SİDAS MEDYA
Akademik Gıda®
ISSN Online: 2148-015X
https://dergipark.org.tr/tr/pub/akademik-gida

Akademik Gıda 21(4) (2023) 375-387, DOI: 10.24323/akademik-gida.1423455

Review Paper / Derleme Makale

Potential Effects of Bilberry (*Vaccinium myrtillus* L.) on Cancer: A Narrative Review

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Received (Geliş Tarihi): 01.08.2023, Accepted (Kabul Tarihi): 29.12.2023
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ABSTRACT

Bilberry (*Vaccinium myrtillus* L.) is a fruit with high polyphenolic content and rich in anthocyanins. Due to its strong antioxidant capacity, it has potential effects in improving human health and reducing the risk of diseases. In addition to its antioxidant effect, it also possesses potential anti-inflammatory, anti-carcinogenic, anti-angiogenic, anti-proliferative, anti-atherogenic, anti-microbial, anti-diabetic, anti-lipidemic, neuroprotective, anti-metastatic, anti-radical effects, as well as preventing lipid oxidation, reducing oxidative stress and improving eye health. Bilberry consumption can potentially protect against and reduce the risks of chronic inflammation, dyslipidemia, hyperglycemia, increased oxidative stress, cardiovascular diseases, diabetes, dementia, and other age-related diseases and cancer. This review focuses on the potential mechanisms of action of bilberry in cancer.

Keywords: *Vaccinium myrtillus* L., Billberry, Cancer, Anthocyanins, Functional food

Yabanmersininin (*Vaccinium myrtillus L.*) Kanser Üzerindeki Potansiyel Etkileri: Geleneksel Derleme

ÖZ

Yabanmersini (*Vaccinium myrtillus L.*) polifenolik içeriği yüksek antosiyaninlerden zengin bir meyvedir. Antioksidan kapasitesi çok güçlü olduğu için sağlığı geliştirici ve hastalık risklerini azaltıcı potansiyel etkileri vardır. Antioksidan etkisinin yanı sıra anti-inflamatuar, anti-kanserojenik, anti-anjiyogenik, anti-proliferatif, anti-aterojenik, anti-mikrobiyal, anti-diyabetik, anti-lipidemik, göz sağlığını geliştirici, nöroprotektif, anti-metastatik, anti-radikal, lipit oksidasyonunu önleyici ve oksidatif stresi azaltıcı potansiyel etkileri de bulunmaktadır. Yabanmersini tüketimi kanser dahil olmak üzere kronik inflamasyon, dislipidemi, hiperglisemi, artmış oksidatif stres, kardiyovasküler hastalıklar, diyabet, demans ve yaşa bağlı diğer hastalıkların risklerinin azaltılmasında, önlenmesinde ve tedavisinde koruyucu potansiyel etkilere sahiptir. Bu derlemede antosiyaninlerden zengin olan yabanmersininin kanser üzerindeki potansiyel etki mekanizmaları anlatılmıştır.

Anahtar Kelimeler: *Vaccinium myrtillus* L., Yabanmersini, Kanser, Antosiyaninler, Fonksiyonel gıda

INTRODUCTION

Cancer is a complex disease characterized by uncontrolled cell division, abnormal cell growth, and influenced by genetic makeup and environmental conditions. Cancer ranks second among the leading causes of death worldwide, following cardiovascular diseases. According to the World Health Organization,

cancer accounts for 10 million deaths worldwide each year. Globally, one in every six deaths is attributed to cancer [1-3]. The factors contributing to cancer etiology include excessive consumption of salty, spicy, and smoked foods, inadequate intake of fruits and vegetables rich in antioxidant vitamins and bioactive compounds, insufficient fiber intake, high-carbohydrate and high-fat diets, and the presence of *Helicobacter pylori*. Other factors influencing cancer etiology include low socioeconomic status, age, gender, race, ethnic, reproductive factors, metabolic factors, environmental factors such as tobacco use, alcohol consumption, ultraviolet exposure, inadequate physical activity, immunity, as well as genetic factors [4-8].

Epidemiological studies have provided strong evidence that a diet rich in fruits and vegetables reduces the incidence of cancer. Fruits and vegetables exert their potential anti-carcinogenic actions through phytochemicals, which are functional food components [9-11]. Phytochemicals include carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds. Phenolic compounds are further categorized as phenolic acids, flavonoids, stilbenes, tannins, and coumarins. Flavonoids, in turn, are divided into six subclasses including flavonols (e.g., quercetin, kaempferol, myricetin), flavones (e.g., apigenin, luteolin), flavanones (e.g., hesperidin, naringenin), flavanols (e.g., catechin, epicatechin, epigallocatechin, theaflavin), isoflavones (e.g., genistein, daidzein, glycitein), and anthocyanins (e.g., delphinidin, cyanidin, peonidin, malvidin, pelargonidin, petunidin) [12-14].

The potential anti-carcinogenic effects of flavonoids have been demonstrated through experimental evidence both *in vitro* and *in vivo*. Flavonoids have been shown to have positive effect various cancer processes, including proliferation, migration, inflammation, angiogenesis, invasion, and metastasis. They exert these effects by modulating mitogen-activated protein kinase (MAPK), protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and beta-catenin (β-catenin) pathways, by inhibiting the activation of nuclear factor kappa B (NF-kB) and tumor activator protein-1 (AP-1), inducing cell cycle arrest, and promoting apoptosis and autophagy [13, 15 - 17].

Bilberry, cranberry, raspberry, mulberry, elderberry, and strawberry are berries that belong to the berry family, and are rich in nutrients and several bioactive compounds including phenolic acids, tannins and flavonoids, especially anthocyanins [4, 10, 18]. Especially, among these berries, the anthocyanin content of bilberry is higher compared to other Vaccinium species and is one of the richest natural sources [19]. Bilberry has the highest antioxidant capacity owing to its phytochemical content. In addition to its antioxidant capacity, studies have shown that it also has anti-inflammatory, anti-proliferative, anti-invasion, anti-angiogenic, anti-metastatic, anti-migration, apoptotic, anti-adhesion, anti-tumor and chemopreventive effects. It has been emphasized that these effects may have strong anti-carcinogenic effects on organ cancers and blood-related cancers [4, 10, 18-25].

