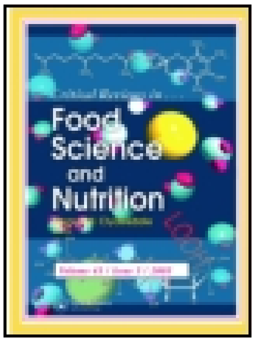

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REVIEW

Grapes and their derivatives in modulation of cognitive decline: a critical review of epidemiological and randomized-controlled trials in humans

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ABSTRACT

With an increase in life expectancy, the incidence of chronic degenerative pathologies such as dementia has progressively risen. Cognitive impairment leads to the gradual loss of skills, which results in substantial personal and financial cost at the individual and societal levels. Grapes and wines are rich in healthy compounds, which may help to maintain homeostasis and reduce the risk of several chronic illnesses, including dementia. This review analyzed papers that were systematically searched in PubMed, MEDLINE, Embase, and CAB-Abstract, using the association between grapes (or their derivatives) and their effects on cognitive functions in humans. Analysis was restricted to epidemiological and randomized-controlled studies. Consumption of grape juice (200-500 mL/day) and/or light-to-moderate wine (one to four glasses/day) was generally associated with improved cognitive performance, while the results for other alcoholic beverages were controversial and inconclusive. Bioactive molecules contained in grapes and wine were also considered, with particular attention paid to resveratrol. Due to the relatively high doses required (150-1000 mg/day) for bioactivity coupled with its low bioavailability, resveratrol is only one of the possible grape-derived compounds that may partly underpin the beneficial effects of grapes on the central nervous system.

KEYWORDS
Alzheimer's disease; cognitive functions; dementia; grapes; resveratrol; wine

Introduction

Aging and cognition

Aging is a well-known risk factor for cognitive decline, which is associated with an inability to maintain independence, physical activity, and social relationships (Murman 2015). An increase in life span is accompanied by both positive and negative effects. Although increased life expectancy enables prolonged relationships with family and friends, the gradual loss of cognitive function leads to problems for individuals, their relatives, and the societies in which they live. An increased life span is specifically associated with a higher incidence of chronic degenerative diseases, including dementias. The WHO (2015) reported 3.1 new cases of dementia in every 1000 inhabitants aged 60-64 years old and 175 new cases in every 1000 inhabitants aged >95 years old for any given year. The incidence is higher in industrialized countries, but this is due at least partly to the difference in accessibility to medical districts and diagnostic criteria. Reduced physical activity, smoking, overweight/obesity, poor diet, and concomitant metabolic diseases can also increase the risk of dementia in developed countries, as reported by WHO (2015). The most common cause of dementia is Alzheimer's disease, which is particularly frequent in those older than 85 years old. Dementia from Alzheimer's disease is progressive, has variable prognosis, and differs from that due to normal decline from aging (Hugo and Ganguli 2014).

To address this "dementia pandemic," preventive strategies have been proposed by both national and international authorities (WHO 2013). Physical exercise and healthy dietary habits have been identified as some of the most efficient therapeutic approaches (Savica and Petersen 2011) and are recommended from early life.

Diet, aging, and cognition

Diet is a critical source of protective compounds, including both caloric (e.g., unsaturated fatty acids) and non-caloric (e.g., vitamins, minerals, phenolic compounds) nutrients. Diet contributes to maintaining homeostasis of the organism and reducing risk factors for several chronic and degenerative diseases.

Sofi et al. (2008) performed a meta-analysis on the impact of Mediterranean diet on health and considered 12 prospective studies including 1,574,299 subjects followed for a period ranging between 3 and 18 years. Adherence to the

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Mediterranean diet was directly associated with better health status as indicated by lower overall mortality (−9%) and decreased prevalence of chronic degenerative diseases, such as cancers (−6%) and Parkinson's/Alzheimer's diseases (−13%). Although the term "Mediterranean diet" does not indicate a unique food pattern, this definition traditionally includes a high consumption of vegetables, legumes, fruits, and fish; the use of olive oil as the main source of lipids; and a moderate intake of red wine during meals (Visioli and Galli 2001; Mezzano et al. 2001; Giacosa et al. 2013).

