The Journal of Nutrition
**Supplement: Grapes and Health**

# Anticancer and Cancer Chemopreventive Potential of Grape Seed Extract and Other Grape-Based Products[1–3]

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## Abstract

With emerging trends in the incidence of cancer of various organ sites, additional approaches are needed to control human malignancies. Intervention or prevention of cancer by dietary constituents, a strategy defined as chemoprevention, holds great promise in our conquest to control cancer, because it can be implemented on a broader population base with less economic burden. Consistent with this, several epidemiological studies have shown that populations that consume diets rich in fruits and vegetables have an overall lower cancer incidence. Based on these encouraging observations, research efforts from across the globe have focused on identifying, characterizing, and providing scientific basis to the efficacy of various phytonutrients in an effort to develop effective strategy to control various human malignancies. Cancer induction, growth, and progression are multi-step events and numerous studies have demonstrated that various dietary agents interfere with these stages of cancer, thus blocking malignancy. Fruits and vegetables represent untapped reservoir of various nutritive and nonnutritive phytochemicals with potential cancer chemopreventive activity. Grapes and grape-based products are one such class of dietary products that have shown cancer chemopreventive potential and are also known to improve overall human health. This review focuses on recent advancements in cancer chemopreventive and anticancer efficacy of grape seed extract and other grape-based products. Overall, completed studies from various scientific groups conclude that both grapes and grape-based products are excellent sources of various anticancer agents and their regular consumption should thus be beneficial to the general population. J. Nutr. 139: 1806S–1812S, 2009.

## Introduction

Cancer is a global health problem with high morbidity and mortality and poses both economic and psychological challenges. Cancer cure and prevention therefore remain a high priority for the scientific community across the world. Insight gained into the etiology of cancer through various epidemiological studies encompassing various parameters such as geographical location, ethnicity, sex, age, and trans-migratory populations have collectively revealed that lifestyle is one of the major influencing factors (1–3). Other factors include environmental aspects such as automobile exhaust pollutants, solar UV radiation, occupational exposure to carcinogens and mutagens, bacterial/viral infection, and genetic susceptibility (4,5). Lifestyle factors are usually classified as modifiable risk factors and include diet intake, smoking, alcohol consumption, and physical activity and body mass. In general, physical activity instead of inactivity, abstinence from smoking and alcohol consumption, low body mass, and diets low in fat/calories are usually recommended for overall good health and have a positive influence on reducing the risk of cancer, especially breast and colorectal cancers (2,6). Because all these factors can be modified, they also provide us with leverage to use them as interventive/preventive measures. Accordingly, the American Cancer Society has suggested guidelines on nutrition and physical activity for the prevention of cancer. Broadly, recommendations suggest the intake of $\geq 5$ servings of fruits and vegetables, chose whole grains instead of

[1] Published in a supplement to *The Journal of Nutrition*. Presented at the conference "Grape Health Workshop," held in San Francisco, CA, December 2–3, 2008. The supplement coordinator for this supplement is John M. Pezzuto, University of Hawaii at Hilo. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact. The conference was organized by the National Grape and Wine Initiative (NGWI) (its contents are solely the responsibility of the authors and do not necessarily represent the official views of NGWI). *Supplement Coordinator disclosure*: John M. Pezzuto serves as Chair of the Grant Review Committee of the California Table Grape Commission. John M. Pezzuto received an honorarium to serve as moderator at the Grapes and Health Workshop. *Supplement Guest Editor disclosure*: Maria-Luz Fernandez has no relationships to disclose. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of *The Journal of Nutrition*.

[2] Supported by the R01 grants CA91883 from the National Cancer Institute and AT003623 from the National Center for Complementary and Alternative Medicine, and the Office of Dietary Supplement, NIH, Bethesda, MD.

[3] Author disclosures: M. Kaur, C. Agarwal, and R. Agarwal, no conflicts of interest.

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First published online July 29, 2009; doi:10.3945/jn.109.106864.

refined grains and sugars, limit the consumption of red meat or diets rich in fat, and finally maintain healthy weight by eating a diet that helps in maintaining proper weight. Other recommendations include guidelines for early detection/screening for cancers of certain sites (7).