Recently, researchers have provided many and different information about the nutrient components contained in bilberry, the properties of these components and their effects on health. It appears to be an important and promising functional food due to its functional nutrient components. The increase in the number of in vitro and in vivo studies examining the relationship between bilberry and cancer has led to a significant increase in the information on the subject in the literature. However, there are limited number of reviews in the literature describing its general potential effect mechanisms of action on cancer. Therefore, the purpose of this review is to evaluate the potential effects of bilberry on cancer.

Search Strategy

The electronic databases of Medline, Pubmed, Web of Science, Science Direct and TUBITAK ULAKBIM Turkish Medical Directory were searched in order to determine the studies on the potential effects of *Vaccinium myrtillus* L. on cancer. “*Vaccinium myrtillus* L.” AND “Cancer”, “Billberry” AND “Cancer”, “*Vaccinium myrtillus* L.” OR AND “Billberry” AND “Anthocyanins” keywords were used. Databases were searched from inception to 2022 without year limitation. Studies examining the relationship between *Vaccinium myrtillus* L. or billberry and cancer were included in this review. This review was prepared by using the Documentary Source Analysis method, including a total of 76 articles.

Bilberry and its Characteristics

Bilberry is a plant species belonging to the *Ericaceae* family, and grows in grasslands, meadows, and moist coniferous forests in Northern Europe, North America, and Asia. It is a small, blue-colored, seed-bearing, fleshy fruit with a diameter of 5-9 mm [18, 26, 27]. It produces its blue-purple fruits from April to June. In Turkey, it grows in mountains and forests, and is known as "çalı çiçeği" or "çoban üzümü" [28].

In traditional medicine, the fruit of bilberry is used for its anti-diarrheal properties, while the leaves are used as a coagulant and diuretic. The leaves of bilberry contain tannins, flavonoids, and a small amount of arbutin [29]. Blueberries are also a fruit rich in dietary fiber content. It is stated that it can prevent and protect against intestinal diseases such as constipation, hemorrhoids and colon cancer [30]. The fruit of bilberry is rich in phenolic compounds such as flavonols (e.g., quercetin, myricetin), flavanols (e.g., catechin, epicatechin), tannins, ellagitannins, phenolic acids (e.g., gallic, caffeic, ferulic, and chlorogenic acids), and anthocyanins. Among the phenolic compounds, bilberry is particularly abundant in anthocyanins, including delphinidin, cyanidin, peonidin, petunidin, and malvidin [18, 27, 31 - 34]. Table 1 shows the anthocyanin content of bilberry [18].

Table 1. The anthocyanin content of bilberries

Anthocyanins	%
Delphinidin	15.17
Delphinidin-3-O-glucoside	5.81
Delphinidin-3-O-galactoside	5.04
Delphinidin-3-O-arabinoside	4.32
Siyanidin	8.36
Cyanidin-3-O- glucoside	3.42
Cyanidin-3-O- galactoside	2.75
Cyanidin-3-O-arabinoside	2.19
Petunidin	6.64
Petunidin-3-O- glucoside	3.67
Petunidin-3-O- galactoside	1.89
Petunidin-3-O-arabinoside	1.08
Malvidin	5.43
Malvidin-3-O- glucoside	3.35
Malvidin-3-O- galactoside	1.27
Malvidin-3-O-arabinoside	0.81
Peonidin	1.87
Peonidin-3-O- glucoside	1.31
Peonidin-3-O- galactoside	0.34
Peonidin-3-O-arabinoside	0.22

Bilberry contains approximately 40% of anthocyanins. Delphinidin and cyanidin contain about 60% of the total anthocyanin content. The anthocyanin content is ranked as follows: delphinidin (15.17%), cyanidin (8.36%), petunidin (6.64%), malvidin (5.43%), peonidin (1.87%). Depending on environmental conditions and ripeness, approximately 100 grams of bilberry contains about 300-700 mg of anthocyanins. In addition to anthocyanins, 100 grams of bilberry contains approximately 3 mg of quercetin, 20 mg of catechins, 100 mcg of beta-carotene, and 64 mcg of lutein [18, 26, 32, 35]. Table 2 shows the energy and nutrient content of 100 grams of bilberry [35].

Table 2. Energy and nutrient content of bilberries

	Component	Unit	Average amount (100 g)
	Energy	kcal	44
	Water	g	87.76
Macro nutrients	Protein	g	0.46
	Total fat	g	0.34
	Carbohydrate	g	8.49
	Total fiber	g	2.73
	Soluble fiber	g	0.30
	Insoluble fiber	g	2.43
Micro nutrients	Iron	mg	0.55
	Phosphorus	mg	20
	Calcium	mg	13
	Magnesium	mg	7
	Potassium	mg	98
	Sodium	mg	6
	Zinc	mg	0.15
	Vitamin C	mg	21.9
	Thiamin	mg	0.009
	Riboflavin	mg	0.025
	Niacin	mg	0.321
	Vitamin B6	mg	0.077
	Vitamin A	RE	8
	Beta-carotene	mcg	100
	Lutein	mcg	64

Bilberry has the highest antioxidant capacity among berries. It shows this effect with the nutrients and functional food components it contains. Also, its beneficial phytochemical content enables it to have potential effects such as anti-inflammatory, antiseptic, anti-lipidemic and anti-radical, as well as antioxidant effects. It can improve nutritional quality, improve health and reduce the risk of chronic diseases [18, 26, 31, 36, 37].

Anthocyanins

Anthocyanins are water-soluble flavonoids commonly included in fruits and vegetables. Essentially, they are the pigments responsible for the pink, red, blue, and purple colors of many flowers, leaves, vegetables, and fruits [7, 18, 38].

