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Chapter

Tannins as Antiviral Agents

Neli Vilhelmova-Ilieva, Angel S. Galabov and Milka Mileva

Abstract

Tannins possess a variety of biological effects, not a small part of which is of medical significance. Tannins, isolated from plants as well as synthetically obtained, manifest activity against a large spectrum of viruses: enteroviruses (polio- and coxsackie-), caliciviruses (feline calicivirus, mouse norovirus), rotavirus, influenza virus A, rhabdo- (vesicular stomatitis virus), paramyxoviruses (Sendai and Newcastle disease viruses), human immunodeficiency virus, herpes simplex virus, and adenoviruses. A special importance merits several ellagitannins manifesting pronounced effects against herpes simplex virus type 1 and 2 and on some herpes viruses affecting domestic animals, causing diseases of economic importance. An advantage of ellagitannins as anti-herpesvirus agents is that they have a non-nucleoside structure. Their targets are virus-specific proteins, so they retain activity against acyclovir-resistant strains of HSV types 1 and 2. Besides, these tannins manifest a synergistic effect with acyclovir when combined. Some initial results on their mechanism of action were carried out. In addition, it was found that most of the tannins have antioxidant properties in experimental models in vitro as well as in experimental influenza viral infection in mice.

Keywords: tannins, antiviral effect, antioxidant, herpes simplex virus, influenza virus

1. Introduction: tannins in medicine

For thousands of years throughout the world, tannins have been used in traditional medicines for the treatment of various health problems. They are used in the form of tea, coffee, and various extracts and in the daily intake of tannin-rich foods. They are also purposefully included as a component of many diets. Tannins are found in all parts of the plant—roots, stems, leaves, fruits, and seeds—which contribute to the existence of numerous natural sources of these substances.

Due to tannins' astringent effects, herbs containing tannins are used to treat injured and inflamed tissues, including burns, and to stop bleeding and prevent infection. Herbs contain tannins. They are also used in the treatment of mouth and throat inflammation, gastritis, enteritis, irritating bowel disorders, and other conditions [1–3], due to their ability to bind very tightly to proteins by forming multiple hydrogen bonds between their phenolic groups and the -NH groups of the peptides. Precipitation or the shrinking of proteins—the so-called tanning effect—then occurs, forming a protective layer on the surface of tissues.

Tannins have the ability to bind to metal ions in the body to form stable compounds called tannates. This property may have both positive and negative significance for human health. On the one hand, tannins can be used as an antidote for heavy metal poisoning. On the other hand, taking tannins daily, for example,

in tea or coffee, can cause calcium and iron deficiencies in the body and may cause osteoporosis and anemia [4].

Tannins are also effective inhibitors of certain enzymes. For example, woodfruticosin (woodfordin C) shows anti-topoisomerase II activity; and eugeniflorin D1 and D2, isolated from *Eugenia uniflora* L., and oenothein B effectively inhibit Epstein-Barr virus (EBV) DNA polymerase. Oenothein A and B, isolated from *Epilobium* species, appear to be potential inhibitors of the enzymes 5α-reductase and aromatase, which play important roles in the development of benign prostatic hyperplasia. Researchers have suggested that the enzyme poly(ADP-ribose) glycohydrolase, an important factor in gene expression, DNA replication, and cell differentiation, can be inhibited by the oligomeric ellagitannins oenothein B and nobotanins B, E, and K. In addition, enzyme α-glucosidase (maltase), which may be important in the development of type-2 diabetes, is inhibited by chebulagic acid (isolated from *Terminalia chebula*), tellimagrandin I, and eugeniin (casuarictin) [5].

Research results indicate that the crude extract of *Terminalia bellerica* fruit (Tb. Cr), which is rich in tannin content, induced a dose-dependent fall in the arterial blood pressure of rats. Tb.Cr inhibited the force and rate of atrial contractions, and this effect was due to a calcium antagonistic mechanism [6]. Tannins also exhibit antihypertensive activity in the body by inhibiting the effect of angiotensin I-converting enzyme (ACE) [7]. Hydrolysable tannins with pronounced antihypertensive activity are castalagin and chebulinic acid as well as corilagin isolated from the leaves of *Lumnitzera racemosa* [8].

