Grapes and Cancer

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Abstract Grape consumption has been linked to beneficial effects in the prevention or treatment of various different cancers in laboratory animals and humans. Several phytochemicals in the skin and seeds of grapes have been implicated in having anticancer activity including resveratrol, quercetin, and proanthocyanidins, among others. These components promote tumor cell apoptosis, have antiproliferative effects through cell cycle arrest, disrupt intracellular signaling including Wnt and PI3K/AKT pathways, suppress inflammatory responses, and display antiangiogenic activity. The best studied individual component of grapes with anticancer properties is resveratrol which can inhibit intestinal tumorigenesis, hepatocellular cancer, and skin cancer in rodent models. Only a handful of human studies have been performed with resveratrol, but these have demonstrated activity on key proliferative pathways in target organs despite questions about bioavailability and attainable serum concentrations of specific grape-derived phytochemicals. Overall, based on epidemiologic evidence, laboratory studies in vitro and in model organisms, and direct human studies, grapes or specific components of grapes hold promise for both cancer prevention and treatment.

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1 Introduction

Up to one-third of all cancers in industrial societies are believed to be attributable to lack of physical activity and dietary factors (Wiseman 2008; Glade 1999). From a dietary perspective, there has been increasing interest in cancer prevention and cancer treatment with natural compounds (Gullett et al. 2010). As far back as 1993, a case control study on oral cancer in Beijing demonstrated that increased consumption of grapes resulted in a reduced risk of oral cancers (Zheng et al. 1993). Several components have been implicated as having active antitumor activity ranging from grape seed extract, shown to reduce the risk of squamous cell carcinoma of the skin (Asgari et al. 2011), to resveratrol, as well as several other phytochemicals in the skin and seeds of grapes. Resveratrol is a key component of grapes with a myriad of actions on cellular processes and possible cancer preventive and treatment activity (Gescher et al. 2013; Gescher 2008). For example, resveratrol from grapes has been associated with reduced risk of breast cancer with an odds ratio of 0.39 for the highest tertile of grape ingestion (Levi et al. 2005). The various active components of grapes, their effects on cellular processes in vitro, and the evidence for anticancer activity in laboratory animal models and in human studies are summarized in this chapter.

2 Components of Grapes with Potential Anticancer Activity

Grapes contain over 100 distinct phytochemicals that may have metabolic activity (Pezzuto 2008). Phytochemicals are defined as nonnutritive chemicals found in plants. The phytochemicals found in grapes that are believed to have significant activity in humans or have been shown to affect cellular processes in vitro include phenolic acids, flavonols, flavan-3-ols, myricetin, peonidin, flavonoids, resveratrol, quercetin, tannins, anthocyanins, kaempferol, cyanidin, ellagic acid, and proanthocyanidins (Yang and Xiao 2013). Flavonoids such as quercetin and stilbenes such as resveratrol and piceatannol (Gullett et al. 2010) are principally localized in the skins of grapes, while flavan-3-ols such as catechin are found in the skins and seeds. Anthocyanins are primarily concentrated in the seeds, though some species of red grapes also contain significant amounts in the skin. Phytochemicals are found in grape products in addition to whole grapes. For example, resveratrol is at its highest in red wine, but white wines and dark red (unprocessed or minimally processed) grape juice also contains some of this compound. The compounds that have been most extensively studied for their anticancer or cancer preventive activity include resveratrol and anthocyanins in grape seed extracts though antiproliferative activity has been reported for many other components. Piceatannol, a stilbenoid, has antiproliferative activity against hepatocellular cancer cells and suppresses metastases of these cells in rats (Kita et al. 2012). Pterostilbene inhibits proliferation of

pancreatic cancer cells in vitro (Mannal et al. 2010). Ellagic acid-containing polyphenolic extracts from grapes are potent inhibitors of proliferation (Mertens-Talcott et al. 2006). Liofenol, a natural red wine lyophilized extract, promotes differentiation and reduces proliferation of HCT116 colon cancer cells (Signorelli et al. 2015).

