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REVIEW

Beyond Conventional Medicine - a Look at Blueberry, a Cancer-Fighting Superfruit

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Abstract
Nearly 40% of men and women will be diagnosed with cancer during their lifetime. Thus, there is a rapidly growing need for novel therapies to combat this deadly disease. One such method is the consumption of blueberries. Long coveted for their powerful antioxidant properties, more recent studies have demonstrated that blueberries also exhibit inherent abilities to prevent carcinogenesis, inhibit the proliferation of neoplastic cells, and reduce the risks of recurrence in patients in remission. This review will focus on the specific activities of blueberry derivatives in cancer cells across many different forms of cancer. Ultimately, such research could be helpful in the development of new strategies to treat cancer.

Keywords Blueberry · Phytochemicals · Cancer · Apoptosis · Anthocyanidin

Introduction

In 2017, an estimated 1,688,780 new cases of cancer will be diagnosed in the United States and nearly 600,920 people will die from the disease [1]. Although conventional treatment methods such as surgery, chemotherapy, and radiation are paramount, the use of therapeutic dietary practices has gained critical emphasis in translational medicine [2]. Foods rich in phytochemicals, such as tomatoes and pineapples, have been found to be beneficial to cancer patients when used as an adjunct treatment [3]. Food derivatives, especially phytochemicals, and their anti-cancerous effects are widespread in medical literature. Some research has displayed phytochemicals to be most effective when used supplementary to primary cancer treatment regimens. However, a growing amount of research is displaying the ability of phytochemicals to act as the principal mechanism in the attenuation of carcinogenesis and the initiation of target cell death and apoptosis [4]. For example, a cranberry-derivative named proanthocyandin has been shown to play a role in the inhibition of esophageal adenocarcinomas in vivo and in vitro in athymic NU/NU mice. Quite significantly, this was the first study demonstrating the efficacy of in vivo orally-delivered proanthocyanidin against esophageal adenocarcinoma cells via the inactivation of AKT/mTOR/MAPK signaling and induction of the autophagic form of LC3B [5].

Other examples of anti-cancer foods are prominent in strawberries, raspberries, blackberries, chokeberries, and most importantly in blueberries. Blueberries are known to be one of the most nutritious foods in the world, containing five major anthocyanidins: cyandin, delphinidin, malvidin, peonidin, and petunidin [6]. These phytochemicals are responsible for the health benefits of blueberries, which include aid in prevention of diabetes, hyperlipidemia, hypertension, neurodegeneration, obesity, and osteoporosis. However, the most notable properties of blueberries are their abilities to inhibit the production of inflammatory molecules, limit oxidative stress preventing DNA damage, and the inhibition of cancer cells though pro-apoptotic, antioxidant, anti-inflammation, and antiangiogenesis effects [7, 8]. This review will thus analyze the actions of blueberry phytochemicals on cancer cell lines across various types of cancers.

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Breast Cancer

The action of blueberry phytochemicals on breast cancer is perhaps the most researched among relevant cancer cell lines. Breast cancer is the most common cause of cancer in American women and the second most common cause of cancer related death [9]. Due to its prevalence and mortality, breast cancer has become a leading topic in cancer research. Novel preventions and treatments are needed and currently being researched. As previously discussed, blueberries are an ideal candidate for future therapeutic use in cancer treatment due to their anticarcinogenic properties. However, since therapeutic levels have been shown to be dose-dependent, bioavailability and administrative routes are in need of further study.

In 2010, Adams et al. examined the ability of blueberry phytochemicals to inhibit growth and metastatic potential in breast cancer cell lines. The study found that dietary phtyochemicals decreased cell proliferation in HCC38, HCC1937, and MDA-MB-231 cells. Using wound-healing assays and migration through a polyethylene terephthalate membrane, decreased metastatic potential of the MDA-MB-231 cells was demonstrated by ingestion of dietary blueberries. Western blotting revealed that treatment with blueberries decreased the activity of matrix metalloproteinase-9 and secretion of urokinase-type plasminogen activator inhibitor 1 in a MDA-MB-231 conditioned medium. These effects were found to be due to phosphatidylinositol 3-kinase (PI3K)/AKT and NKkappaB activation in MDA-MB-231 cells. Furthermore, the study found decreased tumor weight and proliferation, along with increased apoptosis of the blueberry-treated group when compared to controls [10]. Thus, this study could be critical in future breast cancer treatment as it showed the ability of blueberries to inhibit growth and metastasis of breast cancer lines.

