Review

Wine, Polyphenols and the Matrix Effect: Is Alcohol Always the Same?

Elisabetta Miraldi * , Giulia Baini , Marco Biagi , Giorgio Cappellucci , Alessandro Giordano , Federica Vaccaro , Alberto Bertelli

Posted Date: 16 July 2024

doi: 10.20944/preprints202407.1345.v1

Keywords: polyphenols

Review

Wine, Polyphenols and the Matrix Effect: Is Alcohol Always the Same?

Elisabetta Miraldi [1]*, Giulia Baini [1], Marco Biagi [2], Giorgio Cappellucci [1], Alessandro Giordano [1], Federica Vaccaro [1] and Alberto A. E. Bertelli [3,†]

[1] Department of Physical Sciences, Earth and Environment, University of Siena, 53100 Siena, Italy; giulia.baini2@unisi.it (G.B.);giorgi.cappellucci@unisi.it (G.C.); alessandr.giordano@student.unisi.it (A.G.); f.vaccaro@student.unisi.it (F V.)
[2] Departmentof Food and Drug, University of Parma, 43121 Parma, Italy; marco.biagi@unipr.it
[3] Department of Biomedical Sciences for Health, University of Milan, 20133 Milan, Italy; alberto.bertelli@unimi.it
* Correspondence: elisabetta.miraldi@unisi.it
† to whom questions should be asked emailalberto.bertelli@unimi.it.

Abstract: While the number of publications on wine and health is steadily increasing, ranging frommolecular level to epidemiological studies, often with contradictory results, little attention has been given to an holistic approach. In this review some unusual concepts are considered, such as phytocomplex, vehicle and the Matrix effect. As an example,three mono/polyphenols present in wine, Tyrosol, Hydroxytyrosol and Resveratrol, have been selected and the consequences of respecting, disregarding orignoring the Matrix effect are shown. Underestimation of the wine Matrix effect could lead to deceiving results, as in the case of de-alcoholized wine or wine-compound-based nutritional supplements,or in emphasizing a single component toxic activity, in this case alcohol, ignoring the specific protective action at molecular level of other compounds(polyphenols) present in the same Matrix. The dark side of Matrix effect is also discussed. It is suggested that specificity of wine should be always taken in consideration by public health Authorities.

Keywords: keyword 1; keyword 2; keyword 3 (List three to ten pertinent keywords specific to the article; yet reasonably common within the subject discipline.)

1. Introduction

The modern common research methodology on plant-derived molecules tries to isolate the single active compound regardless its interactions with other molecules in the original plant.Furthermore, the choice of carriers, solvents or excipients is often dictated by industrial and/or price constraints.This situation is even more complicated in the case of wine taking into consideration the vast molecular pool that characterize its phytocomplex.

Wine is obtained by fermentation of *Vitis vinifera* L. grapes and contains several hundred of compounds, including polyphenols and ethanol (EtOH).Polyphenols are considered the main responsible for the healthy effect of fruit and vegetables consumption [Rana et al., 2022].

Dietary polyphenols are bioactive compounds especially found in fruit and vegetables that play a crucial role both for plants that produce them and for animals as well, being among the most important antioxidants capable of detoxifying UV-induced oxidative stresses and recognized and biologically active in mammal cells.

These compounds, which include flavonoids, phenolic acids, tannins, and lignans, are widely distributed in plants and contribute to the prevention of exceeding oxidative stress-related dysregulations, such as cardiovascular diseases, type 2 diabetes, and certain types of cancer [Scalbert et al., 2005]. For instance, flavonoids, abundantly found in apples, onions, and tea, have been associated with a reduced risk of cardiovascular diseases through their ability to improve endothelial function and reduce the oxidation of LDL [Hollman and Katan, 1999]. Additionally, the regular intake

 doi:10.20944/preprints202407.1345.v1

of polyphenol-rich fruits and vegetables has been correlated with improved gut health by modulating the gut microbiota and promoting the growth of beneficial bacteria [Cardona et al., 2013].

Beyond their role in disease prevention, polyphenols have also been shown to exert protective effects against neurodegenerative diseases, such as Alzheimer's and Parkinson's, by inhibiting neuroinflammation and oxidative stress in the brain [Vauzour et al., 2008]. Moreover, recent studies have highlighted the potential of polyphenols to improve metabolic health by enhancing insulin sensitivity and reducing inflammation in adipose tissue, thus playing a vital role in obesity management [Williamson G., 2017].

In this review, three well known polyphenols present in wine,tyrosol (Tyr), hydroxytyrosol (HTyr) and resveratrol(Rsv), have been selected for their lipophilicity, but their activity has been evaluated in an holistic way using three uncommon criteria: phytocomplex, matrix effect and vehicle.

2. Fundamental Concepts for the Study of Plant-Derived Bioactive Compounds

2.1. The Importance of the Phytocomplex

The concept of phytocomplex is the fundamental aspect of the use of plants for health, both in the food area and in pharmacology [Biagi et al., 2016]. In fact, the interaction among different molecules in herbal matrixes provides a specific response, clearly different from single constituents in the modulation of microbial populations in the gut [Bertuccioli et al., 2022], in intestinal stability and bioaccessibility [Governa et al., 2021] and, obviously, in evoking biological responses.

The modern, evidence-based phytotherapy, namely the conventional sector of pharmacotherapy in which herbal preparations are used for human (and animal) health, officially recognized by the World Health Organization (WHO)[WHO monographs on selected medicinal plants, 1999-2006] but also, in Europe, by the European Medicines Agency (EMA)[EMA, Herbal Medicinal Products], specifically takes into account the peculiar pharmacokinetics and pharmacodynamics of phytocomplexes in several medical contexts. Examples that explain the role of phytocomplexes and phytotherapy in a clear way could be found in *Ginkgo biloba* L. leaf standardized dry extract, obtained through water (H_2O)/acetone extraction, which has a well-established use in the treatment of mild vascular dementia only because of the multitarget activity of ginkgoflavones and diterpenes [Ahlemeyer and Krieglstein, 2003] or in *Hypericum perforatum* L. aerial parts standardized extracts, obtained through H_2O/EtOH or methanol (MeOH) extraction authorized in the market of almost all European and in several extra-European countries for the treatment of mild depressive symptoms because of the synergistic effect of flavonols, phloroglucinols and hypericins in targeting Na^+-channels and producing a not-specific inhibition of neurotransmitters re-uptake [Butterweck V., 2003]. These two known examples consider two aspects worthy to be better underlined: I) no single molecule of *G. biloba* and *H. perforatum*, even if at very high dosages, could be alternative to the phytocomplex; II) the specific preparation is fundamental and what it is reported for an extract could be not applied to another one, as clearly indicated also by the official monographs of medicinal plants issued by WHO, EMA and official pharmacopoeias.

As initially mentioned, the insight on medicinal plants and phytocomplexes is directly related also to food sciences bearing in mind that safety, as well as potential health benefits of food and food supplements, should be intrinsically related to the specific preparation used; this is so important that the European Commission requires the authorization of novel foods when simple or elaborate processing different from conventional ones are used [European Parliament, Regulation on novel foods]. In the context of plants, the direct consequence to is that nutritional facts, health benefits and therapeutic potential too should not be referred to phytocomplexes and preparationsdifferent from those tested and used.

This concept is worthy to be enlarged by insights from studies on the wine matrix for research about wine and health.

2.2. Vehicle, Matrix and Food Matrix

A pharmaceutical vehicle is a carrier or an inert medium used as a solvent (or diluent) in which the medicinally active agent is formulated and/or administered (Dictionary of Pharmacy, 1986); it is

 doi:10.20944/preprints202407.1345.v1

the most abundant excipient, and as such can influence various aspects of the pharmacokinetics of the active ingredient dissolved/dispersed in it.In the specific case of wine, EtOH represents the vehicle within this beverage matrix.

The notion of "food matrix" has gained a lot of interest recently due to its implications for nutrition, food processing, and general wellness.In the scientific literature, however, the term is used with a range of connotations andoften it is associated with the literal food.

Food matrix, defined by the United States Department of Agriculture (USDA) as "The nutrient and non-nutrient components of food and their molecular relationships, i.e. chemical bonds, to each other"[USDA NAL Thesaurus, 2006], comprises all the micro-, meso- and macroscopic structures in which the food elements are organized. The course of a chemical reaction can be influenced by a number of food-related elements; these effects can be collectively referred as "the food matrix effect". The biological variance thatexists in the kinetics of same reactions taking place within different meals is caused by the food matrix effect itself [Capuano et al., 2018].

Among the many alcoholic beverages, wine has the most peculiar matrix, which can heavily influence the bioavailability of the phytocomplex obtained by the fermentation processes that produces this beverage.

3. Polyphenols: General Properties and Lipophilic Phenols in Wine

Among the countless substances produced by plants, polyphenols represent one of the main classes. Comprising molecules made up of one or more hydroxyl groups linked to aromatic rings, this class, as a consequence of the great number of possible variations in their structure,is one large family of different sub-classes of molecules (flavonoids, phenolic acids, lignans, stilbenes, etc.), some of them in turn divided into vast sub-categories (e.g. anthocyanins and catechins in the sub-class of flavonoids) [Singla et al., 2019].

Their role in the physiopathology of the plant is prominent.In addition to attracting pollinators and having structural functions, polyphenols show many defensive purposes. The antiradical, antioxidant, and antimicrobial activitiesprotect the plant against the over-production of reactive oxygen species (ROS) (induced by UV radiation, drought, exposure to heavy metals, temperature stresses, attacks by herbivores or nematodes, etc.) or possible microbial invasions. Different molecules can interrupt the development of parasitic insects' eggs and/or delay their growth [Bertelli et al., 2021; Stiller et al., 2021].

Together with monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and fibers, polyphenols are one of the main bioactive classes responsible for the beneficial health effects of the Mediterranean Diet, which mainly include great improvementsto the cardiovascular system (actions on the endothelium, on thrombus formation, on the levels of blood lipids, anti-inflammatory and antioxidant activities) and reduction of the risk of type 2 diabetes (insulin-sensibilization effect), cognitive disorders, and cancers (anti-neoplastic activity) [Dinu et al., 2018; Martínez-González et al., 2019; Schwingshackl et al., 2020].

3.1. Bioavailability

A substantial number of studies and research on polyphenols and their properties has confirmed the link between their intake through diet and the positive effects on the overall health state of an individual. Nevertheless, it is fundamental to consider the different forms by which polyphenols are found in food and all the possible modifications which the ingested phenolic pool is subjected to throughout the metabolization process.

It is known that polyphenols are scarcely bioavailable, considerably metabolized by the gut microbiota and quickly absorbed. The concentration of the native molecules in the blood is generally lower than that of their metabolic derivatives due to the additional biotransformation processes of the phenolic hydroxyl groups, exposed mainly to phase II reactions (sulfation, glucuronidation, methylation) [Bernardi et al., 2020].

Before evaluating the biological effects of polyphenolic metabolites, a thorough and precise characterization must be conducted due to the documented instability of many polyphenol molecules

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 July 2024 doi:10.20944/preprints202407.1345.v1

in cell culture media and the co-existence of multiple polyphenol species (unmetabolized, metabolized, and breakdown products) in these conditions. Currently, determining whether the biological effect being observed is the result of the cellular uptake of unmetabolized polyphenol compounds or that of newly formed metabolites [particularly relevant during long exposure studies (> 24 h)] remains a major challenge in evaluating the *in vitro* biological activity of polyphenols [Reis et al., 2021].

Bioavailability of polyphenols varies greatly among them and, for some substances, also among different dietary sources. As exposed by Manach et al. (2005), isoflavones and gallic acid are the polyphenols that humans absorb most readily, followed by quercetin glucosides, catechins, and flavanones with varying kinetics. Anthocyanins, galloylated tea catechins, and proanthocyanidins are the least well-absorbed types of polyphenols.

3.2. Polyphenols as Wine Matrix Constituents

Wine is a hydroalcoholic solution (the EtOH content usually does not exceed 14% *V*/*V*)which contains various substances, such as glycerol, polysaccharides, aldehydes and ketones, organic acids and esters, sugars, soluble proteins, vitamins, minerals, and polyphenols. The whole production procedure can deeply influence the specific composition of this beverage, from the type of grapes used to the specifics of the vinification process and storage. Certainly, the contact with all the parts of the grape during the maceration ensures the higher phenolic extraction in red wines compared to white and rosé ones[Baiano et al., 2009; Buljeta et al., 2023].

