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Commentary

Foodstuffs for Preventing Cancer: The Preclinical and Clinical Development of Berries

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Abstract Laboratory research involving berries is a promising example of food-based cancer prevention. Berries contain many known chemopreventive agents such as anthocyanins and ellagitannins that can be greatly concentrated in freeze-dried berry powders. Based on our program of berry research, this commentary presents the first reported stepwise scheme for the preclinical and clinical development of foodstuffs for cancer prevention. Our preclinical work within this scheme includes promising approaches for assessing the chemopreventive potential of berry powder and berry extracts in preclinical model systems, for determining the mechanisms of action of these agents, and for identifying the active constituents in berries. The commentary also presents preliminary results of clinical trials in the oral cavity, esophagus, and colon using various formulations of freeze-dried berries. The relative merits of berry powders, extracts, or individual constituents (anthocyanins) for cancer prevention are also discussed.

Chemoprevention is the administration of one or more chemical entities, either as individual drugs or as dietary supplements, to prevent the initiation of premalignant lesions or their progression to cancer or cancer recurrence (1). Most chemoprevention studies have been conducted with individual compounds including various nutrients and nonnutrient phytochemicals. Our laboratory has devoted considerable effort in the past toward developing individual compounds for cancer prevention, especially the nonnutrient phytochemicals ellagic acid and phenylethyl isothiocyanate (2, 3). Recently, however, we have devoted most of our effort to developing and applying a "food-based" approach to cancer prevention using freeze-dried, commercially available, edible berries. Our approach to evaluating the efficacy of whole berries (containing numerous compounds) for cancer prevention is nearly identical to that used by chemoprevention scientists working with individual compounds.

Our interest in berries stemmed from early studies with ellagic acid, which is found in the pulp and seeds but not in the juice of berries (4). Because water accounts for ~85% to 90% of the wet weight of berries, we reasoned that the removal of water from berries would result in an ~10-fold concentration of the ellagic acid. Therefore, we began to freeze-dry berries under anoxic conditions to ensure the integrity of their components and to grind the dried berries into powder. Chemical analysis of different berry powders revealed that berries contain multiple chemopreventive agents in addition to ellagic acid (5). Table 1 presents a list of some potential chemopreventive agents in black raspberries (BRB). Blackberries, strawberries, blueberries, and others contain chemopreventive agents similar to those in BRBs (Table 1) but differing in quality and/or quantity.[1] Therefore, berry powders contain a combination of chemoprotective agents that might be expected to act at multiple stages in the carcinogenesis process. This is undoubtedly the case for other foodstuffs as well. Indeed, we were encouraged to test berry powder by early reports on the chemopreventive potential of other foodstuffs such as tea (6, 7), broccoli (8), tomato juice (9), and soybeans (10).

This commentary presents a concise summary of current laboratory work with BRBs and discusses several important topics not detailed in previous reviews as well (11–13). It details a stepwise scheme for assessing the chemopreventive potential of berries and other foodstuffs in preclinical models and clinical trials. It is important to mention that this approach has involved the integrative efforts of numerous basic scientists, physician and dental scientists and practitioners, statisticians, laboratory and clinical trial managers and technicians, postdoctoral trainees, and graduate students. I also discuss the potential advantages and disadvantages of powders, extracts, and individual compounds, including related issues of different formulations and routes of administration; the updated status of clinical BRB trials, including the final polyp-regression results of our trial in familial adenomatous

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polyposis (FAP) patients and a list of all pilot clinical trials (to my knowledge) of BRBs and their specific biomarker end points; and initial batch-to-batch consistency and/or variation of BRB powders from a single source farm.

Scheme for Evaluating the Chemopreventive Potential of Berry Powder

We and others have suggested the following stepwise approach for evaluating the chemopreventive potential of berry powders (Fig. 1): (*a*) develop "standardized" powders using chemical analyses; (*b*) evaluate toxicity in rodents; (*c*) determine antitumorigenic effects and the mechanism(s) for these effects in rodents; (*d*) conduct phase I clinical trials in humans; (*e*) conduct "pilot" trials of different berry powder formulations for effects on precancerous lesions and biomarkers in humans; (*f*) conduct randomized, placebo-controlled phase II biomarker trials; and (*g*) conduct phase III trials to determine cancer prevention efficacy. This approach could easily be applied to the assessment of powders from other foodstuffs and is similar to that described by Kelloff et al. (14) for the preclinical (*in vitro* and animal) and clinical development of individual compounds. The scheme of Kelloff et al. differs from ours principally in their proposed initial step, which is to either synthesize an individual compound or isolate one from naturally occurring sources; a standardized berry powder in our approach contains multiple compounds. Indeed, we and our collaborators also have used the individual-agent approach, isolating anthocyanins (from BRBs) and identifying those with chemopreventive potential in animals (see below; refs. 15, 16). The specific steps of our approach for developing berries and berry components for cancer prevention are summarized in the following sections.

