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Aronia Plants: A Review of Traditional Use, Biological Activities, and Perspectives for Modern Medicine

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ABSTRACT The *Aronia* genus (Rosaceae family, Maloideae subfamily) includes two species of native North American shrubs: *Aronia melanocarpa* (Michx.) Ell. (black chokeberry) and *Aronia arbutifolia* (L.) Pers. (red chokeberry). The fruits of *A. melanocarpa* have been traditionally used by Potawatomi Native Americans to cure colds. In the first half of the 20th century, cultivars of black chokeberry were introduced to the Soviet Union and other European countries, providing fruits used by food industry. At present, it is used mainly for juice, jam, and wine production, as well as an ornamental plant. Among other substances, the berries of *A. melanocarpa* contain anthocyanins and procyanidins, possessing strong antioxidative potential. Numerous health-promoting activities—namely, antioxidative, antimutagenic, anticancer, cardioprotective, hepatoprotective, gastroprotective, antidiabetic, anti-inflammatory, antibacterial, antiviral, radioprotective, and immunomodulatory—have been demonstrated for black chokeberry extracts by both *in vitro* and in *in vivo* studies. The presented review summarizes the information concerning botany, cultivation, chemical composition, and pharmacological activities of *Aronia* plants.

KEY WORDS: • ***anthocyanins*** • ***antihyperlipidemic effect*** • ***antioxidant activity*** • ***polyphenols*** • ***procyanidins***

INTRODUCTION

SHRUBS OF THE *ARONIA* GENUS are native North American plants that have been traditionally used in Native American medicine. Fruits of *Aronia melanocarpa* (Michx.) Ell. (known as chokeberry, wild gooseberry, chokepear, or dogberry), were used by the Forest Potawatomi Native Americans, who called them "nîki'mînûn" or "sakwako'mînûn," to make a tea for treatment of colds.[1,2] *Aronia* berries were also used in the preparation of pemmican, a nutritious and lasting foodstuff prepared from fat, dried powdered meat, and sometimes fruits, in the northeastern United States.[2] Among North American settlers, berries and the bark were used as an astringent.[1]

In the 20th century, *A. melanocarpa* became popular in the Soviet Union and Eastern European countries, mainly for large-scale production of juices, jams, and wines and as a rich source of natural food colorants.[3–6] Black chokeberry gained popularity not only as a food ingredient, but also in herbal medicine, particularly in Russia and Eastern European countries, where it is often used as a natural antihypertensive and anti-atherosclerotic drug.[7,8] Apart from this, *Aronia* preparations are sometimes applied in achlorhydria, avitaminoses, and convalescence and as a remedy against hemorrhoids.[7,9] High anthocyanin contents in chokeberries led to intensive scientific research into biological activities of *Aronia* extracts, as much attention has been recently given to the chemopreventive action of polyphenols, as well as to their role in alleviating the symptoms of diet-related diseases, such as hypertension and atherosclerosis.[10–13]

The following article provides a review of the chemical composition, botany, cultivation, and pharmacological activity of *Aronia* plants.

BOTANY

The genus *Aronia* (Rosaceae family, Maloideae subfamily) includes two species of deciduous North American shrubs: *A. melanocarpa* (Michx.) Ell., known as black chokeberry, and *Aronia arbutifolia* (L.) Pers. (red chokeberry). *A. melanocarpa* is a shrub, 90–180 cm high, with purple-black pomes, about 6 mm in diameter, gathered in clusters of eight to 14 fruits on red pedicels. The berries ripen and drop early. The leaves, 3–7 cm long, are lustrous and glabrous and do not turn red. White-pink flowers open in May.[6,14] *A. arbutifolia* has bright red pomes, which persist into the winter. The dull green leaves are gray pubescent beneath and turn red in the fall.[14] The rangeland of *A. melanocarpa* extends from the northeastern part of North America and the Great Lakes area to the higher parts of the Appalachians in the south, where it occurs in mountain bogs and balds. It is absent from the Piedmont and Coastal Plain. *A. arbutifolia* is centered in the southeastern Coastal Plain

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but is also widespread throughout eastern North America. It occurs in marshes, savannas, and wet woodlands.[14,15]

Apart from the two, fairly distinct species mentioned above, a third controversial entity exists, called *Aronia prunifolia* (purple chokeberry). It has the features of an intermediate between *A. melanocarpa* and *A. arbutifolia*: purple-black fruits and pubescent young leaves, which become glabrous at maturity. The rangeland of *A. prunifolia* is similar to that of black chokeberry, but also extends into the range of red chokeberry. Purple chokeberry is generally considered as a hybrid between *A. melanocarpa* and *A. arbutifolia*, with apomixis being an effective stabilizer of hybridity, enabling *A. prunifolia* to expand into the rangelands of the original species.[14] Black chokeberry is also capable of crossing with closely related rowans (*Sorbus*), and the created hybrids were adapted for cultivation in Russia.[3]

CULTIVATION

Most information concerning *Aronia* cultivation refers to the black chokeberry (*A. melanocarpa*), which is most valuable as food ingredient (berries are used for juice, jam, and wine production) and as the source of natural pigments.[3,4,16,17] The plant became more popular after it had been introduced to Russia in the 19th century, originally intended as a source of berries in home gardens. Large-scale commercial cultivation of black chokeberry in the Soviet Union started in the late 1940s, reaching 17,800 ha in Siberia in 1984.[3,5,17] In 1986, a project of commercial *A. melanocarpa* cultivation was launched in Sweden, in order to obtain an efficient pigment source.[3,5] It is also very popular in Poland, the Czech Republic, Slovakia, and Ukraine.[7,18] In 1976, black chokeberry was introduced to Japan from the former Soviet Union.[19] The most commonly used cultivars include "Viking," "Nero," and "Aron," used for mass fruit production.[3,6]

The cultivation of the black chokeberry is based on cutting or seed propagation and is relatively trouble-free because of lack of serious diseases, pests, or bird problems, probably as a result of the sour taste of the berries. Only occasional rust and ringspot are reported, without serious impact on crop quality.[3,6] Limited generic variation makes seedling populations homogeneous and enables the establishment of large-scale cultures.[3] Besides traditional propagation methods, micropropagation protocols have been prepared for both black and red chokeberry, which may be useful for introduction of new valuable cultivars.[20,21]

