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THE EFFECT OF PHENOLIC ACIDS ON LIVING ORGANISMS

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Abstract

Phenolic acids belong to a numerous group of polyphenolics exhibiting strong antioxidant properties. They are considered to be health-promoting substances and have been proposed as agents in the prevention and control of many diseases, viruses, bacteria, microscopic fungi and yeast. They exhibit different effects on living organisms, slowing or completely limiting their development. In addition to the positive effects of their antioxidant properties, they may also have adverse effects on other living organisms. Literature sources present very limited information on the toxic effect of phenolic acids in relation to animals or humans, although detected LD_{50} values suggest their toxic influence on these organisms. The aim of this study was to clarify the current state of knowledge on toxic properties of phenolic acids, as well as indicate their adverse effect on living organisms starting from plants through microorganisms, animals and humans.

Introduction

The group of phenolic compounds of plant origin, comprising over 8000 polyphenolics identified to date, includes also phenolic acids (Ferrazzano et al. 2011, Strumiłło et al. 2015). These compounds are classified as bioactive components and they are commonly found in the plant world. Present-day medicine, agriculture and various branches of industry have focused on their structure and mode of action. Being compounds with strong antioxidant and radical scavenging properties, these acids are essential elements in the non-enzymatic antioxidant protection system. They participate in many vital functions such as e.g. morphogenesis and photosynthesis. Thanks to their extensive bioactivity phenolic acids are commonly considered to be health-promoting substances. However, in the literature on the subject one can find references to their action against microorganisms. In view of their increasing applications in the agri-food sector and in medicine it was decided to present literature on the subject referring to toxicity of phenolic acids. For this reason the aim of this paper is to present a comprehensive picture of the current state of knowledge on toxic properties of phenolic acids and their adverse effect on living organisms.

General characteristics of phenolic acids

Phenolic acids are a group of organic chemical compounds containing in their structure a phenolic ring and the remaining carboxylic acid. The distribution of phenolic acids depends on their chemical structure. There are distinguished: benzoic acid derivatives and cinnamic acid derivatives. Hydroxylic derivatives of cinnamic acid include p-coumaric, ferulic, synapic and caffeic acids. They are found mainly as esters of glucose or quinic acid, while ferulic and *p*-coumaric acids are bound with arabinoxylans or they are found as hemicelluloses. These acids also form depsides, e.g. chlorogenic acid (an ester of caffeic and quinic acids), which may be contained in hydrolyzing tannins. Cinnamic acid and its derivatives are also important copolymers comprised in lignins. In turn, hydroxyl derivatives are found in plant materials in the form of glycosides. They include protocatechuic, gallic, resorcylic, 4-hydroxysalicylic, vanillic, gentisic, syringic and 4-hydroxybenzoic acids.

Properties of phenolic acids

Phenolic acids may be formed in plants via two metabolic pathways, i.e. the shikimate pathway and the acetic acid metabolic pathway. Analysis of metabolism in the case of phenolic acids synthesized in infected plant cells showed phenylalanine and chorismic acid to be their main precursors. As a result of enzyme action various phenolic acids are formed, e.g. cinnamic acid produced as a result of the action of phenylalanine ammonia lyase (PAL). Through its hydroxylase and reactions catalyzed by the enzymes induced in response to infection coumaric acid or benzoic acid are formed, with salicylic acid formed from the latter via hydroxylation. PAL is a precursor of both the formation of

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salicylic acid and bacteri- and fungicidal phytoalexins, as well as defense plant cells such as lignins. The direct precursors for the formation of salicylic acid include the previously mentioned benzoic acid as well as isochorismic acid, which are susceptible to the action of isochorismate pyruvate lyase (IPL). In turn, by undergoing changes induced by coumaroyl-CoA ligase p-coumaric acid is transformed to the structure of caffeic acid and then to ferulic acid (Kubat 2016).

Phenolic acids found in plants exposed to the action of external biotic and abiotic stressors serve protective functions in those plants. Stress in plants results in the excessive accumulation of free radicals, which are formed under the influence of microorganisms, chemicals, ultraviolet radiation or adverse weather conditions. The interaction of free radicals with cell macromolecules, i.e. proteins, lipids or carbohydrates, leads to DNA damage, mutations or even cell death. Under homeostasis free oxygen radicals disturb biochemical changes and inactivate cell functions damaging tissue structures. In such a case antioxidant compounds are activated as a result of defense responses (Fig. 1.). Antioxidant properties of phenolic acids consist in the elimination of reactive oxygen species, free radical scavenging e.g. in relation to peroxide and hydroxyl radicals, inhibition of oxidase enzymes and chelation of metal ions such as iron and copper (Makarska & Michalak, 2005).

Phenolic acids are capable of proton and electron transfer. These compounds not only undergo oxidation, but they may also mediate in oxidation of compounds not reacting with oxygen. The rate of the antioxidant action of phenolic acids depends on their antioxidant activity, which increases considerably with the growing number of –OH groups in the –ortho or -para configuration. In view of the above the antioxidant activity of phenolic acids depends on the structure and polarity of a given compound, its stability in the reaction medium and the manner of isolation of these phenolic compounds. Acids of high antioxidant activity include e.g. caffeic and gallic acids (Fig. 2., Fig. 3.) (Farmakopea Polska IX, 2011).

