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Red wine, resveratrol, and Alzheimer's disease | Review

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. No effective therapies for AD are yet available, and potentially preventive lifestyle factors, including diet and physical activity, have become a focus of AD research. One such factor is moderate wine consumption, which has been claimed to be neuroprotective, and some studies have suggested a potential role for grapes and wine in retarding cognitive decline and other effects of aging. Polyphenols contained in grapes have been investigated as a preventive measure or potential therapy for dementia. The best-studied fruit polyphenol, the stilbenoid resveratrol (trans-3,5,4'-trihydroxystilbene), is known for its anti-oxidant and anti-inflammatory properties. The present short review evaluates the evidence regarding the role of red wine and resveratrol in the prevention and treatment of AD. Some research findings have suggested that resveratrol may be useful in the treatment of neurodegenerative diseases, including AD, due to its ability to reduce cognitive decline and to inhibit amyloid β aggregation in animal models of dementia. Studies in rodents have demonstrated neuroprotective effects of resveratrol on central features of AD, including decreased amyloid deposition and tau-hyperphosphorylation, enhanced hippocampal neurogenesis, and improved memory functions. The mechanisms through which resveratrol exerts neuroprotective efficacy in animals remain to be established. The potential of resveratrol to act as a nutraceutical targeting neuropathological changes in AD and exerting neuroprotective efficacy may be related to its anti-oxidant activities and its ability to antagonize amyloid aggregation, suppress neuroinflammation, decrease mitochondrial dysfunction, and modulate signaling pathways. In contrast to the neuroprotective activity of resveratrol in various in-vitro and in-vivo models, evidence of the ability of resveratrol to prevent age-associated neurodegeneration in humans and to improve cognitive deficits in AD is lacking. Thus, whether resveratrol has any beneficial effects in humans remains to be established. Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene), an analog of resveratrol, appears to be more effective than resveratrol in ameliorating brain alterations associated with aging and may be a more promising compound for future research. Moderate red wine intake is unable to provide resveratrol in amounts required for clinically relevant effects in AD. Were resveratrol proven to be effective in combatting AD, supplements or a drug should be substituted for wine as a source. Moreover, the toxic effects of alcohol should be considered, since recent evidence suggests that no level of alcohol consumption has beneficial health effects. In particular, long-term alcohol consumption, even in moderate quantities, is associated with multiple markers of abnormal brain structure, including hippocampal atrophy. Moderate drinking to promote brain health is not justified, and any claims regarding the potential efficacy of red wine in the prevention of AD are unsubstantiated and irresponsible.

Key words: Alzheimer's disease; dementia; resveratrol; polyphenols; red wine; alcohol.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a global impairment of cognition including memory, language and other behavioral functions [1]. Neuropathological hallmarks of AD are the extracellular deposition of misfolded amyloid-β (Aβ) in senile plaques and the intracellular accumulation of hyperphosphorylated tau forms in neurofibrillary tangles [2,3]. Chronic oxidative and inflammatory processes in the brain play important roles in the pathophysiology of AD and lead to neuronal dysfunction and cell death [4]. Disease-modifying treatments significantly improving cognitive impairment in individuals with AD or retarding the progression of the disease are currently not available [1]. Nutrition and dietary components have been recognized as factors capable of modulating cerebral structure and connectivity, of producing changes in brain and behavioral functions associated with age and disease, and of modulating cognition and emotion [5,6]. For example, the early decline in brain glucose metabolism in AD has become a potential target for therapeutic intervention and has led to investigations assessing the effects of ketogenic diets, i.e. the supplementation of the normal glucose supply with ketone bodies, which are produced by the body during glucose deprivation and can be metabolized by the brain when glucose utilization is impaired [7].

