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(REVIEW ARTICLE)

A review on antioxidant property containing red grapes of herbal medicine for breast cancer

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Abstract

Breast cancer is a major cause of mortality among women worldwide, making the exploration of novel therapeutic strategies crucial. Among the various alternative treatments, herbal formulations have gained significant attention due to their therapeutic potential. This review focuses on the role of red grape, known for its antioxidant properties, in the prevention and management of breast cancer. The bioactive compounds found in red grapes, particularly resveratrol and polyphenols, exhibit potent anticancer effects through various mechanisms such as oxidative stress reduction, apoptosis induction, and inhibition of cancer cell proliferation. This article discusses the evidence supporting the inclusion of red grape in herbal formulations and its therapeutic potential in breast cancer treatment

Keywords: Red Grape; Antioxidants; Breast Cancer; Oxidative Stress

1. Introduction

Breast cancer, characterized by the uncontrolled growth of breast cells, represents a global health concern. Conventional treatments such as surgery, chemotherapy, and radiation therapy have limitations, including side effects and drug resistance. Herbal formulations have been proposed as complementary or alternative therapies due to their relatively low toxicity and potential health benefits. Red grapes (Vitis vinifera), with their rich composition of antioxidants, particularly resveratrol, have shown promise in cancer prevention and therapy. This review aims to explore the current understanding of red grape's role in combating breast cancer. According to global mortality statistics for 2018, breast cancer was identified as the fifth leading cause of death internationally, accounting for approximately 627,000 fatalities and representing 6.6% of total deaths worldwide. During the last decade, new strategies based on the use of dietary chemo preventive agents for breast cancer management have been developed. Extensive in vitro and in vivo studies have consistently shown that bioactive compounds found in grapes and their derivative products exert numerous beneficial health effects. The health benefits of grapes and red wine have been primarily attributed to their rich content of phenolic compounds, including flavonoids, stilbenes, anthocyanins, and other bioactive molecules. This comprehensive review aims to provide a summary of the current evidence regarding the role of grape-derived bioactive compounds and their metabolites in breast cancer chemoprevention and treatment, with a focus on their molecular targets and underlying mechanisms of action. In breast cancer research, a diverse array of well-established breast cancer cell lines serves as experimental models, recapitulating the heterogeneity of breast cancer subtypes observed in clinical settings. These cell lines provide a virtually limitless source of relatively homogeneous cell populations that can self-replicate in standard cell culture media and are commercially available through cell banks. The MCF-7 cell line, established in 1973 at the Michigan Cancer Foundation, has become the most extensively utilized breast cancer cell line worldwide. Other frequently employed cell lines, including MDA-MB-231,

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MDA-MB-453, MDA-MB-468, and T47D, exhibit distinct molecular characteristics and will be discussed in further detail below.

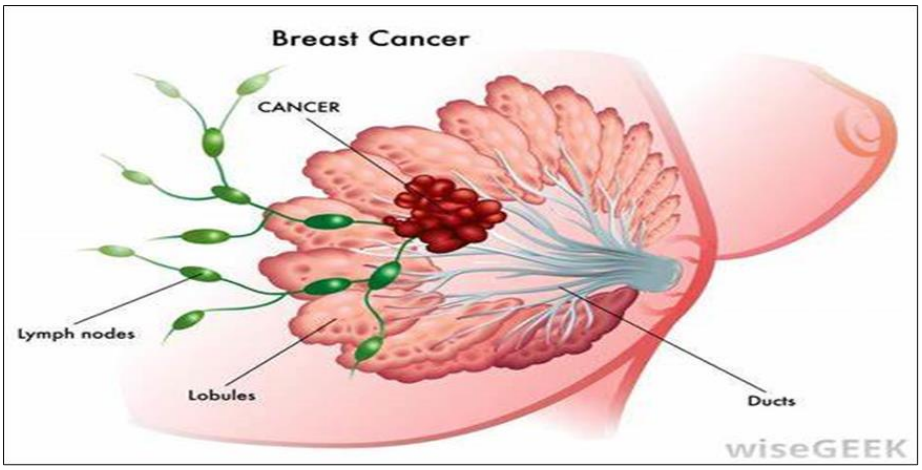

Figure 1 Breast cancer

1.1. Resveratrol

resveratrol is pronounced as rez-VEER-uh-trol. It's a polyphenolic compound found in various plants, including grapes, berries, and peanuts. Resveratrol is particularly known for its presence in red wine and is renowned for its potential antioxidant, anti-inflammatory, and anticancer properties. It has gained attention for its role in promoting cardiovascular health, reducing oxidative stress, and potentially extending lifespan through its effect on cellular processes.

