Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Wine and food

Wine and its association with food have generated an incredible cornucopia of literature. Amazingly, few of the views and assumptions have been subjected to scientific scrutiny. Only a few research papers deal with the topic. This may relate to their subject disciplines (enology and food science) being in separate departments. Also, the funding is different. That for enology and viticulture comes largely from government or industry grants, often based on levies on vineyards and wineries. Funding in the food sciences comes largely from commercial firms, much of it done internally by food companies, and such research remains proprietary. Funding from disparate industries provides little incentive for collaboration on interdisciplinary projects, such as food and wine combination.

Much of what is written is by those with an arts rather than a science background. Sommeliers, for whom the combination of wine and food is their field, are more practitioners than researcher/academicians. Thus, the topic has experienced languor, devoid of scientific rigor. Only recently have scientists ventured into a subject normally the prerogative of the epicurean. Scientists, being inherently doubters, demand experimental verification. The latter is difficult as designing adequate controls is next to impossible. In addition, the laboratory conditions, required for experimentation, make the relevance of finding to “real life” situations dubious. With food and wine combinations, the social context is often more important to perception than actual sensory clues. Finally, social pressures often lead to acceptance of supposed norms.

What follows is a brief discussion of the issue of food and wine combination and what can be said with a
degree of confidence. In addition, it is hoped that it will provide “food for thought” to those seriously interested in wine.

The traditional view is that wine is in some fundamental way designed to be consumed with food. However, when one searches for evidence, it seems to be a myth—a view so oft repeated as to be taken as gospel—an example of social contagion of collective memory. Wine appears to have been the standard food beverage in the Greek or Roman worlds. In the Near East and Egypt, wine was almost the exclusive preserve of the secular and religious oligarchy. In contrast, beer was the beverage of the laboring classes. Wine is mentioned in the Bible but recommended primarily in relation to religious ceremonies and weddings. It is only in regions where wild grapes grew indigenously that vines came to provide the drink for the masses. Its acidity, alcohol, and phenolic contents enhanced its antimicrobial property, making it considerably safer to drink than water. Wine’s mildly antiseptic properties became increasingly important as population numbers grew, hygienic conditions deteriorated, and water supplies became more polluted. Although production was seasonal (unlike beer based on dry grains), wine’s comparative resistance to spoilage (isolated from air) permitted wine to become the preferred beverage. In addition, wine’s higher alcohol content could temporarily numb the afflictions of a peasant life. Although safe and nutritious (calorie rich), there is nothing in its attributes that inherently makes wine ideal as a food beverage. It is actually better suited for one of its ancient secondary roles, a solvent in preparing extracts from medical herbs.

The sharp acidity of many ancient wines, often extended with aged seawater and vinegar (especially for slaves), can hardly be considered an ideal food accompaniment, at least from a modern perspective. The resinous flavor donated by storage in standard amphoras (made watertight with an inner coating of pitch) would not have facilitated detecting any subtle fragrances they might have had. The quality of the ordinary wine available to the average Roman is probably best left to the imagination. Finer wines were available for the patrician classes. These were probably stored in amphoras with a vitreous inner surface, without the need for a pitch lining. The most famous seem to have been or became highly concentrated with age, being almost syrup-like, usually diluted before being consumed. Several Roman poets eulogized the wonders of particular vintages.

Even modern wines, with their predominant acidic, bitterish, and astringent character have little to suggest food compatibility. These characteristics are simply the natural consequence of grape chemistry, not conscious intent. Admittedly, consuming wine with food does mollify its less pleasant aspects, unless one develops an appreciation for sour beverages with a bitter/astringent aspect. Some humans seem adept at coming to appreciate, even crave, perceptions initially repulsive to painful. Black coffee, capsicum peppers, durian, and Limburger cheese are classic examples.

In some instances, the iron content of the wine can induce a metallic sensation, by catalyzing lipid oxidation. This may be masked in combination with food. However, this appears to be unrelated to the fishy aftertaste associated with some white wines taken with seafood (Tamura et al., 2009).

In most “compatible” combinations, both the cheese and wine appear better—not by directly enhancing their respective qualities but by mutually suppressing their less pleasing attributes (Nygren et al., 2002, 2003a, 2003b). Other studies have extended these findings, lending support to the view that red wines pair better with cheeses, due to wine tannins appearing more silky (Bastian et al., 2010). The fatty acid content of the cheese may also contribute to reduced bitterness (Homma et al., 2012), possibly by coating taste receptors. Lipoproteins, typically found in foods, can react with taste receptors, suppressing the perception of bitterness (Katsuragi et al., 1995). However, the bitter-suppressing aspect of cheeses may also relate to its salt content (Frijters and Schifferstein, 1994; Breslin and Beauchamp, 1997; Keast et al., 2001) or the presence of glutamate and adenosine monophosphate (Keast and Breslin, 2002). The fruity aspect of wine may also be enhanced when sampled with cheese (Galmariini et al., 2016).

Although most cheese/wine associations seem mutually beneficial, some are not, for example, sweet wines and cheese (Bastian et al., 2009). That compatibility originates from the negation of unpleasant sensations may not be what wine pundits and sommeliers profess, but it seems closer to the truth. This phenomenon may also apply to many supposedly food and wine “marriages.”

Salt’s suppression of bitterness (Nakamura et al., 2002) might explain the seemingly ancient habit of adding seawater to wine (e.g., *oinos thalassikos* (Younger, 1966, p. 130). Pliny (Historia Naturalis, 14.120) also records that salt enhanced the perceived smoothness of wines. Columella (*De Res Rustica* 12.41) recommends the addition of salt, apparently to avoid moldy tastes. He also notes salt addition in a recipe for preparing “Greek” wine. Salt water was even used until recently in preparing new barrels to receive wine (Nègre and Françoit, 1955).

Salt is well known as a flavor enhancer. This may involve disrupting weak, nonvolatile complexes between matrix and aromatic compounds, promoting their liberation and retronasal detection (Linscott and Lim, 2016). In addition, sodium ion hydration may decrease “free water,” changing solution polarity. Although salt
increases aromatic volatility, saltiness is by itself appreciated (Bolhuis et al., 2016).

When one searches for affinities among the attributes of food and wine, one comes up empty-handed. In contrast, there is extensive incongruity. Table wines possess gustatory attributes predominantly characterized by sourness, bitterness, astringency, and burning sensations. Although pronounced sour tastes are inherently unpleasant, wine’s acidity is of value when used as a marinade—promoting acid-induced hydrolysis of food proteins. Wine phenolics can also act as antioxidants, reducing the toxicity of heterocyclic amines (Viegas et al., 2012) and acrylamide (Qi et al., 2018) generated during frying (Viegas et al., 2012). Phenolics are also antimicrobial (Nisiotou et al., 2013). By comparison, sourness is a rare attribute in most world cuisines (see Moskowitz et al., 1975 for a marked exception). Acids typically are added only as a component in some condiments or flavorants, notably vinegar, lemon juice, or tamarind. They can enhance the flavor of otherwise bland foods. The bitterness and astringency of most red wines also find no equivalent in meat and fish. The protein content of food reacts with both wine acids and phenolics, limiting their activation of taste and touch receptors.

In comparison with wines, solid foods are characterized salty, savory (glutamate), sweet, and sebaceous (fatty acids) sensations. Sour, bitter, astringent, and hot spicy attributes are (or have been) less common in Western cooking and then usually in condiments. The inherent, aversive reactions to such sapid sensations probably arose as a protective response to avoid or limit the consumption of potentially toxic (or rotten) foods. Conversely, bitter/astringent/toxic compounds were probably selected during plant evolution to discourage their consumption, with the principal exception of ripe fruit. During domestication, crop variants with reduced aversive and enhanced pleasant-tasting constituents have been propagated. Thus, lettuce and other vegetables became less bitter; apples, cherries, and other fruits sweeter and less sour or astringent, citrus fruit less acidic, and legumes less flatulent. Food preparation, notably cooking, further facilitated the inactivation or removal of potential food toxins and antimetabolites. Examples include fungal toxins, potato alkaloids, and casava cyanogenic glycosides. Cooking meat also facilitates digestion (promoting collagen and protein fiber breakdown) and enhances flavor. Disappointingly, some cooking processes generate their own toxins, notably roasting and searing. Examples are acrylamide (a Maillard by-product) and a variety of toxic, pyrolytic, smoke by-products. Fermentation is another ancient technique that helped destroy antimetabolites. An example is the action of Rhizopus oligosporus degrading soybean flatulence compounds during tempeh production. Lactobacillus can also destroy soy saponins. Fermentation also has the potential to break down difficult-to-digest oligosaccharides as well as help preserve perishable foods.

The aromatic aspects of food and wine equally show little similarity, on which supposed compatibility could be based. Wine aromas are most frequently described in terms of fresh fruit, jam, or flowers. None of these is characteristic of the main components of a meal and would be considered odd if present. The hints of “apple” in Chardonnay wine may be compatible with chicken, the “pepper” of a Shiraz pair with pepper steak, and the “walnut” of some sherries combine with nut-containing salads (without vinaigrette). However, does the box wood or cat urine of Sauvignon blanc, the rose of Riesling, and the black currant of Cabernet Sauvignon really match with any main course? In addition, does the vanilla/coconut of oak or the leather aspect of aged red wines have any inherent compatibility with food? The supposed spiciness of Gewürztraminer wines is given as a reason for its combination with spicy Asian foods. However, the wine has more litchi aroma than spiciness, making the stated logic dubious. It is only its intense aroma that may permit its presence to remain noticeable. Personally, the best aspect of wine and food association is not their complementary natures but their contrasts. Each cleanses the palate between alternate samplings, allowing fresh perceptions of each. Thus, wine permits swift shifts in savory sensitivity.

Without comparable tastes or flavors, where is the supposed inherent rapport between food and wine? Is its only justification the reduction of undesirable aspects of the partnership and as a palate cleanser? Certainly, wine’s ability to partially rinse the palate between food samples is important. It offers both gustatory, olfactory, and trigeminal receptors time to reestablish their native receptive state, countering adaptation and loss of sensory appeal. Thus, food appreciation is enhanced by being sampled afresh. Wine can, unromantically, be viewed as a savory mouthwash. In addition, volatility of food and wine flavorants is influenced by the dynamically changing concentrations of ethanol, phenols, carbohydrates, etc. supplied with the wine. Conversely, food dilutes, masks, and eliminates most wine flavors. The result being that the next sample can be appreciated to its full, adaptation having been avoided.

The other aspect of potential compatibility arises from their dissimilar attributes. They act in concert, in a manner similar to condiments, providing flavor accents to enhance and maintain flavor interest throughout the meal. The result can be the creation of a stimulating holistic experience. The typical starchy elements in a meal (rice, potatoes, pasta, bread) supplement the synergy, helping to cleanse the palate and generate a feeling of satiation.
However, statements like “wine cuts through fat” are unsupported. If this view has any validity, the partial fat solubility of ethanol may reduce the oily mouth-feel of fats as well as limit the activation of fatty acid taste receptors (Running et al., 2015), but this is no more than speculation. The acids in wine might also have a similar effect. In addition, wine tannins may denature the G protein receptors responsible for detecting fatty acids in the oral epithelium, giving the impression of less fattiness. Conversely, fatty acids can reduce the perception of sourness, astrigency (Peyrot des Gachons et al., 2012), and bitterness (Mattes, 2007), possibly improving mouth-feel.

Wine phenolics can either reduce (Jung et al., 2000) or enhance (Mitropoulou et al., 2011; Villamor et al., 2013) volatility, depending on the phenolic and aromatic involved. Carbohydrates also have the ability to bind aromatics, reducing volatility and significantly modifying wine flavor and its retronasal attributes (Voilley and Lubbers, 1998; Villamor et al., 2013). Thus, both synergies of flavor as well as suppression could be involved in “ideal” pairings. Saliva-induced changes in flavor chemistry is another compounding issue little investigated. Whether such potential reactions are sufficiently marked and rapid to have significance, within the time frame of food consumption, is currently terra incognita.

In all the standard discussions of wine and food combinations, the obvious is rarely if ever mentioned. It limits the rate and maximum amount of alcohol reaching in the blood (Fig. 12.1). Correspondingly, it reduces breath-alcohol content (Sadler and Fox, 2011) and diminishes alcohol’s performance impairment (Millar et al., 1992). In addition, by reducing alcohol uptake, its tendency to promote overeating is repressed—by limiting activation of hypothalamic Agrp neuron activity (Cains et al., 2017).

Many aspects of food preference appear to develop in utero, based on what the mother ate during pregnancy (Mennella et al., 2004) and infancy. Thus, early exposure can play a significant role in developing personal preferences. Subsequently, peer pressure and cultural influences may combine to modify these early dispositions. Habituation may not be imbued with the effusive and social appeal associated with the image of predestined food and wine marriages but far better fits the facts than any supposedly heaven-inspired pairings. Thus, there is little wonder why there has been scant inclination to investigate lovingly held shibboleths about food and wine associations.

However, a dose of reality does not have to destroy long-held views. Knowing that Michelangelo’s Sistine Chapel consists of no more than brush strokes of pigment on plaster, perceived by photoreceptors in the eye, converted to synaptic impulses reconstructed piece-meal into a perception at the back of the brain, need not ruin art appreciation. Ideally, it should enhance the wonder it instills. Scientific understanding augments adds new layers of appreciation. If supplemental knowledge were not considered to augment appreciation, why would connoisseurs be so concerned with vintage dates, wine geography, cultivars, or details of vineyard sites and wine producers? With knowledge, it really is the more the merrier.

**FIGURE 12.1** Blood alcohol concentrations after wine drinking in a single dose. (A) fasting; (B) during a meal; (C) 2 h after a meal; (D) 4 h after a meal; (E) 6 h after a meal. From Serianni, E., Cannizzaro, M., Mariani, A., 1953. Blood alcohol concentrations resulting from wine drinking timed according to the dietary habits of Italians. Q. J. Stud. Alcohol A 14, 165–173, Reproduced by permission.
Admittedly, scientific realism injected at the wrong time may be a despoiler. For special events, psychological appeal can be more significant than sensory reality. As in other aspects of life, science can occasionally be set aside to permit spontaneity and anticipated pleasure presides. The intrigue of magic is being fooled so effectively.

Under most circumstances, though, some basic rules of pairing should be kept in mind, to avoid glaring mistakes. In most fine cuisine, flavor balance, combined with suitable complexity, is central. Nonetheless, the vagueness of this concept is evidenced by the almost infinite variety of combinations seen in cookbooks, food magazines, and culinary shows. Accepted norms also vary markedly among cultures (Rozin, 1977, 1982). Thus, it should not be surprising that almost any wine can pair with almost any meal. There are limits, however, for example a dry Gewürztraminer with dessert or a Riesling Auslese with bouillabaisse. To almost everyone, these would not be considered “marriages made in heaven.” Cabernet Sauvignon and dark chocolate is another clash but seeming appreciated by some connoisseurs. Except where there are clear flavor or intensity disparities, notably sweet/acid or sweet/bitter-astringent, almost any combination will be found pleasing to some and acceptable to most.

Of the generalities oft quoted, the “white with white, red with red” dictum bears logic, within the context of balanced flavor intensity. Nonetheless, it is often the food preparation mode (e.g., poached, fried, baked, broiled, barbequed) or the condiments added (e.g., chilies, curry, relish, olive oil, tomato sauce, garlic, herbs) that often have the greatest influence on flavor intensity, the basic character of the meal, and correspondingly a compatible wine.

In most instances, premium-quality table wines are best sampled prior to the meal and premium-quality dessert wines after the meal. Because of their aromatic complexity, detection of these attributes is compromised by combination with food or dessert. Alternatively, the food or dessert should be designed to be a foil for the wine and be mild in character. In contrast, the more markedly acidic or bitter/astringent the wine, the more effectively these features will be mollified by association with food. Might not this be the most justifiable reason for the pairing most wines with food (other than reduced alcohol uptake)? In addition, a lack in the wine’s aromatic interest can be camouflaged by flavors from the food. Where little attention is likely to be paid to the wine, inexpensive, nondescript red or white wines are both financial and logical choices.

