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# Health-enhancing activity of ellagic acid and ellagitannin of selected species from the genus *Rubus* – Review

Prozdrowotne działanie kwasu elagowego i elagotaniny wybranych gatunków z rodzaju *Rubus* – Przegląd

**Summary**. Numerous species of plants from the genus *Rubus* contain biologically active compounds that can be used in the prophylaxis and phytotherapy of various diseases. Among active compounds ellagic acid and ellagitannin exhibit a broad spectrum of health-enhancing properties, e.g. antioxidant, coagulant, anti-inflammatory, antiviral, anti-bacterial, anti-carcinogenic, and anti-mutagenic activity. Ellagic acid inhibits the activity of such carcinogens as benzo(a)pyrene, aflatoxin B1, and nitroso compounds. It can also be used in the therapy of Alzheimer's disease. Ellagitannins, i.e. precursors of ellagic acid, exert an effect on the activity of enzymes involved in the proper functioning of the circulatory system vessels. The two main ellagitannins, i.e. sanguiin H-6 and lambertianin C, are the major compounds responsible for the antioxidant properties of raspberry fruit. The fruits and leaves of *Rubus* plants containing phytotherapeutic compounds, e.g. ellagic acid and ellagitannins, are used for the production of cakes, sweets, syrup, jam, juice, teas, alcoholic and non-alcoholic beverages. The cultivation of plants from the genus *Rubus* containing ellagic acid and ellagitannins should be propagated due to their health-promoting effects useful for the prevention of many diseases and as natural phytochemicals in the pharmaceutical, cosmetic, and food industries.

**Key words**: Rosaceae, biologically active compounds, phytocompounds, phytotherapy

## INTRODUCTION

Plants from the genus *Rubus* are a source of food and therapeutic raw material in many regions of the world. Their health-enhancing properties were already known in Antiquity. In the Greek and Roman folk tradition as well as Asian, Chinese, and Indian Ayurvedic medicine, different *Rubus* organs (roots, stems, branches, leaves and flowers) were used in the phytotherapy of many diseases [Hummer 2010, Baranowska *et al.*

2015]. The medicinal activity of various species from the genus *Rubus* is associated with e.g. the presence of ellagic acid and ellagitannin. There are literature reports describing the health-promoting properties of many representatives of this genus, e.g. *R. chamaemorus* [Thiem and Goœliñska 2004], *R. coreanus* [Kim *et al.* 2013, Im *et al.* 2013], *R. ellipticus* [Li *et al.* 2009], *R. fairholmianus* [George 2013, 2014], *R. fructicosus* [Riaz *et al.* 2011], *R. lambertianus* [Tanaka *et al.* 1993], *R. roseafolium* [De Souza *et al.* 2017], and *R. unifolius* [Quave *et al.* 2012].

**Roots**. Decoctions from *R. fruticosus* roots were used to treat dysentery and diarrhoea [Jan *et al.* 2008]. When ground and mixed with honey, *R. fruticosus* roots were used to relieve heartache and oedema [Popović *et al.* 2014]. The roots of *R. ellipticus* and *R. fairholmianus* exerts astringent and toning effects due to the high content of tannins and saponins [Li *et al.* 2009, George *et al.* 2013, 2014]. *Rubus ulmifolius* root extracts can be used to inhibit *Staphylococcus aureus* biofilm formation to a degree that can be correlated with increased antibiotic susceptibility without toxic effects on normal mammalian cells. This can therefore be a material for development of a drug for prevention and treatment of *S. aureus* biofilm-associated infections [Quave *et al.* 2012].

**Aboveground parts**. Investigations of various *R. fruticosus* organs in terms of their antimicrobial activity have demonstrated the highest phytotherapeutic efficiency of bioactive compounds present in the shoot, followed by those contained in the root, leaves, and fruits [Riaz *et al.* 2011]. It has been found that the activity against *Staphylococcus aureus* is provided by rubanthrone A, i.e. a compound isolated from aboveground parts of *R. ulmifolius* [Flamini *et al.* 2002]. Shoots of *Rubus* plants are used in treatment of colds, fever, and flu-like infections [Hummer 2010]. Tea from young *R. idaeus* shoots and leaves is applied in treatment of diarrhoea, alleviation of menstrual pains, and mitigation of skin swelling [Popović *et al.* 2014].

