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Review

Pharmacological Effects of Bioactive Compounds from *Vitis vinifera* (Grape)

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Abstract

Recent studies have shown that the most important polyphenols in grapes are anthocyanins, flavanols, flavonoids and resveratrol. These antioxidants have many biological activities such as cardio-protective, anti-cancer, anti-inflammation, anti-aging and antimicrobial properties. Consumption of grape and its products is associated with a lower incidence of degenerative diseases such as cardiovascular disease and certain cancers. Also, extracts from skins, seeds, grape pomace and lees show pharmacological effects of these biomolecules. The review make a presentation of bioactive components in grapes and beneficial effects of the polyphenols..

Keywords: grape; polyphenol; bioactivity; resveratrol; anthocyanidins; flavonoids; bioactivity of phenolic compounds.

1. Introduction

The plants are enshrined sources of pharmaceutical compounds, aromatics, the industrial, the civilization being inseparable from their world for millennia constituted the major source of bio-products obtaining essential for the survival of the entire animal kingdom. The plant kingdom continues to be the leading provider of phytochemicals used in various industries such as the pharmaceutical products, food, cosmetics, agrochemicals, with very high commercial value. Also medical nutrients derived from plants has played an important role in the treatment of various diseases. Grapes can be eaten raw or they can be used for making jam, juice, grape seed extract, raisins, vinegar and grape seed oil [1].

Eating grapes and grape derivatives is beneficial for removing and reversing the harmful effects of oxidative stress, such as cancer, neurodegenerative disorders, aging neuronal communication and behavior [2, 3].

From the pharmaceutical point of view, the polyphenols are the most important group of substances found in the organs of the vine.

They are an important source of natural antioxidant compounds investigated to combat oxidative stress produced by ,,reactive oxygen species", which in moderate amounts, plays a physiological role better outlined, but also have a potentially harmful and destructive to cells.

Although the accumulation of antioxidants in grapes is influenced by non-genetic factors [4], the profile of these substances is genetically determined [5].

It is important to know the individual potential of local varieties in different areas and in different phenological phases, on the concentration of active compounds.

This can be the starting point for the valorisation of lesser known grape varieties in biochemical point of view, contributing to the increase agro-biodiversity.

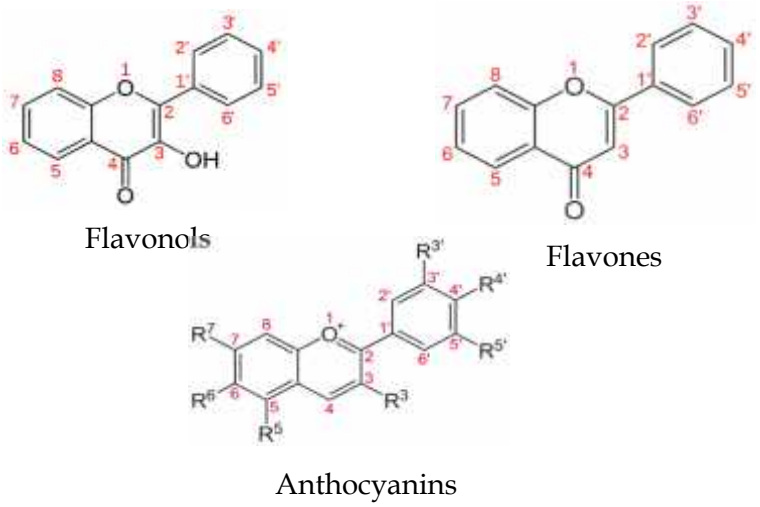
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2. Active constituents

Phenols are substances that are derived from benzene, to which is grafted one or more hydroxyl groups. When the hydroxyl group is attached to a position resulting phenolic arenas. [6]. Chemical activity of this type of molecule is due to phenol function which generates reactions of electrophilic substitutions. Due to phenolic function, phenolic compounds are considered antioxidants [5].

Polyphenols. The phenol compounds are characterized by phenolic function, which is made up of a hydroxyl group directly linked to a benzene ring. Chemical activity of this type of molecule is due phenol function which through mobility of the hydrogen atom has a weak acid character and benzene ring which generates electrophilic substitution reactions [5]. The highly complex molecular structure, phenolic compounds possess chemical properties of oxidation, condensation, polymerization and precipitation. The antioxidant power of the phenolic compounds is greater than vitamins C and E [7]. Phenolic compounds groups together a set of molecules with phenolic character: phenolic acids, volatile phenols, flavones and flavonols, anthocyanins, catechins and tannins a series of microfenoli [5] (fig. 1).

