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Review

Tannins as Natural Helpers in Reinforcement of Human Health

Neli Vilhelmova-Ilieva*, Angel S. Galabov

Department of Virology, The Stephan Angeloff Institute of Microbiology, Bulgarian Academy of Sciences, Sofia, Bulgaria

Abstract

Since ancient times, folk medicine has used the potency of a wide range of plants for treatment of various diseases. In recent years, the development of technology has made it possible to identify the active ingredients determining these properties of plants. One of the largest group of substances isolated from plants are polyphenols. Tannins are a type of polyphenols that have already proven to possess different biological activities important to human health, such as antioxidant, antitumoral, antimicrobial, antiviral, etc.. As an integral part of many food products, tannins are included in the daily diet of many people suffering from various diseases. Tannins can naturally enhance the body's ability to cope with various infections and diseases, improving the immune response and also having a positive effect on patients with heart disease and high blood pressure, which makes them promising therapeutic agents. All of the activities described above allow tannins to be considered as promising therapeutic agents.
Keywords: tannins, ellagitannins, plant substances, biological activities, antiviral effects, therapeutic agents

Резюме

От древни времена народната медицина използва ефективността на голям асортимент от растения за лечение на различни заболявания. През последните години развитието на технологиите направи възможно идентифицирането на активните съставки, които определят тези свойства на растенията. Една от най-големите групи вещества, изолирани от растения, са полифенолите. Танините са вид полифеноли, вече доказали различни свои биологични активности важни за човешкото здраве, като антиоксиданта, антитуморна, антимикробна, антивирусна и други. Като неделима част от много хранителни продукти танините са включени в ежедневната диета на много хора, страдащи от различни заболявания. Танините подобряват способността на организма да се справя с различни инфекции и заболявания, усилвайки имунния отговор. Също така те имат положителен ефект върху сърдечно-съдовите заболявания и високото кръвно налягане. Описаните активности позволяват танините да се смятат за обещаващи лечебни средства.

Introduction

Tannins are a group of polyphenols with molecular weight ranging between 500 and 3000. They are soluble in water and alcohols and are located in the root, bark, stem and outer layers of the plant tissue. They form complexes with proteins, carbohydrates, alkaloids and gelatin (Widsten *et al*., 2014). Tannins are divided into two groups: hydrolysable, which can be hydrolyzed to glucose and gallic acid or other polyphenolic acids, and condensed tannins (proanthocyanidins), composed of flavonoid monomers, mostly (+) catechin or (-) epikatehin connected by carbon-carbon bonds (Okuda *et al.,* 1991). Hydrolysable tannins can be subdivided into gallotannins or ellagitannins, depending on whether they contain gallic or ellagic acid in their structure. Ellagitannins are made up of two galloyl units connected together and forming the basic structural unit of ellagitannins – hexahydroxydifenic acid (HHDP). They are important secondary metabolites of plants because of their property to induce resistance against microorganisms due to their ability to bind with proteins and polysaccharides, there-by blocking their growth.

Many tannins are isolated and structurally characterized from plant species used in traditional medicine. Grape, strawberry, cranberry, blueberry, pomegranate, chestnut, walnut, Brazil nut, pecan nut are with the highest content of tannins (Ascacio-Valdés *et al*., 2011).

This group of plant products has attracted the attention of an increasing number of research teams due to their multifunctional properties that make them promising medicinals.

Antioxidant activity

Free radicals, which are present in the human body, are considered to be responsible for the appearance of more than 100 chronic disorders in humans, including atherosclerosis, arthritis, jaundice, liver damage, central nervous system injury, gastritis, neoplasms, etc. The reasons for their formation are different: environmental pollutants, radiation, chemicals, toxins, fried and spicy foods and physical stress can cause depletion of antioxidants in the immune system, changes in gene expression and production of abnormal proteins. The struggle with degenerative diseases requires increased levels of antioxidants in the body. Foods of plant origin usually contain natural antioxidants. The role of antioxidants is to inactivate reactive oxygen species, and thus slow down or prevent oxidative damage (Jain *et al*., 2015).

Tannins have the ability to prevent the formation of free radicals, as well as to reduce the damage they cause in the cells (Yokozawa *et al*., 2002; Sepúlveda *et al*., 2011). This effect is stronger when tannins contain a greater number of phenolic hydroxyl groups (Hatano *et al*., 1989). Products derived from the metabolism of tannins also possess antioxidant properties (Ito, 2011).

