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Review

Anticancer activities of cranberry phytochemicals: An update

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Studies employing mainly *in vitro* tumor models show that extracts and compounds isolated from cranberry fruit (*Vaccinium macrocarpon*) inhibit the growth and proliferation of several types of tumor including breast, colon, prostate, and lung. Proanthocyanidin oligomers, flavonol and anthocyanin glycosides and triterpenoids are all likely contributors to the observed anticancer properties and may act in a complementary fashion to limit carcinogenesis. Possible chemopreventive mechanisms of action by cranberry phytochemicals include induction of apoptosis in tumor cells, reduced ornithine decarboxylase activity, decreased expression of matrix metalloproteinases associated with prostate tumor metastasis, and anti-inflammatory activities including inhibition of cyclooxygenases. A review of recent studies suggests a potential role for cranberry as a dietary chemopreventive and provides direction for future research.

Keywords: Cancer / Cranberry / Flavonoid / Phytochemical / Tumor cells

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1 Introduction

Cranberry (*Vaccinium macrocarpon* Ait. Ericaceae) is a native fruit of North America that has grown in status as a functional food due to its potential health benefits. Cranberry juice has long been consumed for the prevention of urinary tract infections, a property recently linked to the anti-adhesion properties of cranberry proanthocyanidins (PACs) against certain *Escherichia coli* strains that cause these infections [1]. These studies have highlighted the unique structural features of cranberry PACs [2], and have led researchers to take a closer look at other potential health benefits of cranberry and cranberry products.

Cranberry's role as a potential chemopreventative is gradually emerging from *in vitro* model studies by various researchers, including our collaborations with scientists at the University of Prince Edward Island and the University of Wisconsin. This article summarizes reports over the past ten years on the *in vitro* anticancer properties of cranberry, the phytochemicals contributing to these effects and some possible mechanisms of action, as well as some recent results presented at the National Meeting of the American Chemical Society (ACS) in March of 2007.

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Abbreviations: ACS, American Chemical Society; **COX,** cyclooxygenase; **GI_{50},** growth inhibition by 50%; **MMP,** matrix metalloproteinase; **NF-κB,** nuclear factor kappa B; **ODC,** ornithine decarboxylase; **PAC,** proanthocyanidin; **UA,** ursolic acid

2 Phytochemical composition

Grown primarily in the Northeastern US, Wisconsin, Canada, and the Pacific Northwest, *V. macrocarpon* is a member of the Ericaceae family. Cranberry fruit is high in content of phenolic compounds including three classes of flavonoids (flavonols, anthocyanins, and PACs), catechins or flavan-3-ols; a variety of phenolic acids, among which the major is *p*-hydroxycinnamic acid; and triterpenoids of the ursane type [3]. The major anthocyanins in cranberry (Fig. 1) are galactosides and arabinosides of cyanidin and peonidin [4]. Anthocyanin content can range between 25 and 91 mg *per* 100 g of ripe fruit at harvest depending on cultivar [5, 6]. Fruit of the Early Black cultivar is significantly higher in content of both anthocyanins and PACs than other cranberry cultivars [5, 7]. Quercetin is the major flavonol in cranberries and exists in several glycosidic forms (Fig. 1), primarily the 3-*O*-galactoside [8, 9]. Myricetin glycosides are also present in lesser quantity. The total flavonol content of cranberry fruit averages 20 – 30 mg *per*

