

## Perspective

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## Grape Seeds: Ripe for Cancer Chemoprevention

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## Abstract

A wide variety of phytochemicals, mostly flavonoids or polyphenolics, have been shown to possess anticarcinogenic activities. Among these are the grape seed proanthocyanidins (GSPs), which are the active ingredients of grape seed extract (GSE). Substantial *in vitro* and preclinical *in vivo* studies have shown the chemopreventive efficacy of GSPs against various forms of cancers in different tumor models. In this issue of the journal, Derry and colleagues show that administration of GSE in the diet reduces azoxymethane-induced colon carcinogenesis in an A/J mouse model. The results of this innovative and comprehensive study indicate that inhibition of azoxymethane-induced colon cancer by dietary GSE is mediated through the induction of apoptosis that is associated with alterations in microRNA (miRNA) and cytokine expression profiles as well as  $\beta$ -catenin signaling. Notably, the demonstration that miRNA expression is affected by dietary GSE suggests a novel underlying mechanism for the chemopreventive action of GSE in colon cancer and, potentially, other cancers. *Cancer Prev Res*; 6(7); 617–21. ©2013 AACR.

## Introduction

Natural products including dietary components, herbs, and spices have been used for the prevention of many diseases, including cancer, for centuries. Today, there is renewed interest in natural phytochemicals as promising options for the development of more effective chemopreventive or chemotherapeutic strategies for various types of cancer. Full realization of this potential, however, requires an improved knowledge of the effects of these natural products. Two major lines of enquiry are being pursued: first, identification of the components of the plant, or the dietary agent derived from the plants that are responsible for the anticancer effects and second, elucidation of the mechanisms of action of these components and identification of the specific mechanisms that play a role in reducing the risk of cancer.

Grape seed extract (GSE), which is readily prepared from grape (*Vitis vinifera*) seeds, is a by-product of the grape juice and wine industries. Indeed, it is available in the United States and sold as an over-the-counter health dietary supplement in the form of capsule or tablet formulations containing 100 to 500 mg. It has been shown that GSE is a mixture of several polyphenolic components. Proanthocyanidins, which include dimers, trimers, tetramers, and oligomers/polymers of monomeric catechins and/or (–)-epicatechins, are considered to be a major fraction of

GSE (1, 2). The proanthocyanidins are naturally occurring compounds that are found in numerous different plants. They are distributed variously among the fruits, vegetables, nut, seeds, flowers, and bark. The proanthocyanidins represent the major type of polyphenols in red wine; however, the seeds of grapes are a particularly rich source. The current interest in the biology of GSE originated with reports describing epidemiologic data related to the population of France that showed that despite consumption of a diet high in saturated fat, this population manifests a low incidence of coronary heart disease. To describe these observations, the term "French Paradox" was coined. It was suggested that moderate red wine consumption may be associated with a lower incidence of coronary heart disease in this population. Since red wine is a rich source of GSPs, this prompted interest in testing the cellular effects of GSE and GSPs, including assessment of their chemopreventive or chemotherapeutic efficacy.

Proanthocyanidins are synonymous with condensed tannins and also known as oligomeric proanthocyanidins, pycnogenols or leucocyanidins, and oligomers or polymers of flavan-3-ols. The monomeric units in these oligomers are linked primarily through C4→C8 bond, but the C4→C6 linkages are also present (Fig. 1). These linkages are called B-type linkages (1, 2). The presence of high amounts of oligomeric procyanidins and polymeric compounds (such as tannins) as a result of condensation of flavan-3-ols is responsible for various aesthetic and taste-related qualities of red wine. These agents may also contribute significantly to the pharmacologic properties of grape seeds. The most common types of ingredients and linkages are shown in Fig. 1. The most abundant types of proanthocyanidins in plants are the procyanidins, which consist exclusively of epicatechin units. Various factors can affect the content of the phenolic constituents in grapes. The content is known to be affected by agroecologic factors such as the cultivar; the year

