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Review Article

A Review Article On Antioxidant Profile Of Blueberries In The Treatment Of Various Diseases

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ABSTRACT

The active substances in blueberries are beneficial to health. Blueberry contains flavonoids (only anthocyanins), polyphenols (proanthocyanidins), phenolic acid, pyruvic acid, chlorogenic acid, etc., with anti-cancer, anti-obesity, anti-degenerative diseases, preventing diseases and protecting eyes and liver. It can prevent heart disease, prevent diabetes, improve brain function, protect lung function, strengthen bones, improve immunity, prevent heart disease, and improve intelligence. Anthocyanins and polyphenols in blueberries play an important role in the prevention of chronic diseases. These results support the finding that blueberries may be one of the most effective berries, and also demonstrate the role of anthocyanins and polyphenols in the health and anti-inflammatory effects of blueberries.

INTRODUCTION

Blueberry is one of the most important health foods for human beings, it is recognized as the "king of fruits in the world", which has attracted great interest in the plant-based prebiotics market. Blueberry fruit is valued for its delicious taste and for its variety of functional components (organic acids, phenolics, minerals and vitamins) which have various therapeutic values (antioxidant, anti-inflammatory, anticancer, neuroprotective and vision).1The antioxidants in this berry help the body fight free radicals (reactive oxygen species) that cause premature aging and are toxic to the body.2These species generate oxidative stress within the cell, causing damage to cellular components and leading to cell death.3,4Antioxidants in biological systems control oxidative stress through various mechanisms, such as scavenging of free radicals, inhibition of oxidative enzymes, chelation of metal ions, and cofactor action for antioxidant enzymes.5 It is generally used as Anticancer (Anthocyanins, phenolic acids, pyruvic acid, pterostilbene), Anti-obesity (Anthocyanins, polyphenols), Prevent degenerative diseases (Anthocyanins, chlorogenic acid, polyphenols),

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Anti-inflammation (Anthocyanins, phenolic acids, flavonoids), Protective vision (Anthocyanins, polyphenols), Protective liver (Anthocyanins, polyphenols), Prevent heart diseases (Anthocyanins, procyanidin, polyphenols), Antidiabetic (Anthocyanins, polyphenols), Improve brain functions (Anthocyanins, phenolics), Protective lung (Anthocyanins), Enhance immunity (Polysaccharide, polyphenols), Prevent cardiovascular diseases (Phenolic acids, flavonoid), Improve cognitive decline (Polyphenols).6 This review systematically describes the current status of blueberries as a bioactive component and valuable food with greater potential for nutritional health.

Active Compounds in Blueberry

Blueberry belongs to Genus, Vaccinium, section Cyanococcus and family Ericaceae (related to cranberries and bilberries).7 It originated from North America (both wild and cultivated varieties).8 Blueberry is mainly categorised into two categorised i.e. Lowbush and Highbush. Lowbush also known as dwarf berries that are smaller berries on shorter shrubs, and are mainly wild and highbush berries are larger berries on taller, cultivated shrubs. There are two main countries of blueberry production i.e. Canada and America. Canada leads in lowbush production while US leads in highbush production (40% of global supply).9 Many commercial varieties have English names originating from North America.10,11 There are many nutritional components present in blueberries like Sugars, Dietary fibres, Vitamins - Vitamin A , beta-carotene, Carbohydrates, Fats, Proteins, Thiamine (B1), Riboflavin (B2), Niacin (B3), Pantothenic acid (B5), Vitamin (B6), Folate (B9), Vitamin C, Vitamin E, Vitamin K, Calcium, Iron, Magnesium, Manganese, Phosphorus, Potassium, Sodium, Zinc.12 The bioactive components of blueberries include anthocyanins, polyphenols, and antioxidant properties. Pectin from blueberry powder includes anthocyanin-3-glucoside and anthocyanidins, however anthocyanidins include cyanidins, pelargonidin, malvidin, petunidin and delphinidin, which may represent the accumulation of anthocyanins and the ionic interaction between pectin and anthocyanins, that are two main mechanisms of anthocyanin stacking.13 Blueberries are rich in polyphenols including delphinidins, petunidins, peonidins,3-glucoside/arabinoside/galactoside based polymers.14Antioxidant properties of blueberry juice, contains phenolic compounds, quinine, chlorogenic acid and rutin, ABTS(+) scavenging activity, iron-reducing antioxidant activity, and the oxygen radical absorbance activity.15Oral administration of anthocyanins across the blood-brain barrier may improve visual function by increasing rhodopsin regeneration.16 Wild blueberry polyphenols are degraded by colonic fermentation into syringic acid, cinnamic acid, caffeic acid and protocatechuic acid.17 Blueberry (Vaccinium uliginosum L.) from Changbai Mountains, China, containing five main ingredients (delphinidin, cyanidin, petunia, paeoniflorin and mallow), which could be a promising functional food to inhibit colorectal cancer.18 Acai blueberries are very rich in total phenolic compounds, containing anthocyanins and carotenoids.19