Important for human health is the antitumor activity different tannins show toward various tumors such as cervical and prostate cancer and malignant cells in the skin, breast, stomach, lung, esophagus, liver, and so on [9, 10], with several possible mechanisms of action. Ellagitannins possess the ability to bind to proteins located on the surface of the cell membrane, thus preventing the proliferation of metastatic cells. They can induce also apoptosis in tumor cells by inhibiting factors responsible for the formation of metastases. Another mechanism suggests that during DNA replication, ellagitannins bind carcinogens into a complex, so they cannot cause mutation [11]. There is also evidence that ellagitannins reduce the negative effects of chemotherapy and radiation in cancer treatment [12].

Tannins also show antimicrobial activity, in both plants and animals. In plants, the effect is due to the inhibition of microbial enzymes that degrade the plant cell wall [13]. Inhibition also occurs with other microbial enzymes such as pectinase, xylanase, peroxidase, laccase, and glycosyl transferase. Two possible mechanisms of this antimicrobial activity are tannins binding to the proteins of microbial membranes, damaging their structure and function, and tannins binding with essential metal ions [14]. Due to their antimicrobial activity, tannins can be used in the production and storage of certain foods to increase the shelf life of products [15].

The immunomodulatory activity of tannins has also been demonstrated, with different substances showing different mechanisms of action that enhance the functionality of macrophages [16–18] or stimulate the secretion of cytokines IL-1, IL-β2, and αTNF [18, 19].

2. Tannins as antiviral antioxidants

The overproduction of free radicals and the subsequent development of oxidative stress are implicated as pathogenic factors in a number of viral infections. Oxidative stress is a complex multifaceted biochemical condition, which occurs when there is an increase in oxidative damage to biomolecules and oxidation of nonprotein and protein thiols that regulate a cell's oxidative balance [20].

The cellular injury due to viral diseases caused by over generation of free radicals has been linked to over 200 clinical disorders [21].

It has been clearly established that many of viral infections trigger the production of reactive oxygen (ROS) and nitrogen (RNS) species. This is particularly true for infections caused by the blood-borne hepatitis viruses (B, C and D), human immunodeficiency virus (HIV), influenza virus, herpes simplex virus, Epstein-Barr virus, respiratory syncytial virus, coxsackievirus B3 (CVB3), and others. For acute respiratory viral infections, ROS/RNS have been implicated in lung tissue injury and epithelial barrier dysfunction, which in turn increased susceptibility to secondary infections [22].

A variety of DNA viruses are associated with the increased oxidative stress that promotes DNA damage, high mutagenicity, and initiation and/or progression of neoplasia [23].

Phenolic compounds such as phenolic acids, flavonoids, tannins, and proanthocyanidins are widely distributed in plants and are a protective mechanism against OS. Several studies, including in vivo (in experimental animals) and epidemiological investigations, have demonstrated that phenolic compounds in foods possess positive attributes such as antioxidant potential, which is the basis of antiviral, antimicrobial, and antimutagenic activities. Compounds present in food that have potential antioxidant activity include vitamins C, E, and K, phenols (phenolic acids, flavonoids, thymol, carvacrol, and tannins), and carotenoids [24, 25]. Thus, antioxidants, mainly those originating from natural products, are of great importance for human health.

Antioxidant therapy is becoming an attractive and effective alternative approach for the treatment of viral diseases. The antioxidant properties of apple polyphenol extract, which is rich in tannins, are effective against the development of influenza virus infection in mice—they improve survival rates and also significantly decrease lipid peroxidation and increase oxygen radical absorbance capacity (ORAC) in splenocytes [26].