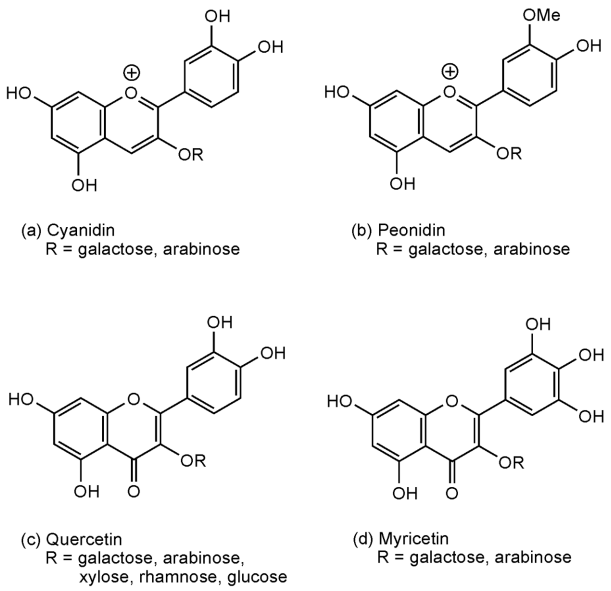

Figure 1. (a), (b) Cyanidin and peonidin are the major anthocyanin glycosides found in cranberry fruit. (c), (d) Quercetin glycosides are the major flavonols in cranberry fruit; myricetin glycosides are also present in lesser quantities.

100 g fresh fruit weight [10]. Content of individual flavonoids and flavan-3-ols in whole fruit as reported by the USDA are summarized in Table 1.

Cranberry PACs are primarily dimers, trimers, and larger oligomers of epicatechin (Fig. 2) or poly-flavan-3-ols. USDA reports that 100 g cranberry fruit typically contains 180 mg of oligomers with 10 degrees of polymerization (DP) or less, and the content of larger polymers is even higher (Table 1). Unlike PACs from other food sources, those found in cranberries contain two types of linkages

Table 1. Content of flavonoids in cranberry fruit by flavonoid class, as reported by the USDA databases on nutrient composition of foods

Flavonoid	Milligram *per* 100 g whole cranberry fruit
Flavonols, total[a)]	21.96
Quercetin[b)]	15.09 ± 1.06
Myricetin[b)]	6.78 ± 1.67
Kaempferol[b)]	0.09 ± 0.03
Anthocyanins, total[a)]	91.57
Cyanidin[b)]	41.81 ± 2.86
Peonidin[b)]	42.10 ± 3.64
Delphinidin[b)]	7.66 ± 1.93
Flavan-3-ol monomers[c)]	7.26
(-)-Epicatechin[b)]	4.37 ± 0.93
(−)-Epigallocatechin[b)]	0.74 ± 0.28
(−)-Epigallocatechin gallate[b)]	0.97 ± 0.48
(+)-Catechin[b)]	0.39 ± 0.16
PACs, total[a)]	411.5
Dimers[c)]	25.93 ± 6.12
Trimers[c)]	18.93 ± 3.39
4 – 6 mers[c)]	70.27 ± 13.07
7 – 10 mers[c)]	62.90 ± 14.71
Polymers[c)]	233.48 ± 49.08

a) Sum of individual flavonoid contents in each class.
b) USDA Database for the Flavonoid Content of Selected Foods, Release 2, August 2006, http://www.ars.usda.gov/nutrientdata.
c) USDA Database for the PAC Content of Selected Foods, August 2004, http://www.nal.usda.gov/fnic/foodcomp/Data/PA/PA.pdf.

between epicatechin units: the more common 4β → 8 (B-type) linkage (also found in apples, grape seed, and cacao), and a less common A-type linkage featuring both 4β → 8 and 2β → O → 7 interflavan bonds. The combination of linkages means that cranberry PACs are very diverse in 3-D

