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Abstract

Heavy alcohol consumption is associated with increased overall mortality, cancer, liver, and cardiovascular diseases; but low doses of alcohol (up to one drink per day) are not associated with the risk of any cancer site with the exception of breast cancer and possibly of oral and pharyngeal cancers. Moreover, recent evidence indicates that moderate alcohol and specifically wine intake provides cardioprotection and neuroprotection and may increase longevity. Various experimental data hypothesize a potential cancer chemopreventive role of some grape extracts, and complete sequence of grapevine genome has revealed genes responsible for the synthesis of healthpromoting compounds (resveratrol and other polyphenols), thus advocating the development of future potential nutraceutical strategies. This focuses on the pros and cons of moderate alcohol and wine consumption and opens a debate on this topic.

Introduction

Heavy alcohol consumption is associated with an increased overall mortality, cardiomyopathy, hypertension, acute cerebrovascular events, liver diseases, and cancer (Baan et al., 2007; Rehm et al., 2009).

In particular, excessive alcohol consumption is associated with cancers of the mouth, pharynx, esophagus, and larynx (Doll et al., 1999). Acceptance of a causal relationship does not however, necessarily imply that ethanol is a complete carcinogen. There is no reason to suppose that tobacco smoke is the only carcinogenic agent to which the human upper respiratory and digestive tracts are exposed, as ethanol may even facilitate the effect of some other unrecognized carcinogenic agents in nonsmokers (Doll et al., 1999). Moreover, heavy alcohol consumption is commonly associated with poor nutrition and this increases the

cancer risk in heavy drinkers (D'Avanzo et al., 1997). Some cohort and case–control studies show a direct relationship between alcohol consumption and colorectal cancer (Fedirko et al., 2011). The relationship is moderate and a two-fold risk for both the colon and rectum cancer can be excluded, even with high levels of alcohol consumption (Fedirko et al., 2011).
Heavy alcohol consumption is also associated with primary liver cancer and pancreatic cancer (La Vecchia, 2007; Maisonneuve and Lowenfels, 2010). Even moderate alcohol consumption has been found to relate to breast cancer risk: this association could explain 12% of breast cancers in Italy (Ferraroni et al., 1998; Hamajima et al., 2002).
A fundamental role is played by the dose of alcohol intake. For instance, Islami et al. (2010) showed, in laryngeal cancer, that consumption versus nonconsumption of alcohol was associated with an approximately twofold increase in the risk of cancer [relative risk (RR)= 1.90; 95% confidence interval: 1.59–2.28], but light alcohol consumption (up to one drink/day) did not show any significant association with the risk of cancer (12 studies, RR=0.88; 95% confidence interval: 0.71 1.08).
Indeed, low doses of alcohol (up to one drink per day) are not associated with the risk of any cancer site, with the exception of breast cancer and possibly of oral and pharyngeal cancers (Hamajima et al., 2002; Tramacere et al., 2010).
Moreover, recent evidence suggests that moderate alcohol and specifically wine intake provides cardioprotection, particularly against coronary heart disease, (Corrao et al., 2004) as well as neuroprotection (Collins et al., 2009) and may increase longevity of life (Farchi et al., 2000; Doll et al., 2005).
Various experimental data suggest a potential cancer chemopreventive role of grape seed extracts and other grape products (Harikumar and Aggarwal, 2008; Nandakumar et al., 2008).
To evaluate the state of the art of these issues, the Italian Observatory for Conscious Wine Consumption, the European Cancer Prevention Organization, and the Oldways Organization (Boston, Massachusetts, USA), organized a workshop on 'The truth about wine', held in Grinzane Cavour (Italy) in February 2010. Three main topics were discussed: grapevine genomics, healthy components in grape berry and wine, and wine and human health.