Antidiabetic activity

According to the World Health Organization (WHO), about 80% of the population uses herbal medicines of traditional medicine for treatment of various diseases (Sani, 2015).

Extracts from various plant species with proved high content of tannins show antidiabetic activity (Rao *et al*., 2003; Raut and Gaikwad, 2006). *C*-glycosidic ellagitannins lagerstroemin, flosin B and reginin A from *Lagerstroemia speciosa* used for treatment of diabetes in the Philippines are activators of glucose transport (Yoshida *et al*., 2010).

Antihypertensive activity

The treatment of hypertension includes many drugs of natural origin, as digitoxin from *Digitalis purpurea* (foxglove), reserpine from *Rauwolfia serpentina* (snakeroot), aspirin from *Salix alba* (willow bark), tetramethylpyrazine, also known as Ligustrazine, from *Jatropha podagrica*, and tetrandrine from *Stephenia tetradra* (Kwan, 1994; O'Kane *et al*., 2003; Iwalokun *et al*., 2011).

Along with other representatives of natural origin, certain types of tannins also show a positive effect against hypertension. Castalagin, chebulinic acid and corilagin isolated from the leaves of *Lumnitzera racemosa* are hydrolysable tannins with pronounced antihypertensive activity (Lin *et al*., 1993).

Antitumor activity

One of the most remarkable abilities of tannins is their activity against various tumors as cervical cancer, prostate cancer, malignant cells in skin, breast, stomach, lung, esophagus, liver, etc. (Barrajon-Catalan *et al*., 2010; Ascacio-Valdés *et al*., 2011; Yildirım and Kutlu, 2015).

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 apoptosis in tumor cells by inhibiting the factors responsible for the formation of metastases. Another mechanism suggests that during DNA replication ellagitannins bind to carcinogens thus preventing their mutation effect (Sepúlveda *et al*., 2011). Corilagin induces cell cycle arrest at the G2/M phase and the apoptosis in cancer cells lines of ovarian cancer SKOv3ip, Hey and HO-8910PM (Jia *et al*., 2013). In literature there are many data on ellagitannins with antitumor activity – geraniin, corilagin (Okabe *et al*., 2001), oenothein A and B, woodfordin C, D and F (Miyamoto *et al*., 1997). Extracts containing tannins induce apoptotic activity in cells of breast and prostate cancer (Bawadi *et al*., 2005).

There is evidence that ellagitannins reduce the negative effects of chemotherapy and mitigate the effects of radiation exposure in anticancer therapy (Varadkar and Dubey, 2001).

Cell proliferation and differentiation activity

Geraniin and furosin isolated from *Phyllanthus muellerianus* stimulated the proliferation and differentiation of human keratinocytes and dermal fibroblasts, as well as the biosynthesis of collagen (Agyare *et al*., 2011).

Immunomodulatory activities

Ellagitannins show immunomodulatory activities using different mechanisms as a promoter of the formation of catechin-polysaccharide complex that is a potential immunostimulant (Monobe *et al*., 2008); enhance the functionality of macrophages (Ushio et al., 1991); for release of nitric oxide (NO), tumour necrosis factor (TNF) and interferon (IFN) (Kolodziej and Kiderlen, 2005); stimulate the secretion of cytokines IL-1 , IL-β2 and αTNF- by human peripheral mononuclear cells (Wang *et al*., 2002).

Enzyme inhibitory activity

Representatives of this group of compounds are also effective inhibitors of certain enzymes. Woodfruticosin (woodfordin C) has atni-topoisomerase II activity; eugeniflorin D1 and D2 isolated from *Eugenia uniflora* L. and oenothein B effectively inhibit Epstein-Barr virus (EBV) DNA polymerase. Enzymes 5α-reductase and aromatase have an important role in the development of benign prostatic hyperplasia, whose potential inhibitors are oenothein A and B isolated from *Epilobium* species.

It has been suggested that an important factor in the expression of genes, DNA replication and differentiation of cells is the enzyme poly(ADP-ribose) glicohydrolase that can be inhibited by oligomeric ellagitannins oenothein B and nobotanin B, E and K. The enzyme α-glucosidase (maltase), possibly important in the development of type-2 diabetes, is inhibited by chebulagic acid (isolated from *Terminalia chebula*), tellimagrandin I and eugeniin (casuarictin) (Yoshida *et al.*,2010).