If some food and wine pairings are ill-conceived, are there seraphic duets? Clearly some do pair better than others, but transcendental experiences? Published accounts of such paradisaical experiences may be no more than figments of a fertile imagination, created to sell wine, newspapers, or magazines. Admittedly there is an incredible range in human sensory sensitivity—those having higher than average acuity tending to prefer milder flavored foods, and those with below average acuity tending to prefer more intensely flavored foods. But these are no more than tendencies, with experience and social pressures capable of inducing significant shifts in preference, if not perception. Psychological influences and a desire to be influenced can distort perception, creating impressions that are “real,” only because of the conditions under which the experience occurred. The more unexpected and astounding the sensation, the stronger the memory trace created. The more the mind is studied, the more we come to realize how the brain can distort perception, based on past experiences. They generate mental models of reality, against which sensations are judged, interpreted, and potentially modified. Thus, it is wise to doubt perceptions and attempt to separate experience-based memory patterns from actuality, unless it is a selective choice to allow the mind to potentially deceive us.

In addition to the sensory pleasure wine can supply when taken with a meal, it also has health benefits. Among other direct benefits noted below, dining with wine can reduce the absorption of oxidized lipids and thereby limit their cardiovascular damage (Natella et al., 2011).

**Moderate wine consumption**

The contrasting social and antisocial effects of alcohol consumption must have become evident shortly after the discovery of winemaking—the negatives being noted early in the Old Testament (Genesis 9.21) and vividly described by Pliny (Historia Naturalis, 14.28). Time has only expanded our understanding of this Dr. Jekyll—Mr. Hyde relationship. It is clear that excessive alcohol consumption, both acute and chronic, can have devastating effects on physical and mental well-being. Abusive ethanol consumption can cause cirrhosis of the liver, increase the likelihood of hypertension and stroke, favor the development of breast and digestive tract cancers, induce fetal alcohol syndrome, among others. Many of these effects seem to arise from excessive alcohol intake activating of free-radical release and associated immune perturbations (Meagher et al., 1999). Other, more severe, negative consequences may arise indirectly, via the accumulation of acetaldehyde, a major breakdown product of ethanol metabolism (Lachenmeier et al., 2009). Because the problems associated with alcoholism (Abrams et al., 1987; Schmitz and Gray, 1998) and its eventual, irreversible, chemical modifications in the brain (Nestler and Malenka, 2004; Heinz, 2006) have been extensively reported, they need not be elaborated here. On the other hand, it is becoming equally clear that moderate wine
consumption (approximately 250 mL/day) can potentially have health benefits. This is considerably less than the two bottles per day that Brillat-Savarin (1848) considered a healthy man could consume and live long; or the amounts considered appropriate in times past (Younger, 1966, p. 367). Mark Twain, in characteristic style, crystalized moderation in his view of the temperance movement: "Temperate temperance is best" (Mark Twain's Notebook, 1896).

Multiple epidemiological studies suggest that daily, moderate, alcohol consumption (Thun et al., 1997; Doll et al., 2005), and notably wine (Grønbæk et al., 2000; Renaud et al., 2004), is associated with a reduction in all-cause mortality. This is expressed in the now famous J-shaped (hormesis) curve (Fig. 12.2), with earlier mortality being associated with both excess alcohol intake and abstinence. This is particularly evident in the reduced incidence of cardiovascular disease in moderate alcohol consumers. In addition, it reduces the likelihood of type 2 diabetes, combats hypertension, and is correlated with reduced frequency of certain cancers (Boffetta and Garfinkel, 1990). Although encouraging to those who enjoy wine, the sharp rise in death risk at much above moderate consumption is of concern. Presumably, this relationship would apply equally to morbidity figures, were such data available. However, morbidity unlike mortality is qualitative rather than quantitative and thus its measurement fraught with difficulty. Additional dangers associated with anything more than moderate consumption, especially alone, comes from alcohol's progressive enhancing of the memory circuitry involving addictive cravings.

These epidemiological correlations are supported by in vivo studies that provide potential molecular explanations for these associations. The principal elements missing, in confirming a causal relationship, involves detailed information on the dynamics of absorption, metabolism, and elimination of the proposed active ingredients.

Faced with a chemical and beverage that can be not only salubrious but also addictive, the fluctuations in society's attitude toward alcohol are not surprising (Musto, 1996; Pittman, 1996; Vallee, 1998). Thankfully for those in the wine industry, wine drinkers appear less likely to become heavy drinkers (Jensen et al., 2002) or to illustrate those alcohol-related problems that have given alcohol a bad reputation (Smart and Walsh, 1999). In addition, wine has a more positive social image than other alcohol-containing beverages (Klein and Pittman, 1990; Unwin, 1992). The major caveat is the derogatory epithet, wino, ascribed to some unfortunate members of society.

The use of wine as a medicine or carrier for herbal extracts has an extensive history. It goes back at least to pharaonic Egypt (Lucia, 1963; Soleas et al., 1997). Ancient Greek and Roman society used wine extensively as a solvent for medicinal infusions. This practice continued largely unabated until the beginning of the twentieth century. The excessive abuse of distilled alcoholic beverages, combined with religious and political conservatism, created a backlash against all beverages containing alcohol, notably in North America. Alcohol was viewed as an agent of corruption to be annihilated. Following the failure of Prohibition, humans themselves, not alcohol, came to be viewed as the source of iniquity. Alcoholism is now viewed as a developmental, multistage, chronic dependence, possessing a complex etiology (Nurnberger and Bierut, 2007), with both genetic and environmental aspects. In this regard, it is similar to other addictions (Ersche et al., 2012). Thus, the social climate is changing and the relationship between wine (as opposed to alcohol) and health is again being reassessed and investigated seriously.

It is unlikely that doctors will soon be prescribing wine for its health benefits. Too often, people have difficulty recognizing the limits of rational use and differ markedly in their metabolism (Gross et al., 2010). In addition,
detrimental influences rapidly counter any benefits at more than light to moderate consumption (often viewed as <30 mg ethanol/day) (Rehm et al., 2010). Erring on the side of restraint seems judicious, without excessively assuaging pleasure, especially if combined with food. Even dietary flavonoid supplements (one of the benefits of wine consumption) can be detrimental, if taken in excess (Skibola and Smith, 2003). Wine can be wonderful in moderation but is no panacea.

Alcohol

Metabolism

Alcohol is the primary by-product of fermentation in many organisms. Ethanol is also an energy source for an even larger number of species. Thus, it is not surprising that enzymes involved in ethanol metabolism are found in most life forms. In humans, ethanol enters the bloodstream either via the consumption of beverages containing alcohol, and/or from ethanol synthesized by members of the intestinal flora. When the concentration of alcohol is low, most of it is metabolized in the liver before it enters the systemic blood supply. Most of the blood coming from the digestive tract passes through the liver before being dispersed to the rest of the body.

The liver metabolizes about 95% of the blood alcohol content, at about 15 mL/h. The rest tends to be lost via the breath or secreted in the urine and other bodily fluids. The rate of alcohol loss is relatively constant over time, with ~50% reduction within 5 h (Fig. 12.3). The liver possesses two ethanol metabolizing pathways. The primary, constitutive mechanism involves the oxidation of ethanol to acetaldehyde, via cytoplasmic alcohol dehydrogenases (ADHs). Of the seven known ADH genes (Crabb et al., 2004), three function in the liver. The others act in the gastric epithelium and other tissues. Subsequent metabolism converts acetaldehyde to acetic acid. This occurs principally under the action of mitochondrial acetaldehyde dehydrogenase (ALDH2). The cytoplasmic acetaldehyde dehydrogenase (ALDH1) is less active. Acetic acid is subsequently secreted into the blood or directly converted to acetyl CoA. From this point, metabolism may flow along any standard biochemical pathway (see Fig. 7.20).

Alcohol metabolizing enzymes frequently occur in allelic forms (isozymes). Their relative occurrence also tends to vary among ethnic groups. Some isozymes possess distinct physiological attributes. For example, ADH1B*1 codes for a subunit that oxidizes ethanol slowly, whereas ADH1B*2 encodes a highly active subunit of the dimeric enzyme (about 30 times more efficient) (Thomasson et al., 1995). Correspondingly, those individuals who are homo- or heterozygous for the ADH1B*2 subunit, eliminate alcohol from the blood more rapidly. Rapid alcohol oxidation may donate a degree of protection against alcoholism, by quickly converting ethanol to acetaldehyde. However, if combined with slow-acting alleles for acetaldehyde dehydrogenase (ALDH2) (Crabb et al., 2004), the accumulation of toxic acetaldehyde is enhanced, predisposing the bearer to cancers of the oropharynx and esophagus. Those also possessing malfunctional glyoxalase and methylglyoxalase repair enzymes are those most susceptible to such damage (see Dingler and Patel, 2017).

A second, ethanol-degradation hepatic pathway becomes activated when blood-alcohol levels become elevated. It involves a microsomal cytochrome, P4502E1 (CYP2E1). It oxidizes ethanol to acetaldehyde, using molecular oxygen rather than NAD⁺. Regrettably, the microsomal pathway generates free oxygen radicals (Meagher et al., 1999)—molecules (or ions) with one or more unpaired electrons. These highly reactive oxidants, or reactive oxygen species (ROS), can be generated long after alcohol intake ceases. Another variant of CYP2E1 occurs in the gastric mucosa, seemingly being more active in

![Figure 12.3](image-url)
Physiological actions

The ability of ethanol to displace water and its unregulated passage across cell membranes explains much of alcohol’s toxicity. In addition, its oxidation to acetaldehyde tends to be more rapid than acetaldehyde’s oxidation to acetate. Thus, acetaldehyde may accumulate in the blood and other bodily fluids. This is often viewed as an important contributor to the toxicity associated with excessive alcohol consumption (Lachenmeier et al., 2009). Differentiating between these direct and indirect toxic effects of excessive ethanol intake has proven difficult.

One of the first physiologic effects of alcohol consumption is a suppression of cognitive brain function. This is most noticeable in enhanced sociability—by blocking social inhibitions regulated by higher brain functions. For others, it quickly induces drowsiness (Stone, 1980). This probably explains why taking a small amount (90–180 mL) of wine before sleeping often helps those suffering from insomnia (Kastenbaum, 1982). This amount often provides the benefits of sleep induction, without causing subsequent agitation and sleep apnea—often associated with greater alcohol consumption. The effect on sleep may arise from alcohol’s modulating the action of inhibitory γ-aminobutyric acid (GABA) receptors, while suppressing the action of excitatory glutamate receptors. GABA and glutamate are estimated to be involved in about 80% of the neurocircuitry of the brain. The level of melatonin in wine is well below those prescribed as an insomnia medication (Rodriguez-Naranjo et al., 2011).

Another effect on brain function results from a reduction in the secretion of vasopressin. As a consequence, urine production increases, producing the frequently reported diuretic effect associated with alcohol consumption. Less well known is how alcohol acts as a crucial regulator of the hypothalamic–pituitary–adrenal axis, modulating the release of hormones such as adrenocorticotropic hormone and corticosterone (Haddad, 2004).

Although alcohol has a general depressive action on brain function, the levels of some brain modulators show transitory increases. Examples are serotonin and histamine. The latter may activate a cascade of reactions leading to headache production.

Another of the multiple influences of alcohol is the conversion of hepatic glycogen to sugar. This results in a short-lived increase in plasma glucose content. This, in turn, can cause glucose loss in the urine as well as an increase in insulin release by the pancreas. Both result in a drop in blood sugar content. If sufficiently marked, hypoglycemia results. This apparently causes the temporary weakness occasionally associated with alcohol consumption, especially excess intake.

In addition to direct effects, the accumulation of acetaldehyde, as a by-product of ethanol metabolism, may have several undesirable consequences. At low rates of alcohol intake, acetaldehyde metabolism is sufficiently rapid to limit its accumulation and liberation from the liver. At higher concentrations, acetaldehyde production rapidly consumes the liver’s glutathione reserves—a central cellular antioxidant. This coincides with activation of the microsomal ethanol oxidation pathway that generates toxic free-oxygen radicals. In the absence of sufficient glutathione, free-oxygen radicals can accumulate, disrupting mitochondrial function. Elsewhere in the body, acetaldehyde can bind with proteins and cellular constituents, forming stable complexes (Niemela and Parkkila, 2004). These can lead to the production of immunogenic determinants, which can stimulate antibody production against acetaldehyde adducts (Romanazzi et al., 2013). This may induce some of the chronic tissue damage associated with alcohol abuse (Niemela and Israel, 1992). The binding of acetaldehyde to the plasma membrane of red blood cells is known to increase rigidity. By limiting their ability to pass through the narrowest capillaries, oxygen supply to tissue cells may be restricted. This could participate in suppressed brain function. It is estimated that the brain consumes up to 20% of the blood’s oxygen supply but constitutes only about 2.5% of body mass. In addition, acetaldehyde can disrupt DNA repair mechanisms. Fortified wines (notably sherries) can be a significant source of acetaldehyde (Lachenmeier and Sohnius, 2008).

Although ethanol and acetaldehyde can produce severe, progressive, and long-term damage to various organs, and incite alcohol dependence, these consequences are minimal to undetectable when alcohol consumption is moderate and taken with meals (Serianni et al., 1953). As the sections below demonstrate, moderate, daily, wine consumption can have health benefits for the majority of people.

Potential health benefits and influences

Food value

Wine’s major nutritional value comes from its rapidly metabolized, ethanolic, caloric content. Alcohol does not
need to be digested, prior to being absorbed through the intestinal wall. In rural viticultural areas, wine historically provided a significant source of metabolic energy for the adult population. The caloric value of ethanol (7.1 kcal/g) is nearly twice that of carbohydrates (4.1 kcal/g). Thus, it constituted a valuable caloric source. It is estimated that alcohol may supply about 6% of the energy in the average American diet (Halsted, 2003). Wine was also a potable beverage and helped disinfest water to which it was added—some bacterial inactivation occurs within seconds (Vaz et al., 2012).

Wine contains small quantities of several vitamins, notably several B vitamins, such as B_{12} (riboflavin), and B_{12} (cobalamin). However, wine is virtually devoid of vitamins A, C, D, and K. In excess, ethanol can impair vitamin uptake.

Wine contains various minerals in readily available forms, especially potassium and iron (in the ferrous state). Nevertheless, excessive alcohol consumption can disturb the uptake of calcium, magnesium, selenium, and zinc and increase the excretion of zinc via the kidneys. The low sodium/high potassium content of wine makes it one of the more effective sources of potassium for individuals on diuretics.

Although wine contains soluble dietary fiber, especially red wines (Díaz-Rubio and Saura-Calixto, 2006), it is insufficient to contribute significantly to the daily recommended fiber content in the human diet.

**Effects on digestion**

Wine has several direct and indirect effects on food digestion. Its phenolic (Hyde and Pangborn, 1978) and alcohol (Martin and Pangborn, 1971) contents activate the release of saliva. In addition, wine promotes the release of gastrin as well as gastric juices. The principal constituent activating the release of gastric juices in red wines is apparently succinic acid, whereas in white wines it is malic acid (Liszt et al., 2012). They do not activate gastrin release, however. The substance(s) involved in stimulating gastrin secretion are unknown. Wine also significantly delays gastric emptying, both on an empty stomach (Franke et al., 2004) or when consumed with food (Benini et al., 2003). The latter favors digestion by extending the duration of acid hydrolysis.

Delayed gastric emptying may be a consequence of wine phenolics activating stanniocalcin-1 cells in the stomach. These possess the same TAS2R system as bitter-sensitive receptors in the mouth (see Finger and Kinnamon, 2011). On stimulus, they release cholecystokinin, a peptide hormone that reduces gut mobility.

In addition, wine slows plasma glucose uptake, independent of any insulin response (Benini et al., 2003). Furthermore, at the levels found in most table wines, ethanol activates bile release. Wine acids and aromatics also have the same effects. In contrast, the high alcohol contents (e.g., distilled spirits) can suppress digestive juice flow, the release of bile, and induce stomach spasms. Wine also aids digestion indirectly by inactivating gastrointestinal pathogens.

Despite the general beneficial effects of moderate amounts of alcohol on digestion, the phenolic content of red wine may counter some of these influences. For example, tannins and phenolic acids can interfere with the action of certain digestive enzymes, notably α-amylase, lipase and trypsin (Rohn et al., 2002; Gu et al., 2011). Digestion may be further slowed by phenolics polymerizing with food proteins. These effects may be mollified by the presence of ionic carbohydrates found in food (Gonçalves et al., 2011) as well as by salivary proteins. Both monomers and proanthocyanidins bind with basic, proline-rich, and histatin proteins in the saliva. Their bonding is reversible, depending on equilibrium conditions. They can become irreversible, though, in the presence of metal ions, upon oxidation, or with pH changes (Luck et al., 1994). Normally, these insoluble saliva/tannin complexes remain stable in the stomach and upper alimentary tract (Lu and Bennick, 1998). Thus, the inactivation of digestive enzymes or the disruption of mineral uptake by tannins may be limited. Degradation of tannin-protein polymers and their moieties subsequently occurs in the colon. In contrast, some pepsin-activated protein breakdown is activated by monomeric phenolics, notably quercetin, resveratrol, catechin, and epigallocatechin gallate (Tagliazucchi et al., 2005). Clearly the action of wine phenolics is complex and much more needs to be known. Not only are the effects potentially different in the stomach from that in the small and large intestines, but also the chemical composition of wine phenolics changes during passage through the digestive tract.