"Standardizing" Berry Powders for Chemoprevention Studies

Early studies revealed that the ellagic acid and anthocyanin contents in berries obtained from different farms in Ohio varied as much as 2- to 4-fold (4, 17). Therefore, to minimize this inherent variability, we obtain all berries from a single farm in Southern Ohio. Most studies have been conducted with BRBs (*Rubus occidentalis*) of a single variety (Jewel) because they have the highest levels of anthocyanins and ellagitannins (18) and exhibit higher antioxidant activity (19) compared with most other commercially available berry types.

Ripe BRBs are picked mechanically, washed with water, and frozen at −20°C on the farm within 2 to 3 hours of picking. The berries are then shipped frozen to Van Drunen Farms in Momence, Illinois, where they are freeze-dried under anoxic conditions to protect the integrity of berry components. Next, seeds are removed by forcing the freeze-dried berries through a small sieve, and the dried pulp is ground into a powder. The berry powder is shipped at a low temperature to Ohio State University, where it is stored at −20°C until use in experimental studies. For standardization purposes, each batch of powder undergoes a quantitative chemical analysis of 26 randomly selected nutrients and nonnutrient components, including some agents with chemopreventive potential (5, 20). The levels of the 26 components remain within 10% to 20% of the initial analyses for at least 2 years in powder stored at −20°C (20).

Table 1 shows some of the potential chemopreventive agent content (5, 21–35) of powders that were prepared from BRBs obtained in 1997, 2001, and 2006; relatively high levels of calcium, β-sitosterol, ellagic acid, quercetin, and anthocyanins are notable. The amounts of calcium, zinc, β-sitosterol, α-carotene, ellagic acid, *ρ*-coumaric acid, quercetin, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, and cyanidin-3-*O*-xylosyl-rutinoside in the yearly powders varied from 10% to 40%, whereas the amounts of other constituents (β-carotene, folate, ferulic acid, and cyanidin-3-*O*-sambubioside) varied from 60% to 90%. The relatively high variability in levels of β-carotene and folate is likely due to difficulties in accurately measuring the low levels of these agents in the powder. Selenium is present in microgram quantities in BRBs; therefore, values for selenium are reported as <5.00 μg/100 g of dry weight. Because we routinely analyze only a small percentage of the overall number of compounds in BRBs, it is likely that BRBs contain known (and perhaps unknown) chemopreventive agents in addition to those listed in Table 1. Therefore, berries, like other foodstuffs, represent combinations of agents that may exhibit chemopreventive potential, particularly when concentrated by freeze-drying.

Toxicity Studies in Rodents

One of the most desirable features of a chemopreventive agent is little or no toxicity at concentrations producing

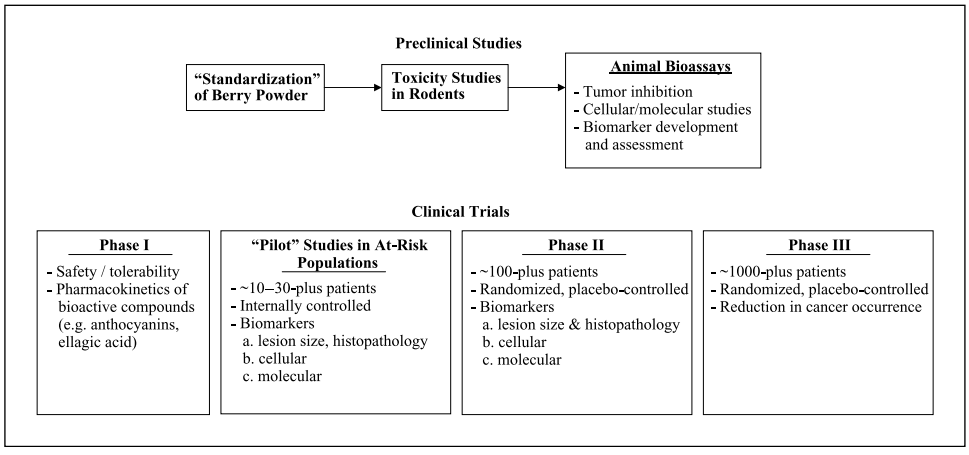

Fig. 1. Scheme for assessing berries (or other foodstuffs) for chemopreventive efficacy.