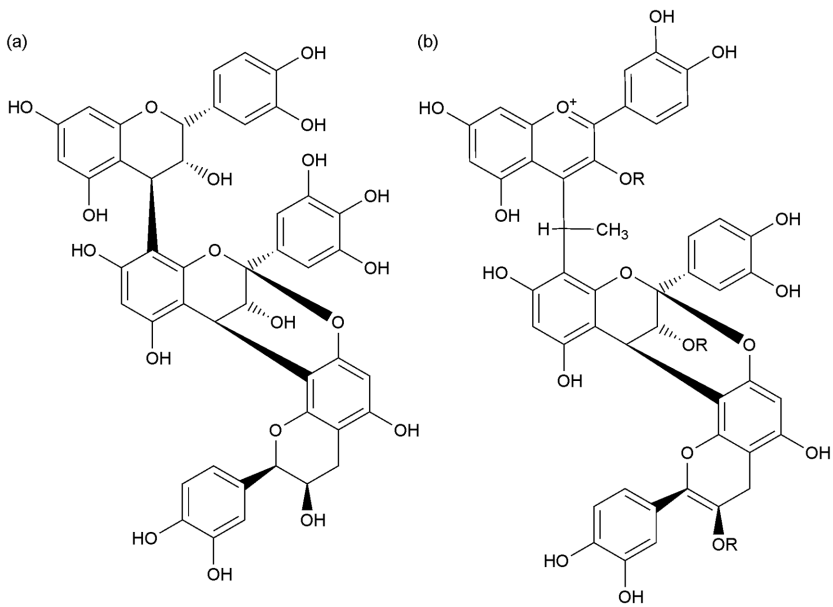

Figure 2. (a) An epicatechin trimer with one A-type linkage isolated from cranberry fruit. (b) Anthocyanin-epicatechin oligomers with masses suggestive of structures such as the trimer shown here have been detected in cranberry juice and fruit.

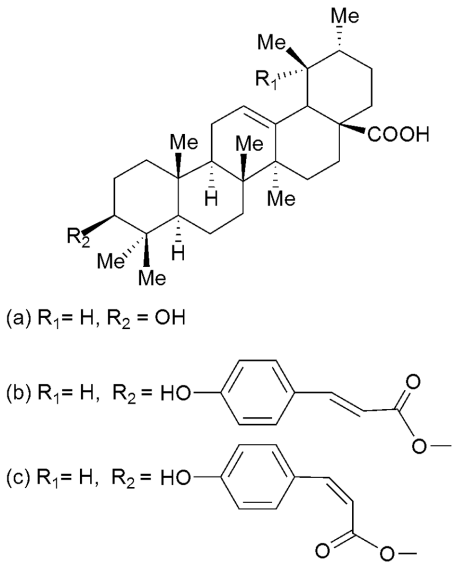

Figure 3. The triterpenoid UA (a) and its hydroxycinnamate esters (b) and (c) have been isolated from whole cranberry fruit and show antiproliferative activity.

structure. PACs reported to inhibit adherence of P-fimbriated *E. coli* include at least three structurally different trimers [2]. We have also detected epicatechin–anthocyanin dimers, trimers, and tetramers in organic cranberry juice and early black fruit by MALDI-TOF MS (Neto *et al.*, unpublished results presented at ACS National Meeting). A representative structure is shown in Fig. 2.

Cranberry fruit contains a significant quantity of ursolic acid (UA) in its peel, in the aglycone form and as the *cis* and *trans p*-hydroxycinnamate esters [11], shown in Fig. 3. Quantitative analysis of cranberry fruit and products by LC-MS found the UA content of whole cranberry fruit of different cultivars to range between 60 and 110 mg *per* 100 g of fresh fruit [12]. A similar content is found in sweetened, dried fruit. Considerably less UA is detected in jellied cranberry sauce. None was detected in commercial cranberry juice. UA has been reported as a constituent of other fruits including apple peels and highbush blueberries [13].

3 Antioxidant properties of cranberry fruit

Due to its high content of the flavonoids and phenolic acids discussed above, cranberry ranks highly among fruit in both antioxidant quality and quantity [14]. Cranberry extracts reportedly inhibit oxidative processes including oxidation of low-density lipoproteins [8, 15], oxidative damage to neurons during simulated ischemia [16], and oxidative and inflammatory damage to the vascular endothelium [17]. These antioxidant properties are likely to contribute to cranberry's overall antitumor potential. Other possible mechanisms of anticancer mechanisms are addressed in this review.

4 Contributors to *in vitro* anticancer activity

The first *in vitro* report of anticancer activity in *Vaccinium* fruit appeared in 1996. A University of Illinois study found that extracts of cranberry, bilberry, and other species inhibited ornithine decarboxylase (ODC) expression and induced the xenobiotic detoxification enzyme quinone reductase (QR) *in vitro* [18]. An initial Canadian report of breast tumor inhibition by cranberry juice [19] was followed by a more detailed study showing that extract of cranberry presscake inhibited proliferation of MCF-7 and MDA-MB-435 breast cancer cells [20]. Later studies by our group and other researchers focused on identifying active constituents.

