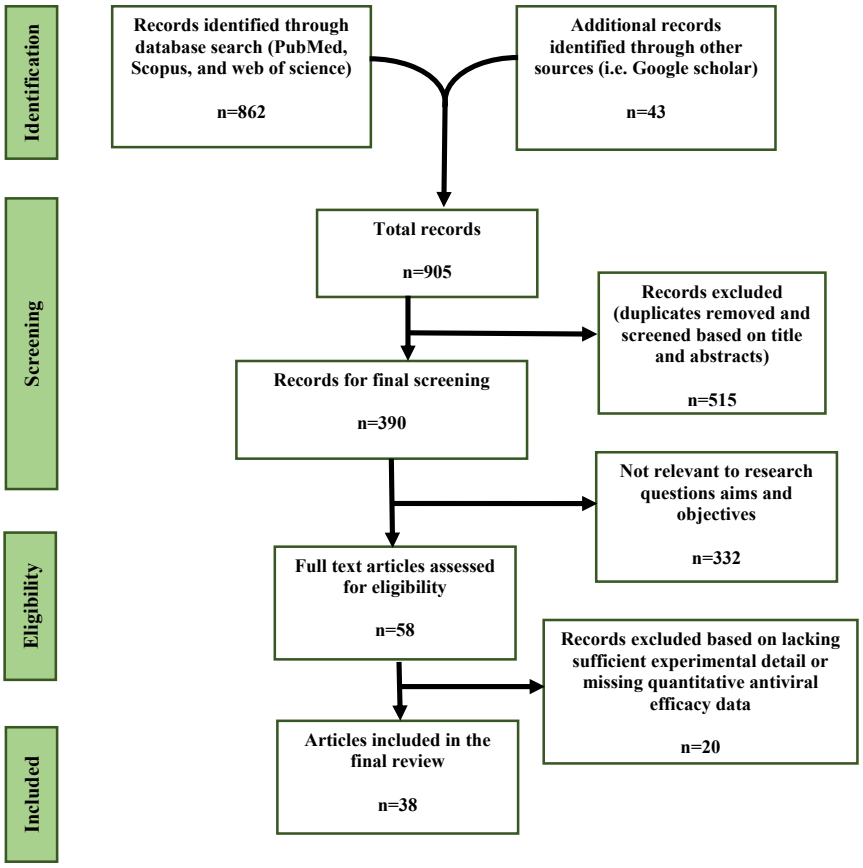

Figure 1. Flow diagram of the study.

(SI). The results, summarized in Table 1, highlight the potential of tannins derived from different plant sources in inhibiting HSV infection (15-27). In Figure 2, the structure of the most important tannins affecting HSV is presented.

Casuarinin from *Terminalia arjuna* (ellagitannin class) exhibited significant activity against HSV-2, with an IC_{50} value of 3.6 μM and an SI value of 25, targeting viral attachment and penetration (15). Gallotannins, such as pentagalloylglucose from *Phyllanthus emblica*, demonstrated potent antiviral effects against multiple HSV-1 strains (IC_{50} values between 3.13 μM and 7.96 μM), with a significant SI > 100. Their antiviral mechanisms linked to the inhibition of nuclear transport and nucleocapsid egress (22,24). Ellagitannins from *Quercus robur*, including castalagin and vescalagin, showed substantial anti-HSV-1 and -2 activities, with IC_{50} values ranging from 0.058 μM to 1.4 μM, suggesting strong potential as antiviral agents (26,27). The SI for these tannins was notably high (up to 681), indicating their selective toxicity against the virus compared to host cells.

Discussion

Ethnomedicinal plants have long served as valuable sources of potential drug candidates for various diseases. Despite the availability of antiviral drugs, their long-term efficacy is often limited by the emergence of viral resistance, along with concerns regarding side effects, disease recurrence, and viral latency. Many ethnomedicinal plants exhibit promising antiviral properties, with overlapping mechanisms of action that target viral replication and genome synthesis. Consequently, there is an urgent need to develop novel antiviral agents derived from natural sources. This systematic review highlights recent advances in the study of tannins with anti-HSV activity and provides insights into their therapeutic potential.