Grapevine and human genomics, and the complexity of secondary metabolism

The complete sequence of the grapevine genome has revealed an unprecedented number of members in the gene families responsible for the synthesis of health- promoting compounds, compared with other plant species. For instance, there are 43 genes encoding stilbene synthesis, the key enzyme that controls the synthesis of resveratrol (Jaillon et al., 2007). Most of them are developmentally regulated at the onset of fruit ripening (Zenoni et al., 2010), and there is much expectation that these genes respond to different environments of cultivation and viticultural practices, in the view of further improving the nutraceutical value of grape products.
The concept of wine quality is continuously evolving, after the improvement of enological techniques and a better understanding of the chemistry of winemaking. The idea of quality has broadened with increasing attention paid to nutraceutical aspects. There exist ample variation in berry nutraceutical value among the most popular grapevine varieties, and the exploration of disgraced and abandoned varieties may reveal high nutraceutical producers.
The human genome has evolved adaptation to metabolize fermented plant materials. Therefore, consumption of low amounts of ethanol has been an integral component of human diet and is physiologically tolerated. Genetic control of human perception of compounds in food and beverages and genetic variability in human populations is being increasingly understood, but needs to be further investigated, as well as how wine compounds interact with each other and with pharmaceutical products and how they are metabolized (Wooding, 2006).

Grape, wine, and human health

The preventive effects of moderate wine consumption on various diseases are summarized in Table 1 (Ellison, 2002). Most of the advantages of wine over other beverages containing alcohol may relate to the biological responses to mainly resveratrol and proanthocyanidins, and to a lesser degree to other polyphenols (mostly present in red wine) including flavonols, monomeric flavan-3-ols, anthocyanins, as well as phenolic acids with antioxidant activity (Fig. 1).

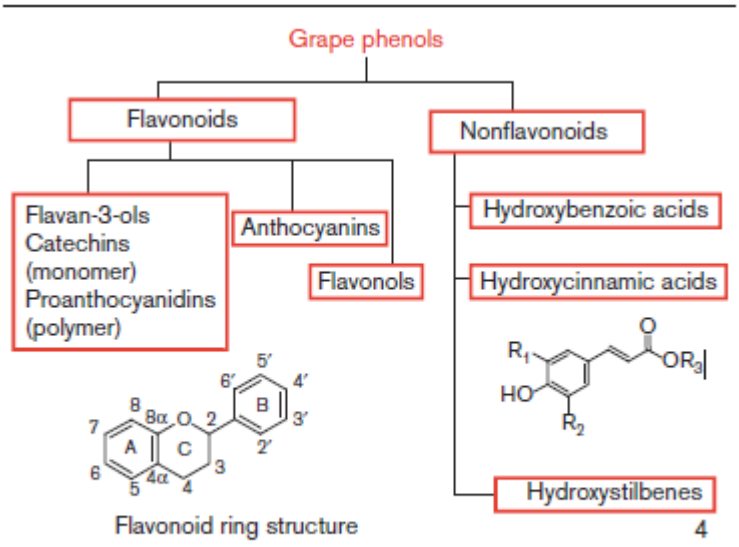
The phenolic substances are not only important com- pounds of defense against pathogens in grapevine but are also responsible for the color of red grapes and wines, oxidative browning of white wines, taste and astringency, and antioxidant action in human body.

Phenolic changes associated with winemaking begin with selective extraction of grape constituents into the must during crushing, maceration, pressing, and continues during wine aging. These phenomena are influenced by reactant concentrations, temperature, pH, ethanol, sulfur dioxide, and by the technological processes.

Table 1 Effects of moderate drinking on various diseases

Cardiovascular diseases (decreases risk of coronary heart disease, ischemic stroke, and peripheral vascular disease)
Metabolic diseases (decreases risk of diabetes, metabolic syndrome, and osteoporosis)
Cognitive disorders (decreases risk of Alzheimer's disease and other dementias) Obesity (emerging data suggest less weight gain over time for moderate drinkers)
Infectious diseases (decreases risk of gall bladder disease and many viral and bacterial diseases)
Cancer (high-alcohol intake increases risk of upper aerodigestive cancers, moderate intake increases risk of breast cancer and perhaps colorectal cancer, decreases risk of kidney and thyroid cancers and lymphomas)

Fig. 1



Grape phenols.

One of the most efficient antimicrobial grapevine phenolics, resveratrol, also appears of relevant importance for human health because it prevents or delays the onset of chronic diseases such as diabetes, inflammation, Alzheimer's disease, and cardiovascular disease;

moreover, it induces neuroprotection and inhibits proliferation of human cancer cell lines (Aggarwal et al., 2004; Baur and Sinclair, 2006; Das and Maulik, 2006; Vidavalur et al., 2006; Das and Das, 2007; Opie and Lecour, 2007; Harikumar and Aggarwal, 2008; Raval et al., 2008; Saiko et al., 2008).