Fruits and wine are important sources of phenolic compounds, which have been suggested to prevent the decay of senescence (for a review, see Gurău et al. 2018). The most important classes of phenolic compounds are:

- flavonoids such as flavones (apigenin), flavanols (catechins), condensed tannins (proanthocyanidins), and flavonols (quercetin, kaempferol, naringenin) and anthocyanins (red grapes)
- non-flavonoids such as stilbenes (resveratrol), lignans, phenolic acids, and hydrolyzable tannins
- other classes of compounds such as ginsenosides, oleuropein, and spermidine

Role of grapes and their derivatives as sources of healthy dietary compounds

Despite geographical and religious differences, grapes and their derivatives (both non-fermented and fermented) are common dietary ingredients world-wide, especially in Mediterranean countries. Grapes are a rich source of bioactive compounds, including anthocyanins (red grapes), flavonols, catechins, procyanidins, organic acids, and stilbenes. The consumption of 100 g of fresh grapes contributes 3-6% of the Recommended Daily Intake (RDI) of vitamins B1, B6, C, and E (FAO-OIV 2016), while phenolic compounds contribute to antioxidant and anti-inflammatory effects in cells and tissues of the body (Colombo et al. 2019).

Although bioactive compounds in grapes differ quantitatively, most are conserved in the juice from grapes depending on the time and temperatures used in the production process, as these factors affect extraction efficiency and concentration of biocompounds. However, several biological effects of both grape and grape juice polyphenols have been observed (Colombo et al. 2019; Xia et al. 2010; Copetti et al. 2018).

Most bioactive properties of grapes are conserved in its juice as well as in raisins (dried grapes), previously described by Restani et al. (2016). Changes in bioactivity are observed in fermented derivatives of grapes, such as red, rosé, and white wines, as oenological processes and alcohol production can affect polyphenol extraction and lead to the production of new phenolic derivatives (e.g., tyrosol, flavanes, free phenolic acids, and hydrolyzable tannins) (Garrido and Borges 2013; Snopek et al. 2018). The higher polyphenol content in wines has been correlated to improvements in several biological parameters and metabolic functions including antioxidant activity and cardiovascular health) (Snopek et al. 2018). Beneficial effects on human health have been reported for all grape-based products (Guilford and Pezzuto 2011), although concerns have been raised for alcoholic beverages due to the adverse outcomes associated with their frequent abuse/misuse among adults and youths (WHO 2010).

To date, only few papers reported data on the effect of wine on cognitive function or diseases, but neither comprehensive review nor data on grape derivatives have been published.

The objective of this review was to perform a critical evaluation of data reported in the scientific literature, where grapes and their derivatives were considered in association with dementia, either as a protective or promoting agent.

Materials and methods

Four of the most established scientific databases of references and abstracts in the life sciences (PubMed, MEDLINE, Embase, and CAB-Abstract) were systematically searched (from database inception to March 2019) using the terms "grape," "raisins," "wine," "Vitis vinifera," "resveratrol," "catechins," "anthocyanins," "quercetin," and "proanthocyanidins" in combination with "cognition," "brain," "dementia," "Alzheimer's disease," "CNS," "memory" "depression" "Parkinson," and "learning." Results were refined for "human studies" and "controlled trials."

The search by title and abstract resulted in the identification of 557 publications on both positive and negative associations between grapes/grape derivatives and cognition functions. Only human studies were included in the systematic review. To ensure the highest standard of scientific evidence, randomized, placebo-controlled (possibly double-blind) trials were selected. In the case of wine, most papers reported epidemiological studies; they were only included in this review if the study design was considered scientifically sound. After removing duplicates such as papers assessing alcohol and irrelevant papers, the final number of publications included in the review was 26.

Results

Grapes as fresh fruit and juice

Importance of fresh grapes, raisins, and juice in the diet

Grape production has demonstrated a progressive global increase from 65 million tons in 2000 to 73.3 million tons in 2017 (OIV 2018). In particular, table grape production increased from 15.7 million tons in 2000 to almost 27 million tons in 2014. The main drivers of this market are the People's Republic of China and India (FAO-OIV 2016). A parallel increase in grape consumption has been observed worldwide from 15,111 to 26,208 million tons, corresponding to an increase of 73% from 2000 to 2014, with certain countries contributing more to this increase. The increase in table grape consumption in the same period exhibits notable differences in the five continents: +59% in Africa, +40% in America, +112% in Asia, +17% in Europe, and +142% in Oceania (FAO-OIV 2016).

Table 1. Studies performed in humans in which grape juice consumption was correlated with cognitive function/dementia.

