Anthocyanins and Flavonols: Therapeutic Implications of Natural Compounds on Cancer

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Therapeutic Implications in ROS-Induced Cancer

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Contents

Abstract

Cancer stands among the main causes of death worldwide characterized by a combination of different factors which drive tumor progression and invasiveness. Oxidative stress has been shown to possess a central involvement in cancer development for promoting an imbalanced microenvironment, favoring DNA

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mutations and damage to biological structures. Flavonoids are naturally occurring compounds present in plant-based foods, mainly fruits and vegetables, which exhibit notable antioxidant and radical scavenging activities. Due to their biological activities and their availability in nature, anthocyanins and flavonols, one of the flavonoids subclasses, have been studied as potential anticarcinogenic agents. This chapter summarizes the main therapeutic implications of some of the most efficacious diet-derivate anthocyanidins and flavonols, and its glycosides, on cancer chemotherapy and chemoprevention.

Keywords

Flavonoids · Anthocyanidins · Glycosides · Cyanidin · Delphinidin · Quercetin · Kaempferol · Oxidative stress

Introduction

Flavonoids are naturally occurring phenolic compounds and ubiquitously present in the plant kingdom. This class of natural molecules is subdivided into flavones, flavonols, isoflavones, flavanones, flavan-3-ols, and anthocyanins. Plant-food flavonoids are known for their remarkable radical scavenging activities, which make them potential compounds for the use against many diseases (George et al. 2017).

Anthocyanins are molecules largely encountered in nature responsible for the blue (açai berry, bilberry, blueberry, eggplant, e.g.), purple (purple carrot, purple corn, e.g.), and red (raspeberry, red cabagge, red onion, red potato, red wine, e.g.) colors of foods. The range of reddish-purple color is attributed to cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin, which stand among the predominant anthocyanidins in food sources (Khoo et al. 2017).

Cyanidin, delphinidin, and their glycosides are the most common anthocyanin compounds found in the plant kingdom with well-understood biological functions including neuroprotective, anti-inflammatory, antioxidant, antimicrobial, antidiabetic, antiobesity, and anticancer properties (Khoo et al. 2017; Lee et al. 2017; Chen et al. 2019).

Quercetin and kaempferol are examples of often-studied dietary flavonoids, being representatives of the flavonols subclass. These molecules, widely present in the human diet, have displayed antioxidant, neuroprotective, anti-inflammatory, and anticancer activity in many *in vitro* and *in vivo* studies (George et al. 2017; D'Andrea 2015; Kashyap et al. 2017).

Cancer is a multifactorial disease characterized by the uncontrolled growth of cells, evading of antiproliferative signals, angiogenesis, invading of surrounding tissues, among others; inflammation and genome instability have been presented as underlying hallmarks that promote tumor development and progression (Hanahan and Weinberg 2011). A large body of evidence has shown that especially inflammation and oxidative stress, mainly by the action of reactive oxygen species (ROS) and inflammatory molecules, trigger damage to important biomolecules and consequently to the cell, and thus possess a close link to tumor formation, driving a healthy cell to a tumor cell (Reuter et al. 2010).

Taking into consideration the healthy benefits of anthocyanins and flavonols, several studies are investigating the potential of these molecules against cancer development (George et al. 2017; Khoo et al. 2017; Chen et al. 2019). In this scenario, this chapter presents some insights on the role *in vitro* and *in vivo* of anthocyanidins, especially cyanidin, delphinidin, and their glycosides, and flavonols, quercetin and kaempferol, on cancer.

Anthocyanins and Anthocyanidins: General Overview

Anthocyanins are pigments soluble in water which provide blue, red, and purple colors to fruits, vegetables, and beverages (e.g., blueberry, cherry, cranberry, eggplant, red cabbage, and red wine, among others) (Khoo et al. 2017). Approximately 700 structurally different anthocyanins have been identified in nature. The aglycone form, called anthocyanidin, which is less frequent in nature, has approximately 30 identified molecules. Among them, six anthocyanidins are usually encountered in food sources: cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin. Meanwhile, anthocyanins are defined as glycosylated anthocyanidins with one or more sugar, and frequently present glucose, galactose, and arabinose in their chemical structure (Khoo et al. 2017; Rodriguez-Amaya 2019).