Wine, one of the foundations of Mediterranean Diet [Willett et al., 1995], has been linked with the healthy benefits of this type of diet for a long time, in particular connected with its phenolic composition. The polyphenols which can be found in wine include many sub-categories of flavonoids (flavones, flavonols, flavan-3-ols, flavanones, anthocyanins, etc.) together with various non-flavonoids, such as stilbenes, hydroxycinnamic and hydroxybenzoic acids. Main examples of molecules are catechin, epicatechin, and proanthocyanidins (flavan-3-ols), Rsv (stilbenes), anthocyanins, Tyr and HTyr, andphenolic acids (caffeic, coumaric, and ferulic acids and esters in the hydroxycinnamic group, gallic, vanillic and salicylic acids in the hydroxybenzoic one)[Ditano-Vázquez et al., 2019; Visioli et al., 2020].

3.3. Tyrosol,Hydroxytyrosol and Resveratrol

In the vast phenolic pool found inside the wine, the Tyr,HTyrand Rsvmolecules are of particular interest in the research field. Due to their particular lipophilicity, these three polyphenols are readily soluble in hydroalcoholic solutions, unlike most other molecules of the same class; this difference in the type of vehicle is one of the reasons for their higher bioavailability.

Their bioavailability is a central theme in the studies regarding their possible use as food supplements mainly in the prevention of different pathologies.Polyphenols should be considered as an integral part of the wine matrix: underestimating their role in this context could have important consequences.

3.3.1. When Matrix Effect is Respected: the case of Tyrosol and Hydroxytyrosol

Even if Tyr and HTyr are extensively studied due to their important levels in olive oil, their presence in wine could corroborate the positive health effects of Rsv and other phenolic compounds. These molecules have numerous health benefits and disease-prevention properties [Karković Marković et al., 2019; Santangelo et al., 2018]: studies conducted *in vitro*, *in vivo*, and in clinical trials have demonstrated their noteworthy bioactivity, both as isolated components and in a phytocomplex [Boronat et al., 2019; D'Angelo et al., 2020].

The simple phenol Tyr is found in fermented drinks like wine and beer, produced as byproduct of tyramine metabolism [Cerrato-Alvarez et al., 2019]. Upon consumption, the human body can endogenously convert Tyr to HTyr [Pérez-Mañá et al., 2015]. Since*in vitro* research has shown that HTyr has a greater antioxidant activity than Tyr, this biotransformation is biologically important,

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 July 2024 doi:10.20944/preprints202407.1345.v1

taking into consideration also that the levels of HTyr in fermented alcoholic beverages is significantly lower than that of Tyr [Warleta et al., 2011; Soldevila-Domenech et al., 2019].

Research on the metabolites of these two phenolic alcohols are exiguous. The levels of absorption after oral administration of Tyr and HTyr are high, even quantitative in some cases [Miró-Casas et al., 2003], but influenced by the food matrixes which convey the substances [Alemán-Jiménez et al., 2021].During digestion, the compounds undergo phase I and II reactions, while,if non-digested, they can also be metabolized by the gut microbiota. HTyrcan be both metabolized and conjugated, while Tyr is mainly conjugated by phase II reactions. Some metabolites were isolated and studied, some of them showing different biological actions, but great part of them is yet unknown or left unstudied [Sakavitsi et al., 2022].

The correct evaluation of HTyr role in the matrix, in the case of olive oil,led to the statement issued by theEuropean Food Safety Agency (EFSA) that "the novel food, hydroxytyrosol, is safe under the proposed uses and use levels"[EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2017]. Even more important was also the authorization for labelling HTyr on food products by the European Commission [European Commission, 2017].

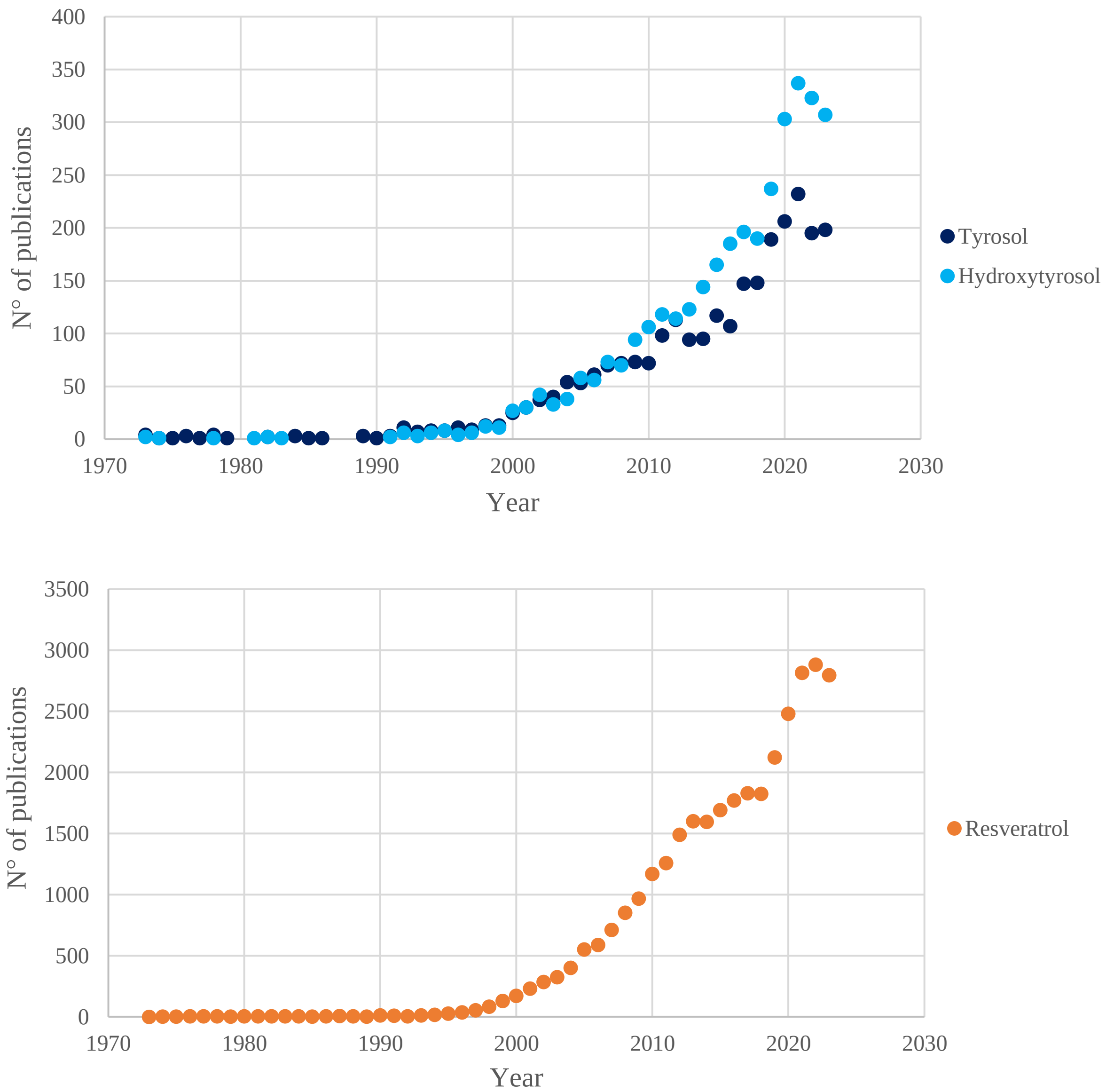

Figure 1. Number of publications, registered in the Scopus database (July 2024), in the past 50 years (1973 – 2023) related to the three main polyphenols analyzed in this review. Results obtained from the queries "tyrosol", "hydroxytyrosol" and "resveratrol", respectively.

3.3.2. When Matrix Effect is Disregarded: Resveratrol

Rsv is the most investigated molecule in the class of the stilbenes. The identification of the molecule and the discovery of the connection of this compound with the beneficial effects of wine consumption on the cardiovascular system are well known [Pezzuto J. M., 2019], as well as its plausible biological role in the so-called "French paradox" [Renaud and de Lorgeril, 1992].

After being taken orally as a pure compound, enterocytes absorb Rsv in enormous amounts; nevertheless, only a small portion (less than 1%) of this dietary ingredient enters the bloodstream and bodily tissues, mainly because of its efficient metabolism in the liver and the intestine [Bandiwadekar et al., 2024]. Some of the most significant restrictions and difficulties associated with the *in vivo* using of Rsv include rapid absorption, low bioavailability, and low solubility in H_2O [Ferraz da Costa et al., 2020].

Rsv is chemically stable at low temperatures, in both acidic [Zupančič et al., 2015] and anoxic [Sessa et al., 2014] environments, and in the dark [Bertelli et al., 1996], all conditions found in bottled wine.

To improve absorption efficacy, solubility, and relative bioavailability, various possibilities in the administration methodologies could be explored, as, for example, the linking with serum albumin [Nair M. S., 2015] or the encapsulation in protein nanoparticles [Geng et al., 2017]. Likewise, the administration strategies should contribute to the "reservoir" effect in order to allowRsv accumulation in tissues and its subsequent mobilization [Lu et al., 2007; Bertelli A. A. E., 2007].

In one of the first kinetic studies in rats in which natural resveratrol in red wine matrix was used, plasma resveratrol concentrations from 100 nM to 1 μM were detected [Bertelli et al., 1996],levels that are sufficient to explicate the cardioprotective activity [Bertelli A. A. E., 2007]. In humans, after red wine intake,Rsv was easily absorbed and detected even in low density lipoproteins (LDLs)[Urpi-Sarda et al., 2007]. It is therefore surprising the trend of increasing synthetic resveratrol dosage, not only in animals but also in humans [Rotches-Ribalta et al., 2012;Wong et al., 2020]. The matrix effect in red wine containing resveratrol was already described as early as in 1995 [Bertelli et al., 1995], just three years after the discovery of the French paradox [Renaud and de Lorgeril, 1992]. The decision to disregard the matrix effect in many researchcould make rather difficult to overcome bioavailability problems.

4. Alcohol and Alcoholic Beverages

As suggested by the adjective, the multitude of existing alcoholic beverages is linked precisely by the presence of alcohol, in different concentrations (from 5 up to 40% *V*/*V* and even more), inside them. Due to its presence in relatively high concentrations compared to other components and the heavy influence that this substance has on the organism, it is obvious that the physiological effects of EtOH play a key role among the consequences of the consumption of these drinks.

4.1. Absorption and Metabolismof Ethanol

Passive diffusion allows alcohol to enter the bloodstream from the digestive system. The duodenum and jejunum absorb most of the EtOH that is taken orally, so the rate at which the stomach empties is a significant factor in determining how quickly alcohol is absorbed. The amount of alcohol consumed, the presence or absence of food in the stomach (food delays gastric emptying and hence reduces EtOH absorption), factors that affect gastric emptying (meals high in fat, carbs, or protein are equally effective in delaying gastric emptying), and the rate of EtOH oxidation all affect blood alcohol concentration. The rate at which the same amount of EtOH is absorbed when given in different alcoholic beverages does not vary significantly. Because alcohol is oxidized more readily than other nutrients, it is crucial to remember that calories from EtOH are obtained preferably instead of those from the metabolism of regular nutrients.[Addolorato et al., 1997; Cederbaum A. I., 2012; Kwo et al., 1988; Lands W. E., 1995; Pikaar et al., 1988; Wilkinson et al., 1977]

Less than 3% of the absorbed EtOH is expelled by sweat, urine, and breath, but more than 90% of it circulates throughout the body and is eventually delivered to the liver via the portal vein. Both oxidative and non-oxidative metabolic processes are used in the liver to break down alcohol. In two stages, the liver converts EtOH into acetate, which is used in the citric acid cycle. When drinking in moderation, specific alcohol-oxidizing enzymes usually drive the elimination of alcohol; when

 doi:10.20944/preprints202407.1345.v1

drinking excessively, nonspecific enzymes may increase alcohol elimination even more. ADH is the primary and most specific alcohol-oxidizing enzyme, transformingEtOH into acetaldehyde. The enzyme ALDH efficiently transforms the extremely poisonous acetaldehyde into the innocuous acetate. In peripheral tissues, acetate is broken down into CO_2, fatty acids, and H_2O. The cytochrome (CY) P2E1 that is part of the microsomal ethanol-oxidizing system (MEOS) is expressed and activated more when alcohol consumption is excessive. Activated CYP2E1 stimulates the synthesis of acetaldehyde by producing ROS. Nonoxidative metabolism produces ethyl glucuronide(EtG), ethyl sulfate(EtS), PEth, and FAEEs from a minor portion of EtOH (<0.1%). TheseEtOH metabolites have a substantially longer half-life than EtOH itself. [Cederbaum A. I., 2012; Comporti et al., 2010; Heier et al., 2016; Holford N. H.; 1987; Laposata and Lange, 1986; Lieber C. S., 1997; Lu and Cederbaum, 2008; Zakhari S., 2006]