Application of combined NPK fertilizer is beneficial as it increases vegetative growth and yield of *A. melanocarpa*; however, it has to be kept at a moderate level because excessive dressing leads to significant decrease in anthocyanin levels.[4] The "alkaline" (N, K, and Si) fertilizer exerts stimulating effect on fruit size and firmness.[22] Supplementation with microelements is beneficial as it increases anthocyanin contents in aronia pomes.[23] Treatment of plants with chlorocholine chloride resulted in increased polysaccharide and anthocyanin concentrations in fruits.[24,25] Experimental application of ornithine decarboxylase inhibitor (ethanolamine phosphate) significantly increased anthocyanin contents and induced transformation of saccharides to phenolics, whereas treatment with polyamine biosynthesis catabolites substantially increased flavonoid concentrations, at the cost of a slight decrease in anthocyanin levels.[26] Berry cracking, resulting from high water uptake during cultivation, should also be avoided as it causes a noticeable reduction in anthocyanin levels and fruit browning.[3] For black chokeberries cultivated in Sweden, the period from September 1 to 8 is optimal for harvesting in terms of berry weight and anthocyanin contents. Prolonged cultivation leads to anthocyanin oxidation and undesirable fruit browning, as does their drying in high temperature.[27,28]

APPLICATION

The pomes of black chokeberry have sour taste and astringent properties, which make them suitable for processing, rather than for direct consumption.[6] Because of high anthocyanin contents, *Aronia* fruits can be used as an ingredient of antioxidant health-promoting juices, teas, and cordial liqueurs.[29–33] It was confirmed that expure of chokeberry juice to a temperature of 60°C for 8 hours resulted in a decrease of 30% in anthocyanin levels and >50% loss of its antioxidant properties. To avoid this, fast and preservative drying methods should be applied.[34] To stabilize the color and anthocyanin compounds in black chokeberry juices, flavone-rich baikal skullcap (*Scutellaria baicalensis*) root was added during production.[35] This process, known as copigmentation, significantly improves the quality of *Aronia* juices in terms of color stability and anthocyanin contents.[35,36] In the pharmaceutical industry, chokeberry extracts are used for production of syrups and dietary supplements.[37] High pectin content makes *Aronia* berries useful for production of mixed jams, together with low-pectin fruits.[6] Chokeberry fruits or preparations can be added to jams to improve their taste, color, or antioxidant properties.[38,39] *A. melanocarpa* berries are, among grapes (*Vitis* sp.) and roselle (*Hibiscus sabdariffa*), an important source of anthocyanins, which can be used as safe, natural food colorants.[16,35,40]

PHARMACOLOGICALLY RELEVANT CONSTITUENTS

Most literature data concerning the chemistry of *A. melanocarpa* refers to its berries being a rich source of pharmacologically relevant compounds. Polyphenols, especially anthocyanins and procyanidins, make up the main group of biologically active constituents in black chokeberry fruits. These compounds are responsible for antioxidant properties of the plant. Other phenolics include chlorogenic and neochlorogenic acid (Fig. 1), as well as a small amount of tannins.[41–43] Total phenolics content ranges from approximately 2,000 to approximately 8,000 mg/100 g dry weight and depends on variety, cultivation conditions, and harvest date.[10,26,42,44–46]

Beside polyphenols, *A. melanocarpa* constitutes a source of sugar (10–18%), pectins (0.6–0.7%), the sugar alcohol

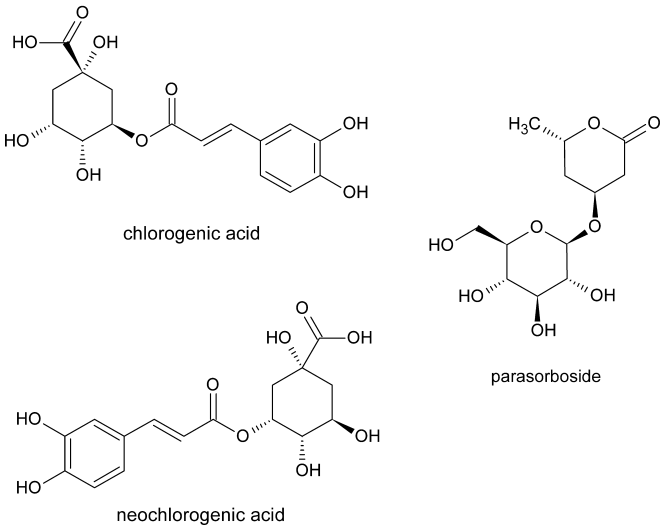


FIG. 1. Chemical structures of organic acids and parasorboside present in *A. melanocarpa*.

sorbitol, and parasorboside (Fig. 1).[37,41,47,48] A low amount of fat (0.14% fresh weight), composed mainly of linoleic acid glycerides and phosphatidylinositol, was also reported in the berries.[20,49] Ash value for fresh fruits was found to be 0.44%.[20] Analyses showed relatively high contents of K and Zn, as well as some amounts of Na, Ca, Mg, and Fe.[20,50] Besides mineral compounds, vitamins B_1, B_2, B_6, and C, niacin, panthotenic acid, folic acid, α- and β-tocopherol, and carotenoids (including β-carotene and β-cryptoxanthine) were identified in *A. melanocarpa* berries.[20,51,52]

Among the triterpenes, β-sitosterol and campesterol were identified in black chokeberry fruits.[49] Seedlings of *A. melanocarpa* were also shown to contain triterpenes, derivatives of betulinic acid, 23-hydroxybetulinic acid, and 2α-hydroxyoleanolic acid.[53]

Among other derivates, black chokeberry fruits contain over 40 volatile compounds, with clear domination of benzaldehyde cyanohydrine, hydrocyanic acid, and benzaldehyde. Other volatile derivates are present in trace amounts.[54] Amygdalin, the presence of which is characteristic for the seeds of many plants from the Rosaceae family, was also found in *A. melanocarpa* fruit extract.[47]

The most important and broadly researched group of pharmacologically relevant black chokeberry compounds are flavonoids, represented mainly by anthocyanins and procyanidins.

