Anthocyanins are a class of water-soluble flavonoids, which show a range of pharmacological effects, such as prevention of cardiovascular disease, obesity control and antitumour activity. Their potential antitumour effects are reported to be based on a wide variety of biological activities including antioxidant; anti-inflammation; anti-mutagenesis; induction of differentiation; inhibiting proliferation by modulating signal transduction pathways, inducing cell cycle arrest and stimulating apoptosis or autophagy of cancer cells; anti-invasion; anti-metastasis; reversing drug resistance of cancer cells and increasing their sensitivity to chemotherapy. In this review, the latest progress on the anticancer activities of anthocyanins and the underlying molecular mechanisms is summarized using data from basic research in vitro and in vivo, from clinical trials and taking into account theory and practice.

Abbreviations
ABC, ATP-binding cassette; AP-1, activator protein-1; APC, adenomatous polyposis coli; ARE, antioxidant response element; Atg5, autophagy-related gene 5; BCRP, breast cancer resistance protein; cAMP, cyclic AMP; C-3-G, cyanidin-3-glucoside; Cy-g, cyanidin-3-O-β-glucopyranoside; FDGP, freeze-dried grape powder; HCC, hepatocellular carcinoma cells; iNOS, inducible NO synthase; 3-MA, 3-methyladenine; MEK, MAPK/ERK kinase; 8-OHdG, 8-hydroxydeoxyguanosine; P-gp, P-glycoprotein; PMBE, Pinus massoniana bark extract; RTK, receptor TK; siRNA, small interfering RNA; TG, Thapsigargin; TPA, 12-O-tetradecanoylphorbol-13-acetate; YGM-3, 3-(6,6′-caffeylferulylsophoroside)-5-glucoside of cyanidin; YGM-6, 3-(6,6′-caffeylferulylsophoroside)-5-glucoside of peonidin
Introduction

Anthocyanins exist widely in plants and are the most abundant flavonoids. Anthocyanins are responsible for the varied colours of flowers and fruit that change with the change of seasons and are cell vacuole components. For example, strawberries, grapes, apples, purple cauliflower and corn can present a red, blue or purple colour respectively (Cooper-Driver, 2001). To date, the number of reported types of anthocyanins exceeds 500, and these different anthocyanins can be detected in 27 families and 72 genera of plants (Sarma et al., 1997). Research since the 1980s has mainly focused on their extraction (Pace et al., 2014; Carbonaro et al., 2015), isolation (Correa-Betanzo et al., 2014), purification and absorption (McGhie and Walton, 2007), metabolism (Jian and Giusti, 2010), bioavailability (Fernandes et al., 2014), pharmacokinetics (Kay, 2006; Semaming et al., 2015) and their analytical techniques (Welch et al., 2008). On the basis of studies in cell lines from the gastrointestinal tract, such as the intestines (Li et al., 2011), oesophageal, stomach, colorectal, liver, breast, cervical and prostate cancers (Bowen-Forbes et al., 2010; Rugina et al., 2012; Hafidh et al., 2013; Jin et al., 2013; Li et al., 2014; Bishayee et al., 2016), animal models (Jiang et al., 2014) and human clinical trials (https://clinicaltrials.gov), anthocyanins have antioxidant (He and Giusti, 2010), bacteriostatic, anti-inflammation, anti-ageing and anticancer functions (Bagchi et al., 2004; Cui and Li, 2014; Chen et al., 2016b). They can be applied for the prevention of cardiovascular disease (Alvarez-Suarez et al., 2014; Cerletti et al., 2016), obesity control (Wu et al., 2013), the alleviation of diabetes (Li et al., 2015a) and cancer therapy (Bobe et al., 2006). Here, we summarize briefly the possible antitumour or anticancer roles of anthocyanins in the different stages of tumourigenesis and carcinogenesis, highlighting their sources, structural characteristics and health effects, and focusing on their pharmacological aspects in the prevention and treatment of cancer in vitro and in vivo.

The chemical structure and characteristics of anthocyanins

Anthocyanin is the common name for a class of flavonoids that are easily dissolved in water. Their basic structural unit is 2-phenylchromenylium (flavylium) (Figure 1) (Hou et al., 2004; Jing and Giusti, 2010). They exist in natural products, mainly in a form combined with glucose, galactose and rhamnose (Liu et al., 2010), and can be divided into at least six common types, such as pelargonidin, cyanidin, delphinidin, peonidin, petunidin and malvidin, according to the different substituent groups on the flavylium B-ring (Holton and Cornish, 1995). The research has indicated that the ortho-dihydroxyphenyl structure on the B-ring is the active site that inhibits tumour growth and metastasis (Hou et al., 2004; Xu et al., 2010). In recent years, because of increased health consciousness (Pascual-Teresa, 2014), people have paid close attention to anthocyanins' roles in...
tumour prevention and cancer therapy because of their extensive sources, low cytotoxicity and safe consumption. This review summarizes the related experimental and clinical data at the cellular and molecular levels in vitro and in clinic trails in vivo, analyses the existing critical questions and provides directions for further research.

The anti-carcinogenic activities of anthocyanins in the initial stage of tumourigenesis

Antioxidant

Anthocyanins can act on the antioxidant system (Bowen-Forbes et al., 2010; Li et al., 2015a), where they scavenge free radicals, thereby reducing damage to the genome of normal cells by oxidative stress and the subsequent malignant transformation by gene mutation, thus preventing the occurrence of tumours (Shih et al., 2007; Yi et al., 2010). Yi et al. (2010) found that the antioxidant effect of anthocyanins is determined by the 3', 4', 5' hydroxyl on the B-ring and the 3' hydroxyl on the C-ring. Shih et al. (2007) and Thoppil et al. (2012) found that anthocyanins (cyanidin, delphinidin and malvidin) could act on antioxidant response element (ARE) through the Keap1-Nrf2 pathway and inhibit the activity of cysteinyl aspartate specific proteinase-3 (caspase-3) by regulating the expression of phase II antioxidants (glutathione reductase, glutathione peroxidase, glutathione transferase and quinone oxidoreductase), thus playing a role in antioxidant protection. In short, it is the promotion of the expressions of ARE-regulated phase II enzymes by anthocyanins that defend normal cells against oxidative stress.

