

Apple Cider Vinegar (ACV) and their Pharmacological Approach towards Alzheimer's Disease (AD): A Review

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ABSTRACT

Alzheimer's disease (AD) is a neurological degenerative condition described by a progressive decline in memory and associated with dementia. This disease arises usually after 65 years in individuals. Oxidative stress is the major cause of dementia connected with Alzheimer's disease. Here there is an imbalance between the creation and clearance of amyloid β protein, which leads to accumulation of amyloid β plaque in the brain and produces neuronal cell death. Anti-Alzheimer's medications help to cover the symptoms of disease but do not cure the cause of disease. Confirmatory studies suggest that a healthy diet of fruits and green vegetables containing phenolic combinations may reduce the risk of Alzheimer's disease (AD). Apple cider vinegar (ACV) contains phenolic compounds like catechin, caffeic acid, gallic acid, chlorogenic acids and p-coumaric acid having high antioxidant potential. Phenolic compounds are not essential for survival but it can protect against various chronic diseases. Various researches showed that phenolic compounds cure β amyloid and tau protein correlated problems associated with AD. Regular consumption of these healthy substances in the diet may prevent the neuronal cells from oxidative stress which leads to AD. The purpose of this review is to highlight the health benefit role, functional property and therapeutic uses of Apple Cider Vinegar.

Key words: Apple Cider Vinegar, Alzheimer's disease, Oxidative stress, Phenolic compounds, A β aggregation, Pharmacological activities.

INTRODUCTION

The lifestyle of humans is mostly connected with the developing of numerous complicated neurological conditions associated with aging. These conditions include intellectual abilities, language problems and memory loss. The prolonged state of these symptoms together develops intellectual deficits in the elderly and is commonly mentioned as dementia. It is predicted that 46.8 million people in this world have dementia and incidences are expected to grow every year and it would be 131.5 million in 2050.^{1,2}

Alzheimer's disease (AD) is the most predominant neural condition associated with dementia. The most troubling complication associated with AD is forgetting daily routine functions. Although the

mechanism behind this neurodegeneration is completely unknown but several genetic and environmental factors, together with vascular pathology have recently shown the growth and progression of Alzheimer's disease.³

In Alzheimer's disease (AD), an individual may seem to be fit but has more and more distress making sense. The problem associated with AD includes memory loss, poor judgment for making decisions, loss of spontaneity, time taking normal daily activity, repeating questions, mood and personality changes and anxiety and aggression. The major cause of AD is due to amyloid β protein (amyloid plaque) aggregation outside the neuronal cells and intracellular Tau protein hyper-phosphorylation

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composed of neurofibrillary tangles (NFTs) and loss of cholinergic system functions⁴ shown in Figure 1.

Occurrence of Alzheimer's disease

In 2005, Alzheimer's disease International Commissioned group spread consensus on dementia and created an epidemiological document acquired over recent years. The outcomes showed that 24.2 million people suffered with dementia and 4.6 million new patients arising every year.⁵

Expected growth rate of dementia incidence from 2001 to 2040 is 172% and 102% in Western Europe and North America higher prevalence of dementia (172% and 102%), China more than 300%, Latin America 400%, North Africa and Middle Eastern Crescent 385%. The annual incidence rates increased exponentially with age after 65 years.⁶ There is nearly a 15-fold increase in the frequency of dementia, predominately Alzheimer's disease between the ages of 65 to 85 years^{5,6} (Figure 2).

Mechanism of Alzheimer's disease

Alzheimer's disease (AD) persuaded dementia is typically represented with synaptic injuries and loss of neurons through propagation of microglial cells.⁷⁻⁹ Based on new studies, neurodegeneration of the hippocampal neurons, cortex and limbic region of brain is a probable mechanism involved in AD.⁹ Alzheimer's disease is characterized by the two major hallmarks: extracellular aggregation of β -amyloid ($A\beta$) and intracellular accumulation of tau protein. Both of these complexes are insoluble in nature. $A\beta$ is the main factor of senile plaques and tau phosphorylation forms neurofibrillary tangles.

