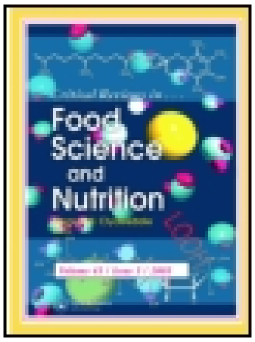

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Anthocyanin supplement as a dietary strategy in cancer prevention and management: A comprehensive review

Jiali Chen, Baojun Xu, Jianxia Sun, Xinwei Jiang & Weibin Bai

To cite this article: Jiali Chen, Baojun Xu, Jianxia Sun, Xinwei Jiang & Weibin Bai (2021): Anthocyanin supplement as a dietary strategy in cancer prevention and management: A comprehensive review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1913092

To link to this article: https://doi.org/10.1080/10408398.2021.1913092

Published online: 19 Apr 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1913092

Taylor & Francis
Taylor & Francis Group

REVIEW

Anthocyanin supplement as a dietary strategy in cancer prevention and management: A comprehensive review

Jiali Chen[a], Baojun Xu[b], Jianxia Sun[c], Xinwei Jiang[a], and Weibin Bai[a]

[a]Department of Food Science and Engineering, Institute of Food Safety and Nutrition, Guangdong Engineering Technology Center of Food Safety Molecular Rapid Detection, Jinan University, Guangzhou, China; [b]Food Science and Technology Program, BNU-HKBU United International College, Zhuhai, China; [c]Faculty of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou, PR China

ABSTRACT
Anthocyanins are natural pigments proven to be beneficial in the vast majority of health problems with no side effects. In this review, the latest progress on the cancer prevention and management of anthocyanins in treating cancers ranked in the top 5 of incidence and mortality was summarized, and the interaction and corresponding mechanisms were established based on a systematic review of electronic libraries. Several studies have revealed that anthocyanins have positive impact on human health with anti-cancer capacity. This review aimed to accumulate the evidence on the anti-cancer effects of anthocyanins, corresponding mechanisms and limitation of anthocyanins on cancer prevention and management. Notably, this review updated the latest studies on cancer prevention and management of anthocyanins and also inputted the future perspectives and the demanding questions for the possible contribution of anthocyanins as anti-cancer adjuvant.

KEYWORDS
Anthocyanin; anti-cancer; immunotherapy; chemotherapy

Introduction

Nowadays, the incidence and mortality of cancer are rapidly increasing worldwide. It is noteworthy that cancer is the first or second leading cause of mortality in most of world regions. It was estimated that there were 18.1 million new cancer cases and 9.6 millon cancer deathes in 2018, reported by the International Agency for Research on Cancer (Bray et al. 2018; Zhang et al. 2020). Bray et al. (2018) also indicated that lung cancer, breast cancer, colorectal cancer, prostate cancer, and stomach cancer were found in the top 5 ranking of incidence. Meanwhile, lung cancer, colorectal cancer, stomach cancer, liver cancer, and breast cancer were ranked in the top 5 for mortality. Cancers ranked in the top 5 of incidence and mortality has become a major health concern worldwide. Therefore, the prevention and management of cancer are extremely important. Several studies have noted a positive correlation between cancer management and healthy diet, contributed by the chemoprevention of vegetables and fruits. Anthocyanin is a group of natural flavonoid, widely distributed in fruits and vegetables. Numerous researches established that anthocyanins possessed potential anti-cancer activity on human health, highly recommended anthocyanins as nutraceutical for cancer prevention and management (Lin et al. 2017; Diaconeasa et al. 2018).

Chemical structures and characteristics of anthocyanins

Anthocyanins occur naturally in vegetables and fruits as glycosides with low cytotoxicity and biosafety. It is a promising substances for cancer prevention and management. The basic structure of anthocyanin is 2-phenylchromenylium (flavylium). It has been identified that the combination with glucose, galatose, and rhamnose could form various types of anthocyanins, including pelargonidin, delphinidin, petunidin, cyanidin, and malvidin, attributed to the different substituent group of B-ring on basic structure (Baby, Antony, and Vijayan 2018; Zhang et al. 2020). Studies also indicated that various types of anthocyanins performed different anti-cancer properties with distinct mechanisms. The following sections systematically summarized the cancer prevention and management of anthocyanins underlying the corresponding mechanisms.

Cancer prevention of anthocyanins

To date, cancer prevention is highly concerned by the citizen and government. A close correlation among the initial stage of tumourigenesis, free radical, and inflammation have been established. Oxidative stress could cause the genomic damage of normal cell, leading to gene mutation. Meanwhile, chronic inflammation has been found that it could promote the growth of cancer cells, treated as the

CONTACT Weibin Bai baiweibin@163.com Department of Food Science and Engineering, Institute of Food Safety and Nutrition, Guangdong Engineering Technology Center of Food Safety Molecular Rapid Detection, Jinan University, Guangzhou 510632, China.

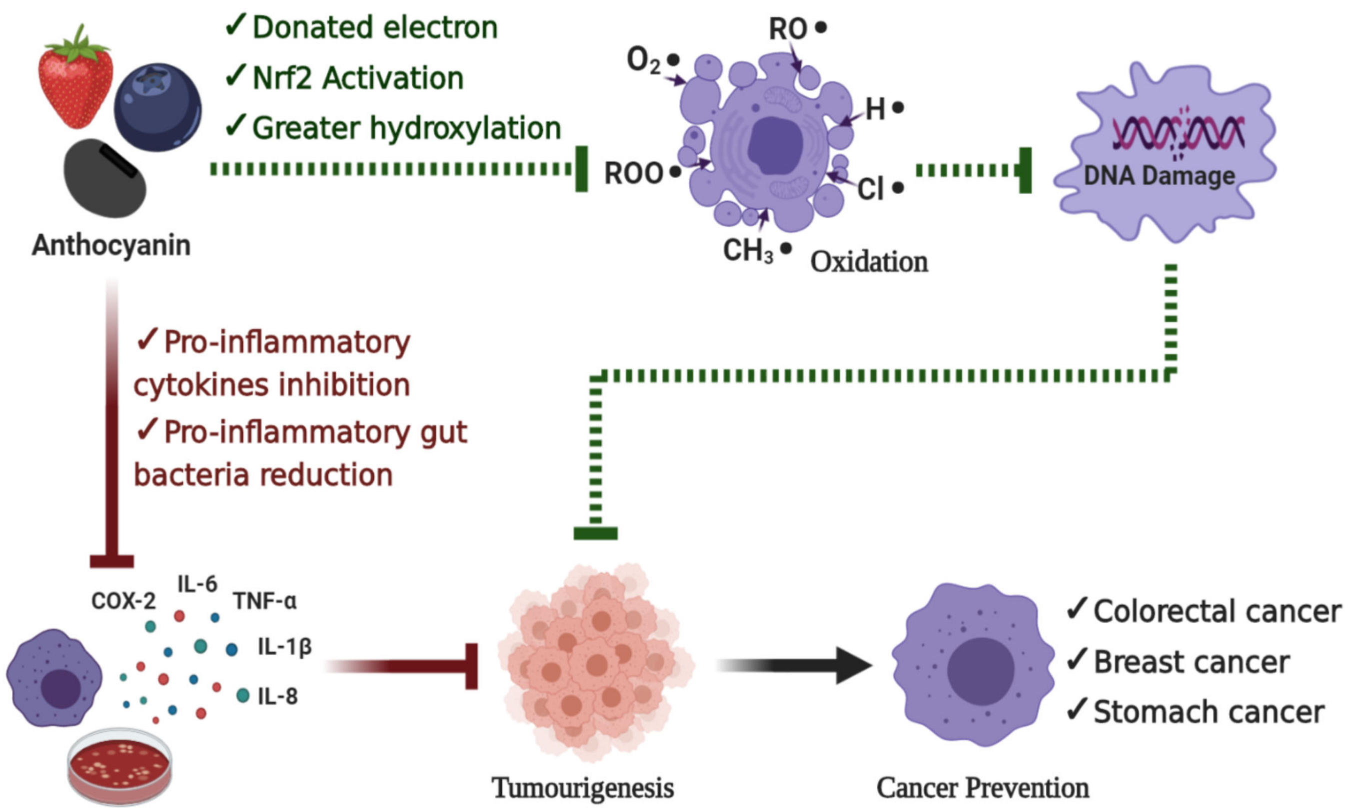

Figure 1. The main potential mechanisms of the cancer prevention of anthocyanins. Anti-oxidation and anti-inflammation were the main mechanism of anthocyanins for cancer prevention. Daily supplement with anthocyanins rich food could effectively prevent cancer by donating electron, Nrf2 activation, and greater hydroxylation. Anthocyanins treatments also could achieve cancer prevention by inhibiting pro-inflammatory cytokines, and reducing pro-inflammatory gut bacteria.

harbinger of tumor. Therefore, antioxidant and anti-inflammatory properties are critical for cancer prevention (Figure 1).