Cohort and study details	Tested product	Objective of the study	Main outcomes	Ref.
35 healthy women (age 69.5 ± 7.0 y; 19 > 70 years) Trial comparing performance before and after intervention	400 mL/day of purple grape juice for 30 days. Juice was characterized for total phenol, catechin, and naringin levels	To verify the effect of chronic consumption of grape juice on cognitive functions	At Mini Mental State Examination (MMSE), cognitive performances were higher after supplementation with purple juice. The effect was more evident in > 70-year-old women.	Cañete da Costa et al. (2017)
20 healthy adults (7 M, 13 F; 21.1 ± 0.89 y) Randomized, double-blind placebo-controlled, crossover study	Active group: purple grape juice (200 mL) plus 30 mL of Schweppes black-currant flavor cordial. Placebo group: 200 mL white grape juice plus 10 mL blackcurrant flavor cordial and 20 mL cold water. Single serving	To study the effect of purple grape juice or sugar-matched control on cognitive functions and mood assessed by Computerized Mental Performance Assessment System	Purple grape juice acutely enhanced aspects of cognition and mood. No significant effects of juice were observed in memory measures. Potential mechanisms to be confirmed: Modulation of cerebral blood flow, gluco-regulation, and inhibition of monoamino oxidase activity.	Haskell-Ramsay et al. (2017)
12 subjects with mild cognitive decline (MCD) without dementia (8 M, 4 F; 78.2 ± 5.0 y) Three times/day for 12 weeks Randomized, double-blind, placebo-controlled study	Active group: Concord grape juice (*Vitis labrusca*) at the daily dose of 6-9 mL/kg bodyweight (bw) Placebo group: similar beverage without polyphenols Three times/day for 12 weeks	To assess the role of Concord grape juice in modulating cognitive functions by treatment (before and after) or placebo: 1. California Verbal Learning Test (verbal learning and retention); 2. Spatial Paired Associate Learning Test (Non-verbal memory); 3. Geriatric Depression Scale (mood)	A significant effect on verbal learning ($p = 0.04$) by Concord grape juice versus placebo was observed, indicating a possible enhancement of cognitive function in older adults with early memory decline. No appreciable effect on depressive symptoms.	Krikorian et al. (2010)
21 subjects with MCD (11 M, 10 F; 68-90 y) Randomized, double-blind placebo-controlled study	Active group: Concord grape juice (*Vitis labrusca*) at the daily dose of 6-9 mL/kg bw Placebo group: similar beverage without polyphenols 16 weeks	To assess the role of Concord grape juice in modulating neurocognitive functions by performing before and after treatment or placebo: • California Verbal Learning Test-II (memory function) • Functional magnetic resonance imaging (fMRI) (brain activation during working memory tests)	A significant enhancement in neurocognitive functions, reduced semantic interference on memory tasks, and greater activation in anterior and posterior regions of the right hemisphere were observed in Concord grape juice group versus placebo	Krikorian et al. (2012)
16 healthy mothers (40-50 years-old) of preteen children (<13 y), working for 30 h/week (stressful lifestyle) Randomized, placebo-controlled, crossover study	Active group: 355 mL/day of Concord grape juice (*Vitis labrusca*) containing 777 mg total polyphenols Placebo group: Energy drink similar for taste and appearance 12 weeks	To study the role of Concord grape juice in modulating neurocognitive functions by performing at 6 and 12 months: • Visual spatial learning test of immediate and delayed recall (verbal memory); • Visual spatial learning test of immediate and delayed recall (nonverbal spatial memory); • Rapid visual information processing (executive function); • Grooved Pegboard (psychomotor skill); • Tower of Hanoi (executive function); Driving performance	Significant improvements in immediate spatial memory and driving performance in active versus placebo group were noted. There was evidence of an enduring effect in the active group when moved to the placebo arm (cross-over).	(Lamport et al. 2016)
10 subjects with MCD (5 M, 5 F; 72.2 ± 4.7 y) Randomized, double-blind placebo-controlled study	Active group: 36 g of freeze-dried grape powder (from fresh red, green, and blue-black California grapes) in 237 mL of water Placebo group: polyphenol-free beverage Twice daily (72 g/day) for 6 months	To study the effects of grapes on cognitive functions by performing at start and 6 months: • A battery of neuropsychological tests (24 tests); Standardized Volume of Interest (sVOI) and statistical parametric mapping methods were applied to Positron	• Placebo versus active group: significant metabolic decline in sVOI of the right posterior cingulate cortex ($p = 0.01$) and left superior temporal cortex ($p = 0.04$) • Placebo group: significant decline in left prefrontal, cingulate, and left superior posterolateral temporal cortex ($p < 0.01$);	Lee, Torosyan, and Silverman (2017)

(*continued*)

Table 1. Continued.