***Leaves***. Extracts from *R. fruticosus* leaves have been used in the treatment of diarrhoea, dysentery, heartaches, cold, cough, fever, and cardiac pain [Popović *et al.* 2014]. Fresh leaves of this species were chewed as part of prophylaxis of gum diseases and scurvy [Patel *et al.* 2004]. *Rubus fruticosus* and *R. idaeus* leaves have been used as an astringent agent to treat throat inflammation, intestinal infections, and inflammatory skin diseases [Pavlovich 2000, Gudej and Tomczyk 2004, Patel *et al.* 2004, Zhang *et al.* 2011, de Souza *et al.* 2017]. Tea from *R. idaeus* leaves and shoots is a diuretic agent and induces respiration [Popović *et al.* 2014]. Given their rich chemical composition, nutritional and dietary values, and antioxidant activity, these organs are a valuable medicinal raw material [Baranowska *et al.* 2015, Chwil and Kostryco 2018].

***Fruits***. Raspberry fruits are known as a pharmacopeal raw material with antimicrobial and anti-inflammatory activity [Hummer 2010]. *Rubus coreanus* fruits have been used in Asian countries as a herbal remedy for alleviation of inflammatory and vascular diseases. *Rubus coreanus* fruit extracts contributed to reduction of atherosclerosis, improved the lipid profile, and inhibited NF-κB activation in mice [Kim *et al.* 2013]. *Rubus cassius* fruits were applied in treatment of diarrhoea and dysentery. *Rubus fruticosus* fruits had a beneficial effect on digestive processes [Popović *et al.* 2014]. Anthocyanins in *R. coreanus* fruits are responsible for the antioxidant capacity of the material [Im *et al.* 2013]. *Rubus* seed extracts exhibited antioxidant and anti-inflammatory properties [Fazio *et al.* 2013]. The rich chemical composition of organs and the wide range of pharmacological activity of various species from the genus *Rubus* have prompted the present at-

tempt to review phytotherapeutic literature reports on two phytotherapeutically important compounds, i.e. ellagic acid and ellagitannins.

The aim of the study was to determine the health-enhancing activity of ellagic acid and ellagitannins contained in various species from the genus *Rubus*.

## LITERATURE REVIEW

*Rubus ideaeus* L. fruits are a rich source of health-enhancing phenolic compounds [Kalt *et al.* 1999], including ellagic acid and hydrolysing tannins (ellagitannins) [Zafrilla *et al.* 2001, Mullen *et al.* 2002]. These compounds are widespread in the plant world [Thiem and Goœliñska 2004].

### Ellagic acid

Ellagic acid (2,3,7,8-tetrahydroxy[1]-benzopyranol[5,4,3-cde]benzo- pyran-5,10-dione) was discovered in 1831 by Bracinnot [Malini *et al.* 2011]. It is a highly thermostable molecule with a melting point of 350°C and a molecular mass of 302,197 g/mol. The compound is easily soluble in water, alcohol, ether, and potassium hydroxide. It is composed of lipophilic and hydrophilic parts. The lipophilic group contains four aromatic rings and four phenolic groups, and the hydrophilic part has two lactone hydrogen bond-forming groups [Sepúlveda *et al.* 2011].

**Occurrence and content of ellagic acid.** In the family Rosaceae, high concentrations of ellagic acid have been found in the fruit of representatives of genera *Fragaria*, *Rubus*, and *Rosa*. It is also present in other fruits, e.g. grapes, pomegranates, black currant, mango, guava, kaki, almonds, as well as Italian, pistachio, and cashew nuts and hazelnuts, and in green tea [Soong and Barlow 2006, Türk *et al.* 2010, Truchado *et al.* 2012].

Raspberries, blackberries, and strawberries have been found to have the highest concentration of ellagic acid. Its content was 2.7–18.1 mg/kg in the fresh weight of raspberry fruit and 300.1–338.1 mg/kg in blackberry fruit. Similarly, ellagic acid has been determined as the main phenolic component of cloudberry fruit (>160 mg/100g), Arctic blackberry (>160 mg/100g), and strawberry (>40 mg/100g) [Häkkinen *et al.* 1999, Segantini *et al.* 2015]. Alcoholic beverages, e.g. nut liquor, brandy, rum, whiskey, and tropical drinks, are a source of ellagic acid as well [Hossen *et al.* 2017].

**Phytotherapeutic activity of ellagic acid.** Ellagic acid is a health-enhancing component of a diet rich in raspberries and other berries. The compound has a wide spectrum of phytotherapeutic effects: it exhibits anti-carcinogenic, anti-mutagenic, and HIV-inhibition activity [Take *et al.* 1989, Maas *et al.* 1991]. It also inhibits avian myeloblastosis virus by interfering with reverse transcriptase and α and β DNA polymerase replication [Take *et al.* 1989]. Ellagic acid has a positive effect on human health, e.g. by its antioxidant activity [Verde *et al.* 2013]. In investigations conducted in mice and rat models (*in vitro*), the compound was found to inhibit tumour DNA polymerases as well as carcinogens, e.g. benzo(a)pyrene, aflatoxin B1, nitroso compounds, 3-methylcholanthrene, and N-2-fluorenylacetamide [Maas *et al.* 1991]. Other carcinogenic compounds, e.g. 1-chloro-2,4-dinitrobenzene and benzo(a)py- rene-4,5-oxide, were inactivated by an

enzyme (glutathione s-transferase) stimulated by ellagic acid [Das *et al.* 1985]. This acid reacted with free radicals forming an inactive complex and with the carcinogenic epoxide benzo(a)pyrene diol, resulting in formation of a new compound with an open epoxide pyrene ring and with no carcinogenic properties [Sayer *et al.* 1982].

