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Effects of anthocyanins on stem/progenitor cell activities: A comprehensive review

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ABSTRACT

Anthocyanins are water-soluble pigments belonging to the flavonoid family vastly found in fruits, vegetables, and flowers. Their antioxidant and anti-inflammatory properties verify therapeutic potential against health conditions including cancer, diabetes, cardiovascular diseases, and neurodegenerative disorders. Recent studies have shown that anthocyanins influence stem/progenitor cell activities. Maintaining stem cell populations in tissues is essential for preserving their regenerative potential and physiological functions. In addition, *in vitro* stem cell proliferation provides sufficient cells for cell therapy. Evidence suggests that anthocyanins could maintain stem cell survival under stressful conditions such as hypoxia, radiation, and inflammation. Also, these compounds can influence the differentiation of various stem and progenitor cells (e.g., mesenchymal, hematopoietic, and neural stem cells) into adipocytes, osteoblasts, chondroblasts, neurons, etc. These effects may vary depending on the chemical structure of the anthocyanins, the anatomical depot of stem cells, and human age. This comprehensive review covers the molecular mechanisms by which anthocyanins impact stem cell survival, proliferation, differentiation, and function. In addition, the natural source, chemical structure, bioavailability, and safety of anthocyanins are discussed. Taken together, the findings discussed in this review highlight the potential of anthocyanins to preserve stem cells and optimize their therapeutic efficacy.

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Introduction

Anthocyanins are water-soluble pigments belonging to the flavonoid family, commonly found in fruits, vegetables, and flowers. These compounds are responsible for the red, blue, and purple colors of many plants. In recent decades, anthocyanins have garnered significant interest in pharmacology and health due to their numerous benefits and therapeutic potential. Recent research highlights their potent anti-oxidant and anti-inflammatory properties, which can help mitigate oxidative stress and chronic inflammation linked to diseases like cancer, diabetes, cardiovascular issues, and neurodegenerative disorders. Studies indicate that anthocyanin consumption is associated with reduced risk of metabolic syndrome, lower blood pressure, improved lipid profiles, and decreased inflammatory markers in high-risk populations (1, 2).

Stem cells play a pivotal role in tissue repair and homeostasis by replenishing cells that are lost during normal turnover, growth, or injury. Additionally, they are essential for the development of organs and tissues during embryogenesis. Currently, stem cells are being utilized increasingly in regenerative medicine and drug development. Numerous studies have explored stem cell applications in regenerative medicine, particularly for highly prevalent conditions such as cardiopulmonary diseases, diabetes, and various neurological disorders (3-5). Despite their promising therapeutic potential, stem cell applications in regenerative medicine face several challenges, including difficulty in effectively differentiating stem cells into the desired cell types and in ensuring their long-term viability and functional integration after transplantation. Additionally, issues related to immunogenicity and the potential for tumorigenesis pose significant risks that need to be addressed before stem cell therapies can be widely implemented.

Nutrition plays a crucial role in the health and functionality of stem cells, influencing their proliferation, differentiation, and overall regenerative potential. A balanced diet rich in essential nutrients, vitamins, minerals, and anti-oxidants can enhance stem cell activity and support their ability to repair damaged tissues. Bioactive compounds from fruits and vegetables, such as polyphenols, have been shown to improve the stem cell microenvironment, thereby enhancing stem cell resilience and longevity (6-9). This article aims to review the effects of anthocyanins

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on stem cell activities and their corresponding molecular mechanisms. It also discusses whether anthocyanins may be used as functional food components to induce desirable changes in stem cell properties.

Search strategy

A comprehensive literature search was performed using the Google Scholar, PubMed/Medline, and Scopus databases, employing keywords such as "anthocyanins", "anthocyanidin", "stem cells", "stemness", "differentiation", and "proliferation." The inclusion criteria focused on both *in vivo* and *in vitro* studies examining the effects of anthocyanins on stem cell activities. Studies that used total plant extracts that were not rich in anthocyanins were excluded. To ensure a thorough exploration of the natural sources, chemical structures, bioavailability, and safety of anthocyanins, as well as the characteristics and functions of stem cells, an extensive review of the relevant literature was undertaken, extending beyond the initial keywords and inclusion/exclusion criteria.

Natural source and chemical structure of anthocyanins

Anthocyanins are a subclass of flavonoids widely distributed in the plant kingdom. They are predominantly found in the vacuoles of plant cells, contributing not only to plant coloration but also to pollinator attraction and fruit dispersal mechanisms. Anthocyanins are present in a variety of fruits (blueberries, blackberries, raspberries, strawberries, cherries, red grapes, etc.), vegetables (e.g., red cabbage, eggplant, and purple sweet potatoes), and grains (e.g., black rice and purple corn) (Figure 1). Anthocyanin concentration varies significantly among different sources, influenced by factors such as plant variety, maturity, and environmental conditions. The six most common anthocyanidins include cyanidin, pelargonidin, peonidin, delphinidin, petunidin, and malvidin (1, 2, 10).

Chemically, anthocyanins are glycosylated derivatives of the anthocyanidin compounds. The anthocyanidin core consists of two aromatic rings (designated A and B) linked by a heterocyclic ring (C) (Fig 1). Variations in the structure of anthocyanidins arise from different substitution patterns on the B-ring. For instance, pelargonidin possesses hydrogen atoms at both the 3' and 5' positions of the B-ring, whereas cyanidin contains a hydroxyl group at the 3' position and a hydrogen atom at the 5' position. The attachment of sugar moieties - such as glucose, galactose, fructose, and xylose - to anthocyanidins can occur at various hydroxyl groups, with the 3-OH position being the most frequently used site for glycosylation. This process leads to the formation of compounds like peonidin-3-O-glucoside and cyanidin-3-O-β-glucoside (11, 12).

Characteristics and classification of stem cells

Stem cells are undifferentiated cells with noteworthy potential to develop into specialized cell types. Their regenerative properties make them pivotal in both therapeutic applications and developmental biology (13). Stem cells are defined by several key characteristics that distinguish them from other cell types. They express specific surface markers that can be used for isolation and identification. For example, CD34 is a marker commonly associated with hematopoietic stem cells (HSCs), whereas OCT4 and NANOG transcription factors are markers of pluripotency in embryonic stem cells (ESCs) (14, 15). Another characteristic of stem cells is their ability to undergo numerous cycles of cell division while maintaining an undifferentiated state. This self-renewal capability is crucial for replenishing cell populations over an organism's lifetime. In addition, stem cells can differentiate into specialized cell lineages. Pluripotent stem cells can give rise to all three germ layers (mesoderm, ectoderm, and endoderm), while multipotent stem cells are limited to specific cell types. The activities of stem cells are heavily influenced by their microenvironment, or niche. Various signals from extracellular matrix components and surrounding cells can influence stem cell fate decisions between self-renewal and differentiation (16, 17).

