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Introduction

Alzheimer's Disease (AD), the most common form of dementia, is a neurodegenerative disease characterized by a progressive loss of neural cells leading to nervous system dysfunction. The hallmark signs are memory loss and decreased abilities to make judgements and perform activities of daily living[1]. Because of the increasing lifespan of humans, the projected number of people 65 years and older diagnosed with AD is expected to reach 13.8 million by the year 2050[2]. Biologically, AD is characterized by deposition of beta-amyloid protein (Aβ) and tau neurofibrillary tangles (NFTs). The deposition of Aβ occurs due to the cleavage of amyloid precursor protein (APP) changing from α-secretase to β-secretase and γ-secretase. This change in enzymatic activity causes larger Aβ molecules to form which then stack on top of one another creating amyloid plaques[3]. NFTs accumulate when isoforms of tau, a microtubule-associated protein, begins to hyperphosphorylate and fold atypically[1]. Over time, these accumulations of amyloid plaques and NFTs lead to brain shrinkage and atrophy causing the well documented signs of AD such as memory problems, impaired judgement, and personality changes[1,4].

AD is classified into two types, Familial Alzheimer's Disease (FAD) and Sporadic Alzheimer's Disease (SAD). FAD, also known as early-onset AD, accounts for approximately 5% of all cases and occurs via genetic inheritance, beginning between the ages of 40 and 60[5]. There are three genetic mutations that account for FAD, these are mutations in the genes that encode for presenilin 1 (a subunit of γ-secretase), presenilin 2 (assist in processing APP), and APP itself[4]. SAD, or late-onset AD, typically occurs after the age of 65. It is not entirely understood what causes SAD, but research indicates genetics, lifestyle, and environmental factors, such as diet, disease state, age, socioeconomic status, and educational level, impact its development[5].

Hypotheses for AD development

Over the past several decades there have been many advances in AD research; however, the cause is still unknown. Development of AD follows a well-documented path, known as Braak staging. First described in 1991, Braak staging has six distinctive phases of AD grouped into three units based on the location of NFTs. Stages I-II occurs in the transentorhinal and entorhinal regions, III-IV are in the limbic allocortex and its adjacent neocortex, and V-VI are in the neocortex[6]. Once AD begins there is no reversing the disease; in order to better understand the disease researchers have hypothesized over the causes of disease progression. The main hypotheses include the amyloid, tau, oxidative stress, cholinergic, N-methyl-D-aspartate (NMDA) receptor, and altered calcium homeostasis[7-11]. More recently, impaired glucose metabolism in the brain, pathogenic virus, and prion disease hypotheses have emerged as possible causes of AD[10,12,13] (Figure 1). Each of these pathways will be explored in more detail but a brief description is included here. The amyloid and tau hypotheses are the most common as the presence of amyloid plaques and NFTs are the definition of AD. The amyloid hypothesis centers around the creation of amyloid plaques formed from longer sheets of $A\beta_{40-42}$ while the tau hypothesis focuses on the accumulation of NFTs leading to neuron death[7]. In oxidative stress, neuronal hypoxia caused by an increase in reactive oxygen species (ROS) occurs[7]. With the cholinergic hypothesis, cholinergic function is lost leading to a decrease in the neurotransmitter acetylcholine (ACh) and subsequent increases in cholinesterase[8]. At the NMDA receptor, neuronal death occurs after excitotoxicity causes increased glutamate and decreased NMDA receptors. The altered calcium homeostasis hypothesis focuses on altered mitochondrial function due to changes in enzymatic activity. This decreased mitochondrial function causes defects in the electron transport chain, leading to production and deposition of $A\beta$[7]. More recently, high

carbohydrate diets causing impaired glucose metabolism in the brain due to a decrease in lipoprotein creation in the liver has been proposed as a possible mechanism of action[10]. In 2018, researchers proposed certain viruses, with emphasis on herpes simplex virus, have the ability to stimulate the accumulation of Aβ[12]. Lastly, prion disease, which occurs when the prion protein causes normal proteins in the brain to misfold, is considered a possibility for AD development[14]. This hypothesis centers around cellular prion protein (PrP^C) acting as a cellular surface receptor for Aβ[13].

AD and nutrition

Not only are researchers divided on the mechanism for AD development, but the research into diet and its impact on these hypotheses is limited. A focus on the daily consumption of complex carbohydrates; including vegetables, whole grains, fruit, nuts, seeds, and legumes has been emphasized, with a strong correlation between adherence to a Mediterranean diet and overall cognitive performance[7,15]. One study reported that consumption of vegetables, fruits, nuts, and fish were associated with improved subjective cognitive function when compared to the intake of meat and dairy[15]. A hybrid of the Mediterranean and Dietary Approach to Stop Hypertension (DASH) diets, the Mediterranean-DASH intervention for Neurodegenerative Delay (MIND) diet, has been developed to help delay the onset of cognitive decline[16,17]. This diet is high in nutrients that research has shown to slow cognitive decline and includes "…folate, vitamin E, carotenoids, and flavonoids"[16]. Therefore, an emphasis is placed on adding berries and dark leafy greens, while not emphasizing large consumption of fruit, dairy, potato, and fish. To date, studies have shown that a high adherence to the MIND diet may play a protective role against AD development[17].

Literature Review

<u>*1. Amyloid Hypothesis*</u>

The large majority of research surrounding diet and AD centers around the amyloid hypothesis and the deposition of amyloid plaques. In healthy brains, α-secretase cleaves the vast majority of APP, releasing shorter, harmless fragments of Aβ, such as $A\beta_{25}$ and $A\beta_{38}$. In the brains of AD patients, β-secretase followed by γ-secretase, are highly active and cleave APP in different locations, releasing longer Aβ proteins, like $A\beta_{40}$ and $A\beta_{42}$[18,19]. Of these two longer proteins, more $A\beta_{40}$ is produced; however, $A\beta_{42}$ is more toxic due to a higher affinity for aggregating caused by its hydrophobic properties[1]. Amyloid plaques are a buildup of these longer Aβ sheets. Experiments have shown nutrients found in common foods can mitigate Aβ-induced damage by increasing α-secretase, decreasing β-secretase and/or γ-secretase, disrupting amyloid plaques, autophagy, and/or clearing Aβ across the blood brain barrier (BBB) (Figure 2)[20-51].

