Anticancer Activity of Anthocyanins: A Comprehensive Review

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Abstract

Anthocyanins, a class of organic pigments that give fruits, vegetables, and flowers their vivid colours, have attracted a lot of interest recently because of their conceivable health advantages. The significance of anthocyanins in the prevention and treatment of cancer has been the subject of numerous studies, and mounting evidence points to their promising anticancer capabilities. The goal of this in-depth review is to compile and evaluate the most recent information on the anticancer properties of anthocyanins. An overview of the molecular pathways behind cancer formation, including cell proliferation, angiogenesis, apoptosis, and metastasis, is given in the review's opening paragraph. The sources of anthocyanins are then examined in detail, including berries, cherries, grapes, and other fruits and vegetables. The review's ensuing parts dig into the vast in vitro and in vivo tests that have looked at anthocyanins' anticancer properties. These studies include a variety of cancer types, including liver, breast, colon, lung, and other types. The review emphasises how anthocyanins can cause cell cycle arrest and apoptosis as well as hinder cancer cell proliferation, invasion, and migration. The review also clarifies the molecular processes through which anthocyanins exert their anticancer effects. Several signalling pathways, including PI3K/Akt, MAPK, NF-B, and STAT3, among others, are modulated by these processes. The review also covers how anthocyanins control oxidative stress, inflammation, and angiogenesis—all of which are crucial for the development of cancer.

Keywords: anthocyanins; anticancer; cell proliferation; angiogenesis; apoptosis; metastasis.

1. Introduction

Plants contain blue, red, or purple pigments called anthocyanins, which are most prevalent in flowers, fruits, and tubers. While anthocyanin is a blue pigment in alkaline conditions, it is a red pigment under acidic settings. Despite having a positive charge on the oxygen atom of the C-ring of the basic flavonoid structure, anthocyanin is nonetheless regarded as one of the flavonoids. The flavylium (2-phenylchromenylium) ion is another name for it. Anthocyanin's stability is influenced by pH, light, temperature, and its structural makeup. [1] Red and purple berries, grapes, apples, plums, cabbage, and other foods high in natural colourants are dietary sources of anthocyanins. The six most prevalent anthocyanidins are cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin. Anthocyanins are absorbed after eating along the digestive tract, with the distal lower colon hosting the majority of absorption and

metabolism. [2] Anthocyanins initially go through substantial microbial degradation, absorption, and human phase II metabolism in the colon. As a result, hybrid microbial-human metabolites are created, which are then ingested and boost the anthocyanins' bioavailability. Anthocyanins provide numerous health advantages, particularly in reducing oxidative stress-related conditions like cardiovascular and neurological illnesses. [3] The glycosylated versions of anthocyanidins (aglycones) are known as anthocyanins. These substances are created when the flavylium cation backbone is hydroxylated in various locations to produce various anthocyanidins. The flavonoid skeleton maintains its ring nomenclature with the charged oxygen atom on the C ring even though these molecules include an oxonium group in their structure. Anthocyanidins can be glycosylated to create various anthocyanins, with 3-OH serving as the most prevalent glycosylation site in nature and resulting in 3-O--glucosides. [4] The glycosides of cyanidin, delphinidin, malvidin, and pelargonidin are among the most frequently found monomeric anthocyanins in nature. Depending on their accumulation and the complementary light absorbance of chlorophyll, these substances exhibit various colours (red, blue, and purple). The ability of some plants to change the characteristic green pigment is a crucial defence mechanism. [5] Light absorbance, pH-dependent colour, and stability of anthocyanins are all closely related characteristics that all include the electronic conjugation qualities that define this class of chemicals' oxonium moiety. Chlorophyll and anthocyanins' combined light absorption is frequently the cause of the colours that various plants (particularly flowers and fruits) can take on. As was already established, some plants' ability to reduce their intensely attractive green coloration serves as a form of defence against potentially deadly herbivorous animals. [6] The intrinsic UV-visible spectral absorption, electronic conjugation, and delocalization characteristics of anthocyanidin and anthocyanin are related. The various ionisation states and electronic rearrangements in the molecules, which are greatly impacted by the protonic concentrations in the environment, are what cause these effects. Anthocyanins exist as flavylium cations (oxonium-charged oxygen) at low pH levels, whereas uncharged quinones are produced at neutral pH levels. All anthocyanins are only marginally stable under basic conditions (a property that rises proportionally with pH), and they can all go through various degradation mechanisms that lead to a loss of colour. [7]