Taking a cue from the epidemiological data indicating that dietary habits influence cancer risk, considerable scientific interest has been generated in developing various preventive measures based on diet, especially those involving fruits and vegetables (8–10). Fruits and vegetables, belonging to plant kingdom, represent a vast source of phytochemicals of varied chemical structure; many of them have already been studied extensively for their potential anticancer or chemopreventive efficacy (10). As such, interventions based on fruits and vegetables are not only "more natural" in lowering cancer risk without posing "any side effects" but also in maintaining good general health based on the fact that they are major sources of vitamins, minerals, and fiber.

A cancer chemopreventive agent could be effective at any of the classically defined stages of carcinogenesis: initiation, promotion, and progression (11–13). The scope of the efficacy of such agents could be profound, because the natural course of the development of full-blown clinically evident cancer is relatively long and sometimes takes a decade or so to develop from initial premalignant/precursor lesions. Because a primary aim of using these agents is the prevention of cancer occurrence where the general population is likely to consume them for a prolonged period, their safety assessment in terms of toxicity and/or other side effects is most vital. A wide range of studies over 2 decades has identified the presence of many potential chemopreventive agents in routinely consumed plant-based diets; mostly, they are nonnutritive phytochemicals spread over different classes based on their chemical structures and include phenolics (tannins, lignans, flavonoids), glucosinolates, terpenoids, carotenoids, and phytoestrogens (14,15). These agents have been found in fruits, vegetables, raisins, nuts, herbal extracts, and commonly consumed beverages such as wine, tea, and coffee. On average, almost 0.2–1 g/d of these agents are consumed as part of a regular healthy diet (16,17). These phytochemicals generate much scientific interest, because they fulfill basic requirements of an ideal chemopreventive agent, such as selective toxicity to cancerous or precancerous cells, efficacy against most types of cancers, oral route of administration, and acceptance by target human population and have a known mechanism of action (18).

In this review, we have focused our discussion on recent advancements largely in grape seed extract (GSE)[6] and to a lesser extent on other grape-based products regarding their cancer chemopreventive and anticancer efficacy and associated molecular mechanisms. GSE is a nutraceutical agent that is commonly consumed as a health/dietary supplement and is sold as an over-the-counter product in the United States in the form of capsules or tablets (100–500 mg). The consumer interest in GSE has been primarily due to the high content of antioxidants in the form of proanthocyanidins in this extract. The antioxidant capacity of this extract has been shown to be greater than known antioxidants such as vitamin C and E (19).

[6] Abbreviations used: DMBA, 7,12-dimethylbenz[*a*]anthracene; GSE, grape seed extract; GSP, polyphenolic fraction from grape seeds; NF-κB, nuclear factor-κB; PCA, prostate cancer; PIN, prostatic intraepithelial neoplasia, TRAMP, transgenic adenocarcinoma of the mouse prostate.

## GSE and cancer: efficacy and mechanisms of action in various epithelial cancer models

Cancer is a disease in which the cell presents itself with unrestricted proliferative potential. As reviewed by Hanahan and Weinberg (20), the transition of normal cell toward cancerous phenotype is due to the occurrence of 6 basic defects in normal cell physiology, which culminate in giving an added growth advantage to the transformed cell (20). Because these defects are mostly due to aberrant signaling cascades involving numerous molecular players, targeting them by chemopreventive agents could be a rationalized approach in cancer control; indeed, GSE targets these signaling cascades for its anticancer and/or chemopreventive efficacy, as briefly discussed in later sections. Additionally, **Table1** summarizes the most relevant studies currently available in the literature related to anticancer efficacy of GSE.

*GSE and skin cancer.* According to the American Cancer Society, >1 million new cases of basal and squamous cell cancers occur annually in the United States alone. Major etiological factors for skin cancer are family history, sun sensitivity, chronic exposure to sun and occupational exposure to carcinogens, and immune suppression (21,22). Whereas several efforts have been made to educate the general population about the strategies to prevent skin cancer, such as avoiding exposure to sun and use of sunscreens, additional approaches are still needed to control and prevent the occurrence of skin cancer. In our first study by Zhao et al. (23) with GSE, we assessed the anti-tumor–promoting effect of GSE polyphenolic fraction (GSP) in a 2-stage SENCAR mouse skin carcinogenesis model where a single 7,12-dimethylbenz[*a*]anthracene (DMBA) application was used as a tumor-initiating event and repeated 12-*O*-tetradecanoylphorbol 13-acetate application was used as a tumor-promoting event. Topical application of GSP to the DMBA-initiated dorsal mouse skin resulted in a highly significant inhibition of 12-*O*-tetradecanoylphorbol 13-acetate-caused skin tumor promotion, as evidenced by a significant reduction in tumor incidence, tumor multiplicity, and tumor volume. We found that procyanidin B5–3′-gallate was the most potent antioxidant compared with other polyphenols isolated from the extract by HPLC (23). Bomser et al. (24,25) also reported antitumor-promoting activity of GSP in a CD-1 mouse model by mechanisms summarized in Table 1.