\LIVER AND ITS FUNCTIONS

The liver, a vital 2% of our body weight, performs diverse tasks like immunity, digestion, and detoxification. Its unique blood supply fuels distinct zones within lobules, specialized hexagonal units. Zone I, closest to incoming blood, excels at processes like sugar production and cholesterol formation. Zone II occupies the middle ground, while Zone III, furthest from fresh blood, handles detoxification and energy production. Bile, produced by the liver, flows in the opposite direction of blood, efficiently removing waste. This complex interplay of zones, blood flow, and bile flow ensures the liver's critical role in our overall health.20 Disse's space, a microscopic gap between liver cells and blood vessels, plays a crucial role in liver function. Its microvilli extensions from liver cells allow interaction with blood, while the extracellular matrix provides structural support and lacks a true basement membrane. This space also houses two important cell types: Kupffer cells, which filter impurities from blood, and Ito cells, which store vitamin A and can convert into scar-forming cells during injury to aid regeneration. This unique microenvironment facilitates vital functions like nutrient exchange, waste removal, and liver repair.21

Factors downregulating liver functions

This passage discusses various factors that can damage the liver, categorized into viral infections, autoimmune diseases, alcohol abuse, and benign changes. Viral infections are generally caused by Hepatitis enzyme causing liver inflammation. Hepatitis A and E leading to acute hepatitis that is self-limiting and can spread through contaminated water/food.22 Hepatitis B, C, and D that can become chronic, spread through contaminated needles or bodily fluids. Vaccination available for A, B, and C.23,24 Then there are autoimmune diseases like Primary biliary cholangitis (PBC) that damages bile ducts, mainly affects women and is treated with ursodeoxycholic acid and immunosuppressants.25 Other factor is alcohol abuse that damages liver cells due to toxic metabolites, leading to cirrhosis and is diagnosed based on history, physical exam, and labs. Treatment involves behaviour modification and medication. Moreover, there are some benign changes also among which Hemangiomas, FNH, hepatocellular adenomas, and liver cysts are most common, usually harmless and monitored with imaging.26

Liver-protecting properties and useful components of blueberries

Blueberry leaf containing oligomeric proanthocyanidins that may inhibit Hepatitis C virus RNA expression thereby showing antiviral properties.27 Protective effects of blueberries may reverse acrylamide-induced liver damage, reduce DNA damage, and protect against mitochondrial damage.28,29 They may inhibit cytochrome P450 enzymes, potentially affecting drug metabolism.30 Blueberry polyphenols offer antioxidant protection against toxic selenite exposure.31 Blueberry extract exhibits antioxidant and anti-inflammatory properties, protecting against cadmium-induced liver damage.32 Blueberries have great potential in treating liver diseases, for instance blueberry and chitosan combination improved liver function in rats with fibrosis. Blueberry anthocyanins may regulate gene expression involved in apoptosis and anti-fibrosis pathways.33,34

