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Review

Apples and Their Products Effect on Neurodegeneration and Alzheimer's Disease

Dora Babić[1], Tomislav Babić[2], Saša Missoni[3]

[1]Croatian Association of Nutritionists, Zagreb, Croatia
[2]Polyclinic Bonifarm, Zagreb, Croatia
[3]Institute for anthropological research, Zagreb, Croatia

ABSTRACT

Neurodegenerative disorders such as Alzheimer's disease (AD) are life-threatening and an economical burden to the health-care system. The current pharmacotherapy of AD is symptomatic and focused almost solely on cognition, with a lot of unmet medical needs, particulary in the area of mood and behavioural symptoms. Therefore the requirement for supportive therapy and nutritive support in the form of nutraceuticals and complex foods has been raised and numerous studies have been conducted for the purpose of identifying the ideal nutritional compund and complex food for the support in treatment of AD. As oxidative stress in the brain is the main symptom of AD, foods that are high in antioxidant activity have been identified as potential nutraceuticals for AD. Due to their nutrient combination and antioxidant effect of the nutrients, apples seem to be one of the most promisable complex foods in the nutritive support of AD. In this article we review the potential benefit of apples on human health, combination of apple compounds and their protective effect on neurodegeneration and AD.

Keywords: *Alzheimer's disease, oxidative stress, apple, apple products, nutritive support*

Introduction

Alzheimer's Disease (AD) is the most common form of dementia in the elderly (50-60% of all dementia)[1] and is one of the major causes of disability in today's population. Only in Europe 10 million[2] people suffer from dementia while the world figure is approximatelly 20-30 million[1]. It is predicted that worldwide prevalence will drastically increase due to an increasing number of elderly in the population[3].

Unfortunatelly, current pharmacotherapy does not provide satisfactory support to AD patients[1] since all available drugs for AD are symptomatic, reducing the extent of cognitive decline in less than 30% of all AD subjects, and typically for only 6-12 months[4,5].

The management of AD has few important goals which include: (1) early diagnosis; (2) optimizing physical health, cognitive status, activity and quality of life; (3) observing and treating psychological symptoms and symptoms of behavior; and (4) providing information and long-term support to caregivers / families[6].

AD is undoubtedly accepted as a complex disease of multiple factors due to the presence of numerous interrelated genetic factors and environmental factors[7]. Basically, risk factors can be divided into two groups: (1) those that can not be modified (age, family history of the disease); and (2) the ones that can be modified[8]. Risk factors that can be modified amongst others include also those that are directly related to the way of life - nutrition, education, physical activity, smoking, alcohol consumption and social relations[9].

Over the past few years, there is growing evidence that nutrition, one of the most important factors of quality of life that we can change, plays a significant role in preventing and / or cessation of cognitive decline and AD that today present one of the major public health issues[10]. Research has shown that the relationship between diet and AD is similar to that of diet and cardiovascular disease(s)[11], but there are still no nutrition guidelines for treatment of AD although we have promising results of isolated food components such as certain vitamins, energy substrates, flavonoids and lipids[12]. Therefore there are increasingly apparent aspirations for dietetics research on AD that will focus not only on isolated components of food but on food as a whole which is present in the ordinary diet of an individual[13].

Apples and apple products

Numerous studies have shown association between the consumption of fruits and vegetables and improved health,

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TABLE 1

A REVIEW OF SCIENTIFIC RESEARCH ON THE EFFECT ON CONSUMATION OF APPLE AND ITS PRODUCTS AND/OR BIOACTIVE COMPONENTS ON THE DELAY OF ONSET, PREVENTION AND/OR THERAPY OF CHRONIC DISEASES