4.1 Activity of ursolic acid and its esters found in whole fruit

We used a bioassay-guided fractionation approach to examine *in vitro* antitumor activities of whole cranberry fruit and juice, extracts and fractions, and finally individual compounds or subfractions within structural classes. Initially, we determined that an ethyl acetate extract of whole cranberry fruit inhibited growth of human tumor cell lines *in vitro* [8]. From ethyl acetate soluble extracts we isolated and identified two hydroxycinnamate esters of UA that inhibited the growth of several types of human tumor cells *in vitro*, including MCF-7 breast, HT-29 colon, DU145 prostate, H460 lung, ME180 cervical epidermoid, and K562 leukemia cell lines [11]. The concentration at which 50% growth inhibition occurred (GI_{50}) for the esters ranged from 11 to 28 μg/mL depending on the cell line. LC-MS analysis of various cranberry cultivars found that in addition to the parent UA, the hydroxycinnamate esters are present in whole cranberry fruit in quantities averaging about 15–20 mg *per* 100 g of fresh fruit [12]. UA isolated from cranberry fruit was recently reported to inhibit the proliferation of HepG2 human liver cancer cells as well as MCF-7 [21].

Preliminary clonogenic assays to assess effects on tumor colony formation over a 2 wk period show that UA inhibits tumor colony formation in a dose-dependent manner in HT-29 and HCT116 colon tumor models [22]. A constituent of several herbal medicines marketed worldwide for inflammatory conditions [23], UA has received relatively scant attention as a functional food factor, perhaps due to the lack of bioavailability data. Although few *in vivo* cancer studies of UA appear in the literature, a mouse model study reported that a dose of 100 mg/kg inhibited murine fibrosarcoma FSaII growth [24]. Numerous reports appear on the *in vitro* antitumor activity of UA, reviewed in 2001 [25]. These suggest a variety of mechanisms of action including an early G1 cytostatic effect [26], induction of apoptosis [27], enhancement of intracellular Ca^{2+} signaling [25], enhanced release of cytochrome c, caspase activation [28] and downregulation of inhibitor of apoptosis proteins (c-IAPs) [29], increased

expression of $p21^{WAF1}$ [30], and decreased matrix metalloproteinase-9 (MMP-9) expression [31]. UA hydroxycinnamate esters isolated by our group from cranberry fruit were evaluated for antitumor activity in a 60 tumor cell line panel through the National Cancer Institute's Developmental Therapeutics program (http://dtp.nci.nih.gov/about.html) and were found to inhibit the growth of several lung, colon, breast, and renal cancer, melanoma and leukemia cell lines with GI_{50} values based on sulforhodamine B (SRB) assay of between 1.2 and 11 μM [12]. The esters were also evaluated by us in a DU-145 prostate tumor model and were found to strongly inhibit expression of both MMP-2 and MMP-9 at micromolar concentrations [32].

4.2 Antiproliferative activity of polyphenolic extracts

The polyphenolic compounds in cranberry can be expected to play a key role in chemoprevention. Studies of polyphenolic cranberry extracts have provided *in vitro* evidence. Cranberry extracts containing PACs and other flavonoids reportedly inhibited ODC activity linked to cell proliferation in mouse epithelial (ME-308) cells [33]. Characterization of an active subfraction revealed the presence of dimers and oligomers of catechin/epicatechin, monomeric catechins, and quercetin glycosides. Water-soluble cranberry polyphenolic extracts prepared from commercial cranberry powder reportedly inhibited proliferation of several human tumor cell lines [34] including two oral (CAL27 and KB), four colon (HT-29, HCT-116, SW480, and SW620), and three prostate (RWPE-1, RWPE-2, and 22Rv1) cancer cell lines. In this study, anthocyanin and PAC subfractions inhibited proliferation but were less effective than the total polyphenolic extract. Since cranberry polyphenolic extracts may contain flavonols, anthocyanins and PACs in varying amounts, these classes of compounds will be considered separately.

