Biomedical Reviews 2021; 32: 1-29

ISSN 1314-1929 (online)

BMR Biomedical Reviews

Review

THERAPEUTIC ROLES OF ANTIOXIDANT AND NUTRACEUTICALS IN THE PREVENTION AND MANAGEMENT OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

Shubhangi Gupta[1], Avinash Shenoy[1], Vinay Chaudhari[1], Harpal S. Buttar[2], Meena Chintamaneni[1], Ginpreet Kaur[1*]

[1]*Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS,Vileparle-West, Mumbai-56, India*

[2]*Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ontario, Canada.*

Alzheimer's disease (AD) has emerged as a serious and challenging neurological disorder in the ageing population worldwide. The progressive decline of mental health in AD patients causes memory loss, cognition decline, and motor impairment, which impacts adversely on the quality of life of afflicted individuls. Health care costs of mental diseases, dementia and AD are escalating globally, because the AD patients need continuous attention either by the family members or by the health care providers. Also, pharmaceutical treatment and hospital cost of AD is very expensive for the society. Therefore, there is an urgent need to develop cost-effective, affordable, and safe alternative remedies for the prevention/mitigation and management of AD. Plant-derived anti-oxidant/anti-inflammation macromolecules (e.g., curcumin, genistein, melatonin, resveratrol, vanillic acid, caffeic acid, berberine) and nutraceuticals (Gingko Biloba) appear to be the safer and cost-effective promising options for the prevention/progression and management of AD patients. The underlying causes and pathological mechanisms of AD are multiple and complex, which include genetic, epigenetic, non-genetic and environmental risk factors. Lifestyle aspects (e.g., excessive tobacco smoking and alcohol abuse), unhealthy dietary habits, accumulation of heavy metals (arsenic, lead, cobalt, mercury) in CNS, and chronic viral infections are considered some other risk factors in memory loss and AD. Brain has relatively low levels of antioxidants and low repair capacity of neuronal cells. Reduced blood supply and impaired mitochondria promote lesser ATP synthesis and energy support in the brain. Many studies have suggested that excessive oxidative stress in the brain leads to the overproduction of free radicals like reactive oxygen species (ROS) and reactive nitrogen species (RNS) from mitochondrial damage and reduction of ATP synthesis. The unabated over production of ROS/RNS cause insults to brain lipids by intiating lipid peroxidation and damage to cellular molecules, resulting in pathological injury and neuronal death. Antioxidant and anti-inflammation phytomolecules,

Received 5 December 2021, revised 19 December 2021, accepted 20 December 2021.

*****Correspondence to: Ginpreet Kaur, PhD**,** Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS,Vileparle-West, Mumbai-56, India. E-mail: Ginpreet.Kaur@nmims.edu

Harpal S. Buttar, DVM, PhD, Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ontario, Canada. E-mail: hsbuttar@bell.net

dietary flavonoids, and nutraceuticals have gained significant importance for scavenging the free radicals and producing neuroprotective and memory-enhancing effects. Systematic searches were done using PUBMED, EMBASE, Scopus, Google Scholar, ResearchGate, and Web of Science databases. Numerous in vitro and in vivo studies have demonstrated that dietary antioxidant/anti-inflammation flavonoids, micronutrients (vitamins, trace metals, amino acids), and plant-derived polyphenols synergistically exhibit neuroprotective activity in AD animal models by stimulating transcription of the endogenous antioxidant system in the brain. The aims and objectives of this review are to recapitulate the current knowledge about the pathophysiology of AD and to shed light on the therapeutic strategies being used for slowing down the progression of dementia and cognitive decline. We will also provide an overview of the proposed underlying mechanisms of different neutraceuticals and their recommended dosages in the prevention/mitigation of AD along with a summary of the antioxidant/anti-inflammation ingredients present in patented formulations. ***Biomed Rev*** **2021; 32: 1-29**

Keywords: *Alzheimer's disease, oxidative stress, dementia, cognition decline, nutraceuticals, phytotherapies, polyphenolic nutrients, antioxidant and anti-inflammation diets.*

ABBREVIATIONS

AD = Alzheimer's Disease
APP = Amyloid Precursor Protein
Aβ = Amyloid Beta
BBB = Blood Brain Barrier
BACE1 = β-secretase
CAT = Catalse
CNS = Central Nervous System
CVD = Cardiovascular Disease
DASH= Dietary Approaches to Stop Hypertension
EGF = Epidermal Growth Factor
eIF2 = Eukaryotic initiation factor -2
GPx = Glutathione Peroxidase
HIF-1α = Hypoxia-Inducible Factor 1α
HK1 = Hexokinase
IRE = Iron responsive element
IREBP = IRE-binding protein
ICB-STZ = Intracerebroventricular streptozotocin
iNOS = nitric oxide synthase
JNK = c-jun N terminal - kinase
LRP1 = Lipoprotein receptor related protein 1
LAMP-1 = Lysosomal - associated membrane protein
MCP-1 = Monocytes chemoattractant protein -1
MED-Diet = Mediterranean diet
NCD = Non-communicable Chronic Diseases
NSAIDs = non-steroidal anti-inflammatory drugs
NO = Nitric Oxide
PPARγ = Proliferators - activated receptor gamma
PKR = Double-stranded RNA-dependent protein kinase
PS1 = Presenilin1
PFKM = Phosphofructokinase
ROS = Reactive Oxygen Species
RNS = Reactive Nitrogen Species
SOD = Superoxide Dismutase
SP1 = Specificity protein 1
TGF = Transforming Growth Factor
TNF = Tumor Necrosis Factor
VOO = Virgin Olive Oil
5'-UTR = 5' - Untranslated Region

INTRODUCTION

The word nutraceutical is derived from the combination of nutrient and pharmaceutical, and is defined as naturally occurring dietary substance that promotes heatlh and well-being, and also prevent ailments. Nutraceuticals are derived from fruits, vegetables, and seed products as well as extracted, isolated, and purified from natural foods, bovine colostrum, dietary fibers, and medicinal herbs for physiological health benefits or to protect against non-communicable chronic diseases (NCDs). Besides promoting health and well-being, nutraceuticals possess strong antioxidant, anti-inflammatory, and anticancer properties. Over the last decades, the nutraceutical market has expanded exponentially due to the rise in consumer awareness created by the lay-press, and importance in the prevention and treatment of many NCDs like diabetes, obesity, cancer, cardiovascular and neurodegenerative disorders [1-2]. Nutraceutical preparations, dietary supplements, and herbal remedies are primarily sold in health food stores for promoting health and well-being and the prevention of NCDs. They are marketed in the form of capsules, tablets, pills, liquid formulations, and powders.

From the historical perspective, Alzheimer's disease (AD) is named after Dr. Alois Alzheimer, a German neurologist, who treated a woman Ms. Auguste Deter with memory loss and

language problems. In 1906, Dr. Alzheimer noticed abnormal histopathological changes in the brain tissue of Ms. Deter who had died of unusual mental illness. Thanks to Dr Alzheimer, also Dr Gaetano Perusini, for documenting the symptoms of their patient, who experienced memory loss, paranoia, and psychological problems, now recognized as the most severe cause of dementia among age-related neurodegenerative diseases [3]. Alzheimer's disease patients have latent and progressive stages of cognitive and memory loss, as well as behavioral and communication problems, which eventually affect lifestyle and socialization capacity [4-5]. Severe dementia and AD patients need continuous attention either by the family members or by the health care providers, which results in very high economic burden on the society. There are two forms of AD: the early onset (before 65-years) and the late-onset (after 65-years). The late-onset accounts for 95 % of the total AD population [6]. For the late-onset of AD, the non-modifiable risk factors consist of genetic, old age, and family history [7-12]. In the recent past, the demographic paradigm of AD has shifted towards the ageing and geriatric populations, where the dementia and cognitive decline have emerged as one of the biggest healthcare challenges globally [13]. Unfortunately, there is no effective drug therapy for this chronic and debilitating disease. Basic researchers and pharmaceutical industry are rigorously exploring for the discovery of cost-effective and affordable alternative therapies for the prevention/progression and management of chronic neurodegenerative illnesses, including AD. Post-mortem examinations have revealed that in AD patients the cerebral cortex shrinks dramatically in volume or gets atrophied due to the death of brain cells, and the gross appearance of the AD brain is very different from the normal brain. Among all the neurological diseases, AD is the most prevalent cause of memory loss and cognitive dysfunction. Toxic protein build-ups in the brain tissue, as well as beta-amyloid plaques and neurofibrillary tangles, are all pathological symptoms of the disease, which are caused by the accumulation of amyloid-beta proteins and the deposition of hyperphosphorylated tau, respectively [14]. These two types of oligomers are neurotoxic, and trigger neuronal oxidative stress, mitochondrial dysfunction, ATP depletion, inflammation of neurons, ER stress, synaptic dysfunction, and eventually cause death and failure of neurons [15-16]. The latest conventional therapy for treating AD was aimed to prevent the formation of Aβ-proteins. However, repeated failures have occurred in antiamyloid therapy clinical trials, suggesting thereby the need to develop sophisticated macromolecules or alternate therapies that would slow down or prevent AD progression [17- 18]. Growing number of research studies have shown that neuro-inflammation lies at the heart of AD pathogenesis [19-20]. Neuro-inflammation in the CNS is caused by the accumulation of toxic proteins, amyloid plaques, neuro fibrillary tangles, and damaged neurons [21]. Several inflammatory biomarkers have been detected in the AD brain tissue: namely increased inflammatory cytokines and chemokines as well as the aggregation of activated microglia cells in the damaged regions [22]. Microglial dysfunction is becoming more widely accepted feature of neuroinflammation, which is closely related to the development of amyloid-beta proteins as a cause of neuronal degeneration [23]. Microglia are resident immune cells in the brain that play a key role in sustaining brain homeostasis and neural circuit plasticity by facilitating the number of functional synapses under normal physiological conditions [24]. However, the persistent pathological stimulation causes neuronal damage and Aβ-proteins aggregation, resulting in the damage of microglial cells and facilitating the pro-inflammatory reaction in the brain [25-26]. Since the microglia plays a crucial role in controlling neuro-inflammation, there is a great interest in understanding the participation of microglia in Alzheimer's disease [27]. It has been suggested that microglia may have both neuroprotective and/or neurotoxicity roles in AD patients and the distinction between the two roles may change over time in the same person [28-29]. The inflammatory response helps to clear the infected or injured area in the brain, and the reactive microglia-induced neuro-inflammation may be helpful, whereas, if persistent inflammation response causes further damage in the surrounding area, it may lead to harmful sequela [30]. In case, the phagocytic removal of the dead protein and neurons microglia aggregation is curtailed, it could contribute to the accumulation of debris, thus causing pro-inflammatory activation of microglia and production of cytokines as has been proposed by Heppner *et al.* (2015) in the immune system-mediated actions in AD pathogenesis [27]. Since inflammasomes can induce neuroinflammation in the CNS, the inflammasome NLRP3 has been linked with AD pathology [31-32].

It is well known that brain is vulnerable to excessive oxidative insults because of its abundant lipid content, weak antioxidant capacity, and high ATP and energy requirements. Oxidative stress-induced imbalance between pro-oxidant and anti-oxidant milieu has been reported to be associated with many diseases, including cardiovascular diseases, osteoarthritis, cancers, dementia, cognition decline, and AD. A large

number of transcription factors are involved in oxidative stress responses. Oxidative stress-induces mitochondrial damage and excessive production of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are considered to play an important role in the pathophysiology of AD. The oxidative stress induced redox imbalance in the brain and decline in the capacity of mitochondrial function and energy, as well as higher production of malondialdehyde and carbonyl protein lead to the dysfunction of intracellular calcium signaling mechanism in the brain [33-35]. It has been observed that in the etiology of neurodegenerative diseases, the biochemical and pathophysiological changes are caused by the unabated excessive production of ROS/RNS that dramatically alter the BDNF-TrkB receptor cascade in the brain, and consequently result in the high influx of calcium into the neural cells that in turn causes an excitotoxic neuronal injury [36]. Arguably, an effective intervention to combat oxidative stress in the brain, the intake of strong antioxidant and anti-inflammation diets and nutraceuticals would be one of the most cost-effective strategies to prevent CNS damage and to manage neurological disorders, including AD. Fresh fruits, vegetables, and spices are rich in naturally occurring flavonoids, polyphenols, retinoids, lycopene, and anthocyanin compounds, and have attracted the worldwide attention of basic researchers and nutrition specialists, because they have been found clinically beneficial in curing chronic NCDs, including neurodegeneration disorders [37].

In summary, oxidative stress-induced neuroinflammation and pro-inflammatory activation of microglia, and production of cytokines seem to play a critical role in the pathology of AD. Because of these observations, slowing down the progression of AD and associated disorders like dementia and cognition decline have become important targets for clinically testing antioxidant and anti-inflammation nutraceuticals, dietary supplements, and functional foods. This review focuses on the neuroprotective impacts of dietary supplements and nutraceuticals as therapeutic strategies for combating oxidative stress in the brain and slowing down the progression of dementia and cognition impairment.

ROLE OF OXIDATIVE STRESS IN THE PATHOPHYSIOLOGICAL MECHANISMS OF NEURONAL CELL DEATH DEATH IN ALZHEIMER'S DISEASE PATIENTS

Regulation of amyloid-β and oxidative stress

When the steady-state equilibrium between pro-oxidant and anti-oxidant is disrupted, oxidative stress occurs. Many illnesses, including AD, have been linked to oxidative stress. As previously mentioned, oxidative stress responses are regulated by a wide number of transcription factors. It plays a major role in AD in the creation of proteinopathy associated with Aβ by controlling both transcriptional and translational levels of the amyloid precursor protein (APP) gene. In response to ROS, various transcription elements, such as HSF-1 and NF-darB attach to the APP gene's promoter region thereby increasing the expression of APP [1, 38-39]. Post-mortem examinations of the AD brains have revealed an increased amount of iron (Fe) in the brain tissue, and Fe can serve as a significant catalyst for the production of ROS in the CNS [40]. The post-transcriptional processing of APP and mRNA interacts with the high Fe concentration. The IRE-binding protein (IREBP) binds to the 5'-untranslated region (5'-UTR) in normal circumstances to downregulate translation, and the APP transcript includes type II iron-responsive component (IRE). An excessive number of intracellular iron is generated and when it binds to (5'-UTR) of APP it results in up-regulation of APP mRNA [41]. Fe's detrimental role in the advancement of AD is shown by this incident. BACE1 and gamma-secretase are the primary processing enzymes for simultaneous proteolysis of APP via the amyloidogenic mechanism [42]. BACE1, a trans-membrane aspartyl protease, cleaves APP and excludes sAPP beta at the N-terminal end, releasing a 99-amino-acid APP C-terminal component. Moreover, the γ-secretase's breakdown results in the generation of Aβ peptides [43]. Thus, the breakage of APP by the third alpha-secretase enzyme limits the formation of harmful Aβ peptides [44]. It has been documented that oxidative stress decreases alpha-secretase activity while increasing BACE1 and secretase stimulation [45-47].

The degree of BACE1 expression is influenced by the adhesion of various redox-sensitive transcriptional regulators such as specificity protein 1 (SP1), hypoxia-inducible factor 1 (HIF-1), NF-B, and peroxisome proliferators-activated receptor-gamma [48]. BACE1 mRNA [49] and its protein concentrations [50] are enhanced by HIF-1, PPARγ, on the other hand, acts as a BACE1 expression repressor. In neuronal cells, NF-βB is indeed a novel transcription factor that controls BACE1 transcription. [51]. It has been documented that NF-βB has a regulatory impact on BACE1 transcription in segregated neuron cultured cells and non-activated glial colonies, but also acts as an activator of BACE1 transcription in astrocytic and Amyloid beta-exposed neuron cultured cells. [52-53]. Apart from these activities, oxidative stress increases

BACE1 activity by stimulating the double-stranded RNA-dependent protein kinase and downstream eIF2 (eukaryotic initiation factor-2) phosphorylation cascades [54-55]. The role of oxidative stress theory in increasing BACE1 activity in Alzheimer's disease is thus demonstrated. Presenilin1 is one of four subunits that make up the gamma-secretase, which generates A42 from APP (PS1). CD1477 nonessential regulator complex with nicastrin, PEN-2, and PH1 catalytic subunits [56]. PS1 and PEN-2 gamma-secretase efficiency are improved by oxidative stress, resulting in a positive feedback loop that contributes to increased BACE1 expression. To cause this positive feedback loop between BACE1 and gamma-secretase, the c-jun N-terminal kinase (JNK) signaling pathway must be triggered to facilitate APP cleavage [57]. Oxidative stress also impairs the management of the brain's toxic-free micro-environment, which is crucial for normal neuronal activity in Alzheimer's patients.