2. Anticancer properties of anthocyanins

Anthocyanins can stop tumorigenesis and cause the terminal differentiation of cancer cells. It was shown that cyanidin-3-O-glucopyranoside (Cyg) may initiate the differentiation of the human acute promyelocytic leukaemia cell line HL-60 in a dose-dependent manner by activating PI3K and PKC. This was done by identifying the markers and kinase inhibitors in the cell differentiation process. By lowering the expression of AP1, anthocyanins can affect the Ras-ERK and PI3K/Akt pathways and hinder cellular transformation. Delphinidin, cyanidin, and petunidin were discovered to be able to stop the TPA-induced transformation of the mouse skin cell line JB6P+. In JB6P+ cells treated with TPA, delphinidin can bind with Raf1 or MEK1 in an ATP-noncompetitive manner to decrease the expression of NFB and AP1, as well as COX2 and PGE2 synthesis. By controlling the phosphorylation of MEK, ERK, ribosomal protein S6 kinase, and mitogen stress activator protein kinase, delphinidin can also reduce the strength of the TPA-induced cellular transformation via the Ras/Raf/MEK/ERK pathway. Although they have little effect on the proliferation of healthy cells, anthocyanins can specifically hinder the growth of cancer cells. They can also stop cancer cells from growing

and multiplying by blocking certain kinase signalling pathways in vitro. [8] Additionally, anthocyanins might start the transcription of p21 and p27. A broad-spectrum CDK inhibitor known as p21 can work in conjunction with CDKs to decrease their activity, causing cancer cells to experience cell cycle arrest. Standardised berry anthocyanin-rich extract reduced Caco2 cells' ability to proliferate by increasing the expression of p21Waf/Cif1, halting the cells' cell cycle, and further triggering death by activating caspase 3. [9] In addition, anthocyanins can stimulate the expression of CDK inhibitors (CDKIs), downregulate the expression of CDK1 and CDK2, inhibit the expression of cyclin B, cyclin A, and cyclin E, and cause cancer cells to arrest at the G0/G1 and G2/M stages. By upregulating the expression of anti-oncogenes and downregulating the expression of oncogenes, along with the expression of various cyclins and their partners CDKs and/or CDKIs, anthocyanins can therefore inhibit cancer cell proliferation. [10] Anthocyanidins may have a synergistic inhibitory effect on human non-small cell lung cancer cells by interfering with the growth and proliferation of these cells via the catenin, Wnt, and Notch pathways and their downstream target proteins. Overall, cancer and tumours are thought of as signal pathway disorders, and this idea aids in the expansion of research and the development of safer, more precise chemopreventive and/or chemotherapeutic therapies, such as anthocyanins and other natural compounds. [11]

