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Review

The Anti-Cancer Effects of Red-Pigmented Foods: Biomarker Modulation and Mechanisms Underlying Cancer Progression

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Abstract: Cancer is one the most malignant diseases that is a leading cause of death worldwide. Vegetables and fruits contain beneficial nutrients such as vitamins, minerals, folates, dietary fibers, and various natural bioactive compounds. These can prevent the pathological processes of many cancers and reduce cancer related mortality. Specifically, the anti-cancer effect of vegetables and fruits is largely attributable to the natural bioactive compounds present within them. A lot of bioactive compounds have very specific colors with pigments and the action of them in the human body varies by their color. Red-pigmented foods, such as apples, oranges, tomatoes, cherries, grapes, berries, and red wine, have been widely reported to elicit beneficial effects and have been investigated for their anti-tumor, anti-inflammatory, and antioxidative properties, as well as anti-cancer effect. Most of the anti-cancer effects of bioactive compounds in red-pigmented foods arise from the suppression of cancer cell invasion and metastasis, as well as the induction of apoptosis and cell cycle arrest. In this review, we assessed publications from the last 10 years and identified 10 bioactive compounds commonly studied in red-pigmented foods: lycopene, anthocyanin, β-carotene, pectin, betaine, rutin, ursolic acid, kaempferol, quercetin, and myricetin. We focused on the mechanisms and targets underlying the anti-cancer effect of the compounds and provided rationale for further investigation of the compounds to develop more potent anti-cancer treatment methods.

Keywords: anti-cancer effects; red-pigmented foods; biomarkers; mechanisms; bioactive compounds

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1. Introduction

Cancer is a leading cause of death worldwide and remains a serious threat to societal development globally. It is generally accepted that cancer arises due to mutations in cancer susceptibility genes and an abnormal stromal environment that is conducive to the neoplastic transformation of cells [1,2]. The overall risk of cancer development depends not only on initiation, but also on sustained progression of tumorigenesis [3].

The National Research Council in the United States and WHO pay attention to foods that have beneficial effects to keeping health and preventing human diseases, such as vascular diseases, cataract, and cancer [4]. Regarding cancer prevention and control, the World Health Organization (WHO) action provides guidance on public health priorities and thus key implementation in science issues. In 2003, WHO and the Food and Agriculture Organization (FAO) strongly suggested a diet rich in vegetables and fruits, and low in sugar, fat, and salt, combined with regular physical activity to reduce mortality caused by chronic diseases [5]. It is very important to remember that 90–95% of all cancers are closely related to lifestyle, such as obesity and diet [6]. Functional foods are defined as those foods and food components that impart beneficial effects on human health beyond basic nutrition. The term originated in Japan in the late 1980s to describe foods fortified with ingredients that elicit additional health benefits [7]. However, the connotated terminology goes beyond the complex, life-maintaining nutritional characteristics of food, which can be referred to

with other popular terms such as 'nutraceuticals', 'dietary supplements', 'immunoceuticals', and 'designer foods' [8,9]. Based on these terms with diverse meanings, it would seem that the precise definition of functional food is somewhere between a conventional nutrient and a medicine [10]. Accumulating evidence has shown the direct impact of food components on health, and research has investigated the intrinsic benefits of natural foods on human diseases, such as cardiovascular diseases, neurodegenerative diseases, and cancers [11–13].

Specifically, such food components are known for their various colorful and dark pigments for which bioactive compounds are responsible. Fruits and vegetables are distinguished by their specific colors and most plant-based pigments typically correspond to a phytonutrient category, for example, red for lycopene, orange and yellow for β-carotene, green for chlorophyll, and blue and purple for anthocyanin [14–18]. It is generally acknowledged that colorful fruits and vegetables are an indicator for food selection of the most nutritious varieties [19]. Numerous reports have shown associations between pigments in colorful foods and human diseases, especially cancer, which occur via the modulation of various mechanisms underlying cancer progression [20]. For example, increased tomato intake can reduce plasma concentrations of IL-10 and vascular cell adhesion molecule-1 (VCAM-1) [21], which can be involved in cancer invasion and metastasis [22]. Carrot inhibits the expression of pro-inflammatory cytokines and cancer-related transcription factors, such as COX-2, IL-6, TNF-α, and NF-κB [23]. A randomized controlled study showed that intervention with green leafy vegetables reduced the risk of red meat-triggered DNA damage and colon cancer by modulating gut microbiota and inflammatory cytokines [24]. An anthocyanin-enriched, purple-fleshed sweet potato was found to decrease cancer cell proliferation by down-regulating proliferative PCNA and up-regulating caspase-3, with further extensive involvement in cell cycle arrest, and the anti-proliferative and apoptotic mechanisms of cancer development [25].

In practice, three colors: red, blue, and yellow, are the most basic, and the combination of these colors generate secondary colors, such as orange, green, and purple [26]. Of particular note, due to red-colored vegetables and fruits tending to be higher in certain bioactive compounds [27], there has been a growing interest in red-pigmented foods in the field of functional food science. In this review, we have selected 10 commonly studied red-pigmented bioactive compounds for publication in the last 10 years (Figure 1): lycopene, anthocyanin, β-carotene, pectin, betaine, rutin, ursolic acid, kaempferol, quercetin, and myricetin, and commented on the diverse mechanisms underlying their suppression of cancer cell progression.

