Mini-review

Anthocyanins and their role in cancer prevention

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Abstract

Anthocyanins are the most abundant flavonoid constituents of fruits and vegetables. The conjugated bonds in their structures, which absorb light at about 500 nm, are the basis for the bright red, blue and purple colors of fruits and vegetables, as well as the autumn foliage of deciduous trees. The daily intake of anthocyanins in residents of the United States is estimated to be about 200 mg or about 9-fold higher than that of other dietary flavonoids. In this review, we summarize the latest developments on the anti-carcinogenic activities of anthocyanins and anthocyanin-rich extracts in cell culture models and in animal model tumor systems, and discuss their molecular mechanisms of action. We also suggest reasons for the apparent lack of correlation between the effectiveness of anthocyanins in laboratory model systems and in humans as evidenced by epidemiological studies. Future studies aimed at enhancing the absorption of anthocyanins and/or their metabolites are likely to be necessary for their ultimate use for chemoprevention of human cancer.

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1. Introduction

Anthocyanins occur ubiquitously in the plant kingdom and confer the bright red, blue and purple colors to fruits and vegetables such as berries, grapes, apples, purple cabbage and corn. Of potential importance to human health is the relatively high concentration of anthocyanins in the diet. The daily intake of anthocyanins in the U.S. diet is estimated to be between 180 and 215 mg whereas, the intake of other dietary flavonoids such as genistein, quercetin and apigenin is only 20–25 mg/day [1]. Epidemiologic studies suggest that the consumption of anthocyanins lowers the risk of cardiovascular disease, diabetes, arthritis and cancer due, at least in part, to their anti-oxidant and anti-inflammatory activities [2].

In the present review, we highlight recent studies on the cancer preventative activities of the anthocyanins, including results from in vitro cell culture and in vivo animal model tumor systems, as well as data from human epidemiological studies. Although laboratory studies have provided some clues on the molecular mechanism(s) by which anthocyanins inhibit carcinogenesis, there is still much to be learned. In addition, the relevance of the in vitro...
studies to the in vivo situation needs to be confirmed in view of the high concentrations of anthocyanins employed in the in vitro studies.

2. Chemistry of anthocyanins

Anthocyanins occur naturally in fruits and vegetables as glycosides, having glucose, galactose, rhamnose, xylose or arabinose attached to an aglycon nucleus [3,4]. In contrast to other flavonoids, the anthocyanins carry a positive charge in acidic solution [3]. They are water-soluble and, depending upon pH and the presence of chelating metal ions, are intensely colored in blue, purple, or red. The de-glycosylated or aglycone forms of anthocyanins are known as anthocyanidins (Fig. 1). The six most common anthocyanidin skeletons are cyanidin, delphinidin, pelargonidin, malvidin, petunidin, and peonidin (Fig. 1). The sugar components of anthocyanins are usually conjugated to the anthocyanidin skeleton via the C3 hydroxyl group in ring C. Several hundred anthocyanins are known varying in the basic anthocyanidin skeleton and the position and extent to which the glycosides are attached to the skeleton [4].

3. Anti-cancer properties of anthocyanins

3.1. In vitro studies

3.1.1. Antioxidant effects

The phenolic structure of anthocyanins is responsible for their antioxidant activity; i.e., ability to scavenge reactive oxygen species (ROS) such as superoxide (O$_2^-$), singlet oxygen (‘O$_2$), peroxide (ROO$^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radical (OH.) [5]. The antioxidant effects of anthocyanins in vitro have been demonstrated using several cell culture systems including colon [6,7], endothelial [8], liver [9,10], breast [11,12] and leukaemic cells [13], and keratinocytes [14]. In these culture systems, anthocyanins have exhibited multiple anti-toxic and anti-carcinogenic effects such as: directly scavenging reactive oxygen species (ROS), increasing the oxygen-radical absorbing capacity of cells, stimulating the expression of Phase II detoxification
enzymes, reducing the formation of oxidative adducts in DNA, decreasing lipid peroxidation, inhibiting mutagenesis by environmental toxins and carcinogens, and reducing cellular proliferation by modulating signal transduction pathways. Although most of the protective effects of anthocyanins are attributed to their ability to scavenge ROS, they also function by chelating metals and by direct binding to proteins [15]. The radical scavenging (antioxidant) activity of anthocyanins is due largely to the presence of hydroxyl groups in position 3 of ring C and also in the 3', 4' and 5' positions in ring B of the molecule. In general, the radical scavenging activity of the anthocyanidins (aglycons) is superior to their respective anthocyanins (glycosides), and it decreases as the number of sugar moieties increase.

