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REVIEW PAPER

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Characteristics of the health-promoting properties of *Cornus mas*

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ABSTRACT

Introduction and aim. The medicinal properties of *Cornus mas L.* have been used in European and Asian folk medicine for many centuries in the prevention and treatment of many diseases. The high biological activity of the plant results primarily from the presence of valuable ingredients, including anthocyanins, flavonoids and iridoid compounds. The aim of the article is to present the role of bioactive ingredients present in *C.mas* that determine its health-promoting properties.

Material and methods. Review and analysis of the scientific literature.

Analysis of the literature. The summarize information about in the field of phytochemical properties and therapeutic effects, among others anticancer, antidiabetic, neuroprotective, cardioprotective and antibacterial**.**

Conclusion. The results of many in vitro and in vivo scientific studies They indicate the possibility of the potential use of Cornelian cherry to obtain valuable nutraceutical and pharmacological substances

Keywords. bioactive compounds, cornelian cherry, *Cornus mas* L., medicinal plant

Introduction

Cornelian cherry (*Cornus mas* L.,) is a fruit plant belonging to the *Cornaceae* family is a tall shrub or a small tree. It occurs naturally mostly in central and south-eastern Europe as well as south-central and western Asia. The latin name *Cornus mas* L. comes from the word „*Cornu*" - horn, and „*maschile*" - hardwood. The beautiful yellow flowers of the edible dogwood develop before the leaves appear and are decisive for its classification as ornamental plants. Ripe, small stone fruits with a dark or cherry-red color, and less often pink or yellow with a sweet and sour taste are used in the kitchen to prepare, among others. marmalades, wines, tinctures.[1,2] Flowers, leaves and fruit have been used in folk medicine for many years due to their numerous medicinal and nutritional values (Fig. 1).[3]

The high biological value results mainly from the content of biologically active substances, mainly antioxidants that determine the antioxidant activity.

The conducted phytochemical studies of Cornelian cherry fruits indicate the presence of numerous valuable bioactive ingredients from the group of polyphenolic compounds (mainly anthocyanins, flavonoids and phenolic acids), triterpenoids and pectin.[4-8] Anthocyanins also affect the color of Cornelian cherry fruits, and the total content of anthocyanins ranges from 35 to 300 mg/100g depending on the color of the fruit. The amount of anthocyanins in the skin fruit can reach even 650-850 mg/100g, while in the flesh it contains only 35-120 mg/100g.[8]

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Whereas *C. mas* leaves contain 113-117 mg/g dry weight of polyphenolic compounds, and flavonols 33-35 mg/g dry weight but no anthocyanins.[9] The richest source of flavonoids are flowers.[10] The presence of other bioactive ingredients was also found in *C. mas* varieties, such as ascorbic acid and iridoid compounds, mainly loganic acid.[11-15]

Fig. 1. *Cornus mas* L. fruit (photograph by Maria Strzępa)

The content of vitamin C varies greatly depending on the variety and ranges from 50 to 100 mg/100 g, and some varieties may even contain 200 mg/100 g of ascorbic acid.[1,13-17] Carotenoids and fatty acids are also present.[17] The largest amount of fat is in the seeds (4.5%) and the main fatty acid is linoleic acid.[7]

The body's defense mechanism reduces the free radicals formed in the body. Long-term, too high level of free radicals that are not neutralized in the body by the antioxidant mechanism is conducive to the formation of oxidative stress.[18] Oxidative stress increases the risk of developing diseases, including cancer, metabolic disorders, and the antioxidants present in the diet prevent the formation of oxidative stress affecting human health.[19]

The presence of bioactive compounds, mainly antioxidants, in *C. mas* determines its biological activity. *C. mas* showing high antioxidant activity, i.e. the ability to neutralize free radicals thanks to numerous bioactive compounds determined by the DDPH, ABTS and FRAP tests.[9,15, 20-26]

Aim

This article presents the results of *in vitro, in vivo* and human studies determining the pro-health effects of *C. mas*: antitumor, supporting diabetes treatment, cardioprotective and antihyperlipidemic, hepatoprotective, neuroprotective, and antimicrobial. Modern scientific research also focuses on important aspects of phytochemical analysis, evaluation of the pharmacological aspect, toxicology of extracts from fruits, leaves, flowers of *C. mas* for the possibility of their use as a safe medicine or supplement for patients.

Material and methods

Review and analysis of the scientific literature.