Anthocyanins. The anthocyanins are glycoside heterocyclic compounds, polyhydroxylic and methoxyl, format from 2-fenil benzo piriliu nucleus, with two sugar molecules. Anthocyanins are natural pigments, responsible for a wide range of colors in grape and red wines. The anthocyanins that have been reported for *V. Vinifera* include 3-glucosides, 3-acetylglucosides, 3-coumaroylglucosides, 3-caffeoylglucosides, 3,5-diglucosides, 3-acetyl-5-diglucosides, 3-coumaroyl-5-diglucosides, and 3-caffeoyl-5-diglucosides of cyanidin, delphinidin, peonidin, petunidin, and malvidin [8].



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Fig 1. *The chemical structures of some phenolic compounds*

Flavonoids. Flavonoids are find in grapes, especially in seeds, and principally contain (+)-catechins, (−)-epicatechin and procyanidin polymers [9].

Grapes contain flavonoids (4–5%), including kaempferol-3-O-glucosides, quercetin-3-Oglucosides, quercetin and myricetin [9] (Fig. 2).

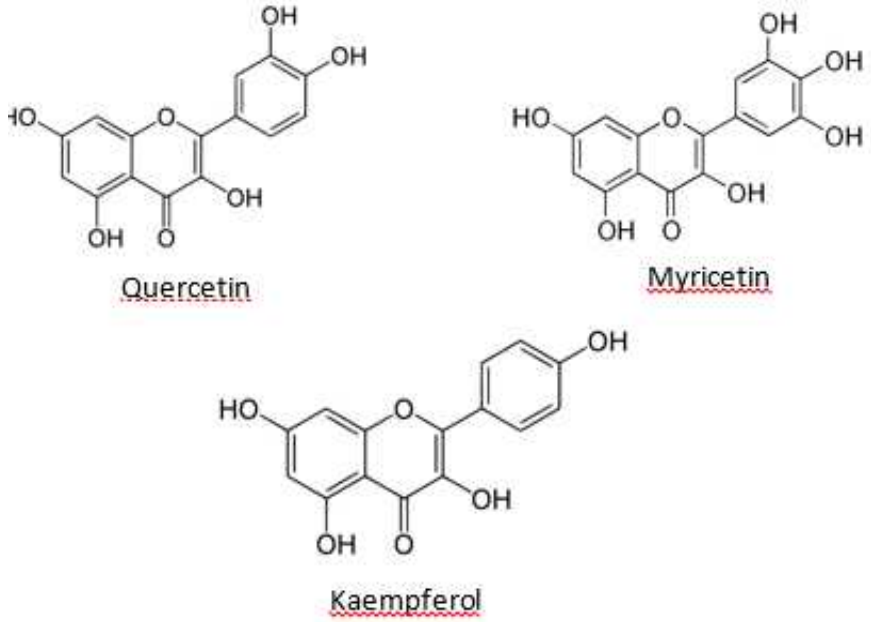


Fig 2. *Some flavonoids found in grape.*

Stilbene derivatives. Stilbenes (1, 2-diarylethenes) belong to non-flavonoid class of phenolic compounds. The resveratrol is present in two isomer forms, but only its *trans*-isomer has been identified in *Vitis vinifera* grapes [10, 11]. The concentration of *trans*-resveratrol (*trans*-3, 5, 40-trihydroxystilbene) in the skins of ripening grapes varied considerably, depending on the variety [12].

3. Bioactivity of Phenolic Compounds

The importance of polyphenols has been put into evidence by research undertaken by Gayon in 1964 [13]. There followed numerous studies, covering areas of health, food and cosmetics, highlighting the character of antioxidant phenolic compounds. Have been reported qualities inflammatory, anticancer and immuno-protective [14, 15]. These connections between the presence of phenolic antioxidants of grapes and beneficial effects on consumer health led to intense research to determine the parameters influencing their presence in different concentrations in grapes and wine [16].