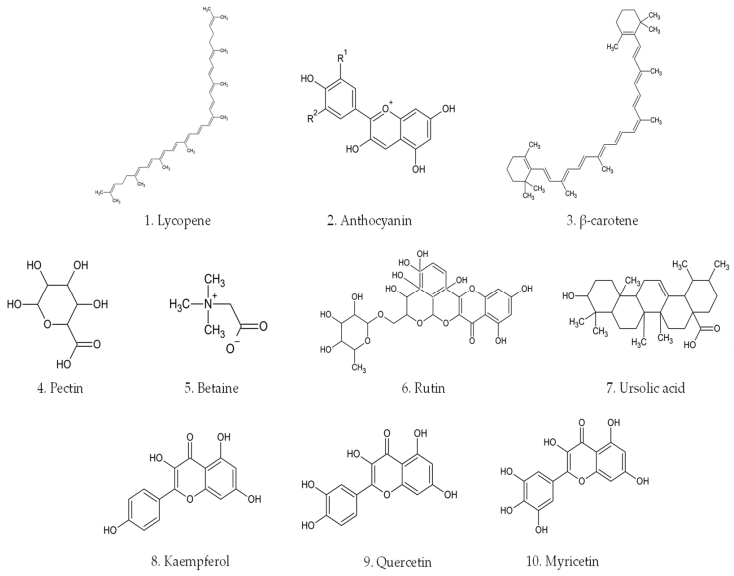

Figure 1. Chemical structures of 10 bioactive compounds in red-pigmented foods. The chemical structures of the compounds were generated using ACD/ChemSketch (Freeware; Ver. 3 January 2021).

2. Bioactive Compounds

2.1. Lycopene

Lycopene is synthesized by plants and microorganisms as a common natural pigment [28]. It is chemically characterized by a highly unsaturated hydrocarbon chain containing 11 conjugated and 2 unconjugated double bonds [29]. Lycopene is found in red fruits and vegetables such as carrots, watermelon, grapefruit, apricot, pink guava, and papaya [30].

Findings from epidemiological studies have suggested the possibility that lycopene can prevent the emergence of cancer cells as well as their progression, with numerous reports shedding light on the molecular mechanisms underlying these effects. A meta-analysis showed that 57 out of 72 studies reported an inverse correlation between lycopene consumption and the risk of diverse cancer types including prostate, breast, colon, and lung cancer [31]. In 2019, Kim et al. demonstrated that lycopene induced apoptosis in gastric cancer cells by inhibiting the nuclear translocation of β-catenin and expression of predominant cancer cell survival genes [32]. In this study, lycopene increased DNA fragmentation and the Bax/Bcl-2 ratio, reducing viability of the AGS cells. Lycopene-mediated ROS reductions also decreased activation of the EGFR/Ras/ERK and p38 MAPK pathways, thereby sequentially attenuating NF-κB mediated COX-2 expression via attenuation of the DNA-binding activity of NF-κB p65/p50 [33]. An in vivo study supported these in vitro anti-gastric cancer findings. Zhou et al. demonstrated that tumor weight was significantly decreased in gastric cancers in nude mice following lycopene treatment, while suggesting that LC3-1 and ERK were involved in the effect [34]. In addition, lycopene reduced the viability of the pancreatic cancer cell line PANC-1 via a similar mechanism of action [35]. In that study, lycopene induced apoptosis of PANC-1 cells by decreasing ROS levels, consequently abrogating NF-κB activity and the expression of its target genes such as clAP1, clAP2, and survivin. MicroRNA (miR)-let-7f was also involved in suppression of the prostate cancer cells. Li et al. demonstrated that lycopene up-regulated miR-let-7f-1 expression and induced the down-regulation of AKT2 in PC3 cells through gain- and loss-of-function experiments [36]. In n-nitrosomethylbenzylamine (NMBzA)-induced esophageal cancer in F344 rats, lycopene intervention (25 mg/kg/day) for 25 weeks not only significantly reduced inflammatory cytokines by suppressing NF-κB and COX-2, but also enhanced apoptotic cytokine expression by increasing PPARγ and caspase-3 activity [37]. Another two studies showed that lycopene enhanced expression of the pro-apoptotic protein BAX, while suppressing the anti-apoptotic protein Bcl-2 in ovarian [38], oral [39], and breast cancers [40]. Furthermore, lycopene improved the efficacy of anti-PD-1 treatment, a cancer immunotherapy. In mice injected with Lewis lung carcinoma cells, the combination of lycopene and anti-PD-1 agent reduced tumor volume and weight to a greater extent than either lycopene or anti-PD-1 alone [41]. As well as inducing cellular apoptosis, the combination elevated the levels of IL-1 and IFN-γ in the spleen of the LCC bearing mice, consequently diminishing PD-L1 expression by activating JAK and increasing phosphorylation of AKT. These studies suggest that lycopene could be used as a nutraceutical or as a potential adjuvant to anti-cancer drugs to synergistically improve their efficacy.