Flavanols

The main flavanols in the chokeberries are procyanidins. Their content varies from 0.66% to 5.18% dry weight.[42,55] The structure of polymeric (–)-epicatechins involves numerous flavan-3-ol subunits, connected mainly with C4→C6 and C4→C8 bonds (so-called B-type) (Fig. 2).[48,56] The degree of polymerization of black chokeberry procyanidins varies from 2 to 23 in the fruits, with the clear domination of >10-mers fraction. High polymerization values of over 30 were recorded for *A. melanocarpa* pomace.[42,55] Free epicatechin is also present in black chokeberry pomes, although its concentration is significantly lower (0.015% dry weight) in comparison with polymeric procyanidins.[42]

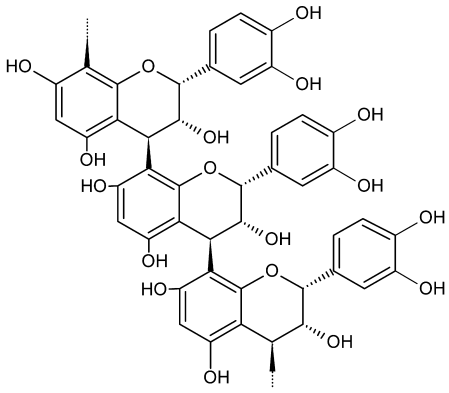


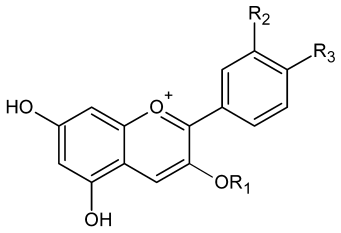
FIG. 2. Chemical structure of polymeric procyanidin with C4→C8 bonds.

Anthocyanins

In chokeberry fruits, anthocyanins are the second largest group of phenolic compounds, with a concentration range from 0.60% to 2.00% dry weight. Anthocyanins present in black chokeberry are a mixture of cyanidin glycosides: 3-galactoside, 3-glucoside, 3-arabinoside, and 3-xyloside (Fig. 3), of which cyanidin 3-galactoside is the main one.[42,55,57–61] Trace amounts of the pelargonidin derivatives 3-*O*-galactoside and 3-*O*-arabinoside were also detected in fruits (Fig. 3).[55]

Other flavonoids

Other flavonoid compounds were also identified in both fruits and flowers of *A. melanocarpa.* In a methanol extract



cyanidin-3-O-galactoside	R_1 = gal	R_2 = OH	R_3 = OH
cyanidin-3-O-glucoside	R_1 = glc	R_2 = OH	R_3 = OH
cyanidin-3-O-xyloside	R_1 = xyl	R_2 = OH	R_3 = OH
cyanidin-3-O-arabinoside	R_1 = ara	R_2 = OH	R_3 = OH
pelargonidin-3-O-arabinoside	R_1 = ara	R_2 = H	R_3 = OH
pelargonidin-3-O-galactoside	R_1 = gal	R_2 = H	R_3 = OH

FIG. 3. Chemical structures of anthocyanins present in *A. melanocarpa*.

from the flowers of black chokeberry[62] one flavanone was identified: eriodictyol 7-*O*-β-glucuronide (Fig. 4). Five flavonol–quercetin derivatives—3-vicianoside (6''-*O*-β-arabinosyl-β-glucoside), 3-robinobioside (6''-α-rhamnosyl-β-galactoside), 3-rutinoside (6''-α-rhamnosyl-β-glucoside), 3-β-galactoside, and 3-β-glucoside—were also identified in flower umbels of *A. melanocarpa* (Fig. 4).[62] Three of these quercetin glycosides—3-rutinoside, 3-β-galactoside, and 3-β-glucoside—were also detected in black chokeberry fruits.[42,59] It is noteworthy that flavonol derivates constituted only 1.30% of all phenolic compounds in the berries.[42]

ANTIOXIDANT ACTIVITY

As various fruits are considered to be rich sources of polyphenolic compounds, numerous studies have been undertaken to establish their antioxidant potential.[59,63] Many of these experiments were of comparative character, and their goal was to determine the differences between distinct berries, in term of chemical composition and free radical scavenging potential.

A comparative study using the oxygen radical absorbing capacity assay showed that acetone extracts from black chokeberries exhibit stronger antioxidant activity than those obtained from blueberries (*Vaccinium corymbosum*) (over five times), cranberries (*Vaccinium macrocarpon*) (over eight times), and lingonberries (*Vaccinium vitis-idaea*) (over four times).[59] The oxygen radical absorbing capacity-based study was further extended to other berries, like black currant (*Ribes nigrum*), red currant (*Ribes rubrum*), gooseberry (*Ribes grossularia*), and elderberry (*Sambucus nigra*) and proved *A. melanocarpa* to be the most potent antioxidant of the species mentioned.[55] Other experiments, based on 2,2-diphenyl-1-picrylhydrazyl radical scavenging ability, demonstrated that *A. melanocarpa* methanolic extracts have greater antioxidant potential than blackberry (*Rubus fruticosus*), red raspberry (*Rubus idaeus*), and strawberry (*Fragaria anannassa*).[64,65] Moreover, antioxidant activity of chokeberry extracts turned out to be stronger than those of synthetic antioxidants butylated hydroxytoluene and butylated hydroxyanisole, but weaker in comparison with α-tocopherol.[64] A similar study, performed on extracts from berries of *A. melanocarpa*, as well as blueberry (*Vaccinium myrtillus*), rabbiteye blueberry (*Vaccinium ashei*), black currant (*R. nigrum*), and elderberry (*S. nigra*), confirmed high anti-2,2-diphenyl-1-picrylhydrazyl radical activity of all the fruits mentioned.[60] Acetone extracts from *A. melanocarpa* berries were also able to inhibit methyl linoleate autooxidation, among numerous other berries, like crowberry (*Empetrum nigrum*), cloudberry (*Rubus chamaemorus*), and whortleberry (*Vaccinium uliginosum*).[10]

Various types of *A. melanocarpa* extracts exhibit significant antioxidative activity *in vitro*, measured by scavenging effect on 2,2-diphenyl-1-picrylhydrazyl and 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radicals. The highest anti-free radical activity was observed in methanolic extracts from freeze-dried pomace; values were slightly lower for methanolic extracts from lyophilized fruits and the lowest for black chokeberry juice (water extract).[42] The above results indicate that pomace constituting a by-product from *Aronia* juice production can be effectively exploited as a source of anthocyanins. Water infusions obtained from dried pomace contained over 10 times more anthocyanins than those prepared from dried chokeberry pomes.[28]

