Health Benefits of Muscadine Grapes

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The Health Benefits of Muscadine Grapes are primarily due to two different mechanisms

1) Antiinflammatory effects
2) Effects on specific genes

Some examples will be provided for 2 Grape nutrients

Resveratrol and Ellagic Acid

Muscadine Grapes

Major source of many different types of Phytonutrient (polyphenolic) compounds

Some are in high concentration and some are not found in other fruits or vegetables

(Acacia, Goji, Pomegranate, Blueberries)

Comparisons

Genus and species:	***Vitis vinifera***	***Vitis rotundifolia***
Common name:	bunch grapes	muscadine grapes
Origin:	Europe	America
Varieties:	Many types	Many types
	Thin skins	Thick skins
	Healthy	More healthy because of more types and higher content of nutrients

Phytonutrients of Muscadine Grapes

selected from a list of > 1000

Ellagic Acid
Chlorogenic Acid
Gallic Acid
Tartaric Acid
Resveratrol
Geraniol
Cyanidin
Piceatannol
Coumaric Acid
Peonidin
Kaempferol
Delphinidin
Cinnamic Acid
Myricetin
Petunidin
Epicatechin
Quercetin
Malvidin
Vitamin C
Anthocyanidins

Many compounds are polyphenolics

Other Components of Muscadine Grapes

- Vitamins
- Oils
- Fibers
- Sugars
- Proteins

Comparisons

Muscadine grape parts

	SKIN	PULP	SEED
	Thick, leathery	Soft, watery	Hard, woody
Nutritional value	first	third	second
Simple sugar content	second	first	third
Most numbers of nutrients for health	first	last	second

Comparison

Muscadine grape

Most abundant phenolics (healthy nutrients)

Skin	**Seed**
Ellagic acid	gallic acid
Myricetin	catechin
Quercetin	epicatechin
Kaempferol	

Other/most distinguishing features:

Skin contains anthocyanidins- none in seeds
Skin contains ellagic acid and ellagitannins – none in seeds
Skin contains kaempherol-none in seeds
Skin contains myricetin and quercetin
Skin contains catechin and epicatechin –more of these in seeds
Skin contains gallic acid- more of this in seeds
Skin contains more resveratrol- very little in seeds
Skin contains several types of resveratrol not only trans-resveratrol

Morbidity and Mortality Data (Estimates for the United States)

	Deaths/year	%Total	Estimated Affected
Heart Disease	783,000	40%	61 Million
Cancer	560,000	28%	10-20 Million
Stroke	167,000	8%	700,000

The leading cause of disability among US adults is

Arthritis 70 Million

Benefit for Heart and Blood Vessel Health

- Reduction of oxidative stress to heart and blood health
- Reduction of inflammation to blood vessels to reduce atherosclerotic plaque formation
- Maintain the dilation mechanisms of blood vessels to keep blood pressure normal
- Protection against inappropriate blood clotting

Benefit for Diabetes

- Reduces Metabolic Syndrome
- Controls blood glucose concentrations
- Reduces metabolic eye damage
- Inhibits AGE protein formation

Muscadine Grapes Provide Anti-inflammatory Effects

Inflammation from any cause

Rheumatoid Arthritis
Gout
Psoriasis
Inflammatory Bowel Disease
Colitis

Atherosclerosis
Diabetes
COPD
Asthma
Allergies
Alzheimer's
Fibromyalgia

Muscadine Grapes Provide Antioxidant Effects

Free radicals are chemical materials formed by cells and tissues and can damage normal tissue. In our tissues free radicals are normally removed if low in number.

When there are more free radicals formed especially in chronic diseases or during inflammation, there is a need for additional protector molecules – Antioxidants- typically taken orally.

Vitamins C and E

The ***first generation*** of antioxidants

Grape Polyphenolics

The ***second generation*** of antioxidants

Are more powerful than vitamin C or E

Muscadine Grape Polyphenolics Regulate Specific Genes

Sirtuin Gene (the longevity Gene)

(Resveratrol)

Resveratrol has a general – non specific effect as antioxidant

Resveratrol has a specific effect on a gene

Resveratrol can regulate cell growth

Resveratrol as a chemo preventive agent: a promising molecule for fighting cancer.

Delmas D, Lançon A, Colin D, Jannin B, Latruffe N.

Laboratory of Cell and Molecular Biology, University of Burgundy, UPRES-EA 2978/GDR-CNRS 2583, 6 Bd Gabriel, 21000 Dijon, France.