2.2. Anthocyanin

Anthocyanins occur ubiquitously in vegetables and fruits as glycosides that are known for their bioactive properties and low cytotoxicity [42]. The base structure is 2-phenylchromenylium (flavolium), which lays the foundation for various types of anthocyanins such as glucose, galactose, and rhamnoses including pelargonidin, delphinidin, petunidin, cyanidin, and malvidin [43,44]. Unlike other flavonoids, the anthocyanins retain a positive charge in acidic solution [45], thus they are water-soluble and, depending on pH and the chelating metal ions present, are intensely colored purple, blue, or red [46]. Numerous studies have indicated that various anthocyanins elicit anti-cancer effects via distinct molecular mechanisms. One of the anthocyanins, cyanidin-3-glucoside (C3G), plays a pivotal role in various cancers including glioblastoma, breast, colon, and prostate

cancer. G3G treatment triggers apoptotic cell death in U87 glioblastoma cells by inducing Bax and p53 gene expression [47]. In breast cancer cells, C3G interferes with activation of the STAT3/VEGF signal pathway by suppressing both mRNA and protein expression and inducing miR-124 expression; as a result, C3G attenuates the angiogenesis of breast cancer cells [48]. The anti-cancer properties of C3G have also been demonstrated in colon cancer. A study showed that C3G has one of the highest binding affinities to ABL1, a key enzyme for cancer cell survival [49]. A molecular docking analysis showed that C3G binds to talin, which is negatively correlated with survival in colon cancer patients, sequentially altering its interactions with β1A-integrin [50]. As a result, 3D spheroid growth of colon cancer cells was significantly inhibited. C3G also showed anti-proliferative properties via activation of caspase-3 in prostate cancer [51] and non-small cell lung cancer cells [52]. C3G reduced the viability and inhibited the invasion and migration ability of oral squamous cell carcinoma cells via activation of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3/caspase-1/IL-1β-mediated pyroptosis [52]. A recent study indicated the possible involvement of epigenetic regulation in the anti-cancer effects of anthocyanin [53]. Pelargonidin, a natural anthocyanidin, reduced DNA methylation levels in the Nrf2 promoter region in JB6P+ cells, consequentially blocking neoplastic transformation of the cells.

2.3. β-Carotene

β-carotene is a major source of vitamin A and is a key member of the carotenoid family [54]. It is a strongly red-orange colored pigment that is common in the human diet. β-carotene is derived from carotenes, which are terpenoids, synthesized biochemically from 8 isoprene units harboring 40 carbon atoms. It is primarily found in carrots, apricots, paprika, and chili powder [55]. In patients with various types of cancer, β-carotene levels in the serum are inversely associated with tumor development [56,57]. In 2020, a study presented the first evidence suggesting that β-carotene regulates the tumor microenvironment through IL-6/STAT3-mediated inhibition of M2 macrophage polarization and fibroblast activation [58]. β-carotene also controls the self-renewal capacity of colon cancer stem cells via epigenetic regulation [59]. In one particular study, a miRNA sequencing array analysis showed that β-carotene regulates miRNA expression associated with histone acetylation; Histone H3 and H4 acetylation status were elevated following β-carotene treatment in colon cancer stem cells. Additionally, DNMT mRNA expression was also down-regulated, consequently reducing global DNA methylation. Additional studies have shown the effect of β-carotene on cancer cell stemness, indicating that β-carotene not only reduces cell growth and induces differentiation of neuronal cells through increasing ERK phosphorylation, but can also inhibit the self-renewal property of cancer stem cells by reducing drosophila delta-like 1 homolog (DLK1), a predominant stem cell marker [60]. Another study supported these findings, demonstrating the anti-stemness properties of β-carotene using a xenograft model [61]. In this study, mice were supplemented with β-carotene for 3 weeks, before receiving a subcutaneous injection of SK-N-BE(2)C neuroblastoma cells. Both tumor growth and incidence were significantly suppressed in the group administrated with β-carotene compared to those in the control group. β-carotene repressed cancer stem cell markers including Oct 3/4 and DLK1. In addition, β-carotene controls cancer development and progression via regulation of various anti-cancer mechanisms. For example, it can trigger apoptosis by inhibiting the caveolin-1-mediated AKT/NF-κB signaling pathway in human esophageal squamous cell carcinoma cells [62]. In breast cancer cells, β-carotene blocks the activation of AKT and ERK1/2, which is mediated by an intracellular growth signaling cascade, and decreases levels of the antioxidant enzyme SOD-2 via down-regulation of its transactivation factor (Nrf-2), thereby suppressing cancer cell survival [63]. In AGS cells (a human stomach cancer cell line), β-carotene induced apoptosis via reduction of Ku70/80, which plays a critical role in DNA double-strand break repair [64], and inhibited MMP-10-mediated cell invasion by suppressing the H. pylori-induced up-regulation of MAPKs and AP-1 [64]. The combination of 5-fluorouracil and

β-carotene was shown to impart greater tumor inhibition in a human esophageal carcinoma cell-xenografted mouse model [65]. The study demonstrated that the combined treatment synergistically down-regulated the expression of Cav-1, p-AKT, p-NF-κB, and mTOR to a greater extent than 5-FU alone. The combination of β-carotene and chemotherapeutic agents remarkably attenuated toxicity in P-glycoprotein-overexpressing and multi-drug resistance cancer cells [66]. By targeting cancer stem cells, β-carotene can also resensitize cells to the anti-cancer drug cisplatin [60].