The table below (Table 1) shows some examples of food sources of anthocyanins and anthocyanidins, and their major molecules.

Literature data has reported that anthocyanins from berries are powerful anticarcinogenic agents mainly due to the protective capacity against genomic instability (Khoo et al. 2017).

In the study conducted by Hogan et al. (Hogan et al. 2010), the antioxidant properties and antiproliferative activity of an anthocyanin-rich açai berry extract *(Euterpe oleracea* Mart.) was investigated against MDA-468 human breast cancer cells and C-6 rat brain glioma cells. The principal anthocyanins identified in the extract were cyanidin-3-glucoside, cyanidin-3-rutinoside, delphinidin 3-(6″-acetoyl) glucoside, and peonidin-3-(6″-malonylglucoside). The açai extract presented effective antioxidant activities and antiproliferative capacity against C-6 brain glioma cells. Besides, DNA damage results suggested that the extract promotes apoptosis in these cells, indicating a correlation between this effect and the antiproliferative capacity.

Shi et al. (Shi et al. 2017) evaluated the anticarcinogenic impact of lyophilized black raspberries (BRB) *(Rubus occidentalis),* which contain anthocyanins as major phenolic components, mainly cyanidin-3-rutinoside, in esophageal squamous cells carcinogenesis in rats. The diet with 5% BRB significantly reduced the rate of esophageal cancer in rats treated with N-nitrosomethylbenzylamine (NMBA) when compared to rats treated with NMBA plus BRB (100% to 81.5%, respectively). Results showed that treatment with NMBA enhanced the levels of hydrogen peroxide (H_2O_2) and lipid hydroperoxide, decreased the expression and activity of glutathione peroxidase (GPx) and superoxide dismutase 2 (SOD2), and triggered the NFκB/MAPK signaling in rat esophagus. Overall, BRB treatment was shown to

Table 1 Anthocyanins and anthocyanidins composition of different fruits and vegetables

Source	Anthocyanins and anthocyanidins	Reference
Açai berry	Cyanidin-3-glucoside, cyanidin-3-rutinoside, and peonidin-3-rutinoside	Hogan et al. (2010)
Purple carrot	Cyanidin-3-(xylosyl)(coumaroyl)glucoside-galactoside, cyanidin-3-(xylosyl)(feruloyl)glucoside-galactoside, cyanidin-3-(xylosyl)(sinapoyl)glucoside-galactoside, and cyanidin-3-(xylosyl)glucoside-galactoside	Montilla et al. (2011), Li et al. (2012)
Red potato	Pelargonidin, pelargonidin-3-(feruloyl)-rutinoside-5-glucoside, pelargonidin-3-rutinoside, pelargonidin-3-rutinoside-5-glucoside, and peonidin-3-(p-coumaroyl)-rutinoside-5-glucoside	Li et al. (2012), Ieri et al. (2011)
Red onion	Cyanidin-3-(6″-malonyl)glucopyranoside, cyanidin-3,5-diglucosides, cyanidin-3-glucosides, and delphinidin-3,5-diglucosides	Zhang et al. (2016a)
Eggplant	Cyanidin-3-rutinoside, delphinidin-3-rutinoside, delphinidin-3-rutinoside-5-glucoside, malvidin-3-rutinoside-5-glucoside, and petunidin-3-rutinoside	Ferarsa et al. (2018)
Blueberry	Cyanidin, cyanidin-3-glucoside, delphinidin, delphinidin 3-arabinoside, delphinidin 3-galactoside, malvidin, malvidin 3-arabinoside, petunidin, and petunidin-3-arabinoside	Li et al. (2016)
Bilberry	Cyanidin-3-O-galactoside, cyanidin-3-O-glucoside, delphinidin-3-O-arabinoside, delphinidin-3-O-galactoside, delphinidin-3-O-glucoside, malvidin-3-O-glucoside, and petunidin-3-O-glucoside	Benvenuti et al. (2018)

reverse oxidative stress and suppress NFκB/MAPK pathways, and these effects were suggested to promote the chemopreventive activity of BRB in esophageal cancer.