Specific nutrients reviewed to determine their effect on amyloid plaques were docosahexaenoic acid (DHA), extra virgin olive oil (EVOO), resveratrol, curcumin, epigallocatechin gallate (EGCG), salvianolic acid B (Sal B), and the fat-soluble vitamins, A, D, E, and K. DHA is an omega-3 fatty acid that is anti-inflammatory and commonly found in flaxseed oil, chia seeds, walnuts, and fish (among other things)[52]. EVOO, a cooking oil used commonly in both the Mediterranean and MIND diets, is an unsaturated fat that contains various isoforms of vitamin E as well as various phenolic compounds, flavonoids, and lignans[53]. Resveratrol, a polyphenol found in nuts, berries, wine, and dark chocolate, has strong antioxidant, anti-inflammatory, anti-cancer, and anti-ageing properties[20]. Curcumin, a nutrient found in turmeric, curry powder, and ginger, displays similar antioxidant, anti-inflammatory, and anti-cancer properties as resveratrol[21]. EGCG, a major polyphenol and catechin found in green

tea has been shown to have neuroprotective effects[22]. Sal B is a water-soluble derivative of caffeic acid that has been commonly used in Chinese medicine to treat coronary artery disease and cerebrovascular diseases[54]. Lastly, multiple research studies have shown a positive correlation between serum and plasma levels of fat-soluble vitamins and cognitive performance[55-68]. Interestingly, an association has also been found between individuals using a vitamin K antagonist for their anticoagulant medication, such as Warfarin, and cognitive impairment[69].

Activation of α-secretase

Compounds that have an ability to activate α-secretase would potentially be able to increase the production of harmless Aβ leading to a decrease in the harmful Aβ[23]. An in-vitro study showed Neuroprotection D1 (NPD1), an enzymatic derivative of DHA, was shown to activate α-secretase in a dose-dependent manner. In this study, overexpression of APP was induced in aging human neuronal-glial cells through transient-transfection with Swedish mutation APP. These cells were treated with NPD1 at concentrations of 0 nM, 50 nM, 100 nM, and 500 nM, with the greatest effect seen at 500 nM[23]. A second in-vitro study analyzed resveratrol's ability to upregulate sirtuin 1 (SIRT1), a silent information regulator that is suppressed by Aβ(25–35). SIRT1 downregulates Rho-associated protein kinase 1 (ROCK1), an inhibitor of α-secretase[20]. This study incubated pheochromocytoma (PC12) cells with resveratrol at concentrations of 12.5 μM, 25 μM, 50 μM, or 100 μM 2 hours prior to the addition of 20 μM Aβ$_{25-35}$[20]. A significant increase of SIRT1 expression and a decrease in ROCK1 expression were seen in western blot analysis showing the potential of resveratrol to upregulate α-secretase[20]. An in-vitro analysis looking into curcumins impact on human embryonic kidney cells (HEK293) overexpressing APP. Curcumin, tetrahydrocurcumin (THC), curcumin-isoleucine (Cur-Ile),

curcumin-phenylalanine (Cur-Phe), or curcumin-valine (Cur-Val) was added at a concentration of 50 µM, with analysis showing Cur-Ile, Cur-Phe, and Cur-Val stimulated α-secretase expression[24]. A second in-vitro study on curcumin conducted on PC12 cells showed that lower concentrations of curcumin were protective against Aβ-induced toxicity while higher concentrations increased toxicity[25].

Decreased activity of β-secretase and/or γ-secretase

Through decreasing enzymatic activity of β-secretase and/or γ-secretase, the continued production of harmful Aβ may decrease[23]. An in-vitro study, looking at EGCG showed a 5-minute incubation of green tea infusion inhibited β-secretase activity by as much as 27%, which increased to 38% after 60 minutes[26]. An in-vivo study utilizing an APP/Prresenilin-1 (PS1) double-transgenic mouse study indicated EGCG was able to ameliorate learning and memory impairment as seen in a Passive Avoidance Test and Morris Water Maze. Mice treated with EGCG showed decreased concentrations of amyloid plaques, decreased concentrations of APP, and decreased apoptosis of neurons with researchers proposing this activity being in part due t EGCGs effects on γ-secretase[70].

When looking at in-vivo research, vitamin A deficiency has been shown to increase deposition of Aβ in the brain and cerebral blood with supplementation of all-trans retinoic acid improving cognitive function[27]. One possible mechanism for this is through inhibiting β-secretase-dependent APP cleavage[28]. In-vivo research into vitamin D has proposed a possible mechanism for clearing Aβ is vitamin D's ability to elevate neprilysin, an enzyme that is shown to degrade Aβ and reduce concentrations of β-secretase[29]. Studies into vitamin D have shown significantly reduced amyloid plaques and improved cognitive performance with

supplementation of a D_3 enriched diet, although it is important to note that rats with normal vitamin D levels did not show improvement in spatial performance with D_3 supplementation[29-32].

Mechanisms by which vitamin E impacts AD include its effect on decreasing cholesterol synthesis. Studies have shown a strong positive correlation between hypercholesterolemia and Aβ production[33]. The relationship between cholesterol and AD centers around cholesterol increasing the activity of β- and γ- secretase[34]. Because vitamin E is a group of eight compounds, it can be confusing to know if it is a combination or just one of these isoforms that has the greatest benefit. Table 1 breaks down some of the research into the various forms of vitamin E as it relates to AD. Unfortunately, outcomes in human studies on vitamin E supplementation have ranged from reduced need of care and slowed disease progression to no effect or an increased cognitive decline[35-38].

Disruption of amyloid plaques

Causing a conformation change in amyloid plaques has shown potential for decreasing overall amyloid load[39-42,45]. An in-vitro analysis on resveratrol using PC12 cells showed 25 µM resveratrol combined with 25 µM purified Aβ42 remodeled three Aβ42 conformers—soluble oligomers, fibrillar intermediates, and amyloid fibrils—into an alternative aggregation that is unstructured and nontoxic[39]. This occurs due to resveratrol binding to the N-terminus of Aβ42 monomers, preventing the formation of oligomers longer than 1–2 nm. Similar results has been seen in-vitro utilizing curcumin[40]. In an in-vitro analysis, Sal B showed a significant inhibition of the formation of Aβ42 that was both dose and time-dependent. Although a mechanism for how Sal B inhibited Aβ42 was not proposed, researchers indicated fibrils of Aβ were converted into deformed aggregates. Incubation with Sal B occurred up to 7 days with 100 µM concentrations[54]. Additional In-vitro studies into vitamin K have indicated it has the potential to be an effective

anti-amyloidogenic drug due to it inhibition of Aβ accumulation and toxicity through binding to the Aβ monomer[41]. Additionally, in-vitro analysis using human neuroblastoma cells (SH-S5Y5) showed DHA interrupted the microenvironment of tyrosine in the Aβ42 backbone, thus reducing levels of soluble Aβ42 oligomers and inhibiting the formation of Aβ42 fibrils. While 5 µM DHA had no significant effect on fibril formation, 10 µM and 20 µM DHA decreased fibril formation by 32% and 41%, respectively[42].

