[Frontiers in Bioscience E4, 1505-1512, January 1, 2012]

Health benefits of wine and alcohol from neuroprotection to heart health

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TABLE OF CONTENTS

1. ABSTRACT

Controversy is common during efforts to define the role of nutrition in health, but few modern reflections of such controversy are as vivid as the debate over wine. There exists no query that chronic alcohol abuse, a leading worldwide problem, causes neuronal dysfunction and brain damage. However, various epidemiologic studies in recent years have indicated that in comparisons with abstainers or never drinkers, light/moderate alcohol/wine consumers have lower risks of age-dependent cognitive decline and/or dementia, including Alzheimer's disease (AD) Neurodegenerative diseases such as AD and Parkinson's (PD) diseases are defined by a progressive neuronal dysfunction and an ensuing behavioral dysfunction. Epidemiologic studies from numerous disparate populations reveal that individuals with the habit of daily moderate wine consumption enjoy significant reductions in all-cause and particularly cardiovascular and neurodegenerative mortality when compared with individuals who abstain or who drink alcohol in excess. Apart from the alcohol present in the wine, other trace compounds and polyphenolic compounds such as resveratrol naturally present in wine and grapes also exert neuroprotective and cardioprotective activities.

2. INTRODUCTION

There is an English saying **"**Wine...is one of the noblest cordials in nature" by John Wesley, English founder of Methodism, (1703-1791) Ancient Sayings of Wine include "Infants should be bathed for long periods in warm water and given wine diluted is not at all cold. Wine should be of a kind which is at least likely to cause distension of the stomach and wind. This should be done to prevent the occurrence of Convulsions and to make the children grow and get good Complexion". The main point in favor of a strong wine "it passes more easily to the bladder than the other kind of and is diuretic and purgative; it is always beneficial for acute diseases". These are good points to note about the beneficial properties of wine said by the predecessor Hippocrates in Regimen for Health and Regimen for Acute diseases. Wine has played an important role in societal development for thousands of years. Hippocrates (450 to 370 BC) was said to be the first physician to understand the healing power of wine.

Wine is a product of the natural fermentation of the juices of grapes and other fruits, such as peaches, pears, plums, and apples, by the action of yeast cells. This biochemical conversion of juice to wine occurs when the

Table 1. Non-polyphenol composition of wine

Percentage by Volume	Ingredients
86	Water
12	Alcohol (ethyl alcohol)
1	Glycerol
0.4	Organic acids, of which: 0.20% Tartaric acid 0.15% Lactic acid 0.05% Succinic acid (plus traces of malic acid citric acid)
0.2	Carbohydrates (Unfermentable sugar)
0.2	Minerals (of which): 0.01% Chloride 0.02% Magnesium 0.075% Potassium 0.05% Phosphate 0.005% Silicic acid 0.02% Sulphate Traces of Aluminium, boron, copper, iron, molybdenum, rubidium, sodium, zinc
0.1	Tannin and color pigments
0.045	Volatile acids (mostly acetic acid)
0.025	Nitrogenous compounds: 0.01% Amino acids (arginine, glutamic acid, proline, serine, threonine, and others) 0.015% Protein and other notrogenous matter (humin, amide, ammonia, and others)
0.025	Ester (mostly ethyl acetate, but traces of numerous others)
0.004	Aldehydes (mostly acetaldehyde, some vanillin, & traces of others)
0.001	Higher alcohols (minute quantities of amyl plus traces of isoamyl, butyl, isobutyl, hexyl, propyl, and methyl may be present)
Traces	Vitamins (thiamine, riboflavin, pyridoxine, pantothenic acid, nicotinic acid, and scobic acid)

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yeast cells enzymatically degrade the fruit sugars fructose and glucose first to acetaldehyde and then to alcohol.

Grapes containing 20-30% sugar concentration will yield wine with an alcohol content of approximately 10-15%. Also present in grapes are acids and minerals whose concentrations are increased in the finished product and that are responsible for the characteristic tastes and bouquets of different wines. For red wine, the crushed grapes must be fermented with their skins to allow extraction of their color into the juice. White wine is produced from the juice of white grapes (1). Many beverages contain alcohol in varying amounts, necessitating standardization of the quantity of alcohol contained in various drinks. In general, the amount of absolute alcohol in grams is determined by the number of beverages consumed per day times the amount of alcohol in each beverage. In general, a 12-ounce bottle of beer, a 4-ounce glass of wine, and a 1 1/2-ounce shot of 80-proof spirits all contain the same amount of alcohol (one half ounce) Each of these is considered a "drink equivalent" (2).

3. CHEMISTRY OF WINE

Wine has a multifaceted chemistry in its composition. Its production takes place on every continent, and its chemical composition is profoundly influenced by enological techniques, the grape cultivar from which it originates, and climatic factors. Wine includes more than 300 components in it, adding up to alcohol, also includes minerals and vitamins which may not be available in certain other fermented beverages (3). The concentration of alcohol shows a discrepancy from 10% to 14% for table wines and up to 20% for certain drinks that stimulate the appetite. The prevalent alcohol is ethanol; glycerol and more than a dozen other alcohols have been isolated from wines (4).The medical literature documents numerous biological properties for wine polyphenols, which include the phenolic acids p-coumaric, cinnamic, caffeic, gentisic, ferulic, and vanillic acids and the trihydroxy stilbenes polydatin and resveratrol and flavonoids (catechin, epicatechin, and quercetin) (5,6). Polyphenolic compounds, such as resveratrol, are naturally present at high concentration in grape skin, seeds, and red wine. It has fascinated the most attention because of its biological activity (7).