3. Anthocyanin and breast cancer

The results demonstrated that anthocyanins greatly reduced the invasion and migration of MDA-MB-231 and MDA-MB-453 cells, whether in enriched extracts or isolated form. Additionally, it has been demonstrated that anthocyanins mainly target the Akt/mTOR pathway rather than the MAPK stress-activated and pro-apoptotic proteins JNK and p38. Additionally, the anthocyanins group's cells fared better during the apoptotic process than the cells in the control group. Both the HER2+ and TNBC subtypes of cancer are aggressive, fast-growing tumours with a high likelihood of spreading at the time of diagnosis. Additionally, these breast cancer subtypes have a significant likelihood of returning after treatment. [12] Understanding the underlying mechanisms to aid in limiting the spread of metastatic breast cancer is a priority due to the dismal prognosis of this type of cancer. The data meta-analysis revealed that separated C-3-O-G and anthocyanin-enriched extracts both decreased cell invasion and migration concerning the mechanisms underlying these processes. Research on the impact of black rice anthocyanins on cell invasion and migration in MDA-MB-453 cells was studied and found that the treatment with 200 g/mL black rice anthocyanins for 24 h reduced invasion and migration by roughly 41% and 45%, respectively. [13] It was discovered that treatment with 200 g/mL black rice anthocyanins for 24 hours was likewise successful in lessening the cell invasion and migration of MDA-MB-453 cells. There was no statistically significant difference even though ACN administration (70 g C3G equivalent/mL) decreased the invasion process in MDA-MB-453 cells by 57.8%. However, the percentage of cells that entered the wound region was statistically reduced by the same extract to 44%. Isolated C-3-O-G was successful in lowering the processes of invasion and migration in MDA-MB-231 and MDA-MB-453 cells, in addition to the potential of anthocyanin-enriched extracts. [14] The downregulation of Akt expression in breast cancer cells has been linked to more anthocyanins found in fruits and vegetables. Anthocyanins from Vitis coignetiae Pulliat, for instance, were found to encourage the downregulation of Akt expression in MCF-7 breast cancer cells, according to a study. The study also showed that anthocyanins increased

cisplatin sensitivity by decreasing the activity of the genes Akt and NF-B in breast cancer cells that have an inherent resistance to treatment. Another study showed that treatment of breast cancer cells with delphinidin-3-glucoside, an anthocyanin typically present in pigmented fruits and vegetables, reduced Akt expression, which in turn led to a decrease in the expression of HOTAIR, an oncogene linked to the growth and metastasis of various cancers, including breast cancer. [15] According to studies, black rice anthocyanins decreased the adhesion, migration, and invasion of MDA-MB-453 human breast cancer cells that were HER-2 positive. The MDA-MB-453 cells' morphology was also considerably changed, switching from a mesenchymal to an epithelial phenotype. Western blot research showed that black rice anthocyanins changed the expression of the mesenchymal markers fibronectin and vimentin while increasing the expression of the epithelial marker E-cadherin. These findings suggest that a significant portion of black rice anthocyanins' anti-metastatic actions come from their inhibition of EMT. The goal of the current investigation was to determine if FAK signalling contributes significantly to the metastasis of MDA-MB-453 cells by examining the adhesion, migration, invasion, and EMT state of cells pretreatment with Y15 using adhesion, wound healing, and Transwell assays. By interacting with the Y397 site, Y15 prevented FAK from being phosphorylated. The Y397 site on FAK is an autophosphorylation site that facilitates the binding of cSrc to FAK, which in turn triggers downstream signalling. A prior investigation found that Y15 slows the development of breast cancer. Y15 decreased the MDA-MB-453 cells' adhesion, migration, invasion, and EMT. [16]

4. Anthocyanin and colorectal cancer

The anthocyanin-enriched extract of BLACK RASPBERRY can inhibit cell growth, trigger apoptosis, lower DNMT1, and DNMT3B activity, and demethylate Wnt pathway proteins CDKN2A, SFRP2, SFRP5, and WIF1. The black raspberry anthocyanin extraction in the diet reduced tumour multiplicity in the AOM/DSS colon cancer mouse model, altered the composition of the commensal gut microbiota, and altered the inflammation index and methylation status of the SFRP2 gene. With an IC50 of 0.78 0.15 mM, the blueberry extract reduced the number of Caco-2 cells that proliferated. [17] Additionally, in HCT116 and HT-29 cells, the blueberry extract reduced cell growth and increased apoptosis. The blueberry anthocyanin extract demonstrated the most antiproliferation benefits when compared to phenolic acids, tannins, and flavonol components. In DLD-1 and COLO205 cells, the anthocyanin extract from China blueberries (Vaccinium uliginosum L) suppressed proliferation. In Caco-2 cells, the bilberry anthocyanin extracts showed antioxidative action with an IC50 of 0.53 0.04 mM. [18] In HT-19 cells, bilberry demonstrated an antiproliferative effect and the processes underlying elevated p21 expression. In the mouse colon cancer cell line MC38, bilberry anthocyanin extract produced mitochondrial damage, activated apoptosis, and reduced cell proliferation. By inhibiting the activity of topoisomerase I and DNA strand breaks, bilberry extract may lessen the negative effects of some chemotherapy medications. The several tumours and inflammation were reduced by the bilberry anthocyanin extract in the CRC animal model caused by AOM/DSS and IBD. The bilberry extract was found to lower total ACF, colonic cellular proliferation, and COX-2 mRNA expression in the AOM rat model. [19] In the AOM rat model, the chokeberry anthocyanin extract decreased the total number of ACF and colonic cellular proliferation and prevented the growth of HT-29 cells. Aronia meloncarpa E, a unique black chokeberry, showed antioxidant properties, suppressed cell