Author	Year	Indication	Materials and methods	Subjects	Result
[26]Feskanisch et al.	2000	Lung cancer	Consumption of fruit and veegtables, apples	77,000 women 47,000 men	21% reduced risk in women
[27]Le Marchand et al.	2000	Lung cancer	Consumation of apples and onions		Reduced risk in women and men
[28]Knekt et al.	2002	Lung cancer	flavonoids	10,00 men and women in Finland	Reduced risk
[29]Arts et al.	2000	Epithelial lung caner	apples	728 men	Reduced incidence
[30]Sesso et al.	2003	Cardiovascular diseases	flavonoids	40,000 women	35% reduced risk of cardiovascular disease
[32]Knekt et al.	2000	Thrombotic effects	apples	Population in Finland	Reduced risk
[32]Knekt et al.	1996	Coronary mortality	flavonoids	Population in Finland	Reduced risk in women but not in men
[29]Arts et al.	2001	Coronary heart disase	Apples and wine	35,000 women in Iowa	Reduced risk from coronary heart disease
[33]Woods et al.	2003	Asthma	Apples and pears	1,600 people in Australia	Reduced risk from asthma and bronchial sensitivity
[34]Shaheen et al.	2001	Asthma	Apples and selenium	600 people in Great Britain	Reduced risk
[28]Knekt et al.	2002	Asthma Diabetes mellitus type II	Apples and oranges	10,000 men and women in Finland	Reduced risk Reduced risk
[35]Tabak et al.	2001	Lung function	Apples	13,000 people in Netherlands	Possible positive correlation in lung function reduced risk from chronic opstructive lung disease
[36]Butland et al.	2000	Lung function	apples	2,500 men in Wales	Positive correlation
[37]de Oliviera et al.	2003	Decrease of body mass Decrease of blood glucose	Apples and pears	Overweight women in Brasil	Positive correlation Positive correlation
[38]Ravn-Haren et al.	2013	Decrease of plasma lipids	Whole apples and apple juice		Positive correlation
[39]Brouns et al.	2012	Hipercholesterolemia	Pectin from apples	Men and women with high cholesterol	Reduced levels of cholesterol
[40]Sanchez et al.	2008	Insulin resistance	Pectin from apples	mice	Improvement of glucose metabolism

especially for the consumption of biologically active substances or phytochemicals from foods of plant origin that play a major role in the modulation of numerous processes in the body responsible for the development of the disease, including AD[14].

The greatest attention is given to flavonoids which are considered responsible for the positive effects of certain foods of plant origin on health in general. The most common flavonoids in fruit and vegetables are quercetin and its conjugates[15].

Since they are one of the first three (3) dietary sources of polyphenols in humans and are available throughout the year it is clear that apples and apple products are one of the main foods for assessing their effects on human

health[14]. In the United States (USA), 22% of total input of fruit phenols comes from apples; in Finland apples and onions are the main sources of flavonoids from food; and in the Netherlands apples are in third place of total flavonoid intake from food, behind tea and onions[16].

Apple (*Malus domestica*) belongs to the Rosaceae family which also includes apricots, spinach, peaches, pears and plums. The annual world apple production in 2011/2012 was estimated at 65.23 million square tons, of which 12.2 million square tons were used to produce apple juice[17].

When looking at the total concentration of phenolic compounds, apples are in second place, immediately behind cranberries. What is more important is that apples have the highest amount of free phenolic compounds compared to other fruits, meaning that phenolic compounds are not related to other fruit components and thus are bioavailable in the human organism after consumption[18].

Numerous studies have been conducted on the potential beneficial effect of apples on human health as well as on the reduction of the risk of chronic illness and as chronic disease therapy (Table 1).

Apple compounds

Apples have low fat content and a high proportion of carbohydrates where fructose is dominant. They are also excellent sources of vitamins (especially vitamin C), minerals (potassium and magnesium), triterpenoids (ursolic acid), dietary fiber (soluble and insoluble) and polyphenols[19].

Apples contain about 2–3% dietary fiber[20]. They are rich in insoluble fiber including cellulose and hemicellulose. From soluble fiber, apples contain pectin - one of the most soluble apple fibers, homogalacturonans and ramnogalacturonans. It is considered that apple pectin has the properties of lowering cholesterol[21] as well as positive effects on glucose metabolism[22].

One of the important quality features of apples is the amount of polyphenols. Five major polyphenolic groups are found in apples: flavanols, phenolic acids, flavonols, dihydrochalcones and anthocyanins[23]. Polyphenols are studied intensively due to many positive effects like their anticancerogenic[24] and antiviral properties[2]

Apples contain a significant amount of phytochemicals especially flavonoids whose concentration is conditioned by numerous factors - cultivation, harvesting, storage and processing of raw materials. The type and concentration of flavonoids are also different depending on whether they are in the apple bark or core. The most prominent apple flavonoids are quercetin-3-galactoside, quercetin-3-glucoside, quercetin-3-ramnoside, catechin, epicatechin, procyanidin, cyanidin-3-galactoside, coumaric acid, chlorogenic acid, gallic acid and florizin[16].

In the apple bark we usually find procyanidines, catechins, epicatechins, chlorogenic acid, florizine and quercetin conjugates. In the apple core the following fitonutrients are present: catechol, epicatechin, procyanidine and florizine but at a significantly lower concentration than in the apple bark. The quercetin conjugates are therefore found only in the bark and the only flavonoid which is found in higher concentration in the apple core in relation to the bark is chlorogenic acid[41].

