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THERAPEUTIC POTENTIAL OF BLUEBERRY ANTHOCYANINS IN CANCER AND INFLAMMATORY DISORDERS: A COMPREHENSIVE REVIEW

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Abstract : Anthocyanins are abundant in blueberry fruits. To date, blueberries (Vaccinium spp.) have been identified to contain 25 different anthocyanidins. Blueberry anthocyanins have garnered a lot of attention due to their exceptional properties as antioxidants, anti-inflammatory, anti-diabetic, anti-obesity, and neuroprotective compounds. They may also be able to prevent cardiovascular diseases, preserve vision, and stop the growth of cancer. However, problems with instability and comparatively low bioavailability limit their use. Therefore, this review offers a thorough summary of the types, roles, stability, bioavailability, and real-world uses of blueberry anthocyanins. The research that is currently available suggests that blueberry anthocyanins have greater potential for industrial production.
Keywords: Blue berry,Anthocyanins,Anti-inflammatory,Anti-oxidant, Flavonoids, Cancer prevention, Nutraceuticals

I. INTRODUCTION

The blue berry, known as the "king of the world fruit," is one of the five main nutritious foods for people and has generated a lot of interest in the market for phytogenic prebiotics. Blueberry fruit juice, wine, vinegar, jam, dried fruit, pulp powder, and flavoring and coloring additives used in bread, cake, biscuits, yogurt, and jelly are examples of novel food innovations that are currently on the market[1]. A common class of water-soluble flavonoids found in fruits and vegetables are called anthocyanins. Red and purple berries, grapes, apples, plums, cabbage, and foods with high concentrations of natural colorants are dietary sources of anthocyanins. The six common anthocyanidins are cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin. Anthocyanins' health benefits have been extensively documented, particularly in relation to preventing oxidative stress-related illnesses like cardiovascular and neurological conditions. Anthocyanins' ability to scavenge free radicals, as well as their effects on a variety of enzymes, including cyclooxygenase, mitogen-activated protein kinase, and inflammatory cytokine signaling, have all been linked to their activities. Because anthocyanin derivatives have no known side effects, even at very high dosages, their application in the prevention or treatment of a wide range of illnesses is an enticing prospect [2].

PLANT PROFILE:

The Ericaceae family, which includes about 450 species worldwide, includes the Vaccinium genus, which includes blueberries [3]. The perennial shrub known as blueberries originated in North America and is now grown in China, Japan, Chile, Europe, Argentina, New Zealand, and Australia [4]. Highbush blueberries (Vaccinium corymbosum L.), lowbush blueberries (V. angustifolium Ait.), and rabbit-eye blueberries (V. ashei Reade) are the three primary types of blueberries that are grown, according to plant size and cold storage needs [5]. The fruits of blueberries are globose, glabrous, dark blue, and whitish [6]. In addition to being low in calories and high in hydration, blueberry fruits are rich in vitamins, prebiotic fibers, essential micronutrients, and bioactive polyphenols [7].

ANTHOCYANIN:

The phenylpropanoid pathway produces the flavonoid derivatives known as anthocyanidins, which are the glucosides of anthocyanins. Higher plants contain them in all of their tissues, including the leaves, stems, roots, flowers, and fruits. Cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin are the six main anthocyanidins that are present in food[8,9]. Anthocyanins' ability to scavenge free radicals, as well as their effects on a variety of enzymes, including cyclooxygenase, mitogen-activated protein kinase, and inflammatory cytokine signalling, have all been linked to their activities. Because anthocyanin derivatives have no known side effects, even at very high dosages, their application in the prevention or treatment of a wide range of illnesses is an enticing prospect.

The presence of hydroxyl or methoxy groups and the B-ring in their structure are also necessary for anthocyanin stability. In fact, anthocyanins are especially vulnerable to nucleophilic attack by substances such as sulfur dioxide, ascorbic acid, hydrogen peroxide, or water because they have an oxonium ion next to carbon 2. Their stability may also be impacted by temperature, light, oxygen, and the presence of metal ions [8].