There has been debate as to which part of the grape has the most anticancer activity. In one study, inhibition of HeLa and 4T1 growth in cell culture and in transplanted tumors in mice was much more effective utilizing a grape skin extract compared to grape pulp, juice, or seeds (Morre and Morre 2006). Grape skin polyphenols also have antimetastatic activities in a murine model of breast cancer (Sun et al. 2012), and numerous studies have been reported with resveratrol (Pirola and Frojdo 2008). However, grape seed extracts demonstrate activity as well, inducing apoptosis in human prostate cancer cells (Agarwal et al. 2002). Grape seed proanthocyanidins induce apoptosis and inhibit metastases in breast cancer cells (Mantena et al. 2006), and gallic acid in grape seed has antiproliferative and proapoptotic activity against pancreatic cancer cells (Cedo et al. 2014). Stilbenes and oligostilbenes found in the leaves and stems of grape plants display antiproliferative effects against cancer cell lines in vitro (Ha do et al. 2009) as do polyphenolic extracts from grape stems (Sahpazidou et al. 2014). Whole grape preparations such as grape powder, containing quercetin, epicatechin, and cyanidin, have been found to have antiapoptotic and antioxidant effects (Jing et al. 2011).

3 In Vitro Mechanisms of Action

Components in grapes, and particularly resveratrol, have a myriad of activities on cellular processes that may translate into anticancer or cancer prevention activity (see reviews: Pirola and Frojdo 2008; Borriello et al. 2014; Aluyen et al. 2012). Resveratrol has been studied extensively and has apoptosis-inducing activity, cell cycle effects, and anti-inflammatory effects and can modulate protein kinase signaling pathways (Shankar et al. 2007). Additional anticancer mechanisms include dysregulation of intracellular signaling including the MAP kinase/Akt pathway, inhibition of Wnt pathway signaling, anti-angiogenic effects, and effects on sirtuin-mediated processes.

Phytochemicals in Grapes Induce Tumor Cell Apoptosis Resveratrol induces apoptosis in liver cancer cells (Choi et al. 2009) and promotes apoptosis by enhancing CD95L expression in HL60 and T47D breast cancer cells (Clement et al. 1998). In T47D breast cancer cells, it also induces apoptosis through activation of p53 (Alkhalaf 2007). Low to moderate concentrations of resveratrol lead to Bax co-localization with mitochondria, activation of caspase-3 and caspase-9, and apoptosis in HCT116 colorectal cancer cells (Mahyar-Roemer et al. 2002; Juan et al. 2008). Resveratrol also activates caspase-2 triggering mitochondrial apoptotic events by inducing conformational changes in Bax/Bak (Mohan et al. 2006). In

multiple myeloma cells, resveratrol downregulates STAT3 and NFκB, leading to apoptosis, BAX release, and activation of caspase-3 (Bhardwaj et al. 2007). It induces apoptosis and inhibits angiogenesis in breast cancer xenografts (Garvin et al. 2006) and induces downregulation of survivin and apoptosis in adult T-cell leukemia (Hayashibara et al. 2002). In HepG2 cells, resveratrol reduces PTEN and increases bcl-xl mRNA expression, inhibiting HepG2 proliferation (Zheng et al. 2012). Pterostilbene, an analog of resveratrol mostly found in blueberries, induces caspase-dependent apoptosis through mitochondrial depolarization (Alosi et al. 2010), and piceatannol induces apoptosis in DU145 prostate cancer cells (Kim et al. 2009).

Grape seed extract has antiproliferative and proapoptotic effects on human colon cancer cell lines (Aghbali et al. 2013; Dinicola et al. 2010, 2012). It leads to caspase activation, mitochondrial membrane potential dissipation, inhibition of NFκB, cytochrome c release, and apoptosis in prostate carcinoma DU145 cells (Agarwal et al. 2002; Dhanalakshmi et al. 2003). Grape seed proanthocyanidin induces apoptosis through activation of p53 (Hu and Qin 2006; Huang et al. 1999). Anthocyanins also have anti-invasive and apoptosis-inducing activity through suppression of matrix metalloproteinases and activation of p38-MAPK, respectively (Shin et al. 2009, 2011).