Ellagitannin geraniin demonstrates virucidal effects against herpesviruses (23,28) and inhibits HSV adsorption (17,29). Similarly, the hydrolyzable tannin casuarinin, isolated from *Terminalia arjuna* Linn., prevents HSV-2 attachment and cellular penetration while also disrupting late-stage infection (15). Chebulagic acid and punicalagin, two hydrolyzable tannins derived from *Terminalia chebula* Retz., inactivate HSV-1 entry and cell-to-cell spread by targeting HSV-1 glycoproteins (20). Putranjivain A, isolated from *Euphorbia jolkini,* inhibits viral entry and late-stage HSV-2 replication in vitro (25). Additionally, three ellagitannins gallic acid, ellagic acid, and punicalagin—exhibit antiviral activity against HSV-1, with punicalagin demonstrating the most potent concentration-dependent reduction in viral plaque formation. Punicalagin also suppresses HSV-1 replication

Table 1. The characteristics and in vitro anti-herpes simplex virus activities of tannins

Tannin name	Tannin class	Source	Type of the virus	CC50 (μg/mL; μM)	IC50 or EC50 (μg/mL; μM)	SI	Mechanism of action	Reference
Casuarinin	Ellagitannin	*Terminalia arjuna* Linn.	HSV-2	89 μM	3.6μM	25	Viral attachment and penetration	(15)
Punicalagin	Ellagitannin	*Punica granatum*	HSV-1	29.51 μg/mL	7.97μg/mL	3.69	-	(16)
Gallic acid	Ellagitannin	*Punica granatum*	HSV-1	19.38 μg/m	10.93 μg/m	1.77	-	
Tannic acid	Gallotannin	-	HSV-1/HF	18 μg/mL	0.034 μg/mL	529	-	(17)
Oenothein B	Ellagitannin	*Oenothera erythrosepala* Borbas	HSV-1/HF	>30 μg/mL	0.036 μg/mL	>833		
Coriariin A	Ellagitannin	*Coriaria japonica* A.	HSV-1/HF	>30 μg/mL	0.038 μg/mL	>789		
Rugosin D	Ellagitannin	*Rosa rugosa* Thunb.	HSV-1/HF	>30 μg/mL	0.034 μg/mL	>882		
Cornusiin A	Ellagitannin	*Cornus officinalis* Sieb.	HSV-1/HF	>30 μg/mL	0.039 μg/mL	>769		
Tellimagrandin	Hydrolyzable tannins	*Casuarina stricta* Ait.	HSV-1/HF	>30 μg/mL	0.036 μg/mL	>833		
Casuarictin	Hydrolyzable tannins	*Casuarina stricta* Ait.	HSV-1/HF	>30 μg/mL	0.044 μg/mL	>681		
Geraniin	Hydrolyzable tannins	*Geranium thunbergii* Sieb.	HSV-1/HF	>30 μg/mL	0.093 μg/mL	>322		
Penta-O-galloyl-13-D-glucose	Gallotannin	-	HSV-1/HF	7 μg/mL	0.047 μg/mL	>148		
4,8-Tetramer of epicatechin gallate	Condensed tannin	*Saxifraga stolonifera* Meerb.	HSV-1/HF	>30 μg/mL	0.14 μg/mL	>820		
Chebulagic acid	Ellagitannin	*Terminalia chebula* Retz	HSV-2/G	>200 μg/mL	1.41 μg/mL	>141	-	(18)
Chebulinic acid	Ellagitannin	*Terminalia chebula* Retz	HSV-2/G	>200 μg/mL	0.06 μg/mL	>3000		
1,2,3,6-tetra-O-galloyl-β-D-glucopyranose	Hydrolysable tannins	*Cornus canadensis*	HSV-1	>25 μM	7 μM	>3.5	The absorption mode.	(19)
1,2,3,4,6-Penta-O-gal-loyl-β-D-glucopyranose	Hydrolysable tannin	*Cornus canadensis*	HSV-1	>25 μM	10 μM	>2.5	The absorption mode.	
Tellima-grandin I	Ellagitannin	*Cornus canadensis*	HSV-1	>25 μM	2.6 μM	>9.6	The absorption mode.	
Tellima-grandin II	Ellagitannin	*Cornus canadensis*	HSV-1	>25 μM	7 μM	>3.5	The absorption mode.	
Punicalagin	Ellagitannin	*Terminalia chebula* Retz.	HSV-1/KOS	318.8 μM	10.25 μM	31.1	Attachment and membrane fusion	(20)
Chebulagic acid	Ellagitannin	*Terminalia chebula* Retz.	HSV-1/KOS	316.8 μM	17 μM	18.6	Attachment and membrane fusion	
Chebulinic acid	Ellagitannin	*Terminalia chebula* Retz.	HSV-1/KOS	330.8 μM	20.8 μM	15.8	Attachment and membrane fusion	
Punicalin	Ellagitannin	*Terminalia chebula* Retz.	HSV-1/KOS	310.8 μM	21.3 μM	14.57	Attachment and membrane fusion	