The blood-brain barrier (BBB), which regulates low-density lipoprotein receptor-related protein 1, is the primary regulator for sustaining A protein homeostasis in the CNS (LRP1 transporter). The membrane-bound type of LRP1 is specifically regulated on the abluminal portion of the BBB and controls the transport of Aβ regulated by the primary receptor through the BBB and into the bloodstream, thus removing this from the brain. The soluble LRP1 variant (sLRP1) binds to free plasma Amyloid beta peptides in the peripheral circulation and is excreted as sLRP1-A complexes by the kidneys and liver. [58-59]. The binding of sLRP1 to A is disrupted by oxidation, increasing plasma concentrations of free A40 and A42 [60-61]. With the aid of the AGE receptor (RAGE), the enhanced amount of free s-plasma A crosses the BBB and reemerges the brain. The BBB's primary Aβ influx receptor i.e., RAGE moves blood to Aβ in the brain [62]. As a result of the rising degree of RAGE expression, AD patients' brains and cerebrovascular areas show Aβ buildup [63-64]. An accumulation in the brain is a combined consequence of decreased membrane-bound and soluble LRP1 expression, which leads to Aβ reemerging into the brain as a result of their oxidation and increased RAGE expression [65].

Relationship between tau and oxidative stress

Tau is a protein correlated with the neuronal microtubule, plays a key role in neuronal polarity production [66-67], The dynamics of microtubules in neurons are influenced by the manipulation of the microtubule assembly and its stabilization [68-69]. The stimulation of numerous tau kinases and tau phosphatases is primarily responsible for the phosphorylation of Tau. The disruption of this equilibrium triggers Tau's irregular phosphorylation, which contributes to the formation of neurofibrillary tangles. The phosphorylation of such a Tau protein is mainly caused by the stimulation of various tau kinases and tau phosphatases. Tau's irregular phosphorylation is triggered when this equilibrium is disrupted, which leads to the formation of neurofibrillary tangles [70].

Oxidative stress-mediated formation of amyloid-beta (aβ) peptides and trace metal dyshomeostasis in the brain of AD patients

The hallmark of AD is the oxidative stress-mediated accumulation of irregular amyloid-beta **(**aβ) peptides and the formation of neurofibrillary tangles in the brain. The dyshomeostasis of trace metals like zinc (Zn) and copper (Cu) is considered to play a significant role play in the neurodegeneration and accumulation of aβ peptides [71]. Both Cu and Zn are involved in the synaptic modulation and synthesis of neurotransmitters in the brain. Since these trace metals are antioxidants and play critical roles in neural functions, their abnormal homeostasis can lead to the production of neurotoxic free-radical [72].

Brain inflammation in Alzheimer's disease

Since the 1980s, immune-related proteins and cells have been found near beta-amyloid plaques [73-74]. Several major epidemiological and observational studies conducted in the 1990s indicate that anti-inflammatory medications used to treat diseases like arthritis have protective effects against the development of AD, with a fifty percent decrease in the fear of advancing the disease in people who have taken non-steroidal anti-inflammatory drugs for a long time (NSAIDs) [75-76]. Such study has led to studies using animal transgenic AD models that show that NSAIDs can reduce the severity of AD pathology [77]. These numerous epidemiological and observational studies lay the groundwork for neuroinflammation support, which plays a key role in the progression of

Neuroinflammation, unlike other risk factors and genetic causes of AD, is usually not considered to be causal on its own, but instead the outcome of one or more or risk factors fpr AD, and it is thought to exacerbate the disease by alleviating beta-amyloid and tau pathophysiology [78,79]. Inflammation in the brain can be neuroprotective in an acute-phase reaction, but it can also be harmful when a chronic response is activated [80]. Several proinflammatory and toxic products, including reactive oxygen species, nitric oxide, and cytokines, release chronically activated microglia. Increased levels of interleukin 1 (IL-1) are responsible for increased development of APP and load of Aβ

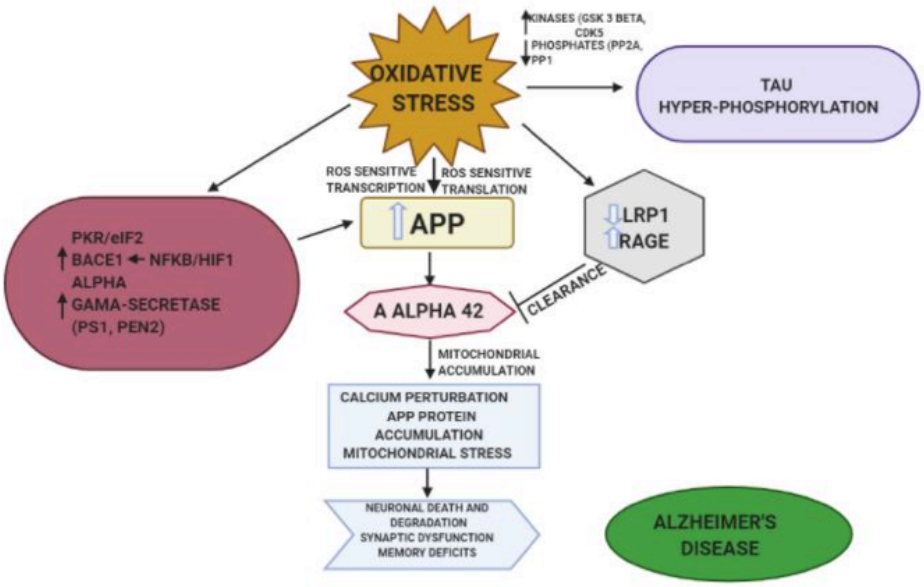

Figure 1. *Diagrammatic representation of Alzheimer's disease pathophysiology.*

in deceased patients with recent head trauma, and increased levels of IL-1 are responsible for increased development of APP and load ofAβ in deceased patients with recent head trauma [81,82]. Increased levels of IL-1b have been linked to the development of other cytokines including IL-6, which has been linked to the activation of CDK5, a kinase that promotes tau hyperphosphorylation [83]. The inflammation of neurons seen in AD tends to play a central role in reducing the burden of Amyloid-beta and tau hyperphosphorylation, implying that this dual role may be a central link between these unrelated AD phenotypes. The immune response mounted through the resident macrophage (microglia) of the brain has become a central tenant of AD's investigation [84].

NLRP3 inflammasome

Many inflammatory mechanisms are linked to the innate immune response and play a key role in the early and late stages of viral and bacterial infections [85-86]. The innate immune response can be activated and sustained by Inflammasome, a cytoplasmic polyprotein complex [87-88]. Several inflammasomes have been discovered recently, including NLRP1, NLRP3, NLRP6, NLRP7, NLRC4, and AIM2 [89-87]. The NLRP3 inflammasome is the most well-studied, with a sensor, an ASC adaptor protein, and an effector protein [90]. The conversion of procaspase-1 to active caspase-1 occurs when the NLRP3 inflammasome is activated, resulting in the formation of pro-inflammatory cytokines IL-18 and IL-1 [91-92]. The cleavage of gasdermin D by active caspase-1 can cause pyroptosis, or inflammatory cell death [93].

Inflammasome NLRP3 activation is regulated by the activation of two canonical stages, along with the first phase of priming and the second phase of activation. Numerous endogenous or microbial molecules activate the priming mechanism by upregulating the levels of NLRP3, pro-IL-18, and pro-IL-1 through the NF-B signaling cascade [94]. The second activation stage is activated by various triggers, such as viral RNA, pore-forming toxins, ATP, or particulate matter, and contributes to the assembly of the Inflammasome NLRP3 [89-87]. Three key upstream pathways trigger the NLRP3 inflammasome: K+ efflux, mitochondrial reactive oxygen species (ROS), and lysosomal membrane degradation [95]. Furthermore, the noncanonical activation manner inflammasome for NLRP3 contains murine caspase-11, which can specifically recognize toxins and lipopolysaccharides before cleaving GSDMD to induce pyroptosis [89-87].

Lately, various novel regulatory mechanisms were thought to be effective in NLRP3 inflammasome activation. The recruitment of NLRP3 to the distributed trans-Golgi network in response to various stimuli is thought to be a generalized and early process that contributes to the accumulation and stimulation of NLRP3 [96,87]. The stress granule protein DDX3X can associate with NLRP3 to cause the formation of the inflammasome [97]. By forming bipartite interactions between adjacent NLRP3 subunits, NIMA-related kinase 7 (NEK7) also plays an important role in facilitating NLRP3 inflammasome activation [98].

A recent study identified several NLRP3 inflammasome negative regulatory mechanisms that may help to improve therapeutic strategies for the treatment of autoimmune and inflammatory diseases [99]. Deacetylation of the inflammasome NLRP3 can also help prevent chronic inflammation and insulin resistance as people get older [100]. As a result, it's critical to look into the NLRP3 function in AD [101].

THERAPEUTIC APPLICATIONS OF NUTRACEUTICALS IN THE MANAGEMENT OF ALZHEIMER'S DISEASE

Turmeric and curcumin

Turmeric is a yellow color spicy herbal product isolated from the tubor of *Curcuma longa*, which is a part of the ginger family *(Zingiberaceae)*. Since ancient times, turmeric has been used as a culinary spice or traditional drug for curing various diseases and may help in slowing the progression of dementia and AD. Dried turmeric roots have been employed in Chinese and Ayurvedic Indian medicines to treat a wide variety of disease conditions such as skin disorders, wounds, rheumatisms, asthma, allergies, sinusitis, hepatic disorders, intestinal worms, general inflammation, and oxidative stress-related diseases [102]. The major bioactive ingredient of turmeric is curcumin with the chemical formula - 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione. Presently, curcumin is one of the 10 most widely used plant products worldwide, especially for its antioxidant and anti-inflammatory activity, either alone or in combination with other herbal drug preparations. The other biologically active components responsible for most of the medicinal properties of turmeric are curcuminoids, which are comprised of a combination of curcumin (75-80%), demethoxycurcumin (15-20%), and bisdemethoxycurcumin (3-5%), and they are marketed as dietary supplements and nutraceuticals [103- 104].

Curcumin's potential actions for the prevention of AD are related to its anti-inflammatory [105-108], and antioxidant properties 109-111]. Curcumin binds to Amyloid Beta in vitro, causing peptide aggregation and inhibiting the formation and elongation of AD fibrils [112]. In addition, curcumin can increase Aβ cellular intake [113], prevent plaque accumulation, and prevent peptide-induced cellular insults [114], and consequently can decrease amyloid-beta production through BACE1 (beta-site APP-cleaving enzyme) expression [115]. Curcumin can repair distorted neuritic morphology around amyloid-beta plaques in vivo [116]. In the AD mouse models, curcumin lowered the levels of Amyloid Beta serum and Amyloid Beta strain in the brain, mainly in the neocortex and hippocampus regions, as well as reduced inflammation and microglia activation [117]. Curcumin can also modulate the processing and phosphorylation of tau protein to prevent the development of NFTs [118-119]. Due to its fluorescent properties and amyloid-beta binding capacity, curcumin has also been proposed as a detection agent for the early diagnosis of plaque deposition in the brain [23].

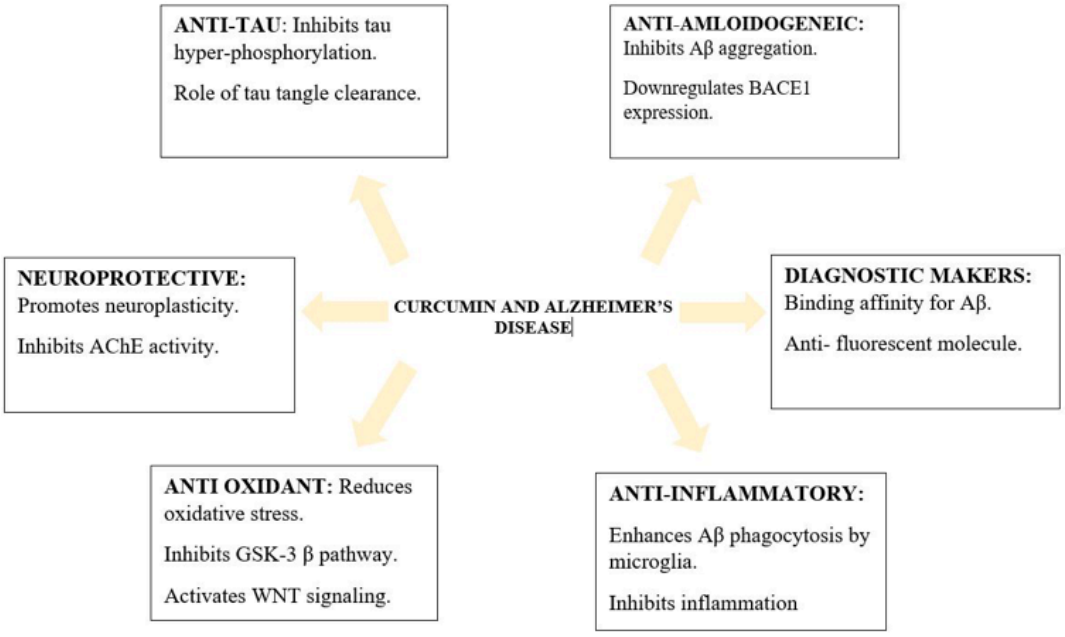

Figure 2. *Antioxidant and anti-inflammation roles of curcumin in neuroprotection and treatment of Alzheimer's disease.*

The function of curcumin and erythropoietin in an ICV-STZ rat model was recently investigated by Samy et al. (2016). The animals are injected with either STZ or saline. For three months, the latter group received either vehicle, curcumin (80 mg/kg/day, p.o.), erythropoietin (500 IU/kg every other day, i.p.), or a mixture of curcumin and erythropoietin. Curcumin and erythropoietin treatment reversed the behavioral, histological, and biochemical changes induced by ICVSTZ. Curcumin, on the other hand, was chosen over erythropoietin because of its less long-term side effects [120].

According to Rainey-Smith *et al.* (2016) participants between 40 and 90 years old without a cognitive disability were assessed on a clinical and cognitive test battery after 12 months of 1500 BiocurcumaxTM or placebo administration. The results of the Montreal cognitive assessment study, which is useful to measure basic cognitive functioning, showed that the placebo group's cognitive function deteriorated after 6 months, whereas the curcumin group's cognitive function remained stable. After a year of follow-up, there was no evidence of this difference in cognitive assessment in the Montreal study. No variations between groups over time were revealed by other cognitive and clinical tests. It was concluded that curcumin does not improve cognition, but slows down its decline. Twenty-three subjects were excluded from the study due to gastrointestinal complications, two of whom were in the placebo group. It appears that the large dosage of BiocurcumaxTM adversely affected the tolerability of this drug [121].

Novel derivatives of curcumin have been synthesized by linking it with a 2-amino-4-phenylpyran-3-carbonitrile system and tested in vitro for their antitumor activities against a panel of three human cancer cell lines (MCF-7, A2780, and U-87MG. Bioassay results demonstrated that L6 (para-Bromo), L9 (para-Nitro), and L12 (meta-Methoxy) analogues had the most potent cytotoxic and apoptosis-inducing activities against A2780 cancer cells [122].

Efforts are being made to enhance the solubility of curcumin with nanotechnology methods and to increase its absorption from the gut. Micronized nanoparticles of curcumin and its encapsulated compounds are being developed to increase curcumin's dissolution rate in the gut and enhance bioavailability for multiple biomedical applications [123].

Tannic acid

A polyphenolic element Tannic acid is extracted from herbs present in various plants, such as legumes, sorghum, banana trees, berries, and tea leaves. Tannic acid has been shown in clinical trials to have anti- oxidative, anti-inflammatory, antiviral, and antibacterial activity. It also prevents BACE1 protein activation, as well as tannic acid's anti-oxidative and anti-inflammatory activity. The main enzyme for generating and depositing Aβ peptides in the brain is BACE1. Tannic acid has been found in an in vitro study to decrease neurotoxic fibrils of Aβ [124-125].