Resveratrol acts on the process of carcinogenesis by affecting the three phases: tumor initiation, promotion and progression phases and suppresses the final steps of carcinogenesis, i.e. angiogenesis and metastasis. It is also able to activate apoptosis, to arrest the cell cycle or to inhibit kinase pathways. Interestingly, resveratrol does not present any cytotoxicity in animal models. Interestingly, low doses of resveratrol can sensitize to low doses of cytotoxic drugs and so provide an innovative strategy to enhance the efficacy of anticancer therapy in various human cancers. By these properties, resveratrol appears to be a good candidate in chemopreventive or chemotherapeutic strategies and is believed to be a novel weapon for new therapeutic strategies.

Curr.Drug Targets 2006 4: 423-442.

Resveratrol can regulate factors that control Genes

Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor-B–regulated antiapoptotic and cell survival gene products in human multiple myeloma cells.

Anjana Bhardwaj, Gautam Sethi, Saroj Vadhan-Raj ,
Carlos Bueso-Ramos, Yasunari Takada, Upasna Gaur,
Asha S. Nair, Shishir Shishodia, and Bharat B. Aggarwal

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center,Houston.

BLOOD, 2007; 109: 2293-2302

Muscadine Grape skin powder kills Prostate Cancer Cells

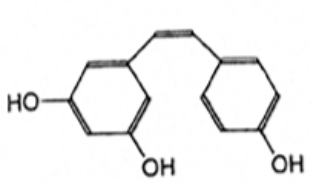
Inhibition of Prostate Cancer Growth by Muscadine Grape Skin Extract and Resveratrol through Distinct Mechanisms

Tamaro S. Hudson, Diane K. Hartle, Stephen D. Hursting,Nomeli P. Nunez, Thomas T.Y. Wang,Heather A. Young, Praveen Arany, and Jeffrey E. Green
Laboratory of Cellular Regulation and Carcinogenesis, National Cancer Institute, NIH, Bethesda, Maryland; College of Pharmacy,Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, Georgia; Division of Nutritional Sciences,

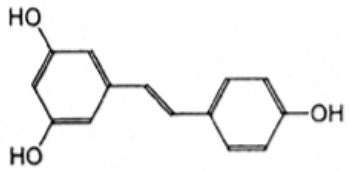
The phytochemical resveratrol contained in red grapes has been shown to inhibit prostate cancer cell growth, in part, through its antioxidant activity. Muscadine grapes contain unique phytochemical constituents compared with other grapes and are potentially a source for novel compounds with antitumor activities. We compared the antitumor. These results show that MSKE and resveratrol target distinct pathways to inhibit prostate cancer cell growth in this system and that the unique properties of MSKE suggest that it may be an important source for further development of chemopreventive or therapeutic agents against prostate cancer.

Cancer Res 2007; 67: 8396–405

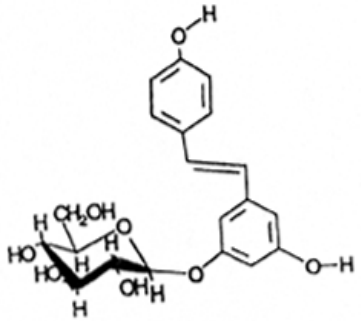
Resveratrol Structures



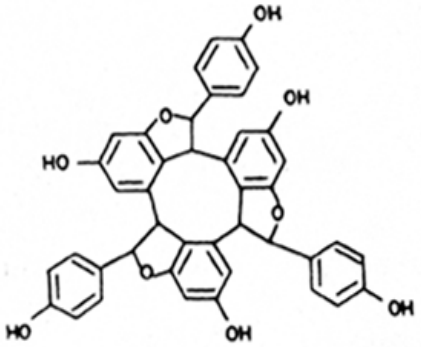
Cis-resveratrol



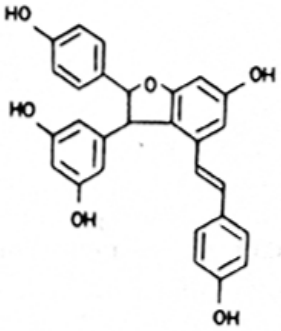
Trans-resveratrol



Trans-resveratrol glucoside



α-viniferin



ε-viniferin

Figure 1 — Chemical structures of resveratrol isomers, *trans*-resveratrol glucoside, α-viniferin and ε-viniferin.