Black chokeberry juice has been shown to inhibit phosphatidylcholine oxidation in a peroxidating liposome system, being approximately twice as efficient as black currant (*R. nigrum*) juice. Moreover, *Aronia* juice clearly exerted a synergistic effect with α-tocopherol in the experiment mentioned, which was not observed in the case of black currant. The results obtained show that black chokeberry can be used not only as a coloring agent, but also as an effective antioxidant, protecting α-tocopherol and unsaturated lipids in food products.[66]

The antioxidant potential of *A. melanocarpa* was demonstrated *in vitro*, as well as in numerous *in vivo* models, where it often combined with other pharmacological activities. Among other effects, the role of black chokeberry extracts in the reduction of oxidative stress, measured by various biochemical markers, is mentioned by several authors.[11,67]

In the experiment on rats, the level of erythrocyte superoxide dismutase was significantly lowered when their

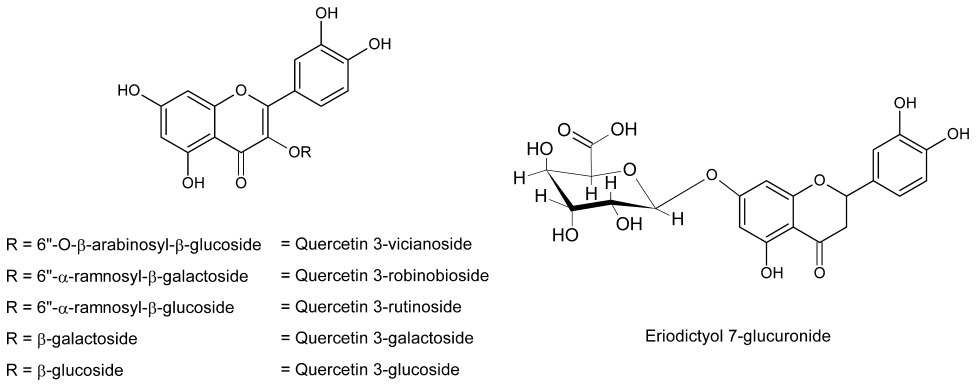


FIG. 4. Chemical structures of quercetin glycosides and eriodictyol glucuronide present in *A. melanocarpa*.

pro-oxidative, hypercholesterolemic diet was supplemented with black chokeberry extract.[11] In a similar experiment, addition of a strongly oxidized fat mixture to the food resulted in an increased thiobarbituric acid-reactive substances (TBARS) level in rat blood. The TBARS concentration was substantially lower in animals receiving chokeberry fruit extract together with oxidized fats, indicating the notable potential of *A. melanocarpa* against lipid peroxidation.[68] Another study, performed on rats with experimentally induced oxidative stress (high-fructose diet and streptozotocin injection), showed that chokeberry extract ingestion leads to noticeable improvement of antioxidant status in liver, kidney, and lungs, measured as the level of TBARS.[67] Streptozotocin-induced oxidative stress in rats, demonstrated by an increased TBARS concentration in kidneys, was significantly lowered in the case of diet supplemented with *A. melanocarpa* juice.[69]

Beside streptozotocin, several chemicals and physical factors can induce oxidative stress, which can be alleviated by black chokeberry extracts. Numerous studies have been undertaken to estimate the protective effect of *A. melanocarpa* phenolics against various oxidative stress-inducing agents.

It has been shown that black chokeberry juice, used as a dietary supplement, substantially prevented lipid peroxidation (measured by TBARS concentration), as well as inhibited the lowering of reduced glutathione (GSH) level in livers of rats exposed to CCl_4.[70] Similar activity was observed for *A. melanocarpa* leaf extract, which inhibited CCl_4-induced hepatic lipid peroxidation.[71] The protective effect of *Aronia* anthocyanins was also observed, when sulfide-2-chloroethyl-3-chloropropyl, an alkylating agent and a member of the sulfur mustards family, was administered to rats, producing serious oxidative damage. Simultaneous application of black chokeberry anthocyanins resulted in decreased TBARS concentration in the lungs and small intestine, as well as in increased catalase activity, compared to intoxicated rats not fed anthocyanins.[72] In another study, supplementation of rat diet with black chokeberry juice reduced increased TBARS level in gastric mucosa and plasma, produced by indomethacin administration.[73] *A. melanocarpa* anthocyanins proved to be effective in alleviating the results of experimental pancreatitis in rats, developed by platelet-activating factor injection. Ingestion of the dye before platelet-activating factor administration inhibited lipid peroxidation, measured as TBARS level.[74] Other experiments showed that the effects of lead intoxication in rats, in terms of lipid peroxidation, can be diminished by simultaneous administration of black chokeberry anthocyanins.[75,76]

A. melanocarpa extracts proved to be effective in alleviating oxidative stress induced by physical factors. Black chokeberry leaf extract effectively reduced lipid and protein peroxidation in brain homogenates obtained from rats subjected to immobilization-induced oxidative stress.[77] In another experiment, supplementation of rat diet with *Aronia* fruits noticeably delayed lipid peroxidation in γ-irradiated animals but had no effect on the antioxidant enzymatic system.[78]

Apart from studies in rat models, the antioxidative activity of *A. melanocarpa* was examined in humans, often in connection with the phenomenon of oxidative stress, which accompanies several metabolic problems, like hypercholesterolemia and diabetes. It has been shown that black chokeberry extracts significantly influenced human platelet functions *in vitro.* Platelet superoxide production was substantially increased in patients with cardiovascular risk factors (hypertension, hypercholesterolemia, smoking, and diabetes); treatment of platelets with *A. melanocarpa* extract caused a significant decrease in superoxide level in patients with cardiovascular risk, whereas no effect was observed in the case of the control group.[79] In another *in vitro* study, black chokeberry juice, as well as the anthocyanin fractions obtained after its digestion in an artificial food canal, significantly inhibited oxidative metabolism of activated polymorphonuclear neutrophils in obese and nonobese patients, leading to substantial reduction of oxidative stress.[80] Supplementing the diet with *A. melanocarpa* anthocyanins for 30 days caused noticeable improvement of oxidative status in blood cells of patients with hypercholesterolemia.[81] Black chokeberry extracts also significantly reduced oxidative stress, manifested by increased levels of autoantibodies to oxidized low-density lipoproteins, in individuals with other metabolic problems, like men with oligospermia and women in pregnancies complicated by intrauterine growth retardation.[82,83]