Analysis of the literature

Antitumor activity

The results of scientific research indicate that these natural substances, among others phenolic compounds, waveguides present in fruits, leaves and flowers of *C. mas* influence the growth of neoplastic cells *in vitro*.[27-29] By inhibiting the proliferation of neoplastic cells (cytostatic effect) and reducing their survival due to induction of apoptosis (cytotoxic effect), they determine the antitumor and cytotoxic properties of *C. mas*.[30-32]

In their research, Savikin et al. assessed the cytotoxicity, antioxidant properties and chemical composition of methanol extracts from *Cornus mas* leaves and flowers. The cytotoxicity was determined on the basis of the metabolic activity of the cells determined by the MTT test. They showed that methanol extracts at a concentration of 200 μg/mL from *C. mas* flowers or leaves inhibited the growth of human cervix adenocarcinoma cells (HeLa) and human colon carcinoma (LS174) cells lines after 72 h of incubation.[33]

In vitro studies by the Yousefi research team demonstrated cytotoxicity of 80% ethanol extracts from *C.mas* fruit against human ovarian cancer cells (SKOV3), breast adenocarcinoma cells (MCF-7), prostate adenocarcinoma cells (PC-3) and lung non small cell cancer (A549). The analyzed doses in the concentration range of 5, 20, 100, 250, 500, 1000 μg/mL showed a high cytotoxic effect on the cells of all types of tested neoplasms.[34] Scientific results of Forman et al. they also showed inhibition of the viability of the aqueous extract of *C. mas* fruit against the MCF-7 cell line.[35] In contrast, *C. mas* juice with a concentration of 0.007-1% shows cytotoxic activity against human liver carcinoma cells (HepG2), human colon cancer cells (Caco2 and HT-29).[36]

Antidiabetic activity

Preparations based on *C. mas* reduce the level of glucose in the blood and increase the sensitivity of tissues to insulin. The results of the research proved the relationship between the presence of polyphenols, such as anthocyanins and flavonoids in fruits, and the inhibition of α-glucosidase activity and the reduction of postprandial blood glucose levels.[37-39]

The studies assessed the effect of an extract derived from the fruit of *C. mas* on glycemic control in people with type 2 diabetes. It has been shown that their daily consumption of these extracts increases insulin levels and thus improves glycemic control. In addition, it also reduces the level of serum triglycerides, which are often abnormal in people with type 2 diabetes.[40] On the other hand, ursolic acid present in *C.mas* fruit causes glucose uptake by activating the insulin receptor.[41]

Cardioprotective activity

Research results indicate an important role of Cornelian cherry fruit in the treatment of metabolic disorders. The results of scientific studies indicate a close relationship between the antioxidant properties of *C. mas*, resulting from the presence of anthocyanins and iridoids in fruits, and the cardioprotective and antihyperlipidemic activity in the human body.

Atherosclerosis is recognized as a civilization disease and the main cause of death all over the world. Due to their valuable pro-health properties, anthocyanins, which are phytochemicals, effectively prevent the development of dyslipidemia.[38,42] The research results indicate that the antioxidant and anti-inflammatory properties of *C. mas* may have a positive effect on the health of patients with hypercholesterolaemia.[43] This effect may be due to the presence of anthocyanins, which inhibit the expression of lipogenic enzymes in adipose tissue and liver, and reduce the activity of lipoprotein lipase in visceral adipose tissue and increase it in muscles.[44,45] Sozański et al. in their *in vivo* studies in an animal model showed that the *C. mas* L. fruit lysate present in the diet for 60 days reduced the level of triglycerides in the blood serum by 44% and effective prevention of atherosclerotic changes in the thoracic aorta by activating the expression of PPARα. Additionally, the significant influence of *C. mas* L. on the oxidative stress in the liver induced by the diet and the normalization of the elevated level of pro-inflammatory cytokines in the serum was assessed.[3]

Hosseinpour et al. observed that after administering the dried powder obtained from the fruit of *C.mas* to rats for a period of 4 weeks, a decrease in the level of triglycerides and LDL-C, an increase in HDL-C and an increase in the antioxidant capacity of the liver.[46] Further studies on an animal model confirm the above results of the effect of the dried powder from *C. mas* fruit for 4 weeks to reduce cholesterol and triglycerides.[47]

Subsequent studies focused on the analysis of bioactive compounds present in *C.mas* fruits and their influence on the activity of pancreatic lipase. Iridoids (loganic acid, cornuside) and anthocyanins (pelargonidin 3-O-galactoside) were identified in the fruit extract of *C. mas* using the HPLC-DAD-MS (high-performance liquid chromatography coupled with diode-array detection and tandem mass spectrometry techniques) technique. A subfraction of *C.mas* extract at a concentration of 7.5 μg/mL which contained pelargonidine 3-O-galactoside decreased pancreatic lipase activity by 28.3±1.5%, but loganic acid and cornucid did not inhibit it. The results of the research suggest that the ability of *C. mas* fruit to inhibit the activity of pancreatic enzymes and their use in the prevention of hyperlipidemia.[48]

In the scientific literature, there is a link between endocrine hormones and metabolic diseases. Cortisol plays a significant role in the metabolism of cholesterol.[49] In animal studies, plasma cortisol levels decreased after the introduction of *C.mas* fruit supplementation.[50] Following the introduction of *C. mas* fruit supplementation to the daily diet of children and adolescents with dyslipidemia for 6 weeks, an improvement in the lipid profile and vascular inflammation was observed.