In addition to the part of the apple the flavonoid content is also affected by the ripening of the fruit itself. Concentrations of quercetine, florizine and catechin glycosides as well as chlorogenic acid are higher at the beginning of the apple season and decrease with fruit ripening[42].

Apples that have higher exposure to sunlight have more flavonoids[43].

Studies have also shown that storage under controlled atmospheric conditions over a year does not significantly affect the concentration of flavonoids in apples[44].

Potentially beneficial effects of apples on health

For apples, especially apple bark, strong antioxidant properties have been proven. The total antioxidant activity of apple with the bark was approximately 83 µmol equivalent of vitamin C (total antioxidant activity of 100g apple is about 1500mg equivalent of vitamin C), although the content of vitamin C in 100g apples is approximately 5.7 mg[45]. Thus it is evident that although vitamin C is a strong antioxidant, almost all antioxidant activity of apples is a result from other compounds while vitamin C antioxidant activity accounts for only 0.6%.[4]

In addition to antioxidant capacity apples also exhibit an antiproliferative effect as they inhibit cell proliferation, probably due to a unique combination of phytochemicals[45], and compared to 11 other frequently consumed fruit foods, are third in antiproliferative activity[47].

Inhibition of lipid peroxidation has been demonstrated for apple phenols in human serum, which is the strongest 3 hours after consumation and initial serum levels are restored after 24 hours[48]. The same has been confirmed after consumption of apple juice in mice, where reduced levels of malonaldehyde (MDA), a lipid peroxidation biomarker, have been demonstrated[49].

One of the main apple flavonoids – quercetin, when isolated did not have any effect on lipid peroxidation in mice suggesting that apple properties in reducing lipid peroxidation are the result of a combination of phytonutrients in the apple itself[49].

Along with the effect on lipid peroxidation, it has been found in humans that after consumption of apple juice there is an increase in glutathione peroxidase levels - biomarkers of oxidative stress[49].

Apples and apple products also show a strong influence on preventing the risk of developing cardiovascular disease(s) due to their ability to reduce cholesterol levels attributable to the combined action of polyphenolic components and apple nutritional fibers[49].

Effect of apple and apple products on AD

Evidence suggests that reactive oxygen species in brain may play a role in the development of age-related neuronal impairments. The increase in the concentration of the proinfl ammatory cytokines in aged brain tissue may also represent a contributory factor[50].

Previous studies on the effect of apples and apple products (ex. juice, concentrate etc.) on oxidative processes and symptoms of AD, primarily due to its high phytochemicals content[14,51], are very good scientific bases for future controlled clinical trials. One of the most important factors involved in age-related cognitive decline is the accumulation and constant repeated exposure to reactive oxygen species (ROS) which leads to a reduction of the ability to mitigate long-term effects of oxidative stress[52]. Oxidative stress has been shown in numerous studies to precede the cardinal neuropathologic manifestations of AD and oxidative modifications are further seen in cerebral tissue in early stages of AD. Oxidation of nucleic acids, proteins and lipids are prominent and early changes in AD[53].

Antioxidant therapy is therefore one of the promising theraputic strategies for AD[54]. Daily consumption of a beverage with high antioxidant power, combining extracts of green tea and apple over a period of 8 months in 100 patients (48 AD patients and 52 controls) has shown prevention of decrease of antioxidant status and increase in antioxidant enzymes values in patients with AD[55].

A vitamin/nutraceutical formulation containing folate, vitamin 12, alpha-tocopherol, S-adenosyl methionine, N-acetyl cysteine and acetyl-L-carnitine (of which all are nutrients found in apples) showed a clinically significant delay in decline in the Dementia Rating Scale and clock-drawing test in patients with AD compared to the placebo group after 9 months of consumation[56].

A formulation of folate, vitamin 6, alpha-tocopherol, S-adenosyl methionine, N-acetyl cysteine and acetyl-L-carnitine in a 12-month, open-label trial with 14 community-dwelling individuals with early-stage Alzheimer's disease showed improvement in the Dementia Rating Scale and Clock-drawing tests. Family caregivers also reported improvement in multiple domains of the Neuropsychiatric Inventory (NPI) where the Performance on the NPI was equivalent to published findings at 3 to 6 months for donepezil and exceeded that of galantamine and their historical placebos[57].

On the other hand, a double-blind, multi-site, phase II study was conducted in which 106 individuals with AD were randomized to a nutraceutical formulation (NF; folate, alpha-tocopherol, B12, S-adenosyl methioinine, N-acetyl cysteine, acetyl-L-carnitine) or placebo for 3 or 6 months, followed by an open-label extension where participants received NF for 6 additional months. Results showed that the NF cohort improved versus the placebo cohort within 3 months[58].