Anti-inflammation

Chronic inflammation is often a harbinger of a tumour. The abnormal overexpression and secretion of inflammatory factors are critical to tumourigenesis. It is reported that anthocyanins can control the expression and secretion of inflammatory factors by inhibiting the transcription factor NF-κB, through multiple pathways to exert their anti-inflammatory function (Estopido et al., 2014; Peiffer et al., 2014). For example, cyanidin-3-glucoside (C-3-G), delphinidin-3-glucoside and petunidin-3-glucoside inhibit the activation of NF-κB induced by external stimuli (e.g. LPS or IFN-γ) by acting on the PI3K/PKB and MAPK pathways (Afaq et al., 2005; Limtrakul et al., 2015) and can inhibit the expression of COX-2 and inducible NO synthase (iNOS), as well as the production of their products PGE2 and NO (Haseeb et al., 2013; Jeong et al., 2013; Peiffer et al., 2014). Miyake et al. (2012) and Burton et al. (2015) found that anthocyanins could also block the activation of STAT3 and inhibit the expression of NF-κB.

Anti-mutagenesis

During the transformation of normal cells towards cancer cells, somatic cell hypermutation can lead to instability of the genome and cause cancer (Martincorena and Campbell, 2015). Yoshimoto et al. (1999) used four different kinds of sweet potato root as experimental materials to investigate their anti-mutation effect and found that Salmonella typhimurium TA98 presented reverse mutation under the action of a heterocyclic mutagen, while adding four different kinds of sweet potato root, whose main ingredients are 3-(6,6'-caffeoylferuloylsophoroside)-5-glucoside of cyanidin (YGM-3) and 3-(6,6'-caffeoylferuloylsophoroside)-5-glucoside of peonidin (YGM-6), could inhibit the reverse mutation of TA98 in a dose-dependent manner. Thus, it was concluded that YGM-3 and YGM-6 could inhibit the reverse mutation of normal cells induced by a mutagen. Oxidative stress from free radical abnormalities can lead to DNA injury and mutation of related genes – oncogenes and anti-oncogenes – resulting in carcinogenesis and finally causing cancer. Therefore, anthocyanins with antioxidant properties may protect human cells from malignant mutation from extreme levels of ROS and free radicals by inhibiting point mutations, thereby exerting their anti-mutagenesis effects in human somatic cells.

The anti-carcinogenic activities of anthocyanins in the cancer formation stage

Differentiation induction

Differentiation induction is a phenomenon whereby malignant cells differentiate towards normal and mature cells under the effect of differentiation inducers. A large number of malignant cells undergo mitosis, and these cells are poorly differentiated (Charepalli et al., 2015; Thwe et al., 2016). Anthocyanins can induce terminal differentiation of tumour cells and block tumourigenesis. Through detecting the markers and kinase inhibitors in the cell differentiation process, Fimognari et al. (2004) found that cyanidin-3-O-β-glucopyranoside (Cyg) could induce the differentiation of human acute promyelocytic leukaemia cell line HL-60 in a dose-dependent way by activating PI3K and PKC. Under treatment by Cy-g (200 mg·mL⁻¹), HL-60 cells presented differentiation characteristics, such as increased adhesion and enhanced activity of esterase, and the expression of oncogene c-Myc was decreased. However, following treatment by PI3K and PKC inhibitors, the effect of Cy-g to induce the differentiation of HL-60 was significantly reduced. Serafini et al. (2004) found that Cy-g could induce the differentiation of melanoma cell line TVM-A12 by up-regulating cAMP levels, and the expressions of tyrosinase and the differentiation marker MART-1. Liu-Smith and Meyskens recently validated Cy-g’s effects on the induction of melanoma cell differentiation (Liu-Smith and Meyskens, 2016). To some extent, the degree of differentiation determines the degree of tumour malignancy, and anthocyanins might play roles in the cancer formation stage by inducing differentiation, further determining the size of final tumour and its malignancy.

Inhibiting cellular transformation

Cellular transformation is one of the mechanisms underlying tumourigenesis. Some carcinogens, such as 12-O-tetradecanoylphorbol-13-acetate (TPA) and EGF, can induce the transformation of various cell lines through the transcription factors AP-1 and NF-κB in the Raf-MEK-ERK and PI3K/Akt pathways (Burton et al., 2015). Limtrakul et al. (2015)
found that black rice whole grain extracts might suppress LPS-induced inflammation via inhibition of the MAPK signalling pathway, leading to decreased NF-κB and AP-1 translocation. In addition, inflammation also has an important relationship with cellular transformation, and high expression of COX-2 and PGE2 can enhance the tumorigenic effect (Hou et al., 2004). Anthocyanins can act on Ras-ERK and PI3K/Akt pathways by decreasing the expression of AP-1 and thus inhibit the cellular transformation. Hou et al. (2004, 2005) found that delphinidin, cyanidin and petunidin could inhibit the transformation of mouse skin cell line JB6P+ induced by TPA. Kang et al. (2008) found that delphinidin could bind with Raf1 or MEK1 in an ATP-non-competitive way to inhibit the expression of AP-1 and NF-κB in JB6P+ cells treated with TPA and further inhibition the expression of COX-2 and the production of PGE2. In addition, delphinidin could also weaken the TPA-induced cellular transformation through the Ras/Raf/MEK/ERK pathway by regulating the phosphorylation level of MEK, ERK, ribosomal protein S6 kinase and mitogen stress activator protein kinase. Early experiments demonstrated that this effect is associated with the antioxidant ability of anthocyanins to scavenge superoxide radicals (Hou et al., 2004). Recently, Song et al. (2012) found that the 1,1-diphenyl-2-picrylhydrazyl radical 2,2-diphenyl-1-(2,4,6-trinitrophényl) hydrazyl and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt of cyanidin and C-3-G showed no significant difference in their free radical scavenging abilities; however, their abilities to inhibit cellular transformation are significantly different: cyanidin has a strong ability to inhibit transformation, while C-3-G has hardly any ability to inhibit transformation, which suggested that the effect of cyanidin to inhibit transformation is not associated with its antioxidant ability. Cyanidin can directly combine with PI3K in an ATP-competitive way to inhibit the expression of AP-1 and NF-κB through the PI3K/Akt/p70S6 pathway and inhibits the cellular transformation of JB6P+ cells by treatment with EGF.