The wine’s phenolic content can also decrease iron and copper absorption in the intestinal tract (Cook et al., 1995). Although nutritionally undesirable, limiting iron bioavailability may reduce the formation of toxic lipid hydroperoxides during digestion. The antioxidant effect of polyphenolics also applies to peroxide generation in the stomach (Kanner and Lapidot, 2001); Fig. 12.4.

The activation of gastric juice release not only aids food digestion but also inactivates enzymes involved in ulceration. Even more significant may be the antibiotic action of wine constituents against Helicobacter pylori (Fugelsang and Muller, 1996). H. pylori is often considered the primary causal agent of stomach ulceration. Thus, moderate wine consumption may have a prophylactic effect in limiting ulcer initiation (Brenner et al., 1997). The bacterium has also been implicated in gastritis, vitamin B_{12} malabsorption, and gastric adenocarcinoma. However, chronic secretion of gastric juice...
Polyphenols

PUFA
LOOH
Mb ↓ Fe
Lipid oxidation
↓
Co-oxidation
ALEs
MDA
Prot-MDA

FIGURE 12.4 Limitation of food-lipid peroxidation (and cytotoxin production) in the stomach by the antioxidant action of polyphenols: PUFA, polyunsaturated fatty acids; LOOH, hydroperoxide; Mb, metmyoglobin; Fe, iron; potential cytotoxins: ALEs, lipid oxidation end-products; MDA, malondialdehyde; Prot-MDA, protein-malondialdehyde. Reproduced with permission from Kanner, J., Gorelik, S., Roman, S., and Kohen, R. (2012) Protection by polyphenols of post-prandial human plasma and low-density lipoprotein modification: The stomach as a bioreactor. J. Agric. Food Chem. 60, 8790–8796., Copyright 2012, American Chemical Society.

can produce irritation and may provoke ulceration, heartburn, and favor the development of adenocarcinomas in the lower esophagus.

Wine may further aid human sustenance by increasing nutrient uptake. Congeners in wine combine with metallic ions, vitamins, and fatty acids, facilitating their transport across the intestinal wall.

Consuming wine with food slows the rate of alcohol uptake in the blood (Fig. 12.1).

In the absence of food, ~80% of the alcohol is absorbed through the intestinal wall. Although the absolute proportion absorbed by the intestines increases when wine is jointly consumed with food, uptake is dispersed over a much longer period. This results primarily by food retarding gastric emptying. Consequently, alcohol transfer into the intestines is delayed. This gives the liver more time to metabolize the alcohol, lowering the maximal blood-alcohol level reached. However, taking sparkling wine on an empty stomach can increase short-term alcohol uptake by about 35% (Ridout et al., 2003). Because the same wine, with its carbon dioxide removed, did not have the same influence, it is suspected that carbon dioxide was the active ingredient (Ridout et al., 2003). It has occasionally been proposed that carbon dioxide relaxes the pyloric sphincter, allowing earlier transfer of fluids from the stomach into the duodenum and thereby its absorption into the blood. The rate of alcohol metabolism differs considerably among individuals, with rates commonly varying between 90 and 130 mg/kg/h. A person’s hormonal and nutritional state also affects their ethanol metabolic rate. Gender is also an influencing factor (Kaltenback et al., 2001). The tendency of women to have a higher body fat content (into which ethanol does not infiltrate), results in their being more rapidly influenced by similar amounts of alcohol (Kalant, 2000).

Additional benefits that may accrue from wine consumption are derived from metabolic by-products of proanthocyanin degradation in the colon. They assist protecting the colonic mucosa from the toxic effects of p-cresol production (generated from l-tyrosine) (Wong et al., 2016). Furthermore, wine phenolics may prevent or delay intestinal diseases associated with inflammation and oxidative stress (e.g., inflammatory bowel disease) (Biasi et al., 2014).

Finally, wine can have a beneficial cultural/psychologic effect on food intake and digestion. The association of wine with refined eating promotes slower food consumption, potentially permitting biofeedback mechanisms to regulate food intake. In addition, wine consumption can promote a more relaxed lifestyle, something increasingly valuable in our overly compulsive society. Whether this explains the reported improved appetite of many elderly and anorectic patients, when wine is taken with the meal, is unknown. Wine taken with a meal can enhance the pleasures derived from both but not necessarily those suffering gastroesophageal reflux (acid reflux). This is apparently correlated more with the consumption of white than red wines (Pehl et al., 1998).

Phenolic bioavailability

Most investigations on the health benefits of moderate wine consumption have involved population (epidemiologic) and tissue-culture studies. However, to be confident in their interpretation, intermediate stages need to be known. This involves details on the uptake and degradation in the intestinal tract, metabolism in the liver, transport, binding, and modification in the blood and lymph, elimination by the kidneys, and cellular uptake and metabolism. Although absorption via the intestinal tract is a priori requirement for most activity, it alone does not imply bioavailability at the cellular level. However, this does not apply to influences in the oral cavity and digestive tract. In the mouth and upper intestinal tract, a wine’s phenolic constituents remain largely unmodified, except for binding with proteins. In contrast, considerable degradation occurs in the colon. Here, large phenolics tend to be metabolized, depending on an individual’s colonic flora. For example, hydrolyzable tannins are converted to more easily absorbed, antiinflammatory/anticarcinogenic urolithins (Tomás-Barberán et al., 2014). If absorbed, most phenolics are quickly metabolized in the liver, conjugated with various moieties (e.g., methyl or sulfur groups) by plasma enzymes, and/or eliminated via the kidneys. Amounts found in the plasma are often ≤1% of that consumed, although this may increase with repeated daily exposure. The proportion of wine-derived flavonoids is estimated at about 4 mg/day/person in the
United States (Chun et al., 2007). This compares with about 200 mg/day/person from all sources. This value would increase to about 37 mg flavan-3-ols and 47 mg procyanidin dimers, based on 180 mL of red wine per day (Forester and Waterhouse, 2009). That volume is near the upper limit of what is typically considered moderate wine consumption.

In the mouth, mid-sized flavonoid polymers often bind to salivary proteins, forming stable complexes (De Freitas and Mateus, 2003; Pizarro and Lissi, 2003), slightly delaying their transport to the stomach. Passage through the stomach does not modify the majority of wine phenolics. Among wine flavonoids, anthocyanins appear to be those that most quickly traverse the stomach and pass into the blood (Passamonti et al., 2003). Flavonoid glucoside uptake is facilitated by gastric glucose transporters (Oliveira et al., 2015), whereas aglycone uptake occurs by passive diffusion. Flavonoids are also effectively translocated across the small intestine lining (Talavéra et al., 2005). Phenolic acids, such as caffeic acid (Simonetti et al., 2001) and resveratrol (Soleas et al., 2001) also readily pass into the plasma via the intestinal tract. In contrast, flavonoid polymers tend to remain in the intestine, until degraded to phenolic acids and aldehydes by the colonic flora (Aura, 2008, Fig. 12.5). Also metabolized in the colon are any anthocyanins or catechins monomers that have not already been absorbed and/or microbially degraded. These may enhance the growth of beneficial bacteria (e.g., Bifidobacterium and Lactobacillus spp.) or their attachment to the intestinal wall (Bustos et al., 2012). Depending on the compound, variable amounts may be absorbed into the blood (Ward et al., 2004).

Studies on the bioavailability of phenolics, once in the bloodstream, are still preliminary (Williamson and Manach, 2005). Although many simple flavonoids are quickly absorbed into the plasma, most appear to be rapidly conjugated (methylated or sulfated), bound to proteins, transformed to glucuronides, or otherwise modified (Williams et al., 2004; Forester and Waterhouse, 2009; Xiao and Högger, 2015). Hydroxycinnamic acids are also rapidly absorbed and metabolized into glucuronide and sulfate conjugates (Nardini et al., 2009). This both reduces their toxicity (potential carcinogenicity) as well as facilitating their excretion by the kidneys. However, the latter reduces their potential beneficial effects. In contrast, anthocyanin seems to be efficiently absorbed via the stomach wall, and their metabolites appear to remain in the plasma for several days (Kalt et al., 2014). Short-term studies primarily detect the uptake of phenolic metabolites, whereas long-term studies detect more parental constituents (Sandoval-Ramírez et al., 2018). Small amounts of cinnamic acid-tartrate esters are also found in the plasma. These transformations could significantly affect their antioxidant and other attributes as well as their ability to move into tissue cells and their surrounding fluids.

Most phenolic metabolites retain one or more hydroxyl groups and thus may still possess antioxidant properties. Nevertheless, there is growing evidence that phenolic metabolites act primarily as signaling molecules, notably in oxygen-stress-related pathways (Williams et al., 2004). Consequently, smaller amounts are needed than for direct antioxidant reactions. This might explain the discrepancy between the low levels of free phenolics in the plasma and their apparent effects. An example may be the increased activity and

---

**FIGURE 12.5** Schematic depiction of metabolic fate of dietary polyphenols in the human—microbial superorganism. Within the colonic compartment, the microbial bioconversion pathways of naringenin are depicted. Within the host, dietary polyphenols and their microbial bioconversion products successively undergo liver phase I and II metabolism, absorption in the systemic circulation, interaction with organs, and excretion in the urine. From van Duynhoven, J., Vaughn, E.E., Jacobs, D.M., Kemperman, R.A., van Velzen, E.J., Gross, G., et al., 2011. Metabolic fate of polyphenols in the human superorganism. Proc. Natl. Acad. Sci. 108, 4531–4538, Reproduced by permission.
gene expression of antioxidant genes in erythrocytes after red wine consumption (Fernández-Pachón et al., 2009). Future studies are needed to investigate the antioxidant efficacy of phenolic metabolites and their conjugated complexes at concentrations found in the plasma. Their binding to and translocation into tissue cells also needs investigation.

The presence of phenolics in the plasma permits their likely uptake into most body tissues. This generality does not necessarily apply to the brain. Except where there are specific transport proteins, most compounds above a molecular weight of 500 Da are excluded from the brain by the blood–brain barrier. The barrier consists of tight connections between the endothelial lining of cerebral capillaries. It prevents the diffusion of most molecules from the blood into the cerebrospinal fluid. However, with anthocyanins (Passamonti et al., 2005) and simple flavonols (Youdim et al., 2004), access to the brain apparently can occur within minutes of consumption. Initial animal studies suggest uptake levels in the brain occur at about 10% that of other tissues (Wu et al., 2012).

Although fascinating, consumers are more interested (if at all) in what wines provide the maximal health benefits and under what conditions. Regrettably, data on these vital concerns are lacking. Grape cultivar, maturity, wine production, maturation and aging conditions all influence the amounts and types of phenolics present and thus their activity.

Antimicrobial action

The prophylactic action of wine against gastrointestinal diseases has been known for millennia, long before their microbial origins were ever suspected. In spite of this, the mechanism(s) by which this occurs remain poorly understood.

The antimicrobial effect of alcohol was discovered in the late 1800s. Nevertheless, alcohol is not particularly antimicrobial, certainly at the concentrations found in wine (its sterilant action is optimal at about 70%). The antimicrobial action of wine is closely related to that of crushed grapes (Öncül and Karabiyikli, 2016). Thus, the antibiotic action of wine likely relates more to its phenolic (Friedman, 2014) and acidic (Vaz et al., 2012) contents, although wine’s alcohol content undoubtedly augments their effectiveness.

Anthocyanins, which are weakly toxic to viruses, protozoans, and bacteria, become more so as a consequence of fermentation. Other phenolic compounds in wine are bacteriostatic and fungistatic. For example, p-coumaric acid is particularly active against gram-positive bacteria (e.g., Staphylococcus and Streptococcus), whereas compounds, such as quercetin, inhibit pathogenic gram-negative bacteria (e.g., Escherichia, Shigella, Proteus, and Vibrio) (Vaquero et al., 2007). Phenolics may also be inhibitory to intestinal pathogens such as Clostridium difficile, C. perfringens, and Bacteroides (Lee et al., 2006). Despite wine being more effective than mildly antimicrobial agents, such as bismuth salicylate (Weisse et al., 1995), full action may take several hours (Møretrø and Daeschel, 2004; Dolara et al., 2005). Although most studies have involved bacteria grown on culture plates, wine has also been shown to be antimicrobial under simulated gastrointestinal conditions (Vaz et al., 2012).

An indirect effect, limiting intestinal problems, is illustrated by the action of the colon flora on anthocyanin structure. It favors the growth of Bifidobacterium and Lactobacillus-Enterococcus spp. (Hidalgo et al., 2012). These have been associated with a healthy gut microflora (Hord, 2008). There is also considerable variation in the effects of different flavanols and procyanidins, both promoting and inhibiting the adhesion of probiotic lactobacilli to the intestinal wall, depending on their metabolic modification during passage through the intestinal tract (Bustos et al., 2012). In addition, viniferin (a resveratrol derivative) can inhibit biofilm formation by pathogenic Pseudomonas aeruginosa and Escherichia coli (Cho et al., 2013). Red wine can suppress biofilm formation by oral pathogens (Muñoz-González et al., 2014).

In most instances, the mechanism by which phenolics have their action is unknown. However, in the case of quercetin, the effect may be partially attributed to its inhibition of DNA gyrase, whereas with epigallocatechin, disruption of cell membrane function appears central to its antibiotic action. Alternative methods of action may involve suppression of cell adherence and colony formation on the gut lining (Selma et al., 2012; Truchado et al., 2012). Adherence is often a prerequisite for the cascade of events leading to disease development. Low pH and the presence of various organic acids appear to accentuate the antimicrobial action of both wine phenolics and ethanol. Organic acids may themselves be antimicrobial, as is the case with Bacillus cereus (Vaz et al., 2012).

Wine is also active against several viruses including the herpes simplex virus, poliovirus, hepatitis A virus as well as rhinoviruses and coronaviruses. The effect on the latter two groups appears reflected in the reduced incidence of the common cold in moderate alcohol consumers (Cohen et al., 1993), particularly those drinking red wines (Takkouche et al., 2002). If you have to gargle, port is certainly one of the more pleasant.

Antioxidant effects

The antioxidant action of wine phenolics not only appears to play an important role in limiting low-density lipoprotein (LDL) peroxidation (Maxwell et al., 1994; Rice-Evans et al., 1996) but also the action of lipoxygenases and enzymes generating ROS. Phenolics can also
directly scavenge (quench) these radicals (e.g., superoxide and hydroxyl radicals), contributing to the action of cellular antioxidants. The oxidized flavonoid by-products are much more stable (nonreactive) and tend to be quickly metabolized or eliminated by the kidneys. A flavonoid’s quenching ability is largely dependent on the location and number of its OH groups as well as its glycosylation, sulfation, methylation, and acylation status (Plaza et al., 2014). In addition, phenolics can chelate iron and copper, limiting their involvement in radical formation (Morel et al., 1994; Rice-Evans et al., 1996) or access to bacterial pathogens. Phenolic can also limit the influx of calcium ions associated with oxidative stress (Ishige et al., 2001).

An antioxidant relatively unique to wine is resveratrol. It is a stilbene phenolic produced in response to plant stresses. It has greater antioxidant activity than common dietary antioxidants, such as vitamin E and ascorbic acid (Frankel et al., 1993). There is also direct evidence that resveratrol can enter the blood system at levels sufficient to suppress cyclooxygenase and 5-lipoxygenase pathways. These are involved in the synthesis of proinflammatory mediators (Bertelli, 1998). In addition, resveratrol can activate proteins involved in nerve cell differentiation, synaptic plasticity, and neuronal survival (Tredici et al., 1999).

Supplemental protection may result from ethanol activating the cellular biosynthesis of hydroxytyrosol (a dopamine metabolite) (de la Torre et al., 2006). Hydroxytyrosol is an important antioxidant and anti-inflammatory agent.

