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The impact of Champagne wine consumption on vascular and cognitive functions

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Running title: Health effects of Champagne wine

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Abstract

Epidemiological evidence suggests an inverse correlation between wine consumption and the incidence of cardiovascular and neurodegenerative disorders. Although white wines are generally low in polyphenol content as compared to red wines, Champagne wine has been shown to contain relatively high amounts of phenolic acids that may exert protective cellular actions *in vivo*. Recent evidence suggest that Champagne phenolic acids may express their beneficial properties through their interaction with cellular signaling pathways and related machinery that mediate cell function under both normal and pathological conditions. In this review we aim to provide an overview of the role that Champagne consumption plays in maintaining cardiovascular health and cognitive function. We discuss epidemiological data, human intervention study findings, as well as animal and *in vitro* studies in support of these actions and we consider how their biological mechanisms at the cellular level may underpin their physiological effects. Together, these data indicate that polyphenols present in Champagne may hold cardioprotective and neuroprotective potential in delaying the onset of degenerative disorders.

Introduction

Despite the well-established harmful effects of heavy alcohol intake [1], epidemiological studies have reported that a low to moderate intake of wine (1-2 glasses per day), may reduce the risk of cardiovascular disease and cognitive impairment [2-5]. In particular, a J-shaped relationship between the amount of wine consumed and the risk of cardiovascular disease, such as hypertension, has been previously described [6-7]. These observations have been further substantiated by series of large scale, cross sectional and prospective studies, which have almost universally demonstrated a strong inverse correlation between wine consumption and the risk of cardiovascular disease [8]. In addition, incidence data from the so-called Personnes Agees Quid [2] study demonstrated that people drinking three to four glasses of wine per day had an 80% decreased incidence of dementia and Alzheimer's disease three years later, compared to those who drank less or did not drink at all [4]. Such protection is believed to be in large part attributable to the intake of specific polyphenols present in great quantity in wine. In particular, flavonoids, a subclass of polyphenols, have been ascribed to exert anti-inflammatory properties [9] and to modulate signalling pathways that regulate nitric oxide production [10] and neuronal survival [11]. As such, there is a great interest in the potential of regular and moderate wine consumption to counteract vascular ageing and to delay the onset of neurological disorders, such as Alzheimer's disease and dementia [12-14].

Although red wines contain high levels of flavonoids and other phenolics relative to white wines [15], Champagne wine is relatively rich in phenolic compounds (Table 1) such as hydroxybenzoic acids, hydroxycinnamic acids (and their tartaric derivative esters), phenolic alcohols and phenolic aldehydes [16-17]. The phenolic composition varies with a wide range of factors, including species, variety, season, growing conditions, and processing practices [18]. The increased levels of phenolic compounds in Champagne wine compared to other white wines, derive predominantly from the two red grapes, Pinot Noir and Pinot Meunier, which are used in its production along with the white grape Chardonnay [19]. Moderate Champagne consumption has been shown to exert a number of effects *in vivo*, including modulation of peripheral serotonin and dopamine release [20] and to increase plasma vitamin A concentration [21]. In addition, Champagne polyphenols have been shown to protect primary neuronal cells against peroxynitrite-induced injury [16], a physiologically relevant oxidizing species which has been implicated in vascular wall pathology [22] and neurodegeneration [23]. As such, Champagne wine

can deliver significant quantities of phenolic compounds capable of mediating changes in cardiovascular health and cognitive performance. In this manuscript, we will review the effects of Champagne wine on vascular health and cognitive functions and we will briefly describe their intracellular targets underlying their protective effects.

Champagne wine and vascular health

Cardiovascular disease (CVD), in particular coronary heart disease and stroke, is a major cause of mortality in the Western countries. Epidemiological and human intervention studies have suggested that a daily and moderate consumption of red or white wine is associated with a lower incidence of CVD [24]. Many of the effects of red wine are compatible with the action of wine-derived polyphenols on endothelium-derived nitric oxide ($NO^{\bullet}$) production [25], whilst white wine effects may result from the synergistic actions of polyphenols and other phenolic constituents on LDL oxidation and platelet function [26]. Moderate red wine intake has also been associated with a reduced coronary artery disease mortality [27-28], through its ability to improve endothelial function [29], to induce an acute increase in endothelium-dependent flow-mediated dilatation [30-31] and to inhibit endothelin-1 synthesis [32-33].