Cohort and study details	Tested product	Objective of the study	Main outcomes	Ref.
		Emission Tomography (PET) scans to identify significant regional cerebral metabolic changes.	• Active group: stable brain metabolism; • Placebo-group: decline in brain regions generally affected in the early stages of Alzheimer's disease; Active group: no decline observed.	

To better define the role of this fruit as a source of compounds with potential beneficial bioactivity, estimation of the average intake of each population was required. Considering the grape intake per capita and per year, the first 10 countries for the highest consumption (in kg/inhabitant) were: Albania (56.7), Turkmenistan (43.3), Macedonia (40.3), Armenia (32.3), Uzbekistan (31.7), Turkey (23.2), Tajikistan (19.1), Afghanistan (18.0), Egypt (16.1), and Greece (14.5) (FAO-OIV 2016).

Several bioactive properties of grapes are conserved in its juice, unless processed at extremely high temperatures (Copetti et al. 2018). The beneficial effects of grape juice in humans are supported by numerous studies. Khadem-Ansari, Rasmi, and Ramezani (2010) reported an association between the consumption of red grape juice and an increase in high-density lipoprotein (HDL) cholesterol and reduction in homocysteine, which are both implicated in the modulation of cardiovascular diseases in healthy people. Moreover, a significant increase in plasma antioxidant capacity was reported in humans after concomitant consumption of grapes and apple juice (Yuan et al. 2011). The present state of the grape juice market and consumption is not easily evaluated due to the different technological processes applied (concentration, dilution, etc.) as well as their multiple destinations (inclusion in mixed juices, sweetener, etc.) (FAO-OIV 2016).

With regard to raisins, the method of drying grapes may differentially affect the phenolic content. The sun drying process (2-3 weeks long) generally reduces phenolic acids and flavonols by 90% and 60%, respectively, due to enzymatic oxidation. Alternatively, raisins can be briefly exposed to hot water and subsequently dehydrated for 20-24 hours. In some cases, grapes can be treated with SO_2 before the drying process to reduce polyphenol oxidase activation and preserve polyphenols. Raisins produced by both methods have demonstrated positive biological effects (Di Lorenzo et al. 2016; Williamson and Carughi 2010), but till now no correlation has been reported with cognitive function.

Grape juice and cognitive function

Studies performed in humans to investigate the effects of grape juice consumption on cognitive decline are listed in Table 1; for each trial, the experimental design, main characteristics, and results are summarized. The papers selected in this review present homogeneous results demonstrating positive effects of grape juices in modulating the early stages of cognitive decline (mild cognitive decline). All studies listed in Table 1 reported an improvement of cognitive functions in the active versus control group after both single dose (Haskell-Ramsay et al. 2017) and long-term (up to 6 months) supplementation (Cañete da Costa et al. 2017; Krikorian et al. 2012, 2010; Lamport et al. 2016; Lee, Torosyan, and Silverman 2017). The most encouraging results were obtained in tests that measured reaction times, verbal skills, degree of orientation, learning, and memory.

A positron emission tomography (PET) study by Lee, Torosyan, and Silverman (2017) demonstrated that subjects in the control group developed significant decline in metabolic activity of the right posterior cingulate cortex and left superior posterolateral temporal cortex, areas significantly affected in the early stages of Alzheimer's disease. These results suggest that grapes and their fresh derivatives may have a protective role against cognitive decline in humans.

Wine

Wine production and consumption

From 2000 to 2017, the global production of wine exhibited a fluctuating trend with a maximum of 298 mhL in 2004 and a minimum of 250 mhL as an estimate of the 2017 production. In the same period, global wine consumption demonstrated a stable trend close to 240 mhL, ranging from 228 in 2001 to 250 in 2017/2018 (OIV 2018). Italy, France, and Spain are the three most important producers of wine in the world, followed by USA, Argentina, China, Australia, Germany, and South Africa. In 2017, the largest consumers were Portugal (58.8 L per capita), France (50.7 L per capita), and Italy (44.0 L per capita) (OIV 2018).