Antiproliferative Activity Through Cell Cycle Arrest Resveratrol (Park et al. 2001) and grape seed extract induce cell cycle arrest in human colon cancer cells (Kaur et al. 2008). The growth inhibitory effects of resveratrol may be mediated through cell cycle arrest, with upregulation of p21Cip1/WAF1, p53, and BAX (Aggarwal et al. 2004). Various cyclins are downregulated, and caspases are activated. In addition, expression of several transcription factors such as NFκB is suppressed, and JNK, MAPK, and Akt protein kinases are inhibited. Resveratrol causes WAF-1/p21 G(1) arrest of cell cycle in A431 cancer cells, with decreased expression of cyclin D1 and cyclin D2 (Ahmad et al. 2001). Irreversible cell cycle arrest then leads to apoptosis. Resveratrol also inhibits cell cycle progression in U937 cells, blocking cells at the S phase checkpoint (Castello and Tessitore 2005), inhibits SW480 colorectal cancer proliferation by modulating cyclin and cyclin-dependent kinase activities (Delmas et al. 2002), and leads to cell cycle arrest and upregulation of cyclins A, E, and B1 (Larrosa et al. 2003).

Disruption of Intracellular Signaling A myriad of intracellular signaling pathways are inhibited by grape components, including resveratrol and anthocyanidins. Grape polyphenols inhibit Akt/mTOR signaling in breast cancer cells (Castillo-Pichardo and Dharmawardhane 2012). Resveratrol leads to the suppression of NFκB and promotion of differentiation in an in vitro leukemia model (Asou et al. 2002) and inhibits protein kinase C, suppressing proliferation of gastric adenocarcinoma cells (Atten et al. 2001). Resveratrol also regulates the PTEN/Akt pathway due to inactivation by MTA1 (Dhar et al. 2015), inhibits IκB kinase activation (Holmes-McNary and Baldwin 2000), and inhibits proliferation of A431 cells by inhibiting MEK1 and suppressing activating protein (AO)-1 activity (Kim et al. 2006). Resveratrol inhibits mTOR signaling via PI3K/PDK1/Akt (Brito et al. 2009) as do

grape seeds that have been reported to increase phosphorylation of MAPK and kinases in the PI3K/Akt pathway, promoting the activity of detoxifying and antioxidant enzymes (Bak et al. 2012). Proanthocyanidin from grape seeds can inactivate the PI3K pathway and induce apoptosis in colon cancer cell lines (Engelbrecht et al. 2007). Grape proanthocyanidin also inhibits pancreatic cancer cell growth via decreased expression of PI3K and p-Akt in tumor xenografts (Prasad et al. 2012) and mouse skin tumors (Roy et al. 2009). Other activities of resveratrol include inhibition of IL-6-dependent transcription of STAT3 in LNCaP cells (Lee et al. 2014); inhibition of EMT in pancreatic cancer cells by suppression of PI3K/Akt/NFκB signaling (Li et al. 2013); inhibition of TGF-β1-induced EMT, suppressing lung cancer invasion and metastases (Wang et al. 2013); and suppression of IGF-1-induced colon cancer cell proliferation by activating p53 and suppressing IGF-1R and Wnt signaling (Vanamala et al. 2010).

Resveratrol Has Inhibitory Effects on Wnt Signaling One of the many other activities of resveratrol is inhibition of Wnt signaling (Hope et al. 2008) (Fig. 1). We have shown that relatively low concentrations of resveratrol can inhibit Wnt signal throughput in colon cancer cell lines. Wnt signaling is central to the development of colon and many other types of cancer (Giles et al. 2003). Specific alterations in the components of the Wnt pathway have been noted by our group in colon cancers arising in the setting of inflammatory bowel disease, providing