In particular, these biological effects have been linked to flavonoids, hydroxycinnamates and phenolic acids present in great concentration in these wines [34]. Following consumption, nanomolar quantities of flavonoids and other polyphenols enter the circulation [34-35] where they may act to improve nitric oxide bioavailability and/or inhibit endothelin-1 (ET-1) [36-37]. In support of this statement, the cardioprotective effects of white wines have been reported [38-39], although they contain lower concentration of flavonoids and induce reduced vascular effects when compared to red wines [40-41]. Moderate Champagne wine consumption has also been shown to exert a number of effects *in vivo*, effecting peripheral serotonin and dopamine release [20] and increasing plasma vitamin A concentration [21]. In addition, Champagne wine polyphenols have also been shown to protect cells against injury induced by peroxynitrite [16], a physiologically relevant oxidizing species which has been implicated in vascular wall pathology [22, 42].

Recently we reported that moderate consumption of Champagne wine, but not a control matched for alcohol, carbohydrate and fruit-derived acid content, improved microvascular blood flow and vascular responsiveness in healthy volunteers [43]. By using Laser Doppler and iontophoresis (LDI), we

demonstrated that absorbed hydroxycinnamates and their metabolites influenced vascular function (Figure 1) by inducing an acute change in endothelium-independent vasodilatation at 4, 6 and 8 h post consumption, whilst the control did not induce any changes in vascular reactivity [43]. These effects were accompanied by an acute decrease in the concentration of matrix metalloproteinase MMP-9 and a significant decrease in plasma levels of oxidising species. These biological effects were paralleled by a urinary excretion of phenolic metabolites. In particular, the mean total excretion of hippuric acid, protocatechuic acid and isoferulic acid were all significantly greater following the Champagne wine intervention compared to control intervention, suggesting that they may be responsible for the observed vascular activity [43]. Together, these data suggest that consumption of Champagne wine phenolic acids may enhance microvascular blood flow for a sustained period of time after consumption, through the maintenance of local nitric oxide levels. Altogether, these results suggest that Champagne wine has some short-term effects on the blood vessels that are not solely caused by its alcohol content. However, it would be premature to extrapolate the "proxy" outcomes of blood vessel dilation to clinical outcomes, such as heart disease.

Champagne wine and cognitive function

Polyphenols-rich foods/beverages have received much attention with regards to their neuroprotective effects [44], including a potential to protect neurons against neurotoxin-induced injury [45-46], to suppress neuroinflammation [47], and to promote memory and learning [48-51]. Despite the well-established harmful effects of heavy alcohol intake [1], epidemiological data suggest that moderate wine consumption may reduce the incidence of age-related dementia, including Alzheimer's disease [4, 52-53]. As such, there is an interest in the potential of regular, moderate wine consumption to counteract normal brain ageing and to improve memory and learning, through its potential to deliver relatively high amounts of flavonoids and phenolic acids [12-13]. Animal data support these findings and indicate that moderate consumption of red wine attenuates Aβ-neuropathology in a mouse model of Alzheimer's disease [54]. In a recent rodent study we reported that Champagne wine is also capable of enhancing spatial working memory (without altering motor performance) in aged animals [55]. In contrast, moderate alcohol intake failed to induce spatial memory changes. These observations are in agreement with those observed following long-term red wine intake in a similar model of hippocampal-

dependent spatial memory [56]. The effects of Champagne on spatial memory (Figure 2) were paralleled by a number of changes in hippocampal and cortical protein expression, which may explain performance on spatial memory tasks. Targeted protein arrays indicated that Champagne induced the differential expression of a number of hippocampal and cortical proteins involved in signal transduction, neuroplasticity, apoptosis and cell cycle regulation [55]. Most notably, we observed the differential modulation of a range of proteins, such as brain-derived neurotrophic factor (BDNF), cAMP response element-binding protein (CREB), p38, dystrophin, 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase), mammalian target of rapamycin (mTOR), B-cell lymphoma2-extra large protein (Bcl-xL) in response to Champagne supplementation compared to the control drink, and the modulation of mTOR, Bcl-xL and CREB in response to alcohol supplementation [55].