An extensive range of phenol concentrations is present in selected wines. A Japanese report analyzed resveratrol and piceid and their isomers content in 42 different wines. The average stilbene content was 4.37 mg/L in red wines and 0.68 mg/L in white wines (8). Red wines have higher concentrations of total phenols, flavonoids, flavanols, and anthocyanins than white or rosé wines (9).Red wines have 6 times the concentration of trans -resveratrol than white wines, while white-grape variety wines contain higher concentrations of cis –resveratrol. Red and white wines contain 0.12 to 0.06 mg/L of cis - resveratrol, while red wines contain a concentration of 12.68 mg/L of trans – resveratrol (10).Wine flavonoids are also present (1 to 3 g/L in red, 0.2 g/L in white) and include flavonols, anthocyanins, flavanols (catechins, quercetin), oligomers (procyanidins), and polymers (tannins) of the catechins (5). Anthocyanins are responsible for the color of wine (11). Champagnes and sparkling wines have approximately 1.5% carbon dioxide. Other wine components include carbonyl compounds, organic acids, tannins, carbohydrates, and esters (3, 4). Table 1 shows the exact composition of non-polyphenolic ingredients present in wine (12).

4. WINE AS “NEUROPROTECTIVE AGENT”

Neurodegeneration is a process involved in both neuropathological conditions and brain ageing. Although the brain accounts for less than 2% of the body weight, it consumes about 20% of the oxygen available through respiration. Amongst a variety of neurodegenerative diseases, Alzheimer's disease (AD) is the most prevalent and devastating disorder and the first cause of institutionalization in the elderly population. Clinical signs of AD are characterized by progressive and irreversible memory deficits, cognitive deterioration and personality changes, usually with an onset after 65 years of age. Memory impairment appears in the early stage of the disease, and motor and sensory functions are not affected until later stages. Parkinson's disease (PD) is the second most common ageing-related neurodegenerative diseases that can greatly impair quality of life. As opposed to cognitive deficits of AD, PD is a movement disorder, whose classical signs include resting tremors, bradykinesia, extrapyramidal rigidity and loss of postural reflexes such as

disturbance in walking or equilibrium. The consequence of these diseases is also very significant in terms of the cost of caring for patients (13, 14). So far epidemiological and investigational reports have associated mild-to-moderate wine and/or grape consumption has been associated with improved cognitive functioning (15-17) a lower risk of Alzheimer disease (AD) (18) and less severe white matter lesions (19,20).

Several studies have recommended that there exists a relationship between alcohol consumption and mortality rates which is characterized by a U-shaped or a J-shaped curve (21, 22). Determinants that suggest the types of Curve are the drinking pattern and the type of alcohol consumed. Certain studies have suggested that wine has a greater protective effect than beer and spirits (23, 24). Alcohol consumption may be associated with many favorable effects, including improved lipid-profile (25). There are studies demonstrating increased antioxidant activity in blood following ingestion of red wines, but not with other beverages (26, 27). Animal and epidemiological studies put forward the notion that polyphenolic constituents of red wine possess antioxidant activities that favor protection against cardiovascular disease – the so-called 'French paradox' – and possibly, central nervous system disorders such as Alzheimer's disease (AD) and ischemia. Stéphane Bastianetto *et al* (28) have suggested the neuroprotective ability of resveratrol, an enriched polyphenolic contents present in wine result from their antioxidant properties rather than their purported modulatory effects on intracellular enzymes such as cycloxygenase, lipoxygenase or nitric oxide synthase. Recent reports suggested that daily consumption of 3-4 glasses of red wine may be linked to lower risks of AD, cognitive impairment and macular degeneration (AMD) (29).

Subirade *et al* (30) and Moosmann *et al* (31) have observed that in cell types such as fibroblasts and HT22 cells red wine-derived phenolic constituents inhibited the lethal events of oxidative stress produced by Nitric oxide generation, a process that may be relevant to neurodegenerative events occurring during chronic inflammation, cerebral ischemia. In a rat model of cerebral infarction resveratrol reduced infarct volume, and the neuroprotection correlated with downregulation of inducible nitric oxide synthase (iNOS) and upregulation of endothelial nitric oxide synthase (eNOS) (32). It is expected that similar effects on serum lipoproteins, coagulation factors, and platelets contribute to the reduced risk of both myocardial infarction and ischemic stroke conferred by low doses of ethanol, and antioxidants such as resveratrol (as well as the antioxidant properties of ethanol itself) might provide neuroprotection to the brain (33). In animal models of ischemic stroke, ethanol reduced delayed neuronal death, neuronal and dendritic degeneration, oxidative DNA damage, glial cell activation, and neutrophil infiltration (34). Monteiro *et al* (35) have suggested that red wine offers neuroprotection by an increased activity of hippocampal aromatase activity and also through an alteration in the relative abundance of estrogen receptor expression. Red wine polyphenolic compounds equivalent to approximately one-twentieth of a glass of red wine reduced brain injury in rats from the onset of cerebral ischemia by decreasing the release of amino acids, increasing the release of free radical scavengers, and improving blood flow restoration and cerebral energy metabolism (36). White wines are generally low in polyphenolic content as compared to red wines. However, Champagne wines have been shown to contain relatively high amounts of phenolic acids that may exert protective cellular actions *in vivo*. It was suggested that the organic and aqueous Champagne wine extracts exhibited potent neuroprotective activity against peroxynitrite-induced injury (37). The alcohol-dependent neuroprotected state appear linked to activation of signal transduction processes potentially involving reactive oxygen species, several key protein kinases, and increased heat shock proteins (33).

