Chapter 11
Anthocyanins and Cancer Prevention

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Abstract Anthocyanins are a class of water-soluble flavonoids, which give the intense color to many fruits and vegetables, such as blueberries and red cabbages. Recent studies have shown that anthocyanins have a range of pharmacological properties, such as prevention of cardiovascular disease, improvement of visual functions, obesity control, and anticancer activity. Their potential anticancer effects are reported to be based on a wide variety of biological activities including anti-oxidative stress; anti-inflammation; anti-mutagenesis; induction of differentiation; inhibition of proliferation; cell cycle arrest and apoptosis; anti-invasion; anti-metastasis; anti-angiogenesis and sensitizing cancer cells to chemotherapy. This chapter summarizes the latest developments on the anticancer activities of anthocyanins and anthocyanin-rich extracts in cell culture models, animal cancer models and some clinical trials. Their chemical structures, molecular mechanisms of action in cancer prevention, and *in vivo* pharmacokinetics-pharmacodynamics (PK-PD) properties will also be discussed.

Keywords Anthocyanins · Anthocyanidins · Cyanidin · Delphinidin · Malvidin · Flavonoids · Cancer prevention · Nrf2-mediated antioxidative stress · Anti-inflammatory · Cellular signaling · Pharmacokinetics (PK)/pharmacodynamics (PD)

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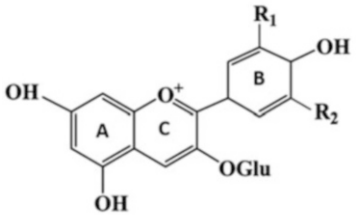
11.1 Introduction

Anthocyanins (from the Greek *Anthos* for flower and *kianos* for blue) are amongst the most utilized vegetable colorants in the food industry because of its water-soluble nature. They are extracted from grapes, berries, red cabbage, apples, radishes, tulips, roses and orchids. Its high dietary consumption makes it important to understand its potential biological effects on human health. The potential dietary intake of anthocyanin is among the greatest of the various classes of flavonoids (Wu et al. 2006). The potential health benefits of anthocyanin as dietary antioxidants, which help to prevent neuronal diseases, cardiovascular illnesses, diabetes, inflammation, and many other diseases including cancer (Prior and Wu 2006). Numerous anthocyanins have been identified from fruits and vegetables can interfere with several cell-signaling pathways to delay the progression of the disease.

In this chapter, we present the latest developments on research regarding potential cancer prevention mechanism of the anthocyanins, including *in vitro* cell culture and *in vivo* animal model at various organ sites, as well as data from human studies, including pharmacokinetics (PK)/pharmacodynamics (PD), bioavailability of anthocyanins. Although *in vitro* and *in vivo* animal studies using anthocyanins have provided convincing evidence about the modulation of various signaling pathways, much still needs to be done to advance the biomarker endpoints into possible human clinical trials.

11.2 Chemical Properties and Structures of Anthocyanins

Thousands of phytochemicals have been identified so far and the number is growing each day (Liu 2004). Flavonoids accounted for approximate 60% of phenolic compounds among all the phytochemicals. Anthocyanins are water-soluble polyphenolic pigments and secondary metabolites of plant products (Bunea et al. 2013). Anthocyanins are a type of flavonoid class of compounds which are found naturally in several foods that give red, purple, and blue plants their rich coloring. The anthocyanidins are the basic structures of the anthocyanins without the sugar moieties. The anthocyanidins (or aglycons) consist of an aromatic ring [A] bonded to an heterocyclic ring [C] that contains oxygen, which is also bonded by a carbon–carbon bond to a third aromatic ring [B] (Konczak and Zhang 2004). When the anthocyanidins are found in their glycoside form (bonded to a sugar moiety) they are known as anthocyanins. There is a huge variety of anthocyanins spread in nature; the most common anthocyanins are represented in Fig. 11.1. The main difference between them are the number of hydroxylated groups, the nature and the number of bonded sugars to their structure, the aliphatic or aromatic carboxylates bonded to the sugar in the molecule and the position of these bonds (Kong et al. 2003). The isolated anthocyanins are highly unstable molecules, susceptible to degradation. Their stability is affected by several factors such as pH, storage temperature, chemical structure, concentration,



