

Supplementary Table of Contents–Framework and Supplementary Tables S1 and S2

Supplementary Table of Contents–Framework

- **Main Section 1. Introduction**
- **Main Section 2. Bio-functional Compounds and Health Benefits of the Fermented Alcoholic Beverage, Wine, and of Its By-Products**
 - *Subsection 2.1. Composition, Nutritional Value, Bio-functional Components, and Functional Properties*
 - ❖ 2.1.1 Composition and Nutritional Value of Wine
 - ❖ 2.1.2 Wineries' By-Products—Composition and Nutritional Value
 - *Subsection 2.2. Bio-functional Components and Associated Health Benefits*
 - ❖ 2.2.1 Wine and Winery By-Products' Phenolic Bioactives with Antioxidant, Anti-Inflammatory and Antithrombotic Health-Promoting Effects
 - Phenolic Bioactives and Antioxidant Health-Promoting Bioactivities
 - Pleiotropic Health-Promoting Effects of Phenolic Bioactives
 - Limitations and Future Perspectives of Phenolic Compounds as Bioactive Ingredients with Health-Promoting Properties
 - ❖ 2.2.2. Bioactive Lipid Compounds of Wine and Wineries' By-Products
 - ❖ 2.2.3. Bio-functional Dietary Fibres from Wineries' By-Products
- **Main Section 3. Health Benefits of Moderate Wine Consumption and Detrimental Effects of Alcohol Abuse;; a Coin with Two Sides**
 - *Subsection 3.1. Health-Promoting Effects of Incorporating Moderate Wine Consumption in Diet*
 - *Subsection 3.2. Alcohol-Containing Wine, Quantity Consumed and Detrimental/Beneficial Effects on Health: Is It Really a Debate or Is It a Matter of Re-Definitions and Re-Education?*
 - *Subsection 3.3. Concluding Remarks on the Health-Promoting Effects of Wine Consumption in Moderation: from Ancient Times (Religion, Philosophy and Scientific Approaches) to Recent Scientific Evaluation*
- **Main Section 4. Recovery and Valorisation of Bioactive Compounds from Wineries' By-Products as Ingredients for Developing Health-Promoting Functional Foods, Supplements and Nutraceuticals**
 - *Subsection 4.1. The Importance of Wineries' By-Products and Their Bioactives in the Functional Foods Sector*
 - *Subsection 4.2. Characteristic Extraction Methods for the Recovery of Bioactive Compounds of Wineries' By-Products*
 - *Subsection 4.3. Applications of Wineries' By-Products and Their Bioactives in the Food Industry as Ingredient(s) for the Fortification/Production of Existing/Novel Functional Food Products*

- ❖ 4.3.1. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Functional Flour/Cereal-Based Foods
- ❖ 4.3.2. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Functional Dairy-Based Foods
- ❖ 4.3.3. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Functional Meat/Fish-Based Foods
- ❖ 4.3.4. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Other Plant-Based Functional Foods and Beverages
- *Subsection 4.4. Health Benefits and Applications of Wineries' By-Products and Their Bioactives as Ingredients of Bio-functional Food Products, Supplements and Nutraceuticals*
 - ❖ 4.4.1. Antioxidant, Anti-Inflammatory and Antithrombotic Health-Promoting Effects of Grape Pomace and of Its Bioactives, Extracts and Relevant Bio-functional Products
 - ❖ 4.4.2. Antioxidant, Anti-Inflammatory and Antithrombotic Health-Promoting Effects of Grape Seeds and of Their Bioactives, Extracts and Relevant Bio-functional Products
 - ❖ 4.4.3. Anticancer Protective Effects of Wineries' By-Products and of Their Bioactives, Extracts and Relevant Bio-functional Products
 - ❖ 4.4.4. Antimicrobial Protective Effects of Wineries' By-Products and of Their Bioactives, Extracts and Relevant Bio-functional Products
 - ❖ 4.4.5. Bodelivery Systems to Improve the Bioavailability and Bio-functionality of Wineries' By-Products and of Their Bioactives, Extracts and Relevant Bio-functional Products
- *Subsection 4.5. Limitations in the Applications of Wineries' By-Products and Their Bioactive Ingredients*
- **Main Section 5. Conclusion**

Supplementary Table S1*. Characteristic studies, interventions and clinical trials on the benefits of moderate consumption of wine and its bio-functional compounds against inflammation, thrombosis, vascular inflammatory activation and adhesion of leukocytes, endothelial dysfunction, atherosclerosis and CVD.

Study	Hypothesis- Intervention	Study design -Factors examined	Main/Concluding Observed Benefit(s)	Specific benefits / other benefits observed - Mechanisms of action(s)	Reference
Lyon Diet Heart Study	To Evaluate the benefits of adherence to the Mediterranean diet compared to the “Westernised diet”	Biomarkers of oxidative stress, thrombo-inflammation and CVD risk (Lipid profile, lipid peroxidation, platelet activation and aggregation, other CVD biomarkers)	Several health benefits in the Mediterranean diet group, which could not be explained by any differences in LDL cholesterol levels between the groups. The potent antioxidant and anti-inflammatory compounds present in wine facilitate these positive health effects	The benefits observed were attributed to bioactive components in Mediterranean diet foods and mainly in alcoholic beverages consumed in this diet, such as red wine, which can prevent platelet aggregation and lipid peroxidation, as main reported mechanisms	[64]
The study of women's health across the nation (SWAN Study)	To evaluate the association between moderate wine consumption and protection against CVD.	An 8-year intervention period of moderate wine consumption (1 glass/day) Plasma levels of hemostatic and inflammatory risk factors	The moderate consumption of wine may provide protection against CVD through reducing inflammatory and clotting pathways	Moderate consumers of wine had remarkably lower levels of CRP, fibrinogen, factor VII, and PAI-1, in contrast to women who drank little (<1 glass/day) or no wine.	[114]
The “Hoorn” study	To investigate the effect of adherence to a healthy diet, high in fruit, vegetables, and fish, low in dairy products, and moderate consumption of alcohol and red wine on endothelial dysfunction and low-grade	A study based on a population cohort of Dutch elderly individuals following a healthy diet combined with moderate consumption of alcohol and red wine. Biomarkers of endothelial dysfunction and low-grade inflammation were examined	Protection against chronic disorders like CVD by reducing the risk of endothelial dysfunction and low grade inflammation	Red wine and alcohol consumption effectively reduced biomarkers of endothelial dysfunction Red wine exclusively reduced the levels of low-grade inflammation biomarkers	[25]

The ATTICA study	inflammation To investigate the benefit of wine consumption against the incidence of CVD over a 10-year period	N = 2583 subjects without CVD at baseline 10-year CVD incidences in these adults in association with wine consumption	The benefit of wine consumption against the incidence of CVD over a 10-year period is dependent on the quantity and pattern of wine consumed by the individual	Inverse relationship was observed between wine consumption (≤ 1 glass/week) and 10-year CVD risk. There was a reduced risk of developing CVD among participants consuming less than or equal to 1 glass of wine per week in comparison to wine abstainers No correlation observed between consumers of more than 1 glass of wine weekly and the 10-year CVD incidence in comparison to abstainers at baseline..	[115]
In Vino Veritas (IVV) study	To compare the effects of red and white wine on classic markers of atherosclerosis	A long-term, prospective, multi-centre, randomized trial in 157 healthy subjects, randomized to white or red wine consumption for one year. Lipid profile, and serum levels of CRP, fasting blood glucose, as well as liver function tests and parameters of oxidative stress were evaluated at baseline and after 12 months for both groups	Both red and white wine beneficially affected all classic blood biomarkers of atherosclerosis, oxidative stress and overall health No clinically relevant differences were observed in the lipid profile, CRP, fasting blood glucose and other markers of atherosclerosis and parameters of oxidative stress between long-term consumption of either red or white wine, suggesting that both wines beneficially moderate these biomarkers at the same level.	At 12 months there was a reduction of LDL-cholesterol in both groups, but with no difference between the groups Nevertheless, drinking of either red or white wine was not associated with any elevation of HDL cholesterol levels There was also no difference between the groups in total cholesterol, CRP, fasting blood glucose and liver function tests. Both groups had comparable differences from baseline in levels of parameters of oxidative stress	[116]
The Aragon	To evaluate the	A prospective cohort design.	Dietary flavonoids, stilbenes, and	A higher intake of flavonoids was	[117]