Stem cells can be categorized based on their origin and differentiation potential. The primary classification includes ESCs, perinatal stem cells, adult stem cells (somatic stem cells), and induced pluripotent stem cells (iPSCs). The ESCs are derived from the inner cell mass of the blastocyst, a pre-implantation stage of the embryo. These stem cells are pluripotent, meaning they can differentiate into nearly all cell types of the body. Perinatal stem cells can be isolated from amniotic fluid, umbilical cord blood, and

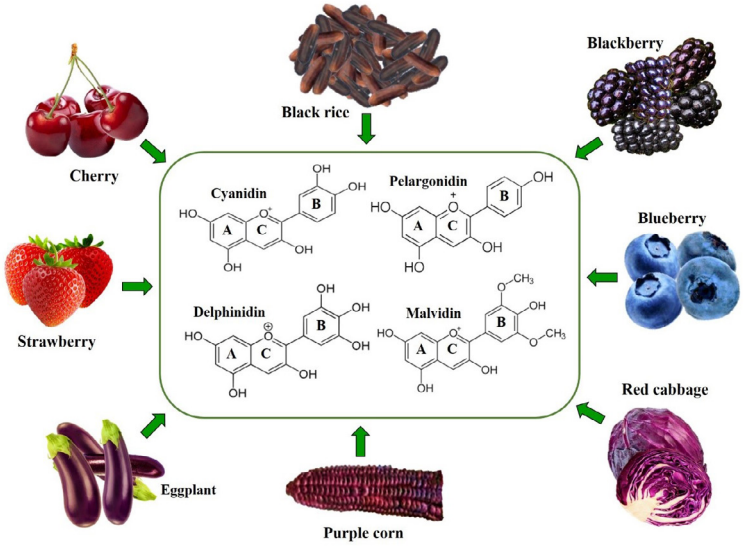

Figure 1. Chemical structures of several abundant anthocyanins and the plants that are rich in them

placenta. They exhibit both pluripotent and multipotent characteristics and have increasingly been investigated for their potential in regenerative medicine. Adult stem cells are found in various tissues throughout the body, including adipose tissue, bone marrow, dental pulp, and skin. They are typically multipotent, meaning they can differentiate into a limited range of cell types related to their tissue of origin. For example, adipose-derived stem cells (ASCs) can differentiate into osteoblasts, chondrocytes, and adipocytes, while bone marrow HSCs can give rise to various blood cell types (3, 18). The iPSCs are adult cells that have been genetically reprogrammed to an ESC-like state. This reprogramming restores their pluripotent capabilities, allowing them to differentiate into various cell types. These stem cells are of significant importance in personalized medicine, as they can be derived from a patient's own cells, thereby reducing the risk of immune rejection (3, 13, 19).

Effects of anthocyanins on stem cells

Effects on proliferation and survival

Maintenance of stem cell populations in the body tissues is essential for preserving their regenerative potential and physiological functions. In addition, *in vitro* proliferation of stem cells is critical for providing sufficient quantities of cells for cell therapy and tissue regeneration. Therefore, optimizing culture conditions with natural compounds to increase cell proliferation may be beneficial (20).

A limited number of studies directly investigated the effects of anthocyanins on stem cell proliferation (Table 1). It has been shown that anthocyanins from *Lycium ruthenicum* Murr can promote the expansion of HSCs isolated from umbilical cord blood, which could be a significant asset for the transplantation of these cells (21). Additionally, Gao *et al.* reported that anthocyanins from Ribes meyeri increased the viability of mouse NSCs. This effect was associated with decreased reactive oxygen species (ROS) levels and down-regulation of the senescence gene p16ink4a; thus, a greater number of cells were observed in the S phase of the cell cycle (22). On the other hand, a report found that blueberry anthocyanin extract dose-dependently inhibited the proliferation of human ASCs (23). Similarly, Jeon *et al.* showed that black soybean anthocyanin extract decreased the proliferation of mouse subcutaneous ASCs. Also, they found that the effect of anthocyanins on stem cell proliferation varied by the anatomical site from which the cells were isolated. For example, the doubling time in ASCs isolated from subcutaneous adipose tissue was shorter than in ASCs isolated from visceral tissue (24). Therefore, it appears that the effect of anthocyanins on the rate of stem cell proliferation depends on the types of anthocyanins, the type of stem cells, and the anatomical origins. Consequently, in different tissues of the body, their effect may be stimulatory or inhibitory.

There is growing evidence suggesting that anthocyanins may maintain stem cell viability under stressful conditions such as hypoxia, radiation, and inflammation. Chen *et al.* administered *Solanum tuberosum* anthocyanin to mice before or after X-ray radiation and isolated their HSCs. They found that this treatment prevented an increase in the G0/G1 phase cell ratio, a decrease in the G2/M and S phase cell ratio, and an increase in the relative mRNA and protein expression of p53 and p21. These findings showed that *S. tuberosum* anthocyanin could protect HSCs against radiation through the p53-p21Waf1/Cip1 pathway (25). The p53 protein plays an important role in regulating the cell cycle. Under destructive situations, such as DNA damage, hypoxia, oncogenic signals, and nutrient deprivation, P53 restricts cell division by stimulating the P21 protein. It induces apoptosis by affecting B-cell lymphoma-2 (Bcl-2) protein and Bcl-2-associated X protein (Bax) (Figure 2). Different classes of flavonoids, including anthocyanins, have been shown to modulate Bcl-2 proteins in the p53 signaling pathway (26).