Anthocyanins are glycosylated forms of anthocyanidins (aglycones). These compounds are formed by the flavylium cation backbone hydroxylated at different positions (usually at C3, C5, C6, C7 and C3', C4', C5' carbons). The properties of anthocyanins depend on the degree and pattern of hydroxylation and methoxylation of the skeletal structure [39, 40]. Anthocyanins exhibit color changes based on pH. They appear red in acidic pH (below pH 2), purple at neutral pH, blue at alkaline pH, and colorless at higher pH levels. The anthocyanin pigments responsible for the red color are primarily included in the form of flavylium cations. The flavylium cation formed at low pH allows anthocyanins to be highly soluble in water. Cyanidin appears red at pH < 3, violet at pH 7-8, and blue at pH > 11, while peonidin is cherry red at low pH and dark blue at pH 8. Anthocyanin molecules consist of an anthocyanidin core with sugar (glucose, galactose, xylose, arabinose, or rhamnose) moieties attached at various positions. Anthocyanins vary based on the number and position of hydroxyl and methoxy groups, depending on the structure of the anthocyanidin [18, 38]. Although there are fewer than twenty naturally occurring anthocyanidins, hundreds of different anthocyanins exist. The most common anthocyanins include cyanidin, delphinidin, pelargonidin, peonidin, malvidin, and petunidin. The distribution of these anthocyanidins in fruits and vegetables is approximately 50% cyanidin, 12% delphinidin, 12% pelargonidin, 12% peonidin, 7% malvidin, and 7% petunidin. Cyanidin is responsible for the purplish-red color and is the main pigment in berries. Delphinidin has a similar chemical structure to anthocyanidins and exhibits a bluish-red color. It is responsible for the blue tones in flowers. Pelargonidin differs from most other anthocyanidins and appears as a red-colored pigment in nature. It gives an orange color to some fruits and a red color to certain flowers. Peonidin is a methylated anthocyanidin included in high amounts in fruits, wines, and berries. It has a violet color. Malvidin is another methylated anthocyanidin with a purple appearance. It is responsible for the red color in red wine and appears as a dark red in unripe wines. Petunidin is a methylated anthocyanidin and is a water-soluble dark red or purple pigment [38].

Regarding the bioavailability of anthocyanins, it has been included that their absorption is rapid but relatively low. Unlike other polyphenolic flavonoids, they are absorbed without structural degradation [18]. Anthocyanins are metabolized in the mouth after consumption. In the mouth, glycosidic groups are removed and chalcones are formed under the influence of the oral microbiota. They start from the stomach and passes through the gastrointestinal tract. Despite the acidic pH of the stomach, they do not undergo significant changes and can be absorbed by bilitranslocase or reach the intestinal epithelium. Anthocyanins reach the liver via portal vein circulation. From here they are directed to the systemic circulation and used by target organs and tissues. Unabsorbed metabolites are excreted in urine and feces [41]. Depending on their structure, anthocyanins are absorbed from the stomach and small intestine at a rate of 11-22%. Anthocyanins can be detected in the plasma shortly after oral intake, typically within a few minutes. They reach its maximum plasma concentration between 30-120 minutes and are eliminated within 6 hours. The maximum plasma concentration ranges from 5 to 50 nmol/L [18, 41].

The anthocyanin content of fruits can vary depending on factors such as sunlight exposure, pH, temperature, soil nitrogen and phosphorus levels, oxygen, processing time, storage conditions, harvest time, and fruit ripeness. Anthocyanins are primarily included on the outer surface of fruits. Damage to the fruit's outer surface during harvest can reduce the anthocyanin content. The optimal harvest time is typically in August and early September. As the fruit ripens, the anthocyanin content increases [18, 26].

Anthocyanins have potential health promoting and disease-preventive effects. Their antioxidant, apoptotic, anti-proliferative, anti-angiogenic, anti-carcinogenic, anti-diabetic, anti-obesity, anti-microbial, cardioprotective, eye health- promoting, neuroprotective, and anti-hypertensive effects contribute to their health benefits [18, 38, 41 - 43].

Potential Effects of Bilberry on Cancer and Relevant Studies

Bilberry plays a crucial role in the prevention and treatment of cancer due to its potential antioxidant, anti-radical, anti-inflammatory, anti-proliferative, anti-carcinogenic, anti-angiogenic, anti-metastatic, and apoptotic effects.

Antioxidant and Anti-radical Effects of Bilberry

When the concentrations of heavy metals exceed optimal levels, they can disrupt the normal functioning of the cell by affecting the cellular components and events. They have been associated with increased reactive oxygen species (ROS). This species can interfere with macromolecules, resulting in impairment of cellular functions and metabolism in normal cells. For example, lipid peroxidation and protein inactivation can result in DNA damage. Detoxification is required to minimize the

damage caused by ROS. Detoxification occurs through two separate pathways: enzymatic and non-enzymatic. The enzymatic pathway involves antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR). The non-enzymatic pathway involves tripeptide glutathione, proline, cysteine, ascorbate, and small molecules containing non-protein compounds rich in sulfhydryl (-SH) groups [27, 44].

Bilberry exhibits antioxidant activity by chelating metals such as iron involved in redox reactions, scavenging hydroxyl radicals, hydrogen peroxide radicals, superoxide anion radicals, and ROS. It increases the levels of glutathione, a powerful antioxidant, and antioxidant enzymes (SOD, CAT, GPX, and GR), thereby enhancing antioxidant capacity [3, 18, 28, 45]. Induction of phase I and phase II antioxidant enzymes involved in detoxification protects against ROS while inhibiting the CYP1A1 gene [33, 34]. Figure 1 shows antioxidant and anti-radical effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 18, 28, 45 - 47]..