It must be mentioned that oxidative stress in humans can be induced not only in the course of serious diseases, but also as a result of physical exercise.[84,85] Supplementation of rowers' diet with black chokeberry juice during a 1-month training camp caused a significant decrease in TBARS concentrations in blood samples collected after the exercise, compared to the control group. The post-training levels of glutathione peroxidase and superoxide dismutase were lower in the case of anthocyanin-receiving subjects, indicating noticeable alleviation of exercise-induced oxidative stress.[86] Similar results were obtained in the former experiment on rats subjected to exercise-induced oxidative stress. Ingestion of chokeberry extract for a few days prior to treadmill exercise resulted in significantly lowered post-training TBARS levels and higher GSH content in rat tissues, compared to the control group.[87,88]

PHARMACOLOGICAL ACTIVITY

For many years, black chokeberry fruits and preparations have been considered as food ingredients, rather than plants of particular medical properties. Since it was discovered that natural polyphenols, including anthocyanins from various berries, exhibit several health-promoting properties like antimutagenic, lipid-lowering, and reducing the risk of cardiovascular diseases, *Aronia* fruits and preparations have been extensively investigated for these properties (Table 1).[113,118–121] No toxicity was observed for black chokeberry extracts.[41] It should also be noted that the results obtained from *in vitro* tests significantly differ from those from *in vivo* studies, as chokeberry anthocyanins are

Table 1. Pharmacological Activities of Black Chokeberry Preparations

Pharmacological effect	*Type of preparation used*[a]	*Scheme of experiment*	*Most important findings*	*References*
Antimutagenic	Dry extract	Ames test	Activity against benzo[*a*]pyrene and 2-aminofluorene	89
	Dry extract	Sister chromatid exchange test, human blood-derived lymphocytes	Decreased genotoxicity of benzo[*a*]pyrene and mitomycin C	89
	Concentrate, isolated anthocyanins	Comet test, human colon tumor HT29 clone 19A cells	Reduced H_2O_2-induced DNA strand breaks	90
Anticancer	Commercial extract	Human colon tumor HT29 cells	Inhibited growth of tumor cells	91–93
	Commercial extract	Rats treated with azoxymethane	Hindered formation of azoxymethane-induced aberrant crypt foci in colonic cells	94
	Juice, subjected to gastric and pancreatic digestion	Human colon carcinoma Caco-2 cells	Inhibited growth of carcinoma cells	95, 96
	Juice	Human colon carcinoma Caco-2 cells	Inhibited sulfoconjugation of 17β-estradiol in carcinoma cells	97
	Acetone extracts	L1210 murine leukemia cell line, human DNA catalytic topoisomerase II assay	Inhibitory effect on L1210 cells, inhibitory action in topoisomerase assay	45
	Leaf extract	Human promyelocytic HL60, HL60/VINC, and HL60/DOX cell lines	Antileukemic activity	98
	Nectar	Rats treated with aminopyrine and sodium nitrite	Inhibited *N*-nitrosamine formation	99
Lipid-lowering	Juice	Rats with diet-induced hypercholesterolemia	Reduced TC, LDL-chol, and TG levels	100, 101
	Commercial dry extract	Rats treated with streptozotocin and on a high-fructose diet	Reduced TC level	67
	Juice	Rats fed with standard diet	Reduced TC and TG levels	102
	Juice	Patients with mild hypercholesterolemia	Reduced TC, LDL-chol, and TG levels; increased HDL-chol level	103
	Commercial dry extract	Patients with metabolic syndrome	Reduced TC, LDL-chol TG, and endothelin-1 levels	104
Cardio-protective	Commercial dry extract	Patients after myocardial infarction, receiving statins	Reduced LDL-chol oxidation status and 8-isoprostanes; increased adiponectin levels	105
	Commercial dry extract	Isolated porcine coronary arterial rings	Endothelium-dependent vasorelaxation	106
Antihypertensive	Commercial dry extract	Patients with metabolic syndrome	Lowered arterial pressure	104
	Juice	Patients with mild hypercholesterolemia	Lowered arterial pressure	103
	Commercial dry extract	Patients after myocardial infarction, receiving statins	Lowered arterial pressure	105
Anti-aggregatory	Commercial dry extract	Platelets of patients with cardiovascular risk and healthy individuals	Anti-aggregatory effect on human platelets *in vitro*	79
Hepatoprotective	Juice	Rats with CCl_4-induced damage	Reduced histopathological changes in liver	70
	Nectar	Rats treated with aminopyrine and sodium nitrite	Reduced histopathological changes in liver	99
Gastroprotective	Juice	Rats with chemically induced gastric lesions	Reduced number, area, and severity of lesions	73, 107, 108
Antidiabetic	Juice	Rats with streptozotocin-induced diabetes	Reduced blood glucose level	109
	Leaf extract	Healthy and streptozotocin-induced diabetic rats	Reduced blood glucose level	110
	Commercial dry extract	Rats treated with streptozotocin and on a high-fructose diet	Reduced blood glucose level	67
	Sugar-free juice	Patients with diabetes mellitus	Reduced fasting blood glucose levels	111

(*continued*)

Table 1. (Continued)

Pharmacological effect	*Type of preparation used*[a]	*Scheme of experiment*	*Most important findings*	*References*
Anti-inflammatory	Dry extract	Rats with endotoxin-induced uveitis	Anti-inflammatory effect	112
	Dry extract	Mouse macrophage cell line RAW 264.7	Suppressed expression of inducible nitric oxide synthase and cyclooxygenase-2	112
Antibacterial, antiviral	Juice	*S. aureus*, *E. coli*, influenza A virus	Bacteriostatic and antiviral activity *in vitro*	113
Radioprotective	Commercial dry extract	γ-Irradiated rats	Diminished lipid peroxidation, hindered reduction of leukocyte levels	114, 115
	Gel	Ultraviolet-irradiated rats	Reduced erythema response	116
Immunomodulatory	Concentrate	Women with breast cancer in the course of postoperative radiation therapy, receiving apple pectins	Increased CD4 and CD8 T cell counts	117

[a]When no other source is specified, the preparation was obtained from *A. melanocarpa* fruits.

sensitive to alkaline pancreatic digestion, which substantially modulates their bioavailability.[122] Moreover, it was proven that the character of both the aglycone and the sugar moiety influences the chemical stability, absorption, and metabolism of anthocyanins, which in great measure determine their *in vivo* activity.[123–125] In the following sections, the pharmacological activities of *A. melanocarpa* are reviewed.

