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# AN OVERVIEW OF THE IMPLICATIONS OF WINE ON HUMAN HEALTH, WITH SPECIAL CONSIDERATION OF THE WINE-DERIVED PHENOLIC COMPOUNDS

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***Abstract***

*Following an ever-increasing tendency to underline the detrimental effects of alcoholic beverages on human health, wine consumption has also recorded a steady decrease. This is despite multiple beneficial effects on health demonstrated by research. This review presents the latest information regarding the effects of wine on human health. While the potential detrimental effect of alcohol is not disregarded, but acknowledged where science clearly demonstrated a negative impact, potential beneficial effects are also presented and discussed. Aside from alcohol, wine contains other compounds which have been shown to serve as antioxidants and anti-blood clotting agents or metabolic signaling molecules, with anti-proliferative, chemoprotective, immunomodulating actions. Accordingly, light to moderate but not heavy wine consumption can complement other dietary effects on human health. Recent research suggests that wine-derived compounds belonging to the phenolic compound classes are important to human health and some of their putative actions are presented in this review.*

***Key words***: *wine, human health, alcohol, phenolic compounds, polyphenols.*

## INTRODUCTION

Wine is an important component of the Mediteranian diet, which means it plays an important role in the protective effect of this diet for human health (Ndlovu et al., 2019). Observational studies, randomized clinical trials and meta-analysis of clinical studies have often demonstrated that wine can lower the risk of developing chronic illnesses and, if not to increase longevity, at least to ensure a longer period of healthy life. Nevertheless, since personal factors – genetic and/or environmental – can also play their part, these effects can vary greatly on personal level and are difficult to be proven and validated for the entire population.

Therefore, it is not surprising that, after a long period of favourable advertising for the implications of red wine for human health, in recent years, due to the sustained anti-alcohol campaigns, the perception regarding wine has started to be affected as well.

Still, unlike beer and spirits, wine is one of the generally recognized components of a healthy diet and lifestyle (Gell and Meier, 2011). For this reason, among health-conscious individuals, wine has remained a popular alcoholic beverage, and especially red wine. Accordingly, a study regarding food buying habits in Denmark concluded that wine consumers are more likely to purchase and consume healthier foods, such as fruits and vegetables, olives, poultry, low fat products, while beer consumers favour precooked/take away food, sugars, cold cuts, chips, pork, sausages, lamb, butter or margarine and soft drinks (Johansen et al., 2006).

### *J-shaped curve and the "French Paradox"*

The rise in awareness about the potential beneficial health effects of wine started with a study which suggested that the rate of mortality from coronary heart disease in France was lower than that of many other countries; this was despite the French traditionally having a high saturated fat diet. This phenomenon was duly called the *"French Paradox"* (Renaud and De Lorgeril, 1992), where most benefit was seen with alcohol consumption of 20-30 g/day.

With clinical and experimental evidence growing, it also became accepted that the risk of mortality from all causes (all-cause mortality) was substantially increased for heavy drinkers, while decreased for light to moderate drinkers compared to both heavy drinkers and abstainers. This relationship is pictorially expressed as a J-shaped curve. It is particularly seen for middle-aged and older adults, associated with both better survival rates and lower risks for certain chronic diseases.

Another well-known study related to the effects of alcohol on human health is the US "Leisure World Cohort Study". The study included 8,877 women and 5,101 men (median age 74 years) who completed a postal health survey in the early 1980s and were thereafter followed for 23 years (1981 to 2004). The initial questionnaire and the follow-ups in 1992 and 1998 included details of their alcohol consumption. When the study was completed in 2007 (Paganini-Hill et al., 2007), 6,930 women and 4,456 men had died at a median age of 87 years. This study, however, showed that both men and women who drank alcohol had a decreased mortality rate compared with abstainers. By using adjustments for age and multivariate risks of death and by calculating 95% confidence intervals, it was concluded that individuals consuming two or more alcoholic drinks per day had a risk of death lower by 14 to 16%. The study tried to take into account the type of alcoholic beverage, and thus consumption of alcoholic beverages was quantified separately for wine, beer and spirits. The observed reduced risk was not correlated, however, to one specific type of alcohol beverage, but with overall alcohol consumption. Consistent drinkers, who consumed alcohol at the beginning of the study as well as in follow-up years, had a significantly decreased risk of death compared with stable abstainers. Moreover, those who did not report drinking in the beginning of the study, but reported drinking later in the study also had a significantly decreased risk of death. Quitters, especially women, who reported drinking in the beginning of the study, but were not drinking at follow-ups, showed an increased risk of death. The 15% reduced risk of death observed in this study was similar to the 20% lower risk observed in the European project HALE, which followed for 10 years women and men aged 70 to 90 years (Knoops et al., 2004). Similar results were provided by other studies showing that overall death rates were lowest in those who consumed one alcoholic drink daily (Thun et al., 1997).

Some study data, however, suggests that the reduction in mortality risk associated with alcohol is more evident from wine consumption, than from beer or spirits. A study performed in California on 128,934 adults monitored between 1978-1985 (Klatsky et al., 2003) confirmed that the J-shaped relationship was valid and remained stable for at least 20 years. The study suggested that lower risk associated with light drinking was primarily associated with wine consumption, as well as independent of the type of wine. The study also showed that wine consumption was independently associated with lower mortality risk, mostly due to beneficial effects on coronary atery disease risk.

Subsequently, the French Paradox has been variously attributed to the effect of certain phenolic compounds abundant in wine acting in conjunction with the alcohol component of wine (Siemann et al., 1992; Ferrieres, 2004; Fei et al., 2018).

*Moderation*

In many although not all countries, "moderate wine consumption" is defined as 2 unit drinks a day for women and 2 to 3 unit drinks a day for men, and never more than 4 unit drinks at a time. A standard drink unit contains an average of 10 g of pure alcohol, irrespective of the type of drink. This would be around 100 ml (96 ml) of wine at 13% vol, 100 ml (104 ml) of sparkling wine at 12% vol, 60 ml (62.5 ml) of fortified wine at 20% vol or 85 ml (83.5 ml) of aromatised wine at 15% vol (Wine in Moderation, 2019; Mongan and Long, 2015).

*Recommendations*

Continuously confronted with the adverse societal, health and economic effects of alcohol abuse, the World Health Organization (WHO) has increased its campaigns against alcohol consumption, although predominantly heavier alcohol consumption. In addition, the robustness of the J-shaped alcohol mortality curve has been questioned. Recent findings from the Global Burden of Diseases, Injuries and Risk Factors Study (2016) led the invetigators to conclude that there is no safe level where alcohol does not cause adverse effects on human health (***GBD, 2016; Alcohol Collaborators, 2018). The study reported the cases of deaths and disabilities attributable to alcohol from 1990 to 2016 for 195 locations, for both sexes and for 5-year age groups between 15 and 95 years old. Among the population aged 15-49 years, alcohol use was found to lead in 2016, 3.8% (95% CI 3.2-4.3) of female deaths and 12.2% (CI 10.8-13.6) of male deaths and 2.3% (CI 2.0–2.6) female and 8.9% (CI 7.8-9.9) male disabilities, including here road and self-harm injuries. For populations aged 50 years and older, the leading cause of alcohol-attributable deaths in 2016 was cancer: 27.1% (95% CI 21.2-33.3) for female deaths and 18.9% (CI 15.3-22.6) for male deaths. While these facts cannot be disregarded, the conclusion of the report, that "the level of alcohol consumption that minimised harm across health outcomes was zero (95% CI 0.0-0.8) standard drinks per week", was not sufficiently supported by the presented data and did not take into account the types of beverages consumed.