Bornsek et al. (Bornsek et al. 2012) tested the cellular antioxidant action of blueberries *(Vaccinium corymbosum* L.) crude extract and bilberries *(Vaccinium myrtillus* L.) crude and purified extract in human colon cancer (Caco-2), human endothelial (EA.hy926), human hepatocarcinoma (HepG2), and rat vascular smooth muscle (A7r5) cells. The anthocyanins represented the majority of all phenolics in both extracts. While cyanidin and delphinidin glycosides were the main anthocyanins in the bilberry extracts, malvidin glycosides were more recurrent in the blueberry extract. Data showed that bilberry and blueberry anthocyanins have potent intracellular antioxidant properties at very small concentrations, however, the antioxidant activity of the bilberry extract was greater when compared to the blueberry extract.

In a recent study performed by Léon-González et al. (León-González et al. 2018), an anthocyanin-rich bilberry extract was able to promote apoptosis in acute lymphoblastic leukemia cells by diminishing the expression levels of Polycomb Group proteins (PcG), and, thus, the following PcG proteins-dependent pro-survival events via a redox-dependent process, after 24 h of exposition.

An investigation performed with anthocyanins from roselle *(Hibiscus sabdariffa* L.) reported antileukemic action in a rat model of chemical-induced leukemia.

Animals were allocated into four groups: control, nitrosomethylurea (NMU), and roselle anthocyanin extract orally supplemented in the diet at 0.1% and 0.2% plus NMU treatment. The results displayed that the administration of anthocyanin extract from roselle (0.2%) orally given to rats significantly suppressed the progression of NMU-induced leukemia by 33.3% (Tsai et al. 2014).

Besides the conventional sources such as fruits, pigment-rich root vegetables are powerful sources of phytochemical antioxidants, notably anthocyanins. Zhang et al. (Zhang et al. 2016b) investigated the antioxidant and anti-inflammatory activity of purple carrots and potato extracts in H_2O_2-exposed Caco-2 cells. These anthocyanin-rich phenolic extracts, mainly in cyanidin and petunidin, besides presenting strong antioxidant actions by direct radical scavenging activity, also stimulated the expression of antioxidant enzymes such as catalase (CAT) and GPx, and reduced the production of pro-inflammatory interleukins mediated by H_2O_2 in Caco-2 cells at low doses (50–100 μg/mL). Results indicate that anthocyanin-rich purple types of potatoes and carrots could improve oxidative stress by intestinal inflammatory responses.

The proliferation inhibitory potential of anthocyanin-rich extracts of cereals was also reported by Mazewski et al. (Mazewski et al. 2017) that analyzed the antiproliferative action of anthocyanin-rich purple and red corn on human colorectal cancer cells (HT-29 and HCT-116). Both extracts increased apoptosis and suppressed angiogenesis.

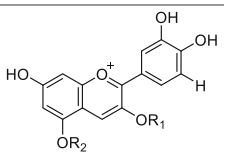
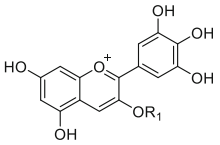
In a recent work performed by Mazewski et al. (Mazewski et al. 2018), the antiproliferative consequence of 11 anthocyanin-rich extracts: black and purple bean, black lentil, black peanut, black rice, blue wheat, purple carrot, purple sweet potato, red and purple grape, and sorghum was tested against human colon cells. The extracts decreased expression of antiapoptotic proteins, induced apoptosis, and promoted cell cycle arrest at the G1 phase. The black lentil, red grape, and sorghum extract inhibited HCT-116 and HT-29 cell proliferation at concentrations of 0.9–2.0 mg/mL (IC50).

Anthocyanins and anthocyanidins act attenuating oxidative stress and inflammation as cellular mechanisms of inhibiting carcinogenesis (Khoo et al. 2017), especially anthocyanins which display more effective anticancer activity than anthocyanidins (Zhou et al. 2018). Among the anthocyanins that have a substantial key role in cancer development are delphinidin, cyanidin and their glycosides, which exhibit potent antioxidant, anti-inflammatory, and anticancer properties (Khoo et al. 2017; Mazewski et al. 2017; Mazewski et al. 2018).