Tannic acid, when taken orally, helps to reduce mental impairment by reducing cerebral amyloidosis and promoting non-amyloidogenic APP development. The accumulation of A peptides in the cerebral parenchyma and cerebral vascular brain region of PSAAP mice is reduced at a dose of 30 mg/kg BW/day. Tannic acid inhibits BACE1 transmission while not affecting $mRNA^{BACE1}$ levels. Tannic acid has been shown to inhibit the growth of Aβ1-40 and Aβ1-42 and prevent β-CTF cleavage in human APP-overexpressing murine neuron-like cells (SweAPP N2a cells) in the in vitro study [126] It also works by inhibiting the expression of proinflammatory cytokines (such as TNF-α and IL-1) and is active towards plaque-coupled gliosis in the presence of Aβ [127-128, 37].

Genistein

Genistein is a simple isoflavonoid present in the Leguminosae family of plants, especially soy plants. It acts against a broad variety of pathophysiological disorders, including cancer, cardiovascular disease, diabetes, and postmenopausal symptoms. It can inhibit DNA topoisomerase and tyrosine-protein kinase operation, as well as having epidermal growth factor (EGF) receptor specificity, a transmembrane regulatory protein that binds to EGF and transforming growth factor (TGF-α) It exhibits strong anti-oxidant properties due to the presence of various phenolic molecules in its composition [129-131]. Most studies have shown that supplementing this biologically active molecule helps enhance learning and memory. This molecule has been shown to have a neuroprotective role in ovariectomized rats by altering cholinergic and dopaminergic functions [132].

Genistein may reduce the synthesis of Amyloid beta by down-regulating BACE1 while concurrently activating the alpha-secretase enzyme, according to an in vitro study of hippocampal neuronal cells. Furthermore, genistein (0.375 g/mL) stimulates the PKC signaling pathway while decreasing the development of Presenilin, which is responsible for APP cleavage [133].

Intracellular ROS levels can be reduced, and mitochondrial dysfunction and an increase in anti-oxidative intracellular

enzymes can be avoided. The negative effects of nucleic acids can be significantly reduced. Activation of the estrogen receptor (ER), estrogen hormone (17-estradiol), receptive intracellular or membrane-bound proteins, which are also G-protein-bound receptors, can down-regulate and control the caspase-dependent intrinsically and extrinsically apoptotic pathways [134-136]. Genistein also regulates pro-survival pathways by triggering Nrf-2 and HO-1-1 [137]. Via calcium influx modulation, genistein can prevent hyperphosphorylation of tau at physiological conditions [138].

The formation of many cytokines and reactive organisms, such as RNS and ROS, is a major cause of AD-related neuro inflammation, and the researchers concluded that genistein has an advantageous part in decreasing Aβ-induced cytotoxicity [139]. Another significant advantage of genistein is that it may act as an estrogen inhibitor and has a neuro protective activity that doesn't conflict against proliferative mechanisms in uterine endometrial cells, unlike hormone replacement therapy, which is currently useful to treat Alzheimer's disease in postmenopausal women [140].

A study revealed that genistein at a dose of 10 mg/kg would prevent the Aβ development in the brain in Aβ-intoxicated rats and boost memory and learning deficits by modulating the estrogenic signaling cascade. Related beneficial effects on brief spatial recognition memory were found in the Y maze and passive voidance tasks.

Melatonin

Melatonin (N-acetyl-5-methoxy-tryptamine) is extensively metabolized in the pineal gland in the brain of vertebrates. It exhibits many functions, such as free radical scavenging, bio-oxidation attenuation, circadian rhythm maintenance, and others. Many other functional features, such as Aβ growth limitation, peptides, amyloid fibril, tau hyperphosphorylation, and neuronal cell apoptosis, make the molecule a major drug product for AD and other treatments [141-144]. In AD patients, there is a lower degree of melatonin in the serum blood samples and cerebrospinal fluid, as well as an abnormal circadian rhythm [145-146]. The direct association of melatonin with, and subsequent clearance of, the Aβ plaques was verified in biophysical research utilizing the thioflavin T fluorescence assay.

Melatonin has a high affinity for Aβ preventing the development of amyloid fibrils [147-148]. Analysis findings indicate that Aβ peptide clearance is not due to its anti-oxidant function increase in anti-oxidative intracellular enzymes can be avoided. The negative effects of nucleic [144]. Melatonin is said to affect the synthesis of APP and COX-2/PGE, as well as other neuro inflammatory and degenerative neural cell pathways, by influencing the role of cAMP [149-150]. Melatonin's anti-AD effect is mediated by MT2 (melatonin receptor 2) signaling pathways. Melatonin may activate protein kinase C also may stimulate phospholipase C via diacylglycerol. As a result, GSK-3's function is diminished, and it

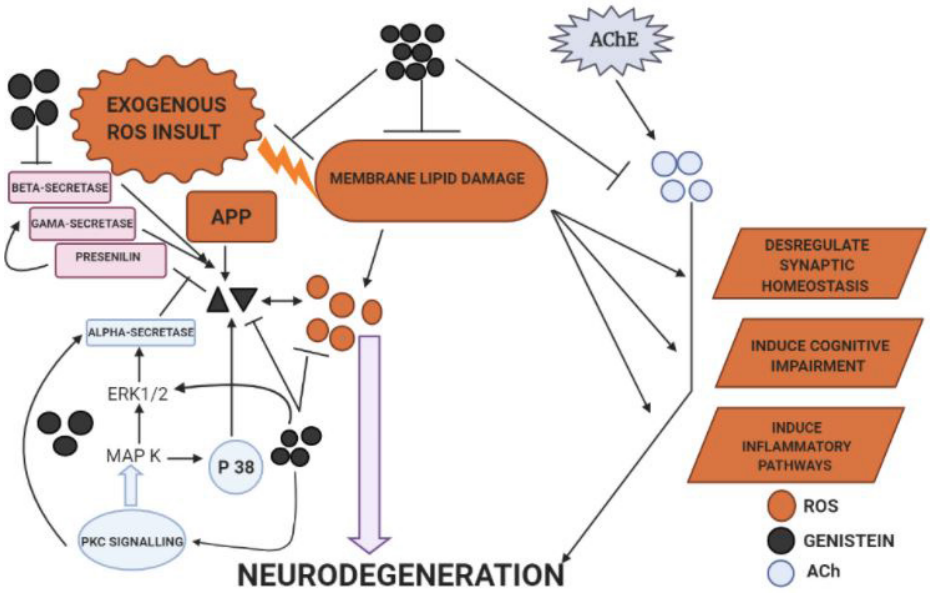

Figure 3. *Schematic representation of the protective role of genistein against Alzheimer's disease.*

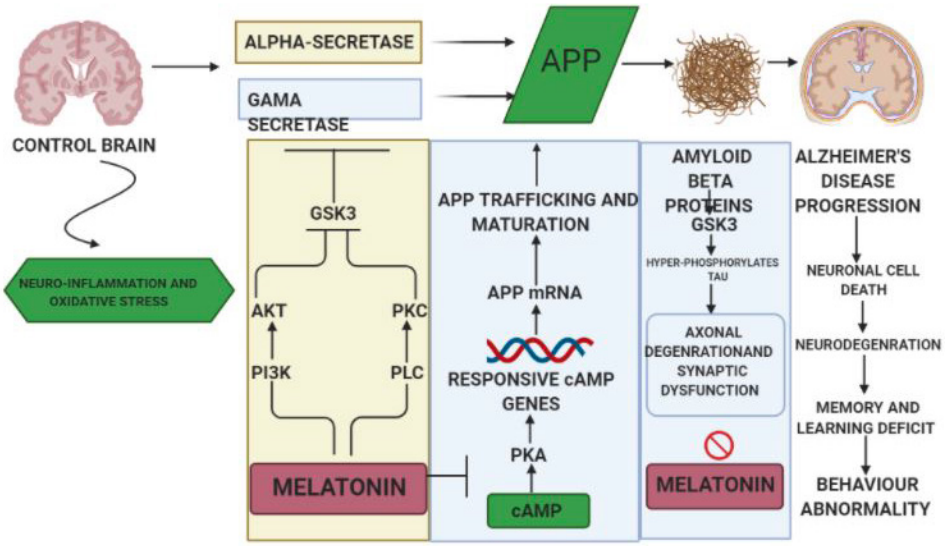

Figure 4. *Schematic representation of the dual role of melatonin in the activation and receptor-mediation of signaling pathways in Alzheimer's disease.*

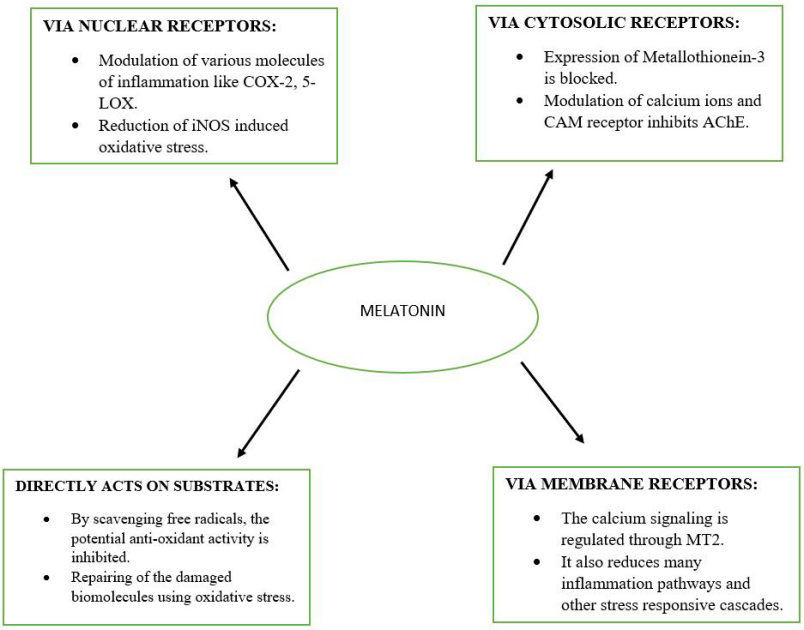

Figure 5. *Schematic illustration about the mechanism of action of melatonin for slowing down the progression of Alzheimer's disease.*

interfaces indirectly with APP synthesis [151-152,58].

Melatonin could also trigger the molecular pathway based on PI3K and Phosphorylates Akt, which can aim at reducing GSK-3 phosphorylation again and can, in turn, modify Aβ aggregation formation through down - regulation of APP [153] and hyper-phosphorylation of the tau is decreased [7]. Melatonin inhibits the expression of HIF-1a and BACE-1 in Alzheimer's micro vessels, which can significantly minimize Amyloid-beta cytotoxicity. [154]. Melatonin can help preserve homeostasis in the cholinergic binding site in AD, in addition to reducing Aβ toxicity. As the disease progresses, acetylcholine activity starts to deteriorate, affecting enzymes such as choline acetyltransferase and acetylcholinesterase [155]. Melatonin significantly reduced Amyloid-beta driven

peroxynitrite-induced disruptive activity in choline and choline acetyltransferase synaptosomes and synaptic vesicles, as well as other neuronal proteins [156].

Long-term melatonin administration improved behavioral skill and biochemical improvements in Tg2576 transgenic mice with Amyloid-beta aggregation. The role of choline acetyltransferase throughout the hippocampus and frontal cortex could be significantly improved, while memory learning and loss can be restored [157]. Melatonin was reported to help reduce immunosenescence as well as cognitive function loss in a mouse transgenic model of AD that expressed Amyloid-beta and tau pathology, similar to that seen in AD patients. In a more nuanced situation, melatonin will effectively prevent Amyloid beta from having a prooxidant effect in the hippocampus in aluminum lactate-fed mice [158]. All of these findings indicated that melatonin could preserve neuron as well as glial cells from oxidative stress-prompt damage via a survival mechanism. It can also reduce Amyloid-beta-mediated oxidative harm in cultured neuroblastoma in models of Alzheimer's. Along with these results, several clinical trials have yielded interesting findings on the therapeutic efficacy of melatonin. The oral administration of 3 mg of melatonin a day improved the behavioral disturbances of 10 AD patients with sleep-wake syndrome in a report [159-162]. Melatonin treatment of three to nine mg a day for nine to eighteen months was found successful in improving patients' behavioral and learning deficits in a study of 25 people undergoing MCI in Argentina [163].

Resveratrol

Resveratrol is a polyphenolic phytoalexin found in grapes and wine. The amounts of resveratrol differ significantly in wine but are present more in red grapes and red wine [164]. Resveratrol diminishes oxidative stress by mopping free radicals and subsequently decreases the risk of heart disease, stroke, dementia, and cognitive decline. It can improve the condition in AD patients by interacting in many metabolic pathways and could delay the onset of this disease [165]. It plays a significant role in preventing the accumulation of Aβ by reducing the aggregation of Aβ. Resveratrol not only protects the loading of lower molecular weight oligomers to higher molecular weight oligomers but also directly interferes with the Aβ aggregation [166-167], as well as indirect reduction effect on Aβ [168]. In addition, resveratrol's inhibitory effect on platelet aggregation has been observed in the medial cortex, hypothalamus, and striatum.

Senile plaques in the brain of people suffering from AD can be stained because it connects to both fibrillary and monomeric amyloid (MA) (1-42) types [169]. Resveratrol's binding energy and specificity in various Amyloid-beta fragments, on the other hand, differs [169-170]. Resveratrol converts soluble oligomers, fibrillary intermediates, and amyloid fibrils into non-toxic aggregate compounds, but not the anti-toxic equivalents, including Aβ-monomer [170]. This resveratrol-specificity for MA plaques can be used to create a resveratrol complex with fluorogenic molecules and graphene oxide for rapid and less expensive Aβ plaque detection in AD tissues [171]. Anti-tauopathy efficacy in AD has also been displayed by Resveratrol. The removal of accumulated tau requires 2 endogenous proteins, lysosomal-associated membrane protein 1 (LAMP-1) and BAG family molecular chaperone regulator 2 (BAG2) [172]. Resveratrol has a strong memory-enhancing influence. By increasing BDNF, it improves the development of eternal memory as well as the power of capacity [173]. The accumulation of formaldehyde increases with age has a significant effect on memory, but resveratrol, a natural formaldehyde scavenger, reverses this deposition as well as reinstates memory [174]. It enhances memory and learning by strengthening damaged hippocampal structures [175].

Inflammatory responses including those mediated by the accumulation of Aβ in AD can be avoided because of the prevention of multiple proinflammatory by Resveratrol. Interleukins, ROS, IL like IL-1, IL-6, IL-12, and IL-23, nitric oxide (NO), and protein-1 monocyte chemoattractant are among the molecules involved (MCP-1) [176-177] as well as nuclear factor-B (NF-B). It inhibits the development of prostaglandin E2, a powerful pro-inflammatory molecule [178]. It prevents AlCl3-produced pro-inflammatory reactions in the brain of rats, including tumor necrosis factor-alpha (TNF alpha) expression as well as inducible nitric oxide synthase (iNOS) activity, by controlling NF-κB alpha expression [179]. It also blocks the effects of the subunits of NADPH oxidase and microglia proliferation, most of which are caused by oligomeric Aβ [180]. In addition, an accumulation increases the activity of another inflammatory enzyme, inducible nitric oxide synthase (iNOS), which causes toxicity of neurons as well as apoptosis. Resveratrol can be used to protect against the damage by lowering the levels of cellular iNOS in a dose-dependent manner [181-182].

Aβ-induced toxicity in the brain is caused by oxidative stress induction. The antioxidant properties of resveratrol, rather than its association with amyloid aggregates, may be the primary reason for its neuroprotective effects [183]. In many other forms, resveratrol also exhibits antioxidant effects on

neurons. It potentially prevents the destruction of the mitochondrial membrane, decreases the development of ROS, and preserves the cells from neurotoxicity induced by Aβ1-42 by retaining levels of imbalanced enzymes like malondialdehyde and glutathione [184]. Aβ induces substantial development of ROS and cellular transition towards apoptosis induced by oxidative stress. It protects cells from the toxicity of neurons as well as cell death [185-186]. It also decreases oxidative stress as well as boosts the number of memory-related proteins.

Table 1. *Purported mechanism of action of resveratrol for treating Alzheimer's disease*.