Regarding alcohol consumption and cancer, study conclusions and recommendations are even more conservative. Among their 12 recommendations to reduce the risk of cancer, the European Code Against Cancer, which is supported by the WHO, suggests avoidance of any consumption of any type of alcoholic beverage (European Code Against Cancer, 2016). As the effect of the alcohol component of wine cannot be separated from the effects of other wine components that may also be beneficial for health, more studies are necessary to determine the effects of the combined and individual wine-derived compounds compared with the alcohol component. Most likely, the effects of the alcohol and other wine components are synergistic on health.

Even so it has been suggested that for older individuals, the calculations made in comparison with abstainers could be biased, as those already affected by diseases have usually ceased consuming alcoholic beverages, including wine (Fillmore et al., 2007). A US survey subsequently showed that wine consumers with better health were more likely to indicate that they consume wine to benefit their health than those with worse health (Higgins and Llanos, 2015).

This review provides an update of published information regarding the effects of wine consumption on human health, principally all-cause morality, cardiovascular disease and cancers, which are the two main causes of death in the developed world and their incidence is increasing in developing countries.

## MATERIALS AND METHODS

A search for relevant research papers and reviews was performed on several scientific literature databases, such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Science Direct, Google Scholar and Scopus.

The search focused on wine and alcohol exposure, chronic diseases, and wine-derived several phenolic compounds. The search terms used for the relevant paper selection were the following: "alcohol", "wine", "mortality", "chronic diseases", "diabetes", "cardiovascular disease", "cancer", "inflammation", "cognitive function", "microbiota", "biological markers", "polyphenols", "resveratrol", "flavonoids", "quercetin", "flavan-3-ols", "anthocyanidins", "antocyanins", "proanthocyanidins".

The selected papers were basic studies, clinical studies, experimental models, observational reports, relevant reviews, preferably with clearly calculated hazard ratios and their corresponding confidence intervals. Priority was given to more recent original articles and systematic reviews, mostly published in the past ten years. The number of publications has increased greatly from one year to another, due to the importance given to wine related phenolic compounds, as well as wine consumption in general.

## RESULTS AND DISCUSSIONS

### 1. Relationship between alcohol consumption and human health

A comprehensive review of the effects of alcoholic beverage consumption on human health (Poli et al., 2013) restated the J-shaped relationship between risk of cardiovascular diseases and alcohol consumption, but also found beneficial health effects for other chronic conditions associated with low to moderate alcohol consumption (Figure 1). Adverse health effects were observed, however, following binge drinking (Figure 2) and heavier alcohol consumption (Figure 3).

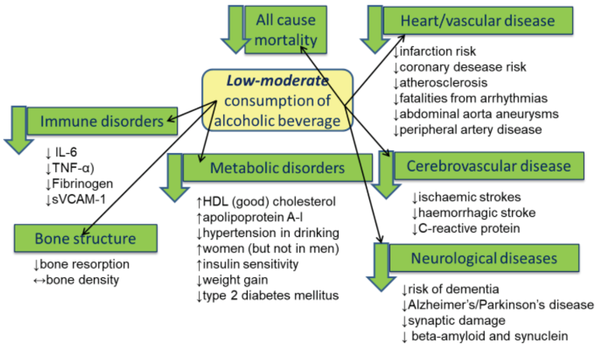


Figure 1. Health conditions and biomarkers associated with low to moderate alcohol consumption

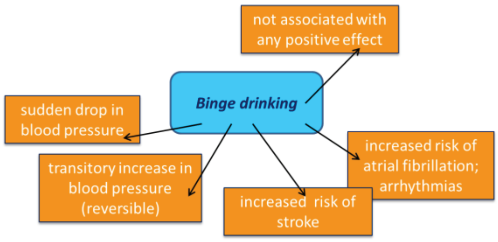


Figure 2. Health conditions associated with binge drinking

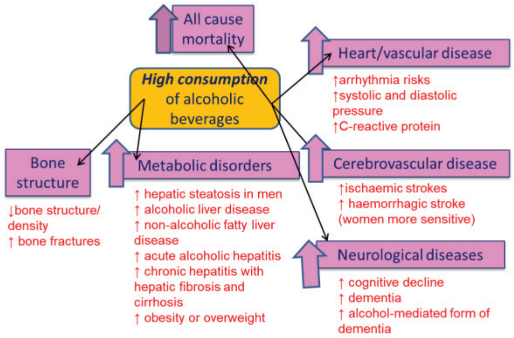


Figure 3. Health conditions and biomarkers associated with heavier alcohol consumption

### 1.1. *Cardiovacular diseases and all-cause mortality*

A 2018 study, which combined large-scale data sources of 83 prospective studies in 19 high income countries, determined dose-response associations and calculated hazard ratios (HRs) for consumption levels of 100 g per week, 100 to 200 g/week and 200 to 350 g/week alcohol. The study focused on the effect of alcohol consumption on all-cause mortality and several types of cardiovascular disease for a number of 599,912 current drinkers. Data were adjusted for age, sex, smoking and diabetes and they showed that the level of alcohol consumption was indeed associated with the all-cause mortality. The minimum mortality risk was approximately or below 100 g per week, a level that is lower than the doses recommended in most guidelines. Except for a slight protection conferred by the dose of 100 g/week for myocardial infarction (HR 0.94, 95% CI 0.91-0.97), for other types of cardiovascular diseases the risk was slightly higher: heart failure 1.09 (95% CI 1.03-1.15); aortic aneurysm 1.15 (CI 1.03-1.28); risk of stroke 1.14 (CI 1.10-1.17); fatal hypertensive disease 1.24 (CI 1.15-1.33) (Wood et al., 2018).

As for cardiovascular disease per se, the beneficial effects of moderate alcohol consumption in reducing risk of, and dying from, have been demonstrated in innumerable studies over the past three decades. Compared with abstainers, moderate alcohol consumers have decreased risk of cardiovascular disease in all age groups, in both men and women, irrespective of ethnicity, but the most benefit is seen for middle-aged and older adults, when risk factors for cardiovascular disease increase.

A study of 192,067 women and 74,919 men from Europe and North America, all healthy at the baseline, showed that hazard ratios among moderately drinking men (5.0 to 29.9 g/day) aged 39-50, 50-59, and 60+ years were 0.58 (95% CI 0.36-0.93), 0.72 (CI 0.60-0.86), and 0.85 (CI 0.75-0.97) compared with abstainers. However, the analyses indicated a smaller incidence rate difference (IRD) between abstainers and moderate consumers in younger adults (IRD = 45 per 100,000; 90% C.I. 8 to 84), than in middle-aged (IRD = 64 per 100,000; 90% CI 24-102) and older adults (IRD = 89 per 100,000; 90% CI 44-140). Similar results were observed in women. The incidence rates of cardiovascular diseases among female abstainers in the three age groups were 11 (95% CI 1-109), 41 (CI 1-400), 103 (CI 9-1018) per 100,000, respectively. In male abstainers, the incidence rates were 114 (95% CI 77-171), 262 (CI 201-343) and 454 (CI 354-553) per 100,000 for the three age groups, respectively. In all age groups, and in both men and women, the incidence rate was lower among participants consuming low to moderate alcohol compared with abstainers. In women, the incidence rate differences between drinking 0 g/day and 5.0-29.9 g/day were 3 (90% CI 1-25), 16 (CI 0-111) and 35 (CI 0-250). For men, corresponding incidence rate differences were 45 (90% CI 8-84), 64 (CI 24-102) and 89 (CI 44-140) per 100,000 (Hvidtfeldt et al., 2010).