A similar study was conducted in 2012, where Montales et al. explored whether dietary blueberries selectively targeted mammary epithelial cells that displayed progenitor subpopulations with previously recognized tumor-initiating potential in MCF-7 and MDA-MB-231 human breast cancer cell lines isolated in MMTV-wnt-1 transgenic mouse tumors. The study found that hippuric acid, a metabolite of blueberry polyphenols, can effectively attenuate mammosphere formation, progression, and renewal of the MDA-MB-231 breast cancer cell line in mice consuming a blueberry containing diet [11]. This has critical implications for future breast cancer treatment in humans because it demonstrates the ability of a blueberry-supplemented diet to inhibit cancer formation.

Kanaya et al. found similar evidence in MDA-MB-231 tumor-bearing mice. This study compared the diets of two groups of mice bearing the same MDA-MB-231 tumor. One group was fed a high fat western diet with 5% whole blueberry powder, while the other group was fed only the high fat western diet. The research showed that mice fed the blueberry diet had significantly smaller tumors, less ulceration, and significantly less metastasis than mice fed a western diet. Furthermore, there was an increased serum level of specific anti-inflammatory cytokines noted in the mice fed with the blueberry diet, leading to the possible conclusion that blueberries act to inhibit MDA-MB-231 metastasis by reducing inflammation [12]. It is well understood that obesity increases the risk factors for multiple cancers and that the standard high fat western diet is a key contributor to the prevalence of obesity. Thus, the impact of the study done by Kanaya et al. could be particularly powerful on Americans due to the prevalence of the western diet in the United States. Further research on the results of this study are needed as it implies that simple blueberry supplementation in the average American diet may improve cancer outcomes.

Jeyabalan et al. examined the activity of dietary blueberry supplementation in a study published in 2013. A multifaceted approach explored both preventive and therapeutic activities of a diet supplemented with blueberry powder against 17β-estradiol (E_2)-mediated mammary tumorigenesis in animals. Two groups received a 5% blueberry blend diet for 2 weeks. The preventative group received the diet prior to treatment, while the therapeutic group received it 12 weeks after treatment. Both the preventative and therapeutic groups showed a delay in tumor latency for palpable mammary tumors by 28 and 37 days, respectively. Moreover, tumor mass and array were also reduced in both groups largely due to down-regulation of CYP 1A1 and ER-α gene expression [6]. Similar outcomes were seen in a study conducted by Ravoori et al. in 2012 where they found that supplementation of 5% blueberry powder reduced mammary tumor proliferation, tumor burden, and downregulation of CYP1A1 expression in an ACI rat mammary model [13]. Together, the previously discussed studies provide overwhelming evidence that blueberry supplementation can inhibit breast carcinogenesis and act therapeutically in established malignancies.

Liver and Colon Cancer

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and is renowned for being a difficult malignancy to treat. Once thought to be a death sentence, the last decade has seen numerous advances in treatment. Now, HCC is a manageable condition with curative potential through surgical resection or radiation [14]. Like any chronic medical condition, prevention is the primary focus in controlling the condition. In a study published in 2006, Yi et al. found that polyphenols in blueberries inhibited growth of HepG2 liver cancer cells by 50% at 70–150 μg/mL. Furthermore, the study showed a 2–4 fold increase in DNA fragmentation and

evidence of apoptosis, suggesting that blueberries have the ability to reduce liver cancer risk [15].

Blueberries were shown to have similar effects in preventing liver cancer in a study published in 2013 by Bingül et al. In this experiment, rats were fed with 5% and 10% blueberry containing diets over a six-week period. The rats were subsequently supplied with N-diethylnitrosamine (DEN), a substance known to induce reactive oxygen species, apoptosis, necrosis, and proliferation in the liver. Overall, the rats displayed decreased hepatic lipid and protein oxidation, as well as decreased apoptotic, necrotic, and proliferative changes in the liver [16]. Because liver injury induced by DEN has shown to lead to liver cancer, the results of this study are significant as they provide yet another example of blueberries playing a role in cancer prevention. Continuing their research on the topic, Bingül et al. published a more recent study in 2015, indicating that blueberries act in the inhibition of DEN-induced cirrhosis and preneoplastic lesions in the liver of DEN-injected rats [17].

The effect of blueberries on liver cancer cells was also studied by Zhan et al. in 2015. In the form of fresh juice, Rabbiteye blueberries were fed to rats at low, moderate, and high doses of 25, 50, and 100% respectively by daily gastric gavage. Blood serum was subsequently obtained for co-culture with HEPG2 cells. Using an MTT assay, Transwell assay, and flowcytometry, the study measured cell proliferation, migration and invasion, as well as cell cycle and apoptosis of the HEPG2 cells. Overall, every measured variable was significantly lower in the rat population fed with Rabbiteye blueberry compared to the control [18]. Moreover, there was a marked decrease in each variable in the high dosage group in comparison to the low dosage group, further exemplifying the anti-cancer effect of the Rabbiteye blueberries. Cancer prevention is a paramount goal. Thus, the previously discussed examples of blueberry-induced attenuation of cancer-promoting conditions in the liver illustrate the need for further research in this area.