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Table 1. Some potential chemopreventive agents in powder made from BRBs harvested in 1997, 2001, and 2006

Component	Crop year*			References
	1997	2001	2006	
Minerals				
Calcium	215.00	175.00	188.00	(21)
Selenium*	<5.00	<5.00	<5.00	(22)
Zinc	2.69	2.34	2.16	(23)
Vitamins				
α-Carotene	<0.02	<0.02	<0.03	(24)
β-Carotene	<0.02	0.06	<0.07	(25)
α-Tocopherol	n.d.	n.d.	10.40	(26)
γ-Tocopherol	n.d.	n.d.	11.20	(27)
Folate	0.06	0.08	0.14	(28)
Sterols				
β-Sitosterol	80.10	88.80	110.00	(29)
Campesterol	3.40	5.90	5.50	(30)
Simple phenols				
Ellagic acid	166.30	185.00	225.00	(2)
Ferulic acid	17.60	<5.00	47.10	(31)
p-Coumaric acid	9.23	6.82	6.92	(32)
Chlorogenic acid	n.d.	n.d.	0.14	(32, 33)
Quercetin	n.d.	43.60	36.50	(32, 34)
Anthocyanins (complex phenols)				
Cyanidin-3-*O*-glucoside	n.d.	250.00	278.50	(13, 35)
Cyanidin-3-*O*-sambubioside	n.d.	220.00	56.00	(13, 35)
Cyanidin-3-*O*-rutinoside	n.d.	2,002.00	1,790.00	(13, 35)
Cyanidin-3-*O*-xylosylrutinoside	n.d.	510.00	853.50	(13, 35)

Abbreviation: n.d., not determined.

*All measures in the crop-year columns are mg/100 g of dry weight, except for that of selenium, which is μg/100 g of dry weight.

chemopreventive efficacy. We have evaluated the toxicity of BRBs in rats fed a synthetic diet (AIN-76A diet) plus either 5% or 10% BRB powder by weight (w/w) for up to 9 months. These percentages of BRB powder in a rat diet would be equivalent to ~0.9 to 1.8 ounces of BRB powder in the daily human diet, as calculated on a body surface area basis (36). Because 1 ounce of berry powder is equivalent in content to ~10 ounces of fresh berries, 0.9 to 1.8 ounces of powder average out to ~0.8 pound of fresh whole BRBs per day overall.

Histopathologic studies indicated that these BRB diets did not produce toxic effects in any major organs of the animals, and there were no significant differences in either body weight or food consumption between rats on either of the BRB-supplemented diets versus control rats on the AIN-76A-alone diet during the 9-month treatment. An unexpected benefit of the berry diets in rats was a 10% reduction in total blood cholesterol.

Inhibition of Carcinogen-Induced Tumors and Mechanistic Studies *In vivo*

Diets containing 5% and 10% BRB powder inhibit carcinogen-induced tumors in the rat esophagus, colon, and mammary gland and the hamster cheek pouch (5, 37–39). The most reliable measure of tumor inhibition in these studies is tumor multiplicity; in general and depending on the temporal sequence of administration of the carcinogen and the berry diet, the extent of inhibition of tumor multiplicity ranges from ~30% to 70%. Optimal tumor inhibition occurs when the BRBs are added to the diet before, during, and after treatment with carcinogens, suggesting that consumption of berries throughout life may maximize their chemopreventive effectiveness in humans. That berry diets do not inhibit 100% of tumorigenesis suggests that the inhibitory components of BRBs are not completely absorbed and/or that berry compounds do not affect certain critical signaling pathways of carcinogenesis. It should be mentioned that diets containing 5% and 10% strawberry and blackberry powders were nearly as effective as BRB powders in inhibiting tumors induced in the rat esophagus by the carcinogen *N*-nitrosomethylbenzylamine (13). In contrast, diet with 5% or 10% blueberry powder was ineffective (13), and studies are under way to determine the basis for this result.