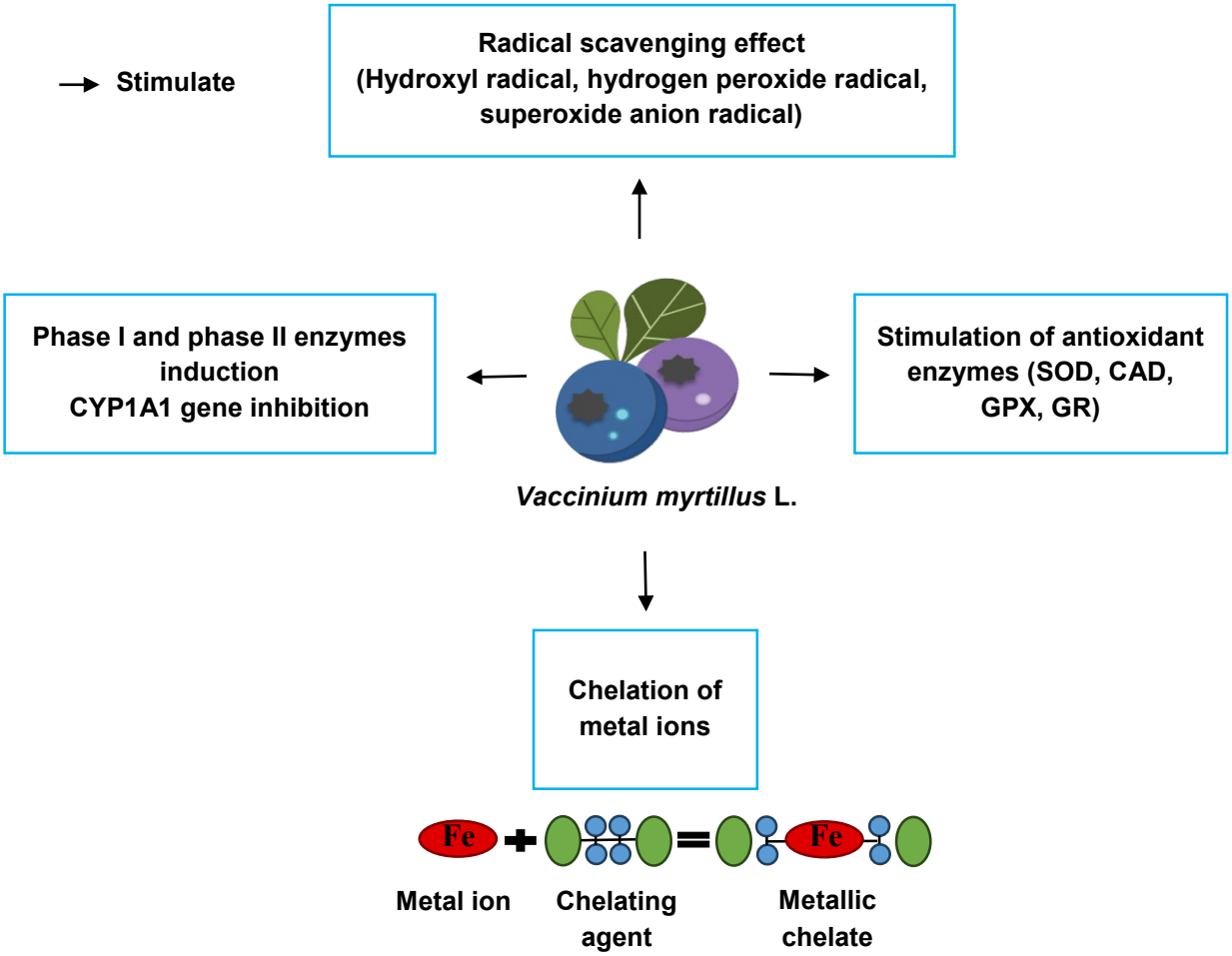

Figure 1. Antioxidant and anti-radical effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 18, 28, 45-47].

In a study by Juadjur et al. [48] on Caco-2 and HT-29 human colon cancer cell lines, 500 mcg/mL of *Vaccinium myrtillus* L. extract significantly reduced ROS levels in Caco-2 cells after 1 hour of incubation. A slight decrease in ROS levels was also observed in HT-29 cells after 24 hours of incubation. Additionally, an increase in total glutathione levels was detected in Caco-2 cells treated with 500 mcg/mL of bilberry extract after 24 hours of incubation. The extract reduced oxidative DNA damage and increased total glutathione levels at high doses. In a study, Šaponjac et al. [49] investigated the antioxidant effects of dried bilberry extract using three different extract fractions. The first extract fraction (Fr1) contained 1.02 mg/100 g of vitamin C, the second extract fraction (Fr2) contained six flavonoids (with quercetin being the most abundant at 243.3 mg/100 g of dried bilberries), and the third extract fraction (Fr3) contained eight phenolic acids, with p-coumaric acid being the most prominent (57.87 mg/100 g of dried bilberry). The most significant effect on the transformation and stabilization of hydroxyl radicals was observed in Fr3 ($EC^{\bullet OH}50$ = 0.117 mg/mL), while the best free radical scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals was observed in Fr2 ($EC^{DPPH\bullet}50$ = 0.025 mg/mL). Fr1 exhibited the lowest free radical scavenging effect on both DPPH and hydroxyl radicals ($EC^{DPPH\bullet}50$ = 0.204 mg/mL, $EC^{\bullet OH}50$ = 1.213 mg/mL). The highest anti-radical effect was observed in Fr2. In addition, Fr2 and Fr3 inhibited the growth of cervical epithelioid carcinoma, breast

adenocarcinoma, and colon adenocarcinoma cell lines. In Bao et al.'s study [50], mice were orally (0.1 mL/10 g of body weight) administered bilberry extract at doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg for 5 days. An increase in mitochondrial membrane potential, an increase in sodium/potassium ATPase activity, and a decrease in ROS levels were observed at the dose of 200 mg/kg. In a study by Esselen et al. [51], when HT-29 colon carcinoma cells were incubated with 500 mg/mL of bilberry extract for 72 hours, cell growth was inhibited. It was reported that at a concentration of 25 mg/mL, topoisomerase I activity was strongly inhibited, and at concentrations ≥50 mcg/mL, topoisomerase I activity was completely suppressed. Topoisomerase II activity was reduced at concentrations ≥1 mcg/mL. The study concluded that bilberry extract suppressed the levels of topoisomerase I and II, which covalently bind to DNA and cause damage to the DNA chain, thus preventing DNA damage. Ancillotti et al. [31] examined the antioxidant and anti-radical activities of *Vaccinium myrtillus* L. and *Vaccinium uliginosum* subsp. gaultherioides, and reported that *Vaccinium myrtillus* L. exhibited greater antioxidant and anti-radical activities due to its delphinidin and cyanidin content. In a study by Kandziora-Ciupa et al. [44], the concentrations of heavy metals (cadmium, lead, zinc, iron, and manganese) in the soil and their bioavailability in *Vaccinium myrtillus* L. were investigated. A positive correlation was found between the concentrations of cadmium, manganese, and zinc in *Vaccinium myrtillus* L. leaves and proline. An increase in manganese accumulation was observed to lead to a decrease in antioxidant response, while an increase in non-protein -SH groups and glutathione content resulted in an increase in antioxidant response. It was also found that bilberry has a high capacity for manganese accumulation.

Anti-inflammatory and Anti-proliferative Effects of *Vaccinium myrtillus* L.