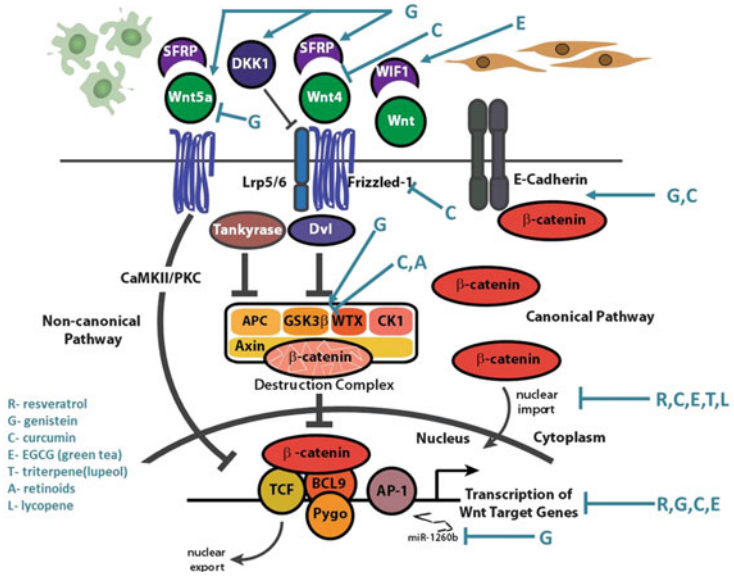

Fig. 1 Wnt pathway schematic, demonstrating roles of extracellular Wnt ligands, cell surface frizzled receptors, the APC-containing complex involved in phosphorylation of β-catenin, and the central role of β-catenin which binds to members of the LEF/TCF transcription factor family to regulate the expression of growth promoting target genes. The various effects of natural products, including resveratrol, are indicated

additional evidence of the confluence of Wnt signaling, inflammation, and colon cancer (You et al. 2007, 2008). In the Wnt pathway, evidence suggests that resveratrol acts downstream of GSK3β, possibly by disrupting the binding between β-catenin and TCF4 (Chen et al. 2012).

Resveratrol Suppresses Inflammatory Responses Resveratrol is a stilbene which has multiple activities in vitro (Pirola and Frojdo 2008) and is purported to have cardioprotective, cancer preventive, and antiaging properties in vivo (Baur and Sinclair 2006). Resveratrol has direct effects on mediators of inflammation. It is an inhibitor of both 5-lipooxygenase (LOX) and cyclooxygenase (COX) (Kimura et al. 1985), enzymes critical for the synthesis of proinflammatory mediators. Resveratrol inhibits COX2 at both a transcriptional and protein expression level, possibly through inhibition of PKCα and Erk1 (Subbaramaiah et al. 1998). Resveratrol also suppresses IKK-mediated phosphorylation of IκB (Kundu et al. 2006a) thereby inhibiting NFκB, an important signal transducer linking inflammation with tumorigenesis (Karin and Greten 2005). IKK is one of the targets most potently inhibited in vivo (Kundu et al. 2006b). Anti-inflammatory effects of resveratrol have also been tied to inhibition of LPS-induced NFκB activation in colon cancer cells (Panaro et al. 2012). Resveratrol has additionally been shown to attenuate the inflammatory response of peripheral blood leukocytes via reduced expression of IL-8 and TNF-α (Richard et al. 2005) and to downregulate iNOS through suppression of NFκB (Surh et al. 2001). Since resveratrol appears to have multiple intracellular targets, global effects such as suppression of inflammation need to be evaluated critically and interpreted within specific experimental contexts.

Anti-angiogenic Properties of Grape Components In vitro, four grape varieties have been tested for anti-angiogenic activity—Concord, Niagara, Chardonnay, and Pinot noir. Those with highest total phenolics and flavonoids displayed the most anti-angiogenic activity (Liu et al. 2010). High dosages of red wine polyphenols decrease VEGF expression and inhibit angiogenesis (Baron-Menguy et al. 2007). Resveratrol has been shown to have anti-angiogenic activity (Cao et al. 2005); it can inhibit angiogenesis in breast cancer xenografts (Garvin et al. 2006) and inhibits VEGF expression in liver cancer cells (Yu et al. 2010). Grape procyanidins have been shown to block tumor angiogenesis in a liver cancer xenograft model (Feng et al. 2014), and grape seed extract inhibits VEGF expression by inhibiting HIF-1α protein (Lu et al. 2009).