2.4. Pectin

Pectin is a complex mixture of linear polysaccharides which is present in the cell walls of fruits and higher plants, especially apples and citrus peels [67]. Although it was discovered over 200 years ago, the structure and composition of pectin are still not well understood due to its diverse sources and extraction methods. Pectin is the most structurally complex of polysaccharides as a structural acidic heteropolysaccharide present in the primary and middle lamella and cell walls of the plant [68]. The anti-tumor effects of dietary pectin may be boosted by formulating the fiber with a chemo-protective food component [69,70]. The mechanisms underlying this effect are associated with modulation of gut microbiota [71], apoptosis [72,73], tumor cell growth [74], and miRNA expression [67]. The anti-tumor efficacy of pectins have been primarily investigated in colon cancer. Pectin supplementation facilitated an anti-PD- mAb effect in humanized C57BL/6 mice harboring colon cancer patient cells by enhancing T cell infiltration into the tumor microenvironment [71]. A study explored the possibility of its use as an adjuvant in irinotecan therapy for both enhancing curative efficacy and ameliorating the side-effects of colon cancer treatment [72]. In the study, a novel enzymatically-extracted apple pectin was shown to induce apoptosis and ROS production, while reducing cell viability and preventing the adhesion of prototype adherent-invasive *E. coli* in colorectal cancer cells, and HCT116 and Caco-2 cells. Apple pectin was also found to suppress breast cancer progression. In 4T1 breast cancer cells, apple pectin obstructed the sub-G1 phase entrance, and reduced the cell attachment and fragmentation of chromatin through p53 overexpression [73]. A further study explored the selective anti-cancer efficacy of apple pectin and citrus pectin in MCF-7, MDA-MB231, and T47D breast cancer cells [74]. The cancer cells treated with citrus pectin and apple pectin were arrested at the S/G1 or G2/M phases of the cell cycle, respectively. Moreover, citrus pectin induced growth inhibition of MDA-MB-231 cells, whereas apple pectin was associated with DNA breaks and DNA damage via oxidation. The anti-cancer phenomena were mediated through pectin's dsDNA binding ability. The pectin oligosaccharides (POS), including homogalacturonan, xylogalaturonan, and rhamnogalacturonan I and II, have been utilized as resources for the development of potential anti-cancer drugs due to these observed beneficial effects [75].

2.5. Betaine

Betaine was first identified in beets and is a nontoxic and stable natural compound. It is primarily found in plants, animals, and microorganisms at higher concentrations [76]. Consumption of dietary betaine plays a crucial role in raising betaine content in the kidneys, liver, and brain [77]. Betaine is a modified amino acid consisting of glycine with three additional methyl groups [78]. Thus, it frequently serves as a methyl donor for several metabolic pathways. Studies of human diseases have shown involvement in cardiovascular disease, metabolic syndrome, Alzheimer's disease [79–82], and cancer. In breast cancer cells, betaine inhibits alcohol-induced transcription of Pol III both in vitro and in vivo. One study showed that betaine inhibited cell growth and colony formation via the down-regulation of Brf1 and Pol III [83]. Betaine enhanced the expression of antioxidants such as GSH, SOD, CAT, and TAS, and reduced the expression of pro-inflammatory cytokines such as TNF-α and IL-6 in the prostate cancer cell line DU-145. Additionally, it induced morphological changes, DNA fragmentation, and apoptosis in a dose-dependent manner [84]. Betaine was also found to enhance the proliferation of HeLa cells, while inhibiting cell growth and

migration by promoting activity of the pro-apoptotic genes p53, Bax, and caspase-3 [85]. It was also shown to directly target mitochondria. A study demonstrated that betaine treatment led to increasing mitochondrial respiration and cytochrome c oxidase activity which were reduced in human pathological diseases including cancer, consequentially producing ATP, cellular energy, and reversal of the Warburg effect in cancer cells [86]. In an AOM/DSS-induced colon cancer model, betaine administration significantly reduced ROS generation and GSSG concentration by down-regulating inflammatory cytokines such as TNF-α, IL-6, iNOS, and COX-2 [87]. It also attenuated cisplatin-induced hepatic injury in rats through regulation of NF-κB and caspase-3-dependent apoptosis [88]. Among the betaines, δ-valerobetaine inhibited the growth of human oral squamous cell carcinoma, Cal 27 cells, and ROS accumulation. SIRT1 up-regulation and apoptosis were found to be responsible for the observations [89]. The study showed that SIRT1 silencing using small interfering RNA reduced apoptosis induced by the combination of δ-valerobetaine with δ-butyrobetaine by modulating procaspase-3 and cyclin B1. Betaine also regulates angiogenesis, the formation of new vessels surrounding the tumor, in vitro and in vivo, and suppressed tube formation, invasion, and migration in HUVECs (human umbilical vein endothelial cells) in a mouse matrigel plug assay [90]. The study demonstrated that following betaine treatment, the mRNA expression of basic fibroblast growth factor, matrix metalloproteinase-2, and matrix metalloproteinase-9 was down-regulated via the suppression of NF-κB and Akt activation. Betaine supplementation in rats bearing diethylinitrosamine-induced liver cancer increased p16 while blocking c-myc expression. Furthermore, in the model, it was observed that increased levels of malondialdehyde and glutathione S-transferase resulted in enhanced antioxidative capacity [91].