Amyloid β protein is composed of 36 to 43 amino acids which are a part of APP (amyloid precursor protein). APP is a trans membrane protein, produced by neurons and other brain cells. This protein is present in extraneuronal tissues. The $A\beta$ is the part of the trans membrane domain of APP and is derived by the cleavage of APP with β and γ -secretase enzymes. An imbalance between the production and metabolism of amyloid β protein produces toxicity in neurons synapses. Formation of $A\beta$ protein is typically mediated by the activity of enzyme including γ -secretase and BACE-1 metabolism of $A\beta$ protein is produced by an active proteolytic enzyme ApoE (chaperone) besides lysosomal and non-lysosomal pathways.¹⁰⁻¹² These $A\beta$ monomers are polymerized into insoluble $A\beta$ 42 oligomers, which participate in amyloid accumulation. These $A\beta$ residues produced microglial infiltration, formation of ROS (reactive oxygen species), synaptic

damage, neurotoxicity and neurodegeneration. Additionally $A\beta$ aggregations also initiate hyperphosphorylation of tau protein and their cleavage (Figure 3). This phosphorylation and cleavage is induced by $A\beta$ activated enzyme such as CDK5, GSK-3 β and caspases. These enzymes induce tau phosphorylation and formation of intracellular neurofibrillary tangles which are insoluble inclusions.¹³⁻¹⁵ Tau accumulates as a pair of fibers which are twisted around one another and formed paired helical filaments structure (PHFs) (Figure 3).

Risk Factors Associated With Alzheimer's

Numerous features have been associated with AD. Diabetes, cardiovascular complications, obesity, dyslipidemia and smoking has found to increase the risk of Alzheimer's disease in old age¹⁶ (Table 1, Figure 4). Remarkably cerebrovascular disease including large cortical infarcts, cerebral hemorrhage, hypoperfusion and other effects produces dementia which is associated with Alzheimer's disease.¹⁷⁻²³

Existing Anti-Alzheimer's Medication

Prescriptions which prescribe to control the improvement of AD indications become comparatively less effective after some time as Alzheimer's turns out to be worse. Specialists are searching for new strategies to treat Alzheimer's disease (AD). There are various clinical medications produced by pharmaceutical companies for the treatment of Alzheimer's disease.²⁴ Rivastigmine, Galantamine and Donepezil mostly act on acetyl cholinesterase and prevent the hydrolysis of acetylcholine, resulting higher concentration of acetylcholine in cerebrum which produces better communication between the neurons. Anti-Alzheimer's medication found in market shown in Table 2.²⁵

Efficacy of Dietary Nutrients in Preventing Alzheimer's disease

Fatty acids

Several examinations have explored the properties of polyunsaturated fatty acids (PUFAs) in avoiding or preventing AD. The PUFAs are the important component of cell membrane and maintain the fluidity of membrane which is significant for synaptic vesicle fusion followed by neurotransmitter communication. The PUFAs contain eicosapentaenoic acid (EPA), omega-3 fatty acids and docosahexaenoic acid (DHA). So PUFAs show a significant dietary involvement in preventing the neuronal loss and improving learning and memory.²⁶

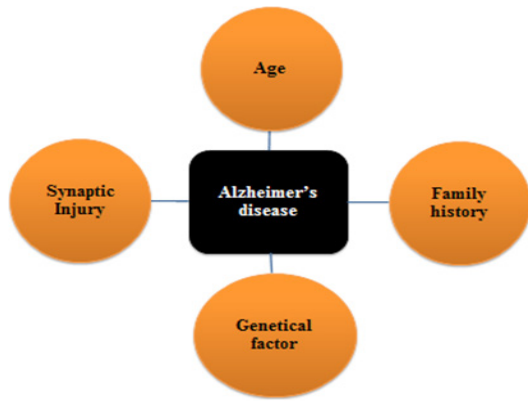


Figure 1: Causes of Alzheimer's disease (AD).