Antioxidant effects of anthocyanins for cancer prevention

Anthocyanin is a subcategory of flavonoids that it also belong to polyphenol compounds. The structure of polyphenol of anthocyanin is critical for the antioxidant activity. Most of the methods applied for antioxidant analysis of anthocyanins were based on its mechanisms, such as anti-radical and reducing activities by 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing antioxidant power (FRAP) assay, inhibition of lipid peroxidation, and the chelation of metal ions. The antioxidant property has been identified for years as the first line defense against the initial stage of mutagenesis process (Amatori et al. 2016). Anthocyanins could perform strong antioxidant capacity via scavenging free radicals, thereby reducing DNA damage, followed by preventing the tumourigenesis (Kalemba-Drożdż, Cierniak, and Cichoń 2020). As shown in Table 1, Jing et al. (2015) indicated that delphinidin derivatives with glycosylation on C3 position exhibited antioxidant effects on colorectal cancer cells through reducing ROS and promoting glutathione reductase (GSR) protein expression. Sousa et al. (2016) and Wang et al. (2019) also found that the antioxidant properties of anthocyanins could contribute in the prevention of stomach and colorectal cancer by donating electrons. Lee et al. (2020) also indicated that anthocyanins could activate the antioxidant siganaling pathway regulated by nuclear factor erythroid 2 (Nrf2) in colon cancer cells, playing role in antioxidant prevention. Grimes et al. (2018) established that anthocyanins perform stronger antioxidant capacity may attribute to greater hydroxylation on the B ring of polyphenols, functioned in colorectal cancer and breast cancer prevention. Anthocyanins possessed antioxidant activity benefit for various kind of cancers prevention but not limited to above mentioned. It is noteworthy that most of the researches were focused on the in vitro cell lines studies for antioxidant prevention. In view of this, in vivo studies for the systematic investigation of anthocyanins with anti-oxidant activities could be focused in the future.

Anti-inflammatory effects of anthocyanins for cancer prevention

Inflammation is the basis of many pathological human diseases and takes important roles in complex immune system. Hyper-response or prolonged inflammation will harmful for many associated diseases (Chen et al. 2019). It has been indicated that inflammation could play roles in promoting many types of cancers (Tan et al. 2020). NF-κB is the crucial part in the regulation of genes involved in immunity and inflammation. It has been found that nuclear factor-kappa B (NF-κB) could promote the invasive phenotype and transcription of oncogenes in cancer cells (Tan et al. 2020). In colorectal cancer, NF-κB could accelerate angiogenesis and

Table 1. Antioxidant and anti-inflammation properties of anthocyanins for cancer prevention.

Properties	Source of anthocyanin	Types of anthocyanin	Methods	Mechanism	References
Antioxidant	Eggplants	Delphinidin, nasunin	Colon cell lines (HT-29 and HCT-116)	ROS reduction and promote glutathione reductase (GSR) protein expression	Jing et al. 2015
Antioxidant	Blackberries	Cyanidin, deoxyanthocyanidins	AGS, MKN-28, Caco-2 (stomach cancer cells and colon cell)	High electron drawing conjugation	Sousa et al. 2016
Antioxidant	–	Anthocyanidins extracts	Meta-analysis of observational studies	Donate electrons, attribute to the glycosides of polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium	Wang et al. 2019
Antioxidant	–	Cyanidin Chloride	Colon cancer cell (HCT116, HT29, and SW620 cells)	Activated antioxidant signaling pathway regulated by Nrf2 in colon cancer cells	Lee et al. 2020
Antioxidant	Grape	Cyanidin, delphinidin	HT-29, Caco-2, and MDA-MB-231 (colon cells and breast cancer cell)	Hydroxylation on the B ring of polyphenols	Grimes et al. 2018
Anti-inflammation	Cocoplum	Anthocyanins extracts	HT-29 (colon cancer cell)	Down-regulated TNF-α, IL-1β, IL-6, and NF-κB expressions	Venancio et al. 2017
Anti-inflammation	Black raspberry	Anthocyanins extracts	HCT-116 (colon cancer cell), Azoxymethane (AOM)/dextran sodium sulfate (DSS) induced colorectal cancer (in vivo)	Down-regulated expression levels of IL-1β, IL-6, COX2 and TNF-α	Chen et al. 2018
Anti-inflammation	Purple and red corn	Anthocyanins extracts	HCT-116, HT-29 (colorectal cancer cells)	Reduction in a proinflammatory marker IL-8	Mazewski, Liang, and Mejia 2017
Anti-inflammation	Dry black pepper, strawberry and blackberry	Anthocyanins extracts	Azoxymethane (AOM)/ dextran sodium sulfate (DSS) induced colorectal cancer (in vivo)	Reduction of pro-inflammatory gut bacteria, such as Bilophila wadsworthia	Fernández et al. 2018

cell proliferation, promote cell invasion and metastasis, and inhibit cell death. Moreover, pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are commonly upregulated in colon cancer cell proliferation, correlated with colitis-associated tumorigenesis (Baby, Antony, and Vijayan 2018; Tan et al. 2020).

Several studies also note a positive correlation between anti-inflammatory property of anthocyanins and cancer prevention. As shown in Table 1, Venancio et al. (2017) found that anthocyanins rich cocoplum exhibited anti-inflammatory effect by down-regulating the expression levels of TNF-α, IL-1β, IL-6, and NF-κB in HT-29 colorectal cell. Chen et al. (2018) also indicated that anthocyanins from black raspberry could effectively down-regulate the expression levels of pro-inflammatory cytokines IL-1β, IL-6, cyclooxygenase (COX-2) and TNF-α for colorectal cancer prevention by in vitro and in vivo studies. Mazewski, Liang, and Mejia (2017) also demonstrated the reduction in a pro-inflammatory marker IL-8 in colorectal cancer cells upon the treatment of anthocyanins rich corn, which correlated with the inhibition of cell proliferation closely related to angiogenesis. Anthocyanins from fruits also possessed anti-inflammatory activities by the reduction of pro-inflammatory gut bacteria for colorectal cancer prevention (Fernández et al. 2018). To date, most of anti-inflammatory studies of anthocyanins for cancer prevention were observed in colorectal cancer. A further investigation for anti-inflammatory effects of anthocyanins for the prevention of other cancers is necessary.

Cancer management of anthocyanins

In the initial stage of tumor, anthocyanins can prevent genomic damage from oxidative stress by anti-oxidation. Meanwhile, anthocyanins also can inhibit the proliferation of cancer cells by down-regulating the pro-inflammatory cytokines. However, studies have already found that the main cause of cancer death is metastasis (Lu et al. 2017). As shown in Figure 2, cancer cells could metastasis through migration, invasion, and proliferation in blood steam. The potential anti-cancer activities of anthocyanins may attribute to the inhibition of migration and proliferation of corresponding cancer cells (Wang and Stoner 2008). Currently, lung cancer, breast cancer, colorectal cancer, prostate cancer, stomach cancer, and liver cancer were the vast majority of cancer, rapidly increased in the world (Bray et al. 2018). Numerous studies have noted a close correlation between cancer management and anthocyanins. In this study, the cancer management of anthocyanins was established in this

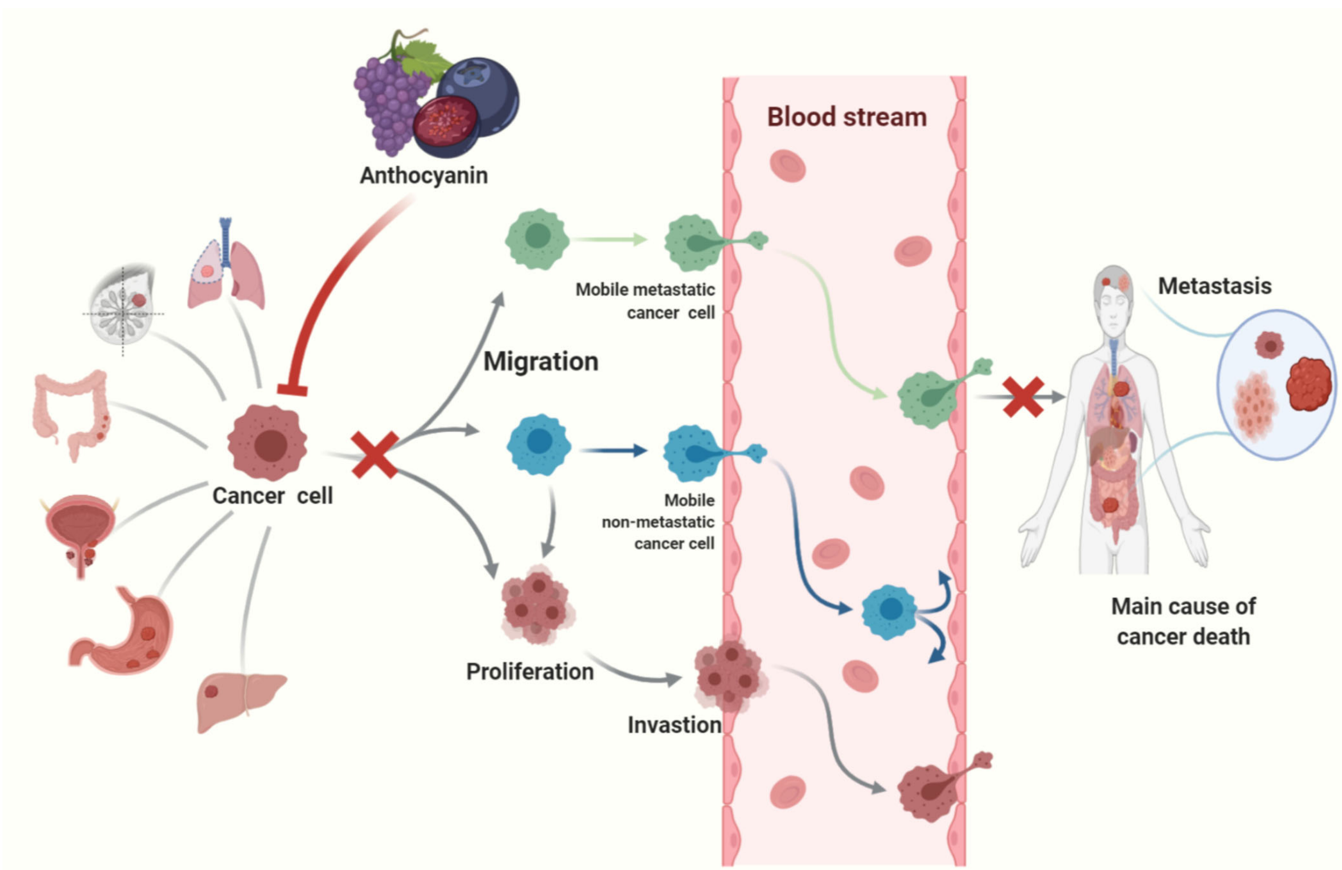

Figure 2. The schematic diagram for the main cause of cancer death. Metastasis of cancer cells is the main cause of cancer death, leading by the migration, proliferation, and invasion of cancer cells through blood stream. The potential anti-cancer activities of anthocyanins may attribute to the inhibition of migration and proliferation of corresponding cancer cells.

sections, including lung cancer, breast cancer, colorectal cancer, prostate cancer, stomach cancer, and liver cancer.