Antimicrobial activity

Many tannins exhibit activity against various bacteria and fungi. Three galotannins: penta-, hexa-, and hepta-O-galloylglucose, isolated from mango (*Mangifera indica* L.), prevent the proliferation of Gram-positive food spoilage bacteria, and reduce the growth of Gram-negative *Escherichia coli* as the most likely inhibitory effects of these hydrolyzable tannins due to their iron-complexing properties (Engels *et al*., 2009). Tannins isolated from *Solanum trilobatum* Linn show antibacterial activity against *Staphylococcus aureus, Streptococcus pyrogens, Salmonella typhi, Pseudomonas aeruginosa, Proteus vulgaris* and *E. coli* (Doss *et al*., 2009).

The growth of *E. coli*, *Candida albicans*, *Crypotococcus neoformans* bacteria and *Aspergillus fumigatus* fungus is affected by the action of pomegranate, punicalagin, punicalin, gallagic and ellagic acids. Derivatives of ellagic acid demonstrated activity against *Klebsiella pneumoniae*, *Bacillus cereus*, *S. typhi* and *S. pyogenes* (Ascacio-Valdés *et al*., 2011).

Antiparasitic activity

Ellagitannins manifested antiparasitic activity against intracellular amastigotes of *Leishmania Donovan* (Kolodziej *et al*., 2001) or direct toxicity for extracellular promastigote *Leishmania donovani* or *L. major* strains (Kolodziej and Kiderlen, 2005). It has been shown that when administered via the feed of the plants rich in tannins they inhibit the development of the various stages of gastrointestinal nematodes of ruminants **(**Hoste *et al*., 2012).

Antiviral activity

In recent years, antiviral activity of various tannins has been increasingly often reported. It is a potential inhibitor of various enveloped viruses due to its capability of binding with different proteins and altering their structure, thus inactivating them.

Many studies have been conducted on tannins against the replication of human immunodeficiency virus (HIV) and the results of the various teams indicate that the targets of action of tannins in replicative cycle of HIV are several. There is evidence of ellagitannins that suppressed HIV replication by inhibiting reverse transcriptase (Asanaka *et al*., 1988; Notka *et al*., 2004). Other authors reported on ellagitannins (geranin and corilagin) that reduce HIV replication by inhibiting the HIV-1 protease and HIV-1 integrase enzyme (Notka *et al*., 2004), and ellagitannins isolated from *Tuberaria lignosa* that inhibit the entry of HIV in MT-2 cells (Bedoya *et al*., 2010).

The replication of human, porcine and duck influenza A virus *in vitro* is prevented by hydrolysable tannin strictinin (Saha *et al*., 2010).

In herpesvirus infections, chemotherapy was developed based on the application of nucleoside analogues that reduce the duration of symptoms and lead to faster healing of the lesions. The most commonly used nucleoside is acyclovir (ACV). The disadvantage of nucleoside analogues is the relatively rapid selection of resistant mutants (Abraham *et al*., 2007). Patients with compromised immune systems, and especially HIV- positive ones, are at the highest risk (Ziyaeyan *et al*., 2007).

Due to the frequent failure of treatment with nucleoside analogues, there is a need for the development of new inhibitors of herpes viruses (Knickelbein *et al*., 2009).

For hundreds of years, man has used natural sources for the treatment of various diseases. Fractions and crude extracts, and isolated and purified compounds from them were tested for antiviral activity against many viruses, including herpes