Mild-to-moderate consumption of ethanol nonetheless appears to reduce the risk of dementia among older people, and the favorable effects of ethanol on cerebrovascular disease do not explain the benefit in non-vascular dementia. Animal models are consistent with these observations. "Alcohol-preferring" rats chronically consuming 15% ethanol/water were protected from apoptosis caused by inflammatory lipopolysaccharide injection (38). In brain cultures non-neurotoxic ethanol exposure protects against excitotoxic NMDA receptor mediated neurodegeneration, and the benefit paralleled induction of heat shock proteins (39, 40). In an *in vitro* study it has been shown that acute ethanol exposure strongly inhibits N – methyl Nmethyl- D-aspartate (NMDA) receptor–mediated excitotoxicity and may therefore be neuroprotective (41).

In contrast to many clinical studies on the detrimental effects of chronic ethanol consumption on liver that have been well documented during the last five decades, beneficial effects of light-to-moderate, non-binge consumption of varied alcoholic beverages in human populations as well as in experimental animal studies have been reported, showing that light-moderate alcohol exposure can initiate cytoprotective mechanisms. Thus, moderate drinking is related to lower incidence of ischemic heart disease, while abstainers or heavy drinkers are at higher risk than light or moderate drinkers. Besides, in middle-aged male survivors of a recent acute myocardial infarction, moderate wine drinking (2-3 standardized drinks per day) was associated with a significant reduction (>50%) in the risk of further cardiovascular complications during a mean follow-up period of 4 years (33). In addition, in animal experiments, a sustained consumption of alcohol (6 weeks; 2.5-36% vol/vol in drinking water) resulted in most species under investigation in a significant reduction in myocardial ischemia/reperfusion injury with improved recovery of function and decreased cardiac enzyme release (42). Finally, chronic low dose alcohol administration can mimic the classical ischemic preconditioning and protect cardiac tissue against ischemic damage (43). Such beneficial effects were at first attributed to the alcohol-induced reduction of platelet aggregation and fibrinogen levels leading to increased fibrinolysis, to increased coronary flow mediated by nitric oxide release and reduced

blood pressure, to increased high density lipoprotein (HDL) and reduced low density lipoprotein (LDL) in the blood, thus reducing the risk due to cholesterol, to a reduction of insulin resistance and increase in insulin sensitivity, and finally to a reduction in blood homocysteine and inflammatory marker levels (33).

In some recent studies, moderate alcohol consumption was associated with a lower risk of dementia, whereas the risk of cognitive decline and Alzheimer' disease was significantly lower (17). This was attributed to alcohol's beneficial hematologic, vascular, and possibly cerebrovascular effects, as well as, in the case of wine-drinkers, to the effect of antioxidant polyphenols, such as resveratrol. In several experimental studies, alcohol-induced preconditioning was reported to induce neuroprotection (44). Moderate alcohol consumption also imparts cardioprotection by adapting the heart to oxidative stress. Indeed alcohol induces a significant amount of oxidative stress to the cardiomyocytes, which is then translated into the induction of expression of several cardioprotective oxidative stress-inducible proteins including heat-shock protein HSP70 (45). Considerable research indicates that HSP can be potential neuroprotective effectors induced by ischemia and other preconditioning approaches (46).

5. WINE, ALCOHOL, AND N-3 PUFAS: THE "FISH LIKE EFFECT" HYPOTHESIS

It has been recently suggested that tissue protection resulting from moderate alcoholic beverage consumption might result at least in part from some interactions between moderate alcoholic beverage drinking and fatty acid metabolism. Thus it was demonstrated that moderate wine drinking was associated with increased plasma concentrations of n-3 PUFAs from marine origin, namely EPA and DHA in patients with cardiovascular disease (47). This phenomenon was observed in patients with either low or high intakes in alpha linolenic acid (ALA), the plant precursor of EPA and DHA. Moreover no dietary or non-dietary factors could explain the association. Since high n-3 PUFA plasma levels have been associated with low mortality from cardiovascular disease (sudden cardiac death), this effect of wine, comparable to that of fish ("fish-like-effect") might also contribute to the cardioprotective effect of alcohol consumption. In 2009, di Giuseppe *et al.* (48) reported that the (EPA+ DHA) index was significantly increased in plasma and red blood cell membranes in moderate wine drinkers, whereas no association was found in those who drink beer and spirits. Recently, Guiraud *et al.* (49) have shown, through a well-controlled experimental study, that a comparable increase in n-3 PUFA plasma levels could also be achieved in rats chronically treated with moderate doses of alcohol. Moreover, long-term dietary intake of plant-derived anthocyanins and actual absorption of these compounds by rats render the myocardium less susceptible to ischemia/reperfusion injury *ex vivo* as well as *in vivo*. This beneficial effect was accompanied by a significant improvement in endogenous antioxidant defenses of the heart and by a 20% increase in myocardial tissue content of EPA and DHA REMOVE (Toufektsian *et al.*, unpublished data) (50). All of these data suggest that moderate wine drinking interacts with fatty acid metabolism. While the exact mechanisms involved in these interactions are not yet elucidated these results provide new insight into the cellular pathways of health benefits afforded by ethanol and non-ethanolic constituents of wine. Studies designed to evaluate whether the preconditioning and neuroprotective effects of light-to-moderate, stable alcohol ingestion are related to alcohol-induced significant changes in n-3 PUFAs concentrations in plasma and/or cell membranes.