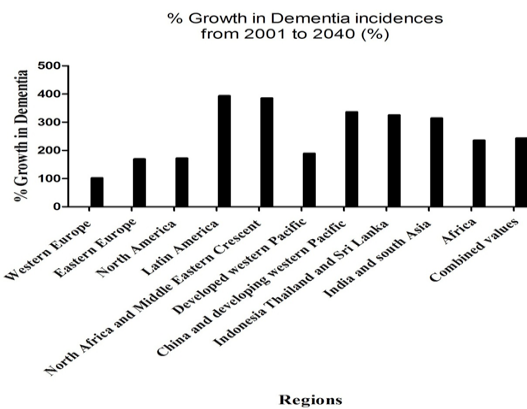


Figure 2: Predictive percentage increase of dementia in developed and developing regions.

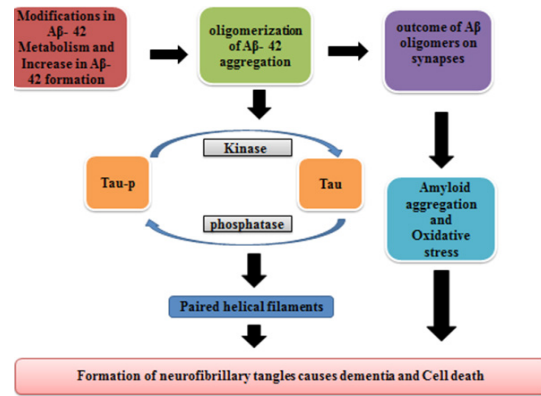


Figure 3: Steps involved in the generation of Alzheimer's disease (AD).

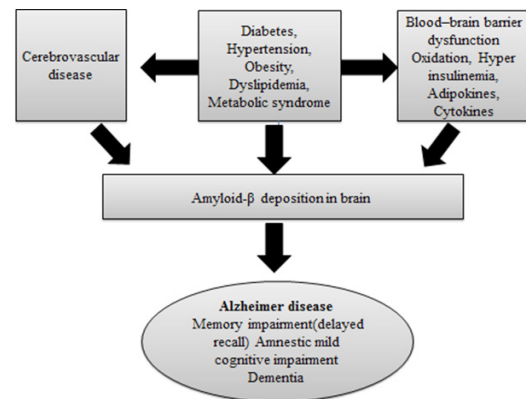


Figure 4: Mechanisms linking vascular risk factors and Alzheimer's disease (AD).

Vitamins

Vitamins have high antioxidants potential and scavenge free radicals effectively. Free radical generation in the brain contributes to progressive failure of cognitive abilities and induces dementia. Clinical trials on vitamin E supplementation carried out for patients with moderate AD confirmed that vitamin E reduces the progression of infection.^{27,28} Other vitamins like Vitamin A and B were found to be lower in the plasma and serum of the geriatric patients with psychological defects.^{29,30} *In vitro* studies have shown a direct correlation of the presence of Vitamin A and β-carotene in case of AD concerning improvement in brain health.³¹

Phenolic compounds

Dietary phenolic compounds have been prescribed as a potential functional food to prevent memory decline.³² Phenolic compounds are regular substances present in plants, natural products, vegetables and fruits. Some polyphenols like 4-O-methyl honokiol, resveratrol, epigallocatechin-3-gallate (EGCG) have been potential

to provide protection against Alzheimer's disease.³³ Their property might be because of antioxidant and anti-inflammatory properties as well as a variety of chemical enzymatic reactions and intracellular signaling pathways. The neuronal signaling changes with aging by acting on CREB/ERK pathway explain synaptic plasticity and long-term potential effects, refining memory in humans.³⁴⁻³⁷

Phenolic Compounds Found in Different Type of Vinegar

Polyphenolic compounds of different groups are found in vegetables and fruits. Their biochemical deviations include thousands of combinations from phenolic acids to flavonoids compound. Phenolic compounds have different health beneficial effects, like strong antimicrobial, anticarcinogenic and antioxidant properties which are already reported.³⁸ The interest is focused on these compounds due to uniformly higher beneficial fitness properties. Fruits and vegetables also possess health-promoting fibers, phenolic acids,

