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PERSPECTIVES

Grapes and Human Health: A Perspective

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Grapes are a valuable source of numerous phytonutrients, including the intensively studied constituent, resveratrol. A question worth addressing is the potential of dietary grape consumption to positively modulate human health. Many studies have suggested cardiovascular benefits, and some work has indicated cancer chemopreventive activity. Data are particularly compelling in the area of skin cancer prevention. With financial support provided by the California Table Grape Commission, novel and exciting preliminary data are emerging from independent research suggesting beneficial activity against other less prevalent but devastating illnesses, such as Alzheimer's disease and urinary bladder dysfunction. It is further suggested that some of the copious amounts of data obtained with resveratrol may be relevant to grape consumption, especially responses that can be mediated by low concentrations of the substance. Whether future specific health claims will be sought from or allowed by regulatory authorities is not known, but based on existing data, it is clear that grapes should be considered an integral component of fruit and vegetable enriched diets that are recommended by health authorities and widely accepted as beneficial for human health and disease prevention.

KEYWORDS: Grapes; resveratrol; phytochemicals; chemoprevention; disease prevention

INTRODUCTION

Early in 1997, while working at the University of Illinois at Chicago, our group published a paper in *Science* describing the cancer chemopreventive potential of resveratrol (*1*). This discovery was the result of an ongoing program project supported by the National Cancer Institute in which the primary goal is the discovery and characterization of the natural product inhibitors of carcinogenesis (http://nic.pharmacy.purdue.edu/) (*2*). The compound was isolated from a nonedible legume originally obtained in Peru; the activity leading to the discovery was inhibition of cyclooxygenase. Resveratrol is a structurally simplistic molecule, a stilbene (**Figure 1**), that does not generally inspire chemists or phytochemists. The chemical structure has been known for decades.

Our excitement stemmed from the interesting and diverse biological responses mediated by the compound, as well as the general knowledge of a more prevalent and perhaps more relevant natural source—the grape. At the time of publication, it must have been a calm time in the world, since intense media coverage ensued very quickly. Since resveratrol in the grape can be extracted during fermentation into the resultant product of wine, it is our understanding that many individuals in the City of Chicago proposed toasts to our discovery the night of the press release, and we suspect similar events occurred throughout the world. In addition to television, radio, newspaper, and magazine coverage, cartoons emerged (**Figure 2**). The compound has become so well-known that it was mentioned on a recent episode of the television series *CSI* and used as part of the evidence to apprehend a criminal.

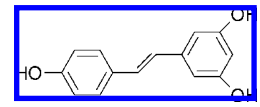

Figure 1. Structure of resveratrol (*trans*-3,4′,5-trihydroxystilbene).

While such attention may not be common in the mainstream world of science, nor particularly appreciated since it distracts from the intensely busy schedule of the day, it seems important to inform the lay public of dietary factors that may be of value for disease prevention. In the case of resveratrol, based on the appearance of nearly 2000 publications over the past few years, it is apparent that the imagination of the scientific community was also captured by our initial report. In addition to a large body of primary scientific papers, symposia have been conducted (*3*), reviews and monographs have been prepared (*4–10*), companies have been created (Royalmount Pharma, http://www.royalmountpharma.com/; Sirtris Pharmaceuticals Inc., http://www.sirtrispharma.com/), and many commercial products are available.

Having greatest interest in cancer chemoprevention, in 1997, I was surprised to notice that the grape was not displayed on a

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Figure 2. Cartoon created by the syndicated artist Chip Bok, Akron Beacon Journal, Akron, OH. Reprinted by permission of Chip Bok and Creators Syndicate.