6. RESVERATROL – AN ACTIVE WINE POLYPHENOL EXERTS NEUROPROTECTION

Sakata *et al* studied that resveratrol, an enriched bioactive polyphenol in red wine, selectively induces heme oxygenase 1 (HO1) in a dose- and time-dependent manner in cultured mouse cortical neuronal cells and provides neuroprotection from free-radical or excitotoxicity damage. Furthermore, resveratrol pretreatment dose-dependently protected mice subjected to an optimized ischemic-reperfusion stroke model (51). Another study has observed that Resveratrol protect against various neurological disorders in experimental models, including brain ischemia, seizures, and neurodegenerative disease models (52). Beta-amyloid (Abeta) aggregation has been strongly associated with the neurodegenerative pathology and a cascade of harmful event rated to Alzheimer's disease (AD) Inhibition of Abeta assembly, destabilization of preformed Abeta aggregates and attenuation of the cytotoxicity of Abeta oligomers and fibrils could be valuable therapeutics of patients with AD. Resveratrol may directly bind to Abeta42 fibrils, interfere in Abeta42 aggregation, change the Abeta42 oligomer conformation and attenuate Abeta42 oligomeric cytotoxicity (53). Recent study shows that treatment with resveratrol may provide multiple benefits leading to reduced inflammation because of its antioxidant activity, activation of SIRT1, and modulation of NF-kB signaling (54). Several studies support resveratrol's role in improving motor and cognitive impairment through its antioxidant activity (55). Resveratrol's activity partially protects against the mitochondrial dysfunction and oxidative damage often seen in Huntington disease (56). Parkinson disease is associated with a depletion of dopamine, often resulting in an imbalance between cholingeric and dopaminergic neurons. Administration of resveratrol in mice protected against a neurotoxin used to induce Parkinsonism or motor coordination impairment, hydroxyl radical overloading, and neuronal loss (57, 58). Dopamine-induced cytotoxicity in neuroblastoma cells was partially reversed by resveratrol. Other studies with resveratrol found cell proliferation at low concentrations versus apoptosis at high concentrations (59). Resveratrol exerts neuroprotection against lipopolysaccharide-induced dopaminergic neurodegeneration, and NADPH oxidase may be a major player in resveratrol-mediated Neuroprotection (60). Trans-resveratrol, a red wine ingredient, inhibits voltage-activated potassium currents in rat hippocampal neurons. It has been observed that superfusion of trans-resveratrol reversibly inhibited both the delayed rectifier (I (K)) and fast transient K (+) current

(I (A)) in rat dissociated hippocampal neurons with IC (50) values of 13.6 +/- 1.0 microM and 45.7 +/- 7.5 microM, respectively (61). Yet another study for the first time demonstrates that trans-resveratrol inhibits the postsynaptic glutamate receptors, which probably works in concert with its antioxidant action for ameliorating the brain ischemic injury. The findings also support the future use of trans-resveratrol in the treatment of various neurodegenerative disorders (62).

7. WINE AND ALCOHOL IN CARDIOPROTECTION

Next to the neurological disorders, heart diseases remain a leading cause of morbidity and mortality worldwide. The important role of wine and alcohol in myocardial preservation became well known when the story of Frence Paradox was first reported by the media in 1991 (63). A great deal of evidence is present in the literature to support the idea that moderate alcohol or wine consumption is capable of providing protection against hypertension, atherosclerosis and myocardial infarction (64). In case of wine, the ethanol content is believed not to be responsible to account for the cardioprotection, rather the polyphenolic constituents are assumed to be responsible for the heart health (65). Resveratrol has been found to provide diverse cardioprotective effects, and likely to be responsible for most of the cardioprotective effects present in wine (66). The cardio protective effects of resveratrol and/or wine are realized through its ability to induce iNOS and eNOS thereby stimulating NO production (67). The extracts of wine increase guanosine 3',5'-monophosphate (cGMP) amounts in intact vascular tissue and both relaxation and the increase in cGMP are reversed by N^G-monomethyl-L-arginine or by N^G-nitro-L-arginine, competitive inhibitors of the synthesis of the endothelium-derived relaxation factor, NO, suggesting that vasorelaxation induced by wine or resveratrol is mediated by NO-cGMP pathway (68). Most importantly, resveratrol maintains the redox homeostasis in the cardiovascular system by manipulating the intracellular antioxidant enzymes including glutathione peroxidase, glutathione –s-transferase and glutathione reductase thereby preventing LDL oxidation in the heart (69). Resveratrol also inhibits platelet aggregation, another major contributor of atherosclerosis (70). Anti-inflammatory functions of wine and resveratrol also play a crucial role in cardioprotection. Suppressed aberrant expression of tissue factor and cytokines in vascular cells achieved by resveratrol is due to the anti inflammatrory role of resveratrol (71). Evidence exists in the literature indicating that resveratrol and wine promote cardioprotection through preconditioning, a state-of-the-art technique of myocardial protection (72). Resveratrol fulfils the defination of preconditioning as it activates adenosine receptors, mitochondrial K_{ATP} channels, MAPKs and protein C kinases (73), which are the mediators of preconditioning (74). Since preconditioning results from an adaptive response, resveratrol also appears to provide cardioprotective responses through the adaption to stress.