Lung cancer management of anthocyanins

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide (Bray et al. 2018). Increasing evidence found that dietary natural products can play an important role in the prevention and management of lung cancer, such as tomatoes, grapes, and pomegranates (Cao et al. 2019). Anthocyanin as a kind of natural nutraceutical with biosafety. Several studies have found a positive correlation between lung cancer prevention and anthocyanin underlying different mechanisms (Table 2, Figure 3). Farrukh et al. (2016) established that anthocyanins rich blueberry can reduce the tumor size to 40% in nude mice against H1299 xenografts, suppressed the proliferation of lung cancer cells. Lu et al. (2017) also indicated that anthocyanins rich blueberry extracts with concentration range from 6.25 to 100 μg/mL were exhibited lung cancer inhibition through suppressing the growth of A549 cells. The main cause of cancer death is metastasis (Lu et al. 2017). Therefore, the control of the metastatic activity through inhibiting proliferation and migration is crucial for the management of lung cancer. Amararathna, Hoskin, and Rupasinghe (2020) established that anthocyanins extracts from berry could effectively reduced nitrosamine induced DNA damage through attenuating the reactive oxygen species (ROS) levels in BEAS-2B cells. Similar to Farrukh et al. (2016) suggested that the anthocyanins extract possessed antitumor effect via inhibiting the migration, invastion, and proliferation of A549 cells through down-regulating the expression level of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), COX-2, C-myc, and cyclin D1. Kausar et al. (2012) also indicated that anthocyanidins from berry could effectively promote apoptosis of A549 or H1299 cells mediated by Bcl2 and poly (ADP-ribose) polymerase (PARP), inhibited the lung tumor through Notch and WNT pathways. Additionally, it was further exhibited that delphinidin (1.5 mg/mice) in anthocyanidins can effectively inhibit the growth of H1299 xenografts in nude mice. Most of methods for lung cancer investigation were focus on the studies of A549, H1299, or xenograft. Anthocyanins in fruits or vegatables are promising chemopreventive substances for managing lung cancer.

Breast cancer management of anthocyanins

Breast cancer is the second most commonly diagnosed cancer worldwide, leading high morbidity and mortality in women (Bray et al. 2018). To date, the most effective treatments are surgical removal of the breast by surgery and chemotherapy to against breast cancer. However, the risk of recurrence is still very high. Consumption of fruits rich in

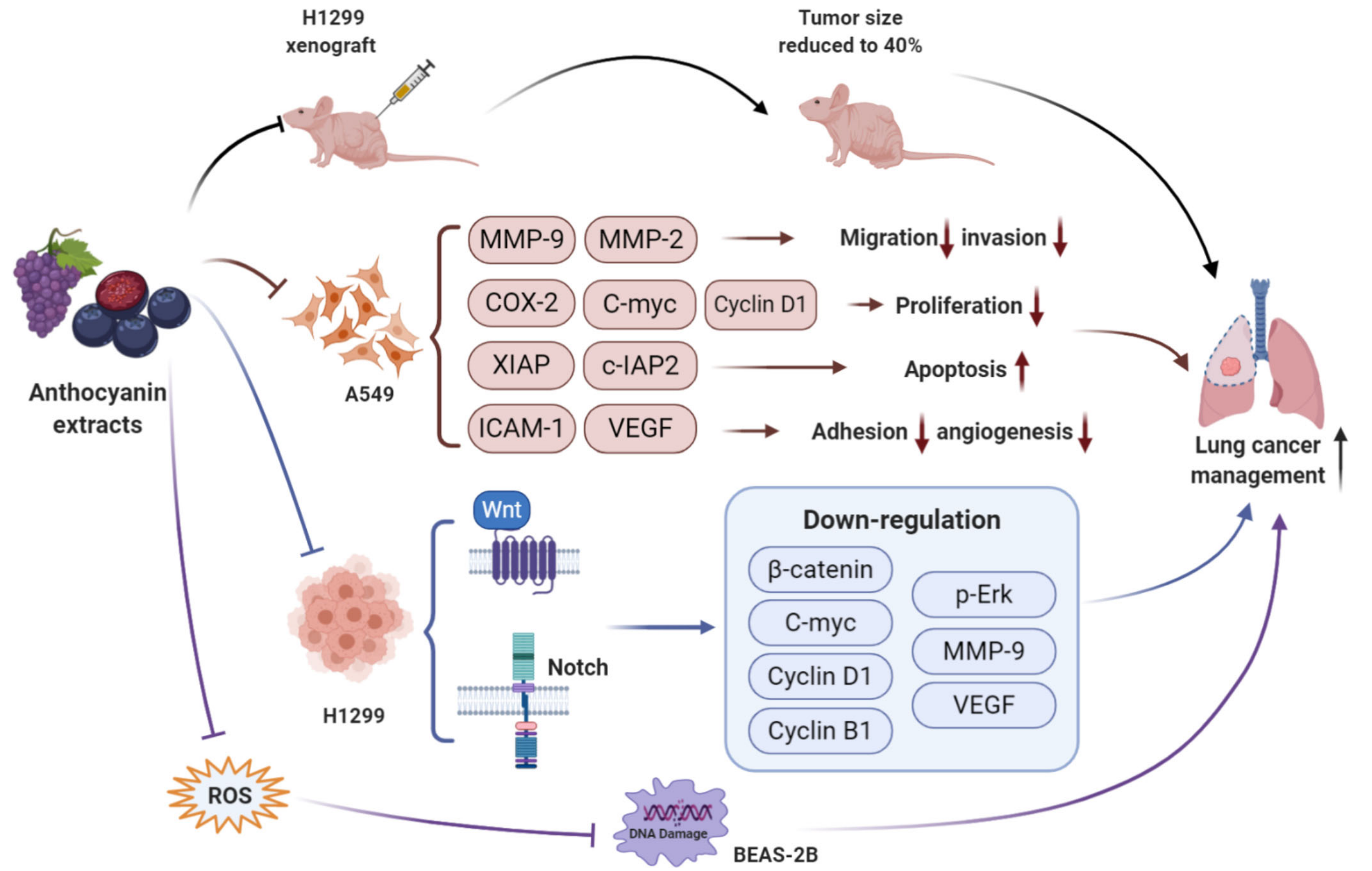

Figure 3. The main potential mechanisms of the lung cancer management of anthocyanins. In vivo and in vitro studies revealed that anthocyanin extracts possessed potential anti-lung cancer activities. It may mainly attribute to the inhibition of migration, invasion, proliferation, anti-apoptosis, adhesion, and angiogenesis by anthocyanins through targeting Wnt, Notch, and PI3/Akt pathway in A549 or H1299 lung cancer cells. The anti-lung cancer activities also may attribute to the anti-oxidant capacity of anthocyanins through reducing ROS levels and DNA damage.

phenolics are highly recommended as a dietary strategy to achieve the risk reduction of breast cancer or as nutraceutical to increase survival rates of breast cancer (Mazzoni et al. 2019; Zhang et al. 2020). Several studies have demonstrated the capacity of anthocyanins in natural food to inhibit the breast cancer (Table 2). Lage et al. (2020) indicated that anthocyanins extracts from dark sweet cherry can significantly suppress the proliferation and induce apoptosis through inhibiting Akt/mTOR and Sirt1/survivin pathways against breast cancers cells. It also could effectively inhibit the metastasis of breast cancer by down-regulating the expression levels of Sp1, Sp4 and VCAM-1. Amatori et al. (2016) also found that anthocyanins extracts from strawberry possessed anticancer activities in inhibiting the growth of A17 xenografts against migration, adhesion, and invasion. Increasing evidences mentioned that the main potential mechanisms of breast cancer management by anthocyanin is to induce apoptosis and inhibit angiogenesis via down-regulating the Akt/mTOR and NF-κB pathway (Figure 4). In the last decades, the capacity of phytochemicals to modulate apoptosis has attracted increasing attention, treated as a potential anti-cancer agent. Some studies also suggested that anthocyanins could be a promising candidate for treating breast cancer in human by inhibiting human breast cancer cells (Qamar et al. 2020). Thus, the consumption of anthocyanins rich fruits or vegetables might be a significant strategy against breast cancer.

Colorectal cancer management of anthocyanins

Chemotherapy, targeted therapy, and immunotherapy were the main drug therapies applied for the treatments of metastatic colorectal cancer. To date, immunotherapy drugs are commonly applied to against colorectal cancer. Several epidemiological studies have found a negative correlation between the risk of colorectal cancer and the consumption of anthocyanins by meta-analysis (Wang et al. 2019). Several studies have noted a close correlation between chemical structures of anthocyanin and chemoprotective activity (Jing et al. 2008). López de Las Hazas et al. (2017) mentioned that anthocyanins extracts from grape and berry were exhibited anti-colon cancer activities by inducing apoptosis in HT-29. Mazewski, Kim, and Mejia (2019) demonstrated that anthocyanins extracts from red grape and black lentil were shown to inhibit angiogenesis pathways by down-regulating the expression levels of PVGF. PD-1 and PD-L1 are treated as part of the immune checkpoints, targeted in activating T cell to combat colorectal cancer. Similar to the studies found that anthocyanins, delphinidin and cyanidin could against colorectal cancer mediated by PD-1 and PD-L1 (Mazewski, Kim, and Mejia 2019, Liu et al. 2020). Lim et al. (2013) also indicated that anthocyanins extracts from purple sweet potato could suppress proliferation and induce apoptosis of SW480 cells by modulating the expression of PCNA and caspase-3. Charepalli et al. (2015) also confirmed that

Table 2. Cancer management of anthocyanins.