### 3.1.2. Phase II enzyme activation

Shih et al. [16] initially demonstrated the ability of anthocyanins to induce phase II antioxidant and detoxifying enzymes in cultured cells. Treatment of rat liver clone 9 cells with 50 μM anthocyanins [9] and non-cancerous breast cells with 10–20 μg/ml anthocyanins [11] enhanced their antioxidant capacity by activating glutathione-related enzymes (glutathione reductase, glutathione peroxidase, and glutathione S-transferase) as well as the activity of NAD(P)H: quinone reductase. The mechanism by which anthocyanins exhibited these effects was through activation of the antioxidant response element (ARE) upstream of genes that code for these enzymes. Shih et al. [9] concluded that the promoting effect of anthocyanins on ARE-regulated phase II enzyme expression is critical for defending cells against oxidative stress.

### 3.1.3. Anti-cell proliferation

Pure anthocyanins and anthocyanin-rich extracts from fruits and vegetables have exhibited anti-proliferative activity towards multiple cancer cell types in vitro [17–22]. Cell proliferation was inhibited by the ability of anthocyanins to block various stages of the cell cycle via effects on cell cycle regulator proteins (e.g., p53, p21, p27, cyclin D1, cyclin A, etc.). Anthocyanidins appear to be more potent inhibitors of cell proliferation than the anthocyanins [22]. Interestingly, several investigations have compared the antiproliferative effects of anthocyanins on normal vs. cancer cells and found that they selectively inhibit the growth of cancer cells with relatively little or no effect on the growth of normal cells [23,24]. The mechanism(s) for the selective effect of the anthocyanins on the growth of cancer cells vs. normal cells is/are not known. However, our laboratory has recently shown that an ethanol extract of black raspberries selectively inhibits the growth and stimulates apoptosis of a highly tumorigenic rat esophageal epithelial cell line (RE-149-DHD) when compared to its low tumorigenic precursor line, RE-149 [25]. These differences in the growth-inhibitory and apoptosis-inducing effects of the black raspberry extract correlated with the finding that the uptake of the three anthocyanins (cyanidin-3-glucoside, cyanidin-3-rutinoside and cyanidin-3-xylosylrutinoside) in black raspberries into RE-149DHD cells exceeded that of their uptake into RE-149 cells by 100-fold. In addition, cyanidin-3-rutinoside, the most abundant anthocyanin in black raspberries, remained at steady state levels in RE-149DHD cells for up-to 12 h whereas, it was not detectable in RE-149 cells after 2 h.

Anthocyanidins have also been evaluated for their effects on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced transformation of cultured mouse JB6 cells [26]. Of the six anthocyanins tested, only those with an ortho-dihydroxyphenyl structure on the B-ring suppressed TPA-induced cell transformation and activator protein-1 transactivation, suggesting that the ortho-dihydroxyphenyl structure may contribute to the inhibitory action. Delphinidin, but not peonidin, blocked the phosphorylation of protein kinases in the extracellular signal-regulated protein kinase (ERK) pathway at early times and the c-Jun N-terminal kinase (JNK) signaling pathway at later times. p38 kinase was not inhibited by delphinidin. These results demonstrate that anthocyanidins contribute to the inhibition of tumorigenesis by blocking activation of the mitogen-activated protein kinase (MAPK) pathway [26].