Cellular and molecular mechanisms of chemoprevention by berries have been studied most often *in vivo* with BRBs in the *N*-nitrosomethylbenzylamine model of rat esophageal carcinogenesis. BRBs influence cellular and molecular events associated with proliferation, apoptosis, inflammation, and angiogenesis (ref. 13, 20; Fig. 2). A recent investigation involving DNA microarray identified *N*-nitrosomethylbenzylamine–dysregulated genes in the initiation stage of rat esophageal

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carcinogenesis that were restored to near normal levels of expression by BRBs (40). These restored genes were associated with multiple cellular functions, indicating that the active components of BRBs elicit a genome-wide effect in modulating genes involved in the early events of esophageal carcinogenesis. Perhaps this is not surprising in view of the array of chemopreventive agents in berries that potentially act on different signaling pathways. Mechanistic data from *in vitro* studies with berry extracts (presented below) confirm the wide range of effects of berry components on cellular and molecular events associated with carcinogenesis.

Phase I Clinical Trial of BRBs in Humans

Clinical trials of BRBs were based on promising preclinical data. A phase I trial evaluated the safety and tolerability of BRB powder (45 g as a slurry in water daily for 7 days) and measured anthocyanins and ellagic acid in the plasma and urine of 11 healthy participants (41). This dose of BRB powder is equivalent to the human consumption of ~16 ounces (1 pound) by weight of fresh whole BRBs daily. BRBs were administered in powder form rather than fresh for two reasons: (*a*) 1 pound of fresh BRBs is a substantial, problematic quantity to consume on a daily basis, particularly for humans who cannot tolerate berry seed; (*b*) fresh BRBs are available in stores only 1 to 2 months of each year, whereas high-quality BRB powder is available during the entire year. For chemoprevention, therefore, berry powder is more feasible. The berry powder was well tolerated, with a low incidence of mild or moderate constipation in 4 of the 11 subjects. Maximum concentrations of anthocyanins and ellagic acid occurred at 1 to 2 hours in plasma and at 1/2 to 4 hours in urine. The overall uptake of anthocyanins and ellagic acid was <1% of the administered dose as determined by measurement of free anthocyanins and ellagic acid in plasma. It is likely, however, that the uptake of these compounds was underestimated because their metabolites and protein-bound forms were not measured in plasma (41, 42). In a subsequent pilot study of oral BRB powder (32 or 45 g/d for 6 months) in Barrett's esophagus patients (43), ~15% of patients reported symptoms of occasional diarrhea, constipation, or epigastric pain, but the symptoms were not severe and all patients continued berry powder consumption throughout the study. The collective human and animal data suggest that BRB powder is well tolerated in humans at doses of up to 45 g/d for at least 6 months and in animals at effective chemopreventive concentrations in the diet.

Pilot Intervention Trials in Humans

A series of pilot clinical trials are being conducted in individuals at higher-than-normal risk for cancer to determine if BRBs have potential for chemoprevention in humans (Table 2). These trials are internally controlled (i.e., each patient serves as his/her own control), involve few patients (15 to 30), and determine the effects of BRBs on dysplastic lesions and relevant biomarkers after relatively short-term (1-9 months) treatment. We view these trials as a time- and cost-effective means of assessing whether berries exhibit effects in specific cohorts with desirable characteristics for further examination in randomized, placebo-controlled, phase II and III clinical trials. Results from pilot trials in patients with Barrett's esophagus or oral dysplasia (43–45) clearly show that topical BRB in a 10% bioadhesive gel was more effective against oral dysplasia than oral BRB powder was against Barrett's esophagus, presumably because the topical treatment facilitated the absorption of berry anthocyanins and other compounds into the oral lesions (44). Ongoing trials are also examining the effects of BRB lozenges on the expression of nuclear factor κB in tumor tissues from patients with oral squamous cell carcinoma and on recurrence in clinically treated patients with oral squamous cell carcinoma (46, 47).

