

## What's in wine? A clinician's perspective<sup>☆☆☆</sup>

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### ABSTRACT

Alcoholic beverages, specifically wine, have been consumed for many years. Wine is postulated to play an important role in the improvement of cardiovascular risk factors. Most epidemiological studies have found sustained consumption at light-to-moderate amounts to increase HDL cholesterol, reduce platelet aggregation, and promote fibrinolysis. Wine consumption has been inversely associated with ischemic heart disease, and the alcohol-blood pressure association, in most studies, follows a J-shaped curve. These outcomes have been attributed to the molecular constituents of wine, namely ethanol and polyphenols. Due to the continued interest in wine as a biological beverage, we review the chemistry of wine as clinicians, including its chemical composition, viticulture and enological practices, and other chemical factors that influence the bioactive components of wine. We also outline the biological effects of wine components and directions for future research.

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### Introduction

Wine is a unique beverage. Its production precedes recorded history, takes place on almost every continent, and is considered both an art and a science [1–3]. The quality of wine is influenced by many oenological factors, including the grape type and grape structure, climatic factors, and fermentation techniques [4–6]. At the molecular level, wine consists of a matrix of hundreds of different molecules encompassing several compounds classes, all suspended in a liquid medium at varying concentrations [7–9]. Wine has historically garnered attention as a healthy beverage after epidemiological evidence found a negative correlation between the light-to-moderate consumption of wine and mortality due to ischemic heart disease (IHD) [10,11]. Despite many multicenter and cross-cultural epidemiological studies reaching similar conclusions, there was conflicting evidence. Some studies observed similar effects with the consumption of beer and spirits, while others reported that the drink type was not important, suggesting that alcohol as a whole was protective [12]. Many studies have examined the wide range of chemical compounds found in wine for their cardioprotective potential. In-vivo and population-based studies pos-

tulate that the bioactive constituents of wine, ethanol and polyphenols, are synergistically responsible for imparting the antioxidant and anti-inflammatory properties of wine [13].

Over the years, the chemistry of grapes and wine, in particular, has contributed to a better understanding of the biological characteristics of wine. Analytical chemistry techniques have allowed for a detailed characterization of the composition of wine [14,15]. Furthermore, the power of Renaud and de Lorgeril's findings on the French paradox have also promoted many investigations into the antioxidant potential of wine [16].

Wine chemistry is a sophisticated branch of interconnected research encompassing the science of winemaking, grape growing, and the analytical, organic, and physical analysis of wine. Wine chemistry allows for an understanding of the taste, aroma, and composition of wine. In this review, we provide a brief historical overview of wine's origins, production and consumption patterns, its compositional analysis, and the biological activity of its constituents on the cardiovascular system. We also discuss the implications of wine and alcohol use on the global disease burden and present directions for future research.

### Brief history: Wine, viticulture, and medicineIntroduction

#### Origins of wine and viticulture

Wine can be simply defined as the fermented juice of grapes. Although other fruits, grains, and even honey have been used to

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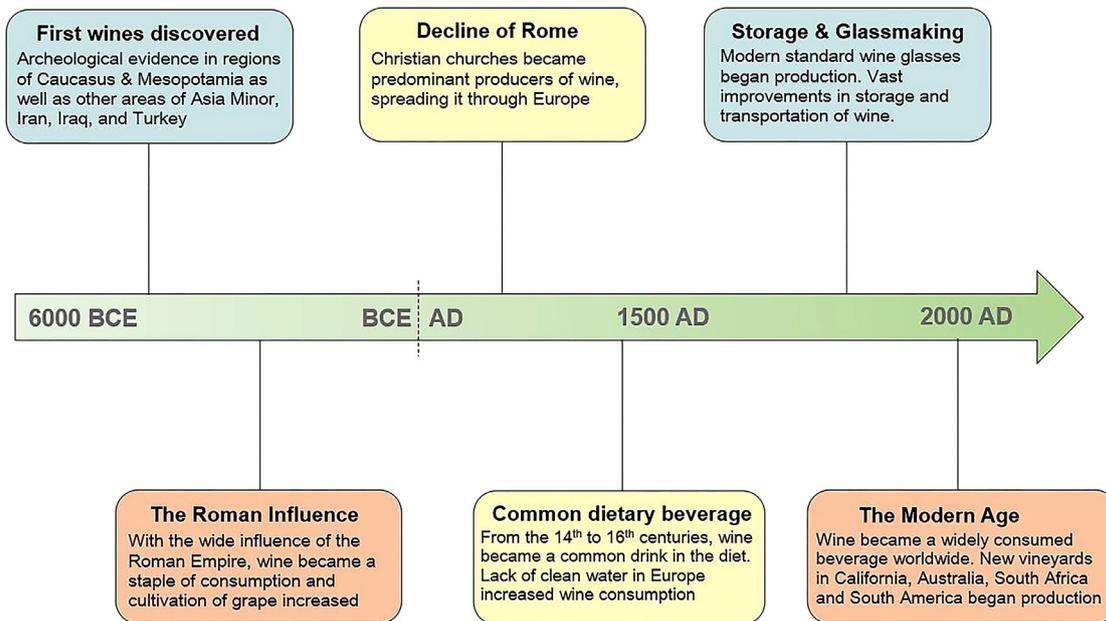