Table 1: Factors linked with Alzheimer's disease (AD).¹⁶

Features	Direction	Mechanisms
Obesity	Increased	Diabetes inflammation
Smoking	Increased	Cardiovascular defects, Oxidative stress
Hypertension	Increased and Decreased	Microvascular disease
Type II Diabetes	Increased	Cerebrovascular effects, Insulin and A β compete for clearance
Cardiovascular Complications	Increased	Parenchymal destruction In brain, leads to increases A β deposition
Traumatic Head injury	Increased	Neuronal Cell death associated with A β Deposition
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Anti-inflammatory and Antioxidant

Table 2: Popular Medications for the treatment of AD.

Popular Medications	Phase of treatment	Targeted Pathway	References
Donepezil	Effective in all phases	AChE Inhibitor	25
Galantamine	Mild to moderate	AChE Inhibitor	25
Memantine	Moderate to severe	N-Methyl-D aspartate Receptor	25
Rivastigmine	Mild to moderate	AChE Inhibitor	25
Tacrine	Mild to moderate	AChE Inhibitor	25

vitamins, minerals and flavonoids. Phenolic compounds are not a fundamental element for survival but can provide long term protection against a number of chronic diseases.³⁹ there are various phenolic compounds present in different vinegar shown in Table 3.⁴⁰⁻⁴³

Apple Cider Vinegar

Apples are essential resources of antioxidants that prevent free radical generation. The apples have high nutritive value and their products are a good source of phenolic compounds, vitamins, minerals, calcium, potassium, phosphorus which are useful in various chronic diseases. Apple cider vinegar is made up from renewed pressed apples, similar to apple juice, treated

Table 3: Vinegars containing phenolic compounds.

Types of different Vinegar	Phenolic compounds	References
Apple Cider Vinegar	Gallic acid, catechin, caffeic acid, epicatechin, chlorogenic acid and p-coumaric acid	40
Grape Vinegar	Catechin, Gallic acid, chlorogenic acid, syringic acid and ferulic acid	41
Sherry Vinegar	Protocatechuic and Gallic acid, protocatechualdehyde, tyrosol, p-OH- benzoic acid, catechin, p-OH-benzaldehyde, syringic acid, vanillin, caftaric acid, cis-p-coutaric acid, trans-p-coutaric acid, fertaric acid, cis-p-coumaric acid, trans-p-coumaric acid, ferulic acid.	42
Traditional Balsamic Vinegar	Gallic acid, Furan-2-carboxylic acid, 5- hydroxyfuran-2-carboxylic acid, 4-hydroxybenzoic acid, vanillic acid, protocatechuic acid, syringic acid, isoferulic acid, p-coumaric acid, ferulic acid and caffeic acid	43

in the same way but it is not filtered. ACV is formed from Cider that has undergone acetous bioconversion and contains low acetic acid (less than 5%), flavonoids, phenolic compounds, organic acids, minerals and vitamins.⁴⁴

Pharmacological Activities of Apple Cider Vinegar ACV act as anticancer

In 2001 Abe *et al.*⁴⁵ assessed the antitumor substance of apple cider vinegar against Meth-A fibrosarcoma using female Balb/c mice. In 2005 Barth *et al.*⁴⁶ used a well-established rodent model for persuading colon damage associated with colon cancer by 1,2-dimethylhydrazine and found that cloudy apple juice reduced the DNA damage, hyperproliferation and act as cancer-preventing agent. Pelingo apple juice suppressed the proliferation of breast cancer cells and made cell accumulation in the cell cycle G2/M phase. In addition the apple juice also inhibited 12-o-tetra-decanoylphorbol-13-acetate (TPA) induced tumor genesis of different cell lines.⁴⁷

Apple polyphenols contain procyanidins, flavonoids, epicatechin, catechin which significantly suppressed

colon cancer cells.⁴⁸ Polyphenols present in apple cider vinegar has cytotoxicity effects in human urinary bladder cancer cells (TSGH-8301) associated with apoptosis and oxidative stress.⁴⁹ In 2008 Clarissa Gerhauser⁵⁰ has written a review article on Cancer chemoprotective potential of apple components and apple juice. This review enclosed *in vivo* animal data, as well as clinical data, showed a targeted mechanism of apple products towards cancer.