FUNCTION	MECHANISM	REFERENCES
Tauopathy retardation	BAG2 Upregulation	[178]
Long-term memory formation enhancement	BDNF level increases also see 232, 233]	[172;
Brain proinflammatory Responses inhibited	NF- κB expression decreased Cellular iNOS levels decreases	[183,184]
Inactivation of astrocyte	GFAP level reduced	[184]
Antioxidative activity	The amount of reactive oxygen species (ROS) in the body has decreased. Glutathione (a free radical scavenger) levels have increased. Downregulation of pro-oxidative stress proteins	[187]

Resveratrol and grape seed extract improved cognitive issues as well as damaged memory linked with Amyloid-beta deposit in animals with Tg2576 (AD experimental mouse model) [188-189]. Resveratrol in two hundred mg/kg bw reduces oxidative stress and inflammation of neural cells in HFD-fed C67BL/6J mice thereby down-regulating TNF-α also stimulating macrophage penetration in the adipose. [190]. Oral resveratrol has been shown to enhance impaired spatial orientation and memory functioning in C57Bl/6 mice by growing microvascular density in the hippocampus region and decreasing vascular defects in the cortical microvascular and hippocampal endothelial cells [191]. It was also shown, in line with the previous results, that HFD fed in both muscular and adipose tissues, can effectively reduce the outpatient locomotor activity and the number of rears in C57Bl/6J mice. This outcome suggests that resveratrol may have the ability to boost mitochondrial function, leading to an improvement in energy metabolism, sensorimotor function, and aerobic capability [191].

Vanillic acid

Vanillic acid is used as a flavoring agent in a variety of foods and medicines. It emerges from the herb *Angelica Sinensis* (Oliv.) Diels (Apiaceae). By reducing oxidative stress, vanillic acid has been found to enhance memory and spatial learning deficiency. The memory of habit is also significantly restored by lowering AChE, corticosterone, and TNF-alpha levels while increasing antioxidant levels [192].

In Aβ1-42 expressing transgenic mice, intraperitoneal administration of vanillic acid at a dosage of thirty mg/kg BW reduces Aβ1-42-mediated ROS initiation, neuro-inflammation, degeneration of neurons, synaptic deficiency, and memory problems. Vanillic acid is the most possible antioxidant that could be useful in AD because of this advanced mechanism. In vitro experiments on neuronal HT22 cells revealed that it protects against Aβ1-42-induced neuronal damage [193].

Vanillic acid is a central component of virgin olive oil (VOO), which is derived from hydroxycinnamic acid (Hc acids). Virgin olive oil and Hydroxycinnamic acids, both of which can reduce the amount of intracellular ROS in SH-SY5Y cells, were used to assess their neuroprotective effects against AD. Virgin olive oil and Hydroxycinnamic acid inhibit pERK1/2 and p-p38 activation while not affecting JNK levels. Furthermore, Virgin olive oil and Hydroxycinnamic stimulate the expression of many glycolytic enzyme genes, including hexokinase (HK1) and phosphofructokinase (PFKM). Virgin olive oil and Hydroxycinnamic acid help protect neurotypical cells from cytotoxicity caused by the Amyloid beta peptide by improving their energy metabolism. Virgin olive oil and Hydroxycinnamic acid are alternative therapeutic routes to improving oxidative stress associated with neuronal disorders such as Alzheimer's disease.

Caffeic acid

Various plant products contain caffeic acid (3,4-dihydroxycinnamic acid). Various pharmaceutical efficiencies are reported to be exhibited by caffeic acids, such as anti-inflammatory, antiviral, anticancer, antihypertensive, antithrombosis, and other therapeutic applications. In an Aβ25-35 injected Alzheimer's disease mouse model, oral administration of caffeic acid recovers spatial, cognitive, and memory capacities It effectively reduces lipid peroxidation and NO production in the kidney, brain as well as liver [194].

If administered, around a 100 mg/kg BW/day, it reduces AChE activity and nitrite generation in Alzheimer's-affected research animals. Caffeic acid has also been shown to reduce caspase-3, p53, phosphorylated MAPK, and NF-κB cleavage in Alzheimer's rats, as well as it shows anti- inflammation effect and reduce oxidative stress [195]. Alzheimer's Tacrine-3-caffeic Acid, a novel multifunctional anti-dimer, protects neurons (HT22 cells) from oxidative stress-induced death of cells by stimulating Nrf2/ARE/HO-1 modulation, an intrinsic anti-oxidative pathway [196].

Berberine

Berberine has a bitter taste and is a yellow alkaloid found in Hydrastis canadensis, Berberis aquifolium, Coptis chinensis, *Berberis aristata and Berberis vulgaris* stems, barks, roots, and rhizomes [197]. Berberine has been shown to modulate the expression of monocyte chemotactic protein-1 and interleukin-6 induced by Aβ and Aβ generation in recent studies. In BV-2 and microglial primary cells. It down-regulates the NOS (nitric oxide synthase) as well as COX-2 by down-regulating the PI3K/PKB and MAPK signaling cascades. Berberine prevents the expression of Aβ peptides and reduces gliosis and cognitive mutilation in neuroglioma H4 cells by regulating APP processing and BACE-1 activity. In pharmacology, berberine is said to be able to pass through the BBB and protect the neurons and neurotrophic effects.

Its administration shows a significant reduction in calyculin Aβ-induced tau hyperphosphorylation at Thr205, Thr231, and Ser198/199/202, Ser396, and Ser404 residues. Because of its phosphorylation at Tyr216 and Ser9, it can also inhibit GSK-3 activation and restore the role of protein phosphatase 2A [198]. Death in the experimental model of intracerebroventricular streptozotocin-induced intermittent AD-like dementia, memory loss, upregulated degree of AChE, and attenuated level of neuronal cells Berberine protects against anxiogenic acts, memory loss, upregulated degree of AChE, and attenuated level of neuronal cells (ICV-STZ) [199]. Berberine reduces memory failure in the AD impaired mouse model by facilitating autophagic clearance of Aβ via the PI3K/beclin-III class. By downregulating BACE1 protein expression in the 3 × Tg-AD mouse brain and primary hippocampal neurons, Berberine also inhibits Aβ production [200].

NUTRACEUTICALS MARKETED FOR THE PREVENTION OF ALZHEIMER'S DISEASE

Continuing vigorous efforts are going on by the basic researchers and pharmaceutical industry to discover blockbuster therapies for curing AD, which would benefit millions of people around the world [201]. Innovation is the main component that characterizes the achievement of the pharmaceutical industry, but the costs associated with identifying a drug, converting this disclosure into an effective drug, and presenting it have increased significantly [202]. Insurance is therefore needed in this way, which can provide pharmaceutical organizations with satisfactory protection for future development and production of innovative medications. A patent is a legal document that enables an innovator to demonstrate selectiveness over another product or drug. Market restrictiveness will give the patent holder cash prizes as it gives the innovator a monopoly over the 20-year patent term growth. Patent security and business investment guarantee for new drug discovery are becoming increasingly common in the pharmaceutical industry [203].

Alzheimer's disease is an elderly brain disorder with a rising incidence due to the high rate of growth in the aging population, especially in developing countries. Due to indirect and direct costs resulting from AD, the economic effect of this disease is rising [204]. Nevertheless, the lack of successful treatment for this debilitating disease has driven pharmaceutical firms to raise their R&D budgets to find a suitable solution. However, given recent clinical trials, several molecules that have been selected as potential AD treatment targets have yielded negative results [205-206]. On the other hand, the use of natural products like nutraceutical products has a promising future [207]. Several reports of cognitive function and behavioral activity in experimental murine suggest that nutraceutical administration can significantly attenuate various prevailing AD biomarkers [208]. Nutraceuticals can also be used to avoid or slow down the worsening of cognitive and behavioral activities in laboratory animals, according to these findings [209].

SUMMARY AND CONCLUSIONS

Global incidences of AD are increasing in the aging populations. As opposed to men, women have an increased risk of AD, depression, and stress-related illnesses. The pathophysiological mechanisms involved in causing neurotransmitter deficiency, neuronal and glial abnormalities, apoptosis/necrosis, and cell death remain largely unknown. The AD-associated progressive decline in mental health not only causes memory loss and motor impairment but also adversely impacts the quality of life of elderly subjects and makes them dysfunctional from making important decisions in their daily life activities.

Table 2. *Summary of patented nutraceuticals marketed for the prevention and management of Alzheimer's disease.*

Serial number	Application year	Patent number	Product title	Inventors' name	Product ingredients and indications	Reference
1	2017-12-21	WO2017215791A1	Resveratrol solubilization product for pharmaceutical purposes	Dariush et al.	Consists of resveratrol, polysorbate 80, and polysorbate 20, plus at least one medium-chain triglyceride and tocopherol. Useful in the prevention of Alzheimer's disease (AD). Dose: 2,000 mg/day	[210]
2	2017-06-20	US9682048B1	Multi-component formulations for the treatment of cognitive decline including Alzheimer's disease	Gene Rosen	A multi-component formulation containing one embodiment methylsulfonylmethane, one energy source i.e., fructose 1,6-diphosphate, and herbal component turmeric for the treatment and prevention of AD. Dose- Combination of 250 mg/kg resveratrol, 70 mg/kg curcumin, 10 mg/kg *Ningxia gouqizi,* 500 mg/kg blueberry, 250 mg/kg cinnamon, 500 mg/kg DHA, 250 mg/kg DMSO, and 170 mg/kg F6P.	[211]
3	2014-12-18	CA2914767A1	A marine oil formulation comprising resveratrol or derivatives thereof for use in treating, delaying, and/or preventing AD.	Janne et al.	Drink formulation containing resveratrol and other derivatives along with marine oil for treating, delaying, and/or preventing AD. Dose: 50-300 ml	[212]
4	2014-07-22	US20120269794A1	Nutraceutical composition that comprises an extract of shilajit, folic acid, vitamin B12, and vitamin B6 and the use thereof for preventing and/or treating neurodegenerative diseases and/or the cognitive deterioration associated with cerebral aging	Ricardo et al.	Nutraceutical composition containing Shilajit, folic acid along a small amount of vitamins B6 and B12 which are useful in preventing AD. Dose: 350 mg capsule 1 every 12 hours.	[213]
5	2011-03-15	US7906643B2	Methylene blue-curcumin analog for the treatment of AD	Thomas & DiMauro	For AD treatment with a methylene blue-curcumin blend. Dose: < 4000 mg/day.	[214]
6	2010-07-01	WO2010074971A1	Use of nitrogen-containing curcumin analogs for the treatment of AD.	Thomas & Dimauro	Natural curcumin was modified with an amino acid moiety to improve the analog's transport through the blood-brain barrier by the LAT1 transporter, which was used to treat AD. Dose: < 4000 mg/day.	[215]

Serial number	Application year	Patent number	Product title	Inventors' name	Product ingredients and indications	Reference
7	2016-07-19	US9393198B2	Intravenous curcumin derivatives for treatment of neurodegenerative and stress disorders	Lawrence et al.	Curcumin crosses the blood-brain barrier and localizes in the hippocampus and striata, preventing stress-induced neuronal cell damage and stimulating neurogenesis and the repair of impaired neural circuits. The parenteral administration of liposomal formulations and polymer conjugates of curcumin, curcumin analogs, and derivatives are used for curing AD. Dose: 50 nM/kg	[216]
8	2017-08-01	US20150031653A1	Useful for treating, delaying, and/or preventing AD.	Janne et al.	A liquid formulation comprising fresh marine omega-3 oil and resveratrol for treating/delaying and/or preventing AD. Dose: 50-300ml	[217]
9	2015-03-05	US20150065449A1	Treating amyloidoses with vitamin B12, plus the composition includes melatonin, resveratrol, and EGCG	Ewa et al.	Composition containing melatonin, resveratrol, EGCG, and vitamin B12 for the treatment of AD.	[218]
10	2017-08-22	US9738605B2	Hybrid compounds of curcumin and melatonin as neuroprotectants and for neurodegenerative disorders	Shijun Zhang	Curcumin and the melatonin-based hybrid compound are considered useful in the prevention of AD. Dose: 1-20 mg/kg	[219]
11	2012-02-09	WO2012017451A1	A bio-stabilized resveratrol formulation	Khandelwal et al.	Bio-stabilized resveratrol formulation containing virtus resveratrol, lotus seed powder, grape seed extract, sesame seed, sunflower seed, pumpkin seed, kelp, carrot seed powder, onion seed, *Medicago sativa*, *Amaranthus spinosus,* and mulberry for the treatment of AD.	[220]
12	2012-08-01	CN102617465A	Tacrine-caffeic acid hetero-blends are used for the preparation method and medicinal compositions	Rongbiao et al.	Tacrine-caffeic acid hetero-blends and derivatives can be used in appropriate dosage form for the treatment of AD. Dose: 80 mg/day	[221]
13	2013-09-12	US20130237556A1	Berberine alkaloid is used as a medicament for the prevention and treatment of neural diseases.	Li et al.	Oral administration of berberine inhibits the accumulation of β-amyloid- plaque, phospho-amyloid precursor protein (p-APP), and tau hyperphosphorylation in a mammalian brain and hence is useful in the treatment of AD. Dose: 25-100mg/kg	[222]
14	2014-07-24	WO2014111028A1	Genistein alkylamine compound is used for the preparation and used thereof for AD treatment	Yong et al.	Genistein alkylamine compound and its pharmaceutically acceptable salt is useful in the treatment and delay of AD. Dose: 2.5-5 mg/kg	[223]

Serial number	Application year	Patent number	Product title	Inventors' name	Product ingredients and indications	Reference
15	2020-09-02	EP3174874A1	Berberine salts, ursodeoxycholic salts, and combinations, methods of preparation, and application thereof	Liping Liu	Berberine in combination with pharmacologically active organic acids helps in the treatment of AD. Dose: Combination of berberine (150 mg/kg) and UA (150 mg/kg) Combination of berberine (150 mg/kg) , EPA (75 mg/kg) and DHA (75mg/kg)	[224]
16	2013-05-09	US20130115202A1	Anti-inflammatory compositions for treating neuro-inflammation	Theoharis Theoharides	The composition of berberine, a flavonoid, olive kernel extract, hydroxytyrosol is useful in the treatment and prevention of AD. Dose: Berberine- 50-500 mg, Olive kernel extract – 100-1000 mg, Hydroxytyrosol- 200-2000 mg	[225]
17	2020-10-07	EP3057437A1	Protective effects of oil palm composition on Alzheimer's disease	Weinberg et al.	Palm oil preparation is useful in impending and making the neurotoxic peptides and thus can be used for the treatment of AD. Dose: 0.9 mg/mL	[226]
18	2015-11-24	US9192644B2	Bioavailable curcuminoid formulations for treating AD and other age-related neurological disorders.	Frautschy and Cole	Curcuminoid preparation with enhanced bioavailability comprising of an antioxidant curcuminoid, glucuronidation inhibitor, and water-soluble, and pharmaceutically acceptable inhibitor is useful for the treatment of AD. Dose: 33.3 mg/kg	[227]
19	2014-10-07	US8853261B2	Nutraceutical composition made from *Garcinia mangostana*	Gokaraju et al.	Nutraceutical and dietary preparations of *Garcinia mangostana* are rich in γ-mangostin or other demethylated xanthones and they exhibit potent antioxidative activity and reduce inflammation, which helps in the treatment/prevention of AD. Dose: 50 mg/kg/day	[228]
20	2011-09-20	US8021701B1	The intended composition retards the onset of AD.	Stephen Perry	A preparation containing curcumin, piperine, oleic acid, oleanolic acid, ursolic acid, galantamine, and huperzine A is useful for the delay of AD. Dose: Combination of 10.0-40.0 mg curcumin; 5.0-10.0 mg piperine; 40.0 mg oleic acid 40.0 mg oleanolic acid; 40.0 mg ursolic acid; 16.0-24.0 mg galantamine; 50.0-100 ug huperzine A; 20.0-50.0 mg choline; and 50.0-100.00 mg vitamin B	[229]

It is well documented that men are at higher risk of Parkinson's disease, autism, and schizophrenia, whereas women have an increased risk of AD, depression, and stress-related illnesses. The incidences of chronic neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, depression, schizophrenia, and anxiety associated disorders are greater in postmenopausal women. The gender differences are attributed to sex hormone effects (testosterone, estrogens) on the CNS. Androgens and estrogens have neuroprotective actions on neuronal and glial cell viability. Neuroprotection caused by sex hormones is decreased in elderly men and women. Oxidative stress is also enhanced in aged men and women, and sex hormones protect against oxidative stress in both genders [230].

NoguchiShinohara *et al.* performed a randomized, placebo-controlled, double-blind 24-week trial in a group of 23 patients to evaluate the safety and efficacy of *Melissa officinalis* extract containing 500 mg rosmarinic acid for the prevention of dementia and AD progression. No significant differences were observed in disease-related biomarkers between the two groups. However, the results suggested that *M. Officinalis* extract containing 500 mg taken daily may help to prevent the worsening of AD-related neuropsychiatric symptoms [231].