Ellagic acid exerts an anti-carcinogenic effect on the VEGF-A factor, which is involved in the growth, proliferation, and migration of endothelial cells in bladder cancer [Pinto *et al.* 2010, Aldebasi *et al.* 2013]. The compound prevents metastasis and development of various types of cancer through inhibition of the proliferation of tumour cells, induction of their apoptosis, effects on inflammatory processes, and disruption of angiogenesis processes [Talcott and Lee 2002, Zhang *et al.* 2014]. As reported by Juranic [2005], an aqueous extract of raspberry seeds exhibited an anti-proliferative effect on colon cancer cells in *in vitro* cultures. This activity has been assigned to ellagic acid by Olsson *et al.* [2004].

Consumption of foods containing ellagic acid and ellagitannins in the daily diet has antiviral and antioxidant activity and prevents development of colorectal and oesophageal cancers [Corthout *et al.* 1991, Rao *et al.* 1991, Stoner and Morse 1997, Kalt *et al.* 1999, Whitley *et al.* 2003, Han *et al.* 2005]. Ellagic acid has aroused researchers' interest as a compound for potential used in the treatment of Alzheimer's disease [Papoutsi *et al.* 2008], as it has a beneficial effect on the nervous system as well as antidepressant and anxiolytic activity [Farbood *et al.* 2015, de Oliveira *et al.* 2016]. The mechanism of action of this acid consists in stimulation of the formation of β-amyloid peptide fibrils and inhibition of the neurotoxicity of peptide monomers playing a key role in the pathogenesis of inhibiting Alzheimer's disease [Feng *et al.* 2009]. Ellagic acid reduces the blood glucose level, thereby preventing diabetes development [Hossen *et al.* 2017]. It is also an effective antioxidant due to its ability to bind free radicals and protect tissues and physiologically important compounds from oxidation [Tulyatham *et al.* 1989]. It is a better antioxidant than α-tocopherol [Dziedzic and Hudson 1984, Kurechi and Kunugi 1983]. It protects mitochondrial and microsomal lipids from harmful oxidation [Okuda *et al.* 1983].

## Ellagitannins

Ellagitannins represent a group of biologically active compounds, i.e. tannins; they are esters of hexahydroxydiphenoic acid, gallic acid, their derivatives, and usually beta-D-glucose monosaccharides. The ellagitannin group comprises monomeric (nupharin A, geraniin, tellimagrandin II), oligomeric (nupharin E, nupharin C, hirtellin A), and C-glycosidic (vescalagin, castalgin) ellagitannins. The compounds are characterised by high molar mass [Grundhöfer *et al.* 2001, Seeram *et al.* 2004, Pinto *et al.* 2008].

**Health-enhancing activity of ellagitannins**. Besides ellagic acid, the health-enhancing *R. idaeus* fruits contain ellagitannins and ellagic acid glycosides as well as a number of other bioactive compounds, e.g. anthocyanins, flavonoids, phenolic acids, and flavan-3-ols [Rommel and Wrolstad 1993, Ancos *et al.* 2000, Mullen *et al.* 2002, Maatta-Riihinen *et al.* 2004].

Ellagitannins are present in plants from the family Rosaceae. The ellagitannins contained in the representatives of the genus *Rubus* are dominated by sanguuin H-6 and lambertianin C [Tanaka *et al.* 1993, Sparzak *et al.* 2010]. Investigations of the antimicrobial activity of raspberry shoot extracts containing phenolic compounds, e.g. sanguiin

H-6 and ellagic acid, in comparison with ampicillin, have demonstrated inhibitory activity towards various bacterial strains (*Bacillus subtilis*, *Clostridium sporogenes*, *Staphylococcus epidermidis*, *Neisseria meningitis*, *Moraxella catarrhalis*, and *Helicobacter pylori*) [Krauze-Baranowska 2014]. Due to the high content of sanguiin H-6, raspberry fruits exert an anti-proliferative effect on the cervical cancer cell line (HeLa). Cytotoxic activity of sanguiin H-6 has been shown in investigations of a leukaemia cell line (HL-60) [Ross *et al.* 2007].