Avian influenza is usually accompanied by virus invasion followed by the occurrence of oxidative stress and serious inflammation. The anti-inflammatory and antioxidant properties of tannin-rich extracts of *Chaenomeles speciosa* showed that the multiple effects of the isolates might play a cocktail-like role in the treatment of avian influenza, and *C. speciosa* components might be a potent source for antiviral and anti-inflammatory agents [27].

Pomegranate juice consumption reduces oxidative stress during influenza infection [28].

Green tea is an important source of polyphenol antioxidants, which are also rich in tannins. Tea polyphenols possess antiviral properties believed to help protect against influenza virus. Oxidative stress and inflammation in the oral cavity, due to cigarette smoking and cigarettes' deleterious compounds nicotine and acrolein, can be reduced by green tea polyphenols. Generally, green tea defends healthy cells from malignant transformation, and locally, it has the ability to induce apoptosis in oral cancer cells [29].

Finally, oxidative stress and the stress-mediated complications of viral infections successfully respond to antioxidant prevention. However, it should be kept in mind that antioxidants are not antivirals. Their function is more auxiliary, and they are particularly beneficial when used in combination therapy with specific viral inhibitors.

3. Tannins as antivirals

For a small fraction of today's known viral diseases, there are vaccines that can be successfully applied. Medicaments that are used are also limited in number, and

in most cases, their use is accompanied by the appearance of side effects or the formation of resistant viral mutants, making therapy ineffective. Therefore, turning to nature to find effective therapies is a good solution to this problem. As mentioned earlier, tannins are a component of many plants. They are found in relatively high concentrations and exhibit significant biological activities. Tannin attack targets can carry out different stages of viral replication, including the extracellular virions themselves, their attachment to the cell, their penetration into the cell and the replication process in the host cell, as well as the assembling of new viral particles, transport proteins, polysaccharides, and viral enzymes [30, 31]. In almost all of the abovementioned stages, the tannin activity is due to their ability to bind permanently to the proteins of the capsid or supercapside, either to specific viral enzymes required for viral replication or to newly synthesized viral proteins involved in the composition of the new viral particles.

Numerous plant extracts have been studied, in which tannins are the main component, and they have shown good results against the replication of different viruses. The resulting effects have been on both coated viruses (influenza viruses A/H3N2 and A/H5N3, herpes simplex virus type 1 (HSV-1), vesicular stomatitis virus, Sendai virus and Newcastle disease viruses) [32, 33] and non-enveloped viruses (poliovirus, coxsackievirus, adenovirus, rotavirus, feline calicivirus, and mouse norovirus) [34].

The antiretroviral activity of *Euphorbia hirta* extracts with high tannin content has indicated a dose-dependent inhibition of reverse transcriptase activity in vitro [35].

Extracts of *Hamamelis virginiana* L. bark, with differing concentrations of tannins and individual tannins of defined structures, including pseudotannins, have been tested for effect against influenza A virus (IAV) and human papillomavirus (HPV) type 16 infections. The study demonstrated that the IAV life cycle is inhibited in the early and, to a minor extent, later steps and that HPV attachment is tannin-dependently inhibited. Of the investigated substances high molecular weight tannin inhibited both IAV receptor binding and neuraminidase activity. However, those with low molecular weight tannin inhibited neuraminidase but not hemagglutination [36].

Many tannins showing antiviral activity have been isolated and characterized. The hydrolyzable tannins chebulagic acid and punicalagin were identified as potent inhibitors of HCV entry [37]. The replication of human, porcine, and duck influenza A virus in vitro was prevented by the hydrolyzable tannin strictinin [38].

Finally, many studies have been conducted on tannins' effects against the replication of human immunodeficiency virus (HIV), and the results of the various teams indicate that tannins have several targets of action in the HIV replicative cycle. Ellagitannins isolated from *Tuberaria lignosa* inhibited HIV's entry into MT-2 cells [39]. There is evidence that ellagitannins suppressed HIV replication by inhibiting reverse transcriptase [40–44]. Other authors have reported on ellagitannins (geraniin and corilagin) that reduced HIV replication by inhibiting the HIV-1 protease and HIV-1 integrase enzymes [43].