Although the clinical histopathological findings and animal models research has contributed a great deal in enhancing our understanding of the underlying cellular and molecular mechanisms involved in the development of dementia and AD, yet there remain several gaps in our knowledge regarding the impact of genetic/epigenetic and environmental factors causing neurodegenerative abnormalities in the aging population. Recently, scholarly review articles have suggested that bioactive proteins produced by adipose and muscle tissue (adipokines and myokines respectively) may be involved in the pathogenesis and therapy of cardiometabolic and neurodegenerative diseases, including AD [232, 233]. For slowing the onset, progression, and prevention of chronic CNS disorders, it is generally recommended that people should make lifestyle changes, eat wholesome foods rich in antioxidant and anti-inflammatory flavonoids and polyphenols, retinoids, do physical exercise, reduce excessive use of alcohol, and avoid tobacco smoking, including E-cigarettes. Consumption of various diets, such as the Med-diet, Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean-DASH Interventions for Neurodegenerative Delay (MIND) diet have proven useful for the primary prevention of cardiovascular diseases (CVDs), and to delay the onset of neurodegenerative disorders. Genetic/epigenetic factors, exposure to environmental toxicants, socio-economic conditions, mental stress, and neuronal inflammation are considered to be the triggers for initiating chronic old-age-related brain diseases. The consumption of anti-inflammation and antioxidant wholesome diets and lifestyle modifications appear to be the most cost-effective strategies for delaying the onset and prevention of chronic brain diseases in the aging population. Natural health products, functional foods, and antioxidants present in fresh vegetables and fruits, and medicinal herbs prevent oxidative stress and lipid peroxidation in the brain, and prevent neuronal/glial injury by scavenging free radicals in the CNS, and consequently protect against neuronal impairment. Recently, numerous medicinal herbs, plant products, nutraceuticals with strong antioxidant/anti-inflammation abilities, such as *Gingko Biloba*, curcumin, resveratrol, epigallocic acid, tannic acid, berberine, vanillic acid, caffeic acid have proven helpful in the prevention and management of Alzheimer's disease.

In this review, we have addressed several antioxidants and anti-inflammation macromolecules to prevent oxidative stress-induced injury by scavenging free radicals in the brain. The phytochemicals present in dietary products and nutraceuticals discussed in this review may not only promote the resolution of existing cerebral Aβ-plaques but also chelate the metals like copper and iron implicated in causing AD. In addition, we have attempted to provide current information about the recent patents filed regarding the usefulness of nutraceuticals in the prevention/mitigation and management of AD and other neurological diseases.

CONFLICT OF INTEREST STATEMENT

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGEMENTS

The authors are grateful to SVKM's NMIMS Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management for providing opportunity, support, and desired assistance.

AUTHOR CONTRIBUTIONS STATEMENT

GK and HSB visualized the idea for this review paper and contributed to manuscript writing. GK also supervised the project. SG, VC, and AS contributed to doing literature searches and preparing the draft manuscript. GK revised and approved the manuscript. GK, HSB, MB, MC, and SW corrected, revised, and approved the manuscript.

REFERENCES

1. Farias G. A, Guzman-Martinez L, Delgado C, Maccioni R. B. Nutraceuticals: a novel concept in prevention and treatment of Alzheimer's disease and related disorders. *J Alzheimer's Dis* 2014; 42(2):357-367. doi: 10.3233/JAD-132741
2. Ganesh V, Hettiarachchy NS. Nutriproteomics: a promising tool to link diet and diseases in nutritional research. *Biochim Biophys Acta Proteins Proteomics* 2012; 1824(10):1107-1117. doi:10.1016/j.bbapap.2012.06.006
3. Ma Y, Yang MW, Li XW, Yue JW, Chen JZ, Yang MW, *et al*. Therapeutic effects of natural drugs on Alzheimer's disease. *Front Pharmacol* 2019; 10:1355. doi:10.3389/fphar.2019.01355
4. Scheltens P, Blennow K, Breteler MM, de Strooper, B, Frisoni, GB, Salloway, S, *et al*. Alzheimer's disease. *Lancet* 2016; 388: 505–517. doi:10.1016/ S0140-6736(15)01124-1
5. Von Gunten A, Bouras C, Kövari E, Giannakopoulos P, Hof P. R. Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease. *Brain Res Rev* 2006; 51(2):176-211. doi:10.1016/j.brainresrev.2005.11.003
6. Reitz C, Mayeux R. Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochem Pharmacol* 2014; 88(4):640-651. doi:10.1016/j.bcp.2013.12.024]
7. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, *et al.* Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. 1997. *JAMA*. doi: 10.1001/jama.1997.03550160069041
8. Saunders AM, Strittmatter WJ, Schmechel D, St. George-Hyslop PH, Pericak-Vance MA, Joo SH. Association of apolipoprotein E allele E4 with late onset familial and sporadic Alzheimer's disease. *Neurology* 1993; 43:1467-1472. doi:10.1212/WNL.43.8.1467
9. Hebert L. E, Bienias J. L, Aggarwal N. T, Wilson R. S, Bennett D. A, Shah R. C*, et al*. Change in risk of Alzheimer disease over time. *Neurology* 2010; 75(9):786-791. doi:10.1212/WNL.0b013e3181f0754f
10. Hebert L. E, Weuve J, Scherr P. A, Evans D. A. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology* 2013; 80(19):1778-1783. doi: https://doi.org/10.1212/WNL.0b013e31828726f5
11. Fratiglioni L, Ahlbom A, Viitanen M, Winblad, B. Risk factors for late–onset Alzheimer's disease: A population-based, case-control study. *Annals Neurol* 1993; 33(3):258-266. doi: 10.1002/ana.410330306
12. Green R. C, Cupples L. A, Go, R, Benke, K. S, Edeki, T, Griffith, P. A, *et al*. Risk of dementia among white and African American relatives of patients with Alzheimer disease. *JAMA* 2002; 287(3):329-336. doi: 10.1001/jama.287.3.329
13. Pereira CF, Santos AE, Moreira PI, Pereira AC, Sousa FJ, Cardoso SM, *et al.* Is Alzheimer's disease an inflammasomopathy? *Ageing Res Rev* 2019; 56:100966. doi:10.1016/j.arr.2019.100966
14. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegen* 2019; 14(1):1-18. doi:10.1186/s13024-019-0333-5
15. Gowrishankar S, Yuan P, Wu Y, Schrag M, Paradise S, Grutzendler J, Ferguson S. M. Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques. *Proc Nat Acad Sci USA* 2015; 112(28):E3699-E3708. doi:10.1073/pnas.1510329112
16. Irvine GB, El-Agnaf, O. M, Shankar, G. M, Walsh DM. Protein aggregation in the brain: the molecular basis for Alzheimer's and Parkinson's diseases. *Mol Med* 2008; 14(7):451-464. doi: https://doi.org/10.2119/2007-00100.Irvine
17. Cedernaes J, Schiöth, H. B, Benedict C. Efficacy of antibody-based therapies to treat Alzheimer's disease: Just a matter of timing?. Experimental gerontology. 2014; 57:104-106. doi: https://doi.org/10.1016/j.exger.2014.05.002
18. Ganjei J. K. Targeting amyloid precursor protein secretases: Alzheimer's disease and beyond. Drug news & perspectives. 2010; 23(9):573-584. doi: 10.1358/dnp.2010.23.9.1507297
19. Rosenblum W. I. Why Alzheimer trials fail: removing soluble oligomeric beta amyloid is essential, inconsistent, and difficult. Neurobiology of aging. 2014; 35(5):969-974. doi: https://doi.org/10.1016/j.neurobiolaging.2013.10.085
20. Huang C, Dong, D, Jiao, Q, Pan, H, Ma, L, Wang R. Sarsasapogenin–AA 13 ameliorates Aβ-induced cognitive deficits via improving neuroglial capacity on Aβ clearance and antiinflammation. *CNS Neurosc Ther* 2017; 23(6):498-509. doi: https://doi.org/10.1111/cns.12697

21. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann, N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatr* 2010; 68(10):930-941. doi: https://doi.org/10.1111/cns.12697
22. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole, G. M, Wyss–Coray T, *et al.* Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000; 21(3):383-421. doi: https://doi.org/10.1016/S0197-4580(00)00124-X
23. Lee Y. J, Han S. B, Nam S. Y, Oh, K. W, Hong, J. T. Inflammation and Alzheimer's disease. Archives of pharmacal research. 2010; 33(10):1539-1556. doi: https://doi.org/10.1007/s12272-010-1006-7
24. Park M. H, Lee M, Nam G, Kim M, Kang J, Choi B. J, Lim M. H, *et al.* N, N′-Diacetyl-p-phenylenediamine restores microglial phagocytosis and improves cognitive defects in Alzheimer's disease transgenic mice. Proceedings of the National Academy of Sciences. 2019; 116(47):23426-23436. doi: https://doi.org/10.1073/pnas.1916318116
25. Ji K, Akgul G, Wollmuth L. P, Tsirka S. E. Microglia actively regulate the number of functional synapses. PloS one. 2013; 8(2): 56293. doi:10.1371/journal.pone.0056293
26. Heneka M. T, Carson M. J, El Khoury J, Landreth G. E, Brosseron F, Feinstein D, Kummer M. P, *et al.* Neuroinflammation in Alzheimer's disease. *Lancet Neurol* 2015; 14(4):388-405. doi:10.1016/S1474-4422(15)70016-5
27. Heppner F. L, Ransohoff R. M, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci* 2015; 16(6):358-372. doi:10.1038/nrn3880
28. Nizami S, Hall-Roberts H, Warrier S, Cowley S. A, Di Danie E. Microglial inflammation and phagocytosis in Alzheimer's disease: Potential therapeutic targets. *Br J Pharmacol* 2019; 176(18):3515-3532. doi:10.1111/bph.14618
29. Du L, Zhang Y, Chen Y, Zhu J, Yang Y, Zhang, H. L. Role of microglia in neurological disorders and their potentials as a therapeutic target. *Mol Neurobiol* 2017; 54(10):7567-7584. doi:10.1007/s12035-016-0245-0
30. Labzin L. I, Heneka M. T, Latz, E. Innate immunity and neurodegeneration. *Annual Rev Med* 2018; 69:437-449. doi: https://doi.org/10.1146/annurev-med-050725-104343
31. dos Santos G, Kutuzov M. A, Ridge K. M. The inflammasome in lung diseases. *Am J Physiol Lung Cell Mol Physiol* 2012; 303(8):L627-L633. doi:10.1146/annurev-med-050725-104343
32. Heneka M. T, Kummer M. P, Latz E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol* 2014; 14(7):463-477. doi:10.1152/ajplung.00225.2012
33. Domijan A. M, Kovac S, Abramov A. Y. Lipid peroxidation is essential for phospholipase C activity and the inositol-trisphosphate-related Ca2+ signal. *J Cell Sci* 2014; 127(1):21-26. doi:10.1038/nri3705
34. Turillazzi E, Neri M, Cerretani D, Cantatore S, Frati P, Moltoni L, Fineschi V, *et al.* Lipid peroxidation and apoptotic response in rat brain areas induced by long-term administration of nandrolone: the mutual cross-talk between ROS and NF-kB. *J Cell Mol Med* 2016; 20(4):601-612. doi: 10.1242/jcs.138370
35. Chowdhury S, Sinha K, Banerjee S, Sil P. C. Taurine protects cisplatin induced cardiotoxicity by modulating inflammatory and endoplasmic reticulum stress responses. *Biofactors* 2016; 42(6):647-664. doi:10.1111/jcmm.12748
36. Saha S, Sadhukhan P, C Sil P. Genistein: a phytoestrogen with multifaceted therapeutic properties. *Mini Rev Med Chem* 2014; 14(11):920-940. doi:10.1002/biof.1301
37. Sadhukhan P, Saha S, Dutta S, Mahalanobish S, Sil P. C. Nutraceuticals: An emerging therapeutic approach against the pathogenesis of Alzheimer's disease. *Pharmacol Res* 2018; 129:100-114. doi:10.2174/1389557514666141029233442
38. Ko SY, Lin YP, Lin YS, Chang SS. Advanced glycation end products enhance amyloid precursor protein expression by inducing reactive oxygen species. *Free Radical Biol Med* 2010; 49(3):474-480. doi:10.1016/j.phrs.2017.11.028
39. Shi Z. M, Han Y. W, Han X. H, Zhang K, Chang Y. N, Hu, Z. M, Hong W, *et al.* Upstream regulators and downstream effectors of NF-κB in Alzheimer's disease. *J Neurol Sci* 2016; 366:127-134. doi:10.1016/j.freeradbiomed.2010.05.005
40. Kaur U, Banerjee P, Bir A, Sinha M, Biswas A, Chakrabarti S. Reactive oxygen species, redox signaling and neuroinflammation in Alzheimer's disease: The NF-κB connection. *Curr Topics Med Chem* 2015; 15(5):446-457. doi: https://doi.org/10.1016/j.jns.2016.05.022
41. Wang X, Wang W, Li L, Perry G, Lee H. G, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim Biophys Acta Mol Basis Dis* 2014; 1842(8):1240-1247. doi: 10.2174/1568026615666150114160543.

42. Lu M. A, Rajanala S, Mikkilineni S. V, Cahill C. M, Brown R, Berry J. D, Rogers J. T. The 5'-untranslated region of the C9orf72 mRNA exhibits a phylogenetic alignment to the cis-aconitase iron-responsive element; novel therapies for amytrophic lateral sclerosis. *Neurosci Med* 2016; 7(01):15. doi:10.1016/j.bbadis.2013.10.015
43. Yan R, Vassar R. Targeting the β secretase BACE1 for Alzheimer's disease therapy. *Lancet Neurol* 2014; 13(3):319-329. doi: 10.4236/nm.2016.71003
44. Cheng Z, Shang Y, Gao S, Zhang T. Overexpression of U1 snRNA induces decrease of U1 spliceosome function associated with Alzheimer's disease. *J Neurogenet* 2017; 31(4):337-343. doi:10.1016/S1474-4422(13)70276-X
45. Goedert M. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. *Science* 2015; 349(6248). doi: https://doi.org/10.1080/01677063.2017.1395425
46. Ghosh A. K, Osswald H. L. BACE1 (β-secretase) inhibitors for the treatment of Alzheimer's disease. *Chem Soc Rev* 2014; 43(19):6765-6813. doi: 10.1126/science.1255555
47. Ran Y, Hossain F, Pannuti A, Lessard, C. B, Ladd G. Z, Jung, J. I, Golde T. E, *et al.* γ-Secretase inhibitors in cancer clinical trials are pharmacologically and functionally distinct. *EMBO Mol Med* 2017; 9(7):950-966. doi: 10.1039/c3cs60460h.
48. Bastianetto S, Ménard C, Quirion R. Neuroprotective action of resveratrol. *Biochim Biophys Acta Mol Basis Dis* 2015; 1852(6):1195-1201. doi:10.1016/j.bbadis.2014.09.011
49. Chen X. F, Zhang Y. W, Xu H, Bu G. Transcriptional regulation and its misregulation in Alzheimer's disease. *Mol Brain* 2013; 6(1):1-9. doi:10.1186/1756-6606-6-44
50. Lee H. J, Ryu J. M, Jung Y. H, Lee S. J, Kim J. Y, Lee S. H, Han H. J, *et al.* High glucose upregulates BACE1-mediated Aβ production through ROS-dependent HIF-1α and LXRα/ABCA1-regulated lipid raft reorganization in SK-N-MC cells. *Sci Rep* 2016; 6(1):1-15. doi:10.1038/srep36746
51. Chen R. F, Zhang T, Sun Y. Y, Sun Y. M, Chen W. Q, Shi N, Sun X. J, *et al*. Oxygen-glucose deprivation regulates BACE1 expression through induction of autophagy in Neuro-2a/APP695 cells. *Neural Regen Res* 2015; 10(9):1433. doi: 10.4103/1673-5374.165511
52. Ganguly G, Chakrabarti S, Chatterjee U, Saso L. Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. *Drug Design Dev Ther* 2017; 11:797. doi: 10.2147/DDDT.S130514
53. Shi Z. M, Han Y. W, Han X. H, Zhang K, Chang Y. N, Hu Z. M, Hong W, *et al.* Upstream regulators and downstream effectors of NF-κB in Alzheimer's disease. *J Neurol Sci* 2016; 366:127-134. doi:10.1016/j.jns.2016.05.022
54. Hwang C. J, Park M. H, Choi M. K, Choi J. S, Oh K. W, Hwang D. Y, Hong J. T, *et al.* Acceleration of amyloidogenesis and memory impairment by estrogen deficiency through NF-κB dependent beta-secretase activation in presenilin 2 mutant mice. *Brain Behav Immun* 2016; 53:113-122. doi:10.1016/j.bbi.2015.11.013
55. Marchal J. A, Lopez G. J, Peran M, Comino A, Delgado J. R, García-García JA, Garcia M. A, *et al.* The impact of PKR activation: from neurodegeneration to cancer. *FASEB J* 2014; 28(5):1965-1974. doi:10.1096/fj.13-248294
56. Paquet C, Dumurgier J, Hugon J. Pro-apoptotic kinase levels in cerebrospinal fluid as potential future biomarkers in Alzheimer's disease. *Front Neurol* 2015; 6:168. doi:10.3389/fneur.2015.00168
57. Sun L, Zhou R, Yang G, Shi Y. Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Aβ42 and Aβ40 peptides by γ-secretase. *Proc Nat Acad Sci USA* 2017; 114(4):E476-E485. doi:10.1073/pnas.1618657114
58. Zhou Q, Wang M, Du Y, Zhang W, Bai M, Zhang Z, Miao J, *et al.* Inhibition of c-J un N-terminal kinase activation reverses Alzheimer disease phenotypes in APP swe/PS 1dE 9 mice. *Annals Neurol* 2015; 77(4):637-654. doi:10.1002/ana.24361
59. Pohlkamp T, Wasser C. R, Herz J. Functional roles of the interaction of APP and lipoprotein receptors. *Front Mol Neurosci* 2017; 10:54. doi:10.3389/fnmol.2017.00054
60. Martiskainen H, Haapasalo A, Kurkinen K. M, Pihlajamäki J, Soininen H, Hiltunen M. Targeting ApoE4/ApoE receptor LRP1 in Alzheimer's disease. *Expert Opin Theur Targets* 2013; 17(7):781-794. doi:10.1517/14728222.2013.789862
61. Xue-Shan Z, Qi W, Zhong R, Li-hong P, Zhi-han T, Zhi-sheng J, Lu-shan L, *et al.* Imbalanced cholesterol metabolism in Alzheimer's disease. *Clinica Chim Acta* 2016; 456:107-114. doi:10.1016/j.cca.2016.02.024