**Inhibiting cell proliferation**

A significant characteristic of cancer cells is their uncontrollable cell cycle, which leads to continuous division and proliferation (Lee et al., 2010; Li et al., 2016a). Anthocyanins can selectively inhibit the proliferation of cancer cells but have little influence on the proliferation of normal cells (Malik et al., 2003). The main manifestations of anthocyanins’ inhibition of the growth and proliferation of cancer cells are summarized below from three aspects.

**Inhibition of signalling pathways to block signal transduction**

Syed et al. (2008) found that delphinidin could inhibit the hepatocyte growth factor-induced phosphorylation and activation of hepatocyte growth factor receptors on human normal mammary cell line MCF-10 A and could block the Ras–ERK MAPK and PI3K/Akt pathways. Teller et al. (2009b) found that anthocyanins could also inhibit the autophosphorylation of receptor TKs (RTKs) extensively in cancer cells, and the inhibitory effect on oncogene ErbB3 was the most effective. Anthocyanins, especially malvidin, could inhibit the activity of PDE and the hydrolysis of cAMP effectively in human colon cancer HT29 cells and thus inhibit the MAPK signalling pathway (Marko et al., 2004). In short, anthocyanins can inhibit the growth and proliferation of cancer cells by inhibiting different kinase signalling pathways in vitro.

**Regulating the expression of anti-oncogenes and relevant proteins**

Malik et al. (2003) and Ha et al. (2015) found that in addition to up-regulating p53 in colon and prostate cancer cells to activate the DNA repair system, anthocyanins could also inhibit the transcription of p21 and p27. p21, a broad-spectrum inhibitor of cyclin-dependent kinases (CDKs), can combine with CDKs and inhibit their activity to induce the cell cycle arrest of cancer cells. Anwar et al. (2016) found that a standardized berry anthocyanin rich extract inhibited the proliferation of Caco-2 cells by up-regulating the expression of p21Waf/Cip1, arresting their cell cycle, and further inducing them to undergo apoptosis by caspase-3 activation. Meanwhile, anthocyanins can also down-regulate the expressions of CDK-1 and CDK-2, inhibit the expressions of cyclin-B, cyclin-A and cyclin-E, promote the expressions of CDK inhibitors (CDKIs) and induce cancer cells to arrest at the G0/G1 and G2/M stages (Chen et al., 2005). Thus, anthocyanins can inhibit cancer cell proliferation mainly by arresting the cell cycle at different division phases via up-regulating the expressions of anti-oncogenes and down-regulating the expressions of oncogenes, accompanied by the expressions of different cyclins and their partners CDKs and/or CDKIs.

**Other signalling pathways**

Kausar et al. (2012) found that berry anthocyanidins could act on the β-catenin, Wnt and Notch pathways, as well as their downstream target proteins, to inhibit the growth and proliferation of human non-small-cell lung cancer cells synergistically.

Overall, tumours and cancer are referred to as signal pathway diseases, and this concept helps researchers to broaden their research and develop safer, targeted chemopreventive and/or chemotherapeutic treatments, including anthocyanins and other natural products.

**The anti-carcinogenic activities of anthocyanins in the cancer development stage**

**Inducing apoptosis of tumour cells**

Malignantly transformed cells display uncontrollable growth, and their excessive proliferation leads to the formation of a tumour (Četojević-Simin et al., 2015). Apoptosis of tumour cells is inhibited; therefore, dying cells cannot be eliminated normally (Naomi et al., 2003). Anthocyanins can induce the apoptosis of cancer cells through the internal mitochondrial pathway and the external death receptor pathway (Figure 2).

**The death receptor pathway**

Huang et al. (2012) determined the phosphorylation levels of p38, p53, protein Fas and Fasl after treatment with the p38 inhibitor SB203580 and demonstrated that mulberry
Anthocyanin could induce the apoptosis of gastric cancer cells through the external receptor p38/Fas/FasL/Caspase-8 pathway. Chang et al. (2005) found that delphinidin could activate p38-FasL and the pro-apoptosis protein Bid pathway, thereby inducing the apoptosis of HL-60 cells in a time-dependent and dose-dependent manner.

The mitochondrial signalling pathway
Mitochondria-mediated apoptosis include the caspase-dependent and caspase-independent pathways.

Caspase-dependent pathway
Anthocyanins can act on proteins of the Bcl family and the inhibitor of apoptosis protein family to activate the apoptosis response through the caspase-dependent cascade (Shih et al., 2007; Lee et al., 2009; Charepalli et al., 2016).

Caspase-independent pathway
Anthocyanins extracted from potato could induce mitochondria to release endonuclease G and apoptosis-inducing factor through the JNK pathway to trigger caspase-independent apoptosis of prostate cancer LNCaP and PC-3 cell lines (Reddivari et al., 2007; Liu et al., 2016).

The endoplasmic reticulum signalling pathway
Yu et al. (2011) investigated the mechanism underlying the anti-apoptotic effects of freeze-dried grape powder (FDGP) on human hepatocarcinoma Huh7 cells. Pretreatment with FDGP could inhibit the thapsigargin (TG)-induced expression of binding immunoglobulin protein/glucose-regulated protein 78 and cytochrome c and increased the TG-reduced expression of PCNA and caspase-12. Caspase-7 can be transported to the endoplasmic reticulum (ER) to react with caspase-12 to induce the apoptosis of cancer cells. By contrast, the protein Bax is also abundant in the ER, and research has confirmed that anthocyanins can cause down-regulation or up-regulation of pro-apoptotic proteins, such as Bax and Bcl-2 homologous antagonist/killer (Bak) (Pal et al., 2013; Liu et al., 2016). Therefore, anthocyanins might achieve their functions via the ER signalling pathway.