EGCG has shown the ability to decrease Aβ generation in a dose-dependent manner, protect against Aβ-induced apoptosis, and inhibit fibrillization of Aβ[22,43,44]. A proposed mechanism for how EGCG is able to do this is via covalent bonding with Aβ, preventing its accumulation[45]. It is important to note that EGCG is not the only catechin in green tea nor is it the only antioxidant. It is likely the inhibition activity seen in the green tea infusion is due to the cumulative effect of all of the bioactive compounds found in green tea. In one in-vivo study, α-secretase activity increased, overall plaque load was reduced by 50% and β-secretase and γ-secretase activity decreased. Researchers concluded oral administration of EGCG was more effective then injection[24,43,46].

Autophagy

Curcumin has also been shown to reduce Aβ42 toxicity through an in-vivo study comparing the effects of curcumin supplementation in mice[47]. After sacrifice, control mice showed well-formed amyloid plaques where treatment mice showed significantly reduced plaques in a dose dependent manner in both the hippocampus and cortex[47]. This same in-vivo study showed an increase in autophagy of APP-rich organelles. Additionally, Morris water maze test after six months of treatment with either control, low concentration, or high concentration of curcumin revealed that mice completed the maze faster in a dose dependent manner. When the

brains of the mice were extracted and analyzed it was determined that curcumin acts through the PI3K/Akt/mTOR pathway to stimulate the autophagy of APP-rich organelles allowing for the survival and proliferation of cells[47]. Although in-vitro and in-vivo research has shown the benefit of curcumin, two human studies, one a 6-month clinical trial and one a phase 2 double-blind study did not show any improvement in cognitive performance or levels of amyloid plaques[48,49]. This can potentially be caused by curcumin's low bioavailability[21].

In one study on ambulatory AD patients, peripheral blood mononuclear cells (PBMCs) were collected and differentiated into macrophages. These macrophages were incubated overnight with either 1,25-dihydroxyvitamin D_3 (1,25D3) at a final concentration of 0.01 to 0.1 μM or curcuminoids at a concentration of 0.001 μM to 1 μM. Fluorescently labeled Aβ was also added, and fluorescence microscopy and enzyme-linked immunosorbent assay (ELISA) both revealed that 1,25D3 increased clearance of Aβ through phagocytosis in all cells, and curcuminoids significantly assisted in only 50% of cells. 1,25D3 stimulates transport of Aβ within the cell, while curcuminoids stimulate surface binding. It was determined *in silico* that 1,25D3 binds to the genomic pocket of the vitamin D receptor (VDR), while curcuminoids binds to the non-genomic pocket[50].

Clearing Aβ across the Blood Brain Barrier

One in-vivo study looking at the effects of EVOO on Aβ burden, showed after three and six months of EVOO consumption, Aβ concentrations in mice brains were significantly reduced by 24% and 29% respectively. Researchers found this reduction in Aβ load was possibly associated with clearance across the blood brain barrier. Additionally, mice in the six-month treatment group showed improvement in the burrowing and nest construction test compared to control where mice in the three-month treatment group showed no improvement. Researchers

proposed that clearing Aβ across the BBB could potentially prevent an accumulation of amyloid plaques in the brain[51].

2. Tau Hypothesis

The Tau hypothesis for AD development goes hand in hand with Aβ accumulation; the presence of both being the definitive diagnosis of AD[7]. Tau proteins assist in the formation of microtubules, promotion of microtubule stability, and synaptic plasticity. In the tau hypothesis, NFTs are produced in the brain. This occurs through a chain reaction starting with tau protein developing an unhealthy ratio of repeating amino acid sequences in the microtubule-binding domain. A normal tau protein has around 77 serine/threonine sites that allow for phosphorylation of the protein. When hyperphosphorylation occurs, tau's affinity for microtubules is decreased along with the overall stability of microtubules. As more tau proteins are hyperphosphorylated, they accumulate, forming NFTs. This accumulation of NFTs leads to neuron death and cognitive decline[71].

In-vitro studies have demonstrated that grape seed phenol extract, tannic acid, and oleuropein (a compound found in olives) has the ability to inhibit the accumulation of tau by breaking up preformed tau peptide aggregates and inhibiting their accumulation[72-74]. Additionally, in-vitro studies have shown grape seed phenol extract was able to breakdown preformed tau peptides[72]. In-vivo studies showed the effectiveness of grape seed phenol extract at reducing the phosphorylation of tau and EGCG at suppressing phosphorylated tau isoforms[46,75,76].

Similar to its effects on Aβ plaques, vitamins A and E have shown the potential to reduce the concentration of NFTs. Vitamin A shows this activity with supplementation of all-trans retinoic acid in in-vivo studies and is possibly due to retinoic acid's ability to prevent tau

phosphorylation[27,77,78]. Vitamin E shows this action via trolox, an analog of vitamin E that is water soluble[79]. A second in-vivo study showed supplementation with α-tocopherol caused suppressed development of NFTs[80].

3. Oxidative Stress

During oxidative stress, there is an imbalance between the production of ROS and their clearance from the body. As a result, neuronal hypoxia may occur, leading to neurodegeneration. Because the brain is more susceptible to free radical damage then other organs, oxidative damage can be both a potential cause of and result of Aβ deposition. The amyloid and oxidative stress hypotheses are closely linked due to APP and its derivatives causing excessive generation of ROS in mitochondria. This, coupled with oxidative stress, potentially causing increases in β-secretase and γ-secretase, leading to increased plaque deposition[7].

ROS play a pivotal role in immune response and cell signaling and are created during normal physiological processes. In a healthy individual, endogenous antioxidant defense systems keep ROS at healthy levels[7]. Various mechanisms are known to increase the levels of ROS in the brains of patients with AD, including increasing amyloid plaque load and increasing excitotoxicity from the NMDA receptor[81-83]. In order to maintain a healthy equilibrium between creation and degradation of ROS, a diet high in antioxidants is crucial[7]. Antioxidants scavenge ROS and inhibit their continued formation. By including antioxidants in the diet, they increase the effects of endogenous antioxidants[84].

Many vitamins, minerals, and polyphenols display antioxidant activity, including vitamins A, C, and E; selenium; and polyphenols such as resveratrol[85]. Antioxidants are primarily found in plant-based foods, such as teas, nuts, berries, dark chocolate, and fruit[81]. Due to the importance of antioxidants, the creators of the MIND diet emphasized consumption of

complex carbohydrates. The MIND diet includes ten categories of brain healthy foods ("…green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine…") and five categories of unhealthy foods ("…red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast foods…")[16]. In one study of preclinical AD patients, the MIND diet was significantly associated with a decreased risk of developing AD. Individuals in the highest quartile of compliance had a 53% reduction in AD compared to the lowest quartile[17].