1.2. *Cancer*

Less clear cut is the relationship between alcohol consumption and cancer, although there have been a significant number of studies published. Some of these have shown an increase in the incidence of some but not all types of cancers among alcohol consumers. Associations with alcohol consumption, and even low and moderate amounts, are found for liver cancer, oral and pharyngeal cancer, oesophageal squamous cell carcinoma and breast cancer (Poli et al., 2013).

A 1997, US study suggested (Thun et al., 1997) that mortality from breast cancer was 30% higher (1.3 relative risk; 95% CI 1.1-1.6) among women reporting at least one drink daily than among abstainers. However, taking into account the specific tumor characteristics, another study performed between 1993-2001 showed that alcohol consumption was not associated with all breast cancer subtypes (Falk et al., 2014). Significant hazard ratios (HR) were observed especially for hormone receptor-positive tumors, such as estrogen receptor–positive (ER+) and progesteron receptor–positive (PR+) cancers. Hazard ratios for women consuming one or more drinks per day versus non-drinkers were: 1.48 (95% CI 1.19-1.83) for ER+ cancer; 1.64 (CI 1.31-2.06) for PR+ cancer; 1.63 (CI 1.30-2.05) for ER+/PR+ cancer; and 2.51 (CI 1.20-5.24) for mixed ductal/lobular cancer. Similar results were presented in 2009 in a study of 184,418 postmenopausal women aged 50–71 years in the National Institute of Health-AARP Diet and Health Study conducted between 1995-2003 (Lew et al., 2009).

For men, consuming more than 3 drinks daily showed a small increase in the risk of non-advanced prostate cancer, risk which increases with the alcohol consumption: HR 1.06 for men consuming up to 3 drinks daily, compared with abstainers, HT 1.19 for men consuming 3-6 drinks daily and HR 1.25 in case of more than 6 drinks daily (Watters et al., 2010).

In 2016, after reviewing 89 international studies and a total of 17.5 million individuals, of which approximately 77,000 were stomach cancer patients, the American Cancer Society warned (ACS, 2016) that consuming 3 or more alcoholic drinks a day may increase the risk of cancer of the lower stomach.

To give another example, a study conducted between 1993 and 2013 calculated, by applying a Multivariate Cox regression model, that the relative risk to develop a colon cancer is increased to 1.16 for men consuming 15 g of alcohol/day and 1.28 for men consuming 30 g of alcohol/day, and is slightly less for women, the hazard rate being 1.06 for women 15 g alcohol/day and 1.15 for women consuming 30 g alcohol/day. This predisposition is higher in the case of individuals with a BMI under 25, especially when dietary folate and fibre intake are low. Surprisingly, this relative risk increase was higher in the case of beer and wine consumption than for stronger alcoholic beverages. Interesting as well was the fact that the association was higher for left colon and rectum tumors, as compared to the right colon ones (Park et al., 2018). A Japanese study also (Mizoue et al., 2008) showed that consumption of more than 23 g/day of alcohol may increase the risk for men of developing both colon and the rectum cancers (HR of 1.42, 1.95, 2.15, 2.96 respectively for groups of consumers drinking 23-45.9 g/day, 46-68.9 g/day, 69-91.9 g/day and >= 92 g/day).

Conversely, for some other types of cancer, such as lung, pancreatic and colorectal cancers, no overall association has been observed with moderate alcohol consumption. Some cancers, such as kidney cancer and non-Hodgkin lymphoma, were actually found to be inversely associated to low or moderate alcohol consumption, in other words the risk was higher for abstainers, suggesting a protective effect conferred by alcohol. Laryngeal cancer was also associated only with heavy drinking (Poli et al., 2013).

In addition, for head and neck cancers, wine has been shown to not increase risk compared with other types of alcoholic beverages (Purdue et al., 2009). In a meta-analysis of 15 controlled studies, independently assessing the association of beer, wine and liquor consumption with these cancers, only for moderate wine drinkers was no increase in risk observed. The data also showed that the relative risks of head and neck cancer for beer and liquor are comparable (HR 1.6-5.4 for beer, 1.6-3.6 for liquor), with direct correlation with the quantity consumed. Relative risks also increased for heavier wine consumption, however, comparable to that of the other types of alcoholic beverages.

A recent study (Chen et al., 2018) attempted to elucidate the effect of wine and its components on cancer cells, *in vitro* and *in vivo*. The study showed that alcohol can promote cell proliferation, as well as tumor formation by increasing the transcription of a specific gene, RNA Pol III. The effect is higher at a low alcohol concentration (12.5 to 25 mM), which enhanced cell proliferation of breast and esophageal cancer lines. Surprisingly, a higher alcohol concentration (100 mM to 200 mM) slightly decreased the proliferation rates. Moreover, red wines significantly repressed cell proliferation of different human cancer lines, in a dose-dependent manner, by reducing the RNA Pol III gene transcription. Red wine also inhibited colony formation of human breast cancer and esophageal carcinoma cells. Even more interesting is the reported stronger inhibitory effect of aged wines compared with younger wines. Thus, the study suggests that phenolic compounds may be inhibitory, in contrast to the alcohol component of wine.

Moderation is key. A USA study (White et al., 2017), performed on women who had a sister with breast cancer, showed that even in low-level drinkers (< 60 drinks/year), hazard ratios increased for every binge drinking (HR = 1.29, 95% CI 1.15-1.45) or blacking out (HR = 1.39, CI 1.17-1.64). Compared with low-level drinkers who never binged, moderate drinkers (60-229 drinks/year) who binged had a higher risk (HR = 1.25, CI 1.08-1.44). Increased breast cancer risk was observed for higher lifetime alcohol drinkers, with more than 230 drinks/year (HR = 1.35, CI 1.15-1.58).

An individual's response to alcohol, however, depends on their genetic profile. By exposure to predisposing factors (external or internal) the genetic material, DNA, can be damaged. In normal, young persons, efficient mechanisms are in place to repare some of the damage. However, with age and in case of some of genetic deficiencies, damaged DNA tends to accumulate in the cells, increasing the risks of leukemia or other cancers. From the alcoholic beverages, the main aggressor is not alcohol itself, but one of its metabolites, the acetaldehyde, a known and recognized carcinogen. Produced during the transformation of ethanol to acetic acid, when the ethanol quantity is higher than the capacity of the organism to completely metabolize it, acetaldehyde accumulates in the cells and, due to its higher reactivity, cross-links the DNA, damaging it.

In case of persons deficient in one of the enzymes involved in the transformation of acetaldehyde in acetic acid (the enzyme ALDH, acetaldehyde-dehydrogenase), acetaldehyde accumulates in even higher quantities (Shrotriya et al., 2015). The toxicity of the acetaldehyde is thus dependent on its rate of accumulation and also on each person's capacity to repair DNA.

It is also known that genetic polymorphisms of alcohol dehydrogenase and of the other genes implicated in free radicals generation and/or scavenging determine the susceptibility to alcoholic liver disease (Ratziu et al., 2010).

In wine, the presence of phenolic compounds may block or counteract the carcinogenic effect of acetaldehyde and alcohol. It was demonstrated that resveratrol induces the death (apoptosis) of the cells in which damaged DNA accumulates and is beyond repair (Shrotriya et al., 2015).

## 2. Phenolic compounds may be key to many of the beneficial health effect of wines

As opposed to strong distilled alcoholic beverages, wine is a more complex matrix, with a more balanced chemical composition, which, aside of ethanol, includes acids, polyphenols, glucides, proteins and several classes of aroma compounds, in various concentrations.