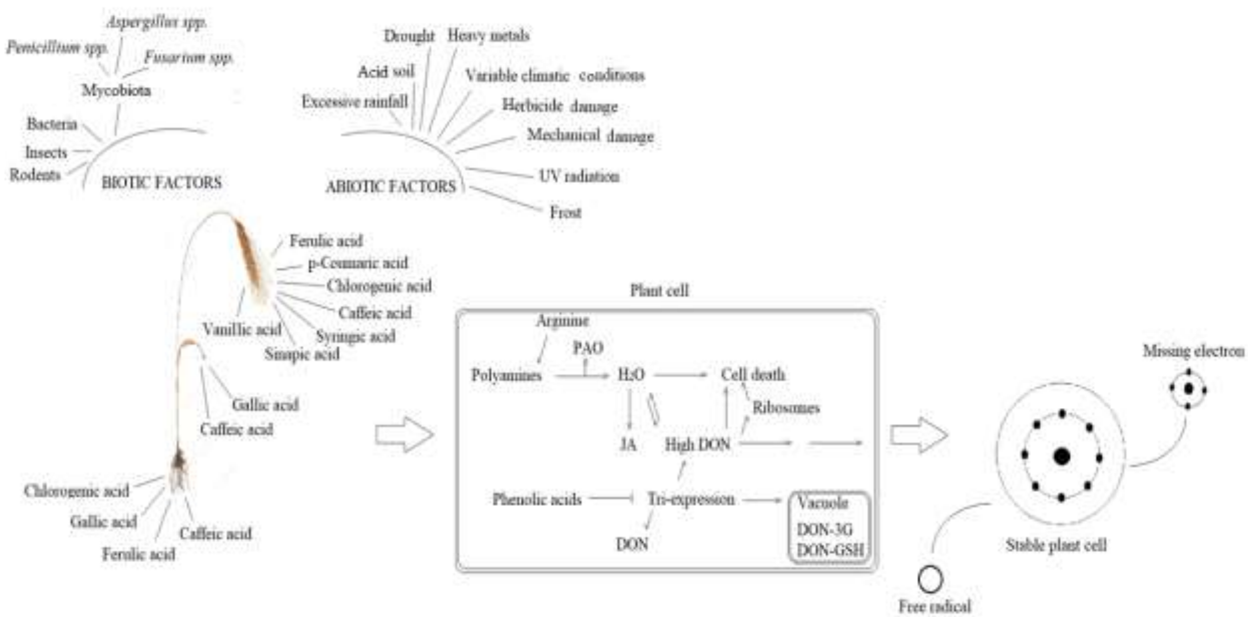

Figure 1. Defense mechanism against the action of stressors (Audenaert et al. 2013, Stuper-Szablewska et al. 2017)

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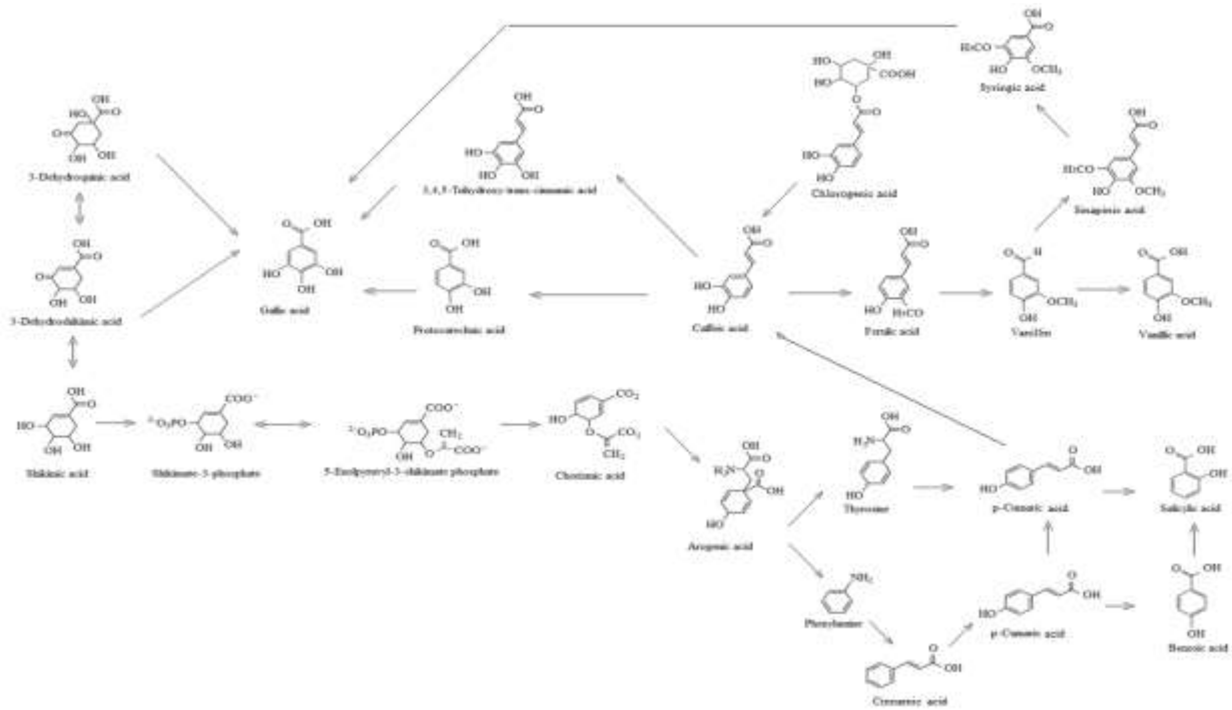