2.6. Rutin

Rutin is a flavonol mainly found in citrus plants, including the peel of orange fruit (*Citrus sinensis*) [92], wine, and grapes [92]. Rutin has been shown to have anti-cancer effects by promoting apoptosis and inducing G2/M cell cycle arrest in human neuroblastoma cells by reducing Bcl2 and the Bcl2/Bax ratio [93]. In a preventive study of cervical cancer, rutin downregulated Notch-1 and Hes-1, thereby inducing apoptotic cell death [94], which is attributable to the activation of caspase-3/9, induction of ROS, and alteration of Bax/Bcl2 mRNA expression [94]. Rutin also induced caspase-dependent apoptosis in HeLa cells [94], which was mediated by HPV-E6 and E7 down-regulation. E6 and E7 were shown to inactivate the tumor suppressor proteins p53 and pRB, which was reversed with rutin treatment in cervical cancer [94]. Rutin has also been demonstrated to mitigate breast cancer cell growth via regulation of the microRNA-129-1-3p-mediated calcium signaling pathway. Overexpression of microRNA-129-1-3p mediated by rutin suppressed the proliferation, invasion, migration, and calcium overload of mouse breast cancer cells (4T1), thereby enhancing apoptosis in 4T1 cells [95]. Rutin has also been shown to have a protective effect against colorectal cancer. Transcriptome analysis using bioinformatics tools indicated that rutin interferes with cancer progression via the alteration of glucose, lipid, and protein metabolism, modulation of endoplasmic reticulum stress responses, negative regulation of cell cycle processes, and induction of the extrinsic and intrinsic apoptotic signaling pathways [94]. Rutin is also well known to exhibit anti-inflammatory properties, which are mediated by the down-regulation of COX-2 and TNF-α in HPV16-transgenic mice [96]. This anti-inflammatory activity contributes to protection against lung cancer. Wu et al. (2017) demonstrated that rutin attenuates TNF-alpha, thereby inducing apoptosis while also reducing GSK-3b expression in A549 human lung cancer cells [97]. Rutin also mitigates inflammatory responses via NF-κB, COX-2, IL-6, TNF-α down-regulation induced by benzo(a)pyrene in the lungs of mice [98]. Rutin-mediated induction of apoptosis via modulation of p53 gene expression in PC3 cancer cells has also been shown to protect against prostate cancer [99].

2.7. Ursolic Acid

Ursolic acid is a pentacyclic triterpenoid found in apple peels (*Malus domestica*) [100,101]. Ursolic acid protects against breast cancer by activating SFRP4 (Wnt agonist), inhibiting miRNA-499A-5p in MCF7, MDA-MB-231, and CSC cells [102], and also activates SP1/Caveoli-1 signaling, thereby inhibiting breast cancer metastasis [103]. Ursolic acid also protects against intestinal cancer progression, where it dose-dependently attenuates the number and growth of cells while down-regulating FN1, CDH2, CTNNB1, and TWSIT gene expression. Ursolic acid also down-regulates expression of the cancer cell survival markers BCL-2, SURVIVIN, NFKB, and SP1, while upregulating BAX, P21, and P53, markers of cancer cells growth inhibition [104]. The anti-tumor activity of ursolic acid can be partly attributed to its binding to EGFR and subsequent down-regulation of phospho-EGFR and inhibition of the JAK2/STAT3 signaling pathway. In addition, ursolic acid reduces VEGF, MMP, and PD-L1 expression, as well as STAT3/MMP2 and STAT3/PD-L1 complex formation, observations reported in non-small cell lung cancer cells [105]. Conway et al. noted that ursolic acid inhibited collective cell migration while promoting lysosome-associated cell death, outcomes that were JNK-dependent in glioblastoma multiforme cells [106]. Conway et al. also found that ursolic acid-mediated increased cell toxicity causing the formation of AVO, which likely contributed to eventual apoptosis [106]. Analysis of data from the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) databases found that colon adenocarcinoma patients have increased expression of cyclin B1 that acts as a tumor promoting gene, and this overexpression can be reversed with treatment of ursolic acid in HCT-116 and SW-480 cells [107]. A number of other studies have demonstrated that ursolic acid has anti-cancer effects against various cancer types including esophageal cancer [108], pancreatic cancer [109], and colorectal cancer [110] via a number of different mechanisms, including the induction of ROS-mediated autophagy [108] and ER stress-mediated RAGE inhibition, promoting apoptosis and autophagy [109], and up-regulation of ROS and caspase-3, -8, and -9, thereby inducing apoptosis [92]. Further anti-tumor effects of ursolic acid have been observed in papillary thyroid carcinoma cells, mediated via enhancement of fibronectin-1 expression and subsequent induction of apoptosis [111].