Oxidative stress, along with the stimulation of the microenvironment, activates several pathways such as NF-kB, signal transducer and transcription activator 3 (STAT3), hypoxia-inducible factor-1 alpha (HIF-1α), AP-1, and nuclear factor erythroid 2-related factor 2 (Nrf2), leading to increased release of inflammatory cytokines such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), interleukin-10 (IL-10) and tumor necrosis factor (TNF)-α. Chronic inflammation, coupled with increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), may result in malignant cell transformation in healthy cells and tissues, thereby increasing the risk of cancer occurrence [3, 33, 46, 52]. Bilberry with its phytochemical content, particularly anthocyanins, exhibits anti-inflammatory and anti-proliferative effects, inhibiting the formation and proliferation of cancer cells. It exerts this effect by scavenging ROS, inhibiting the NF-kB pathway, activating the Nrf2-antioxidant response element (ARE) signaling pathway, inhibiting STAT3, and reducing inflammatory markers [TNF-α, IL-1β, IL-6, IL-10, iNOS, COX-2, prostaglandin E2 (PGE2), phosphoprotein 65 (p-p65)] [47, 53-56]. Figure 2 shows anti-inflammatory and anti-proliferative effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 33, 46, 47, 52-56].

In a study by Schantz et al. [57] using Caco-2 and HT-29 human colon cancer cell lines, *Vaccinium myrtillus* L. exhibited anti-inflammatory effects on HT-29 cells (after 24-hour incubation at 250 mcg/mL) and Caco-2 cell lines (after 1-hour incubation at 50 mcg/mL), and significantly reduced ROS levels. They also observed a significant reduction in DNA damage in Caco-2 cells after 24-hour incubation at 5 mcg/mL. In a randomized controlled study by Karlsen and coworkers [58], the control group (n=31) was given water, while the experimental group (n=31) received 330 mL/day of bilberry juice (diluted with 1 liter of water) for 4 weeks. The study found a significant decrease in plasma concentrations of C-reactive protein (CRP), IL-6, and IL-15 as well as an increase in TNF-α level in the group that was given bilberry juice. The increase in TNF-α stimulates the release of IL-10, an anti-inflammatory cytokine. It was concluded that the polyphenols present in bilberry can modulate inflammatory processes.

Anti-carcinogenic and Apoptotic Effects of *Vaccinium myrtillus* L.

The potential anti-carcinogenic, anti-invasion, anti-adhesion, anti-migration, anti-angiogenic, and anti-metastatic effects of *Vaccinium myrtillus* L. include protection of cells against oxidative damage, suppression of inflammation, regulation of cell cycle, induction of apoptosis leading to inhibition of cell proliferation, inhibition of angiogenesis, prevention of cell migration and adhesion, and prevention and repair of DNA damage [3, 54, 59]. *Vaccinium myrtillus* L. exhibits anti-angiogenic effects by inhibiting the release of vascular endothelial growth factor (VEGF) induced by stress and cytokines [60, 61]. It reduces the release of pro-angiogenic factors such as c-Myc, c-jun, and c-fos. It also exhibits a potential preventive effect against cell adhesion by downregulating the expression of cell adhesion molecules such as β-catenin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), while upregulating the expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) [54]. By suppressing matrix metalloproteinases (MMPs) (MMP-2 and MMP-9) and urokinase-type plasminogen activator (u-PA), *Vaccinium myrtillus* L. can prevent cell invasion [3, 46]. Tumor cells promote angiogenesis by creating new blood vessels from existing ones to access oxygen and nutrients, and they induce metastasis by migrating to other tissues through blood and lymphatic vessels [62]. *Vaccinium myrtillus* L. exhibits anti-metastatic effects by inhibiting AP-1, which accelerates the epithelial-mesenchymal transition of tumor cells (the first step in metastasis) [46]. Figure 3 shows anti-invasion, anti-adhesion, anti-migration, anti-angiogenic and anti-metastatic effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 46, 54, 59 - 61].

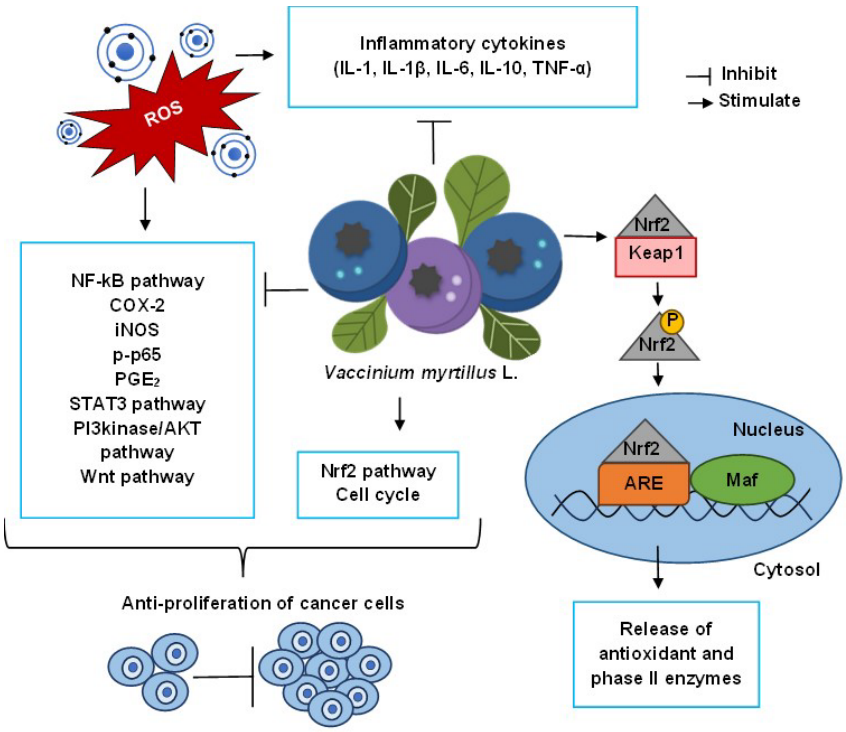

Figure 2. Anti-inflammatory and Anti-proliferative Effects Mechanisms of *Vaccinium myrtillus* L. in Cancer Cells [3, 33, 46, 47, 52-56].