Among various anthocyanidins, delphinidin is one of the best-known cytoprotective compounds. Pretreatment with delphinidin was shown to prevent hypoxia-induced apoptosis in ESCs. This effect of delphinidin was due to inhibition of ROS production, inhibition of JNK and NF-jB, as well as decrease of Bax, cleaved caspase-9, and cleaved caspase-3. It also prevented the decline of Bcl-2 and Akt (27). This cytoprotective effect was observed at a concentration of 0.1 μM of delphinidin. The c-JUN N-terminal kinases (JNKs) belong to the family of mitogen-activated protein kinases (MAPKs). Various factors, including inflammatory cytokines, environmental stressors, and growth factors, can trigger them. Once activated, JNKs phosphorylate

Table 1. Effect of anthocyanins on stem cell proliferation and survival

Anthocyanins	Type of stem/progenitor cells	Effects	Ref.
Lycium ruthenicum anthocyanin extract	Umbilical cord blood HSCs	↑Cell proliferation	(21)
Cyanidin-3-glucoside	Human primary osteoblast isolated from femoral heads	↑Cell proliferation	(40)
Ribes meyeri anthocyanins	Mouse NSCs	↑Cell proliferation	(22)
Black soybean anthocyanin extracts	3T3-L1 preadipocytes	↓Cell proliferation	(34)
	Mouse ASCs	↓Cell proliferation	(24)
Blueberry anthocyanin extract	Human ASCs	↓Cell proliferation	(23)
Delphinidin	Mouse embryonic stem cells	↓Hypoxia-induced apoptosis	(27)
Delphinidin-3-glucoside	MSCs lineage (C3H/10T1/2)	↑Cell cycle progression in the presence of lipopolysaccharide	(31)
Solanum tuberosum anthocyanins	Mouse HSCs	↓Radiation-induced decrease of cell cycle progression	(25)

ASCs: Adipose-derived stem cells; HSCs: Hematopoietic stem cells; MSCs: Mesenchymal stem cells; NSCs: Neural stem cells

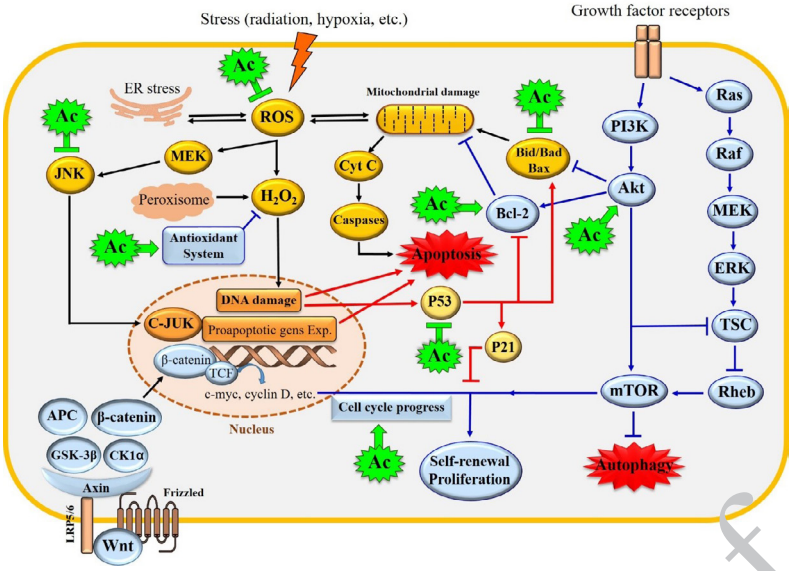

Figure 2. Intracellular pathways regulating the self-renewal and survival of stem cells
The effects of anthocyanins are shown by green stars
Ac: Anthocyanins; APC: Adenomatous polyposis coli; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma-2; Cyt C: Cytochrome C; ER: Endoplasmic reticulum; ERK: Extracellular signal regulated kinase; GSK-3ß: Glycogen synthase kinase 3β; JNK: Jun-N-terminal kinase; LRP: Lipoprotein receptor-related protein; MEK: Mitogen-activated protein kinase kinase; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase; Ras: Rat sarcoma; Raf: Rapidly accelerated fibrosarcoma; Rheb: Ras homolog enriched in brain; ROS: Reactive oxygen species; TSC: Tuberous sclerosis complex; TCF: T-cell specific factor

numerous substrates, altering gene expression and driving diverse cellular signaling activities, including apoptosis, self-renewal, migration, and cell differentiation. Furthermore, JNKs play important roles in processes such as embryonic development, immune response, wound healing, neural function, metabolic disorders, and tumorigenesis (28). The phosphoinositide 3-kinase (PI3K)/Akt pathway is one of the main regulators of cell survival and proliferation in different cell types. Once activated, Akt can stimulate various downstream targets, including Bcl-2 and mTOR, which in turn enhance cell survival and proliferation (29) (Figure 2). It has been shown that delphinidin pretreatment modulated the PI3K/Akt signaling pathway and induced cytoprotective effects on bone marrow-derived hepatocyte stem cells exposed to a pro-apoptotic microenvironment induced by TGF-β (30).

In another study, it was shown that when mesenchymal stem cells (MSCs) are treated with lipopolysaccharide, delphinidin at a concentration of 50 μM increases cell cycle progression by promoting the S, G2, and M phases. This suggests that delphinidin may play a beneficial role in enhancing stem cell activity, particularly in inflammatory or traumatic conditions. However, it should be noted that the effects of this anthocyanidin on the cell viability may be reversed in high concentrations. For example, delphinidin at concentrations of 100 μM or higher induces apoptosis in MSCs (31). However, such high concentrations are unlikely to be achieved in blood with normal dietary intake and are likely to be achieved by administering high doses of pure delphinidin.

Effects on differentiation

Studies have shown that common anthocyanidins, such as cyanidin, malvidin, and delphinidin, may influence the differentiation of various stem and progenitor cells, such as bone marrow-derived stem cells (BMSCs), ASCs, and amniotic cells (Table 2). As observed in the case of proliferation, the effect of anthocyanins on differentiation may vary with anthocyanin chemical structure, the anatomical depot of stem cells, and developmental stage (embryonic, adult, etc.).

Adipocyte differentiation

Cyanidin-3-glucoside (Cy3G) has been investigated for its effects on human amniotic epithelial cells, a promising source of pluripotent stem cells. Microarray analysis revealed that Cy3G influences gene expression, with 109 genes up-regulated and 232 down-regulated upon treatment. Notably, genes associated with adipogenesis were modulated, indicating Cy3G's potential to steer differentiation of amniotic epithelial cells toward adipocytes (32). Although findings on adipogenic differentiation of these cells vary in the literature, Cy3G's ability to enhance this process in the absence of growth factors could be an appealing avenue for future studies.