### 2.1. *Wine-derived phenolic compounds*

The phenolic content of white wine ranges from 50 to 400 mg/l and that of red wines from 900 up to 3000 mg/l for highly tannic wines (Waterhouse, 2002), the variation being determined by grape variety, growth region conditions, winemaking techniques and the age of the wine. Grape seeds contain much higher

quantities of total polyphenols in comparison with the skin. About 60-70% of the grape polyphenols, containing especially phenolic acids, flavonols, flavan-3-ols such as catechins and their isomers, proanthocyanidins and the stilbene resveratrol are found in seeds, thus also in grape seed extracts (Nowshehri et al., 2015).
The phenolic content of wine significantly varies with the grape variety and winemaking technology, thus the values reported in several journal also vary, although they do convey a general idea about the degree of magnitude. For example, a study of 2015 reported that in red wines the average concentrations of caffeic acid, gallic acid, resveratrol, and rutin were 2.15, 30.17, 0.59 and 2.47 mg/L, respectively, while in the white wine samples the concentrations were below limit of the HPLC method (Agatonovic-Kustrin et al., 2015).
Gallic acid is the most abundant simple phenol in wines and it is transferred easily in wines from grapes. For example, in Negroamaro and Primitivo wines its level was of about 28-29 mg/kg (Ragusa et al., 2019). The concentration of the catechin isomers in red wine was reported in a study to be in the range of 20-200 μM for (-)-epicatechin and 200-500 μM (+)-catechin (Burns et al., 2000).
The concentration of resveratrol, the most reserched wine-related phenol, varies considerably with the grape variety, region, weather, disease pressure, winemaking technique etc. The range is from non-detectable to 14.9 mg/l (Stervbo et al., 2007), but those upper limits are rather the exception, not the norm. Usually, the normal level does not exceed 2 mg/l. For example, in Serbian wines, *trans*-resveratrol concentration ranged from 0.11 to 1.69 mg/l and *cis*-resveratrol from 0.12 to 1.49 mg/l (Dekic et al., 2008). In Greek red wines *trans*-resveratrol ranged from 0.35 to 1.99 mg/l and from 0.005-0.57 mg/l in white varieties (Gerogiannaki-Christopoulou et al., 2006). Some studies reported that wines from grapes of the Pinot Noir and St. Laurent showed the highest level of *trans*-resveratrol (Stervbo et al., 2007), other that Cabernet and Shiraz (Agatonovic-Kustrin et al., 2015). Oligomers of stilbens, such as pallidol (resveratrol dimers) (He et al., 2009) viniferins (resveratrol dimers, trimers or tetramers) and vitisins (tertramers) are also found in grapes and wines. In French wines viniferin was found only in red and botrytized sweet white wines, ranging from 0.1 and 1.63 mg/l. Levels of pallidol from 0.38 to 2.22 mg/l were found only in wines obtained by maceration in the presence of stems (Landrault et al., 2002). Other phenolic compounds, such as tyrosol and hydroxytyrosol, present in wine and virgin olive oil, may play a role in prevention of certain pathologies including cancer (Rodriguez-Morato et al., 2016).
Although wine-derived phenolic compounds belong to several chemical classes and their structure is strictly related to their biochemical and physiological effect, the scientific community generally agrees that the higher the concentration of total phenolic compounds, the greater the potential beneficial effect on human health.
Many researchers have concentrated their efforts toward showing that the presence of phenolic compounds in wines can counter-balance the possible negative impact of the alcohol component. Although wine consumption has been shown to exert a J-shaped effect on the relative risk of cardiovascular disease (Arranz et al., 2012; Costanzo et al., 2011), the degree to which this putative protection is conferred by the alcohol component, wine-derived phenolic compounds or both remains to be clarified. Considering hypertension specifically, a double blind interventional study in 2015 (Draijer et al., 2015) showed that alcohol-free red wine extract intake lowered significantly 24-hour ambulatory systolic/diastolic BPs (135.9 ± 1.3/84.7 ± 0.8 mmHg) in mildly hypertensive people compared to placebo (138.9 ± 1.3/86.6 ± 1.2 mmHg), although grape-extract did not have a similar effect, possibly because the polyphenolic composition differed in grape-extract and in wine-extract due to the maceration process of the grape seeds in the latter.

2.2. *Specific phenolic compounds*

The phenolic components of grapes and wine are numerous, some belonging to non-flavonoid classes of compounds (i.e. hydroxycinnamates, hydroxybenzoates and stilbenes), but most of them belong to flavonoid classes, with a C6-C3-C6 skeleton, consisting of two phenyl rings and a heterocyclic ring (Del Rio et al., 2013). Flavonoids of grapes and wines are represented by flavonols, flavones, flavanones, flavan-3-ols and anthocyanins. Proanthocyanidins are oligomers of catechine, epicatechine (flavan-3-ols) esterified with gallic acid. Proanthocyanidins with larger molecules (polymers of these flavan-3-ols) are commonly named tannins.

The proanthocyanidins adsorption in the gut is variable, in direct connection to their molecular size/polymerization degree (Ou and Gu, 2014). As compared to (-)-epicatechin, the absorption rate of proanthocyanidin dimers is only 5-10%; trimers and tetramers have even lower absorption rates, while proanthocyanidin with higher polymerization rates are not absorbable anymore. Moreover, these proanthocyanidins do not depolymerize in the gastrointestinal tract, to have a direct effect on human health. However, athough proanthocyanidins are not absorbed in the intestine, they are metabolized by the gut microbiota. The proanthocyanidins are known to reduce glucose metabolism and lower the caloric impact of foods (Amoako and Awika, 2016), while their capacity to bind with proteins can lower the content of absorbed gluten, with a benefit for those with gluten sensitivity (Dias et al., 2015).

Anthocyanins too are relatively stable, with only a small portion being hydrolyzed. Although they can also be absorbed in the stomach, the intestinal epithelium is the main site for their absorption, either as such or as degraded products, the later having also their share of beneficial effects on health. (Han et al., 2019). Although studies on anthocyanins alone are fewer than for total or other individual flavonoids, they have started to attract more and more attention (Cassidy, 2018). Jennings team showed in 2014 (Jennings et al., 2014) that high habitual anthocyanin intakes (35 mg) resulted in a 0.7 mIU/l reduction in insulin levels in women, effect which is similar to that of a low-fat diet (Shikany et al., 2011) or walking one hour a day (Fung et al., 2000).

### 2.3. *Phenolic compounds and all-cause-mortality risk*

Regarding the effect of dietary flavonoids, a recent meta-analysis (Grosso et al., 2017) indicated that they are indeed associated with decreased risk of all-cause mortality, as well as decreased risk of cardiovascular disease. Dietary intake of individual flavonoid classes was assessed and all showed an average decrease of relative risk, with confidence intervals rarely over 1.0. Thus, the calculated relative risks for overall mortality cases were, for total flavonoids, flavonols, flavones, flavanones, anthocyanidins, falvan-3-ols, proanthocianydines, as follows: 0.74 (CI 0.55-0.99), 0.88 (CI 0.69-1.11), 0.86 (CI 0.80-0.93), 0.75 (CI 0.57-0.97), 0.89 (CI 0.85-0.94), 0.88 (CI 0.72-1.09), 0.85 (CI 0.70-1.03), respectively.

### *2.4. Phenolic compounds and cardiovascular disease*

As already presented, the effects of wine and wine components on cardiovascular disease have been extensively researched so far, thus there is abundant scientific literature on this topic. Most of the studies and reviews clearly demonstrated the protection conferred in ischemic heart disease and atherosclerosis by the major compounds present in grapes and wines (Bertelli and Das, 2009). The positive effects of wines are not limited, however, to cardiovascular protection, as wine can also reduce the risk and intensity of other chronic diseases, such as cancers, diabetes, liver function and cognitive function.