### Cardiovascular disease

The most clearly established benefit of moderate alcohol consumption, notably wine, relates to a nearly 30%–35% reduction in death rate due to cardiovascular disease (Klatsky et al., 1974, 2003; Renaud and de Lorgeril, 1992, Fig. 12.6). Alcohol consumption is also correlated with a decrease in the likelihood of intermittent claudication (pain or cramping in the calf of the leg). Claudication is a common indicator of peripheral arterial disease. Recent studies have confirmed that incidental factors, such as gender, race, lifestyle, educational level, etc. do not affect these results (see Mukamal et al., 2006). Studies have also demonstrated that daily consumption of alcohol significantly reduces the incidence of other cardiovascular diseases, such as hypertension (Keil et al., 1998), heart attack (Gaziano et al., 1999), stroke (Truelsen et al., 1998; Hillbom, 1999), and peripheral arterial disease (Camargo et al., 1997). Those who consume wine moderately live, on average, 2.5–3.5 years longer than teetotalers and considerably longer than heavy drinkers. The prime area of contention is the degree to which these benefits accrue from the effects of ethanol vs. phenolic and/or other constituents (Rimm et al., 1996).

Atherosclerosis is the principal cause of most cardiovascular disease (Libby, 2001). It apparently results from chronic injury to the arteries (Fig. 12.7). Although associated with several independent factors, most damage is correlated with lipid oxidation—a subgroup of cholesterol-apoproteins complexes (LDLs). Because of the hydrophobic nature of cholesterol and triglycerides, their transport in the plasma requires a special structure. As illustrated in Fig. 12.8, lipoprotein complexes consist of an outer membrane of phospholipids, within which apoproteins and free cholesterol occur. They enclose a hydrophobic core possessing numerous triglycerides and cholesteryl esters. Metabolism of the enclosed lipids is regulated by the apoproteins in the outer membrane.

Normally, LDLs supply cholesterol for cellular membrane repair and steroid synthesis. However, in high concentrations, they may accumulate in the artery

![Figure 12.6 Relationship of per capita alcohol consumption with 1972 heart disease death rates in men aged 55–64 in 20 countries.](image-url)
wall. If they remain there for an extended period, their lipid content tends to become oxidized. In an oxidized state, lipids are cytotoxic and indirectly irritate the artery wall. As a consequence, special adhesion proteins attach to the artery wall. Monocytes and helper T-cells of the immune system bond to these proteins. In addition, affected endothelial cells may secrete compounds, such as endothelin-1. Endothelin-1 activates monocyte and T-cell migration into the artery wall. Procyanidins, principally found in red wines, are particularly effective in suppressing the production of endothelin-1 (Corder et al., 2001). Anthocyanin metabolites are also effective modulators of endothelial function (Edwards et al., 2015). In the layer just underneath the endothelial lining (intima), accumulated monocytes mature into macrophages. Both macrophages and T-cells may release a range of cytokines that further activate the immune system, involving localized inflammation. Activated macrophages tend to engulf oxidized LDLs. However, as the LDLs are not degraded, their progressive accumulation gives the macrophage the appearance of being full of bubbles (termed foam cells). They are the first clear evidence of localized arterial swelling (plaques). Occasionally plaques bulge into the vessel. More frequently, they initially enlarge outward into the surrounding tissue. Action of immune cells in the plaque also induces migration of smooth muscle cells from the artery wall into the intima. Here they proliferate and produce collagen, forming a fibrous cap over the plaque. Additional LDLs slowly collect, provoking further rounds of inflammation and plaque enlargement. These accretions may develop their own vasculature, becoming fibrous and inelastic. As the plaques enlarge, they may produce irregular protrusions into and block the artery lumen.

Even without restricting blood flow, plaques set the stage for platelet aggregation, clot formation (thrombus) and the blockage that can precipitate a heart attack or stroke. In the later phases of plaque formation, unknown factors enhance inflammatory changes in the plaque. These disrupt the integrity of the cap. For example, collagenases secreted by macrophages inhibit collagen synthesis by smooth muscle cells. Sudden rupture of a plaque permits blood infiltration into the plaque. Because plaques contain potent blood clotting factors, thrombus development is almost instantaneous. It is currently thought that plaque rupture is the principal factor inducting thrombus formation and precipitating a heart attack, stroke, or other cardiovascular trauma.

Atherosclerosis appears to be at least partially reversible, if risk factors such as smoking, high blood pressure, high dietary sources of cholesterol, and possibly infection by pathogens such as Chlamydia pneumoniae and cytomegalovirus are eliminated. Part of the reversal process involves the action of high-density lipoproteins (HDLs). Of the two principal forms, ethanol augments the presence of HDL₃, whereas exercise increases the level of HDL₂. The effect of ethanol on HDL concentration appears independent of beverage type (van der Gaag et al., 2001). Either form of HDL favors the removal of cholesterol from the arteries, transferring it to the liver for metabolism. HDLs also appear to interfere with LDL
oxidation. Because the HDL/LDL ratio affects the degree and rate of cholesterol turnover, the slower the rate, the greater the likelihood of oxidation (Walzem et al., 1995) and eventual plaque formation.

The beneficial effect of moderate alcohol consumption on the HDL/LDL ratio is now relatively clearly established. Less well understood is its effect in lowering the concentration of C-reactive protein (CRP) (Levitan et al., 2005). CRP is an indicator of inflammation. Its level usually rises in correlation with the risk of atherosclerosis.

Moderate alcohol consumption also reduces the incidence of another risk factor for cardiovascular disease—type 2 diabetes. Chronically high values of circulatory glucose, associated with type 2 diabetes, appear to generate high plasma triglyceride and LDL levels. However, the benefits of wine’s alcohol content on glucose and insulin metabolism appear not to occur if intake is not coincident with meal consumption (Augustin et al., 2004). Phytoestrogens, such as resveratrol, have a similar effect in reducing triglyceride and LDL contents in the circulatory system (see Bisson et al., 1995).

Another of alcohol’s beneficial influences involves disruption of events leading to clot formation. Platelets are less “sticky” in the presence of alcohol and thus less likely to aggregate, limiting clot formation. Alcohol also increases the level of prostacyclin (interferes with clotting) and raises the level of plasminogen activator (a clot-dissolving enzyme).

Clots, adhering or becoming stuck to the roughened surfaces of narrowed atherosclerotic vessels, may block blood flow. The oxygen deficiency and cell death that result are central to the damage caused by a heart attack or stroke. Thus, it is not surprising that inhibitors of platelet aggregation reduce the frequency of these cardiovascular crises and their sequelae. It is the rationale for recommending the daily consumption of acetylsalicylic acid (an inhibitor of platelet aggregation). Ethanol (Renaud and Ruf, 1996) as well as wine phenolics, such as resveratrol and anthocyanins, have similar effects (Fig. 12.9).

An additional example of the beneficial effects of limited alcohol intake is the relation between alcohol dehydrogenase (ADH) genotype and the incidence of myocardial infarction. Individuals homozygous for ADH1C*2 (slow metabolizers of ethanol) are significantly less likely to have a heart attack than heterozygous individuals and even less likely than homozygous individuals for ADH1C*1 (fast metabolizers of ethanol) (Hines et al., 2001).

Individually, many phenolics, such as resveratrol, catechin, epicatechin, and quercetin appear to have inhibitory effects on platelet aggregation (Keli et al., 1994). In an in vitro study, though, monomeric or low-molecular-weight flavonoids and hydroxycinnamic acids enhanced platelet aggregation and LDL oxidation, with only large polymers being inhibitory (Shanmuganayagam et al., 2012). In another investigation, the combined effect of several phenolics was superior to single compounds (Wallerath et al., 2005). The action partially results from the enhanced synthesis and release of nitric oxide by endothelial cells. This has been found to occur at resveratrol concentrations associated with moderate wine consumption (Gresele et al., 2008). Chlorogenic acid also appears to activate nitric oxide production (Mubarak et al., 2012). Nitric oxide induces vasodilation (by relaxing vascular smooth muscle), reduces blood pressure, and limits platelet adhesion to blood vessel endothelia. Indicative of the complexities of such interactions is the observation that flavonoids may also inactivate nitric oxide (Verhagen et al., 1997). In addition, nitric oxide, notably as peroxynitrite, oxidizes LDLs. Clearly, much more still needs to be known before a clear picture emerges.

In addition to affecting platelet aggregation, wine phenolics can bind directly with LDLs (limiting their oxidation), indirectly reduce macrophage-mediated oxidation and preserve the action of paraoxonase (further protecting LDLs from oxidation) (Aviram and Fuhrman, 2002). Furthermore, red wine phenolics directly or indirectly limit the migration of smooth muscle cells into the intima of artery walls. These influences probably explain some of the added benefits of wine vs. other alcoholic beverages in reducing the incidence and severity of cardiovascular disease. Although flavonoids tend to suppress inflammation, conflicting observations

![FIGURE 12.9](image-url) Inhibition of platelet aggregation induced by several red wine fractions (barrel- or bottle-aged, their dealcoholized versions, total ethanol extracts (EtOAc's) and ethanol extracts at pHs 7 and 2, and anthocyanin extracts from the wines. From Baldi, A., Romani, A., Mulinacci, N., Vincieri, F.F., Ghiselli, A., 1997. The relative antioxidant potencies of some polyphenols in grapes and wines. In: Watkins, T.R. (ed.), Wine: Nutritional and Therapeutic Benefits. American Chemical Society, Washington, DC, pp. 166–179. ACS Symposium Series No. 661, Reproduced by permission.)
put the clinical significance of their antiinflammatory action to atherosclerosis in question. Whether this might also apply to the antiinflammatory effects of wine phyto-
prostanes (degradation products of linolenic acid) is unknown.

Red wines have usually been credited with superior health-related benefits than white wines, especially relative to cardiovascular disease. This presumably results from their higher flavonoid content (Tian et al., 2011). This view is supported by studies where white wine has shown the same effects as red wine, when supplemented with grape polyphenolics (Fuhrman et al., 2001). Nevertheless, prolonged skin contact, or choice of particular cultivars, can enhance the presence of phenolic acids in white wine. Common phenolics in white wine, such as caffeic and coumaric acids as well as flavonols such as quercetin, are well-known potent antioxidants.

The low sodium content of wine is an incidental benefit. It may permit wine consumption by those on a low-sodium diet, for example those with high blood pressure or heart attack victims. The high potassium to sodium ratio of wine (20:1) is also advantageous.

Vision

As noted, many of the beneficial influences of alcohol and wine consumption show a J-shaped curve (Fig. 12.2). This also applies to its effect on age-related macular degeneration (Obisesan, 2003; Fraser-Bell et al., 2006). The disease expresses itself as a progressive degeneration of the central region of the retina (macula), leading to blurred or distorted vision. It results as a consequence of local atherosclerosis that deprives the retina of oxygen and nutrients. It is the leading cause of blindness in adults over the age of 65. A similar relationship has been found for cataract development. In both conditions wine antioxidants are suspected to be the active protective agent. In this regard, quercetin appears to be more protective (against light-induced lipid peroxidation) than either anthocyanin- or phenolic acid-rich constituents (Liu et al., 2016). However, wines high in ethanol content may undo these benefits, by promoting pro-oxidant action.

Neurodegenerative diseases

Alzheimer’s, a devastating neurodegenerative disease, affects more than 15 million people. Not surprisingly, researchers have investigated whether wine consumption affects the incidence of this and other neurodegenerative diseases (Barnham et al., 2004). Flavonoids not only activate key respiratory enzymes in mitochondria (Schmitt-Schillig et al., 2005), but also decrease the production of reactive oxygen species, by stimulating the production of catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase (Martín et al., 2011). A pattern appears to apply here, as with most health-related benefits of wine and alcohol consumption—moderate intake being beneficial, whereas high consumption or abstinence is deleterious.

Alzheimer’s disease has been correlated with the accumulation of extracellular amyloid β-peptide (plaque) and the formation of intracellular neurofibrillary tangles containing tau-protein. Many in vitro studies have shown that antioxidant compounds, such as vitamin E, protect neurons from β-amyloid accumulation. Tannins also inhibit the formation of and destabilize preexisting β-amyloid fibrils (Ono et al., 2008; Guéroux et al., 2015), whereas resveratrol promotes the degradation of amyloid β-peptides (Marambaud et al., 2005). Wine consumption is also linked to a reduction in the incidence of Alzheimer’s disease (Truelsen et al., 2002; Letenneur, 2004; Luchsinger et al., 2004). Even mild cognitive impairment and the progression of idiopathic dementia may be reduced with moderate alcohol consumption (Solfrizzi et al., 2007). Grape juice has also been found to be effective in this regard (Krikorian et al., 2012). Like other health benefits, these finding may not, in and by themselves, justify wine consumption, but they are encouraging to those who choose wine as part of their preferred lifestyle.

Osteoporosis

Age-related bone mass loss affects both sexes but is more frequent in postmenopausal women. Many risk factors including dietary influences and hormonal supplements, can affect its progress and severity. Of these factors, moderate alcohol consumption has been found to favor bone retention (Ganry et al., 2000; Ilich et al., 2002). Tucker et al. (2009) found data consistent with higher benefits from wine than other alcohol-containing beverages. The source of these benefits may be a combination of enhanced calcium uptake, associated with alcohol consumption (Ilich et al., 2002), the phytoestrogen effects of phenolics, such as resveratrol and kaempferol, or other unsuspected influences.

Arthritis

A number of drugs used in treating arthritis tend to irritate the stomach lining. This side-effect may be counteracted by the mildly acidic, dilute alcohol content of table wines. Other beneficial effects connected with moderate wine consumption may accrue from its mildly diuretic and muscle relaxant properties. The diuretic action of wine can help reduce water retention and minimize joint swelling. Wine can also directly reduce muscle spasms and the stiffness associated with
arthritis. The antiinflammatory influences of wine phenolics, notably resveratrol (Yang et al., 2018), may also play a role in diminishing the suffering associated with arthritis and other diseases associated with chronic inflammation (Schueller et al., 2015).

**Diabetes**

Wine consumption has been shown to attenuate insulin-resistance in type 2 diabetes (Dixon et al., 2001; Napoli et al., 2005). This may result from wine phenolics quenching oxygen radicals, thought to be pivotal in the damage associated with the disease. Type 2 diabetes appears to result when body cells fail to respond properly to the presence of insulin. The incidence of metabolic syndrome is also lower in wine drinkers (Rosell et al., 2003). These effects may be due to one or more of the following: the influences of alcohol on metabolism; the antidiabetic properties of the element vanadium (for which wine is a significant source) (Brichard and Henquin, 1995; Teissèdre et al., 1996); the hypoglycemic and hypolipidemic effects of phenolics such as resveratrol (Su et al., 2006); and/or through some effect on endothelial nitric oxidase synthase (Leighton et al., 2006). It appears there may be considerable specificity. For example, in a comparison between malvidin- and delphinidin-3-O-glucosides, only the predominant anthocyanin in grapes (malvidin) seems to have a significant hypoglycemic effect (Lida et al., 2012).

Relative to diabetes mellitus (type 1 diabetes), moderate consumption of dry wine was found to present no adverse effects on sugar control (Gin et al., 1992; Bell, 1996). Although wine does contain residual sugars, the most common, fructose, is poorly transported across the gastrointestinal tract. Most of what is absorbed is rapidly removed from the blood by the liver, where it is metabolized into glycerol and often stored as fat. It does not stimulate pancreatic insulin release.

Red wine (and a diet rich in antioxidants) appear to slow the progression of kidney damage (necropathy), occasionally associated with diabetes (Zhu et al., 2017).

**Goiter**

In an epidemiological study, Knudsen et al. (2001) found a strong link between alcohol consumption and a reduced prevalence of goiter and solitary thyroid nodules. The origin of this apparent protective effect is unknown.

**Kidney stones**

Drinking water has long been associated with reducing the development of kidney stones. Increased urine production is thought to limit calcium oxalate crystallization. What is new is the observation that wine consumption further reduces the production of these painful and dangerous inclusions (Curhan, 2007).

---

**Potential health issues**

**Cancer**

Moderate wine consumption has been correlated with reduced incidence in some cancers (see Bianchini and Vainio, 2004) (e.g., the kidney) but increased risk for others (notably the throat and gastrointestinal tract) (Ebeler and Weber, 1996; Parry et al., 2011). This potential varies markedly, primarily based on the amounts habitually consumed. For other cancers, moderate consumption appears to be neither protective nor a risk factor (e.g., prostate cancer) (Chao et al., 2010). Conversely, excessive consumption of alcoholic beverages increases the risk of a range of cancers, notably those of the oropharynx, larynx, esophagus, liver, colon, rectum, and breast (Connor, 2017).