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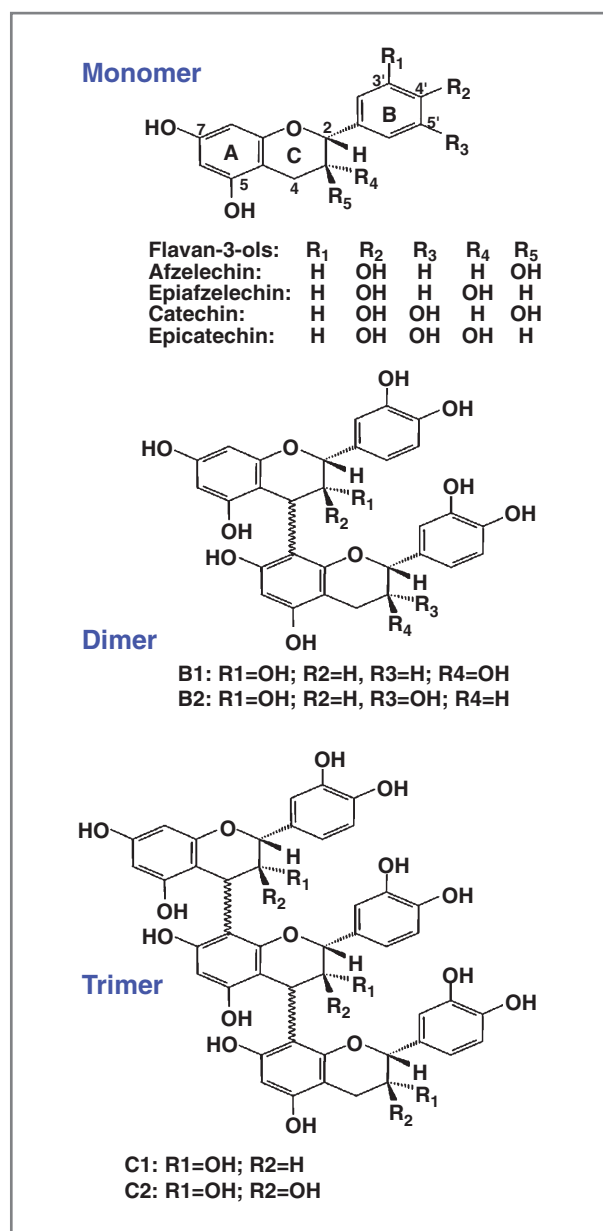


Figure 1. Chemical structures of the monomers (flavan-3-ols), dimers (B1, B2), and trimers (C1, C2) present in GSE.

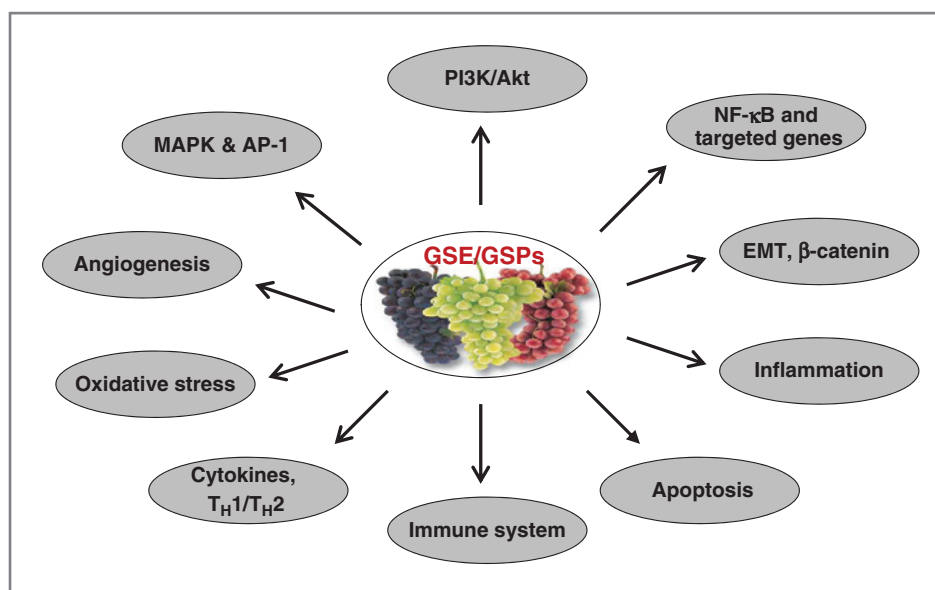
of production, which is of interest for the most part because of the climatic condition during that year; the geographic location, which affects soil chemistry, the use of fertilizers, etc.; and the degree of fruit maturation. The GSPs have been subjected to toxicity testing, including analysis of the acute and subchronic toxicity in rats and genotoxicity testing. The results of this testing indicate that these compounds are of low toxicity and have no genotoxic potential (2, 3).