Resveratrol can also act in combination with melatonin to attenuate oxidative stress associated with Aβ42. An in-vitro study using HT22 hippocampal cells determined Aβ_{1-42} induced cell death via oxidative stress in a dose dependent manner. Researchers measured levels of ROS as well as cell viability to show the effects of Aβ_{1-42} without treatment groups. The cell line was infected with 2 μM Aβ_{1-42} and treated with 0.1 μM to 20 μM resveratrol and/or 1 μM to 500 μM melatonin. Using DCF fluorescence, it was determined that the maximum reduction of oxidative stress was achieved at concentrations of 20 μM resveratrol and 500 μM melatonin, and that co-treatment revealed synergistic effects. Spectrophotometry revealed that resveratrol and melatonin may reduce oxidative stress by preventing the depletion of glutathione, another antioxidant. Aβ treatment resulted in a glutathione decrease of 20%, and the addition of resveratrol and melatonin increased glutathione to at least control levels[86]. Another in-vitro study conducted rat primary cortex neurons using resveratrol as well as two other stilbenes, trans-4-hydroxystilbene (THS) and trans-3'4',3,5-tetrahydroxy-stilbene (PIC) showed the free radical scavenging ability of these compounds. THS showed the lowest effectiveness on ROS at 6.25%, followed by resveratrol at 13.07% and PIC at 26.82%. When compared with Aβ_{25-35}, stilbenes

showed a significant dose-dependent decrease in ROS showing a possible neuroprotective effect of these nutraceuticals[87].

Cocoa extract is another high antioxidant/high polyphenol compound that can reduce the oligomer formation of Aβ42. In the presence of equimolar cocoa extracts, dimers, pentamers, and hexamers of Aβ42 were not formed while trimers and tetramers were greatly reduced. When looking at Aβ40 similar decreases were seen; trimers and tetramers were completely blocked by Levado extract and reduced by natural and Dutch cocoa extracts while dimers were reduced by Levado, natural, and Dutch cocoa extracts[88]. A second in-vitro study looked at supplementation of cocoa extract and its protection from Aβ cytotoxicity due to oxidative stress. Researchers found the toxicity was attenuated and cell viability was increased with treatment of cocoa extract[89].

Lycopene, found in tomatoes and tomato products, is a carotenoid with strong neuroprotective, antioxidant, and anti-inflammatory activity. Lycopene is also studied due to its ability to cross the blood brain barrier and to specifically act as an antioxidant in the brain. One in-vitro study pre-treated primary cultured cortical neurons with lycopene, followed by Aβ25-35. Although researchers utilized the shorter, less toxic form of Aβ, they stated the peptide utilized in their experiments is shown to "…retain the toxicity of the full length Aβ…"[90]. What researchers found was the pre-treatment of lycopene significantly protected against neurotoxicity by reducing apoptosis and decreasing concentrations of ROS's in a dose dependent manner[90].

4. Cholinergic Hypothesis

The cholinergic hypothesis of AD is based on ACh, the major neurotransmitter within the cholinergic system, playing an important role in memory and learning[7]. ACh synthesis occurs in the presynaptic nerve terminal and is the byproduct of the enzyme choline acetyltransferase on

Acetyl Coenzyme A (Acetyl CoA) and choline. After ACh is synthesized, it is released into the synaptic cleft where it attaches to presynaptic and postsynaptic receptors, which in turn regulates both neurotransmission and further release of ACh. At this point ACh is broken down by acetylcholinesterase (AChE) into acetate and choline which go back into circulation to produce additional ACh[91]. During the development of AD (as well as in the ageing process), a loss of cholinergic function in the central nervous system (CNS) occurs and is associated with a measurable decrease in the amount of ACh and an increase in total cholinesterase in the brain[7,92]. This loss of ACh is hypothesized to contribute to cognitive decline[7]. Currently, the majority of pharmacological treatments for AD focus on AChE inhibition in order to slow down the breakdown of ACh which subsequently causes an increase in synaptic concentration of ACh as well as its neurotransmission regulatory effects. At this time, AChE inhibitors offer only modest, short-term relief during the early stages of cognitive decline[91].

Butyrylcholinesterase (BuChE) is a second neurotransmitter within the cholinergic system that is important in cholinergic neurotransmission regulation as well as the development of the nervous system[8]. In 41-80% of patients with advanced AD, BuChE activity is significantly enhanced while AChE is decreased by 10-60% in the area of amyloid plaques and NFTs. Traditional treatment for AD targets AChE in order to prevent the breakdown of ACh, which delays the onset of AD but does not stop the progression of the disease[8]. Interestingly, when BuChE is inhibited, a dose-dependent increase of ACh is seen in the brain with BuChE remaining unaffected by increasing concentrations of ACh[91]. See Table 2 for examples of dietary components that may play a role in the cholinergic hypothesis for AD development.

5. NMDA Receptor

NMDA receptors plays an important role in short and long-term memory, synaptic plasticity, and learning. When overstimulated it can produce free radicals and cause cognitive defects through neuron death[7,93]. NMDA receptor is a glutamate receptor that can either be bound to glutamate (an excitatory neurotransmitter) or glycine (an allosteric modulator)[93]. In normal conditions, glutamate homeostasis prevents the overaccumulation of glutamate. Additionally, NMDA receptors are highly sensitive with regulation occurring via PrP^C. Higher concentrations of PrP^C reduces the expression of NMDA receptors. During the pathogenesis of AD, increasing concentrations of Aβ in the brain causes overstimulation of glutamate, simultaneously Aβ binds to PrP^C, removing its inhibitory role on NMDA receptor causing its concentration to increase. Excitotoxicity then causes the production of ROS, leading to neuron death, cognitive dysfunction, and ultimately AD[94].

Simultaneously, excitotoxicity causes an influx of calcium through the NMDA receptor which disrupts learning and memory and causes death to the cell[7,94]. In one study, walnuts were found to simultaneously increase NMDA receptor activity while decreasing excitotoxicity[95]. Researchers believed it was the combination of polyunsaturated fatty acids, antioxidants, and polyphenols found in walnuts that provided this neuroprotective effect as seen through decreasing concentrations of lipid peroxidation[95]. Similarly, another study looking at supplementation of vitamin D in rats found that rats consuming vitamin D had an increase in the expression of NMDA receptors which was positively associated with cognitive function[96].