Because ethanol is not directly carcinogenic, negative associations with alcohol consumption presumably relate to carcinogens potentially present in wines (e.g., ethyl carbamate). Thankfully, its carcinogenicity is reduced at the alcohol concentration typical of table wines. More significant, though, maybe acetaldehyde, a common denominator in gastrointestinal cancers (Salaspuro, 2009). Depending on the type of wine consumed, short-term but high concentrations of acetaldehyde may occur in the saliva and gastric juice (Lachenmeier and Sohnius, 2008). Acetaldehyde may also accumulate due to the action of alcohol dehydrogenase in the digestive tract, microbial alcohol metabolism (notably the colon), and malfunction of cellular acetaldehyde dehydrogenase.

Certain wine phenolics can be protective, whereas others mutagenic, especially at high concentrations. For example, quercetin can induce mutations in laboratory tissue cultures but is a potent anticarcinogen in whole-animal studies (Fazal et al., 1990). This apparent anomaly may result from differences in the concentrations of quercetin used, and/or the low levels of metal ions and free oxygen found in the body (vs. tissue culture). In addition, quercetin, along with several other phenolics that are potential carcinogens, lose this attribute when present as a glycoside. Most phenolics in the plasma occur in some conjugated state, not as free phenolics. In addition, phenolics may detoxify the small quantities of nitrites commonly found in food. However, in the presence of high nitrite concentrations (a preservative found in smoked and pickled foods), nitrites are converted into diazophenols (Weisburger, 1991). These appear to favor the development of oral and stomach cancers.
Several phenolics can limit or prevent cancer development through a diversity of effects, such as DNA repair, carcinogen detoxification, enhanced apoptosis (programmed cell death), disrupted cell division (Hou, 2003; Aggarwal et al., 2004), or enhanced immunostimulation (Tong et al., 2011). For example, resveratrol induces the redistribution of the Fas receptor. It is a cellular attachment site for TNF (tumor necrosis factor). Its action is part of a sequence that can lead to cancer cell apoptosis (Delmas et al., 2003). Resveratrol is an inhibitor of angiogenesis—the production of new vasculature essential for most tumor growth. Other effects of resveratrol include inhibition of cyclooxygenase-2 (Subbaramaiah et al., 1998) and cytochrome P450 1A1 (Chun et al., 1999). Cyclooxygenase-2 is thought to be involved in carcinogenesis, whereas P450 1A1 is an important hydroxylase. It can convert several environmental toxicants and procarcinogens into active carcinogens.

Flavones and flavonols strongly restrict the action of common dietary carcinogens, notably heterocyclic amines (Kanazawa et al., 1998). It is estimated that these amines, produced during cooking, are consumed at a rate of approximately 0.4–16 µg per day (Wakabayashi et al., 1992). Antitumor activity is also associated with acutissimin, a flavono-ellagitannin found in oak-matured red wine. The antiallergic and antiinflammatory properties of flavonoid phenolics probably also contribute to the anticancer aspects of these flavonoids (see Middleton, 1998).

The major exception to the general benefit of moderate wine consumption may be breast cancer (Viel et al., 1997). The connection is more evident in those with the ADH1C*1 (fast metabolizers of ethanol to acetaldehyde) (Terry et al., 2006). However, findings from the long-duration Framingham Study indicate no relationship between moderate alcohol consumption and the incidence of breast cancer (Zhang et al., 1999). Ethanol, although not itself a carcinogen, can enhance the transforming effect of some carcinogens.

Another example of a negative effect of wine consumption, at least in excess of moderate intake, is to increase the incidence of mouth and throat cancers (Barra et al., 1990).

Allergies and hypersensitivity

Alcoholic beverages may also induce a diversity of allergic and allergy-like reactions. In sensitive individuals, these may express as rhinitis, itching, facial swelling, headache, cough, or asthma. The primary culprit inducing bronchial constriction, at least in some asthmatics, is sulfur dioxide (Dahl et al., 1986). Wine containing an abnormally high sulfur dioxide concentration (300 ppm sulfite) induce a rapid drop in forced expiratory volume (Vally and Thompson, 2001), recovery taking about 15–60 min. The same individuals did not respond to wine containing 20, 75, or 150 ppm sulfite. Fig. 12.10 illustrates the range of sulfur dioxide contents potentially found in Californian wine. Thus, the sulfite levels normally found in wine seem not to be a major factor in wine-induced asthmatic responses (Vally et al., 2007). Why sensitive asthmatics episodically react to wines with low SO2 content may be related to changes in their asthma control. Surprisingly, red wines appear to provoke more asthma problems than white wines, even though red wines typically have lower sulfur dioxide contents than white wines.
The rapidity of the reaction to sulfite suggests some malfunction in the amount of glutathione in lung tissue or the activity of glutathione S-transferase in reducing sulfite to glutathione S-sulfonate. Normally, sulfite is rapidly converted to sulfate by sulfite oxidase in the blood. However, low levels of this enzyme could permit sulfite to persist, provoking a heightened response in hypersensitive individuals.

At greater risk are individuals afflicted with a rare, autosomal, genetic disease, caused by a deficiency in sulfite oxidase (Shih et al., 1977; Crawhall, 1985). Affected individuals must live on a very restricted diet, low in sulfur-containing proteins. It is estimated that the synthesis of sulfite, associated with normal food metabolism, generates approximately 2.4 g sulfite/day. The sulfites in wine contribute only marginally to this amount but may be temporally significant. Because of the gravity of sulfite oxidase deficiency, most affected individuals do not reach adulthood.

Another allergy-like reaction provokes rapid facial and neck flushing (cutaneous erythema). It develops shortly after alcohol consumption. Other symptoms often include peripheral vasodilation, elevated heart rate, nausea, abdominal discomfort, and bronchoconstriction. The syndrome is associated with a dysfunctional form of mitochondrial acetaldehyde dehydrogenase (ALDH2*2) (Enomoto et al., 1991; Eriksson et al., 2001) and is particularly pronounced in the homozygous state. ALDH2 is the principal enzyme oxidizing acetaldehyde to acetic acid. It is estimated that up to 50% of eastern Asians possess at least one dysfunctional ALDH2 allele and express some degree of allergy-like reaction to alcohol consumption. It has been suggested that the ALDH2 mutant, frequently found in eastern Asians, may reflect an evolutionary adaptation to the endemic occurrence of hepatitis B (Lin and Cheng, 2002). The mutation could have induced alcohol aversion, thereby avoiding synergism between alcohol and hepatitis B-induced liver damage.

Elevated levels of acetaldehyde appears to activate the release of histamine from mast cells. It subsequently induces vasodilation and an associated influx of blood (flushing). The connection between acetaldehyde and histamine is supported by the action of antihistamines in reducing the reaction, if taken in advance of an alcohol challenge (Miller et al., 1988). An alternative proposal is that this flushing reaction results from a direct, cutaneous, alcohol-induced vasodilation. The phenomenon tends to be suppressed by acetysalicylic acid (aspirin), if taken in advance (Truitt et al., 1987). The unpleasant side-effects of acetaldehyde accumulation is used in treating alcoholism. It involves taking disulfiram (a potent inhibitor of ALDH) prior to alcohol consumption. A facial flushing, concomitant with alcohol consumption but devoid of other symptoms, is occasionally experienced by Caucasians. Whether this is related to an ALDH malfunction is unclear.

The histamine content of wine has frequently been thought to contribute to several allergy-like reactions. However, wine is typically low in histamine content. Fig. 12.11 illustrates the range found in some wines. Thus, it seems unlikely that a wine’s histamine content is a major inducer of allergy-like reactions. This is supported by a double-blind study of people, self-reportedly wine intolerant. Reactions to two Pinot noir wines, differing in histamine content (13.8 vs. 0.4 mg/L) were not significantly different (Kanny et al., 2001). Other common foods are considerably higher in histamine content, for example cheeses.

This does not necessarily exonerate biogenic amines from being somehow involved. People vary in diamine oxidase activity (a histamine inactivator) (Wantke et al., 1991).
1996) and how alcohol (via acetaldehyde) suppresses its action (Jarisch and Wantke, 1996). Alcohol also can enhance the permeability of the intestinal lining to histamine. In addition, acetaldehyde accumulation can activate histamine release (Harada et al., 1981). This may explain the benefit antihistamines have in diminishing the rhinitis occasionally associated with wine consumption (Andersson et al., 2003). In addition, antihistamines counteract the broncho constriction in individuals showing histamine intolerance.

Idiopathic allergic and other immune hypersensitive responses to wine are difficult to predict or diagnose. Reactions may include the induction of headaches, nausea, vomiting, general malaise, or a combination of these. In a few instances, IgE-related anaphylaxis reactions have been reported to grape PR proteins (endochitinase and thaumatin) (Pastorello et al., 2003). The effects may involve urticaria/angioedema (red patches or wheals on the skin/swelling) and occasionally shock. Residual amounts of fining agents, such as egg whites, have also been implicated in some allergic reactions (Marinkovich, 1982). In a double-blind, placebo-controlled trial, wines fined with egg white, isinglass, or nongrape derived tannins presented “an extremely low risk of anaphylaxis” to egg-, fish-, or peanut-allergic consumers (Rolland et al., 2006). In an ELISA analysis, only egg white and lysozyme could be detected in wine samples (Weber et al., 2007). Nevertheless, with more than 1000 compounds potentially occurring in wine, it is not surprising that some individuals may occasionally show some form of adverse reaction to some wines.

In addition to physiological reactions to wine constituents, there is a wide range of equally important psychological responses (Rozin and Tuorila, 1993), both positive and negative. Traumatic memories, associated with the first exposure to, or excessive consumption of, a particular beverage can create an association that lasts a lifetime. Other people have come to associate certain products with social groups, lifestyles, or behaviors. Such attitudes can make the beverage either unacceptable or desirable as the case may be.

Gout

In the 1800s, there were many reports linking gout with wine consumption, notably port. Gout is caused by the localized accumulation of uric acid crystals in the synovium of joints. Their presence stimulates the synthesis and release of humoral and cellular inflammatory mediators (Choi et al., 2005). Gout is also associated with reduced excretion of uric acid in the kidneys. Mutations in the gene that encodes urease, the enzyme that metabolizes uric acid to allantoin (a soluble by-product), is often implicated in gout.

Dietary predisposing factors for gout include red meat, seafood, and beer. This is presumably because purines, the principal source of uric acid, are found in higher concentrations in these products than many other foods or beverages. Alcohol consumption may occasionally aggravate gout by increasing lactic acid synthesis. It, in turn, favors uric acid reabsorption by the kidneys. Despite this, wine consumption appears not be associated with an increased risk for gout. In contrast, it seems to favor reduced serum urate levels (Choi and Curhan, 2004).

Medical historians suspect the nineteenth century gout–port association was connected with lead-induced kidney damage (Yu, 1983; Emsley, 1986/1987). Samples of port from the nineteenth century show high lead contents. Lead contamination probably came from the stills used in preparing the wine spirits added in port production. In addition, the former use of pewter and lead-glazed drinking cups and prolonged storage of port in lead crystal decanters or stemware could have further augmented lead content (Falcone, 1991; Guadagnino et al., 1998).

Headaches

People occasionally avoid wine because it induces headaches. Regrettably, the wine/headache connection is still poorly understood. However, effective differentiation between wine-induced headaches may be pivotal to discovering their causes and possible solutions.

One of the most severe headache syndromes, potentially associated with wine consumption, is the migraine. Migraines appear to be induced, but inconsistently, by a wide range of environmental stimuli, often in tandem. An association between it and red wine consumption has been noted since Roman times. The dilation of cerebral blood vessels, partially associated with histamine release, appears to be a common element in many headache syndromes. Migraines may be one of them, although current thought suggests a neurological rather than a vascular origin. In addition, a double-blind study seemingly has exonerated histamine in most redwine-induced migraine headaches (Masycek and Ough, 1983). In addition, migraine attacks are more often associated with consuming spirits and sparkling wines, both lower in histamine content that table wines or beer (Nicoletti and Sicuteri, 1999). However, the former are often taken alone, leading to more rapid and higher spikes in blood alcohol content.

Alcohol may be directly involved in migraine induction through vasodilation—by activating meningeal vessel-associated trigeminal neurons (Nicoletti et al., 2007). Alcohol’s potential to reduce cerebral glucose metabolism (Volkow et al., 2006) could also be a contributing factor. Other potential disruptive aspects on brain
function may relate to the slow rate of alcohol metabolism by cerebral ADH. Thus, more alcohol may be metabolized by cytochrome P4502E, a process that generates acetaldehyde as well as ROS.

The more frequent association of red wines with several headache sequelae may be due to their higher phenolic content. On average, red wines contain about 1200 mg/L phenolics, vs. 200 mg/L for white wines. Some phenolics can suppress the action of platelet phenol sulfotransferase (PST) (Jones et al., 1995; Yeh and Yen, 2003), several isozymic forms (M and P) of which detoxify biogenic amines and phenolics via sulfation. Low levels of platelet-bound PST-P have been correlated with migraine susceptibility (Alam et al., 1997). The accumulation of small phenolics (those readily absorbed) in the blood could prolong the action of potent hormones and nerve transmitters (e.g., histamine, serotonin, dopamine, adrenaline, and noradrenaline). Small phenolics can also promote platelet aggregation and blood vessel dilation. The associated increase in intracranial pressure may participate in a migraine attack (Pattichis et al., 1995). Abnormal and cyclical patterns in platelet sensitivity to 5-HT release in migraine-prone individuals (Jones et al., 1982; Peatfield et al., 1995) may explain the inconsistent association of wine consumption with migraine induction.

In the treatment of cluster-headaches, small doses of lithium have been suggested as preventive (Steiner et al., 1997). Because some red wines have a higher than average lithium content, the possibility exists that they might limit the development of, rather than induce, this headache syndrome.

Another recognized headache syndrome is called the red wine headache (Kaufman, 1986). It may develop within minutes of consuming red wine, often being dose-related. The headache reaches its peak within ~2 h, tends to fade but returns roughly 8 h later. The headache seems related to the release of type E prostaglandins, important chemicals involved in dilating blood vessels. Their release can be activated by phenolics (Padilla et al., 2005) as well as alcohol (Parantainen, 1983). Prostaglandins may also activate pain receptors around blood vessels (Wienecke et al., 2009). This association may explain why prostaglandin synthesis inhibitors (e.g., acetylsalicylic acid, acetaminophen, or ibuprofen) may limit the development of some wine-related headaches (if taken about 1 h before consumption) (Kaufman, 1992).

A separate wine-related headache has been dubbed the red head (Goldberg, 1981). It develops within an hour of waking, after drinking no more than two glasses of red wine the previous evening. The headache, associated with nausea, is particularly severe when reclining. Although the headache is somewhat relieved by standing, it itself exacerbates the nausea. The headache usually lasts a few hours before dissipating. A similar phenomenon has been reported with some white wines, or mixtures of white wine, taken alone or with coffee or chocolates. Its chemical cause is unknown (Kaufman, 1986).

Because tannins are poorly absorbed in the upper digestive tract, in contrast to monomeric phenolics, the latter are likely the primary phenolic headache acti-vants. This may explain why aged red wines (in which most phenolics occur as large polymers) tend to be less associated with headaches than their younger counterparts. Large tannin polymers remain largely unmodified until reaching the colon, where bacteria degrade them (Deprez et al., 2000). Because this can take up to 2 days, they presumably are not (or not recognized to be) involved in wine-induced headaches.

Phenolic absorbed into the blood are primarily detoxified by being methylated or sulfated but may also become more “toxic” (to o-quinones). The latter can retard the breakdown of dopamine and restrict access to μ-opioid (painkilling) receptors, exacerbating the pain associated with cerebral blood vessel dilation. Nonetheless, some phenolics (e.g., resveratrol) limit, rather than augment, headache development. It inhibits the expression of cyclooxygenases, involved in the synthesis of prostaglandins (Jang and Pezzuto, 1998).

Although red wines are generally associated with headache production, white wines are occasionally associated with their production (Relja et al., 1993). Their characteristics and etiology are even less well understood than those evoked by red wines. In some individuals, this situation may be associated with a sensitivity to sulfites but atypically.