2. Antioxidants and breast cancer

This review focuses on dietary, synthetic, and endogenous antioxidants with high therapeutic potential for breast cancer, as evidenced by preclinical and clinical studies. Specifically, we examine natural dietary antioxidants such as melatonin, resveratrol, curcumin, vitamins C, D, and E, carotenoids, hydroxytyrosol, epigallocatechin gallate, and selenium, as well as select synthetic antioxidants. We provide an overview of clinical trials (registered on (link unavailable) or otherwise) investigating antioxidant supplementation as a potential monotherapy or adjuvant therapy, and highlight key studies aimed at mitigating treatment-related side effects. A substance found in the skins of grapes and in certain other plants, fruits, and seed.

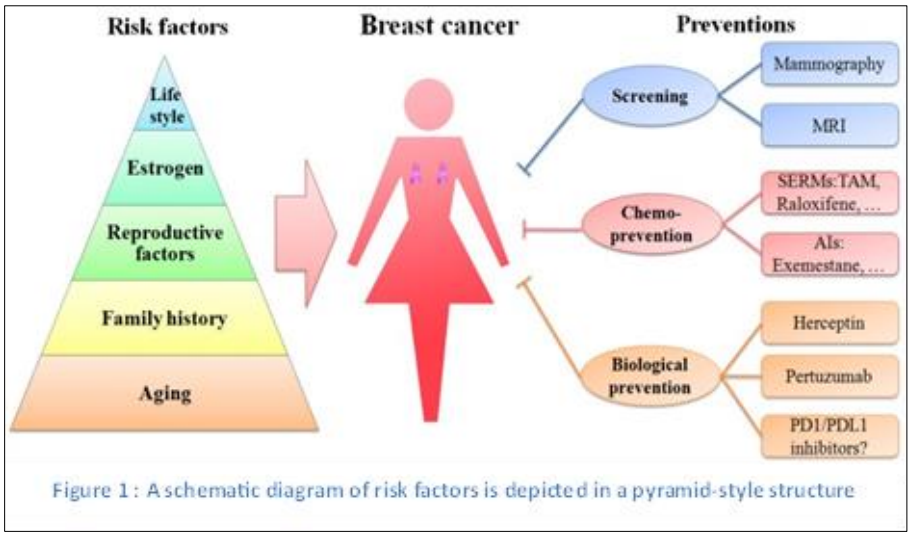

Figure 2 A schematic diagram of risk factors is depicted in a pyramid-style structure

3. Causes and risk factor

3.1. Aging

Aging is a significant risk factor for breast cancer, second only to sex. The incidence of breast cancer demonstrates a significant positive correlation with advancing age. According to 2016 statistics, a staggering 99.3% and 71.2% of breast cancer-related deaths in the United States occurred in women aged 40 and above, and 60 and above, respectively. Consequently, it is essential for women aged 40 and older to undergo regular mammography screenings as a proactive measure for early detection and prevention.

3.2. Family history

Family history plays a significant role in breast cancer, with approximately 25% of cases attributed to familial factors. Women with a first-degree relative (mother or sister) diagnosed with breast cancer are at increased risk of developing the disease. A large cohort study of over 113,000 women in the UK revealed that having one first-degree relative with breast cancer elevates the risk by 1.75-fold compared to women without affected relatives. Notably, the risk increases to 2.5-fold or higher when two or more first-degree relatives are diagnosed with breast cancer. The inherited susceptibility to breast cancer is partially attributed to mutations in breast cancer-related genes, such as BRCA1 and BRCA2.