Cyanidin and Cyanidin-3-O-Glicoside

Cyanidins and their glycosides are one of the main groups of anthocyanins that occur naturally, being considered one of the most abundant in the plant kingdom (Khoo et al. 2017). They are compounds with well-understood biological properties, being widely researched mainly for their antioxidant and anti-inflammatory properties. Cyanidin rarely occurs in nature, on the other hand, its glycosides (Table 2) are

Table 2 Names, molecular characteristics, and chemical structures of cyanidin, delphinidin and their O-glycosides

Name	Abbr.	Substitution pattern		Structure
		R_1	R2	
Cyanidin and its O-glycosides[a]				
Cyanidin	C	H	H	
Cyanidin-3-5-O-diglucoside	CDG	Glucose	Glucose	
Cyanidin-3-O-arabinoside	CA	Arabinose	H	
Cyanidin-3-O-galactoside	CGA	Galactose	H	
Cyanidin-3-O-glucoside	CG	Glucose	H	
Cyanidin-3-O-rutinoside	CR	Rutinose	H	
Delphinidin and its O-glycosides[b]				
Delphinidin	D	H	–	
Delphinidin-3-O-arabinoside	DA	Arabinose	–	
Delphinidin-3-O-galactoside	DGA	Galactose	–	
Delphinidin-3-O-glucoside	DG	Glucose	–	
Delphinidin-3-O-rutinoside	DR	Rutinose	–	
Delphinidin-3-O-sambubioside	DS	Sambubiose	–	

[a]Adapted from Cyboran-Mikolajczyk et al. (Cyboran-Mikolajczyk et al. 2019)
[b]Adapted from Chen et al. (Chen et al. 2019)

widely found in the plant kingdom, among these glycosides is cyanidin-3-glucoside (CG) (Liu et al. 2018; Cyboran-Mikolajczyk et al. 2019).

Cyboran-Mikolajczyk et al. (Cyboran-Mikolajczyk et al. 2019), when analyzing the significance of O-glycosylation on the interplay of cyanidin with red blood cells and human microvascular endothelial cells (HMEC-1), reported that the bioactive properties of cyanidin and its glycosides relies on the type and number of sugar substituents and differs according to the cell type and extracellular milieu. Furthermore, the results showed that the compounds did not present cytotoxicity, not induced apoptosis or altered the promotion of the cell cycle in HMEC-1 cells. In addition, despite the compounds having altered the shape of red blood cells, they did not impair their transmembrane potential, also protecting erythrocytes against free radicals and reducing the generation of ROS (Cyboran-Mikolajczyk et al. 2019).

Hosseini et al. (Hosseini et al. 2017) analyzed the cytotoxic and apoptotic effect of CG on the U87 glioblastoma cell line at different concentrations showing that treatment with 40 μg/mL of the compound caused the apoptosis of 32% of the cells after 24 h. More recently, Liu et al. (Liu et al. 2018) conducted a study to investigate the effects of cyanidin at different concentrations on the proliferation, invasion, cell cycle, and apoptosis *in vitro* using renal cell carcinoma lines (786-O and ACHN). Data reported that cyanidin inhibited cell proliferation and migration in a wide range of concentrations, significantly reducing tumorigenesis independent of the concentration. In addition, cyanidin promoted cell apoptosis in treated cells (786-O and ACHN) and induced cell cycle arrest. Furthermore, protocols were also carried out *in vivo* injecting mice with the suspension of ACHN cells and administering cyanidin at the dose of 6 mg/Kg two times a week. After 4 weeks, tumors were

collected and evaluated, and results showed that the mice treated with cyanidin significantly reduced tumor growth.

In another study performed by Takeuchi et al. (Takeuchi et al. 2011), cyanidin diminished the intracellular levels of ROS in several cell cancer lines such as MCF-7, Huh-7, HepG2, and Caco2, also inhibiting the proliferation of these cells. However, while cyanidin suppressed the growth of cells, CG did not. In the same way, peonidin, peonidin-3-glucoside, and cyanidin-3-rutinoside (CR) were also tested, though the glycosylated structure inhibited the biological effects.

Delphinidin and Delphinidin-3-O-Glucoside

Delphinidin, one of the major anthocyanidins found in plants, and its glycosides, have displayed several health benefits, especially antioxidant and anti-inflammatory properties (Lee et al. 2017; Chen et al. 2019). Research has also presented that these compounds have anticarcinogenic activities. The chemical structure of delphinidin affects its stability and bioavailability and the addition of distinct sugar substituents originates different delphinidin glycosides, as shown in Table 2 (Chen et al. 2019).