4. Ellagitannins as antiherpesvirus agents

Various tannins have been tested for antiherpesviral activity. Ellagitannin geraniin possesses a virucidal effect against herpesviruses [45], and it inhibits the adsorption of HSV and HTLV-IIIB [46–49]. The hydrolyzable tannin casuarinin isolated from *Terminalia arjuna* Linn prevents the attachment of HSV-2 and its penetration into the cell, and it also disturbs the late stages of infection [1]. Chebulagic acid and punicalagin—two hydrolysable tannins isolated from *Terminalia chebula*

Retz.—inactivate HSV-1 entry and the cell-to-cell spread of the virus by targeting HSV-1 glycoproteins [50]. Putranjivain A isolated from *Euphorbia jolkini* inhibits the entry of the virus and the late stages of HSV-2 replication in vitro [51].

Seven ellagitannins isolated from *Phyllanthus myrtifolius* and *Phyllanthus urinary*, and eugeniflorin D (1) and D (2) isolated from *Eugenia uniflora* L., are active against the DNA polymerase of EBV [52, 53]. *Eucalyptus grandis* extract containing euglobal-G1 and euglobal-G3 shows antiviral activity against EBV, as do quassinoids (ailantinol B, ailantinol C, and ailanthone). Eugenol and eugenin isolated from *Geum japonicum* or *Syzygium aromaticum* show inactivating activity on viral DNA polymerase and thus inhibit acyclovir-resistant TK-deficient HSV-1 virus, wild HSV-2, and EBV [52, 54–56]. The EBV DNA polymerase is also inhibited by ellagitannins contained in *Phyllanthus myrtifolius* extracts and *Phyllanthus urinaria* (*Euphorbiaceae*), probably due to the corilagin moiety of these tannins. The tannin samarangenin B contained in the alcoholic extract of *Limonium sinensis* significantly suppresses HSV-1 multiplication [57]. And cowaniin isolated from *Cowania mexicana* (*Rosaceae*) exhibits an inhibitory effect on the activation of EBV early antigens [58].

Our studies on the antiviral activity of tannins have been mainly related to substances that belong to the group of nonahydroxyterphenoil-bearing C-glucosidic ellagitannins. We investigated the activity of three compounds—castalagin, vescalagin, and grandin isolated from powdered pedunculate oak (i.e., *Quercus robur*)—against the replication of two strains of HSV-1 (DA and Victoria) susceptible to acyclovir (ACV), one HSV-1 strain resistant to ACV (R-100), two HSV-2 strains susceptible to ACV (XA and Bja), and one HSV-2 strain resistant to ACV (PU) (**Table 1**) [59, 60].

Currently existing therapy against HSV infections is based on the administration of nucleoside analogues, among which ACV has had the broadest application. A disadvantage of this therapy is the rapid formation of resistant mutants [61].

All three investigated ellagitannins showed remarkable antiviral activity against all strains of HSV-1, the strongest being castalagin's action against the DA strain (SI = 5390.0) followed by vescalagin's action against that strain (SI = 4546.0), and these effects were greater than that of ACV. The effects on the replication of HSV-2 strains, although less pronounced than those on HSV-1, were significant. The strongest effects were seen on strain XA, with the following SI values: vescalagin = 378.9, castalagin = 336.9, and grandinin = 208.8.

The activity of the three ellagitannins was also determined in relation to the replication of three of the most common and important HSV-1 strains of economic importance, namely, pseudorabies virus or Suid herpesvirus 1 (SuHV-1), bovine

Compounds	**SI = CC_{50}/IC_{50}**					
	HSV-1			**HSV-2**		
	Strains sensitive to ACV		**Strain resistant to ACV**	**Strains sensitive to ACV**		**Strain resistant to ACV**
	DA	**Victoria**	**R-100**	**XA**	**Bja**	**PU**
Castalagin	5390.0	4498.0	1047.5	336.9	89.9	97.4
Vescalagin	4546.0	909.0	900.0	378.9	123.9	117.4
Grandinin	1183.0	88.7	650.0	208.8	71.0	103.1
ACV	1270.5	972.8	25.3	790.2	810.5	29.0

