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Application of medicinal properties of blueberries (Vaccinium myrtillus)

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Abstract

Introduction: The blueberry (Vaccinium myrtillus) is a fruit that is widely consumed and is harvested from mid-June to late July. It is among the earliest berries to be gathered from the wild during the summer season. Blueberries have traditionally been recognised not only for their palatability but also as a source of medicinal raw materials in folk medicine. The use of blueberry berries and leaves as a therapeutic agent dates back to the 16th century, with applications in the treatment of various ailments, including diarrhoea, inflammation of the mouth and throat, poor circulation and vision disorders.

Material and Methods: The objective of this study was to examine the biologically active compounds of Vaccinium myrtillus and their contemporary applications in the management of prevalent illnesses. The narrative review employed scientific and research articles that were devoted to the study of the biologically active substances present in blueberries, as well as the utilisation of berries and leaves from the plant in the treatment of a range of diseases, including cardiovascular, oncological, and neurodegenerative conditions.

Results and discussion: A review of the literature revealed that the biologically active substances present in blueberries and their leaves belong to the tannin-anthocyanin category of raw materials. Furthermore the plant contains a range of organic acids, vitamins and trace elements. Previously blueberry berries were more frequently utilised for the treatment of

gastroenteritis and scurvy. Currently the extract derived from blueberry leaves represents a significant component of plant-based raw materials employed in the prevention and management of diverse ocular conditions, as well as in the prevention of gastric and duodenal cancers. Aqueous extracts of blueberries, whether derived from berries or leaves, have been demonstrated to possess pronounced immunostimulating properties due to the presence of polyphenols, which exert a multidirectional influence on mediators associated with the immune response.

Conclusion: The assertion that a diet abundant in blueberries offers protection against the detrimental effects of the external environment is corroborated by multiple studies comprising in vitro cell culture studies, animal models, and clinical investigations involving both healthy volunteers and patients. The considerable number of antioxidant compounds present in this plant suggests a potential role in the prevention of a range of diseases, including cardiovascular disease, inflammation, diabetes and cancer.

Key words: blueberry berries and leaves; anthocyanins; polyphenols; oxidative stress.

Annotation. The blueberry (Vaccinium myrtillus) is a fruit that is widely consumed and is harvested from mid-June to late July. It is one of the first berries to be harvested from the wild during the summer season. Blueberries have traditionally been recognised not only for their palatability but also as a source of medicinal raw materials in folk medicine. The use of bilberry berries and leaves as a therapeutic agent dates back to the 16th century, with applications in the treatment of various ailments, including diarrhoea, inflammation of the mouth and throat, poor circulation, and vision disorders. The objective of this study was to examine the biologically active compounds of Vaccinium myrtillus and their contemporary applications in the management of prevalent illnesses. The narrative review employed scientific and research articles that were devoted to the study of the biologically active substances present in blueberries, as well as the utilisation of berries and leaves from the plant in the treatment of a range of diseases, including cardiovascular, oncological, and neurodegenerative conditions. A review of the literature revealed that the biologically active substances present in blueberries and their leaves belong to the tannin-anthocyanin category of raw materials. Furthermore, the plant contains a range of organic acids, vitamins and trace elements. Previously, blueberry berries were more frequently utilised for the treatment of gastroenteritis and scurvy. Currently, the extract derived from blueberry leaves represents a significant component of plant-based raw

materials employed in the prevention and management of diverse ocular conditions, as well as in the prevention of gastric and duodenal cancers. Aqueous extracts of blueberries, whether derived from berries or leaves, have been demonstrated to possess pronounced immunostimulating properties due to the presence of polyphenols, which exert a multidirectional influence on mediators associated with the immune response. A substantial body of literature comprising studies utilising cell cultures in vitro, animal models and clinical studies involving both healthy volunteers and patients, corroborates the assertion that a diet rich in blueberries offers protection against the detrimental effects of the external environment. The considerable number of antioxidant compounds present in this plant suggests a potential role in the prevention of a range of diseases, including cardiovascular disease, inflammation, diabetes and cancer.