Effect of blueberry pre-treatment on diethyl-nitrosamine induced oxidative stress in rats

This study investigated how blueberries (BB) might protect the liver from damage caused by a harmful chemical (DEN). Some technical details and references were omitted for clarity. Observations generated through this research were that High-dose BB diet reduced DEN-induced liver damage, including death of liver cells and uncontrolled cell growth.35 Blueberries reduced harmful molecules associated with oxidative stress and inflammation in the liver.36,37 They also boosted the activity of an enzyme (GST) that helps detoxify harmful substances.38 Liver tissue analysis showed less damage in groups fed blueberries compared to those only receiving DEN.39 Hence, Blueberries show promise in protecting the liver from damage caused by harmful substances.BB can have an inhibitory effect on acute liver damage by reducing apoptosis, necrosis, proliferation, oxidative and nitrosative stress in DEN-treated rats.40,41,42 However, this study was conducted in rats, and more research is needed to confirm these findings in humans.

BRAIN AND THE GEOGRAPHY OF THOUGHTS

The brain is the most complex part of the human body. This 3-pound organ is the seat of intelligence, the interpreter of the senses, the initiator of bodily movement, and the controller of behaviour. The different roles of its major lobes that containing Cerebral hemispheres that is divided into four lobes-frontal, parietal, occipital, and temporal. Frontal lobes are responsible for planning, imagination, reasoning, and short-term memory. Parietal lobes process sensory information like touch, temperature, and taste. Occipital lobes process visual information and create visual memories. Temporal lobes are responsible for hearing, music perception, memory formation, and sensory integration. Each lobe further comprises specialized areas with specific tasks. Damage to different lobes can lead to various impairments.43

Role of acetylcholine in Alzheimer's disease

The most common form of dementia, Alzheimer's disease is a neurological condition that develops over time and is often misdiagnosed.44,45,46

Alzheimer's disease, the most common dementia, steals memories and clouds minds. This age-related illness, often misdiagnosed, affects around 12% of the elderly worldwide.47,48,49 Hallmark symptoms include disorientation, memory decline, and behavioral changes. While the exact cause remains a mystery, multiple culprits are suspected, including protein buildups, neuron loss, and a lack of the brain chemical acetylcholine, crucial for memory.50,51 One leading theory, the cholinergic hypothesis, focuses on this acetylcholine deficiency and its link to degenerating brain cells.52 This understanding helps guide treatment approaches using acetylcholine therapy, but the fight against Alzheimer's continues as researchers delve deeper into the complexities of this challenging disease.53,54