One of the most recognized alcohol-related headache phenomena is associated with binge drinking—the hangover (veisalgia) (Wiese et al., 2000). Although not consistently associated with a headache, it is frequently part of the sequelae. Hangovers are characterized by tremulousness, palpitations, tachycardia, sweating, loss of appetite, anxiety, nausea, and possibly vomiting and amnesia (Penning et al., 2010). When accompanied with a headache, it possesses symptoms resembling a migraine. The headache may be global but frequently concentrated anteriorly, associated with heavy, pulse-synchronous throbbing. It usually starts a few (~3 h) after the cessation of drinking, when blood alcohol level is declining and other hangover symptoms have already developed (Sjaastad and Bakkeiteig, 2004; Verster et al., 2010). Duration is seldom more than 12 h.

Despite its all-too-frequent occurrence, the causal mechanism(s) remains unclear. Most data suggest that alcohol-induced cerebral inflammation is the primary cause (Penning et al., 2010). This may operate directly via tissue dehydration and electrolyte imbalance (due to vasopressin enhanced urination) or indirectly via...
the toxic effects of acetaldehyde (Quertemont et al., 2005). Ethanol can also promote hepatic glycogen breakdown, glucose release, loss via the kidneys, and induction of hypoglycemia. In addition, activation of the liver’s microsomal ethanol oxidation pathway releases ROS, causing cellular damage and multiple metabolic disruptions. That the severity of a hangover may be reduced by prostaglandin synthesis inhibitors suggests that they may also play a role in hangover sequelae (Kaivola et al., 1983). As the old Spanish proverb noted:

Wine hath drowned more men than the sea

Because glutathione inactivates free radicals, taking an amino acid supplement (N-acetyl-cysteine) has been suggested as a partial remedy. It is rich in cysteine, an amino acid that forms the core of glutathione. In addition, glutathione facilitates the conversion of acetaldehyde to acetic acid. Disruption of membrane function and cerebral neurotransmitter action by acetaldehyde is presumably the rationale for commercial products, such as Hangover Helper and Rebound. They are designed to counter the effects of acetaldehyde.

Congeners (such as fusel alcohols and methanol) could exacerbate the effects of ethanol and acetaldehyde. However, because their content in wine is low, they are unlikely to be involved in wine-induced hangovers.

Some purported remedies, such as artichoke extract, have not stood up to rigorous clinical testing (Pittler et al., 2003), but others, such as an Opuntia fiscus-indica (Prickly Pear) extract, apparently reduced the severity of some hangover symptoms (Wiese et al., 2004).

That hangovers have been associated with deregulation of cytokine pathways (Kim et al., 2003), may explain the reported value of pyritinol (a vitamin B₆ derivative) as a treatment (Khan et al., 1973). Mineral deficiencies have also been correlated with hangovers (Min et al., 2010).

Combined with restraint, taking wine with a meal is probably the best means by which to avoid a hangover. Food delays the movement of alcohol into the intestinal tract, thereby slowing alcohol uptake (Fig. 12.1) and correlating uptake closer to the liver’s ability to metabolize ethanol. In addition, delayed transfer to the intestinal tract slows phenolic uptake (and other potential provocateurs).

Dental erosion

Wine tasting is not normally considered a hazardous occupation. However, recent studies show that dental erosion is an occupational hazard (Mok et al., 2001; Mandel, 2005; Mulic et al., 2011). Damage results from the frequent and extended exposure to wine acids, correspondingly, white wines are generally more corrosive than reds (Willershausen et al., 2009). Saliva is diluted and washed away, resulting in the oral pH falling to that of the wine (Obreque-Slier et al., 2016). This causes calcium to dissolve out of tooth enamel, softening and making it susceptible to erosion by masticatory forces and tooth brushing. Exposure times as short as 2 min can be harmful (Lupi-Pegurier et al., 2003). Demineralization commences at about pH 5.7. Dental erosion is unlikely to be a significant problem for the typical consumer who takes wine with meals. Food and salivary secretion limit, if not prevent, tooth enamel demineralization.

After many years, professional wine tasters may experience tooth disfiguration, affecting both tooth shape and size. Cupping, a depression in the enamel, exposing dentine at the tip of molar cusps, is a frequent clinical sign. Erosion can also contribute to severe root abrasion at the gum line. The good news is that not all tasters are equally at risk (Mulic et al., 2011).

Protection is partially achieved by rinsing the mouth with an alkaline mouthwash after tasting, application of a fluoride gel (such as APF) and refraining from tooth brushing for at least 1 h after tasting. The delay permits minerals in the saliva to rebind with enamel. For more protective protocols see Ranjitkar et al. (2012). The use of remineralizing agents, such as Tooth Mousse, also helps prevent dental erosion (Piekarz et al., 2008).

In contrast to this risk factor, consuming red wine may have some direct oral benefits. Proanthocyanidins can limit the adherence and biofilm-forming activity of caries-inducing Streptococcus mutans (Daglia et al., 2010). Gibbons (2013) provides a fascinating insight into the association of this bacterium with changes in human diet which resulted from a switch from a hunter-gather to an agriculture lifestyle. Mark Twain also made pronouncements about dental health, which might be equally applied to wine: “I always take it (Scotch whiskey) at night as a preventive of toothache. I have never had the toothache; and what is more, I never intend to have it”. From Europe and Elsewhere.

Fetal alcohol syndrome

Fetal alcohol syndrome refers to a set of phenomena including suppressed growth, mild mental retardation, and subtle facial abnormalities (Wattendorf and Muenke, 2005). It was first described in 1973 and appeared most markedly in the children of alcoholic mothers. They tended also to be heavy smokers, users of illicit drugs, consumers of large amounts of coffee, had poor nutrition, or a combination of these (Scholten, 1982; Whitten, 1996). Although associated with alcohol
uptake, the accumulation of acetaldehyde may be the principal toxicant. Even more subtle effects have now been associated with alcohol consumption, generating the fetal alcohol spectrum disorders. Because the consequences may be lifelong, it is generally recommended that pregnant women, or those desirous of becoming pregnant, refrain from alcohol consumption. Although abstinence may be unnecessary (Kesmodel et al., 2012), erring on the side of caution can supply desired peace-of-mind. This also applies to breast feeding—alcohol in breast milk could be detrimental to infant development.

Toxins

The presence of toxins in wine is seldom mentioned, outside academic circles, presumably because of their minimal presence. The only mycotoxin for which there may be regular analysis is ochratoxin A (O’Brien and Dietrich, 2005; Varga and Kozakiewicz, 2006), produced by several black Aspergilli (notably Aspergillus carbonarius) (Somma et al., 2012). Preliminary data suggests that most ochratoxin A is eliminated (destroyed/precipitated) during and after fermentation/maturation (Fernandes et al., 2007). Other potential mycotoxins that could occur in wine include isofumigaclavine, festuclavine, and roquefortine, all produced by Penicillium spp. (Moller et al., 1997), aflatoxins (El Khoury et al., 2008) from Aspergillus flavus, fumonisins from Aspergillus niger (Mogensen et al., 2010), and trichothecenes by Trichothecium roseum (Schwenk et al., 1989). Because these fungi are secondary saprophytes, they typically occur only on rotted grapes (thankfully, unlikely on noble-rotted grapes). Although the exclusion of all diseased grapes is essentially impossible, their inclusion is limited as much as feasibly possible.

Pesticide residues are other potential toxins. Their levels are usually below those known to be toxic, partially due to regulations limiting their use, precipitation or metabolism during winemaking and degradation during maturation. In addition, most importing countries possess regulations on permissible levels and systems to check for compliance. Achieving a zero concentration is probably impossible, if only because of our increasing technical ability to detect their presence at increasingly infinitesimal levels.

Methanol is present but in amounts insufficient to have any known negative consequences. The same also appears to be true for diacetyl and other potentially toxic compounds. Ethyl carbamate, a carcinogen, is no longer likely to occur, since its origin during wine production can be effectively avoided.

It may initially be disconcerting to think of trace amounts of toxins in wine, but this situation applies to all food, water, and air. Xenobiotics are an inescapable aspect of life, both modern and ancient. Their universal presence in the natural environment presumably provided the selective pressures that favored the evolution of organs of detoxification (e.g., the liver and kidneys) and the presence of multiple detoxifying enzyme systems. Thankfully, our bodies inactivate most xenobiotics rapidly and effectively, without our conscious knowledge. In addition, governmental agencies set regulations and assess compliance to limit most toxicants to well below known safe limits. As long as exposure to toxicants is kept to a bare minimum, consumers can basically forget they exist.

Contraindications

The most important wine contraindication relates to those with a past history of alcohol abuse. For the majority of adults (except pregnant women), moderate wine consumption appears to have significant health benefits. Nevertheless, there are several situations in which wine consumption, even in moderate amounts, can complicate or diminish the effectiveness of disease treatment.

The acidic nature of wine can aggravate inflammation and slow the healing of ulcers in the mouth, throat, stomach, and intestinal tract. Other constituents in wine may also be detrimental in this regard. Thus, all beverages containing alcohol are usually contraindicated in cases of gastritis, gastric cancer, and bleeding ulcers. The consumption of wine increases the burden on an already weakened vital organ. Chronic alcohol abuse can lead to cirrhosis of the liver.

Wine, along with other alcoholic beverages, may provoke gastroesophageal (acid) reflux in individuals prone to this syndrome.

With liver disease, the consumption of wine is normally contraindicated. The presence of alcohol puts additional stress on an already weakened vital organ. Chronic alcohol abuse can lead to cirrhosis of the liver.

In acute kidney infection, wine should be avoided. The consumption of alcohol increases the burden on an organ essential to eliminating toxic metabolic wastes. With prostatitis or genitourinary infections, the consumption of alcohol can complicate matters. The diuretic action of wine may increase the frequency of urination, or conversely it may induce highly painful urinary retention.
In epilepsy, the consumption of even moderate amounts of wine may increase the frequency of seizures. Consumption should be strictly limited in most situations of hypertension, hemorrhagic stroke, or atrial fibrillation.

Patients, about to undergo surgery, are advised to avoid all alcoholic beverages well before surgery. This avoids increasing any tendency to enhance intra- and postoperative bleeding (Wolfert et al., 1996), due to alcohol’s reduction of platelet clotting.

The consumption of alcohol is also ill advised when eating certain mushrooms. The most well-known example is the antabuse reaction associated if alcohol is consumed with *Cephalosporinum atramentarius* (Inky Cap). Another mushroom generating the same response is *Boletus luridus* (Budmiger and Kocher, 1982). The antabuse reaction derives its name from the trade name of disulfiram, a medication used in the treatment of alcoholism. It functions as an inhibitor of acetaldehyde dehydrogenase. Even small amounts of alcohol consumed while taking disulfiram can generate very unnerving reactions (e.g., flushing, sweating, weakness, vertigo, blurred vision, difficulty breathing, nausea, chest pain, palpitation, and tachycardia). In severe cases, the reaction can provoke acute congestive heart failure, convulsion, and death. Similar symptoms may develop in sensitive individuals when alcohol beverages are consumed while taking certain medications (e.g., cephalosporins, griseofulvin, chloramphenicol, sulfonylurea, metronidazole).

**Medication interactions**

In addition to the reactions noted above, consumption of alcohol while taking certain medications can generate dangerous conditions. Most of the literature comes from studies on alcoholics or binge drinkers. This limits the potential applicability of the data to conditions of moderate consumption and when taken with food. Nevertheless, even small amounts of alcohol may cause loss of muscle control in people taking tricyclic antidepressants. In addition, red wines can reduce the effectiveness of MAO (monoamine oxidase) inhibitors, used in controlling hypertension. Long-term acetaminophen use can enhance alcohol-induced kidney damage.

Other contraindications involve the intensification of the effects of barbiturates and narcotics. In combination with certain antidiabetic agents, such as tolbutamide and chlorpropamide, alcohol can cause dizziness, hot flushes, and nausea. Mild reactions may occur with a wide range of other medications, such as sulfanilamide, isoniazid, and aminopyrine. Additional details may be found in Adams (1995), Fraser (1997), and Weathermon and Crabb (1999).

In conclusion, Mark Twain crystallizes what so often seems to be the relationship between food, wine, and health:

*The only way to keep your health is to eat what you don’t want, drink what you don’t like, and do what you’d druther not.* —Mark Twain in Following the Equator.

**References**

Abrams, A., Aronson, M.D., Delbanco, T., Barnes, H.N. (Eds.), 1987. Alcoholism. Springer-Verlag, New York, NY.

Adams, W.L., 1995. Interactions between alcohol and other drugs. Int. J. Addict. 30, 1903–1923.

Aggarwal, B.B., Bhardwaj, A., Aggarwal, R.S., Seeram, N.P., Shishodia, S., Takada, Y., 2004. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Res. 24 (5A), 2783–2840.

Alam, Z., Coombes, N., Waring, R.H., Williams, A.C., Steventon, G.B., 1997. Platelet sulphotransferase activity, plasma sulfate levels, and sulphation capacity in patients with migraine and tension headache. Cephalalgia 17, 761–764.

Andersson, M., Persson, C.G.A., Persson, G.G., Svensson, C., Cervin-Hoberg, C., Greiff, L., 2003. Effects of loratadine in red wine-induced symptoms and signs of rhinitis. Acta Otolarystogol. 123, 1087–1093.

Augustin, L.S.A., Gallus, S., Tavani, A., Bosetti, C., Negri, E., La Vecchia, C., 2004. Alcohol consumption and acute myocardial infarction: a benefit of alcohol consumed with meals? Epidemiology 15, 767–769.

Aura, A.-M., 2008. Microbial metabolism of dietary phenolic compounds in the colon. Phytochem. Rev. 7, 407–429.

Aviram, M., Fuhrman, B., 2002. Wine flavonoids protect against LDL oxidation and atherosclerosis. Ann. NY Acad. Sci. 957, 146–161.

Baldi, A., Romani, A., Mulinacci, N., Vincieri, F.F., Ghiselli, A., 1997. The relative antioxidant potencies of some polyphenols in grapes and wines. In: Watkins, T.R. (Ed.), Wine: Nutritional and Therapeutic Benefits. American Chemical Society, Washington, DC, pp. 166–179. ACS Symposium Series No. 661.

Barnham, K.J., Masters, C.L., Bush, A.I., 2004. Neurodegenerative disease and oxidative stress. Nat. Rev. Drug Discov. 3, 205–214.

Barra, S., Franceschi, S., Negri, E., Talamini, R., La Vecchia, C., 1990. Type of alcoholic beverage and cancer of the oral cavity, pharynx and oesophagus in an Italian area with high wine consumption. Int. J. Cancer 46, 1017–1020.

Bartowski, E.J., Stockley, C.S., 2010. Waiter, is there histamine in my wine? Histamine in Australian wines – a survey over 27 years (1982 to 2009). Aust. NZ Grapegrower Winemaker 557a, 69–72.

Bastian, S.E.P., Payne, C.M., Perrenoud, B., Joseyne, V.L., Johnson, T.E., 2009. Comparisons between Australian consumers’ and industry experts’ perceptions of ideal wine and cheese combinations. Aust. J. Grape Wine Res. 15, 175–184.

Bastian, S.E.P., Collins, C., Johnson, T.E., 2010. Understanding consumer preferences for Shiraz wine and Cheddar cheese pairings. Food Qual. Prefer. 21, 668–678.

Bell, D.S.H., 1996. Alcohol and the NIDDM patient. Diabetes Care 19, 509–513.

Benini, L., Salandini, L., Rigon, G., Tacchella, N., Brighenti, F., Vantini, L., 2003. Effect of red wine, minor constituents, and alcohol on the gastric emptying and the metabolic effects of a solid digestible meal. Gut 52 (Suppl. 1), pA79–pA80.

Bertelli, A.A.E., 1998. Modulatory effect of resveratrol, a natural phytoalexin, on endothelial adhesion molecules and intracellular signal transduction. Pharm. Biol. 36 (Suppl. 1), 44–52.
References

Bianchini, F., Vainio, H., 2004. Wine and resveratrol: mechanisms of cancer prevention? Eur. J. Cancer Prev. 12, 417–425.

Biasi, F., Deiana, M., Guina, T., Gamba, P., Leonardiuzzi, G., 2014. Wine consumption and intestinal redox homeostasis. Redox Biol. 2, 795–802.

Bisson, L.F., Butzke, C.E., Ebeler, S.E., 1995. The role of moderate ethanol consumption in health and human nutrition. Am. J. Enol. Vitic. 46, 449–462.

bolhuis, D.P., Newman, L.P., Keast, R.S.J., 2016. Effects of salt and fat combinations on taste preference and perception. Chem. Senses 41, 189–195.