Recent results from two pilot trials in colorectal cancer or FAP suggest that berries may be useful for chemoprevention of colon cancer. BRB powder (20 g, 3× a day) administered orally in a slurry of water for a short term (2-4 weeks) produced a positive trend for changes in the expression of Ki-67 (marking cell proliferation), terminal deoxyribonucleotidyl transferase–mediated dUTP nick end labeling (apoptosis), CD105 (angiogenesis), and genes associated with the Wnt pathway (β-catenin, E-cadherin, c-Myc, and cyclin D1) in colorectal tumors (and not in normal colon; ref. 48). Only the reduction in Ki-67 cell proliferation rates, however, was

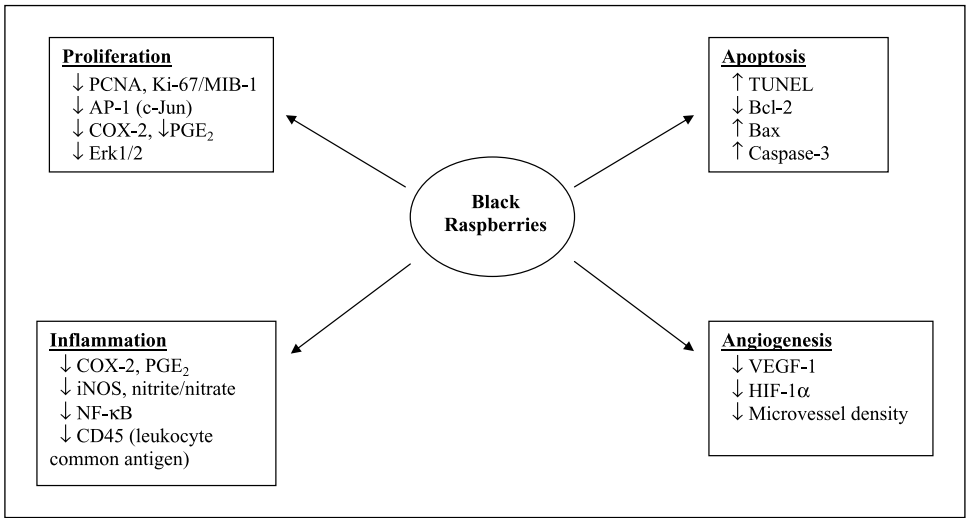

Fig. 2. Effects of BRBs on cellular events and associated genes in the *N*-nitrosomethylbenzylamine (*NMBA*)–treated rat esophagus. PCNA, proliferating cell nuclear antigen; COX-2, cyclooxygenase-2; PGE_2, prostaglandin E_2; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor κB; VEGF-1, vascular endothelial growth factor-1; HIF-1α, hypoxia-inducible factor-1α.

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Table 2. Pilot clinical trials of BRBs in at-risk populations

Trial	Delivery route	No. patients	Biomarkers	Status	References
Barrett's esophagus	Oral	20	Lesion size Histopathology Cell proliferation Oxidative stress Phase II enzymes	Complete	(43)
Esophageal dysplasia	Oral	60	Lesion size Histopathology Cell proliferation COX-2, iNOS	Ongoing	—
Oral dysplasia	Berry gel	27	Lesion size Histopathology Loss of heterozygosity COX-2, iNOS Gene modulation (microarray)	Complete	(44, 45)
Colon cancer	Oral	30	Cell proliferation Apoptosis Angiogenesis β-Catenin E-cadherin c-myc Cyclin D1	Complete	(48)
Rectal polyps	Oral and rectal suppository	14	Polyp number Polyp size	Complete	(49)
Prostate cancer	Oral	20	Cell proliferation Prostate-specific antigen	Ongoing	—
Oral cancer	Lozenge	35	NF-κB and other genes	Ongoing	(46, 47)

Abbreviations: COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor κB.

significant ($P < 0.05$). The positive modulation of a key biomarker such as Ki-67 of tumor development after short-term treatment with BRBs is encouraging. The recovery of BRB anthocyanins from normal colon tissues obtained from berry-treated patients indicated that the anthocyanins reached the target tissue and were absorbed locally.

FAP is a dominantly inherited disease characterized by the early onset of colonic polyposis and a nearly 100% risk of colon cancer by the age of 40. The traditional management of FAP is colectomy followed by lifelong endoscopic surveillance of the rectum and removal of rectal polyps. In a pilot study involving FAP patients who had undergone a colectomy (49), seven patients received BRB powder (20 g, 3× a day) in a slurry of water plus two rectal suppositories (700 mg BRBs each) inserted 1 hour before bedtime; the other seven patients received an oral powder placebo in a slurry of water plus the two active BRB suppositories; treatment lasted 9 months. The number of polyps was reduced by a median of 38% overall after 9 months (compared with polyp counts at baseline), including a median reduction of 53% in patients receiving both routes of berry treatment and 25% in patients treated with suppositories only. Studies are under way to determine the molecular mechanism(s) for BRB-induced polyp regression in these patients. The pilot results suggest that BRBs may be as or more effective than nonsteroidal anti-inflammatory drugs in regressing rectal polyps in FAP patients. Four other patients in this trial in 18 total patients, however, dropped out early because of rectal fissures caused by the suppositories. Therefore, the use of BRB suppositories for future trials to prevent rectal cancers is questionable.