Fig. 1. A timeline of the major events linked to the spread of wine and viticulture around the world.

make alcoholic beverages, the grape produces a diverse and chemically complex drink with an array of flavors. Wine has been consumed for many years. The ancient Romans and Greeks trace wine back to their prehistoric days, with interesting myths of its origins [17]. The earliest evidence of oenology, or winemaking, from cultivated grapevines can be dated back to between 5400 and 5000 BCE in Iran [18]. However, some investigators credit other regions of Caucasus, located at the border of Europe and Asia, as the place of discovery and domestication of the wine grape. The presence of the calcium salt of tartaric acid, a naturally occurring acid in grapes, was used as a marker to identify the presence of wine [5]. From its reported origins, winemaking spread throughout Mesopotamia, Syria, Egypt, and around the Mediterranean region. When the Romans conquered Greece, wine became an important staple of consumption that was consumed with almost every meal and was connected to figures like Dionysus the God. The wide influence of the Romans distributed winemaking to parts of Europe. With the fall of the Roman Empire and the subsequent spread of Christianity, monasteries across Europe began protecting and maintaining vineyards, slowly refining the chemical process. As wine-making and its consumption disappeared from the Middle East and Northern Africa due to the spread of Islam, Europeans expanded the practice to the Americas via the Spanish missionaries, starting with Mexico and then southward to Peru, Chile and Argentina [19]. Viticulture was later adapted to the climatic and agricultural conditions of North America, which has since seen an enormous growth in consumption (Fig. 1).

#### Wine as a medicine

Early medicine was closely tied to religious practices, with wine retaining an important role for medicinal purposes. The earliest known Mesopotamians recommended the use of wine for various treatments, such as mixing it with honey to treat coughs [20]. The ancient Egyptians used wine as a solvent, as an agent to increase appetite, as a remedy for weakness, or as an applicant to wounds [21]. Hippocrates, the ancient Greek physician, considered wine to be a nourishing part of a healthy diet and also advocated its use as a disinfectant and a sedative [22].

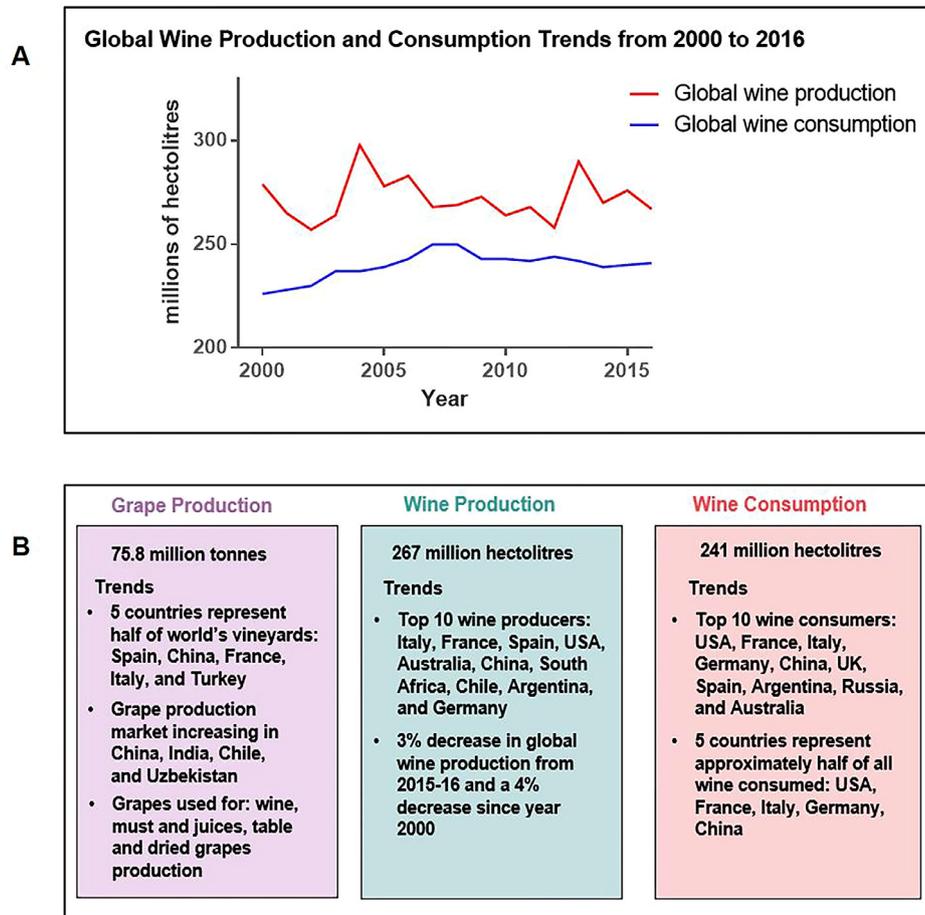
#### The French paradox

Modern scientific intrigue for wine grew as epidemiological studies found that light-to-moderate intake of regular amounts of alcohol may possibly confer cardioprotective effects [10]. A negative correlation between the light-to-moderate consumption of alcohol and IHD incidence and mortality was described using epidemiological studies, first appearing in the 1960s [23]. These results were individually reported for wine, specifically red wine [11], and this phenomenon became known as the French Paradox after two researchers, Serge Renaud and Michel de Lorgeril, observed a relatively low risk of IHD-associated mortality among drinkers of red wine in France, despite a high intake of saturated fat [24]. With the empirical associations already established, the debate pertaining to wine and cardiovascular health now revolves around causality and how to deal with the public health aspects [25].