Boffetta, P., Garfinkel, L., 1990. Alcohol drinking and mortality among human cytochrome P450 1A1 inhibitor. Biochem. Biophys. Res. Commun. 180, 107–110.

Bogdarev, S.M., Henquin, J.-C., 1995. The role of vanadium in the management of diabetes. Trends Pharmacol. Sci. 16, 265–270.

Brillat-Savarin, J.A., 1848. Physiologie du Gout. Gabriel de Gonet, Paris, France, p. 87.

Budmiger, H., Kocher, F., 1982. Boletus luridus and alcohol. Case report (in German). Schweiz. Med. Wochenschr. 112, 1179–1181.

Bustos, I., Garcia-Cayuela, T., Hernández-Ledesma, B., Peláez, C., Requena, T., Martínez-Cuesta, M.C., 2012. Effect of flavan-3-ols on the adhesion of potential probiotic lactobacilli in intestinal cells. J. Agric. Food Chem. 60, 9082–9088.

Cains, S., Blomeyer, C., Kollo, M., Rácz, R., Burdakov, D., 2017. Agpr neuron activity is required for alcohol-induced overeating. Nat. Commun. 8, 14014.

Camargo Jr., C.A., Stampfer, M.J., Glynn, R.J., Gaziano, J.M., Manson, J.E., Goldhaber, S.Z., et al., 1997. Prospective study of moderate alcohol consumption and risk of peripheral arterial disease in US male physicians. Circulation 95, 577–580.

Chao, C., Haque, R., Van Den Eeden, S.K., Caan, B.J., Poony, K.-Y., Quinn, V.P., 2010. Red wine consumption and risk of prostate cancer: the California Men's Health Study. Int. J. Cancer 126, 171–179.

Cho, H.S., Lee, J.-H., Ryu, S.Y., Joo, S.W., Cho, M.H., Lee, J., 2013. Inhibition of Pseudomonas aeruginosa and Escherichia coli 0157:H7 biol film formation by plant metabolite e-viniferin. J. Agric. Food Chem. 61, 4189–4196.

Choi, H., Curhan, G., 2004. Beer, liquor, and wine consumption and stone disease. Urol. Clin. N. Am. 31, 278, 41427–41431.

Daglia, M., Stauder, M., Papetti, A., Signoretto, C., Giusto, G., Canepari, P., et al., 2010. Isolation of red wine components with anti-adhesion and anti-biofilm activity against Streptococcus mutans. Food Chem. 119, 1182–1188.

Dahl, R., Henriksen, J.M., Harving, H., 1986. Red wine asthma: a controlled study. J. Allergy Clin. Immunol. 78, 1126–1129.

De Freitas, V., Mateus, N., 2003. Nephelometric study of salivary protein-tannin aggregates. J. Sci. Food Agric. 83, 113–119.

Delmas, D., Rébé, C., Lacours, S., Filomenko, R., Athias, A., Cambert, P., et al., 2003. Resveratrol-induced apoptosis is associated with Fal redistribution in the rats and the formation of a death-inducing signaling complex in colon cancer cells. J. Biol. Chem. 278, 41482–41490.

Déprez, S., Bressillon, C., Rabot, S., Philippe, C., Mila, I., Lapierre, C., et al., 2004. Polymeric proanthocyanidins are catabolized by human colonic microflora into low-molecular-weight phenolic acids. J. Nutr. 130, 2733–2738.

Díaz-Rubio, M.E., Saura-Calixto, F., 2006. Dietary fiber in wine. Am. J. Enol. Vitic. 57, 69–72.

Dingler, F.A., Patel, K.J., 2017. Of sizzling steaks and DNA repair. Science 357, 130–131.

Dixon, J.B., Dixon, M.F., O’Brien, P.E., 2001. Alcohol consumption in the severely obese: relationship with the metabolic syndrome. Obes. Res. 10, 245–252.

Dolara, P., Arrigucci, S., Cassetta, M.I., Fallani, S., Novelli, A., 2005. Inhibitory activity of diluted wine on bacterial growth: the secret of water purification in antiquity. Int. J. Antimicrob. Agents. 26, 338–341.

Doll, R., Peto, R., Boreham, J., Sutherland, I., 2005. Mortality in relation to alcohol consumption: a prospective study among male British doctors. Int. J. Epidemiol. 34, 199–204.

Ebel, S.E., Weber, M.A., 1996. Wine and cancer. In: Waterhouse, A.L., Rantiz, J.M. (Eds.), Wine in Context: Nutrition, Physiology, Policy. Proc. Symp. Wine & Health. American Society for Enology and Viticulture, Davis, CA, pp. 16–18.

Edward, M., Czank, C., Woodward, G.M., Cassidy, A., Kay, C.D., 2015. Phenolic metabolites of anthocyanins modulate mechanisms of endothelial function. J. Agric. Food Chem. 63, 2423–2431.

El Khoury, A., Rizk, T., Lteif, R., Azouri, H., Delia, M.-L., Lebrihi, A., 2008. Fungal contamination and aflatoxin B1 and ochratoxin A in Lebanese wine—grapes and musts. Food Chem. Toxicol. 46, 2244–2250.

Enomoto, N., Takada, A., Date, T., 1991. Genotyping of the aldehyde dehydrogenase 2 (ALDH2) gene using the polymerase chain reaction: evidence for single point mutation in the ALDH2 gene for ALDH2-deficiency. Gastroenterol. Jpn. 26, 440–447.

Eriksson, C.J.P., Fukunaga, T., Sarkola, T., Chen, W.J., Chen, C.C., Ju, J.M., et al., 2001. Functional relevance of human ADH polymorphism. Alcohol Clin. Exp. Res. 25, 1578–1635.

Ersche, K.D., Jones, P.S., Williams, G.B., Burton, A.J., Robbins, T.W., Bullmore, E.T., 2012. Abnormal brain structure implicated in stimulant drug addiction. Science 335, 601–604.

Falcone, E., 1991. Migration of lead into alcoholic beverages during storage in lead crystal decanters. J. Food Prot. 54, 378–380.

Fazli, F., Rahman, A., Greensill, J., Ainley, K., Hasi, S.M., Parish, J.H., 1990. Strand scission in DNA by quercetin and Cu(II): identification...
of free radical intermediates and biological consequences of scission. Carcinogenesis 11, 2005–2008.

Fernandes, A., Ratola, N., Cerdeira, A., Alves, A., Venâncio, A., 2007. Changes in ochratoxin A concentration during winemaking. Am. J. Enol. Vitic. 58, 92–96.

Fernández-Pachón, M.S., Bema, G., Otaolaurruchi, E., Troncoso, A.M., Martin, F., García-Parrilla, M.C., 2009. Changes in antioxidant endogenous enzymes (activity and gene expression levels) after repeated red wine intake. J. Agric. Food Chem. 57, 6578–6583.

Finger, T.E., Kinnaman, S.C., 2011. Taste isn’t just for taste buds anymore. F1000 Biol. Rept. 3, 20. http://f1000.com/reports/b/3/20.

Forester, S.C., Waterhouse, A.L., 2009. Metabolites are key to understanding health effects of wine polyphenolics. J. Nutr. 138, 18245–18315.

Franke, A., Teyssen, S., Harder, H., Singer, M.V., 2004. Effects of ethanol and some alcoholic beverages on gastric emptying in humans. Scand. J. Gastroenterol. 39, 638–645.

Frankel, E.N., Waterhouse, A.L., Kinsella, J.E., 1993. Inhibition of human LDL oxidation by resveratrol. Lancet 341, 1103–1104.

Fraser, A.G., 1997. Pharmacokinetic interactions between alcohol and other drugs. Clin. Pharmacokinet. 33, 79–90.

Fraser-Bell, S., Wu, J., Klein, R., Azen, S.P., Varma, R., 2006. Smoking, alcohol intake, estrogen use, and age related macular degeneration in Latinos: the Los Angeles Latino Eye Study. Am. J. Ophthalmol. 141, 79–87.

Friedman, M., 2014. Antibacterial, antiviral, and antimicrobial properties of wines and winery products in relation to their flavonoid content. J. Agric. Food Chem. 62, 6025–6042.

Frijters, J.E.R., Schifferstein, H.N.J., 1994. Perceptual interactions in mixtures containing bitter tasting substances. Physiol. Behav. 56, 1243–1249.

Fugelsang, K.C., Muller, C.J., 1996. The in vitro effect of red wine on Helicobacter pylori. In: Waterhouse, A.L., Rantz, J.M. (Eds.), Wine in Context: Nutrition, Physiology, Policy. Proc. Symp. Wine & Health. American Society for Enology and Viticulture, Davis, CA, pp. 43–45.

Fuhrman, B., Volkova, N., Suraski, A., Aviram, M., 2001. White wine with red wine-like properties: increased extraction of grape skin polyphenols improves the antioxidant capacity of the derived white wine. J. Agric. Food Chem. 49, 3164–3168.

Galmarini, M.V., Loiseau, A.-L., Visalli, M., Schlich, P., 2016. Use of multi-intake temporal dominance of sensations (TDS) to evaluate the influence of cheese on wine perception. J. Food Sci. 81, S2566–S2577.

Ganry, O., Baudoin, C., Fardellone, P., 2000. Effect of alcohol intake on bone mineral density in elderly women: the EPIDOS Study. Epidemiol..rbrella 71, 3163–3170.

Haddad, J.J., 2004. Alcoholism and neuro-immune–endoctrine interactions: biochemical aspects. Biochem. Biophys. Res. Commun. 325, 361–371.

Halsted, C.H., 2003. Alcohol: effects of consumption on diet and nutritional status. In: Caballero, B., Finglas, P., Toldra, F. (Eds.), Encyclopedia of Food Sciences and Nutrition, second ed. Academic Press, London, UK.

Harada, S., Agarwal, D.P., Goedde, H.W., 1981. Aldehyde dehydrogenase deficiency as cause of facial flushing reaction to alcohol in Japanese. Lancet 318, 982.

Heinz, A., 2006. Staying sober. Sci. Am. Mind 17, 57–61.

Hidalgo, M., Oruna-Concha, M.J., Kolida, S., Walton, G.E., Callibratha, S., Spencer, J.P., et al., 2012. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. J. Agric. Food Chem. 60, 3882–3890.

Hillbom, M., 1999. Oxidants, antioxidants, alcohol and stroke. Front. Biosci. 4, 67–77.

Hines, L.M., Stamper, M.J., Ma, J., Gazzano, J.M., Ridker, P.M., Hankinson, S.E., et al., 2001. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. N. Engl. J. Med. 344, 549–555.

Homma, R., Yamashita, H., Funaki, J., Ueda, R., Sakurai, T., Ishimaru, Y., et al., 2012. Identification of bitterness-masking compounds from cheese. J. Agric. Food Chem. 60, 4492–4499.

Hord, N.G., 2008. Eukaryotic-microbiota crosstalk: potential mechanisms for health benefits of prebiotics and probiotics. Annu. Rev. Nutr. 28, 215–231.

Hou, D.-X., 2003. Potential mechanism of cancer chemoprevention by anthocyanins. Curr. Mol. Med. 3, 149–159.

Hyde, R.J., Pangborn, R.M., 1978. Parodit salivation in response to tasting wine. Am. J. Enol. Vitic. 29, 87–91.

Ilich, J.Z., Brownbill, R.A., Tamborini, L., CrnecvicOrlic, Z., 2002. To drink or not to drink: how are alcohol, caffeine and past smoking related to bone mineral density in elderly women? J. Am. Coll. Nutr. 21, 536–544.

Ishige, K., Schubert, D., Sagara, Y., 2001. Flavonoids protect neuronal cells from oxidative stress by three distinct mechanisms. Free Radic. Biol. Med. 30, 433–446.

Jang, M., Pezzuto, J.M., 1998. Resveratrol blocks eicosanoid production and chemically-induced cellular transformation: implications for cancer chemoprevention. Pharm. Biol. 36 (Suppl. p), 28–34.

Jarisch, R., Wantke, F., 1996. Wine and headache. Int. Arch. Allergy Immunol. 110, 7–12.

Jensen, M.K., Andersen, A.T., Sørensen, T.L.A., Becker, U., Thorsen, T., Gronbaek, M., 2002. Alcoholic beverage preference and risk of becoming a heavy drinker. Epidemiology 13, 127–132.

Jones, A.L., Roberts, R.C., Colvin, D.W., Rubin, G.L., Coughtrie, M.W.H., 1995. Reduced platelet phospholipase A₂ activity towards dopamine and 5-hydroxytryptamine in migraine. Eur. J. Clin. Pharmacol. 49, 109–114.
Martin, S., Pangborn, R.M., 1971. Human parotid secretion in response to ethyl alcohol. J. Dent. Res. 50, 485–490.

Martin, S., González-Burgos, E., Carretero, M.E., Gómez-Serrallones, M.P., 2011. Neuropeptotrophic properties of Spanish red wine and its isolated polyphenols on astrocytes. Food Chem. 128, 40–48.

Masquelier, J., 1986. Azione portettrice del vino sull’ulcera gastrica. Ind. Bevande 81, 13–16.

Masyczew, R., Ough, C.S., 1983. The red wine reaction syndrome. Am. J. Enol. Vitic. 32, 260–264.

Mates, R.D., 2007. Effects of linoleic acid on sweet, sour, salty, and bitter taste thresholds and intensity ratings of adults. Am. J. Physiol. Gastroutest. Liver Physiol. 292, G1245–G1248.

Maxwell, S.R.J., 1997. Wine antioxidants and their impact on antioxidant activity in vivo. In: Watkins, T.R. (Ed.), Wine: Nutritional and Therapeutic Benefits American Chemical Society, pp. 150–165.

Washington, DC: ACS Symposium Series No. 661.

Maxwell, S.R.J., Cruickshank, A., Thorpe, G.H.G., 1994. Red wine and antioxidant activity in serum. Lancet 334, 193–194.

Meagher, E.A., Barry, O.P., Burke, A., Lucey, M.R., Lawson, J.A., Rokach, J., et al., 1999. Alcohol-induced generation of lipid peroxidation products in humans. J. Clin. Investig. 104, 805–813.

Mennella, J.A., Griffin, C.E., Beauchamp, G.K., 2004. Prenatal and post-natal flavor learning by human infants. Adv. Exp. Med. Biol. 439, 175–182.

Middleton Jr., E., 1998. Effect of plant flavonoids on immune and antioxidant activity in serum. Lancet 334, 193

Milewski, J., 1986. Azione portettrice del vino sull’ulcera gastrica. Ind. Bevande 81, 13–16.

Mayer, N.S., Goodwin, D.W., Jones, F.C., Gabrielle, W.F., Pardo, M.P., Anand, M.M., et al., 1988. Antihistamine blockade of alcohol-induced flushing in orientals. J. Stud. Alcohol 49, 16–20.

Min, J.-A., Lee, K., Kim, D.-J., 2010. The application of minerals in man-induced performance impairment by prior ingestion of food. Br. J. Psychol. 83, 261–278.

Miller, N.S., Goodwin, D.W., Jones, F.C., Gabrielle, W.F., Pardo, M.P., Anand, M.M., et al., 1988. Antihistamine blockade of alcohol-induced flushing in orientals. J. Stud. Alcohol 49, 16–20.

Nygren, I.T., Gustafsson, I.-B., Johansson, L., 2003b. Perceived flavour changes in blue mould cheese after tasting white wine. Food Serv. Rev. 3, 110–115.

Mitropoulou, A., Hatzidimitriou, E., Paraskevopoulou, A., 2011. Aroma release of a model wine solution as influenced by the presence of non-volatile components. Effect of commercial tannin extracts, poly saccharides and artificial saliva. Food Res. Int. 44, 1561–1570.

Mogensen, J.M., Larsen, T.O., Nielsen, K.F., 2010. Widespread occurrence of the mycotoxin fumonisin B2 in wine. J. Agric. Food Chem. 58, 4853–4857.

Mok, T.B., McIntyre, J., Hunt, D., 2001. Dental erosion: In vitro model of a wine assessor’s erosion. Aust. Dent. J. 46, 263–268.

Moller, T., Akerstrand, K., Massoud, T., 1997. Toxin-producing species and our genes. Sci. Am. 296 (4), 46–53.

Nakamura, T., Tanigake, A., Miyanaga, Y., Ogawa, T., Akiyoshi, T., Matsuyama, K., et al., 2002. The effect of various substances on the suppression of the bitterness of quinine-human gustatory sensation, and binding and taste sensor studies. Chem. Pharm. Bull. 50, 1589–1593.