Several studies have suggested that moderate wine consumption can slow age-related cognitive decline [8−10]. The findings of epidemiological studies suggest possible neuroprotective effects of wine, since an inverse relationship was observed between a moderate (250–500 ml) daily intake of red wine and the incidence of AD in elderly individuals [11,12]. It has been suggested that red wine may attenuate cognitive deterioration and amyloid neuropathology in animal models of dementia and protect against AD [8,13]. While moderate ethanol intake has been proposed to be beneficial in this regard, greater protective effects have been claimed for red wine intake compared to other ethanol containing beverages [15]. These potential health benefits are attributed to the polyphenolics abundantly present in red wines. Of these, the stilbenoid resveratrol (trans-3,5,4'-trihydroxystilbene) has been proposed as a major constituent responsible for the positive effects [16]. Several polyphenols, including resveratrol from edible plants, have been shown to possess neuroprotective properties in various experimental settings and to reduce toxic Aβ aggregation [17−19]. Sources of resveratrol are primarily peanuts, pistachios, berries and grapes; the most important dietary source of resveratrol is red wine [20].

Mechanisms involved in AD include oxidative stress, generated by free radicals in the brain, and reduced anti-inflammatory processes associated with aging [21,22]. Flavonoids and related polyphenols from grape, grape seeds and wine have been shown to have free radical scavenging, anti-oxidant, and anti-inflammatory activities [23]. Grapes may therefore be beneficial in slowing the development of neuronal deficits associated with aging. Resveratrol possesses a wide range of biological effects, including anti-oxidative [24], anti-inflammatory [25], anti-apoptotic [26,27], and anti-carcinogenic properties [28]. Neuroprotective effects of resveratrol have been shown in animal models of various diseases, such as cerebral ischemia [29,30], kainic acid-induced excitotoxicity [31], Huntington's disease [32], Parkinson's disease [33], and AD [34]. Resveratrol and other polyphenols have been shown to be capable of directly interfering with the hallmark of AD, i.e. toxic β-amyloid protein (Aβ) aggregation [17,18].

2. Resveratrol in animal intervention studies

The therapeutic potential in AD of in-vitro resveratrol has been examined in several studies (see [19]). However, the findings of these studies cannot readily be extrapolated to the in-vivo situation, since they used non-physiological concentrations of resveratrol and did not apply the metabolites produced in vivo following digestion and metabolic processing.

Several studies have investigated the effects of resveratrol in models of impaired learning/memory and AD. The effects of resveratrol on cognitive impairment induced by the muscarinic antagonist scopolamine were examined in mice [35]. Pre-treatment with resveratrol (10 mg/kg and 20 mg/kg) for 21 days showed no improvement of scopolamine-induced cognitive deficits in learning and memory (Morris water maze, elevated plus maze, and passive avoidance task) [35]. Dietary resveratrol effects were investigated in a model of age-related AD (SAMP8 mice) [36]. The administration of resveratrol increased both mean life expectancy and maximum life span in SAMP8. In addition, long-term supplementation of resveratrol over seven months decreased cognitive impairment, as assessed using an object recognition task [36]. In the Aβ protein precursor/presenilin 1 mouse model of AD, chronic oral administration of resveratrol over 10 months significantly reduced memory loss, as assessed with an object recognition test [37]. Following the microinfusion of Aβ1-42 bilaterally into hippocampal CA1 subregions,

resveratrol reversed Aβ-induced memory impairment in the Morris water maze task [38]. In another study, resveratrol protected rats from Aβ-induced hippocampal neuron loss and markedly improved spatial memory in the Morris water maze [39]. Resveratrol was also demonstrated to reverse a decline in working and nonspatial memory caused by lipopolysaccharide induction in mice [40]. Furthermore, resveratrol improved spatial memory in a rat model of AD (ovariectomized rats chronically treated with D-galactose) [41]. Positive effects of resveratrol supplementation on cognitive functions were also shown in male grey mouse lemurs [42]. Compared to controls, oral administration of resveratrol over 18 months improved working memory and spatial memory performance [42].