The lysosome signalling pathway – cooperation with an autophagy inhibitor
Autophagy is a process whereby intracellular substances are degraded by the lysosome, which has a dual function in carcinogenesis: on the one hand, autophagy deficiency can promote malignant transformation and carcinogenesis; on the other hand, autophagy can restrict the necrosis and inflammation of a tumour, thereby relieving chromosome injury and the metabolic stress response in tumour cells. Anthocyanins can induce autophagy of cells in an autophagy-related protein 5 (encoded by Atg5)-dependent manner (Tsuyuki et al., 2012; Schiavano et al., 2015). Longo et al. (2008) found that after human hepatocellular
carcinoma (HCC) cell line PLC/PRF/5 was treated with anthocyanins, the expressions of downstream Bcl-2 family and rapamycin target proteins were down-regulated, while the expressions of eukaryotic initiation factor 2α and autophagy related gene LC3-II were up-regulated, which all suggested that anthocyanins can induce autophagy of human HCC cells. Using small interfering RNA (siRNA) to interfere to silence the Atg5 gene or using autophagy inhibitor 3-methyladenine (3-MA) to act on HCC cells treated with anthocyanins causes transfer of apoptin Bax into mitochondria, the release of cytochrome c and cleavage of caspase-3, leading to the apoptosis cascade response. Feng et al. (2010) found that cyanidin-3-rutinoside and delphinidin could not induce the apoptosis of HCC cells and could only cause growth retardation of cells via vacuolisation, which could be inhibited by the type III PI3K inhibitor 3-MA and proton pump inhibitors that blocked lysosome degradation. After using 3-MA and siRNA to interfere with autophagy marker LC3 and using delphinidin to treat human HCC SMMC7721 cells, delphinidin could induce autophagy of SMMC7721 cells. In addition, 3-MA and delphinidin acting together on SMMC7721 cells could lead to significant cell death.

Inhibiting angiogenesis of tumours

Tumour angiogenesis is a restrictive condition for the growth and metastasis of malignant tumours. The process of angiogenesis is controlled by many cytokines, of which the most important positive regulatory factor is VEGF. Therefore, inhibiting the receptor of angiogenesis VEGF receptor (VEGFR) could inhibit the metastasis of tumours effectively (Chen et al., 2015). Anthocyanins can inhibit RTK extensively, and the inhibitory effect on VEGFR-3 is especially significant (Teller et al., 2009a). Delphinidin and cyanidin could strongly inhibit the expression of VEGF in vascular smooth muscle cells induced by PDGF by blocking the p38-MAPK and JNK pathways (Oak et al., 2006). The inhibitory effect of delphinidin on angiogenesis is associated with not only VEGF inhibition but also inhibition of the PDGFR-β (Lamy et al., 2008). Delphinidin could inhibit PDGF induced phosphorylation of PDGFR-β in pulmonary artery smooth muscle cells in a time-dependent and dose-dependent manner, thus inhibiting VEGF-induced microvessel formation in HUVECs. Hypoxia is a general pathophysiological characteristic of solid tumours. It is likely to induce angiogenesis of the tumour, and this process is mainly completed via the VEGF signalling pathway, mediated by hypoxia inducible factor-1α (HIF-1α). Inhibiting the protein level of HIF-1α could lead to decreased transcription activity of HIF-1α target genes, including VEGF (Huang et al., 2011). Freeze-dried blackberry anthocyanins could reduce the expression of HIF-1α and VEGF in oesophageum tumour cells of F344 rats induced by N-nitrosomethylbenzylamine and thus inhibit angiogenesis of oesophageal tumours (Wang et al., 2009).

Inhibiting the invasion and metastasis of tumours

Invasion and metastasis are the two main aspects of cancer cells that threaten patients’ health and life. Cyanidin could inhibit effectively the invasion and metastasis of breast cancer cells (BT474, MDA-MB231 and MCF-7) with high expression of ErbB2 by blocking the ErbB2/cSrc/FAK pathway (Xu et al., 2010; Li et al., 2016a). Syed et al. (2008) found that delphinidin could reduce the membrane translocation of PKCa and the phosphorylation of STAT3 in MCF-10 A cell lines mediated by hepatocyte growth factor, inhibit the nuclear translocation of NF-κB/p65 and thus inhibit the invasion of cells. Invasion and metastasis involve three main processes: adhesion, degradation and movement. Anthocyanins can act on some adhesion molecules and proteolytic enzymes to inhibit the adhesion and degradation of cells (Zhu et al., 2008; Mauray et al., 2012).

Adhesion

Chen et al. (2011) found that delphinidin could reduce the expression of cell adhesion molecule-1 and P-selectin induced by oxidized LDL through the ROS/p38-MAPK/NF-κB pathway in a dose-dependent manner, thus inhibiting the adhesion of monocytes to endothelial cells.

Degradation

Undecyl phosphate adenosine (uPA) and MMPs are two key components for extracellular matrix degradation, which can promote the invasion of tumour cells and increase their migration ability. Anthocyanins can target uPA and MMPs and thus play a role in inhibiting tumour metastasis. Delphinidin could influence the expression of the uPA receptor and LDL receptor related protein, as well as the production of plasmin, by interfering with the clearance of uPA-plasmin activator inhibitor complex in malignant glioma U-87 cells, thus inhibiting the invasion of U-87 cells (Lamy et al., 2007). In MDA-MB-453 cells, the capacity for migration, adhesion, motility and invasion was inhibited by black rice anthocyanins in a concentration-dependent manner, accompanied by decreased activity of a transfer promoting factor, urokinase-type plasminogen activator (Luo et al., 2014). Ho et al. (2010) found that peonidin could reduce the expression of uPA in lung cancer cells by inhibiting the phosphorylation of ERK1/2 and thus inhibited the invasion of cancer cells. Delphinidin could target reduced nicotinamide adenine dinucleotide phosphate oxidase to inhibit the phosphorylation of MAPK-JNK1/2, MKK3/6-p38 and MEK-ERK1/2 and thus inhibit the expression of MMP-1 in human epidermal fibroblasts induced by UV-B radiation (Lim et al., 2013b). In addition, cyanidin and pelargonidin could inhibit the expression of MMP-2 and MMP-9 by inhibiting the PI3K/Akt pathway in cancer cells and thus reducing the invasion of cancer cells (Shin et al., 2011; Kuntz et al., 2015). A study also found that Vitis coignetiae anthocyanins could inhibit the expression of MMP-2 and MMP-9 through inhibiting the activation of NF-κB in cancer cells (Yun et al., 2010). In addition, it is reported that anthocyanins (including delphinidin-3-glucoside, cyaniding-3-glucoside and malvidin-3-glucoside) could inhibit the expression of the tight junction proteins, claudin-1 and claudin-3, by activating the p38-MAPK pathway in human colon cancer HCT-116 cells, thus inhibiting their invasion (Shin et al., 2011).
Reversal of multidrug resistance