Research into the effects of vitamin E on NMDA receptors has also been conducted. In-vitro research on mouse embryonic stem cells induced toxicity of glutmate followed by treatment with either α-tocopherol or tocotrienol rich fraction (TRF) which was composed of 25% tocopherol and 75% tocotrienol. This post treatment of cells with vitamin E was conducted in

order to assess the neurorecovery properties of vitamin E against glutamate toxicity. Researchers found posttreatment with α-tocopherol and TRF reduced cell death in a dose-dependent manner with TRF having a greater effect then α-tocopherol alone. This increase in cell viability occurred due to α-tocopherol and TRF acting as antioxidants and reducing levels of ROS[82].

6. Altered Calcium Homeostasis

Research into mitochondrial health has indicated that as we age the function of the mitochondria declines. This is important because the mitochondria are not only the site where bodies produce the majority of ATP for energy, but they also assist in maintaining calcium homeostasis[7]. Research has shown a decrease in mitochondrial function in AD patients within brain, fibroblasts, and blood cells[97,98]. Mitochondria dysfunction begins with a reduction in enzymatic activity within the mitochondria. This leads to defects in the electron transport chain, altered calcium homeostasis, and eventually AD due to increasing the likelihood of Aβ production and deposition[7].

Effect of nutraceuticals on mitochondria

The composition of lipids in the mitochondrial membrane changes with age. One study suggests that as people grow older, the percentage of phospholipids containing DHA in the mitochondrial membrane increases[99]. The ability of mitochondrial membranes to change lipid composition as a result of a change in diet has been demonstrated in 8-month-old zebrafish, whose mitochondrial membranes contained a higher percentage of DHA after a diet high in DHA[100]. The same effect was found in eicosapentaenoic acid (EPA), another omega-3 fatty acid[101]; although additional research suggests that while DHA and EPA exhibit many similar biological effects, research has indicated that EPA, but not DHA, improved protein quality in mitochondria and mitigated loss of mitochondrial function in aged mice[102]. One human study

showed a substantial reduction in the risk of all-cause dementia for individuals who were in the highest quartile of plasma DHA levels[103].

Resveratrol (as an antioxidant) has been found to pick up electrons that have been leaked from the respiratory chain, increase the formation of antioxidant species, and participate in mitochondrial energy biogenesis[104]. One study showed resveratrol increased cell survival by mitigating the levels of ROS in the mitochondria, although the same study suggested that resveratrol increases the total amount of ROS in the cell[83]. As stated previously, resveratrol activates SIRT1, which in addition to its anti-amyloid properties, regulates mitochondria function and energy metabolism[105]. Several polyphenols, including resveratrol, were found to affect mitochondrial biogenesis by upregulating the promoter of mitochondrial transcription factor A (Tfam)[106]. Other studies, however, suggest resveratrol actually induces apoptosis by upregulating the release of cytochrome c from the mitochondria, and increasing the expression of proapoptotic proteins while downregulating antiapoptotic proteins [107].

Like resveratrol, curcumin is an antioxidant that has demonstrated neuroprotective effects by mitigating oxidative stress caused by mitochondrial dysfunction[108]. In the kidneys of diabetic mice, curcumin also protects mitochondria from the effects of hyperglycemia by modifying oxygen consumption rate, nitric oxide synthesis, and the levels of thiobarbituric acid-reactive substances (TBARS)[109]. A hybrid compound of curcumin and melatonin has been found to upregulate the expression of complexes I, II, and IV of the electron transport chain in mitochondria in the brain tissue of APP/PS1 mice[110]. Experiments with cancer cells in-vivo and adipocytes in-vitro have suggested that curcumin, as well as several derivatives, including bisdemethoxycurcumin (BDMC), can induce apoptosis by inducing the release of cytochrome c

from the mitochondria[111,112]. In contrast, a study using diabetic rat testicular cells has suggested that curcumin protects against mitochondria-dependent apoptosis[113].

In an in-vitro study, researchers indicated that vitamin D downregulates respiratory chain transcription in these cells and upregulates biosynthetic pathways instead, thus increasing cell growth and proliferation[114]. A similar study indicated vitamin D acts as a gatekeeper for the mitochondrial respiratory chain by suppressing the transcription of cytochrome c oxidase subunits II and IV. This downregulates the Krebs cycle and directs the cell toward biosynthetic pathways[115]. Interestingly, vitamin D receptors can be transferred from the nucleus to the mitochondria which would help to increase the biosynthetic pathways[116].

One in-vivo study on lycopene injected rats with Aβ42 and observed how treatment with lycopene at doses of 1, 2, and 4 mg/kg orally impacted their mitochondrial activity. What researchers found was a significant increase in mitochondrial complex enzyme (I, II, and IV) in both the cerebral cortex and hippocampus along with a significant restoration of mitochondrial redox activity. Additionally, lycopene treated rats performed better then control in a Morris water maze test[117].

A high-resolution respirometry system revealed Aβ and tau may work synergistically to reduce the oxidative phosphorylation capacity of mitochondria through chronic oxidative stress[118]. It has also been suggested that Aβ derived from the endoplasmic reticulum (ER), Golgi apparatus, or mitochondria-associates ER membranes (MAM) accumulates in the mitochondria, which disrupts Ca^{2+} homeostasis and increases the production of free radicals[119]. The above listed research into the effect of nutraceuticals on apoptosis has been conducted murine muscle cells, breast and gastric cancer cells, human adipocytes, diabetic rats with testicular abnormalities, and human proliferating keratinocytescells[106,107,111-115]. The variety of cell types

used can possibly explain some of the opposing effects seen in resveratrol and curcumin (Figure 3).

7. Impaired Glucose Metabolism

A more recent hypothesis on the development of AD is it is caused by impaired glucose metabolism in the brain. Individuals diagnosed with type 2 diabetes in their mid-life as opposed to later in life are 1.5 times more likely to develop AD. Brain glucose hypometabolism can be detected through tomography imaging and is proposed as a possible tool for early diagnosis of AD. This link between glucose hypometabolism and AD development focuses on diets that are high in carbohydrates (with an emphasis on fructose and fructose-containing carbohydrates), inhibiting the liver from creating lipoproteins. This decrease in lipoprotein formation starve neurons of these nutrients causing the cascade effect of neurodegeneration[10]. One study showed a negative correlation between glycemic load dietary pattern and overall cognition and performance on various neuropsychometric tests[120].

In one in-vitro study, cultured rat hippocampal cells were exposed to Aβ42, causing a reduction in the number of cells and neurite length. For cells simultaneously exposed to β-hydroxybutyrate (a ketone body) they doubled the number of surviving cells and increased neurite overgrowth[121]. In two in-vivo studies, a ketogenic diet was found to reduce the overall volume of formed Aβ with one showing decreased concentrations of NFTs and improved cognitive function[122,123]. In one human study, 15 participants maintained a ketogenic diet with medium chain triglyceride (MCT) oil supplementation. In participants who maintained ketosis, a significant improvement in the AD Assessment Scale cognitive subscale score was observed. After participants returned to their previous diet their cognitive functions returned to baseline[124].