Cancer	Source of anthocyanin	Types of anthocyanin	Method	Mechanism	References
Lung cancer	Blueberry, black raspberry	Anthocyanins extracts, Cyanidin, cyanidin-3-glucoside (100-400 μM)	A549, H1299 (lung cancer cells), tumor xenograft in nude mice	Anti-proliferation of lung cancer cells, reduce the tumor size	Farrukh et al. 2016
	Vitis coignetiae pulliat	Anthocyanins extracts (400 μg/mL)	A549 (lung cancer cells)	Suppress cancer migration, and invasion (MMP-2 and MMP-9), anti-proliferation (COX-2, C-myc, cyclin D1)	Lu et al. 2017
	Blueberry	Anthocyanins (6.25-100 μg/mL)	A549 (lung cancer cells)	Cell viability inhibition	Kazan et al. 2016
	Berry	Anthocyanidins, cyanidin, malvidin, peonidin, petunidin and delphinidin (12.5-100 μM)	A549, H1299 (lung cancer cells)	Promote apoptosis (Bcl2, PARP), Inhibited the oncogenic Notch and WNT pathways (b-catenin, c-myc, cyclin D1, cyclin B1, pERK, MMP9 and VEGF)	Kausar et al. 2012
	Berry	Anthocyanins extracts	BEAS-2B (lung epithelial cells)	Reduced nitrosamine induced DNA damage	Amararathna et al. 2020
Breast cancer	Dark sweet cherry	Anthocyanins extracts (40–320 μg GAE/mL, equivalent to 10.8–86.2 μg C3G/mL)	BT4747, MDA-MB-453, MDA-MB-231(Breast cancer cells)	Downregulation of Akt/mTOR pathway and pro-survival Sirt1/survivin pathways, leading to anti-proliferation and apoptosis; reduction of invasive/metastatic markers Sp1, Sp4, and VCAM-1	Lage et al. 2020
	Strawberry	Anthocyanins extracts (0.5-5 mg/mL)	A17 (breast cancer cell), orthotopically injected with A17 cells to form tumor in mice	Against migration, adhesion, and invasion	Amatori et al. 2016
	Strawberry	Anthocyanins extracts	N202/1A、N202/1E	Against oxidative damage (ROS)、pro-apoptosis	Mazzoni et al. 2019
	Blue corn/Tortilla	Anthocyanins extracts (200-1000 µg/mL)	MDA-MB-453	Inhibited cell viability、induced apoptosis	Herrera-Sotero et al. 2020
Colorectal cancer	–	Anthocyanin	Meta analysis	Inhibited colon cancer by interfering in the cell cycle, proliferation, and apoptosis	Wang et al. 2019
	Red grape, black lentil	Anthocyanins extracts, delphinidin, cyanidin (100–600 µg/mL)	HCT-116, HT-29 (colon cancer cells), in silico analysis	Down-regulated the expression levels of PD-1, PD-L1, and PVGF	Mazewski et al. 2019
	Purple sweet potato	Anthocyanins (10-40 μM)	SW480 (colon cancer cell), carcinogen azoxymethane (AOM) induced colon carcinogenesis in mice	Suppressed proliferation (PCNA), induced apoptosis (caspase-3)	Lim et al. 2013
	Lyophilized açaí pulp	Cyanidin 3-rutinoside (C3R)	RKO (human colon adenocarcinoma cells)	Interfered the motility	Fragoso et al. 2018
	Bilberry	Anthocyanin extracts	MC38 (colon cancer cells)	Gut microbiome modulation, enhanced the therapeutic efficiency of PD-L1 blockade	Liu et al. 2020
	Purple corn, chokeberry, bilberry, purple carrot, grape, radish, and elderberry	Anthocyanin extracts	HT-29	Growth inhibition	Jing et al. 2008
	Grape, strawberry	Anthocyanin extracts	HT-29	Trigger apoptosis (cell viability; caspase-3)	López de Las Hazas et al. 2017
	Bilberry	Anthocyanin extracts (156 µg/mouse)	MC38 xenograft	Enhanced anti-PD-L1 efficiency, gut microbiota modulation	Wang et al. 2020

	Potato	Anthocyanin extracts (5 µg/mL; 5 mg/kg)	Colon cancer stem cells; AOM induced carcinogen in A/J mice	Downregulation of Wnt/β-catenin signalingand induction of apoptosis	Charepalli et al. 2015
Prostate cancer	–	Anthocyanin	Molecular docking	binding affinity of androgen receptor (AR)	Singh et al. 2017
	Black raspberry	Anthocyanins extracts (10–1000 µg/mL)	22Rv1, PC-3, C4-2 (prostate cancer cells), tumor xenograft in nude mice	Decreased tubulin polymerization	Eskra et al. 2019
	Black soybean	Anthocyanins (60-120 µM)	DU-145 (prostate cancer cell), tumor xenograft in nude mice	Trigger apoptosis (p53, Bax, and Bcl-2), inhibited androgen signaling (AR)	Ha et al. 2015
	Muscadine grape skin	Anthocyanins extracts (5-20 µg/mL)	C4-2	Trigger apoptosis (Bax, and Bcl-2), induced apoptosis (caspase-3)	Burton et al. 2016
	Blue corn/Tortilla	Anthocyanins extracts (200-1000 µg/mL)	LNCaP	Inhibited cell viability 、induced apoptosis	Herrera-Sotero et al. 2020
Stomach cancer	Mulberry	Anthocyanins (cyanidin)	AGS (gastric cancer cell), tumor xenograft in nude mice	Induced apoptosis via p38/Fas/FasL/caspase 8 signaling and p38/p53/Bax signaling, tumor inhibition	Huang et al. 2011
	Black currant	Anthocyanins extracts (6.25-100 mg/mL)	SGC-7901 (gastric cancer cell)	Inhibited cell viability and proliferation, induced apoptosis	Jia et al. 2012
	Vitis coignetiae pulliat	Anthocyanins extracts (400 μg/mL)	SNU-1, SNU-16 (gastric cancer cell)	Induced apoptosis (Akt, Caspase-3, Bax, XIAP)	Lu et al. 2015
Liver cancer	Black currant	Anthocyanins (cyanidin) (100-500 mg/kg body weight	Diethylnitrosamine-induced hepatocellular carcinogenesis in rats	Inhibition of cell proliferation and induction of apoptosis (Bax. Bcl-2)	Bishayee et al. 2011
	Black chokeberry	Anthocyanins extracts (100-200 μg/mL)	SK-Hep1 (liver cancer cell)	Decreased adhesion, suppressed proliferation, migration for inhibiting metastasis (MMP-2, MMP-9)	Thi and Hwang, 2018
	Wild grown berries	Anthocyanins extracts (0.2 mg/mL)	PLC/PRF/5, HepG2, McArdle (liver cancer cell)	Induced apoptosis (Bax, cytochrome C, caspase 3) by inhibiting autophagy (eIF2α, mTOR, Bcl-2)	Longo et al. 2008
	Red jambo peel	Anthocyanin extracts (1-50 mg/mL)	HepG2	Anti-proliferation	Vuolo et al. 2019

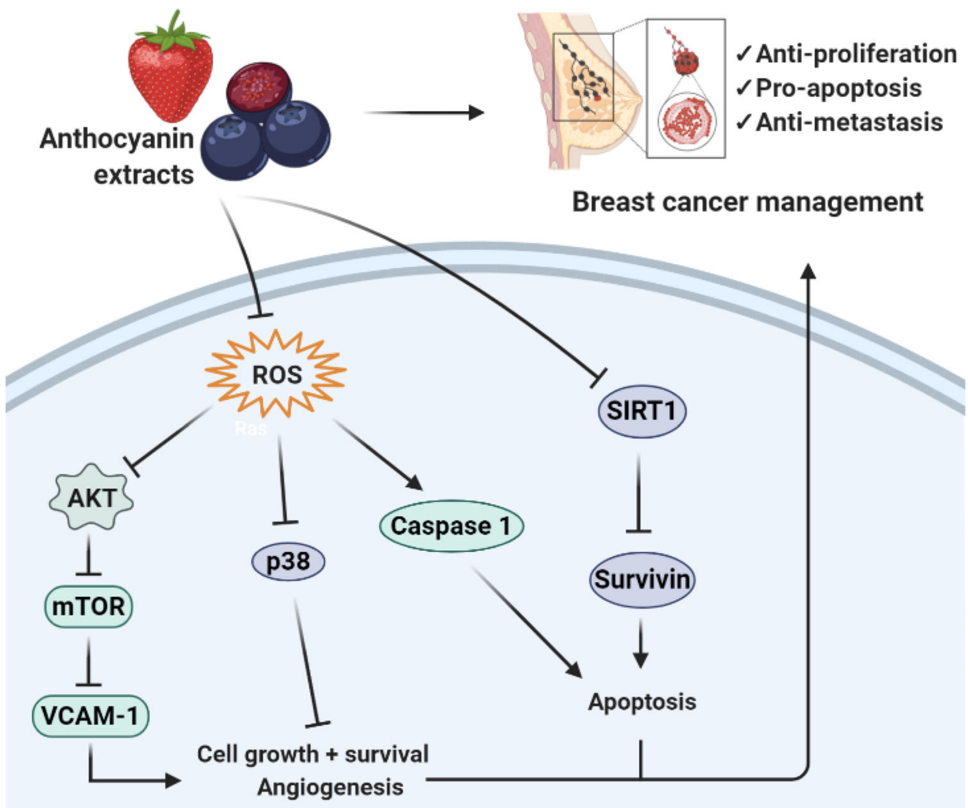

Figure 4. The main potential mechanisms of the breast cancer management of anthocyanins. Cancer cells growth and angiogenesis might be inhibited by anthocyanin extracts via down-regulating the Akt/mTOR and NF-κB pathway. The lung cancer cells also may be induced apoptosis by anthocyanin extracts through caspase 1 activation and down-regulating the expression levels of SIRT1 and survivin. Breast cancer management by anthocyanin extracts is mainly attribute to the anti-oxidant capacity of anthocyanin to attenuate the ROS levels.