### *2.5. Phenolic compounds and cancers*

Regarding cancer, although there are studies suggesting a possible protection conferred by flavonoids, due to the vast number of cancer types and mechanisms involved, direct evidence for humans has not been reliably provided yet.

An example is the case of prostate cancer. A study on a Netherlands cohort including 58,279 men followed between 1986 to 2003 the association of the flavonoids intake (from black tea) and the risk of developing prostate cancer. Intake of total catechin, epicatechin, kaempferol and myricetin were associated with a decreased risk of advanced prostate cancer. Risk ratios of stage III/IV and stage IV prostate cancer for the highest versus the lowest flavonoid consumption as tea (more than 5 cups/day versus less or equal 1 cup/day) were 0.75 (95% CI 0.59-0.97) and 0.67 (CI 0.50-0.91), respectively. However, for non-advanced prostate cancer no protection effect was observed (Geybels et al., 2013).

For prostate cancer, higher flavonoids and proanthocyanidins intake was associated with lower risk. The diet of the surveyed men who consumed higher amounts of flavonoids and proanthocyanidins was richer in wine, tea, fruits and vegetables. The study on a cohort of 43,268 men with a mean age of 70 years showed a positive association with overall prostate cancer risk, but only in the case of fifth quintile vs. first quintile of total flavonoids intake. The authors concluded that this possible influence of total flavonoids and proanthocyanidins in the evolution of prostate cancer deserves further study (Wang et al., 2014).

For non-Hodgkin's lymphoma an investigation on 960 selected cases of 32-60 year old men already diagnosed vs. 1717 men recruited randomly showed that consumption of wine, but not of beer or spirits, is associated with a reduced risk for this type of cancer (Briggs et al., 2002). Compared with non-drinkers, hazard ratios for men who consumed less than one glass of wine per day were 0.8 (95% CI 0.5-1.3), while for those who consumed one or more glasses of wine they were 0.4 (CI 0.2-0.9). This effect was not confirmed for beer or spirits, pointing out to a possible polyphenol effect.

*2.6. Phenolic compounds and diabetes and diabetes-related co-morbidities*

Moderate consumption of white and fortified wine is associated with a reduced incidence of diabetic retinopathy (DR), either vision-threatening (VT) or not. In one study, of the 395 participants (65.9 ± 10.4 years old; 253 males), 188 (47.6%) consumed alcohol and 235 (59.5%) had some form of diabetic retinopathy. Compared to no alcohol consumption, an overall moderate one was significantly associated with reduced odds of any diabetic retinopathy (OR = 0.47, 95% CI 0.26-0.85). Moderate consumption of white wine/ champagne or fortified wine was also associated with reduced odds of any diabetic retinopathy (OR = 0.48, 95% CI 0.25-0.91, and OR = 0.15, CI 0.04-0.62, respectively), either non-VTDR or VTDR (Fenwick et al., 2015).

Glucose metabolism has been proven to be positively affected by polyphenols, which reduce the incidence of diabetes (Luz et al., 2018). Long-maceration wine improved glucose tolerance and hepatic lipid accumulation involved in metabolic syndrome in mice. Long maceration improved total phenols, but the concentration of the main phenols related to health, such as quercetin, routin and resveratrol, did not increase significantly as compared to regular maceration, the concentration of resveratrol actually decreasing with the maceration time. However, regular-maceration wine did not appear to have the same beneficial effect on glucose tolerance and hepatic lipid accumulation, which means other phenols (catechin, epicatechin, gallic acid) are also important. Pomace as well improved glucose tolerance, insulin sensitivity and reduced hepatic triglycerides (Rosenzweig et al., 2017).

Based on clinical trials selected in accordance to very restrictive criteria, however, not enough evidence was found to firmly demonstrate that grape polyphenols can positively influence glycemia, blood pressure or lipid levels, although an improvement of insulin sensitivity was confirmed (Woerdeman et al., 2017).

An Australian study assessing influences on the level of inflammation in diabetes showed that neither wine nor alcohol per se have a significant effect on inflammation resolution. For example, red wine did not differently affect any of the measured pro-resolving mediators of inflammation, when compared with equivalent volumes of dealcoholized red wine or water (Bardena et al., 2018).

*2.7. Effects of phenolic compounds on liver function*

As a study performed in USA between 2005-2010 showed, polyphenols can also protect the liver. Nonalcoholic fatty liver disease was correlated with lower intake of flavonoids in the diet, 111.3 ± 3.6 vs. 201.3 ± 2.3 mg/day (Mazidi et al., 2019).

*2.8. Effects of phenolic compounds on cognitive function*

Flavonoids are known to protect against cognitive dysfunction or decline. A study started in 1988 in Bordeaux, France on persons of 65 years or older, with follow-up of 13 years, showed that the decline in cognitive function was lowest in the case of those with the higher intake of flavonoids (Letenneur et al., 2007). In this study, the quartiles of flavonoid intake were 0-10.39, 10.40-13.59, 13.60-17.69 and 17.70-36.94 mg/day. Subjects in the two highest quartiles had a significantly better evolution than did subjects in the first quartile. The evaluation was based on the evolution of the square root of the number of errors to the Mini-Mental State Examination (MMSE) over a 10 years period. Subjects with the lowest flavonoid intake lost in 10 years an average of 2.1 points on the MMSE, whereas subjects with the highest quartile lost only 1.2 points.

Wine, one of the foods richest in flavonoids, has also demonstrated protection. A 34 years study performed from 1968 in Sweden only on women (Mehlig et al., 2008) showed that wine consumtion was protective for dementia (HR 0.6, 95% CI 0.4-0.8) and the association was even stronger for women who only consumed wine (HR 0.3, CI 0.1-0.8). In contrast, consumption of spirits was associated with increased risk of dementia (HR 1.5, CI 1.0-2.2).

Several flavonoids, among which quercitine, was reported to be protective in demyelinating disease by preventing the oxidative damage of oligodendrocytes (van Meeteren et al., 2004). Also, gallic acid, a hydroxybenzoic acid abundant in wine, inhibited the formation of amyloid fibrils by α-synuclein, having a potential neuroprotective effect (Liu et al., 2013).

*2.9. Effects of phenolic compounds on microbiota and other microbial-related diseases*

Microbiota too plays a main role in the gut as regards the absorption of dietary polyphenols. Also, the consumption of dietary polyphenols modifies the gut microbiota (Nash et al., 2018). After intake of red wine or de-alcoholized red wine, modulation of gut bacteria was observed. Consumption of 272 ml/day of red wine significantly increased the gut bacterial concentrations of four phyla: *Proteobacteria, Fusobacteria, Firmicutes* and *Bacteroidetes*, as well as in *Prevotella, Bacteroides, Bacteroides uniformis, Bifobacterium* and *Eggerthella lenta* while intake of 272 ml of de-alcoholized red wine per day increased the concentration of *Fusobacteria* only (Queipo-Ortuno et al., 2012).

A recent study suggested that the main phenolic compound metabolites found in feces, phenyl-acetic and phenylpropionic acids, may be used as markers of gut health. Phenylacetic acid was related with more pro-inflammatory and pro-oxidant status, being associated with increased *Lactobacillus* and reduced *Clostridia* and *Bacterioides* group. Presence of phenylpropionic acids is correlated with proanthocyanidins ingestion (Gutiérrez-Díaz et al., 2018).

Wine-derived phenolic compounds also have desirable antimicrobial effects. Plant products including resveratrol inhibited *Helicobacter pylori* colonization of gastrointestinal tract, inhibited mutagenesis and repressed pre-cancerous changes by inhibiting NF-κB DNA binding (Lee et al., 2008). The rate of infection with *H. pylori* was found to be only 0.31 (95% CI 0.12–0.81) for people consuming an equivalent of 75 g of alcohol per week as compared to non-consumers, the effect being stronger for consumption of wine rather than beer (Brenner et al., 1999).