growth, encouraged cell phase arrest, and increased the expression of numerous genes involved in the cell cycle. [20] The antioxidant, antiproliferative, and anti-inflammatory properties of the blackberry anthocyanin extract were demonstrated in HT-29 and Caco-2 cells by reducing cell proliferation and the release of interleukin (IL)-12 by dendritic cells obtained from mouse bone marrow. Inhibiting cell development and inducing cell death, lingonberry, elderberry, black currant, and raspberry, and strawberry extracts all show anticancer effects in CRC cell lines. [21] Prunus spinosa drupes (blackthorn), for example, contain anthocyanin extract that has been shown to decrease colony formation, increase apoptosis in HCT-116 cells, and lessen tumour growth in xenograft mice. [22] The anthocyanin-rich grape extracts may suppress cell development and encourage apoptosis in HT-29 and CaCo-2 cells. By inhibiting the activity of topoisomerase I and DNA strand breaks, the grape extract may lessen the negative effects of some chemotherapy medications. The grape anthocyanin extract demonstrated the best antiproliferation benefits when compared to phenolic acids, tannins, and flavonol components. However, in a different investigation, the researchers discovered that the non-anthocyanin fraction showed superior anticancer activity. The grape extract decreased the overall burden of ACF and COX-2 mRNA expression in the AOM rat model. The grape pomace extract reduced AKT and Ki-67 expression, adenoma burden, and adenoma number in APCmin mice. [23] Anthocyanins, flavonoids, and their derivatives are all present in red wine, which also exhibits several intriguing biological effects. The S, G2, and M phases of HCT-15 cells may be blocked by the methanol extracts of red wine. Compared to the non-anthocyanin fractions, the anthocyanin fraction demonstrated greater efficiency. The lyophilized red wine extract inhibited cell proliferation in HCT-116 cells, increased the expression of the cell cycle regulators p53 and p21, induced an antioxidant response by triggering the nuclear factor erythroid 2-related factor 2 (Nrf2) transcriptional factors, and promoted differentiation via E-cadherin and the epithelial-mesenchymal transition (EMT) pathway. [24] When coupled with sulindac, an anthocyanin-rich tart cherry extract can reduce bodyweight loss and tumour burden in APCmin mice. In HT-29 cells, a polyphenol-rich extract from the Illawarra plum (Podocarpus elatus Endl.) inhibited cell growth, stopped S cell phase progression, enhanced apoptosis, and reduced telomerase activity and telomere length. [25] In HCT-116 cells, the anthocyanin extract from Java plum (Eugenia jambolana) increased the fraction of colon cancer stem cells while reducing cell proliferation and promoting death. A Podocarpus elatus Endl. extract high in polyphenols inhibited cell growth, stopped the S cell phase, enhanced apoptosis, and reduced telomerase activity and telomere length in HT-29 cells. The Java plum, Eugenia jambolana, and anthocyanin extract reduced cell proliferation boosted apoptosis, and increased the fraction of colon cancer stem cells in HCT-116 cells. [26] Vitis coignetiae Pulliat has long been used in traditional Korean medicine to treat cancer and inflammatory diseases. The amount of anthocyanin pigments are shown by the vivid dark red colour of Vitis coignetiae Pulliat. In HCT-116 and HT-29 cells, anthocyanins extracted from Meoru decreased cell viability, proliferation, motility, and invasiveness and triggered cell death. The anthocyanins extracted from Meoru dramatically reduced tumour growth in the HT-29 xenograft mice model. [27] A particular variety of sweet potatoes high in anthocyanins is purple-fleshed. In WiDr and SW480 cells, the anthocyanin extract from purple-fleshed sweet potatoes reduced the number of cells, prevented cell proliferation, and encouraged cell cycle arrest. Anthocyanin extraction in colon cancer stem cells decreased