Anthocyanins	R1	R2
Cyanidin	OH	H
Malvidin	OCH_3	OCH_3
Peonidin	OCH_3	H
Delphinidin	OH	OH
Pelargonidin	H	H
Petunidin	OCH_3	OH

Fig. 11.1 Structure of most common anthocyanins [adopted and modified from Tadesse et al. (2012)]

light, oxygen, solvents, the presence of enzymes, flavonoids, proteins and metallic ions. Cyanidin, delphinidin and malvidin are three major compounds of anthocyanidins and the content of these compounds have been found mainly in berries consumed in United States (blackberries, cherries and blueberries) (Khoo et al. 2017). The range of anthocyanidins is at the 30–120 mg per 100 g of fresh weight. Numerous studies have been conducted on anthocyanidins or anthocyanins and their anticancer, antibacterial and activity in scavenging free radicals will be discussed in the following sections.

11.3 Cancer Preventive Properties of Anthocyanins

11.3.1 In Vitro *Studies*

11.3.1.1 Anti-initiation Mechanism of Anthocyanins

Cellular metabolism plays a pivotal role in the process of initiation during carcinogenesis. Xenobiotic molecules entering the cellular environment are metabolized by metabolizing [phase I (functionalization) and phase II (conjugation)] xenobiotic metabolizing enzymes (XMEs), rendering them into water-soluble compounds to make it less reactive towards different biomolecules. Hence, these XMEs could be one of the potential targets for cancer chemoprevention by anthocyanins.

Anthocyanins have demonstrated multiple anti-carcinogenic effects such as: direct scavenging of reactive oxygen species (ROS), stimulating the expression of Phase II detoxification enzymes, reducing the formation of oxidative adducts in DNA by acting as blocking agents (Maru et al. 2016). The antioxidant potential of anthocyanins is governed by scavenging ROS such as superoxide, singlet oxygen, peroxide, hydrogen peroxide, and hydroxyl radical (Wang and Jiao 2000). Anthocyanins scavenge free radicals, thereby reducing damage to the genome of normal cells by oxidative stress and the subsequent malignant transformation by gene mutation, ultimately preventing tumor formation (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)

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 enzymes (glutathione reductase, glutathione peroxidase, glutathione transferase and quinone oxidoreductase), thus playing a role in antioxidant protection. Although most of the protective effects of anthocyanins are attributed to their ability to scavenge ROS, they also function by chelating metals and by direct binding to proteins (Kong et al. 2003). Although modulation of cytochrome P450 activity has been observed by constituents of fruit extracts including several flavonoids, anthocyanins happened to be one of the weak inhibitors of the CYPs isozymes including 3A4 (Dreiseitel et al. 2008), and CYP2C9, CYP2A6, CYP2B6 (Srovnalova et al. 2014).

The expression of phase II enzymes is governed by a cis-acting regulatory element named the anti-oxidant response element (ARE). ARE containing genes are regulated by nuclear factor erythroid 2-related factor 2 (Nfe2l2 or Nrf2), a member of the cap 'n' collar family basic-leucine-zipper family of transcription factors via ARE. The protective effect of pelargonidin have demonstrated to decrease oxidative stress in HepG2 cells by the activation of detoxification enzyme levels through Keap1/Nrf2 signaling pathway (Sharath Babu et al. 2017). Cyanidin-3-*O*-glucoside has protective effects through the inhibition of NF-κB signaling in Caco-2 cells by activated cellular protective responses modulated by Nrf2 (Ferrari et al. 2016). Shih et al. (2007) shows that anthocyanins induction of ARE-regulated phase II enzyme expression is crucial for protecting cells against oxidative stress-induced apoptosis.

11.3.1.2 Anti-promotion Mechanism of Anthocyanins

Chronic inflammation is often a harbinger in the process of tumorigenesis (Maru et al. 2016). 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 (Esposito 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 (Limtrakul et al. 2015) and can inhibit the expression of COX-2 and inducible NO synthase (iNOS), as well as the production of PGE2 and NO (Jeong et al. 2013). Treatment of JB-6 Cl 41 mouse epidermal cells with black raspberries anthocyanin resulted in down-regulation of benzopyrene diol-epoxide (BaPDE)-induced expression of NF-κB (Huang et al. 2002).