Research on 3T3-L1 preadipocytes has shown that anthocyanins may inhibit terminal differentiation into adipocytes. Treatment with anthocyanins extracted from *Vitis coignetiae* reduced lipid droplet formation and triglyceride production, likely via activation of AMP-activated protein kinase (AMPK). Additionally, anthocyanins inhibited key adipogenic transcription factors, suggesting that they may serve as functional food agents in managing obesity by preventing adipocyte differentiation (33). In line with these findings, black soybean anthocyanin extracts containing 68% Cy3G, 25% delphinidin-3-O-glucoside, and 6.5% petunidin-3-O-glucoside have been shown to inhibit adipocyte differentiation and peroxisome proliferator-activated receptor γ (PPARγ) expression (34). In another study, this plant also suppressed the differentiation of subcutaneous ASCs into the precursors and mature adipocytes (24). In addition, it has been reported that 3T3-Ll cells treated with black soybean extract and Cy3G differentiated into smaller adipocytes. These small fat cells released less tumor necrosis factor-α (TNF- α) and more adiponectin. Also, they expressed higher levels of PPARγ

Table 2. Effect of anthocyanins on stem cell differentiation

Differentiation	Anthocyanins	Type of stem/ progenitor cells	Effects	Ref.
Adipogenesis	Cyanidin-3-glucoside	Human amniotic cells	↑Differentiation	(32)
	Black soybean anthocyanin extract	Mouse subcutaneous ASCs	↓Differentiation	(24)
	Delphinidin, malvidin, and cyanidin	Human ASCs	↓Differentiation by delphinidin	(37)
	Anthocyanins isolated from *Vitis coignetiae*	3T3-L1 preadipocytes	↓Terminal differentiation	(33)
	Black soybean anthocyanin extract		↓Differentiation	(34)
	Cyanidin-3-glucoside and black soybean anthocyanin extract		Differentiation into smaller adipocytes	(35)
	Cyanidin-3-glucoside		Differentiation into beige adipocyte phenotypes	(36)
Osteogenesis	Proanthocyanidin-rich extract of grape	Human BMSCs	↑Differentiation (early stage)	(42)
	Cyanidin-3-glucoside	Human primary osteoblast isolated from femoral heads	↑Differentiation	(40)
	Cyanidin-3-glucoside	Murine calvaria-derived osteoblasts	↑Differentiation	(41)
	Cyanidin	Primary bone marrow monocytes and RAW264.7 cells	↑Differentiation in low concentrations but opposite effect in high concentrations	(43)
	Delphinidin, malvidin, and cyanidin	Human ASCs	↑Differentiation by malvidin	(37)
Chondrogenesis	Cyanidin	MSCs	↓Expression of chondrogenic-related genes (Col2a1, Sox9)	(45)
	Delphinidin, malvidin, and cyanidin	Human ASCs	↑Differentiation by cyanidin and delphinidin	(37)
Neurogenesis	*R. meyeri* anthocyanins	Mouse NSCs	↑Differentiation of NSCs into neurons	(22)
	Anthocyanins from bilberry and black currant	Human hippocampal progenitor cells (HPC03A/07 line)	↑Neurogenesis	(53)
	Cyanidin	Mice underwent chronic unpredictable mild stress	Preserving neuronal differentiation and dendritic maturation	(52)
Other cell lineages	Aronia berry anthocyanins	Murine muscle satellite cells	Promoting early and late stages of myogenic differentiation	(55)
	Anthocyanidin mixture (peonidin, cyanidin and pelargonidin)	Primary myogenic cells isolated from the skeletal muscle of rainbow trout	Induced delayed myogenic differentiation (↑Expression of Pax7 gene; ↓myogenic regulatory factors; ↑Expression of Gpx1 involved in defense against oxidative stress)	(57)
	Cyanidin-3-glucoside and vitisin A	HSCs	↓Differentiation into inflammatory monocytes	(54)

ASCs: Adipose-derived stem cells; BMSCs: Bone marrow-derived stem cells; HSCs: Hematopoietic stem cells; MSCs: Mesenchymal stem cells; NSCs: Neural stem cells

and CCAAT/enhancer-binding protein α (C/EBPα) and showed increased glucose uptake (35). The level of cAMP and C/EBPβ, and the expression of beige adipocyte markers (CITED1 and TBX1) and mitochondrial genes (such as SOD2, UCP-1, and UCP-2) were increased by Cy3G (36). Therefore, it appears that some anthocyanins induce the differentiation of preadipocytes into beige adipocyte phenotypes (brown-shaped adipocyte) and may have beneficial effects for the prevention and treatment of obesity-related metabolic diseases (35, 36). Some studies have shown that an anthocyanin can inhibit the differentiation of a stem cell into one lineage while stimulating it into another. Saulite *et al*. investigated the effect of different anthocyanins on the differentiation of MSCs. Their results showed that delphinidin decreased MSC adipogenesis while stimulating chondrogenesis. The effect of delphinidin on adipogenesis was associated with decreased expression of the adipose tissue-related genes FABP4 and adiponectin (37).

Osteogenic differentiation

Differentiation of stem cells into osteoblasts involves several stages (from the precursor stage to early and mature osteoblasts). It is regulated by several signaling pathways including Wnt/β-catenin, transforming growth factor-β (TGF-β)/(SMAD), parathyroid hormone/camp/protein kinase a (PKA), fibroblast growth factor (FGF)/rapidly accelerated fibrosarcoma (RAF)/extracellular signal regulated kinase (ERK), and insulin-like growth factor-1 (IGF-1)/PI3K/Akt (Figure 3) (38, 39).

Studies have reported that anthocyanins can induce

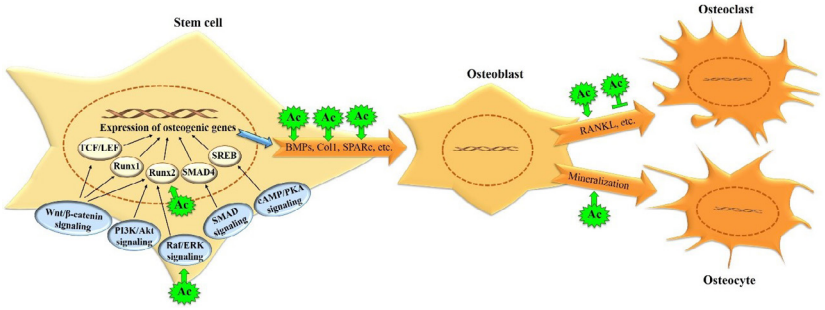

Figure 3. Signaling pathways regulating the differentiation of stem cells into osteoblasts
The effects of anthocyanins are shown by green stars
Ac: Anthocyanins; BMP: Bone morphogenetic protein; Col1: Collagen type I; ERK: Extracellular signal regulated kinase; LEF: Lymphoid enhancer factor; PKA: Protein kinase A; PI3K: Phosphoinositide 3-kinase; Raf: Rapidly accelerated fibrosarcoma; Runx: Runt-related transcription factor 2; SPARc: Secreted protein acidic and rich in cysteine; SREB: Super-conserved receptor expressed in brain; RANKL: Receptor activator of nuclear factor kappa-B ligand; TCF: T-cell specific factor