WNT signalling, increased apoptosis, and decreased proliferation. Anthocyanin extraction lowered the frequency of ACF and cell proliferation while promoting apoptosis in the animal model of AOM-induced CRC. Apple, curly kale, Chinese aubergine, Pistacia atlantica sub kurdica, and purple-shoot tea anthocyanin extracts showed anticancer activity in cell lines or carcinogenic animal models. Cell proliferation suppression, apoptosis induction, cell migration inhibition, cell cycle arrest, DNA damage protection, and antioxidation are all linked to anticancer actions. [28]

5. Anthocyanin and liver cancer

Anthocyanin from Beile fruiti was linked to the suppression of the growth of the HCC cell line SMMC-7721, according to a study. It may stop the cell cycle at stage G2/M, causing DNA damage and apoptosis in SMMC-7721 cells. Additionally, it may boost antioxidase activity, lower lipid peroxidation levels, control immune cytokine levels, kill tumour cells, slow tumour growth, and increase the survival of mice with the H22 tumour. The ABL-2 family of L. caerulea 'Beilei' fruits contains the highest concentration of anti-tumor anthocyanins, with cyanidin-3-glucoside (42.91%) as its major anthocyanin. [29] The ability of a drug to treat tumours is influenced by tumour cell apoptosis as well as its ability to limit cell proliferation. Apoptosis is a biological process that is essential for many biological processes, including development, growth, and equilibrium in multicellular animals. It is a feature that has been conserved throughout evolution. Cell shrinkage, chromatin condensation, DNA fragmentation, membrane blebbing, and the development of an apoptotic body are among the molecular characteristics that may be used to identify it. The intrinsic mitochondrial pathway and the extrinsic death receptor pathway are now the two main pathways for apoptosis, and they can both be initiated by a variety of chemical, physical, and biological signals, including chemical reagents, free radicals, radiation, viral infection, etc. [30] The receptors, signalling pathways, and effectors that make up the cell cycle checkpoint undergo aberrant occurrences. G1/S, S, G2/M, and mid-late inspection points are among the primary inspection locations. Tumour cells frequently lack the G1 checkpoint and are inclined to hang around in the G2 phase after DNA damage. G2/M checkpoints are now a focus for cancer therapy as a result. On the one hand, tumour cells that have been kept in G2/M for a long time can slow the growth of the tumour. On the other hand, they lead to DNA damage accumulation and apoptosis in tumour cells, which has a curative effect on cancer. The findings demonstrate that ABL can successfully inhibit SMMC-7721 cells from entering the G2/M phase, damage DNA, and impede mitosis, which leads to apoptosis to have an anti-tumor effect. [31] Currently, the majority of therapeutic medicines function as anticancer agents by enhancing host immune response, inhibiting the development of tumour cells, and interrupting the cell cycle at a certain phase, consequently triggering cell apoptosis in vivo or in vitro. For instance, in vitro HepG2 cell apoptosis could be induced by maize peptides via the mitochondrial apoptosis pathway, and in H22 tumor-bearing mice, the host immune response might be improved. [32] By inhibiting the cellular signal transducer and activating transcription factor 3 (STAT3), both in vitro and in vivo, kurarinol caused HCC cells to die. As a result, it has been established that inducing apoptosis is a promising method for preventing and treating hepatocellular cancer. Recent research has demonstrated that anthocyanin can cause apoptosis in a variety of tumour cell types, preventing the growth of cancerous tumour cells. By causing the apoptosis of tumour cells, cyanidin-3-glucoside can successfully slow the growth of a range of malignant tumours; however, there was no overt harm toward

normal cells. This study supported the earlier findings by demonstrating that the primary component of ABL-2 was cyanidin-3-glucoside, which may cause SMMC-7721 cells to undergo apoptosis. [33]