#### Production and consumption patterns

##### Global production of wine

The intercontinental trade of wine has influenced its production and consumption patterns [26]. According to the International Organization of Vine and Wine (OIV) [27], an intergovernmental group on vine and wine products, reported that in 2016, 7.5 million hectares of land was covered under vineyards, with an annual production of 75.8 million tonnes of grapes. Approximately half of those grapes produced were used in the production of wine. In 2016, the global wine production was 267 million hectoliters (mhl), a 3% decrease compared to the previous year, and a 4% decrease since the year 2000. Italy was the largest global producer (gp) (50.9 mhl), producing 19.1% of the world's wine, followed by France (43.5 mhl; 16.3% gp), Spain (39.3 mhl; 14.7% gp), United States (23.9 mhl; 8.9% gp), and Australia (13.0 mhl; 4.9% gp). Trends in wine production are presented in Fig. 2 [27].



**Fig. 2.** The global status of wine and viticulture represented by the (A) production and consumption patterns, and (B) observed global trends. Data are from the 2017 International Organization of Vine and Wine Statistical Report [27].

### Global consumption of wine

The global consumption of wine in 2016 was 241 mhl, a 7% increase since the year 2000 [27]. Five countries consumed approximately half of the world's wine. The United States was the largest global consumer with 31.8 mhl (13.2% of global consumption (gc)), followed by France (27.0 mhl; 11.2% gc), Italy (22.5 mhl; 9.4% gc), Germany (19.5 mhl; 8.1% gc), and China (17.3 mhl; 7.2%). The United States has been the largest global consumer since 2011. Italy and China have experienced a growth in consumption, and France, Spain and Russia are at a stable consumption rate. Trends in wine consumption are presented in Fig. 2 [27].

### Alcohol-attributable global disease burden

Excessive wine or alcohol consumption is regarded as a major risk factor for disease and mortality. Globally, more than 1.8 million deaths, and approximately 52 million disability-adjusted life years, were attributable to annual alcohol use [28]. Alcohol is connected to more than 200 International Classification of Disease (ICD-10) codes which include non-communicable diseases, infectious diseases, and acute adverse injuries [28–30]. The disease burden attributable to wine and alcohol, is related, in large part, to the frequency, volume, and patterns of consumption. Alcohol dependence in the United States remains highly prevalent, affecting 4–5% of the population at a given time. Alcohol abuse was more prevalent among young and unmarried individuals, and more prevalent among males than females [31,32]. Approximately one-third of the United States population that consumed alcohol did so excessively,

accounting for an annual average of 87,798 deaths and 2.5 million years of potential life lost [33]. Individuals consuming alcohol excessively have steadily increased, with this pattern of consumption carrying a significantly higher mortality risk than the light-to-moderate intake of alcohol [34].

The majority of deaths and years of life lost due to premature mortality (YLLs), in the context of alcohol and resulting non-communicable diseases, are attributable to cardiovascular diseases, gastrointestinal diseases, and cancers [28]. Looking specifically at alcohol-associated mortality and YLLs due to cardiovascular disease, contributors include hypertension, IHD, alcoholic cardiomyopathy, stroke, and dysarrhythmias. It is of note, however, that for years of life lost due to disability (YLDs), alcohol exerted a net protective effect, plausibly due to the negative correlation between the light-to-moderate intake of alcohol and IHD [28,35].

### Wine terminology

*Oenology* is defined as the study of wine and winemaking, whereas *viticulture* is the study or science of grape growing [36]. *Ethanol* is the chemical compound in wine that is formed as the by-product of yeast fermentation [37]. *Fermentation* is the chemical process whereby grape sugars are converted to ethanol and carbon dioxide (CO<sub>2</sub>), turning grape juice into wine [38]. *Carbonic maceration* is a specific fermentation technique where whole grapes are fermented in a CO<sub>2</sub>-rich environment prior to crushing [38]. *Must* refers to the unfermented grape juice that has been freshly extracted by pressing the grapes, a precursor to wine [38]. A dry wine has no perception of sweetness, a consequence of the fermentation

of residual sugars [37]. *Fortification*, in the context of winemaking, denotes a wine where the alcoholic content is increased by the addition of distilled spirits [37].

### What is wine? A definition and analysis

The term wine originates from the Latin word, *vinum*, which translates to “wine” or “vine”. Wine is an alcoholic beverage produced from the fermentation of must or grape juice, without the addition of enzymes, sugars, acids, or other nutrients. Yeast consumes the grape sugars to yield ethanol and CO<sub>2</sub> [39]. The process of winemaking and its subsequent storage result in a number of chemical additions and perturbations that contribute to the aroma, taste, and the antioxidant and cytoprotective properties of wine.

#### *Grapevines: influence on wine chemistry*

Grapevines, or *Vitis vinifera*, are plants from which wine is produced. They belong to the genus *Vitis*, within the botanical family *Vitaceae*, which retains approximately 1,000 species of grapes [40]. Grapes can be divided into 2 categories: red and white. Different subspecies of grapevines are most often identified with their geographical regions of origin. Grapes are one of the major naturally occurring fruits that are cultivated in large fields with a temperate climate [41]. The most popular regions of grape cultivation and wine production are in Italy, France, Australia, South Africa, Argentina, Chile, and the United States, specifically California.