Figure 2. The biosynthesis pathway for phenolic acids (Stuper-Szablewska et al. 2017, Goleniowski et al. 2013)

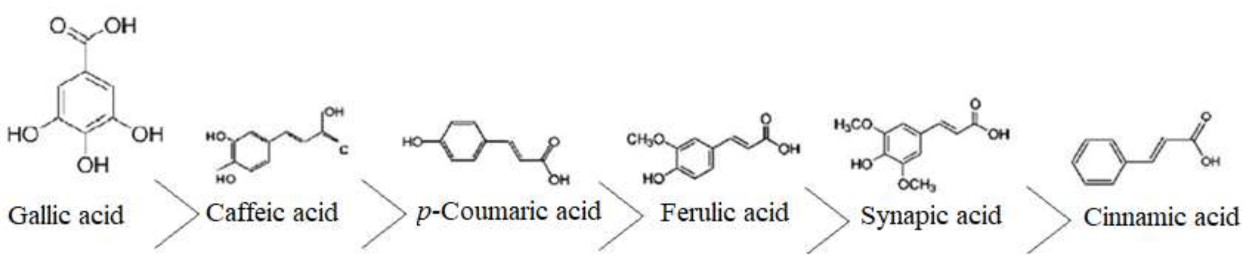

Figure 3. Antioxidant activity series of phenolic acids (Szajdek & Borowska, 2004)

Occurrence of phenolic acids

Phenolic acids are commonly found in plant tissues in bound form in the form of esters or glycosides, which are part of lignin and hydrolysing tannins (Table 1). In addition, they combine with flavonoids, fatty acids, sterols and cell wall polymers.

Table 1. Examples of ester bound phenolic acids in plant tissues

Acid	Plant	Form
Glucaric	tomato leaves	caffeoylglucaric acid
Tartaric	chicory	chicoric acid (2R,3R-O-dicaffeoyltartaric acid)
Tartaric	grapes	α-hydroxy-hydrocaffeic acid
Tartronic	mung bean cotyledons	p-coumaroyl-, feruloyl- and caffeoyltartronic acids
Shikimic	palm tree	3-O-caffeoylshikimic acid

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Phenolic acids differ considerably in terms of their structure and physico-chemical properties, as well as the concentration, at which they are found in tested plant materials. Example contents of phenolic acids are presented in Table 2 and Fig. 4. These acids have been detected in all plant parts, e.g. the pericarp, leaves, shoots and roots. They are accumulated in the vacuoles, guard and epidermal cells. The highest concentrations among phenolic acids were recorded for derivatives of hydroxycinnamic acid in red fruits and vegetables as well as green, unroasted coffee beans and in green tea infusion. Cereal kernels are also rich sources of phenolic acids, with the highest concentrations of ferulic acid, followed by syringic and p-coumaric acids. Cereal germ contains esters of caffeic and ferulic acids (Gawlik-Dziki 2004, Zieliński 2002, Baublis et al. 2000, Slavin et al. 2000). Ferulic acid and its dimers constitute the primary structural material for the primary cell wall. The monomer is covalently bound with mono-, di- and polysaccharides of the plant cell wall, glycoproteins, polyamines, lignin and fatty acids, forming suberin or cutin (Gawlik-Dziki 2004, Bourne & Rice-Evans 1998, Sen et al. 1994).

Table 2. Contents of phenolicacids [mg/kg] in various food products (Przybylska et al. 2017, Przybylska et al. 2017, Kazimierczak et al. 2010, Piątkowska et al. 2010, Ferruzzi 2010, Stuper-Szablewska et al. 2016, Przybylska-Balcerek et al. 2019)

Food product	Chlorogenic	p-Coumaric	Ferulic	Syringic	Synapic	Caffeic
Blueberry	2000	10	10	NDA	NDA	NDA
Apple	180-200	100	10	NDA	NDA	NDA
Lovage	248	114	147	NDA	NDA	623
Wheat flour type 1850	155	30	853	16	76	19
Rye flour type 720	191	47	993	23	92	18
Oat bran	1880	117	2500	NDA	180	17
Tomato	290	280	700	130	130	380
Sage	320	289	311	NDA	NDA	59
Thyme	170	397	869	NDA	NDA	96
Coffee brew	500*	NDA	50*	NDA	NDA	250*
Herb extracts digested by bees	125	816	66	35	73	95
Grains of barley	15	34	798	71	12	18
Grains of triticale	3	65	865	37	184	5
Oat grain	51	20	970	17	52	19
Rye grain	28	12	1140	11	16	20
Wheat grain	40	39	1280	60	30	35