Tumor promotion involves the clonal expansion of initiated cells giving rise to tumor comprised pre-neoplastic cells. This stage is mainly characterized by two important cellular events, viz., cellular proliferation and apoptosis. Pure anthocyanins and anthocyanin-rich extracts from fruits and vegetables have exhibited anti-proliferative activity towards multiple cancer cell types *in vitro* including oral squamous cell carcinoma (Rodrigo et al. 2006), breast (MCF-7), colon (HT-29,

HCT116), and prostate (LNCaP) (Seeram et al. 2006). Interestingly, several investigations have compared the antiproliferative effects of anthocyanins on normal vs. cancer cells and found that they selectively inhibit the growth of cancer cells with relatively little or no effect on the growth of normal cells (Hakimuddin et al. 2004; Galvano et al. 2004). 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.

Extracts from blueberries, black currant, black chokeberries, apple, sea buckthorn, plum, lingonberries, cherries, and raspberries decreased the proliferation of both colon cancer HT29 cells and breast cancer MCF-7 cells and the effect was concentration dependent (Olsson et al. 2004). Cyanidin-3-*O*-glucoside was the most potent anthocyanin on kinase inhibition (Mazewski and Liang 2018). Standardized anthocyanin-rich extract demonstrated marked decreased Caco-2 cell proliferation, induced apoptosis by activating caspase-3 cleavage, and upregulated cyclin-dependent kinase inhibitor 1 (p21Waf/Cif1) expression in a dose-dependent manner (Anwar et al. 2016). Anthocyanin-rich grape and strawberry extracts and their generated metabolites such as hydroxyphenyl acetic acid showed apoptotic effects in HT-29 colon cancer cells (Lopez de Las Hazas et al. 2017).

Under normal conditions, cell proliferation is tightly regulated by proliferative signals. However, in transformed cells, they are over ridden to cause hyper proliferation under the influence of promotion signals. Promotion can be initiated by mitogenic stimuli like growth factors, oxidative stress, hormones, etc. Cyanidin and delphinidin have demonstrated to decrease EGFR kinase activity and phosphorylation of the transcription factor Elk-1 thereby inhibiting the activation of the GAL4-Elk-1 fusion protein in human vulva carcinoma cell line A431 (Meiers et al. 2001). Delphinidin inhibited VEGF-induced tyrosine phosphorylation of VEGFR-2, by attenuating VEGF-induced ERK phosphorylation in human umbilical vein endothelial cells (Lamy et al. 2006). Mouse skin epidermal (JB6 P+) cells can be inhibited by delphinidin at <40 μM concentration by suppressing Raf1 and MEK1 kinase activity and attenuation of (ERK), p90RSK, and MSK (Kang et al. 2008). Peonidin-3-glucoside inhibits the phospho-HER2, phospho-AKT and phopspho-p44/42MAPK levels and induces HER2-positive cells specific apoptosis (Liu et al. 2013). Malvidin-3-galactoside modulates regulation of cyclin D1, cyclin B, cyclin E, caspase-3, cleaved caspase-3, Bax, p-JNK, and p-P38. It also was demonstrated to activate phosphatase and tensin homolog deleted on chromosome ten (PTEN), accompanied by a decrease in the p-AKT level and lowering the protein expression of MMP-2 and MMP-9 in HepG2 cells (Wang et al. 2018). Overall, anthocyanins decreased carcinogen induced proliferation and induces apoptosis which have been closely linked to the modulation of the signaling kinases in the promotion phase of carcinogenesis.