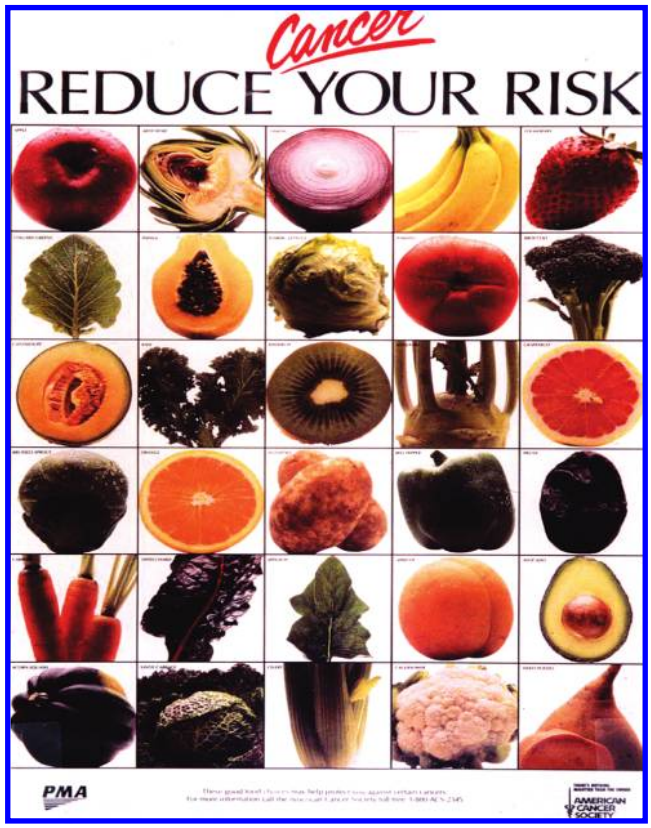

Figure 3. Poster suggesting consumption of fruits and vegetables leads to reduced risk of cancer. Reprinted by the permission of the American Cancer Society, Inc.

popular poster created by the American Cancer Society that simply stated Reduce Your Risk (**Figure 3**). Perhaps I was not the only person to notice the conspicuous absence of the grape, since I was invited by and eventually accepted an invitation from the California Table Grape Commission to present our work on resveratrol at a meeting of the Board of Directors. As described herein for the first time, over the past 10 years, a variety of studies investigating the biological activity of fresh grapes spawned from this visit. In addition, a review and perspective of the relevance of this work is provided.

WORK OF THE CALIFORNIA TABLE GRAPE COMMISSION

Following my presentation at the Board of Directors meeting in April 1997, held in Bakersfield, CA, the California Table Grape Commission created a grant program that continues today (http://www.freshCaliforniagrapes.com/). Applications are investigator initiated and subject to rigorous scientific review. In order to help ensure solid, reproducible data, starting with fresh whole grapes, the Commission sponsors the preparation of standardized grape powder preparations. The preparation is analyzed and supplied to investigators who receive unrestricted grants from the Commission. A list of the projects supported over the past several years is given in **Table 1**. Clearly, the California Table Grape Commission has demonstrated an unyielding and laudable commitment to the pure, basic, and applied science of the grape.

SOME BACKGROUND ON GRAPE RESEARCH

As a scientist involved in natural product research for many years, it is sometimes difficult to appreciate some of the finer aspects of life. As one small example, I can no longer look at a grape and observe its tactual properties, or even think so much about its organoleptic qualities. I see it as a crude source of phytochemicals, some of which may be of value for human health. Of course all natural products are composed of many chemical constituents, and, in addition to resveratrol, some of those having been associated with the grape are listed in **Table 2**. Over 1600 compounds have been identified in grapes, including anthocyanins, catechins, ellagic acid, lutein, lycopene, quercetin, and other potent antioxidants. Of additional interest, melatonin has been discovered recently as a component of the grape (*11*), and this substance could act in a synergistic manner with other active constituents. Obviously, when we consume a food or beverage, we are consuming its matrix of chemicals, and there is little doubt that some will affect our well being.