Antioxidant activity. Phenolic compounds from grapes have more biological activities linking to human health benefits, such as antioxidant, cardio protective, anticancer, anti-inflammation, antiaging and antimicrobial properties. Experimental studies in the medical field, with the aim to clarify the mechanism of action of the polyphenols in general, have shown: chemoprevention and chemo protective effects both in vivo and in vitro [17, 18]; antioxidant effect, by protecting the cells from lipid peroxidation and induction of DNA damage by free radicals reagents [19]; anti-proliferative effect, the selective induction of apoptosis in tumor cell lines [20]; effects of combating of the invasion and metastasis by inhibiting the activity of metalloproteinases MMP [21]. Evaluation of the antioxidant capacity of different phenolic compounds extracted from grapes or grape different parts is done by several methods: oxygen radical absorbance capacity (ORAC), crocin bleaching assay (CBA), 1, 1-diphenyl-2-picryhidrazyl (DPPH), Trolox equivalent antioxidant capacity (TEAC), superoxide radical scavenging activity (SOD), hydroxyl radical averting capacity (HORAC) method and the ferric reducing antioxidant power (FRAP) assay [23]. Using these methods the values of antioxidant capacities were very different between the parties and grape seed extracts, indicating that some antioxidants in the extraction process is deteriorating (Table 1). High antioxidant capacity had seeds and grape pomace.

Cardioprotection action. Some of the potential mechanisms of preventing cardiovascular disease after consumption of grape polyphenols could be related to their antioxidant activity. Grape seed extract showed a protective activity against cardiovascular disease and myocardial infarction in rats [22]. It is considered that procyanidins may exert a protective effect against cardiovascular diseases [24]. In addition we also speak of the antithrombotic properties of these compounds [24, 25]. It seems that wine procyanidins are more

related to the protection of the thrombotic processes with atherosclerosis [26], reaching 50% reduction in the risk of such diseases, mainly due to the antithrombotic effects and antioxidant procyanidins [27].

Anticancer activities. Eating foods rich in polyphenolic shown to significantly reduce the incidence of breast, lung, prostate and gastrointestinal human cancer. Grape antioxidants have been shown to prevent carcinogenesis and progression of cancer through cell cycle arrest and apoptosis in cancer cells [29]. Also anti-inflammatory activity exerted by the antioxidants of grapes is believed to be associated with chemopreventive effects [28]. Preventive effect by dietary supplementation with grape juice, reduced lymphocyte DNA damage by reducing the formation of reactive oxygen species [30]. The beneficial effects of antioxidants on breast cancer were highlighted by altering estrogen receptor. Use of grape skin and seed extracts in preventing cancer has great potential, and further investigation is justified in this exciting field.

Anti-inflammation Activities. Different authors describe that procyanidins diet may have anti-inflammatory effect [24]. These have described a protective action against gastric ulcer and also in rats seems to be protect against gastric damage induced by alcohol [31]. Recio et al (1995) disclose that different quercetin glycosides they possess anti-inflammatory effects in mice with inflammation [35], while Sanchez de Medina et al (1996) experimenting with the anti-inflammatory effect of quercitrin [36]. It is believed that to have an anti-inflammatory effect, procyanidins should have a methoxy substitution position 5 and a methoxy or methyl substitution in position 7.

Antimicrobial Effects. Some researches showed that phenolic compounds from grapes have different antimicrobial effects [32, 33, 34]. The phenolic compounds of grapes displayed different antimicrobial effects. The grapes contain antimicrobial phytochemicals capable of suppressing oral pathogens associated with caries or periodontal diseases. Wu et al. (2009) showed in vitro study that fluoride treatment inhibited further demineralization of existed artificial root lesions and increased the microhardness value of lesions [32]. Treatment with grape seed extract was also found to increase the microhardness of the lesions compared with the untreated control group. Grape seed extract may be a potential adjunct or alternative to fluoride in the treatment of root caries during minimally invasive therapy [32].

4. Conclusions

Studies have shown an inverse association between the intake of grapes and grape products and mortality in age-related diseases such as coronary heart disease. Grapes and its main components anthocyanins, resveratrol and flavonoids have bioactivities: antioxidant, cardioprotective, anti-cancer, anti-inflammatory, antimicrobial activity and antiaging, which are closely linked to the prevention of diseases. These results suggest that the active compounds of the grapes should be studied in more detail to aid development as agents for the treatment of cardiovascular, gastrointestinal, and neurodegenerative diseases. This shows greater potential for grapes in the food and pharmaceutical applications.