Bioactive components of the blueberry that improve brain health

As an irreversible and progressive neurodegenerative disease common in the elderly, Alzheimer's disease (AD) is the leading cause of dementia and is characterized by the formation of insoluble plaques of beta-amyloid (A).55,56 Various therapeutic approaches have been used to improve central nervous system (CNS) function, but the underlying mechanism of AD pathogenesis remains unclear. It is known that plants synthesize many chemical compounds that are not involved in their primary metabolism. These “secondary compounds”, called phytochemicals, can maintain plant viability and are responsible for numerous beneficial effects on a number of health conditions.57 Numerous studies have shown that some phytochemicals can protect the brain from neurotoxicity.58-61 As a strain of Vaccinium, blueberry (BB) has significant antioxidant power and high levels of flavonoids and polyphenolic compounds such as anthocyanidins.62 Studies have shown that short-term nutritional supplementation in older animals is effective in reversing age-related cognitive and motor deficits.63 Previous studies also showed that BB extracts have beneficial effects in reversing the effects of aging in mice, including improving 's cognitive and behavioral functions.64 Josef et al. reported that BB extracts could improve Y-maze performance in AD mice. It appears that BB extracts can enhance memory-related neuronal signalling, although Joseph et al. did not observe that the BB extracts had a significant effect on conversion to A, beta burden.57 However, it provided strong evidence that BB extracts may contain potent substances that can alleviate the pathology of AD. More work is needed to understand the details of the mechanism. In the study, APP/PS1 transgenic mice were fed a normal diet and an experimental diet containing BB extracts for a period of time. The effect of BB extracts on enhancing cognitive and behavioral functions in AD mice was examined and investigated the mechanism that might be involved in these effects. This provides valuable clues for using an ingredient, a food, and even a cure for AD with BB. Whole fresh cranberry reduced apoptosis and attenuated histopathological findings in the brain of a rat administered D-galactose.65 The L-galactose pathway was the major pathway for ascorbic acid biosynthesis, and its highest levels of expression are associated with five genes [guanosine diphosphate mannose-3,5-epimerase (GME), guanosine diphosphate L-galactose phosphorylase (GGP), L -galactose dehydrogenase-1,4-lactone (GLDH), monodehydroascorbate reductase (MDHAR), and dehydroascorbate reductase (DHAR)] in blueberries.66 Blueberry anthocyanin diets can prevent radiation by reducing oxidative stress and inflammation, improving neuronal signaling, and protecting neuronal function when exposed to high-energy particles.67 Blueberry anthocyanins improve cognition by promoting cerebral perfusion and activation in healthy older adults.68,69 The antidepressant effect of bilberry extract may be mediated through the control of the monoaminergic and glucocorticoid systems, which are due to neuroprotective effects and 5-HT receptor antagonism.70The cyanant-3-O-galactoside in bilberry may protect the central nervous system and improve cognitive and behavioral functions in aging by increasing antioxidant capacity and altering stress signaling.71 Blueberry anthocyanins and the ethyl acetate fraction of blueberry leaves have been associated with increased neuronal signaling in the brain, mediating memory function and glucose clearance as well as delaying neurodegeneration.72,73 The contribution of dogs to the improvement in cognitive function was greater in dogs fed bilberry polyphenol extract.74 Cranberry phenols can reduce gastrointestinal infections in patients with cerebral venous thrombosis by potentiating antidepressant effects by upregulating brain-induced neurotrophic factor regulated by miR-155.75 Increased neural activation by blueberries shows neurocognitive benefits in this at-risk population.76 The neurocognitive benefits of blueberries are mainly due to the anthocyanin's eicosapentaenoic acid and docosahexaenoic acid.77 Six blueberry extracts, especially blueberry anthocyanins, have free radical scavenging effects, reactive carbonyl, glycosylation resistance, anti-Aβ, flicker and anti-microglia neuroprotective effects Alzheimer.78

BLUEBERRY INGREDIENTS THAT FIGHT CANCER AND SERVE PURPOSES

Being a good source of anthocyanins and phenolic acids, blueberries not only show tumors longer and show lower levels of proliferative, antiapoptotic and angiogenic transcripts79, but also prevent carcinogenesis and reduce the risk of relapse and as a potential radiosensitizer for cancer therapy.80,81 Blueberry anthocyanins and their products containing pyruvate may slow cancer by inhibiting the proliferation of cancer cells.82 Fresh weight of blueberry anthocyanins contains malvidin-3-glucoside, which has antiproliferative and apoptotic properties in cancer cells and can be used as chemoprevention of metastasis83, but using HepG2 Cov. The anticancer ability of cells is related to the concentration of anthocyanins.84 Mitochondria benefited from the protection of blueberry anthocyanin extract against acrylamide toxicity.85 Pterostilbene in blueberry protects primary curative myeloma in the treatment of clinical/refractory myeloma and bortezomib chemotherapy.86 Lowbush blueberry proanthocyanidins can increase apoptosis induction in human colon cancer cells, representing an important dietary factor for cancer prevention.87 Dietary treatment of blueberry peel and probiotics may delay the occurrence of cancer.88 Cranberry juice has antipromutagenic activity similar to vitamin C and also acts as a methylation inhibitor of human methylenetetrahydrofolate reductase and DNA methyltransferase.89 Anthocyanins and anthocyanin extracted from blueberries can inhibit the growth of B16F10 cells and induce apoptosis.90 Eating blueberries (400mg daily) reduced tumor size in mice and inhibited the growth of ovarian cancer by lowering cyclooxygenase-1 and cyclooxygenase-2 levels.91