The antioxidant properties of *R. idaeus* leaf extract are provided in 50% by ellagitannins (sanguiin H-6 and lambertianin C) [Beekwilder *et al.* 2005]. As shown by Larrosa *et al.* [2005], daily consumption of ellagitannins and ellagic acid induces apoptosis of cancer cells via an effect on mitochondria. The antiviral activity of ellagitannins involves inhibition of HIV adsorption to cells and inhibition of reverse transcriptase. The oenotherin B ellagitannin is particularly active in this respect [Maas *et al.* 1991].

Ellagitannin-rich extracts have been found to inhibit oxidation of LDL cholesterol and reduce its accumulation in macrophages [Aviram *et al.* 2008]. Ellagitannins have a positive effect on the function of blood vessels by induction of formation of nitric oxide synthase in the circulatory system endothelium [Nigris *et al.* 2005, 2007]. Ellagitannins prevent processes associated with the pathogenesis of Alzheimer's disease by prevention of platelet aggregation and adhesion of monocytes and endothelial cells [Papoutsi *et al.* 2008]. Ellagitannin metabolites exhibit anti-atherosclerotic properties. Similar to ellagitannin, ellagic acid inhibits the expression of the VCAM-1 factor, which plays a key role in the early stages of atherosclerosis [Cybulsky 2001, Papotusi *et al.* 2008].

Ellagic acid is produced during hydrolysis of ellagitannins in the small intestine. It is metabolised in 99% by intestinal microflora. The process results in formation of bioavailable urolithins. These compounds are composed of 6H-dibenzo[*b,d*]pyran-6-one in the basic part and a lower number of hydroxyl groups [Espin *et al.* 2007, Gonzales--Bario *et al.* 2011]. Urolithins are metabolised by phase II enzymes, mainly in enterocytes and hepatocytes [Gonzales-Sarrias *et al.* 2010].

An increase in the ellagic acid content can be noted during fruit processing, probably due to hydrolysis of ellagitannins into free ellagic acid [Zafrilla *et al.* 2001]. Addition of sugar and pectins and thermal treatment applied in jam production was found to result in a 2.5-fold increase in the ellagic acid content, in comparison with its concentration in fresh fruits [Maghradze *et al.* 2011].

## CONCLUSIONS

Ellagic acid and ellagitannins are phytocompounds with a broad spectrum of health--enhancing phytotherapeutic activity. Given their content of health-enhancing ellagic acid and ellagitannins, cultivation of the medicinal plants from the genus *Rubus* should be recommended. As bioactive compounds, ellagic acid and ellagitannins can be used in pharmaceutical, cosmetic, and food industries.

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**Streszczenie.** Liczne gatunki roślin z rodzaju *Rubus* zawierają substancje biologicznie czynne stosowane w profilaktyce i leczeniu fitoterapeutycznym różnych schorzeń. Wśród tych związków aktywnych kwas elagowy i elagotaniny wykazują szerokie różnorodne właściwości prozdrowotne, m.in. antyoksydacyjne, zwiększające krzepnięcie krwi, przeciwzapalne, przeciwwirusowe (hamujące aktywność wirusa HIV), antybakteryjne, antykancerogenne, antymutagenne. Kwas elagowy hamuje aktywność czynników rakotwórczych: benzo(a)pyrene, aflatoksyny $B_1$, związków nitrozowych. Może być stosowany w leczeniu choroby Alzheimera. Elagotaniny będące prekursorami kwasu elagowego wpływają na aktywność enzymów zaangażowanych w prawidłowe funkcjonowanie naczyń systemu krwionośnego. Dwie główne elagotaniny, sangwina H-6 i lambertianina C, są najważniejszymi związkami zapewniającymi własności antyoksydacyjne owoców malin. Owoce i liście roślin z rodzaju *Rubus*, zawierające fitoterapeutyczne związki, m.in. kwas elagowy i elagotaniny, są wykorzystywane do produkcji ciastek, słodyczy, dżemów, syropów, soków, herbatek, napojów alkoholowych i niealkoholowych. Należy propagować uprawę roślin z rodzaju *Rubus* i spożycie owoców zawierających kwas elagowy i elagotaniny ze względu na ich prozdrowotne działanie, które może być wykorzystane w profilaktyce wielu chorób. Rośliny z rodzaju *Rubus* mogą być także wykorzystywane jako źródło fitozwiązków w przemyśle farmaceutycznym, kosmetycznym i spożywczym.

**Słowa kluczowe:** Rosaceae, substancje biologicznie czynne, fitozwiązki, fitoterapia

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