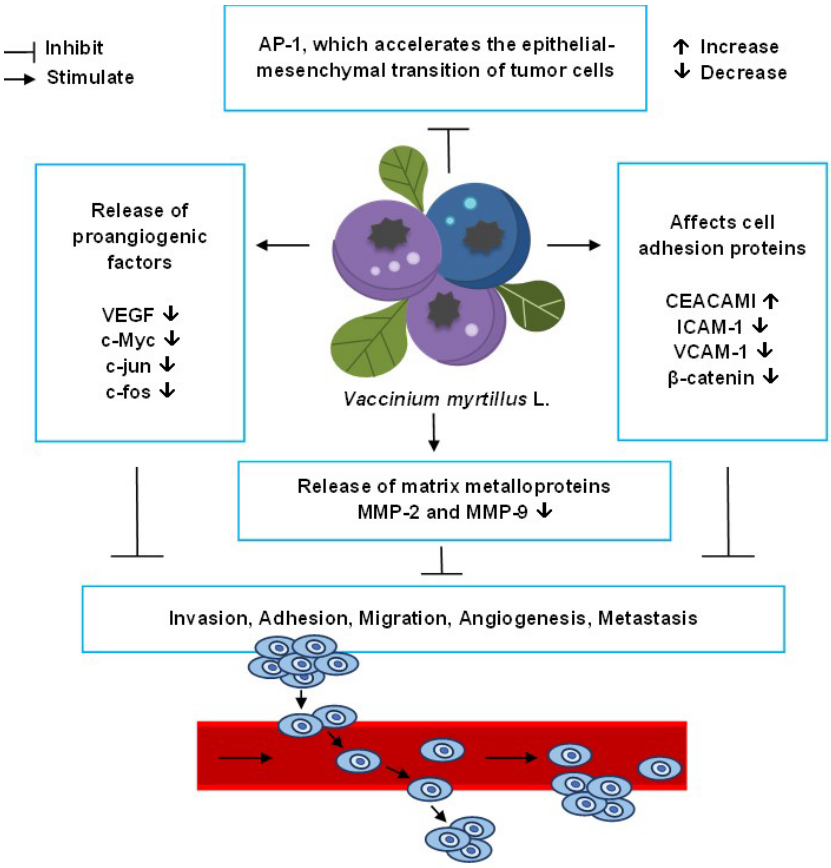

Figure 3. Anti-invasion, anti-adhesion, anti-migration, anti-angiogenic and anti-metastatic effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 46, 54, 59-61].

The cell division cycle is a biochemical phase controlled by cyclin-dependent kinases (CDKs). They are regulated by the synthesis and degradation of cyclins, as well as the phosphorylation and inhibition of CDKs. There are also several transcription factors that control the cell cycle. p53 is a gene that increases the release of CDK inhibitors, thereby halting the cell cycle. Uncontrolled cell division, aberrant signaling pathways, anti-apoptotic effects, metastatic effects, immortality, increased angiogenesis, and mutations in tumor suppressor genes such as proto-oncogenes and p53 are observed in tumor cells [63]. Bilberry exhibits potential anti-proliferative and cell cycle regulatory effects, preventing the uncontrolled growth and proliferation of tumor cells. It reduces the activity of CDK-2, CDK4, cyclin A, cyclin B1, cyclin D1, cyclin E, protein phosphatase 2 (Cdc2), and Cdc25C, while increasing the activity of CDK inhibitors p16, p21, and p27 [3, 54].

Genetic alterations and mutations in cancer cells are associated with signaling pathways that control tumor formation. DNA mutations can lead to overexpression of affected genes or production of mutated proteins with erratic activity. Proteins found in signaling pathways that are widely activated in various physiological responses include growth factor receptor tyrosine kinases (e.g., epidermal growth factor receptor), guanosine triphosphatases (e.g., Ras), serine/threonine kinases (e.g., Raf and Akt), cytoplasmic tyrosine kinases (e.g., Src and Abl), lipid kinases (e.g., Phosphatidylinositol-3-kinase or PI3K), and nucleotide receptors (e.g., estrogen receptor). The components of the signaling pathways such as Wnt, Hedgehog, Hippo, and Notch can also be affected. The most important pathways regulating cell proliferation are PI3K-Akt and Ras-Raf-ERK. Ribosomal S kinase (RSK) and MAPK are phosphorylated by ERK. Akt and RSK lead to activation of the mammalian target of rapamycin (mTOR) pathway [62]. In addition to its anti-inflammatory and anti-proliferative actions, anthocyanin-rich *Vaccinium myrtillus* L. suppresses Ras-Raf-MAPK-ERK, PI3K-Akt-mTOR, and Wnt signaling pathways [54].

p53 is a transcription factor that regulates the cell cycle and controls DNA repair mechanisms and apoptosis. Mutate p53 loses its tumor suppressor function, leading to increased cancer cell formation and proliferation [3, 54]. Through its anthocyanin content, *Vaccinium myrtillus* L., exhibits potential effects in preventing p53 mutation and DNA damage, promoting DNA repair, and inducing phase II enzymes such as quinone reductase. These effects contribute to the inhibition of cell proliferation and induction of apoptosis [18, 47, 64]. Apoptosis is programmed cell death. There are two main pathways for apoptosis: the extrinsic pathway (death receptor pathway) and the intrinsic pathway (mitochondrial pathway). In the extrinsic pathway, TNF is induced by the interaction of extracellular ligands such as the Fas ligand (Fas-L) and TNF-related apoptosis-inducing ligand (TRAIL) with transmembrane receptors (death receptors). Binding of the Fas-associated death domain (FADD) and the TNF receptor-associated death domain (TRADD) results in the formation of the death-inducing signaling complex (DISC). The resulting DISC activates pro-caspase-8, which in turn activates pro-caspase-3, an effector caspase that initiates apoptosis [65, 66]. In the intrinsic pathway, the mitochondria play a crucial role. Cytochrome c (Cyo-c), an electron transport chain protein involved in adenosine triphosphate (ATP) production is located in the inner mitochondrial membrane. tBid is formed when active caspase-8 cleaves the pro-apoptotic protein Bid. The resulting tBid integrates into the mitochondrial membrane and increases its permeability. Increased membrane permeability allows the release of Cyo-c into the cytoplasm through the pores formed in the membrane. The release of Cyo-c from the mitochondria into the cytoplasm indicates that apoptosis is irreversible. Cyo-c, ATP, procaspase-9 and apoptosis protease activating factor 1 (APAF-1) together form a complex known as apoptosome. Procaspase-3 is converted to active caspase-3. The caspase-dependent mechanism of apoptosis is activated [60, 63, 67]. Apoptosis is induced by activation of caspase-3, caspase-8, and caspase-9, induction of Bax and Cyo-c release, suppression of Bcl-2 and poly ADP ribose polymerase (PARP) release, mitochondrial damage, and stimulation of Cyo-c release [46, 47, 54]. Anthocyanins also exert an apoptotic effect by inhibiting the NF-kB pathway and arresting the cell cycle in the G2/M phase [5, 68, 69]. In addition to these effects, they inhibit the expression of polycomb group (PcG) proteins. PcG proteins are epigenetic regulators that downregulate tumor suppressor genes and ensure cancer cell survival [59]. Figure 4 shows anti-angiogenic and apoptotic effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 5, 18, 47, 54, 64, 68-70].