11.3.1.3 Anti-progression Mechanism

Effect on Invasion and Metastasis

Tumor metastasis is one the most common causes of cancer death and various treatment strategies have targeted on preventing the occurrence of metastasis. 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 (Xia et al. 2009). Cyanidin 3-rutinoside and cyanidin 3-glucoside (extracted from *Morus alba L.*) exhibited a dose-dependent inhibitory effect on the migration and invasion, of highly metastatic A549 human lung carcinoma cells without any toxicity. It acts by decreasing the expressions of matrix matalloprotinase-2 (MMP-2) and urokinase-plasminogen activator (u-PA) in a dose-dependent manner and enhancing the expression of tissue inhibitor of matrix matalloprotinase-2 (TIMP-2) and plasminogen activator inhibitor (PAI) (Chen et al. 2006a). A similar effect was demonstrated by peonidin 3-glucoside and cyanidin 3-glucoside by modulating matrix metalloproteinase (MMP)-9 and urokinase-type plasminogen activator (u-PA) in SKHep-1 cells (Chen et al. 2006b) and lung cancer cells (Ho et al. 2010).

11.3.2 In Vivo *Studies*

Anthocyanins has shown to exert chemoprevention effect through an array of biological activities and signaling pathways *in vitro*. To translate to clinical research, the therapeutic efficacy, mechanism of action, and the metabolic processes are needed to be further examined in *in vivo* models. Anthocyanins isolated from diverse fruits and vegetables have been administrated to experimental animals mainly in the form of extracts or (lyophilized) powder. For delivery of the anthocyanins, diverse administrative routes were used including the oral route for esophageal, small intestine, and colon cancers, or the topical route for skin cancer models.

11.3.2.1 Gastro-intestinal Cancer

In the *N*-nitrosomethylbenzylamine (NMBA) induced esophageal cancer model, rats fed diets containing black/red raspberries, strawberries, blueberries, noni, and wolfberry demonstrated a significant reduction in multiplicity of esophageal squamous cell carcinoma by downregulation of serum cytokines (IL-5 and GRO/KC) (Stoner et al. 2007, 2010). Peiffer et al. (2016) demonstrated a novel mechanism linking the chemopreventive effect of anthocyanin rich berry powder, anthocyanins, and protocatechuic acid (metabolite of anthocyanin) to the innate immune system. The chemoprevention activity of 10% bilberry-extracted anthocyanin against colitis-associated cancers was examined by Lippert et al. (2017) in the azoxymethan

(AOM)/dextran sodium sulfate (DSS) model. The 10% anthocyanins diet significantly ($P < 0.004$) reversed the reduction of colon length (from 12.1 to 11.2 cm, average tumor number decreased by 89–91%) caused by inflammation. Lala et al. (2006) reported the chemopreventive potential of monomeric anthocyanin on the specific pathogen-free F344 male rats subcutaneously injected with AOM. Rats fed with diet containing anthocyanin from bilberry, chokeberry, or grape showed a significant reduction of AOM-mediated aberrant crypt foci by 26–29% compared with AOM only group; particularly, the aberrant crypt foci were mainly observed in the distal colon (Lala et al. 2006). Another colorectal carcinogenesis model were adopted by applying initiator, 1,2-dimethylhydrazine (DMH), and promoter, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (Hagiwara et al. 2001; Hagiwara et al. 2002). Male F344/DuCrj rats orally administered commercial anthocyanins from purple sweet potatoes, red cabbage and purple corn have presented suppression of average number of colon tumors (both benign and malignant) by 48, 63 and 89% compared with DMH/PhIP control group. In addition to chemopreventive effect of anthocyanins on colon cancers, several small intestinal cancer studies have also shown the chemopreventive effect. APCmin mice fed with anthocyanin-rich tart cherry extract with sulindac showed a significant decrease in total small intestine tumor number and total tumor area by 22 and 20% compared with mice fed sulindac alone (Bobe et al. 2006).