CNPase is a myelin-associated enzyme that constitutes around 4% of total CNS myelin protein, and is thought to undergo significant age-associated changes [57], and is reduced in Alzheimer's disease and Down's syndrome patients [58]. Furthermore, Champagne-induced hippocampal increases in the cytoskeletal associated protein, dystrophin, may be beneficial as a lack of this protein in the hippocampus has been associated with impaired cognitive function [59], spatial memory [60] and long-term potentiation [61]. Indeed, patients lacking dystrophin in the hippocampus and neocortex (due to mutation in the dystrophin gene) display a range of cognitive deficits [62]. Intervention with the phenolic rich Champagne also led to the increased expression of a range of 'other' cytoskeletal proteins, including plakoglobin (γ-catenin), spectrin, calponin, cytokeratin pep4 and pep19, myosin Va and Focal Adhesion Kinase [55]. Such proteins facilitate complex neuronal network formation in the brain and operate with neuronal membrane proteins (e.g., ion channels, scaffolding proteins, and adaptor proteins) at sites of synaptic contacts to regulate synaptogenesis and coordinate synaptic strength [63-64]. Our data therefore suggest that smaller phenolics such as gallic acid, protocatechuic acid, tyrosol, caftaric acid and caffeic acid, in addition to flavonoids, are capable of exerting improvements in spatial memory via the modulation in hippocampal signalling and protein expression.

Mechanisms of action

Champagne wine consumption has been observed to improve acute vascular function [43], in a similar manner to that of red wine [65-66]. Champagne wine and specifically its phenolic metabolites may affect

vascular function by improving local nitric oxide bioavailability by two potential mechanisms. Firstly, they may increase the local half-life of $NO^{\bullet}$ via reaction with reactive oxygen species, such as superoxide [67]. Secondly, phenolic metabolites, such as those excreted post champagne consumption, may mimic NADPH oxidase inhibitors [68], such as apocynin thereby reducing the cellular production of superoxide and increasing the half-life of $NO^{\bullet}$, without any change in the rate of $NO^{\bullet}$ synthesis [69]. Furthermore, tyrosol, caffeic acid, and gallic acid, phenolic compounds found at relatively high concentrations in Champagne, have been shown to potently inhibit peroxynitrite-induced cellular injury at physiologically relevant concentrations (0.1 to 10 μM) [16], whilst nanomolar levels of tyrosol, caffeic acid and *p*-coumaric acid protect cortical neurons against 5-S-cysteinyl-dopamine induced injury [70]. Indeed, the level of protection induced by these phenolics was equal to, if not greater than, that observed for similar concentration of the flavonoids, (+)-catechin, (-)-epicatechin and quercetin [70]. The hydroxycinnamate, caffeic acid, has also been shown to be neuroprotective, counteracting inflammatory injury induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by decreasing the production of a number of inflammatory cytokines, down-regulating the expression of iNOS, COX-2 and glial fibrillary acidic protein and lowering the production of NO and PGE_2 [71]. In addition, caffeic acid phenethyl ester may protect cerebellar granule neurons against glutamate-induced neuronal death via inhibition of p38 phosphorylation and caspase-3 activation [72] and significantly prevents hypoxic-ischaemic-induced neonatal rat brain damage in the cortex, hippocampus and thalamus [73]. Indeed, for any polyphenol to exert direct neuroprotective actions they must also undergo permeation of the blood brain barrier (BBB), something that has been reported for both flavonoids and hydroxycinnamates [74]. However, whilst the ability of flavonoids to cross the BBB is believed to be dependent on lipophilicity, small phenolics are thought to transverse the BBB via amino acid transporters, such as has been reported for 4-ethylcatechol [75]. Furthermore, caffeic acid shares structural similarities with L-DOPA and, as such, may undergo BBB transport via catecholamine transporter systems.

It is well reported that flavonoids may exert cellular action by interacting with the PI 3-kinase, Akt/PKB and MAP kinase signalling pathways [11]. Smaller phenolics, such as caffeic acid or tyrosol, may also participate in cellular interactions of this nature [76], or may directly react with toxic intermediates, as has been observed for *p*-coumaric acid [77]. All together, these processes act to maintain the number

and quality of synaptic connections in the brain, a factor known to be essential for efficient long term potentiation (LTP), synaptic plasticity and ultimately the efficient working of memory.