*in solution [mg/L]
NDA – no data available

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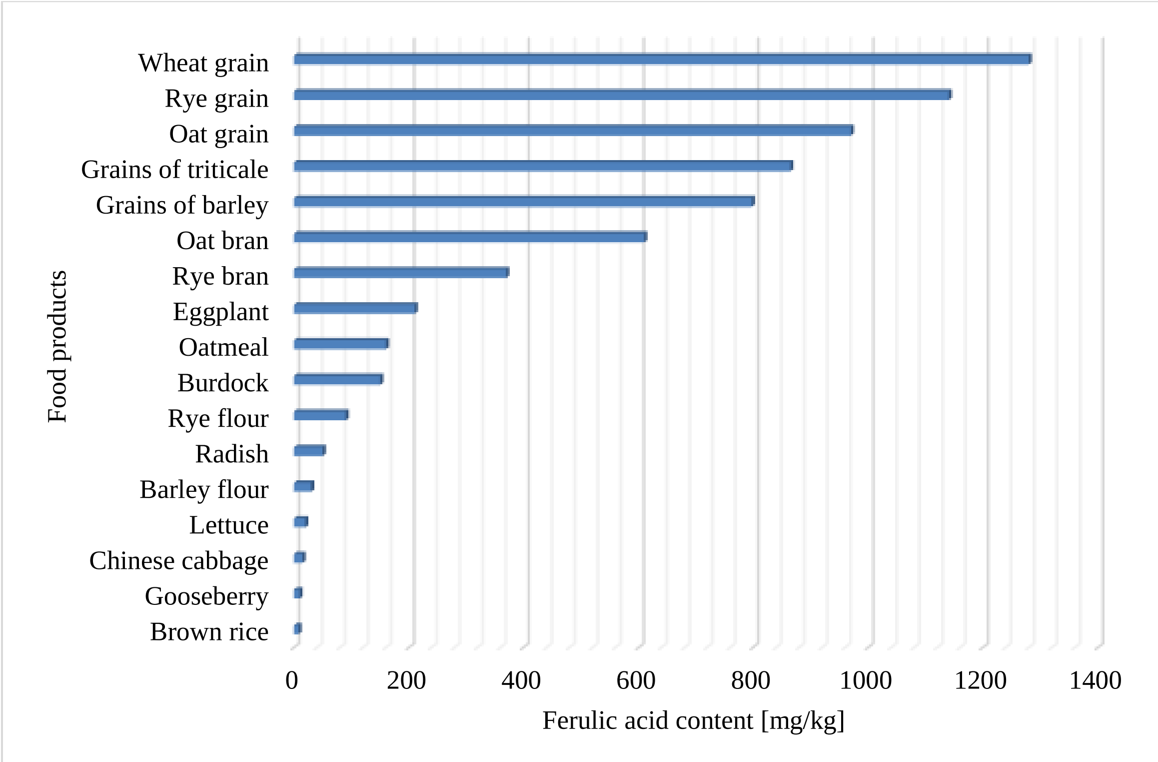

Figure 4. Ferulic acid content in selected raw materials (Stuper-Szablewska et al. 2017, Przybylska-Balcerek et al. 2019)

Phenolic acids are responsible e.g. for the characteristic sour, bitter (ferulic, o- and p-coumaric acids) or slightly sweet taste of certain food products of plant origin, such as flour produced from blue maize grain (slight sweet) (Przybylska et al. 2017) and products from maize germ flour (bitter) (Parus, 2013).

The properties of phenolic acids

Phenolic acids, thanks to the above-mentioned properties, are natural pesticides protecting plants against pathogens, while at the same time they have a beneficial effect on the plant producing them as well as hinder germination, growth and development of neighboring plants. Examples in this respect may be provided by water soluble herbicidal allelochemicals isolated from clover (*Medicago sativa L.*), including primarily cinnamic acids and their derivatives, i.e. vanillic, ferulic and p-coumaric acids. Caffeic acid exhibits a characteristic action in relation to some plant species, such as e.g. growth stimulation in lettuce or growth inhibition in common heather (*C. vulgaris*). As a consequence it shows phytotoxic action in relation to root growth in monocots and dicots. It inhibits energy metabolism in chloroplasts and mitochondria and hinders modification of bond affinity to the membrane receptors. The chemical mechanism of phenolic acid phytotoxicity has not been thoroughly clarified; nevertheless, based on literature data and experiments conducted by the authors of the study it may be stated that the toxic action on seed germination may be partly connected with their lipophilic character. It is also known that carboxylic acids and phenols induce conjugations of forms oxidized during photosynthetic photophosphorylation in mitochondria and chloroplasts (Bravo et al. 2013). Literature sources on the subject also indicated a dual action of phenolic acids. Phenolic acids found singly or in combination with other polyphenolics exhibit a phytotoxic effect on plants. This mechanism may be based on their synergistic or antagonistic action (Peyrat-Maillard&Cuvelier, 2003). In plant cells this leads to a reduction of e.g. the rate of photosynthesis, stomatal conductivity and transpiration. Methyl ester of salicylic acid serves the function of a carrier triggering the defense mechanism against infections within the plant and between plants. Studies conducted to date also indicate that a too low concentration of phenolic acids in plant cells may also intensify the effects of oxidative stress.

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Antiviral properties

The most extensive body of information is available on antimicrobial properties of phenolic acids. They are inhibitors of virus development, e.g. gallic acid and its derivatives inhibit the development of Herpes Simplex Virus (HSV), including HSV-1, which is acquired in childhood and causes blisters, and HIV-1 (Human Immunodeficiency Virus) from the retrovirus family being a causative agent of AIDS (Acquired Immune Deficiency Syndrome). Gallic acid and its derivatives affect infectivity of HSV-1 by deactivation of viruses, which have been bound with cells, via disturbing viral glycoproteins (ICP27, GC, GD and VP5) blocking their expression, thus limiting virus penetration and replication. In the case of infection with HIV-1 inhibition consists in blocking viral integrase activity (Edenis et al. 1995, Kratz et al. 2008).