Phase II and III Clinical Trials

To date, a single phase II clinical trial of BRBs in the oral cavity has been undertaken and is ongoing;[2] no phase III trials have been initiated. The pilot trial results suggest that there are sufficient positive data to initiate the first phase II clinical trials of BRBs in the colon and more studies in the oral cavity.

Berry Extracts and Bioactive Constituents

Water- and/or solvent-soluble extracts obtained from foods such as tea, grape seed, and pomegranate have been studied extensively for chemoprevention (50–52). Although they contain mixtures of compounds, extracts are thought to be more easily standardized than are whole foodstuffs, and they usually can be prepared with minimal difficulty. Extracts from different berry types, including BRBs, produce *in vitro* effects

[2] C. Weghorst, personal communication, January 7, 2009.

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Table 3. Some advantages and disadvantages of berry powders, extracts, and individual anthocyanins for cancer chemoprevention

	Advantages	Disadvantages
Powders	Contain multiple chemopreventive agents	Difficult to standardize
	Modulate multiple events in carcinogenesis	Stability of berry components influenced by several factors
	Seem to cause little or no toxicity	Potential contamination with microbes and chemicals
	Can be administered in different formulations	Apparent need for high consumption to be effective
	Relatively inexpensive	Seasonal availability of some berry types
Extracts	Potentially contain several chemopreventive agents	More difficult to prepare than powders
	Modulate multiple carcinogenic events *in vitro*	Some components unstable
	More easily standardized than powders	Efficacy *in vitro* is variable-high doses usually required
	Seem to cause little toxicity	High doses required for *in vivo* efficacy when given orally
	Can be administered in different formulations	May be expensive
	Useful for topical application to precancerous lesions	
Anthocyanins	Easily standardized	Unstable at alkaline pH
	Can be modified to improve bioavailability	Difficult to synthesize
	Influence multiple events in carcinogenesis	High doses required for *in vitro* efficacy
	Can be administered in different formulations	Poor bioavailability
	Cause little toxicity	Expensive

associated with chemoprevention including inhibition of cell transformation, proliferation, and carcinogen-induced gene expression, and stimulation of apoptosis and differentiation (13). Huang et al. (53) have shown that an alcohol extract of BRB powder reduces the activities of multiple carcinogen-induced genes in JB-6 mouse epidermal cells, including genes associated with the signal transduction pathways of phosphoinositide-3 kinase/Akt, activator protein-1, extracellular signal–regulated kinases/p38 kinase, and nuclear factor κB. An ethanol-water extract of BRBs was fractionated using high-performance liquid chromatography, and the subfractions were tested for their ability to down-regulate carcinogen-induced activator protein-1 and nuclear factor-κB activities in JB-6 cells; the major constituents of the most active subfractions were three (of the four) anthocyanins in BRBs: cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside, and cyanidin 3-*O*-(2^G)-xylosylrutinoside (15). We recently assessed these anthocyanins for *in vivo* activity, finding that a diet containing an anthocyanin-rich fraction of BRBs was as effective in inhibiting *N*-nitrosomethylbenzylamine–induced esophageal tumorigenesis in rats as was a diet containing 5% whole (not fractionated) BRB powder (16). Both diets contained the same, relatively small amount of anthocyanins (3.8 μmol/g diet), suggesting that relatively small doses of anthocyanins have important chemopreventive effects and that an anthocyanin-rich fraction of BRBs might be useful for cancer chemoprevention.

Pure anthocyanins, including cyanidin-3-*O*-glucoside and cyanidin-3-*O*-rutinoside in BRBs, exhibit multiple anticarcinogenic effects *in vitro*, as summarized by Wang and Stoner (54). *In vivo*, cyanidin-3-*O*-glucoside (at 0.3% of the diet) inhibits adenoma development in APC^{min} mice (55), and the anthocyanin delphinidin (found in pomegranates) inhibits biomarkers of skin tumorigenesis in CD-1 mice (52). These data suggest that additional studies of pure anthocyanins as potential chemopreventive agents are warranted.