Resveratrol and Sirtuins Many reports have linked resveratrol to improved life expectancy through its effects on sirtuins (Baur et al. 2006). Sirtuin-activating capacity by resveratrol may explain the beneficial effects of the Mediterranean diet (Russo et al. 2014). This activity may also play a role in cancer treatment or prevention (Kelly 2010a, b). Sirt7 is implicated in cancer due to its effects on chromatin signaling (Paredes et al. 2014), sirt3 is implicated in cancer as regulator of mitochondrial adaptive responses to stress (Chen et al. 2014), and sirt3 is associated with survival in esophageal cancer (Zhao et al. 2013). More research is necessary to define whether this activity of resveratrol can be linked directly to cancer prevention or treatment.

Other Mechanisms of Action of Grape Components Relevant to Cancer Several other activities of grape components suggest a role in cancer prevention and treatment. Matrix metalloproteinases promote tumor growth, invasion, and metastases and are inhibited by grape seed proanthocyanidins (Katiyar 2006). Grape seed extract can function as an aromatase inhibitor (Kijima et al. 2006) so may be useful in the treatment of estrogen-responsive tumors. Resveratrol induces DNA double-strand breaks through interaction with topoisomerase II (Leone et al. 2010). Topoisomerase II inhibitors are frequently utilized chemotherapy agents. Finally, resveratrol inhibits ornithine decarboxylase (ODC) activity (Wolter et al. 2004). ODC is the rate-limiting step in polyamine synthesis which is closely linked to colon carcinogenesis (Zell et al. 2007).

4 Anticancer Activity in Laboratory Animals

Systemic administration of resveratrol has been shown to inhibit the growth of tumors in several different rodent cancer models (Baur and Sinclair 2006) and for multiple different tumor types (Carter et al. 2014). For colon cancer prevention, effects are seen over a wide variety of dose ranges depending on individual studies. Tessitore demonstrated activity of very low-dose resveratrol of 0.2 mg/kg/day in reducing aberrant crypt foci (ACF) in the colon in an azoxymethane-induced tumor model (Tessitore et al. 2000). In another carcinogen-based model, utilizing 1,2-dimethylhydrazine, resveratrol at 8 mg/kg/day reduced both ACF and colonic tumors (Sengottuvelan and Nalini 2006; Sengottuvelan et al. 2006). In genetic models utilizing the $APC^{min/+}$ mouse, which harbors a single allele mutation in *apc* and therefore has intrinsically activated Wnt signaling, Schneider demonstrated profound activity at dosages as low as 0.3 mg/mouse/day in reducing intestinal tumors (Schneider et al. 2001). In this study, expression of Wnt target gene *cyclinD1* as well as other markers of cell cycling was reduced. However, Ziegler (Ziegler et al. 2004) found resveratrol up to 90 mg/kg ineffective, and Gignac and Bourquin (2001) demonstrated an effect only at 500 mg/kg and, in this case, only in male mice. Sale utilized dosages of 60 and 240 mg/kg and found the former ineffective but the latter effective in inducing a more modest reduction in intestinal tumorigenesis (Sale et al. 2005). In DMH-treated Sprague-Dawley rats, administration of 60 mg/kg *trans*-resveratrol orally for 49 days decreased aberrant crypt foci by 52 % (Alfaras et al. 2010). Utilizing a SCID xenograft model implanted with HCT-116 colon cancer cells, Majumdar found that the combination of curcumin with resveratrol led to a reduction in proliferation accompanied by attenuation of NFκB activity (Majumdar et al. 2009).