From a chemical perspective, *V. vinifera* are ideal for red and white wines. For red wines, fermentation is performed with the grape skin intact, allowing for the release of tannin and anthocyanin polyphenols, which gives the juice its acidity, red colour, and antioxidant potential. For white wines, the skin of the grape is removed before allowing the grape to ferment, which abstracts the polyphenols, thereby decreasing the acidity and removing the red colour [37]. Temperature during grape ripening (optimal: 12 to 15 °C), humidity (optimal: 70 to 80%), and storage time are a few crucial external factors that influence wine maturity during vinification [40,42].

#### *Grapes to wine: the process chemistry*

Generally, grapes consist of a clear juice, pulp, skin, seeds, and stem. The process of winemaking results in the variable extraction, or maceration, of compounds from the grape, adding to the final composition of wine. Maceration occurs pre-fermentation, and is influenced by variables such as time and temperature, and chemical and physical processes such as mixing, pressing, heating, freezing, and enzymatic treatments [43]. Harvesting is a pre-fermentation process where time is the most important variable that influences the sugar and acid concentrations of the grape, thereby affecting the ethanol content of wine [44]. Crushing and de-stemming are performed subsequent to the harvest, where the stems are removed and the grapes are pressed to extract the juice, pulp and seeds. Sulfur dioxide is added pre-fermentation to inhibit oxidation and kill any microbes [45]. Yeast fermentation is the second phase of vinification. Under inert conditions, fermentable grape sugars are converted to ethanol and byproducts. Post-fermentation operations that influence wine composition include storage, filtration, and bottling.

### Classification of wines

Wines, in the broadest sense, are divided into four categories: still, sparkling, fortified, and dealcoholized. They can further be subdivided based on the ethanol, CO<sub>2</sub>, and sugar content, and then

on colour, grape variety, or the place of origin and age. The classification by colour gives an indication of the wine's intensity, with the classification by geographic origin being the most common. [38,46].

Still wines have an alcoholic content of ≤ 14 vol%, with fortified wines ranging between 17–22 vol%. Conversely, the differentiation between still and sparkling wines depend on the CO<sub>2</sub> content of the wine. Still wines are referred to as “table” wines, having lower ethanol content, appropriate to be consumed with meals. Fortified wines are referred to as “dessert/appetizer” wines, having a higher ethanol content, and usually consumed before or after meals. The ethanol concentrations within wines represent the limitations of the yeast strains' fermentation potential [47] and also play a role in a country's taxation laws for alcoholic beverages [48].

#### *Still wines*

The most accepted division within still wines is by color: red, white, and rosé wines. For red wines, the color is determined by the presence of the grape skin during the fermentation process [40]. Red wines are rich in flavor, acidic, and dry compared to white wines. The dryness arises from the wines having no remaining fermentable grape sugars. After production, red wines are stored in oak barrels or inert tanks for maturation [38]. White wines, in comparison, are fermented without the grape skin, have a varying sugar concentration, and are estimated to be 10-fold lower in polyphenolic content than red wines [49]. Rosé wines are produced from very dark grapes where the grape skin is left intact for a short period.

#### *Sparkling wines*

Sparkling wines are characterized by the production method. The term “sparkling” refers to the wines where excess CO<sub>2</sub> has been produced due to yeast fermentation. These wines are usually fermented twice, and are bottled and packaged under pressure. The three most common techniques are: the traditional method (champagne), tank method (Lambrusco), and transfer method [37,38]. Sparkling wines are subdivided based on color: white, pink, and red. The most common consumer product of this category is the “white” sparkling wine.

#### *Fortified wines*

Fortified wines are usually consumed in smaller amounts. They have microbiological stability and a long storage life. These wines are sweet and have an elevated ethanol content (17–22 vol%), which is achieved by the addition of distilled spirits at the beginning or end of the fermentation process. The high ethanol content allows for limited oxidation, greater stability, and hence, limited spoilage. Fortified wines are subdivided into three groups: maderized wines, sweet wines, and flavored wines [37,38].