In DU145 human prostate cancer cells, blueberry flavonoids reduce matrix metalloproteinase activity

The role of extracellular matrix (ECM) integrity and ECM-degrading enzymes such as matrix metalloproteinases (MMPs or matrix proteins) in cancer metastasis has been shown to be extensive because ECM destruction is important for tumor metastasis to occur.92 MMP expression and activity are tightly regulated processes that demonstrate their importance in everyday cellular dynamics and interactions.93 While not only contributing to cancer metastasis, it is clear that many cancer cells have increased MMP activities and that expansion of MMPs may be an important factor in tumor angiogenesis in tumors and foreign tissues.92,93 As MMPs play an important role in tumorigenesis and metastasis, MMP expression and regulation may be important targets in developing cancer-fighting and therapeutic strategies.93 Recent studies have shown that blueberry (Vaccinium angustifolium) is good for some chronic diseases.94 Blueberries contain high levels of polyphenolic compounds such as flavonoids and phenolic acids.95 Flavonoids found in plants of the Vaccinium genus (blueberries, cranberries, cranberries, and blueberries) have anticancer properties; they modulate ornithine decarboxylase, whose activity or expression changes in different tumor types.94 In this study, 3 varieties of blueberries were tested to examine their effects on MMP activity in DU145 human prostate cancer cells. These fractions represent the main flavonoids in the fruit: the raw fraction contains all flavonoids; anthocyanin-rich fraction (AN); and the proanthocyanidin-rich fraction (PAC). Anthocyanins and proanthocyanidins are a group of flavonoids believed to be the main agents responsible for the anti-inflammatory effects of many fruit and vegetable flavonoids.94,96 Therefore, in this study, it is hypothesized that the gelatinolytic activity of MMPs in DU145 cells would be affected after exposure to various flavonoid-rich fractions; This indicates that the flavonoid-rich fraction isolated from the lower blueberry chunks can inhibit and regulate matrix metalloproteinases. This study showed that MMP activity in human prostate cancer cells, specifically DU145 cells, was reduced after exposure to the flavonoid-rich fraction of blueberry. Although the gelatinolytic activity of MMPs in DU145 cells was reduced by blueberry fraction treatment, each flavonoid-rich fraction affected MMP activity differently. To our knowledge, this is the first study to demonstrate a link between bioactive compounds isolated from blueberry and inhibition of MMP expression. The PAC moiety contains a variety of proanthocyanidins, from monomers to decamers. The AN fraction contains several potential bioactive compounds, including the 4 major glycosides (malvalenin, petunin, delphinidin, and quercetin), quercetin-3-galactoside, and quercetin-rhamnoside glycosides. Anthocyanins and proanthocyanidins from other sources have been shown to affect MMP activity. Delfinidin has been shown to reduce the activity of MMP-2 (in human neuroblastoma cells) and MMP-9 (in HT-1080 human fibrosarcoma cells). Epigallocatechin 3-gallate has been reported to inhibit MMP-2 and MMP9 activity. Myricetin, a proanthocyanidin, also potently inhibits the activity of MMPs.97 The results presented in this study are consistent with these observations. It is important to note that this blueberry constituents do not cause necrotic cell death in these cells. These findings demonstrate the specificity of the effects of the bioactive components found in the blueberry fraction and inhibition of MMP (MMP-2 and MMP-9) activity in DU145 cells. In this study, the mechanisms involved in these inhibitory processes were investigated. MMP-2 and MMP-9 are important mediators of basement membrane damage and are thus potential targets for the development of new anti-inflammatory drugs from onwards.98 Studies suggest that the flavonoid-rich fraction of blueberries can reduce the activity of MMPs in particular. In conclusion, results describe for the first time the potential modulatory effects of flavonoids isolated from blueberry on human prostate cancer. This regulation targets the activity of MMP-2 and MMP-9. These activities may be one of many targets for the anti-inflammatory potential associated with flavonoid-related isolates from blueberry.99