11.3.2.2 Skin Cancer

Razina et al. (2016) reported in 2016 the skin cancer prevention effect of anthocyanin extract isolated from mountain ash fruit (*Fructus Sorbi aucupariae*). Injected with melanoma B-16 intramuscularly as a model of metastatic melanoma, C57Bl/6 mice administered intragastrically with anthocyanin extract have shown the inhibition in the primary melanoma growth by 35% and decrease the incidence of metastases by 25%, by inhibiting cell proliferation. Afaq et al. (2007) reported a skin carcinogenesis model using UVB as the carcinogen in female SKH-1 hairless mice. Topical application (pretreatment or post-treatment) with delphinidin onto the dorsal skin decreased the apoptotic cell numbers in the epidermis and reversed the markers of DNA damage observed in skin biopsies from mice. Similar results were observed by using DMBA- and TPA-induced two-stage skin tumorigenesis model by inhibiting ornithine decarboxylase (ODC) activity and inhibiting phosphorylation of MAPKs proteins (ERK1/2, p38 and JNK1/2) (Afaq et al. 2005). More studies including mixed exposures will help to understand the detailed mechanism of anthocyanins in inhibition of skin carcinogenesis.

11.3.2.3 Breast Cancer

Liu et al. (2014) reported the chemopreventive efficacy of anthocyanin in a human breast carcinoma xenograft model was demonstrated by subcutaneous injection of

BT474 cells, with overexpressed human epidermal growth factors receptors 2 (HER-2) and estrogen receptors (ER) into the flank region of female nude mice. Anthocyanins have been shown to decrease Ki67 and HER2 expression in the xenograft as compared to control group. HER2-positive trastuzumab-resistant BT474 xenograft were studied using female nude mice by i.p. administration of peonidin-3-glucoside. It was demonstrated that tumor volume was reduced by 88% by decreasing HER2 and Ki67 expression (Li et al. 2016). The chemopreventive effect of anthocyanin-rich extract from black rice was reported against skin cancer by injecting HER2 overexpressed MDA-MB-453 cells subcutaneously into the right axilla of female BALB/c nude mice reversing the tumor growth mediated by VEGF (Hui et al. 2010). The possible mechanism was interpreted by decreased expression of nuclear antigen Ki67, angiogenesis factors (MMP9, MMP-2, and uPA). In another study using MDA-MB-453 xenografts model on BALB/c nude mice fed with distilled water containing commercial anthocyanins have shown a significant reduction in tumor volumes and tumor weight and a significant inhibition of Ki67 positive tumor cells (Luo et al. 2014). However, more studies using breast cancer *in vivo* models and various study parameters will help to assess the chemoprevention effect and the mechanism of action of anthocyanins in breast cancers.

11.3.2.4 Lung Cancer

Cyanidin-3-glucoside (C3G) from blackberry has been shown to suppress lung tumor growth by 50% and inhibit tumor metastasis in A549 xenograft as a human lung carcinoma model (Ding et al. 2006). In another study, C57BL/6 male mice implanted with Lewis lung carcinoma cells administered orally with cyanidin-3-glucoside (C3G) or peonidine-3-glucoside (P3G)-rich anthocyanins extracted from black rice by oral gavage significantly reduced tumor volume by 52% (Chen et al. 2005). Aqil et al. (2016) also showed the chemopreventive efficacy of anthocyanins (glycones of delphinidin, cyanidin, malvidin, peonidin and petunidin) suppressed tumor volume by 42% against lung cancer xenografts using A549 and H1299. The therapeutic effects of the anthocyanins against lung cancer reported in these independent studies are promising. However, additional examination into the mechanism of action of anthocyanin or anthocyanin/polyphenolics combination in lung cancers will be valuable to achieve clinical application.

11.3.3 Human Studies

Many clinical studies investigating the impact of anthocyanins on human health have been conducted to translate whether preclinical findings have real benefit in humans (Wallace and Giusti 2015). Varying compositions of anthocyanins from different plant sources have been tested in a range of different conditions. Common conditions testing anthocyanins include but are not limited to the following:

cardiovascular disease, vision improvement, neuroprotection, diabetes, obesity, cancer chemoprevention, and inflammation (Prior and Wu 2006; Mitscher 2007; Reis et al. 2016; Pojer et al. 2013). The majority of clinical studies on anthocyanins have used extracts and mixtures enriched with anthocyanins from different sources, berries among the most common. The complex mixtures of each source and different batches from producers make direct comparisons more challenging (Pojer et al. 2013). Though many sources of anthocyanins have been tested, consumption of anthocyanins is considered relatively safe (Wallace and Giusti 2015; Pojer et al. 2013) and currently there are no specific dietary recommendations on anthocyanin intake.