One case study placed the participant on a ketogenic diet along with high intensity interval training (HIIT) until ketosis was reached. After sustained ketosis their Hemoglobin A1C was within normal limits and an improvement in spatial awareness and self-efficacy was evident each week[125]. A second case study had a patient consume a ketogenic and calorie restricted diet in addition to HIIT exercises. This patient entered ketosis within three weeks and saw a 26% increase in memory function score from baseline[126].

8. Pathogenic Viral

The pathogenic viral hypothesis on AD progression is fairly new, with research conducted in 2018 suggesting certain viruses, like herpes simplex virus, may be responsible for the long and slow progression of AD[12]. Research had previously indicated that microbes are able to stimulate the formation of Aβ as a defense mechanism to stop the infectious process[127]. In genetic analysis, researchers found differential gene expression associated with various viruses like Epstein-Barr virus (EBV) and human herpesvirus 6A (HHV-6A) and sought to determine if patients diagnosed with AD showed genetic changes caused by viruses. What researchers found was an increased quantity of HHV-6A and human herpesvirus 7 (HHV-7) in the brains of patients who had passed away from AD[12]. Conducting a quick PubMed review of herpes simplex virus & diet brings up 58 articles but research into the way diet can reduce the impact of herpes simplex virus is lacking.

9. Prion Disease

In the prion disease hypothesis, Aβ oligomers bind to PrP^c receptors on neurons and initiate signaling transduction pathways that ultimately lead to neuronal death[128-131]. In-vitro analysis has indicated PrP^c is capable of mediating the toxic effects of Aβ due to $Aβ_{42}$ having a high affinity for PrP^{c}[132]. Subsequent in-vivo analysis determined PrP^c was essential for the

toxicity caused by Aβ and mice lacking PrP[c] who had amyloid plaques showed no spatial learning or memory impairment[133]. When conducting a PubMed review of PrP[c] associated with AD and diet only three articles came back[134-136]. None of these articles discussed the impact diet has on the development of AD via prion disease.

Summary

In 1906, Dr. Alois Alzheimer first described amyloid plaques and NFTs[137]. What has become clear since that time is AD is more confusing then researchers initially imagined. In this paper, a discussion was had on some of the more popular hypotheses surrounding AD development, many of which are hard to distinguish from each other due to their similarities. Between the amyloid, tau, oxidative stress, cholinergic, NMDA, altered calcium homeostasis, impaired glucose metabolism in the brain, pathogenic virus, and prion disease hypotheses it becomes apparent how interconnected many of them are. For instance, does the generation of amyloid plaques cause ROS to form or does oxidative stress form ROS leading to the development of amyloid plaques? With all of the compelling research on the nine potential pathways it becomes apparent that AD likely utilizes multiple pathways simultaneously, creating some type of interconnected loop.

Even more confusing than the cause of AD, is the role that diet plays on protecting humans from developing it. Human studies on diet and AD are limited and typically occur after an individual is already displaying signs of cognitive dysfunction[35-38,48,49,103,124-126]. At that point in time, all of the research is focused on slowing the pace of cognitive decline because of AD's irreversible nature. Many of the bioactive compounds found commonly in plants, such as walnuts, berries, and dark leafy greens, can potentially modulate the formation of AD in multiple ways. Through this research we've learned the importance of antioxidants to remove ROS and

decrease amyloid load by targeting the various enzymes in the accumulation of amyloid plaques. Although the large majority of studies are looking at how diet impacts AD after it has already begun, the question remains, what is the right diet for a prolonged healthy life? While the evidence points towards the Mediterranean diet as an excellent option for long term health, does the MIND diet help slow the rate of cognitive decline once AD has started? What these diets have in common is a high consumption of antioxidant, anti-inflammatory, whole plant-based foods. Consuming these foods, like EVOO and resveratrol may help the body fight AD by decreasing the amount of ROS, keeping the mitochondria healthy, and reducing the potential build-up of amyloid plaques. One human study analyzed dietary patterns in patients over the course of 3.9 years and compared it to their degree of AD risk. What researchers found was a dietary pattern that was significantly associated with reduced risk of AD. It was also positively correlated with consumption of "…salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits and dark and green leafy vegetables…" and negatively correlated with a consumption of "…high-fat dairy, red meat, organ meat, and butter…"[138].

Looking forward, research needs to focus more on all of the lifestyle factors that contribute to AD. A question remains about whether individuals genetically predisposed to AD can impact its development through modifying their lifestyle. Garcia-Escudero et al and Weuve et al have written about how not only diet, but disease state, age, socioeconomic status, and educational level all impact the development of AD[5]. African Americans are 2-3 times more likely than whites to have cognitive impairment as they age[139]. In fact, one study showed that stress over the course of your lifetime is associated with decreased cognition later in life with African Americans reporting higher stressful events in their lives[140]. In addition, a quick search of K-12 nutrition education programs shows that nutrition education comes from after school

programs and the school nutrition program, who is responsible for providing meals to children. From a nutritional standpoint it is easy to emphasis consuming a diet that is high in antioxidant, anti-inflammatory, whole foods; however, before recommending this, it is important to recognize what the possible barriers are to an individual getting what they need. Knowing whether they live in a food desert, what their financial/transportation situation is, and what education they have received about eating healthy can lead the conversation. In the previous study linking dietary patterns with risk of AD, the population consuming the diet with the lowest risk of AD tended to be younger, more educated, non-current smokers[141]. Future research needs to focus on bringing nutrition education to everyone and reducing the health disparities. Through incorporating education in the classrooms from a young age, a longitudinal study could show us the impact of a low-risk AD healthy diet throughout the life instead of focusing on preventing the further development of a disease that currently has no cure.