3.3. Reproductive factors

Reproductive factors play a significant role in modulating breast cancer risk. Specifically, early menarche, late menopause, delayed age at first pregnancy, and low parity have all been linked to an increased risk of breast cancer. Notably, each one-year delay in menopause is associated with a 3% increase in breast cancer risk. Conversely, each 1-year delay in menarche or each additional birth decreases the risk of breast cancer by 5% or 10%, respectively. A recent Norwegian cohort study found a significant association between age at first birth and breast cancer risk. The study identified a hazard ratio (HR) of 1.54, indicating an increased risk associated with a late age at first birth (≥35 years) compared to an early age at first birth (<20 years). Reproductive factors also exhibit a strong association with estrogen receptor (ER) status in breast cancer. Notably, significant differences in odds ratios (OR) are observed between ER-positive (ER+) and ER-negative (ER-) breast cancer for parity and age at first birth. Specifically, the odds ratio (OR) for parity is 0.7 for ER-positive (ER+) breast cancer, compared to 0.9 for ER-negative (ER−) breast cancer, when comparing women with three or more births to nulliparous women. Similarly, the OR for age at first birth is 1.6 for ER+ breast cancer versus 1.2 for ER− breast cancer, when comparing women who gave birth at age 30 or older to those who gave birth before age 25.

4. Estrogen

4.1. The Role of Estrogen in Breast Cancer Risk

Estrogen, both endogenous and exogenous, plays a significant role in modulating breast cancer risk. In premenopausal women, the ovaries serve as the primary source of endogenous estrogen production. Notably, ovariectomy has been shown to decrease breast cancer risk, highlighting the association between endogenous estrogen levels and breast cancer susceptibility.

4.2. Sources of Exogenous Estrogen

Exogenous estrogen sources primarily include oral contraceptives and hormone replacement therapy (HRT). Oral contraceptives have been widely used since the 1960s, with continually evolving formulations to minimize adverse effects. However, epidemiological studies have revealed an elevated odds ratio (OR) for breast cancer risk, exceeding 1.5, among specific populations, including African American women and Iranian populations. However, oral contraceptives do not elevate the risk of breast cancer in women who discontinue their use for more than 10 years.

4.3. Lifestyle

Certain aspects of modern lifestyles, including excessive alcohol consumption and high dietary fat intake, have been linked to an increased risk of breast cancer. Specifically, alcohol consumption has been shown to elevate blood levels of estrogen-related hormones, thereby activating estrogen receptor pathways and potentially contributing to breast carcinogenesis. A meta-analysis of 53 epidemiological studies revealed that consuming 35–44 grams of alcohol per day

increases the risk of breast cancer by 32%, with a 7.1% rise in relative risk (RR) for every additional 10 grams of alcohol consumed daily.

4.4. Anticancer Effects of Resveratrol

Resveratrol has demonstrated anticancer potential in preclinical studies, influencing multiple aspects of cancer cell behavior. The compound's ability to modulate cellular processes and molecular pathways is crucial in understanding its therapeutic benefits for breast cancer treatment.