6. Anthocyanins and lung cancer

Anthocyanins can be found in a variety of plant-based diets and/or medicinal plants, and they have anti-NSCLC properties. Anthocyanins from plant-based diets and medicinal plants may have anti-tumor effects with therapeutic potential in nicotine-induced NSCLC, although the probable molecular mechanisms by which they do so have not yet been fully understood. Several anti-nicotine-induced NSCLC effects, including anti-proliferative, anti-migration, anti-metastatic, anti-invasive, anti-angiogenic, and apoptosis/autophagy activation, have been seen following treatment with anthocyanins at different nontoxic doses. By improving the chemosensitivity and/or radiosensitivity of NSCLC cells, delphinidin, and cyanidin may increase apoptotic/autophagic activity. [34] By encouraging cell proliferation, migration, invasion, and angiogenesis, nicotine and/or NNK may aid in the growth of NSCLC. The stimulation of 7nAChR-mediated signalling pathways may result in such consequences. Anthocyanins have the potential to serve as 7nAChR selective agonists, inhibiting the activation of 7nAChR in NSCLC cells. Anthocyanins may directly bind to the 7nAChR, indicating that these substances may be effective in influencing a variety of signalling pathways and transcription/growth factors. [35] Given that it is implicated in the antiproliferative and apoptotic/autophagic effects against NSCLC cells, the -R enzyme responsible for the deglycosylation of anthocyanins in plant-based foods may have a significant therapeutic role in nicotine-induced NSCLC. Due to their anti-proliferative, anti-angiogenic, anti-migration, anti-invasive, anti-inflammation, anti-metastatic, and apoptosis/autophagy activities, plant-based foods and/or medicinal plants-derived PCs and anthocyanins may be therapeutically effective as anti-NSCLC medicinal agents in smokers; however, more research is required to fully understand the underlying mechanisms. [36]

7. Anthocyanins and prostate cancer

The antiproliferative effects of plant extracts from the flowers and fruits of Opuntia ficus Indica, also known as black rice, as well as their combined effects on the proliferation of BPH-1 cells, which are the epithelial cells of benign prostatic hypertrophy, LNCaP cells, which are androgen-dependent tumoral prostatic cells, and DU145 cells, which are androgen-resistant tumoral prostatic cells. With a geometric mean of 70% and 80% cell viability, respectively, the flower extract of O. ficus Indica (10 g/mL) and the extract of black rice (100 g/mL) were each able to cause a decrease in the cellular vitality of the BPH-1, LNCaP, and DU145 cell lines. The use of two extracts in combination (210 g/mL) on identical cell lines resulted in a statistically significant reduction in cellular vitality (geometric mean of about 36%) compared to the use of the individual extracts. [37] Until the main chemical was obtained, the rice bran fraction that was richer in ACNs was isolated and processed. Using immunohistochemical staining and immunoblotting techniques, the isolate cyanidin 3-O-glucoside (C3G) and the sub-fraction of rice bran were examined against PC3. On PC3 cells, the extract and the purified substance both demonstrated cell viability with an IC50 value of 168 M. By inhibiting tumour transformation, C3G decreased the expression of Smad/Snail signalling molecules at 100 M and increased the expression of E-cadherin as a cell surface protein. In addition to decreasing the levels of nuclear factor kappa B (NF-B) expression and the activity of the enzyme in PC3 cells, this ACN was also able to inhibit MMP-9, which slowed the process of cell invasion and