Table 1. Continued

Tannin name	Tannin class	Source	Type of the virus	CC50 (μg/mL; μM)	IC50 or EC50 (μg/mL; μM)	SI	Mechanism of action	Reference
Castalin	Ellagitannin	-	HSV-1	163 μM	NA	-	-	(21)
Vescalin	Ellagitannins	-	HSV-1	118 μM	NA	-	-	
Epiacutissimin A	Ellagitannins	-	HSV-1	>1000 μM	18 μM	>55.5	-	
Epiacutissimin B	Ellagitannins	-	HSV-1	>1000 μM	16.5 μM	>60.6	-	
Acutissimin A	Ellagitannins	-	HSV-1	>640 μM	18.4 μM	>34.8	-	
Mongolicain	Ellagitannins	-	HSV-1	>640 μM	19.7 μM	32.5	-	
VgSBuSH	Ellagitannins	-	HSV-1	>640 μM	26 μM	>24.6	-	
VgSOctSH	Ellagitannins	-	HSV-1	324.5 μM	86.6 μM	3.7	-	
VgOMe	Ellagitannins	-	HSV-1	>640 μM	29 μM	>22	-	
α-glucogallin	Gallotannins	-	HSV-1	545 μM	124 μM	4.4	-	
β-glucogallin		-	HSV-1	632 μM	308 μM	2	-	
α/β-1-O-digalloyl-D-glucopyranose	Gallotannins	-	HSV-1	640 μM	192 μM	3.3	-	
1,2,3,4,5-penta-O-digalloyl-α-D-glucopyranose	Gallotannins	-	HSV-1	>200 μM	7 μM	>28.3	-	
1,2,3,4,5-penta-O-digalloyl-β-D-glucopyranose	Gallotannins	-	HSV-1	>100 μM	2.8 μM	>35.7	-	
α/β-3-O-digalloyl-D-glucopyranose	Gallotannins	-	HSV-1	610 μM	39 μM	15.6	-	
3,4,6-tris-O-digalloyl-1,2-O-isopropylidene-α-D-Glucofuranose	Gallotannins	-	HSV-1	34.5 μM	3.7 μM	9.3	-	
Commercial tannic acid	Gallotannins	-	HSV-1	>100 μM	4 μM	>25	-	
Pentagalloylglucose	Gallotannin	*Phyllanthus emblica*	HSV-1/F	611.3 μM	7.96 μM	76.79	Induction of autophagy	(22)
Geraniin	Ellagitannin	*Phyllanthus urinaria*	HSV-1/KOS	51.4 μM	35 μM	1.5	-	(23)
Geraniin	Ellagitannin	*Phyllanthus urinaria*	HSV-2/196	51.4 μM	18.4 μM	2.8	-	
Pentagalloylglucose	Gallotannin	*Phyllanthus emblica*	HSV-1	745 μM	4.12 μM	180.8	Down-regulating cofilin1	(22)