2.8. Kaempferol

Kaempferol is a flavonol found in numerous plants and plant-derived foods such as apple (0.14 mg/g fresh weight), blueberry (3.17 mg/g fresh weight), cherry (5.14 mg/g fresh weight), and cranberry (0.21 mg/g fresh weight). Black tea (1.70 mg/100 mL) and red wine (0.25 mg/100 mL) also contain significant levels of kaempferol [112]. The anti-carcinogenic activity of the compound has been investigated in various cancer cell models. Kaempferol reduces metalloproteinase-2 (MMP-2) protein expression and activity in 786-O renal cancer cells, effects that are thought to be mediated by the phosphorylation of Akt and down-regulation of focal adhesive kinase (FAK) [113]. Kaempferol arrests cell cycle progression at the G2/M stage, which is mediated by the down-regulation of CDK1 in human breast cancer MDA-MB-453 cells. This contributes to the inhibition of cancer cell growth [114]. Kaempferol also elicits a protective effect against triple-negative breast cancer cells (TNBC) [115]. Indeed, kaempferol suppresses the migration and invasion of TNBC cells, mediated by the mitigation of RhoA and Rac1 activity [115]. Zhao et al. investigated the induction of TRAIL-mediated apoptosis induced by kaempferol in human ovarian cancer cells, which was found to be mediated via the ERK/JNK/CHOP-related signaling pathways [116]. Kaempferol increased the expression of DR4, DR5, CHOP, JNK, ERK1/2, and p38, as well as apoptosis-related proteins, contributing to the induction of chemosensitivity in the human ovarian cancer cells OVCAR-3 and SKOV-3 to TRAIL-induced apoptosis [116]. In the study conducted by Da et al., kaempferol suppressed the growth of LNCaP cells that were sensitive to androgen by up to almost 100%, while inhibiting androgen receptor activity induced by DHT, collectively suggesting the possibility that kaempferol acts against cancers associated with the androgen signaling pathway, including prostate cancer [117]. Kaempferol and 5-fluorouracil together protected against

colorectal cancer by inhibiting PI3K/Akt signaling [118], and the anti-carcinogenic activity was greater compared to the use of either agent alone [118]. Kaempferol's ability to overcome 5-FU resistance has also been investigated in treatment-resistant LS174 colon cancer cells [119].

Kaempferol and 5-FU together increased apoptosis and induced cell cycle arrest in chemo-resistant and -sensitive cells. Kaempferol also blocked ROS formation and inhibited the JAK/STAT3, MAPK, PI3K/Akt, and NF-KB pathways [119]. According to an in silico docking analysis, the anti-tumor effect of kaempferol is attributable to the deletion of a glycosyl group in contrast to other derivatives, including kaempferol 3-O-glucoside and kaempferol 3-O-rutinoside [119]. Similarly, kaempferol promoted apoptosis and autophagy by inhibiting the phosphorylation of PI3K and Akt and increasing PTEN expression, as well as up-regulating miR-340 in human lung cancer cells [120]. Kaempferol also provides potential protection against gastric cancer cell growth [58]. Kaempferol up-regulates miR-181a and inactivates the MAPK/ERK and PI3K-mediated pathways, contributing to suppression of the growth of SNU-216 cells and promoting cell autophagy [58]. Chuwa et al. evaluated the anti-tumor effects of kaempferol in endometrial cancer [121], and found that kaempferol dose-dependently induced sub-G1 cell accumulation and cell apoptosis significantly. In particular, kaempferol-mediated apoptosis was associated with the inhibition of 17 β-estradiol-induced ERα and survivin, two important targets in the development of endometrial cancer [121].

2.9. Quercetin

Quercetin is found in a variety of foods such as apple (4.01 mg/g fresh weight), chili pepper (32.6 mg/100 g fresh weight), blueberry (14.6 mg/g fresh weight), cherry (17.4 mg/g fresh weight), and cranberry (25.0 mg/g fresh weight). Quercetin is also present in black tea (2.50 mg/100 mL) and red wine (3.16 mg/100 mL) [112]. The anti-cancer effects of quercetin have been widely studied using different models of cancer including liver, prostate, breast, lung, ovarian and cervical. Quercetin suppresses tumor growth and increases the survival rate of nude mice grafted with HepG2 human hepatocarcinoma cells, which is likely via the reduction of cyclinD1 expression in the tumors [122]. In addition, quercetin induces apoptosis by interfering with the cell cycle of human hepatocellular carcinoma LM3 cells, and simultaneously induces autophagy by down-regulating JAK2 and STAT3 activity, thereby protecting against the progress of hepatocarcinoma [123]. Quercetin reverses docetaxel resistance by modulating the androgen receptor expression and the PI3K/Akt signaling pathway in prostate cancer cells (LNCaP/R, PC-3/R) [123]. Moreover, quercetin treatment markedly decreases MALAT1 protein expression dose- and time-dependently in PC cells, thus inhibiting epithelial-to-mesenchymal transition (EMT) and inducing apoptosis [124]. This indicates that quercetin has protective effects against prostate cancer development [124]. The anti-cancer effects of quercetin are likely attributable to its induction of apoptosis, which has been evaluated in 9 different tumor cell lines [125]. Annexin V/PI staining indicates that quercetin significantly promotes apoptosis, especially in CT-26, LNCaP, MOLT-4, and Raji cell lines, while also reducing tumor volume significantly in MCF-7 and CT-26 mice [125]. Liu et al. investigated the possibility that quercetin can overcome cisplatin-induced side effects. Interestingly, quercetin mitigated kidney toxicity, a potential side effect of cisplatin treatment, while cisplatin and quercetin together increased anti-tumor effects compared to the controls in EMT6 breast tumor-bearing mice [126]. ln addition to the mitigation of side effects, quercetin also enhanced the anti-tumor effects of BET inhibitors in a xenograft model of pancreatic cancer [127]. Simultaneous treatment with quercetin and a BET inhibitor induced apoptosis and suppressed cell growth, while reducing hnRNPA1 expression in vivo, thereby enhancing the anti-tumor effect of the BET inhibitor [127]. These studies suggest that quercetin can be synergistically used with current cancer treatments under development. Quercetin also suppressed cancer metastasis including lung cancer via inhibition of Snail-dependent Akt activation and Snail-independent ADAM9 expression pathways [128]. Quercetin also increased radio-sensitivity of human