Anthocyanins have been shown to mediate apoptosis in various cancer cells, including non-small-cell lung cancer (NSCLC) (Pal et al. 2013) and colon cancer cells (Shin et al. 2009). Delphinidin was shown to suppress the expression of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor 2 (VEGFR2) in NSCLC cells. The effects of this molecule *in vitro* and *in vivo* on NSCLC cells and in athymic nude mice, respectively, were investigated. Data showed that delphinidin significantly inhibited cell growth *in vitro* without harmful effects on healthy human bronchial epithelial cells. In nude mice, treatment with the compound suppressed tumor growth, inducing apoptosis, and decreasing angiogenesis and markers of cell proliferation compared to control animals (Pal et al. 2013). In human colon cancer cells (HCT-116), anthocyanins isolated from *Vitis coignetiae* Pulliat were proposed to regulate apoptosis proteins by stimulating p38-MAPK and inhibiting Akt proteins (Shin et al. 2009).

In another study, the outcome of different anthocyanins was tested *in vitro* on the viability of human fibrosarcoma HT1080 cells. Results showed that at the concentration of 100 μM, delphinidin-3-glucoside (DG) significantly decreased cell viability, whereas other anthocyanins (3-glucosides of malvidin, cyanidin, pelargonidin, and peonidin) did not affect this parameter; also, DG only presented a 20% decrease in the viability of normal fibroblast cells (NIH 3T3) (Filipiak et al. 2014).

Recent investigation performed *in vivo* using NMU as a model to induce breast carcinogenesis in rats suggested that delphinidin might possibly inhibit breast tumor formation and present its anticancer effects by modulating the HOTAIR/miR-34a axis (Han et al. 2019).

Another recent work addressed the effect on cell viability of DG and delphinidin on human colorectal cancer cells (HT-29 and HCT-116). Overall, results demonstrated that DG and delphinidin promoted apoptosis and inhibited colorectal cancer cell survival according to the dose. Furthermore, DG also was shown to potentially

suppress immune checkpoints, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Overexpressed PD-L1 in cancer cells contributes to escape immune destruction, and its binding to PD-1 on T cells disables these cells to recognize and kill cancer cells. Therefore, these proteins are being used as targets for colon cancer treatment once inhibiting their expression could boost immune response in order to promote cancer cell death (Mazewski et al. 2019).

Thus, anthocyanins such as delphinidin and its glycosides appear to be effective in reducing oxidative stress and decreasing proinflammatory factors, as well as positively interfering with some cancers.

Flavonols: General Overview

Among flavonoids, flavonols are one of the most abundant classes in nature. Flavonols are present in considerable amounts in the human diet, through edible portions of many food plants, leafy vegetables, tubers and bulbs, several fruits, tea, and wine (Perez-Vizcaino and Duarte 2010). Flavonols show a broad range of biological actions: antioxidant, neuroprotective, anti-inflammatory, and anticancer activity (George et al. 2017; Kashyap et al. 2017).

The main representant of the flavonol class is quercetin (Fig. 1B), which is the most abundant and most often studied dietary flavonol, found especially in glucoside forms. Another common flavonol is kaempferol (Fig. 1A), also present in many foods (Perez-Vizcaino and Duarte 2010).

Due to its availability in nature, presence in the human diet, and biological activities, quercetin and kaempferol are compounds of interest in research against cancer development.

Kaempferol

Kaempferol (Fig. 1A) is a flavonol, belonging to the large group of flavonoids, found in several species of plants around the world. Some examples of food sources that contain this compound are: garlic, chives, broccoli, mustard, turnip, grapefruit,