osteoblastic differentiation. Specifically, Cy3G was shown to enhance osteoblast mineralization, which was associated with increased expression of osteocalcin (at the mRNA and protein levels) and phosphorylation of ERK (40, 41). In a study by Saulite *et al.*, the effect of cyanidin on stem cell differentiation into osteoblasts was less than the effect of malvidin. The latter showed an osteogenesis-promoting activity and led to a significant increase in the expression of bone morphogenetic protein-2 and Runx2 transcription factor (37). In another study, Torre *et al.* investigated the effects of a proanthocyanidin-rich grape extract on the osteogenic differentiation of MSCs isolated from human bone marrow. The extract stimulated early osteoblast differentiation by enhancing the expression of the SPARc (secreted protein acidic and rich in cysteine) and col1a1 (pro-alpha1 chains of type I collagen) genes, which are involved in extracellular matrix deposition. In addition, the plant extract could decrease the metalloproteinase (MMP) to tissue inhibitor of MMP (TIMP) ratio, which favors MSCs' osteogenic differentiation. On the other hand, the expression of mineralization-related genes (osteocalcin and alkaline phosphatase) that are activated at mature stages of osteoblast differentiation was decreased (42).

There is growing evidence that anthocyanins may also modify osteoclastic differentiation of progenitor cells. In a study by Park *et al.*, murine bone marrow-derived macrophages (as osteoclast precursors) were cultured in the presence of C3G. They found that C3G inhibited receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated osteoclast differentiation and decreased the expression of ERK, JNK, and p38 MAPK. Also, it down-regulated the expression of c-Fos and nuclear factor of activated T-cells, which are master transcription factors for osteoclastogenesis (41). In another study, Dou *et al.* treated primary bone marrow monocytes and RAW264.7 cells with RANKL and M-CSF in the presence of cyanidin. The results showed that cyanidin had a dual effect on osteoclast differentiation. At low concentrations (< 1 mg/ml), it promoted both differentiation and fusion of osteoclasts, whereas at higher concentrations (> 10 mg/ml), it had the opposite effect (43). Therefore, further studies are needed to confirm the importance of cyanidin's effect on the balance between osteocyte and osteoclast production.

These findings indicate that anthocyanins may play a modulatory role in bone tissues, and some of these compounds may have regenerative potential for bone architecture. In addition, it has been shown that oxidative stress and inflammatory factors can impair osteogenesis, thereby aggravating bone loss in osteoporosis progress (44). Because of their anti-oxidant and anti-inflammatory effects, anthocyanins have the potential to prevent osteoporosis.

Chondrogenic differentiation

As mentioned above, Saulite *et al.* showed that delphinidin stimulated chondrogenic differentiation of human ASCs. This effect was also induced by cyanidin. Up-regulation of aggrecan and Col2a1 (a gene encoding the alpha-1 chain of type II collagen) was associated with the chondrogenic effects of cyanidin and delphinidin (37). On the other hand, Cao *et al.* evaluated the effect of cyanidin on chondrogenic differentiation in MSCs. They found that the expression of both hypertrophic marker genes (Col10a1, Runx2) and chondrogenic-related genes (Col2a1, Sox9) was inhibited by this anthocyanin. By promoting Nrf2 expression and inhibiting autophagy, cyanidin demonstrated its potential to maintain chondrocyte function and prevent hypertrophic changes in tissue-engineered cartilage (45). Therefore, insufficient evidence of anthocyanins' effects on chondrocyte differentiation prevents a definitive conclusion and leaves the matter unsettled.

Neurogenesis

Brain tissue and neural stem cells (NSCs) are notably vulnerable to oxidative stress due to high metabolic activity, high levels of unsaturated fatty acids, and relatively limited anti-oxidant defense mechanisms. Consequently, averting this damage and the subsequent risk of neurodegeneration is a significant area of focus in aging studies (46, 47). Adult hippocampal neurogenesis, the process of generating new neurons from NSCs throughout adulthood, plays a crucial role in cognitive functions related to learning and memory. Neurogenic alterations can be observed before the typical pathological features of dementia, indicating their fundamental role in the disease pathogenesis. As a result, compounds that promote neurogenesis may promote disease prevention. Concurrently, diets rich in anti-oxidants are being studied for their potential to mitigate age-related conditions. Investigating how these dietary anti-oxidants affect NSCs and hippocampal neurogenesis will enhance our understanding of their therapeutic potential (48).

Preclinical studies have shown that anthocyanin-rich products modulate synaptic plasticity, inhibit the intracellular and extracellular accumulation of toxic proteins, and improve learning and memory (49). Gao *et al.* demonstrated that *R. meyeri* anthocyanins positively affect aged NSCs. Anthocyanins promoted NSC differentiation into neurons and improved memory and learning in aged mice (22). Suresh and Vellapandian showed that cyanidin could restore impaired neurogenesis in cortical and hippocampal regions of rats treated with bisphenol, a known neurotoxic compound. The mechanisms proposed for this protective effect are alleviating oxidative stress and interactions with Wnt signaling proteins (50). Another signaling pathway involved in neurogenesis is the PI3K/AKT/Foxg1 cascade. Foxg1 (formerly BF-1) belongs to the Forkhead box family of transcription factors and is expressed in the postnatal and adult telencephalon (51). Cyanidin was shown to preserve neurogenesis in mice that underwent chronic unpredictable mild stress through the PI3K/AKT/FoxG1/FGF-2 signaling pathway and therefore alleviated depression-like symptoms (52).

Recently, it has been reported that serum collected from adult participants who consumed anthocyanins (from bilberry and black currant) increased *in vitro* neurogenesis in hippocampal progenitor cells. The cells treated with post-treatment serum (from the intervention group) showed lower levels of the stemness marker Sox2 than cells treated with pre-treatment (baseline) serum samples. This observation suggests that dietary supplementation with anthocyanins can modify the composition of the systemic environment, thereby differentiating neural progenitor cells (53).

Differentiation into other cell lineages

In murine models of atherosclerosis and ulcerative colitis, vitisin A (an anthocyanin derivative) and Cy3G exhibited immunomodulatory effects by restricting HSC differentiation toward inflammatory monocytes (54). This

suggests that anthocyanins can influence stem cell fate in inflammatory contexts, further revealing their potential as therapeutic agents in managing chronic inflammatory diseases.