In a study by Misikangas et al. [71] on Min/1 mice to investigate the chemopreventive properties of *Vaccinium myrtillus* L. (rich in anthocyanins), *Vaccinium vitis-idaea* (rich in proanthocyanidins), and *Rubus chamaemorus* (rich in ellagic acid) with different phenolic contents on intestinal tumor formation, four different groups were constructed: *Vaccinium myrtillus* L., *Vaccinium vitis-idaea*, *Rubus chamaemorus*, and a control group. The control group was fed a high-fat diet consisting of 41% fat, 39% carbohydrates, and 19% proteins, while the other groups were fed high-fat diets containing 10% berries for 10 weeks. Berries inhibited the formation of intestinal adenomas by 15-30% and suppressed cell growth. They also reduced β-catenin and showed chemopreventive activity, resulting in a decrease in tumor formation by 60%.

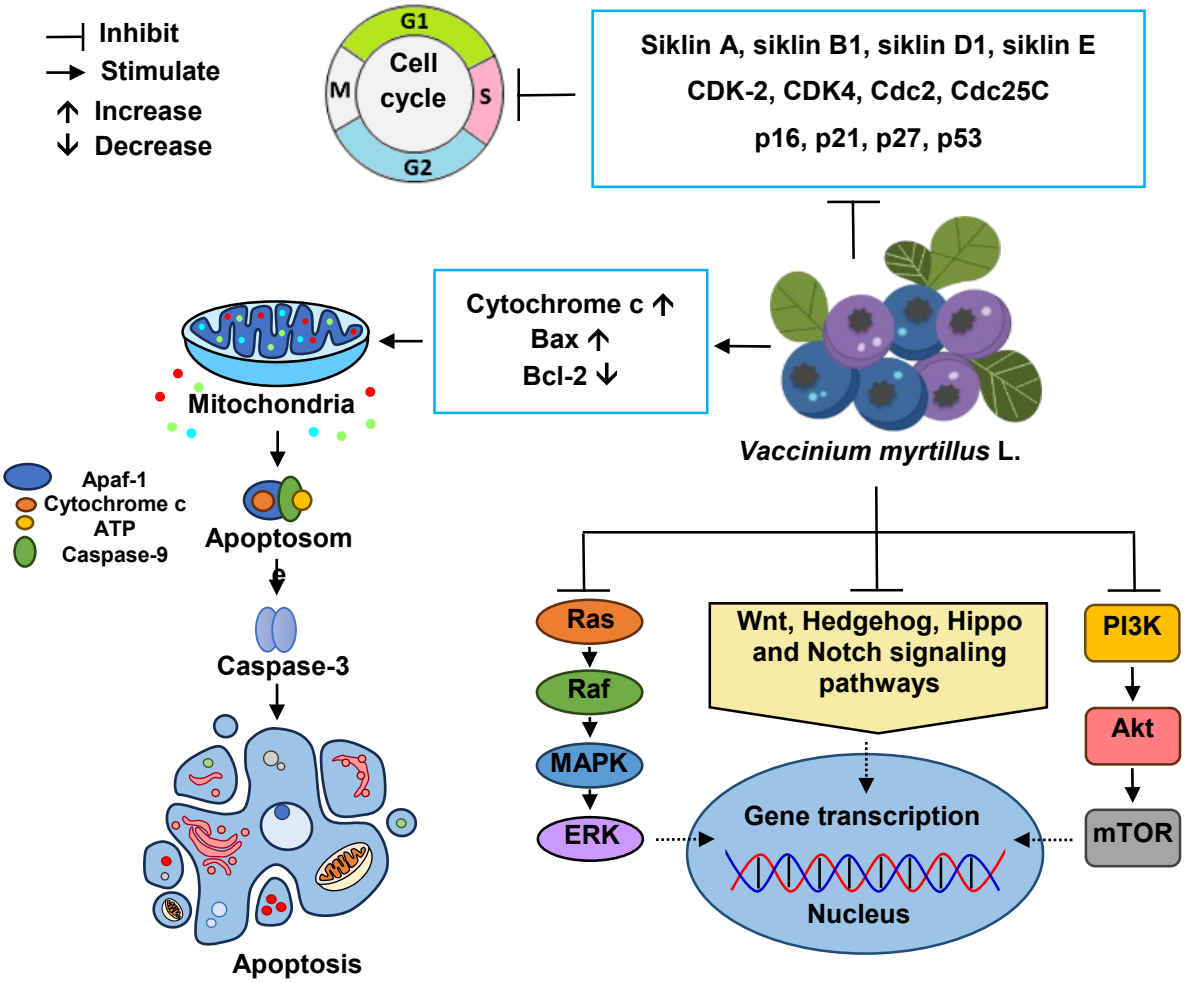

Figure 4. Anti-carcinogenic and apoptotic effects mechanisms of *Vaccinium myrtillus* L. in cancer cells [3, 5, 18, 47, 54, 64, 68 - 70].