#### *Dealcoholized wines*

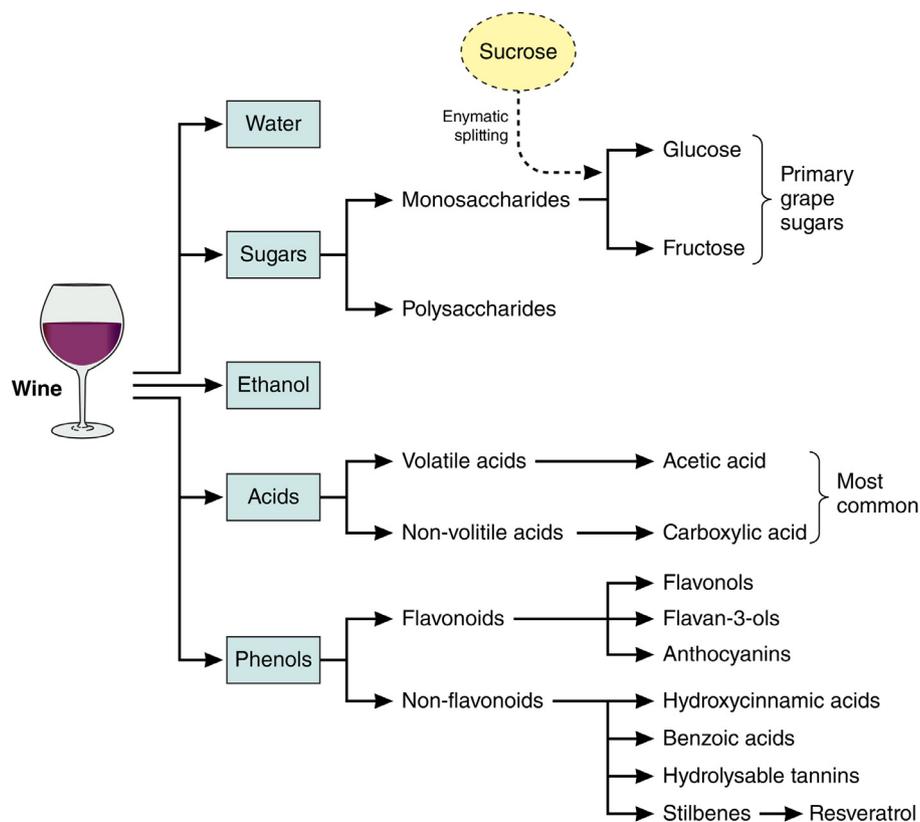
Dealcoholized wines are produced by taking alcoholic wine, and removing the ethanol content. The main dealcoholizing techniques that are employed post-fermentation include: reverse osmosis, a membrane separation technique that removes ethanol but retains polyphenols [50], and vacuum distillation, a heat induced separation technique that removes water and ethanol [51]. Dealcoholized wines are generally lower in total caloric content compared to other wines, beers, and spirits (Table 1), but are less stable compared to conventional wine.

**Table 1**  
Total caloric value, standard drinks, and common examples for alcoholic beverages.

Type of Beverage	Beverage serving size (fl. oz.) <sup>a</sup>	Strength (% alc/vol)	Average calories	Standard drinks <sup>b</sup>	Examples
Beer	12	5	153	1	Lagers, Ales, Malts, Stouts and Porters
Red Wine	5	12	125	1	Pinot Noir, Cabernet sauvignon, Dolcetto
White Wine	5	12	121	1	Chardonnay, Sauvignon blanc, Frontignac
Dealcoholized wine	5	–	30	–	–
Distilled spirits	1.5	40	97	1	Gin, Vodka, Whiskey, Tequila

<sup>a</sup> Beverage containers vary in size but are commonly within this range.

<sup>b</sup> The National Institute of Health definition of 1 standard drink = 14 g of pure ethanol.



**Fig. 3.** An overview of the main chemical constituents of wine. Reproduced with permission from Ref # [1].

## Composition of wine

The composition of wine is based on the grape constituents, products from yeast fermentation, and compounds formed during wine storage and maturation. More than 500 compounds have been analytically identified in wine, most ranging in concentrations between  $10^{-1}$  to  $10^{-6}$  mg per liter (mg/L) [5,52], which are not sufficient to individually play a role in the taste profile of wine, but collectively could be of significance [53]. The taste, fragrance, and texture are estimated to be largely due to a few constituents that occur in detectable concentrations of grams per liter (g/L) [54].

The major constituents of wine are water and ethanol, accounting for approximately 97% on a weight-by-weight (%w/w) basis. The remaining components of abundance are sugars, acids, other alcohols, and phenolics, present in concentrations of g/L. They play an important role in the sweetness, acidity, color, and the sensory and taste profiles of wine. Phenolics, particularly polyphenols, are of particular interest as they impart antioxidant activity to wine, and have been found to be biologically active in the human body [55]. Wines also contain esters, acetals, and other trace molecules, including minerals, vitamins, and nitrogen and sulfur containing compounds in much smaller concentrations [56]. Fig. 3 represents the main chemical constituents of wine.

## Water

Water is a major constituent of grapes and wine. It acts as a medium of chemical reactions during grape maturation, must fermentation, and wine aging. Many compounds important to the taste and aroma of wine are only soluble in water due to its unique intermolecular chemical properties [54]. Water is critical in establishing the basic flow characteristics, and is a fundamental chemical constituent of wine.

## Alcohols

The typical ethanol concentrations range from 10–15 vol%, with higher concentrations thereafter achieved through fortification [39]. Ethanol influences the stability, maturation, and taste and aroma profiles of wine. Increasing ethanol concentration generally increases the perception of bitterness and sweetness of wines [57,58], decreases the intensity of other odorants [59], and suppresses microorganisms growth during fermentation [60]. It also reduces the evaporation of other volatile compounds such as phenols, and improves the overall stability of wine through the production of esters [61]. Red wine grapes generally have a higher ethanol concentration than white wine grapes. In regards to other