There is also a report about the potential effect of anthocyanidins on myogenic differentiation. Liu and colleagues evaluated the effects of Aronia berry anthocyanins on muscle myogenesis in a cell model of chronic muscle inflammation. These anthocyanins were able to enhance both the early and late stages of myogenesis, indicating the anti-atrophy potential of Aaronia berry anthocyanins (55). In another study, a mixture of three anthocyanidins (cyanidin, peonidin, and pelargonidin) was shown to delay myogenic differentiation in primary myogenic cells. This effect was accompanied by increased expression of the genes involved in myogenic programming (pax7), Notch signaling (her6 and hey2), and the anti-oxidant enzyme (gpx1) (56). Although the significance of these effects in humans needs to be determined by future studies, it seems that anthocyanidins contribute to the defense of muscle tissue against oxidative stress.

Effects on stem cell function

Anthocyanins' effects on stem cell function have attracted increasing interest in recent years, particularly due to the anti-inflammatory, anti-oxidant, and cell-metabolism-modulating properties attributed to these compounds. Unlike speculative approaches, available studies provide concrete, though still fragmented, evidence that anthocyanins can modulate specific functions of different stem cell populations in ways strongly dependent on cell type, experimental context, and the nature of the inflammatory or oxidative stimulus. Relevant evidence was obtained from embryonic models to investigate the effects of anthocyanins on organismal development. Kundap *et al.*, although not specifically studying embryonic stem cells, demonstrated in a zebrafish developmental model that pelargonidin directly affected embryonic development, resulting in a significant reduction in aortic formation and suggesting effective inhibition of angiogenesis (57). In addition, Neves *et al.* demonstrated that anthocyanins affect the immunomodulatory function of MSCs. When MSCs were challenged with lipopolysaccharide, delphinidin modulated the secretory profile, increasing the release of anti-inflammatory cytokines, particularly IL-10 and TGF-β. No significant changes were observed in the production of pro-inflammatory cytokines such as IL-1β and IL-6, but delphinidin reduced NF-κB phosphorylation (31). Additional studies further reinforce this anti-inflammatory profile in MSCs. Perut *et al.* observed that exposure of ASCs to strawberry-derived exosome-like nanoparticles (anthocyanin-rich product) did not negatively affect cell viability, and pretreatment of the stem cells prevented oxidative stress in a dose-dependent manner (58). Similarly, Freitas *et al.* reported that Cy3G attenuated the impact of inflammatory stress on MSCs, maintaining cell viability and reducing activation of pathways associated with chronic inflammation, particularly NF-κB signaling. In addition, conditioned medium from MSCs pretreated with Cy3G reduced the production of IL-1β, IL-6, and IL-12 in lipopolysaccharide-stimulated macrophages, suppressed IL-2 production, and increased IL-10 levels in lymphocytes. These results suggest that anthocyanins can preserve essential MSC functions in adverse environments without inducing undesirable phenotypic changes (59). The classical study by Zhou *et al.* provides one of the most direct and specific pieces of evidence regarding the effects of anthocyanins on ASCs. In their work, these cells were stimulated with lipopolysaccharide to induce inflammation, and treatment with tart cherry extract, a rich source of anthocyanins, and purified Cy3G resulted in a significant reduction in IL-6. Importantly, this effect was observed without cytotoxicity and was enhanced when combined with statins, demonstrating a direct anti-inflammatory effect in ASCs (60). Additionally, Pei *et al.* evaluated the effects of Cy3G on murine MSCs differentiated into brown adipocytes *in vitro*. During differentiation, MSCs progressively acquired characteristics of brown adipocytes, including lipid accumulation and increased UCP1 expression. Treatment with Cy3G did not significantly restore intracellular UCP1 expression. Clearly, it modulated the secretory function of these cells, demonstrating a direct impact on the secretory activity of their differentiated progeny under lipotoxic stress (61). She *et al.* showed that a high-fat diet induced aberrant proliferation and functional dysregulation of intestinal stem cells in mice, and administration of an anthocyanin-rich lingonberry extract for nine weeks reduced hyperproliferation and excessive activation of intestinal stem cells induced by the high-fat diet. Lingonberry extract negatively modulated central pathways involved in intestinal stem cell homeostasis by suppressing activation of the Wnt and JAK/STAT pathways. These effects contributed to the restoration of the balance between intestinal stem cell proliferation and differentiation. They were accompanied by remodeling of the gut microbiota, thereby controlling pathological proliferation and preserving functional integrity of the intestinal epithelium under a fat-rich diet (62). The Wnt/β-catenin pathway is essential for various cellular functions, including survival, proliferation, cell polarity, and cellular migration. Additionally, this signaling pathway is vital for early embryonic development, as it is a primary regulator of ESC self-renewal and maintenance of their pluripotent state (63). Finally, some frequently cited studies have investigated the effects of anthocyanins in cells not classified as stem cells, but they provide important contextual information. For example, Kaewmool *et al.* analyzed somatic cells exposed to anthocyanins and observed reductions in inflammation and oxidative stress (64). At the same time, Chuntakaruk *et al.* reported similar anti-inflammatory effects in differentiated cellular models (65). Although these studies do not involve stem cells, their findings help contextualize the general mechanisms of action of anthocyanins, which may indirectly influence the niches where stem cells reside.

Effects on cancer stem cells

Cancer stem cells (CSCs) are a highly adaptable, treatment-resistant subset of cells within tumors that play a significant role in tumor initiation, progression, metastasis, and recurrence. Their capacity to evade standard treatments, adjust to metabolic challenges, and engage with the tumor microenvironment positions them as essential targets for novel therapeutic approaches (66).

Many studies have suggested that anthocyanins have cancer-preventive properties and inhibit the growth and metastasis of tumor cells (67). For example, in an animal model of liver cancer, an anthocyanin-rich blackberry extract inhibited diethylnitrosamine-induced hepatocellular

carcinoma in rats. It prolonged their survival by inhibiting oxidative stress and the Wnt4/β-catenin pathway (68). In the nervous system, Xue *et al.* reported that cyanidin restrains glioma cell growth by down-regulating Wnt/β-catenin signaling, thereby decreasing β-catenin and c-Myc protein levels by altering WNT1 and MYC gene expression and Twist1 and Snail1 expression (69). Köchling *et al.* evaluated the effects of isolated anthocyanins, such as cyanidin-3-rutinoside and delphinidin-3-glucoside, as well as a standardized anthocyanin-rich berry extract, on different leukemic cell types. The authors observed that anthocyanins inhibited leukemic cell proliferation in a dose-dependent manner (70). In another study, the effect of an anthocyanin-rich extract of black raspberry was evaluated on the epithelial-to-mesenchymal transition, pluripotency, and other characteristics in pancreatic CSCs. The extract suppressed stemness properties, inhibited epithelial-to-mesenchymal transition, and decreased aggressive behavior of these cells (71). The inhibitory effect of anthocyanins on epithelial-to-mesenchymal transition was also reported in breast cancer cells, where Cy3G suppressed this transition and the cancer invasion property by up-regulating Krüppel-like factor-4. This transcription factor can function as either a tumor suppressor or an oncogene, depending on the cellular context (72).