In a UVB radiation-induced mouse skin carcinogenesis model, dietary feeding of GSP was effective in preventing photocarcinogenesis at both initiation and promotion stages and malignant transformation of skin papillomas to carcinomas (26–28). The mechanisms of chemopreventive effects of GSP against UVB-induced skin carcinogenesis are summarized in Table 1 (26–28). Together, the studies summarized above provide clear evidence for the potential chemopreventive efficacy of GSE/proanthocyanidins against skin cancer with some mechanistic insights.

*GSE and colorectal cancer.* Colon cancer is the 3rd most prevalent cancer in both men and women and accounts for 9% of total deaths due to cancers of all organ sites (21). Colorectal cancer is preventable, as healthy changes in life style especially in dietary habits could help reduce the risk of this malignancy. Thus, nutritional recommendations from the American Cancer Society include adequate intake of fruits and vegetable in a regular diet (7).

In our efforts to evaluate the chemopreventive potential of GSE against colorectal cancer, we investigated its in vitro and in

**TABLE 1** In vivo and in vitro studies showing chemopreventive/anticancer efficacy of GSE

| Organ site | In vivo/in vitro model | Mechanism of action | Reference |
|---|---|---|---|
| Skin | DMBA initiated and TPA promoted skin carcinogenesis in SENCAR mouse | Antioxidant | 23 |
| | TPA promotion in CD1 mouse skin[1] | Inhibition of ornithine decarboxylase and myeloperoxidase activities | 24,25 |
| | UV-B induced skin carcinogenesis | Antioxidant, ↓MAPK,[2] ↓NF-κB, ↓lipid peroxidation, Immunosuppression | 26,27,28 |
| Colorectal cancer | LoVo and HT-29 cells, HT-29 cells as tumor xenografts | ↓Cell growth, ↑apoptosis, ↑p21 levels | 29 |
| | Azoxymethane-DMBA dual organ rat model | ↓Aberrant crypt foci formation | 30 |
| | TNBS-induced ulcerative colitis rat model[3] | Antiinflammatory | 31 |
| | Human cancerous/noncancerous colon tissues | ↓Adenosine deaminase activity<br>↓5′-nucleotidase activity | 32 |
| | Caco-2 cells | ↓PI3Kinase, ↑apoptosis | 33 |
| | HT-29 cells | ↓Proliferation, ↑apoptosis, ↓cholesterol uptake, ↓5-lipoxygenase activity | 34 |
| PCA | DU145 cells | ↑Apoptosis | 35 |
| | DU145 cells | ↓EGFR-Shc-ERK1/2-ELK1-AP1 pathway | 36 |
| | DU145 tumor xenografts, DU145 cells | ↓VEGF,[4] ↑IGFBP-3[5] in tumors ↑IGFBP3 in plasma ↑apoptosis, ↓NF-κB, ↓VEGF secretion | 40, 41 |
| | LNCaP cells | ↑Apoptosis (anoikis) | 44 |
| | TRAMP model | Cell cycle arrest | 46 |
| Breast cancer | Aromatase transfected MCF-7 cells | ↓Aromatase activity and expression | 48,49 |
| | MCF-7, MDA-MB468, MDA-MB231 cells | Synergistic effects with doxorubicin | 50 |
| | MCF-7 cells | Cytotoxic | 51 |
| | MCF-7, MDA-MB-231 cells | Antiangiogenic | 53 |
| | 4T1 Breast cancer cells | Antimetastatic effects | 54 |
| Other cancers | A427 lung cancer cells, gastric adenocarcinoma CRL-1739 cells; A549 and H1299 lung cancer cells; Cal27 and SCC25 oral squamous cell carcinoma cells; Jurkat cells | Cytotoxic | 51, 55–57 |

[1] 12-*O*-tetradecanoylphorbol 13-acetate.
[2] Mitogen-activated protein kinases.
[3] Trinitrobenzene sulfonic acid.
[4] Vascular endothelial growth factor.
[5] Insulin growth factor binding protein-3.

vivo anticancer effects in LoVo and HT-29 human colorectal carcinoma cell lines (29). Our completed studies showed that GSE halts the growth of these cancer cells and, more importantly, inhibits the growth of HT-29 cells in culture as well as when grown as tumor xenografts in athymic nude mice (29). In animal models for colon cancer chemoprevention, grape seed proanthocyanidins significantly inhibited azoxymethane-induced colonic aberrant crypt foci, a precursor lesion for colon cancer in rat dual-organ tumor model (30) and reduced the colonic macroscopic and microscopic damage in 2,4,6-trinitrobenzene sulfonic acid-induced ulcerative colitis in rats (31).