Workers' Health Study (AWHS)	association of specific types of dietary polyphenols mainly consumed through red wine and virgin olive oil (flavonoids, stilbenes, and tyrosols) with prevalent subclinical atherosclerosis in middle-aged subjects	<p>Participants (middle-aged workers free of CVD at baseline) were invited between 2011-2014 to undergo noninvasive subclinical atherosclerosis imaging as well as questionnaires on cardiovascular and lifestyle factors.</p> <p>Presence of plaques in carotid and femoral arteries and coronary calcium were assessed by ultrasonography and computed tomography</p> <p>Polyphenol intake was assessed using a validated semi-quantitative 136-item food frequency questionnaire.</p> <p>The Phenol Explorer database was used to derive polyphenol class intake.</p> <p>Logistic and linear regressions were used to estimate the cross-sectional association of polyphenols intake with femoral and carotid subclinical atherosclerosis and coronary calcium</p>	tyrosols, whose main sources are red wine and virgin olive oil, are associated with lower prevalence of subclinical atherosclerosis in middle-aged subjects	<p>associated with a lower risk of both carotid and femoral subclinical atherosclerosis.</p> <p>A higher intake of stilbenes was associated with a lower risk of femoral subclinical atherosclerosis and positive coronary calcium</p> <p>A higher intake of tyrosols was also associated with a lower risk of positive coronary calcium</p> <p>The associations remained similar when adjusted for blood lipids and blood pressure</p>	
Chiva-Blanch et al. (2011)	To evaluate the effects of ethanol and phenolic constituents of red wine on the expression of of adhesion	<p>Randomized, crossover control trial N = 67 male subjects at high risk for CVD.</p> <p>After a washout period they received red wine (30g alcohol/d),</p>	Only the phenolic content of red wine was able to reduce serum concentrations of ICAM-1, E-selectin, and IL-6 demonstrating its regulatory effect on leukocyte	Both alcohol and phenolic components of red wine may regulate soluble inflammatory markers-mediators (CD40 antigen, CD40 ligand, IL-16, MCP-1, VCAM-1) in patients at high	[118]

	molecules and inflammatory cytokines linked to atherosclerosis	the same amount of dealcoholized red wine or gin (30g alcohol/d) over a course of four weeks. The cellular and serum inflammatory biomarkers were assessed prior to and post each intervention period	adhesion molecules and thus reducing the inflammatory process of endothelial dysfunction in patients at high risk of CVD	risk of CVD.	
Canali et al. (2010)	Investigated the effects of human serum following red wine consumption on cell adhesion or fibrinolysis in human endothelial cells	Effects of isolated human serum containing red wine metabolites (after 40 minutes of acute wine consumption; 5ml/kg body weight), on the activation of TNF- α -dependent transcription factors (NF- κ b, AP-1, and cAMP binding proteins) and the expression of specific genes related to the processes of cell adhesion or fibrinolysis in human endothelial cells cultured in a setting that replicates the biological environment in vivo	Red wine metabolites beneficially influence the actions of several cytokines-depended transcription factors and genes that modulate inflammatory processes in endothelial cells	Red wine consumption promoted nuclear translocation of NF- κ b and AP-1, as well as c-jun binding to the plasminogen activator cAMP, a process that downregulated specific gene expression downstream related to the processes of cell adhesion or fibrinolysis in human endothelial cells	[119]
Calabriso et al. (2016)	Evaluated the activities of polyphenolic extracts from two varieties of Italian red wine, as well as the contribution of individual polyphenols and their relevant mode of action against vascular inflammatory	Studying the effects of red wine compounds on LPS-induced vascular inflammatory stimulation in a model of human endothelial cells pre-incubated with increasing levels (1-50 μ g/ml) of polyphenolic extracts from red wine or pure polyphenols (1-25 μ mol/L) such as hydroxycinnamic acids, flavonols,	Red wine and its biofunctional compounds inhibited monocyte adhesion to endothelial cells following their inflammatory stimulation	Both varieties of red wine reduced the expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin, MCP-1, M-CSF)	[2]

	activation	or stilbenes			
Nallasamy et al. (2021)	Studied the effect of physiologically feasible quantities of resveratrol on vascular inflammation in human and mice endothelial cells.	Biomarkers of inflammatory induced endothelial dysfunction in both human and mice aortic endothelial cells and aortas following dietary supplementation of resveratrol	Low concentrations (~1µM) of resveratrol attenuated TNF-α-induced monocyte adhesion and vascular dysfunction in both human and mice endothelial cells	Decline in levels of TNF-α induced adhesion molecules and cytokines, as well as weakened TNF-α induced mRNA expressions of major mediators of endothelial cell-monocyte cytokines and adhesion molecules required for the formation of cardiovascular plaque (MCP-1/CCL2, ICAM-1 and VCAM-1), which resulted in reduced monocyte adhesion to endothelial cells	[120]
Kechagias et al (2010)	Evaluated the effects of moderate wine consumption on liver fat and blood lipid profile	Prospective randomised study in healthy subjects (n=44). 32 healthy women and 12 healthy men (34 ± 9 years of age) were randomized to consume 150 ml of red wine/day for women (16 g ethanol/day) or double that amount for men (33 g ethanol/day), or to alcohol abstention for 90 days. Nuclear magnetic-resonance spectroscopy for measurement of hepatic triglyceride content (HTGC) and collection of blood samples for assessment of cardiovascular risk were performed before and after the intervention.	Even though moderate consumption of red wine during 3 months increased HTGC in subjects without steatosis at baseline, still no subject developed hepatic steatosis. Red wine consumption had no effect on the levels of HDL cholesterol or insulin throughout the trial, while there was a significant reduction in LDL cholesterol	Since not a single participant developed steatosis the authors proposed that the threshold of alcohol consumption to define nonalcoholic fatty liver disease should not be lower than the amount used in this study	[121]
Apostolidou et al (2015)	The role of red wine in the prevention of	Controlled clinical trial based on 40 healthy male and female volunteers,	Asymptomatic hypercholesterolemic individuals	TAC, fasting LDL/HDL ratio and Vitamin E/TC ratio were beneficially	[53]

	atherosclerosis and CVD in hypercholesterolemic individuals free of CVD.	divided in 2 age-adjusted groups of asymptomatic hypercholesterolemic, and normocholesterolemic, according to their TC levels Serum TAC, Lipid profile, Vitamin E, and cardiovascular risk indexes (LDL/ HDL cholesterol and Vitamin E/ TC) were evaluated prior to and 1 month after once daily consumption of red wine or a placebo drink (following a 1 month wash out period)	are more likely to develop CVD as presented by high cholesterol levels and low baseline serum α -tocopherol (vitamin E) concentrations, leading to higher risk for atherosclerosis. When these individuals follow an early dietary intervention, seem likely to reduce the risk factors for CVD by beneficially increasing TAC, α -tocopherol (vitamin E) and vitamin E/TC ratio	increased after the intervention in all subjects in comparison to drinking the placebo, while vitamin E was significantly increased especially in the asymptomatic hypercholesterolemic group	
Roth et al (2019)	Investigated the effects of aged white wine on various atherosclerosis risk factors.	Evaluated the effects of moderate consumption of aged white wine on levels of inflammatory cytokines and inflammation-induced expression of adhesion molecules in endothelial cells and in their circulating progenitor cells, as well as on classic biomarkers of CVD such as systolic and diastolic blood pressure and lipid profile, in comparison to other white alcoholic drinks (gin)	Protective effects of white wine subjected to an extended aging process, against the development of atherosclerosis. The extended aging process of white wine resulted in a higher polyphenolic content than standard white wine with more potent anti-inflammatory and protective effects. Consumption of such aged white wine modulates cardiovascular risk factors via circulating endothelial progenitor cells and inflammatory biomarkers	Significantly downregulated biomarkers linked to the expression of inflammatory vascular and intercellular adhesion molecules, the expression of EPC, and levels of pro-inflammatory molecules (IL-8 and IL-18) Effectively decreased systolic and diastolic blood pressure and increased the concentrations of HDL-cholesterol and Apo A-I	[122]
Huang et al. (2010)	Intake of red wine may stimulate the	Plasma levels of NO and levels and functionality of circulating EPC and	Intake of red wine increases the number and functional capacity	Significant improvement of plasma nitric oxide levels, while endothelial	[123]