Antimicrobial properties

Phenolic acids exhibit also bactericidal properties. In the case of a bacterium *Clostridium botulinumi* gallic acid inhibits the production of the botulin toxin and impairs bacterial adhesion to the substrate by damaging enzymes and transport proteins. Phenolic acids and their esters are growth inhibitors for bacteria from the genera *Yersinia, Bacillus, Corynebacterium, Proteus, Staphylococcus, Enterococcus, Klebsiella, Micrococcus, Escherichia* and *Pseudomonas* as well as yeast from the genera *Candida, Malassezia* and *Trichosporon*. Gallic, vanillic, synapic and protocatechuic acids limit growth of Gram-positive bacteria, e.g. *Staphylococcus aureus* and *Staphylococcus epidermidis*, and Gram-negative bacteria e.g. *Escherichia coli, Enterobacter cloacae DG-6* and *Pseudomonas acidovorans* (Czechowska et al. 2009, Nowak et al. 1992). These acids exhibit a more effective destructive effect on cells of Gram-positive rather than Gram-negative bacteria. This results from the fact that cells of Gram-negative bacteria are equipped with an outer envelope surrounding the cell wall, which hinders diffusion of hydrophobic compounds into the cell through the liposaccharide membrane. Such bioactive compounds as caffeic, ferulic and protocatechuic acids also inhibit growth of bacteria responsible for food poisoning, e.g. *Bacillus subtilis* and *Bacillus cereus.* Derivatives of phenolic acids also exhibit bactericidal properties against rods of *Yersinia enterocolitica*. Among them compounds of o-coumaric acid are more effective than m-coumaric acid derivatives, which may be connected both with the chemical structure of these phenolic acids and resistance of these bacteria (Stachelska et al. 2012).

Antifungal properties

Benzoic acid and its derivatives exhibit antimicrobial activity also in relation to microscopic fungi and yeast at pH <5.0. Phenolic acids limit growth of microscopic fungi e.g. *Fusarium* spp., *Aspergillus* spp. And *Penicillium* spp. Benzoic acid in the presence of other polyphenolics shows a synergistic fungicidal effect against *Cryptococcus neoformans* (Czechowska et al. 2009). Moreover, phenolic acids inhibit growth also in yeast from the *Candida* family, e.g. *Candida albicans*. Kulik et al. (2015) in his research showed that *Fusarium* spp. produces phenolic acids. The production of trans-cinnamon and chlorogenic acid inhibits the production of trichothecenes. Mushroom strains reduce exogenous phenolic acids, which leads to their conversion or degradation. Exogenous trans-cinnamic acid and chlorogenic acid inhibit the production of mycotoxins by *Fusarium* spp., which seems to be largely dependent on the phenolic compound and its concentration and the test strain. The production of ergosterol is stimulated by trans-cinnamic acid, while chlorogenic acid negatively affects ergosterol biosynthesis. Changes in ergosterol biosynthesis can be explained by various antifungal effects of phenolic acids (Kulik et al. 2015).

The action of phenolic acids on plants

Metabolites most often produced by plant cells are phenolic compounds, very often have allelopathic potential, including cinnamic acid and benzoic acid and their phenolic derivatives. In the biological literature you can find a lot of information on the effect of phenolic compounds on plants. The effects of allelopathins induced at the cellular level can be divided into primary and secondary (Wójcik-Wojtkowiak et al. 1998). Finally, it was considered that the damage of the cell membrane is the first and the most basic one of the harmful effects of the allelic compounds, thus also cinnamic or benzoic acid and their phenolic derivatives. As a result of contact with this structure, they immediately reduce the transmembrane electrochemical potential. The range of action of these compounds depends on the concentration and solubility of the lipid in it. The rate of action is also dependent on the pH of the environment, and penetration through the membrane is most intense at lower pH and higher external concentrations (Shann & Blum, 1987). Depolarisation of the membrane caused by the presence of phenolic acids causes an unlikely outflow of both anions and cations, accompanying the increased permeability of these structures. These effects are related to the