Other types of resveratrols found in Muscadine Grape Skin powder

In addition to **trans-resveratrol** and **cis-resveratrol** Muscadine skin contains:

trans-piceid	(glycosylated t-resveratrol)
cis-piceid	(glycosylated c-resveratrol)
Piceatannol	(hydroxylated resveratrol)
Scirpusin	(dimer of piceatannol)
Astringin	(glycosylated piceatannol)
Pterostilbene	(methylated resveratrol)
ε-vineferin	(dimer of resveratrol)
α-vineferin	(trimer of resveratrol)

Each type of Resveratrol may act in different ways

Piceatannol attenuates 4-hydroxynonenal-induced apoptosis of PC12 cells by blocking activation of c-Jun N-terminal kinase

- **Jang YJ**, **Kim JE**, **Kang NJ**, **Lee KW**, **Lee HJ**.
- Major in Biomodulation, Department of Agricultural Biotechnology, Seoul National University, Seoul, Korea.
- Alzheimer's disease (AD) is an age-related neurodegenerative disorder in which apoptosis plays a potentially important role. 4-Hydroxynonenal (HNE) is a major lipid peroxidation product produced by oxidative stress, and its level is elevated in the AD brain. In the present study, piceatannol (but not resveratrol) at the concentration of 20 micromol/L inhibited HNE-induced PC12 cell death. Treatment with HNE induced nuclear condensation in PC12 cells, and this was attenuated by piceatannol treatment. HNE induced poly(ADP-ribose) polymerase cleavage and decreased Bcl-2 expression, with both of these effects being attenuated by piceatannol. Piceatannol also inhibited the phosphorylation of c-Jun N-terminal kinase, which is a key regulator of HNE-induced PC12 cell death. These results indicate that piceatannol has therapeutic potential in the prevention of AD.

Ref: Natural Compounds and Their role in Apoptotic Cell Signaling Pathways: Ann. N.Y. Acad. Sci. 1171: 176-182, 2009.

Heart Disease

Grape Polyphenols Exert a Cardioprotective Effect in Pre- and Postmenopausal Women by Lowering Plasma Lipids and Reducing Oxidative Stress1

Tosca L. Zern, Richard J. Wood, Christine Greene, Kristy L. West, Yanzhu Liu, Dimple Aggarwal,* Neil S. Shachter,* and Maria Luz Fernandez2
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**Department of Medicine, Columbia University, New York, NY 10032*

ABSTRACT To evaluate the effects of grape polyphenols on plasma lipids, inflammatory cytokines, and oxidative stress, 24 pre- and 20 postmenopausal women were randomly assigned to consume 36 g of a lyophilized grape powder (LGP) or a placebo for 4 wk. The LGP consisted of 92% carbohydrate and was rich in flavans, anthocyanins, quercetin, myricetin, kaempferol, and resveratrol. After a 3-wk washout period, subjects were assigned to the alternate treatment for an additional 4 wk. The placebo consisted of an equal ratio of fructose and dextrose andwas similar in appearance and energy content (554 kJ) to LGP. Plasma triglyceride concentrations were reduced by 15 and 6% in pre- and postmenopausal women, respectively (*P* 0.01) after LGP supplementation. In addition, plasma LDL cholesterol and apolipoproteins B and E were lower due to LGP treatment (*P* 0.05). Further, cholesterol ester transfer protein activity was decreased by 15% with intake of LGP (*P* 0.05). In contrast to these beneficial effects on plasma lipids, LDL oxidation was not modified by LGP treatment. However, whole-body oxidative stress as measured by urinary F2-isoprostanes was significantly reduced after LGP supplementation. LGP also decreased the levels of plasma tumor necrosis factor-, which plays a major role in the inflammation process. Through alterations in lipoprotein metabolism, oxidative stress, and inflammatory markers, LGP intake beneficially affected key risk factors for coronary heart disease in both pre- and postmenopausal women.

J. Nutr.135: 1911–1917, 2005.

Cancer

Muscadine Grape Ellagic Acid kills colon cancer cells

Induction of Cell Death in Caco-2 Human Colon Carcinoma Cells by Ellagic Acid Rich Fractions from Muscadine Grapes (Vitis rotundifolia)

SUSANNE U. MERTENS-TALCOTT,JOON-HEE LEE, SUSAN S. PERCIVAL, AND STEPHEN T. TALCOTT Department of Pharmaceutics, University of Florida, Gainesville, Florida and Department of Food Science and Human Nutrition