### 3.1.4. Induction of apoptosis

Apoptosis, or programmed cell death, plays a key role in the development and growth regulation of normal cells, and is often dysregulated in cancer cells. Some of the most effective chemopreventive agents are strong inducers of apoptosis in premalignant and malignant cells. Anthocyanin-rich extracts from berries and grapes, and several pure anthocyanins and anthocyanidins, have exhibited pro-apoptotic effects in multiple cell types in vitro [12,14,18,19,27,28]. They induce apoptosis through both intrinsic (mitochondrial) and extrinsic (FAS) pathways [27,29]. In the intrinsic pathway, anthocyanin
treatment of cancer cells results in an increase in mitochondrial membrane potential, cytochrome c release and modulation of caspase-dependent anti- and pro-apoptotic proteins. In the extrinsic pathway, anthocyanins modulate the expression of FAS and FASL (FAS ligand) in cancer cells resulting in apoptosis. In addition, treatment of cancer cells, but not normal cells, with anthocyanins leads to an accumulation of ROS and subsequent apoptosis, suggesting that the ROS-mediated mitochondrial caspase-independent pathway is important for anthocyanin-induced apoptosis [13].

3.1.5. Anti-inflammatory effects

Inflammation has been shown to play a role in the promotion of some types of cancer in animals, and probably in humans [30]. Abnormal up-regulation of two inflammatory proteins, nuclear factor-kappa B (NF-κB) and cyclooxygenase-2 (COX-2), is a common occurrence in many cancers, and inhibitors of these proteins usually exhibit significant chemopreventive potential [28,29]. Interestingly, through their ability to inhibit the mRNA and/or protein expression levels of COX-2, NF-κB and various interleukins, the anthocyanins have exhibited anti-inflammatory effects in multiple cell types in vitro [17,20,31–33]. For example, treatment of JB-6 Cl 41 mouse epidermal cells with an anthocyanin-rich extract from black raspberries resulted in down-regulation of benzoapyrene diol-epoxide (BaPDE)-induced expression of NF-κB [33].

3.1.6. Anti-angiogenesis

Angiogenesis is the process of forming new blood vessels from the existing vascular network, and is an important factor in tumor growth and metastasis [34]. Some of the most potent angiogenesis-activating molecules are members of a family of vascular endothelial growth factors (VEGF), and VEGF expression is frequently enhanced in developing tumors [34]. The anti-angiogenic effects of anthocyanins have been investigated using cultured endothelial cells [8], oral cancer cells [17] and mouse epidermal JB6 cells [34]. Anthocyanins have been shown to suppress angiogenesis through several mechanisms such as: inhibition of H2O2- and tumor necrosis factor alpha (TNF-α)-induced VEGF expression in epidermal keratinocytes [8], and by reducing VEGF and VEGF receptor expression in endothelial cells [8]. In addition, anthocyanins inhibit neovascularisation by endothelial cells in the chick chorioallantoic membrane and in Matrigel [35]. Furthermore, treatment of mouse epidermal JB6 cells with an anthocyanin-rich extract from black raspberries resulted in down-regulation of VEGF expression through inhibition of the phosphoinositide 3-kinase (PI3K)/Akt pathway [34].

3.1.7. Anti-invasiveness

Degradation of basement membrane collagen by proteolysis is an early and critical invasion event. Tumor and stromal cells have to secrete proteolytic enzymes to facilitate degradation of the extracellular matrix barriers for successful tumor cell invasation. Degradation of the basement membrane is not dependent solely on the amount of proteolytic enzymes present but on the balance of activated proteases and their naturally occurring inhibitors. Matrix metalloproteinases (MMP) and plasminogen activators are families that regulate the degradation of the basement membrane [36]. Anthocyanin extracts (2.5–100 μM) from different berry types, black rice and eggplant have been evaluated for their ability to inhibit the invasion of multiple cancer cell types in Matrigel [37–39]. The extracts were found to inhibit cancer cell invasion through reducing the expression of MMP and urokinase-plasminogen activator (u-PA), both of which degrade extracellular matrix as part of the invasive process and, by stimulating the expression of a tissue inhibitor of matrix metalloproteinase-2 (TIMP-2) and of an inhibitor of plasminogen activator (PAI), both of which counteract the action of MMP and u-PA [36].