Wu et al. [72] reported that 10 mg/mL of bilberry extract reduced cell proliferation by 30% in HT-29 colon cancer cells. They observed that the extract resulted in an increase in Bax expression and a decrease in Bcl-2 expression. In a study, Alhosin et al. [73] investigated the apoptotic effects of a bilberry extract containing 50% anthocyanins (Antho 50) on B-cell chronic lymphocytic leukemia cells. They found that Antho 50 increased ROS generation, caspase-3 activation, and levels of p21 and p73, while decreasing p-Akt, histone deacetylase (HDAC), and DNA methyltransferase 1 (DNMT1). It was observed that ROS generation induced by hydrogen peroxide and Antho 50 was prevented by catalase. The study concluded that Antho 50 inhibited the expression of PcG proteins in Jurkat cells and increased apoptosis by 75% at a concentration of 75 mg/mL. León-González et al. [59] examined the effects of Antho 50 on the expression of PcG proteins in Jurkat cells in which Jurkat cells were treated with different concentrations of Antho 50 (10, 25, 50, 75, and 100 µg/mL) for 24 hours. It was observed that apoptosis began in 50% of the cells treated with 100 µg/mL Antho 50, and there was a loss of mitochondrial membrane potential and a significant increase in intracellular ROS levels. Additionally, there was a 60% decrease in the expression levels of HDAC1, DNMAT1, and UHRF1, which are proteins that act in conjunction with PcG. Also, HDAC2 expression was reduced by 40%. Furthermore, significant increases were observed in the expression levels of the tumor suppressor p73, cell cycle regulator p21, and caspase-3 in cells treated with 75 and 100 µg/mL Antho 50. In an *in vitro* study by Katsube et al. [74] investigating the effects of 10 different berry extracts, including *Vaccinium myrtillus* L., on HL60 human leukemia cells and HCT116 human colon carcinoma cells, it was found that at a concentration of 4-6 mg/mL, bilberry extract reduced the cell viability of HL60 human leukemia cells by 84-88%, and at a concentration of 2-4 mg/mL, it reduced the cell viability of HCT116 human colon carcinoma cells by 66-97%. In the same study, 4 mg/mL bilberry extract was observed to induce apoptosis in HCT116 human colon carcinoma cells, while its apoptotic effect was greater in HL60 human leukemia cells. In another study by Nguyen et al. [75], the effects of *Vaccinium myrtillus* L. on MCF7 human breast cancer cells were assessed. It was reported that, at a concentration of 0.3-0.4 mg/mL, *Vaccinium myrtillus* L. induced apoptosis and reduced cell proliferation by 50%. In a study by Aaby et al. [76], anti-proliferative effects of bilberry extracts obtained at different temperatures (22, 40, 60, 80, and 100°C) for 4, 15, 30, and 45 minutes were investigated in three different colon cancer cell lines (Caco-2, HT-29, and

HCT 116). It was found that, at a concentration of 125 mg/L, the extract obtained at 100 °C inhibited cell proliferation in Caco-2 cells 1.4 and 1.7 times more than the extracts obtained at 60°C and 40°C, respectively. In HT-29 cells, when the extract obtained at 100°C was given at a concentration of 250 mg/L, 2.2 and 2.5 times greater anti-proliferative effect was observed compared to the extracts obtained at 60°C and 40°C, respectively. In HCT 116 cells, at a concentration of 250 mg/L, the extract obtained at 100 °C and exhibited 4.0 and 5.6 times more anti-proliferative activity compared to the extracts obtained at 60°C and 40°C, respectively. These findings indicate that extracts obtained at higher temperatures (80-100°C) have a greater inhibitory effect on colon cancer cell proliferation compared to extracts obtained at lower temperatures. In a pilot study by Thomasset et al. [42] involving 15 patients with colorectal adenocarcinoma and 10 patients with colorectal liver metastasis, 10 patients received 1.4 g of a standardized bilberry extract (containing 36% of anthocyanins), 8 patients received 2.8 g and 7 patients received 5.6 g of the standardized extract three times a day for 7 days. 1.4 g of the standardized extract contained 0.5 g of anthocyanins, equivalent to 370 g of fresh bilberries. A 9% reduction in cancer cell proliferation was observed in the group receiving 1.4 g of the standardized extract, while the reductions in the other groups were nonsignificant. In a study by Zhao et al. [36] on HT-29 colorectal adenocarcinoma cell line and NCM460 colon cell line, *Vaccinium myrtillus* L. extract was reported to inhibit cell proliferation by 7% at 48 and 72 hours.

CONCLUSION

Vaccinium myrtillus L. has an anti-oxidant effect by stimulating the chelation of metal ions, scavenging of reactive oxygen species and releasing of anti-oxidant enzymes. It can prevent oxidative stress and inflammation by activating the Nrf2 pathway and suppressing the NF-kB, STAT3, Wnt, PI3kinase/AKT pathways and inflammatory markers (TNF-α, IL-1β, IL-6, IL-10, IL-1 etc.). Moreover, it has a potential preventive effect against cell adhesion by decreasing cell adhesion molecules such as ICAM-1, VCAM-1, b-catenin and increasing CEACAM1. It has a potential inhibitory effect on angiogenesis and metastasis by reducing VEGF, c-Myc, c-jun, c-fos, MMP-2 and MMP-9. It also prevents the uncontrolled growth and proliferation of tumor cells by showing anti-proliferative and cell cycle regulatory potential. It reduces the activity of CDK-2, CDK-4, cyclin A, cyclin B1, cyclin D1, Cdc2 and Cdc25C, while it increases CDK inhibitors p16, p21 and p27. Additionally, it provides activation of caspase-3, caspase-8 and caspase-9, induction of the release of p53, Bax and Cyo-c, suppression of Bcl-2 and PARP release, formation of mitochondrial damage and stimulation of cytochrome c release and stimulates apoptosis. Thus, it has been shown to have potential anti-oxidative, anti-inflammatory, anti-carcinogenic, anti-proliferative, anti-angiogenic, anti-radical, anti-mutagenic, anti-metastatic and apoptosis-inducing effects on cancer. There are studies examining the effects of *Vaccinium myrtillus* L. on types of cancer on organ cancers such as colorectal, colon and breast, and blood-related cancers such as leukemia and lymphoma. According to the Turkey Nutrition Guide, at least 5 portions (at least 400 g/day) of fruits and vegetables should be consumed per day. At least 2-3 portions of these should be fruit. Consuming fruits of different colors is necessary to absorb different nutrients and bioactive nutritional components. In addition, cancer patients can choose blueberries as one portion of their daily fruit consumption in order to get the nutrients and components found in bilberry. This review is a precursor for future studies that will examine the relationship between *Vaccinium myrtillus* L. and cancer. There is a need for larger prospective, large-scale clinical and human studies describing the relationship between *Vaccinium myrtillus* L. and cancer. New studies should be planned as specified.

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