	circulating endothelial progenitor cell (EPC) level and function	EPC colony forming units	of circulating EPC by enhancing NO bioavailability, which may contribute to its distinct cardioprotective effect	function was remarkably enhanced by intake of red wine leading to an increase in levels of circulating EPC and EPC colony-forming units.	
Weseler et al (2011)	To investigate the putative beneficial effects of wine-grape phenolics on improvement of overall vascular health	A double-blind, randomized, placebo-controlled intervention study in 28 male smokers supplemented with 200 mg per day of grape-wine flavanols. Macro- and microvascular function and a cluster of systemic biomarkers for major pathological processes occurring in the vasculature: disturbances in lipid metabolism and cellular redox balance, and activation of inflammatory cells and platelets were measured at At baseline, after 4 and 8 weeks	Integration of all measured effects into a global, so-called vascular health index revealed a significant pleiotropic vascular health benefit by such an 8 weeks supplementation of grape-wine flavanols in humans compared to placebo	Total and LDL cholesterol were decreased significantly in volunteers with high baseline levels. The ratio of glutathione to glutathione disulphide in erythrocytes was increased from baseline. Anti-inflammatory effects in blood and a reduction of the expression of inflammatory genes in leukocytes. No alterations in macro- and microvascular function, platelet aggregation, plasma levels of nitric oxide surrogates, endothelin-1, CRP, fibrinogen, PGF(2 α), plasma antioxidant capacity and gene expression levels of antioxidant defense enzymes	[62]
Di Renzo et al (2015)	Evaluated the outcome of consumption of a McDonald's Meal and a Mediterranean Meal, with and without the additive effect of red wine, in order to ascertain whether the addition of the latter	A randomized controlled trial in a total of 24 subjects ox-LDL, CAT, GPX1, SOD2, SIRT2, and CCL5 gene expression levels, were assessed before and after consumption of the 4 different meal combinations with washout intervals between each meal.	A positive effect of red wine intake combined with two different (a well established "healthy" and an "unhealthy") but widely consumed meal types on ox-LDL and gene expression was observed	When red wine was included in any of the diets the values of ox-LDL are lowered and expression of antioxidant genes is increased, while CCL5 expression is decreased. In the Mediterranean diet group with red wine SIRT2 expression is significantly correlated with downregulation of CCL5 and	[60]

	has a positive impact on oxidized (ox-) LDL and on expression of oxidative and inflammatory genes.		upregulation of CAT GPX1 increased significantly in the comparison between baseline and all conditions with red wine		
Schrieke et al (2013)	To evaluate the effect of acute and chronic consumption of red wine or de-alcoholized red wine with a similar antioxidant capacity on plasma TAC, NF-κB activity and F2-isoprostanes (8-iso-PGF(2α)) in healthy men	A randomized, controlled crossover design trial in 19 healthy men with an increased waist circumference (≥94 cm) and a BMI above 25 kg/m². They daily consumed 450 ml of red wine (four drinks; 41.4 g alcohol) or 450 ml of de-alcoholized red wine during dinner for 4 weeks each. On the last day of each treatment period, blood was collected before and 1 h after a standardized dinner with red wine or de-alcoholized red wine and also 24-h urine was collected	Consumption of a moderate dose of red wine can acutely increase plasma TAC and suppress NF-κB activation induced by a meal. In contrast, 4 weeks of red wine consumption compared with de-alcoholized red wine consumption increases the oxidative lipid damage marker 8-iso-PGF(2α), suggesting that the antioxidant effect of wine intake is exclusive to acute moderate consumption, since chronic consumption may induce detrimental effects to health	Absolute TAC levels were higher 1 h after dinner with red wine compared to dinner with de-alcoholized wine. Consumption of dinner together with de-alcoholized red wine acutely stimulated NF-κB activity in peripheral blood mononuclear cells, whereas this increase was completely suppressed when the dinner was combined with red wine. A chronic increase in urinary 8-iso-PGF(2α) after 4 weeks of red wine consumption compared with de-alcoholized red wine consumption was also observed.	[55]
Tomé-Carneiro et al (2013)	To investigate dose-dependent effects of the grape and wine polyphenol resveratrol on stable patients with CAD treated according to currently accepted guidelines for secondary prevention of CVD	A triple-blind, randomized, placebo-controlled, one-year follow-up, 3-arm pilot clinical trial, in 75 stable-CAD patients received 350 mg/day of placebo, resveratrol-containing extract or conventional phenolics extract lacking resveratrol during 6 months, and a double dose for the following 6 months. Changes in circulating inflammatory and	Chronic daily consumption of a resveratrol-containing nutraceutical could exert cardiovascular benefits in stable-CAD patients treated according to current evidence-based standards, by increasing serum adiponectin, preventing PAI-1 increase and inhibiting atherothrombotic signals in	After 1 year, in contrast to the placebo and conventional phenolics extract groups, the resveratrol-containing extract group showed an increase of the anti-inflammatory serum adiponectin and a decrease of the thrombogenic PAI-1. 6 key inflammation-related transcription factors were predicted to be significantly activated or inhibited,	[124]

		fibrinolytic biomarkers were analyzed. The transcriptional profiling of inflammatory genes in PBMCs was explored using microarrays and functional gene expression analysis	PBMCs These findings may lead to controversy as the bioavailability of resveratrol in wine may not be as potent as a resveratrol-containing grape extract, in this case. Thus, emphasis must be placed on the reduced bioavailability of dietary phenolic compounds obtained from wine, which subsequently limits their beneficial effects	with 27 extracellular-space acting genes involved in inflammation, cell migration and T-cell interaction signals presenting downregulation in PBMCs. No adverse effects were detected in relation to the study products.	
Cosmi et al (2015)	To evaluate the relations between wine consumption, health status, circulating biomarkers, and clinical outcomes in a large Italian population of patients with chronic heart failure enrolled in a multicenter clinical trial	A brief questionnaire on dietary habits was administered at baseline to 6973 patients enrolled in the trial. The relations between wine consumption, fatal and nonfatal clinical end points, quality of life, symptoms of depression, and circulating biomarkers of cardiac function and inflammation (in subsets of patients) were evaluated with simple and multivariable-adjusted statistical models.	Moderate wine consumption is associated with a better perceived and objective health status, lower prevalence of depression, and less vascular inflammation, but does not translate into more favorable clinical 4-year outcomes in a large cohort of patients with chronic heart failure	More than half of the patients reported drinking at least 1 glass of wine per day. After adjustment, clinical outcomes were not significantly different in different groups of wine consumption. Patients with more frequent wine consumption had a significantly better perception of health status, less frequent symptoms of depression, and lower plasma levels of biomarkers of vascular inflammation (osteoprotegerin and C-terminal proendothelin-1, and pentraxin-3) after adjusting for possible confounders.	[125]
Haas et al (2022)	To investigate the effects of red wine consumption on the gut	A randomized, crossover, controlled trial involving 42 men (average age, 60 y) with documented CAD	Modulation of the gut microbiota may contribute to the putative cardiovascular benefits and	Plasma TMAO did not differ between red wine intervention and alcohol abstention, while TMAO concentrations	[99]

	microbiota, plasma TMAO, and the plasma metabolome in CAD male patients	comparing 3-week red wine consumption (250 mL/d, 5 drinks/weekk) with an equal period of alcohol abstention, both preceded by a 2-week washout period. The gut microbiota was analyzed via 16S rRNA high-throughput sequencing, while plasma TMAO and metabolome of 20 randomly selected participants were also evaluated using a multiomics assessment. The effect of red wine consumption was assessed by individual comparisons using paired tests during the abstention and wine periods.	redox homeostasis induced by moderate red wine consumption. The low intraindividual concordance of TMAO, a metabolite with deleterious effects that has been studied as diagnostic and therapeutic targets in several pathologies, presents challenges regarding its role as a cardiovascular risk biomarker of wine consumption at the individual level	showed low intraindividual concordance over time. After red wine consumption, there was significant remodeling of the gut microbiota, with a difference in β diversity. Plasma metabolomic analysis revealed significant changes in metabolites after red wine consumption, consistent with improved redox homeostasis.	
Xanthopoulos et al (2017) & Argyrou et al (2017)	To evaluate the potential postprandial effect of wine consumption on platelet aggregation induced by the inflammatory and thrombotic mediator, PAF, on PAF-metabolism and on other circulating biomarkers of inflammation,	A cross-over study design 10 healthy men participated in four daily trials on separate days: They consumed a standardized meal along with white wine (Robola), or red wine (Cabernet Sauvignon), or an ethanol solution, or water. Blood samples were collected before and after meal consumption and at several time points during 6 h. Platelet aggregation against PAF (EC50 values) and several blood biomarkers, were measured, and	Wine consumption improved platelet sensitivity independently of alcohol, kept TAGs at lower levels during their postprandial elevation, and did not affect PAI-1 levels more adversely than ethanol per se. The protective effect of wine consumption could partly be explained through the modulation of PAF metabolism by wine micro-constituents that lead to lower PAF levels and	A significant trial effect was found in platelet sensitivity against PAF. The iAUC-PAF EC50 of red wine trial was higher compared to both iAUC-PAF EC50 of Ethanol and Water trials. PAI-1 iAUC was higher in all alcoholic beverages compared with the one of Water trial. Triacylglycerol iAUC increased significantly only in Ethanol compared to Water trial and were significantly lower at 60-120 min in wine trials. In the wine trials, the enzyme activities	[12-13]