Berry Powders versus Extracts versus Anthocyanins

Table 3 lists some advantages and disadvantages of using berry powders, berry extracts (water and solvent soluble), and pure anthocyanins (as examples of individual berry compounds) for cancer chemoprevention. Similar advantages and disadvantages undoubtedly apply to other foodstuffs and their derivatives. The choice of berry formulation (powder, extract, and anthocyanin) for specific chemoprevention studies depends, in part, on the target tissue. For example, BRB gels applied topically to oral lesions optimize the delivery of anthocyanins to target tissues (44), and the topical application of an alcohol-water extract of BRB powder to mouse skin inhibits UVB-induced skin tumorigenesis.[3] The oral consumption of berry powders may prove to be effective for colon cancer prevention (48, 49). A major advantage of berries and their component anthocyanins and of other foodstuffs and their components (e.g., tea/epigallocatechin-3-gallate, grapes/resveratrol, tumeric/curcumin, and tomatoes/lycopene) for chemoprevention is their apparent lack of toxicity in animals and in humans in comparison with toxicity of certain retinoids, selenium compounds, nonsteroidal anti-inflammatory drugs, and β-carotene (56–59). The various berry formulations, however, have not been administered to humans in multiyear trials, where toxicity is more likely and has occurred with many other preventive agents. Therefore, it may be premature to assume that berry formulations will be nontoxic in multiyear trials.

A disadvantage of whole berries and other foodstuffs for cancer prevention is the requirement for standardized formulations that provide reproducible chemopreventive effects. As indicated above, we found that the contents of ellagic acid and

[3] F.J. Duncan, J.R. Martin, B.C. Wulff, K.L. Tober, T.M. Oberyszyn, D.F. Kusewitt, A.M. VanBuskirk, unpublished data.

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anthocyanins in BRBs from different Ohio farms varied significantly. This variability is likely to be even greater in specific berry types grown throughout the world. Although we have tried to remedy variability by procuring berries from a single farm, this is not a "real-world" solution. Using a single lot of berry powder for an entire animal experiment or human trial, however, should allow a close determination of the amount of a specific chemopreventive agent(s) that will be needed to reproduce potential chemopreventive effects; therefore, we are using single lots to derive values for the amounts of anthocyanins, ellagitannins, and other berry components that may be expected to reproduce similar effects in humans.

Conclusions

A major objective of cancer therapy and prevention investigators is to develop individual therapeutic agents that markedly affect the expression of only one or a very few genes. The objective of this approach is to selectively kill specific types of cancer cells with minimal effects on their normal counterparts. In contrast, berry powders contain a mixture of compounds that seem to affect the expression levels of a wide range of cancer-related genes (to lesser extents than therapeutic agents; ref. 40), thus preventing the conversion of premalignant cells to malignancy at doses that cause minimal or no cytotoxicity. In this regard, berries seem to fulfill the requirement of an "ideal" chemopreventive agent (60). The same is undoubtedly true of many other foodstuffs; for example, a freeze-dried aqueous extract of broccoli sprouts was effective at dietary levels in inhibiting chemically induced bladder cancer with no observable toxicity in rats (61).

From a practical standpoint, we have found that high-risk individuals are usually willing to participate in clinical trials of berry formulations, and compliance in these trials is excellent. Moreover, the general public is intrigued with food-based approaches for the prevention of diseases including cancer. With potentially lower toxicity and costs, effective food-based approaches not only would be attractive for developed countries but would also offer greater portability (versus highly synthesized agents) to underdeveloped countries as well. Therefore, in my opinion, food-based approaches with rational developmental schemes such as the one outlined in this commentary should be an integral part of the overall strategies for the prevention of cancer and other diseases.

The future of food-based chemoprevention will benefit, indeed may rely, on the close collaboration and cooperation of basic scientists, nutritional epidemiologists, and clinical researchers. Mechanistic understandings of foodstuffs can only enhance their prospects for successful interventions in human populations at risk of cancer. Indeed, collaborative research of this nature can even help inform directions for the development of molecular-targeted approaches. As a related example, mechanistic studies indicate that the strong cancer-preventive effects of caloric restriction involve inhibition of the mammalian target of rapamycin (62). This information is potentially valuable to the large enterprise of preclinical and clinical development of mammalian target of rapamycin inhibitors.

Disclosure of Potential Conflicts of Interest

The author has no conflicts of interest relative to the information in this article.

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