Antimutagenic and anticancer activity

Among other health-promoting natural products, various berry preparations are often mentioned as important chemopreventive diet ingredients. Numerous investigations have demonstrated their significant antimutagenic and anticancer potential in various *in vitro* and *in vivo* models.[120,121,126–128]

Anthocyanins from *A. melanocarpa* berries exhibit antimutagenic activity *in vitro*, which can be attributed to their free radical scavenging properties, as well as inhibition of enzymes that are responsible for promutagen activation. In the Ames test, mutagenic activities of benzo[*a*]pyrene and 2-aminofluorene were almost completely eliminated in the presence of anthocyanins isolated from black chokeberry fruits. The sister chromatid exchange test, performed with the use of human blood-derived lymphocytes cultured *in vitro*, also revealed significant antimutagenic activity of *A. melanocarpa* extracts. A high anthocyanin dose decreased the genotoxicity of benzo[*a*]pyrene by nearly 30% and that of mitomycin C by about 10%.[89]

The experiment with human colon tumor HT29 clone 19A cells, performed with the use of the microgel electrophoresis assay (comet test), proved that H_2O_2-induced DNA strand breaks were significantly reduced in the presence of *A. melanocarpa* extract. On the other hand, endogenous generation of oxidized DNA bases remained unchanged. The results obtained suggested that the cancer-preventing potential of anthocyanins may be attributed to systemic protection, manifested, for example, by free radical scavenging in the blood, rather than to antimutagenic activity within specific tissues.[90]

Anticancer properties of black chokeberry extract against the HT29 cell line were confirmed, as it significantly (>60%) inhibited the growth of above-mentioned colon cancer cells at G_1/G_0 and G_2/M phases during a 24-hour exposure. No changes in cell number were observed during prolonged exposure to anthocyanin-rich extract, indicating that growth inhibition was of cytostatic character. Less than 10% growth inhibition was observed in the case of NCM460 normal colon cells.[91] The comparative study showed that *A. melanocarpa* extracts were the most potent HT29 cells growth inhibitor (approximately 50%), exhibiting stronger chemopreventive action than grape (*Vitis vinifera*) and blueberry (*V. myrtillus*) preparations. As in a previous survey, a much lower inhibitory effect was observed in the case of NCM460 cells.[92] In another experiment, chokeberry extracts also significantly inhibited growth of HT29 cells, displaying stronger activity than many other antioxidant-rich products, such as purple carrot (*Daucus carota*), grape (*V. vinifera*), elderberry (*S. nigra*), and radish (*Raphanus sativus*). It was also suggested that the chemoprotective effect of anthocyanins is strongly affected by their chemical structure. More distinct carcinoma growth inhibition was observed for nonacetylated monoglycosylated anthocyanins than for triglycosidated, cinnamic acid-acylated, or pelargonidin derivatives.[93]

In an *in vivo* experiment in rats, ingestion of chokeberry extracts resulted in significant inhibition of azoxymethane-induced aberrant crypt foci (a colon cancer biomarker) formation in colonic cells, confirming the chemopreventive potential of *A. melanocarpa* anthocyanins. Moreover, rats fed with anthocyanin-rich diet had substantially higher fecal bulk and moisture content in excrement compared to the control group. This may significantly contribute to decreased

concentrations of endogenous tumor-promoting agents, such as bile acids, and to alleviation of colon irritation. It is possible that ingested anthocyanins may act directly on colon cells as well as on the gastrointestinal environment, making it less harmful for mucosal membrane.[94]

Black chokeberry juice, subjected to gastric and pancreatic digestion with the purpose of simulating physiological conditions, proved to effectively inhibit the growth of Caco-2 human colon carcinoma cells. Repetitive applications of anthocyanin extract during a 4-day period inhibited the growth of Caco-2 cells at the G_2/M phase. As a result of chokeberry juice treatment, tumor suppressor carcinoembryonic antigen-related cell adhesion molecule 1, whose reduced expression often accompanies early-stage carcinomas, was up-regulated in Caco-2 cells, suggesting its potential role as a target in colon cancer chemoprevention.[95,96] In another experiment, *A. melanocarpa* juice was shown to strongly inhibit sulfoconjugation of 17β-estradiol in Caco-2 cells and also to exhibit an inhibitory effect on cytosolic sulfotransferase, the enzyme involved in estrogen deactivation, from human carcinoma cells *in vitro*. These results indicate that black chokeberry extracts might influence the growth of some breast and colon cancers through sulfotransferase inhibition, and therefore alter estrogen availability to their receptors.[97] This is remarkable, as it was proven that exposure to estrogens reduces the risk of colon cancer in women.[129]

Chemopreventive activity of black chokeberry fruit extracts was examined with the use of L1210 murine leukemia cell and human DNA catalytic topoisomerase II assays. Acetone extracts, obtained from European plantation-bred and wild (Illinois, USA) *A. melanocarpa* berries, were separated into several subfractions and tested for antileukemic activity *in vitro*. The most active fractions, from both wild and cultivated plants, exhibited a >90% inhibitory effect on L1210 cells and was shown to be rich in oligomeric procyanidins and anthocyanins. Fractions, especially from the wild genotype, also proved to act as catalytic inhibitors in the topoisomerase assay.[45]

In another *in vitro* study, extracts from *A. melanocarpa* exhibited antileukemic activity against the human promyelocytic HL60 line and its multidrug-resistant sublines, HL60/VINC and HL60/DOX. It should be noted that the resistance factors determined in the above lines were relatively low compared to clinical antitumor drugs like doxorubicin or vincristine.[98]

Among other chemopreventive actions, black chokeberry nectar efficiently inhibited carcinogenic *N*-nitrosamine formation in rats subjected to the application of aminopyrine and sodium nitrite. Reduced *N*-nitrosamine generation was manifested by reduced transaminase activity in the serum and alleviated liver damage.[99]

Cardioprotective activity

The broadly understood cardioprotective activity of *A. melanocarpa* can be attributed to lipid-lowering, antiaggregative, and direct vasoactive action of its anthocyanin-rich extracts. It should also be mentioned that black chokeberry fruits contain significant amounts of niacin, the beneficial effects of which in cardiovascular diseases, especially in terms of lipid-lowering activity, are well recognized.[130] As a result, the observed effects of *A. melanocarpa* juice may be attributed to the presence of anthocyanins, as well as niacin.