anthocyanins rich potatoes possessed anti-proliferation effects via down-regulating the expression levels of c-Myc and cyclin D1 in colon cancer stem cells. It also exhibited pro-apoptosis effects through elevating the expression levels of Bax and cytochromein. In vivo results further revealed that anthocyanins rich potatoes could effectively suppress the colorectal cancer by suppressing the levels of β-catenin. Additionally, supplementation with anthocyanins has been proven that it could effectively suppress the colon cancer through gut microbiota modulation and immunotherapy (Liu et al. 2020). Taken together, chemotherapy and immunotherapy were the main pathways for the anthocyanins treatments of metastatic colorectal cancer (Figure 5). Additionally, it is noteworthy that encapsulated method has already been applied for enhancing the digestive stability of anthocyanins in treating colon cancer (Liu et al. 2020). However, studies on the chemical basis and systematic mechanism of encapsulated anthocyanins against colon cancer remain scarce. It would be a promising orientation for improving the anti-cancer activities of anthocyanins.

Prostate cancer management of anthocyanins

Prostate cancer is the second most common cancer amongst men with high incidence worldwide (Bray et al. 2018). It is a serious problem with highly concern by the government in consideration of the influence of fertility in men. Dietary administration of natural nutraceutical in preventing prostate cancer is popular in commercial market. Increasing evidence indicated that anthocyanins have benefits for preventing prostate cancer. Data of molecular docking revealed that anthocyanins are closely link to prostate cancer prevention or management through binding affinity analysis of androgen receptor (AR) (Singh, Baruah, and Sharma 2017). Eskra, Schlicht, and Bosland (2019) showed that anthocyanins extracts (10–1000 μg/mL) of black raspberry could interfere prostate cancer by reducing tubulin polymerization. Ha et al. (2015) also found that anthocyanins-rich black soybean could trigger apoptosis and inhibit androgen signaling in DU-45 cells by modulating the expression of p53, Bax, Bcl-2, and AR. Studies also further revealed that anthocyanins could effectively reduce the tumor size in nude mice against DU-45 xenografts. Several studies have noted a positive correlation between anthocyanins and prostate cancer management. However, it is noteworthy that the studies of anthocyanins against prostate cancer still lack of systematic investigation and remain elusive. Further evaluation on the capacity and mechanisms of anthocyanins against prostate cancer is needed.

Stomach cancer management of anthocyanins

As reported by Bray et al. (2018), gastric cancer is one of the most common tumors in the world, ranking the 5th in incidence and the 3rd in mortality. Numerous researches were revealed a positive relation between anthocyanin and gastric cancer prevention underlying different potential

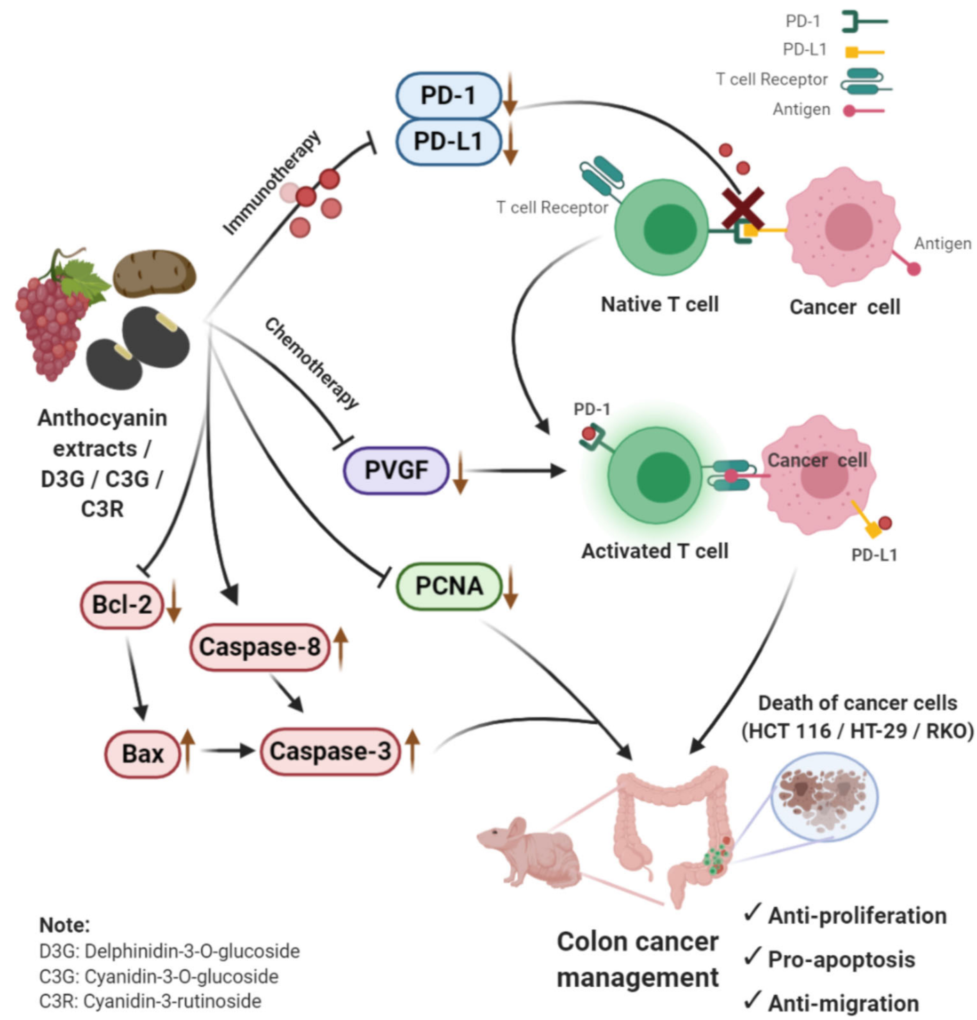

Figure 5. The main potential mechanisms of the colon cancer management of anthocyanins. Chemotherapy and immunotherapy were the main pathways for the anthocyanins treatments of metastatic colorectal cancer. Anthocaynins could against colon cancer cells mediated by PD-1 and PD-L1 for targeting the activation of T cells. The colon cancer cells could be inhibited by anthocyanins through regulating apoptosis-related mediators Bcl-2, Bax, Caspase-8, and Caspase-3. Anthocyanins also might down-regulate the expression level of proliferation associated protein PCNA for colon cancer management.

mechanisms (Figure 6). It was reported that anthocyanins-rich extracts (1–3 mg/mL) could induce apoptosis in AGS cells through the activation of p38/caspase 8 and p38/Bax signaling (Huang et al. 2011). Studies also further indicated that anthocyanins could reduce the tumor size with up to 80% in nude mice against AGS xenografts (Huang et al. 2011). Jia et al. (2012) also demonstrated that anthocyanins extracts from black currant have anticancer activities through inducing apoptosis and anti-proliferation in SGC-7901 cells. Moreover, anthocyanins extracts with concentration 400 μg/mL could significantly induce the apoptosis in SNU-1and SNU-16 cells via regulating the expression levels of Akt, Caspase-3, Bax, and XIAP (Lu et al. 2015). Studies suggested that anthocyanins rich extracts from food could be a promising candidature for managing gastric cancer with biosafety.

Liver cancer management of anthocyanins

Liver cancer was predicted to be the 6th most commonly diagnosed cancer and the 4th in mortality worldwide in 2018. Liver is the crucial organ in human body, functioned in metabolism and detoxification. Several studies have documented that anthocyanins has a close correlation in managing liver cancer (Shin et al. 2009; Giampieri et al. 2018; Vuolo et al. 2019). Bishayee et al. (2011) has demonstrated an anticancer effect of anthocyanins in rats through anti-proliferation and induction of apoptosis by regulating Bax and Bcl-2 expressions. Anthocyanins derived from black chokberry with concentration of 100–200 μg/mL also exhibit an anticancer capacity in SK-Hep1 cells through inhibiting proliferation, adhesion, migration, and metastasis (Thi and Hwang 2018). Similarly, Longo et al. (2008) also indicated that anthocyanins derived from berries possessed anticancer activity through inducing apoptosis (Bax, cytochrome C, caspase 3) in HepG2 and McArdle cells by inhibiting autophagy (eIF2α, mTOR, Bcl-2). Most results were revealed that anthocyanins could significantly against liver cancer though inducing the apoptotic pathway. Thus, dietary administration of anthocyanins could be developed as a significant strategy against liver cancer.