These substances are water-soluble vacuolar pigments that are found in vegetative organs as well as fruits and flowers. Because they give fruits and vegetables their distinctive red to blue hue, they have a significant effect on the sensory qualities of food. They are essential for pollination and, by absorbing light, shield plants from cold stress and UV ray damage[10,11,12]

Figure 1: Structure of anthocyanidins

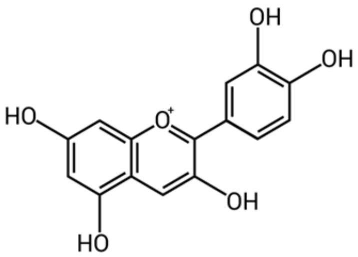

Figure 2: Constituents of anthocyanidins[13,14,15]

Anthocyanin profiles	R1	R2	R3	CONTENT (mg/100g)	
				Fresh fruits	Dried fruits
Cyanidin-3-O-arabinoside	OH	H	Are	14.33	1.08-52.8
Cyanidin-3-O-gyucoside	OH	H	Glc	0.62-11.7	0.12-10.5
Delphinidin-3-O-arabinoside	OH	OH	Ara	3.73-13.3	0.48-39.2
Delphinidin-3-O-galactoside	OH	OH	Gal	5.61-26.9	1.08-81.4
Delphinidin-3-O(6”-acetyl)glucoside	OH	OH	$_{6''}{}^{Ac}$Glc	-	0-25.1
Malvidin-3-O-arabinoside	OCH3	OCH3	Ara	13.3-42.38	2.52-54.3
Malvidin-3-O-galactoside	OCH3	OCH3	Gal	23.4-66.68	5.29-108.8
Paeonidin-3-O-galactoside	OCH3	H	Gal	12.46-20.9	1.32-19.8
Paeonidin-3-O-glucoside	OCH3	H	Glc	11.9-12.0	-
Petunidin-3-O-arabinoside	OCH3	OH	Ara	5.61-9.05	0.48-21.3
Petunidin-3-O-glucoside	OCH3	OH	Glc	3.5-28.1	0.5-37.9

ANTI-OXIDANT PROPERTIES:
Its natural formation of antioxidants during food processing or storage makes its antioxidant activity especially intriguing. Although the exact mechanism of these MRPs' antioxidant activity is unknown, it is thought to be based on their capacity to hold onto positively charged electrophilic species, eliminate oxygen radicals, and/or chelate metals to create inactive complexes[16]

The protection of the human body from the damaging effects of free radicals and the degradation of fats and other food ingredients is achieved through antioxidant activity. Glutathione peroxidase, ferroxidase, superoxide dismutase, catalase, and other antioxidant enzymes scavenge free radicals and shield the body from stressor offenses[17]

ANTI-OXIDANT ACTIVITY OF ANTHOCYANINS:
Similar to other polyphenols and flavonoids, anthocyanins and anthocyanidins have the capacity to scavenge free radicals and protect against dangerous oxidants like reactive oxygen and nitrogen species (ROS and RNS) [18].

Anthocyanins with specific characteristics involving radical electron delocalization on the sp2 orbitals of the oxonium moiety are provided by the flavylium skeleton. The oxidation of phenolic hydroxyl groups found in anthocyanins is a key component of antioxidant activity; para- and ortho-phenolic groups, in particular, are crucial for the production of semiquinones and the stabilization of products of one-electron oxidation[18,19]

Through hydrogen atom abstraction from phenolic groups and a single electron transfer reaction, anthocyanins can neutralize reactive radical species. Positions 3´ and 4´ are essential for these compounds' antioxidant potential, as seen in Figure 5. Because they can form ortho-semiquinones and then ortho-quinones through two consecutive one electron transfer reactions, catechol moieties (3´ and 4´ dihydroxyphenyl groups) on ring B are responsible for the antioxidant power of a variety of polyphenols and flavonoids [18,20,21,22]

Carotenoids, phenolic compounds, anthocyanins, and other synthetic antioxidants are among the many natural products whose antioxidant activity is assessed by bleaching of the ABTS+•, which is quantified by the reduction of the radical cation as the percentage inhibition of absorbance at 734 nm [23,24]

Chronic illness	Phytoconstituents	MOA	Ref
Antioxidant	Polyphenols, anthocyanins, chlorogenic acid	Anthocyanins (malvidin-3-glucoside)/phenolic metabolism inhibited by methyl jasmonate	25

ANTI-INFLAMMATORY ACTIVITY:

Proinflammatory cytokines are synthesized and released as a result of inflammation, which is linked to oxidative stress and excessive reactive oxygen species (ROS) production. Nowadays, there are a lot of natural products with anti-inflammatory properties. Chitosan and its derivatives have a number of biological benefits, including an anti-inflammatory effect, the mechanisms underlying which are only partially understood [26].

In this phenomenon, keratinocytes, B lymphocytes, T lymphocytes, and macrophages produce immune-responsive substances (cytokinins and interleukins). Inflammatory enzymes and antibodies are released by the endocrine system. The primary immune organs' anti-inflammatory components, cytokines, IL-2, and IL-1, act as mediators to bring about the healing process [27].