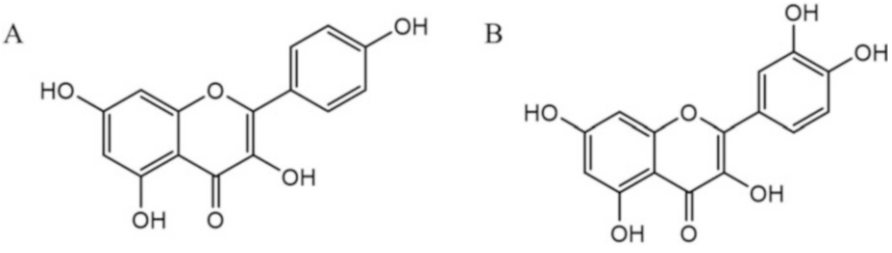


Fig. 1 Chemical structure of the main flavonols: kaempferol (**A**) and quercetin (**B**)

cucumber, strawberry, sweet potato, lettuce, apple, peach, spinach, tomatoes, grape, raspberry, aloe vera, capers, and saffron, among others (Calderón-Montaño et al. 2011).

The interest in the kaempferol compound has increased due to its antioxidant, cardio- and neuroprotective, and anti-inflammatory activities, demonstrated in many *in vitro* and *in vivo* studies (Kashyap et al. 2017). Regarding kaempferol antitumor activity, several investigations have addressed and highlighted possible mechanisms of this compound through cellular and *in vivo* models (Imran et al. 2019).

For example, in the case of breast cancer, kaempferol anticancer activity was explored in the cell cycle of MCF-7 cancer cells and verified to inhibit cyclins D and E in the G1 phase, possibly by suppressing estrogen activity (Kim et al. 2016). Another study showed that kaempferol triggered apoptosis of human cervical cancer (HeLa) cells by positively regulating pro-apoptotic genes such as TP53, P21, caspase 3, caspase 9, Bax, and PTEN and negative modulation of survival genes, including AKT, Bcl-2, and PI3K (Kashafi et al. 2017).

Han et al. (Han et al. 2018), studying pulmonary adenocarcinoma (A549 cells) found that kaempferol reduced cell viability and proliferation, while inducing autophagy and apoptosis. Additionally, the compound also upregulated PTEN expression besides inactivating the PI3K/AKT pathway. Besides, in another study, Heo et al. (Heo et al. 2018) investigated kaempferol in melanoma cells (A375SM) and verified the inhibition of the Bcl-2 protein and the stimulus of the pro-apoptotic protein Bax, the activation of the P21 gene expression, promoting the arrest of the cell cycle and cell progression at the G1 phase by inhibiting cyclin B and E. In addition, cells treated with kaempferol increased the generation of ROS, which may contribute to apoptosis and suppress cell growth in melanoma cells.

Quercetin

Quercetin (Fig. 1B) is a polyphenolic flavonoid that possesses antioxidant properties and is usually found in several fruits and vegetables, including green vegetables, berries, green tea, citrus fruits, legumes, onions, and parsley (Hashemzaei et al. 2017). Researches have shown several health benefits of quercetin such as improvement of endothelial function, antihypertensive, antioxidant, antithrombotic, anti-inflammatory, anti-obesity, and anticancer activity (D'Andrea 2015). Due to its wide distribution in nature, quercetin is a flavonol with potential as an anticancer agent against several cancer types and by being a further candidate for anticancer drug design.

An investigation addressed the action of natural products such as quercetin and green tea on the efficacy of inoculated androgen-independent prostate PC-3 cancer cells in mice. Results showed that quercetin and green tea in combination with docetaxel (Doc) increased its efficacy and considerably decreased tumor progression.

Also, blood concentrations of growth factors, such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) were found decreased after the intervention by the mixture of quercetin, green tea, and Doc (Wang et al. 2016a).

Zhao and coworkers investigated the action of quercetin against HepG2 human liver cancer cells. Results showed that quercetin was able to trigger apoptosis in these cells which was followed by the decrease in fatty acid synthase (FASN) activity. In this sense, suggesting that apoptosis may be triggered by quercetin via the suppression of FASN and that this compound could help to prevent human liver cancer (Zhao et al. 2014).