Most human beings have some cognitive concern about diseases that claim the largest number of lives. In the USA, the dominant diseases are heart disease and cancer, followed by pneumonia/influenza, cerebrovascular, respiratory, diabetes, and Alzheimer's disease. In considering the potential impact of grapes, a good deal of evidence suggests an association with reducing the risk of cardiovascular disease. Many studies have been conducted with phytochemicals employing *in vitro* or cell culture models, and an overwhelming majority of these studies show that grape constituents inhibit the atherosclerotic process (*12–21*). Similarly, in recent work conducted with a Dahl-Salt Sensitive rat model, Seymour et al. have reported a reduction of heart failure pathogenesis as the result of administering grape powder-enriched diets (*22*). While preliminary, work of this type is important since it helps to establish plausible biological mechanisms by which resveratrol and other phytochemicals in grapes may reduce the risk of cardiovascular disease. Perhaps of greater interest, however, are human intervention trials. As examples, in studies conducted with grapes and grape juice, clinical trials have demonstrated decreased platelet aggregation (*23–26*), improved endothelial function (*27–29*), reduced blood pressure (*30*), and positive influences on biomarkers such as HDL, LDL, apo-B, and MCP-1 (*18, 31, 32*). Accordingly, it is apparent that grape consumption can modulate a number of factors that are associated with health benefits.

In the case of cancer prevention, fewer studies of such a direct nature are available. Again, a variety of animal, cell culture, and *in vitro* studies have investigated the effect of grape phytochemicals on cancer-related processes (*33–36*), mostly suggesting beneficial activity. Recently, Holcombe et al. have observed a reduction in Wnt target gene expression in normal mucosa of patients treated with resveratrol and grape powder, suggesting potential to prevent colorectal cancer (*37*). In addition, the antioxidant potential of grapes and grape juice has been studied in human trials (*18, 27, 32, 38–40*). These studies

Table 1. Projects Funded by the California Table Grape Commission (1999−present) (http://www.freshCaliforniagrape.com/)

investigator	institution	funded proposals
John Bauer	Ohio State University	Vasoprotective Effects of a Standardized Grape Product
Dipak Das	University of Connecticut	Grapes and Cardioprotection
Giovanni Manfredi	Weill Medical College of Cornell University	Therapeutic Effect of Grape Intake in Animal Models of Neurodegeneration
Kathryn McMahon	Texas Tech University of Health Sciences Center	Anti-Atherogenic Activity of Grapes in Hypercholesteremic Transgenic Mice
John Pezzuto	University of Illinois at Chicago	Evaluation of Cancer Chemoprevention Potential of Standardized Grape Extract
Ronald Prior	Arkansas Children's Nutrition Center	Absorption, Metabolism, and Antioxidant Capacity of Grape Polyphenols
Chung Yang	College of Pharmacy, Rutgers University	Bioavailability of Grape Constituents
Constance Brinkerhoff	Dartmouth Medical School	Inhibition of Metalloproteinase Gene Expression by Extract of Fresh Grapes
Maria Luz Fernandez	University of Connecticut	Favorable Effects of Grapes on LDL Oxidation and Atherosclerotic Lesions. Studies in Ovariectomized Guinea Pigs, a Model for Menopause
Michael Seidman	Henry Ford Health System	The Effects of Standardized Grape Preparation on Presbyacusis
Bao Ting Zhu	University of South Carolina	Polyphenolic Grape Constituents Increase Bioavailability of L-DOPA: Benefits in the Treatment of Parkinson's Disease
Bianca Fuhrman	Lipid Research Laboratory, Rambam Medical Center Israel	Prevention of Atherosclerosis by Standardized Grape Preparation: Mechanistical Studies in Cell Culture, Atherosclerotic Mice, and Humans
Donald Godwin	University of New Mexico Health Sciences Center	Oral Administration of Freeze-Dried Powder to Prevent Photodamage to Skin
Robert Klein	University of Kansas Medical Center Research Institute	Can Grapes Prevent Brain Aging?
Albert Sun	University of Missouri School of Medicine	The Neuroprotective Effects of Grape Polyphenols
Margaret Hanausek	AMC Cancer Research Center	Inhibition of Different Stages of Skin Carcinogenesis with Freeze-Dried Grape Powder
Robert Levin	Albany College of Pharmacy	Protection of Urinary Bladder Function by Grape Extracts
Dorothy Morre	Purdue University	The Protective Effect of Standardized Grape Preparation Against Cancer/ Anticancer Activity of Grape and Grape Skin Extracts Combined with Catechins Based on Inhibition of tNOX and Growth of HeLa Cells in Culture and 4T1 Mouse Mammary Tumors in Mice
Maria Luz-Fernandez	University of Connecticut	Cardioprotective Effects of Grape Polyphenols in Pre- and Post-Menopausal Women
Herman Schut	Medical College of Ohio	Inhibition of PhIP-DNA Adduct Formation in Female F344 Rats by Dietary Freeze-Dried Grape Powder
Johanna Slavin	University of Minnesota	Effects of Grape Powder on Inflammation Markers in Post-Menopausal Women
Jerry Exon	Holm Research Center, University of Idaho	Interactive and Synergistic Effects of Grape Powder, Grape Seed Proanthocyanidins, Resveratrol, and Quercetin in a Colon Cancer Model
Robert Levin	Albany College of Pharmacy	Ischemic Bladder Dysfunction: Protection by Grape Suspension
Joseph M. Wu	New York Medical College	Cardioprotection by Resveratrol and Freeze-Dried Grape Preparation
Steven Bolling	University of Michigan	Grape Antioxidant Impact on Heart Failure Pathogenesis
Randall Holcombe	University of California, Irvine	Effects of Freeze-Dried Powder on WNT Signaling and Colon Cancer
Silvia Finneman	Weill Medical College	Age-Related Blindness: Possible Prevention or Delay by Grape Powder
Janet Olson	Mayo Clinic	Evaluation of Aromatase Inhibition Potential of Standardized Grape Powder
Tammy Dugas	Louisiana State University	Effects of Resveratrol and/or Grape Powder on Estrogen Dependent Modulation of Lesion Area in a Rodent Model for atherosclerosis and restinosis
Srinvasa Raja	John Hopkins Hospital	Freeze-Dried Grape Powder as a Potential Adjuvant in the Treatment of Rheumatoid Arthritis
Carl Keen	University of California, Davis	Effects of Freeze-Dried Table Grape Powder on Vascular Health in Post-Menopausal Women
Ishwarlal Jialal	University of California Davis and VA N. California Healthcare System	Effect of Grape Powder Supplementation on Inflammation Biomarkers in Human Volunteers