62. Walker D, Lue L. F, Paul G, Patel A, Sabbagh M. N. Receptor for advanced glycation endproduct modulators: a new therapeutic target in Alzheimer's disease. *Expert Opin Invest Drugs* 2015; 24(3):393-399. doi:10.1517/13543784.2015.1001490
63. Xu X. Y, Deng C. Q, Wang J, Deng X. J, Xiao Q, Li Y, Chen G. J, *et al*. Plasma levels of soluble receptor for advanced glycation end products in Alzheimer's disease. *Int J Neurosci* 2017; 127(5):454-458. doi:10.1080/00207454.2016.1193861
64. Choi B. R, Cho W. H, Kim J, Lee H. J, Chung C, Jeon W. K, Han J. S. Increased expression of the receptor for advanced glycation end products in neurons and astrocytes in a triple transgenic mouse model of Alzheimer's disease. Experimental & molecular medicine. 2014; 46(2):e75-e75. doi: https://doi.org/10.1038/emm.2013.147
65. Chiarini A, Armato U, Liu D, Dal Prà I. Calcium-sensing receptors of human neural cells play crucial roles in Alzheimer's disease. *Front Physiol* 2016; 7:134. doi: 10.3389/fphys.2016.00134
66. Zempel H, Mandelkow E. Lost after translation: missorting of Tau protein and consequences for Alzheimer disease. *Trends Neurosci* 2014; 37(12):721-732. doi:10.1016/j.tins.2014.08.004
67. Khan S. S, Bloom G. S. Tau: the center of a signaling nexus in Alzheimer's disease. *Front Neurosci* 2016; 10:31. doi:10.3389/fnins.2016.00031
68. Avila J, Pallas N, Bolós M, Sayas C. L, Hernandez F. Intracellular and extracellular microtubule associated protein tau as a therapeutic target in Alzheimer disease and other tauopathies. *Expert Opin Ther Targets* 2016; 20(6):653-661. doi:10.1517/14728222.2016.1131269
69. Kadavath H, Hofele R. V, Biernat J, Kumar S, Tepper K, Urlaub H, Zweckstetter M, *et al*. Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. *Proc Nat Acad Sci USA* 2015; 112(24):7501-7506. doi:10.1073/pnas.1504081112
70. Marti L, Latypova X, Wilson C. M, Magnaudeix A, Perrin M. L, Yardin C, *et al*. Tau protein kinases: involvement in Alzheimer's disease. *Ageing Research Rev* 2013; 12(1):289-309. doi:10.1016/j.arr.2012.06.003
71. Robert A, Liu Y, Nguyen M, Meunier B. Regulation of copper and iron homeostasis by metal chelators: A possible chemotherapy for Alzheimer's disease. *Accounts Chem Res* 2015; 48(5):1332-1339. doi:10.1021/acs.accounts.5b00119
72. Lee H. J, Korshavn K. J, Kochi A, Derrick J. S, Lim M. H. Cholesterol and metal ions in Alzheimer's disease. *Chem Soc Rev* 2014; 43(19):6672-6682. doi: https://doi.org/10.1039/C4CS00005F
73. Griffin W. S, Stanley L. C, Ling C. H. E. N, White L, MacLeod V, Perrot L. J, Araoz C, *et al*. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Nat Acad Sci USA* 1989; 86(19):7611-7615. doi:10.1073/pnas.86.19.7611
74. Rogers J, Luber-Narod J, Styren S. D, Civin W. H. Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. Neurobiology of aging. 1988; 9:339-349. doi: 10.1016/s0197-4580(88)80079-4
75. Wyss-Coray T, Yan F, Lin A. H. T, Lambris J. D, Alexander J. J, Quigg, R. J, Masliah E. Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. Proceedings of the National Academy of Sciences. 2002; 99(16):10837-10842. doi: https://doi.org/10.1073/pnas.162350199
76. Beard C. M, Waring S. C, O'Brien P. C, Kurland L. T, Kokmen E. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease: a case-control study in Rochester, Minnesota, 1980 through 1984. In Mayo Clinic Proceedings. Elsevier. 1998; 73(10):951-955. doi: https://doi.org/10.4065/73.10.951
77. Breitner J. C, Gau B. A, Welsh K. A, Plassman B. L, McDonald W. M, Helms M. J, Anthony J. C. Inverse association of anti–inflammatory treatments and Alzheimer's disease: initial results of a co–twin control study. *Neurology* 1994; 44(2): 227-227. doi:10.1212/WNL.44.2.227
78. Rich JB, Rasmusson D. X, Folstein M. F, Carson K. A, Kawas C, Brandt J. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. *Neurology* 1995; 45(1): 51-55. doi:10.1212/WNL.45.1.51
79. McGeer, P. L., & McGeer, E. G. NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. *Neurobiol Aging* 2007; 28(5):639-647. doi:10.1016/j.neurobiolaging.2006.03.013
80. McGeer, P. L., & Rogers, J. Anti-inflammatory agents as a therapeutic approach to Alzheimer's disease. Neurology. 1992; 42(2):447-449. doi: 10.1212/wnl.42.2.447

81. Zotova, E., Nicoll, J. A., Kalaria, R., Holmes, C., & Boche, D. Inflammation in Alzheimer's disease: relevance to pathogenesis and therapy. Alzheimers Res Ther. 2010; 2(1):1-9. doi: https://doi.org/10.1186/alzrt24
82. Kim, Y. S., Joh, T. H. Microglia, major player in the brain inflammation: their roles in the pathogenesis of Parkinson's disease. *Exp Mol Med* 2006; 38(4):333-347. doi:10.1038/ emm.2006.40
83. Goldgaber, D., Harris, H. W., Hla, T., Maciag, T., Donnelly, R. J., Jacobsen, J. S, Gajdusek D. C, *et al.* Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells. Proceedings of the National Academy of Sciences. 1989; 86(19):7606-7610. doi: https://doi.org/10.1073/pnas.86.19.7606
84. Plassman, B. L., Havlik, R. J., Steffens, D. C., Helms, M. J., Newman, T. N., Drosdick, D., Breitner J. C, *et al.* Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology.* 2000; 55(8):1158-1166. doi: https://doi.org/10.1212/WNL.55.8.1158
85. Quintanilla, R. A., Orellana, D. I., González-Billault, C., Maccioni, R. B. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. *Exp Cell Res* 2004; 295(1):245-257. doi: https://doi.org/10.1016/j.yexcr.2004.01.002
86. Kinney, J. W., Bemiller, S. M., Murtishaw, A. S., Leisgang, A. M., Salazar, A. M., Lamb, B. T. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's Demen: Transl Res Clin Interv* 2018; 4:575-590. doi: 10.1016/j. trci.2018.06.014
87. Feng, YS., Tan, Z. X., Wu, L. Y., Dong, F., Zhang, F. The involvement of NLRP3 inflammasome in the treatment of Alzheimer's disease. *Ageing Res Rev* 2020;101192. doi:10.1016/j.arr.2020.101192
88. Pennisi, M., Crupi, R., Di Paola, R., Ontario, M. L., Bella, R., Calabrese, E. J., Calabrese V, *et al*. Inflammasomes, hormesis, and antioxidants in neuroinflammation: Role of NRLP3 in Alzheimer disease. *J Neurosci Res* 2017; 95(7):1360-1372. doi: https://doi.org/10.1002/jnr.23986
89. Guo, H., Callaway, J. B., Ting, J. P. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med* 2015; 21(7):677-687. doi: https://doi.org/10.1038/nm.3893
90. Walsh, J. G., Muruve, D. A., Power, C. Inflammasomes in the CNS. Nature Reviews Neuroscience. 2014; 15(2):84-97. doi: https://doi.org/10.1038/nrn3638
91. Strowig, T., Henao-Mejia, J., Elinav, E., Flavell, R. Inflammasomes in health and disease. *Nature* 2012; 481(7381):278-286. doi: https://doi.org/10.1038/nature10759
92. Thawkar, B. S., Kaur, G. Inhibitors of NF-κB and P2X7/NLRP3/Caspase 1 pathway in microglia: Novel therapeutic opportunities in neuroinflammation induced early-stage Alzheimer's disease. *J Neuroimmunol* 2019; 326:62-74. doi: https://doi.org/10.1016/j.jneuroim.2018.11.010
93. Brydges, S. D., Broderick, L., McGeough, M. D., Pena, C. A., Mueller, J. L., Hoffman, H. M. Divergence of IL-1, IL-18, and cell death in NLRP3 inflammasomopathies. *J Clin Invest* 2013; 123(11):4695-4705. doi: 10.1172/JCI71543
94. Wree, A., Eguchi, A., McGeough, M. D., Pena, C. A., Johnson, C. D., Canbay, A., Feldstein A. E, *et al.* NLRP3 inflammasome activation results in hepatocyte pyroptosis, liver inflammation, and fibrosis in mice. *Hepatology* 2014; 59(3):898-910. doi:10.1002/hep.26592
95. Malik, A., & Kanneganti, T. D. Inflammasome activation and assembly at a glance. *J Cell Sci* 2017; 130(23):3955-3963. doi: 10.1242/jcs.207365
96. Bauernfeind, F. G., Horvath, G., Stutz, A., Alnemri, E. S., MacDonald, K., Speert, D., Latz E, *et al.* Cutting edge: NF-κB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J Immunol* 2009; 183(2):787-791. doi:10.4049/ jimmunol.0901363
97. Muñoz-Planillo, R., Kuffa, P., Martínez-Colón, G., Smith, B. L., Rajendiran, T. M., Núñez, GK. efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity* 2013; 38(6):1142-1153. doi:10.1016/j.immuni.2013.05.016
98. Chen J, Chen Z. J. PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation. *Nature* 2018; 564(7734):71-76. doi:10.1038/s41586-018-0761-3
99. Samir P, Kesavardhana S, Patmore D. M, Gingras S, Malireddi R. S, Karki R, Kanneganti T. D, *et al.* DDX3X acts as a live-or-die checkpoint in stressed cells by regulating NLRP3 inflammasome. *Nature* 2019; 573(7775):590-594. doi:10.1038/s41586-019-1551-2

100. Sharif, H., Wang, L., Wang, W. L., Magupalli, V. G., Andreeva, L., Qiao, Q., Wu H, *et al.* Structural mechanism for NEK7-licensed activation of NLRP3 inflammasome. *Nature* 2019; 570(7761):338-343. doi:10.1038/s41586-019-1295-z
101. Afonina, I. S., Zhong, Z., Karin, M., Beyaert, R. Limiting inflammation—the negative regulation of NF-κB and the NLRP3 inflammasome. *Nat Immunol* 2017; 18(8):861. doi:10.1038/ni.3772
102. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. *Planta Med* 1991;57(1):1-7. doi: 10.1055/s-2006-960004.
103. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: The Indian solid gold. *Adv Exp Med Biol* 2007;595:1–75. doi:10.1007/978-0-387-46401-5_1
104. Wichitnithad W, Jongaroonngamsang N, Pummangura S, Rojsitthisak P. A simple isocratic HPLC method for the simultaneous determination of curcuminoids in commercial turmeric extracts. Phytochem Anal. 2009;20:314–319. doi: https://doi.org/10.1002/pca.1129
105. Shi X, Zheng Z, Li J, Xiao Z, Qi W, Zhang A, Wu Q, Fang Y. Curcumin inhibits Aβ- induced microglial inflammatory responses in vitro: Involvement of ERK1/2 and p38 signaling pathways. *Neurosci Lett* 2015; 594:105-10. doi: 10.1016/j.neulet.2015.03.045.
106. Cianciulli A, Calvello R, Porro C, Trotta T, Salvatore R, Panaro MA. PI3k/Akt signalling pathway plays a crucial role in the anti-inflammatory effects of curcumin in LPS-activated microglia. *Int Immunopathol* 2016; 36:282-90. doi: 10.1016/j.intimp.2016.05.007.
107. Liu ZJ, Li ZH, Liu L, Tang WX, Wang Y, Dong MR, Xiao C. Curcumin Attenuates Beta- Amyloid-Induced Neuroinflammation via Activation of Peroxisome Proliferator-Activated Receptor-Gamma Function in a Rat Model of Alzheimer's Disease. *Front Pharmacol* 2016; 7:261. doi: 10.3389/fphar.2016.00261.
108. Sahebkar A, Cicero AF, Simental-Mendía LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis Of randomized controlled trials. *Pharmacol Res* 2016; 107:234-42. doi: 10.1016/j.phrs.2016.03.026.
109. Derosa G, Maffioli P, Simental-Mendía LE, Bo S, Sahebkar A. Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2016; 111:394-404. doi: 10.1016/j.phrs.2016.07.004.
110. Gibellini L, Bianchini E, De Biasi S, Nasi M, Cossarizza A, Pinti M. Natural Compounds Modulating Mitochondrial Functions. *Evid Based Complement Alternat Med* 2015. doi: 10.1155/2015/527209.
111. Uğuz AC, Öz A, Nazıroğlu M. Curcumin inhibits apoptosis by regulating intracellular calcium release, reactive oxygen species and mitochondrial depolarization levels in SHSY5Y neuronal cells. *J Recept Signal Transduct Res* 2016;36(4):395-401. doi: 10.3109/10799893.2015.1108337.
112. Fan CD, Li Y, Fu XT, Wu QJ, Hou YJ, Yang MF, Sun JY, Fu XY, Zheng ZC, Sun BL. Reversal of Beta-Amyloid-Induced Neurotoxicity in PC12 Cells by Curcumin, the Important Role of ROS-Mediated Signaling and ERK Pathway. *Cell Mol Neurobiol*. 2017;37(2):211-222. doi: 10.1007/s10571-016-0362-3.
113. Ono K, Hasegawa K, Naiki H, Yamada M. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils in vitro. *J Neurosci Res* 2004;75(6):742-50. doi: 10.1002/jnr.20025.
114. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, *et al*. Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients. *J Alzheimers Dis.* 2006;10(1):1-7. doi: 10.3233/JAD-2006-10101.
115. Kim H, Park BS, Lee KG, Choi CY, Jang SS, Kim YH, Lee SE. Effects of naturally occurring compounds on fibril formation and oxidative stress of beta-amyloid. *J Agric Food Chem.* 2005;53(22):8537-41. doi: 10.1021/ jf051985c.
116. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Epigallocatechin-3-gallate and curcumin suppress amyloid beta-induced beta-site APP cleaving enzyme-1 upregulation. *Neuroreport.* 2008;19(13):1329-33. doi: 10.1097/WNR.0b013e32830b8ae1
117. Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. J Neurochem. 2007;102(4):1095-104. doi:10.1111/j.1471-4159.2007.04613.x.
118. Wang YJ, Thomas P, Zhong JH, Bi FF, Kosaraju S, Pollard A, Fenech M, Zhou XF. Consumption of grape seed extract prevents amyloid-beta deposition and attenuates inflammation in brain of an Alzheimer's disease mouse. Neurotox Res. 2009;15(1):3- 14. doi: 10.1007/s12640-009-9000-x.