4.2. Physiological Effects and Toxicity of Alcohol

Alcohol enters the brain and momentarily alters signal transduction. After moderate alcohol consumption, the neurotransmitters glutamate, dopamine, serotonin, and γ-aminobutyric acid (GABA) undergo the most significant short-term alterations. EtOH reduces glutamate activity and increases GABA activity, which promotes tranquility, relaxation, pleasure, and a reduction in tension. EtOH also causes a spike in serotonin and increases the release of dopamine, further enhancing the pleasant effects. [Hendriks H. F. J., 2020]

Alcohol metabolic byproducts harm the liver and are a major factor in the progression of alcohol-related liver diseases (ALD), from alcoholic steatosis to alcoholic cirrhosis. Acetaldehyde is the most well-known harmful substance that results from the metabolism of EtOH. Direct interactions between acetaldehyde and DNA result in chromosomal damage and point mutations. Additionally, it forms acetaldehyde adducts via binding to a series of proteins, which alters the structure and function of the liver. These protein adducts increase oxidative stress and upregulate CYP2E1 expression. Furthermore, it has been shown by Holstege et al. (1994) that protein adducts are important in the pathophysiology of different phases of ALD by promoting lipid accumulation, inflammation, and fibrosis. EtOH toxicity is also known to be caused by metabolites produced from nonoxidative pathways, such asphosphatidylethanol(PEth) and fatty acid ethyl esters (FAEEs), although the exact processes are still unknown. [Hyun et al., 2021; Lieber C. S., 1994; Setshedi et al., 2010; Tuma and Casey, 2003; Wu and Cederbaum, 2003; Seth et al., 2011]

4.2.1. The Dark Side of the Matrix Effect: Alcohol and Smoke

The toxic effects of ethanol consumption on the organism are also synergic with those of other harmful substances.

There is a strong dose-response association between alcohol intake and the development of head and neck cancer (HNC), making it an independent risk factor [Goldstein et al., 2010; Pelucchi et al., 2008]. Acetaldehyde and alcoholic beverages are categorized as class I carcinogens [IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012]. After being metabolized, alcohol may contribute to HNC carcinogenesis directly or indirectly. The latter may occur, for instance, due to alcohol acting as a solvent for other potential carcinogens, such as those found in tobacco [Boffetta and Hashibe, 2006; Clinton et al., 2020]. The risk between drinking beer, wine, or liquor and developing HNC is comparable, suggesting that ethanol, rather than other components in alcoholic beverages, is likely the most significant factor in determining HNC risk [Freedman et al., 2007]. However, the risk of HNC was generally inversely correlated with wine consumption [Purdue et al., 2009]. Numerous studies have already proven the strong correlations between smoking cigarettes and an elevated risk of HNC in general and all subtypes [Freedman et al., 2007; Gandini et al., 2008]. Furthermore, there seems to be a correlation between the risk of HNC overall and cigarette smoking status, frequency, and duration, and quitting smoking also lowers the risk of HNCs [Hashibe et al., 2007; Lubin et al., 2009; Marron et al., 2010]. A multiplicative interaction between the categories of cigarette smoking and alcohol intake was established in the HNC as a whole [Hashibe et al., 2009; Zeka et al., 2003]. Since alcohol can function as a solvent for carcinogens in cigarette smoke and increase the mucosa's permeability to these carcinogens, the interaction effect between alcohol

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 July 2024 doi:10.20944/preprints202407.1345.v1

consumption and cigarette smoking is biologically plausible. As a result, the carcinogenic properties of both factors are likely to be enhanced in the presence of one another [Maasland et al., 2014; Varoni et al., 2015].

4.3. When the Matrix Effect Is Ignored: Alcohol Beverages Specificity

In the search for the biological motivation for the pro-carcinogenic effect of alcoholic beverages, acetaldehyde resulting from the metabolism of EtOH has been indicated as a cause of malignant tumors, particularly those affecting the esophagus [Baan et al., 2007].However, the specificity of the distinct types of alcoholic beverages is not considered since in most studies no distinctions are usually made. Therefore, there is a tendency to consider also wine as a responsible for the onset of esophageal tumors through a mechanism of action mediated by acetaldehyde. Nevertheless, several studies on the upper digestive tract not only do not confirm this hypothesis, but even suggest a protective effect of wine in these pathologies [Kubo et al., 2009; Vioque et al., 2008;Anderson et al., 2009; Pandeya et al., 2009; Gammon et al., 1997; Grønbaek M., 2004]. A recent review about moderate red wine intake also pointed to its association with a positive effect on mortality and dementia, as well as specific malignancies, like non-Hodgkin lymphoma, and circulatory diseases, while the correlation for other medical conditions was insignificant [Wojtowicz J. S., 2023].

Is there a biological plausibility for this protective effect of wine? It would seem so, since the polyphenols in the wine itself are responsible. As already known, acetaldehyde can react in wine with other phenolic-type components to the detriment of the quality of the product [Cucciniello et al., 2023].At least thirteen polyphenols present in wine have been shown to be “potent inhibitors of the mammary tissue microsomal pathway of EtOH metabolism to acetaldehyde”[Maciel et al., 2011]. Three other polyphenols (epicatechin, epicatechin gallate and epigallocatechin) extracted from the fruit of *Diospyros kaki*L.f., the persimmon,“attenuate acetaldehyde-induced DNA double-strand breaks by scavenging acetaldehyde”[Matsuzaki et al., 2022]. The three mentioned polyphenols are also present in wine [Arranz et al., 2012]. Furthermore, epigallocatechin can silence the activation of hepatic stellate cells induced by acetaldehyde, which plays a key role in hepatic fibrogenesis [Chen et al., 2002].

Rsv“decreases acetaldehyde generation and increases the metabolism of acetaldehyde to acetic acid by enhancing acetaldehyde dehydrogenase 2 (ALDH2)” in cultures of human peripheral lymphocytes[Yan et al., 2012]. It must be underlined that the activation of ALDH2 is also of cardiovascular interest as it “reduces ischemic damage to the heart” and may be beneficial for patients subjected to cardiac ischemia [Chen et al., 2008].Rsv and other flavonoids showed promising results in pre-clinical trials by lowering blood pressure, increasing vascular health, and attenuating left ventricular remodeling and hypertrophy, while enhancing its functionality. These polyphenols can also have a beneficial impact on a number of cardiovascular risk factors, including vascular inflammation, diabetes, and lipid profiles, while also exhibiting strong anti-atherogenic properties [Gál et al., 2023].

The prevention of cardiovascular disease has been linked to procyanidins (tetra-epicatechin-gallate, procyanidin trimer-, tetramer- and pentamer-gallate). These polyphenols are particularly abundant in red wines from south-west France (Gers) and Sardinia (Nuoro) and can be linked to the peculiar increased longevity in these two regions [Corder et al., 2006]. Furthermore, other studies showed the possible preventive action of red wine against weight gain and health hazards associated with obesity [Moreno-Indias et al., 2016; van Bussel et al., 2018], clearly connected also with those affecting the circulatory system, as opposed to spirits and beer [Larsen et al., 2022; Wannamethee et al., 2005].

Recent epidemiological research confirms the cardiovascular protective effect of moderate wine consumption [Krittanawong et al., 2022], although for some researchers it seems to be limited to the prevention of ischemic heart disease [Schutte et al., 2020]. Moreover, in the latter cited study the authors underline the importance of distinguishing between the several types of alcoholic drinks, a distinction that is rarely considered in most of this type of research.In a recent systematic analysis for the Global Burden of Disease Study 2020, the authors themselves admit that a limitation in the report is precisely that of not having differentiation between the various types of alcoholic beverages [GBD 2020 Alcohol Collaborators, 2022].

The recommendations for research by the WHO Scientific Group, which suggests"to investigate the possible protective effects of ingredients other than alcohol in alcoholic beverages"["Cardiovascular Disease Risk Factors: New Areas for Research. Report of a WHO Scientific Group.", 1994],considering the most recent studies seem not only relevant, but also capable of directing future researchtowards innovative points of view that have so far been too neglected.

5. *In Vivo* Studies on Polyphenols Biological Activities

The modest bioavailability and high biotransformation of most polyphenols in the organism cast doubt on the possibility that their antioxidant activity can play a major role in their *in vivo* effects, even though*in vitro*it is well-substantiated and has been repeatedly linked in the literature to their health effects [Santos-Buelga et al., 2019].

Despite the fact that *in vivo* polyphenols have a mild but significant direct antioxidant activity[Forman et al., 2014], other factors are now thought to be involved in their biological effects. They might, for instance, regulate the expression of genes and intracellular signaling pathways that are essential to the protection and functioning of cells [Barrajón-Catalán et al., 2014;Joven et al., 2014]. Additionally, there is mounting evidence that the interactions between gut microbiota and polyphenols play a vital role in explaining the health advantages of polyphenol ingestion. In fact, the range of substances that can have a biological impact was substantially expanded by the discovery of metabolites produced by the microbiota [González-Domínguez et al., 2020].

A comprehensive revision including *in vivo* investigations on the impact of proanthocyanidins on lipid metabolism was done by Bladéet al.(2010). A number of dietary anthocyanins, including cyanidin-3-rutinoside and pelargonidin-3-glucoside, as well as the flavanones hesperetin and naringenin and their corresponding*in vivo* metabolites, have been shown to be able to penetrate the blood-brain barrier (BBB) [Faria et al., 2014; Talavéra et al., 2005]. Regretfully, the results of these numerous investigations into neuroprotective processes typically use flavonoids in their natural state rather than those that are more likely to penetrate the bloodstream [Fernandes et al., 2017].

According to *in vitro* and *in vivo* studies, phenolics from olive oil can activate the 5′ adenosine monophosphate-activated protein kinase(AMPK), which then inhibits the mTOR signaling pathway [Barrajón-Catalán et al., 2014]. This pathway is involved in the control of several adipose tissue activities, such as lipid metabolism, thermogenesis, and adipogenesis. Moreover, it alters cell cycle progression, hypoxia signaling, autophagy, mitochondrial biogenesis, and functioning [Cai et al., 2016]. Due in part to their high polyphenol content, virgin olive oil-rich Mediterranean diets were found to be beneficial in lowering a number of inflammatory markers in intervention studies, includingtumor necrosis factor (TNF) α, interleukin (IL) 6,chemokines like the monocyte chemoattractant protein(MCP), etc.[Medina-Remón et al., 2017; Urpi-Sarda et al., 2012]. [Santos-Buelga et al., 2021]

There is a multitude of research on*in vivo* human studiesabout the connections between wine, phenolic components and health (Table 1). A study by Welch et al. (2012) looked at how various wine flavonoids affected the bone mineral density (BMD) of more than three thousand female twins from the United Kingdom. Anthocyanins and flavones had good effects on hip and spine BMD, and total flavonoid intake had a positive association with spine BMD,implying that phenolics may be advantageous for human bone health. [Kutleša and Budimir Mršić, 2016]

Althoughwine polyphenols shouldn't be viewed as direct antioxidants*in vivo*, under certain circumstances they may act in that way. Lipid peroxides are formed in the stomach during digestion, particularly after consuming red meat, and can reach concentrations of up to mM [Gorelik et al., 2008; Timmers et al., 2020]. Foods and drinks high in polyphenols, such as extra virgin olive oil and red wine, can scavenge lipid peroxides and stop and lessen the development of such peroxides.

By blocking the sphingosine kinase 1/sphingosine phosphate pathway, green tea and wine polyphenols limit prostate cancer cell proliferation both *in vitro* and *in vivo*, according to a study that employed a grapevine extract [Brizuela et al., 2010].