The breadth of the therapeutic potential of resveratrol is shown by the extension of the lifespan and improved motor function in mice given resveratrol who were fed a high-calorie diet as shown by Baur et al. (2006). This study indicates new approaches for treating obesity- related diseases and the age-related diseases. This study shows that resveratrol produces changes associated with longer lifespan including increased insulin sensitivity, reduced insulin-like growth factor-1 levels, increased adenosine monophosphate-activated protein kinase, in- creased peroxisome proliferator-activated receptor-g coactivator 1 a (PGC-1a) activity, increased mitochon- drial number, and improved motor function.

Resveratrol is usually considered as an antioxidant, primarily by increasing nitric oxide bioavailability, but resveratrol can also exhibit prooxidant properties in the presence of transition metal ions such as copper, leading to oxidative breakage of cellular DNA (De la Lastra and Villegas, 2007). This prooxidant action could be the common mechanism for anticancer and chemopreventive properties of plant polyphenols. Resveratrol at lower doses (5 mg/kg) activates survival signals by upregulating the antiapoptotic and redox proteins, Akt and Bcl-2, whereas a higher dose of 25 mg/kg potentiates a death signal by downregulating redox proteins and upregulating proapop- totic proteins (Mukherjee et al., 2010) thus inducing hormetic dose–responses (Calabrese et al., 2010).

Many of the same compounds including resveratrol, cur- cumin, and epigallocatechin gallate, modulate the effects of deregulated cell cycle checkpoints, and this could con- tribute to the prevention of cancer (Meeran and Katiyar, 2008). Clinical trials with resveratrol in human cancers are needed, but none of them have been reported, although five trials on human cancers supported by National Institutes of Health are underway (Bishayee, 2009).

Wine catechins and proanthocyanidins also appear to be of relevant importance due to their ability to improve endothelial function, vascular tone, and platelet reactivity in vivo (Corder et al., 2006).

It is necessary to invest in research (study of the genetic basis of stilbene synthesis and interaction with the environment) to increase the production of resveratrol and other stilbenes in order to achieve a better production of grapes and wine in terms of health beneficial properties (Bavaresco et al., 2009). The recent progresses in grapevine genomics open the road for such a goal.

Grapevine genomics for the understanding of the mechanisms of production of neutracetical compounds in grapevine

The recent concern for the development of a more sustainable agriculture was translated in viticulture by two major goals: (i) drastically reduce the quantity of chemicals used in viticulture, which are mainly represented by fungicides and (ii) adapt the viticulture to global climatic changes (Bisson et al., 2002; Jones et al., 2005). These two goals have to be reached while maintaining a high quality of the grapevine production. One of the ‘bricks’ that will allow reaching these objectives is the use of grapevine genetic diversity including the creation of new varieties better adapted to these new conditions (Bisson et al., 2002; Duchene et al., 2010). The content in phenolic compounds of these new varieties will certainly be among the major traits to be improved because of their importance for wine quality and human health.

In this context, the scientific community has focused its efforts, during the last 10 years, to develop modern genomic tools for the deciphering of the molecular mechanisms underlying traits of interest and their regulation and for the development of efficient breeding programs

assisted by markers. The grapevine genome is now sequenced (Jaillon et al., 2007) and this resource as well as intermediate ones first allowed completing the ground knowledge on the gene families coding the proteins involved in the polyphenols biosynthetic path- way (Castellarin et al., 2006; Jaillon et al., 2007). In parallel, the accumulation of a wealth of information on the regulation of these metabolic pathways during berry development (Terrier et al., 2005; Bogs et al., 2007; Deluc et al., 2007; Cutanda-Perez et al., 2009; Terrier et al., 2009; Zamboni et al., 2010; Zenoni et al., 2010), in relation to environmental stresses (Cramer et al., 2007; Pilati et al., 2007; Castellarin et al., 2007a, 2007b) and to genetic diversity (Vincent et al., 2007; Samuelian et al., 2009) is now well advanced. This already guides genetic studies for the content in phenolic compounds (Fournier-Level et al., 2009) and the understandings of the links between the functioning of these pathways and wine quality (Conde et al., 2007).