Wine and cognitive function

The correlation between positive or negative effects of wine and cognition has been considered in different papers. A paper by Stockley indicated that light to moderate wine consumption was neuroprotective, although heavy or abusive alcohol consumption was neurotoxic (Stockley 2016). Several papers have examined the association between alcoholic beverage consumption and depression with conflicting results (Gea et al. 2012, 2013; Wang and Patten 2001). As the association between depression and dementia is far from conclusive (for a review, see Muliyala and Varghese 2010), depression will not be considered in this review. The most significant papers considering wine consumption and dementia are summarized in Table 2. For ethical reasons, clinical trials with alcoholic beverages cannot be performed.

Table 2. Studies performed in humans in which wine consumption was correlated with cognitive function/dementia.

Cohort and study details	Beverages included	Objective of the study	Main outcomes	Ref.
5,033 stroke-free people (2,227 M; 2,806 F; age 25-85 y) Longitudinal population-based study	Consumption of wine, beer, or spirits for 14 days: None $<$ 1 glass 3-4 glasses $\geq$ 5 glasses	Impact of consumption of different alcoholic beverages on cognitive function after 7 years of follow-up. Tests performed: verbal memory test, digit-symbol coding test, and tapping test	Moderate wine consumption was independently associated with improved performance on all cognitive tests in both men and women. No significant improvement was observed with beer or spirits.	Arntzen et al. (2010)
589 multi-ethnic community residents in New York. (130 M; 265 F; Age $>$ 60 years; mean age 80.1 $\pm$ 5.5 y) Cross-sectional study	Consumption of wine, beer, or liquor over the prior year: • None (n= 409) • Light to moderate: 0-30 drinks/month for females; 0-60 drinks/month for males (n = 180) • Heavy: $>$ 30 drinks/month for females: $>$ 60 drinks/month for males) (n = 14) 1 drink = 10 g alcohol equiv. 113 g wine	To evaluate the association between alcoholic beverages and brain structure measured by magnetic resonance imaging (MRI)	Compared to non-drinking, light-to-moderate total alcohol (b = 0.007, p = 0.04) or wine (b= 0.008, p = 0.05) intake, but not beer or liquor intake, was associated with larger total brain volume (TBV). Further analysis showed a dose-response association between alcohol (p-trend = 0.03) or wine (p-trend = 0.006) and TBV. Overall, alcohol intake was not associated with white matter hyperintensity volume (WMHV) or brain infarcts.	Gu et al. (2014)
259 subjects (age: >60 y) with deterioration in cognitive functions Longitudinal study Population-based study	3-4 glasses/day × 3 years No detail on types of wine consumed	To assess the relationship between wine and tobacco consumption and cognitive changes using an extensive battery of cognitive tests: attention, primary memory, secondary memory, implicit memory, visuospatial ability, and language	Moderate wine consumption (3-4 glasses per day) was associated with a fourfold reduction in the risk of Alzheimer's disease (OR = 0.26) in non-institutionalized subjects. Wine consumption was associated with an increased risk of decline over time in attention (p = 0.06) and secondary memory (p = 0.09). No clear combined effect of smoking and drinking was observed, although smoking increased the risk of decline in language performance when adjusted for wine consumption.	Leibovici et al. (1999)
4,615 subjects without dementia at baseline (>65 y) Longitudinal population-based study	Questionnaire reporting risk factors for Alzheimer's disease, including wine consumption	Role of risk factors on the induction of Alzheimer's disease (AD)	At 5 years after enrollment: 194 AD cases, 3,894 subjects cognitively normal. Increasing age, low education, and napolipoprotein E e4 allele were significantly associated with increased risk of AD. Use of non-steroidal anti-inflammatory drugs, alcoholic drink consumption, coffee consumption, and physical activity were associated with a reduced risk of AD. Odds ratio were 0.68 for all alcoholic drinks; 0.49 for wine; 0.78 for spirits; and 0.84 for beer.	Lindsay et al. (2002)
980 community subjects without dementia at baseline with and without APO-ε4 allele (age $\geq$ 65 y) Prospective study	Weekly consumption of wine, beer, liquor: • 1-3 serving/month • 1 serving/week • 1-2 serving/week • 5-6 serving/week • 1 serving/day • 2-3 serving/day • 4-5 serving/day • 6 serving/day (1 serving of wine = 11 g alcohol)	Prospective relationship for 4 years of alcoholic beverage consumption and risk of AD disease and dementia associated with stroke	Light to moderate intake (0.1-36 g alcohol/day, up to three servings/day) of wine was associated with a lower risk of AD in elderly people without APO-ε4 allele. Intake of liquor, beer, and total alcohol was not associated with lower risk of AD.	Luchsinger et al. (2004)

(*continued*)

Table 2. Continued.