Other cancer management of anthocyanins

Apart from the impact of anthocyanins on lung cancer, breast cancer, colorectal cancer, prostate cancer, stomach

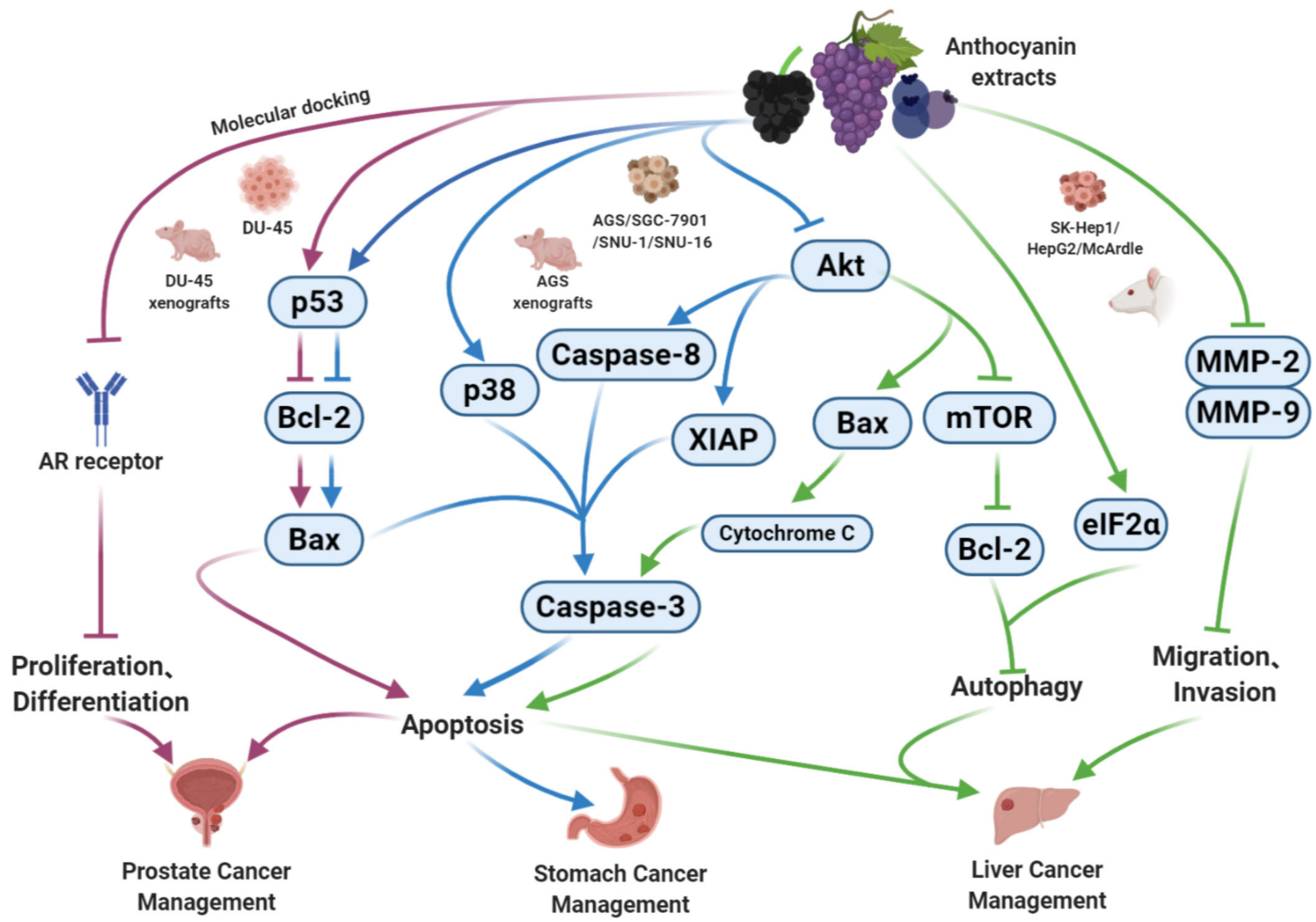

Figure 6. The main potential mechanisms of the prostate, stomach, and liver cancer management of anthocyanins. Prostate cancer might be inhibited by anthocyanin extracts through targeting AR receptor. Treatments with anthocyanin extracts also might against the stomach cancer cells or prostate cancer cells or liver cancer cells by regulating the apoptosis-related mediators (e.g. p53, Bcl-2, Bax, cytochrome C, Akt, and Caspase-3). Anthocyanins could inhibit the autophagy, migration, and invasion of liver cancer cells through regulating the expression levels of mTOR, Bcl-2, eIF2α, MMP-2, and MMP-9.

cancer, and liver cancer. It also possesses healthy benefits in inhibiting bladder cancer, cervical cancer, skin cancer, oral squamous cell carcinoma, and esophageal cancer (Peiffer et al. 2016; Wang et al. 2017; Li et al. 2018; Pan et al. 2019; Yue et al. 2019). The study of other cancer managements by anthocyanins were mainly stayed at the initial in vitro investigation. A further study on the exact molecular mechanisms for this cancer management of anthocyanins remain needed. Besides for the top 5 cancers, Qamar et al. (2020) also mentioned that anthocyanins as supplement in human may possess anti-cancer activity by inhibiting the cell viability of cancer cells, including human cervical cancer cells, human larynx carcinoma cells, human lung cancer cells, and human embryonic kidney cancer cells. However, studies on the cancer therapy of anthocyanins still lack of epidemiological studies in human.

Conclusions

Cancers ranked in the top 5 of incidence and mortality have become a major health concern worldwide. Therefore, the prevention and management of cancer are extremely important. Chemoprevention is one of the most promising and realistic approaches in the prevention of cancer. Anthocyanins are natural pigment proven to be beneficial in the vast majority of cancers. In this review, the cancer prevention and management of anthocyanins in treating cancers ranked in the top 5 of incidence and mortality were summarized, and the interaction and corresponding mechanisms were established. Review revealed that anti-oxidation and anti-inflammation were the main mechanism of anthocyanins for cancer prevention. Daily supplement with anthocyanins rich food could effectively prevent cancer by donating electron, Nrf2 activation, and greater hydroxylation. Anthocyanins treatments also could achieve cancer prevention by inhibiting pro-inflammatory cytokines, and reducing pro-inflammatory gut bacteria. Chemotherapy and immunotherapy were the main pathways for cancer management by anthocyanins. As shown in Figures 3–6, increasing evidences indicated that the mechanisms of cancer management of anthocyanins are mainly attributed to anti-proliferation, anti-migration, and pro-apoptosis through down-regulating PI3/Akt/mTOR, Wnt, Notch, or NF-κB signaling pathways.

Pelargonidin, delphinidin, petunidin, cyanidin, and malvidin were identified as the main types of anthocyanin. Though numerous in vitro and in vivo studies established that anthocyanins extracts have positive impact on human health with anticancer capacity, a complete study on the exact molecular mechanisms of various types of anthocyanin associated with the corresponding anticancer capacity remain lack of investigation. Additionally, anthocyanin notoriously possessed poor bio-availability in human body, limited to exert its anti-cancer activities and clinical use (He et al. 2017; Han et al. 2019; Lila et al. 2016). As mentioned in this review that encapsulated method has already been applied for enhancing the digestive stability of anthocyanin in treating colon cancer (Liu et al. 2020). Forbes-Hernández (2020) and Cao et al. (2021) also revealed that encapsulation could be an effective technique for improving the stability and potential in cancer therapy. However, studies on the chemical basis and systematic mechanism of encapsulated anthocyanin against cancer remain scarce. Taken together, the future perspectives on cancer prevention and management of anthocyanins have vast openings to figure out, which may include a. exact elucidation for the molecular mechanisms of various types of anthocyanins associated with the corresponding anticancer capacity; b. optimize the encapsulated method for enhancing the bio-availability to against cancer; c. establish the clinical study of anthocyanins supplement to convince the anti-caner activities. Notably, anthocyanins derived from natural food can be highly recommended as the nutraceutical for cancer prevention and management with no side effects.

Abbreviations

AR	Androgen receptor
COX-2	Cyclooxygenase-2
DPPH	2, 2-diphenyl-1-picrylhydrazyl
FRAP	Ferric reducing antioxidant power
GSR	Glutathione reductase
IL-1β	Interleukin-1β
IL-6	Interleukin-6
MMP-2	Matrix metalloproteinase-2
MMP-9	Matrix metalloproteinase-9
NF-κB	Nuclear factor-kappa B
Nrf2	Nuclear factor erythroid 2
PARP	Poly (ADP-ribose) polymerase
ROS	Reactive oxygen species
TNF	Tumor necrosis factor-α.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by Guangzhou Science and Technology Program key projects (No. 201903010082); and the National Natural Science Foundation of China (NSFC, No. 31771983); and Program for Research and Development in Key areas of Guangdong Province (2019B020210003); and one grant from BNU-HKBU United International College (UIC202007); and one research grant from Natural Science Foundation of Guangdong Province (No. 2017A030310176).

ORCID

Jiali Chen http://orcid.org/0000-0002-7317-4146
Baojun Xu http://orcid.org/0000-0003-0739-3735
Xinwei Jiang http://orcid.org/0000-0003-4484-1293
Weibin Bai http://orcid.org/0000-0003-1729-2970

References

Amararathna, M., D. W. Hoskin, and H. V. Rupasinghe. 2020. Anthocyanin-rich haskap (*Lonicera caerulea* L.) berry extracts reduce nitrosamine-induced DNA damage in human normal lung epithelial cells *in vitro*. *Food and Chemical Toxicology* 141:111404.

Amatori, S., L. Mazzoni, J. M. Alvarez-Suarez, F. Giampieri, M. Gasparrini, T. Y. Forbes-Hernandez, S. Afrin, A. E. Provenzano, G. Persico, B. Mezzetti, et al. 2016. Polyphenol-rich strawberry extract (PRSE) shows *in vitro* and *in vivo* biological activity against invasive breast cancer cells. *Scientific Reports* 6 (1):30917. doi: 10.1038/srep30917.

Baby, B., P. Antony, and R. Vijayan. 2018. Antioxidant and anticancer properties of berries. *Critical Reviews in Food Science and Nutrition* 58 (15):2491–507. doi: 10.1080/10408398.2017.1329198.

Bishayee, A., T. Mbimba, R. J. Thoppil, E. H. Radnai, P. Sipos, S. Darvesh, H. G. Folkesson, and J. Hohmann. 2011. Anthocyanin-rich black currant (*Ribes nigrum* L.) extract affords chemoprevention against diethylnitrosamine-induced hepatocellular carcinogenesis in rats. *The Journal of Nutritional Biochemistry* 22 (11):1035–46. doi: 10.1016/j.jnutbio.2010.09.001.