alcohols in wine, methanol is present in ranges of 0.01–0.2 g/L, making it a minor constituent [61]. The maximum safe limit of ingestion is 2 g, with acute toxicity estimated at 8 g [62]. Wine has the lowest methanol concentrations out of all fermented beverages, and it exerts no direct sensory effects. Other higher alcohols of importance include methyl-propanols, butanols, and phenols, occurring as byproducts of yeast amino acid metabolism which contribute to aromas of wine [39]. A light-to-moderate consumption of wine at regular intervals has been reported to be inversely correlated with IHD [11], reduced systolic and diastolic blood pressure [63], and improved HDL-LDL cholesterol ratio [64]. These effects are postulated to be imparted, apart from the polyphenols, from the ethanol content of wine [1]. A meta-analysis by Gallagher et al. [65] characterized the association between different patterns of sustained alcohol consumption and atrial fibrillation (AF), finding that low-levels of alcohol intake were not associated with an increased risk of incident AF (Hazard ratio (HR): 1.03, 95% CI: 0.98–1.09,  $p=0.22$ ), with moderate consumption increasing the risk in males, but not females (Males: HR: 1.26, 95% CI: 1.04–1.54,  $p=0.02$ ; Females: HR: 1.03, 95% CI: 0.86–1.25,  $p=0.74$ ), and excessive consumption associated with an increased risk in both genders (Males: HR: 1.68, 95% CI: 1.18–2.41,  $p=0.004$ ; Females: HR: 1.29, 95% CI: 1.01–1.65,  $p=0.04$ ).

### Sugars

Sugars are the primary substrate for the production of ethanol in wine during fermentation. Residual sugars, from incomplete fermentation or non-fermentable sugars, add to the sweetness of wines. In grapes, the primary sugars are hexoses: fructose and glucose, typically occurring in concentrations of 0.2–4.0 and 0.5–1.0 g/L respectively. Sucrose is enzymatically split into fructose and glucose, and is typically found in concentrations of 0–0.2 g/L, making it a minor, and rare constituent of wine [39]. Grape sugars provide metabolic energy to the primary wine yeast, *Saccharomyces cerevisiae*, which converts the primary grape sugars to ethanol and CO<sub>2</sub>, in cases leaving some residual sugar content behind [38]. Dry table wines have a residual sugar content of 1–4 g/L, which is the threshold for classifying wines as “dry” [66]. Sugars can also be metabolized to higher alcohols, aldehydes, and fatty-acid esters, which add to the aromatic character of wine. While direct evidence of wine sugars on the cardiovascular risk profile is limited, observational studies support the findings that high intake of dietary sugars is associated with several metabolic abnormalities that unfavorably affect the cardiovascular system [67].

### Phenols

Phenols are a class of compounds with hydroxyl groups attached to an aromatic ring, while polyphenols are compounds with multiple rings. Phenolics are commonly found in dietary sources such as coffee, tea, fruits, and wine. Phenols contribute to the appearance, fragrance, taste, and antioxidant properties of wine, especially red wine [68]. Red wines have a substantially higher total phenolic content than white wines (2 g/L vs. 200 mg/L) [39].

Wine phenolics can be divided into two categories: the flavonoids and non-flavonoids. The flavonoids account for most of the polyphenolic component in red wine (>85%,  $\geq 1$  g/L) and comprise of compounds such as flavonols, flavan-3-ols, and anthocyanins. The non-flavonoid portion includes derivatives of carboxylic acids, hydroxycinnamates, hydrolysable tannins, and most importantly resveratrol, a stilbene derivative [69]. The flavonoids are extracted from the grape skin, seeds, and stem. Anthocyanins contribute to the colour of red wine. The non-flavonoid, tannins, are found in oak barrels and can appear in wine during storage,

adding to the astringency of the wine. Resveratrol is biosynthesized throughout the grape as a response to injury, mechanical trauma, fungal infection, or ultraviolet radiation [70].

Red wine extract of polyphenols, in experimental thrombosis rat models, was found to significantly reduce stasis-induced venous thrombosis [71]. Another extract of polyphenols prevented endothelial dysfunction and hypertension in Angiotensin-II induced hypertensive rats by improving nitric oxide (NO) bioavailability [72]. Short-term ingestion of grape juice was associated with improved flow-mediated vasodilation and reduced LDL-oxidation in patients with coronary artery disease (CAD) [73]. Both regular and dealcoholized red wine, in human subjects with CAD, were acutely demonstrated to reduce arterial stiffness, attenuate increased wave reflections, and decrease central systolic blood pressures [74]. Indirect observational evidence found the high intake of anthocyanins, a flavonoid, to reduce the risk of acute myocardial infarction in a cohort of 760 non-fatal AMI and 682 control Italian patients [75].

### Acids

The major organic acids in grapes and wine are: acetic (0.1–0.5 g/L), malic (2–7 g/L), tartaric (2–6 g/L), succinic (0.5–1.0 g/L), lactic (0–3 g/L), and citric acids (0.1–0.7 g/L) [39]. They represent >95% of the total acidic content of wine. The acids are responsible for determining the pH of the wine, which impacts its color, taste, and stability. Red wines have ideal pH ranges of 3.3 to 3.5, with white wines ranging between 3.0 and 3.3. External measures to correct the pH in wine adds significant costs to the industry [56].