ANTI- INFLAMMATORY ACTIVITY OF ANTHOCYNINS:

Serum levels of vascular endothelial growth factor (VEGF) and interleukin-1β (IL-1β) were significantly decreased in STZ-induced diabetic rats when blueberry anthocyanins were given orally at a dosage of 80 mg/kg [28].

Blueberry fruits and their anthocyanins have been shown in numerous studies to have the ability to regulate inflammation. Consequently, blueberry anthocyanins have the potential to prevent and/or alleviate associated chronic diseases. By blocking the mRNA levels of inflammatory biomarkers such as IL-1β, COX-2, and iNOS, the blueberry anthocyanin extract effectively reduced the inflammatory response of Raw 264.7 macrophages triggered by lipopolysaccharide (LPS) in cellular tests [29].

In rats with collagen-induced arthritis, the application of blueberry extract with 0.58 mg/mL of anthocyanin reduced the development of acute inflammation and arthritis clinical symptoms (including soft tissue swelling, osteophyte formation, and bone absorption) [30].

When mice were given a combination of blueberry pectin and high hydrostatic pressure cyanidin-3-glucoside, they demonstrated a successful anti-inflammatory response to ulcerative colitis caused by dextran sodium sulfate [31].

Blueberry polyphenol extract was found to reduce TNF-α and IL-6 in Raw 264.7 macrophages by blocking the activation of the NF-κB and MAPK pathways [32].

Chronic illness	Phytoconstituents	MOA	Ref
Anti-inflammation	Phenolic acids, Anthocyanins, flavonoids	The remarkable properties of blueberry proanthocyanidins make them promising candidates for potential therapeutic agents. These substances work together to protect the oral keratinocyte barrier by neutralizing leukotoxins, having antibacterial properties, and having anti-inflammatory properties. Malvidin-3-glucoside and malvidin-3-galactoside from blueberries have anti-inflammatory properties in endothelial cells that are regulated by the nuclear factor-kappa B pathway.	33

ANTI-CANCER ACTIVITY OF ANTHOCYNIN

In a dose-dependent manner, anthocyanin caused HepG-2 cells to undergo apoptosis. The apoptosis mechanism is associated with the TGF-β signaling pathway, the mitochondrial apoptosis pathway, the MAPK signaling pathway, the p53 signaling pathway, the apoptosis signaling pathway in the endoplasmic reticulum (ER) stress response, and so forth. Because medications can harm cells, research has also been done on how blueberry anthocyanin, when combined with existing medications, can inhibit tumor cells while protecting healthy cells. In mouse tumor liver tissue, acylated blueberry anthocyanin and cyclophosphamide were found to enha nce T-SOD, cat, and GSH PX enzyme activities [34].

Research has shown that after being treated with 250 µg/mL blueberry anthocyanin extract and anthocyanin pyruvate adduct for 24 hours, the development of MDA-MB-231 and MCF7 breast cancer cells was successfully reduced.[35]

It has been demonstrated that blueberry extract efficiently inhibits cell growth and initiates programmed cell death in HT-29 colon cancer cells through the COX-2 pathway [36]

The extract of blueberry polyphenols was demonstrated to improve specific immune activities and inhibit the formation of tumors in mice with CD-1 tumors in an animal model research.[37,38]

found that feeding ACI rats a 5% freeze-dried blueberry powder diet with 21 mg/g of anthocyanin decreased the number and size of breast tumors while delaying their formation. At concentrations between 2.5 and 7.5%, European blueberry anthocyanins, including their separate components, were found to efficiently inhibit the growth of human lung cancer A549 and H1299 cells.[39]

Following a six-week period of daily blueberry fruit eating, 25 individuals exhibited increased levels of the anti-inflammatory cytokine IL-10 and a significant rise in the number of natural killer (NK) cells, a particular type of lymphocyte that targets aberrant cellular immune responses.[40]

Malvidin-3-glucoside and malvidin-3-galactoside, which are derived from blueberries, might reduce the production of the inflammatory markers monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) at the protein and mRNA levels that are induced by TNF-α when 50 µM of these substances is present. It functions by dissolving IκBα and bringing p65 into the nucleus, which regulates the NF-κB pathway and gives it anti-inflammatory qualities.[41]