The anticancer effects of whole black grape (seeds included) extract are also reported in the cancerous colon tissues of humans via inhibition in DNA turnover enzymes (32). The anticancer effects of proanthocyanidins from grape seeds against colon cancer Caco2 cells have also been demonstrated through inhibition of the survival pathway and induction of apoptosis (33). Almost similar anticancer effects of GSE or red wine polyphenolic extract were also observed in HT-29 cells (34). The mechanisms of GSE action in these studies are summarized in Table 1.

*GSE and prostate cancer.* As per the statistics provided by the American Cancer Society for 2008, prostate cancer (PCA) remains the most commonly diagnosed cancer in men. There has been considerable improvement in the diagnosis and treatment options for PCA patients, which has resulted in stabilization in the rate of incidence of this cancer in recent years (21); however, PCA is still the most deadly malignancy in the elderly male population. Our research program has made major efforts in assessing and establishing chemopreventive and anticancer efficacy of GSE against PCA as summarized in Table 1. In our first study by Agarwal et al. (35) with the DU145 cell line, which represents advanced metastatic hormone refractory human PCA, GSE induced apoptotic death. We also found that GSE inhibited both ligand epidermal growth factor (EGF)-induced and constitutively active EGFR–Shc–ERK1/2–Elk1–AP1 pathway in DU145 cells (36).

Treatment of advanced-stage PCA with chemo- or radiotherapy is often limited by resistance to apoptosis (37). Further, in the advanced stage, PCA cells acquire angiogenic potential, which promotes the growth and metastasis to distant sites. Therefore, agents that can either induce apoptosis or inhibit angiogenic capacity of cancer cells can have profound effects on limiting the progression of cancer to a more advanced stage (37–39). In this regard, we found that GSE exerts antiproliferative and antiangiogenic effects and interferes with IGF-1 signaling in DU145 xenografts by the mechanisms summarized in Table 1, thereby exerting an overall growth inhibitory effect against DU145 xenografts in nude mice (40).

In more detailed mechanistic studies, we observed that GSE inhibits the nuclear factor-κB (NF-κB) pathway and thus results in induction of apoptosis in DU145 cells (41). Constitutive

activation of this pathway contributes to the resistance to chemotherapeutic drugs and radiotherapy in various malignancies, including PCA (42,43). Thus, inhibition of this pathway by GSE in DU145 PCA cells could be used as an effective therapeutic target for PCA. In another study with androgen-dependent human PCA LNCaP cells, we observed that GSE causes detachment-induced apoptosis (anoikis) in these cells. The induction of death by GSE in these cells was triggered due to reactive oxygen species induced-DNA damage (44).

In our continued efforts to characterize the chemopreventive efficacy of GSE against PCA, we also conducted the studies in a transgenic adenocarcinoma of the mouse prostate (TRAMP) mouse model, wherein spontaneous neoplastic epithelial transformation occurs in the mouse prostate starting from early lesions of prostatic intraepithelial neoplasia (PIN) to late-stage metastatic adenocarcinoma in a manner that mimics human PCA (45). We observed that oral feeding of GSE to TRAMP mice resulted in higher incidence of PIN with a concomitant decrease in the progression of these initial lesions (PIN) to adenocarcinoma by inhibition of aberrant cell cycle progression (46).