**The data for strains DA and DX are the original ones; the rest are from references [59, 60].*

Table 1.
*Effect of ellagitannins on HSV replication.**

herpesvirus-1 (BoHV-1), and caprine herpesvirus-1 (CapHV-1). The effect of the three ellagitannins was strongest against SuHV-1, with the activity of castalagin (SI = 336.8) and vescalagin (SI = 309) being on the order of ACV, while grandinin exhibited a moderate effect (SI = 40.8). The activity of the three ellagitannins against BoHV-1 was comparatively weaker but still significant (castalagin SI = 45, vescalagin SI = 42.5, grandinin SI = 32.3). Activity against the CapHV-1 strain had limited values.

Antiviral activity against HSV-1 (Victoria strain) was also determined for nine ellagitannins, of which six are natural compounds (castalin, vescalin, acutissimin A, epiacutissimins (EPI) A and B, mongolicain) and three are vescalagin synthetic derivatives (VgSBuSH, VgSOctSH, VgOMe). Thirteen gallotannin-type compounds [Gal-01A, Gal-01B, Gal-02A, Gal-02B, Gal-03 M, Gal-04A, Gal-04B, Gal-05 M, Gal-07, Gal-08, Gal-09, Gal-11 M (tannic acid), Gal-12 (gallic acid)] as well as Gal-13 and Gal-14 (ellagic acid)] were also tested. Generally, the group of ellagitannins exhibited greater activity, with only castalin and vescalin, from the natural products, and one of the synthetic derivatives (VgSOctSH) showing no activity. The remaining four natural components exhibited more pronounced activity than did the synthetic products, with the strongest effect showing for Epi B and Epi A (**Table 2**). Only three of the gallotannins—Gal-04A, Gal-04B, and Gal-11 M—showed activity against HSV-1 replication (**Table 2**) [62].

In order to control HSV infections, especially in immunosuppressed patients, it is necessary to treat them with antiherpetic preparations. However, their systemic use leads to the selection and/or formation of resistant strains. Given the heterogeneity of the viral population, naturally resistant variants are present. Therefore, the use of new approaches to the treatment of HSV infections [63, 64], namely, by combination therapy with two or more chemotherapeutics with synergistic action, is being sought. In these new approaches, synergistic combinations of two and more preparations are used to attack multiple viral targets simultaneously. This reduces the possibility of the formation and/or selection of resistant mutants. Even more, the therapeutic doses are abruptly reduced, eliminating any side effects. Data have been reported for combinations of antiviral agents showing a synergistic or additive effect on HSV [65–68].

Each of the three ellagitannins—castalagin, vescalagin, and grandinin—was administered in combination with ACV, and their effects against the replication

Compound	MM (g/mol)	CC_{50} (μM)	IC_{50} (μM)	SI = CC_{50}/IC_{50}
Epi A	1207	>1000***	18.0 ± 0.77***	>55.5
Epi B	1207	>1000***	16.5 ± 0.14***	>60.6
Acutissimin	1207	>640***	18.4 ± 1.2***	>34.78
Mongolicain	1177	>640***	19.7 ± 0.84***	>32.5
VgSBuSH	1039	>640***	26.0 ± 1.76***	>24.6
VgOMe	949	>640***	29.0 ± 2.89***	>22.0
Gal-04A	1701	>200***	7.0 ± 1.2**	>28.5
Gal-04B	1701	>100***	2.8 ± 0.53*	>35.7
Gal-11 M(TA)	1701	>100***	4.0 ± 0.07*	>25.0

*The table presents data partially contained in Ref. [62].*p > 0.05.*
***p < 0.05.*
****p < 0.001, when comparing the value of each gallotannin against ACV (CC_{50} = 1296.0 μM; IC_{50} = 1.47 μM) [59].*

Table 2.
Effect of tannins on the replication of HSV-1 in MDBK cell.