4.3 Properties of quercetin and its occurrence in cranberry

Quercetin, present in many fruits and vegetables, is widely reported to have antiproliferative and antineoplastic activities *in vitro* against a variety of cell lines [34 – 40]. Its mechanisms of action include induction of apoptosis, with cell cycle arrest in G_1 phase [35 – 37]; inhibition of epidermal growth factor (EGF) receptor expression and associated tyrosine kinase activity [37, 38]; reduced Ras protein expression [39]; increased expression of endogenous inhibitors of MMPs [40] and phytoestrogenic interaction with estrogen receptors alpha and beta (ERα and EBβ of human mammary MCF-7 cells [41]. In our studies of antiproliferative compounds from cranberry, quercetin inhibited the growth of MCF-7 human breast adenocarcinoma, HT-29 human colon adenocarcinoma, and K562 human chronic myelogenous leukemia cell lines almost as effectively as the UA esters [11]. Quercetin and its glucoside were also recently reported to inhibit the proliferation of HepG2 liver cancer cells [21].

Based on quercetin's antiproliferative activity and abundance in the fruit, it is likely that quercetin contributes to the observed anticancer activity of whole cranberry extracts. *In vivo*, quercetin glycosides are usually metabolized to sulfates or glucuronides [42]. A study of quercetin's ability to suppress the formation of colon cancer precursor aberrant crypt foci (ACF) in rats found that a quercetin-enriched diet decreased ACF incidence four-fold, and evidence of apoptosis induction *via* a mitochondrial pathway involving modulation of Bax and Bcl-2 protein expression was found in colon tissue [43].

4.4 Possible roles of cranberry anthocyanins in fighting cancer

As powerful antioxidants, anthocyanins may be expected to inhibit oxidative processes linked to tumorigenesis. Compared to other compounds in cranberry fruit, the anthocyanins showed little direct antiproliferative or growth-inhibitory properties in our *in vitro* models. Purified cyanidin-3-galactoside was evaluated by us in eight tumor cell lines *in vitro* using the SRB assay. In all cell lines, the highest concentration tested (250 μg/mL) did not inhibit growth by 50%, suggesting GI_{50} values at least that high [11]. Similarly, a mixed anthocyanin fraction demonstrated little tumor growth inhibition. In another study, anthocyanin subfraction from cranberry limited growth in three prostate tumor lines (RWPE-1, RWPE-2, and 22Rv1) by 50 – 70% but did not significantly inhibit oral or colon tumor cell line proliferation [34]. A follow-up study of six anthocyanin-rich fruit extracts confirmed that cranberry extracts were less effective at inhibiting proliferation in these cell lines than other berry extracts [44]. However anthocyanins, including those from cranberry, have been implicated in the observed anti-angiogenic properties of mixed berry extracts [45, 46]. Mixed anthocyanin-rich extracts inhibited tumor necrosis factor alpha (TNF-α-induced vascular endothelial growth factor (VEGF) expression, and decreased hemangioma formation and tumor growth [47]. So, although the anthocyanins do not appear to be highly cytotoxic or antiproliferative to most tumor cells, they may play a role in limiting carcinogenesis by inhibiting other activities related to tumor formation.

4.5 Structure and activity of cranberry proanthocyanidins

Several studies of cranberry extracts with anticancer activities implicate the PACs as major contributors [20, 33, 34]. In our fractionation studies of whole fruit, a PAC fraction selectively inhibited the proliferation of H460 human large

cell lung carcinoma, HT-29 colon adenocarcinoma, and K562 chronic myelogenous leukemia cells *in vitro*. A subfraction retaining the activity in those three cell lines was isolated and characterized by MALDI-TOF MS and found to contain PAC oligomers composed primarily of four to seven epicatechin units with at least one or two A-type linkages between the units [48].

In our clonogenic assays of tumor colony formation with HT-29 and HCT-116 colon tumor cell lines, the number of new tumor colonies present at the end of a 2-wk period decreased in these cell lines in a dose-dependent manner when treated with a PAC fraction prepared from Early Black variety cranberry fruit [49]. MALDI-TOF MS characterization of this PAC fraction revealed that it was composed primarily of trimers through hexamers of epicatechin with both A and B-type linkages. The fraction was more effective than the whole polyphenolic extract, with over 50% inhibition of colony formation in HCT116 observed at concentrations of less than 10 μg/mL [22].