3.1.8. Induction of differentiation

Prevention and treatment of cancer through the induction of cellular differentiation offers a cell-specific approach to cancer prevention and treatment that is likely to be less toxic than standard radio/chemotherapy [40]. In this regard, treatment of leukemic cells in vitro with anthocyanins (25–200 μg/ml) leads to induction of differentiation as evidenced by: (a) increased reduction of nitroblue tetrazolium (NBT), a functional marker for granulocyte/monocyte differentiation; (b) increased adherence of cells to plastic, suggesting differentiation of leukemic cells into a monocyte/macrophage-like phenotype; (c) induction of naphthol AS-D chloroacetate activity, a marker for granulocytic differentiation; and, (d) an increase in the number of α-naphthyl acetate esterase positive cells, further indicating differentiation toward the monocytic/macrophagic lineage [40]. Stimulation of leukemic cell differentiation was accompanied by reduced cell proliferation and
down-regulation of c-myc. Anthocyanins also induced differentiation in melanoma cells characterized by a marked increase in dendritic outgrowth accompanied by a remodeling of the microtubular network [41]. This was associated with a significant increase in the expression of “brain specific” cytoskeletal components such as NF-160 and NF-200 neurofilament proteins in the cells [41]. In oral cancer cells, anthocyanins (100 µg/ml) induced the activation of transglutaminase enzymes involved in keratin production [17].

3.2. In vivo studies in animals

Anthocyanins have been shown to inhibit the development of cancer in carcinogen-treated animals and in animals with a hereditary predisposition to cancer. In most studies, the molecular mechanism(s) of tumor inhibition were not investigated in detail. A summary of the available data on the prevention of cancer in animals by anthocyanins is as follows.

3.2.1. Esophageal cancer

In a model of squamous cell carcinoma of the esophagus, Fischer-344 rats are treated repeatedly with the carcinogen, N-nitrosomethylbenzylamine (NMBA), after which esophageal tumors appear in all treated animals within 20–25 weeks [42]. Using this model, our laboratory has demonstrated the ability of multiple chemopreventive agents, including lyophilized black raspberries, to prevent the development of NMBA-induced esophageal tumors and determined their mechanism(s) of action [43]. In a recent study, we compared the ability of diets containing either 5% black raspberry powder, an anthocyanin-rich fraction isolated from black raspberries, or an ethanol:H2O extract from black raspberries, to inhibit esophageal tumorigenesis in NMBA-treated rats [42]. All three diets contained approximately the same quantity of anthocyanins (3.5 µmole/g diet). The results of this study indicated that all three diets were equally effective in preventing the development of esophageal tumors, reducing tumor numbers by 42–47%, suggesting that the anthocyanins in black raspberries are important for their chemopreventive activity [43]. The mechanism(s) by which the anthocyanin-rich diet prevented esophageal tumorigenesis is under investigation, however, we have shown that whole 5% black raspberry diets inhibit the mRNA and protein expression levels of COX-2, inducible nitric oxide synthase (iNOS), c-Jun, VEGF and other genes associated with cell proliferation, inflammation and angiogenesis [43].

3.2.2. Colon cancer

In the APC(Min) mouse model of intestinal cancer, animals fed an anthocyanin-rich tart cherry extract (375–3000 mg/kg diet) had 74% fewer cecal tumors (p < 0.05) than untreated mice, but the percent changes in colon tumors (17%) and small intestinal tumors (30%) in treated versus untreated mice were not significant [44]. In a subsequent study using a similar protocol, Min mice fed the anthocyanin-rich tart cherry extract (375–3000 mg/kg diet) plus the non-steroidal anti-inflammatory drug (NSAID), sulindac (100 mg/kg diet), had significantly (p < 0.05) fewer tumors in the proximal and medial thirds of the small intestine, but not in the distal third, than mice fed sulindac alone [45]. In the same model, animals fed the anthocyanin, cyanidin-3-glucoside (0.3% of the diet), or an anthocyanin mixture from bilberry at the same dietary concentration (0.3%) decreased adenoma numbers by 45% and 30%, respectively [46]. In this study, anthocyanins were detected in plasma, and both glucuronide and methyl metabolites of anthocyanins were detectable in the intestinal mucosa and urine. In the azoxymethane (AOM)-induced model of colon cancer in F344 rats, diets containing 2.5%, 5% and 10% lyophilized black raspberries significantly decreased total tumors (adenomas and adenocarcinomas) by 42%, 45% and 71%, and urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels by 73%, 81% and 83%, respectively [47]. The reduction in urinary 8-OHdG levels indicated that berries reduce ROS-induced DNA damage in animals. Lala et al. [48], using the AOM-induced rat colon cancer model, reported that an anthocyanin-rich extract from bilberry, chokeberry and grape (containing 3.85 g anthocyanins per kg diet) significantly reduced AOM-induced aberrant crypt foci by 26–29%. This reduction was associated with decreased cell proliferation and COX-2 gene expression, however, the levels of urinary 8-OHdG were similar among rats fed the different diets. Anthocyanins from purple sweet potatoes, red cabbage and purple corn (at 5% in the diet), significantly reduced colorectal carcinogenesis by 48, 63 and 89%, respectively, in rats treated with 1,2-dimethylhydrazine, but the mechanism(s) of tumor inhibition were not investigated [49,50].
3.2.3. Skin cancer