### Other compounds

Grapes and wine contain nitrogenous compounds, with the most important one being amino acids, present in concentrations of mg/L. Amino acids are derivatives of amines. They play a role as subunits in enzyme biosynthesis and are important sources of nitrogen and energy during fermentation. Approximately 50 inorganic constituents are also found in wine. The most important inorganic element is considered to be potassium, which can exist in concentrations of g/L [56]. Despite minerals being minor components in the overall composition of wine, they play a role during fermentation, and also add to the chemical stability of wine. Dietary studies have identified potassium intake to be beneficial for blood-pressure regulation, endothelial function, vascular compliance, and other structural and functional cardiovascular parameters [76]. Since wine also confers these benefits during regulated intake, potassium may be a contributor to the bioactive properties of wine [56]. Sulfur containing compounds also contribute to the quality and the sensory properties of wine. They are derived via wine fermentation or through the external addition of sulfur dioxide, a universally added compound in wine production [77]. Inorganic sulphites in wines are typically found in concentrations of  $\mu\text{g/L}$ , with some yeasts able to produce 10–30 mg/L [38,77]. Sulphite exposure has been associated with adverse reactions including anaphylaxis, headaches, dermatitis, hypotension, cardiac dysfunction, and gastric and intestinal disorders [78]. While the addition of sulfur in wine is allowed in most countries, following reports of sulphite-related adverse events, the United States Food and Drug Administration prohibited its use on raw fruits and vegetables, and declared that concentrations of >10 mg/L must be reported on labels, including wines [78,79].

### External influences on the composition of wine

External influences that affect the quality and composition of wine include aspects of the soil such as water accumulation,

nutrient content and pH, as well as topographical influences such as temperature and sunlight [80]. A high nitrogen content of the soil has been found to suppress the production of anthocyanins, but promote amino acid production. High potassium levels in soil can perturb the pH ranges of the grape, impacting the stability of wine [81]. Excess water accumulation in the soil can reduce sugar concentrations and increase the grape's acidity, thereby influencing the ethanol content of wine during fermentation [82]. Temperature can affect yeast fermentation, polyphenolic concentration, and the stability of wine. Solar exposure is an important climatic factor affecting grape production, with a sloped orientation of the vineyard considered ideal [5,38].

### Wine phenolics and cardiovascular health

Wine phenolics have been found to limit LDL oxidation by scavenging radicals, an effect attributed to the phenol ring, reduce platelet aggregation, promote fibrinolysis, and prevent endothelial dysfunction through increased bioavailability of NO [1,83].

#### *Polyphenolic bioavailability*

Polyphenols can only exert biological effects if they are detectable in the plasma. Specific wine polyphenols have been quantitatively detected in the human body after acute and chronic consumption of wine [84,85]. The most important polyphenols include flavonoids (quercetin, catechin, anthocyanins) and non-flavonoids (resveratrol). There is considerable evidence that wine polyphenols act as powerful antioxidants and are bioavailable after acute and chronic consumption of red wine to exert biological effects in vivo [86]. Vitaglione et al. [85] reported that trans-resveratrol bioavailability in humans was independent from meal content, suggesting that detected concentrations in serum samples were due to the acute consumption of red wine. Even though the bioavailability of resveratrol is low, it is not reduced by simultaneous consumption of food. Giovinazzo et al. [87] review the means of increasing resveratrol bioavailability, which can be done by producing synthesized analogues or administration of enzyme inhibitors to increase available serum concentrations. Analogous to resveratrol, flavonoids are also absorbed into the circulation, however acute consumption of wine may not be a plentiful source compared to food items [88]. With prolonged red and white wine consumption however, plasma concentrations of resveratrol and catechin, a flavonoid, are significantly elevated [89]. Upon entering the body, polyphenols appear to be conjugated, with the metabolized forms possessing antioxidant properties [90]. Limitations of gastrointestinal absorption in humans means that it would potentially require large doses of red wine to have a biological effect.

#### *Non-flavonoids*

Resveratrol, a stilbene derivative, is considered to be an important bioactive constituent of wine. Resveratrol exists in two forms, cis (Z) and trans (E), with the cis-isomer able to isomerize to trans in a process known as photoisomerization [91]. The cardiovascular effects of resveratrol have largely been reported in animal models, with limited but increasing literature in humans. As a polyphenolic compound, resveratrol is an effective radical scavenger, protecting against oxidative stress [92]. Resveratrol is postulated to upregulate endothelial NO synthase (eNOS), which increases NO levels, causing vasodilation and an elevated blood flow [93]. Resveratrol has been reported to cause vasodilation of isolated human arteries through a NO-mediated mechanism [94]. Links between resveratrol and reduced platelet aggregation have also been reported [95]. The effects of resveratrol on several cardiovascular pathologies has been investigated [96]. In hypertensive animal

models, low doses of resveratrol (5–10 mg/kg/day) were sufficient to lower blood pressure under different conditions [97–99]. Several animal studies have shown the intake of dietary resveratrol to lower LDL cholesterol, triglycerides, and increases HDL cholesterol [100–102], however clinical studies have been more variable, and this effect cannot be causally attributed to resveratrol alone [103–106]. Resveratrol has been shown to protect against ischemia-reperfusion injury and myocardial damage [107–110]. In general, preclinical and clinical studies have shown interesting but inconsistent results.