One of the interesting effects of anthocyanins that has received increasing attention is their effect on CSCs. Charepalli *et al.* reported that anthocyanin-containing extract of purple-fleshed potatoes decreased proliferation and increased apoptosis in colon CSCs. The extract inhibited the Wnt/β-catenin pathway and its downstream proteins (cyclin D1 and c-Myc), while inducing mitochondrial apoptosis by increasing the level of Bax and cytochrome c. Also, they showed that the plant extract decreased the incidence of colon cancer in mice and decreased the number of crypts containing cells (73). Similarly, it has been shown that proanthocyanidins decreased CSC marker, proliferation, and colony formation in colorectal cancer cells through modulating Wnt/β-catenin signaling, down-regulating β-catenin and related stemness pathways, and suppressing tumor growth in mice (74). In another work on colon cancer cells, Mazewski *et al.* investigated the effects of Cy3G and delphinidin-3-O-glucoside on immune checkpoint regulation in HT-29 and HCT-116 cells. The anthocyanins decreased cell proliferation and the expression of immune checkpoint proteins implicated in tumor immune evasion, suggesting modulation of their stem-like phenotypes (75). Further studies on the mechanisms of apoptosis have demonstrated that anthocyanins may induce apoptosis in colon CSCs through p53-independent signaling pathways (76).

Clinical translation

Bioavailability of anthocyanins

Although *in vitro* experiments and animal studies have indicated promising health benefits of anthocyanins, their limited stability and bioavailability may hinder effectiveness in humans. The bioavailability of anthocyanins may vary among individuals and is influenced by factors such as anthocyanin chemical structure, food matrix (the fibers, proteins, and lipids surrounding the anthocyanins), gastrointestinal health, and interactions with the gut microbiota (77, 78). The stability of anthocyanins may decrease under non-acidic pH (neutral and alkaline conditions), light exposure, oxygen, and high humidity, leading to degradation or conversion into less bioactive forms (79).

Some anthocyanins are primarily absorbed in the upper part of the gastrointestinal tract. It seems that the mechanism of absorption involves both passive diffusion and active transport mechanisms. In the oral cavity, anthocyanins undergo partial hydrolysis by the microbiota, yielding aglycones. In the stomach, anthocyanins could be absorbed without deglycosylation through specific transporters (e.g., sodium-dependent glucose co-transporter 1 and facilitative glucose transporter 1). However, in the small intestine, they are primarily absorbed as aglycones. The gut microbiota facilitates the breakdown of high-polymeric anthocyanins into lower-polymeric forms or smaller phenolic acids, enhancing their overall absorption. Inside the cells, anthocyanins and their derivatives are modified by metabolic enzymes involved in phases I and II of metabolism and subsequently enter the bloodstream (80). A study utilizing isotope tracers showed that Cy3G has a minimum relative bioavailability of 12.6 ± 1.9%, with significant variability among individuals (81). This variability can be attributed to differences in gastrointestinal microbiota composition, which may influence the degree of anthocyanin metabolism and absorption (77). Even some of the systemic health effects we attribute to anthocyanins may actually be the result of changes brought about by microbiota.

Following absorption, anthocyanins undergo hepatic first-pass metabolism. After administering 500 mg of isotopically labeled Cy3G, researchers identified 24 metabolites at concentrations ranging from 0.1 to 42 μmol/L. About 44 ± 26% of the ^{13}C was found in urine, feces, and breath, while the fate of the remaining ^{13}C was unidentified. A wide range of metabolites is produced from C3G post-ingestion, including phenolic acids and other degradation products, suggesting that anthocyanins do not remain intact in the bloodstream for extended periods but are instead rapidly metabolized (81).

Enhancing the bioavailability of anthocyanins can significantly improve their health benefits. Several methods have been suggested to achieve this goal. One approach involves encapsulating anthocyanins within liposomes or nanoparticles, thereby preventing their degradation and facilitating their absorption in the digestive tract (82). Also, incorporating anthocyanins into nanogels facilitates targeted drug delivery to specific areas, including the brain, while improving the chemical stability of anthocyanins, their intestinal absorption, and their anti-oxidant effectiveness at the cellular level. Another strategy is chemical modification, such as acylation of hydroxyl groups, to increase stability and decrease water solubility. Acylation decreases the polarity of anthocyanins and modifies their molecular dimensions. This process also creates a steric effect that reduces anthocyanins' vulnerability to nucleophilic attack, thereby enhancing their structural and chemical stability (83). Using the copigmentation technique can create more stable anthocyanin colors. In this method, anthocyanins interact in solution with colorless or lightly colored organic substances. These substances are referred to as co-pigments and include a diverse range of compounds, such as amino acids, phenolic acids, flavonoids, alkaloids, organic acids, tannins, and anthocyanins themselves. This interaction enhances the stability of anthocyanins, particularly by protecting them from degradation caused by light, heat,

and oxygen. Copigmentation offers the advantages of high synthesis rate and ease of implementation, making it an effective method for improving anthocyanin stability (83, 84).

Each of these techniques has its limitations, and a combination of methods can be used to improve anthocyanin bioavailability. For example, a combination of encapsulation and copigmentation strategies may lead to synergistic stabilization of anthocyanins (85).