of HSV-1 and HSV-2 strains sensitive and resistant to ACV's effect were markedly synergistic [59, 60]. To evaluate the effect of the combinations, we employed the three-dimensional model system developed by Prichard and Shipman [69] using the computer program MacSynergy ™ II [70]. The program calculates the volume of synergy in $\mu M^2\%$, where values between 50 and 100 $\mu M^2\%$ indicate moderate synergy (this interaction may be important in vivo) and values over 100 $\mu M^2\%$ indicate strong synergy (these are more likely to be important in vivo). The strongest synergistic effect was seen in the combinations administered against the ACV-resistant HSV-1 strain, and the effect was also pronounced in the ACV-sensitive HSV-1 strain. The combined effect on the HSV-2 strains was weaker but also significant: in both the resistant and sensitive strains, the effect was on the same order of magnitude (**Table 3**).

The telling synergistic effect of all three ellagitannins shows that they have a different mechanism of action against HSV reproduction compared to that of ACV. The exact mechanism of antiviral activity of tannins has not been studied in detail.

To elucidate the mechanism of anti-herpes activity of tannins, we used a substance that showed activity similar to that of acyclovir, namely, castalagin.

When monitoring castalagin's effect on extracellular virions, we found that it was markedly time dependent. At the first time interval—15 min—the effect was negligible, but at 30 min, the effect was already significant, and as time increased, the virucidal effect intensified. This effect was also influenced by the temperature at which it occurred, with the effect at 37°C being stronger than that at room temperature [71].

Castalagin's effect on the attachment of HSV-1 virions to MDBK cells was time dependent, and it was also dependent on the concentration of castalagin and the number of infectious viral particles. The inhibitory effect was reported at 30 min (Δlog 1.7), and it increased with the time of impact, reaching a value of Δlog 3.2 at 60 min. The most remarkable effect was observed when using castalagin at a maximum non-toxic concentration of 10 μM and then reducing its effect with a decrease in its concentration [71].

Using a one-staged viral replicative cycle in a timing-of-addition study, we tested castalagin's effect on the production of infectious virions during the replication cycle of ACV-sensitive HSV-1, Victoria strain. The effect of adding castalagin at 0 hours was most pronounced, and the effect remained significant when adding the ellagitannin at up to 4 hours. After this period of time, the addition of the substance had no particular effect, and after 15 hours, a statistically significant effect was not observed. From these results, it can be concluded that castalagin affects earlier stages of the viral replicative cycle [71].

These results demonstrate a very high activity of the ellagitannin derivative castalagin toward human herpes simplex viruses 1 and 2. Its effect is on the order of the most efficient anti-HSV compound, acyclovir, which is widely used in clinical practice. In addition, castalagin manifested a marked activity against ACV-resistant

Compound	**HSV-1**		**HSV-2**	
	Victoria	**R-100**	**Bja**	**PU**
Castalagin	222.06	222.13	71.62	97.78
Vescalagin	205.09	324.44	87.56	79.11
Grandinin	106.0	314.53	132.78	106.12

**The table is originally constructed with results presented in Refs. [59, 60].*

Table 3.
*Synergistic effect between ellagitannins and acyclovir ($\mu M^2\%$).**

HSV strains, and its combination effects with ACV could be characterized as synergistic. Another advantage of this substance is its non-nucleoside chemical structure.

Castalagin could be considered as a candidate for in vivo testing on experimental HSV infections in laboratory animals, such as HSV-1-induced skin infection in mice, encephalitis in newborn mice, eye infection in rabbits, as well as HSV-2 genital infection in mice. A very important step in the characterization of the anti-HSV effect of castalagin is the determination of its target in the herpesvirus replication cycle via molecular genetic analysis.

Author details

Neli Vilhelmova-Ilieva, Angel S. Galabov* and Milka Mileva
Bulgarian Academy of Sciences, The Stephan Angeloff Institute of Microbiology, Sofia, Bulgaria

*Address all correspondence to: galabov@microbio.bas.bg

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