Chemotherapy can inhibit proliferation or induce apoptosis of tumour cells by interfering with the DNA replication of tumour cells; however, multidrug resistance of tumour cells is a common reason for chemotherapy failure. A classical pathway for multidrug resistance of tumour cells is mediated by an ATP-binding cassette (ABC) transmembrane protein superfamily, which mainly includes P-glycoprotein (P-gp), multidrug resistance associated protein and breast cancer resistance protein (BCRP). The ABC superfamily is highly expressed in the pharmacological barrier. Therefore, targeting these proteins to reverse multidrug resistance could be used to assist chemotherapy to treat cancer. The anthocyanins have MWs low enough to penetrate the blood–brain barrier (Andres-Lacueva et al., 2005). A further study found that cyanidin could inhibit the expression of P-gp in human epidermal carcinoma KB-C2 cells that overexpressed P-gp (Kitagawa, 2006). Anthocyanins have high affinity for BCRP, and among the anthocyanins determined, seven kinds (malvidin, petunidin, malvidin-3-galactoside, malvidin, cyaniding-3-galactoside, peonidin-3-glucoside and C-3-G) were BCRP inhibitors and three kinds (malvidin, peonidin-3-glucoside and malvidin-3-diglucoside, cyanidin-3-rutinoside, malvidin-3-diglucoside, malvidin, pelargonidin, delphinidin, petunidin, delphinidin-3-glucoside, cyanidin-3-rutinoside, malvidin-3-glucoside, pelargonidin-3,5-diglucoside and malvidin-3-galactoside) were BCRP inhibitors and three kinds (malvidin, malvidin-3-galactoside and petunidin) demonstrated dual biological activity (Dreiseitel et al., 2009). In vitro, black rice anthocyanin could inhibit the activity of topoisomerase and the formation of topoisomerase-DNA complex in colon cancer HT29 cells (Esselen et al., 2011). All these results suggested that anthocyanins might function to change pharmacokinetics and reverse multidrug resistance.

Experiments performed in different models

Animal models

In a BALB/c nude mice model that received a transplant of human breast cancer cell line MDA-MB-453, growth of cancer and the formation of its blood vessels were clearly inhibited by oral delivery of an anthocyanin-rich extract from black rice (100 mg·kg\(^{-1}\) in the diet) (Chang et al., 2010). The study observed lower expressions of COX-2, iNOS and c-Jun, and angiogenic factors such as MMP-9, MMP-2 and uPA in tumour tissue (Chang et al., 2010). In a mouse model of adenomatous polyposis coli (APC) intestinal cancer, the number of mice that developed caecum cancer was reduced significantly (\(P < 0.05\)) (Lim et al., 2013a), compared with the control group, when they were fed with purple sweet potatoes rich in anthocyanins. Another mouse model of APC showed that mucosal expression of COX-2 and cPLA2 was significantly decreased in the 0.5% anthocyanin-rich extract group, by 32 and 62%, respectively, compared with the control group (Park et al., 2015). In a rat model of F344 colon cancer, the number of all tumours, which included glandular tumours and cancers, was reduced by 42, 45 and 71% compared with the control group, after a diet with 2.5, 5 and 10% freeze-dried powders from black raspberries, and the 8-hydroxydeoxyguanosine (8-OHdG) level in urine was reduced by 73, 81 and 83% respectively (Kocic et al., 2011). Treatment with Hibiscus anthocyanins (HAs) caused reduction in the levels of aspartate transaminase, alanine transaminase, uric acid and myeloperoxidase. In addition, the results showed that oral administration of HAs (0.2%) \(\times\) inhibited the progression of N-nitrosomethylurea-induced leukaemia by approximately 33.3% in rats (Tsai et al., 2014). Bishayee et al. (2011) tested the effects of black currant extract rich in anthocyanins on the prevention of liver cancer. Mice were fed with preventive anthocyanin for 4 weeks and fed for another 22 weeks after injecting diethylnitrosamine into the abdominal cavity to induce liver cancer. The result indicated that black currant anthocyanins could reduce the risk of abnormal proliferation before cancers formation, reduce the number of hyperplastic nodules and decrease in the sizes any nodules that did form. The effect was dose-dependent, which was confirmed by later pathological examinations.

Human research

Epidemiological studies have demonstrated that consumption of fruit and vegetables rich in polyphenols is associated with reduced risk of colorectal cancer, while a recent study conducted by Nimptsch et al. (2016) did not support the hypothesis that a higher habitual intake of any flavonoid subclass decreases the risk of colorectal cancer. Although epidemiological studies do not show a lower risk of most human cancers after taking anthocyanins, anthocyanin intake might reduce oxidative damage (Wang and Stoner, 2008). DNA oxidative damage decreased in human subjects who had drunk a juice rich in anthocyanins and showed significant increases in reduced glutathione, compared with the control group (Weisel et al., 2006). Recently, Cerletti et al. (2016) summarized the results of two EU-funded projects, which indicated that in breast cancer patients, moderate wine consumption may have a protective effect on skin toxicity induced by radiotherapy, attributing this effect to the possible antioxidant effect of the polyphenols contained in wine. In another study, the treatment group drank freeze-dried powders from black raspberries every day, and after 6 months, 8-iso-PGF\(_2\) and 8-OHdG levels were both decreased in their urine (Kresty et al., 2006). Urinary 8-OHdG is considered a marker of total DNA damage in humans, while 8-ISO-PGF\(_2\), a prostaglandin-like compound produced via COX-independent enzymes, is used as a marker of lipid peroxidation. Both 8-OHdG and 8-ISO-PGF\(_2\) are indicators of oxidative status in vivo (Kresty et al., 2006; Cocate et al., 2014). A randomized, placebo-controlled, double blind, monocentric evaluation, including 300 patients, is reported in Table S1 of Cerletti et al.’s report in 2016 (ClinicalTrials.gov ID: NCT0195960). This trial is ongoing and will be completed in the coming months (Cerletti et al., 2016).