5. Mechanisms of Action

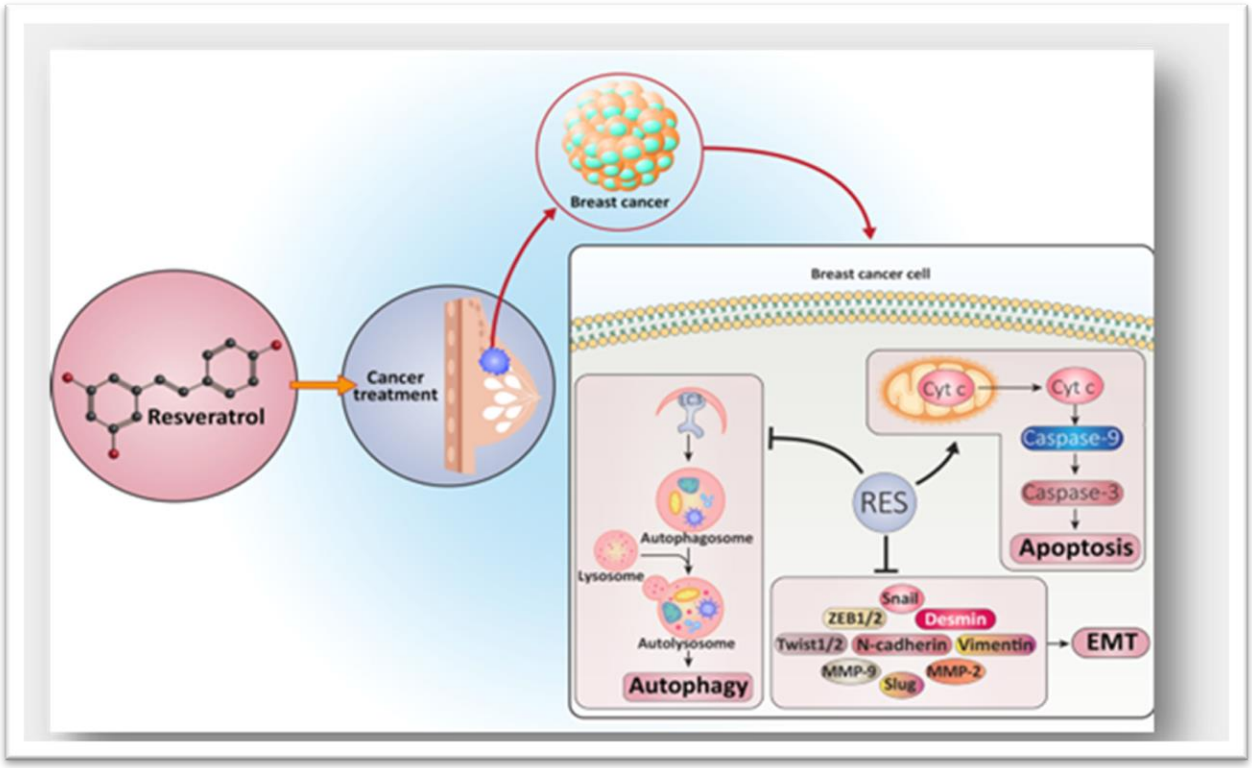

Figure 3 Resveratrol in breast cancer treatment: from cellular effects to molecular mechanisms of action.

Resveratrol exerts its effects through various molecular and cellular mechanisms, including:

- **Induction of Apoptosis (Programmed Cell Death):** Resveratrol promotes apoptosis in breast cancer cells by activating intrinsic and extrinsic apoptotic pathways. It upregulates pro-apoptotic proteins such as Bax, and downregulates anti-apoptotic proteins like Bcl-2. Additionally, resveratrol induces caspase activation, leading to cell death in breast cancer cells.
- **Cell Cycle Arrest:** Resveratrol exerts its anti-cancer effects by arresting the cell cycle at specific phases, notably the G1/S transition. It achieves this by modulating cyclin-dependent kinases (CDKs) and cyclins, thereby inhibiting the progression of cancer cells through the cell cycle and preventing their proliferation. Additionally, resveratrol enhances the accumulation of p53, a tumor suppressor protein that plays a critical role in regulating cell cycle arrest.
- **Inhibition of Angiogenesis:** Resveratrol inhibits angiogenesis, the process by which new blood vessels are formed to supply tumors with oxygen and nutrients. It reduces the expression of vascular endothelial growth factor (VEGF), a key molecule that promotes angiogenesis, thereby limiting the growth and spread of tumors.
- **Inhibition of Invasion and Metastasis:** Resveratrol has been shown to reduce the invasive potential of breast cancer cells. It inhibits matrix metalloproteinase (MMPs) that degrade extracellular matrix components, thus preventing the migration of cancer cells to other tissues. Additionally, resveratrol affects epithelial-mesenchymal transition (EMT), a process that plays a critical role in metastasis.
- **Modulation of Estrogen Receptor Signaling:** Estrogen plays a significant role in the development and progression of breast cancer, particularly in estrogen receptor-positive (ER+) breast cancer. Resveratrol acts

as a phytoestrogen, meaning it can bind to estrogen receptors and exert estrogenic or anti-estrogenic effects, depending on the concentration and cellular context. It may inhibit estrogen receptor signaling, suppressing tumor growth in ER+ breast cancers.

- **Epigenetic Modulation:** Resveratrol can influence epigenetic modifications, such as DNA methylation, histone acetylation, and miRNA expression. These modifications can alter the expression of genes involved in cancer progression, apoptosis, and metastasis. Resveratrol's ability to regulate these epigenetic changes further contributes to its anticancer properties
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5.1. Resveratrol's Effect on Different Breast Cancer Subtypes

Resveratrol has shown potential against different subtypes of breast cancer, including:

ER-positive (Estrogen Receptor Positive) Breast Cancer: Resveratrol acts through both estrogenic and anti-estrogenic mechanisms, modulating estrogen receptor activity and interfering with estrogen-induced cancer cell proliferation.