Table 1. Continued

Tannin name	Tannin class	Source	Type of the virus	CC50 (μg/mL; μM)	IC50 or EC50 (μg/mL; μM)	SI	Mechanism of action	Reference
Pentagalloylglucose	Gallotannin	*Phyllanthus emblica*	HSV-1/F	401.15 μM	3.13 μM	128	Inhibition of nuclear transport and nucleocapsid egress	(24)
Pentagalloylglucose	Gallotannin	*Phyllanthus emblica*	HSV-1/153*	401.15 μM	3.19 μM	125	Inhibition of nuclear transport and nucleocapsid egress	
Pentagalloylglucose	Gallotannin	*Phyllanthus emblica*	HSV-1/106*	401.15 μM	3.26 μM	123	Inhibition of nuclear transport and nucleocapsid egress	
Pentagalloylglucose	Gallotannin	*Phyllanthus emblica*	HSV-1/Blue*	401.15 μM	3.49 μM	114	Inhibition of nuclear transport and nucleocapsid egress	
Putranjivain A	Ellagitannin	*Euphorbia jolkinin* Bioss.	HSV-2/196	80.3 μM	6.3 μM	12.7	Inhibiting viral attachment and penetration	(25)
Castalagin	Ellagitannin	*Quercus robur*	HSV-1/ Victoria	39.5 μM	0.058 μM	681	--	(26)
Castalagin	Ellagitannin	*Quercus robur*	HSV-2/ Bja	39.5 μM	0.88 μM	44.8	-	
Vescalagin	Ellagitannin	*Quercus robur*	HSV-1/ Victoria	27 μM	0.18 μM	150	-	
Vescalagin	Ellagitannin	*Quercus robur*	HSV-2/ Bja	27 μM	0.94	28.7	-	
Grandinin	Ellagitannin	*Quercus robur*	HSV-1/ Victoria	36.6 μM	0.88 μM	41.5	-	
Grandinin	Ellagitannin	*Quercus robur*	HSV-2/ Bja	36.6 μM	0.78 μM	46.9	-	
Castalagin	Ellagitannin	*Quercus robur*	HSV-1/ R-100*	39.5 μM	1.1 μM	35.9	-	(27)
Castalagin	Ellagitannin	*Quercus robur*	HSV-2/PU*	39.5 μM	1.2 μM	32.9	-	
Vescalagin	Ellagitannin	*Quercus robur*	HSV-1/ R-100*	27 μM	1.4 μM	22.5	-	
Vescalagin	Ellagitannin	*Quercus robur*	HSV-2/PU*	27 μM	1.1 μM	19.3	-	
Grandinin	Ellagitannin	*Quercus robur*	HSV-1/ R-100*	36.6 μM	1.5 μM	24.4	-	
Grandinin	Ellagitannin	*Quercus robur*	HSV-2/PU*	36.6 μM	1.2 μM	30.5	-	

*ACV: resistant strains; IC50: 50% inhibition of viral cytopathic; EC50: 50% cytotoxic effective concentration; CC50: 50% concentration; SI: selectivity index (CC50/IC50 or EC50); -: its source has not been mentioned in the study, or it has been synthesized.