Cohort and study details	Beverages included	Objective of the study	Main outcomes	Ref.
1,462 women (age 38-60 y) Prospective study	Frequency of alcohol consumption: • Never • Not in the last 10 years • Not in the last year • Monthly • Weekly • Several times/week Daily	To evaluate the association between different types of alcoholic beverages and 34-year incidence of dementia.	Wine was protective for dementia (OR = 0.6) and the association was strongest when wine was the only beverage consumed (OR = 0.3). The protective effect of wine was stronger in smokers. Consumption of spirits at baseline was associated with an increase in dementia (OR = 1.5).	Mehlig et al. (2007)
373 subjects with incident dementia (age 77.8 ± 5.5 y) and 373 controls (age 77.5 ± 5.2 y) Prospective study	Weekly consumption of wine, beer, or spirits: • < 1 drink, • 1 to 6 drinks, > 7 drinks	Prospective relationship for 6 years of alcoholic beverage consumption and risk of dementia.	The lowest odd ratios of dementia were in old adults who consumed: > 7 drinks/weekly of wine (0.62); 1 to 6 of beer (0.74); <1 of liquor (0.84). A higher consumption of beer and spirit increased the odds ratio.	Mukamal et al. (2003)
2,273 community residents without dementia at baseline (age ≥ 65 y) Prospective study	Wine consumption: • None (< 1 drink/week) • Mild (2 drinks/week to 2 drinks/day • Moderate (3-4 drinks/day) Heavy (≥ 5 drinks/day)	Prospective relationship for 3 years of wine consumption and risk of dementia.	The lowest risk of incident dementia was observed in moderate wine consumers (OR = 0.19, $p < 0.01$) and that of Alzheimer's disease (OR = 0.28, $p < 0.05$)	Orgogozo et al. (1997)
5,395 subjects (age ≥ 55 y) without dementia at baseline Prospective study 6 years	Consumption of wine, beer, liquor, or fortified wine: • None • < 1 drink/week • 1 to 7 drinks/week • 1 to 3 drinks/day > 4 drinks/day	Association between alcohol consumption and risk of dementia.	Light-to-moderate drinking (one to three drinks per day) was significantly associated with a lower risk of any dementia (hazard ratio 0.58), Alzheimer's disease (0.72), and vascular dementia (hazard ratio 0.30). No evidence of different dementia risk in relation to the alcoholic beverage consumed.	Ruitenberg et al. (2002)
11,102 women from the Nurses' Health Study (age 70-81 y) Prospective study 2 years	Alcohol intake (as wine, beer, or liquor)	To assess cognitive scores with the level of alcohol consumption (<5 up to 30 g/day)	Moderate drinkers (< 15 g/day of alcohol) demonstrated better cognitive scores than that of nondrinkers and a reduced risk of decline in performance over a 2-year period (RR = 0.85). No statistically significant difference was observed between data due to the different type of alcoholic beverages.	Stampfer et al. (2005)
83 subjects with dementia and 1,626 nondemented controls (age ≥ 65 y) Case-control nested in a cohort study	Intake of alcohol, type of alcoholic beverage in the previous 15 years	Effect of alcohol and wine on risk of dementia	Average weekly total alcohol intake had no significant effect on risk of dementia. Monthly and weekly intake of wine was significantly associated with a lower risk of dementia. For beer and spirits, only a monthly intake of beer was associated with an increased risk. Odds ratio for wine were: monthly intake 0.56; weekly intake 0.36; daily intake 0.49.	Truelsen, Thudium, and Grønbaek (2002)

As such, the selected studies were conducted using epidemiological approaches. All studies supported positive effects of light to moderate wine consumption on dementia, although crucial details were often lacking; for example, some studies did not discriminate between the consumption of white and red wines or their alcoholic content.