Triple-negative Breast Cancer (TNBC): Resveratrol shows promise in treating TNBC, a more aggressive subtype of breast cancer with limited treatment options. It has been reported to inhibit the growth and migration of TNBC cells by modulating multiple signaling pathways such as NF-kB, PI3K/Akt, and MAPK.

Resveratrol: Pharmacology and Therapeutic Potential-
This section highlights the prominent biological actions and therapeutic potential of resveratrol. The subsequent sub-sections will delve into its pharmacological effects, with a particular emphasis on its anti-diabetic properties, cardiovascular benefits, neuroprotective functions, and anticancer activities.

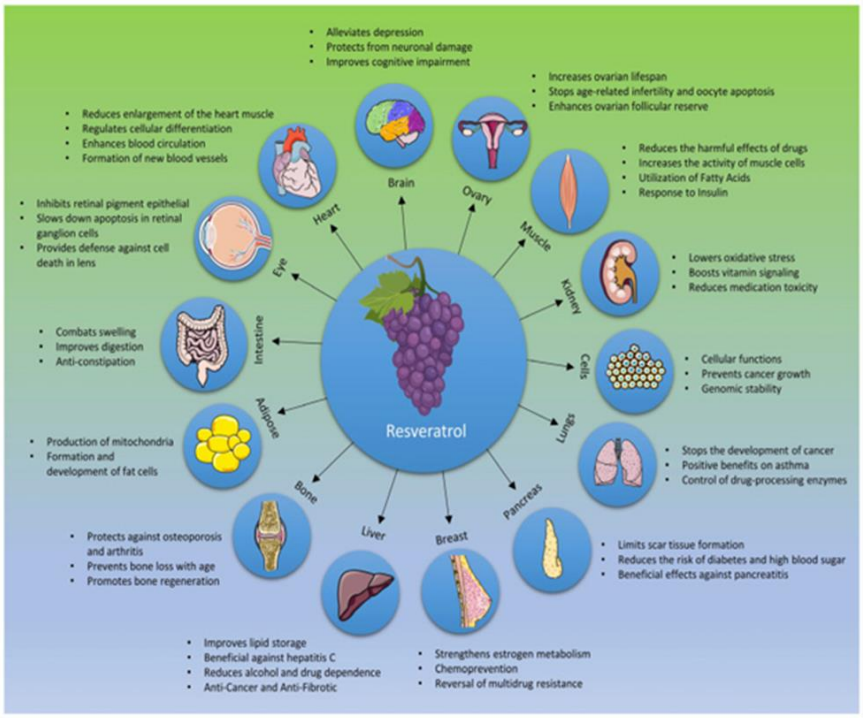

Figure 4 The health benefits of resveratrol consumption in humans.

5.2. Method of preparation

Grapes and their derivative products are a rich source of bioactive molecules, including flavonoid compounds (flavanols, monomeric catechins, proanthocyanidins, anthocyanins, anthocyanidins) and non-flavonoid phenolic compounds

(resveratrol), as well as their metabolites. Several molecular pathways involved in breast cancer cell signalling and differentiation, cell cycle arrest, apoptosis, and metastasis can be modulated compound.