Resveratrol may affect AD pathology not only by blocking inflammatory processes but also by direct inhibition of the accumulation of Aβ peptides [43]. The biochemical mechanisms associated with beneficial effects of resveratrol on cognitive functions include a reduction of amyloid burden [36,37,43] and tau-hyperphosphorylation [36], a reduction in Aβ deposition due to an increase in estradiol and neprilysin [40], protection from oxidative stress [39,41], a decrease in the cellular levels of inducible nitric oxide synthase and lipid peroxidation [39], an enhancement of mitochondrial complex IV protein levels [37], an activation of 5-adenosine monophosphate-activated protein kinase pathways and sirtuin 1 [36], the regulation of neuronal inflammation and apoptosis via phosphodiesterase-4 subtypes related cAMP-CREB-BDNF signaling [38], and protection of the integrity of the blood-brain barrier [43].

In summary, investigations in rodent models of AD have demonstrated neuroprotective effects of resveratrol on central features of AD including decreased amyloid deposition and tau-hyperphosphorylation, enhanced hippocampal neurogenesis, and improved memory functions. The translational relevance of these findings for dementia in humans needs to be examined.

3. Resveratrol in human intervention trials

Although much is known concerning potential anti-oxidant and neuroprotective effects of resveratrol, few clinical studies have been conducted in healthy humans or individuals with AD [44]. The evidence regarding potential benefits of resveratrol in healthy humans is inconclusive [45−47]. While resveratrol has been shown to have beneficial effects on cerebral blood flow [48], glucose control [49−51], and verbal episodic memory [46], positive effects on brain volume could not be found [46,52]. The short intervention durations of 4 to 6 weeks are a major limitation of the studies failing to reveal favorable results [45,47].

A 5-year follow-up epidemiological study of 1357 elderly individuals aged 65 years or older demonstrated a significant inverse association between flavonoid intake and the risk of dementia [53]. Since high grape intake may be potentially useful in delaying the onset or reducing the incidence of dementia, the effects of grapes on cognitive performance and regional cerebral metabolism were examined in five females and five males with mild cognitive impairment (mean age 72.2 ± 4.7 years) [54]. The participants were randomly assigned to a group consuming a grape formulation (table grapes consumed twice a day) for six months or a placebo group receiving a formulation free of polyphenols. Both at baseline and six months after the initiation of treatment, cognitive performance and brain metabolism were assessed. Individuals in the placebo group showed a statistically significant metabolic decline, as assessed using fluorodeoxyglucose positron emission tomography, in the right posterior cingulate cortex and left superior posterolateral temporal cortex, whereas no significant decline in brain metabolism could be found in the active formulation group [54]. No significant differences were found between the two groups in the neuropsychological test battery used. Improvements in attention and working memory in the active formulation group were correlated with brain metabolism in the right superior parietal cortex and left inferior anterior temporal cortex [54]. In summary, the placebo group showed a decline in metabolism in brain areas known to be affected in the early stages of AD, while no such changes were seen in the group consuming grapes. These protective effects were associated with improved attention and working memory. The neuroprotective effects of grapes in regard to metabolic decline in elderly people with mild cognitive impairment should be investigated in larger samples over extended treatment periods. Moreover, the compounds underlying the effects observed need to be identified.

The effects of resveratrol supplementation have been studied in both healthy elderly adults and individuals with mild cognitive impairment. The administration of resveratrol (200 mg daily) in healthy adults for 26 weeks enhanced verbal episodic memory, long-term glucose control, and resting-state functional connectivity between hippocampus and neocortical brain areas [46]. In individuals with mild cognitive impairment, resveratrol supplementation (200 mg daily, n = 18) over 26 weeks reduced glycated hemoglobin A1c, preserved hippocampus volume, and improved resting-state functional connectivity of the hippocampus when

compared with controls (n = 22) [55]. Whether these benefits following administration of resveratrol can be extended to cognitive function should be examined.

An increase in the risk of cognitive decline and dementia is found in postmenopausal women. In comparison to placebo, the administration of resveratrol (75 mg twice daily) for 14 weeks in healthy post-menopausal women (aged 45–85 years) elicited increases by 17% in cerebrovascular responsiveness to both hypercapnic and cognitive stimuli [56]. Significant improvements following resveratrol administration were found in verbal memory and in overall cognitive performance, which correlated with the increase in cerebrovascular responsiveness [56]. These results suggest that resveratrol may reduce the increased risk of accelerated cognitive decline in post-menopausal women.