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inhibition of ion uptake. It has been shown that phenolic acids suppress the absorption of phosphorus, potassium, magnesium and nitrate ions. Thus, changes in ion content of mineral substances in plant tissues may be one of the evidence for the presence of phenolic acids in the. Benzoic and cinnamic acids also damage the integrity of cell membranes by reducing the sulfhydryl groups. Both substances induce lipid oxidation caused by the presence of free radicals in the membranes as a result of inhibition of the enzymes catalase and peroxidase. Oxidation of the sulfhydryl groups of the plasma membrane is the first way they work. Derivatives of the abovementioned acids cause structural changes in membranes, including, in turn. Cations of membrane proteins - inter alia, membrane channels and conveyors and proton pumps. Many plant physiologists emphasize the negative impact of phenolic compounds with allelopathic potential on the water ratios prevailing in the plant. The influence of phenolic acids on the retention and flow of ions through plasma membranes is directly related to changes in the water management of plants. These compounds reduce the water conductivity of the root tissues, as evidenced by changes in the parameters characterizing the water management of plants. Blum and his colleagues investigated the allelopathic effect of feluric acid. They showed that this substance limits water uptake by cucumber, tomato and bean seedlings and was not caused by the osmotic effect of the nutrients used for plant breeding. In addition, they also found that ferulic acid is a more potent growth inhibitor than p-coumaric acid and that the lower the pH of the environment, the more negative is the ferulic acid effect on water intake (Wójcik-Wojtkowiak et al. 1998). In turn, in other studies carried out using soybean cuttings (they were from 10 days to 4 weeks) it turned out that the phenolic acids tested for ferulic, p-coumaric, coffee, salicylic, p-hydroxybenzoic, gallic and chlorogenic have changed normal water balance of plants, which was characterized by a decrease in water potential in leaves, turgor pressure, or changes in the content of radioactive carbon isotope in tissues. The radioactive carbon isotope in C3 plants is an indicator of the degree of water stress during growth. The results of these studies also indicated that the concentration that caused the inhibition of seedling growth testifies to water stress. Available data suggest that polyphenols, such as chlorogenic and coffee acids, synergistically induce an increase in IAA (indolyl-3-acetic acid oxidase) to compensate for its level. The growth of germinating seeds is inhibited to a greater extent by trans cinnamon derivatives than the benzoic acid derivatives, which also showed a connection with the regulation of the oxidase activity of IAA, and consequently with the concentration of auxins in plant cells. P-coumaric acid and ferulic acid lead to increased L-phenylalanine ammonia activity, which in turn leads to inhibition of cucumber root growth. This enzyme is responsible for the beginning of synthesis of lignin deposited in the cell walls. However, its deposition caused by previous induction causes a loss of plasticity of the cell walls, and thus - limitation of cell enlargement and elongation. Other studies have shown that when reducing the amount of polyphenol oxidases in the seedlings of maize (Zea mays), ferulic acid increases the activity of peroxidase, catalase, as well as indole-3-acetic acid oxidase. Although numerous research studies have shown the influence of many natural phenols on the frequency of enzymatic oxidation of IAA, it has not yet been determined how this action is associated with allelopathic growth inhibition. It is also known that ferulic acid compounds stimulate root formation in a "casual" way. It is therefore common to observe that distorted, short and stocky roots are found in seedlings that have been subjected to phenolic acids during the tests. This morphology probably results, at least in part, from the interaction of phenolic allelics with IAA responsible for plant growth (Einhellig 2004). The presence of phenolic compounds and their precursors in plant tissues undoubtedly affects their photosynthetic potential. Cinnamic acid and benzoic acid contribute to the reduction of the net profit of photosynthesis, which is caused by the slowdown of its pace. The reason for this is primarily the reduced conductivity of stomata, and partly also the reduction of chlorophyll. Studies carried out in this area allowed to conclude that the: ferulic and p-coumaric acids with a concentration of 0.5 mM decreased the amount of chlorophyll a and chlorophyll b in soybean leaves, and this conclusion was based on the mass of leaves before and after the use of these substances. On the other hand, other studies have shown that benzoic, syringic, protocatechuic, trans-cinnamon and caffeic acids reduce the concentration of chlorophyll in the leaves of both soy and Chinese bean with a significant effect on chloro-liquid (Einhellig 2004). All phenolic compounds produced by plants have a negative effect on the structure of mitochondria as well as on the metabolic processes of these organelles. This applies above all to intracellular respiration, thanks to which the whole body obtains energy enclosed in the form of high-energy adenosine triphosphate (ATP) bonds. Numerous research works on the influence of allelopathins on the respiration process in plant-acceptors have shown that phenolic acids and their mixtures modulate its rate, disturbing the structure of the internal mitochondrial membrane. It was established, among others in studies conducted with isolated mitochondria using benzoic and cinnamic acids. Subsequent experiments using salicylic acid, gentisin and p-hydroxybenzaldehyde (salicylaldehyde) carried out in this respect showed blocking electron transport in the cytochrome b / c1 complex after using these substances. In comparison to other inhibitors, the level of phenolic

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compounds required to attenuate oxygen uptake by the mitochondria is quite high. Thus, it is undoubtedly the conclusion that the cytotoxic action of these substances does not pass without trace of such important cellular structures as the mitochondria (Quah 1990). One of the effects of exposure of plant cells to cinnamon and benzoic acids is that normal cell synthesis patterns change. Cell cultures treated with 0.01 mM cinnamic acid and 0.1 mM ferulic acid limit protein biosynthesis, which is also indicated by studies using lettuce seedlings (Lactuca sativa). However, both of these acids have different effects on the amount of other organic cell compounds. Ferulic acid increases the production of lipids and reduces organic acids, while cinnamic acid does not change the percentage of these fractions. Available data show that the phenolic compounds described in the effects on the physiological processes of plants depend on both their quality and quantity, and hence their concentration. A particular problem is the modification in the synthesis and allocation of stored organic compounds, and later their mobilization and conversion to compounds necessary during germination and development of seedlings. Thus, the action of phenolic acids on carbon metabolism helps explain why early seedling growth is so sensitive to allelochemistry (Einhellig 2004).