have largely yielded positive results, and modulation of the biomarkers investigated in this work is known to correlate with disease prevention. Notably, in recent clinical trials, Prior et al. have reported that consumption of standardized grape powder increases plasma antioxidant capacity (*41*).

Further, it is worth recalling the many studies that have been conducted with resveratrol, since the predominant dietary source of resveratrol is the grape and it is found in grapes of all colors. In our original report (*1*), antiinflammatory activity was observed in rats, and inhibition of tumorigenesis was observed in the two-stage mouse skin model. Importantly, in the rat inflammation model, resveratrol was administered orally, so a preliminary indication of bioavailability and systemic activity was provided. Inhibition in the two-stage mouse skin system has been confirmed (*42*) and greatly expanded with activity being observed in UV-induced skin cancer models (*43–46*). These data are very promising and suggest potential utility for the prevention of skin cancer.

As a logical extension of the numerous mechanistic studies performed with resveratrol in cell culture systems, many animal studies have been reported in the literature. In part, these studies have been designed to examine some biomarkers of carcinogenesis (*47–50*), a few derivatives of resveratrol (*51, 52*), and to investigate absorption and metabolism (*51, 53–55*). In addition, of course, a variety of antitumor models have been employed. Resveratrol reduced biomarkers of lung carcinogenesis produced in benzo(*a*)pyrene-treated mice (*56*) but not tumorigenesis (*57*). We also found that resveratrol was not active in the benzo(*a*)pyrene mouse lung tumorigenesis model (unpublished data), nor was it active in a mixed-carcinogen lung cancer model (*58*). A positive response was observed, however, with Lewis lung carcinoma-bearing mice (*59*). This response may have been due to an antiangiogenic response mediated by resveratrol (*59*), as has been noted in various other antitumor models (*60–62*).