The fact that resveratrol or wine mediated cardioprotection is an adaptive response receives further support from the recent findings that resveratrol induces autophagy, another example of adaptive response to cope with the stress (75) Several recent studies have confirmed that resveratrol triggers the expression of several genes and transcription factors related to autophagy (76). Another recent study has shown that resveratrol potentiates the regeneration of infracted heart (77). Maintaining a reduced tissue environment by treatment with resveratrol in rats appears to enhance the cardiac regeneration by adult cardiac stem cells via improved cell survival, proliferation and differentiation leading to improved cardiac function.

8.CONCLUSION

Identification of the mechanisms of alcohol and wine's multiple effects on cognition—including neurotoxicity, neuroprotection and cardiac preservaion—will have obvious bearing not only on medical management but also on public policy. Although accumulating evidence on the health properties of Wine and its polyphenolic contents is associated with their well-known antioxidant properties, other mechanisms involving modulatory effects on signal transduction pathways and gene expression also likely to play predominant roles. These multiple mechanisms of actions – that may be synergistic or additive; and may explain the variability of their clinical efficacy.

9. REFERENCES

1. J.G. Cappuccino, N. Sherman: "Wine Production" In Microbiology: A Laboratory Manual. Benjamin Cummings: San Francisco, (2002)

2. Provisional Table on the Nutrient Content of Beverages. Washington, DC: Department of Agriculture, Human Nutrition Information Service, (1982)

3. Emeryville: Wine and America. Winegrowers of California. (1986)

4. Uses of Wine in Medical Practice. Wine Advisory Board San Francisco (1975)

5. G.J. Soleas, E.P. Diamandis, D.M. Goldberg: Wine as a biological fluid: history, production, and role in disease prevention. *J Clin Lab Anal* 11, 287-313 (1997)

6. M.J. Halpern, A.L. Dahlgren, I. Laakso, T. Seppänen-Laakso, J. Dahlgren, P. A. McAnulty: Red-wine polyphenols and inhibition of platelet aggregation: possible mechanisms, and potential use in health promotion and disease prevention. *J Int Med Res* 26, 171-180 (1998)

7. L.H. Opie, S. Lecour: The red wine hypothesis: from concepts to protective signalling molecules. *Eur Heart J* 28, 1683-1693 (2007)

8. M. Sato, Y. Suzuki, T. Okuda, K. Yokotsuka: Contents of resveratrol, piceid, and their isomers in commercially available wines made from grapes cultivated in Japan. *Biosci Biotechnol Biochem* 61, 1800-1805 (1997)

9. H. Li, X. Wang, Y. Li, P. Li, H. Wang: Polyphenolic compounds and antioxidant properties of selected China wines. *Food Chem* 112, 454-460 (2009)

10. O. Feijóo, A. Moreno, E. Falqué: Content of trans - and cis -resveratrol in Galician white and red wines. *J Food Comp Analysis* 21, 608-613 (2008)

11. R.F. Guerreroa, A. Liazid, M. Palma, B. Puertas, R. González-Barrio, Á. Gil-Izquierdo, C. García-Barroso, E. Cantos-Villar: Phenolic characterization of red grapes autochthonous to Andalusia. *Food Chem* 112, 949-955 (2009)

12. Phil Crews: Introduction to Wines and Wine Chemistry. U.C. Santa Cruz (2009)

13. B. Pillon, B. Deweer, Y. Agid, B. Dubois: Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases. *Arch. Neurol* 50, 374–379 (1993)

14. A.M. Paolo, A.I. Tröster, S.L. Glatt, J.P. Hubble, W.C. Koller: Differentiation of the dementias of Alzheimer's and Parkinson's disease with the dementia rating scale. *J Geriatr Psychiatry Neurol* 8, 184–188 (1995)

15. M.A. Espeland, L. Gu, K.H. Masaki: Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. *Am J Epidemiol* 161, 228-238 (2005)

16. D J Galanis, C Joseph, K H Masaki, Petrovitch H, Ross GW, White L: A longitudinal study of drinking and cognitive performance in elderly Japanese American men: the Honolulu-Asia Aging Study. *Am J Public Health* 90, 1254-1259 (2000)

17. K.J. Mukamal, L.H. Kuller, A.L. Fitzpatrick, W.T. Longstreth Jr, M.A. Mittleman, D.S. Siscovick: Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA* 289, 1405- 1413 (2003)

18. J.A. Luchsinger, M.X. Tang, M. Siddiqui, S. Shea, R. Mayeux Alcohol intake and risk of dementia. *J Am Geriatr* Soc 52, 540-546 (2004)