Bray, F., J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 68 (6):394–424. doi: 10.3322/caac.21492.

Burton, L. J., M. Rivera, O. Hawsawi, J. Zou, T. Hudson, G. Wang, Q. Zhang, L. Cubano, N. Boukli, and V. Odero-Marah. 2016. Muscadine grape skin extract induces an unfolded protein response-mediated autophagy in prostate cancer cells: A TMT-based quantitative proteomic analysis. *PLoS One* 11 (10):e0164115. doi: 10.1371/journal.pone.0164115.

Cao, S. Y., Y. Li, X. Meng, C. N. Zhao, S. Li, R. Y. Gan, and H. B. Li. 2019. Dietary natural products and lung cancer: Effects and mechanisms of action. *Journal of Functional Foods* 52:316–31. doi: 10.1016/j.jff.2018.11.004.

Cao, H., O. Saroglu, A. Karadag, Z. Diaconeasa, G. Zoccatelli, C. A. Conte-Junior, J. Y. Ou, W. B. Bai, C. M. Zamarioli, L. A. P. Freitas, et al. 2021. Available technologies on improving the stability of polyphenols in food processing. *Food Frontiers 2*:1–31.

Charepalli, V., L. Reddivari, S. Radhakrishnan, R. Vadde, R. Agarwal, and J. K. Vanamala. 2015. Anthocyanin-containing purple-fleshed potatoes suppress colon tumorigenesis via elimination of colon cancer stem cells. *The Journal of Nutritional Biochemistry* 26 (12):1641–9. doi: 10.1016/j.jnutbio.2015.08.005.

Chen, J., M. Jayachandran, B. Xu, and Z. Yu. 2019. Sea bass (*Lateolabrax maculatus*) accelerates wound healing: A transition from inflammation to proliferation. *Journal of Ethnopharmacology* 236:263–76. doi: 10.1016/j.jep.2019.03.012.

Chen, L. L., B. Jiang, C. G. Zhong, J. Guo, L. Zhang, T. Mu, Q. H. Zhang, and X. L. Bi. 2018. Chemoprevention of colorectal cancer by black raspberry anthocyanins involved the modulation of gut microbiota and SFRP2 demethylation. *Carcinogenesis* 39 (3):471–81. doi: 10.1093/carcin/bgy009.

Diaconeasa, Z. M., A. D. Frond, I. Ştirbu, D. Rugina, and C. Socaciu. 2018. *Anthocyanins-smart Molecules for Cancer Prevention*, 75. BoD–Books on Demand. London, UK: InTech Open Access Publisher.

Eskra, J. N., M. J. Schlicht, and M. C. Bosland. 2019. Effects of black raspberries and their ellagic acid and anthocyanin constituents on taxane chemotherapy of castration-resistant prostate cancer cells. *Scientific Reports* 9 (1):1–12. doi: 10.1038/s41598-019-39589-1.

Farrukh, A., J. Jeyaprakash, K. Hina, M. Radha, S. Inderpal, and G. Ramesh. 2016. Lung cancer inhibitory activity of dietary berries and berry polyphenolics. *Journal of Berry Research* 6 (2):105–14.

Fernández, J., L. García, J. Monte, C. J. Villar, and F. Lombó. 2018. Functional anthocyanin-rich sausages diminish colorectal cancer in an animal model and reduce pro-inflammatory bacteria in the intestinal microbiota. *Genes* 9 (3):133. doi: 10.3390/genes9030133.

Forbes-Hernández, T. Y. 2020. Berries polyphenols: Nano-delivery systems to improve their potential in cancer therapy. *Journal of Berry Research* 10 (1):45–60. doi: 10.3233/JBR-200547.

Fragoso, M. F., G. R. Romualdo, L. A. Vanderveer, J. Franco-Barraza, E. Cukierman, M. L. Clapper, R. F. Carvalho, and L. F. Barbisan. 2018. Lyophilized açaí pulp (*Euterpe oleracea Mart*) attenuates colitis-associated colon carcinogenesis while its main anthocyanin has the potential to affect the motility of colon cancer cells. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 121:237–45. doi: 10.1016/j.fct.2018.08.078.

Giampieri, F., M. Gasparrini, T. Y. Forbes-Hernandez, L. Mazzoni, F. Capocasa, S. Sabbadini, J. M. Alvarez-Suarez, S. Afrin, C. Rosati, T. Pandolfini, et al. 2018. Overexpression of the anthocyanidin synthase gene in strawberry enhances antioxidant capacity and cytotoxic effects on human hepatic cancer cells. *Journal of Agricultural and Food Chemistry* 66 (3):581–92. doi: 10.1021/acs.jafc.7b04177.

Grimes, K. L., C. M. Stuart, J. J. McCarthy, B. Kaur, E. J. Cantu, and S. C. Forester. 2018. Enhancing the cancer cell growth inhibitory effects of table grape anthocyanins. *Journal of Food Science* 83 (9): 2369–74. doi: 10.1111/1750-3841.14294.

Ha, U., W. J. Bae, S. J. Kim, B. I. Yoon, S. H. Hong, J. Y. Lee, T. K. Hwang, S. Y. Hwang, Z. P. Wang, and S. W. Kim. 2015. Anthocyanin induces apoptosis of DU-145 cells *in vitro* and inhibits xenograft growth of prostate cancer. *Yonsei Medical Journal* 56 (1): 16–23. doi: 10.3349/ymj.2015.56.1.16.

Han, F., P. Yang, H. Wang, I. Fernandes, N. Mateus, and Y. Liu. 2019. Digestion and absorption of red grape and wine anthocyanins through the gastrointestinal tract. *Trends in Food Science & Technology* 83:211–24. doi: 10.1016/j.tifs.2018.11.025.

He, B., J. Ge, P. Yue, X. Yue, R. Fu, J. Liang, and X. Gao. 2017. Loading of anthocyanins on chitosan nanoparticles influences anthocyanin degradation in gastrointestinal fluids and stability in a beverage. *Food Chemistry* 221:1671–7. doi: 10.1016/j.foodchem.2016.10.120.

Herrera-Sotero, M. Y., C. D. Cruz-Hernández, R. M. Oliart-Ros, J. L. Chávez-Servia, R. I. Guzmán-Gerónimo, V. González-Covarrubias, M. Cruz-Burgos, and M. Rodríguez-Dorantes. 2020. Anthocyanins of blue corn and tortilla arrest cell cycle and induce apoptosis on breast and prostate cancer cells. *Nutrition and Cancer* 72 (5):768–77. doi: 10.1080/01635581.2019.1654529.

Huang, H. P., Y. C. Chang, C. H. Wu, C. N. Hung, and C. J. Wang. 2011. Anthocyanin-rich mulberry extract inhibit the gastric cancer cell growth in vitro and xenograft mice by inducing signals of p38/p53 and c-jun. *Food Chemistry* 129 (4):1703–9. doi: 10.1016/j.foodchem.2011.06.035.

Jia, N., Y. L. Xiong, B. Kong, Q. Liu, and X. Xia. 2012. Radical scavenging activity of black currant (*Ribes nigrum* L.) extract and its inhibitory effect on gastric cancer cell proliferation via induction of apoptosis. *Journal of Functional Foods* 4 (1):382–90. doi: 10.1016/j.jff.2012.01.009.

Jing, P., J. A. Bomser, S. J. Schwartz, J. He, B. A. Magnuson, and M. M. Giusti. 2008. Structure-function relationships of anthocyanins from various anthocyanin-rich extracts on the inhibition of colon cancer cell growth . *Journal of Agricultural and Food Chemistry* 56 (20):9391–8. doi: 10.1021/jf8005917.

Jing, P., B. J. Qian, S. J. Zhao, X. Qi, L. Ye, M. M. Giusti, and X. Y. Wang. 2015. Effect of glycosylation patterns of Chinese eggplant anthocyanins and other derivatives on antioxidant effectiveness in human colon cell lines. *Food Chemistry* 172:183–9. doi: 10.1016/j.foodchem.2014.08.100.

Kalemba-Drożdż, M., A. Cierniak, and I. Cichoń. 2020. Berry fruit juices protect lymphocytes against DNA damage and ROS formation induced with heterocyclic aromatic amine PhIP. *Journal of Berry Research* 10 (1):95–113. doi: 10.3233/JBR-190429.

Kausar, H., J. Jeyabalan, F. Aqil, D. Chabba, J. Sidana, I. P. Singh, and R. C. Gupta. 2012. Berry anthocyanidins synergistically suppress growth and invasive potential of human non-small-cell lung cancer cells. *Cancer Letters* 325 (1):54–62. doi: 10.1016/j.canlet.2012.05.029.

Kazan, A., C. Sevimli-Gur, O. Yesil-Celiktas, and N. T. Dunford. 2016. Investigating anthocyanin contents and in vitro tumor suppression properties of blueberry extracts prepared by various processes. *European Food Research and Technology* 242 (5):693–701. doi: 10.1007/s00217-015-2577-9.

Lage, N. N., M. A. A. Layosa, S. Arbizu, B. P. Chew, M. L. Pedrosa, S. Mertens-Talcott, S. Talcott, and G. D. Noratto. 2020. Dark sweet cherry (*Prunus avium*) phenolics enriched in anthocyanins exhibit enhanced activity against the most aggressive breast cancer subtypes without toxicity to normal breast cells. *Journal of Functional Foods* 64:103710. doi: 10.1016/j.jff.2019.103710.

Lee, D. Y., S. M. Yun, M. Y. Song, K. Jung, and E. H. Kim. 2020. Cyanidin chloride induces apoptosis by inhibiting NF-κB signaling through activation of Nrf2 in colorectal cancer cells. *Antioxidants* 9 (4):285. doi: 10.3390/antiox9040285.