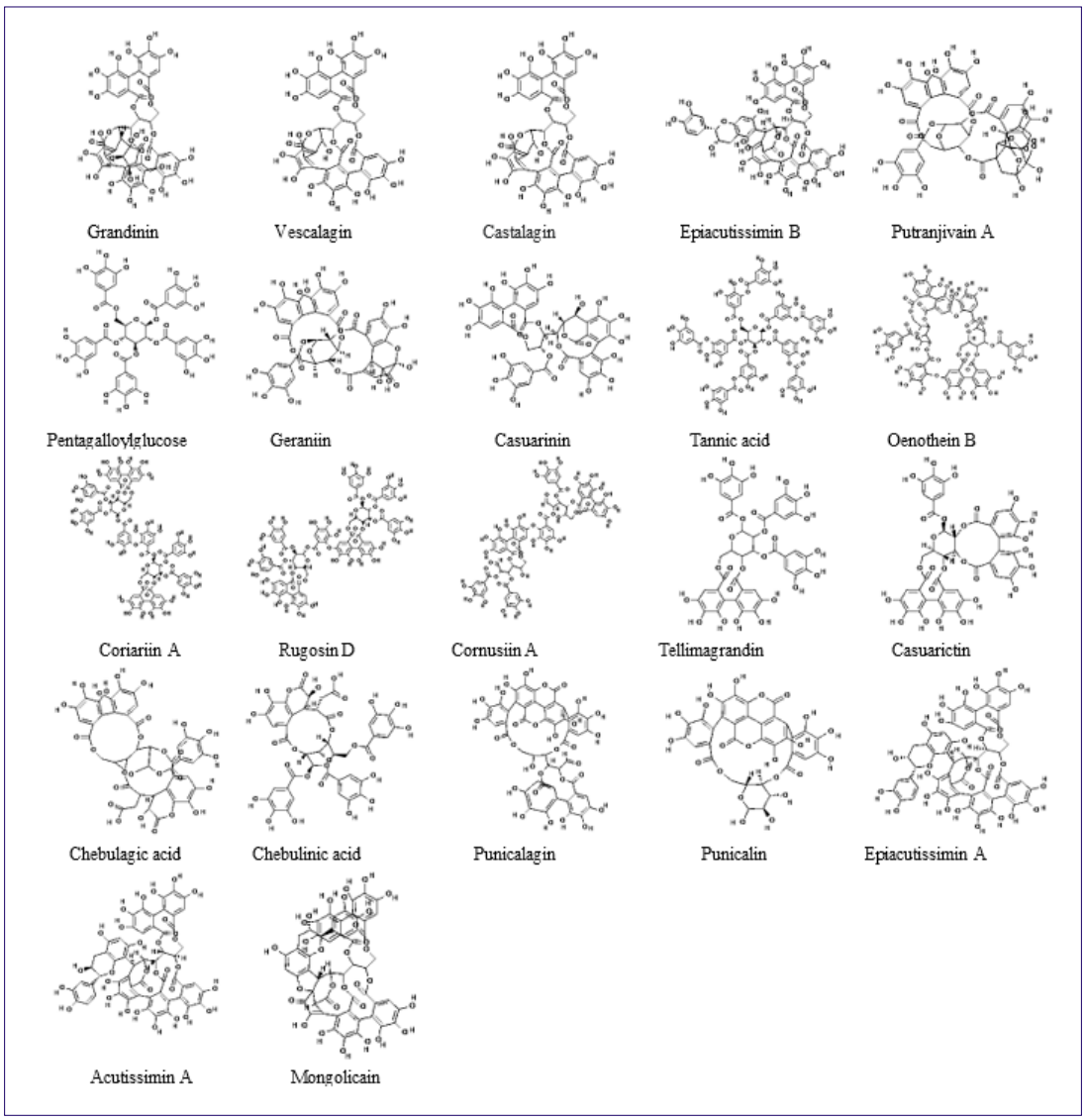

Figure 2. Chemical structures of tannins with anti-HSV properties.

by reducing viral DNA, transcript accumulation, and proteins across all three phases of the viral replication cascade (16). Fukuchi et al demonstrated that chemically defined tannins significantly inhibit plaque formation in various HSV strains, suggesting that polyphenol groups play a crucial role in their anti-HSV activity (17).

Vilhelmova-Ilieva et al investigated the anti-HSV activity of three C-glucosidic ellagitannins—castalagin, vescalagin, and grandinin—isolated from *Quercus robur* (pedunculate oak). These compounds exhibited significant antiviral effects against both ACV-sensitive and ACV-resistant HSV-1 and HSV-2 strains (26,27). In a separate study, nine ellagitannins—including six natural compounds (castalin, vescalin, acutissimin A, epiacutissimins A and B, mongolicain) and three synthetic vescalagin derivatives (VgSBuSH, VgSOctSH, VgOMe)—were evaluated for anti-HSV-1 activity. Among these, ellagitannins generally displayed stronger activity, with only castalin, vescalin, and one synthetic derivative (VgSOctSH) showing no effect. The remaining natural compounds outperformed the synthetic derivatives in potency. Additionally, only three out of thirteen tested gallotannins (Gal-04A, Gal-04B, and Gal-11M) exhibited inhibitory effects on HSV-1 replication (21). Further studies on chebulagic acid and punicalagin confirmed their ability to target and inactivate HSV-1 particles, preventing viral binding, penetration, cell-to-cell spread, and secondary infection. Notably, their antiviral effects were significantly reduced in mutant cell lines deficient in heparan sulfate and chondroitin sulfate production, but activity was restored upon heparan sulfate biosynthesis reconstitution (20). Jin et al reported that pentagalloylglucose, a gallotannin, effectively inhibits the proliferation of clinical ACV-resistant HSV-1 strains by blocking viral nuclear transport and suppressing nucleocapsid egress, suggesting its potential as a therapeutic agent against drug-resistant HSV (24). Vilhelmova et al also explored the synergistic effects of combining three ellagitannins (castalagin, vescalagin, and

grandinin) with ACV against ACV-sensitive and ACV-resistant HSV-1 and HSV-2. The strongest synergistic effects were observed against ACV-resistant and ACV-sensitive HSV-1 strains (26,27).

Tannins target various stages of viral replication, from extracellular virions to their attachment and penetration into host cells, and the replication process within the host. Furthermore, tannins can interfere with the assembly of new viral particles, transport proteins, polysaccharides, and viral enzymes (30). For instance, ellagitannin geraniin has demonstrated virucidal effects against herpes viruses, inhibiting HSV adsorption (23). Similarly, hydrolyzable tannin casuarinin has been shown to prevent HSV-2 attachment and penetration into host cells while affecting the later stages of infection (15). Chebulagic acid and punicalagin, both hydrolysable tannins, disrupt HSV-1 entry and viral spread by targeting the virus's glycoproteins (20). Putranjivain A is also known to block viral entry and impede late replication stages in HSV-2 (25). Punicalagin has been further shown to reduce HSV-1 replication by limiting viral DNA accumulation and inhibiting protein synthesis across all phases of the viral replication cycle (16). Studies have shown that both chebulagic acid and punicalagin inhibit HSV-1 entry through interactions with the viral glycoproteins involved in attachment and fusion, specifically by blocking cell surface glycosaminoglycan interactions. Notably, their antiviral activities were significantly reduced in cell lines lacking heparan sulfate and chondroitin sulfate, underscoring the importance of these molecules in the antiviral effects of tannins (20).