ACV act as Anti diabetic

Apple cider vinegar (ACV) that is made from fermentation of Apple juice has been used as a folk medicine for diabetes. Diabetes is the metabolic disorder characterized by the hyperglycemic effect. In 2008, studies of shishehbor *et al.*⁵¹ showed the protective effect of ACV on lipid profile in normal and diabetic rats model. Apple derived products modulate the gut microbiota and improved high fat diet-induced body weight gain, hyperglycemia, hyperinsulinemia and other metabolic disorders in rodent models.⁵²

The metabolic disorders caused by high fat diet were improved by ACV, which proved antihyperlipidemic effect and prevented the atherogenic effects.⁵³ Apple cider vinegar (ACV) produced antihyperglycemic effect by the reduction of inflammatory response, reduced the oxidative stress-related markers and normalized the lipid profiles in the complication of Diabetes.⁵⁴ In 2016, studies of Morgan *et al.*⁵⁵ observed the protective effect of ACV on type II diabetes management.

Based on the Meta analysis, it has been reported that apple products consumption (apple juice, sauce) was connected with a lower prevalence of obesity.⁵⁶ In 2016 Fathy and Drees⁵⁷ performed a study of cloudy apple juice and apple peel extract on rat pancreas. The apple juice induced antihyperglycemic effects by the reduction of inflammation, modification of the oxidative stress and reduced the lipid profile, proposing a useful target for diabetes mellitus.

ACV act as Anti-inflammatory

In 2014 Naziroglu *et al.*⁵⁸ showed that ACV modified serum lipid profile, erythrocyte and liver membrane oxidative stress in mice. Dietary flavonoids isolated from apples reduced the inflammation related markers like interleukin-11, interleukin-2 in intestinal tissue of mice.⁵⁹ Apple polyphenolic compounds reduced the inflammatory response of kidney via decrease the expression and activity of COX-2 in rodent model.⁶⁰

Apple cider vinegar has a number of flavonoids and highly effective polyphenolic compounds (Yang *et al.* 2010; Budak *et al.* 2011; Denis *et al.* 2013),⁶¹⁻⁶³ which elucidate the antioxidant potential against oxidative

stress, free radical generation in tissues and erythrocytes. In 2011 Budak *et al.*⁶² determined the cholesterol lowering effect of apple vinegar in rats fed on high fat diets and estimated the serum triglyceride levels, total cholesterol, lipoproteins (HDL, LDL, VLDL) of different groups.

ACV act as Hepatoprotective

Extract of apple polyphenolic compounds reduced the noxious effect of Aluminum in the liver of rodent species.⁶⁴ Polyphenolic compounds improved the SOD (Superoxide dismutase) and catalase activity associated with ATP synthesis. In 2015 Kuzniak *et al.*⁶⁵ observed the effect of apple juice on hepatocarcinogenic activity induced in rats. These results indicated that apple juice protects liver damage. In 2015 Moura *et al.*⁶⁶ conducted a study on rats that exhibited that apple juice was able to prevent genotoxicity and oxidative stress persuaded by Cadmium.

ACV act as the reduction in cardiotoxicity

Atherosclerosis is a chronic disease connected with inflammatory stimulation and oxidative stress which generates the cardio vascular diseases. In 2018 Wu⁶⁷ proposed a study and results showed that cardiovascular health products produced potential effects with apple cider vinegar to improve atherogenesis, ameliorate inflammation and reduced triacylglycerol in mice serum. Polyphenolic compounds in apple peel extract reduced arsenic trioxide induced cardiotoxicity in H9c2 cells. The extract altered the activity of SOD, catalase, glutathione, GSH (Glutathione reductase) and caspase 3.⁶⁸

Apple intake was associated with lower risk of all chronic diseases.⁶⁹ In 1994 Laranjinha *et al.*⁷⁰ observed that Polyphenolic compounds like chlorogenic acid found in apple cider vinegar which reduced the oxidation of lipoproteins (especially LDLs) and prevented cardiovascular complications.