119. Voulgaropoulou, S. D., van Amelsvoort, T. A. M. J., Prickaerts, J., & Vingerhoets, C. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. Brain research. 2019; 1725:146476. doi: https://doi.org/10.1016/j.brainres.2019.146476.

120. Serafini, MM., Catanzaro, M., Rosini, M., Racchi, M., Lanni, C. Curcumin in Alzheimer's disease: Can we think to new strategies and perspectives for this molecule? *Pharmacol Res* 2017. 124:146-155. doi: https://doi.org/10.1016/j.phrs.2017.08.004

121. Goozee KG, Shah TM, Sohrabi HR, Rainey-Smith SR, Brown B, Verdile G, Martins RN. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. *Br J Nutr* 2016;115(3):449-65. doi: 10.1017/S0007114515004687.

122. Arjomandi OK, Almasi S, Hosseinzadeh L, Kavoosi M and Adibi H. Preparation, Characterization and In Vitro Biological Evaluation of Novel Curcumin Derivatives as Cytotoxic and Apoptosis-Inducing Agents. *Anti-Cancer Agents Med Chem* 2021. 21:1309-1322. doi: 10.2174/1871520620666201002111205

123. Baiji Xue , Jinxiang Huang , Haoxiang Zhang , Bingliang Li , Man Xu , Yuelan Zhang, *et al.*. Micronized curcumin fabricated by supercritical CO2 to improve antibacterial activity against Pseudomonas aeruginosa. *Artif Cells Nanomed Biotechnol* 2020;48:1,1135-1143. doi:10.1080/21691401.2020.1815755

124. Braidy, N., Jugder, B. E., Poljak, A., Jayasena, T., Mohammad Nabavi, S., Sachdev, P., Grant, R. Molecular targets of tannic acid in Alzheimer's disease. *Curr Alzheimer Res* 2017; 14(8):861-869. doi:10.2174/1567205014666170206163158

125. Sylla, T., Pouységu, L., Da Costa, G., Deffieux, D., Monti, J. P., & Quideau, S. Gallotannins and Tannic Acid: First Chemical Syntheses and In Vitro Inhibitory Activity on Alzheimer's Amyloid β–Peptide Aggregation. Angewandte Chemie International Edition. 2015; 54(28):8217-8221. doi: https://doi.org/10.1002/anie.201411606

126. Garcia-Alloza, M., Robbins, E. M., Zhang-Nunes, S. X., Purcell, S. M., Betensky, R. A., Raju, S., Frosch M. P, *et al.* Characterization of amyloid deposition in the APPswe/PS1dE9 mouse model of Alzheimer disease. Neurobiology of disease. 2006; 24(3):516-524. doi: https://doi.org/10.1016/j.nbd.2006.08.017

127. Mori, T., Rezai-Zadeh, K., Koyama, N., Arendash, G. W., Yamaguchi, H., Kakuda, N., Town T, *et al.* Tannic acid is a natural β-secretase inhibitor that prevents cognitive impairment and mitigates Alzheimer-like pathology in transgenic mice. *J Biol Chem* 2012; 287(9):6912-6927. doi: https://doi.org/10.1074/jbc.M111.294025

128. Rezai-Zadeh, K., Shytle, D., Sun, N., Mori, T., Hou, H., Jeanniton, D., Tan J, *et al.* Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice. *J Neurosci* 2005; 25(38):8807-8814. doi: https://doi.org/10.1523/JNEUROSCI.1521-05.2005

129. Menze, E. T., Esmat, A., Tadros, M. G., Abdel-Naim, A. B., Khalifa, A. E. Genistein improves 3-NPA-induced memory impairment in ovariectomized rats: impact of its antioxidant, anti-inflammatory and acetylcholinesterase modulatory properties. *PLoS One* 2015; 10(2):e0117223. doi: 10.1371/journal.pone.0117223

130. Mazumder, M. A. R., Hongsprabhas, P. Genistein as antioxidant and antibrowning agents in in vivo and in vitro: A review. *Biomed Pharmacother* 2016; 82:379-392. doi: https://doi.org/10.1016/j.biopha.2016.05.023

131. Gong, DK., Liu, BH., Tan, XH. Genistein prevents cadmium-induced neurotoxic effects through its antioxidant mechanisms. *Drug Res* 2015; 65(02): 65-69. doi: 10.1055/s-0034-1372595

132. Soni, M., White, L. R., Kridawati, A., Bandelow, S., Hogervorst, E. Phytoestrogen consumption and risk for cognitive decline and dementia: with consideration of thyroid status and other possible mediators. The Journal of steroid biochemistry and molecular biology. 2016; 160:67-77. doi: https://doi.org/10.1016/j.jsbmb.2015.10.024

133. Liao, W., Jin, G., Zhao, M., Yang, H. The Effect of Genistein on the Content and Activity of α–and β–Secretase and Protein Kinase C in Aβ–Injured Hippocampal Neurons. Basic & clinical pharmacology & toxicology. 2013; 112(3):182-185. doi: https://doi.org/10.1111/bcpt.12009

134. Radi E, P. Formichi, C. Battisti, A. Federico, Apoptosis and oxidative stress in neurodegenerative diseases, Journal of Alzheimer's Disease. 2014; S125-S152. doi: 10.3233/JAD-132738

135. Fazel Nabavi, S., Daglia, M., Tundis, R., Rosa Loizzo, M., Sobarzo-Sanchez, E., Erdogan Orhan, I., & Mohammad Nabavi, S. Genistein: A boon for mitigating ischemic stroke. Current topics in medicinal chemistry. 2015; 15(17):1714-1721. DOI: 10.2174/1568026615666150427122709
136. Ahmed, T., Javed, S., Tariq, A., Onofrio, G., Daglia, M., Fazel Nabavi, S., & Mohammad Nabavi, S. Daidzein and its effects on brain. Current medicinal chemistry, 2017; 24(4):365-375. DOI: 10.2174/0929867323666161101140214
137. Xi YD, Zhang, D. D., Ding, J., Yu, H. L., Yuan, L. H., Ma, W. W, *et al.* Genistein inhibits Aβ25–35-induced synaptic toxicity and regulates CaMKII/CREB pathway in SH-SY5Y cells. *Cell Mol Neurobiol* 2016; 36(7):1151-1159.doi:10.1007/s10571-015-0311-6
138. Bagheri, M., Rezakhani, A., Nyström, S., Turkina, M. V., Roghani, M., Hammarström, P, *et al.* Amyloid beta 1-40-induced astrogliosis and the effect of genistein treatment in rat: a three-dimensional confocal morphometric and proteomic study. *PLoS One* 2013; 8(10):e76526. doi: 10.1371/journal.pone.0076526
139. Devi, K. P., Shanmuganathan, B., Manayi, A., Nabavi, S. F., & Nabavi, S. M. Molecular and therapeutic targets of genistein in Alzheimer's disease. Molecular neurobiology. 2017; 54(9):7028-7041. doi: ttps://doi.org/10.1007/s12035-016-0215-6
140. Henderson, V. W. Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *J Steroid Biochem Mol Biol* 2014; 142:99-106. doi: https://doi.org/10.1016/j.jsbmb.2013.05.010
141. Bagheri, M., Joghataei, M. T., Mohseni, S., & Roghani, M. Genistein ameliorates learning and memory deficits in amyloid β (1–40) rat model of Alzheimer's disease. Neurobiology of Learning and Memory. 2011; 95(3):270-276. doi: https://doi.org/10.1016/j.nlm.2010.12.001
142. Wang, Y. Y., Zheng, W., Ng, C. H., Ungvari, G. S., Wei, W., Xiang, Y. T. Meta–analysis of randomized, double–blind, placebo–controlled trials of melatonin in Alzheimer's disease. *Int J Geriat Psychiatry* 2017; 32(1):50-57. doi:10.1002/gps.4571
143. Miller, E., Morel, A., Saso, L., Saluk, J. Melatonin redox activity. Its potential clinical applications in neurodegenerative disorders. *Curr Topics Med Chem* 2015; 15(2):163-169. DOI: 10.2174/1568026615666141209160556
144. Reiter, R. J., Tan, D. X., & Galano, A. Melatonin: exceeding expectations. Physiology. 2014. doi: https://doi.org/10.1152/physiol.00011.2014
145. Perez, A., Li, T., Hernandez, S., Zhang, R., & Cao, C. The rationale of using coffee and melatonin as an alternative treatment for alzheimer's disease. J Alzheimers Dis Parkinsonism. 2016; 6(205):2161-0460. doi: 10.4172/2161-0460.1000205
146. Gunasingh Masilamoni, J., Philip Jesudason, E., Dhandayuthapani, S., Ashok, B. S., Vignesh, S., Jebaraj, W. C. E., ... & Jayakumar, R. The neuroprotective role of melatonin against amyloid β peptide injected mice. Free radical research. 2008; 42(7):661-673. doi: https://doi.org/10.1080/10715760802277388
147. Ali, T., & Kim, M. O. Melatonin ameliorates amyloid beta–induced memory deficits, tau hyperphosphorylation and neurodegeneration via PI 3/Akt/GS k3β pathway in the mouse hippocampus. Journal of pineal research. 2015; 59(1):47-59. doi: https://doi.org/10.1111/jpi.12238
148. Jaworek, J., Szklarczyk, J., Bonior, J., Kot, M., Góralska, M., Pierzchalski, P., ... & Tomaszewska, R. Melatonin metabolite, N (1)-acetyl-N (1)-formyl-5-methoxykynuramine (AFMK), attenuates acute pancreatitis in the rat: in vivo and in vitro studies. *J Physiol Pharmacol* 2016; 676:411. doi: 10.3390/ ijms18051014
149. Zhang, HM., Zhang, Y. Melatonin: a well–documented antioxidant with conditional pro–oxidant actions. *J Pineal Res* 2014; 57(2):131-146. doi: https://doi.org/10.1111/jpi.12162
150. Kandalepas, P. C., Mitchell, J. W., & Gillette, M. U. Melatonin signal transduction pathways require E-box-mediated transcription of Per1 and Per2 to reset the SCN clock at dusk. 2016; 11(6):e0157824. DOI: 10.1371/journal.pone.0157824
151. Waly, N. E., & Hallworth, R. Circadian pattern of melatonin MT1 and MT2 receptor localization in the rat suprachiasmatic nucleus. Journal of circadian rhythms, 2015; 13. doi: 10.5334/jcr.ab
152. Kong, P. J., Byun, J. S., Lim, S. Y., Lee, J. J., Hong, S. J., Kwon, K. J., & Kim, S. S. Melatonin induces Akt phosphorylation through melatonin receptor-and PI3K-dependent pathways in primary astrocytes. *Korean J Physiol Pharmacol* 2008; 12(2):37. doi: 10.4196/kjpp.2008.12.2.37

153. Muche, A., Bürger, S., Arendt, T., Schliebs, R. Hypoxic stress, brain vascular system, and β-amyloid: a primary cell culture study. *Nutr Neurosci* 2015; 18(1):1-11. doi: 10.1179/1476830513Z.000000000112
154. Shi, J., Tian, J., Zhang, X., Wei, M., Ni, J., Li, T., ... & Wang, P. P1–407: INFLUENCE OF GEPT EXTRACT ON HIPPOCAMPAL EXPRESSION OF CHOLINE ACETYLTRANSFERASE AND ACETYLCHOLINESTERASE OF APP/PS1 TRANSGENIC MICE. Alzheimer's & Dementia. 2014; 10:P462-P463. doi: https://doi.org/10.1016/j.jalz.2014.05.650
155. Cardinali, D. P., Vigo, D. E., Olivar, N., Vidal, M. F., & Brusco, L. I. Melatonin therapy in patients with Alzheimer's disease. Antioxidants. 2014; 3(2):245-277. doi: https://doi.org/10.3390/antiox3020245
156. Lin, L., Huang, Q. X., Yang, S. S., Chu, J., Wang, J. Z., & Tian, Q. Melatonin in Alzheimer's disease. International journal of molecular sciences. 2013; 14(7): 14575-14593. doi: https://doi.org/10.3390/ijms140714575
157. Revilla, S., Suñol, C., García-Mesa, Y., Giménez-Llort, L., Sanfeliu, C., & Cristòfol, R. Physical exercise improves synaptic dysfunction and recovers the loss of survival factors in 3xTg-AD mouse brain. Neuropharmacology. 2014; 81:55-63. doi: https://doi.org/10.1016/j.neuropharm.2014.01.037
158. Cohen-Mansfield, J., Garfinkel, D., Lipson, S. Melatonin for treatment of sundowning in elderly persons with dementia – a preliminary study. *Arch Gerontol Geriatr* 2000; 31(1):65-76. doi:10.1016/S0167-4943(00)00068-6
159. Fainstein, I., Bonetto, A. J., Brusco, L. I., Cardinali, D. P. Effects of melatonin in elderly patients with sleep disturbance: a pilot study. *Curr Ther Res* 1997; 58(12):990-1000. doi:10.1016/S0011-393X(97)80066-5
160. Mahlberg, R., Kunz, D., Sutej, I., Kühl, K. P., & Hellweg, R. Melatonin treatment of day-night rhythm disturbances and sundowning in Alzheimer disease: an open-label pilot study using actigraphy. *J Clin Psychopharmacol* 2004; 24(4):456-459. doi: 10.1097/01.jcp.0000132443.12607.fd
161. Mahlberg, R., & Walther, S. Actigraphy in agitated patients with dementia. *Zeitschrift Gerontol Geriatrie* 2007; 40(3):178-184. doi:10.1007/s00391-007-0420-z
162. Furio, A. M., Brusco, L. I., Cardinali, D. P. Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study. *J Pineal Res* 2007; 43(4):404-409. doi:10.1111/j.1600-079X.2007.00491.x
163. Vingtdeux, V., Dreses-Werringloer, U., Zhao, H., Davies, P., & Marambaud, P. Therapeutic potential of resveratrol in Alzheimer's disease. *BMC Neurosci* 2008; 9(2):1-5. doi:10.1186/1471-2202-9-S2-S6
164. Ahmed T, Javed, S., Javed, S., Tariq, A., Šamec, D., Tejada, S., *et al.* Resveratrol and Alzheimer's disease: mechanistic insights. *Mol Neurobiol* 2017; 54(4):2622-2635. doi:10.1007/s12035-016-9839-9
165. Fu, Z., Aucoin, D., Ahmed, M., Ziliox, M., Van Nostrand, W. E., & Smith, S. O. Capping of Aβ42 oligomers by small molecule inhibitors. Biochemistry. 2014; 53(50):7893-7903. doi: https://doi.org/10.1021/bi500910b
166. Ghobeh, M., Ahmadian, S., Meratan, A. A., Ebrahim–Habibi, A., Ghasemi, A., Shafizadeh, M., Nemat-Gorgani, M. Interaction of Aβ (25–35) fibrillation products with mitochondria: Effect of small-molecule natural products. *Peptide Sci* 2014; 102(6):473-486. doi: https://doi.org/10.1002/bip.22572
167. Ribeiro, C. A., Saraiva, M. J., Cardoso, I. Stability of the transthyretin molecule as a key factor in the interaction with A-beta peptide-relevance in Alzheimer's disease. *PloS one* 2012; 7(9):e45368. doi: https://doi.org/10.1371/journal.pone.0045368
168. Ge, J. F., Qiao, J. P., Qi, C. C., Wang, C. W., Zhou, J. N. The binding of resveratrol to monomer and fibril amyloid beta. *Neurochem Int* 2012; 61(7):1192-1201. doi: https://doi.org/10.1016/j.neuint.2012.08.012
169. Ladiwala, A. R. A., Lin, J. C., Bale, S. S., Marcelino-Cruz, A. M., Bhattacharya, M., Dordick, J. S., & Tessier, P. M. Resveratrol selectively remodels soluble oligomers and fibrils of amyloid Aβ into off-pathway conformers. Journal of Biological Chemistry. 2010; 285(31):24228-24237. doi: https://doi.org/10.1074/jbc.M110.133108
170. He, X. P., Deng, Q., Cai, L., Wang, C. Z., Zang, Y., Li, J., Tian, H, *et al.* Fluorogenic resveratrol-confined graphene oxide for economic and rapid detection of Alzheimer's disease. ACS applied materials & interfaces. 2014; 6(8):5379-5382. doi: https://doi.org/10.1021/am5010909
171. Patil, S. P., Tran, N., Geekiyanage, H., Liu, L., Chan, C. Curcumin-induced upregulation of the anti-tau cochaperone BAG2 in primary rat cortical neurons. *Neurosci Lett* 2013; 554:121-125. doi: https://doi.org/10.1016/j.neulet.2013.09.008