For controlling HSV infections, particularly in immunosuppressed individuals, antiviral treatments are essential. However, the systemic use of conventional antivirals often leads to the development of resistant strains. Given the diversity of the viral population, naturally resistant variants are frequently encountered. Thus, novel treatment strategies, including combination therapies using multiple antiviral agents with synergistic effects, are being explored to overcome resistance. These combinations target various stages of the viral life cycle, reducing the likelihood of resistance development and minimizing side effects by allowing for lower therapeutic doses. Recent studies have highlighted the potential of pentagalloylglucose, a gallotannin, in inhibiting the proliferation of clinical ACV-resistant HSV-1 strains, suggesting its applicability in drug-resistant HSV therapy (24). Additionally, the synergistic effects of ellagitannins have been shown to enhance antiviral activity against both ACV-sensitive and -resistant HSV-1 strains, further supporting their utility in combination treatments (26,27). These ellagitannins exhibit a distinct antiviral mechanism that differs from ACV, but the exact molecular mechanisms underlying their activity remain to be fully elucidated.

The presence of polyphenolic groups in tannins has been identified as a key factor in their anti-HSV activity (31). The number of hydroxyl groups within the benzene ring plays a critical role in determining antiviral potency (32). Moreover, the molecular weight of tannins, along with the presence of galloyl or hexahydroxydiphenoyl groups, is crucial for their effectiveness (17,33).

Conclusion

Tannins have shown significant potential as antiviral agents, primarily due to their capacity to form stable complexes with proteins in viral capsids or supercapsids. Tannins from diverse plant sources exhibit potent anti-HSV activities, with mechanisms including inhibition of viral attachment, penetration, and membrane fusion. These compounds can also target specific viral enzymes essential for replication or newly synthesized viral proteins crucial for assembling new viral particles. Such properties make tannins particularly promising as anti-HSV drugs, especially in cases of drug resistance. The compounds like Punicalagin, Castalagin, and Vescalagin exhibit the most significant potential as anti-HSV agents, warranting further investigation for therapeutic development.

Authors' contribution

Conceptualization: Mohammad-Taghi Moradi, Alizamen Salehifard Jouneghani.
Data curation: Majid Asadi-Samani, Mohammad-Taghi Moradi.
Formal analysis: Mohammad-Taghi Moradi, Dhiya Altememy.
Funding acquisition: Dhiya Altememy
Investigation: All authors.
Methodology: Majid Asadi-Samani, Mohammad-Taghi Moradi
Project administration: Majid Asadi-Samani, Mohammad-aghi Moradi
Resources: Alizamen Salehifard Jouneghani, Dhiya Altememy, Majid Asadi-Samani, Mohammad-Taghi Moradi.
Software: Mohammad-Taghi Moradi
Supervision: Majid Asadi-Samani, Mohammad-Taghi Moradi.
Validation: All authors.
Visualization: Majid Asadi-Samani, Mohammad-Taghi Moradi
Writing–original draft: Dhiya Altememy, Majid Asadi-Samani, Mohammad-Taghi Moradi.
Writing–review & editing: All authors.

Conflict of interests

There is no conflict of interest to declare.

Ethical considerations

Authors have carefully monitored ethical issues such as text plagiarism, duplicated publication, misconduct, data fabrication, and falsification.

Funding/Support

None.

