

A Review on Antitumor and Antiviral Potential of Cranberries (*Vaccinium Vitis-Idaea*) Origin from Bulgaria

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Abstract

A major goal in antitumor and antiviral therapy is to find active ingredients that selectively suppress the proliferation of tumor cells or inhibit viral replication and proliferation. In this connection, the antitumor and antiviral activity of natural products with proven phytochemical properties and pharmacological significance are actively investigated. A promising candidate are Bulgarian cranberries from high mountain plant populations, which are a valuable natural source of food and have proven healing properties in urinary tract infections, eye diseases and cardiovascular disorders, as well as prevention of hypertension and diabetes. The active components of *Vaccinium vitis-idaea* L. are polyphenols and anthocyanins which belong to classes of plant components with high antioxidant, antimicrobial, cytotoxic and antiproliferative activity. Cranberries contain a high percentage and variety of vitamins (A, E, C, etc.) and a number of minerals (K, Ca, Mg, P, Na). In the world regions where endemic measles outbreaks occur, for secondary prevention and avoidance of complications including blindness, WHO recommends the use of high doses of vitamin A in children under 5 years of age. Bulgarian cranberries are a valuable source of vitamins A and C.

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The assessment of biological activity of the individual components and fractions in the composition of the Bulgarian cranberries may help to identify substances with antitumor and/or antiviral activity that could potentially be useful in future development of new therapeutic agents.

Keywords: Bulgarian cranberries; measles; antitumor and antiviral activity.

1. Introduction

Cancer is a serious problem for modern science, considering late diagnosis, inadequately effective therapy and prevention. Despite the combined efforts of the scientific community, the mechanisms of tumorigenesis have not yet been fully elucidated. The frequency of these diseases for the last decades has been steadily increasing. One of the main reasons for the lack of effective therapy is the molecular heterogeneity of the malignant process. Along with efforts to understand the complex genetic and epigenetic factors and mechanisms that trigger a carcinogenic process, it is also necessary to analyze the potential active substances that may delay or even stop the progression of carcinogenesis.

Viral infections in humans are common, characterized by high mortality and development of complications of varying clinical severity requiring hospital treatment. These pathogens are responsible for neoplastic transformations, including the development of a number of severe diseases. Some difficult to treat and complex syndromes are associated with viral infections, including type 1 diabetes and hepatocellular carcinoma [1]. Due to the increasing number of travelling and fast urbanization there is a higher risk of rapidly expanding and emerging new epidemic outbreaks. The rapid spread of emerging viruses with pandemic potential is a threat to public health, especially in the absence of preventive vaccines and effective antiviral therapy. Examples in this relation, is the appearance and rapid spread of Severe acute Respiratory Syndrome (SARS), the Middle East Respiratory Syndrome MERS- SoV, measles, West Nile [2; 3] and the avian influenza viruses.

The Paramyxoviridae family includes morbillivirus (MV, genus Morbillivirus), along with human parainfluenza viruses (hPIV) and mumps virus. In early childhood these pathogens are important and represent a serious problem for the pediatric practice. The MV remains a serious threat to children's health, despite the presence of an effective attenuated vaccine [4; 5]. Approximately 30% of the reported patients with measles infection have one or more complications and the debilitating effects are most common among children under the age of five years. Data for 2014 shows about 115,000 deaths in children (mostly under 5 years of age) as a result of measles infection. Although most newly diagnosed patients are registered in countries with limited access to vaccination, outbreaks still occur in some countries that have failed to maintain high levels of vaccine coverage or those with enhanced migratory status. Since 2004, Bulgaria has been included in the WHO Program for the elimination of measles and rubella (including Congenital rubella) in the European Region and is active in seroepidemiological surveillance. Nevertheless, in 2009-2011, after a long inter-epidemic period (7 years), one of the largest epidemics in the European Region breaks out – with more than 24,000 people infected (morbidity - 324%) and 24 dead (Mortality - 0.3%, lethality - 0.1%) [6]. During the period 2011-2013, large epidemics of measles have also been registered in France, Ukraine, Georgia and Turkey. In the end of 2016 and the beginning of 2017, an epidemic of measles in Romania has been reported, affecting for several months all the regions of the country,

with over 4,000 affected so far, including 17 deaths, mostly children under 1 year of age. In Bulgaria, after a period of three years when only sporadic cases of measles occurred, in the beginning of 2017 there was a high jump of the people affected, with more than 200 cases in three regional cities and their adjacent areas in the country, namely Plovdiv, Pazardzhik and Montana. The reasons for the new epidemic outbreaks of measles are very complex. These include weaker vaccine immunity, naturally acquired protection and lower vaccine coverage levels in children in developed countries due to the unwillingness of parents to vaccinate them because of safety concerns for the components in the trivalent vaccine [7].

Currently, no specific antiviral therapy is available for treatment of measles, although drugs such as ribavirin and interferon α are used predominantly in severe forms of the disease.

At present, a number of highly pathogenic viruses remain without effective immunization, and the availability of licensed antivirals with real use in clinical practice is insufficient. The situation is further aggravated by the possibility of development of drug-resistant pathogens [8]. Therefore, it is especially important to develop new antivirals with high efficacy, low toxicity and cost, especially in cases when there are no vaccines and standard therapeutical approaches.