Possible anticancer mechanisms exerted by polyphenolic compounds contained in fruits and vegetables include antioxidant activity, the inhibition of proliferation, and the induction of apoptosis in cancer cells. This study examined the effects of four isolated polyphenolic extracts from red muscadine grapes (Vitis rotundifolia) on vital cell parameters and the induction of apoptosis in Caco-2 colon carcinoma cells. The magnitude of effects in cell culture was then correlated to polyphenolic composition and antioxidant capacity. Whereas anticancer effects of individual polyphenolic compounds have been demonstrated multiple times, information relating to anticancer effects of polyphenolic extracts is not available in abundance. All four extracts induced apoptosis, decreased cell number, and caused alterations in cell cycle kinetics in a concentration-dependent manner. The efficacy of the polyphenolics on vital cell parameters correlated well to the presence of ellagic acid glycosides and flavonoids and also to the antioxidant capacity. This study demonstrated the anticancer properties of ellagic acid rich extracts from red muscadine juice. J. Agric. Food Chem. **2006,** 54: 5336-5343

Ellagic acid protects normal tissues from chemotherapy drugs

Ellagic Acid Prevents Cisplatin-Induced Oxidative Stress in Liver and Heart Tissue of Rats

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Abstract: Cisplatin is one of the most active cytotoxic agents in the treatment of cancer. High doses of cisplatin have also been known to produce hepatotoxicity, and several studies suggest that supplemental antioxidants can reduce cisplatin-induced hepatotoxicity. The present study was designed to determine the effects on the liver and heart oxidant/antioxidant system and the possible protective effects of ellagic acid on liver and heart toxicity induced by cisplatin. The control group received 0.9% saline; animals in the ellagic acid group received only ellagic acid (10 mg/kg); animals in the cisplatin group received only cisplatin (7 mg/kg); animals in cisplatin + ellagic acid group received ellagic acid for 10 days after cisplatin. The rats were killed at the end of the treatment period. Malondialdehyde (MDA) and glutathione (GSH) levels, glutathione-peroxidase (GSH-Px) and catalase (CAT) activities were determined in liver and heart tissue. While administration of cisplatin increased the MDA levels in liver and heart tissues, it decreased the GSH, GSH-Px and CAT in these samples when compared to the control group. The administration of ellagic acid to cisplatin-treated rats decreased the MDA levels, and increased GSH, GSH-Px and CAT in these samples. Cisplatin caused marked damages in the histopathological status of liver and heart tissues. These damages were ameliorated by ellagic acid administration. In conclusion, ellagic acid may be used in combination with cisplatin in chemotherapy to improve cisplatin-induced oxidative stress parameters.

Basic Clin. Pharmacol. Toxicol. 2007,101: 345-349.

American Association of Cancer Research Annual Meeting
April 18-22, 2009; Denver, CO

Muscadine Grape skin powder protects against leukemia

Resveratrol and muscadine grape extract reduce radiation-induced bone marrow PU.1 gene loss and chromosome aberration frequency.

Ronald E. Carsten, Annette M. Bachand, Susan M. Bailey, Phuong N. Le, Robert L. Ullrich. Colorado State University, Fort Collins, CO.

Resveratrol and MGE initiated before irradiation and resveratrol started after irradiation significantly ($p<0.0001$) reduced PU.1 gene loss at 1 and 30 days in mice. The optimum dose range of resveratrol for reducing chromosome aberrations was 3.12-25 mg/kg and for the MGE it was 2.10-7.13 µg/kg. These results demonstrate that resveratrol alone, or as found in combination with other bioactive factors in MGE is capable of significantly reducing radiation-induced PU.1 gene loss. The µg/kg doses of MGE resveratrol are superior to resveratrol alone in mg/kg or equivalent µg/kg doses of resveratrol as a single agent. Reduction of PU.1 gene loss and chromosome aberration frequencies in irradiated bone marrow cells suggests that resveratrol and MGE may protect against development of radiation-induced acute myeloid leukemia. Muscadine grape skin protects against radiation damage to bone marrow cells and possible blood cancers such as leukemia.

A Synergistic effect of the polyphenols in Muscadine Grapes is important for health

Combined Resveratrol, Quercetin, and Catechin Treatment Reduces Breast Tumor Growth in a Nude Mouse Model[1]

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Transl.Oncol 2008, 1: 19-27.

SUMMARY

- Muscadine grapes contain many phytonutrients which scientifically have been shown to benefit health.
- The natural and complex interaction or synergy of the phytonutrients is important for health.
- The phytonutrients can act as antioxidants, anti-inflammatory agents and/or on specific genes to reduce the effects of chronic diseases and promote health.

Review Articles and Key Research Papers Available

www.muscadinenaturals.com

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