Conclusions

The development of cardiovascular and cognitive impairment is a complex process that begins even in the absence of a symptomatic disease [78]. Human clinical trials and animal studies have identified polyphenol-rich foods and beverages as being capable of delaying the onset of age-related vascular and cognitive impairment [44, 79-83]. Polyphenols present in such foods have been postulated to evoke protection through the actions of absorbed flavonoids and their metabolites at the cellular level, enhancing existing endothelial and neuronal function and/or stimulating cell regeneration [44, 79, 83-84]. Although antioxidant mechanisms cannot be excluded [85], recent data sets suggest that such effects are mediated by their ability to modulate endothelial and neuronal signalling [86-87], to stimulate neurotransmitter release [88], to increase vascular blood flow [89] and even to stimulate hippocampal neurogenesis [90]. We previously provided evidence that moderate Champagne wine consumption induces improvements in vascular health and cognitive function, dependent on the potential of Champagne phenolic compounds to modulate endothelial and neuronal cell signalling [70, 91], and to enhance blood flow *in vivo*. Altogether, these results suggest that Champagne wine consumption holds a potential to limit neurodegeneration and is capable of vascular improvements [43, 55, 92]. However, the pharmacological potential of these natural compounds still remains to be translated in humans in clinical conditions. The challenge ahead therefore, is to proceed cautiously until rigorous randomized controlled clinical trials have been undertaken to determine whether Champagne wine polyphenols and/or their *in vivo* metabolites have efficacy in patients suffering from cardiovascular episodes or from loss of neuronal function.

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Table 1. Phenolic compounds in Champagne wine

Phenolic compounds	(mg/L)
gallic acid	0.66
protocatechuic acid	0.50
tyrosol	8.46
caftaric acid	5.01
caffeic acid	1.43
total phenolics	16.06

Figure legends

Figure 1. Postulated effects of Champagne wine phenolics on the cardiovascular system

Figure 2. Postulated effects of Champagne wine phenolics on memory and cognition

List of Figures

Figure 1.

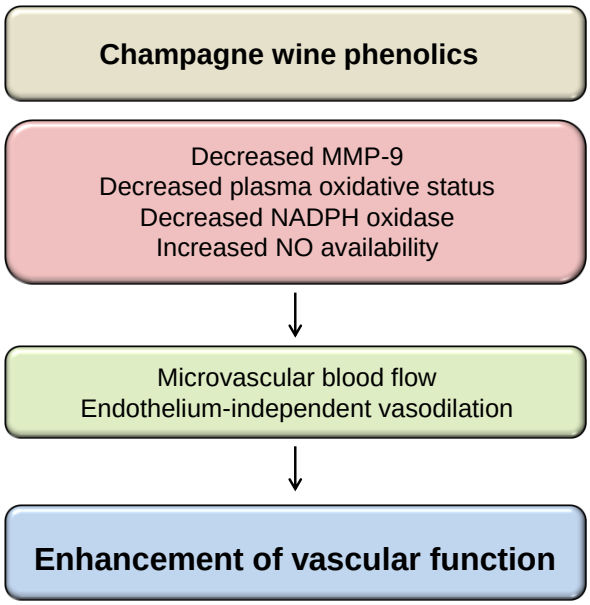
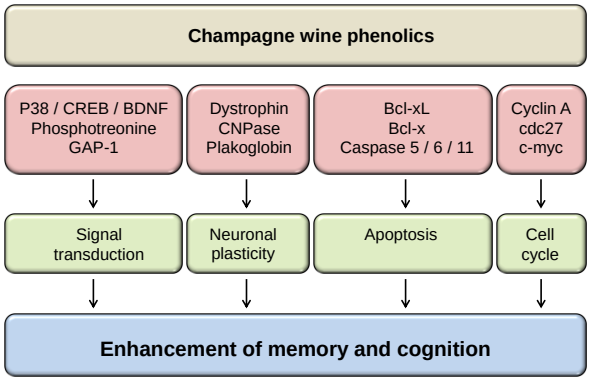


Figure 2.


Champagne wine phenolics
P38 / CREB / BDNF
Phosphotreonine
GAP-1
Dystrophin
CNPase
Plakoglobin
Bcl-xL
Bcl-x
Caspase 5 / 6 / 11
Cyclin A
cdc27
c-myc
Signal transduction
Neuronal plasticity
Apoptosis
Cell cycle
Enhancement of memory and cognition