19. T. Den Heijer, S.E. Vermeer, E.J. van Dijk: Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. *Am J Clin Nutr* 80, 992-997 (2004)

20. K.J. Mukamal, W.T. Longstreth, M.A. Mittleman, R.M. Crum, D.S. Siscovick: Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the Cardiovascular Health Study. *Stroke* 32, 1939-1946 (2001)

21. P. Bofetta, L. Garfinkel: Alcohol drinking and mortality among men enrolled in an american cancer society prospective study. *Epidemiology* 1, 342–348 (1990)

22. C.S. Fuchs, M.J. Stampfer, G.A. Colditz, E.L. Giovannucci, J.E. Manson, I. Kawachi, D.J. Hunter, S.E. Hankinson, C.H. Hennekens, B. Rosner, F.E. Speizer, W.C. Willett: Acohol consumption and mortality among women. *N Engl J Med* 332, 1245-1250 (1995)

23. A.L. Klatsky, M.A. Armstrong: Alcoholic beverage choice and risk of coronary artery disease mortality: Do red wine drinkers fare best? *Am J Cardiol* 71, 467–469 (1993)

24. M. Grønbeck, A. Deis, T.I.A. Sørensen, U. Becker, P. Schnohr, G. Jensen: Mortality associated with moderate intake of wine, beer or spirits. *BMJ* 310, 1165–1169 (1995)

25. E.N. Frankel, J. Kanmer, J.B. German, E. Parks, J.K. Binsella: Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 341, 454–457 (1993)

26. S. Maxwell, A. Cruikshank, G. Thorpe: Red wine and antioxidant activity in serum. *Lancet* 344 193–194, (1994)

27. T.P. Whitehead, D. Robinson, S. Allaway, J. Syms, A. Hale: Effect of red wine ingestion on the antioxidant capacity of serum. *Clin Chem* 41, 32–35 (1995)

28. S. Bastianetto, W.H. Zheng, R. Quirion: Neuroprotective abilities of resveratrol and other red wine constituents against nitric oxide- related toxicity in cultured hippocampal neurons. *Br J Pharmacol* 131: 711–720, (2000P.

29. J.A. Luchsinger, M.X. Tang, M. Siddiqui, S. Shea, R. Mayeux: Alcohol intake and risk of dementia. *J Am Geriatr Soc* 52, 540-546 (2004)

30. I. Subirade, I. Fernandez, Y. Fernandez, A. Periquet, S. Mitjavila: Catechin protection of 3T3 Swiss fibroblasts in culture under oxidative stress. *Biol Trace Element Res* 47, 313 – 319 (1995)

31. B. Moosmann, C. Behl: The antioxidant Neuroprotective effects of estrogens and phenolic compounds are independent from their estrogenic properties. *Proc Natl Acad Sci* 96, 8867 – 8872 (1999)

32. S.K. Tsai, L.M. Hung, Y.T. Fu, H. Cheng, M.W. Nien, H.Y. Liu, F.B. Zhang, S.S. Huang: Resveratrol neuroprotective effects during focal cerebral ischemia injury via nitric oxide mechanism in rats. *J Vasc Surg* 46, 346-353 (2007)

33. M.A. Collins, E.J. Neafsey, K.J. Mukamal, M.O. Gray, D.A. Parks, D.K. Das, R.J. Korthuis: Alcohol in moderation, cardioprotection, and neuroprotection: epidemiological considerations and mechanistic studies. *Alcohol Clin. Exp Res* 33, 206-219 (2009)

34. Q. Wang, A.Y. Sun, A. Simonyi, T.J. Kalogeris, D.K. Miller, G.Y. Sun, R.J. Korthuis: Ethanol preconditioning protects against ischemia/reperfusion-induced brain damage: role of NADPH oxidase-derived ROS. *Free Radic Biol Med* 43, 1048-1060 (2007)

35. R. Monteiro, A. Faria, N. Mateus, C. Calhau, I. Azevedo: Red wine interferes with oestrogen signalling in

rat hippocampus. *J Steroid Biochem Mol Biol* 111, 74-79 (2008)

36. M.F. Ritz, Y. Curin, A. Mendelowitsch, R. Andriantsitohaina: Acute treatment with red wine polyphenols protects from ischemia-induced excitotoxicity, energy failure and oxidative stress in rats. *Brain Res* 1239, 226 – 234 (2008)

37. V. David, V. Katerina, G. Corona, S.E. Pollard, X. Tzounis, P.E. Jeremy Spencer: Champagne Wine Polyphenols Protect Primary Cortical Neurons against Peroxynitrite-Induced Injury. *J Agric Food Chem* 55, 2854–2860 (2007)

38. A.K Singh, Y. Jiang, S. Gupta, E. Benlhabib: Effects of chronic ethanol drinking on the blood brain barrier and ensuing neuronal toxicity in alcohol-preferring rats subjected to intraperitoneal LPS injection. *Alcohol* 42, 385-399 *(*2007)

39. A. Belmadani, E.J. Neafsey, M.A. Collins: Human immunodeficiency virus type 1 gp120 and ethanol coexposure in rat organotypic brain slice cultures: curtailment of gp120-induced neurotoxicity and neurotoxic mediators by moderate but not high ethanol concentrations. *J Neurovirol* 9, 45-54 (2003)