While numerous clinical investigations on anthocyanins have been performed on other conditions such as cardiovascular disease (Cassidy et al. 2013; Curtis et al. 2009; Yang et al. 2017; Fairlie-Jones et al. 2017; Vetrani et al. 2018; Huang et al. 2016; Hassellund et al. 2012, 2013; Dohadwala et al. 2011), dyslipidemia (Shah and Shah 2018; Qin et al. 2009; Broncel et al. 2010; Kusunoki et al. 2015; Li et al. 2015; Zhu et al. 2011), and inflammation (Jennings et al. 2014; Martin et al. 2018; Lynn et al. 2014; Coelho Rabello Lima et al. 2015; Seymour et al. 2009; Kim et al. 2018; Lee et al. 2017; Edirisinghe et al. 2011), in comparison, limited clinical research has been done on the potential of anthocyanins for cancer chemoprevention. Most studies involving human cancer subjects and anthocyanins have primarily focused on gastrointestinal cancer prevention (Bishayee et al. 2016).

Results surrounding intake of anthocyanins and colorectal cancer (CRC) prevention have been mixed. Epidemiological evidence suggests higher intake of flavonoids such as anthocyanins can reduce CRC risk but some studies have found no support for higher anthocyanin intake and decreased CRC risk (Nimptsch et al. 2016). Though the evidence for anthocyanin intake and cancer risk is not conclusive, several studies suggest anthocyanins can decrease oxidative damage. An intervention of mixed berry juice rich in anthocyanins in healthy male volunteers showed an increase in reduced glutathione and decrease in oxidative DNA damage (Weisel et al. 2006) compared to control. A phase II study in patients with esophageal dysplastic lesions who are at higher risk for esophageal cancer received freeze-dried strawberry powder at 30 or 60 g/day. 80.6% of patients in the 60 g/day arm had lower histologic grade of precancerous esophageal lesions. Patients in the high-dose strawberry group also had significant reductions in iNOS, COX-2, p-NF-κB-p65, and pS6 protein expression, while the lower-dose groups were not significantly reduced. Cell proliferation, as measured by Ki-67, was also reduced in patients receiving 60 g/day of strawberry powder compared to baseline. In a phase I study of CRC patients, oral freeze-dried black raspberries decreased Ki-67 staining and suggest IL-8 and GM-CSF are potential indicators of response to berry-based CRC chemoprevention (Mentor-Marcel et al. 2012). Interestingly, black raspberry treatment could influence epigenetic markers in tissues with demethylation of tumor suppressor genes, possibly by decreasing DNMT1 (Wang et al. 2011). Observations of anthocyanins reducing oxidative stress and inflammation have been reported for other conditions (Li et al. 2015; Traustadottir et al. 2009; Alvarez-Suarez et al. 2014; Riso et al. 2005; Davinelli et al. 2015; Lyall et al. 2009; Kuntz et al. 2014; Kaspar

et al. 2011; Seymour et al. 2014) though conflicting findings on oxidative stress have also been reported (Moller et al. 2004; Mertens-Talcott et al. 2008; Ellinger et al. 2012; Desai et al. 2018; Duthie et al. 2006). Further studies are needed to standardize preparations to anthocyanin contents and more rigorous study designs may help determine the effects of anthocyanins on cancer chemoprevention in humans.

In addition to esophageal and colorectal cancer, oral cancer prevention studies on patients with premalignant oral lesions have been conducted using freeze-dried black raspberry gel. Patients receiving topical application of raspberry gel on intraepithelial neoplasia had significant reduction in loss of heterozygosity of tumor suppressor genes and histological regression in a patient subpopulation (Shumway et al. 2008). A separate report from the same research group also observed significant reductions in epithelial COX-2 and lower but non-significant decreases in iNOS (Mallery et al. 2008). In both studies, the black raspberry gel was well-tolerated with no observed adverse effects.