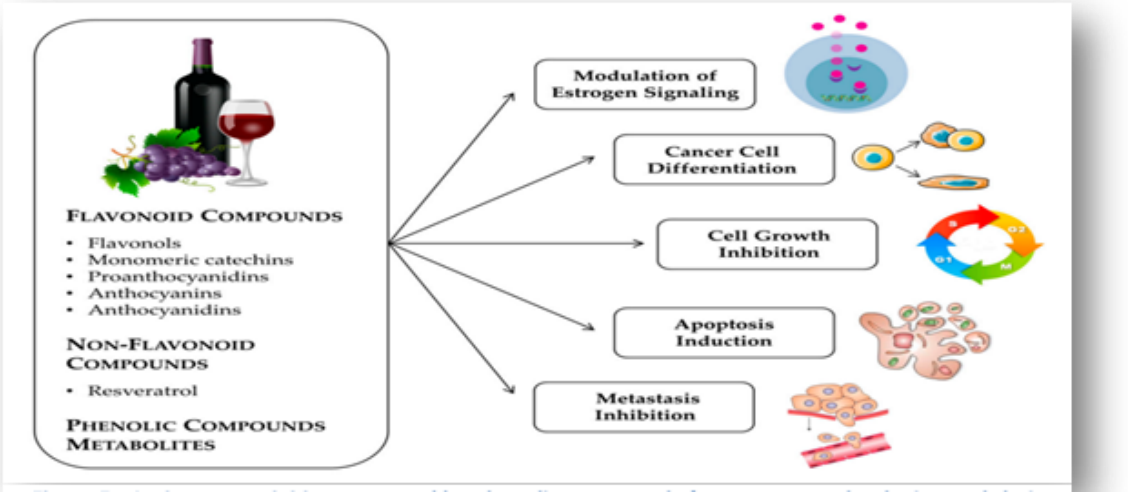

Figure 5 Anticancer activities promoted by phenolic compounds from grapes and red wine and their metabolites.

6. Impact and Novelty

1. Potential Therapeutic Use These compounds have demonstrated anti-cancer properties by reducing oxidative stress, a key factor in cancer progression. Understanding their effects in breast cancer opens new avenues for developing less toxic, complementary therapies**.**

2. Antioxidant Mechanisms: By inhibiting oxidative stress pathways, red grape compounds may prevent DNA damage, reduce tumour growth, and enhance the effectiveness of conventional treatments like chemotherapy and radiation.

3. Targeted Therapy: The compounds specifically modulate pathways like NF-κB and PI3K/Akt, which are crucial in breast cancer development. This targeted action offers a potentially more precise and safer therapeutic strategy compared to traditional cancer treatments.

4. Prevention and Chemoprevention: The inclusion of red grape polyphenols in diet could be used for breast cancer prevention, particularly for high-risk groups. This makes it valuable for public health initiatives focused on cancer prevention.

6.1. Novelty

Natural Antioxidant Approach: The focus on plant-based, natural compounds like resveratrol is novel compared to synthetic drugs, providing a more biocompatible alternative with fewer side effects.

Combination with Conventional Therapies: Combining red grape compounds with conventional cancer treatments is an emerging strategy, which can improve therapeutic outcomes by reducing oxidative damage from therapies like chemotherapy while simultaneously enhancing cancer cell death.

Focus on Specific Pathways: Exploring how these compounds interact with specific oxidative stress and cancer signaling pathways adds novelty to understanding the molecular basis of their anti-cancer effects. This can lead to the discovery of new drug targets or biomarkers for breast cancer prognosis.

In Vivo and Clinical Trials: While in vitro studies are abundant, translating these effects to in vivo models and clinical trials is still a developing area. Advancements here will establish the clinical relevance of these compounds in breast cancer treatment

7. Conclusion

The therapeutic potential of red grape, particularly its antioxidant compounds, in breast cancer prevention and treatment is significant. The evidence supports the inclusion of red grape extracts in herbal formulations as an adjunctive or alternative treatment strategy. However, further clinical studies are needed to establish the optimal doses, formulations, and long-term safety of these herbal interventions. As research progresses, red grape may become an integral part of breast cancer management.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Vivier MA, Pretorius IS. Genetically tailored grapevines for the wine industry. Trends in Biotechnology. 2002;20(11):472–478. doi: 10.1016/s0167-7799(02)02058-9.

[2] This P, Lacombe T, Thomas MR. Historical origins and genetic diversity of wine grapes. Trends in Genetics. 2006;22(9):511–519. doi: 10.1016/j.tig.2006.07.008.

[3] Hankinson B, Rao VNM, Smit CJB. Viscoelastic and histological properties of grape skins. Journal of Food Science. 1977;42:632–635.

[4] Bellincontro A, De Santis D, Botondi R, Villa I, Mencarelli F. Different postharvest dehydration rates affect quality characteristics and volatile compounds of Malvasia, Trebbiano and Sangiovese grapes for wine production. Journal of the Science of Food and Agriculture. 2004;84(13):1791–1800.

[5] Feringa HHH, Laskey DA, Dickson JE, Coleman CI. The effect of grape seed extract on cardiovascular risk markers: a meta-analysis of randomized controlled trials. Journal of the American Dietetic Association. 2011;111(8):1173–1181. doi: 10.1016/j.jada.2011.05.015.

[6] Mellen PB, Daniel KR, Brosnihan KB, Hansen KJ, Herrington DM. Effect of muscadine grape seed supplementation on vascular function in subjects with or at risk for cardiovascular disease: a randomized crossover trial. Journal of the American College of Nutrition. 2010;29(5):469–475. doi: 10.1080/07315724.2010.10719883.