	thrombosis and lipid profile	incremental areas under the curve (iAUC) were calculated The activity of PAF metabolic enzymes and IL-6 levels as a cytokine inflammatory marker were also assessed	reduced inflammatory status	of PAF-biosynthetic enzymes (Lyso-PAF-AT and PAF-CPT) were reduced compared to Ethanol trial No time either trial effect was observed in the enzyme activity of PAF-catabolic enzyme (LpPLA2). A significant time effect was found in IL-6 levels, while no trial effect was revealed in this inflammatory biomarker	
Fragopoulou et al (2021) & Choleva et al (2022)	To examine the effects of wine consumption on the inflammatory response, on the oxidation-induced macromolecular damage and on the endogenous antioxidant enzyme activities, as well as to compare these effects with the consumption of similar amount of alcohol without the wine micro-constituents in CVD patients	A randomized, single-blind, controlled, ntervention study in CVD patients (n = 64; in group A participants consumed no alcohol, the participants of the ethanol B group and wine group C consumed 27 g of alcohol/day for 8 weeks). Biological samples were collected at the beginning (baseline), on the 4th and 8th week and several biomarkers of inflammation and oxidative stress were measured, such as urine oxidized guanine species levels, protein carbonyls, TBARS levels, and SOD and GPx enzyme activities Inflammatory cytokines secretion (IL-1 β and TNF α) measured in PBMCs from patients incubated under basal and inflammatory	The light to moderate wine consumption for 8 weeks revealed an attenuation of the ethanol consumption effect on cytokine secretion at basal conditions from the patients' PBMCs These results support the idea that wine's bioactive compounds may exert antioxidant actions that counteract the macromolecular oxidative damage induced by alcohol in CHD patients	No significant difference was observed among the three groups before the initiation or during the intervention in the most soluble biomarkers. Oxidized guanine species and protein carbonyl levels were significantly decreased in the wine group, while they were increased in the ethanol group Higher TNF α secretion by PBMCs was observed at basal conditions in the ethanol group both at 4 and 24 h of incubation versus baseline secretion. In contrast, lower secretion of the TNF α was observed after 8 weeks of intake in the wine group versus the ethanol group, both at 4 and 24 h of PBMCs' incubation	[19-20]

conditions for 4 and 24 h

Abbreviations: CVD = cardiovascular disorders; CAD = coronary artery disease; PAF = platelet-activating factor; Lyso-PAF AT = lyso-PAF acetyltransferase (main enzyme of the remodeling synthesis of PAF)); PAF-CPT = PAF-cholinephosphotransferase (main enzyme of the *de novo* synthesis of PAF); LpPLA2 = lipoprotein-associated phospholipase A2 (main enzyme of PAF-catabolism); CRP = C-reactive protein; NO = nitric oxide; EPC = endothelial progenitor cells; PBMCs = peripheral blood mononuclear cells; PAI-1 = plasminogen activator inhibitor type 1; IL- = interleukin-; MCP-1 = monocyte chemoattractant protein; VCAM-1 = Vascular cell adhesion protein 1; ICAM-1 = intercellular adhesion molecule-1; M-CSF = macrophage colony-stimulating factor; TNF- α = tumor necrosis factor; NF- κ b = nuclear factor kappa beta; AP-1 = activator protein-1; LPS = lipopolysaccharide; Total Antioxidant Capacity (TAC), LDL = low density lipoproteins; HDL = high density lipoprotein; TC = total cholesterol; ox-LDL = oxidized-LDL; TAGs = triacylglycerols; PG = prostaglandin; BMI = body mass index;; TBARS = thiobarbituric acid substances; SOD = superoxide dismutase; GPx = glutathione peroxidase; TMAO = trimethylamine N-oxide.

Supplementary Table S2*. Characteristic studies, interventions and clinical trials on the benefits of moderate consumption of wine and its bio-functional compounds against other inflammatory and thrombotic manifestations and inflammation-related chronic disorders and all cause of mortality, including cancer, metabolic syndrome and diabetes mellitus, .gastrointestinal disorders, chronic obstructive pulmonary disease, stroke, neurodegenerative diseases and depression

Study	Hypothesis- Intervention	Study design -Factors examined	Main/Concluding Observed Benefit(s)	Specific benefits / other benefits observed - Mechanisms of action(s)	Reference
The Health Professionals Follow-Up Study	To examine (1) whether alcohol intake among men at risk of prostate cancer is associated with diagnosis of lethal prostate cancer and (2) whether intake among men with nonmetastatic prostate cancer is associated with metastasis or death	A prospective cohort study based on the Health Professionals Follow-Up Study (1986 to 2012). Analysis of alcohol intake assessed among men at risk of prostate cancer included 47,568 cancer-free men, while among men with prostate cancer was restricted to 5,182 men diagnosed with nonmetastatic prostate cancer during follow-up. The association of total alcohol, red and white wine, beer, and liquor with lethal prostate cancer and death were assessed by multivariate Cox proportional hazards regression that estimated hazard ratios (HRs) and 95% confident intervals.	Cancer-free men who consumed alcohol had a slightly lower risk of lethal prostate cancer compared with abstainers. Among men with prostate cancer, red wine was associated with a lower risk of progression to lethal disease. These observed associations provide assurance that moderate alcohol consumption is safe for patients with prostate cancer.	Alcohol drinkers had a lower risk of lethal prostate cancer without a dose-response relationship. Total alcohol intake among patients with prostate cancer was not associated with progression to lethal prostate cancer, whereas moderate red wine intake was associated with a lower risk. Compared with none, 15 to 30 g/d of total alcohol after prostate cancer diagnosis was associated with a lower risk of death, as was red wine	[126]
The North Carolina Colon Cancer Study	To evaluate whether alcohol consumption is associated with distal colorectal cancer and rectal cancer specifically	A retrospective, observational study Data on alcohol intake were examined from the North Carolina Colon Cancer Study, a population-based case-control study of distal colorectal cancer, encompassing 33 counties in the central and eastern part of North	Moderate alcohol intake (especially wine) was inversely associated with distal colorectal cancer	The odds ratio for rectal cancer comparing any vs no alcohol intake was low (0.73), adjusted for age, sex, race, smoking status, obesity, education, red meat intake, use of nonsteroidal anti-inflammatory medications, and family history of colorectal cancer.	[127]

		<p>Carolina</p> <p>Cases (n=1033) had adenocarcinoma of the rectum, rectosigmoid, and sigmoid colon. Controls (n=1011) were frequency-matched on age, race, and sex.</p> <p>Demographic and dietary intake data were collected with use of a validated questionnaire.</p> <p>Logistic regression was used to estimate odds ratios for the relationship between alcohol consumption and distal colorectal cancer</p>		<p>The odds ratio for moderate alcohol (14 g/day) was even lower (0.66), whereas the odds ratio for heavy alcohol (>14 g/day) was higher (0.93)</p> <p>Moderate beer and wine intakes were also inversely associated with distal colorectal cancer, with odds ratios being amongst the lowest ones (0.76 and 0.69, respectively)</p>	
Liu et al (2022)	To evaluate the effect of low-to-moderate wine drinking on hepatocellular carcinoma (HCC)	<p>Participants from the UK Biobank with detailed information on alcohol use and free of common diseases were included. Daily pure alcohol intake (g/day) was calculated, and the predominant alcoholic beverage type was assigned for each participant. Additive Cox regression model and nonlinear Mendelian randomization (NLMR) analyses were performed to evaluate the association of alcohol intake with HCC</p> <p>Of 329,164 participants (52.3% females of mean age = 56.7 ± 8.0 years), 201 incident HCC cases were recorded during the median follow-up of 12.6</p>	<p>Low-to-moderate drinking may be inversely associated with the risk of HCC in low-risk populations, which may be largely driven by wine drinking.</p> <p>However, those in high-risk populations of HCC, such as men and older people, and those with abnormal alanine transaminase (ALT) levels and/or those who carry genetic risk variants, should abstain from drinking alcohol</p>	<p>A J-shaped relationship between daily alcohol intake level and HCC risk was observed, but not during nonlinear Mendelian randomization</p> <p>The J-shaped correlation pattern was detected only in subjects who mainly drank wine but not in those who mainly drank beer, spirits, etc.</p> <p>Moderate wine drinking showed a significant ALT and aspartate aminotransferase lowering effect compared to that of the nondrinkers.</p>	[128]