migration. [38] In a study, the effects of muscadine grape skin extract on the prostate (LNCaP, ARCaP-E) and breast (MCF-7) cancer cells that overexpress snail transcription factors were examined. It has been shown that snail overexpression boosted pSTAT-3, cathepsin L expression/activity, and invasion and migration. At concentrations of 5 g/mL and 20 g/mL, muscadine grape skin extract reduced snail overexpression, which resulted in less cell invasion and migration. [39] By adjusting the expression of cell cycle regulators, researchers were able to confirm the American cranberry's ability to pause the cell cycle. The proportion of cells in the G2/M phase was reduced and the proportion of cells in the G1 phase was enhanced when DU145 was treated for 6 hours with cranberry extract at 25 and 50 mg/mL. According to a molecular investigation, the extract raised the expression of p27 while decreasing the expression of CDK4, cyclin A, cyclin B1, cyclin D1, and cyclin E. Additionally, p16INK4a expression levels were down and pRBp107 expression levels were up, even though the differences weren't statistically significant in comparison to the control. [40] Against prostate, (RWPE-1, RWPE-2, and 22Rv1) cancer cell lines, 200 g/mL of total cranberry extract and all fractions, including extract high in sugars, organic acids, and polyphenols, were tested in a different investigation. The strong efficacy of natural acids and polyphenols, including ACDs/ACNs in the extract, was confirmed by the crude extract and all fractions, except for the sugar-rich fraction, representing at least 50% anti-proliferative activity against prostate cancer cells. [41]

8. Anthocyanins and ovarian cancer

Berry bio-actives point to therapeutic and preventative effects against different cancer types. We looked at the ability of berry anthocyanidins (Anthos) to inhibit the growth of both drug-sensitive (A2780) and drug-resistant (A2780/CP70, OVCA432, and OVCA433) ovarian cancer cells. In comparison to A2780, these cisplatin-resistant ovarian cancer cell lines overexpress p-glycoproteins (PgP) and exhibit >100-fold resistance to the chemotherapeutic treatment. Anthos inhibits the development of ovarian cancer cells in a dose-dependent manner. Furthermore, cisplatin in conjunction with anthocyanin (75 M) dramatically increased cell death when applied to drug-resistant ovarian cancer (OVCA433) cells. [42] It took 10 to 15 times less cisplatin than the IC50 of cisplatin alone to have this effect. Anthos, like other plant bio-actives, struggle with poor oral bioavailability and stability. In comparison to Anthos alone and vehicle control, the exosomal Anthos (ExoAnthos) greatly improved the antiproliferative activity against the growth of ovarian cancer cells and more effectively reduced tumour growth. Patients with cisplatin-resistant tumours frequently nevertheless exhibit paclitaxel (PAC) sensitivity. Since systemic administration of PAC has serious side effects, exosomal versions of PAC (ExoPAC) are used for oral delivery. ExoPAC administered orally showed a therapeutic efficacy comparable to that of free PAC administered intraperitoneally. [43] In OVCA432 cells, the Anthos and PAC combination reduced the PgP level in a dose-dependent manner. ExoPAC and ExoAnthos together greatly increased the anticancer activity against A2780 tumour xenografts. For the treatment of ovarian cancer, the berry Anthos is very successful, and milk exosomes work well as a nano-carrier to increase the drug's oral bioavailability. [44]

9. Anthocyanin and skin cancer

Preliminary evidence for the extract's capacity to inhibit growth and promote differentiation in a melanoma cancer cell line was provided by a study that examined the antiproliferative activity of anthocyanin-rich strawberry extracts on the