Similarly, drinkers of more than 14 glasses of wine per week showed a relative risk for catching common cold of only 0.6 (95% CI 0.4-0.8), the association being stronger for red wine. Beer, spirits and total alcohol intakes did not affect the risk of common cold, the effect being rather due to the wine polyphenols than to alcohol. After adjusting for alcohol consumption, the conclusion that wine, and especially red wine, is protective against the common cold may still be valid (Takkouche et al., 2002). Several effects are also exerted by wine and wine extracts on oral microbiota, either by direct inhibitory effects or indirect actions against inflammation caused by pathogens involved in periodontal disease (Esteban-Fernández et al., 2017). Bacteria responsible for tooth cavities and periodontis can form on teeth self-protective biofilms and generate detrimental acidity and plaque. Wine-derived phenolic compounds reduce the growth of these bacteria in spite of the formed biofilms (Munoz-Gonzalez et al., 2014).

In spite of the vast majority of studies pointing out the beneficial effect of phenolic compounds, excessive intake may also promote unwanted biochemical mechanisms. An analysis of a US cohort of 43,268 men, with a mean age of 70 years questioned between 1999-2000 and followed up for an average of 7.8 years, showed that in some cases of prostate cancer the relative risk is slightly increased by higher doses of flavonoids (Wang et al., 2014).

Within the first 2 years of follow-up, men in the top quintile of dietary total flavonoids (about 500 mg/day on average) had a higher risk of high-grade prostate cancer compared with men in the bottom quintile (about 100 mg/day). The calculated relative risks were for this top quintile 2.68 (95% CI 1.50-4.79) for total flavonoids, 2.04 (CI 1.14-3.65) for flavan-3-ols and 2.72, (CI 1.53-4.85) for proanthocyanidins.

However, the observed associations were inverse after excluding the first 2 years of follow-up. Although inconclusive, this study suggests that with polyphenols too, moderation is important.

Also it cannot be excluded that many beneficial effects correlated with flavonoid intake from wine, grape or other sources may also be a marker of overall healthy dietary habits.

## CONCLUSIONS

Significant research has been carried out over the years regarding the effects of wine on human health and the quality and quantity of data obtained has been steadily increasing. The fact that alcohol per se can be harmful to human health cannot be ignored; against this background, however, numerous studies have been conducted to determine the beneficial effects of wine and that of wine components. While this research is on-going, a wealth of information has been gathered which speaks with strong scientific arguments in favor of a low and moderate consumption of wine as a part of a healthy diet and lifestyle. Reviewing research results highlights, however, the complexity of the relationship between wine and human health. A challenge continues to be the integration of results and the efficient interpretation of the large amounts of data, in a way that can be useful at an individual or personal level.

Overall, wine consumers should be advised that to avoid the harmful physiological and pharmacological effects of rapid accumulation of alcohol and acetaldehyde in the body, it is important to consume alcoholic beverages with food and to stay hydrated to dilute these compounds. Consuming lower alcohol beverages is also good advice. A team of neuroscientists (Frost et al., 2015) assessed consumer reactions to different types of wine using functional magnetic imaging of the brain regions associated with flavor processing and food reward. Pairs of high- and low- alcohol content red wines, otherwise similar in attributes, were given to the participants. Contrary to expectation, significantly greater activation was recorded in brain regions sensitive to taste intensity for low-alcohol rather than for high-alcohol wines. Although there are limited choices on offer of low-alcohol wine and consumer acceptance and demand also remains limited, this wine category has the potential for increased market shares in the future (Bucher et al., 2018).

## REFERENCES


Agatonovic-Kustrin S., Hettiarachchi C.G., Morton D.W., Razic S., 2015. Analysis of phenolics in wine by high performance thin-layer chromatography with gradient elution and high resolution plate imaging, J Pharm Biomed Anal., Vol. 102, 93-99.

Amoako D., Awika J. M., 2016. Polyphenol interaction with food carbohydrates and consequences on availability of dietary glucose, Current Opinion in Food Science, Vol. 8, 14-18.

Arranz S., Chiva-Blanch G., Valderas-Martínez P. et al., 2012. Wine, beer, alcohol and polyphenols on cardiovascular disease and cancer, Nutrients, 4 (7), 759-781.

Bardena A., Shinde S., Phillips M., Beilin L., Mas E., Hodgson J.M., Puddey I., Mori T.A., 2018. The effects of alcohol on plasma lipid mediators of inflammation resolution in patients with Type 2 diabetes mellitus, Prostaglandins, Leukotrienes and Essential Fatty Acids, Vol. 133, 29-34.

Bertelli A.A., Das D.K., 2009. Grapes, Wines, Resveratrol, and Heart Health, Journal of Cardiovascular Pharmacology, 54 (6): 468-476.

Brenner H., Rothenbacher D., Bode G., Adler G.,1999. Inverse Graded Relation between Alcohol Consumption and Active Infection with Helicobacter pylori, American Journal of Epidemiology, Vol. 149, Issue 6, 571-576.

Briggs N.C., Levine R.S., Bobo L.D., Haliburton W.P., Brann E.A. et al., 2002. Wine Drinking and Risk of Non-Hodgkin's Lymphoma among Men in the United States: A Population-based Case-Control Study, Am. J. of Epidemiology, Vol. 156, Issue 5, 454-462.

Bucher T., Deroover K.and Stockley C., 2018. Low-alcohol wine: A narrative review on consumer perception and behaviour, Beverages, Vol. 4, 82-91.

Burns J., Gardner P.T., O'Neil J., Crawford S., Morecroft I., McPhail D.B., Lister C., Matthews D., MacLean M.R., Lean M.E., Duthie G.G., Crozier A., 2000. Relationship among antioxidant activity, vasodilation capacity, and phenolic content of red wines, J Agric Food Chem., Vol. 48 (2), 220-230.

Cassidy A., 2018. Berry anthocyanin intake and cardiovascular health, Molecular Aspects of Medicine, Vol. 61, 76-82.

Chen S., Xia T., Hong Z., Zhang Y., Shi G., He Z., Zhong S., 2018. The influences of red wine in phenotypes of human cancer cells, Gene, In press corrected proof Available online 23 October.

Costanzo S., Di Castelnuovo A., Donati M.B. et al., 2011. Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis, Eur J Epidemiol, 26 (11), 833-850.

Dekic S., Milosavljevic S., Vajs V., Jovic S., Petrovic A., Nikicevic N., Manojlovic V., Nedovic V., Tesevic V., 2008. *Trans*- and *cis*-resveratrol concentration in wines produced in Serbia, Journal of the Serbian Chemical Society, 73 (11), 1027-1037.

Del Rio D., Rodriguez-Mateos A., Spencer J.P. et al., 2013. Dietary (poly) phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases, Antioxid Redox Signal, 18 (14), 1818-1892.

Dias R., Perez-Gregorio R., Mateus N., De Freitas V., 2015. The interaction between tannins and gliadin derived peptides in a celiac disease perspective. RSC Advances, 5 (41), 32151-32158.

Draijer R., de Graaf Y., Slettenaar M., de Groot E., Wright C.I., 2015. Consumption of a polyphenol-rich grape-wine extract lowers ambulatory blood pressure in mildly hypertensive subjects. Nutrients, 7 (5), 3138-3153.

Esteban-Fernández A., Zorraquín-Peña I., González de Llano D., Bartolomé B., Moreno-Arribas M.V., 2017. The role of wine and food polyphenols in oral health. Trends in Food Science & Technology, Vol. 69, Part A, 118-130.