Although it is universally accepted that fruit and vegetables intake is protective, there is no clear consensus about the effects of consuming the juices that are extracted from them[59,60]. Concerns about the lower fiber content and the higher caloric density of fruit juices when compared to fruit suggesting that fruit juices are comparable to sugar-sweetened beverages has been denied when evidence published in 2006 suggested that the 100% fruit juices (with no added nonjuice components, sweeteners etc.) retain the majority of nutrients and phytochemicals of whole fruit and therefore show potential benefit on human health[59].

With the exception of fiber and vitamin C, one small fruit or half a cup of fruit is similar in vitamin and mineral content to one half of a cup of 100% fruit juice[61].

Fruit and vegetable juices may play an important role in delaying the onset of Alzheimer's disease, particularly among those who are at high risk for the disease. These results may lead to a new avenue of inquiry in the prevention of Alzheimer's disease[62].

As different polyphenol forms have been studied for cognitive benefits in the elderly, it has been demonstrated that apple, grape and wine extracts rich in antocyanins and flavan-3-ols show the ability to minimize cognitive decline in rodent models of AD.[2] Interventional studies in people older than 45 years with mild cognitive decline display potential improvement in several assessment tools, in particular verbal memory and word recognition[64].

It has been shown that regular consumption of fresh apples increases the level of antioxidative enzymes in erythrocytes of the elderly and thus raises total antioxidative potential of the organism[65]. An antioxidant effect can be registered as soon as 30 minutes after consuming 150 ml of apple juice and is present for about 60 minutes[66]. Although 43 apple juice components have been isolated, it is not quite clear which of them attribute to the antioxidant effect the most since all of them exhibit an antioxidant effect at some level[67]. Quercetin and floretine seem to be the most effective[68].

Quercetin has also shown decreases in extracellular ß-amyloidosis, tauopathy, astrogliosis and microgliosis in the hippocampus and the amygdala and has induced improved performance on learning and spatial memory tasks and greater risk assessment behaviour based on the elevated plus maze test[70].

In all likelihood, the antioxidative potential of apple juice is responsible for the repairment of behavioral disorders and learning abilities on animal models with AD[71,72,73], while the same model shows regenerative effects of apple juice on damaged synapses[74] whose damage is considered the key to functional neuropathology of AD.

Apple juice concentrate, administered ad libitum in drinking water has been found to compensate for the increased reactive oxygen species and decline in cognitive performance in maze trials observed when normal and transgenic mice lacking apolipoprotein E are deprived of folate and vitamin E[71].

Supplementation with apple juice concentrate also prevents the increases in glutathione synthase transcription and activity which provides further evidence that the antioxidant potential of apple juice concentrate can compensate for dietary and genetic deficiencies that otherwise promote neurodegeneration[72,75].

Apple juice concentrate administered in drinking water maintains acetylcholine levels that otherwise decline when adult and aged mice are maintained on a diet deficient in folate and vitamin E and containing iron as a pro-oxidant which shows that the consumption of antioxidant-rich foods such as apples can prevent the decline in cognitive performance that accompanies dietary and genetic deficiencies and aging[76].

It also appears that apple juice reduces the expression of presenilin-1[73], proteins responsible for the deposition of insoluble ß-amyloid, whose brain accumulation is pathognomic to AD. Apolipoprotein E function increases the oxidative stress and potentiates the deleterious activity of preseniline-1 as well as folate deficiency increases preseniline-1 expression, a study was conducted to review the effect of apple juice concentrate on presenilin-1 expression in ApoE deficient mice. Study results showed that apple juice concentrate prevented or decreased these increases[77].

S-adenosylmethionine (SAM) is another compound that is easily depleted due to lack of folate and also leads to preseniline-1 overexpression thus neurodegeneration. Direct supplementation of SAM has shown to attenuate preseniline-1 overexpression and since apple juice concentrate contains levels of SAM that are sufficient to prevent preseniline-1 overexpression, more evidence is available that apple juice concentrate is beneficial in prevention of cognitive decline[77].

Since a portion of neurotoxicity of amyloid-beta is due to oxidative stress, a study was conducted to review the effect of apple juice on amyloid-beta in patients with AD through an apple juice concentrate. Apple juice concentrate prevented the increased generation of reactive oxygen species (ROS) normally induced by amyloid-beta treatment under these conditions and it also prevented amyloid-beta-induced calcium influx and apoptosis, each of which results in part due to increased ROS. These findings suggest that the antioxidant potential of apple products can prevent amyloid-beta-induced oxidative damage[78].