Safety of anthocyanins

Although anthocyanins are natural compounds and the traditional belief is that they have no adverse effects, the safety of natural products should be evaluated as carefully as that of synthetic drugs. Current data from animal studies and clinical research suggest that anthocyanins are generally nontoxic when consumed at typical doses, and there is even a negative correlation between their intake and the incidence of serious diseases, including cancer and cardiovascular disease (86, 87). For example, as mentioned above, an anthocyanin-rich extract of blackberry improved liver oxidant/anti-oxidant status in rats and inhibited diethylnitrosamine-induced hepatocellular carcinoma (88). Shuping *et al.* evaluated acute and subacute toxicity of an anthocyanin extract of *L. ruthenicum* in mice and rats. Findings indicated that the highest extract dose that could be safely administered to mice in a single intragastric dose was at least 8000 mg/kg. Furthermore, during continuous intragastric administration for 30 days, no toxic reactions were observed in the rats (89). Bagchi *et al.* examined the safety of an anthocyanin-rich formulation of edible berries (containing wild blueberry, cranberry, bilberry, raspberry, elderberry, and strawberry). Acute oral toxicity in rats revealed an LD_{50} greater than 5 g/kg. No significant adverse effects were detected after necropsy. In rabbits, only slight eye irritation and slight skin irritation were observed (90). In the case of pure anthocyanins, administration of cyanidin to rats showed an LD_{50} exceeding 500 mg/kg in acute toxicity tests. A subacute toxicity assessment, using doses ranging from 7.5 to 30 mg/kg over 28 days, revealed a "no observed adverse effect level" (NOAEL) of at least 30 mg/kg/day. Furthermore, no significant histological changes were detected in vital organs such as the liver, kidneys, or brain (91).

The number of clinical studies primarily aimed at investigating the safety of these compounds is small. Biedermann *et al.* investigated the efficacy and safety of an anthocyanin-rich bilberry extract in patients with ulcerative colitis (800-1000 mg for 8 weeks). The extract contained glycosylated derivatives of various anthocyanidins, including cyanidin, delphinidin, peonidin, and malvidin. The findings indicated that the extract was generally well tolerated, and no severe side effects or systemic toxicity were attributed to the intervention. Some patients showed mild nausea and fatigue, which resolved without needing medical intervention (92). An open-label clinical trial in patients with type 2 diabetes showed that administration of dietary anthocyanins (320 mg per day for 4 weeks) induced anti-inflammatory effects (decreases in IL-6, IL-18, and TNF-α) and did not lead to severe side effects (93). In a randomized, open-label study, 12 healthy participants received 1 g/day of a black bean seed extract for 2 weeks. This extract is notable for its high concentration of functional ingredients, with the black pigment attributed to a significant amount of anthocyanins. The findings indicated that the extract was generally well tolerated, with no severe adverse reactions reported (94).

Joo *et al.* assessed the safety and effectiveness of a Cy3G-rich extract from black rice for improving cognitive function among individuals with memory issues. This double-masked randomized controlled trial (n = 48) administered black rice capsules for 12 weeks. Results indicated no significant adverse effects on blood chemistry, blood cell counts, or urine analysis. Participants reported no side effects throughout the trial, and the Cy3G-rich extract appeared to enhance subjective memory in older participants (95). In another clinical trial, 42 participants were randomly assigned to take anthocyanin extract or a placebo 3 times daily for 4 weeks. Extract supplementation was associated with improved oxidative status and did not cause toxic side effects (96).

In summary, anthocyanins do not seem to present major adverse effects at typical dietary levels. However, it is important to note that the available toxicological research, both in animal and human studies, remains limited, warranting further investigation to substantiate their safety. Additionally, no long-term studies have yet been performed on humans, and the potential for drug interactions involving anthocyanins, as well as their safety during pregnancy and lactation, remains to be explored.

Dosage discrepancies

The consumption of anthocyanins varies significantly depending on the context, whether it is as a dietary supplement or at pharmacological doses intended for therapeutic effects. Dietary consumption typically results in lower plasma concentrations of anthocyanins due to the complex interplay of digestion, metabolism, and absorption. The presence of other food components may further affect the solubility and stability of anthocyanins, leading to variations in individual responses. Conversely, pharmacological administration is designed to achieve higher and more consistent plasma levels of anthocyanins, thereby potentially enhancing their therapeutic effects on stem/progenitor cells. This disparity is critical as many preclinical studies investigating the effects of anthocyanins often utilize concentrations that exceed those obtainable through diet alone. As a result, while dietary anthocyanins may confer general health benefits and help maintain stem cell health, pharmacological doses may be necessary to sufficiently stimulate specific signaling pathways, such as those involved in proliferation and differentiation.

The optimal dose required for successful therapeutic outcomes in humans is not yet well defined. Animal studies investigating the effects of anthocyanins on stem cells have used varying doses (25 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, 250 mg/kg, 400 mg/kg, etc.) of these compounds (22, 52, 61, 62, 88). This wide range of doses may raise concerns about a translational gap between laboratory results and clinical applications. By applying conversion formulas that relate animal dosages to human dosages according to body surface area, the administration of 25 mg/kg - 400 mg/kg of anthocyanins in mice translates to roughly 2 mg/kg - 32 mg/kg for humans (i.e., 140 mg to 2240 mg for a 70-kg individual) (97). Randomized clinical trials are required to define which dose is most effective for which effect on stem cells.

Future directions

Future studies should focus on elucidating the precise molecular mechanisms underlying anthocyanin-mediated differentiation and examining the impact of anthocyanins in *in vivo* models. Incorporating anthocyanins into stem cell therapies has the potential to enhance their therapeutic efficacy. This may involve pre-treating stem cells with specific anthocyanins before transplantation to enhance their functional capacity. Anthocyanins may also be employed to help preserve stem cells during their expansion and storage outside the body. This strategy may not only increase stem cell survival rates but also improve their functional characteristics for therapeutic uses. Also, priming of stem cells with specific anthocyanins may improve their differentiation potential towards the desired cell lineage. Investigating the synergistic effects of these compounds in combination with other bioactive agents may provide valuable information on how to maximize their therapeutic potential. Additionally, conducting clinical trials to evaluate the efficacy of anthocyanin-rich products in regenerative medicine will be essential for translating these findings into clinical practice.

Conclusion

Based on available evidence, anthocyanins may modulate various aspects of stem cell biology, including self-renewal, differentiation, and secretory/immunomodulatory function. This modulation is important from cellular and physiological perspectives, as it shows that dietary phytochemicals can affect stem cell activity across different stages of human life, from embryonic development to old age. Also, this evidence underscores the potential of anthocyanins in enhancing the efficacy of stem cells in regenerative medicine by optimizing *in vitro* culture conditions for stem cell expansion and differentiation. Nevertheless, translational application remains hypothetical until issues of bioavailability, effective dosage, standardization, safety, *in vivo* efficacy, and clinical validation are fully addressed.

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Data Availability Statement

This is a narrative review, and all data included are referenced within the article.

Authors' Contributions

F S contributed to the literature search, interpretation, and table preparation. R A F, M A, and A H contributed to the literature search, interpretation, and manuscript drafting. A G conceived, designed, and supervised the review and helped draft the manuscript. All authors approved the final version.

Conflicts o Interest

The authors declared no conflicts of interest.

Declaration

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