In oncology and clinical virology, most of the current drug agents are costly and have quite negative toxic effects on a number of organs and systems in the human body [9]. It is necessary to find therapeutic agents, which selectively and locally suppress tumor growth or viral invasion and replication without harming the body as a whole, in order to avoid the negative effect of the drugs used in oncology and for treatment of a number of viral diseases. One of the main approaches to achieving these goals is based on a study of the antitumor and antiviral properties of biologically active ingredients in whole extracts as well as various purified fractions of plants known and used for therapeutic purposes in traditional medicine. Based on such approach, an alkaloid inhibitor of acetylcholinesterase was found in a snowdrop (*Galanthus nivalis* L. var. *Gracilis*), which, in the form of the Nivalin preparation, was successfully used for the treatment of poliomyelitis, neuritis and radiculitis. Currently, many of the drugs used in the oncology practice have a natural origin. Achievement in this regard is the development of medicinal products based on paclitaxel (isolated from *T. brevifolia*), vincristine and vinblastine (derived from *C. roseus*) and podophyllotoxin (obtained from the roots of *Podophyllum* sp.) [10] (and others. Data obtained from highly sensitive methods and technologies indicate that some of the active ingredients in herbs can induce apoptosis in target cells only [11], but the mechanisms that lead to this effect are still too unclear.

1.1. Current state of the research on the problem area

There are about 3600 plant species in Bulgaria, and approximately 650 of them are considered to be healing. As a result of the favorable and varied climatic and soil conditions, Bulgarian plant species contain a high percentage of biologically active substances. They are rich in alkaloids, flavonoids, anthocyanins, glycosides, saponins, polysaccharides, polyphenols, tannins, and others. For some of the active substances in plants, there is evidence that they induce apoptosis in different types of cancer cells [12]. Epidemiological clinical trials show that antioxidants play a key role in the prevention of viral and cancer diseases [13]. They protect human cells

from oxidative damage by interacting with active oxygen radicals and metal-binding agents.

In recent years, intensive studies of the phytochemical properties and pharmacological significance of the Bulgarian flora have resulted in natural products with antitumor, antioxidant, antimicrobial and immunomodulating effect. An example in this regard is Thaliblastine (an original Bulgarian medical product with antineoplastic effect obtained from *Th. Aquilegifolium*) and Hyperatomarin (*H. annulatum*) with proven inhibitory effect on chronic myeloid leukemia cell lines [14].

At this moment, antiviral therapy for infections caused by the measles virus is not available. In regions of the world where cases of epidemic outbreaks of measles developed, World Health Organization (WHO) and the UN Children's Fund recommend receiving two large doses of vitamin A, in the post-diagnosis infection in children under 5 years of age [15]. Vitamin A is associated with a 50% reduction in complications and mortality due to measles infection, although its mechanism of action remains unclear [16].

In this respect, the development of new therapeutics on a natural basis, effective and as innocuous as possible for children's health, is indispensable. Potential sources of such antiviral substances may be plants rich in vitamins and microelements.

Wild berries have long been known for their antiseptic properties, antioxidant and antimicrobial activities and are widely used in traditional medicine in eye and cardiovascular disorders, as well as urinary tract infections [17]. Major representative of wild berries are cranberries (family *Ericaceae*, genus *Vaccinium*). More than 450 species are known, mostly shrubs distributed in colder regions of the northern hemisphere. In Bulgaria are distributed mainly 3 types - red (*Vaccinium vitis-idaea L.*), black (*Vaccinium myrtillus L.*) and blue (*Vaccinium uliginosum L.*). Currently cranberries belong to a group of functional foods, as experimental studies have demonstrated their beneficial effects on different functions in the body related to reducing the risk of a number of pathological conditions, including socially important cancer, diabetes, osteoporosis.

Nowadays a lot of drugs for the treatment of urogenital infections [18], atherosclerosis, including nervous system diseases such as Alzheimer's disease, contain cranberry as an active substance. Its fruits are rich in bioactive compounds such as pectin, tannins, provitamin A, vitamin B, C, PP, anthocyanins, polyphenols, Mn, Mg, Fe, organic acids [19] which have a proven effect against a wide range of human pathogenic bacteria and are beneficial to human health. Although the antimicrobial activity of the fruit has long been known and widely studied [20], antiviral properties have not been characterized in detail. There are separate publications reporting on the antiviral activity of the aqueous extracts from cranberry and black currant with respect to virus tick-borne encephalitis [21], of polyphenols and anthocyanins in cranberry juice against rotavirus and influenza virus [22 - 25].

In recent years, the available literature data shows that there is a strong interest and active analyzes of the antitumor potential of various active fractions of cranberry [26; 27]. Articles exposing data from *in vitro* studies of the effects of various anthocyanins and polyphenolic substances of berries extract on human carcinoma lines, were found [28 - 31].

Until now, data on the antiproliferative potential of extracts and purified cranberry fractions has not been published in Bulgaria, nor on primary cell cultures nor on immortal cell lines, and the antiviral potential data is exhausted by a single publication of Nikolaeva-Glomb and a team [32]. The authors analyze the antiviral potential of various wild berries, including blackberries and cranberries, against members of the families Picornaviridae - polyovirus type 1 (PV-1) and Coxsackievirus type B1 (CV-B1), Paramyxoviridae - respiratory syncytial virus subgroup A1 (human respiratory syncytial virus) and the family Orthomyxoviridae - influenza virus A (H3N2) virus, and detect the antiviral effect of total extracts on the replication of CV-B1 and influenza A (H3N2) viruses.

2. Conclusion

In this respect, the use of modern methods for detecting potential antitumor and antiviral activity of Bulgarian cranberries will contribute to enriching the scientific information with modern data about the biological activities useful for the human health of plant populations from Bulgarian flora. Cranberries refer to the category of medical foods with a wide range of useful active ingredients, including vitamins and microelements. A large number of food products and medicinal substances contain cranberries, and the conservation of their natural populations, as well as the building of cultural institutions in small municipalities rich in natural habitats, is a priority on both national and European level.

The control of viral pathogens posing a threat to human health, such as measles, and the efforts of the scientific community to enrich the therapeutic resources, is also an important and priority international destination.

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