The methods for extracting polyphenols from grapes should be improved in the future for getting as pure bioactive components and their use in medicine.

Is also, important to know the individual potential of some indigenous varieties, the lesser known, contributing to agro-biodiversity in the field of viticultural and the starting base for identifying natural sources rich in antioxidant substances.

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References

[1] Hashemi, J. M. (2014). Biomedical Effects of Grape Products. Middle-East Journal of Scientific Research, 21(12), 2222-2225.

[2] Ames, B. N., Shigenaga, M. K., & Hagen, T. M. (1993). Oxidants, antioxidants, and the degenerative diseases of aging. Proceedings of the National Academy of Sciences, 90 (17), 7915-7922.

[3] Lau, F.C., Shukitt-Hale, B. and Joseph, J. A. (2006). The beneficial effects of fruit polyphenols on juice on cognitive and motor deficits in aging. Nutrition 22, 295–302.

[4] Castillo-Muñoz, N., Gómez-Alonso, S., García-Romero, E., & Hermosín-Gutiérrez, I. (2007). Flavonol profiles of Vitis vinifera red grapes and their single-cultivar wines. Journal of agricultural and food chemistry, 55(3), 992-1002.

[5] Țârdea, C. 2007. Chimia și analiza vinului. Ion Ionescu de la Brad, Iași.

[6] Cotea, V. D., C. V. Zănoagă, and V. V. Cotea. 2009. Tratat de Oenochimie. Ed. Academiei Române, Bucureşti.

[7] Vinson, J.A. and A. Hontz-Barbara. 1995b. Phenol antioxidant index: comparative antioxidant effectives of red and white wines. Journal of Agric. Food Chemistry 43:401-403.

[8] Wang, H., Race, E. J., & Shrikhande, A. J. (2003). Characterization of anthocyanins in grape juices by ion trap liquid chromatography-mass spectrometry. Journal of Agricultural and Food Chemistry, 51(7), 1839-1844.

[9] Gruenwald J, Brendler BA, Jaenicke C. 2004. PDR for Herbal Medicines. 3rd ed. Thomson PDR: Montvale, NJ

[10] Jeandet, P., Bessis, R., & Gautheron, B. (1991). The production of resveratrol (3, 5, 4'-trihydroxystilbene) by grape berries in different developmental stages. American Journal of Enology and Viticulture, 42(1), 41-46.

[11] Vrhovsek, U., Wendelin, S., & Eder, R. (1997). Effects of various vinification techniques on the concentration of *cis*-and *trans*-resveratrol and resveratrol glucoside isomers in wine. American Journal of Enology and Viticulture, 48(2), 214-219.

[12] Okuda, T., & Yokotsuka, K. (1996). *Trans*-resveratrol concentrations in berry skins and wines from grapes grown in Japan. American Journal of Enology and Viticulture, 47(1), 93-99.

[13] Ribereau-Gayon, P. (1964) Les Composes Phenoliques du Raisin et du Vin, Institut Nationale de la Recherche Agronomique, Paris.

[14] Matito, C., Mastorakou, F., Centelles, J. J., Torres, J. L., & Cascante, M. (2003). Antiproliferative effect of antioxidant polyphenols from grape in murine Hepa-1c1c7. European Journal of Nutrition, 42(1), 43-49

[15] Mitjans, M., del Campo, J., Abajo, C., Martínez, V., Selga, A., Lozano, C., ... & Vinardell, M. P. (2004). Immunomodulatory activity of a new family of antioxidants obtained from grape polyphenols. Journal of agricultural and food chemistry, 52(24), 7297-7299.

[16] Kinsella, J. E., Frankel, E., German, B., & Kanner, J. (1993). Possible mechanisms for the protective role of antioxidants in wine and plant foods. Food Technology.

[17] Surh, Y. J. (2003). Cancer chemoprevention with dietary phytochemicals. Nature Reviews Cancer, 3(10), 768-780

[18] Radhakrishnan, S., Reddivari, L., Sclafani, R., Das, U. N., & Vanamala, J. (2011). Resveratrol potentiates grape seed extract induced human colon cancer cell apoptosis. Front Biosci (Elite Ed), 3, 1509-1523.

[19] Mittal, A., Elmets, C. A., & Katiyar, S. K. (2003). Dietary feeding of proanthocyanidins from grape seeds prevents photocarcinogenesis in SKH-1 hairless mice: relationship to decreased fat and lipid peroxidation. Carcinogenesis, 24(8), 1379-1388.