The effect of quercetin has been also investigated against colorectal lung metastasis. In a study conducted both *in vitro* and *in vivo,* quercetin suppressed the viability of colon 26 (CT26) and colon 38 (MC38) cells. Besides, it triggered apoptosis by regulating the MAPKs pathway in CT26 cells and also suppressed the migration and invasion abilities of these cells by the modulation of tissue inhibitor of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs) expression. Quercetin also reduced lung metastasis of CT26 cells in a mouse model. This result suggested that this compound was able to suppress the ability of CT26 cells to metastasize and it also inhibited lung metastasis *in vivo* (Kee et al. 2016). In the case of cervical cancer, research showed that quercetin could inhibit the viability and proliferation of HeLa cells by promoting apoptosis through a p53-dependent mechanism and also inducing G2/M phase cell cycle arrest (Priyadarsini et al. 2010; Wang et al. 2016b).

Quercetin has been also indicated to enhance the chemosensitivity of breast cancer cells (MCF-7) to the chemotherapeutic drug doxorubicin (Dox) and the mechanism has been suggested to be through enhanced cell apoptosis, suppression of cell invasion and proliferation, downregulation of p-Akt expression, and upregulation of PTEN expression (Li et al. 2015). Besides, in another study using human breast cancer cell lines (MCF-7 and MDA-MB-231), quercetin showed inhibitory effects on cell proliferation, suppressed invasion by the downregulation of the epidermal growth factor receptor (EGFR) expression, promoted apoptosis by caspase-3 activation, and an upregulation in the miR-146a expression (Tao et al. 2015).

Balakrishnan et al. (Balakrishnan et al. 2016) investigated the antitumor potential of a gold nanoparticle-conjugated quercetin system against breast cancer cells and also in an induced mammary carcinoma in rats. Results showed that the combination of quercetin and gold nanoparticles suppressed invasion and migration of MDA-MB and MCF-7 cells and formation of blood vessels using *in vivo* and *in vitro* angiogenesis assays. Besides, the combination inhibited tumor growth in the rat model. Overall, findings indicated that the conjugation of quercetin with gold nanoparticles was able to inhibit metastasis and angiogenesis of breast cancer cells.

Figure 2 summarizes some biological effects and central mechanisms by which anthocyanins and flavonols, presented in this chapter, demonstrate their anticancer properties acting at stages of carcinogenesis, such as angiogenesis, metastasis, migration, inhibition of the cell cycle phases, and promoting apoptosis.

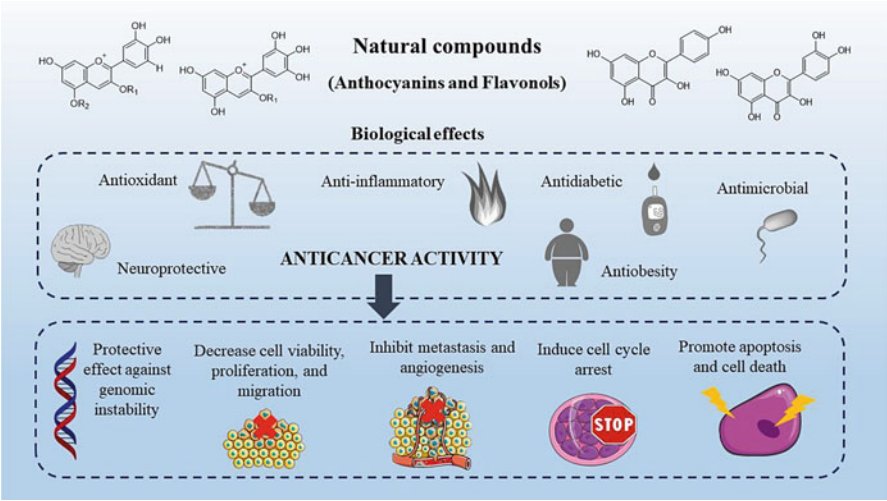


Fig. 2 Overview of some of the biological activities and general anticancer mechanisms of action induced by the anthocyanins and flavonols discussed in this chapter

Conclusion

In summary, literature data using *in vitro* cellular models and *in vivo* protocols provides evidence on the anticancer properties of anthocyanins and flavonols, showing that some of the main underlying mechanisms of action are related to the antiproliferative activity, apoptosis induction, suppression of angiogenesis and migration, and improvement of oxidative stress. Furthermore, these molecules did not show or showed reduced negative effects on healthy cellular models. Therefore, isolated anthocyanins and flavonols or derived from extracts could potentially be used as chemopreventive or adjuvant agents in cancer treatment.

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Conflict of Interest None.

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