Napol, R., Cozzolino, D., Guardasole, V., Angelini, V., Zarra, E., Matarazzo, M., et al., 2005. Red wine consumption improves insulin resistance but not endothelial function in type 2 diabetic patients. Metabolism 54, 306–313.

Nardini, M., Forte, M., Vrouvek, U., Mattivi, F., Viola, R., Scaccini, C., 2009. White wine phenolics are absorbed and extensively metabolized in humans. J. Agric. Food Chem. 57, 2711–2718.

Natella, F., Macone, A., Ramberti, A., Forte, M., Mattivi, F., Matarese, R.M., Scaccini, C., 2011. Red wine prevents the postprandial increase in plasma cholesterol oxidation products: a pilot study. Br. J. Nutr. 105, 1718–1723.

Negre, E., Françoït, P., 1955. Manuel Pratique de Vinification et de Conservation des Vins. Flammarion, Paris (cited by Younger, 1966, pg. 131).

Nestler, E.J., Malenka, R.C., 2004. The addicted brain. Sci. Am. 290 (3), 78–85.

Nicoletti, P., Trevisani, M., Manconi, M., Gatti, R., De Siena, G., Zagli, G., et al., 2007. Ethanol causes neurogenic vasodilation by TRPV1 activation and CGRP release in the trigeminovascular system of the Guinea pig. Cephalgia 28, 9–17.

Nicolodi, M., Sicutieri, F., 1999. Wine and migraine: compatibility or incompatibility? Drugs Exp. Clin. Res. 25, 147–153.

Nielsen, O., Israel, Y., 1992. Hemoglobinacetaldehyde adducts in human alcohol abusers. Lab. Invest. 67, 246–152.

Nielleicht, A., Parkkila, S., 2004. Alcoholic macrocytosis — is there a role for acetaldehyde and adducts? Addict. Biol. 9, 3–10.

Nisiotou, A., Chorianopoulos, N.G., Gounadaki, A., Panagou, E.Z., Nychas, G.H.E., 2013. Effect of wine-based marinades on the behavior of Salmonella typhimurium and background flora in beef fillets. Int. J. Food Microbiol. 164, 119–127.

Nurnberger, J.I., Bierut, L.J., 2007. Seeking the connections: alcoholism and our genes. Sci. Am. 296 (4), 46–53.

Nygren, I.T., Gustafsson, I.-B., Johansson, L., 2002. Perceived flavour changes in white wine after tasting blue mould cheese. Food Serv. Technol. 2, 163–171.

Nygren, I.T., Gustafsson, I.-B., Johansson, L., 2003a. Effects of tasting technique — sequential tasting vs. mixed tasting — on perception of dry white wine and blue mould cheese. Food Serv. Technol. 3, 61–69.

Nygren, I.T., Gustafsson, I.-B., Johansson, L., 2003b. Perceived flavour changes in blue mould cheese after tasting white wine. Food Serv. Technol. 3, 61–69.

Obisesan, T.O., 2003. Wine: protective in macular degeneration. In: Sandler, M., Finder, R. (Eds.), Wine: A Scientific Exploration. Taylor & Francis, London, UK, pp. 285–298.

Obreque-Slier, E., Espinola-Espinola, V., López-Solís, R., 2016. Wine pH prevails over buffering capacity of human saliva. J. Agric. Food Chem. 64, 8154–8159.

Oliveira, H., Fernandes, I., Brás, N., Faria, A., De Freitas, V., Calhau, C., Mateur, N., 2015. Experimental and theoretical data on the mechanism by which red wine anthocyanins are transported through a human MKN-28 gastric cell model. J. Agric. Food Chem. 63, 7685–7692.

Öncül, N., Karabiyikli, S., 2016. Survival of food-borne pathogens in unripe grape products. LWT — Food Sci. Technol. 74, 168–175.

Ono, K., Condon, M.M., Ho, L., Wang, J., Zhao, W., Pasinetti, G.M., et al., 2008. Effects of grape seed-derived polyphenols on amyloid β-protein self-assembly and cytotoxicity. J. Biol. Chem. 283, 32176–32187.

O’Brien, E., Dietrich, D.R., 2005. Ochratoxin A: the continuing enigma. Crit. Rev. Toxicol. 35, 33–60.

Padilla, R., Ruiz, E., Redondo, S., Gordillo-Moscoso, A., Slowing, K., Tejerina, T., 2005. Relationship between vasodilation capacity and phenolic content of Spanish wines. Eur. J. Pharmacol. 517, 84–91.

Parantainen, J., 1983. Prostaglandins in alcohol intolerance and hangover. Drug Alcohol Depend. 11, 239–248.
Vaquero, M.J.R., Alberto, M.R., de Nadra, M.C.M., 2007. Antibacterial effect of phenolic compounds from different wines. Food Control 18, 93–101.

Varga, J., Kozakiewicz, Z., 2006. Ochratoxin A in grapes and grape-derived products. Trends Food Sci. Technol. 17, 72–81.

Vaz, M., Hogg, T., Couto, J.A., 2012. The antimicrobial effect of wine on Bacillus cereus in simulated gastro-intestinal conditions. Food Control 28, 230–236.

Verhagen, J.V., Haenen, G.R.M.M., Bast, A., 1997. Nitric oxide radical scavenging by wines. J. Agric. Food Chem. 45, 3733–3734.

Verster, J.C., Stephens, R., Penning, R., Rohsenow, D., McGeary, J., Levy, D., McKimney, A., Finnigan, F., et al., 2010. The alcohol hangover research group consensus statement on best practice in alcohol hangover research. Curr. Drug Abuse Rev. 3, 113–126.

Viegas, O., Amaro, L.F., Ferreira, J.M., Pinho, O., 2012. Inhibitory effect of antioxidant-rich marinades on the formation of heterocyclic aromatic amines in pan-fried beef. J. Agric. Food Chem. 60, 6235–6240.

Viel, J.F., Perarnau, J.M., Challier, B., Faivrenappez, I., 1997. Alcoholic calories, red wine consumption and breast cancer among premenopausal women. Eur. J. Epidemiol. 13, 639–643.

Villamor, R.R., Evans, M.A., Mattinson, D.S., Ross, C.F., 2013. Effect of ethanol, tannin and fructose on the headspace concentration and potential sensory significance of odorants in a model wine. Food Res. Int. 50, 38–45.

Voilley, A., Lubbers, S., 1998. Flavor–matrix interactions in wine. In: Waterhouse, A.L., Ebele, S.E. (Eds.), Chemistry of Wine Flavor. American Chemical Society, Washington, DC, pp. 217–229.

Volkow, N.D., Wang, G.J., Franceschi, D., Fowler, J.S., Thanos, P.K., Maynard, L., et al., 2006. Low doses of alcohol substantially decrease glucose metabolism in the human brain. Neuroimage 29, 295–301.

Wakabayashi, M., Nagao, M., Esumi, H., Sugimura, T., 1992. Food derived mutagens and carcinogens. Cancer Res. 52, 2092s–2098s.

Wallerath, T., Li, H., GodtelAmbrust, U., Schwarz, P.M., Forstermann, U., 2005. A blend of polyphenolic compounds explains the stimulatory effect of red wine on human endothelial NO synthase. Nitric Oxide 2005 (12), 97–104.

Walzem, R.L., Hansen, R.J., 1996. Atherosclerotic cardiovascular disease and antioxidants. In: Waterhouse, A.L., Rantz, J.M. (Eds.), Wine in Context: Nutrition, Physiology, Policy, Proc. Symp. Wine & Health. American Society for Enology and Viticulture, Davis, CA, pp. 6–12.

Walzem, R.L., Watkins, S., Frankel, E.N., Hansen, R.J., German, J.B., 1995. Older plasma lipoproteins are more susceptible to oxidation: a linking mechanism for the lipid and oxidation theories of atherosclerotic cardiovascular disease. Proc. Natl. Acad. Sci. U.S.A. 92, 7460–7464.

Wantke, F., Hemmer, W., Hagmüller, T., Gotz, M., Jarisch, R., 1996. Histamine in wine – bronchoconstriction after a double-blind placebo-controlled red wine provocation test. Int. Arch. Allergy Immunol. 110, 397–400.

Ward, N.C., Croft, K.D., Puddye, L.B., Hodgson, J.M., 2004. Supplementation with grape seed polyphenols results in increased urinary excretion of 3-hydroxyphenylpropionic acid, an important metabolite of proanthocyanidins in humans. J. Agric. Food Chem. 52, 5545–5549.

Wattendorf, D.J., Muenke, M., 2005. Fetal alcohol spectrum disorders. Am. Fam. Physician 72, 279–282. 285.

Weathermon, R., Crabb, D.W., 1999. Alcohol and medication interactions. Alcohol Res. Health 23, 40–54.

Weber, P., Steinhart, H., Paschke, A., 2007. Investigation of the allergenic potential of wines fined with various proteinogenic fining agents by ELISA. J. Agric. Food Chem. 55, 3127–3133.

Weisburger, J.H., 1991. Nutritional approach to cancer prevention with emphasis on vitamins, antioxidants, and carotenoids. Am. J. Clin. Nutr. 53 (Suppl. p.), 2265–2375.

Weisse, M.E., Eberly, B., Person, D.A., 1995. Wine as a digestive aid: comparative antimicrobial effects of bismuth salicylate and red and white wine. Br. Med. J. 311, 1657–1660.

Whitten, D., 1996. Fetal alcohol risk: a current perspective. In: Waterhouse, A.L., Rantz, J.M. (Eds.), Wine in Context: Nutrition, Physiology, Policy. In: Proc. Symp. Wine & Health. American Society for Enology and Viticulture, Davis, CA, pp. 46–49.

Wiemcke, T., Olesen, J., Oturai, P.S., Ashina, M., 2009. Prostaglandin E2 (PGE2) induces headache in healthy subjects. Cephalalgia 29, 509–519.

Wiese, J., McPherson, S., Odden, M.C., Shipak, M.G., 2004. Effect of Opuntia fiscus indica on symptoms of the alcohol hangover. Arch. Intern. Med. 164, 1334–1340.

Wiese, J.G., Shipak, M.G., Browner, W.S., 2000. The alcohol hangover. Ann. Intern. Med. 132, 897–902.

Willershansen, B., Callaway, A., Azrak, B., Kloß, C., Schulz-Dobrick, B., 2009. Prolonged in vitro exposure to white wines enhances the erosive damage on human permanent teeth compared with red wines. Nutr. Res. 29, 558–567.

Williams, R.J., Spencer, J.P., Rice-Evans, C., 2004. Flavonoids: antioxidants or signaling molecules? Free Radic. Biol. Med. 36, 838–849.

Williamson, G., Manach, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am. J. Clin. Nutr. 81, 243S–255S.

Wolfort, F.G., Pan, D., Gee, J., 1996. Alcohol and preoperative management. Plastic Reconstruct. Surg. 98, 1306–1309.

Wong, X., Carrasco-Pozo, C., Escobar, E., Navarrete, P., Blachier, F., Andrianmihaja, M., et al., 2016. Deleterious effect of p-cresol on human colononic epithelial cells prevented by proanthocyanin-containing polyphenol extracts from fruits and proanthocyanin bacterial metabolites. J. Agric. Food Chem. 64, 3574–3583.

Wu, L., Zhang, Q.-L., Wang, S., Li, J., Yuan, Y., et al., 2012. Pharmacokinetics and blood-brain barrier penetration of (+)-catechin and (−)-epicatechin in rats by microdialysis sampling coupled to high-performance liquid chromatography with chemiluminescence detection. J. Agric. Food Chem. 60, 9377–9383.

Xiao, J., Höög, P., 2015. Stability of dietary polyphenols under the cell culture conditions: avoiding erroneous conclusions. J. Agric. Food Chem. 63, 1547–1557.

Yang, G., Chang, C.-C., Yang, Y., Yuan, L., Xu, L., Ho, C.-T., Li, S., 2018. Resveratrol alleviates rheumatoid arthritis via reducing ROS and inflammation, inhibiting MAPK signaling pathways, and suppressing angiogenesis. J. Agric. Food Chem. 12953–12960, 2018.

Yeh, C.T., Yen, G.-C., 2003. Effects of phenolic acids on human phenol-sulfotransferase in relation to their antioxidant activity. J. Agric. Food Chem. 51, 1474–1479.

Youdim, K.A., Quiser, M.Z., Begley, D.J., RiceEvans, C.A., Abbott, N.J., 2009. Nitric Oxide (PGE2) induces headache in healthy subjects. Cephalalgia 29, 509–519.

Yu, T., 1983. Lead nephropathy and gout. Am. J. Kidney Dis. 11, 555–558.

Zhang, Y., Kreger, B.E., Dorgan, J.F., Splansky, G.L., Cupples, L.A., Ellison, R.C., 1999. Alcohol consumption and risk of breast cancer: the Framingham Study revisited. Am. J. Epidemiol. 149, 93–101.

Zhu, W., Meng, Y.-F., Wu, Y., Xu, M., Lu, J., 2017. Association of alcohol intake with risk of diabetic retinopathy: a meta-analysis of observational studies. Sci. Rep. 7, 1–9.
Suggested reading

Wine and Food
Hayes, J.E., 2015. Measuring sensory perception in relation to consumer behavior. In: Delarue, J., Lawlor, J.B., Rogeaux, M. (Eds.), Rapid Sensory Profiling Techniques. Woodhead Publishing, Cambridge, UK, pp. 53–69.
McGee, H., 2004. On Food and Cooking — the Science and Lore of the Kitchen, second ed. Scribners, New York, NY.
This, H., deBevoise, M., 2008. Molecular Gastronomy: Exploring the Science of Flavor. Columbia University Press, New York, NY.
Voilley, A., Etiévant, P. (Eds.), 2006. Flavor in Food. Woodhead Publishing Ltd., Cambridge, UK.

Wine and Health
Chuang, C.C., McIntosh, M.K., 2011. Potential mechanisms by which polyphenol-rich grapes prevent obesity-mediated inflammation and metabolic diseases. Annu. Rev. Nutr. 31, 155–176.
Friedman, M., 2014. Antibacterial, antiviral, and antifungal properties of wines and winery products in relation to their flavonoid content. J. Agric. Food Chem. 62, 6025–6042.
Krga, I., Milenkovic, D., 2019. Anthocyanins: from sources and bioavailability to cardiovascular-health benefits and molecular mechanisms of action. J. Agric. Food Chem. 67, 1771–1783.
Krymchantowski, A.V., Cunha Jevoux, C., 2014. Wine and headache. Headache 54, 967–975.
Nash, V., Ranadheera, C.S., Georgousopoulou, E.N., Mellor, D.D., Panagiotakos, D.B., McKune, A.J., et al., 2018. The effects of grape and red wine polyphenols on gut microbiota—a systematic review. Food Res. Int. 113, 277–287.
Presti, R.L., Carollo, C., Caimi, G., 2007. Wine consumption and renal diseases: new perspectives. Nutrition 23, 598–602.
Rauf, A., Imran, M., Butt, M.S., Nadeem, M., Peters, D.G., Mubarak, M.S., 2018. Resveratrol as an anti-cancer agent: a review. Crit. Rev. Food Sci. Nutr. 58, 1428–1447.
Romeo, J., Wärnberg, J., Nova, E., Diaz, L.E., Gómez, S., Marcos, A., 2007. Moderate alcohol consumption and the immune system. A review. Br. J. Nutr. 98 (Suppl. 1), S111–S115.
Smoliga, J.M., Baur, J.A., Hausenblas, H.A., 2011. Resveratrol and health — a comprehensive review of human clinical trials. Mol. Nutr. Food Res. 55, 1129–1141.
Stockley, C., Teissedre, P.L., Boban, M., Di Lorenzo, C., Restani, P., 2012. Bioavailability of wine-derived phenolic compounds in humans: a review. Food Funct. 3, 995–1007.
Vally, H., Thompson, P.J., 2003. Allergic and asthmatic reactions to alcoholic drinks. Addict. Biol. 8, 3–11.
Vauzour, D., 2014. Effect of flavonoids on learning, memory and neurocognitive performance: relevance and potential implications for Alzheimer’s disease pathophysiology. J. Sci. Food Agric. 94, 1042–1056.
Verster, J.C., 2010. The alcohol hangover. Curr. Drug Abuse Rev., Special Issue. 3, 64–126.
Vinson, J.A., 2019. Intracellular polyphenols: how little we know. J. Agric. Food Chem. 67, 3865–3870.