The lipid-lowering activity of black chokeberry preparations has been well documented with the use of rat models with artificially induced hypercholesterolemia. Supplementation of hypercholesterolemic (1–4% cholesterol) diet with *A. melanocarpa* juice for 30 days resulted in substantially decreased levels of total cholesterol (TC) and its fractions in low-density lipoprotein cholesterol (LDL-chol) and triglycerides (TG) in blood plasma, in comparison to control rats not fed *Aronia*. Neither high-cholesterol diet nor black chokeberry juice significantly influenced the concentration of high-density lipoprotein cholesterol (HDL-chol).[100,101] In another study, symptoms mimicking those observed in metabolic syndrome (increased levels of lipids and glucose in the blood) were induced by application of diet rich in fructose and intraperitoneal injection of streptozotocin. Addition of chokeberry extract to the rat high-fructose diet substantially reduced the high TC level. Moreover, in the experiment described no effect of chokeberry extract on elevated TG concentration was observed.[67] It should also be noted that the TC- and TG-lowering activity of *A. melanocarpa* extracts was found in the case of rats fed with standard, non-hypercholesterolemic diet supplemented with high doses of chokeberry anthocyanins for 4 weeks.[102]

Beneficial effects of *A. melanocarpa* on blood lipid concentration were observed in hypercholesterolemic patients receiving black chokeberry anthocyanins in the form of juice or dry extracts. It was shown that regular (>6 weeks) drinking of *Aronia* juice significantly lowered TC, LDL-chol, and TG blood levels and increased the HDL-chol concentration in patients with mild hypercholesterolemia and without pharmacological treatment.[103] In another study, 2-month supplementation of the diet with *Aronia* extracts resulted in significantly lowered TC, LDL-chol, TG, and endothelin-1 levels in patients with metabolic syndrome.[104]

In a combined therapy, chokeberry extracts were given as supplements with the diet of patients after myocardial infarction, as an addition to the statin treatment. Compared to the control group, treated only with statins, patients receiving additional *Aronia* extract for 6 weeks had significantly lower LDL-chol oxidation status as well as reduced levels of serum 8-isoprostanes and increased adiponectin levels, which indicate diminished oxidative stress and reduced endothelial inflammation.[105]

Direct vasoactive properties of *A. melanocarpa* extracts were determined with the use of isolated porcine coronary arterial rings. Application of black chokeberry extract induced dose- and endothelium-dependent vasorelaxation.[106,131] In addition, at concentrations too low to exert direct vasorelaxation, *A. melanocarpa* extracts protected coronary arteries from loss of relaxation induced by reactive

oxygen species.[106] The results obtained are promising as they point out the potential role of anthocyanin extracts in vascular disease treatment.

A. melanocarpa extracts possess noticeable antihypertensive activity, which was established in several clinical trials. In patients with metabolic syndrome, 2-month anthocyanin treatment resulted in lowered values of arterial pressure compared to the control group.[104] Similar antihypertensive effects were observed in men with mild hypercholesterolemia consuming chokeberry juice for 6 weeks.[103] Significant reduction of systolic and diastolic blood pressure was also obtained during 6-week combined therapy with the use of statins and *Aronia* extracts compared to treatment based only on statins.[105]

Beside lipid-lowering, vasorelaxative, and antihypertensive activities, black chokeberry extract can exert a significant anti-aggregatory effect on human platelets *in vitro*. Interestingly, this activity of *Aronia* extract seems to be independent of its ability to inhibit platelet superoxide production in patients at risk of cardiovascular disease. An anti-aggregatory effect was observed both in patients from the risk group and in healthy individuals.[79] In a comparative *in vitro* study, extract of *A. melanocarpa* was shown to exhibit anti-aggregatory activity similar to that of grape (*V. vinifera*) seed extract and lower than that of extract from bark of *Yucca schidigera*. All the extracts mentioned inhibited platelet aggregation and adhesion and superoxide generation, exhibiting stronger effects than the solution of pure resveratrol.[132]

Hepatoprotective activity

Hepatoprotective activity of *A. melanocarpa* juice was established in an experiment in rats with CCl_4-induced liver damage. Addition of black chokeberry juice to the diet of rats prior to CCl_4 treatment significantly reduced histopathological changes in the liver, such as necrosis, ballooning degeneration, and inflammatory infiltration of lymphocytes. The protective effect of *A. melanocarpa* is in great measure related to its antioxidative properties and the scavenging of free radicals formed during CCl_4 intoxication.[70]

Beneficial effects of black chokeberry nectar were observed in rats treated with aminopyrine and sodium nitrite, in order to induce *N*-nitrosamine formation. Ingestion of *A. melanocarpa* nectar together with *N*-nitrosamine precursors substantially reduced their hepatotoxic activity compared to the control group. Dystrophic changes, like centrolobular necrosis, exangia, and enlarged cells, were almost completely absent in the livers of chokeberry-fed rats.[99]

In another experiment, anthocyanins from *A. melanocarpa* proved to be useful in alleviating the effects of cadmium chloride intoxication in rats. Administration of black chokeberry extract resulted in decreased accumulation of cadmium in livers and kidneys, lowered concentrations of bilirubin and urea in blood serum, and reduced activities of aminotransferases.[133] Moreover, dietary fiber from *Aronia* fruits can act as a weak cadmium sorbent and thus reduce its absorption in the digestive tract.[134]