Chronic illness	Phytoconstituent	MOA	Ref
Anticancer	Phenolic acids, pyruvic acid, anthocyanins, pterostilbene	Experiments on ML cell lines reveal that blueberry plant extracts have anti-AML (acute myeloid leukemia) qualities. Protein kinase B (Akt) and extracellular signal-regulated kinase (Erk) are partially responsible for these effects, which are most noticeable in the leukemia stem cell subpopulation. Antioxidant and anti-inflammatory qualities are associated with blueberries' anticancer effects. Additionally, they regulate the proliferation of cells by monitoring signal transduction pathways. The bioactive components of blueberries efficiently inhibit the development and metastasis of breast cancer cells by modifying the PI3K/AKT/NF-κB pathway; blueberry anthocyanins have been shown to affect cytochrome c and caspase-9 production, as well as lowering p53 methylation. In oral cancer, these actions taken together inhibit growth, cause G2/M cell cycle arrest, and promote apoptosis.	42

BLUE BERRY IN AYURVEDIC MEDICINE OF TREATMENT :

Blueberries have an astringent taste and balance the Pitta dosha because they are Kashaya Rasa. This characteristic lowers blood sugar levels and aids in wound healing. Blueberries are perfect for summer because of their Pitta-calming qualities. It helps the eyes, which are linked to Pitta dosha, and gives the body a cooling sensation. Fresh, whole blueberries are the most popular way to eat them. They can also be eaten with other vegetables and fruits [43].

Blueberries calm the Pitta dosha and have an astringent taste, or Kashaya Rasa. This characteristic of blueberries is used to lower blood sugar levels and promote wound healing. Its Pitta-pacifying qualities make it perfect for summer. It helps with eye conditions that are linked to Pitta dosha and has a cooling effect on the body [44].

SOME OTHER HELATH BENEFITS OF BLUE BERRY:

1) One of the best foods for antioxidants is blueberries. Your body is shielded by antioxidants against free radicals, which are unstable chemicals that can harm cells and play a role in aging and illnesses like cancer.

   Among all common fruits and vegetables, blueberries have one of the highest quantities of antioxidants. The primary antioxidants found in blueberries are flavonoids, a family of polyphenol antioxidants.

   Many of the positive health effects of these berries are believed to be caused by a particular class of flavonoids called anthocyanins.
2) Oxidative DNA damage is a natural part of life and is thought to happen in every cell in your body every day. It contributes to aging and is a major factor in the development of diseases like cancer. Blueberries may help neutralize some of the free radicals that damage your DNA because they are high in antioxidants.
3) People with high blood pressure, a key risk factor for heart disease, seem to benefit greatly from blueberries.

   A review for 2024 According to a reliable source, eating blueberries daily for a month could greatly increase blood vessel dilatation and blood flow.
4) Oxidative stress can hasten the aging process of your brain and impair its functionality.

   According to a 2023 study, older persons' memory and brain function may be preserved by regularly taking blueberry powder, which is equivalent to around one cup of fresh blueberries.[45]

5) The sugar content of blueberries is minimal when compared to other fruits.

   An orange's worth of sugar, or 14 grams, is included in one cup (150 grams) (Trusted Source). Blueberries include bioactive chemicals that may help control blood sugar.

   According to research, blueberry anthocyanins may improve glucose metabolism and insulin sensitivity (Trusted Source). Both fresh and freeze-dried berries have been shown to have these anti-diabetic benefits.

   Increased insulin sensitivity may reduce the incidence of type 2 diabetes and metabolic syndrome, both of which are linked to a number of detrimental health consequences.
6) Weariness and muscle discomfort can result from intense activity. Oxidative stress and local inflammation in your muscle tissue are partially to blame for this. By reducing molecular damage, blueberry supplements may minimize muscle discomfort and decreased performance.According to a small 2018 study, blueberries can help with recovery by enhancing exercise performance and lowering specific inflammatory markers. [45]

CONCLUSION:

Blueberries have shown great promise in the prevention and treatment of a number of chronic disorders, including cancer and inflammatory diseases, especially because of their high anthocyanin concentration. Their therapeutic adaptability is demonstrated by the wide range of pharmacological activities, including anti-inflammatory, anti-diabetic, anti-cancer, and antioxidant properties. Blueberries are positioned as a beneficial nutraceutical component because of scientific studies that highlight their capacity to affect important cellular pathways, reduce oxidative stress, and regulate immunological responses. The incorporation of blueberry-based treatments into both conventional and contemporary medical practices is still supported by research, despite issues including bioavailability and chemical stability. Blueberries are an effective ally in promoting health and preventing disease because of their potential in complementary medicines, particularly when combined with traditional therapies.

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CONFLICT OF INTEREST:

We declare that we have no conflict of interest.

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43) Pitta Pacifying Blueberry Recipes For Summer

by Dr. Arya Krishna
44)Article by Dr. Karanvir Singh (M.D in AYURVEDA, PANCHAKARMA FAGE) and reviewed by Vaidya Jagjit Singh (B.A.M.S)

45) 7 Proven Health Benefits of Blueberries

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