In one study, a lack of activity was observed in the C57BL/6J $Apc^{Min/+}$ mouse (*63*). In an earlier study conducted with the same model, however, resveratrol was found to mediate a reduction of intestinal tumors (*64*). Aberrant crypts were also reduced in carcinogen-treated rats (*65*), as were colon tumors in 1,2-dimethylhydrazine-treated rats (*66*).

An increase in tumorigenesis was reported when resveratrol

Table 2. Phytochemical Components Reported from the Genus *Vitis*[a]

actinidiolide
acuminoside
ampelopsin A−F
amurensin A−M
amurensisin
amyrin
anisole
antheraxanthin
anthocyanins
astilbin
astragalin
astringin
benzoic acid
benzyl alcohol
betaine
betulifol A, B
betulin
betulinic acid
blumenol C
borneol
brevilagin 1
butyric acid
cadaverine
caffeic acid
caffeoyl tartrate
caftaric acid
caproic acid
carotene
castavinol
catechin dimers, trimers, tetramers, etc.
catechins
catechol
chlorogenic acid
chrysanthemin
chrysophanic acid
cineol
cinnamaldehyde, 3,4-dimethoxy
citronellol
coxmosiin
coumaric acid
coutaric acid
crotonic acid ethyl ester
cryptoxanthin
cyanidin
cycloartenol
cynaroside
damascenone
davidol A
decanoic acid ethyl ester
delphin
delphinidin
elemol acetate
ellagic acid
emodin
engeletin
enomelanin
enotannin
ergosterol
eugenol methyl ether
fenchyl alcohol
trans-fertaric acid
ferulic acid
feruloyl tartrate
flexuosol A
friedelan-3-one
furanone
furfural
furoic acid
gallic acid
gallocatechin
gentisic acid
geranic acid
geraniol
germanicol
gnetin
heptanoic acid ethyl ester
hopeaphenol
hyperoside
indole-3-acetic acid
ionone
iso-amyl acetate
jasmonic acid
kaempferol
lauric acid ethyl ester
leptosidin-6-*O*-β-D-glucopyranoside
leucopelrrgonidin
limonene
linalool
linoleic acid
lupenone
lupeol
lutein
luteolin
luteoxanthin
lycopene
malibatol A
malvidin
miquelianin
miyabenol A
mulberroside E
mutatoxanthin
myrcenol
myricetin
neoxanthin
nerol
nicotiflorin
nonan-1-al
obtusifoliol
ocimenol
octanoic Acid
oenin
oleanolic acid
oleic acid
orientin
paeonidin
pallidol
palmitic acid
pelargonidin
pentan-1-ol
petunidin
phenethyl acetate
phenylethanol
phloroglucinol-(4-α-2)-catechin
physcion
phytoene
Phytofluene
piceatannol
piceid
populnin
proanthocyanidin
procyanidin dimers
protocatechuic acid
pterostilbene
putrescine
pyrrolidine
quercetin
quercetrin
quercimeritrin
quercitrin
quinic acid
resveratrol
rhamnetin
roseoside
rutin
salicylic acid
scyllitol
shikimic acid
sinapic acid
β-sitosterol
spermidine
spermine
squalene
stearic acid
stenophyllol C
stigmasterol
syringaldehyde
syringic acid
tannin
taraxasterol
taraxerol
tartaric acid
terpinen-4-ol
terpinene
theaspirane, 8-hydroxy
triacontan-1-ol
trilobatin
ursolic aldehyde
vanillic acid
vinferin
viniferol A−E
viniferone A−C
violaxanthin
vitexin
vitilagin
vitisin A−E
vitisinol A−D
vitisinol B
vitispirane
vomifoliol
zeatin
zeaxanthin

[a] The chemical components listed in the table were obtained by searching the NAPRALERT database (www.napralert.org). A search of the term *Vitis* yielded 272 citations with a total of 1610 compound records. Major classes of compounds are summarized in the table.