Gastroprotective activity

Gastroprotective activity of *A. melanocarpa* extracts was examined in rats with chemically induced gastric lesions. Ingestion of black chokeberry juice before indomethacin administration significantly reduced the number, area, and severity of lesions caused by the anti-inflammatory drug. It is likely that the protective effect of *Aronia* juice results from increased production of gastric mucus and from diminishing the oxidative stress evoked by indomethacin.[73] Similar anti-ulcerative activity of *A. melanocarpa* anthocyanin fractions was established in *in vivo* studies in rats with ethanol-induced gastric hemorrhagic damage. Like in the formerly described experiment, the observed effects can be attributed to oxidative stress reduction and free radical scavenging activity of black chokeberry anthocyanins.[107,108]

Antidiabetic activity

Antidiabetic activity was established for fruit as well as for leaf extracts of *A. melanocarpa*, often in animal models with experimentally induced diabetes.[109,135] Black chokeberry juice, administered perorally for 6 weeks, exhibited a substantial (>40%) glucose level-reducing effect in rats with streptozotocin-induced diabetes, whereas no such effect was observed in healthy rats.[109] Intraperitoneal or peroral administration of *Aronia* leaf extract significantly reduced blood glucose levels in healthy rats, as well as in streptozotocin-induced diabetic animals.[110] Furthermore, it was proven that *Aronia* leaf extract stimulates glucose uptake by PC12 and L929 cells.[136] In another study, where high-fructose diet in connection with streptozotocin injection caused prediabetes in rats, the glycemia-lowering activity was also demonstrated for the extract from black chokeberries.[67] It was suggested that the antidiabetic potential of *A. malanocarpa* may result from decreased mucosal maltase and sucrase activities in the small intestine, but other mechanisms, such as stimulation of glucose uptake, increased insulin secretion, or reduction of oxidative stress, can also be involved.[67,109]

Beside animal models, the antidiabetic activity of *A. melanocarpa* juice was demonstrated in patients with diabetes mellitus. It was shown that daily ingestion of 200 mL of sugar-free black chokeberry juice over a 3-month period resulted in substantially lower fasting blood glucose levels in patients with non–insulin-dependent diabetes compared to the control group. The observed results indicate that supplementation of the diet with *Aronia* juice may exert beneficial supporting effects in diabetic patients.[111]

Anti-inflammatory activity

Anti-inflammatory activity of black chokeberry extracts was demonstrated mainly in rat models. *A. melanocarpa* juice significantly reduced rat paw swelling evoked by administration of histamine or serotonin solutions. The observed anti-inflammatory effect was stronger than those obtained for rutin or rutin–magnesium complex.[137] In

another *in vivo* study, intravenous administration of *Aronia* extract exerted substantial anti-inflammatory activity on endotoxin-induced uveitis in rats.[112] A particularly strong effect, comparable to that of 10 mg of prednisolone, was obtained for 100 mg of black chokeberry extract. The complementary *in vitro* experiment, performed with use of the mouse macrophage cell line RAW 264.7, indicates that anti-ocular inflammatory action of *A. melanocarpa* extract may involve inhibition of nitric oxide, prostaglandin (E_2), and tumor necrosis factor-α production, resulting from suppressed expression of inducible nitric oxide synthase and cyclooxygenase-2 enzymes.[112]

Antibacterial and antiviral activity

Antimicrobial properties of phenolic compounds from numerous berry species, such as cranberry, blueberry, and raspberry, are well known and have been demonstrated *in vitro*. *A. melanocarpa* berry extracts exhibited bacteriostatic activity *in vitro* against *Staphylococcus aureus* and *Escherichia coli*. Moreover, they were shown to possess antiviral activity against influenza A virus.[113]

A particularly strong inhibitory effect was observed for human intestinal pathogens from the genuses *Staphylococcus* and *Salmonella*.[138–140] Because of high phenolic contents, some antimicrobial action in small intestine was also noted in the case of *A. melanocarpa* extracts.[7,18]

Radioprotective and immunomodulatory activities

A. melanocarpa extracts exerted beneficial effects in rats with experimentally induced radiation illness. The survival rate of γ-irradiated animals fed with chokeberry extract was significantly increased compared to the control group. It was also observed that *Aronia* anthocyanins substantially hindered lipid peroxidation, manifested by increased generation of free radicals, as well as the reduction of leukocyte levels in γ-irradiated rats.[114,115] In another experiment, gels containing *A. melanocarpa* anthocyanins have been shown to effectively protect the skin from ultraviolet radiation, which was applied in amounts much higher than the erythema dose.[116]

The immunomodulatory activity of black chokeberry extracts was examined in women with breast cancer in the course of postoperative radiation therapy. Ingestion of *Aronia* extracts together with apple pectins during the irradiation period resulted in significantly increased CD4 and CD8 T cell counts compared to the control group.[117]

CONCLUSIONS

Modern pharmacological research presents *A. melanocarpa* as a plant with numerous health-promoting activities. Biological activities of anthocyanin-rich chokeberry fruit extracts include antioxidative, antimutagenic, cardioprotective, and antihyperglycemic, among others. Initially used by Native Americans for treatment of colds, the plant became more popular after it had been introduced to Russia and Eastern European countries as a crop plant in the early 20th century. Traditional use of the black chokeberry as an antihypertensive drug in Russian herbal medicine was supported by modern pharmacological research. Interestingly, this application of black chokeberry was not reported in western countries.[8] The broadly defined cardioprotective action of *Aronia* extracts was also confirmed in several studies. However, the use of *A. melanocarpa* in treatment of colds practiced by Native Americans was not scientifically supported. It may be suggested that this activity is somehow related to antioxidative properties of *Aronia*, as some oxidative stress symptoms have been reported during viral infections, such as the common cold and influenza.[141,142] So far no research has been undertaken to support this hypothesis, although some antiviral activity of chokeberry extracts has been reported.[113] The use of *Aronia* fruits in hemorrhoid treatment, although not clinically supported, may be attributed to the hemostatic properties of tannins, as well as the improvement of microcirculation by polyphenolic compounds.[143] Many of the pharmacological activities of the black chokeberry, such as antimutagenic, hepatoprotective, and cardioprotective, are directly or indirectly related to its antioxidative properties, resulting from the high polyphenol content. Because of their health-promoting effects, *A. melanocarpa* extracts may constitute a valuable dietary supplement for people with risk factors of cardiovascular diseases or metabolic syndrome. Moreover, regular consumption of black chokeberry products, considering their high antioxidant and antimutagenic potential, may exert some long-term effects such as cancer prevention.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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