The chronic administration of resveratrol in patients with mild to moderate AD for 52 weeks (500 mg orally once daily with dose escalation by 500-mg increments every 13 weeks, i.e. final dose of 1,000 mg twice daily) showed no effects of resveratrol in regard to hippocampal volume, entorhinal cortex thickness, Aβ42 in plasma or cerebrospinal fluid, or tau or phospho-tau 181 in cerebrospinal fluid [52]. However, resveratrol administration increased brain volume loss compared to placebo [52]. These results suggest no benefits of long-term resveratrol supplementation.

In summary, the findings of published intervention trials of resveratrol in individuals with mild cognitive impairment [55] or mild to moderate AD [52] are disappointing and do not provide evidence of neuroprotective or therapeutic effects.

4. Alcohol and AD

Better health in moderate drinkers compared to those who abstain from alcohol has frequently been reported. For example, population studies have demonstrated protective effects of moderate alcohol consumption against cardiovascular disease and total mortality [57]. This relationship is described as a "J-shaped curve", which is the graphical appearance of health measures plotted against consumption and, in the case of alcohol consumption, shows a lower risk of disease for moderate drinkers compared to non-drinkers, but an increase in risk for heavy drinkers. A J-shaped curve has also been posited to reflect the relationship between alcohol consumption and the risk of dementia, including AD. In a comprehensive meta-analysis, the average ratio of risk for cognitive risk (dementia or cognitive impairment/decline) associated with moderate "social" (not alcoholic) drinking of alcohol was shown to be 0.77, with nondrinkers as the reference group [58]. The benefit of moderate drinking applied to all forms of dementia (dementia unspecified, AD, and vascular dementia) and to cognitive impairment, while no significant benefit against cognitive decline was found [58]. Both light and moderate drinking provided a similar benefit, but heavy drinking was associated with a non-significantly elevated risk of dementia and cognitive impairment. A dose-response meta-analysis of prospective studies found that modest alcohol consumption (≤12.5 g/day) was associated with a reduced risk of dementia, with 6 g/day of alcohol conferring a lower risk than other levels, while excessive drinking (≥38 g/day) may elevate the risk [59]. A weakness of this study [59] is that "current non-drinkers", or the lowest category of intake in each study, were used as a reference group, and no distinction was made between ex-drinkers and life-time abstainers. If the reference group is defined as "current non-drinkers" (without knowledge of previous drinking), this group will include a variable number of former heavy drinkers, who tend to have a higher risk of many disease outcomes ("sick quitters") than lifetime abstainers. If a large percentage of ex-drinkers consist of former heavy drinkers, an apparently protective effect observed in moderate drinkers may be misleading. The findings of other studies did not support the hypothesis that low-to-moderate alcohol consumption prevents cognitive decline (e.g. [60]).

When assessing the effects of alcohol consumption on cognitive risk, most studies did not distinguish between different types of alcoholic beverages. Light-to-moderate wine consumption was associated with better performance in various cognitive tests after a follow-up of 7 years compared to low alcohol intake in both men and women, while no consistent association was found between consumption of beer and spirits and cognitive test results [61]. A meta-analysis indicated that wine consumed in moderate quantities provided a significant reduction in cognitive risk, while beer and spirits did not [58]. However, this result was based on a relatively small number of studies. The mechanisms through which alcohol consumption may protect against cognitive decline are unclear. The positive effect of wine could be due to specific favorable biological effects of wine, but could also be related to confounding variables, such as socioeconomic status and healthier dietary or other lifestyle habits [62].

Even if potentially positive effects of alcohol intake on cognitive risk could be proven, it needs to be emphasized that these effects are likely to be outweighed by general health hazards of alcohol. An analysis of nearly 600,000 people with no history of cardiovascular disease found an

increase in all causes of death when more than 100 g of alcohol (e.g. five 175 ml glasses of wine) was consumed every week [63]. Drinking more alcohol was also associated with a greater likelihood of stroke, heart failure, and fatal aneurysm [63]. These findings provide clear evidence to support a lowering of the recommended limits of alcohol consumption in many countries. In an observational cohort study, weekly alcohol intake and cognitive performance were measured repeatedly over 30 years [64]. Alcohol consumption, even at moderate levels, was associated with adverse brain outcomes including dose-dependent hippocampal atrophy [64]. No protective effect of light drinking compared to abstinence was observed.