Anticancer Properties in Breast Cancer Cell Lines from Blueberry Anthocyanins and Pyruvic Acid Adducts

Breast cancer is one of the most frequently diagnosed cancers in women in the world today and is the second leading cause of cancer.100 Many studies have revealed that estrogen is often involved in the growth and development of the breast, and efforts are currently being made to develop drugs that block estrogen production and action. The malignancy invades normal tissues and involves three processes: degradation of the extracellular matrix (ECM), cell metastasis, and proliferation.101,102 It plays an important role in determining the risk of many cancers, including breast cancer. In addition, fruit and vegetable consumption has been associated with a reduced risk of breast cancer.103 Interest in anthocyanins, the flavonoid compounds that provide most of the flavor and color to these fruits and vegetables, has grown over the years with evidence of their anti-cancer properties.104 Previous studies have shown that anthocyanins and other phenolic compounds may have beneficial effects, including reducing the risk of heart disease and cancer through antioxidant, anti-inflammatory, and medicinal immunity.105 The mechanisms involved are still unclear, but they may inhibit growth106 and angiogenesis as well as cause apoptosis in cancer cells may contribute to these beneficial effects.107 These compounds have also been reported to scavenge reactive oxygen species, inhibit low-density lipoprotein oxidation in vitro, inhibit platelet aggregation, and reduce blood lipids.108,109 Anthocyanins and anthocyanin-derived pigments, such as anthocyanin-pyruvate adducts, may be important not only because they are derived from natural precursors but also have pronounced antioxidant properties.110 This study investigated the anti-cancer potential of two extracts: anthocyanins and anthocyanin-pyruvate adducts, on two breast cancer cell lines.111,112,113 The study highlights the importance of investigating new, non-toxic approaches to cancer treatment. The key findings were that both extracts inhibited the growth and proliferation of both estrogen-dependent and estrogen-independent breast cancer cells, even at non-toxic concentrations.114,115,116 The anthocyanin-pyruvate adduct activated caspase-3 in one cell line, suggesting it may induce apoptosis.117 Both extracts inhibited the ability of cancer cells to invade, a crucial step in metastasis.118,119 Neither extract attracted cancer cells, but instead acted as repellents, potentially slowing their spread. These findings suggest that both anthocyanins and anthocyanin-pyruvate adduct have potential as anti-cancer agents, regardless of the presence of estrogen receptors. The mechanisms by which these extracts work is not fully understood and require further investigation.120,121 While further research is needed to understand their effectiveness in humans, these extracts show promise for future breast cancer treatment and prevention strategies.

Effect of combining blueberry extracts with oxaliplatin on human colon cancer cells

Colon cancer (CRC) is the third most common cancer in men and the second most common in women worldwide, putting a heavy burden on our health system.122 Oxaliplatin (OX) is widely used in combination with other chemotherapeutic drugs to treat CRC by inducing apoptosis.123 However, the use of OX is not 100% effective and is often associated with side effects. Evidence shows that natural remedies can be effective/synergistic with pharmaceutical drugs by changing different targets.124 Therefore, there is a growing interest in developing effective treatment strategies, including treatment with natural and medicinal drugs, to overcome some of the challenges faced with the use of chemotherapeutic drugs in cancer treatment. Previous studies have reported the anti-inflammatory effects of bilberry extract (BE). Anthocyanin-rich BE inhibits apoptosis in HT-29 cells by increasing DNA fragmentation and caspase-3 activity.125 Previous studies have shown that many anthocyanins fail to protect HCT-116 and HT-29 human cancer cells.126 In vivo and in vitro experiments show that whole foods can have the advantages of individual nutrients, and that the anthocyanins and other phenolic compounds in plant extract can work synergistically. Previous studies have shown that anthocyanin-rich plants have a cytotoxic effect on OX on CRC cells. Recently, the combined treatment of cancer drugs and nutritional products has received a lot of attention because of the therapeutic effects127 where the interaction between drugs and phytochemicals can be enhanced (synergistic) or reduced (antagonistic).128 In addition, diet can reduce the risk of cancer, increase the survival of cancer patients, and reduce chemotherapy-related side effects. Although much attention has been paid to the effects of BE, little research has been done on the effects of BE and chemotherapeutic drugs on cancer cells. To our knowledge, the anticancer effect of BE combined with OX has not been studied. The aim of this study was to investigate the effect of BE on OX-conjugated HCT-116 cells by measuring cell viability, apoptosis, intracellular reactive oxygen species (ROS) and mitochondrial membrane potential (MMP). In addition, it was aimed to elucidate the underlying molecular mechanisms by investigating the regulation of cell cycle and apoptosis-related inflammatory cytokines and proteins in cells.