Public health implications

Taking into account the favorable and unfavorable effects of alcohol on health, a sensible individual advice should be given for recommended limits to alcohol consumption. National guidelines often state that alcohol intake for men should not exceed 30 g of ethanol per day (i.e. approximately two drinks of beer, wine, or spirits a day, including with meals) and 15 g per day for women (La Vecchia, 1995).

Wine is an important component of the Mediterranean diet, and may be responsible for part of the reduced incidence of cardiovascular diseases in these countries (La Vecchia, 1995). Alcohol consumption including wine, has substantially declined in Italy and other Mediterra- nean countries over the last three decades, a decrease that may relate to the simultaneous decrease in mortality rates for hepatic cirrhosis that has also occurred in these countries (Bosetti et al., 2007).

Total alcohol-related deaths (liver disease, cancer, and car accidents) were estimated in the 1990s at approximately 25 000 per year in Italy (5% of all deaths), and over 50 000 (10% of all deaths) in France and now these estimates are approximately 50% lower, due to the substantial (over 50%) fall in alcohol consumption (La Vecchia, 1995; Bosetti et al., 2007; Boffetta et al., 2009).

In contrast, in moderate wine drinkers there are substantial advantages incardiovascular disease and coro- nary heart disease mortality. Thus, the total balance is open to discussion because a vast number of studies have evaluated the relation between alcohol consumption and total mortality, and numerous reviews and meta-analyses have tried to summarize the results. In most studies the relation between alcohol consumption and mortality is a 'J-shaped curve' showing a maximum protective effect at 20 g of average pure alcohol intake per day: the RR = 1 line, equivalent to abstainers' risk, is crossed at 72 g average intake and there is a significant detrimental effect after 89 g of average intake per day (Rehm et al., 2003).

In addition, there is a pronounced sex effect showing that women have less favorable effects at the same level of consumption, and an earlier upturn of the curve.

Wine intake may have a beneficial effect on all-cause mortality, that is, additive to that of alcohol as shown by the Copenhagen Prospective Population Studies (Grønbaek et al., 2000). In the Italian Rural Cohort Seven Countries Study, the relationship between life expec- tancy and alcohol consumption (97% wine in this cohort and mostly red wine) is nonlinear. Men aged between 45 and 64 years at their entry in the cohort study who consumed five drinks per day, showed a longer life expectancy than occasional and heavy drinkers (Farchi et al., 2000).

Consensus statement

The Grinzane Cavour workshop developed a consensus statement for the public, the media, and the governments on the basis of 10 items:

(1) Wine has been a part of human life throughout recorded history;

(2) Wine is increasingly enjoyed by a large number of cultures;

(3) Wine is a component of the Mediterranean diet;

(4) Wine is a natural product obtained from the fermentation of crushed grapes, and its components include many health-promoting bioactive com- pounds, especially polyphenols such as resveratrol, anthocyanins, and tannins.

(5) These substances contribute to flavor and sensorial qualities, and make each wine unique and the ideal complement to food;

(6) In recent decades scientific research has shown that moderate wine consumption has significant health benefits, especially in promoting longevity and reducing the risks of most of the age-related diseases. These include coronary heart disease, stroke, dementia, and diabetes;

(7) The mechanisms responsible for the beneficial health effects include the antioxidant and anti- inflammatory activities of a large number of bioactive components, as well as favorable impacts on coagula- tion, blood lipids, and endothelial function;

(8) The alcohol derived from the fermentation of grapes, together with these bioactive components, has favorable health effects when wine is consumed in a moderate pattern, but has detrimental health effects when consumed excessively or inappropri- ately;

(9) Governments and private institutions should (i) support research on the effect of moderate con- sumption of wine on health and (ii) promote consumer educational programs about moderate consumption of wine;

(10) These educational programs should help prevent alcohol abuse, particularly for young people. These programs should include information on: (i) the individual variability in tolerating alcohol; (ii) the dangers of alcohol misuse, including binge con- sumption; (iii) the increased risk of injuries from driving, when the legal consumption limits are exceeded, and (iv) the favorable effects of regular and moderate wine consumption, as part of the daily diet, and in conjunction with other aspects of a healthy lifestyle.

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