During the last decade, multiple preclinical studies have been carried out using *in vitro* approaches and *in vivo* analyses in animal models that show the protective effects of GSE and its active constituents grape seed proanthocya-

nidins (GSPs) against skin (4, 5), breast (6), prostate (7, 8), head and necks (9, 10), and lung (11, 12) cancers. The grape seed constituents possess antioxidant and antiinflammatory properties. A number of studies, including those from our laboratories, have identified multiple molecular targets that are affected by treatment with GSPs. Specific molecules that have been shown to be affected include mitogen-activated protein kinases (MAPK), nuclear factor-kappaB (NF- $\kappa$ B), phosphatidylinositol-3 kinase (PI3K), 5-lipoxygenase, cytokines, vascular endothelial growth factor (VEGF), angiogenic factors, immunomodulatory factors, and the epidermal growth factor receptor (EGFR)-Shc-ERK1/2-ELK1-AP-1 pathway (2). Collectively, these studies suggest that GSPs can affect tumor cell proliferation, apoptosis, invasion, angiogenesis, cell-cycle regulators, and the generation of inflammatory mediators (Fig. 2).

Both topical treatment of GSE or dietary administration of GSPs have been shown to prevent 7,12-dimethylbenz(a)anthracene (DMBA)-initiated and 12-O-tetradecanoyl phorbol-13-acetate (TPA)-promoted 2-stage chemical carcinogenesis in mice in terms of tumor incidence, tumor multiplicity, and tumor size (4, 13). Extensive work has shown the chemopreventive effect of GSPs against ultraviolet (UV) radiation-induced skin carcinogenesis and its related molecular mechanisms. In these studies, the diet of the test animals was supplemented with GSPs and the effect on UV-induced skin tumors was determined. Dietary GSPs inhibit UV-induced skin tumor development in SKH-1 hairless mice in terms of a reduction in percentage of mice with tumors, tumor multiplicity per animal, and the size of the tumors (5), which was associated with the inhibition of UV-induced oxidative stress and inflammatory responses, such as suppression of inducible cyclooxygenase-2 (COX-2) and its prostaglandin (PG) metabolites (14). Further, the molecular targets involved in prevention of photocarcinogenesis by dietary GSPs were shown to involve the enhancement of DNA repair and xeroderma pigmentosum group A-dependent mechanisms (15). As UV-induced suppression of the immune system has been implicated as a risk factor for nonmelanoma and melanoma skin cancers (16), prevention of UV-induced immunosuppression represents a potential strategy for the prevention of skin cancers. Dietary administration of GSPs significantly inhibits UV-induced suppression of the contact hypersensitivity response to contact sensitizer, 2, 4-dinitrofluorobenzene, and this effect has been shown to be associated with the enhanced production of the immunostimulatory cytokine, interleukin (IL)-12, and reduced expression of the immunosuppressive cytokine, IL-10, in mouse skin and draining lymph nodes of UV-exposed mice (17). Protection of the immune system by GSPs in this model also was mediated through IL-12-dependent stimulation of CD8<sup>+</sup> effector T cells and inactivation of CD4<sup>+</sup> T cells (18), and functional activation of dendritic cells in mice and these effects of GSPs have been associated with the enhanced repair of UVB-induced DNA damage in mouse skin compared with those mice that were not given a diet supplemented with GSPs (19). Of particular interest, chemoprevention by GSPs also

Figure 2. Molecular targets of GSE or GSPs in prevention of cancers of different organs.



involved reactivation of silenced tumor suppressor genes in skin cancer cells as a consequence of epigenetic reprogramming (20).