Proliferation inhibition by BE AND OX in HCT 116 cells

The outcome of all cancers is associated with cell proliferation and apoptosis.129 To determine the protective activity of BE on breast cancer cells, HCT-116 human breast cancer cells were chosen as an in-vitro cell model. BE and OX inhibited the growth of HCT-116 cells in a dose-dependent manner. Inhibition of HCT-116 cell proliferation by BE can be attributed to the presence of anthocyanins, phenolic acids and flavonoids previously shown to inhibit the growth of CRC cells.130 After 48 hours of treatment, BE and OX inhibited the growth of HCT-116 cells individually. The combination of BE and OX caused a greater effect on the viability of HCT-116 cancer cells. At the lowest BE and OX combination, success was reduced by 61%. The synergistic effect of BE and OX on the viability of HCT-116 cancer cells after 48 hours of treatment was observed. The results show that BE has the ability to inhibit the growth of CRC cells. Single and combined treatment of BE and OX on IC50 values showed that the growth of HCT-116 cells treated with BE, OX and OX/BE combination was inhibited by 52%,37% and 69.59%, respectively. Similar results were obtained by131 demonstrated the synergistic anti-inflammatory activity of a combination of clofarabine and resveratrol on human malignant mesothelioma cells. The results of the study confirmed the low toxicity of BE and OX/BE treatment for normal cells at strong concentrations against HCT-116 cells. Studies on anthocyanin-rich plant extracts also did not show cytotoxic effects on the normal body and showed that the extracts protected against apoptosis.126 Based on the results of previous studies and this study, BE may have the potential to act as an anti-cancer agent alone or in combination with OX.

HCT 116 cells were subjected to an OX/BE combo therapy that caused apoptosis via the caspase apoptotic pathway

Chemotherapy drugs work effectively to target specific proteins, usually membrane receptors or kinases. Cleavage of caspase-9 and its downstream effector caspase-3 play an important role in the activation of apoptosis.132 In HCT-116 cells, treatment with OX or BE alone or in combination increased cleaved caspase-3 levels by 1.99-,2.01-fold and 2.99-fold, respectively, compared to control cells. The level of cleaved caspase-9 was the same as the level of cleaved caspase-3 in the three treatment groups above. Caspases are important mediators of apoptosis and ultimately lead to irreversible cell death.133 HCT-116 cells treated with BE or OX alone or in combination showed lower levels of procaspase-3 compared to untreated controls. In addition, all treatment groups showed a reduction in procaspase-9 expression compared to control cells; this indicates that the apoptotic caspase pathway is involved in apoptosis due to BE or OX treatment. More importantly, OX/BE combined treatment had a significantly stronger effect in activating caspase cascade apoptosis compared to the effect of OX or BE treatment alone. In addition, caspase expression levels may explain why the combination treatment showed greater apoptosis induction and cell cycle arrest in HCT-116 cells than OX or BE treatment alone.