Pharmacokinetics

Yang et al. (2011) summarized the bioavailability, pharmacokinetics and metabolism of anthocyanins in their published review. De Ferrars et al. (2014) identified 17 \(^{13}\)C-labelled compounds in serum, which are metabolized to a structurally diverse range of metabolites that exhibit dynamic kinetic profiles. Research on the metabolites suggested that
**Table 1**
Summary of the experimental data on the health effects of anthocyanins from cancer cell lines *in vitro* and from animal models *in vivo*

<table>
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<th>Anthocyanins</th>
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<td>Blackberry</td>
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<td>Synergistically or additively in producing</td>
<td>Anthocyanins and non-anthocyanin phenolics in anthocyanin-containing</td>
<td>Human colon cancer</td>
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<td>anticancer effects</td>
<td>blackberry extracts act synergistically or additively in producing</td>
<td>HT-29, breast cancer</td>
<td>(Dai et al., 2009)</td>
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<td>anticancer effects</td>
<td>MCF-7 and leukaemia</td>
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<td>Black currant</td>
<td></td>
<td>Up-regulation of Bax and down-regulation of</td>
<td>Mechanistic studies revealed that the anthocyanin-rich black currant</td>
<td>Rats treated with diethylnitrosamine and human liver cancer HepG2 cells</td>
<td>(Bishayee et al., 2011)</td>
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<td>Bax and down-regulation of Bcl-2 expression</td>
<td>extract-mediated pro-apoptotic signal during experimental hepatocarcinogenesis might be propagated via the up-regulation of Bax and down-regulation of Bcl-2 expression at the translational level</td>
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<td>Chokeberry</td>
<td></td>
<td>Antioxidant, anti-proliferative</td>
<td>Cyanidin glycosides inhibited HeLa human cervical tumour cell</td>
<td>Human colon cancer</td>
<td>(Rugina et al., 2012)</td>
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<td>proliferation and increased the generation of reactive oxygen species</td>
<td>HT-29 cells</td>
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<td>after 48 h of treatment, suggesting that they could be responsible for</td>
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<td>the anti-proliferative activity</td>
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<td>Tart cherry</td>
<td></td>
<td>Anti-inflammatory, anti-carcinogenesis</td>
<td>Mice that were fed anthocyanin-rich extract (at any dose) in combination</td>
<td>APC (Min) mice</td>
<td>(Bobe et al., 2006)</td>
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<thead>
<tr>
<th>Anthocyanins</th>
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<th>Laboratory model</th>
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<tbody>
<tr>
<td>Wild-grown berries</td>
<td>Induction of autophagy</td>
<td>Anthocyanin-induced autophagy switched to apoptosis, as shown by the activation of Bax, cytochrome c and caspase 3, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling-positive fragmented nuclei and cells with sub-G(1) DNA content, which were prevented by z-VAD</td>
<td>Human liver cancer PLC/PRF/Sand HepG2 cells</td>
<td>(Longo et al., 2008)</td>
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<tr>
<td>Black rice</td>
<td>Suppress metastasis</td>
<td>Black rice anthocyanins suppress metastasis in breast cancer cells by targeting the RAS/RAF/MAPK pathway</td>
<td>Human breast cancer cell lines MCF-10A and MCF-7</td>
<td>(Chen et al., 2015)</td>
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<td>Black rice whole grain</td>
<td>Anti-inflammation</td>
<td>Polar fraction of black rice whole grain extracts might suppress LPS-induced inflammation via the inhibition of the MAPK signalling pathway, leading to decrease of NF-kB and AP-1 translocation</td>
<td>RAW 264.7 macrophage cells</td>
<td>(Limtrakul et al., 2015)</td>
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<tr>
<td>Black currant</td>
<td>Antioxidant</td>
<td>Blackcurrant bioactive anthocyanins exert chemo-preventive actions against diethylnitrosamine-inflicted hepatocarcinogenesis by attenuating oxidative stress through activation of the Nrf2 signalling pathway</td>
<td>Rats</td>
<td>(Thoppil et al., 2012)</td>
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<td>Delphinidin</td>
<td>Grape</td>
<td>Block carcinogen-DNA adduct formation</td>
<td>Concord grape extract and a component grape anthocyanin have breast cancer chemo-preventive potential caused in part</td>
<td>Block carcinogen-DNA human breast epithelial MCF-10F cells treated with benzo[a]pyrene adduct formation</td>
<td>(Singletary et al., 2007)</td>
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<tr>
<td>Blueberry</td>
<td>Inhibit MMP-2 and MMP-9 proteolytic activity</td>
<td>Gallic acid inhibited MMP-2 and MMP-9 proteolytic activity with very similar potency. NMR and molecular modelling experiments confirmed the interaction of Gallic acid with MMP-2 and suggested that it takes place within the catalytic centre</td>
<td>Human fibrosarcoma HT1080 cells</td>
<td>(Filipiak et al., 2014)</td>
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<tr>
<td>Roselle</td>
<td>Antitumour</td>
<td>Treatment with HAs caused reduced levels of AST, ALT, uric acid and MPO. The results showed that oral administration of HAs (0.2%) remarkably inhibited progression of NMU-induced leukaemia by approximately 33.3% in rats</td>
<td>N-nitrosomethylurea-induced leukaemia in rats</td>
<td>(Tsai et al., 2014)</td>
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<tr>
<td>Muscadine grape skin Mediated invasion, migration and osteoclastogenesis</td>
<td>Snail regulation of CatL might occur via STAT3 signalling and can be antagonized by Muscadine grape skin extract, leading to decreased cell invasion, migration and bone turnover</td>
<td>LNCP prostate and MCF-7 breast human cancer cells</td>
<td>(Burton et al., 2015)</td>
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<tr>
<td>Malvidin Blueberry</td>
<td>Antioxidant, anti-proliferative, stimulate apoptosis</td>