The structures of PACs in cranberry fruit and cranberry products are complex, and further investigation is needed to determine any link between structure and activity. MALDI-TOF MS analysis found that PAC oligomer fractions from whole cranberry contained molecules up to 12 DP in size with as many as four A-type linkages. Most contained exclusively epicatechin units, but some epigallocatechin unit masses were also detected [48]. Preliminary MALDI-TOF MS analysis of fractions prepared from organic 100% cranberry juice also detected masses that can be attributed to the presence of anthocyanin–epicatechin dimers, trimers, and tetramers with direct linkages or an acetaldehyde-derived bridge (Fig. 3). Some of these structures are also detected in extracts of Early Black fruit (Amoroso *et al.*, unpublished results). The effect of A-type linkages, size, and the presence of anthocyanin units on antitumor activity of PACs is the subject of current studies in our laboratory. Prior reports suggest that A-type linkages may influence tumor inhibitory and selectivity properties of PACs from other sources. A screening of small polyflavan-3-ols from different plants against GLC4 lung and Colo 320 colon carcinomas found that a trimer with an A-type linkage was more cytotoxic than dimers with A-type linkages and trimers with only B-type linkages [50]. PACs containing A-type linkages isolated from wild blueberries reportedly had a greater growth inhibitory effect on androgen-sensitive LNCaP prostate cancer cells than androgen-insensitive DU145 cells [51], which is consistent with our observation that PACs with A-type linkages show stronger antiproliferative activity in some cell lines than others [48].

5 Possible chemopreventive mechanisms

Bioactive compounds found in berries are thought to act individually, additively, and even synergistically in chemoprevention [52]. Tumor inhibition by cranberry could involve complementary or synergistic activities between the flavonols (primarily quercetin), PACs, UA, and anthocyanins, since all are capable of inhibiting proliferation on their own, as discussed in the preceding sections. Possible mechanisms of action supported by *in vitro* evidence are reviewed below, including induction of apoptosis in cancer cells, decreased invasion, and metastasis due to MMP inhibition, decreased ODC expression and activity, and inhibition of inflammatory processes including cyclooxygenase-2 (COX-2) activity.

5.1 Induction of apoptosis in breast and colon tumor cells

Induction of apoptosis plays a role in the tumor-inhibitory activity of many dietary phytochemicals, for example, resveratrol [53] and epigallocatechin gallate (EGCG) [54]. Evidence is emerging suggesting that apoptosis may play a key role in cranberry's ability to limit tumor cell growth. This activity may be associated with the presence of quercetin, UA, and/or the PACs. Dose-dependent induction of apoptosis by cranberry has been observed in breast tumor models. An antiproliferative fraction from cranberry presscake also induced apoptosis in MDA-MB-435 breast tumor cells as determined by Annexin-V staining [20]. An 80% aqueous acetone extract of whole cranberry fruit was reported to increase apoptosis in MCF-7 cells by 25% [55], albeit at a concentration (50 mg/mL) much higher than would likely be encountered *in vivo*.

We used a fluorescent TUNEL (terminal dUTP nick end labeling) assay to compare the effects of a whole polyphenolic extract of cranberry fruit on apoptosis rates in tumorigenic (MCF-7) *versus* nontumorigenic (MCF-10A) breast cell lines. At 250 μg/mL, cranberry extract increased the baseline apoptosis rate to 92% in MCF-7 cells, while not increasing apoptosis in MCF-10A cells to a significant extent [56]. An extract of organic 100% cranberry juice also increased apoptotic rates in MCF-7 breast tumor cells (Neto *et al.*, unpublished data): at a treatment concentration of 25 μg/mL, rates of apoptosis in MCF-7 cells doubled when treated with whole cranberry polyphenolic extract and nearly tripled when treated with juice extract. MALDI-TOF MS analysis of a PAC fraction prepared from the juice extract detected the presence of compounds believed to be novel anthocyanin–epicatechin oligomers, in addition to the primarily epicatechin-based oligomers found in the fractions prepared from whole fruit extract (Amoroso *et al.*, unpublished results presented at 2007 meeting of the ACS in Chicago, IL). It is unknown whether these compounds arose through processing or occur naturally in juice. In colon tumor cell lines HCT116 and HT-29, little increase in apoptosis was observed to occur in response to treatment with crude polyphenolic extract at or below 100 μg/mL, but when tested separately, UA and cranberry PACs both

induced significant rates of apoptosis at these concentrations [22].