Figure 1: Summary of hypothesis leading to the development of Alzheimer's Disease.
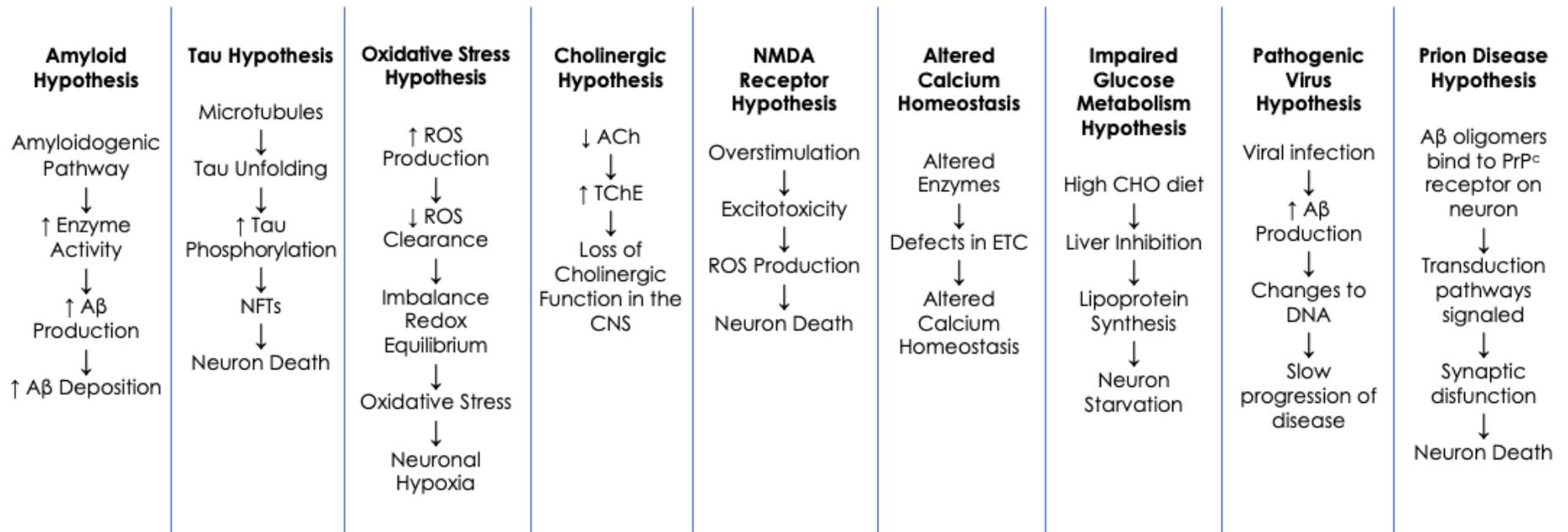
Aβ: beta-amyloid protein; ROS: reactive oxygen species; ETC: electron transport chain; ACh: Acetylcholine; TChE: Total Cholinesterase; CNS: Central Nervous System: NMDA: N-methyl-d-aspartate

Figure 2: Effects of diet on the amyloid hypothesis of Alzheimer's Disease development
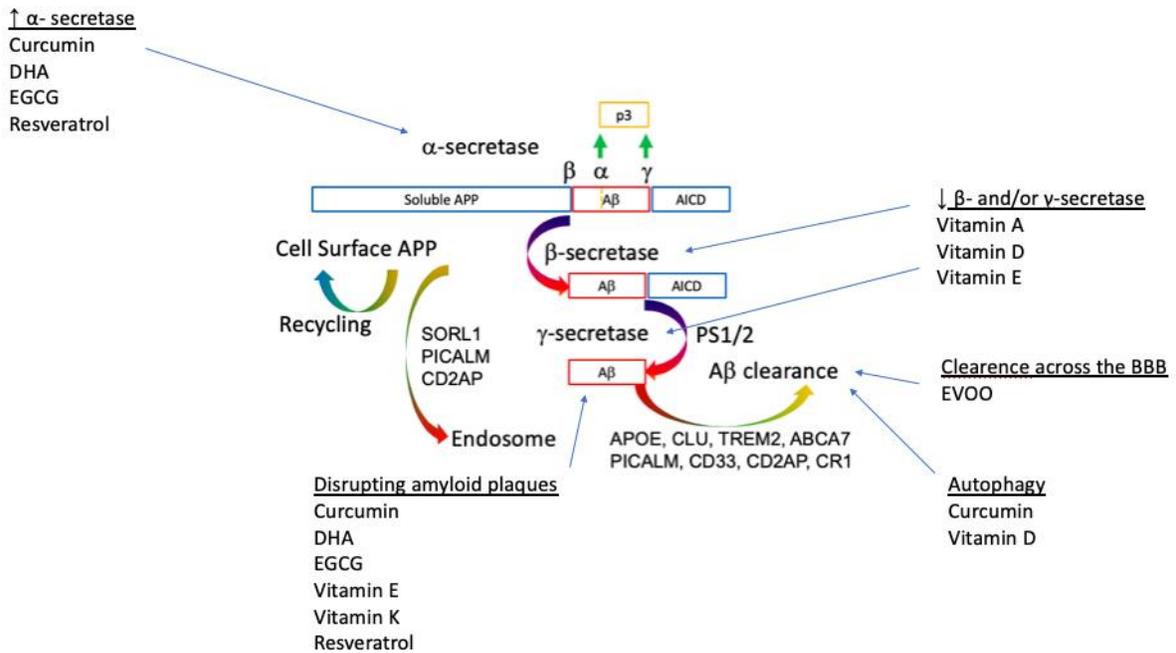
Adapted from Rosenberg, et al[18]. DHA: docosahexaenoic acid; EGCG: epigallocatechin gallate; EVOO: extra virgin olive oil

Table 1: Summary of research into the impact of vitamin E isoforms on the amyloid hypothesis.

| α-tocopherol	• Higher intake associated with reduced AD risk[62-64] • If γ-tocopherol levels are low, higher α-tocopherol levels are associated with higher Aβ load[64] • In-vivo study showed dietary supplementation along with N-acetylcysteine and alpha-lipoic acid prevented cognitive decline[142] • α-tocopherol quinine is an oxidative metabolite of α-tocopherol and has been shown to improve memory in in-vitro studies[143] • α-tocopherol + α-tocopherol quinine shown to decrease Aβ accumulation and toxicity[142]
γ-tocopherol	• Higher plasma levels associated with lowered AD neuropathology[144] • One in-vitro study showed increased Aβ secretion with treatment due to increased expression of β- and γ- secretase[145]
δ -tocopherol	• One in-vitro study showed increased Aβ secretion with treatment due to increased expression of β- and γ-secretase[145]
α-tocopherol + α-, β-, γ-, δ-tocotrienol supplement	• In-vitro analysis indicates it disrupts formation of Aβ42[146] • In-vivo analysis indicated an improvement in cognitive impairment and a decrease in Aβ deposition with supplementation[146]

AD: Alzheimer's Disease; Aβ: beta-amyloid protein

Table 2: Summary of research into dietary nutrients impact on the cholinergic hypothesis.