It has been demonstrated that resveratrol increases bone growth and inhibits bone loss. By using a number of molecular mechanisms that have all been demonstrated in*in vitro* studies, it prevented osteoclast differentiation and bone loss [He et al., 2010]. Its preventive benefits in bones are confirmed by *in vivo* animal investigations [Habold et al., 2011; Zhao et al., 2023].

Scientists studying human health have recently become interested in trans-epsilon-viniferin, also known as "ε-viniferin", a trans-resveratrol dimer. Red wine is its primary food source, withthe highest concentrations foundroughly around1 mg/L [Guerrero et al., 2020].Numerous studies have examined the biological effects of viniferin over the past fifteen years, and its anti-inflammatory and antioxidant qualities have been documented [Beaumont et al., 2022]. Certain reports claim that the biological properties of ε-viniferin are often even higher than those of resveratrol. It has been shown to have positive benefits in both *in vivo* and *in vitro* models of cancer, obesity, disorders connected to obesity, and neurological or cardiovascular diseases. [Hrelia et al., 2022]

Table 1. References from different meta-analysis, referred to human studies, which highlight the positive effects of wine / grape products assumption.

Reference	N° of studies	Treatment	Results	Outcomes
Sheng et al., 2024	12	Wine (242 – 94.308 mg/L/die)	↓ CICAM-1 ↓ VCAM-1 ↓ TNF-α ↓ CCR2 ↑ αMβ2 (Mac-1)	Improvement of the markers associated with atherosclerotic inflammation in healthy patients, but not in those with CVD
Xie and Feng, 2022	4	Red wine vs white wine and/or other alcoholic beverages	/	Red wine decreased the risk of Alzheimer's Disease
Weaver et al., 2021	4	Grape extract (700 – 1 400 mg/die)	↓ blood pressure ↑ FMD	Improvement of vascular health, particularly in at risk human populations
Hong et al., 2020	11	Wine (0 – 84.9 g/die)	/	There isn't a statical significant correlation between wine assumption and prostate cancer
Ye et al., 2019	9	Wine (118 – 300 mL/die)	↓ total cholesterol ↓ diastolic blood pressure	Improvement of some cardiovascular parameters in type 2 diabetes mellitus patients
García-Conesa et al., 2018	99	Red wine / grape extract (100 – 2 000 mg/die) Red wine (250 – 400 mL/die)	↓ total cholesterol ↓ blood pressure ↑ HDL-C ↑ FMD ↓ TAGs	Improvement of cardiovascular health Support in the treatment of metabolic disorders
Sancho and Mach, 2014	6	Red wine (moderate consumption, max one glass/die)	/	Decrease in the risk of developing Non-Hodgkin Lymphoma, epithelial ovarian cancer, prostate cancer, lung cancer, breast cancer, esophageal adenocarcinoma (Barret's esophagus)

6. When Natural Vehicle in Wine is Targeted: Wine Non-Alcoholic Alternatives

If in the future the consumption of wine will also be penalized from a regulatory point of view due to the alcohol content, various scenarios will have to be hypothesized in which wine is replaced by other, non-alcoholic products.

One feasible alternative could be grape juice, which, however, is ineffective as a matrix in the absorption of two polyphenols of interest like quercetin and Rsv, both in animals and humans. It was observed that when administration occurs by adding 10% EtOH or whiskey, polyphenols are present both in plasma and urine, pointing to a good level of absorption of the molecules [Meng et al., 2004].

A perhaps more rational substitute would be dealcoholized wine, but the experimentation of this product in post-menopausal women gave underwhelming results [Giovannelli et al., 2011], while unmodified red wine instead reduces the risk of cardiovascular diseases [Pal et al., 2004]. A study in humans on different circulatory functions, with particular attention to the flow mediated dilatation (FMD), reaches the same conclusions, confirming once again the functioning of red wine but not of the dealcoholized one[Boban et al., 2006].

Another product used as a wine substitute is red wine extract (RWE), which formulation is highly variable in quantity and quality. Comparing the action of RWEs in humans, the results are conflicting and with completely different FMD values [Lekakis et al., 2005; van Mierlo et al., 2010].

Considering wine as a phytocomplex, there must be an interaction between its components, in particular polyphenols. This has been observed both *in vitro*[Wallerath et al., 2005] and *in vivo*[Zhou et al., 2012]. However, even if a perfect correspondence with the wine's phytocomplex was possible in the formulation of the extracts, the role of EtOH always remains, indispensable, according to some authors, as a synergistic element [Chan et al., 2000] or even considered as the sole responsible for the protective effect of wine [Spaak et al., 2010].

The synergistic effect between the components of RWEs was observed on an intracellular level and is considered "not the result of a single phytochemical activity, but that of all the components of wine extracts that crossed cell membranes"[Stranieri et al., 2022]. It should be noted that in this study the extracts are dissolved in a hydroalcoholic matrix before use to facilitate penetration. The presence of EtOH is also a principal factor in the bioavailability of Tyr in humans.

Many doubts therefore remain not only on the effectiveness, but also on the logic with which RWEs are formulated: for example, the effect mediated by the Sirtuin 1 enzyme (expressed from the gene SIRT1)[Kitada et al., 2020] should have been better calibrated by giving less importance to Rsv but also considering only malvidin [Mannari et al., 2010], already present in RWEs.

7. Conclusions and future perspectives

The concept of matrix effect in food is not a widespread one.Usually the pharmacological aspect prevails, leading to the isolation of specific molecules to be sold as drugs or food supplementation.This procedure, being already quite difficult with a normal phytocomplex, becomes even more puzzling when products of natural fermentation are present, like EtOH and bacterial/yeast byproducts in wine matrix. In this review, failures in targeting a single molecule or in artificially modulating the vehicle have been discussed.

On the other hand, wine matrix plays an instrumental role in improving beneficial compounds bioavailability or in inhibiting alcohol metabolites carcinogenicity. Indeed, wine specificity and scientific research have already been recommended even by intergovernmental Organizations [Office International de la Vigne et du Vin,2003].

With the public health interest as objective, wine specificity should be finally giventhe consideration it deserves.

Author Contributions:

Funding:

Conflicts of Interest:

Abbreviations

ADH	Alcohol dehydrogenase
ALD	Alcohol-related liver disease
ALDH	Acetaldehyde dehydrogenase
AMPK	5′ adenosine monophosphate-activated protein kinase
BBB	Blood-Brain Barrier
BMD	Bone Mineral Density

CO_2	Carbon dioxide
CYP2E1	Cytochrome P450 isoform 2E1
EFSA	European Food Safety Agency
EMA	European Medicines Agency
EtG	Ethyl glucuronide
EtOH	Ethanol
EtS	Ethyl sulfate
FAEE	Fatty acid ethyl ester
FMD	Flow Mediated Dilatation
GABA	Gamma-aminobutyric acid
H_2O	Water
HDL-C	High Density Lipoprotein – Cholesterol
HNC	Head and Neck Cancer
HTyr	Hydroxytyrosol
IL	Interleukin
LDL	Low Density Lipoprotein
MCP	Monocyte Chemoattractant Protein
MeOH	Methanol
MEOS	Microsomal ethanol-oxidizing system
MUFAs	Mono-Unsaturated Fatty Acids
PEth	Phosphatidylethanol
PUFAs	Poly-Unsaturated Fatty Acids
ROS	Reactive Oxygen Species
Rsv	Resveratrol
RWE	Red Wine Extract
TAG	Triacylglycerol
TNF	Tumor Necrosis Factor
Tyr	Tyrosol
USDA	United States Department of Agriculture
UV	Ultraviolet
WHO	World Health Organization

References

1. Addolorato, G., Capristo, E., Greco, A. V., Stefanini, G. F., &Gasbarrini, G. (1997). Energy expenditure, substrate oxidation, and body composition in subjects with chronic alcoholism: new findings from metabolic assessment. *Alcoholism, clinical and experimental research*, *21*(6), 962–967.
2. Ahlemeyer, B., &Krieglstein, J. (2003). Pharmacological studies supporting the therapeutic use of Ginkgo biloba extract for Alzheimer's disease. *Pharmacopsychiatry*, *36 Suppl 1*, S8–S14. https://doi.org/10.1055/s-2003-40454
3. Alemán-Jiménez, C., Domínguez-Perles, R., Medina, S., Prgomet, I., López-González, I., Simonelli-Muñoz, A., Campillo-Cano, M., Auñón, D., Ferreres, F., & Gil-Izquierdo, Á. (2021). Pharmacokinetics and bioavailability of hydroxytyrosol are dependent on the food matrix in humans. *European journal of nutrition*, *60*(2), 905–915. https://doi.org/10.1007/s00394-020-02295-0
4. Anderson, L. A., Cantwell, M. M., Watson, R. G., Johnston, B. T., Murphy, S. J., Ferguson, H. R., McGuigan, J., Comber, H., Reynolds, J. V., & Murray, L. J. (2009). The association between alcohol and reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. *Gastroenterology*, *136*(3), 799–805. https://doi.org/10.1053/j.gastro.2008.12.005
5. Arranz, S., Chiva-Blanch, G., Valderas-Martínez, P., Medina-Remón, A., Lamuela-Raventós, R. M., & Estruch, R. (2012). Wine, beer, alcohol and polyphenols on cardiovascular disease and cancer. *Nutrients*, *4*(7), 759–781. https://doi.org/10.3390/nu4070759
6. Baan, R., Straif, K., Grosse, Y., Secretan, B., Ghissassi, F. E., Bouvard, V., Altieri, A., &Cogliano, V. (2007). Carcinogenicity of alcoholic beverages. *Lancet Oncology/Lancet. Oncology*, *8*(4), 292–293. https://doi.org/10.1016/s1470-2045(07)70099-2
7. Baiano, A., Terracone, C., Gambacorta, G., & La Notte, E. (2009). Phenolic content and antioxidant activity of Primitivo wine: comparison among winemaking technologies. *Journal of food science*, *74*(3), C258–C267. https://doi.org/10.1111/j.1750-3841.2009.01101.x