Generally speaking, light to moderate wine consumption seems to be associated with an improvement in cognitive performance (Arntzen et al. 2010; Leibovici et al. 1999) and a reduced risk of developing any dementia (Lindsay et al. 2002; Luchsinger et al. 2004; Mehlig et al. 2007; Mukamal et al. 2003; Orgogozo et al. 1997; Ruitenberg et al. 2002; Truelsen, Thudium, and Grønbaek 2002). The effects of wine were typically greater than those obtained with an equivalent quantity of alcohol from other alcoholic beverages, such as beer or spirits (Arntzen et al. 2010; Gu et al. 2014; Lindsay et al. 2002; Luchsinger et al. 2004; Mehlig et al. 2007; Mukamal et al. 2003; Truelsen, Thudium, and Grønbaek 2002).

Alcohol and other active molecules in wine

Alcohol and cognitive functions

Studies have reported that alcohol consumption was associated with effects on cognitive function; a subset of these studies distinguished the type of beverage used, whereas others did not. In the studies assessing the effects on cognition according to type of beverage (wine, beer, or spirits) (Panza et al. 2009), wine was generally more effective than other alcoholic beverages for improving cognitive performance.

A review of papers considering alcohol consumption per se by Panza et al. (2009) indicated that the current evidence for protective effects of light to moderate consumption of alcohol on cognitive decline (including dementia) was suggestive only. Indeed, several papers considering alcohol per se (mainly defined as number of drinks) showed positive cognitive effects in abstainers compared to those in light to moderate drinkers (Espeland et al. 2005; Ganguli et al. 2005; Zuccalà et al. 2001; Rehm et al. 2019), but the quality of the studies did not always permit definitive conclusions to be drawn or to identify a dose of alcohol that could be considered neuro-protective without associated negative effects. Moreover, in such "unspecified" approaches, bias may be more probable in terms of effects of habits (alcohol with or without a meal), lifestyle, or other factors that could contribute to the improvement or deterioration of cognitive functions.

Phenolic compounds and cognitive functions

Since the first report on the "French paradox," wine has been studied widely. Particular interest has been paid to the role of phenolic compounds in providing beneficial health effects, with special emphasis on resveratrol. Wine-derived resveratrol has been frequently associated with a reduced risk of cardiovascular diseases, in a J-shaped relationship. However, the data obtained from *in vitro* studies are being reconsidered, as a consequence of the low bioavailability of resveratrol (Stockley et al. 2012). Data from studies assessing the efficacy of phenolic compounds on cognitive performance are listed in Table 3. Most studies on resveratrol have reported positive effects on cognitive function, but the doses used (150-1000 mg/day) are far from the usual intake associated with food and wine consumption. The content of resveratrol in grapes and wines has been reported by different authors; according to a review by Weiskirchen and Weiskirchen (2016), these levels are: 92-1604 and 59-1759 μg/kg fresh weight for red and white grapes, respectively, and 0.36-1.97, 0-1.09, and 0.29 mg/L for red, white, and rosé wines, respectively. As such, the lowest active level of resveratrol (150 mg/day) reported by Evans, Howe, and Wong (2016, 2017) would be reached with an intake of approximately 85 kg/day of grapes or at least 76 L/day of red wine and more than 130 L/day of white or rosé wines.

Discussion

The studies examined in this review suggest the following:

- Consumption of 200-500 mL/day of grape juice is correlated with positive effects on cognitive performance;
- Light to moderate wine consumption (one to four glasses/day, in which the effective volume was not always defined) is associated with improved cognitive performance in older individuals compared to that in abstainers with a lower risk of dementia, especially Alzheimer's disease;
- Some studies indicate that beneficial effects on cognitive performance are independent of the type of alcoholic beverage consumed, which is in contrast to most studies where better performance was associated with wine consumption; and
- When searching for bioactive molecules involved in the protective effects of wine on cognitive performance, most authors performed studies with polyphenolic compounds, especially resveratrol. The studies included in this review suggest that, given the high doses required and low bioavailability of resveratrol, this compound should be considered as only one of the possible effectors of beneficial outcomes on the central nervous system.

It is important to highlight that wine contains a complex mixture of molecules, the total activity of which can be represented by the sum of the activity of single compounds, synergistic, or antagonistic effects. Studies performed *in vivo* or *in vitro* with purified molecules have limited biological significance, and their extrapolation to human *in vivo* settings may lead to erroneous conclusions.

Finally, it should be kept in mind that the number of papers identified was limited. It is therefore essential to consider the observations reported in this review critically and be aware that further observational studies are necessary for confirmation of bioactivity.

Table 3. Studies performed in humans in which the intake of active compounds from wine was correlated to cognitive function/dementia.