Blueberries have been found to have similar effects in colon cancer as well. Preceding the previously mentioned study on the effects of phenolic blueberry compounds on HepG2 liver cancer cells, Yi et al. found that the same phenolic compounds inhibited proliferation and induced apoptosis in HT-29 and Caco-2 colon cancer cell lines in 2015 [19]. Similarly, in a study published in 2007, Suh et al. demonstrated that the F344 rats fed with Pterostilbene, a blueberry derivative, showed inhibition of azoxymethane-induced colonic aberrant foci preneoplastic lesions [20]. These findings are significant, as they suggest that a diet supplemented by blueberries has the potential to reduce the risk of colon cancer.

Minker et al. also researched the effect of blueberries in colon cancer in 2014, investigating the impact of procyanidins derived from multiple types of berries on caspase-8 activation in colon cancer. Among the studied berries, lowbush blueberries were shown to induce the strongest apoptotic activity in SW480-TRAIL-sensitive and SW620-TRAIL-resistant human colon cancer cell lines [21]. Ultimately, the research of Minker et al. presented some of the most conclusive evidence that lowbush blueberries should be considered a primary prevention strategy for human colon cancer.

Other Cancers

Blueberry phytochemicals have shown positive impacts on other notable forms of cancer. In a 2014 study carried out by Qi et al., researchers found that wild blueberries from Inner Mongolia suppressed the growth of the oral cancer cell line KB. Specifically, the study revealed that blueberry anthocyanin extracts suppressed the proliferation of KB cells in a dose-dependent manner. Furthermore, these extracts were found to induce G2/M cell cycle arrest and apoptosis of oral cancer KB cells. Upon treatment with blueberry anthocyanin, results showed that caspase-9, cytochrome-c, and p53 levels were substantially increased. Interestingly, the experiment also noted a marked increase in unmethylated p53, indicating that anthocyanins down-regulated the methylation, or silencing, of the p53 molecule [22].

Blueberry inhibition on oral cancer was also studied by Baba et al. in 2016. In this study, oral squamous cell carcinomas were induced in hamsters in the hamster buccal pouch (HBP) by 7,12-dimethylbenz[a]anthracene (DMBA). The results of the study showed that blueberry supplementation inhibited the development and progression of HBP carcinomas by interrupting the TGF-β and PI3K/Akt pathways, suggesting that targeting oncogenic signaling pathways using dietary blueberries can be an effective form of treatment of oral cancer [23].

Blueberries have been shown to pose a benefit in prostate cancer as well. According to The American Cancer Society there are over 2 million men in the United States that are known prostate cancer survivors. Second only to skin cancer, it is most common cancer among American men [1]. In 2006, Schmidt et al. published a study that examined the effects of wild and cultivated blueberries on the proliferation of LNCaP, an androgen-sensitive prostate cancer cell line, and DU145, a more aggressive androgen-insensitive prostate cancer cell line, in order to assess similarities between the two. The study found that cultures in the LNCap cell line saw growth inhibited to 11%, 26%, and 57% of control with an IC50 of 13.3 μg/mL, 5.8 μg/mL, and 22.7 μg/mL, respectively. For the DU145 cells, significantly reduced growth was only observed in one culture, with an IC50 of 74.4 μg/mL, indicating limited inhibitory action. These results suggest that blueberries possess an inhibitory effect primarily on androgen-dependent growth of prostate cancer [24]. With this in mind,

blueberries may have a future role in cell-line specific treatment of androgen-dependent prostate cancers.

In a related study, Matchett et al. explored the effect of lowbush blueberry flavonoids on matrix metalloproteinases (MMPs) in DU145 human prostate cancer cells. Flavonoids were found to down-regulate MMPs, which are essential in metastasis-regulation. The study also observed an increase in endogenous tissue inhibitors of metalloproteinases (TMP-1 and TMP-2) [25]. Thus, the simultaneous inhibition of MMPs and increase in TMPs suggests that lowbush blueberry-derived flavonoids regulate metastasis in multiple ways.