Keywords: blueberry berries and leaves, anthocyanins, polyphenols, oxidative stress.

Introduction

Blueberries are a flavorful berry that are typically available from mid-June to late July, representing one of the earliest summer berries to be harvested from the wild. Blueberries are consumed in a variety of forms including fresh and frozen, in juices, jams, and desserts, and more recently as an ingredient in dietary supplements. The blueberry (Vaccinium myrtillus) is a species belonging to the heather family that is native to Northern and Central Europe, North America, and the northern part of Asia [1]. The species is native to northern Ukraine and is found growing on moist, acidic soils, forming an important component of the undergrowth in pine and spruce forests. Lokhina is a diminutive shrub, reaching a maximum height of 30 cm, which flowers between April and mid-June. The fruit is a black berry with a wax coating, red pulp and dark purple juice. The leaves are small, thin, and egg-shaped, with finely toothed edges [1]. Traditionally, blackberry gained recognition not only as a tasty berry, but also as a medicinal raw material in folk medicine. Both the fruit and the leaves have been used since the 16th century to treat various ailments, especially diarrhoea, inflammation of the mouth and throat, poor circulation and vision disorders [1].

The aim of the work was to study data on biologically active compounds of Vaccinium myrtillus and their modern use for the treatment of the most common diseases.

Materials and methods

We used a narrative review of the scientific literature, since there is a lot of material accumulated in this field, but the data of researchers is very often contradictory. The review drew upon a substantial corpus of scientific literature in Polish and English, encompassing both articles and other academic works, which collectively explore the biologically active properties of blueberries and the potential therapeutic applications of the plant's berries and leaves in the treatment of a range of diseases, including cardiovascular, oncological, and neurodegenerative conditions.

Results and discussion

At the present time, the principal pharmacological agent is derived from the fruits of the blueberry (Vaccinium myrtillus), which are collected at the turn of June and July, and, on occasion, the leaves of the plant (Folium myrtilli), which are collected between June and August. For pharmaceutical purposes, the fruits are dried in a natural environment, in the shade and in the air, or in drying chambers at a temperature of 50-60°C, while the leaves are dried in a natural environment or at a temperature of 40°C. Blueberry, a traditional folk medicine, has three pharmacopoeial monographs. The Polish Pharmacopoeia, ninth edition, volume I, page 1336, contains monograph 01/2008:1602, entitled "Myrtilli Fructus Recens" and describing the properties of fresh blueberry fruits. The definition of the raw material includes a description of its characteristics: fresh or frozen ripe Vaccinium myrtillus fruits, containing a minimum of 0.30% anthocyanins in terms of cyanidin 3-0-glucoside chloride. Furthermore, the monograph delineates the intrinsic characteristics of the raw material, the methodology for its authentication, and the cyanidin 3-0-glucoside content. Similarly, within the same volume, on page 1337, there is a monograph (07/2008:2394) entitled "Myrtilli Fructus Recentis Extractum Siccum Raffinatum et Normatum" which describes a dry extract of fresh blueberry fruits, purified and standardised. The extract should contain a cyanidin 3-0-glucoside chloride concentration ranging from 32.4% to 39.6%. The third monograph is located on page 1338 and is identified as 01/2008. 1588 pertains to the dried fruits of blueberries, specifically Myrtilla Fructus Siccus, which is the Latin name for dried blueberries. The raw material must contain a