OX/BE-induced apoptosis in HCT-116 cells was evidenced by high levels of cleaved caspase-3 and caspase-9. This study demonstrates that OX/BE-induced activation of caspase-3/9 is associated with reduced phosphorylation of Akt and bad proteins. Similar results were obtained by León-González et al. (2015), who found that anthocyanin-rich blackcurrant-derived products induce p-53 and caspase-3 activation and downregulate the UHRF1 and p-Akt/p-Bad/Bcl-2 pathways in Jurkat cells.134 These findings are consistent with other studies showing that polyphenol-rich extracts from the Centipede plant induce down-regulation of p-Akt, p-Bad and Bcl-2 and caspase-3 in inflammation, lymphoblastic leukemia.[135] In conclusion, combined OX/BE treatment of HCT-116 cells can inhibit cell proliferation by downregulating cyclin-D1 and CDK4. In addition, treatment induces apoptosis via the caspase-3/9-dependent apoptotic pathway, which is associated with Bcl-2 family proteins involved in mitochondrial membrane permeability and the p-Akt/p-Bad/Bcl-2 pathways and downregulation. In the European Union, Australia and New Zealand, anthocyanins have been approved as food additives with the "E-mark" E163. In this study, it was found that anthocyanins, the main components of BE, have the desired inhibitory effect on HCT-116 cells. BE treatment with IC50 had similar effects with OX treatment with IC50 on cell viability and apoptosis in HCT-116 cells.

CONCLUSION

Blueberries are one of the top food crops with a total production of 629,720 tons in 2016 and the main international exporters are the United States, Chile, Spain and China. Blueberry contains flavonoids, polyphenols, phenolic acids, pyruvic acid, chlorogenic acid, etc. rich in terms of

Blueberries are rich in anthocyanins and polyphenols, currently recommended in China and the international market. Anthocyanins in blueberries include anthocyanins (red, purple, and blue depending on pH), geranoids (orange), hibiscus (blue), petunine (dark red, purple), and delphinidin (blue, blue-red); It contains polyphenols 3-glucoside. / arabinoside / galactoside-based polymers of delphinidin, petunienin, paeoniflorin, mallow and anthocyanins; antioxidant properties A total of phenols, quinic acid, chlorogenic acid and rutin. A descriptive review describes the mechanisms by which blueberry anthocyanins and polyphenols protect against chronic disease. Blueberry anthocyanins are beneficial to human health as anti-cancer, anti-obesity, anti-degenerative diseases, anti-infection, anti-aging of liver, preventing heart disease, preventing diabetes, protecting brain health, protecting lung, etc. it has many benefits. The main mechanisms of blueberry anthocyanins in the prevention of chronic diseases are as follows: The anticancer effect of anthocyanins is mediated by suppressing the JAK/STAT-3 signaling pathway and regulating PI3K/AKT/Erk/Akt/P53/NF-κB. The anti-obesity effects of anthocyanins are mediated by downregulation of our gene and downregulation of the phosphorylated Akt adipogenic factor. Prevents degenerative diseases associated with higher antioxidant capacity of malvidin-3-glycoside in blueberries; anti-inflammatory effects of anthocyanins controlled by the nuclear factor-kappa B pathway; In retinal pigment epithelial cells, anthocyanin-3-glucoside glycosides protect the eye by reducing vascular endothelial growth factor and activating Akt signaling; anthocyanins protect the liver by down-regulating TIMP1, PCNA, Col -III, α-SMA and up-regulating MMP-9 and hnRNP A2/B1 inhibitors; anti-anthocyanins heart disease-related immunity and anti-oxidation; The anti-diabetic effect of anthocyanins is to increase insulin secretion, reduce insulin resistance and improve β-cell regeneration. The protective effect of anthocyanins on the brain is mediated by extracellular signal-dependent kinase and cAMP response element binding protein, as well as the brain-derived neurotrophic factor pathway and gene expression in the brain. The protective effect of anthocyanins on the lungs is mediated by inhibition of the NF-kB signaling pathway. This review provides important information for future research, especially the role of anthocyanins and polyphenols in the prevention or treatment of chronic diseases.

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