ACV act as Antioxidants, Antimicrobial and Antifungal

It was found that ACV consumption increased antioxidants enzymes including SOD and glutathione peroxidase. In 2000 Lu and Foo⁷¹ carried out a study that showed the antioxidant and free radical scavenging activity of apple cider vinegar containing polyphenolic compounds. In 2016 Seydim *et al.*⁷² made an experimental model on rats for evaluation of the antioxidant potential of apple cider vinegar and grape vinegar. In 2018 Yagnik *et al.*⁷³ observed the antimicrobial activity of ACV against various bacteria like *E. coli*, *Staphylococcus aureus* and *Candida albicans* and also checked microbial protein expression.

Apple cider vinegar (ACV) also has antifungal activity against candida species involved in denture stomatitis.⁷⁴ In 2011 Hyson wrote a comprehensive review on apples and apples constituents followed by a connective link between the apple products with different chronic diseases and their relationship with human health.⁷⁵ This review contained various *in vitro* studies and clinical data analysis supported to apple products.

ACV act as the reduction in Cognitive impairments, Immunomodulator

A number of studies from the Shea *et al.*⁷⁶⁻⁸² produced valuable results of apple juice focused on Alzheimer's disease linked with ageing. In this study aging showed impaired memory functions and oxidative markers in the mice brain. When aged mice received the dilute form of apple cider vinegar in drinking water, there was a significant improvement in cognitive functions and increased antioxidant activity.⁷⁶

Memory impairment, oxidative stress and reduction of acetyl choline signaling are the major symbols of Alzheimer's disease. Apple juice also prevents the reduction of acetylcholine depletion connected with aging and oxidative stress and maintains the neuronal communications.⁷⁹ In 2017 Safari *et al.*⁸³ performed a study to investigate the Immunomodulatory potency of ACV and found ACV more effective, act as an immunomodulator on the systemic and mucosal immune response.

CONCLUSION

ACV (Apple cider vinegar) is a natural health-promoting food which includes various potential health benefits. Due to the existence of various polyphenolic compounds, it has high antioxidant, anti-inflammatory action, hepatoprotective and anti-cancer action. The antioxidant mechanism defined essential suggestions for a protective effect of ACV not only cancer but also cardiovascular diseases, asthma and potentially diabetes. Similarly, oxidative stress and mutation in gene coding amyloid precursor protein (APP) and aging are the main origins of Alzheimer's disease. However, research data signifying that antioxidant effects are imperative, including the suppression of neurotoxic mediators in Alzheimer's diseases. So regular consumption of ACV as a part of a healthy diet may prevent the oxidative effect of cells which is the main cause of Alzheimer's disease and it could be an economical and recurrent source of dietary antioxidant. Ongoing work continues to define mechanisms behind this followed by *in vivo* and *in vitro* experiment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AD: Alzheimer's Disease; **ACV:** Apple Cider vinegar; **NFTs:** Neurofibrillary tangles; **A β :** β -amyloid; **APP:** Amyloid precursor protein; **BACE 1:** Beta-secretase 1; **GSK3 β :** Glycogen synthase kinase 3 β ; **CDK5:** Cyclin-dependent kinase 5; **PHFs:** Paired helical filaments structure; **PUFAs:** Polyunsaturated fatty acids; **ERK:** Extracellular-signal regulated kinase; **CREB:** Cyclic AMP response element binding protein; **COX-2:** Cyclooxygenase-2; **LDL:** Low density lipoprotein; **HDL:** High density lipoprotein; **VLDL:** Very low density lipoprotein.

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