minimum of 1.0% tannins in total. The biologically active compounds of Fructus Myrtilli are classified as tannin-anthocyanin raw materials. The tannin content of raw materials is typically within the range of 5-12%, predominantly comprising condensed tannins, namely catechins, which are derivatives of catechin and epicatechin. Anthocyanin compounds comprise derivatives of delphinidin, cyanidin, malvidin, peonidin and petunidin. In addition, the raw materials contain ursolic acid, phenolic acids (chlorogenic, ferulic and caffeine), and vitamins. Additionally, the raw materials contain vitamin C, PP, A and B, organic acids, sugars and pectins, as well as trace elements such as calcium, magnesium, phosphorus, manganese, copper and potassium. Myrtilli folium has been found to contain up to 7% of catechin tannins, procyanidins, flavonoids (derivatives of quercetin and kaempferol), iridoids (aspemlozide, monotropein), triterpene compounds, phenolic acids (quininic, chlorogenic, caffeic, salicylic, p-coumaric), and quinolizidine alkaloids. Additionally, it has been determined that this plant contains compounds of manganese and chromium [1]. The primary structure of catechin tannins is the catechin molecule, or more specifically, the catechol hydroxyflavanol-3. There are four potential optical isomers: (+) catechin, (-) catechin, (+) epicatechin and (-) epicatechin. The result of catechin oxidation is the formation of leucoanthocyanidins (catechins yield leucoanthocyanidins upon oxidation). Furthermore, leucoanthocyanidins may undergo decay and transformation into anthocyanins or tannins. It is erroneous to categorise catechins and leucoanthocyanidins as tannins, as they lack the capacity to bind proteins [1].

Blueberries are a rich source of anthocyanins which are polyphenolic compounds. It is likely that these compounds are responsible for the healing effects of this medicinal plant. In comparison to other berry raw materials, the anthocyanin content of blueberries is significantly higher, with concentrations reaching 300-700 mg/100 g of fresh fruit. In addition to anthocyanins, 100 grams of fresh berries also contain 3 milligrams of vitamin C, 3 milligrams of quercetin, and 20 milligrams of catechin [2]. The majority of commercial products derived from blueberries are standardised for anthocyanin content, with a minimum requirement of 25%. The bioavailability of anthocyanins is contingent upon their absorption in the gastrointestinal tract in an unaltered form, whereby the aglycon is combined with the remainder of the sugar. The absorption of these compounds occurs in the stomach and small intestine, but with relatively low efficiency, with approximately 11% of malvidin-3-glucoside and approximately 20% of cyanidin-3-glucoside being absorbed. The plasma concentration of these compounds can be detected within minutes of oral administration [3,4]. Data on the bioavailability of anthocyanins were obtained in comparative studies using raw materials other than blueberries, mainly from grapes, as well as in animal studies [5].

The authors observe that historically, blueberry berries have been employed as an antidiarrheal agent, particularly in children, to treat gastroenteritis. Due to its vitamin C content, it was also prescribed for the treatment of scurvy and used externally for the treatment of inflammation of the mouth and throat. Additionally, raw materials were employed to enhance the functionality of the vascular system and address issues related to night vision. In scientific sources, it is noted that blueberry leaves were also employed in the treatment of enteritis, inflammation of the urinary tract and kidney stones, as well as in the management of diabetes. Leaf infusions were employed in the treatment of arthritis, poor blood circulation, haemorrhoids and skin inflammation. The American Herbal Products Association (AHPA) classifies blueberries in Group I (Class 1), indicating that they are suitable for use without contraindications [4]. The recommended dosage varies considerably depending on the source. In the case of the phytopreparation, an additional dose of 20–60 g of dried berries or 60–160 mg of dry extract is recommended, depending on the severity of the disease [4].

Today blueberry extract is one of the most important components of plant raw materials used for the prevention and treatment of various eye diseases: twilight amblyopia, cataracts, macular degeneration, and diabetic retinopathy [3]. The results obtained from in vitro studies, as well as from studies conducted on animals and humans, corroborate the beneficial effects of blueberries in the aforementioned cases of disease. Furthermore, observations made by Air Force pilots during the Second World War were corroborated: their night vision improved after consuming blueberry jam. It is postulated that this may be due to the fact that this raw material strengthens blood vessels, improves ocular microcirculation, reduces the permeability of blood vessels, and lowers intraocular pressure [6]. Researchers agree that anthocyanins contained in blueberries are most likely responsible for this effect [7]. The specific relationship between the action of the active substances present in this raw material and the resulting effects remains to be elucidated through further research. A review of the scientific sources reveals that it is challenging to draw definitive conclusions, as the majority of the studies conducted do not meet the standards required for clinical trials. The products administered are not standardised in terms of their active substance content. They are administered in conjunction with other compounds, for example, vitamin E. Administration periods vary, and adequate control systems are not provided [7]. Recently, a lot of attention in scientific works has been paid to anthocyanins, the main active substances of blueberries, which show a wide range of biological activity, including a strong antioxidant effect, neutralizing reactive oxygen species [7,8]. The compounds in question display stability in an acidic environment. As the pH rises, they undergo a chemical transformation, forming phenolic compounds. At pH 10-11, irreversible structural changes