Research by the team of Asgary et al. and Rafieian-Kopaei et al. indicate a very valuable anticoagulant effect of *C. mas*. The results of *in vivo* studies on an animal model showed that consumption of *C. mas* dried fruit powder may be beneficial in the group of patients with atherosclerosis due to its lowering effect on plasma fibrinogen levels.[52,53]

Gholamrezayi et al. in their research on the effect of *C. mas* fruit extract on lipid profiles and leptin parameters in postmenopausal women. After 8 weeks of daily supplementation, the weight of the group of women did not change, as did the waist circumference, the ratio of LDL/HDL and TC/HDL and the leptin concentration, but the HDL levels increased compared to the control group.[54]

Hepatoprotective activity

The metabolism of xenobiotics in the body can lead to liver damage, resulting in carcinogenic transformation or inflammation. *In vivo* studies on an animal model have proven the protective effect of *C. mas* fruit extract on the liver by maintaining its biological functions and reducing the degree of damage.[55-58]

Alavian et al. demonstrated the protective effect of *C. mas* fruit extract, rich in antioxidants and anthocyanins, on the liver of male rats against hepatotoxicity induced by CCl_4. After 14 days of oral administration of *C. mas* fruit extract (200 and 500 mg/kg body weight/d) to these rats, they observed a reduction in elevated levels of the following enzymes: aspartate transaminase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP).[55]

In subsequent *in vivo* studies, the protective effect of *Cornus mas* fruit extract on the liver of healthy rats was indicated. These extracts (50, 200 and 400 mg/kg body weight) administered daily for 3 weeks to rats caused a decrease in the levels of the enzymes: AST, ALT and ALP in the blood serum at doses of 200 and 400 mg/kg. There were also no pathological changes in the liver tissues.[56]

Some drugs used in the treatment of cancer and autoimmune diseases cause side effects by toxic to the liver and lead to its damage. Scientists have attempted to evaluate the medicinal effect of *C. mas* fruit extract on drug-induced liver damage.

In vivo studies were conducted with the administration of the anti-cancer drug Methotrexate to hepatoxic rats. Rats were simultaneously administered the drug and the extract of freeze-dried fruit *C. mas* (300, 700, 1400 mg/kg body weight). The levels of some enzymes in the liver were determined: direct and indirect total bilirubin, AST, ALT, ALP, and lactate dehydrogenase (LDH). It was observed that the dose of 700 and 1400 mg/kg of body weight of *C. mas* extract significantly counteracted the changes caused by this drug, including: the levels of AST, ALT, ALP enzymes; direct bilirubin and LDH demonstrating a hepatoprotective effect.[57]

On the other hand, Abasi et al. undertook an evaluation of the effect of *C. mas* fruit extracts (CMFE) on liver changes caused by the anticancer drug cisplatin. The drug administered to rats caused a decrease in the antioxidant activity of the liver enzymes: SOD, GPx, TAC and CAT, and increased the activity of MDA and decreased the levels of AST, ALT and ALP in the serum. For 16 days, the administration of freeze-dried fruit extract of *C. mas* (300 and 700 mg/kg body weight) to rats increased the level of antioxidant activity of liver enzymes and enzymes in the serum in relation to changes caused by the action of cisplatin. It was also observed that after treatment with *C. mas* extract, the histological structure of the liver tissue was close to that of normal histology. The content of antioxidants and phenolic compounds in *C. mas* fruit counteracts oxidative stress and histological changes in the liver in rats caused by the action of this drug.[58]

Neuroprotective activity

Neurological disorders are caused by excess free radicals in the body. The excess of free radicals promotes the development of oxidative stress negatively affecting the human body, especially brain tissue.[59] *C. mas* as a rich source of antioxidants from the group of polyphenols mainly flavonoids, anthocyanins and vitamin C may reduce the level of free radicals. Flavonoid derivatives as antioxidants play an important role in pathophysiology of many diseases, including neurological disorders (eg. Alzheimer's disease). Resveratrol, belonging to the flavonoid group, protects neurons from the toxic effects of beta-amyloid protein, which plays a role in the development of Alzheimer's disease, and reduces the frequency of neuronal death in the hippocampus.[59] In contrast, catechin and epicatechin flavonoids protect brain cells against damage caused by free radicals. Vitamin C actively participates in the process of myelination of the brain and is a neuromodulator.[59] As an antioxidant, it reduces lipid peroxidation and strengthens the structure of cell membranes. neuroprotective.[3,4,22,60]