At least three studies have demonstrated the ability of anthocyanins to influence parameters of skin tumor development in mice. Using the SKH-1 hairless mouse, Afaq et al. [14] investigated the photopreventive effect of delphinidin, a major anthocyanidin present in many pigmented fruits and vegetables, on UVB-induced biomarkers of skin cancer development. Topical application of delphinidin (1 mg/application) to mouse skin inhibited apoptosis and markers of DNA damage such as cyclobutane pyrimidine dimers and 8-OHdG. These results suggest that delphinidin inhibited UVB-mediated oxidative stress and reduced DNA damage, thereby protecting the cells from UVB-induced apoptosis. In another study by the same laboratory, topical application of anthocyanin- and tannin-rich pomegranate extracts (2 mg/mouse) to the skin of CD-1 mice significantly inhibited TPA-mediated increases in skin edema and hyperplasia, ornithine decarboxylase (ODC) activity and protein expression of both ODC and COX-2 [51]. In addition, the extracts inhibited TPA-induced phosphorylation of ERK1/2, p38 and JNK1/2, as well as the activation of NF-κB, and IKKα, and phosphorylation and degradation of IκBα. Finally, the pomegranate fruit extracts produced significant (p < 0.05) decreases in TPA-induced skin tumor incidence (70% reduction) and tumor multiplicity (64% reduction) at 16 and 30 weeks of the bioassay, respectively.

3.2.4. Lung cancer

Anthocyanins have been shown to inhibit the development of tumors induced in mice following the subcutaneous injection of lung tumor cells. Cyanindin-3-glucoside, administered i.p. to nude mice at a dose of 9.5 mg/kg, reduced the size and inhibited metastasis of tumors produced by xenotransplantation of A549 human lung carcinoma cells [52]. Similarly, anthocyanins from black rice administered in a dose of 0.5% (wt/wt) by oral gavage, suppressed the growth of Lewis lung carcinoma cells following s.c. injection into C57BL/6 male mice [19]. The mechanism(s) by which these anthocyanins suppressed tumor development was not investigated.

3.3. Human studies

Unlike the in vivo animal model studies, epidemiological studies in humans have not provided convincing evidence of the anti-cancer effects of anthocyanins. For example, a case-control study involving 805 subjects with oral and pharyngeal cancer and 2,081 hospital controls without neoplasia was conducted in Italy to examine the relationship between anthocyanin intake and cancer risk [53]. The results indicated no significant association between anthocyanin intake and risk for oral or pharyngeal cancer. Also in Italy, the role of six principal classes of flavonoids, including the anthocyanidins, on prostate cancer risk was studied using data from a multicentric case-control study [54]. This study included 1294 incident cases of prostate cancer, and 1451 hospital controls without neoplasia. The results did not support a protective effect of flavonoids, including anthocyanidins, on prostate cancer in this population [54]. Supplementation of anthocyanins in the diet of cancer patients receiving chemotherapy did not result in increased inhibition of tumor development when compared to chemotherapy alone [55].

Although epidemiological studies have not shown that anthocyanin intake reduces cancer risk in humans, they suggest that anthocyanin intake may reduce certain parameters of oxidative damage. A study in Germany showed that individuals who consumed an anthocyanin/polyphenolic-rich fruit juice had reduced oxidative DNA damage and a significant increase in reduced glutathione when compared to controls [56]. In addition, in an investigation of patients with Barrett’s esophagus, the oral administration of 45 or 32 g (males and females, respectively) of lyophilized black raspberry powder (which contains about 5–7% anthocyanins) in a slurry of water daily for six months reduced levels of 8-epi-prostaglandin F2α (8-Isop-PGF2) and 8-OHdG in urine [57]. In contrast, a study conducted in the United Kingdom indicated that dietary anthocyanins from cranberry juice had no effect on basal or induced oxidative DNA damage or cellular antioxidant status in leukocytes taken from treated individuals [58].