8. Bandiwadekar, A., Jose, J., Gopan, G., Augustin, V., Ashtekar, H., & Khot, K. B. (2024). Transdermal delivery of resveratrol loaded solid lipid nanoparticle as a microneedle patch: a novel approach for the treatment of Parkinson's disease. *Drug delivery and translational research*, 10.1007/s13346-024-01656-0. Advance online publication. https://doi.org/10.1007/s13346-024-01656-0
9. Barrajón-Catalán, E., Herranz-López, M., Joven, J., Segura-Carretero, A., Alonso-Villaverde, C., Menéndez, J. A., & Micol, V. (2014). Molecular promiscuity of plant polyphenols in the management of age-related diseases: far beyond their antioxidant properties. *Advances in experimental medicine and biology*, *824*, 141–159. https://doi.org/10.1007/978-3-319-07320-0_11
10. Beaumont, P., Courtois, A., Atgié, C., Richard, T., & Krisa, S. (2022). In the shadow of resveratrol: biological activities of epsilon-viniferin. *Journal of physiology and biochemistry*, *78*(2), 465–484. https://doi.org/10.1007/s13105-022-00880-x
11. Bernardi, S., Del Bo', C., Marino, M., Gargari, G., Cherubini, A., Andrés-Lacueva, C., Hidalgo-Liberona, N., Peron, G., González-Dominguez, R., Kroon, P., Kirkup, B., Porrini, M., Guglielmetti, S., & Riso, P. (2020). Polyphenols and Intestinal Permeability: Rationale and Future Perspectives. *Journal of agricultural and food chemistry*, *68*(7), 1816–1829. https://doi.org/10.1021/acs.jafc.9b02283
12. Bertelli, A. A. E. (2007). Wine, research and cardiovascular disease: instructions for use. *Atherosclerosis*, *195*(2), 242–247. https://doi.org/10.1016/j.atherosclerosis.2007.04.006
13. Bertelli, A. A., Giovannini, L., Bernini, W., Migliori, M., Fregoni, M., Bavaresco, L., & Bertelli, A. (1996). Antiplatelet activity of cis-resveratrol. *Drugs under experimental and clinical research*, *22*(2), 61–63.
14. Bertelli, A. A., Giovannini, L., Giannessi, D., Migliori, M., Bernini, W., Fregoni, M., & Bertelli, A. (1995). Antiplatelet activity of synthetic and natural resveratrol in red wine. *International journal of tissue reactions*, *17*(1), 1–3.
15. Bertelli, A. A., Giovannini, L., Stradi, R., Urien, S., Tillement, J. P., & Bertelli, A. (1996). Kinetics of trans- and cis-resveratrol (3,4',5-trihydroxystilbene) after red wine oral administration in rats. *International journal of clinical pharmacology research*, *16*(4-5), 77–81.
16. Bertelli, A., Biagi, M., Corsini, M., Baini, G., Cappellucci, G., & Miraldi, E. (2021). Polyphenols: From Theory to Practice. *Foods (Basel, Switzerland)*, *10*(11), 2595. https://doi.org/10.3390/foods10112595
17. Bertuccioli, A., Cardinali, M., Di Pierro, F., Zonzini, G. B., & Matera, M. R. (2022). Ketogenic and Low FODMAP Diet in Therapeutic Management of a Young Autistic Patient with Epilepsy and Dysmetabolism Poorly Responsive to Therapies: Clinical Response and Effects of Intestinal Microbiota. *International journal of molecular sciences*, *23*(15), 8829. https://doi.org/10.3390/ijms23158829
18. Biagi, M., Pecorari, R., Appendino, G., Miraldi, E., Magnano, A. R., Governa, P., Cettolin, G., & Giachetti, D. (2016). Herbal Products in Italy: The Thin Line between Phytotherapy, Nutrition and Parapharmaceuticals; A Normative Overview of the Fastest Growing Market in Europe. *Pharmaceuticals (Basel, Switzerland)*, *9*(4), 65. https://doi.org/10.3390/ph9040065
19. Bladé, C., Arola, L., &Salvadó, M. J. (2010). Hypolipidemic effects of proanthocyanidins and their underlying biochemical and molecular mechanisms. *Molecular nutrition & food research*, *54*(1), 37–59. https://doi.org/10.1002/mnfr.200900476
20. Boban, M., Modun, D., Music, I., Vukovic, J., Brizic, I., Salamunic, I., Obad, A., Palada, I., &Dujic, Z. (2006). Red wine induced modulation of vascular function: separating the role of polyphenols, ethanol, and urates. *Journal of cardiovascular pharmacology*, *47*(5), 695–701. https://doi.org/10.1097/01.fjc.0000211762.06271.ce
21. Boffetta, P., &Hashibe, M. (2006). Alcohol and cancer. *The Lancet. Oncology*, *7*(2), 149–156. https://doi.org/10.1016/S1470-2045(06)70577-0
22. Boronat, A., Mateus, J., Soldevila-Domenech, N., Guerra, M., Rodríguez-Morató, J., Varon, C., Muñoz, D., Barbosa, F., Morales, J. C., Gaedigk, A., Langohr, K., Covas, M. I., Pérez-Mañá, C., Fitó, M., Tyndale, R. F., & de la Torre, R. (2019). Cardiovascular benefits of tyrosol and its endogenous conversion into hydroxytyrosol in humans. A randomized, controlled trial. *Free radical biology & medicine*, *143*, 471–481. https://doi.org/10.1016/j.freeradbiomed.2019.08.032
23. Brizuela, L., Dayon, A., Doumerc, N., Ader, I., Golzio, M., Izard, J. C., Hara, Y., Malavaud, B., & Cuvillier, O. (2010). The sphingosine kinase-1 survival pathway is a molecular target for the tumor-suppressive tea and wine polyphenols in prostate cancer. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, *24*(10), 3882–3894. https://doi.org/10.1096/fj.10-160838

24. Buljeta, I., Pichler, A., Šimunović, J., &Kopjar, M. (2023). Beneficial Effects of Red Wine Polyphenols on Human Health: Comprehensive Review. *Current issues in molecular biology*, *45*(2), 782–798. https://doi.org/10.3390/cimb45020052
25. Butterweck V. (2003). Mechanism of action of St John's wort in depression : what is known?. *CNS drugs*, *17*(8), 539–562. https://doi.org/10.2165/00023210-200317080-00001
26. Cai, Y., Yang, L., Hu, G., Chen, X., Niu, F., Yuan, L., Liu, H., Xiong, H., Arikkath, J., & Buch, S. (2016). Regulation of morphine-induced synaptic alterations: Role of oxidative stress, ER stress, and autophagy. *The Journal of cell biology*, *215*(2), 245–258. https://doi.org/10.1083/jcb.201605065
27. Capuano, E., Oliviero, T., & van Boekel, M. A. J. S. (2018). Modeling food matrix effects on chemical reactivity: Challenges and perspectives. *Critical reviews in food science and nutrition*, *58*(16), 2814–2828. https://doi.org/10.1080/10408398.2017.1342595
28. Cardiovascular disease risk factors: new areas for research. Report of a WHO Scientific Group. (1994). *PubMed*, *841*, 1–53. https://pubmed.ncbi.nlm.nih.gov/8184600
29. Cardona, F., Andrés-Lacueva, C., Tulipani, S., Tinahones, F. J., & Queipo-Ortuño, M. I. (2013). Benefits of polyphenols on gut microbiota and implications in human health. *The Journal of nutritional biochemistry*, *24*(8), 1415–1422. https://doi.org/10.1016/j.jnutbio.2013.05.001
30. Cederbaum A. I. (2012). Alcohol metabolism. *Clinics in liver disease*, *16*(4), 667–685. https://doi.org/10.1016/j.cld.2012.08.002
31. Cerrato-Alvarez, M., Bernalte, E., Bernalte-García, M. J., & Pinilla-Gil, E. (2019). Fast and direct amperometric analysis of polyphenols in beers using tyrosinase-modified screen-printed gold nanoparticles biosensors. *Talanta*, *193*, 93–99. https://doi.org/10.1016/j.talanta.2018.09.093
32. Chan, M. M., Mattiacci, J. A., Hwang, H. S., Shah, A., &Fong, D. (2000). Synergy between ethanol and grape polyphenols, quercetin, and resveratrol, in the inhibition of the inducible nitric oxide synthase pathway. *Biochemicalpharmacology*, *60*(10), 1539–1548. https://doi.org/10.1016/s0006-2952(00)00471-8
33. Chen, A., Zhang, L., Xu, J., & Tang, J. (2002). The antioxidant (-)-epigallocatechin-3-gallate inhibits activated hepatic stellate cell growth and suppresses acetaldehyde-induced gene expression. *The Biochemical journal*, *368*(Pt 3), 695–704. https://doi.org/10.1042/BJ20020894
34. Chen, C. H., Budas, G. R., Churchill, E. N., Disatnik, M. H., Hurley, T. D., &Mochly-Rosen, D. (2008). Activation of aldehyde dehydrogenase-2 reduces ischemic damage to the heart. *Science (New York, N.Y.)*, *321*(5895), 1493–1495. https://doi.org/10.1126/science.1158554
35. Clinton, S. K., Giovannucci, E. L., &Hursting, S. D. (2020). The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: Impact and Future Directions. *The Journal of nutrition*, *150*(4), 663–671. https://doi.org/10.1093/jn/nxz268
36. Comporti, M., Signorini, C., Leoncini, S., Gardi, C., Ciccoli, L., Giardini, A., Vecchio, D., & Arezzini, B. (2010). Ethanol-induced oxidative stress: basic knowledge. *Genes & nutrition*, *5*(2), 101–109. https://doi.org/10.1007/s12263-009-0159-9
37. Corder, R., Mullen, W., Khan, N. Q., Marks, S. C., Wood, E. G., Carrier, M. J., & Crozier, A. (2006). Oenology: red wine procyanidins and vascular health. *Nature*, *444*(7119), 566. https://doi.org/10.1038/444566a
38. Cucciniello, R., Tomasini, M., Russo, A., Falivene, L., Gambuti, A., & Forino, M. (2023). Experimental and theoretical studies on the acetaldehyde reaction with (+)-catechin. *Food chemistry*, *426*, 136556. https://doi.org/10.1016/j.foodchem.2023.136556
39. D'Angelo, C., Franceschelli, S., Quiles, J. L., & Speranza, L. (2020). Wide Biological Role of Hydroxytyrosol: Possible Therapeutic and Preventive Properties in Cardiovascular Diseases. *Cells*, *9*(9), 1932. https://doi.org/10.3390/cells9091932
40. Dinu, M., Pagliai, G., Casini, A., & Sofi, F. (2018). Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *European journal of clinical nutrition*, *72*(1), 30–43. https://doi.org/10.1038/ejcn.2017.58
41. Ditano-Vázquez, P., Torres-Peña, J. D., Galeano-Valle, F., Pérez-Caballero, A. I., Demelo-Rodríguez, P., Lopez-Miranda, J., Katsiki, N., Delgado-Lista, J., & Alvarez-Sala-Walther, L. A. (2019). The Fluid Aspect of the Mediterranean Diet in the Prevention and Management of Cardiovascular Disease and Diabetes: The Role of Polyphenol Content in Moderate Consumption of Wine and Olive Oil. *Nutrients*, *11*(11), 2833. https://doi.org/10.3390/nu11112833
42. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Turck, D., Bresson, J. L., Burlingame, B., Dean, T., Fairweather-Tait, S., Heinonen, M., Hirsch-Ernst, K. I., Mangelsdorf, I., McArdle, H. J., Naska, A.,

Neuhäuser-Berthold, M., Nowicka, G., Pentieva, K., Sanz, Y., Siani, A., Sjödin, A., Stern, M., Tomé, D., Vinceti, M., … van Loveren, H. (2017). Safety of hydroxytyrosol as a novel food pursuant to Regulation (EC) No 258/97. *EFSA journal. European Food Safety Authority*, *15*(3), e04728. https://doi.org/10.2903/j.efsa.2017.4728

43. European Commission. (2017). Commission Implementing Decision (EU) 2017/2373 of 14 December 2017 authorising the placing on the market of hydroxytyrosol as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council. *Off. J. Eur. Union*, *50*, 56-59.
44. European Medicines Agency; *Herbal Medicinal Products*; (n.d.). https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products
45. European Parliament; Consolidated text: Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (Text with EEA relevance) Text with EEA relevance. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02015R2283-20210327
46. Faria, A., Meireles, M., Fernandes, I., Santos-Buelga, C., Gonzalez-Manzano, S., Dueñas, M., de Freitas, V., Mateus, N., &Calhau, C. (2014). Flavonoid metabolites transport across a human BBB model. *Food chemistry*, *149*, 190–196. https://doi.org/10.1016/j.foodchem.2013.10.095
47. Fernandes, I., Pérez-Gregorio, R., Soares, S., Mateus, N., & de Freitas, V. (2017). Wine Flavonoids in Health and Disease Prevention. *Molecules (Basel, Switzerland)*, *22*(2), 292. https://doi.org/10.3390/molecules22020292
48. Ferraz da Costa, D. C., Pereira Rangel, L., Quarti, J., Santos, R. A., Silva, J. L., & Fialho, E. (2020). Bioactive Compounds and Metabolites from Grapes and Red Wine in Breast Cancer Chemoprevention and Therapy. *Molecules (Basel, Switzerland)*, *25*(15), 3531. https://doi.org/10.3390/molecules25153531
49. Forman, H. J., Davies, K. J., &Ursini, F. (2014). How do nutritional antioxidants really work: nucleophilic tone and para-hormesis versus free radical scavenging in vivo. *Free radical biology & medicine*, *66*, 24–35. https://doi.org/10.1016/j.freeradbiomed.2013.05.045
50. Freedman, N. D., Abnet, C. C., Leitzmann, M. F., Hollenbeck, A. R., &Schatzkin, A. (2007). Prospective investigation of the cigarette smoking-head and neck cancer association by sex. *Cancer*, *110*(7), 1593–1601. https://doi.org/10.1002/cncr.22957
51. Freedman, N. D., Schatzkin, A., Leitzmann, M. F., Hollenbeck, A. R., & Abnet, C. C. (2007). Alcohol and head and neck cancer risk in a prospective study. *British journal of cancer*, *96*(9), 1469–1474. https://doi.org/10.1038/sj.bjc.6603713
52. GBD 2020 Alcohol Collaborators (2022). Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *Lancet*, *400*(10347), 185–235. https://doi.org/10.1016/s0140-6736(22)00847-9
53. Gál, R., Halmosi, R., Gallyas, F., Jr, Tschida, M., Mutirangura, P., Tóth, K., Alexy, T., & Czopf, L. (2023). Resveratrol and beyond: The Effect of Natural Polyphenols on the Cardiovascular System: A Narrative Review. *Biomedicines*, *11*(11), 2888. https://doi.org/10.3390/biomedicines11112888
54. Gammon, M. D., Schoenberg, J. B., Ahsan, H., Risch, H. A., Vaughan, T. L., Chow, W. H., Rotterdam, H., West, A. B., Dubrow, R., Stanford, J. L., Mayne, S. T., Farrow, D. C., Niwa, S., Blot, W. J., & Fraumeni, J. F., Jr (1997). Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *Journal of the National Cancer Institute*, *89*(17), 1277–1284. https://doi.org/10.1093/jnci/89.17.1277
55. Gandini, S., Botteri, E., Iodice, S., Boniol, M., Lowenfels, A. B., Maisonneuve, P., & Boyle, P. (2008). Tobacco smoking and cancer: a meta-analysis. *International journal of cancer*, *122*(1), 155–164. https://doi.org/10.1002/ijc.23033
56. García-Conesa, M. T., Chambers, K., Combet, E., Pinto, P., Garcia-Aloy, M., Andrés-Lacueva, C., de Pascual-Teresa, S., Mena, P., Konic Ristic, A., Hollands, W. J., Kroon, P. A., Rodríguez-Mateos, A., Istas, G., Kontogiorgis, C. A., Rai, D. K., Gibney, E. R., Morand, C., Espín, J. C., & González-Sarrías, A. (2018). Meta-Analysis of the Effects of Foods and Derived Products Containing Ellagitannins and Anthocyanins on Cardiometabolic Biomarkers: Analysis of Factors Influencing Variability of the Individual Responses. *International journal of molecular sciences*, *19*(3), 694. https://doi.org/10.3390/ijms19030694
57. Geng, T., Zhao, X., Ma, M., Zhu, G., & Yin, L. (2017). Resveratrol-Loaded Albumin Nanoparticles with Prolonged Blood Circulation and Improved Biocompatibility for Highly Effective Targeted Pancreatic Tumor Therapy. *Nanoscale researchletters*, *12*(1), 437. https://doi.org/10.1186/s11671-017-2206-6