Francik et al. evaluated the effect of freeze-dried *C. mas* fruit on the diets of control, fructose and high fat rats. The addition of dried fruit of *C. mas* to the diet led to an increase in the activity of catalase (an antioxidant enzyme) present in the brain tissue and inhibition of the process of protein oxidation, leading to a reduced amount of carbonyl and thiol groups in the brain tissue and plasma.[59] The results of studies assessing the activity of paraoxonase-1 (PON1) in rats after a 5-week diet with 10% of *C.mas* fruit juice showed its increase in plasma, but not in the liver. The increase in the activity of PON1 protects the LDL fraction and prevents its oxidation caused by oxidative stress. Because PON1 is an enzyme that plays a role in protecting against oxidation of, inter alia, two cholesterol fractions; LDL and HDL ensure the hydrolysis of activated phospholipids and lipid peroxides.[61]

The results of the research show that *C. mas*, a rich source of antioxidants, can be used to support treatment and to prevent neurological diseases.

Antimicrobial activity

The results of scientific works also indicate the antimicrobial properties of *C. mas*.[9,62-65] The results indicate that after the incubation of water extracts of *C. mas* fruit with the strains of bacteria *Staphylococcus aureus* and *Pseudomonas aeruginosa* causing infectious diseases, their growth was inhibited.[64] Milenković-Andjelković et al. analyzed the antibacterial and antifungal activity of fruit, leaves and seeds, bark of *C. mas*. They observed that only methanol and ethanol extracts from seeds, leaves and bark showed antimicrobial activity. The greatest effect was shown by leaf extracts against the bacteria *S. aureus* and the fungus *Candida albicans* compared to methanol extracts from seeds and bark of *C. mas*.[24] Subsequent studies indicate high antimicrobial activity against *Bacillus subtilis, B. cereus, Escherichia coli* and *Serratia marcescens* juice, methanolic and aqueous fruit extracts of *C. mas*.[66]

Krzystak et al. assessed the antimicrobial potential of extracts derived from seeds, leaves, bark and fruit. Among the tested microorganisms, the most susceptible strains were: *S. aureus, E. coli* and the fungus *C. albicans*.[67] Additionally, Antolak et al. indicated that phytochemicals found in plant raw materials may re-

duce the adhesion bacteria of the genus *Asaia spp.* present in food products and juices. Identified by HPLC and LC-MS techniques in the juice of *C. mas* anthocyanins (cyanidin-3-glucoside: 0.28 ± 0.039 μg/mL, petunidin-3-glucoside: 0.380±0.052 μg/mL, cyanidin-3-robinobioside: 0.321±0.041 μg/mL, pelargonidin-3-robinobioside: 0.302±0.022 μg/mL) and phenolic compounds (quercetin, quercetin-3-glucoside, myricetin-3-galactoside) prevent the loss of the organoleptic quality of food and plant preparations [68]

Toxic activity

It is very important to define the safe amount of use of medicinal products derived from *C. mas* for patients as a herbal medicine. The results of clinical trials with human subjects indicate that daily consumption of 100 g of fresh *C. mas* fruit for 6 weeks does not show any toxic effects on the human body.[51] Subsequent studies investigated the safety of taking anthocyanins isolated from *C. mas* as supplements. They showed no adverse effects at the amount of 600 mg/day taken by adult diabetic patients over a period of 6 weeks. [40]

Conclusion

C. mas is a very popular plant in Europe and Asia with high biological activity. Its beneficial pro-health effects are confirmed by the results of many *in vitro* and *in vivo* scientific studies presented in this article. They indicate the possibility of the potential use of Cornelian cherry to obtain valuable nutraceutical and pharmacological substances. However, it is necessary to conduct further scientific research, mainly clinical on a large study group and long-term, together with an assessment of possible levels of toxicity, in order to consider leaves, fruits, flowers as a safe herbal medicine. It is also important to analyze the aspect of interaction of *C. mas* extracts with drugs already used in the treatment of a given disease entity.

Declarations

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Author contributions

Conceptualization, K.N., E.P.S. and A.E.S.; Writing – Original Draft Preparation, K.N., E.P.S., A.E.S.; Writing – Review & Editing, E.P.S. and A.E.S.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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