In summary, alcohol cannot be recommended as a means to decrease the risk of developing AD.

5. Conclusions

Many naturally occurring polyphenol anti-oxidants have properties that may be useful in the treatment of neurodegenerative diseases. They are not only active scavengers of free radicals but also modulators of pro-survival or pro-apoptotic signaling pathways [65]. Wine-related compounds, including resveratrol, appear to be able to exert neuroprotective or neurorescuing effects through anti-oxidant activities and the ability to antagonize amyloid aggregation, suppress neuro-inflammation, decrease mitochondrial dysfunction, and modulate signaling pathways. The findings of both in-vitro and in-vivo studies suggest that resveratrol has potential in the therapy of AD [19]. Resveratrol has been shown to be safe and reasonably well-tolerated at doses of up to 5 g/day in humans; nausea, diarrhea, and weight loss were the most common adverse events observed [52,66]. However, the clinical efficacy of resveratrol is limited by its poor solubility and ability to cross the brain blood barrier [67]. Future studies need to investigate correlations between the biological/clinical efficacy of resveratrol and its bioavailability in the brain.

The concentration of resveratrol in most wines and grape juices is in the range of 0.05 to 25 mg/L [68]. The bioavailability of exogenous resveratrol ranges from 20% to 50% and the plasma concentrations are around 2 μM [69]. It is difficult to estimate the concentrations in tissues, which are in the nanomolar range and much lower than those used in vitro. It has been calculated that 25 glasses of red wine per day would be necessary to provide a potentially therapeutic dose of 25 mg of resveratrol [70]. Thus, if resveratrol were proven to be useful against AD, it should be provided in supplement form rather than diet. In addition, possible adverse effects of long-term administration of resveratrol should be assessed.

The translation of experimental findings regarding resveratrol into therapeutic benefits requires further characterization of its metabolism, absorption profile, and bioavailability [71]. The demonstration of benefits in human treatment studies will determine the relevance of resveratrol in clinical practice or as a dietary component as a means of modulating the onset or progression of AD. Human trials should consider the poor bioavailability of resveratrol, the need to initiate the experimental therapy long before the onset of symptoms, and the limited knowledge concerning the appropriate form of administration. In view of the slow progression of AD, clinical trials face the challenge of assessing both short and long-term outcomes.

The association between light-to-moderate wine consumption and a reduced risk of developing AD is commonly attributed to a protective effect of resveratrol, which is present in relatively small concentrations in wine. Other phenolic compounds found in wine include flavonoids such as quercitin, anthocyanidins, and catechins, which are all anti-oxidants that may be effective in preventing the effects of aging on brain functions [72]. The role of individual polyphenols in AD prevention requires further investigation. Moreover, resveratrol analogs such as pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene) may have greater therapeutic potential in AD [19,73−75]. This may be due to the more lipophilic nature of pterostilbene, with its two methoxyl groups compared to the two hydroxyl groups of resveratrol. Therefore, the potential clinical benefits of pterostilbene and of combinations of different polyphenols should be investigated in future studies.

In summary, several studies have linked resveratrol to protection against neurodegenerative diseases. However, it is unclear whether the onset of AD can be delayed or the disease mitigated by dietary resveratrol.

6. The bottom line

Despite the neuroprotective activity of resveratrol in various in-vitro and in-vivo models, clinical studies have demonstrated either minimal or no beneficial effects in humans with cognitive impairment or mild-to-moderate AD. Resveratrol analogs such as pterostilbene may have greater therapeutic potential in AD. Wine is not an appropriate source of resveratrol or other potentially neuroprotective compounds, since even moderate drinking poses various health risks, is associated with an increase in all causes of death and is linked to pathological changes in the brain including hippocampal atrophy.

Conflict of interest

The author declares no conflict of interest.

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