ovarian cancer cells, which was mediated by p53-dependent endoplasmic reticulum stress pathways [129]. The anti-cancer effects included the induction of apoptosis, DNA damage, and inhibition of G2-M cell cycle arrest, which were associated with the up-regulation of caspase and pro-apoptosis genes, as well as the down-regulation of PI3K, MAPK, and WNT-mediated signaling pathways [130].

2.10. Myricetin

Myricetin is a flavonol found in a number of common foods including tomatoes [131], oranges, berries, and grapes [132]. Myricetin's antioxidant properties and anti-cancer effects have been widely studied [133]. Ye et al. (2018) demonstrated that myricetin kills prostate cancer cells, with ONCOMINE database mining and prostate cancer tissue immunochemistry analysis indicating that the compound suppresses PIM1 while interrupting the PIM1/CXCR4 interaction, thereby inducing selective cell toxicity and apoptosis [134]. The flavonoid thereby enhanced chemosensitivity in A2780 and OVCAR3 ovarian cancer cells (IC50 value = 25 μM), with treatment also regulating specific pro- and anti-apoptotic markers resulting in the induction of apoptosis. Such effects mediated by myricetin appear to be associated with MDR-1 down-regulation in these cell models [135]. Sun et al. (2018) investigated the anti-carcinogenic effects of myricetin in skin cancer using the A431 cell line and found that myricetin-mediated anti-cancer activity was attributable to reactive oxygen species (ROS)-prompted mitochondrial membrane potential modulation and the initiation of apoptosis, events that were associated with myricetin-mediated alterations in Bcl-2 and Bax expression. Myricetin also caused cell cycle arrest and inhibited the migration and invasion of A431 cells [136]. The compound has also been reported to inhibit angiogenesis, as well as breast tumor growth via down-regulation of VEGF/VEGFR2 and the p38MAPK signaling pathway [137]. Myricetin also inhibits mTOR activation in HepG2 cells, thereby inducing protective autophagy, providing another avenue for potential anti-cancer effects [138]. Treatment with an inflammatory cytokine mixture (IL-6, interferon-γ, and TNF-α) in CCA KKU-100 cells induced migration and invasion via activation of the STAT3 pathway, which was reversed by myricetin treatment. Myricetin also suppressed STAT3-mediated downstream genes, including intercellular adhesion molecule-1, matrix metalloproteinase-9, iNOS, and COX-2 in CCA KKU-100 cells [139]. The myricetin derivative M10 exhibits protective effects against ulcerative colitis and colorectal cancer, with the chronic anti-inflammatory activity of M10 protecting against colorectal tumorigenesis while increasing CD8+ and CD4+ T cells, as well as reducing IL-6 and TNF-α levels [140]. Myricetin-induced cell apoptosis has been observed in T47D breast cancer cells, associated with increased expression of apoptotic genes including caspase-3, -8, -9, BAX/Bcl-2, p53, BRCA1, and GADD45. In particular, the BRCA1-GADD45 pathway was involved in the apoptotic death of the T47D cells [141]. Myricetin has also been reported to inhibit the migration and invasion of hepatocellular carcinoma MHCC97H cells and weaken filopodia and lamellipodia [142]. Myricetin also up-regulates E-cadherin expression while down-regulating N-cadherin [142]. Collectively, these findings suggest that myricetin suppresses the process of epithelial-mesenchymal transition (EMT), thereby impeding the migration and invasion of hepatocellular carcinoma cells [142]. Myricetin also protects against thyroid cancer cells by inducing apoptosis, which is associated with caspase activation and enhancement of the Bax/Bcl-2 ratio, while regulating mitochondrial dysfunction [143].

3. Conclusions

Recent evidence shows that red-pigmented foods containing bioactive compounds described in this review elicit anti-cancer effects via diverse mechanisms, which have been investigated using various cancer cells and animal models (Table 1).

Table 1. Bioactive compounds in red food, and their target in various cancer types.