58. Giovannelli, L., Pitozzi, V., Luceri, C., Giannini, L., Toti, S., Salvini, S., Sera, F., Souquet, J. M., Cheynier, V., Sofi, F., Mannini, L., Gori, A. M., Abbate, R., Palli, D., &Dolara, P. (2011). Effects of de-alcoholised wines with different polyphenol content on DNA oxidative damage, gene expression of peripheral lymphocytes, and haemorheology: an intervention study in post-menopausal women. *European journal of nutrition*, *50*(1), 19–29. https://doi.org/10.1007/s00394-010-0111-1
59. Goldstein, B. Y., Chang, S. C., Hashibe, M., La Vecchia, C., & Zhang, Z. F. (2010). Alcohol consumption and cancers of the oral cavity and pharynx from 1988 to 2009: an update. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)*, *19*(6), 431–465. https://doi.org/10.1097/CEJ.0b013e32833d936d
60. González-Domínguez, R., Jáuregui, O., Mena, P., Hanhineva, K., Tinahones, F. J., Angelino, D., & Andrés-Lacueva, C. (2020). Quantifying the human diet in the crosstalk between nutrition and health by multi-targeted metabolomics of food and microbiota-derived metabolites. *International journal of obesity (2005)*, *44*(12), 2372–2381. https://doi.org/10.1038/s41366-020-0628-1
61. Gorelik, S., Ligumsky, M., Kohen, R., & Kanner, J. (2008). The stomach as a "bioreactor": when red meat meets red wine. *Journal of agricultural and food chemistry*, *56*(13), 5002–5007. https://doi.org/10.1021/jf703700d
62. Governa, P., Manetti, F., Miraldi, E., & Biagi, M. (2021). Effects of in vitro simulated digestion on the antioxidant activity of different Camellia sinensis (L.) Kuntze leaves extracts. *European Food Research & Technology*, *248*(1), 119–128. https://doi.org/10.1007/s00217-021-03864-1
63. Grønbaek M. (2004). Epidemiologic evidence for the cardioprotective effects associated with consumption of alcoholic beverages. *Pathophysiology : the official journal of the International Society for Pathophysiology*, *10*(2), 83–92. https://doi.org/10.1016/j.pathophys.2003.10.004
64. Guerrero, R. F., Valls-Fonayet, J., Richard, T., & Cantos-Villar, E. (2020). A rapid quantification of stilbene content in wine by ultra-high pressure liquid chromatography–Mass spectrometry. *Food Control*, *108*, 106821.https://doi.org/10.1016/j.foodcont.2019.106821
65. Habold, C., Momken, I., Ouadi, A., Bekaert, V., & Brasse, D. (2011). Effect of prior treatment with resveratrol on density and structure of rat long bones under tail-suspension. *Journal of bone and mineral metabolism*, *29*(1), 15–22. https://doi.org/10.1007/s00774-010-0187-y
66. Hashibe, M., Brennan, P., Benhamou, S., Castellsague, X., Chen, C., Curado, M. P., Dal Maso, L., Daudt, A. W., Fabianova, E., Fernandez, L., Wünsch-Filho, V., Franceschi, S., Hayes, R. B., Herrero, R., Koifman, S., La Vecchia, C., Lazarus, P., Levi, F., Mates, D., Matos, E., … Boffetta, P. (2007). Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Journal of the National Cancer Institute*, *99*(10), 777–789. https://doi.org/10.1093/jnci/djk179
67. Hashibe, M., Brennan, P., Chuang, S. C., Boccia, S., Castellsague, X., Chen, C., Curado, M. P., Dal Maso, L., Daudt, A. W., Fabianova, E., Fernandez, L., Wünsch-Filho, V., Franceschi, S., Hayes, R. B., Herrero, R., Kelsey, K., Koifman, S., La Vecchia, C., Lazarus, P., Levi, F., … Boffetta, P. (2009). Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, *18*(2), 541–550. https://doi.org/10.1158/1055-9965.EPI-08-0347
68. He, X., Andersson, G., Lindgren, U., & Li, Y. (2010). Resveratrol prevents RANKL-induced osteoclast differentiation of murine osteoclast progenitor RAW 264.7 cells through inhibition of ROS production. *Biochemical and biophysical research communications*, *401*(3), 356–362. https://doi.org/10.1016/j.bbrc.2010.09.053
69. Heier, C., Xie, H., & Zimmermann, R. (2016). Nonoxidative ethanol metabolism in humans-from biomarkers to bioactive lipids. *IUBMB life*, *68*(12), 916–923. https://doi.org/10.1002/iub.1569
70. Hendriks H. F. J. (2020). Alcohol and Human Health: What Is the Evidence?. *Annual review of food science and technology*, *11*, 1–21. https://doi.org/10.1146/annurev-food-032519-051827
71. Holford N. H. (1987). Clinical pharmacokinetics of ethanol. *Clinical pharmacokinetics*, *13*(5), 273–292. https://doi.org/10.2165/00003088-198713050-00001
72. Hollman, P. C., & Katan, M. B. (1999). Dietary flavonoids: intake, health effects and bioavailability. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, *37*(9-10), 937–942. https://doi.org/10.1016/s0278-6915(99)00079-4

73. Holstege, A., Bedossa, P., Poynard, T., Kollinger, M., Chaput, J. C., Houglum, K., &Chojkier, M. (1994). Acetaldehyde-modified epitopes in liver biopsy specimens of alcoholic and nonalcoholic patients: localization and association with progression of liver fibrosis. *Hepatology (Baltimore, Md.)*, *19*(2), 367–374.
74. Hong, S., Khil, H., Lee, D. H., Keum, N., & Giovannucci, E. L. (2020). Alcohol Consumption and the Risk of Prostate Cancer: A Dose-Response Meta-Analysis. *Nutrients*, *12*(8), 2188. https://doi.org/10.3390/nu12082188
75. Hrelia, S., Di Renzo, L., Bavaresco, L., Bernardi, E., Malaguti, M., & Giacosa, A. (2022). Moderate Wine Consumption and Health: A Narrative Review. *Nutrients*, *15*(1), 175. https://doi.org/10.3390/nu15010175
76. Hyun, J., Han, J., Lee, C., Yoon, M., & Jung, Y. (2021). Pathophysiological Aspects of Alcohol Metabolism in the Liver. *International journal of molecular sciences*, *22*(11), 5717. https://doi.org/10.3390/ijms22115717
77. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2012). Personal habits and indoor combustions. *IARC monographs on the evaluation of carcinogenic risks to humans*, *100*(Pt E), 1–538.
78. Joven, J., Micol, V., Segura-Carretero, A., Alonso-Villaverde, C., Menéndez, J. A., & Bioactive Food Components Platform (2014). Polyphenols and the modulation of gene expression pathways: can we eat our way out of the danger of chronic disease?. *Critical reviews in food science and nutrition*, *54*(8), 985–1001. https://doi.org/10.1080/10408398.2011.621772
79. Karković Marković, A., Torić, J., Barbarić, M., &Jakobušić Brala, C. (2019). Hydroxytyrosol, Tyrosol and Derivatives and Their Potential Effects on Human Health. *Molecules (Basel, Switzerland)*, *24*(10), 2001. https://doi.org/10.3390/molecules24102001
80. Kitada, M., Ogura, Y., Monno, I., &Koya, D. (2020). Supplementation with Red Wine Extract Increases Insulin Sensitivity and Peripheral Blood Mononuclear Sirt1 Expression in Nondiabetic Humans. *Nutrients*, *12*(10), 3108. https://doi.org/10.3390/nu12103108
81. Krittanawong, C., Isath, A., Rosenson, R. S., Khawaja, M., Wang, Z., Fogg, S. E., Virani, S. S., Qi, L., Cao, Y., Long, M. T., Tangney, C. C., & Lavie, C. J. (2022). Alcohol Consumption and Cardiovascular Health. *The American journal of medicine*, *135*(10), 1213–1230.e3. https://doi.org/10.1016/j.amjmed.2022.04.021
82. Kubo, A., Levin, T. R., Block, G., Rumore, G. J., Quesenberry, C. P., Jr, Buffler, P., & Corley, D. A. (2009). Alcohol types and sociodemographic characteristics as risk factors for Barrett's esophagus. *Gastroenterology*, *136*(3), 806–815. https://doi.org/10.1053/j.gastro.2008.11.042
83. Kutleša, Z., & Budimir Mršić, D. (2016). Wine and bone health: a review. *Journal of bone and mineral metabolism*, *34*(1), 11–22. https://doi.org/10.1007/s00774-015-0660-8
84. Kwo, P. Y., Ramchandani, V. A., O'Connor, S., Amann, D., Carr, L. G., Sandrasegaran, K., Kopecky, K. K., & Li, T. K. (1998). Gender differences in alcohol metabolism: relationship to liver volume and effect of adjusting for body mass. *Gastroenterology*, *115*(6), 1552–1557. https://doi.org/10.1016/s0016-5085(98)70035-6
85. Lands W. E. (1995). Alcohol and energy intake. *The American journal of clinical nutrition*, *62*(5 Suppl), 1101S–1106S. https://doi.org/10.1093/ajcn/62.5.1101S
86. Laposata, E. A., & Lange, L. G. (1986). Presence of nonoxidative ethanol metabolism in human organs commonly damaged by ethanol abuse. *Science (New York, N.Y.)*, *231*(4737), 497–499. https://doi.org/10.1126/science.3941913
87. Larsen, B. A., Klinedinst, B. S., Le, S. T., Pappas, C., Wolf, T., Meier, N. F., Lim, Y. L., & Willette, A. A. (2022). Beer, wine, and spirits differentially influence body composition in older white adults-a United Kingdom Biobank study. *Obesity science & practice*, *8*(5), 641–656. https://doi.org/10.1002/osp4.598
88. Lekakis, J., Rallidis, L. S., Andreadou, I., Vamvakou, G., Kazantzoglou, G., Magiatis, P., Skaltsounis, A. L., &Kremastinos, D. T. (2005). Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, *12*(6), 596–600. https://doi.org/10.1097/00149831-200512000-00013
89. Lieber C. S. (1994). Hepatic and metabolic effects of ethanol: pathogenesis and prevention. *Annals of medicine*, *26*(5), 325–330. https://doi.org/10.3109/07853899409148346
90. Lieber C. S. (1997). Ethanol metabolism, cirrhosis and alcoholism. *Clinicachimica acta; international journal of clinical chemistry*, *257*(1), 59–84. https://doi.org/10.1016/s0009-8981(96)06434-0
91. Lu, Y., &Cederbaum, A. I. (2008). CYP2E1 and oxidative liver injury by alcohol. *Free radical biology & medicine*, *44*(5), 723–738. https://doi.org/10.1016/j.freeradbiomed.2007.11.004