Falk R.T., Maas P., Schairer C., Chatterjee N., Mabie J.E. et al., 2014. Alcohol and risk of breast cancer in postmenopausal women: an analysis of etiological heterogeneity by multiple tumor characteristics. American Journal of Epidemiology, Vol. 180, Issue 7, 705-717.

Fei Q., Kent D., Botello-Smith W.M., Nur F., Nur S., Alsamarah A., Chatterjee P., Lambros M. and Luo Y., 2018. Molecular mechanism of resveratrol’s lipid membrane protection. Scientific Reports, Vol. 8, 158.

Fenwick E.K., Xie J., Man R.E.K., Lim L.L., Flood V.M., Finger R.P., Wong T.Y., Lamoureux E.L., 2015. Moderate consumption of white and fortified wine is associated with reduced odds of diabetic retinopathy. Journal of Diabetes and its Complications, Vol. 29, Issue 8, 1009-1014.

Ferrieres J., 2004. The French Paradox; Lessons for other countries. Heart, 90 (1), 107-111.

Fillmore K.M., Stockwell T., Chikritzhs T., Bostrom A., Kerr W., 2007. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann. Epidemiol. 17, S16-S23.

Frost R., Quiñones I., Veldhuizen M., Alava J.I., Small D., Carreiras M., 2015. What can the brain teach us about winemaking? An fMRI study of alcohol level preferences. Plos One, Vol. 10 (3).

Fung T.T., Hu F.B., Yu J., Chu N.F., Spiegelman D., Tofler G.H., Willett W.C., Rimm E.B., 2000. Leisure-time physical activity, television watching, and plasma biomarkers of obesity and cardiovascular disease risk. Am. J. Epidemiol., Vol. 152, 1171-1178.

Gell L., Meier P., 2011. The nature and strength of the relationship between expenditure on alcohol and food: an analysis of adult-only households in the UK. Drug Alcohol Rev., 31 (4), 422-430.

Gerogiannaki-Christopoulou M., Athanasopoulos P., Kyriakidis N., Gerogiannaki I.A., Spanos M., 2006. trans-Resveratrol in wines from the major Greek red and white grape varieties. Food Control, Vol. 17, 700-706.

Geybels M.S., Verhage B.A.J., Arts I.C.W., van Schooten F.J., Goldbohm R.A. et al., 2013. Dietary Flavonoid Intake, Black Tea Consumption, and Risk of Overall and Advanced Stage Prostate Cancer. Am. J. of Epidemiology, Vol. 177 (12), 1388-1398.

Grosso G., Micek A., Godos J., Pajak A., Sciacca S., Galvano F., Giovannucci E.L., 2017. Dietary Flavonoid and Lignan Intake and Mortality in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis. American Journal of Epidemiology, Vol. 185, Issue 12, 1304-1316.

Gutiérrez-Díaz I., Fernández-Navarro T., Salazar N., Bartolomé B., Moreno-Arribas M.V., López P., Suárez A., de Los Reyes-Gavilán C.G., Gueimonde M., González S., 2018. Could fecal phenylacetic and phenylpropionic acids be used as indicators of health status? J Agric Food Chem, 66 (40), 10438-10446.

Han F., Yang P., Wang H., Fernandes I., Liu Y., 2019. Digestion and absorption of red grape and wine anthocyanins through the gastrointestinal tract. Trends in Food Sci & Technol., Vol. 83, 211-224.

He S., Jiang L., Wu B., Pan Y. and Sun C., 2009. Pallidol, a resveratrol dimer from red wine, is a selective singlet oxygen quencher. Biochemical and Biophysical Research Communications, Vol. 379, Issue 2, 283-287.

Higgins L.M., Llanos E., 2015. A healthy indulgence? Wine consumers and the health benefits of wine. Wine Economics and Policy, Vol. 4, 3-11.

Hvidtfeldt U.A., Tolstrup J.S., Jakobsen M.U., Heitmann B.L., Gronbaek M. et al., 2010. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. Circulation, 121, 1589-1597.

Jackson R.S., 2016. Wines: Wine and Health. Reference module in food science encyclopedia of food and health, 562-570.

Jennings A., Welch A.A., Spector T., Macgregor A., Cassidy A., 2014. Intakes of anthocyanins and flavones are associated with biomarkers of insulin resistance and inflammation in women. J. Nutr., Vol. 144, 202-208.

Johansen D., Friis K., Skovenborg E., Gronbaek M., 2006. Food buying habits of people who buy wine or beer: cross sectional study. BMJ, 332, 519-523.

Knoops K.T.B., de Groot L.C.P., Kromhout D. et al., 2004. Mediterranean diet, lifestyle factofs, and 10-year mortality in elderly European men and women. The HALE Project. JAMA, Vol. 292, 1433-1439.

Kropp S., Becher H., Nieters A., Chang-Claude J., 2001. Low-to-moderate alcohol consumption and breast cancerrisk by age 50 years among women in

Germany. American Journal of Epidemiology, Vol. 154, Issue 7, 624-634.

Landrault N., Larronde F., Delaunay J.C., Castagnino C., Vercauteren J., Merillon J.M., Gasc F., Cros G., Teissedre P.L., 2002. Levels of stilbene oligomers and astilbin in French varietal wines and in grapes during noble rot development. J Agric Food Chem., 50 (7), 2046-52.

Lee S.Y., Shin Y.W., Hahm K.B., 2008. Phytoceuticals: mighty but ignored weapons against Helicobacter pylori infection. J Dig Dis., Vol. 9 (3), 129-39.

Leger A.S.St., Cochrane A.L., Moore E., 1979. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. Lancet, 1 (8124), 1017-1020.

Lew J.Q., Freedman N.D., Leitzmann M.F., Brinton L.A., Hoover R.N. et al., 2009. Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: The NIH-AARP Diet and Health Study. American Journal of Epidemiology, Vol. 170, Issue 3, 308-317.

Li Y., Zhang L., Wang X., Wu W., Qin R., 2018. Effect of Syringic acid on antioxidant biomarkers and associated inflammatory markers in mice model of asthma. Drug Dev. Res., 1-9.

Liu C.M., Zheng G.H., Ming Q.L. et al., 2013. Protective effect of quercetin on lead-induced oxidative stress and endoplasmic reticulum stress in rat liver via the IRE1/JNK and PI3K/Akt pathway. Free Radic Res, Vol. 47 issue 3, 192-201.

Luz P.L., Favarato D., Berwanger O., 2018. Endothelium and Cardiovascular Diseases Vascular Biology and Clinical Syndromes. Chapter 26 - Action of red wine and polyphenols upon endothelial function and clinical events, 391-418.

Mehlig K., Skoog I., Guo X., Schütze M., Gustafson D. et al., 2008. Alcoholic Beverages and Incidence of Dementia: 34-Year Follow-up of the Prospective Population Study of Women in Göteborg. American Journal of Epidemiology, Vol. 167, Issue 6, 684-691.

Mizoue T., Inoue M., Wakai K., Nagata C., Shimazu T. et al., 2008. Alcohol drinking and colorectal cancer in japanese: A pooled analysis of results from five cohort studies. Am. J. Epidemiol., Vol. 167, Issue 12, 1397-1406.

Mongan D., Long J., 2015. Standard drink measures throughout europe; peoples' understanding of standard drinks and their use in drinking guidelines, alcohol surveys and labelling. Health Research Board, Dublin, Ireland.

Muñoz-Gonzalez I., Thurnheer T., Bartolome B., Moreno-Arribas M.V., 2014. Red wine and oenological extracts display antimicrobial effects in an oral bacteria biofilm model. J. Agric. Food Chem., Vol. 62 (20), 4731-4737.