occur, resulting in the formation of phenolic products through the rearrangement of double bonds and subsequent disintegration of the heterocyclic ring C. In the digestive system, they decompose, among other things, to phenolcarboxylic acid, which is responsible for the biological effect of raw materials.

It is established that oxidative stress is a significant contributing factor to the aetiology of a range of diseases, including neurodegenerative disorders such as Parkinson's and Alzheimer's diseases, cardiovascular diseases, oncological diseases and age-related degenerative processes. The antioxidant action of blueberry anthocyanins inhibits a number of oxidative reactions caused by oxidative stress, which can lead to degenerative changes in the dopaminergic system [9]. The preceding argument is thus concluded. A number of studies have demonstrated that a product containing blueberry extract exerts potent antioxidant, anti-angiogenic and anti-atherosclerotic effects. The product has been demonstrated to inhibit the induction of transcription factors AP-1 and NF-κB, as well as post-inflammatory cytokines, including IL-8. In vitro research conducted by Chinese scientists has confirmed the protective effect of the active compounds against oxidative stress. However, the concentrations of these compounds used in the research are many times higher than those that can be used in vivo [10]. In addition, studies in healthy volunteers have shown no effect of a diet high in blueberries on lipid peroxidation [11]. Only studies involving people with an increased risk of cardiovascular disease or diabetes have confirmed the protective effect of berries or juices obtained from them in relation to oxidative stress [12].

A significant focus of the literature under examination is the prevention of oncological diseases. It is postulated that cancer is a disease that results from mutations in key genes involved in the cell cycle and proliferation. The occurrence of DNA damage caused by a defective or ineffective cellular repair system increases the probability of irreversible alterations to the genetic material. It is postulated that oxygen radicals damage the genetic material of the cell, which in turn leads to mutation and represents a significant factor in the aetiology of cancer. The literature highlights the significance of incorporating berries into the regular diet as a strategy for cancer prevention [13]. The multidirectional antitumour effect of anthocyanins can be attributed primarily to their high antioxidant potential, which manifests in the following ways: The direct neutralisation of reactive oxygen species, stimulation of the expression of enzymes involved in the second phase of xenobiotic metabolism, limitation of the formation of oxidative adducts with DNA, and reduction of lipid peroxidation, which inhibits mutagenesis induced by exogenous carcinogens, are all processes that contribute to the multidirectional antitumour effect of anthocyanins [14]. Researchers have demonstrated that anthocyanins have the ability

to block the cell cycle in its various phases by affecting cycle regulatory proteins (for example, p 52, p 21, p 27, cyclin D 1, cyclin A) [15]. Scientists are sure that these compounds are characterized by a selective effect on cancer cells and little or no effect on the growth of normal cells [16]. Additionally, the pro-apoptotic effect of anthocyanin extracts has been documented. Furthermore, the anticancer potential of anthocyanins is linked to their anti-inflammatory effect. This is particularly relevant in the context of colorectal cancer, given the well-established link between inflammation and the process of carcinogenesis [16]. It has also been proven that the anticancer effect of anthocyanins may include inhibition of the process of angiogenesis and the ability to form metastases [17]. The literature emphasizes the existence of another effect in therapy with anthocyanin drugs - the induction of the process of differentiation and suppression of the proliferation of cancer cells [18]. The antitumour effects of anthocyanins have been corroborated in vivo, as evidenced by the results of animal model experiments. A study of cancerous and normal tissues collected before and after therapy demonstrated that an anthocyanin-enriched diet resulted in a reduction in the proliferation rate of cancer cells and an increase in apoptosis, while no effect was observed on normal cells. Additionally, a reduction in angiogenesis was observed [19].