Overall, these studies indicate that resveratrol has activity in both carcinogen-induced tumor models and in the Wnt-activated $APC^{min/+}$ mouse, but that the effective dose is unclear, with activity reported utilizing dosages ranging from <1 to 500 mg/kg/day. Results of animal model studies related to resveratrol and intestinal/colorectal cancer are summarized in Table 1. Proanthocyanidins have

Table 1 Summary of studies of resveratrol in rodent models on intestinal tumorigenesis

Author (year)	Animal model	Carcinogen	Outcome measure	Resveratrol concentration	Route	Duration (weeks)	Result
Tessitore et al. (2000)	F334 rat	AOM	ACF	0.2 mg/kg/day	Water	12	Significant decrease in # and multiplicity of ACFs
Schneider et al. (2001)	$APC^{min/+}$ mouse	Genetic	Tumors	0.01 % in H_2O (0.3–0.4 mg/mouse/day)	Water	7	Reduction by 70 %. ↓cyclinD1, ↑immune response genes
Gignac and Bourquin (2001)[a]	$APC^{min/+}$ mouse	Genetic	Tumors	500 mg/kg	Diet	2	Reduction by 50 %, males only
Ziegler et al. (2004)	$APC^{min/+}$ mouse	Genetic	Tumors	0, 4, 20 or 90 mg/kg	Diet	7	No change
Sale et al. (2005)	$APC^{min/+}$ mouse	Genetic	Adenomas (tumors)	0.05 % (60 mg/kg)	Diet	10–14	No change
				0.2 % (240 mg/kg)	Diet	10–14	Reduction by 27 %. Conc. ~36 nmol/g intestinal tissue
Sengottuvelan and Nalini (2006)[b]	Wistar rats	DMH	ACF	8 mg/kg/day	GG	15–30	50–75 % reduction
			Tumors	8 mg/kg/day	GG	15–30	35–70 % reduction
Sengottuvelan et al. (2006)[b]	Wistar rats	DMH	ACF	8 mg/kg/day	GG	15–30	50–75 % reduction
			Tumors	8 mg/kg/day	GG	15–30	35–70 % reduction
Majumdar et al. (2009)	SCID mice	HCT-116 cells	Tumor growth	150 mg/kg daily	GG	3	40 % inhibition with curcumin
Alfaras et al. (2010)	Sprague-Dawley rats	DMH	ACF	60 mg/kg	Oral	7	52 % reduction

[a]Information based on abstract only
[b]These two reports do not appear to describe independent data sets
AOM azoxymethane, *ACF* aberrant crypt foci, *DMH* 1,2-dimethylhydrazine, *GG* gastric gavages

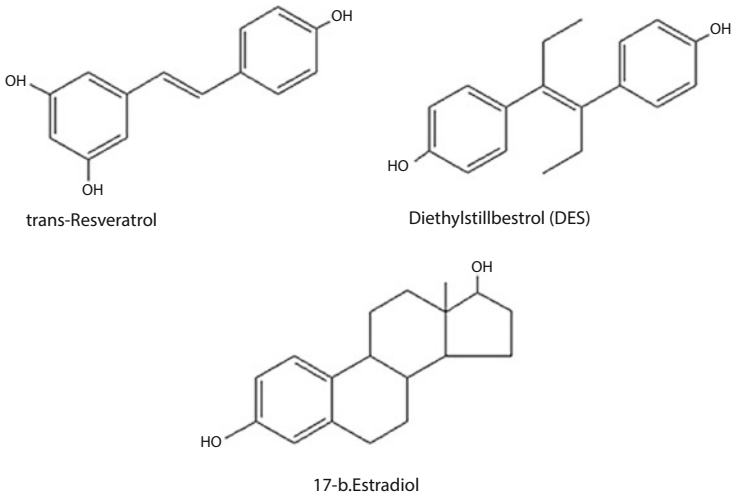

Fig. 2 Chemical structure of *trans*-resveratrol in comparison to diethylstilbestrol (DES) and estradiol

also been demonstrated to have anti-colon cancer activity. In an azoxymethane cancer model in F344 rats, a decreased frequency of aberrant crypt foci was demonstrated (Nomoto et al. 2004; Singletary and Meline 2001).