(Hassan *et al*., 2015). A significant part of these extracts showed remarkable anti-herpesvirus activity. Grape, apple, strawberry juices and extract of *Azadirachta indica* possess anti-HSV activities. The aqueous extract of *Carissa edulis* root from Kenya shows *in vitro* and *in vivo* antiviral activity against acyclovir (ACV) sensitive and ACV resistant strain of HSV-1 and HSV-2. The extract of *Ceratostigma willmattianum* demonstrates suppression of viral adsorption, replication and transcription of HSV-1 and HSV-2 (Chattopadhyay *et al*., 2010). Essential oils of ginger, thyme, hyssop and sandalwood effectively inhibit drug-resistant clinical HSV-1 strain (Schnitzler *et al*., 2007). Extracts of *Cardamine angulata*, *Conocephalum conicum*, *Lysichiton americanum*, *Polypodium glycyrrhiza* and *Verbascum thapsus* exhibit antiviral activity against HSV (Jassim and Naji, 2003), extracts of the Taiwanese folk remedy *Boussingaultia gracilis* and *Serissa japonica* and the extract of Senna petersiana are used for sexually transmitted diseases (Chattopadhyay *et al*., 2010). The methanolic crude extract of *Mallotus peltatus* possesses weak anti-HSV activity (Bag *et al*., 2012). *Eucalyptus globulus* is a traditional herb that has been used in Iran for many years. The methanolic extract of this plant inhibits HSV-1 replication in cell cultures in various dilutions (Davood *et al*., 2012). Acetone, ethanol and methanol extracts of *Phyllanthus urinaria* inhibit HSV-2 infection *in vitro* (Yang *et al*., 2005). An extract of *Ribes nigrum* L., known as blackcurrant in Europe and Kurokarin® in Japan, inhibits HSV-1 attachment to the cell membrane and inhibits virus replication of HSV-1, HSV-2 and VZV by suppression of protein synthesis in infected cells in the early stage of infection (Suzutani *et al.*, 2003). The ethanolic extract of *Rheum officinale* and methanol extract of *Paeonia suffruticosa* inhibit the attachment and penetration of HSV-1, and other studies show that the aqueous extract of *P. suffruticosa* and ethanolic extract of *Melia toosendan* affect the attachment and replication of HSV -1 and HSV-2. A garlic extract and an extract of *Terminalia chebula* showed anti-HCMV activity (Chattopadhyay *et al*., 2010), as well as extracts of *Euphorbia australis* and *Scaevola spinescens* (Jassim and Naji, 2003).

Various tannins were tested for anti-herpesviral activity. Seven ellagitannins isolated from *Phyllantus myrtifolius* and *P. urinary,* and eugeniflorin D (1) and D (2) isolated from *Eugenia uniflora* L. are active against DNA polymerase of EBV (Lee *et al*., 2000). Ellagitannin geraniin possesses a virucidal effect against herpesviruses (Notka *et al*., 2004). Chebulagic acid and punicalagin – two hydrolysable tannins isolated from *Terminalia chebula* Retz. inactivated HSV-1 entry and the cell-to-cell spread as their targets are HSV-1 glycoproteins (Lin *et al*., 2011). Hydrolyzable tannin casuarinin from *Terminalia arjuna* Linn prevent the attachment of HSV-2 in the cell, and also violates the late stages of infection (Cheng *et al*., 2002). Eugeniin (from *Geum japonicum* and *Syzygium aromaticum*) showed a significant inhibitory effect on the activity of DNA polymerase of HSV-1 (Kurokawa *et al*., 1998).

Our research in this area is mainly related to a substance that belongs to the group of nonahydroxyterphenoil-bearing C-glucosidic ellagitannins. This substance is castalagin and is extracted from powdered pedunculate oak (*i.e.*, *Quercus robur*). It provides an activity against the replication of HSV-1 greater than that of acyclovir and well-defined, but relatively lower activity against HSV-2 replication (Vilhelmova *et al*., 2011). Successfully combined with acyclovir, castalagin exerts a strong synergistic effect (Vilhelmova *et al*., 2011). In addition, castalagin shows clear activity against strains of HSV-1 and HSV-2 resistant to acyclovir and its combination with acyclovir has a clear synergistic effect (Vilhelmova-Ilieva *et al*., 2014).

We have also studied the two substances vescalagin and grandinin from the same group, whose activity is not as as strong as that of castalagin, but is significant and selective. They also demonstrate a synergistic effect when combined with ACV as in sensitive and in resistant to ACV strains of HSV -1 and HSV-2 (Vilhelmova *et al*., 2011; Vilhelmova-Ilieva *et al*., 2014).

Conclusion

Plant species from almost all plant families are at the heart of alternative medicine in different countries. Roots, stems, bark, leaves, flowers, fruits and grains possess medicinal properties, from which substances with different structure are isolated,an important part of which is occupied by tannins. They possess various biological activities, including anti-herpetic activity results in a damage at different stages of the virus replicative cycle. Further research remains to be conducted to discover new active substances, as well to establish the exact mechanism of action and the optimal concentrations in which active ingredients can be applied. With its diversity Nature provides a vast world in which future antiviral agents are hiding.

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