Toxic effects on other organisms

Phenolic acids are increasingly often used in various branches of industry (Stuper-Szablewska et al. 2017), including the chemical industry. Waste products containing these compounds penetrate to surface waters, ground waters and soil, thus contaminating the aquatic environment. There as a result of multiple transformations and reactions with other organic and inorganic compounds they form toxic products disqualifying water in terms of its potability (Shahidi & Chandrasekara 2010, Nakajima et al. 2007, Burris et al. 2012). In the food industry phenolic acids are frequently used as natural preservatives (Ozcan et al. 2014). Studies conducted to date indicate that phenolic acids have been used in food technology to increase product shelf life since the mid-19th century, initially it was salicylic acid and next benzoic acid and its derivatives (p-hydroxybenzoic acid, sodium benzoate, calcium benzoate, potassium sorbate) as well as cinnamic acid. These acids are naturally found first of all in berry fruits and cereal grain, providing them with high storage quality. Benzoic acid due to its poor water solubility has been replaced by its readily soluble salts. Their addition to food at a concentration of 0.02-0.08% constitutes a barrier to microbial growth (primarily microscopic fungi). Excess benzoic compounds are not accumulated in the human organism; however, they may lead to irritation of gastric and intestinal mucosa and allergic skin lesions (Stachowicz 2015, Dec 2016). In the case of milk the presence of phenolic acids has a negative effect on its production process, since milk contains an enzyme lactoperoxidase, which catalyzes oxidation of organic and inorganic substrates (Br^-, I^-, SCN^-), as a result of which they gain antibacterial properties. This enzyme, together with its substrates and products, forms the so-called lactoperoxidase system, which plays an important role in the immune system thanks to is antibacterial action in milk and secretions of the mucous membranes. These properties may be disturbed by the presence of phenolic acids in cow milk. All phenolic acids are inhibitors of the lactoperoxidase in milk. A particularly strong action inhibiting activity of this enzyme is observed for 3,4-dihydroxybenzoic, 3,5-dihydroxybenzoic, chlorogenic, synapic, 4-hydroxybenzoic and vanillic acids. For this reason phenolic acids may weaken the immune system, leading to deactivation of lactoperoxidase (Koksal et al. 2016).

In addition to the desired antiviral, antibacterial and antifungal effects, phenolic acids can adversely affect the health of the consumer. Table 3 presents the toxicity limit values for selected phenolic acids. Based on these data, they were compared with the Hodge and Sterner classification (Table 4). It was found that phenolic acids are within the limits of toxicity from medium to very toxic.

Table 3. Toxicity of selected phenolic acids and their derivatives (mg/kg b.w.)

Acid	LD_{50}	Test object	Route of administration	Literature
4-Hydroxybenzoic	> 10000 mg/kg b.w. 2200 mg/kg b.w.	rat mouse	p.o.	Data sheet (A), 2017,
Gallic	2800 mg/ kg b.w. 5000 mg/ kg b.w.	rabbit rat	p.o.	Data sheet (B), 2016,

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Ferulic	>194 mg/kg b.w. 3200 mg/kg b.w. 2113 mg/kg b.w. 2445 mg/kg b.w.	mouse mouse rat - female rat - male	i.p. p.o. p.o. p.o.	Data sheet (D), 2015, Tada et al. 1999, Wang & Ou-Yang, 2005,
p-Coumaric	2850 mg/kg b.w.	mouse	p.o.	Data sheet (C), 2017,
Protocatechuic	800 mg/kg b.w. 3500 mg/kg m.c	mouse	i.p. i.v.	Kakkar & Souravh, 2014,
Acetylsalicylic	300-500 mg/kg b.w. 2500-3500 mg/kg b.w.	children adult	p.o.	Dreisbach & Robertson, 1995, Wójcik-Skierucha, 2000,

Table 4. Classification of toxicity according to Hodge and Stemer (mg/kg b.w.)

Degree of toxicity	Level of substancetoxicity	LD_{50} (mg/kg b.w.) after per os administration to rats
3	highly toxic	50
4	medium toxic	500
5	weakly toxic	5000
6	practically non-toxic	15000
7	relatively non-toxic	>15000

Toxicity of phenolic compounds is determined based on the so-called acute toxicity (LD_{50}; lethal dose), with the tested substances administered by ingestion (per os - p.o.), intraperitoneally (i.p.), subcutaneously, or intravenously (i.v.) (Kędzia & Hołderna-Kędzia 2011).

Ferulic acid is the most thoroughly investigated phenolic acid. This is connected with the fact that it is found in high concentrations (even several hundred fold than those of the other acids) in plant origin raw materials and products of considerable importance for the human and animal diets. Ferulic acid exhibits antioxidant properties enhancing e.g. anti-inflammatory, antiviral and anticancer action. In is used in many branches of medicine as well as the cosmetics and bakery industries (Zhao & Moghadasian 2008, Akihisa et al. 2000, Graf 1992, Rukkumani et al. 2004, Ou & Kwok 2004, Srinivasan et al. 2007, Kumar & Pruthi 2014, Stuper-Szablewska et al. 2017). Ferulic acid and its metabolites are found at high concentrations in cereal grain, fruit, vegetables, nuts and unroasted coffee beans. It is readily absorbed from the intestinal lumen; however, esterification occurring in the duodenum limits intestinal absorption. Metabolites of ferulic acid are eliminated from the blood plasma, which indicates that the daily consumption of plant products is necessary to maintain their high blood concentrations (Manach et al. 2004).This was stated based on studies concerning the relation of its excretion to intake. It was observed that the maximum period of its excretion with urine is approx. 7 hours, thus it was stated that it is not accumulated in the animal organism (Bourne & Rice-Evans 1999, Chang et al. 1993). Moreover, it was reported that its free form is absorbed by the intestines at 8 μmol/kg body weight (Zhao et al. 2004). The range of metabolites and their relative proportions depend on many factors, including the dose, administration route and animal species. Literature sources on the subject report low toxicity of ferulic acid, which has been confirmed in experimental studies. However, Tada et al. (1999) in their study determined its LD_{50}, with the lethal dose in the case of rats exceeding that for mice. Tada et al. (1999) also observed reduced mobility as well as lacrimation followed by death in rats administered ferulic acid (1929 mg/kg) as early as within the first 24 h during the 14-day observation period (Tada et al. 1999). In turn, intestinal hemorrhage followed by death was observed within 24 h after the administration of LD_{50}. Nevertheless, ferulic acid has been approved in the USA, Japan and most European countries as a food additive and it is used as a natural antioxidant in food, beverages and cosmetics (Tada et al. 1999, Graf 1992). It has also been reported that ferulic acid forms 4-vinylguaiacol through decarboxylation during processing, contributing to a deterioration of taste in cooked dishes, beer and orange juice (Medina et al. 2002, Narziss et al. 1990). Lattanzio et al. stated that this acid inhibits development and growth of five microscopic fungi (*Sclerotinia sclerotiorum, Fusarium oxysporum, Alternia* spp., *Botrytis cinerea, Penicillium*