[20] Yi, W., Akoh, C. C., Fischer, J., & Krewer, G. (2006). Effects of phenolic compounds in blueberries and muscadine grapes on HepG2 cell viability and apoptosis. Food research international, 39(5), 628-638.

[21] La, V. D., Bergeron, C., Gafner, S., & Grenier, D. (2009). Grape seed extract suppresses lipopolysaccharide-induced matrix metalloproteinase (MMP) secretion by macrophages and inhibits human MMP-1 and-9 activities. Journal of periodontology, 80(11), 1875-1882.

[22] Bagchi, D., Bagchi, M., Stohs, S. J., Das, D. K., Ray, S. D., Kuszynski, C. A., ... & Pruess, H. G. (2000). Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. Toxicology, 148(2), 187-197.

[23] Alam, M. N., Bristi, N. J., & Rafiquzzaman, M. (2013). Review on in vivo and in vitro methods evaluation of antioxidant activity. Saudi Pharmaceutical Journal, 21(2), 143-152

[24] Cooper, J. S., Pajak, T. F., Forastiere, A. A., Jacobs, J., Campbell, B. H., Saxman, S. B., ... & Fu, K. K. (2004). Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. New England Journal of Medicine, 350(19), 1937-1944.

[25] Pignatelli, P., Pulcinelli, F. M., Celestini, A., Lenti, L., Ghiselli, A., Gazzaniga, P. P., & Violi, F. (2000). The flavonoids quercetin and catechin synergistically inhibit platelet function by antagonizing the intracellular production of hydrogen peroxide. The American journal of clinical nutrition, 72(5), 1150-1155.

[26] Hertog, M. G. (1996). Epidemiological evidence on potential health properties of flavonoids. Proceedings of the Nutrition society, 55(1B), 385-397.

[27] Hollman, P. C., Gaag, M. V., Mengelers, M. J., Van Trijp, J. M., De Vries, J. H., & Katan, M. B. (1996). Absorption and disposition kinetics of the dietary antioxidant quercetin in man. Free Radical Biology and Medicine, 21(5), 703-707.

[28] Hogan, S., Canning, C., Sun, S., Sun, X., & Zhou, K. (2010). Effects of grape pomace antioxidant extract on oxidative stress and inflammation in diet induced obese mice. Journal of agricultural and food chemistry, 58(21), 11250-11256.

[29] Aggarwal, B. B., Bhardwaj, A., Aggarwal, R. S., Seeram, N. P., Shishodia, S., & Takada, Y. (2004). Role

of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer research, 24(5A), 2783-2840.

[30] Park, Y. K., Park, E., Kim, J. S., & Kang, M. H. (2003). Daily grape juice consumption reduces oxidative DNA damage and plasma free radical levels in healthy Koreans. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 529(1), 77-86.

[31] Ares, J. J., Outt, P. E., Randall, J. L., Murray, P. D., Weisshaar, P. S., O'Brien, L. M., ... & Kelm, G. R. (1995). Synthesis and biological evaluation of substituted flavones as gastroprotective agents. Journal of medicinal chemistry, 38(25), 4937-4943.

[32] Wu, C. D. (2009). Grape Products and Oral Health. The Journal of Nutrition, 139(9), 1818–1823.

[33] Jung, H. J., Hwang, I. A., Sung, W. S., Kang, H., Kang, B. S., Seu, Y. B., Lee, D. G. (2005). Fungicidal effect of resveratrol on human infectious fungi. Arch. Pharm. Res. 2, 557–560

[34] Garcia-Alonso, J., Ros, G., Vidal-Guevara, M. L., Periago, M. J. (2006). Acute intake of phenolic-rich juice improves antioxidant status in healthy subjects. Nutr. Res., 26, 330–339.

[35] Recio, M. D. C., Giner, R. M., Manez, S., Gueho, J., Julien, H. R., Hostettmann, K., & Rios, J. L. (1995). Investigations on the steroidal anti-inflammatory activity of triterpenoids from Diospyros leucomelas. Planta medica, (61), 9-12.

[36] de Medina, F. S., Gálvez, J., Romero, J. A., & Zarzuelo, A. (1996). Effect of quercitrin on acute and chronic experimental colitis in the rat. Journal of Pharmacology and Experimental Therapeutics, 278(2), 771-779.