5.2 Invasion and metastasis: Inhibition of matrix metalloproteinases

Phytochemicals from whole cranberry fruit may act against cancers by limiting processes involved in tumor invasion and metastasis, particularly the expression of the MMPs involved in remodeling of the extracellular matrix [57]. Both whole cranberry polyphenolic extract and a cranberry PAC fraction inhibited the expression of MMPs MMP-2 and MMP-9 in the DU145 prostate tumor cell line in a dose-dependent manner [48]. The crude extract was more effective, suggesting that other flavonoids in the fruit also contribute to the activity along with the oligomers. Similar activity has been observed with a flavonoid-rich extract of cranberry's close relative the highbush blueberry (*V. angustifolium*) [58]. Hydroxycinnamate esters of UA isolated from whole cranberry fruit were strong inhibitors of MMP-2 and MMP-9 protein expression, inhibiting expression significantly at concentrations of 10 μM or less [32]. This finding was consistent with the observed ability of UA to inhibit MMP expression in fibrosarcoma cells [31]. Further studies are needed to determine the efficacy of cranberry and its PACs against tumor metastasis compared to that of oligomers from other sources such as grape seed that demonstrate antimetastasis activity both *in vitro* and *in vivo* [59].

5.3 Ornithine decarboxylase: Induction and inhibition

The biosynthesis and metabolism of polyamines (spermidine and spermine) involved in cell proliferation is controlled by enzymes such as ODC and spermidine/spermine N1-acetyltransferase (SSAT). The activity of ODC can be affected by dietary polyphenolics, as has been reported for grape seed PACs, which reduced colonic ODC activity in female rats [60]. Overexpression of these enzymes is observed in models of cancer where ODC can play a regulatory role in transformation, invasion, and angiogenesis [61] and can be induced by pro-inflammatory agents such as LPSs or tumor promotors such as 12-*O*-tetradecanoyl phorbol-13-acetate (TPA). A cranberry fruit flavonoid fraction inhibits the activity of ODC in a mouse epidermal cell line (ME-308) as determined by an assay measuring conversion of substrate [33]. Cranberry was also found to influence the expression of ODC induced by LPS in an H-ras transformed mouse fibroblast model [62]. Whole cranberry polyphenolic extract produced a dose-dependent inhibition of LPS-induced ODC expression, and induction by LPS was abolished at extract concentrations of 100 μg/mL or less [62].

5.4 Anti-inflammatory activities

COX is a key enzyme in the biosynthetic pathway to prostaglandins, which have many physiological roles including production of an inflammatory response. The COX-1 isozyme is expressed constitutively in all cells, while expression of COX-2 can be induced in response to inflammatory stimuli. COX-2 is highly expressed in tumor tissues [63] and studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs), for example Sulindac, have a chemopreventive effect against colon cancer in cellular and animal models [63 – 65]. Since COX-2 overexpression is thought to play a role in promoting certain cancers, inhibition of COX-2 activity or expression presents another potential route to chemoprevention. Several individual constituents of cranberry may have anti-inflammatory properties. Inhibition of COX activity by anthocyanins, including those found in cranberry, was reported [66]. Pure cyanidin was an effective COX-2 inhibitor, reducing activity by 47%, with activity superior to other anthocyanins or catechins [67]. The observed COX-1 inhibition may also be relevant to cancer, since some evidence suggests that COX-1 specific inhibitors are as effective as COX-2 specific inhibitors in decreasing events related to tumor development [63].