Wang et al (2022)	To determine the effect of very-light alcohol consumption on cancer	<p>years.</p> <p>The manner of gavage was used to control the alcohol consumption accurately in a breast metastasis mouse model.</p> <p>The impacts of age and time of drinking on cancer progression were also evaluated</p> <p>8 commercial alcohol types were investigated at a dosage of 1.0% w/v</p> <p>RNA sequencing analyses were performed in primary tumors and related metastases from the NC group and 1.0% w/v group</p>	<p>A certain range of very light alcohol dosages might have a potential human-cancer inhibition effect</p> <p>Red wine (made in France) and baijiu (made in China), exerted excellent primary tumor and metastasis inhibitory effects.</p> <p>The untargeted metabolomic analysis by LC-MS indicated that differences in compositions can lead to different anti-cancer effects</p>	<p>A certain range of alcohol consumption (from 0.5% w/v to 2.0% w/v) can suppress tumor development in the breast metastasis mouse model by controlling the alcohol consumption dosage accurately</p> <p>The results of primary tumors and related metastases indicated that chronic very-light alcohol consumption downregulates breast tumor-associated oncogenes in primary tumors and regulates the immune system and metabolic system in metastatic carcinoma</p>	[129]
Schaefer et al (2022)	To examines how alcohol intake from wine and non-wine alcoholic beverages (non-wine) in g/day are associated with all-cause, cancer, non-cancer and CVD mortality	<p>A prospective cohort study in 354,386 participants of the UK Biobank cohort who drank alcohol at least occasionally and survived at least 2 years after baseline with 20 201 deaths occurring over 4.2 million person-years.</p> <p>Hazard ratios (HR) for mortality were assessed with Cox proportional hazard regression models and beverage intake fitted as penalised cubic splines</p>	<p>light to moderate consumption of wine but not non-wine is associated with decreased all-cause and non-cancer mortality..</p>	<p>A significant U-shaped association was detected between wine consumption and all-cause, non-cancer and CVD mortality.</p> <p>Wine consumption with lowest risk of death ranged from 19 to 23 g alcohol/day in all participants and both sexes separately.</p> <p>Non-wine intake was significantly and positively associated in a dose-dependent manner with all mortality types studied except for CVD (0 and 12 g alcohol/day).</p>	[130]
Turati et al (2018)	To investigate the association between	3034 breast cancer cases and 3392 controls admitted to the same	Adherence to the Mediterranean diet was	Low adherence to the Mediterranean Diet (low Mediterranean Diet Score) showed	[131]

	adherence to the Mediterranean diet, including moderate wine consumption, and breast cancer risk by means of a hospital-based case-control study conducted in Italy and Switzerland	network of hospitals for acute, non-neoplastic and non-gynaecologic diseases were studied. Adherence to the Mediterranean diet was quantitatively measured through a Mediterranean Diet Score, summarizing the major characteristics of the Mediterranean dietary pattern and ranging from 0 (lowest adherence) to 9 (highest adherence). Odds ratios of breast cancer were evaluated using multiple logistic regression models, adjusting for several covariates.	associated with a reduced breast cancer risk. The exclusion of the ethanol component from the MDS, mostly from wine, did not materially modify the Mediterranean diet score and thus had little impact on odds ratios for breast cancer	higher odds ratios for breast cancer, whereas higher adherence to the Mediterranean Diet (high Mediterranean Diet Score) showed lower odds ratios for breast cancer	
Shufelt et al (2012)	To evaluate if red wine is a nutritional aromatase inhibitor that can prevent the conversion of androgens to estrogen and thus breast cancer in premenopausal women	In a cross-over design, 36 women (mean age 36 ± 8 years) were assigned to 8 ounces (237 mL) of red wine daily then white wine for 1 month each, or the reverse. Blood was collected twice during the menstrual cycle for measurement of estradiol (E2), estrone (E1), androstenedione (A), total and free testosterone (T), sex hormone binding globulin (SHBG), luteinizing hormone (LH), and follicle stimulating hormone (FSH)	Red wine is associated with significantly higher free testosterone and lower sex hormone binding globulin levels, as well as a significant higher Luteinizing hormone level vs. white wine in healthy premenopausal women, suggesting that red wine is a nutritional aromatase inhibitor and may explain the observation that red wine does not appear to increase breast cancer risk.	Red wine demonstrated higher free testosterone vs. white wine and lower sex hormone binding globulin. Estradiol levels were lower in red vs. white wine but not statistically significant. Luteinizing hormone was significantly higher in red vs. white wine, however, follicle stimulating hormone was not	[132]
Armstrong et al (2018)	To assess the role of modest alcohol	A well-characterised single centre cohort of nearly 200 patients with	Modest, non-binge wine consumption (<70 g/week)	Modest, non-binge wine consumption may reduce the risk of hepatocellular carcinoma	[[133]

	consumption in patients with non-alcohol induced fatty liver disease (NAFLD) related to chronic liver disease, including hepatocellular carcinoma	non-alcohol induced fatty liver disease	was associated with significantly lower risk of advanced hepatic fibrosis on biopsy compared with complete abstinence in non-alcohol induced fatty liver disease patients		
Zhu et al (2012)	To determine if trans-resveratrol had a dose-related antitumor effect on DNA methylation and prostaglandin expression in humans at increased breast cancer risk	A randomized double blind controlled trial in 39 adult women at increased breast cancer risk, administrated placebo or 5 or 50 mg trans-resveratrol twice daily for 12 weeks. Methylation assessment of 4 cancer-related genes (p16, RASSF-1 α , APC, CCND2) was performed on mammary ductoscopy specimens.	Beneficial effects of trans-resveratrol on the breast of women at increased breast cancer risk, including a decrease in methylation of the tumor suppressor gene RASSF-1 α	The predominant resveratrol species in serum was the glucuronide metabolite. Total trans-resveratrol and glucuronide metabolite serum levels increased after consuming both trans-resveratrol doses RASSF-1 α methylation decreased with increasing levels of serum trans-resveratrol The change in RASSF-1 α methylation was directly related to the change in PGE(2).	[134]
The PREDIMED (Prevención con Dieta Mediterránea) study on Metabolic Syndrome	To investigate if moderate red wine consumption could be associated with a lower prevalence of the Metabolic Syndrome	A cross-sectional study of 5801 elderly participants at a high cardiovascular risk included in the PREDIMED (Prevención con Dieta Mediterránea) study 3897 fulfilled the criteria of the Metabolic Syndrome at baseline. Red wine intake was recorded using a validated 137-item food frequency questionnaire. Multiple logistic regression analysis	Moderate red wine consumption is associated with a lower prevalence of the Metabolic Syndrome in an elderly Mediterranean population at a high cardiovascular risk	Compared with non-drinkers, moderate red wine drinkers (≥ 1 drink/day) were found to have a reduced risk of prevalent Metabolic Syndrome, a lower risk of having an abnormal waist circumference, low HDL-cholesterol concentrations, high blood pressure and high fasting plasma glucose concentrations after adjusting for several confounders. This association was found to be stronger in female participants, in participants aged	[135]