Resveratrol is considered a phytoestrogen (Fig. 2) and appears to have both antagonistic and agonistic effects through the estrogen receptor (Bowers et al. 2000; Bhat et al. 2001). Therefore, it is not surprising that studies in laboratory animals related to breast cancer have been contradictory. Several studies have demonstrated a reduction in breast cancer tumors or a delay in their initiation following DMBA [7,12-dimethylbenz(*a*)anthracene] administration (Banerjee et al. 2002; Whitsett et al. 2006; Chatterjee et al. 2011) or NMU (*N*-nitroso-*N*-methylurea) administration (Bhat et al. 2001). Other studies have not demonstrated benefit or even suggested that resveratrol may increase tumor formation when given to prepubescent rats (Sato et al. 2003; Castillo-Pichardo et al. 2013). These studies suggest that the phytoestrogen effects of resveratrol may counteract any cancer inhibitory activity under certain circumstances and that caution should be used prior to extrapolating to human use.

Induction of hepatocellular carcinoma with diethylnitrosamine (DENA) followed by phenobarbital can be inhibited by resveratrol, often associated with increased apoptosis in liver cancer cells (Bishayee 2009; Luther et al. 2011; Rajasekaran et al. 2011). Interestingly, a reduction in hepatocellular cancer development was also seen in a hepatitis B virus X protein model (Lin et al. 2012) suggesting a potential preventive role in virally mediated liver cancer. An activity of resveratrol for pancreatic cancer prevention in immune-deficient mice has also been reported (Harikumar et al. 2010; Oi et al. 2010; Roy et al. 2011). Resveratrol appears to inhibit prostate cancer growth in TRAP rats and TRAMP mice (Harper

et al. 2007; Seeni et al. 2008) but has no effect in a nude mouse xerograph model (Seeni et al. 2008; Wang et al. 2008).

Several different skin cancer models have suggested that resveratrol may be beneficial in prevention of this disease. Its administration inhibits skin cancer in a two-stage mouse model (Kapadia et al. 2002). Similar activity has been reported in UV-induced skin cancer as well (Aziz et al. 2005; Reagan-Shaw et al. 2004; Adhami et al. 2003; Afaq et al. 2003). A beneficial effect has also been seen in a Lewis lung carcinoma murine model (Kimura and Okuda 2001), possibly through inhibition of angiogenesis, an effect seen in other tumor model systems as well (Garvin et al. 2006; Chen et al. 2006; Mousa and Mousa 2005).

5 Human Studies for Cancer Treatment and Prevention

Multiple dietary agents have been purported to possess anticancer or cancer preventive activity (Aggarwal and Shishodia 2006) though there have been few controlled trials in humans on which to form conclusions regarding efficacy. Most of the trials relevant to grapes have focused on the activities of resveratrol, though a few have examined whole grapes or combinations of grape components. Several clinical trials have focused on the pharmacokinetics, pharmacodynamics, and safety of moderate to large oral dosages of resveratrol (Patel et al. 2011). Safety is always a concern when administering high dosages. At 5 g/day, nausea, diarrhea, fatigue, and renal insufficiency were noted in a patient with multiple myeloma (Popat et al. 2013). Others have found resveratrol to be well tolerated in high dosages for short periods of time (29 days of resveratrol supplementation at 2.5 g/day) and to reduce IGF-1 and IGFBP3 levels (Brown et al. 2010). Thus, resveratrol may have effects on energy metabolism and metabolic profiles similar to caloric restriction (Timmers et al. 2011), processes suggested as important for both primary and secondary cancer prevention (Voskuil et al. 2005). Howells et al. (2011) showed that 5 g resveratrol daily for 10–21 days increased apoptosis in colorectal cancer metastases in the liver. Of note, resveratrol may increase the activity levels of cancer-detoxifying enzymes such as glucuronosyltransferase (Chow et al. 2010). The authors of this study caution that a similar effect on inhibition of cytochrome P450 activity might counterbalance an antineoplastic effect.