The question of whether cranberry can decrease the expression of COX-1 or COX-2 in cellular models remains to be answered; to date, no published studies appear evaluating the effects of cranberry on COX expression in cancer models. Inhibition of COX-2 expression, if it is observed, could contribute to anticancer activity. Considering the known effects of compounds found in cranberry fruit, modulation of COX-2 expression, and associated pathways is likely. Both UA and quercetin are established inhibitors of cellular COX expression [68, 69]. The anti-inflammatory actions of triterpenes including UA have been reviewed [70] and studies support an anti-inflammatory role both *in vitro* [68, 71] and *in vivo* [72, 73]. UA inhibited COX-2 transcription in a human mammary oncogenic epithelial cell line (184B5/HER), through a mechanism believed to involve the protein kinase C signal transduction pathway [68]. Several anti-inflammatory activities of quercetin have also been reported. Quercetin reduced COX-2 mRNA expression in Caco-2 colon cancer cells, and both quercetin and its metabolite quercetin-3′-sulfate inhibited COX-2 activity [69]. In a rat model of colitis, quercetin delivered in the form of rutin inhibited the TNF-α-dependent activation of nuclear factor kappa B (NF-κB), a transcription factor involved in the control of cell proliferation as well as inflammation, in a dose-dependent manner [74]. UA likewise has been reported to suppress NF-κB activation [75]. Quercetin has been reported to inhibit expression of inducible nitric oxide synthase (iNOS), a promotor of inflammation that has also been linked to tumor angiogenesis, in cel-

lular models [76]. Given the variety of anti-inflammatory activities attributed to quercetin and UA, the effects of cranberry extracts on inflammatory pathways would be an interesting subject for future study.

5.5 *Helicobacter pylori* inhibition

H. pylori infection is positively associated with the incidence of gastric cancer [77]; thus, prevention of these infections may reduce cancer risk. Antibacterial adhesion studies demonstrated that in addition to inhibiting *E. coli* adhesion, cranberry components also inhibit adhesion of *H. pylori* to human gastric mucus [78]. A randomized, double-blind placebo-controlled trial provided some clinical support for this finding, with significantly lower levels of *H. pylori* infection observed in adults consuming cranberry juice [79].

6 Recent evidence from an animal model

The first report of tumor growth inhibition by cranberry in an animal model appeared recently [80] from researchers who had earlier reported on the effects of cranberry presscake extracts on breast tumor cells *in vitro* [20]. In the animal model study, explants of U87 glioblastoma, HT-29 colon carcinoma, or DU145 prostate carcinoma were established in female Balb/c mice. Mice in the treatment groups were intraperitoneally injected with either a flavonoid-rich aqueous extract from cranberry presscake or a PAC fraction prepared from whole fruit extract. Dosages previously determined as tolerable to the mice of 100 mg/kg body weight PAC fraction or 250 mg/kg presscake extract were administered ten times over a period of 24 days. Both treatments resulted in up to 40% slower growth of U87 glioblastoma based on the time taken for tumors to reach milestone sizes. Flow cytometry experiments suggested that both extracts arrest U87 cells in G1 phase after 24 h, reducing the number of cells going on to S phase. In mice given HT-29 tumor explants, the PAC treatment group exhibited significantly reduced tumor volume over the first 40 days compared to control. PAC treatment also slowed the growth of tumors in the DU145 group and induced complete regression of these tumors in two treatment mice [80].

7 Future directions for cranberry research

Evidence from *in vitro* studies suggests that phytochemicals from cranberry, including PACs, quercetin, anthocyanins, and UA, may have a mitigating effect on tumor development through induction of apoptosis, inhibition of cell proliferation and tumor colony formation, and limiting the ability of cancer cells to invade and metastasize. Anti-inflammatory properties of cranberry phytochemicals may also decrease the risk of developing some cancers. Future research should continue to examine cranberry's role in regulating cellular processes related to apoptosis, inflammation, and proliferation, including the expression of key genes in these pathways, and begin to address how the unique blend of phytochemicals may best work together. For example, elucidation of apoptosis pathways by which cranberry phytochemicals operate in human tumor cell lines may provide some insight into their potential to decrease growth and proliferation of existing tumors. Since many of the individual compounds have been demonstrated to possess anti-inflammatory properties, it may also be worthwhile to determine cranberry's effects on inflammation-linked pathways that promote carcinogenesis, including the activity and expression of COX, or to examine its effects on the activation of transcription factor NF-κB. Cranberry's efficacy against tumor development *in vivo* will depend largely on the bioavailability of its phytochemicals to the various tissues, a topic which is yet to be thoroughly researched. An effort should be made to design studies that examine the effect of dietary cranberry on animal models of breast and colon cancer, as well as those which examine prostate tumor growth and metastasis. Design of such studies should pay close attention to chemical composition in order to maximize the diversity of available phytochemicals and take advantage of any complementary biological effects.

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