Many studies have investigated the effects of anthocyanins on oxidative stress and inflammation as a possible mechanism for cancer chemoprevention. However, recent findings have suggested that the effects of black raspberries (Gu et al. 2019) and tart cherries (Mayta-Apaza et al. 2018) may be mediated by influencing the gut microbiome. Anthocyanins may impact gut microbiota to modulate inflammation (Morais et al. 2016) and control obesity (Jamar et al. 2017). In one recent study, black raspberry anthocyanins altered gut microbiota in an *in vivo* CRC mouse model and through epigenetic demethylation of SFRP2 (Chen et al. 2018). Recent advances in gut microbiome and anthocyanin interactions should be considered in future human clinical studies investigating anthocyanins in cancer chemoprevention. The influence of anthocyanins on gut microbiota may shed new insights into the chemopreventive mechanisms of dietary anthocyanins.

11.4 Pharmacokinetics (PK)/Pharmacodynamics (PD) and Metabolism of Anthocyanins, Food Source and Bioavailability

The fate of anthocyanins after oral administration follows a unique pattern as compared to the other flavonoids since they could be absorbed from the stomach as well as intestine and colon. Also, active transporters may play a role in the absorption of anthocyanins from the stomach as well as in their transport in the kidney or liver. In a cell culture study, anthocyanins were found to be able to cross MKN-28 cell monolayers (differentiated adenocarcinoma stomach cells) through glucose transporters 1 (GLUT1) and 3 (GLUT3) (Fang 2014; Oliveira et al. 2015). Many Studies of individual anthocyanins reveal their oral bioavailability is generally $<1\%$ (Milbury et al. 2010). Anthocyanins can be absorbed intact from the stomach as well as the intestine despite having different physicochemical properties including molecular size and type of sugar or acylated groups attached (Stalmach et al. 2012;

Matsumoto et al. 2001; Kurilich et al. 2005). Some factors such as glycated groups, glycine and sugar moiety (Wu et al. 2004, 2005; Tian et al. 2006; Milbury et al. 2002) can affect the absorption rate and extent of anthocyanins. Anthocyanins were found in the blood stream within minutes of consumption in human (Tian et al. 2006), suggesting that anthocyanins can be quickly absorbed from the stomach, which has also been confirmed in animal studies. Furthermore, in human studies, anthocyanins were absorbed when introduced through nasal intubation directly into the jejunum (Passamonti et al. 2009; Cai et al. 2011). Anthocyanins were absorbed efficiently after *in situ* perfusion of the jejunum and ileum in rats (Talavera et al. 2004). Another study using chamber mounted with mouse intestine sections showed that the highest absorption of anthocyanins occurred with jejunum tissue ($55.3 \pm 7.6\%$) (Matuschek et al. 2006). Minor absorption occurred with duodenal tissue ($10.4 \pm 7.6\%$), and no absorption was detected from the ileum or colon. The absorption of anthocyanin was usually influenced by their chemical structure and varied between malvidine-3-glucoside (10.7%) and cynidine-3-glucoside (22.4%).

Anthocyanins are the largest group of water-soluble pigments in the fruits and vegetables. The uptake of anthocyanins from the gastrointestinal lumen into the blood depends on the structure of the absorbed molecules (Hribar and Ulrih 2014). Research over the past decade suggested that the majority of conjugation reactions involved in the metabolism of flavonoids include glucuronidation, methylation and sulfation (Mullen et al. 2006; Hollman and Katan 1998; Donovan et al. 2001; Shimoi et al. 1998) with only 0.1–1.5% of ingested dietary anthocyanidins reported to be excreted unmetabolized (Mullen et al. 2006; Hollman et al. 1995). Glucuronide conjugation is usually regarded as the major conjugation reaction involved in flavonoid metabolism (Shimoi et al. 1998; Kuhnle et al. 2000; Oliveira et al. 2002; Spencer et al. 1999). The glucuronidation reaction is catalyzed by UDP-glucuronosyltranferases (UGT) which is found in high concentrations in the liver, intestine and kidneys. Of all these tissues, the liver has the largest capability for glucuronidation (Mojarrabi and Mackenzie 1998; Strassburg et al. 1998) but increasing evidence suggests that the intestine as being the initial and principal site for flavonoid glucuronidation in clinical trials following dietary consumption. Methylation appears as the second most significant metabolism conjugation reaction involved in flavonoids (Kuhnle et al. 2000; Williamson et al. 2000).