<td>The ARF-T was shown to have the highest anthocyanin content and antioxidant activity and inhibited B16-F10 melanoma murine cells proliferation at concentrations higher than 500 μg·mL⁻¹. In addition, ARF-T stimulated apoptosis and increased</td>
<td>Mouse melanoma B16-F10 cells</td>
<td>(Bunea et al., 2013)</td>
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<tr>
<td>Blueberry</td>
<td>Increase apoptosis through DNA fragmentation and caspase-3 activity</td>
<td>total LDH activity in metastatic B16-F10 melanoma murine cells</td>
<td>Apoptosis was confirmed in HT-29 cells when treated with anthocyanins from blueberry cultivars at 50–150 μg·mL⁻¹ concentrations; however, these same concentrations decreased quinone reductase and glutathione-S-transferase activities rather than induced them</td>
<td>Human colon cancer HT-29 cells</td>
<td>(Srivastava et al., 2007)</td>
</tr>
<tr>
<td>Blackberry</td>
<td>Antioxidant, anti-proliferative and anti-inflammatory activities</td>
<td>The hydrolysed pulp and seed extracts showed significant antiproliferative activity. However, non-hydrolysed extracts showed much less activity</td>
<td></td>
<td>Human lung cancer A549 cells</td>
<td>(Aqil et al., 2012)</td>
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<tr>
<td>Bilberries and blueberries</td>
<td>Antioxidant</td>
<td>Anthocyanins had intracellular antioxidant activity if applied at very low concentrations (&lt;1 μg·L⁻¹; nM range), thereby providing a long-sought rationale for their health protecting effects in spite of their unfavourable pharmacokinetic properties</td>
<td></td>
<td>Human colon cancer (Caco-2), human hepatocarcinoma (HepG2), human endothelial (EA.hy926) and rat vascular smooth muscle (A7r5)</td>
<td>(Romsek et al., 2012)</td>
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<tr>
<td>Pelargonidin</td>
<td>Pomegranate</td>
<td>Antioxidant, antitumour and anti-inflammatory</td>
<td>Pomegranate fruit extract possesses anti-skin tumour-promoting effects in CD-1 mouse. Pomegranate fruit extract is capable of inhibiting conventional, as well as novel, biomarkers of TPA-induced tumour promotion; therefore, it may possess chemopreventive activity in a wide range of tumour models</td>
<td>TPA-induced skin tumour in CD-1 mice</td>
<td>(Afaq et al., 2005)</td>
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<td>Peonidin</td>
<td>Sweet potato P40</td>
<td>Antioxidant, anti-proliferative, induce cell-cycle arrest, apoptosis</td>
<td>Dietary P40 at 10–30% significantly suppressed azoxymethane-induced formation of aberrant crypt foci in the colons of CF-1 mice in conjunction with the inhibition of tumour-promoting effects</td>
<td>Human colonic SW480 cancer cells</td>
<td>(Lim et al., 2013a)</td>
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<td>Eugenia jambolana</td>
<td>Anti-proliferative, pro-apoptotic</td>
<td>with, at least in part, a lesser proliferative PCNA and a greater apoptotic caspase-3 expression in the colon mucosal epithelial cells</td>
<td>Java plum fruit extract anthocyanins suppressed ( (P &lt; 0.05) ) proliferation in HCT-116 cells and elevated ( (P &lt; 0.05) ) apoptosis in both HCT-116 cells and colon CSCs</td>
<td>HCT-116 colon cancer cell line and colon CSCs</td>
<td>(Charepalli et al., 2016)</td>
</tr>
<tr>
<td>Petunidin</td>
<td>Jamun, Blackberry</td>
<td>Antioxidant and anti-proliferative</td>
<td>The hydrolysed pulp and seed extracts showed significant anti-proliferative activity. However, non-hydrolysed extracts showed much less activity</td>
<td>Human lung cancer A549 cells.</td>
<td>(Aqil et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Blueberry</td>
<td>Antiproliferative, antioxidant, metastasis control</td>
<td>The ARF-T had the highest anthocyanin content and antioxidant activity and inhibited B16-F10 melanoma murine cells proliferation at concentrations higher than 500 ( \mu \text{g·mL}^{-1} ). In addition, ARF-T stimulated apoptosis and increased total LDH activity in metastatic B16-F10 melanoma murine cells</td>
<td>B16-F10 metastatic melanoma murine cells</td>
<td>(Bunea et al., 2013)</td>
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<td></td>
<td>Black soybean</td>
<td>Suppress oxidative stresses, decreasing inflammatory responses</td>
<td>Mucosal expression of COX-2 and cPLA2 were decreased significantly in the 0.5% AE group, by 32 and 62%, respectively, compared with the control group</td>
<td>APC (Min/+ ) mice</td>
<td>(Park et al., 2015)</td>
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AE, anthocyanin-rich extract; ALT, alanine transaminase; ARF-T, anthocyanin rich-fraction obtained from cultivar Torro; AST, aspartate transaminase; MPO, myeloperoxidase; NMU, N-nitroso-N-methylurea.
anthocyanins have longer enterohepatic recycling, which leads to prolonged residence time (Lila et al., 2016). Cerletti et al. (2016) also found three main metabolites in urine, namely, delphinidin-3-glucoside, C-3-G and cyanidin-3-(6-malonylglucoside), reached a plateau level after the first week of ingestion of red orange juice. These compounds were considered markers of anthocyanin bioavailability in subsequent human studies. The peak plasma concentration of the four anthocyanins in black raspberries could be detected 2 h after taking oral black raspberries, whose elimination fits first-order kinetics (Stoner et al., 2005). Four to eight hours after taking black raspberries, the anthocyanins are excreted through the urine in the form of complete anthocyanin or methyl derivatives. Experiments in vitro proved that anthocyanins in the range of $10^{-6}$ to $10^{-4}$ M could inhibit the growth of malignant tumours, regulate cell signal transduction and induce apoptosis (Cooke et al., 2005; Wang and Stoner, 2008). When anthocyanins are taken, their concentration can reach a level of $10^{-8}$ M to $10^{-7}$ M or it can be far lower than that in vivo to have an anticancer effect (Yang et al., 2011). The bioavailability of anthocyanins is very low (<1% in plasma); however, their presence in their native form has been described recently in colonic tissues of patients, suggesting they can directly interact with colonic tissues (Núñez-Sánchez et al., 2015). It remains unclear whether anthocyanins in experimental concentrations can play a role against cancer in the human body and whether they function as the original molecules or as metabolites.