A pilot study was performed in colon cancer patients who received either resveratrol or freeze-dried grape powder orally (Nguyen et al. 2009). Normal colonic mucosa and colon tumors were evaluated before and after the intervention. A reduction in Wnt pathway target genes was noted, primarily on the normal mucosa with minimal effect on Wnt signaling in tumor tissue. The most significant effects were observed with low-dose grape powder. These data suggest that the primary clinical efficacy may be in cancer prevention and not treatment of established colon cancer. A more recent study involved the administration of 1/3 to 1 pound of whole red grapes per day for 2 weeks to normal volunteers' diet

(Martinez et al. 2010). Colorectal mucosal biopsies were obtained pre- and post-grape supplementation and evaluated for markers of proliferation and Wnt signaling. Following grape ingestion, the mucosal proliferation rate was significantly reduced as measured by Ki67 staining at the base of crypts. In addition, Wnt target gene expression was reduced similar to the prior study with grape powder. The reduction in Wnt signaling and proliferation was seen primarily in individuals over the age of 50 and those on a high-arginine diet (Holcombe et al. 2014), two groups that are at increased risk for the development of colon cancer.

6 Bioavailability

While resveratrol effects multiple molecular targets, the concentrations attained in vivo are significantly lower than the concentrations required for activity in vitro, raising the question as to how resveratrol exhibits this activity in animal models and perhaps in humans (Gescher and Steward 2003). Selection of the correct dose is problematic as the concentrations noted in vitro to exhibit activity are much higher than can be achieved in humans (Scott et al. 2012). A recent pharmacokinetic study of single-dose resveratrol confirmed that peak plasma concentrations of the parent compound following a single large 5 g ingestion reached only 539 ng/ml (2.4 μM), significantly lower than the 5.0 μM expected to be necessary for cancer prevention activity (Boocock et al. 2007). The peak levels of conjugated metabolites resveratrol-3-sulfate and two monoglucuronides were 3–8× higher, raising the possibility that cancer prevention activity may be, at least in part, attributable to resveratrol's glucuronide and sulfate metabolites (Walle 2011). Sulfated metabolites have been shown to have antitumor activity against breast cancer cells in vitro (Miksits et al. 2009).

While well absorbed, resveratrol has low bioavailability (Walle et al. 2004). Lower-dose ingestions of resveratrol in the range of 25 mg yield systemic levels of only 7.5–40 nM (Soleas et al. 2001; Goldberg et al. 1995). One explanation of the in vivo activity of resveratrol may be that, even though serum concentrations are low, local concentrations in the gut are sufficient to provide activity (Patel et al. 2010). Still, it appears that the effective dose of the parent compound required to attain sufficient concentrations for activity is large and achieving this is not straightforward. Alternatively, the suspected mechanisms of action requiring high micromolar concentrations in vitro may not be those operative in vivo. Even low concentrations of resveratrol have been shown to affect signaling pathways in vitro and in the human GI tract (Hope et al. 2008; Nguyen et al. 2009).

7 Whole Food vs. Component Considerations

A significant issue when considering the benefits of dietary interventions is whether single components provided as supplements are as effective as consuming phytochemicals from whole food sources. For example, Burton-Freeman and Sesso found that ingestion of tomatoes had a superior effect on cardiovascular risk endpoints compared to lycopene supplementation (Burton-Freeman and Sesso 2014). In a study comparing freeze-dried grape powder or resveratrol on Wnt signaling endpoints in the colonic mucosa, Nguyen et al. reported a greater effect by the whole food source product, suggesting that other compounds found in grapes might be synergistic with resveratrol resulting in greater effectiveness than the isolated compound (Nguyen et al. 2009). Other studies have demonstrated synergy of resveratrol and curcumin in inhibition of colon cancer cell growth (Majumdar et al. 2009), and it is reasonable to assume that synergy exists among the myriad of phytochemicals present in grapes.

Grape juice prepared from whole grapes has been shown to increase plasma total antioxidant capacity (Yuan et al. 2011) and to have chemopreventive activity in a two-stage mouse skin cancer model, possibly by blocking activation of COX2 (Arimoto-Kobayashi et al. 2013). Similarly, consumption of grape powder increases plasma antioxidant activity (Prior et al. 2007). Finally, in a recent study looking at dietary supplementation of up to a pound daily of whole red grapes which is reported (Holcombe et al. 2015), significant effects were reported showing a reduction in the proliferation rate and in the extent of Wnt signaling in colonic mucosa. More research on the utility of whole grapes on cancer prevention and cancer treatment endpoints, in addition to further investigations with individual components and defined combinations of components, is needed.

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