92. Lu, Z., Zhang, Y., Liu, H., Yuan, J., Zheng, Z., & Zou, G. (2007). Transport of a Cancer Chemopreventive Polyphenol, Resveratrol: Interaction with Serum Albumin and Hemoglobin. *Journal of Fluorescence*, *17*(5), 580–587. https://doi.org/10.1007/s10895-007-0220-2
93. Lubin, J. H., Purdue, M., Kelsey, K., Zhang, Z. F., Winn, D., Wei, Q., Talamini, R., Szeszenia-Dabrowska, N., Sturgis, E. M., Smith, E., Shangina, O., Schwartz, S. M., Rudnai, P., Neto, J. E., Muscat, J., Morgenstern, H., Menezes, A., Matos, E., Mates, I. N., Lissowska, J., … Hayes, R. B. (2009). Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. *American journal of epidemiology*, *170*(8), 937–947. https://doi.org/10.1093/aje/kwp222
94. Maasland, D. H., van den Brandt, P. A., Kremer, B., Goldbohm, R. A., & Schouten, L. J. (2014). Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. *BMC cancer*, *14*, 187. https://doi.org/10.1186/1471-2407-14-187
95. Maciel, M. E., Castro, J. A., & Castro, G. D. (2011). Inhibition of rat mammary microsomal oxidation of ethanol to acetaldehyde by plant polyphenols. *Human & experimental toxicology*, *30*(7), 656–664. https://doi.org/10.1177/0960327110377522
96. Manach, C., Williamson, G., Morand, C., Scalbert, A., &Rémésy, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American journal of clinical nutrition*, *81*(1 Suppl), 230S–242S. https://doi.org/10.1093/ajcn/81.1.230S
97. Mannari, C., Bertelli, A. A. E., Stiaccini, G., & Giovannini, L. (2010). Wine, sirtuins and nephroprotection: not only resveratrol. *Medical hypotheses*, *75*(6), 636–638. https://doi.org/10.1016/j.mehy.2010.08.004
98. Marron, M., Boffetta, P., Zhang, Z. F., Zaridze, D., Wünsch-Filho, V., Winn, D. M., Wei, Q., Talamini, R., Szeszenia-Dabrowska, N., Sturgis, E. M., Smith, E., Schwartz, S. M., Rudnai, P., Purdue, M. P., Olshan, A. F., Eluf-Neto, J., Muscat, J., Morgenstern, H., Menezes, A., McClean, M., … Hashibe, M. (2010). Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International journal of epidemiology*, *39*(1), 182–196. https://doi.org/10.1093/ije/dyp291
99. Martínez-González, M. A., Gea, A., & Ruiz-Canela, M. (2019). The Mediterranean Diet and Cardiovascular Health. *Circulation research*, *124*(5), 779–798. https://doi.org/10.1161/CIRCRESAHA.118.313348
100. Matsuzaki, K., Kumatoriya, K., Tando, M., Kometani, T., &Shinohara, M. (2022). Polyphenols from persimmon fruit attenuate acetaldehyde-induced DNA double-strand breaks by scavenging acetaldehyde. *Scientific reports*, *12*(1), 10300. https://doi.org/10.1038/s41598-022-14374-9
101. Medina-Remón, A., Casas, R., Tressserra-Rimbau, A., Ros, E., Martínez-González, M. A., Fitó, M., Corella, D., Salas-Salvadó, J., Lamuela-Raventos, R. M., Estruch, R., & PREDIMED Study Investigators (2017). Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: a substudy of the PREDIMED trial. *British journal of clinical pharmacology*, *83*(1), 114–128. https://doi.org/10.1111/bcp.12986
102. Meng, X., Maliakal, P., Lu, H., Lee, M. J., & Yang, C. S. (2004). Urinary and plasma levels of resveratrol and quercetin in humans, mice, and rats after ingestion of pure compounds and grape juice. *Journal of agricultural and food chemistry*, *52*(4), 935–942. https://doi.org/10.1021/jf030582e
103. Miró-Casas, E., Covas, M. I., Fitó, M., Farré-Albadalejo, M., Marrugat, J., & de la Torre, R. (2003). Tyrosol and hydroxytyrosol are absorbed from moderate and sustained doses of virgin olive oil in humans. *European journal of clinical nutrition*, *57*(1), 186–190. https://doi.org/10.1038/sj.ejcn.1601532
104. Moreno-Indias, I., Sánchez-Alcoholado, L., Pérez-Martínez, P., Andrés-Lacueva, C., Cardona, F., Tinahones, F., & Queipo-Ortuño, M. I. (2016). Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. *Food & function*, *7*(4), 1775–1787. https://doi.org/10.1039/c5fo00886g
105. Nair M. S. (2015). Spectroscopic study on the interaction of resveratrol and pterostilbene with human serum albumin. *Journal of photochemistry and photobiology. B, Biology*, *149*, 58–67. https://doi.org/10.1016/j.jphotobiol.2015.05.001
106. Office International de la Vigne et du Vin (OIV) (2003). Specificity of wine and scientific research. Resolution OENO 8/2003.
107. Pal, S., Naissides, M., & Mamo, J. (2004). Polyphenolics and fat absorption. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*, *28*(2), 324–326. https://doi.org/10.1038/sj.ijo.0802577

108. Pandeya, N., Williams, G., Green, A. C., Webb, P. M., Whiteman, D. C., & Australian Cancer Study (2009). Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. *Gastroenterology*, *136*(4), 1215–e2. https://doi.org/10.1053/j.gastro.2008.12.052
109. Pelucchi, C., Gallus, S., Garavello, W., Bosetti, C., & La Vecchia, C. (2008). Alcohol and tobacco use, and cancer risk for upper aerodigestive tract and liver. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)*, *17*(4), 340–344. https://doi.org/10.1097/CEJ.0b013e3282f75e91
110. Pérez-Mañá, C., Farré, M., Rodríguez-Morató, J., Papaseit, E., Pujadas, M., Fitó, M., Robledo, P., Covas, M. I., Cheynier, V., Meudec, E., Escudier, J. L., & de la Torre, R. (2015). Moderate consumption of wine, through both its phenolic compounds and alcohol content, promotes hydroxytyrosol endogenous generation in humans. A randomized controlled trial. *Molecular nutrition & food research*, *59*(6), 1213–1216. https://doi.org/10.1002/mnfr.201400842
111. Pezzuto J. M. (2019). Resveratrol: Twenty Years of Growth, Development and Controversy. *Biomolecules & therapeutics*, *27*(1), 1–14. https://doi.org/10.4062/biomolther.2018.176
112. Pikaar, N. A., Wedel, M., & Hermus, R. J. (1988). Influence of several factors on blood alcohol concentrations after drinking alcohol. *Alcohol and alcoholism (Oxford, Oxfordshire)*, *23*(4), 289–297.
113. Purdue, M. P., Hashibe, M., Berthiller, J., La Vecchia, C., Dal Maso, L., Herrero, R., Franceschi, S., Castellsague, X., Wei, Q., Sturgis, E. M., Morgenstern, H., Zhang, Z. F., Levi, F., Talamini, R., Smith, E., Muscat, J., Lazarus, P., Schwartz, S. M., Chen, C., Neto, J. E., … Hayes, R. B. (2009). Type of alcoholic beverage and risk of head and neck cancer--a pooled analysis within the INHANCE Consortium. *American journal of epidemiology*, *169*(2), 132–142. https://doi.org/10.1093/aje/kwn306
114. Rana, A., Samtiya, M., Dhewa, T., Mishra, V., & Aluko, R. E. (2022). Health benefits of polyphenols: A concise review. *Journal of food biochemistry*, *46*(10), e14264. https://doi.org/10.1111/jfbc.14264
115. Reis, A., Perez-Gregorio, R., Mateus, N., & de Freitas, V. (2021). Interactions of dietary polyphenols with epithelial lipids: advances from membrane and cell models in the study of polyphenol absorption, transport and delivery to the epithelium. *Critical reviews in food science and nutrition*, *61*(18), 3007–3030. https://doi.org/10.1080/10408398.2020.1791794
116. Renaud, S., & de Lorgeril, M. (1992). Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet (London, England)*, *339*(8808), 1523–1526. https://doi.org/10.1016/0140-6736(92)91277-f
117. Rotches-Ribalta, M., Andres-Lacueva, C., Estruch, R., Escribano, E., & Urpi-Sarda, M. (2012). Pharmacokinetics of resveratrol metabolic profile in healthy humans after moderate consumption of red wine and grape extract tablets. *Pharmacological research*, *66*(5), 375–382. https://doi.org/10.1016/j.phrs.2012.08.001
118. Sakavitsi, M. E., Breynaert, A., Nikou, T., Lauwers, S., Pieters, L., Hermans, N., &Halabalaki, M. (2022). Availability and Metabolic Fate of Olive Phenolic Alcohols Hydroxytyrosol and Tyrosol in the Human GI Tract Simulated by the *In Vitro* GIDM-Colon Model. *Metabolites*, *12*(5), 391. https://doi.org/10.3390/metabo12050391
119. Sancho, M., & Mach, N. (2014). Efecto de lospolifenoles del vino sobre la prevención del cáncer [Effects of wine polyphenols on cancer prevention]. *Nutricionhospitalaria*, *31*(2), 535–551. https://doi.org/10.3305/nh.2015.31.2.8091
120. Santangelo, C., Vari, R., Scazzocchio, B., De Sanctis, P., Giovannini, C., D'Archivio, M., & Masella, R. (2018). Anti-inflammatory Activity of Extra Virgin Olive Oil Polyphenols: Which Role in the Prevention and Treatment of Immune-Mediated Inflammatory Diseases?. *Endocrine, metabolic & immune disorders drug targets*, *18*(1), 36–50. https://doi.org/10.2174/1871530317666171114114321
121. Santos-Buelga, C., González-Manzano, S., & González-Paramás, A. M. (2021). Wine, Polyphenols, and Mediterranean Diets. What Else Is There to Say?. *Molecules (Basel, Switzerland)*, *26*(18), 5537. https://doi.org/10.3390/molecules26185537
122. Santos-Buelga, C., González-Paramás, A. M., Oludemi, T., Ayuda-Durán, B., & González-Manzano, S. (2019). Plant phenolics as functional food ingredients. *Advances in food and nutrition research*, *90*, 183–257. https://doi.org/10.1016/bs.afnr.2019.02.012
123. Scalbert, A., Johnson, I. T., & Saltmarsh, M. (2005). Polyphenols: antioxidants and beyond. *The American journal of clinical nutrition*, *81*(1 Suppl), 215S–217S. https://doi.org/10.1093/ajcn/81.1.215S
124. Schutte, R., Papageorgiou, M., Najlah, M., Huisman, H. W., Ricci, C., Zhang, J., Milner, N., & Schutte, A. E. (2020). Drink types unmask the health risks associated with alcohol intake - Prospective evidence from the