Cohort and study details	Tested product	Objective of the study	Main outcomes	Ref.
2,574 participants (mean age at evaluation = 66 y) Cohort study	Total polyphenol intake: • Males: 1.28 ± 0.51 • Females: 1.12 ± 0.48	To assess the role of polyphenol supplementation in improving cognitive functions tested by phonemic semantic fluency, the RI-48 Cued Recall test, the Trail Making test, and Forward and Backward Digit Span.	High intake of specific polyphenols, including flavonoids and phenolic acids, could play a role in maintaining verbal memory, which is frequently impaired in pathological brain aging.	Kesse-Guyot et al. (2012)
32 healthy, community-dwelling, overweight old adult (age 79 ± 14 y, 65-93 y) Double-blind, Phase IIa randomized, placebo-controlled trial	Three groups: • Placebo • 300 mg/day resveratrol • 1000 mg/day resveratrol	To study the effect of 90 days of chronic treatment with resveratrol on cognitive function Cognitive functions were assessed with a battery of tests	Supplementation with resveratrol at a dose of 1000 mg/day selectively improved psychomotor speed when compared to supplementation with placebo or 300 mg/day of resveratrol. No further significant effects on other cognitive domains in older adults were observed.	Anton et al. (2018)
80 post-menopausal women (age: 61.5 ± 1.1 y; 45-85 y) Randomized placebo-controlled intervention trial	Placebo or two capsules/day of resveratrol (2 × 75 mg) for 14 weeks	Effect of chronic supplementation with resveratrol on cerebrovascular function, cognition, and mood in post-menopausal women.	Resveratrol improved cerebrovascular responsiveness (17%) to both hypercapnic ($p = 0.010$) and cognitive stimuli ($p = 0.002$). Significant improvements in performance of cognitive tasks related to verbal memory ($p = 0.041$) and overall cognitive performance ($p = 0.020$) were observed. A trend for improvement in mood was observed but this did not reach statistical significance.	Evans, Howe, and Wong (2017); Evans, Howe, and Wong (2016)
22 healthy adults (age 24.8 y; 21-29 y) Randomized, placebo-controlled, double-blind, crossover study	Placebo or 2 doses of resveratrol (250 and 500 mg) on separate days	To assess the effect of resveratrol on cognitive performance and localized cerebral blood flow variables.	Resveratrol dose-dependently increased cerebral blood flow measured during task performance. Cognitive functions were not affected.	Kennedy et al. (2010)
40 participants with mild cognitive impairment (21 F; age 50-80 y) Randomized, double-blind interventional study	Placebo or resveratrol (200 mg/day) for 26 weeks	To evaluate the effect of resveratrol on neuropsychological testing for assessing learning and memory.	No significant differences in memory performance.	Köbe et al. (2017)
119 patients with mild-moderate Alzheimer's disease Randomized, placebo-controlled, double-blind, multi-site study	Placebo or resveratrol 500 mg orally once daily (with a dose escalation by 500-mg increments every 13 weeks, ending with 1,000 mg twice daily). 52 weeks	To evaluate if resveratrol regulated neuro-inflammation and induced adaptive immunity in AD.	Markers of neurodegenerative disease and metalloproteinase (MMP) in cerebrospinal fluid (CSF) and plasma were measured. At 52 weeks, resveratrol-treated group showed several changes in CSF and plasma biomarkers, indicating that resveratrol modulated neuroinflammation and induced adaptive immunity.	Moussa et al. (2017)
60 healthy subjects (51 F; age 18-29 y) Randomized, placebo-controlled, double-blind, parallel-groups study	Placebo or resveratrol 500 mg with 10 mg piperine for 28 days	To assess the role of resveratrol supplementation on performance of cognitively demanding tasks (serial subtractions, rapid visual information processing, and 3-back)	The only cognitive improvement at day 28 was a beneficial effect of resveratrol on the accuracy of the 3-back task, and subjective rating of "fatigue" was significantly lower.	Wightman et al. (2015)
46 healthy adults (18 F; age: 50-80 y; BMI: 25-30 kg/m^2) Randomized intervention/ control study	Placebo or 200 mg/day resveratrol for 26 weeks	To assess if supplementation with resveratrol would enhance memory performances	Before and after placebo/RES, subjects underwent memory tasks and neuroimaging. Participants receiving RES showed a significant improvement in retention of words over 30 min ($p = 0.038$) that correlated with increased hippocampal functional connectivity.	Witte et al. (2014)

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Disclosure statement

Authors have no conflict of interests to declare.

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