Bioactive Compounds	Red Foods	Target Regulation		Cancer Types & Ref.
Lycopene	Carrots, watermelon, grapefruit, apricot, pink guava, and papaya	↑	Bax, PPARγ, and Caspase- 3	Gastric [30–32], pancreatic [33], prostate [34], esophageal [35], ovarian [36], oral [37], breast [38], and lung [39] cancer
		↓	EGFR, Ras ERK, p38, NFκB, Cox2, clAP1, clAP2, and Bcl2	
Anthocyanin	Grapes, berries, black bean, black rice, porunn, potatos, and red onion	↑	Bax and p53	Glioblastoma [45], breast [46], colon [47,48], oral squamous [50], and prostate [49] cancer
		↓	STAT3/VEGF, caspase-1, caspase-3, and IL-1β	
β-carotene	Carrots, apricots, paprika, and chili powder	↓	IL-6, STAT3, DNMT, DLK1, Oct3, Oct4, AKT, NFκB, SOD2, Nrf2, Ku70/80, MMP-10, AP-1, Cav-1, and mTOR	Neuroblastoma [58,59], colon [57] esophageal squamous cell carcinoma [60,63], breast [61], and gastric [62] cancer
Pectin	Apple and citrus	↑	p53, AMPK, and Nrf2	Colorectal [69,70] and breast [71,72] cancer
		↓	β-glucuronidase, β-glucosidase, tryptophanase, PTK2B, PDE4B, and TCF4	
Betaine	Sugar cane, Guji berries, and beets	↑	GSH, SOD, CAT, TAS, p53, Bax, caspase-3, cytochrome c oxidase, SIRT1, and p16,	colon [85], and liver [86,89] cancer, and oral squamous cell carcinoma [87] Breast [81] , prostate [82], cervical [83],
		↓	PolIII, Brf1, TNFα, iNOS, Cox2, MMP-2, MMP-9, Akt, NFκB, and c-myc	
Rutin	Oranges, wine, and grapes	↑	Caspase-3, Caspase-9, Bax, TNF-α, GSK3-β, and p53	Neuroblastoma [91], cervical [92,94], breast [93], colorectal, lung [95,96], and prostate [97] cancer
		↓	Notch-1, Hes-1, Bcl2, HPV-E6, HPV-E7, Cox2, and IL-6	
Ursolic acid	Apple peels	↑	sFRP4, sp1, Caveolin-1, Bax, p21, p53, Cyclin B1, Caspase-3, Caspase-8, Caspase-9, fibronectin-1, E-Cad, and LC3-II	Gliolastoma [104], breast [100,101], intestinal [102], lung [103], colorectal [105], esophageal [106], and pancreatic [107] cancer, and papillary thyroid [109] carcinoma
		↓	FN1, CDH2, CTNNB1, TWSIT, Bcl2, Servivin, NFκB, VEGF, MMP, PD-L1, RAGE, N-Cad, p62, and p-AKT	
Kaempferol	Apple, blueberry, cherry, cranberry, black tea, and red wine	↑	DR4, DR5, CHOP, JNK, ERK1/2, p38, and Bax	Renal [111], breast [112,113], prostate [115], ovarian [114], colorectal [116,117], lung [118], gastric [56], and endometrial [119] cancer
		↓	MMP-2, FAK, CDK1, PSA, TMPRSS2, TMEPA1, PI3K, Akt, Bcl-2, TS, RhoA, Rac1, JAK/STAT3, MAPK, and NFκB	
Quercetin	Apple, chili pepper, blueberry, cherry, cranberry, black tea, and red wine	↑	p53	Liver [120,121], prostate [122,123], colon [123], leukemia [123], lymphoma [123], breast [123,124], pancreatic [125], lung [126], and ovarian [127] cancer
		↓	Cyclin D1, JAK2, STAT3, MALAT1, PI3K, Akt, hnRNPA1, Bcl-2, PI3K, MAPK, and Wnt	

Table 1. *Cont.*

Bioactive Compounds	Red Foods	Target Regulation		Cancer Types & Ref.
Myricetin	Tomatoes, oranges, berries, and grapes	↑	Bax, Caspase-3, Caspase-8, Caspase-9, p53, BRCA1, GADD45, and E-Cad	Prostate [132], ovarian [133], skin [134], breast [135,139], liver [136,137,140], colorectal [138], and thyroid [141] cancer
		↓	PIM1, CXCR4, MDR-1, Bcl-2, VEGFR2, p38, p-STAT3, COX2, IL-6, TNF-α, NFκB, and N-Cad	

The anti-cancer activities of natural bioactive compounds in red-pigmented foods are largely attributable to the suppression of cancer cell invasion and metastasis, induction of apoptosis and cell cycle arrest, as well as the inhibition of proliferation and survival signaling. These effects are often closely related with the anti-inflammatory and antioxidant properties. However, few of these findings have been translatable to measurable outcomes in human clinical studies since individuals show different pharmacokinetics and/or gene specificity. Not only including red-pigmented foods but also including vegetables and fruits that are rich in bioactive compounds as part of a healthful diet is safe for most people, and it is also very good in terms of prevention of diseases. Although bioactive compounds clearly shows to have various beneficial effects, excessive intake has the potential to cause side effects such as liver damage, kidney damage, alterlation of thyroid hormone production, obstruction of the absorption of certain nutrients, and interaction with multiple medications [144]. Therefore, people with certain medical conditions, such as cancers, may need to avoid excessive intake of certain bioactive compounds. These issues should be more closely investigated to support the therapeutic development and disease prevention of the more promising anti-cancer bioactive compounds derived from natural colored foods.

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