The anticancer potential of berries, including blueberries, is associated not only with the presence of anthocyanins, but also with the presence of proanthocyanidins, also known as tannins. During their passage through the gastrointestinal tract, due to their polymer structure, they are partially absorbed, with their concentration in the colon reaching several hundred micromoles per litre of intestinal content. This creates an opportunity for effective local antitumour action [20]. It seems pertinent to mention the recent discovery of the compound resveratrol in blueberries. It is an aromatic compound derived from diphenylethane. Resveratrol has been demonstrated to possess potent antioxidant properties, and it is postulated that it exerts an antitumour effect at various stages of carcinogenesis, including initiation, promotion and progression. It is likely that the compound inhibits the activity of phase I enzymes of metabolism and stimulates the activity of phase II enzymes, thereby reducing the number of active metabolites of xenobiotics and facilitating their elimination. During the progression stage, the compound stimulates a number of processes, including apoptosis [21].

In traditional folk medicine, blueberries have been employed for the treatment of various inflammatory conditions, particularly those affecting the mucous membranes of the mouth and throat. The bactericidal and disinfecting effects of natural phenolic compounds, as well as their strong anti-inflammatory effects, are well documented [22]. The research indicates that a mixture of berry extracts exerts a toxic effect on the stomach bacterium Helicobacter pylori.

This bacterium is thought to be a probable cause of various gastrointestinal tract diseases, including stomach and duodenal cancer, and the findings have significant implications in the context of public health. A study of the Finnish population, in which berries constitute a significant component of the diet, has demonstrated that berries, which contain a substantial quantity of tannins, exhibit antibacterial properties and provide protection against pathogens. This discovery offers novel avenues for the utilisation of berries in the food industry [23, 24].

Studies described in the literature have shown that some types of plant raw materials and products obtained from them both in vivo and in vitro show significant immunostimulating activity [25]. A comparison of the immunological activity of synthetic immunomodulators: levamisole and isoprinosine with the activity of aqueous extracts of Fructus Myrtilli indicates a pronounced immunostimulating effect of the extract [26]. It is hypothesised that the polyphenols present in berries exert a multifaceted influence on the mediators implicated in the immune response, specifically through the modulation of the release of pro-inflammatory cytokines. Phenolic acids also exert an influence on the effector phase of antibody production. In particular, chlorogenic, ellagic, gallic, caffeic and salicylic acids have been observed to stimulate the production of IgG antibodies [26, 27]. Stimulation of the immune system with the combined use of antibiotics and extracts of plant raw materials, in particular blueberries, indicates the possibility of their use to improve the condition of the immune system of patients treated with antibiotics [28, 29]. It can thus be postulated that the incorporation of blueberries into a maintenance therapy regimen, in conjunction with an appropriate antibiotic treatment, may prove advantageous for the patient's immune system.

A number of literature reports, which present the results of studies using cell cultures in vitro, studies on animal models and clinical studies with the participation of both healthy volunteers and sick people, confirm the hypothesis that a diet rich in blueberries protects the human body from the harmful effects of the environment [30, 31].

Conclusions and recommendations

Blueberry berries and leaves represent a traditional component of the diet and a source of antioxidant substances, including anthocyanins and phenolic acids. The chemical and pharmacological properties of these substances make it possible to utilise blueberries in the prevention and complex therapy of the most common diseases of civilisation, including cardiovascular disease, diabetes, oncological disease, neurodegenerative disease and other diseases affecting the elderly. The precise relationship between the action of the active

substances present in this raw material and the observed effects remains to be elucidated through further research.

Author's contribution:
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