was administered to rats treated with *N*-methyl-*N*-nitrosourea (*67*), but this is contrary to our results wherein an inhibition was observed (*47*). Activity was also reported in two studies conducted with the 7,12-dimethylbenz(*a*)anthracene rat mammary carcinogenesis model (*68, 69*), as well as the HER-2/Neu spontaneous breast cancer model (*70*). A positive response was reported with the *N*-nitrosomethylbenzylamine-esophageal model (*71*), as well as some combination regimens (*72, 73*). Finally, although activity was not observed with 4T1 breast cancer (*74*), B16 melanoma (*55*) or leukemia (*75*), resveratrol was found to mediate positive responses with tumor transplant models for hepatoma (*72, 76–79*), neuroblastoma (*80*), sarcoma (*81*), pancreatic (*82*), mammary (*61*), lung (*59*), glioma (*60*), laryngeal (*83*), and gastric (*84*) cancers.

Thus, the majority of animal studies conducted with resveratrol indicate promising activity. As a logical extension, some limited data are now available from studies conducted with human beings (*28, 53, 85, 86*), and four small-scale phase trials are underway (*87*). First and foremost, as anticipated from animal and cell culture studies, resveratrol is readily absorbed following oral administration, and rapidly metabolized (*53, 85, 86*). The primary metabolites are sulfates and glucuronides. These metabolites require further investigation since they are probably responsible for the biological response mediated by resveratrol administration. Further, resveratrol is present, albeit in low concentrations, so physiological responses could be facilitated by the parent compound with targets exemplifying high specificity and avidy. Finally, a combination effect involving resveratrol and metabolites is feasible, especially since so many possible targets have been identified.

EMERGING DATA: PRELIMINARY BUT EXCITING

As noted above and summarized in **Table 1**, a number of pilot studies have been performed utilizing a standardized grape powder. Of these studies, approximately 50% have yielded a positive response of one type or another. A few of the more exciting and interesting effects are briefly summarized below.

As the first example, urinary bladder dysfunction is a serious problem for older men with benign prostatic hyperplasia (BPH). Using rabbits as a model, Levin and co-workers have found that ischemia/reperfusion results in significant reductions in

contractile response. Interestingly, dietary administration of grape powder provided significant protection against the hypoxic effects of ischemia and ischemia/reperfusion (*88, 89*). The grape preparation could function through the up-regulation of superoxide dismutase and catalase (*90*). Since over 80% of men over the age of 50 may require some type of medical attention for BPH (*91*), these results suggest the importance of further investigation in this area.

Next, the most prevalent type of cancer is skin cancer, with over 1 000 000 cases each year in the USA (*92*). As demonstrated in our original studies, using the two-stage mouse skin model, resveratrol was an effective inhibitor of tumorigenesis (*1*). This observation has been confirmed by others (*42*). Now, employing SENCAR mice treated with 7,12-dimethylbenz(*a*)anthracene as a complete carcinogen, Hanausek and co-workers have demonstrated significant inhibition of skin tumorigenesis by treatment with grape powder. For example, with 5% standardized grape powder in the diet, after 12 weeks, the number of papillomas was reduced from 7.8 per mouse in the control group, to 0.7 per mouse in the treatment group. Notably, this reduction was found to correlate with a decrease in Ha-ras mutation at codon 61 (Hanausek, personal communication). Furthermore, in studies conducted by Godwin and co-workers employing UV-irradiated SKH:hr-1 hairless mice, oral administration of grape powder equivalent to two servings of fresh grapes five times per week, significantly reduced edema. After one week, a reduction of about 50% was observed. The reduction increased with time, reaching about 90% after eight weeks. The decrease correlated with photoprotection of lipids in the epidermis (Godwin, personal communication). These data provide preliminary, yet intriguing evidence for the potential of grape consumption to prevent severe skin damage.