References

1. Álvarez DM, Castillo E, Duarte LF, Arriagada J, Corrales N, Farías MA, et al. Current antivirals and novel botanical molecules interfering with herpes simplex virus

infection. Front Microbiol. 2020;11:139. doi: 10.3389/fmicb.2020.00139.
2. Chayavichitsilp P, Buckwalter JV, Krakowski AC, Friedlander SF. Herpes simplex. Pediatr Rev. 2009;30(4):119-30. doi: 10.1542/pir.30-4-119.
3. Alareeki A, Osman AM, Khandakji MN, Looker KJ, Harfouche M, Abu-Raddad LJ. Epidemiology of herpes simplex virus type 2 in Europe: systematic review, meta-analyses, and meta-regressions. Lancet Reg Health Eur. 2023;25:100558. doi: 10.1016/j.lanepe.2022.100558.
4. Patil S, Beck P, Nelson TB, Bran A, Roland W. Herpes simplex virus-2 meningoencephalitis with abducens nerve palsy with literature review. Cureus. 2021;13(6):e15523. doi: 10.7759/cureus.15523.
5. Van Wagoner N, Qushair F, Johnston C. Genital herpes infection: progress and problems. Infect Dis Clin North Am. 2023;37(2):351-67. doi: 10.1016/j.idc.2023.02.011.
6. Musa M, Enaholo E, Aluyi-Osa G, Atuanya GN, Spadea L, Salati C, et al. Herpes simplex keratitis: a brief clinical overview. World J Virol. 2024;13(1):89934. doi: 10.5501/wjv.v13.i1.89934.
7. Sadowski LA, Upadhyay R, Greeley ZW, Margulies BJ. Current drugs to treat infections with herpes simplex viruses-1 and -2. Viruses. 2021;13(7):1228. doi: 10.3390/v13071228.
8. Piperi E, Papadopoulou E, Georgaki M, Dovrat S, Bar Illan M, Nikitakis NG, et al. Management of oral herpes simplex virus infections: the problem of resistance. A narrative review. Oral Dis. 2024;30(3):877-94. doi: 10.1111/odi.14635.
9. Moradi MT, Rafieian-Kopaei M, Karimi A. A review study on the effect of Iranian herbal medicines against in vitro replication of herpes simplex virus. Avicenna J Phytomed. 2016;6(5):506-15.
10. Treml J, Gazdová M, Šmejkal K, Šudomová M, Kubatka P, Hassan ST. Natural products-derived chemicals: breaking barriers to novel anti-HSV drug development. Viruses. 2020;12(2):154. doi: 10.3390/v12020154.
11. Fraga-Corral M, García-Oliveira P, Pereira AG, Lourenço-Lopes C, Jimenez-Lopez C, Prieto MA, et al. Technological application of tannin-based extracts. Molecules. 2020;25(3):614. doi: 10.3390/molecules25030614.
12. Khanbabaee K, van Ree T. Tannins: classification and definition. Nat Prod Rep. 2001;18(6):641-9. doi: 10.1039/b101061l.
13. de Melo LF, de Queiroz Aquino-Martins VG, da Silva AP, Oliveira Rocha HA, Scortecci KC. Biological and pharmacological aspects of tannins and potential biotechnological applications. Food Chem. 2023;414:135645. doi: 10.1016/j.foodchem.2023.135645.
14. Hossain MT, Furhatun-Noor, Asadujjaman M, Abdul Matin M, Tabassum F, Harun-Ar Rashid M. A review study on the pharmacological effects and mechanism of action of tannins. Eur J Pharm Med Res. 2021;8(8):5-10.
15. Cheng HY, Lin CC, Lin TC. Antiherpes simplex virus type 2 activity of casuarinin from the bark of *Terminalia arjuna* Linn. Antiviral Res. 2002;55(3):447-55. doi: 10.1016/s0166-3542(02)00077-3.
16. El-Aguel A, Pennisi R, Smeriglio A, Kallel I, Tamburello MP, D'Arrigo M, et al. *Punica granatum* peel and leaf extracts as promising strategies for HSV-1 treatment. Viruses. 2022;14(12):2639. doi: 10.3390/v14122639.
17. Fukuchi K, Sakagami H, Okuda T, Hatano T, Tanuma S, Kitajima K, et al. Inhibition of herpes simplex virus infection by tannins and related compounds. Antiviral Res. 1989;11(5-6):285-97. doi: 10.1016/0166-3542(89)90038-7.
18. Kesharwani A, Polachira SK, Nair R, Agarwal A, Mishra NN, Gupta SK. Anti-HSV-2 activity of *Terminalia chebula* Retz extract and its constituents, chebulagic and chebulinic acids. BMC Complement Altern Med. 2017;17(1):110. doi: 10.1186/s12906-017-1620-8.