It has been shown that apple juice concentrate dose not alter overall signaling, but fosters an organization of signals into less frequent and longer »bursts« of activity. It seems that apple juice concentrate modulates signaling patterns by stimulating the activity of inhibitory neurons which shows that apple juice concentrate may foster improved cognition at least in part by stimulation of inhibitory activity in situ[79].

Aged rats fed with a diet enriched with fresh apples showed a significant decrease in anxiety levels and they improved their ability to sustain long-term potentiation (LTP) by reaching the level of young rats. Furthermore, superoxide dismutase (SOD) activity was increased in aged rats who were fed with a standard diet, while the SOD activity of aged rats fed with the fresh apple-enriched diets was at a level of young animals[74].Apple juice also reduces the neurotoxicity of soluble ß-amyloid oligomers in vitro, which is attributed to the effect of S-adenosyl methionine (SAM) in apple juice[80]. SAM can exert a direct effect on glutathione S-transferase (GST) activity. AD is accompanied by reduced GST activity, diminished SAM, and increased S-adenosylhomocysteine (SAH), the downstream metabolic product resulting from SAM-mediated transmethylation reactions, when deprived of folate. Due to this, it is believed that SAM plays a critical role in maintenance of neuronal health and suggesting a possible role of SAM as a neuroprotective dietary supplement for AD patients[81].

Caffeic acid which is also one of the nutrients found in apple juice has shown beneficial effects on learning ability in rat models with AD where caffeic acid significantly reduced learning deficits and increased cognitive function in the rats with AD. Caffeic acid administration also resulted in a significant decrease in acetylcholinesterase activity and nitrite generation and suppressed oxidative stress, inflammation, nuclear factor-κB-p65 protein expression and caspase-3 activity as well as regulating the protein expression of p53 and phosphorylated (p-)p38 MAPK expression in the rats with AD. Thus it seems that the beneficial effects of caffeic acid on learning deficits in a model of AD were due to the suppression of oxidative stress and inflammation through the p38 MAPK signaling pathway[82].

A study that reviewed protective effects of coffee components determined that quercetin reduced oxidative/nitrative damage to DNA, as well as to the lipids and proteins of SH-SY5Y cells. There was also a resultant increase in GSH, an antioxidant enzyme, in SH-SY5Y cells which all indicates that quercetin, which is also a major component in apples, is the major neuroprotective component in coffee against Parkinson's disease and Alzheimer's disease[82].

Conclusion

Numerous epidemiologic studies have shown the potential benefit of apples and their products on various chronic diseases including neurodegenerative diseases such as AD. In vitro and animal studies have demonstrated that apples, apple juices and apple juice concentrates have high antioxidant activity and therefore the ability to alter neurodegenerative processes in AD brains.

Although the isolated compounds and phytonutrients in apples such as quercetine each for themselves show significant antioxidant and protective activity, it seems that the combination of phytonutrients in apples is responsible for the beneficial effects on neurodegeneration.

Through different in vitro, animal and human studies, apples and their products have shown numerous different effects on AD clinical signs and symptoms thus showing their potential benefit and supportive use in the treatment of AD for which the requirement of randomized clinical trials is necessary in the future.

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Dora Babić

Croatian Association of Nutritionists, Ilica 134/I, 10 000 Zagreb, Croatia
e-mail: dora@windowslive.com

UTJECAJ JABUKE I NJEZINIH PROIZVODA NA NEURODEGENERACIJU I ALZHEIMEROVU BOLEST

S A Ž E T A K

Neurodegenerativni poremećaji kao što je Alzheimerova bolest (AB) opasni su po život i veliki ekonomski teret zdravstvenom sustavu. Sadašnja farmakoterapija AB je simptomatska i usredotočena gotovo isključivo na bihevioralne smetnje dok puno simptoma nije liječeno osobito u području promjena raspoloženja i simptoma ponašanja. Stoga se pokazala potreba za potpornom terapijom i nutritivnom podrškom u obliku nutraceutika i kompleksnih namirnica, te su provedena brojna istraživanja s ciljem utvrđivanja idealnog prehrambenog kompleksa i složene hrane za podršku u liječenju AB. Budući da je oksidativni stres u mozgu glavni simptom AB, hrana bogata antioksidantima identificirana je kao potencijalni nutraceutik za AB. Zbog sadržaja hranjivih tvari i njihovog antioksidacijskog učinka, čini se da jabuka predstavlja jednu od najboljih složenih namirnica u nutritivnoj potpori AB. U ovom članku ćemo prikazati pregled istraživanja koji pokazuju potencijalnu dobrobit jabuka na ljudsko zdravlje, kombinaciju spojeva jabuka i njihov zaštitni učinak na neurodegeneraciju i AB.