		was carried out to estimate the association between red wine intake and the prevalence of the Metabolic Syndrome		< 70 years and in participants who were former or current smokers. No significant association was found between red wine intake (≥ 1 drink/day) and TAG concentrations.	
The longitudinal UK Biobank study	to investigate whether different alcohol types (beer/cider, red wine, white wine/Champagne, spirits) differentially associated with body composition, adipogenesis, metabolic syndrome and obesity-related health risks in elderly people	1869 White participants (40-80 years; 59% male) of the UK Biobank self-reported demographic, alcohol/dietary consumption, and lifestyle factors using a touchscreen questionnaire Anthropometrics and serum for proteomics were collected Body composition was obtained via dual-energy X-ray absorptiometry Structural equation modeling was used to probe direct/indirect associations between alcohol types, cardiometabolic biomarkers, and body composition.	Red wine in moderation seems to protect against adipogenesis and thus against weight gain, metabolic syndrome and obesity-related health risks, due to its anti-inflammatory and eulipidemic effects, especially in older adults White wine in moderation may help curb age-associated bone mineral loss and thus benefit bone health in older White adults, and especially in older adult drinkers who have an elevated risk for osteopenia-associated diseases	Drinking more red wine was associated with less visceral adipose mass, which was driven by reduced inflammation and elevated high-density lipoproteins. White wine consumption predicted greater bone density. In contrast, greater beer/spirit consumptions were associated with greater visceral adiposity, which was driven by dyslipidemia and insulin resistance	[136]
The CASCADE (CARDiovascular Diabetes and Ethanol) Study	To assess cardiometabolic effects and progression of carotid atherosclerosis by initiating moderate consumption of wine	A 2-year randomized controlled trial in abstainers with well-controlled type 2 diabetes with 150 ml daily intake of either red wine, white wine, or water, in a Mediterranean diet design. 2-year changes in carotid total plaque	No progression in carotid-TPV was observed by wine consumption. Only in patients with the greatest plaque burden assigned to drink wine a small regression of plaque	After 2 years, no significant progression in carotid total plaque volume was observed in all groups. Participants with the higher baseline plaque burden reduced their plaque volume significantly after 2 years drinking wine, compared to baseline.	[137-138]

	for 2 years in patients with type 2 diabetes, and whether the type of wine matters	volume and carotid vessel wall volume were evaluated in 174 of the 224 participants (with 45% having detectable plaque at baseline), using 3D ultrasound Follow-up data at 2 years were also collected in 195 out of 224 participants for lipid and glycemic control profiles, genetic measurements, blood pressure, liver biomarkers, medication use, symptoms, and quality of life.	burden was observed Compared with the changes in the water group, red wine further increased HDL-cholesterol and reduced the number of components of the metabolic syndrome	Two-year reductions in Apo(B)/Apo(A) ratio(s) were independently associated with regression in carotid total plaque volume. Two-year decreases in systolic blood pressure were independently associated with regression in carotid vessel wall volume. Red wine significantly increased HDL-cholesterol and decreased the TC/HDL-cholesterol ratio	
Ma et al (2022)	To investigate the joint associations of the timing of alcohol intake with respect to meals (i.e., with meals or outside of meals) and the amount of alcohol consumed with the risk of type 2 diabetes	A total of 312,388 current drinkers from the UK Biobank without type 2 diabetes at baseline were included. Cox proportional hazards models were used to examine the association between the timing of alcohol intake with respect to meals and the risk of type 2 diabetes	In current drinkers, moderate drinking of alcohol, especially wine, with meals is associated with a lower risk of type 2 diabetes The beneficial association of moderate drinking with type 2 diabetes risk was only observed in participants who consumed alcohol with meals, but not in others Further analyses on various types of alcoholic beverages indicated that the beneficial associations between alcohol drinking with meals and type 2 diabetes were mainly driven by wine consumption	During a median of 10.9 y of follow-up, 8598 incident cases of type 2 diabetes were documented. After adjustment for covariates and the amount of alcohol consumed, consuming alcohol with meals was significantly associated with a lower risk of type 2 diabetes, than was consuming alcohol outside of meals The timing of alcohol intake with respect to meals significantly modified the relations between the amount of alcohol consumed and risk of type 2 diabetes When consumed together with meals, drinking more wine, rather than other alcoholic beverages, was related to lower CRP concentrations	[139]

Chiva-Blanch et al (2013)	To compare the effects of moderate consumption of red wine, dealcoholized red wine, and gin on glucose metabolism and the lipid profile and thus on diabetes and cardiovascular risk	A randomized crossover trial in 67 men at high cardiovascular risk. After a run-in period, all received each of red wine (30 g alcohol/d), the equivalent amount of dealcoholized red wine, and gin (30 g alcohol/d) for 4 week periods, in a randomized order. Fasting plasma glucose and insulin, homeostasis model assessment of insulin resistance (HOMA-IR), plasma lipoproteins, apolipoproteins and adipokines were determined at baseline and after each intervention	A beneficial effect of the non-alcoholic fraction of red wine (mainly polyphenols) on insulin resistance was observed, conferring greater protective effects on CVD to red wine than other alcoholic beverages	Fasting glucose remained constant throughout the study, while mean adjusted plasma insulin and HOMA-IR decreased after red wine and dealcoholized red wine. HDL cholesterol, Apolipoprotein A-I and A-II increased after red wine and gin. Lipoprotein(a) decreased after the red wine intervention	[140]
Ismail et al (2022)	To compare acute effects of red wine with or without alcohol and moist snuff with or without nicotine on prandial hormones and metabolism.	A cross over study in 14 healthy women and men with 200mL of wine, with or without alcohol, together with a standardized supervised meal. All participants also combined the meal with usage of with moist snuff, with or without nicotine. The snuff was replaced hourly at each of the four settings, i.e. snuff with or without nicotine combined with red wine with or without alcohol, that started at 0800 o'clock and were finished at noon.	Alcohol in red wine augmented the postprandial suppression of ghrelin and it also lowered postprandial glucose 3 h post-meal, linking regular intake of moderate amounts of red wine with lower risk for diabetes	Drinking red wine with alcohol suppressed more efficiently ghrelin levels compared to non-alcoholic wine. The postprandial metabolic rate was further elevated following alcohol containing red wine compared with non-alcoholic red wine. Lowered glucose levels were observed 3h after the meal with alcoholic red wine. Nicotine-containing moist snuff (AUC: 1406 ± 149 nmol/ml x hours) elevated the levels of serum cortisol compared with nicotine-free snuff. No effects of nicotine or alcohol on feelings of satiety were observed.	[141]

Sattarinezhad et al (2019)	To evaluate the effects of grape and wine resveratrol on diabetic nephropathy	A randomized, double-blind, placebo-controlled clinical trial in 60 patients with type 2 diabetes and albuminuria that received resveratrol (500mg/day) or placebo for 90 days. Losartan (12.5mg/day) was also administered to all participants Primary outcomes were urinary albumin/creatinine ratio, estimated glomerular filtration rate (eGFR) and serum creatinine levels. Secondary outcomes were oxidative stress markers, and anthropometric and biochemical measures.	Wine resveratrol may be an effective adjunct to angiotensin receptor blockers for reducing urinary albumin excretion in patients with diabetic nephropathy	Urine albumin/creatinine ratio was significantly reduced in the resveratrol group vs placebo After adjusting for confounding variables, the effect of resveratrol in reducing urinary albumin excretion was still significant Every 1-cm decrease in waist circumference and 1- μ mol/L increase in nitric oxide (NO) was associated with reductions of urine albumin/creatinine ratio Serum antioxidant enzymes were increased with resveratrol . eGFR and serum creatinine were unchanged.	[142]
Tian et al (2016)	To test the influence of wine resveratrol against cognitive dysfunction as well as on hippocampal structural synaptic plasticity in streptozotocin-induced diabetic rats	Rats were randomly selected and divided into 5 groups of 15 animals each, i.e. control, diabetic control, diabetic/RV 10 mg/kg, diabetic/RV 20 mg/kg, and control/RV 20 mg/kg.per day for 8 weeks All animals were then tested for learning and memory task in Morris water maze for 5 consecutive days. Isolated blood, serum, brains and both hippocampi were assessed for synapses, oxidative stress and inflammatory biomarkers	oral supplementation of resveratrol might be a potential therapeutic strategy for the treatment and/or prevention of diabetic encephalopathy	In the diabetic group the cognitive performances were markedly deteriorated, accompanied by noticeable alterations in oxidative as well as inflammation parameters. In contrast, chronic treatment with resveratrol (10, 20mg/kg) in the diabetic rats groups improved neuronal injury and cognitive performance by attenuating oxidative stress and inflammation, as well as by inhibiting synapse loss	[143]
The German Study on	To investigate whether dietary	A prospective cohort study in participants aged 75+ of the AgeCoDe	From all the single foods assessed, only red wine was	Only higher red wine intake was associated with a lower incidence of	[144]

Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe)	intake of red wine and other single foods, assessed by a single-food-questionnaire, would be associated with either incident Alzheimer's dementia or verbal memory decline in elderly people	cohort, which were regularly followed over 10 years (n = 2622; n = 418 incident AD cases) Multivariable-adjusted joint modeling of repeated-measures and survival analysis was used, taking gender and Apolipoprotein E4 (APOE 4) genotype into account as possible effect modifiers.	found to be protective against cognitive decline Red wine reduced the risk for Alzheimer's dementia only in men. Women could be more susceptible to detrimental effects of alcohol	Alzheimer's dementia. This was true only for men, while in women higher red wine intake was associated with a higher incidence of Alzheimer's dementia, and higher white wine intake with a more pronounced memory decline over time	
Mendes et al (2018)	To investigate whether dietary intake of white wine polyphenolic extract can be used as effective nutraceuticals to break or delay the progressive brain degeneration underlying cognitive decline and dementia that characterize Alzheimer's disease (AD)	A selective pool of polyphenols, obtained from the white wine by adsorption to polyvinylpyrrolidone polymer (PVPP), was used to prepare a polyphenols-enriched diet, supplementing the drinking water with 100 mg/L (expressed as gallic acid equivalent) of wine polyphenolic extract. The impact of the daily consumption of water supplemented with polyphenols for 2 months on brain of 10-month-old 3xTg-AD and NonTg mice was evaluated, considering effects on the redox state of cells, levels of amyloid- β peptides, mitochondrial bioenergetics and fatty acid profile of whole membrane phospholipids	Oral administration of a wine polyphenols-enriched diet promotes significant benefits in multiple aspects of the pathophysiological cascade associated with the neuropathology developed by 3xTg-AD mice	The polyphenols-enriched diet promoted brain accumulation of catechin and hydroxybenzoic acid derivatives, and modulated the redox state of 3xTg-AD brain cells, increasing both glutathione/glutathione disulfide ratio and catalase activity and decreasing membrane lipids oxidation. The functional diet decreased the 3xTg-AD brain levels of both amyloid- β peptides, A β 1-40 and A β 1-42 The brain mitochondrial bioenergetic dysfunction of 3xTg-AD animals was not attenuated by the polyphenols-enriched diet. Lipidomic studies showed that this functional diet modulates membrane lipid composition of brain cells, increasing C22:6n-3 (docosahexanoic acid) and	[145]

				decreasing C20:4n-6 (arachidonic acid) levels, which may have beneficial impact on the chronic inflammatory process associated with AD pathology.	
Hu et al (2017)	To investigate the potential dose-response association between alcohol consumption and risk of dementia	A dose-response meta-analysis of prospective studies A systematic search was conducted in electronic databases to identify relevant studies. Risk estimates were combined using a random-effect model. 11 studies with 73,330 participants and 4586 cases for all-cause dementia, 5 studies with 52,715 participants and 1267 cases for Alzheimer's dementia and 4 studies with 49,535 participants and 542 cases for vascular dementia were included.	Modest alcohol consumption (≤ 12.5 g/day) is associated with a reduced risk of dementia with 6 g/day of alcohol conferring a lower risk than other levels while excessive drinking (≥ 38 g/day) may instead elevate the risk	A nonlinear association between alcohol consumption and all-cause dementia risk. The alcohol dose associated with lower risk of dementia was confined to at most 12.5 g/day, with the risk hitting bottom at roughly 6 g/day. The all-cause dementia risk seemed to be elevated when the dose surpasses certain levels: 23 drinks/week or 38 g/day. For the alcohol type, recommendation for wine is prioritized. The subgroup analysis further indicated that the effect of alcohol may be greater in younger adults (< 60 years old) with regard to fighting against dementia.	[146]
Ho et al (2013)	To evaluate the specific biological activities and cellular and molecular mechanisms by which wine polyphenolic components from moderate consumption of red wines may lower the relative risk for	Accumulations of polyphenols were assessed in the rat brain following oral dosage with a Cabernet Sauvignon red wine and tested brain-targeted polyphenols for potential beneficial Alzheimer's disease - modifying activities	Brain-targeted quercetin-3-O-glucuronide may simultaneously modulate multiple independent Alzheimer's disease - modifying mechanisms and, as such, may contribute to the benefits of dietary supplementation with red wines as an effective intervention for Alzheimer's	Accumulations of select polyphenolic metabolites were identified in the brain of animals. In comparison to vehicle-control treatment, one of the brain-targeted polyphenol metabolites, quercetin-3-O-glucuronide, significantly reduced the generation of β -amyloid ($A\beta$) peptides by primary neuron cultures generated from the Tg2576 AD mouse model Quercetin-3-O-glucuronide is also capable	[147]

developing Alzheimer's disease (AD) dementia		disease		of interfering with the initial protein-protein interaction of A β (1-40) and A β (1-42) that is necessary for the formation of neurotoxic oligomeric A β species. Quercetin-3-O-glucuronide treatment, compared to vehicle-control treatment, significantly improved Alzheimer's disease -type deficits in hippocampal formation basal synaptic transmission and long-term potentiation, possibly through mechanisms involving the activation of the c-Jun N-terminal kinases and the mitogen-activated protein kinase signaling pathways	
The PREDIMED (Prevención con Dieta Mediterránea) study on cognitive function in the elderly	To assess whether consumption of antioxidant-rich foods in the Mediterranean diet, including wine, relates to cognitive function in elderly subjects at high cardiovascular risk	A cross-sectional study in asymptomatic subjects at high cardiovascular risk (n = 447; 52% women; age 55-80 y) enrolled in the PREDIMED study, a primary prevention dietary-intervention trial, food intake and cardiovascular risk profile was assessed Apolipoprotein E genotype was also determined Neuropsychological tests were used to evaluate cognitive function. Urinary polyphenols were also measured as an objective biomarker of intake. Associations between energy-adjusted	. Increased consumption of antioxidant-rich foods in general and of polyphenols in particular, such as wine, is associated with better cognitive performance in elderly subjects at high cardiovascular risk. The results reinforce the notion that Mediterranean diet components, including wine, might counteract age-related cognitive decline	Higher education years and higher wine intake were associated with better performance in the neuropsychological tests Participants who consumed alcohol were mostly moderate wine drinkers, and the daily dose of wine related to a better overall cognitive function in them.	[148]

		food consumption, urinary polyphenols, and cognitive scores were assessed by multiple linear regression models adjusted for potential confounders.			
The INTERSTRO KE Study	To explore the association between alcohol consumption and stroke, particularly for low-moderate intake of wine	A case-control international study of risk factors for acute stroke. Alcohol consumption was self-reported and categorized by drinks/week as low (1-7), moderate (7-14 for females and 7-21 for males), or high (>14 for females and >21 for males). Heavy episodic drinking was defined as >5 drinks on ≥1 day per month. Multivariable conditional logistic regression was used to determine associations. 12,913 cases and 12,935 controls were included; 25.0% (n = 6,449) were current drinkers, 16.7% (n = 4,318) former drinkers, and 58.3% (n = 15,076) never drinkers. Current drinkers were younger, male, smokers, active, and with higher-paid occupations.	High and moderate alcohol intake were associated with increased odds of stroke, whereas low intake was not associated with stroke. However, there were important regional variations, which may relate to differences in population characteristics of alcohol consumers, types or patterns of consumption. Wine consumption was associated with reduced odds of all stroke and ischemic stroke but not intracerebral hemorrhage. The magnitudes of association were greatest in those without hypertension and current smokers.	Current drinking was associated with all stroke and intracerebral hemorrhage but not ischemic stroke. High level of alcohol intake and Heavy episodic drinking pattern was consistently associated with all stroke, ischemic stroke and intracerebral hemorrhage. Moderate intake was associated with all stroke and intracerebral hemorrhage, but not ischemic stroke. Low alcohol intake was not associated with stroke overall, but there were regional differences; low intake was associated with reduced odds of stroke in Western Europe/North America and increased odds in India.	[149]
Kaluza et al (2019)	To investigate the associations of total alcohol consumption	A population-based prospective cohort study, the Cohort of Swedish Men (n = 44,254).	Moderate beer and wine consumption, but not liquor consumption, may decrease	Moderate alcohol consumption was associated with the lowest risk of chronic obstructive pulmonary disease.	[150]