In a pre-surgical model, 25 colon cancer patients that had not received prior therapy consumed 60 g/day (20g/3×/day) of black raspberry powder daily for 2–4 weeks. Biopsies of normal-appearing and tumor tissues were taken before and after berry treatment. The berries reduced proliferation rates and increased apoptosis in colon tumors but not in normal-appearing crypts. The number of CD 105 stained blood vessels was also reduced in berry-treated colon tumors suggesting an anti-
angiogenic effect of short-term berry treatment. The contribution of the anthocyanins in the berries to these effects is under investigation [59].

4. Pharmacokinetics and metabolism of anthocyanins

The bioavailability, pharmacokinetics of distribution, and metabolism of anthocyanins in animals and in humans have been summarized in a recent review [60]. In general, in both animals and humans, the anthocyanins are absorbed as intact glycosides, and their absorption and elimination is rapid. However, the efficiency of their absorption is relatively poor [60,61]. We investigated the absorption and metabolism of black raspberry anthocyanins in humans when administered orally at high doses (2.69 ± 0.085 g/day) [62]. Peak plasma levels of the four anthocyanins in black raspberries were observed within 2 h of oral berry treatment and their elimination from plasma followed first-order kinetics. They were excreted both as intact anthocyanins and as methylated derivatives in the urine within 4–8 h of berry ingestion. Overall, less than 1% of the administered dose of the berry anthocyanins was absorbed and excreted in urine. Similar results have been obtained in studies of the absorption and metabolism of anthocyanins in rodents [61].

Anthocyanins have been shown to inhibit malignant cell growth, stimulate apoptosis and modulate oncogenic signaling events in vitro in the $10^{-6}$ to $10^{-4}$ M concentration range. Studies of the uptake of anthocyanins in humans after their consumption as mixtures suggest that they reach levels of $10^{-8}$ to $10^{-7}$ M in human blood, or far below the levels required to exhibit anti-carcinogenic effects in vitro. Thus, it is unclear whether the concentrations in vivo are sufficient to elicit anti-carcinogenic effects in humans, and whether they exert chemopreventive efficacy by themselves or if they need to undergo hydrolysis to their aglyconic counterparts to be effective [63].

5. Conclusions

Anthocyanins have been shown to exhibit anti-carcinogenic activity against multiple cancer cell types in vitro and tumor types in vivo. Potential cancer chemopreventive activities of anthocyanins revealed from in vitro studies include radical scavenging activity, stimulation of phase II detoxifying enzymes, reduced cell proliferation, inflammation, angiogenesis and invasiveness, and induction of apoptosis and differentiation. The anthocyanins modulate the expression and activation of multiple genes associated with these cellular functions including genes involved in the PI3K/Akt, ERK, JNK, and MAPK pathways (Fig. 2). In vivo studies have shown that dietary anthocyanins inhibit cancers of the gastrointestinal (G.I.) tract and topically applied anthocyanins inhibit skin cancer. Pharmacokinetic data indicate that the absorption of anthocyanins into the bloodstream of rodents and humans is minimal, suggesting that they may have little efficacy in tissues other than the G.I. tract and skin, where they can be absorbed locally. Measuring tissue-bound anthocyanins should be done to predict the chemopreventive effects of anthocyanins in different organ sites. The role of gut bacteria in the metabolism and uptake of anthocyanins should also be investigated. Finally, studies should be undertaken to determine if the anti-cancer effects of anthocyanins are due to the parent compounds and/or to their metabolites.

Although experimental studies have clearly demonstrated the anti-cancer activity of anthocyanins, epidemiological studies have not revealed protective effects of anthocyanin consumption on cancer risk in humans, and their antioxidant activity in humans remains questionable. Moreover, the amounts of anthocyanins needed to elicit effects in vitro far exceed the amounts observed in human plasma in vivo. Future studies aimed at enhancing the absorption of anthocyanins and/or their metabolites therefore, may be necessary for their optimal use in the chemoprevention of human cancer, particularly in tissues other than the G.I. tract and skin.
References