An innovative study published in 2012 by Kausar et al. examined the combinatorial effects of berry anthocyanidins (cyanidin, malvidin, peonidin, petunidin and delphinidin) as found naturally in blueberries, bilberries, and Indian blackberries. Results showed that suboptimal concentrations of equimolar anthocyanidins synergistically inhibit the growth of two aggressive non-small-cell lung cancer cell (NSCLC) lines, with minimal effects on non-tumorigenic cell viability. The study showed that cell-cycle arrest, apoptosis, and suppression of NSCLC invasion and migration were all significantly greater in samples treated with the mixture [26]. Due to the aggressive nature of NSCLC, the research by Kausar et al. is of critical importance for the future use of blueberries in the treatment, prevention, recurrence, and metastasis of NSCLC.

In 2015, Diaconeasa et al. found that the high anthocyanin content and antioxidant activity of blueberries inhibited proliferation and stimulated apoptosis in murine melanoma cells [27]. These results indicate that the blueberry-derived anthocyanins have properties that could allow them to be utilized as a chemopreventive or adjuvant treatment in the prevention of metastasis. In 2015, a subsequent study by Diaconeasa et al. reevaluated the antiproliferative effects of anthocyanin-rich extracts on tumor cell lines in correlation with their antioxidant properties. In order to test the antiproliferative effects of the blueberry-derived extracts, a MTT assay was used on the murine melanoma cell line B16F10, along with blackcurrant juice. A similar assay was also done on ovarian cancer cell line (A2780) and the cervical cancer cell line (HeLa). The results of this study confirm the link between the antiproliferative potential of anthocyanin-rich extracts and their antioxidant properties. This is significant as it indicates that intake of both blueberries and blackcurrants can be beneficial in the prevention of various neoplastic diseases [27, 28]. Our lab has studied the potential roles of phytochemicals as radiosensitizers for years [29–32]. We previously showed that resveratrol, a compound in red grapes or red wine, could be used as a radiosensitizer for prostate cancer and melanoma. In 2017, by using cervical cancer cell line SiHa, we found that the percentage of colonies, PCNA expression level and the OD value of cells from SiHa cells were decreased in the group of radiation together with blueberry extract when compared with those in the radiation alone group. We further found that TUNEL+ cells and the relative caspase-3 activity in SiHa cells were increased in the group of radiation together with blueberry extract when compared with those in the radiation alone group. The anti-proliferative effect of addition of blueberry extract to radiation on SiHa cells correlated with decreased levels of pro-proliferative molecules cyclin D and cyclin E. The pro-apoptotic effect addition of blueberry extract to radiation on SiHa cells correlated with increased level of the pro-apoptotic molecule TRAIL. Our study strongly indicates that blue berry could sensitize cervical cancer cells to radiation by inhibition of proliferation and promotion of apoptosis. This is consistent with its anti-cancer findings in cervical cancer by others [27, 28].

Other examples of blueberry phytochemicals inhibiting proliferation and/or inducing apoptosis can be found in regards to endothelial cell neoplasms in mice, as well as seven human adult T-cell leukemia-related cell lines. As demonstrated by Gordillo et al. in 2009. subcutaneous injection of spontaneously transformed murine endothelial (EOMA) cells leads to the development of hemangioendothelioma (HE). Results of the study saw a dose dependent decrease in HE tumor size in mice that received daily oral gavage feeds of blueberry extract [33]. Thus, this study could be critical in future cancer treatment, as it implies that blueberry extracts have potential therapeutic antiangiogenic treatment ability in cell neoplasms. Finally, in 2011, Kai et al. evaluated inhibitory effects of several agricultural plants on the proliferation of seven human adult T-cell leukemia-related cell lines. The highest inhibitory effect on the adult T-cell leukemia lines was seen from leaves of *Vaccinium virgatum* Aiton, a species of blueberry that is common in the southeastern United States [34].

Conclusion

Thus, through the review of previous literature, it is clear that blueberry-derived phytochemicals display significant anticancerous effects across multiple cancer cell lines. Blueberries present a type of adjunct treatment that healthcare providers can utilize in prevention, treatment, and reduction in recurrence risk in current and future cancer patients. Though the initial research is promising, more work needs to be done in order to explore any possible adverse drug interactions between high biological levels of blueberry derivatives and antineoplastic agents. However, in patients undergoing radiation therapy, or in those with neoplasms that can only be cured by surgical resection, there is likely little to no risk in encouraging the regular consumption of blueberries.

Our lab has demonstrated the possibility that blueberries can be used as a radiosensitizer to weaken cancer cells prior to radiation therapy. Ultimately, such a treatment would allow sensitized cancer cells to be destroyed at lower levels of

radiation, preserving competent host tissues, and lowering the costs of treatment. Finally, the use of blueberries as a radiosensitizer could allow the use of radiation in high-risk patients that would otherwise not be eligible for such therapy.

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