*GSE and breast cancer.* Breast cancer is the second leading cause of cancer-related deaths after lung cancer in women. Even though the incidence of breast cancer has declined at a rate of 3.5%/y from 2001 to 2004, the mortality associated with this malignancy is still high (21). Therefore, more efforts are required to develop effective therapeutic or interventive approaches to conquer this malignancy. One effective approach is to target abnormal protein(s) or signaling pathways involved in the progression of this malignancy. One such target could be enzyme aromatase, which is highly expressed in cancerous compared with normal breast tissue (47). Studies conducted by Eng et al. (48) and Kijima et al. (49) revealed that procyanidin dimers, especially procyanidin B2 dimer from wine extract and also found in high quantities in grape seeds, inhibited the activity and expression of this enzyme, which is responsible for the conversion of androgens into estrogens in aromatase-transfected MCF-7 breast cancer cells and their xenografts in athymic nude mice. In another study conducted by Sharma et al. (50), GSE exerted a synergistic effect with doxorubicin in inhibiting the growth of estrogen-receptor–expressing MCF-7 cells as well as estrogen-receptor negative MDA-MB468 cells. The findings of this study revealed that GSE could be used in combination with doxorubicin to enhance the efficacy of this drug (50). Further, cytotoxic effects of IH636 GSE were observed against MCF-7 human breast cancer cells (51). In a chemoprevention setting, supplementation of GSE in rodent diet resulted in a significant reduction in DMBA-induced mammary tumor multiplicity in female rats; however, the protective effect was dependent on the composition of the diet to which it was added (52). Antiangiogenic effects of GSE were observed in MDA-MB-231 human breast cancer cells and in U251 human glioma cells (53). In the study conducted by Mantena et al. (54), the metastatic potential of 4T1 breast cancer cells was inhibited by grape seed proanthocyanidins.

*GSE and other cancers.* Apart from the anticancer and chemopreventive efficacy of GSE against skin, colorectal, prostate, and breast cancers discussed above in detail, anticancer efficacy of this extract has also been observed against human lung cancer A427, A549, and H1299 cells, human gastric adenocarcinoma CRL-1739 cells, oral squamous cell carcinoma CAL27 and SCC25 cells, Jurkat, U937, and HL-60 as summarized in Table 1 (51,55–57). GSE as well as red wine have been shown to significantly reduce the number of metastatic nodules on the surface of lung in Swiss mice inoculated with B16F10 melanoma cells, although at a microscopic level, GSE increased the implantation and growth of these cells (58), clearly suggesting that more studies are needed to address these contradictory findings.

### Anticancer and chemopreventive efficacy of other grape-related products

Although the above-cited literature strongly suggests that grape seeds are a potential source of anticancer and cancer chemopreventive phytochemicals, the other parts of the grape such as the skin, the whole grape by itself, grape-derived raisins, and phytochemicals present within the grapes have also demonstrated potential anticancer efficacy in various preclinical and clinical studies, as summarized in **Table 2**. One such phytochemical is resveratrol, which is found abundantly in the skin of grapes; peanuts, itadori tea, and wine also contain resveratrol in appreciable amounts (59). With the discovery of the chemopreventive potential of resveratrol by Jang et al. (60) employing a mouse skin model, there have been thousands of publications showing anticancer and cancer chemopreventive efficacy of this natural product in numerous cancer models in cell culture and animals (61–64). Summarizing those is beyond the scope of the present review; however, some of the most recent findings are mentioned in Table 2.

Regarding other grape-based products, another phytochemical, piceatannol, a stilbene present in grapes, has been shown to attenuate dextran sulfate sodium-induced colitis in BALB/c mice (65). Further, a skin extract of muscadine grapes, which does not contain resveratrol, has been shown to selectively inhibit the growth of RWPE-1, WPE1-NA22, WPE1-NB14, and WPE1-NB26 PCA cells compared with normal prostate epithelial PrEC cells (66), whereas anthocyanin-rich extract from Concord grapes blocked the formation of carcinogen-DNA adduct formation in noncancerous immortalized human breast epithelial MCF-10F cells (67) by the mechanisms summarized in Table 2.

In another study with purple grape juice extract, inhibition of carcinogen DMBA-induced mammary tumorigenesis was observed in rats (68). Further mechanistic studies revealed that consumption of grape juice phenolics inhibited in vivo DMBA-DNA adduct formation (68). Stagos et al. (69) showed that grape extracts from 2 Greek varieties of *Vitis vinefera* inhibit mitomycin C-induced DNA strand breakage and were potent inhibitors of topoisomerase I, which might be responsible for their anticancer effects. In other studies, the extract from dried Greek raisins (currants and sultanas) inhibited the proliferation of AGS gastric cancer cells (70). Shirataki et al. (71) have reported the selective cytotoxicity of grape peel and seed extract against oral tumor cells, although GSE was more potent in terms of cytotoxic efficacy. The underlying mechanisms of action of these grape-based products are summarized in Table 2. In a case control study conducted by Do et al., increased consumption of grapes was linked to significant protective effect against risk of breast cancer in Korean women, although no association was found between the intake of total fruits, vegetables, or soy food and breast cancer risk (72). In yet another study conducted in Korea, daily grape juice consumption resulted in reduced levels of oxidative DNA damage as measured in peripheral lymphocytes and increased plasma antioxidant capacity in healthy Korean participants (73). The findings of these studies strongly suggest that grapes and grape-based products are the sources of many potential anticancer and cancer chemopreventive agents