In short, we have summarized the chemical structure of anthocyanins, their potential molecular mechanisms in tumour prevention and anticancer therapy, and the current research status of their pharmacological effects on both cell lines in vitro and animal model in vivo and in human clinical trials. Notably, their precursors, proanthocyanidins, share many of the same functions with anthocyanins. Proanthocyanidins are molecules polymerized with flavan-3-ols (Chen et al., 2016a) and are extracted from flowers, fruit, leaves and barks of many plants. Proanthocyanidins, especially proanthocyanidin B from Pinus massoniana bark extract (PMBE), can scavenge free radicals and has antioxidant (Cui et al., 2005b), anti-inflammation, antitumour and apoptosis induction and anti-invasion effects at the cellular level in vitro (Cui et al., 2005a; Li et al., 2015b, 2016b) and in a mouse model in vivo (Li et al., 2007; Zhang et al., 2012). Animal experiments by Li et al. (2007) showed that Pinus koraiensis bark procyanidins extract has antitumour activity against U12 cervical cancer mice. Treatment with 100, 200 and 300 mg·kg⁻¹ PMBE reduced the tumour weight and volume of S180-bearing NIH mice by 9–67% and 13–68%, respectively (Zhang et al., 2012). In human trials, according to the No.NCT00100893 (https://clinicaltrials.gov), IF636 grape seed extract, which is rich in proanthocyanidins, has been used in a phase I clinical trial to study its side effects and the best dose to prevent breast cancer in postmenopausal women (40–75 years old) at risk of developing breast cancer.

**Conclusions**

The anticancer effect of anthocyanins differs according to the different substituents on their B-rings. Anthocyanins with ortho-dihydroxyphenyl on their B-rings show the most obvious anticancer activity. Table 1 summarizes all the experimental data from cancer cell lines in vitro and animal models in vivo. Increasing evidence indicates that the main molecular mechanism of their antitumour effects lies in inhibiting the cancer cell growth and metastasis by targeting RTKs (EGFR, PDGFR and VEGF/VEGFR) by acting on Ras-MAPK and PI3K/Akt signal cascade pathways. At the initial stage, anthocyanin inhibits inflammation by acting on the PI3K/Akt and NF-κB pathway to suppress the expression of COX-2 and iNOS, thus preventing normal cells from transformation by regulating the expression of phase II antioxidant enzymes to achieve antioxidation through Nrf2/ARE signal system. During the formation phase, anthocyanins prevent carcinogenesis by targeting the MAPK pathway and AP-1 and by inhibiting RTK activity and its signal cascade pathway to regulate the expression of cancer-related genes, which leads to cell cycle arrest and DNA repair. At the development stage, anthocyanins induce apoptosis of cancer cells by activating caspase, mediated by ROS and JNK/p38-MAPK. In addition, anthocyanins inhibit cancer metastasis by targeting the VEGF signal pathway and extracellular matrix degradation. Furthermore, anthocyanins can reverse the multidrug resistance of cancer cells to improve their chemotherapy sensitivity. Figure 2 briefly summarizes the above related signal pathways.

Increasing in vitro experimental data have shown that anthocyanins can interfere with multiple signal pathways to exert their anticancer activities. However, it must be pointed out that most of these experiments were performed in vitro, and there is not necessarily an epidemiological connection between intake of anthocyanin and risk of carcinogenesis (Wang and Stoner, 2008). Data from animal models and in vitro and in vivo experiments indicated that anthocyanins have the potential to prevent and treat cancers; however, the metabolism of anthocyanins remains unclear. Considering that anthocyanins are rapidly metabolized into several active metabolites by the host and/or by gut microbiota and the evaluation of bioavailability of anthocyanins is complex (Núñez-Sánchez et al., 2015), more sensitive instruments and efficient methods should be developed to further this research. More clinical trials are required to validate the potential anticancer activities of anthocyanins before their wide clinical use. In addition, experiments show that their availability in the human body is lower than that in vivo (Cooke et al., 2005, Núñez-Sánchez et al., 2015). Therefore, improving the availability and the stability of anthocyanin in vivo represents another challenge to researchers. The latest review of preclinical and clinical evidence for the potential benefits of edible berries for human aerodigestive and gastrointestinal tract cancers indicated that the exact mechanisms of actions of phytochemicals (including anthocyanins) remain largely unexplained. These mechanisms include chronic inflammation and cancer; modulation of carcinogenesis; phytochemical interaction with vital proteins; signal pathways; and regulation of cancer cell proliferation, immortality and metastasis, and have attracted significant research attention (Bishayee et al., 2016). The mechanism of action of anthocyanins is summarized in Figure 2. Limited evidence from clinical data indicates that the use of anthocyanins can improve life quality (Bishayee et al., 2016) and might provide
a survival advantage in terminal care for cancer patients. However, further rigorous scientific investigation and more clinical proof are required.

Acknowledgements

This work was supported by the University Students Innovation Training Program of Shanghai Municipal Government [grant number 201610247134 to HF Song] and the Yangfan Project of Tongji University School of Medicine [grant number 2012YF05 to YY Cui]. The authors thank the staff of the Key Laboratory of Arrhythmias, Ministry of Education (Tongji University) for their technical assistance. We also thank the editor and reviewers for their comments and suggestions, which have improved this review considerably.

Conflict of interest

The authors declare no conflicts of interest.

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Anthocyanins and prevention & treatment of cancer


Chen MH, McClung AM, Bergman CJ (2016a). Bran data of total flavonoid and total phenolic contents, oxygen radical absorbance capacity, and profiles of proanthocyanidins and whole grain physical traits of 32 red and purple rice varieties. Data Brief 8: 6–13.