#### *Flavonoids*

Flavonoids are a class of plant pigments that also occur in the grapes used for the production of wine. Research on flavonoid chemistry and its associated effects on cardiovascular diseases has steadily increased over the past 20 years [111], with preclinical and clinical data reporting the intake of flavonoids, particularly quercetin, to be beneficial for patients with CAD [112], decrease LDL-oxidation [113], and improve vasodilation [114]. A dietary investigation of 10,054 Finnish men and women found that the risk of mortality from IHD was lower with a high quercetin intake (RR 0.79; 95% CI 0.63–0.99; P=0.02) [115]. Quercetin is a type of flavonoid known to be an effective radical scavenger. Studies have demonstrated that intake of quercetin can increase the antioxidant capacity of blood plasma [116], improve endothelial dysfunction through a NO dependent pathway [117], and reduce atherosclerotic lesions in apolipoprotein E knockout mice models [118].

### Frequency and patterns of consumption: An important consideration

There is no doubt that the excessive and binge-consumption of wine, or alcohol, is detrimentally associated with cardiovascular outcomes and all-cause mortality. As for the light-to-moderate consumption, its protective effects with respect to IHD and all-cause mortality have been well demonstrated. Similar findings have also been reported for beer and spirits [119,120]. However, these observations have methodological variabilities. Rehm et al. [121] discuss this issue in detail, making several important observations. Firstly, these studies are largely epidemiological, however, much of the data points into the direction of a light-to-moderate consumption being cardioprotective. The authors present the “sick quitter” argument, where former drinkers who give up consumption due to health reasons, are included into the control group, making the group artificially sicker [121]. The observed effects of a light-to-moderate intake can be exaggerated in this case. The authors state that even Mendelian randomization studies, where instrumental variables are used as genetic variants, are prone to their own selection biases that may overestimate the protective effects [122]. Although causality cannot be absolutely established, the evidence should not be discarded, and for drinkers, safe-consumption guidelines constituted by national and international bodies should be followed.

#### **Future directions**

General awareness of alcohol misuse is prevalent, however many misconceptions remain regarding recommendations of appropriate intake, and risks and benefits of consumption [123,124]. While it is clear to physicians what to recommend to their patients in terms of diet, exercise, and smoking, it is important to question whether the same be said about providing recommendations for alcohol and wine use. Alcohol consumption guidelines are publicly misunderstood, highly variable between literature, and

**Table 2**  
Low-risk consumption guidelines of national and international organizations.

Type of beverage	Year of publication	Low risk consumption guidelines	Guidelines by gender	Standard drink size, g	Standard drink equivalents
World Health Organization [127]	2001	≤2 std./day for men and women; at least 2 non-drinking days per week	–	10	11 oz. of 5% beer, 5 oz. of 12% wine, or 1.3 oz. of 40% spirits
American Heart Association [132]	2015	≤ 1–2 drinks/day for men, and ≤ 1 drink/day for women	+	Not defined	12 oz. beer, 4 oz. wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits
Dietary Guidelines for Americans [128]	2015	≤ 2 std./day men and ≤ 1 std./day women	+	14	12 oz. of 5% beer, 5 oz. of 12% wine, or 1.5 oz. of 40% spirits
Canadian Centre for Substance Abuse & Addiction [129]	2011	≤3 std./day (and ≤ 15 std./week) for men, and ≤ 2 std./day (and 10 std./week) for women	+	13.45	12 oz. of 5% beer, 5 oz. of 12% wine, or 1.5 oz. of 40% spirits

Abbreviations: std. = standard drink; oz. = fluid ounces.

across country borders [125]. Low-risk consumption limits for alcohol vary across national and international guidelines, as seen in Table 2. These guidelines are commonly reported by governments and/or national institutions to quantify alcohol consumption, monitor associated risks, and to encourage safe drinking practices. They are defined in at least 37 countries [126]. The World Health Organization (WHO) [127] assumes 1 standard drink to equal 10 g of pure ethanol, with a recommendation to not exceed 2 std./day for both men and women, with at least 2 non-drinking days per week. In the United States, 1 standard drink equates to 14 g of pure ethanol (40% greater than the WHO definition), with a recommendation to not exceed 2 std./day for men and 1 std./day for women [128]. The Canadian guidelines [129], also vary when compared to the WHO and the United States. A study by Wood et al. [130] analyzed individual-participant data for alcohol use across 83 prospective studies, aiming to characterize risk thresholds for all-cause mortality and cardiovascular disease subtypes. With 599,912 current drinkers, the lowest risk of premature mortality was observed in drinkers consuming alcohol at ≤ 100 g/week. This threshold is substantially lower than many international guidelines, particularly of the United States. With such variation in policy, there is little evidence regarding the physician demographic and their knowledge of consumption guidelines, how to decipher them, and whether or not they are comfortable counselling a patient, within their standard of care, on alcohol consumption patterns and safe levels of alcohol intake. Studies have shown that screening for hazardous drinking along with physician intervention at the primary healthcare level can result in reduced patient consumption [131], however it is not very well-known how much primary care practitioners are aware of alcohol consumption guidelines. Given the variability in the guidelines, recommendations for consumption may be less obvious, and this area may present a knowledge gap to address in the future.

## Conclusions

Despite the conflicting arguments regarding the cardioprotective nature of wine and other alcoholic beverages, the ethanol and polyphenolic components of wine have demonstrated desirable biological activity against cardiovascular diseases. Wine is a chemically complex beverage where each chemical compound contributes to the overall matrix to influence flavor, perception, taste, and mouthfeel. As the alcohol-attributable global disease burden rises and guidelines vary, the detriments of alcohol consumption become exacerbated, with heavy drinking being the most-detrimental.

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