**TABLE 2** Preclinical and clinical studies showing chemopreventive/anticancer efficacy of whole grape or grape-based products

| Chemopreventive agent | Preclinical and clinical studies | Mechanism of action/study end points | Reference |
|---|---|---|---|
| Resveratrol (grape skin, wine, whole grape) | MCF-7 cells | Autophagy | 62 |
| | MCF-10F | Inhibition of estrogen-DNA adduct | 63 |
| | Two-stage mouse skin cancer model; DMBA-induced mammary cancer, | ↓Tumor incidence and burden | 60 |
| | Carrageenan-induced inflammation | ↓Preneoplastic lesions, ↓Edema; inflammation | |
| | Human mammary and oral epithelial cells | Cycloxygenase-2 inhibitory activity | 64 |
| Piceatannol | Dextran sodium sulfate-induced colitis in mice | ↓Colonic myeloperoxidase activity, ↓production of inflammatory mediators such as nitric oxide, prostaglandin $E_2$, and pro-inflammatory cytokines | 65 |
| Muscadine grape skin extract | RWPE-1, WPE1-NA22, WPE1-NB14, WPE1-NB26 PCA cells | Growth Inhibition, ↓PI3Kinase-Akt, ↓MAPK | 66 |
| Concord grape extract | Carcinogen-DNA adduct formation in MCF-10F cells | ↓Carcinogen-DNA adduct formation; ↑Phase-II Glutathione-s-transferase and NAD(P)H: quinine reductase-1 | 67 |
| Purple grape juice | DMBA-induced rat mammary tumorigenesis | ↓Carcinogen-DNA adduct formation | 68 |
| Greek raisins | AGS gastric cancer cells | ↓Cell proliferation, ↓TNF-$\alpha$[1]-induced ICAM[2] expression | 70 |
| Grape peel and seed extract | Oral tumor cells | Cytotoxicity | 71 |
| Grapes | Korean women | Protection against risk of breast cancer | 72 |
| Grape juice | Healthy Korean participants | Reduced oxidative DNA damage in peripheral lymphocytes; ↑Plasma antioxidant capacity | 73 |

[1] Tumor necrosis factor-$\alpha$.
[2] Intercellular adhesion molecule-1.

and more efforts are needed to identify both the agents and efficacy in cancer models.

In conclusion, prevention of cancer either by chemopreventive strategies based on naturally occurring agents or simply by advocating healthy dietary habits should have far reaching effects on lowering the incidence of cancer and reducing the socioeconomic burden, as these strategies are most cost effective and practical in their translational potentials. Additionally, being natural with increased affordability, they have much broader access to populations at large. Naturally occurring phytochemicals have shown promising chemopreventive effects in various in vitro and preclinical models and in several cases, their mechanisms of action at the molecular level have been characterized. However, most of them are in the infancy stage due to lack of extensive clinical studies yet to be conducted with these agents. Therefore, more studies are needed in high-risk populations for cancer of specific organs or sites with standardized GSE preparations to establish the dose regimen and to determine pharmacologically achievable levels of biologically active constituents in the plasma/target organ. These studies would also help establish any toxicity associated with long-term administration of GSE. Caution is also needed in the use of GSE and any other given agent in clinical settings until all of their adverse effects, even as a chemopreventive agent, are evaluated and established comprehensively. Once such information is available, it would also be helpful in using these agents as adjuvants to conventional therapeutic drugs to augment their therapeutic effect at relatively lower doses, thereby limiting their toxic side effects to some extent. Based on the evidence from currently available literature, vegetable- and fruit-based diets/extracts can be viewed in general as healthy and nutritive with the additional benefit of being cancer preventive. Together, it can be concluded that consumption of grapes and/or grape-related products in diets along with maintaining an active healthy lifestyle has both practical and translation potential in the fight against cancer and is thus beneficial to the general population.

Other articles in this supplement include (74–80).

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