40. A. Belmadani, Kumar S, Schipma M, Collins MA, Neafsey EJ. Inhibition of amyloid-beta-induced neurotoxicity and apoptosis by moderate ethanol preconditioning. *Neuroreport* 15, 2093-2096 (2004)

41. L.J. Chandler, C. Sumners, F.T. Crews: Ethanol inhibits NMDA receptor-mediated excitotoxicity in rat primary neuronal cultures. *Alcohol Clin Exp Res* 17, 54–60 (1993)

42. L.H. Abou-Agag, N.K. Khoo, R. Binsack, C.R. White, V. Darley-Usmar, H.E. Grenett, F.M. Booyse, S.B. Digerness, F. Zhou, D.A. Parks: Evidence of cardiovascular protection by moderate alcohol: role of nitric oxide. *Free Radic Biol Med* 39, 540–548 (2005)

43. M. Miyamae, I. Diamond, M.W. Weiner, S.A. Camacho, V.M. Figueredo: Regular alcohol consumption mimics cardiac preconditioning by protecting against ischemia-reperfusion injury. *Proc Natl Acad Sci* 94, 3235–3239 (1997)

44. A. Belmadani, J.Y. Zou, M.J. Schipma, E.J. Neafsey, M.A. Collins: Ethanol pre-exposure suppresses HIV-1 glycoprotein 120-induced neuronal degeneration by abrogating endogenous glutamate / Ca2+-mediated neurotoxicity. *Neuroscience* 104, 769–781 (2001)

45. M. Sato, C. Fraga, D.K. Das: Induction of the expression of cardioprotective proteins after mild-to-moderate consumption of alcohol. *Pathophysiology* 10, 139–145 (2004)

46. J.M. Gidday: Cerebral preconditioning and ischaemic tolerance. *Nat Rev Neurosci* 7, 437–448 (2006)

47. M. De Lorgeril, P. Salen, J.L. Martin, F. Boucher, J. de Leiris: Interactions of wine drinking with omega-3 fatty acids in patients with coronary artery disease. *Am Heart J* 155, 175-181 (2008)

48. R. Di Giuseppe, M. de Lorgeril, P. Salen, F. Laporte, A. di Castenuovo, V. Krogh, A. Siani, J. Arnout, F.P. Cappuccio, M. van Dongen, M.B. Donati, G. de Gaetano, L. Iacoviello: Alcohol consumption and n-3 polyunsaturated fatty acids in healthy men and women from 3 European populations. *Am J Clin Nutr* 89, 354-362: 2009.

49. A. Guiraud, M. de Lorgeril, S. Zeghichi, F. Laporte, P. Salen, V. Saks, N. Berraud, F. Boucher, J. de Leiris. Interactions of ethanol drinking with n-3 fatty acids in rats: potential consequences for the cardiovascular system. *Brit J Nutr* 100, 1237-1244 (2008)

50. M.C. Toufektsian, M. de Lorgeril, N. Nagy, P. Salen, M.B. Donati, L. Giordano, H.P. Mock, S. Peterek, A. Matros, K. Petroni, R. Pilu, D. Rotilio, C. Tonelli, J. de Leiris, F. Boucher, C. Martin: Chronic dietary intake of plant-derived antocyanins protects the rat heart against ischemia/reperfusion injury. *J Nutr* 138, 747-752 (2008)

51. Y. Sakata, H. Zhuang, H. Kwansa, R.C. Koehler, S. Doré: Resveratrol protects against experimental stroke: putative neuroprotective role. *Exp Neurol* 224, 325-329 (2010)

52. F. Zhang, J. Liu, J.S. Shi: Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation. *Eur J Pharmacol* 63, 1-7 (2010)

53. Y. Feng, X.P. Wang, S.G. Yang, Y.J. Wang, X. Zhang, X.T. Du, X.X. Sun, M. Zhao, L. Huang, R.T. Liu: Resveratrol inhibits beta-amyloid oligomeric cytotoxicity but does not prevent oligomer formation. *Neurotoxicology* 6, 986-995 (2009)

54. B.L. Tang, C.E. Chua: SIRT1 and neuronal diseases. *Mol Aspects Med* 29, 187-200 (2008)

55. P. Kumar, S.S. Padi, P.S. Naidu, A. Kumar: Effect of resveratrol on 3-nitropropionic acid-induced biochemical and behavioural changes: possible neuroprotective mechanisms. *Behav Pharmacol* 17, 485-492 (2006)

56. A. Solans, A. Zambrano, M. Rodríguez, A. Barrientos: Cytotoxicity of a mutant huntingtin fragment in yeast involves early alterations in mitochondrial OXPHOS complexes II and III. *Hum Mol Genet* 15, 3063-3081 (2006)

57. K.T. Lu, M.C. Ko, B.Y. Chen. Neuroprotective effects of resveratrol on MPTP-induced neuron loss mediated by free radical scavenging. *J Agric Food Chem* 56, 6910-6913 (2008)

58. J. Blanchet, F. Longpré, G. Bureau: Resveratrol, a red wine polyphenol, protects dopaminergic neurons in MPTP-

treated mice. *Prog Neuropsychopharmacol Biol Psychiatry* 32, 1243-1250 (2008)