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digitatum) and it exhibits the greatest activity among all investigated acids. In the course of other studies it was shown that ferulic acid at a concentration of 500 mg/l may inhibit growth of yeast (*Pichia anomala, Debaryomyces hansenii*, *Saccharomyces cerevisiae*), although it is less effective than derivatives of benzoic acid (Lattanzio et al. 1994).

Animal studies showed an adverse effect of long-term application of large amounts of chlorogenic acid, which may enhance inflammatory response. This acid administered to laboratory rats caused abnormal musculoskeletal development. It was also shown that the application of chlorogenic acid together with high-fat diet contributes to a reduction of body weight, while it does not protect against the adverse metabolic effect of such a diet. In turn, discontinuation of chlorogenic acid administration after the slimming therapy does not guarantee maintenance of constant body weight.

Most phenolic acids, e.g. 4-hydroxybenzoic and gallic acids, irritate the skin and eyes, which may cause dyspnea and coughing. Gallic acid shows the cytotoxic action in the cytotoxicity test in relation to healthy human skin fibroblasts (Czechowska et al. 2009). In turn, synapic acid applied at very high concentrations exhibits cytotoxic effect against cervical cancer cells.

Synapic acid is the most effective phenolic acid in terms of DNA damage during proliferation of human leukemia. When administered at low concentrations it increases cell viability, while at a high concentration it almost completely inhibits proliferation of cancer cells. Moreover, synapic acid exhibits genotoxic properties in relation to human colon adenocarcinoma (Hameed et al. 2016, Zhang et al. 2008).

In the presence of manganese chelate caffeic acid induces mutations in bacteria *Salmonella typhimurium*, contributing to *Saccharomyces cerevisiae* D7 gene conversion. This acid may also cause chromosomal aberration in ovaries (Stich et al. 1981 (A,B)). Caffeic acid supplied to humans per os is found mostly in the bound form and thus its bioavailability is dependent on absorption in the small intestine (Olthof et al. 2001). Caffeic acid produced in the intestinal microflora may penetrate to cells with the participation of monocarboxylic acid transporter (MCT) proteins (Favre & Powell 2014). In intestinal mucosa cells and in the liver caffeic acid undergoes glucuronidation involving UDP-glucurone transferase, sulfonation or *o*-methylation, resulting in weakening of its antioxidant properties. Caffeic acid inhibits also the enzymatic action of lipoxygenase, and thus it inhibits biosynthesis of leucotrienes, lipids related with the immune system and participating in inflammatory processes in asthma and allergies (Koshihara et al. 1984, Murita & Kashihara, 1985). This acid blocks aggregation of platelets by slowing the production of thromboxanes exhibiting antithrombotic action and contributing to attacks of dyspnea (Andueza et al. 2009, Chesson et al. 1999, Cheng et al. 2007, Budryn & Nebesny 2006). Toxic effects on living organisms were also shown for protocatechuic acid (PCA). PCA applied orally in mice leads to a reduction of GSH concentration in the liver and kidneys; however, no mortality was reported.

Phenolic acids found in propolis extracts in the form of ester combinations exhibit allergenic properties. The most active allergens include benzyl esters of caffeic and ferulic acids.

Phenolic acids may disturb uptake and action of allelopathic substances, e.g. cinnamic acid supplied together with polygodial inhibits root growth in seedlings of lettuce (*Lactuca sativa*) by limiting proton transport from the cytoplasm to apoplasts (Fujita & Kubo 2003)**,** which is regulated by the activity of ATP-dependent proton pumps (Sanswik 1981). Some phenolic acids, i.e. p-hydroxybenzoic, p-coumaric and ferulic acids, inhibit uptake of micro- and macroelements through changes in cell membrane conductivity (Streibig & Olofsdotter 2002, Duke 2003).

Concluding remarks

Phenolic acids, being compounds exhibiting strong bioactive properties, have a considerable beneficial effect on living organisms. Their primary role is to counter the effects of oxidative stress induced by biotic and abiotic factors. However, depending on their concentration and synergistic action their action may sometimes be adverse and undesirable. Knowledge on the subject gained to date is limited. Nevertheless, the diverse structure, biological activity and the mechanism of action of phenolic acids facilitate their extensive application in many fields of science and branches of industry. Due to a lack of definite data concerning the synergistic toxic action of phenolic acids on plants,

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animals and humans administration of these compounds at high doses may cause health consequences which are difficult to predict.

The limited body of data on the toxic action of phenolic acids on animals and humans indicates the need to conduct such research in order to supplement the current state of knowledge on the subject. Justification for additional, comprehensive studies is related with the scarce remarks on the negative effect of phenolic acids applied at various doses on cells of living organisms.

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