B16-F10 murine melanoma cell line. The highly metastatic B16-F10 murine melanoma cell line was treated with the extract and numerous parameters of the melanoma cells were altered, demonstrating the anticancer actions. As a result, the research has unmistakably shown that the treated B16-F10 cells had significantly less cell growth than the control application (approximately 30% after 48 hours and by about 27% after 72 hours). Additionally, the strawberry extract caused no cell damage, and the toxicity level was less than 5% in the B16-F10 cell line, according to a Trypan Blue exclusion test. [45] Later, it was revealed that extracts from cell suspensions (strawberry, strawberry tree, blackberry, and red raspberry) had an anti-proliferative effect on murine melanoma cells. Cell proliferation was observed to be decreased by anthocyanin-containing extracts (between 30% and 38% less than the control). Another study looked into how delphinidin affected the growth of tumours. [46] The data from the in vitro experiment showed that delphinidin considerably reduced the growth of the melanoma-induced tumour, and endothelial cell proliferation was also reduced. Investigated was the effect of cyanidin-3-O-glucopyranoside (C-3-G) on the TVM-A12 human melanoma cell line. The nutrient C-3-G is found in large quantities in plants and is consumed. The study looked at how C-3-G affected melanin synthesis, cell proliferation, and shape. It has been demonstrated that C-3-G therapy affects cell proliferation and causes morphological differentiation. Additionally, melanosome maturation and melanin synthesis were improved. Another study used SKH-1 hairless mice to examine the photo-chemopreventive effects of delphinidin against UVB-induced indicators of skin cancer development. Delphinidin may shield cells from UVB-induced apoptosis, according to the study's findings that it can suppress UVB-mediated oxidative stress and minimise DNA damage. Anthocyanins from mulberries were looked into for their antimetastatic properties. [47] The information gained revealed that mulberry anthocyanins have potent anticancer properties and prevented B16-F1 cells from spreading. These substances' antimetastatic effects were also discernible in a mouse model using C57BL/6 mice. Anthocyanins have strong antioxidant properties, but they are also quite vulnerable to the effects of the environment. Therefore, it was discovered that encasing anthocyanin in liposomes successfully stabilised these molecules. The development of melanoma in human A357 melanocytes was examined in a study to determine the inhibitory effects of liposome-encapsulated anthocyanin (LCA), which was extracted from Hibiscus sabadariffa Linn. The study showed that anthocyanin with liposome encapsulation boosted anthocyanin stabilisation and melanogenesis inhibition. [48] Anthocyanins have been found to have antiproliferative and proapoptotic properties, according to numerous researches. Elderberries were recently used in a study to produce anthocyanin-enriched extracts (AEE), which were used to treat B16-F10 murine melanoma cells. Following the therapy, AEE boosted LDH activity and reduced cell growth in a concentration-dependent manner. Dual staining AO/EB and TUNEL assays were also used to confirm that AEE caused melanoma cells to undergo apoptosis. The results of this study show that the high anthocyanin concentration of elderberries makes their anthocyanin-derived compounds potentially useful in the treatment of skin cancer. [49] The high anthocyanin content of blueberries is well recognised and has been linked to several processes related to cancer. In a recent study, the B16-F10 melanoma cell line was used to examine the chemopreventive potential of blueberry anthocyanin extracts. Both anthocyanin and anthocyanidin extracts prevented the viability and growth of melanoma cells after the treatment. This study also

examined the cytotoxicity of anthocyanin extract from the same berries on murine melanoma cells and discovered that it was more harmful than anthocyanin extracts. At concentrations lower than 400 and 200 g/mL, both extracts prevented cell cycle progression at the G0/G1 phase. Through the use of flow cytometric analysis, the induction of apoptosis was discovered. According to the results, topical applications of anthocyanin and anthocyanidin extracts for the treatment of skin cancer are possible. It has been demonstrated that anthocyanins and their aglycones have several biological effects, including the ability to be anticarcinogenic to several cancer cell lines. In a study, liquid chromatography was used to examine the phytochemical composition of nine distinct fruit samples. The investigation concentrated on melanoma cell lines and the effects of specific chokeberry and red grape anthocyanin extracts. Both anthocyanins had a deleterious impact on the normal cells after treatment with the extract, but they had no adverse effects on cell proliferation, oxidative stress biomarkers, or mitochondrial membrane potential. The five different aglycones made the treatment more successful. To increase oxidative stress and decrease cancer cell proliferation, anthocyanins may be useful.

Conclusion

In conclusion, the research examined offers compelling evidence in favour of anthocyanins' ability to fight skin, ovarian, lung, liver, breast, and colorectal cancers, as well as other types of cancer. Anthocyanins have proven their ability to induce cell cycle arrest and apoptosis in a variety of cancer types. They have also shown inhibitory effects on cancer cell proliferation, invasion, and migration. Additionally, they have the potential to be potent therapeutic agents due to their modulation of important signalling pathways, control of oxidative stress and inflammation, and prevention of angiogenesis. These results point to the potential of anthocyanins as natural substances for the prevention and treatment of many malignancies, paving the way for further study and potential therapeutic uses. However, additional research is required.

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