Li, W. L., H. Y. Yu, X. J. Zhang, M. Ke, and T. Hong. 2018. Purple sweet potato anthocyanin exerts antitumor effect in bladder cancer. *Oncology Reports* 40 (1):73–82. doi: 10.3892/or.2018.6421.

Lila, M. A., B. Burton-Freeman, M. Grace, and W. Kalt. 2016. Unraveling anthocyanin bioavailability for human health. *Annual Review of Food Science and Technology* 7:375–93. doi: 10.1146/annurev-food-041715-033346.

Lim, S., J. Xu, J. Kim, T.-Y. Chen, X. Su, J. Standard, E. Carey, J. Griffin, B. Herndon, B. Katz, et al. 2013. Role of anthocyanin-enriched purple-fleshed sweet potato p40 in colorectal cancer prevention. *Molecular Nutrition & Food Research* 57 (11):1908–17. doi: 10.1002/mnfr.201300040.

Lin, B. W., C. C. Gong, H. F. Song, and Y. Y. Cui. 2017. Effects of anthocyanins on the prevention and treatment of cancer. *British Journal of Pharmacology* 174 (11):1226–43. doi: 10.1111/bph.13627.

Liu, X., L. Wang, N. Jing, G. Jiang, and Z. Liu. 2020. Biostimulating gut microbiome with bilberry anthocyanin combo to enhance anti-PD-L1 efficiency against murine colon cancer. *Microorganisms* 8 (2): 175. doi: 10.3390/microorganisms8020175.

Longo, L., F. Platini, A. Scardino, O. Alabiso, G. Vasapollo, and L. Tessitore. 2008. Autophagy inhibition enhances anthocyanin-induced apoptosis in hepatocellular carcinoma. *Molecular Cancer Therapeutics* 7 (8):2476–85. doi: 10.1158/1535-7163.MCT-08-0361.

López de Las Hazas, M.-C., J. I. Mosele, A. Macià, I. A. Ludwig, and M.-J. Motilva. 2017. Exploring the colonic metabolism of grape and strawberry anthocyanins and their in vitro apoptotic effects in HT-29 colon cancer cells. *Journal of Agricultural and Food Chemistry* 65 (31):6477–87. doi: 10.1021/acs.jafc.6b04096.

Lu, J. N., W. S. Lee, A. Nagappan, S. H. Chang, Y. H. Choi, H. J. Kim, G. S. Kim, C. H. Ryu, S. C. Shin, J. M. Jung, et al. 2015. Anthocyanins from the fruit of *vitis coignetiae pulliat* potentiate the cisplatin activity by inhibiting PI3K/Akt signaling pathways in human gastric cancer cells. *Journal of Cancer Prevention* 20 (1):50–6. doi: 10.15430/JCP.2015.20.1.50.

Lu, J. N., R. Panchanathan, W. S. Lee, H. J. Kim, D. H. Kim, Y. H. Choi, G. S. Kim, S. C. Shin, and S. C. Hong. 2017. Anthocyanins from the fruit of vitis coignetiae pulliat inhibit tnf-augmented cancer proliferation, migration, and invasion in a549 cells. *Asian Pacific Journal of Cancer Prevention: APJCP* 18 (11):2919–23. doi: 10.22034/APJCP.2017.18.11.2919.

Mazewski, C., M. S. Kim, and E. G. D. Mejia. 2019. Anthocyanins, delphinidin-3-O-glucoside and cyanidin-3-O-glucoside, inhibit immune checkpoints in human colorectal cancer cells in vitro and in silico. *Scientific Reports* 9 (1):1–15. doi: 10.1038/s41598-019-47903-0.

Mazewski, C., K. Liang, and E. G. D. Mejia. 2017. Inhibitory potential of anthocyanin-rich purple and red corn extracts on human colorectal cancer cell proliferation in vitro. *Journal of Functional Foods* 34: 254–65. doi: 10.1016/j.jff.2017.04.038.

Mazzoni, L., F. Giampieri, J. M. A. Suarez, M. Gasparrini, B. Mezzetti, T. Y. F. Hernandez, and M. A. Battino. 2019. Isolation of strawberry anthocyanin-rich fractions and their mechanisms of action against murine breast cancer cell lines. *Food & Function* 10 (11):7103–20. doi: 10.1039/c9fo01721f.

Pan, F., Y. Liu, J. Liu, and E. Wang. 2019. Stability of blueberry anthocyanin, anthocyanidin and pyranoanthocyanidin pigments and their inhibitory effects and mechanisms in human cervical cancer HeLa cells. *RSC Advances* 9 (19):10842–53. doi: 10.1039/C9RA01772K.

Peiffer, D. S., L.-S. Wang, N. P. Zimmerman, B. W. S. Ransom, S. G. Carmella, C.-T. Kuo, J.-H. Chen, K. Oshima, Y.-W. Huang, S. S. Hecht, et al. 2016. Dietary consumption of black raspberries or their anthocyanin constituents alters innate immune cell trafficking in esophageal cancer. *Cancer Immunology Research* 4 (1):72–82. doi: 10.1158/2326-6066.CIR-15-0091.

Qamar, M., S. Akhtar, T. Ismail, P. Sestili, A. Tawab, and N. Ahmed. 2020. Anticancer and anti-inflammatory perspectives of Pakistan's indigenous berry Grewia asiatica Linn (Phalsa). *Journal of Berry Research* 10 (1):115–31. doi: 10.3233/JBR-190459.

Shin, D. Y., C. H. Ryu, W. S. Lee, D. C. Kim, S. H. Kim, Y. S. Hah, S. J. Lee, S. C. Shin, H. S. Kang, and Y. H. Choi. 2009. Induction of apoptosis and inhibition of invasion in human hepatoma cells by anthocyanins from meoru. *Annals of the New York Academy of Sciences* 1171 (1):137–48. doi: 10.1111/j.1749-6632.2009.04689.x.

Singh, A. N., M. M. Baruah, and N. Sharma. 2017. Structure-based docking studies towards exploring potential anti-androgen activity of selected phytochemicals against prostate cancer. *Scientific Reports* 7 (1):1–8. doi: 10.1038/s41598-017-02023-5.

Sousa, A., P. Araújo, J. Azevedo, L. Cruz, I. Fernandes, N. Mateus, and V. de Freitas. 2016. Antioxidant and antiproliferative properties of 3-deoxyanthocyanidins . *Food Chemistry* 192:142–8. doi: 10.1016/j.foodchem.2015.06.108.

Tan, Y. F., M. Wang, Z. Y. Chen, L. Wang, and X. H. Liu. 2020. Inhibition of BRD4 prevents proliferation and epithelial–mesenchymal transition in renal cell carcinoma via NLRP3 inflammasome-induced pyroptosis. *Cell Death & Disease* 11 (4):239. doi: 10.1038/s41419-020-2431-2.

Thi, N. D., and E. S. Hwang. 2018. Effects of black chokeberry extracts on metastasis and cell-cycle arrest in sk-hep1 human liver cancer cell line. *Asian Pacific Journal of Tropical Biomedicine* 8 (6):285–91. doi: 10.4103/2221-1691.235313.

Venancio, V. P., P. A. Cipriano, H. Kim, L. M. Antunes, S. T. Talcott, and S. U. Mertens-Talcott. 2017. Cocoplum (*Chrysobalanus icaco* L.) anthocyanins exert anti-inflammatory activity in human colon cancer and non-malignant colon cells. *Food & Function* 8 (1):307–14. doi: 10.1039/c6fo01498d.

Vuolo, M. M., Â. G. Batista, A. C. T. Biasoto, L. C. Correa, M. R. M. Júnior, and R. H. Liu. 2019. Red-jambo peel extract shows antiproliferative activity against HepG2 human hepatoma cells. *Food Research International (Ottawa, Ont.)* 124:93–100. doi: 10.1016/j.foodres.2018.08.040.

Wang, L., G. Jiang, N. Jing, X. Liu, Q. Li, W. Liang, and Z. Liu. 2020. Bilberry anthocyanin extracts enhance anti-PD-L1 efficiency by modulating gut microbiota. *Food & Function* 11 (4):3180–90. doi:10.1039/D0FO00255K.

Wang, E., Y. Liu, C. Xu, and J. Liu. 2017. Antiproliferative and proapoptotic activities of anthocyanin and anthocyanidin extracts from blueberry fruits on B16-F10 melanoma cells. *Food & Nutrition Research* 61 (1):1325308. doi: 10.1080/16546628.2017.1325308.

Wang, L. S., and G. D. Stoner. 2008. Anthocyanins and their role in cancer prevention. *Cancer Letters* 269 (2):281–90. doi: 10.1016/j.canlet.2008.05.020.

Wang, X., D. Y. Yang, L. Q. Yang, W. Z. Zhao, L. Y. Cai, and H. P. Shi. 2019. Anthocyanin consumption and risk of colorectal cancer: A meta-analysis of observational studies. *Journal of the American College of Nutrition* 38 (5):470–7. doi: 10.1080/07315724.2018.1531084.

Yue, E., G. Tuguzbaeva, X. Chen, Y. Qin, A. Li, X. Sun, C. Dong, Y. Liu, Y. Yu, S. M. Zahra, et al. 2019. Anthocyanin is involved in the activation of pyroptosis in oral squamous cell carcinoma. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 56:286–94. doi: 10.1016/j.phymed.2018.09.223.

Zhang, Y. B., X. F. Pan, J. Chen, A. Cao, Y. G. Zhang, L. Xia, J. Wang, H. Q. Li, G. Liu, and A. Pan. 2020. Combined lifestyle factors, incident cancer, and cancer mortality: A systematic review and meta-analysis of prospective cohort studies. *British Journal of Cancer* 122 (7):1085–9. doi: 10.1038/s41416-020-0741-x.