59. M.K. Lee, S.J. Kang, M. Poncz, K.J. Song, K.S. Park: Resveratrol protects SH-SY5Y neuroblastoma cells from apoptosis induced by dopamine. *Exp Mol Med* 39, 376-384 (2007)

60. F. Zhang, J.S. Shi, H. Zhou, B. Wilson, J.S. Hong, H.M. Gao: Resveratrol protects dopamine neurons against lipopolysaccharide-induced neurotoxicity through its anti-inflammatory actions. *Mol Pharmacol* 78, 466-477 (2010)

61. Z.B. Gao, G.Y. Hu: Trans-resveratrol, a red wine ingredient, inhibits voltage-activated potassium currents in rat hippocampal neurons. *Brain Res* 1056, 68-75 (2005)

62. Z.B. Gao, X.Q. Chen, G.Y. Hu: Inhibition of excitatory synaptic transmission by trans-resveratrol in rat hippocampus. *Brain Res* 1111, 41-47 (2006)

63. S. Renaud, M. de Lorgeril: Wine, alcohol, platelets and the French Paradox for coronary heart disease. *Lancet* 339, 1523-1526 (1992)

64. D. Aguilar, H. Skali, L.A. Moyé, E.F. Lewis, J.M. Gaziano, J.D. Rutherford, L.H. Hartley, O.S. Randall, E.M. Geltman, G.A. Lamas, J.L. Rouleau, M.A. Pfeffer, S.D. Solomon: Alcohol consumption and prognosis in patients with left ventricular dysfunction after a myocardial infarction. *J Am Coll Cardiol* 43, 2015–2021 (2004)

65. M. Seigneur, J. Bonnet, B. Dorian, D. Benchimol, F. Drouillet, G. Gouverneur: Effect of consumption of alcohol, white wine and red wine on platelet function and serum lipids. *J Appl Cardiol* 5, 215-222 (1990)

66. D.K. Das, N. Maulik: Resveratrol in cardioprotection: A therapeutic promise of alternative medicine. *Mol Interventions* 6, 36-47 (2006)

67. G. Imamura, A.A. Bertelli, A. Bertelli, H. Otani, N. Maulik, D.K. Das. Pharmacologic preconditioning with resveratrol: an insight with iNOS knockout mice. *Am J Physiol* 282, 1996-2003 (2002)

68. D.F. Fitzpatrick, S.L. Hirschfield, R.G. Coffey: Endothelium-dependent vasorelaxing activity of wine or other grape products. *Am J Physiol* 265, 774–748 (1993)

69. S. Das, N. Khan, S. Mukherjee, D. Bagchi, N. Gurusamy, H. Swartz, D.K. Das: Redox regulation of resveratrol-mediated switching of death signal into survival signal. *Free Radical Biol Med* 44, 82–90 *(*2008)

70. S. Shigematsu, S. Ishida, M. Hara, N. Takahashi, H. Yoshimatsu, T. Sakata, R.J. Korthuis: Resveratrol, a red wine constituent polyphenol, prevents superoxide-dependent inflammatory responses induced by ischemia/reperfusion, platelet-activating factor, or oxidants. *Free Radic Biol Med* 34, 810–817 (2003)

71. U.R. Pendurthi, J.T. Williams, L.V. Rao: Resveratrol, a polyphenolic compound found in wine, inhibits tissue factor expression in vascular cells: A possible mechanism for the cardiovascular benefits associated with moderate consumption of wine. *Arterioscler Throm Vasc Biol* 19, 419–426 (1999)

72. D.K. Das, S. Mukherjee, D. Ray: Resveratrol and red wine, healthy heart and longevity. *Heart Fail Rev* 15, 467-77 (2010)

73. S. Das, V.K. Alagappan, D. Bagchi, H.S. Sharma, N. Maulik, Das DK: Co-ordinated induction of inOS-VEGF-KDR-eNOS after resveratrol consumption. A potential mechanism of resveratrol preconditioning of the heart. *Vasc Pharmacol* 42, 281-289 (2005)

74. R. Hattori, H. Otani, N. Maulik, D.K. Das: Pharmacological preconditioning with resveratrol: role of nitric oxide. *Am J Physiol* 1988-1995, 2002.

75. I. Lekli, D. Ray, S. Mukherjee, N. Gurusamy, M.K. Ahsan, B. Juhasz, I. Bak, A. Tosaki, M. Gherghiceanu, L.M. Popescu, D.K. Das: Co-ordinated autophagy with resveratrol and gamma-tocotrienol confers synergetic cardioprotection. *J Cell Mol Med* 14, 2506-2518 (2009)

76. N. Gurusamy, I. Lekli, S. Mukherjee, D. Ray, M.K. Ahsan, M. Gherghiceanu, L.M. Popescu, D.K. Das: Cardioprotection by resveratrol: a novel mechanism via autophagy involving the mTORC2 pathway. *Cardiovasc Res* 86, 103-112 (2010)

77. N. Gurusamy, D. Ray, I. Lekli, D.K. Das: Red wine antioxidant resveratrol-modified cardiac stem cells regenerate infarcted myocardium. *J Cell Mol Med* 14, 2235-2239 (2010)

Key Words: Tocotrienol, Hypocholesterolemia, Antioxidant, Cardioprotection, Review

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