Both *in vitro* studies and *in vivo* studies in animals have generated additional insights into the mechanisms underlying the anticancer effects of GSPs/GSE. Recently, we provided compelling evidence that GSPs have the ability to reverse the epithelial-mesenchymal transition (EMT) in cancer cells by affecting the expression of various proteins that orchestrate the migration of invasive cancer cells during metastasis. Using *in vitro* cell culture models, we have shown that treatment of melanoma (21), non-small cell lung cancer (NSCLC) cells (22), pancreatic cancer cells (23), and head and neck squamous cell carcinoma (HNSCC) cells (9) with GSPs significantly inhibited the migration ability or invasive potential of these cells. GSPs inhibit melanoma cell invasiveness by reduction of COX-2 expression, PGE<sub>2</sub> production, and reversal of EMT in these cells (21). This characteristic of GSPs is important because melanoma is the leading cause of death from skin disease due, in large part, to its propensity to metastasize (24). Moreover, its incidence in children is increasing rapidly (25). HNSCC is responsible for approximately 20,000 deaths and affects more than 40,000 people in the United States annually (26). EGFR is overexpressed in 90% of HNSCCs and is considered as a critical target in its treatment. Using a cell invasion assay, we found that treatment of HNSCC cells with GSPs resulted in inhibition of cell invasion, which was associated with the reduced levels of EGFR and its downstream target NF-κB (9). Overexpression of EGFR and high NFκB activity play key roles in the EMT, which is of critical importance in the processes underlying metastasis, and it was found that treatment of cancer cells with GSPs reversed the EMT process and promoted the mesenchymal-epithelial transition instead. Bioactive components of GSPs also inhibit the growth of HNSCC cells *in vitro* as well as *in vivo* in an athymic nude mouse model by targeting multiple sig-

naling molecules/pathways (10). These targets include: (i) inhibition of cell proliferation, (ii) induction of apoptosis, (iii) regulation of dysregulated cell cycle and its checkpoints, and (iv) reactivation of tumor suppressor proteins. Similar effects of GSPs also were observed when pancreatic cancer cells were treated with GSPs (23). Pancreatic cancer is an aggressive malignancy that is frequently diagnosed at an advanced stage with poor prognosis (27). Using *in vitro* studies and an *in vivo* athymic nude mouse model, Prasad and colleagues (28) have shown that GSPs inhibit pancreatic cancer cell growth through induction of apoptosis and by targeting the PI3K/Akt pathway. The PI3K/Akt pathway is a fundamental signaling pathway that mediates several cellular processes, including cell proliferation, growth, cell survival, and motility (29). Lung cancer remains the leading cause of cancer related deaths in the United States and worldwide. NSCLC represents approximately 80% of all types of lung cancer. Although a combination of chemotherapy and radiation therapy can improve survival of the patients, most patients die of disease progression, often resulting from acquired or intrinsic resistance to chemotherapeutic drugs (30). Thus, it is of interest that the results of a recent study revealed that treatment of human NSCLC cells with GSPs induces apoptosis by loss of mitochondrial membrane potential in both *in vitro* and *in vivo* models (31). This preclinical study also indicated that dietary GSPs inhibit the growth of human NSCLC xenografts by targeting insulin-like growth factor binding protein-3 and inhibition of tumor angiogenesis (11). The previously mentioned GSPs-induced inhibitory effects on PGE<sub>2</sub> and PGE<sub>2</sub> receptors also have been associated with the inhibition of human NSCLC cells growth (12). As the metastasis of lung cancer cells is considered as a major cause of death, the effect of GSPs on lung cancer cell migration/invasion was also investigated. Punathil and Katiyar have reported that treatment of human NSCLC cells with GSPs resulted in inhibition of migration of these cells, and the inhibition of cancer cell

migration by GSPs was associated with the sequential inhibition of nitric oxide, guanylate cyclase, and MAPK pathways (22). Similarly, administration of dietary GSE inhibited the growth and progression of prostate cancer in the TRAMP mouse model with these effects being associated with its inhibition of prostate cancer cell proliferation and angiogenesis (7, 8). These studies indicate that GSPs may be highly efficacious if used as an adjuvant during the therapeutic intervention of highly aggressive metastatic cancers in humans. Collectively, the information derived from these studies provide important leads in terms of potential chemopreventive strategies and the identification of specific molecular markers that could be used to evaluate the chemopreventive efficacy of the GSPs against various form of cancers.