	and intake of specific alcoholic beverages with risk of chronic obstructive pulmonary disease	Alcohol consumption was assessed with a self-administered questionnaire in 1997. During follow-up (1998-2014), 2,177 chronic obstructive pulmonary disease cases were ascertained.	risk of chronic obstructive pulmonary disease	A J-shaped association was observed for ethanol and beer consumption; while for wine consumption, a U-shaped association was observed	
Sánchez-Fidalgo et al. (2010)	Examined the protective or preventative effects of dietary resveratrol consumption in a chronic colitis model caused by dextran sulfate sodium (DSS) in mice.	6-week-old C57BL/6 mice were randomly assigned to one of two diets: a conventional diet or one supplemented with resveratrol.	Dietary supplementation of resveratrol attenuated chronic colonic inflammation in mice. Reduced signs of abnormal body weight and diarrhea, as well as improvement of the inflammatory score and disease activity index in the resveratrol group	Three weeks following the removal of DSS, there was an apparent reduction of pro-inflammatory cytokines, TNF- α and IL-1 β , and a rise in the anti-inflammatory cytokine IL-10	[3]
Queipo-Ortuño et al (2012)	to evaluate the effect of a moderate intake of red wine polyphenols on select gut microbial groups implicated in host health benefits	A randomized, crossover, controlled intervention study in 10 healthy male volunteers. After a washout period, all of the subjects received red wine, the equivalent amount of de-alcoholized red wine, or gin for 20 d each and several biomarkers were measured.. Monitoring and quantification of changes in fecal microbiota was performed by PCR-denaturing gradient gel electrophoresis and real-time quantitative PCR.	Red wine consumption can significantly modulate the growth of select gut microbiota in humans, which suggests possible prebiotic benefits associated with the inclusion of red wine polyphenols in the diet	In parallel, systolic and diastolic blood pressures and triglyceride, CRP and total and HDL cholesterol concentrations decreased significantly, in association to changes in the <i>bifidobacteria</i> number.	[26]
The Mediterranean	To assess the association between	Demographic and dietary characteristics of 1572 adults living in	When taking into consideration the major	. Total polyphenol intake was not associated with depressive symptoms.	[151]

n healthy Eating, Lifestyle and Aging (MEAL) study	habitual dietary intake of total polyphenols, their classes, subclasses and individual compounds and depressive symptoms among the participants of the Mediterranean healthy Eating, Lifestyle and Aging (MEAL) study	southern Italy were analyzed. Food frequency questionnaires and Phenol-Explorer were used to calculate habitual dietary intakes of polyphenols. The Center for Epidemiologic Studies Depression Scale (CES-D-10) was used as screening tool for depressive symptoms; a total of 509 individuals reported having depressive symptoms. Multivariate logistic regression analyses were used to test associations and were expressed as odds ratio (OR) and 95% confidence intervals (CI).	sources of the polyphenols, only citrus fruits and wine consumption was inversely associated with depressive symptoms. Higher dietary intake of flavonoid may be inversely associated with depressive symptoms.	After adjustment for potential confounding factors, dietary intake of phenolic acid, flavanones, and anthocyanins showed significant inverse association with depressive symptoms, when comparing the highest with the lowest quartile, in a dose-response manner. Among individual compounds, inverse association was observed for quercetin and naringenin for the highest versus lowest quartile of intake.	
The "Seguimiento Universidad de Navarra" (SUN) Cohort Study	To evaluate the effects of the adherence to the Mediterranean Alcohol Drinking Pattern (MADP) of alcohol consumption against all cause mortality in people of older ages	A prospective cohort study with a follow-up in 2226 participants (men older than 50 years and women older than 55 years at baseline) in the Seguimiento Universidad de Navarra (SUN) cohort. Participants were classified into 3 categories of adherence to the MADP score (low, moderate, and high), and we added a fourth category for abstainers. Cox regression models estimated multivariable-adjusted hazard ratios (HR) of all-cause death and 95% confidence intervals (CI)	High adherence to the (MADP) score, which integrates several dimensions of drinking patterns (moderation, preference for red wine, drinking with meals, and avoiding binge drinking), could substantially reduce the risk of all-cause mortality among people older than 50 years who drink alcohol	The strongest reduction in risk of mortality was observed for those with high adherence to the MADP score. The moderate adherence group and the abstention group also exhibited lower risks of mortality than the low MADP adherence group.	[152]

		using low MADP adherence as the reference category.			
The Southern European Atlantic Diet (SEAD) study	To examine the association between adherence to the traditional diet of Northern Portugal and North-Western Spain, Southern European Atlantic Diet (SEAD), and all-cause mortality in older adults	<p>A cohort study based on data taken from the Seniors-ENRICA-1 cohort with 3165 individuals representative of the non-institutionalized population aged ≥ 60 years in Spain (646 deaths occurred in a 10.9 years follow up)</p> <p>Food consumption was assessed with a validated diet history, and adherence to the diet was measured with an index comprising 9 food components: fresh fish, cod, red meat and pork products, dairy products, legumes and vegetables, vegetable soup, potatoes, whole-grain bread, and wine.</p> <p>Vital status was ascertained with the National Death Index of Spain. Cox regression models were performed, adjusted for the main confounders.</p>	Moderate wine consumption lowered all-cause mortality. Adherence to the Southern European Atlantic Diet is associated with a lower risk of all-cause death among older adults in Spain	<p>Most food components of the diet showed some tendency to lower all-cause mortality, especially moderate wine consumption.</p> <p>Higher adherence to the diet was associated with lower all-cause mortality. The protective association between this diet and all-cause death was of similar magnitude to that found for the Mediterranean Diet Adherence Screener and the Alternate Healthy Eating Index.</p>	[153]
Grønbaek et al (2000)	To examine the relation between intake of different types of alcohol and death from all causes, coronary heart disease, and cancer	Pooled cohort studies in which intake of beer, wine, and spirits; smoking status; educational level; physical activity; and BMI were assessed at baseline in 13 064 men and 11 459 women 20 to 98 years of age in Copenhagen, Denmark.	<p>Wine drinkers had significantly lower mortality from both coronary heart disease and cancer than did non-wine drinkers</p> <p>Thus, wine intake may have a beneficial effect on all-cause</p>	<p>During 257859 person-years of follow-up, 4833 participants died. J-shaped relations were found between total alcohol intake and mortality at various levels of wine intake. Compared with nondrinkers, light drinkers who avoided wine had a relative risk for death from all causes of 0.90 and</p>	[154]

		Number of deaths and time to death from all causes, coronary heart disease, and cancer were measured during follow-up.	mortality that is additive to that of alcohol	those who drank wine had a relative risk of 0.66 Heavy drinkers who avoided wine were at higher risk for death from all causes than were heavy drinkers who included wine in their alcohol intake.	
Noguer et al (2012)	To evaluate whether alcohol-free wine has any effect on antioxidant enzyme activities that contribute to the overall antioxidant properties of wine.	A randomized cross-over human intervention A low phenolic diet was designed to prevent interference from polyphenols in other food sources. In the first period, the volunteers ate only this low phenolic diet; in the second, they ate this diet and also drank 300 mL of alcohol-free wine. Superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase were assessed.	The increase in the activity of the antioxidant enzymes is not due to the alcohol content in wine but to its bioactives' composition like polyphenols. Alcohol-free wine could be an excellent source of antioxidants to protect people suffering from oxidative stress (cancer, diabetes, alzheimer, etc.) who should not consume alcohol.	The activities of glutathione reductase, superoxide dismutase and catalase decreased during the low phenolic diet period and increased in the period when dealcoholized wine was also consumed within this diet On the 3 rd day of intervention, significant changes were observed in glutathione reductase and superoxide dismutase activity for both intervention periods under study. Catalase activity changed significantly on the 7 th day of intervention Antioxidant enzymes modulated their activity more easily than the endogenous antioxidants, which did not undergo any changes	[155]

Abbreviations: CVD = cardiovascular diseases; CRP = C-reactive protein; HDL = high density lipoprotein; HCC = hepatocellular carcinoma; ALT = alanine transaminase;; TAG = triacylglycerols; homeostasis model assessment of insulin resistance (HOMA-IR); Alzheimer's disease (AD); The Mediterranean Alcohol Drinking Pattern (MADP) LC-MS = liquid chromatography mass spectrometry

***All references cited in both Supplementary Tables S1 and S2 have been incorporated (with the exact numbering) within the main References' list of the Manuscript**