19. Lavoie S, Côté I, Pichette A, Gauthier C, Ouellet M, Nagau-Lavoie F, et al. Chemical composition and anti-herpes simplex virus type 1 (HSV-1) activity of extracts from *Cornus canadensis*. BMC Complement Altern Med. 2017;17(1):123. doi: 10.1186/s12906-017-1618-2.
20. Lin LT, Chen TY, Chung CY, Noyce RS, Grindley TB, McCormick C, et al. Hydrolyzable tannins (chebulagic acid and punicalagin) target viral glycoprotein-glycosaminoglycan interactions to inhibit herpes simplex virus 1 entry and cell-to-cell spread. J Virol. 2011;85(9):4386-98. doi: 10.1128/jvi.01492-10.
21. Vilhelmova-Ilieva N, Jacquet R, Deffieux D, Pouységu L, Sylla T, Chassaing S, et al. Anti-herpes simplex virus type 1 activity of specially selected groups of tannins. Drug Res (Stuttg). 2019;69(7):374-3. doi: 10.1055/a-0640-2557.
22. Pei Y, Xiang YF, Chen JN, Lu CH, Hao J, Du Q, et al. Pentagalloylglucose downregulates cofilin1 and inhibits HSV-1 infection. Antiviral Res. 2011;89(1):98-108. doi: 10.1016/j.antiviral.2010.11.012.
23. Yang CM, Cheng HY, Lin TC, Chiang LC, Lin CC. The in vitro activity of geraniin and 1,3,4,6-tetra-O-galloyl-beta-D-glucose isolated from *Phyllanthus urinaria* against herpes simplex virus type 1 and type 2 infection. J Ethnopharmacol. 2007;110(3):555-8.doi:10.1016/j.jep.2006.09.039.
24. Jin F, Ma K, Chen M, Zou M, Wu Y, Li F, et al. Pentagalloylglucose blocks the nuclear transport and the process of nucleocapsid egress to inhibit HSV-1 infection. Jpn J Infect Dis. 2016;69(2):135-42. doi: 10.7883/yoken.JJID.2015.137.
25. Cheng HY, Lin TC, Yang CM, Wang KC, Lin LT, Lin CC. Putranjivain A from *Euphorbia jolkini* inhibits both virus entry and late stage replication of herpes simplex virus type 2 in vitro. J Antimicrob Chemother. 2004;53(4):577-83. doi: 10.1093/jac/dkh136.
26. Vilhelmova N, Jacquet R, Quideau S, Stoyanova A, Galabov AS. Three-dimensional analysis of combination effect of ellagitannins and acyclovir on herpes simplex virus types 1 and 2. Antiviral Res. 2011;89(2):174-81. doi: 10.1016/j.antiviral.2010.11.014.
27. Vilhelmova-Ilieva N, Jacquet R, Quideau S, Galabov AS. Ellagitannins as synergists of ACV on the replication of ACV-resistant strains of HSV 1 and 2. Antiviral Res. 2014;110:104-14. doi: 10.1016/j.antiviral.2014.07.017.
28. Lee YG, Park DW, Kwon JE, Kim H, Kang SC. *Elaeocarpus sylvestris* var. *ellipticus* extract and its major component, geraniin, inhibit herpes simplex virus-1 replication. Plants (Basel). 2024;13(11):1437. doi: 10.3390/plants13111437.
29. Elendran S, Shiva Kumar V, Sundralingam U, Tow WK, Palanisamy UD. Enhancing the bioavailability of the

ellagitannin, geraniin: formulation, characterization, and in vivo evaluation. Int J Pharm. 2024;660:124333. doi: 10.1016/j.ijpharm.2024.124333.
30. Chattopadhyay D, Naik TN. Antivirals of ethnomedicinal origin: structure-activity relationship and scope. Mini Rev Med Chem. 2007;7(3):275-301. doi: 10.2174/138955707780059844.
31. Hassan STS, Šudomová M, Mazurakova A, Kubatka P. Insights into antiviral properties and molecular mechanisms of non-flavonoid polyphenols against human herpesviruses. Int J Mol Sci. 2022;23(22):13891. doi: 10.3390/ijms232213891.
32. Haapakoski M, Emelianov A, Reshamwala D, Laajala M, Tienaho J, Kilpeläinen P, et al. Antiviral functionalization of cellulose using tannic acid and tannin-rich extracts. Front Microbiol. 2023;14:1287167. doi: 10.3389/fmicb.2023.1287167.
33. Engström MT, Virtanen V, Salminen JP. Influence of the hydrolyzable tannin structure on the characteristics of insoluble hydrolyzable tannin-protein complexes. J Agric Food Chem. 2022;70(41):13036-48. doi: 10.1021/acs.jafc.2c01765.