Nash V., Ranadheera C.S., Georgousopoulou E.N., Mellor D.D., Naumovski N., 2018. The effects of grape and red wine polyphenols on gut microbiota – A systematic review. Food Research International, Vol. 113, 277-287.

Ndlovu T., van Jaarsveld F., Caleb O.J., 2019. French and Mediterranean-style diets: Contradictions, misconceptions and scientific facts-A review. Food Res Int., 116, 840-858.

Nowshehri J.A., Bhat Z.A., Shah M.Y., 2015. Blessings in disguise: Bio-functional benefits of grape seed extracts. Food Res. Intl., Vol. 77 (Part 3), 333-348.

Ou K., Gu L., 2014. Absorption and metabolism of proanthocyanidins. Journal of Functional Foods, Vol. 7, 43-53.

Paganini-Hill A., Kawas C.H., Corrada M.M., 2007. Type of alcohol consumed, changes in intake over time and mortality: the Leisure World Cohort Study. Age and Ageing, Vol. 36, 203-209.

Park S.Y., Wilkens L.R., Setiawan V.W., Monroe K.R., Haiman C.A., 2018. Alcohol intake and colorectal cancer risk in the multiethnic cohort study. Am.J. of Epidemiology, Vol. 188, Issue 1, 67-76.

Poli A., Marangoni F., Avogaro A. et al., 2013. Moderate alcohol use and health: A consensus document. Nutrition, Metabolism & Cardiovascular Diseases, Vol. 23, 487-504.

Prescott E., Grønbæk M., Becker U., Sørensen T.I.A., 1999. Alcohol intake and the risk of lung cancer: influence of type of alcoholic beverage. Am J. of Epidemiology, Vol. 149, Issue 5, 463-470.

Purdue M.P., Hashibe M., Berthiller J., La Vecchia C., Dal Maso L. et al., 2009. Type of alcoholic beverage and risk of head and neck cancer-a pooled analysis within the INHANCE Consortium. American Journal of Epidemiology, Vol. 169, Issue 2, 132-142.

Queipo-Ortuno M.I., Boto-Ordonez M., Murri M., Gomez-Zumaquero J.M., .... Tinahones F.J., 2012. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. The Am J. of Clinical Nutrition, 95 (6), 1323-1334.

Ragusa A., Centonze C., Grasso M.E., Latronico M.F., Mastrangelo P.F., Sparascio F. and Maffia M., 2019. HPLC analysis of phenols in Negroamaro and Primitivo red wines from Salento. Foods, 8 (2), 45-57.

Ratziu V., Bellentani S., Cortez-Pinto H., Day C., Marchesini G., 2010. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J. of Hepatology, Vol. 53 (2), 372-84.

Renaud S., De Lorgeril M., 1992. Wine alcohol, platelets, and the French paradox for coronary, heart disease. Lancet, 339, 1523-1526.

Rodriguez-Morato J., Boronat A., Kotronoulas A., Pujadas M., Pastor A., Olesti E., Perez-Mana C., Khymenets O., Fito M., Farre Magi et al., 2016. Metabolic disposition and biological significance of simple phenols of dietary origin: hydroxytyrosol and tyrosol. Drug Metabolism Reviews, 48 (2), 218-236.

Rohrmann S., Linseisen J., Boshuizen H.C., Whittaker J., Agudo A. et al., 2006. Ethanol intake and risk of lung cancer in the european prospective investigation, into cancer and nutrition (EPIC). American Journal of Epidemiology, Vol. 164, Issue 11, 1103-1114.

Rosenzweig T., Skalka N., Rozenberg K., Elyasiyan U., Pinkus A., Green B., Stanevsky M., Drori E., 2017. Red wine and wine pomace reduced the development of insulin resistance and liver steatosis in HFD-fed mice. Journal of Functional Foods, Vol. 34, 379-389.

Shikany J.M., Margolis K.L., Pettinger M., Jackso, R.D., Limacher M.C., Liu S., Phillips L.S., Tinker L.F., 2011. Effects of a low-fat dietary intervention on glucose, insulin, and insulin resistance in the Women's Health Initiative (WHI) Dietary Modification trial. Am. J. Clin. Nutr., Vol. 94, 75-85.

Shrotriya S., Agarwal R., Sclafani R.A., 2015. A Perspective on chemoprevention by resveratrol in head and neck squamous cell carcinoma. In: Vasiliou V., Zakhari S., Seitz H., Hoek J. (eds) Biological basis of alcohol-induced cancer. Advances in Experimental Medicine and Biology, Vol. 815, Springer.

Siemann E.H., Creasy L.L., 1992. Concentration of the phytoalexin resveratrol in wine. Am J Enol Vitic. 43, 49-52.

Stervbo U., Vang O., Bonnesen C., 2007. A review of the content of the putative chemopreventive phytoalexin resveratrol in red wine. Food Chem., Vol. 101, 449-457.

Takkouche B., Regueira-Méndez C., García-Closas R., Figueiras A., Gestal-Otero J.J., 2002. Intake of Wine, Beer, and Spirits and the Risk of Clinical Common Cold. Am. Journal of Epidemiology, Vol. 155, Issue 9, 853-858.

Thun M.J., Peto R., Lopez A.D., Monaco J.H., Henley S.J., Heath C.W.Jr., Doll R., 1997. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med, Vol. 337, 1705-14.

van Meeteren M.E., Hendriks J.J., Dijkstra C.D., van Tol E.A., 2004. Dietary compounds prevent oxidative damage and nitric oxide production by cells involved in demyelinating disease,. Biochem. Pharmacol., 67, 967-975.

Wang Y., Stevens V.L., Shah R., Peterson J.J., Dwyer J.T. et al., 2014. Dietary Flavonoid and Proanthocyanidin Intakes and ProstateCancer Risk in a Prospective Cohort of US Men. Am. J. Epidemiol., Vol. 179, (8) 15, 974-986.

Waterhouse A.L., 2002. Wine phenolics. Ann N Y Acad Sci., Vol. 957, 21-36.

Watters J.L., Park Y., Hollenbeck A., Schatzkin A., Albanes D., 2010. Alcoholic beverages and prostate cancer in a prospective us cohort study. Am J. of Epidemiology, Vol. 172, Issue 7, 773-780.

White A.J., DeRoo L.A., Weinberg C.R., Sandler D.P., 2017. Lifetime alcohol intake, binge drinking behaviors, and breast cancer risk. American Journal of Epidemiology, Vol. 186, Issue 5, 541-549.

Woerdeman J., van Poelgeest E., Ket J.C.F., Eringa E.C., Serné E.H. and Smulders Y.M., 2017. Do grape polyphenols improve metabolic syndrome components? A systematic review. European Journal of Clinical Nutrition, Vol. 71, 1381-1392.

Wood M.A., Kaptoge S. et al., 2018. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599912 current drinkers in 83 prospective studies. Lancet, Vol. 391, 1513-23.

***American Cancer Society, 2016. Report links alcohol, processed meats, and excess weight to stomach cancer, https://www.cancer.org/latest-news/report-links-alcohol-processed-meats-and-excess-weight-to-stomach-cancer.html, online on 3/1/2019.

***European Code Against Cancer, 2016. online at 02/02/2019; http://cancer-code-europe.iarc.fr/index.php/en/.

***GBD, 2016 Alcohol Collaborators, 2018. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, The Lancet, Vol. 392, Issue 10152, 1015-1035.

***Wine in Moderation. How Much is Moderate? online 02/02/2019 https://www.wineinmoderation.eu/en/content/How-much-wine-is-too-much.66/.