In human pharmacokinetic (PK) study including both male and female, it is observed that the maximum plasma concentration is achieved within 0.5–2 h after consumption of anthocyanin-rich fruits (Charron et al. 2009). The systemic bioavailability of anthocyanins is estimated to be 0.26–1.8% in animal studies (Ichiyanagi et al. 2006; Borges et al. 2007; Felgines et al. 2002, 2003). Maximum plasma concentration levels of total anthocyanins are in the range of 1–100 nmol/l following consumption of berries or grapes in human studies (Prior and Wu 2006) . Despite low bioavailability, plasma concentrations of anthocyanins appear sufficient to induce changes in signal transduction and gene expression *in vivo* (Karlsen et al. 2007; DeFuria et al. 2009) in a manner that suggests their potential effects in physiological functions and health outcomes. The absorbed anthocyanins are rapidly eliminated from the circulation. The anthocyanins are detected in the blood stream

within very short time (minutes) after administration in human suggesting that its quick absorption (Milbury et al. 2002). Furthermore, when anthocyanins were introduced through nasal tubes, the anthocyanin urine concentrations were fivefold higher as opposed to stomach administration in patients (Cai et al. 2011). Many studies demonstrated that around 7.5% of ingested anthocyanins were detected in the small intestine tissue in their native form 2 h following administration of black raspberries to rats (He et al. 2009). Other study also mentioned that the cynidine-3-glucoside and its methylated and glucuronosyl-conjugated metabolites in jejunum tissue reached 605 nmol/g after administration of an anthocyanin enriched diet for 15 days in rats (Karlsen et al. 2007). Furthermore, several studies have shown that anthocyanins exhibit a complex dose-response, with decreased absorption efficiencies with increased doses (Kurilich et al. 2005; Borges et al. 2007; Charron et al. 2007). The health benefits of anthocyanins have been suggested to be associated with their oral bioavailability and other pharmacokinetic behaviors, such as peak plasma concentration (Cmax) and exposure (AUC) of anthocyanins or their metabolites at peripheral tissue (Milbury et al. 2010; Xiao et al. 2017; de Ferrars et al. 2014). The oral bioavailability of dietary anthocyanins that maintain their parent C6-C3-C6 structure has been reported to be relatively low and various dietary factors such as mixed nutrient meals may have an impact (de Ferrars et al. 2014). Future *in vivo* PKPD studies would be needed to clarify these issues.

11.5 Conclusions

The preponderance of evidence indicates that polyphenolic compounds found in fruits and vegetables have potential chemopreventive properties in various organ specific cancers. There are a significant number of studies with anthocyanins that indicate they can decrease the incidence of some cancers. Anthocyanins have been shown to exert chemopreventive effects *in vitro* on cellular differentiation/cell cycle and cellular growth, apoptosis, activation or deactivation of various enzyme systems such as the phase I biotransformation enzymes, antioxidant action, antimutagenic, antimetastatic activities, interacting with various signaling pathways or direct interaction with the carcinogen. *In vivo* studies have shown that dietary anthocyanins inhibit cancers of the gastrointestinal tract, breast, lung cancer and topically applied anthocyanins inhibited skin cancer. Along with xenograft models, carcinogen induced and patient derived xenograft (PDX) models will help to generate the relevant evidence for the chemopreventive efficacy of anthocyanins. Along with human epidemiological studies, PK-PD data indicate that the minimal absorption of anthocyanins into the bloodstream, complicate the potential efficacy in tissues other than the directly exposing the GI tract and skin. Hence, measuring tissue-bound and circulating anthocyanins would be needed to ascertain the potential chemopreventive effects of anthocyanins at various organ sites. Further studies of individual or combination of the anthocyanins at physiological concentrations and quantifying the metabolites, and the role of gut microbiome, will contribute to the overall knowledge of potential cancer chemoprevention of anthocynanins in humans.

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