Another example of great interest involves neuroprotection. As the population continues to achieve a longer lifespan, notable increases have been observed in the incidence of Alzheimer's disease, for example. The effects of administering grape powder in the diet of 24-month-old C57/B1K6 mice, as a model of aging, has been investigated. Of the various data obtained, modulation of transthyretin, a transporter of thyroid hormones and vitamin A in cerebrospinal fluid, known to bind to Alzheimer β-amyloid and thereby reduce plaque formation during neural aging, is particularly notable. As shown by Klein and colleagues, relative to control animals, oral treatment of these mice with grape powder upregulated transthyretin mRNA 246-fold. These very promising data indicate a that grape-enriched diet may augment antiaging/Alzheimer pathways and reduce inflammation in the brain (*93*).

Thus, in addition to demonstrating promise in prevalent diseases such as skin cancer, exciting data are emerging in systems designed to model other devastating illnesses such as Alzheimer's disease, age-related blindness, and urinary bladder dysfunction. As mentioned above, about half of the studies listed in **Table 1** have demonstrated positive responses with standardized grape powder. Clearly, the full biologic potential of the grape has yet to be realized, and excellent progress is being achieved.

A QUESTION OF DOSE

Many of the studies conducted with grapes, standardized grape powder, or grape constituents have been conducted with physiologically relevant doses, i.e., quantities that can easily be consumed by human beings, such as the equivalent of two servings (3/4 cup each) of grapes per day. These studies are least subject to scrutiny. Some other studies have been conducted with high dose regimens which the lay press likes to mention would be equivalent to consuming some large quantity such as 50 pounds of grapes per day. A factor that should be borne in mind, however, relates to the extreme nature of certain test systems. In the case of cancer chemoprevention, for example, test animals may be treated with chemical carcinogens. This is necessary to generate a sufficient number of tumors for establishing statistical significance and to accomplish this task in a reasonable time frame. So, of course, a high dose of test substance may be necessary to block or inhibit such an intense adverse reaction. What is established in such test systems, in a valid and acceptable scientific manner, is the potential of a test substance to demonstrate efficacy. In a real life situation, where the challenge is not nearly as direct or acute, it is reasonable to speculate that a lower dose, a dose that can be achieved in a regular dietary regimen, could be efficacious.

CONCLUSION

As healthcare costs continue to escalate, the concept of disease prevention is becoming more and more attractive. The use of vaccines is well accepted by all reasonable people and even mandated by law in some cases. In terms of drug therapy, the use of tamoxifen for the prevention of breast cancer, celebrex for the prevention of colon familial polyps, and aspirin for the prevention of cardiovascular disease or cancer is well established. It is likely that additional vaccines will be developed in due course, and it is likely that new drug therapies will be implemented as part of overall disease prevention strategies.

In terms of disease prevention, a concept that must constantly be remembered is the creed of the physician: first, do no harm. This concept is distinctly related to the 5-A-Day for Better Health campaign. Should the grape be included among the group of fruits and vegetables recommended for health maintenance or disease prevention? Based on existing data, the answer is yes. The power of the grape is at least on par with other fruits and vegetables: it rightly deserves membership on the *Reduce Your Risk* poster illustrated in **Figure 3**.

A unique aspect of the grape is the presence of resveratrol which, as described herein, has received a tremendous amount of attention. Are papers and data obtained or produced using resveratrol applicable to the grape? This is certainly a logical conclusion, especially when low concentrations of resveratrol can mediate biological responses (*94, 95*). In addition, the grape could easily produce copious quantities of resveratrol either through environmental stress (*96–98*), preharvest treatment with a plant activator (*99*), or genetic manipulation (*100, 101*). This is a polemic beyond the scope of this discussion, but the potential exists. In any event, in addition to resveratrol, many other phytochemicals are present in the grape (**Table 2**), and several of these constituents have been associated with health benefits. Overall, based on research conducted to date, it is reasonable to conclude that regular daily consumption of grapes could help maintain heart health, and potentially help to protect against the onset of aging, as well as the onset of some diseases associated with aging, such as certain cancers and neurodegeneration. It is also worth noting that very few people have a problem with grape consumption, such as an allergy. In summary, for the vast majority, including the grape in a normal dietary regimen is a sensible approach from a scientific viewpoint. Besides, who does not like grapes?

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