[7] Castilla P, Dávalos A, Teruel JL, et al. Comparative effects of dietary supplementation with red grape juice and vitamin E on production of superoxide by circulating neutrophil NADPH oxidase in hemodialysis patients. American Journal of Clinical Nutrition. 2008;87(4):1053–1061. doi: 10.1093/ajcn/87.4.1053.

[8] Castilla P, Echarri R, Dávalos A, et al. Concentrated red grape juice exerts antioxidant, hypolipidemic, and antiinflammatory effects in both hemodialysis patients and healthy subjects. American Journal of Clinical Nutrition. 2006;84(1):252–262. doi: 10.1093/ajcn/84.1.252.

[9] Brooker S, Martin S, Pearson A, et al. Double-blind, placebo-controlled, randomised phase II trial of IH636 grape seed proanthocyanidin extract (GSPE) in patients with radiation-induced breast induration. Radiotherapy and Oncology. 2006;79(1):45–51. doi: 10.1016/j.radonc.2006.02.008.

[10] Preuss HG, Wallerstedt D, Talpur N, et al. Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study. Journal of Medicine. 2000;31(5-6):227–246.

[11] Vislocky LM, Fernandez ML. Biomedical effects of grape products. Nutrition Reviews. 2010;68(11):656–670. doi: 10.1111/j.1753-4887.2010.00335.x.

[12] Prasain JK, Carlson SH, Wyss JM. Flavonoids and age-related disease: risk, benefits and critical windows. Maturitas. 2010;66(2):163–171. doi: 10.1016/j.maturitas.2010.01.010.

[13] Frayne RF. Direct analysis of the major organic components in grape must and wine using high performance liquid chromatography. American Journal of Enology and Viticulture. 1986;37:281–287.

[14] Hogan S, Zhang L, Li J, Zoecklein B, Zhou K. Antioxidant properties and bioactive components of Norton (Vitis aestivalis) and Cabernet Franc (Vitis vinifera) wine grapes. LWT—Food Science and Technology. 2009;42(7):1269–1274.

[15] Careri M, Corradini C, Elviri L, Nicoletti I, Zagnoni I. Direct HPLC analysis of quercetin and trans-resveratrol in red wine, grape, and winemaking byproducts. Journal of Agricultural and Food Chemistry. 2003;51(18):5226–5231. doi: 10.1021/jf034149g.

[16] Kammerer D, Claus A, Carle R, Schieber A. Polyphenol screening of pomace from red and white grape varieties (Vitis vinifera L.) by HPLC-DAD-MS/MS. Journal of Agricultural and Food Chemistry. 2004;52(14):4360–4367. doi: 10.1021/jf049613b.

[17] Lu Y, Yeap Foo L. The polyphenol constituents of grape pomace. Food Chemistry. 1999;65(1):1–8.

[18] Zhao J, Wang J, Chen Y, Agarwal R. Anti-tumor-promoting activity of a polyphenolic fraction isolated from grape seeds in the mouse skin two-stage initiation-promotion protocol and identification of procyanidin B5-3'-gallate as the most effective antioxidant constituent. Carcinogenesis. 1999;20(9):1737–1745. doi: 10.1093/carcin/20.9.1737.

[19] Prieur C, Rigaud J, Cheynier V, Moutounet M. Oligomeric and polymeric procyanidins from grape seeds. Phytochemistry. 1994;36(3):781–784.

[20] Jayaprakasha GK, Singh RP, Sakariah KK. Antioxidant activity of grape seed (Vitis vinifera) extracts on peroxidation models in vitro . Food Chemistry. 2001;73(3):285–290.

[21] Ye X, Krohn RL, Liu W, et al. The cytotoxic effects of a novel IH636 grape seed proanthocyanidin extract on cultured human cancer cells. Molecular and Cellular Biochemistry. 1999;196(1-2):99–108.

[22] Fuleki T, Da Silva JMR. Catechin and procyanidin composition of seeds from grape cultivars grown in Ontario. Journal of Agricultural and Food Chemistry. 1997;45(4):1156–1160.

[23] Negro C, Tommasi L, Miceli A. Phenolic compounds and antioxidant activity from red grape marc extracts. Bioresource Technology. 2003;87(1):41–44. doi: 10.1016/s0960-8524(02)00202-x