Alkaloids	Largest group of metabolites with ChE inhibitory activity at lower concentrations. Examples include physostigmine which decreases AChE but not BuChE and berberine, an isoquinoline alkaloid that inhibits ChEs and β-secretase activity in rabbits, and galantamine[8]
Brava Oil	Showed dose dependent inhibition of BuChE and AChE[147]
Coumarins	Display AChE inhibition with some showing good BuChE inhibition[8]
Flavonoids	Along with isoflavones have higher AChE activity. The number of hydroxyl groups on the B ring of a flavonoid influences the potency of BuChE inhibition with an increase in the number of hydroxyl groups decreasing BuChE inhibition. Examples include Galangin, a type of flavanol had strong anti-ChE activity with the most potent activity against BuChE[8]
Lycopene	In-vivo study showed reversal of AChE activity and improved performance on Morris water maze test[117]
Mansa Oil	Showed dose dependent inhibition of BuChE but not AChE[147]
Prenyltransferase Inhibitors	Have been used to rescue synaptic and cognitive deficits caused by overactivation of farnesylated proteins. GGTIs can act directly on neuronal cells and the CNS[148]
Quinones	Pro-oxidants needed for mitochondria respiration. Redox reactions may occur creating semiquinones and hydroquinones which can create additional ROS. Some also work as AChEi[8]
Spanish Sage	Inhibit AChE, is an antioxidant, anti-inflammatory, and displays estrogenic effects. Estrogenic agents are potentially protective in preventing or delaying neurodegeneration in AD[149]
Stilbenes	Secondary metabolites derived from phenylpropanoid pathway and includes Resveratrol. Stilbenes other than resveratrol (like Gnetol) have better AChE and BuChEi activity[8]
Terpenic Compounds	Built up from isoprene subunits and are the most numerous and structurally diverse group of secondary metabolites produced by plants. It takes higher concentrations of terpenes to inhibit ChE. Dihydrotanshinone and cryptotanshinone have the potential to cross the BBB[8]
Tocotrienols	Tocotrienols appear to be superior to tocopherols because of their better distribution in the fatty layers of the cell membrane. Overall reduces free radical markers decreases AChE[150]
Xanthones	Secondary metabolites produced by plants, fungi, and lichens. Generally weak ChE inhibitors but with a lipophilic side chain it improves[8]
Vitamin A	In-vivo studies indicate restored AChE activity with supplementation of all-trans retinoic acid[151]

AChE: Acetylcholinesterase; AChEi: Acetylcholinesterase inhibitor; AD: Alzheimer's Disease; BBB: Blood Brain Barrier; BuChE: Butyrylcholinesterase; BuChEi: Butyrylcholinesterase inhibitor; ChE: Cholinesterase;: GGTIs: Geranylgeranyl Transferase Inhibitor; ROS: Reactive Oxygen Species

Figure 3: Cell type dependent effect of nutraceuticals on apoptosis
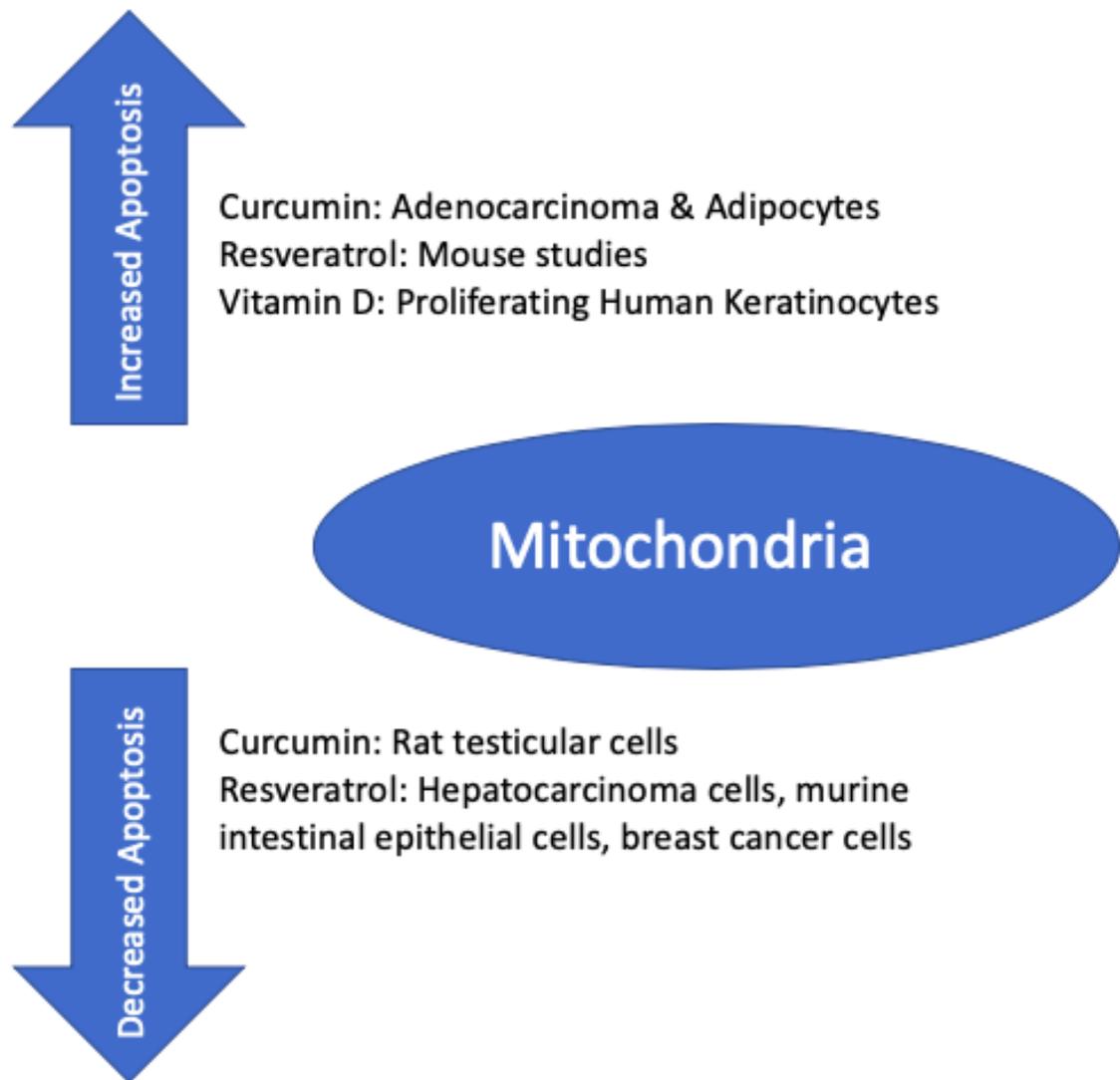
Curcumin and resveratrol have shown opposing effects on mitochondria apoptosis depending on cell type. Vitamin D on the other hand has been shown to increase apoptosis.

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