general population. *Clinical nutrition (Edinburgh, Scotland)*, *39*(10), 3168–3174. https://doi.org/10.1016/j.clnu.2020.02.009
125. Schwingshackl, L., Morze, J., & Hoffmann, G. (2020). Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. *British journal of pharmacology*, *177*(6), 1241–1257. https://doi.org/10.1111/bph.14778
126. Sessa, M., Balestrieri, M. L., Ferrari, G., Servillo, L., Castaldo, D., D'Onofrio, N., Donsì, F., & Tsao, R. (2014). Bioavailability of encapsulated resveratrol into nanoemulsion-based delivery systems. *Food chemistry*, *147*, 42–50. https://doi.org/10.1016/j.foodchem.2013.09.088
127. Seth, D., Haber, P. S., Syn, W. K., Diehl, A. M., & Day, C. P. (2011). Pathogenesis of alcohol-induced liver disease: classical concepts and recent advances. *Journal of gastroenterology and hepatology*, *26*(7), 1089–1105. https://doi.org/10.1111/j.1440-1746.2011.06756.x
128. Setshedi, M., Wands, J. R., & Monte, S. M. (2010). Acetaldehyde adducts in alcoholic liver disease. *Oxidative medicine and cellular longevity*, *3*(3), 178–185. https://doi.org/10.4161/oxim.3.3.12288
129. Sheng, Y., Meng, G., Li, G., & Wang, J. (2024). Red wine alleviates atherosclerosis-related inflammatory markers in healthy subjects rather than in high cardiovascular risk subjects: A systematic review and meta-analysis. *Medicine*, *103*(23), e38229. https://doi.org/10.1097/MD.0000000000038229
130. Singla, R. K., Dubey, A. K., Garg, A., Sharma, R. K., Fiorino, M., Ameen, S. M., Haddad, M. A., & Al-Hiary, M. (2019). Natural Polyphenols: Chemical Classification, Definition of Classes, Subcategories, and Structures. *Journal of AOAC International*, *102*(5), 1397–1400. https://doi.org/10.5740/jaoacint.19-0133
131. Soldevila-Domenech, N., Boronat, A., Mateus, J., Diaz-Pellicer, P., Matilla, I., Pérez-Otero, M., Aldea-Perona, A., & de la Torre, R. (2019). Generation of the Antioxidant Hydroxytyrosol from Tyrosol Present in Beer and Red Wine in a Randomized Clinical Trial. *Nutrients*, *11*(9), 2241. https://doi.org/10.3390/nu11092241
132. Spaak, J., Tomlinson, G., McGowan, C. L., Soleas, G. J., Morris, B. L., Picton, P., Notarius, C. F., & Floras, J. S. (2010). Dose-related effects of red wine and alcohol on heart rate variability. *American journal of physiology. Heart and circulatory physiology*, *298*(6), H2226–H2231. https://doi.org/10.1152/ajpheart.00700.2009
133. Stiller, A., Garrison, K., Gurdyumov, K., Kenner, J., Yasmin, F., Yates, P., & Song, B. H. (2021). From Fighting Critters to Saving Lives: Polyphenols in Plant Defense and Human Health. *International journal of molecular sciences*, *22*(16), 8995. https://doi.org/10.3390/ijms22168995
134. Stranieri, C., Guzzo, F., Gambini, S., Cominacini, L., & Fratta Pasini, A. M. (2022). Intracellular Polyphenol Wine Metabolites Oppose Oxidative Stress and Upregulate Nrf2/ARE Pathway. *Antioxidants (Basel, Switzerland)*, *11*(10), 2055. https://doi.org/10.3390/antiox11102055
135. Talavéra, S., Felgines, C., Texier, O., Besson, C., Gil-Izquierdo, A., Lamaison, J. L., &Rémésy, C. (2005). Anthocyanin metabolism in rats and their distribution to digestive area, kidney, and brain. *Journal of agricultural and food chemistry*, *53*(10), 3902–3908. https://doi.org/10.1021/jf050145v
136. Timmers, P. R. H. J., Wilson, J. F., Joshi, P. K., &Deelen, J. (2020). Multivariate genomic scan implicates novel loci and haem metabolism in human ageing. *Nature communications*, *11*(1), 3570. https://doi.org/10.1038/s41467-020-17312-3
137. Tuma, D. J., & Casey, C. A. (2003). Dangerous byproducts of alcohol breakdown--focus on adducts. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, *27*(4), 285–290.
138. United States Department of Agriculture (USDA), National Agricultural Library (NAL) Thesaurus (Created 2006-01-19, last modified 2015-12-22). Food matrix. https://agclass.nal.usda.gov/vocabularies/nalt/concept?uri=https://lod.nal.usda.gov/nalt/17238
139. Urpi-Sarda, M., Casas, R., Chiva-Blanch, G., Romero-Mamani, E. S., Valderas-Martínez, P., Arranz, S., Andres-Lacueva, C., Llorach, R., Medina-Remón, A., Lamuela-Raventos, R. M., & Estruch, R. (2012). Virgin olive oil and nuts as key foods of the Mediterranean diet effects on inflammatory biomakers related to atherosclerosis. *Pharmacological research*, *65*(6), 577–583. https://doi.org/10.1016/j.phrs.2012.03.006
140. Urpi-Sarda, M., Zamora-Ros, R., Lamuela-Raventos, R., Cherubini, A., Jauregui, O., de la Torre, R., Covas, M. I., Estruch, R., Jaeger, W., & Andres-Lacueva, C. (2007). HPLC-tandem mass spectrometric method to characterize resveratrol metabolism in humans. *Clinical chemistry*, *53*(2), 292–299. https://doi.org/10.1373/clinchem.2006.071936
141. van Bussel, B. C. T., Henry, R. M. A., Schalkwijk, C. G., Dekker, J. M., Nijpels, G., Feskens, E. J. M., & Stehouwer, C. D. A. (2018). Alcohol and red wine consumption, but not fruit, vegetables, fish or dairy products, are associated with less endothelial dysfunction and less low-grade inflammation: the Hoorn Study. *European journal of nutrition*, *57*(4), 1409–1419. https://doi.org/10.1007/s00394-017-1420-4

142. van Mierlo, L. A., Zock, P. L., van der Knaap, H. C., & Draijer, R. (2010). Grape polyphenols do not affect vascular function in healthy men. *The Journal of nutrition*, *140*(10), 1769–1773. https://doi.org/10.3945/jn.110.125518
143. Varoni, E. M., Lodi, G., & Iriti, M. (2015). Ethanol versus Phytochemicals in Wine: Oral Cancer Risk in a Light Drinking Perspective. *International journal of molecular sciences*, *16*(8), 17029–17047. https://doi.org/10.3390/ijms160817029
144. Vauzour, D., Vafeiadou, K., Rodriguez-Mateos, A., Rendeiro, C., & Spencer, J. P. (2008). The neuroprotective potential of flavonoids: a multiplicity of effects. *Genes & nutrition*, *3*(3-4), 115–126. https://doi.org/10.1007/s12263-008-0091-4
145. Vioque, J., Barber, X., Bolumar, F., Porta, M., Santibáñez, M., de la Hera, M. G., Moreno-Osset, E., & PANESOES Study Group (2008). Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC cancer*, *8*, 221. https://doi.org/10.1186/1471-2407-8-221
146. Visioli, F., Panaite, S. A., & Tomé-Carneiro, J. (2020). Wine's Phenolic Compounds and Health: A Pythagorean View. *Molecules (Basel, Switzerland)*, *25*(18), 4105. https://doi.org/10.3390/molecules25184105
147. Wallerath, T., Li, H., Gödtel-Ambrust, U., Schwarz, P. M., &Förstermann, U. (2005). A blend of polyphenolic compounds explains the stimulatory effect of red wine on human endothelial NO synthase. *Nitric oxide : biology and chemistry*, *12*(2), 97–104. https://doi.org/10.1016/j.niox.2004.12.004
148. Wannamethee, S. G., Shaper, A. G., & Whincup, P. H. (2005). Alcohol and adiposity: effects of quantity and type of drink and time relation with meals. *International journal of obesity (2005)*, *29*(12), 1436–1444. https://doi.org/10.1038/sj.ijo.0803034
149. Warleta, F., Quesada, C. S., Campos, M., Allouche, Y., Beltrán, G., &Gaforio, J. J. (2011). Hydroxytyrosol protects against oxidative DNA damage in human breast cells. *Nutrients*, *3*(10), 839–857. https://doi.org/10.3390/nu3100839
150. Weaver, S. R., Rendeiro, C., McGettrick, H. M., Philp, A., & Lucas, S. J. E. (2021). Fine wine or sour grapes? A systematic review and meta-analysis of the impact of red wine polyphenols on vascular health. *European journal of nutrition*, *60*(1), 1–28. https://doi.org/10.1007/s00394-020-02247-8
151. Welch, A., MacGregor, A., Jennings, A., Fairweather-Tait, S., Spector, T., & Cassidy, A. (2012). Habitual flavonoid intakes are positively associated with bone mineral density in women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, *27*(9), 1872–1878. https://doi.org/10.1002/jbmr.1649
152. Wilkinson, P. K., Sedman, A. J., Sakmar, E., Kay, D. R., & Wagner, J. G. (1977). Pharmacokinetics of ethanol after oral administration in the fasting state. *Journal of pharmacokinetics and biopharmaceutics*, *5*(3), 207–224. https://doi.org/10.1007/BF01065396
153. Willett, W. C., Sacks, F., Trichopoulou, A., Drescher, G., Ferro-Luzzi, A., Helsing, E., &Trichopoulos, D. (1995). Mediterranean diet pyramid: a cultural model for healthy eating. *The American journal of clinical nutrition*, *61*(6 Suppl), 1402S–1406S. https://doi.org/10.1093/ajcn/61.6.1402S
154. Williamson G. (2017). The role of polyphenols in modern nutrition. *Nutrition bulletin*, *42*(3), 226–235. https://doi.org/10.1111/nbu.12278
155. Wojtowicz J. S. (2023). Long-Term Health Outcomes of Regular, Moderate Red Wine Consumption. *Cureus*, *15*(10), e46786. https://doi.org/10.7759/cureus.46786
156. Wong, R. H., Thaung Zaw, J. J., Xian, C. J., & Howe, P. R. (2020). Regular Supplementation With Resveratrol Improves Bone Mineral Density in Postmenopausal Women: A Randomized, Placebo-Controlled Trial. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, *35*(11), 2121–2131. https://doi.org/10.1002/jbmr.4115
157. World Health Organization, WHO Consultation on Selected Medicinal Plants, WHO Consultation on Selected Medicinal Plants (2nd: 1999; Ravello-Salerno, Italy), WHO Consultation on Selected Medicinal Plants (3rd: 2001; Ottawa, Ont.) & WHO Consultation on Selected Medicinal Plants (4th: 2005; Salerno-Paestum, Italy). (2006). WHO monographs on selected medicinal plants. World Health Organization. https://iris.who.int/handle/10665/42052
158. Wu, D., & Cederbaum, A. I. (2003). Alcohol, oxidative stress, and free radical damage. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, *27*(4), 277–284.
159. Xie, C., & Feng, Y. (2022). Alcohol consumption and risk of Alzheimer's disease: A dose-response meta-analysis. *Geriatrics & gerontology international*, *22*(4), 278–285. https://doi.org/10.1111/ggi.14357

 doi:10.20944/preprints202407.1345.v1

160. Yan, Y., Yang, J. Y., Mou, Y. H., Wang, L. H., Zhou, Y. N., & Wu, C. F. (2012). Differences in the activities of resveratrol and ascorbic acid in protection of ethanol-induced oxidative DNA damage in human peripheral lymphocytes. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*, *50*(2), 168–174. https://doi.org/10.1016/j.fct.2011.10.046
161. Ye, J., Chen, X., & Bao, L. (2019). Effects of wine on blood pressure, glucose parameters, and lipid profile in type 2 diabetes mellitus: A meta-analysis of randomized interventional trials (PRISMA Compliant). *Medicine*, *98*(23), e15771. https://doi.org/10.1097/MD.0000000000015771
162. Zakhari S. (2006). Overview: how is alcohol metabolized by the body?. *Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism*, *29*(4), 245–254.
163. Zeka, A., Gore, R., & Kriebel, D. (2003). Effects of alcohol and tobacco on aerodigestive cancer risks: a meta-regression analysis. *Cancer causes & control : CCC*, *14*(9), 897–906. https://doi.org/10.1023/b:caco.0000003854.34221.a8
164. Zhao, J., Zhou, G., Yang, J., Pan, J., Sha, B., Luo, M., Yang, W., Liu, J., & Zeng, L. (2023). Effects of resveratrol in an animal model of osteoporosis: a meta-analysis of preclinical evidence. *Frontiers in nutrition*, *10*, 1234756. https://doi.org/10.3389/fnut.2023.1234756
165. Zhou, M., Wang, S., Zhao, A., Wang, K., Fan, Z., Yang, H., Liao, W., Bao, S., Zhao, L., Zhang, Y., Yang, Y., Qiu, Y., Xie, G., Li, H., & Jia, W. (2012). Transcriptomic and metabonomic profiling reveal synergistic effects of quercetin and resveratrol supplementation in high fat diet fed mice. *Journal of proteome research*, *11*(10), 4961–4971. https://doi.org/10.1021/pr3004826
166. Zupančič, Š., Lavrič, Z., & Kristl, J. (2015). Stability and solubility of trans-resveratrol are strongly influenced by pH and temperature. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur PharmazeutischeVerfahrenstechnike.V*, *93*, 196–204. https://doi.org/10.1016/j.ejpb.2015.04.002