With respect to chemoprevention of colon cancer by GSE, *in vivo* studies using Fischer 344 rats have shown that dietary GSE significantly inhibits azoxymethane (AOM)-induced formation of colonic aberrant crypt foci (ACF) in terms of crypt multiplicity (32). This study also showed that feeding of GSE inhibited AOM-induced cell proliferation and enhanced apoptosis in colon including ACF, which was associated with the reduction in the expression of COX-2, iNOS, cyclin D1, and survivin. The reduction in colonic ACF by GSE also was correlated with a reduction in AOM-induced increase in  $\beta$ -catenin and NF- $\kappa$ B as compared with the group of rats that were not given GSE in diet. In another study, the same group showed that treatment of colon carcinoma HT29 cells with GSE inhibited cell growth and induced apoptotic cell death, which was associated with the induction of Cip1/p21 protein and phosphorylation of ERK1/2 (33).

In this issue, Agarwal and colleagues (34) report the results of an extension of their previous studies and show a mechanism-based chemopreventive action of GSE in models of colorectal carcinogenesis. Employing the A/J mouse model, these authors showed that dietary GSE prevents AOM-induced colon carcinogenesis and that this was associated with the antiproliferative and proapoptotic activities of GSE. This study provides elegant mechanistic evidence to support the concept that GSE targets cytokine/inflammation signaling pathways by modulating the expression of microRNAs (miRNA). Notably, the authors employed a highly relevant model, *i.e.*, AOM-induced colon tumorigenesis in A/J mice that resembles inflammation-associated human colorectal carcinogenesis in terms of the progression of disease from aberrant crypt foci to polyps, adenoma, and carcinomas (34). Treatment of dietary GSE resulted in a significant reduction in both colon and small intestine tumor multiplicity and size with a concomitant reduction in proliferation-related biomarkers and increase in apoptosis-related proteins. A unique aspect of this study is the application of anatomical gadolinium-enhanced T1-weighted magnetic resonance imaging noninvasive technology to track the progression of the disease. This showed the slow progression of the disease in real time with respect to GSE feeding. A second important aspect of this study is the comprehensive evaluation of potential targets. The authors verified that NF- $\kappa$ B,  $\beta$ -catenin, and MAPKs signal-

ing pathways are targeted by GSE as well as a significant reduction in the expression of cytokines/chemokines and other inflammation-predicting biomarkers. Notably, they also extended the analyses to include analysis of miRNAs. The importance of miRNA in cancer biology is becoming increasingly apparent with numerous reports now showing a correlation between their expression and disease prognosis in a variety of cancers. It is therefore of considerable importance that these authors found that GSE modulated the expression profile of a broad spectrum of miRNAs (miR-19a, miR-20a, miR-let7a, miR-205, miR-135b, miR-196a, miR-21, miR-148a, and miR-103), as well as the miRNA processing machinery. Further in-depth investigations, which were not a part of this current study, are required to understand the mechanism by which phytochemicals like GSE may affect miRNA homeostasis. Undoubtedly, this study provides a direction for further translational investigations with a view to develop chemopreventive agents that can specifically modulate the expression of miRNA and abrogate colon cancer development. In addition, the angiogenesis regulatory pathway, another important target pathway of these bioactive GSE, needs to be further investigated.

The chemopreventive studies employing various dietary polyphenols conducted in various cell culture and murine models of multiple cancer types are of great interest and suggest that these complex mixtures that are present as secondary metabolites in plants are pharmacologically active and important. It should be noted, however, that the results of clinical trials of these phytochemicals are often not very encouraging (35). Major questions have been raised about their bioavailability and degradation profiles in human tissues and must be resolved. This issue is complicated by the difficulties inherent in obtaining pharmacokinetic values for complex mixtures. Safety issues, particularly the possibility of heavy metal contamination of the agents and the estrogenic activities associated with many of the phytochemicals, are other impediments in the development of these agents. From the *in vitro* and *in vivo* animal data and molecular target identification studies, it seems that the use of GSE/GSPs alone or in an adjuvant setting with other chemotherapeutic agents or drugs in patients with cancer may be highly promising. Thus, the current challenge is to accelerate laboratory studies that will advance the knowledge of the mechanisms of action of GSE in a manner that facilitates clinical applications.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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# Cancer Prevention Research

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