172. Zhao YN, Li, W F., Li, F., Zhang, Z., Dai, YD., Xu, AL, *et al*. Resveratrol improves learning and memory in normally aged mice through microRNA-CREB pathway. *Biochem Biophys Res Commun* 2013; 435(4):597-602. doi:10.1016/j.bbrc.2013.05.025
173. Mei, Y., Jiang, C., Wan, Y., Lv, J., Jia, J., Wang, X., Tong Z, et al. Aging–associated formaldehyde–induced norepinephrine deficiency contributes to age–related memory decline. Aging cell. 2015; 14(4):659-668. doi: https://doi.org/10.1111/acel.12345
174. Moorthi, P., Premkumar, P., Priyanka, R., Jayachandran, K. S., & Anusuyadevi, M. Pathological changes in hippocampal neuronal circuits underlie age-associated neurodegeneration and memory loss: positive clue toward SAD. Neuroscience. 2015; 301:90-105. doi: https://doi.org/10.1016/j.neuroscience.2015.05.062
175. Wight, R. D., Tull, C. A., Deel, M. W., Stroope, B. L., Eubanks, A. G., Chavis, J. A., Hensley L. L, et al. Resveratrol effects on astrocyte function: relevance to neurodegenerative diseases. Biochemical and biophysical research communications. 2012; 426(1):112-115. doi: https://doi.org/10.1016/j.bbrc.2012.08.045
176. Yao, Y., Li, J., Niu, Y., Yu, J. Q., Yan, L., Miao, Z. H., Li, W. Q, et al. Resveratrol inhibits oligomeric Aβ-induced microglial activation via NADPH oxidase. *Mol Med Rep* 2015; 12(4):6133-6139. doi: https://doi.org/10.3892/mmr.2015.4199
177. Kim, Y., Lim, S. Y., Rhee, S. H., Park, K. Y., Kim, C. H., Choi, B. T., Choi Y. H, et al. Resveratrol inhibits inducible nitric oxide synthase and cyclooxygenase-2 expression in β-amyloid-treated C6 glioma cells. International journal of molecular medicine. 2006; 17(6):1069-1075. doi: https://doi.org/10.3892/ijmm.17.6.1069
178. Zhang, Y., Dong, R., Yang, Q., Zhang, L., Li, J., & Zhao, H. (2019). [Resveratrol upregulates the gene and protein expressions of N-methyl-D-aspartate receptor 1 and protein kinase C in the hippocampus in Alzheimer's disease rats]. *Journal of Hygiene Research*, *48*(2), 269–278. https://europepmc.org/article/med/31133106
179. Huang, T. C., Lu, K. T., Wo, Y. Y. P., Wu, Y. J., & Yang, Y. L. Resveratrol protects rats from Aβ-induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation. 2011; 6(12):e29102. doi: 0.1371/journal.pone.0029102
180. Granzotto, A., & Zatta, P. Resveratrol acts not through anti-aggregative pathways but mainly via its scavenging properties against Aβ and Aβ-metal complexes toxicity. 2011; 6(6):e21565. doi: 10.1371/journal.pone.0021565
181. Kwon, K. J., Kim, H. J., Shin, C. Y., & Han, S. H. Melatonin potentiates the neuroprotective properties of resveratrol against beta-amyloid-induced neurodegeneration by modulating AMP-activated protein kinase pathways. Journal of clinical neurology. 2010; 6(3):127. doi: 10.3988/jcn.2010.6.3.127
182. Koukoulitsa C, Villalonga-Barber, C., Csonka, R., Alexi, X., Leonis, G., Dellis, D*, et al*. Biological and computational evaluation of resveratrol inhibitors against Alzheimer's disease. *J Enz Inhib Med Chem* 2016; 31(1):67-77. doi: 10.3109/14756366.2014.1003928
183. Jang, J. H., Surh, Y. J. Protective effect of resveratrol on β-amyloid-induced oxidative PC12 cell death. *Free Rad Biol Med* 2003; 34(8):1100-1110. doi: https://doi.org/10.1016/s0891-5849(03)00062-5
184. D Rege, S., Geetha, T., L Broderick, T., & Ramesh Babu, J. Resveratrol protects β amyloid-induced oxidative damage and memory associated proteins in H19-7 hippocampal neuronal cells. Current Alzheimer Research. 2015; 12(2):147-156. doi: https://doi.org/10.1007/s12035-016-9839-9
186. Braidy, N., Jugder, B. E., Poljak, A., Jayasena, T., Mansour, H., Mohammad Nabavi, S., Grant R, et al. Resveratrol as a potential therapeutic candidate for the treatment and management of Alzheimer's disease. Current topics in medicinal chemistry. 2016; 16(17):1951-1960. DOI: 10.2174/1568026616666160204121431
187. Jeon, B. T., Jeong, E. A., Shin, H. J., Lee, Y., Lee, D. H., Kim, H. J., Roh G. S, et al. Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet. *Diabetes* 2012; 61(6):1444-1454. doi:10.2337/db11-1498
188. Toth P, Tarantini, S., Tucsek, Z., Ashpole, N. M., Sosnowska, D., Gautam, T, *et al*. Resveratrol treatment rescues neurovascular coupling in aged mice: role of improved cerebromicrovascular endothelial function and downregulation of NADPH oxidase. *Am J Physiol Heart Circ Physiol* 2014; 306(3), H299:H308. doi:10.1152/ajpheart.00744.2013

189. Higashida K, Kim, S. H., Jung, S. R., Asaka, M., Holloszy, J. O., Han, DH. Effects of resveratrol and SIRT1 on PGC-1α activity and mitochondrial biogenesis: a reevaluation. *PLoS Biol.* 2013; 11(7):e1001603. doi: 10.1371/journal.pbio.1001603
190. Singh, J. C. H., Kakalij, R. M., Kshirsagar, R. P., Kumar, B. H., Komakula, S. S. B., & Diwan, P. V. Cognitive effects of vanillic acid against streptozotocin-induced neurodegeneration in mice. Pharmaceutical biology. 2015; 53(5):630-636. doi: https://doi.org/10.3109/13880209.2014.935866
191. Amin, F. U., Shah, S. A., & Kim, M. O. Vanillic acid attenuates Aβ 1-42-induced oxidative stress and cognitive impairment in mice. Scientific reports. 2017; 7(1):1-15. doi: https://doi.org/10.1038/srep40753
192. Villareal, M. O., Sasaki, K., Margout, D., Savry, C., Almaksour, Z., Larroque, M., & Isoda, H. Neuroprotective effect of Picholine virgin olive oil and its hydroxycinnamic acids component against β-amyloid-induced toxicity in SH-SY5Y neurotypic cells. *Cytotechnology* 2016; 68(6):2567-2578. doi:10.1007/s10616-016-9980-3
193. Wang, Y., Wang, Y., Li, J., Hua, L., Han, B., Zhang, Y., *et al*. Effects of caffeic acid on learning deficits in a model of Alzheimer's disease. *Int J Mol Med* 2016; 38(3):869-875. doi: https://doi.org/10.3892/ijmm.2016.2683
194. Chao, X. J., Chen, Z. W., Liu, A. M., He, X. X., Wang, S. G., *et al*. Effect of Tacrine–3–caffeic Acid, A Novel Multifunctional Anti–Alzheimer's Dimer, Against Oxidative–Stress–Induced Cell Death in HT 22 Hippocampal Neurons: Involvement of Nrf2/HO–1 Pathway. *CNS Neurosci Ther* 2014; 20(9):840-850. doi:10.1111/cns.12286
195. Cai, Z., Wang, C., Yang, W. Role of berberine in Alzheimer's disease. Neuropsychiatric disease and treatment. 2016; 12:2509. doi: 10.2147/NDT.S114846
196. Haghani, M., Shabani, M., & Tondar, M. The therapeutic potential of berberine against the altered intrinsic properties of the CA1 neurons induced by Aβ neurotoxicity. European journal of pharmacology. 2015; 758, 82-88. doi: https://doi.org/10.1016/j.ejphar.2015.03.016
197. Jia, L., Liu, J., Song, Z., Pan, X., Chen, L., Cui, X., & Wang, M. Berberine suppresses amyloid–beta–induced inflammatory response in microglia by inhibiting nuclear factor–kappaB and mitogen–activated protein kinase signalling pathways. *J Pharm Pharmacol* 2012; 64(10):1510-1521. doi:10.1111/j.2042-7158.2012.01529.x
198. Yu, G., Li, Y., Tian, Q., Liu, R., Wang, Q., Wang, J. Z, *et al.* Berberine attenuates calyculin A-induced cytotoxicity and Tau hyperphosphorylation in HEK293 cells. *J Alzheimer's Dis* 2011; 24(3):525-535. doi: 10.3233/JAD-2011-101779
199. Luo, T., Jiang, W., Kong, Y., Li, S., He, F., Xu, J, *et al.* The protective effects of jatrorrhizine on β-amyloid (25-35)-induced neurotoxicity in rat cortical neurons. *CNS Neurol Disor-Drug Targets* 2012; 11(8):1030-1037. doi: https://doi.org/10.2174/187152712804870928
200. de Oliveira JS., Abdalla, F. H., Dornelles, G. L., Adefegha, S. A., Palma, T. V., Signor, C, *et al.* Berberine protects against memory impairment and anxiogenic-like behavior in rats submitted to sporadic Alzheimer's-like dementia: involvement of acetylcholinesterase and cell death. *Neurotoxicology* 2016; 57:241-250. doi: https://doi.org/10.1016/j.neuro.2016.10.008
201. Huang, M., Jiang, X., Liang, Y., Liu, Q., Chen, S., & Guo, Y. I. Berberine improves cognitive impairment by promoting autophagic clearance and inhibiting production of β-amyloid in APP/tau/PS1 mouse model of Alzheimer's disease. Experimental gerontology. 2017; 91:25-33. doi: https://doi.org/10.1016/j.exger.2017.02.004
202. Taylor, D. The pharmaceutical industry and the future of drug development, 2015. doi: 10.1039/9781782622345-00001
203. Hara, T. (2003). *Innovation in the pharmaceutical industry : the process of drug discovery and development*. 271. https://www.e-elgar.com/shop/gbp/innovation-in-the-pharmaceutical-industry-9781843760504.html
204. Hu, X. Filing Patent Applications. In Smoothing a Critical Transition. Springer, Singapore. 2020; 87-100) doi: https://doi.org/10.1007/978-981-15-4035-6_8
205. Sambamurti, K., Greig, N. H., Utsuki, T., Barnwell, E. L., Sharma, E., Mazell, C., ... & Pappolla, M. A. Targets for AD treatment: conflicting messages from γ–secretase inhibitors. Journal of neurochemistry. 2011; 117(3):359-374. doi: https://doi.org/10.1111/j.1471-4159.2011.07213.x
206. Saxena, U. Alzheimer's disease amyloid hypothesis at crossroads: where do we go from here?. Expert opinion on therapeutic targets. 2010; 14(12):1273-1277. doi: https://doi.org/10.1517/14728222.2010.528285
207. Ji HF, Zhang HY. Multipotent natural agents to combat Alzheimer's disease. Functional spectrum and structural features 1. *Acta Pharmacol Sinica* 2008; 29(2):143-151. doi:10.1111/j.1745-7254.2008.00752.x
208. Mecocci, P., Tinarelli, C., Schulz, R. J., Polidori, M. C. Nutraceuticals in cognitive impairment and Alzheimer's disease. *Front Pharmacol* 2014; 5:147. doi: https://doi.

org/10.3389/fphar.2014.00147

209. Polidori, M. C. Preventive benefits of natural nutrition and lifestyle counseling against Alzheimer's disease onset. *J Alzheimer's Dis* 2014; 42(s4):S475-S482. doi: 10.3233/JAD-141539
210. Behnam, D.; Hayward, M.A. Resveratrol solubilisation product for pharmaceutical purposes. *WO Patent* 2017215791A1. December 21, 2017.
211. Rosen G.S. Multi-component formulations for the treatment of cognitive decline including Alzheimer's disease. *US Patent* 9682048B1. June 20, 2017.
212. Mathisen J.S.; Mathisen, H. A marine oil formulation comprising resveratrol or derivatives thereof for use in treating, delaying and/or preventing alzheimer's disease. *CA Patent* 2914767A1. December 18, 2014.
213. Baraona RM, Sepúlveda, L.Q.; Saavedra, I.S.; Salas, R.S.; Salas, V.S. Nutraceutical composition that comprises extract of shilajit, folic acid, vitamin b12 and vitamin b6 and the use thereof for preventing and/or treating neurodegenerative diseases and/or the cognitive deterioration associated with cerebral ageing. *US Patent* 20120269794A1. July 22, 2014.
214. DiMauro, T.M. Methylene blue-curcumin analog for the treatment of Alzheimer's Disease. *US Patent* 7906643B2. March 15 2011.
215. DiMauro, T.M. Use of nitrogen-containing curcumin analogs for the treatment alzheimer's disease. July 01, 2010.
216. Helson, L.; Chiu, S.; Intravenous curcumin and derivatives for treatment of neurodegenerative and stress disorders. *US Patent* 9393198B2. July 19, 2016.
217. Mathisen, J.S.; Mathisen, H. Method of treating, delaying and/or preventing Alzheimer's disease. *US Patent* 20150031653A1. August 01, 2017.
218. Bienkiewicz, E.A. Treating Amyloidoses With A Vitamin B12 Composition Including Melatonin, Resveratrol, and EGCG. *US Patent* 20150065449A1. March 05, 2015.
219. Zhang, S. Hybrid compounds of curcumin and melatonin as neuroprotectants for neurodegenerative disorders. *US Patent* 9738605B2. August 22, 2017.
220. Khandelwal, S.; Omray, P.; Tripathi V.K. A bio-stabilized resveratrol formulation. *WO Patent* 2012017451A1. February 09, 2012.
221. Rongbiao, P, Xiaojuan, C, Xixin, H, Zhiyi, C, Yilin, Y, Yifan, H, *et al*. Tacrine-caffeic acid heteroblends, their preparation method and medicinal compositions. *CN Patent* 102617465A. August 01, 2012.
222. Siva, M.L.; Durairajan, S.K.; Liu, L.; Jiahong, L.U. Berberine alkaloid as a medicament for prevention and treatment of neural disease. *US Patent* 20130237556A1. September 12, 2013.
223. Yong, D.; Zhenghuai, T.; Xiaoming, Q.; Wen, Y.; Zhipei, S.; Qiang, L.; Yan L. Genistein alkylamine compound, preparation method and use thereof. *WO Patent* 2014111028A1. July 24, 2014.
224. Liu L. Berberine salts, ursodeoxycholic salts and combinations, methods of preparation and application thereof. *EP Patent* 3174874A1. September 02, 2020.
225. Theoharis C. Anti-inflammatory compositions for treating neuro-inflammation, *US Patent* 20130115202A1. May 09. 2013.
226. Weinberg, R.P.; Rha, C.; Sinskey, A.J.; Tan Y.A.; Sambanthamurthi, R. Protective effects of oil palm composition on alzheimer's disease. EP Patent 3057437A1. October 07, 2020.
227. Frautschy, S.A.; Cole, G.M. Bioavailable curcuminoid formulations for treating Alzheimer's disease and other age-related disorders. US Patent 9192644B2. November 24, 2015.
228. Gokaraju, G.R.; Gokaraju, R.R.; Golakoti, T.; Chirravuri, V.R.; Bhupathiraju, V. Nutraceutical composition from Garcinia mangostana. US Patent 8853261B2. October 07, 2014.
229. Perry, S.C. Composition to retard the onset of symptoms of alzheimer's disease. US Patent 8021701B1. September 20, 2011.
230. Duong, P., Tenkorang, M. A., Trieu, J., McCuiston, C., Rybalchenko, N., & Cunningham, R. L. Neuroprotective and neurotoxic outcomes of androgens and estrogens in an oxidative stress environment. *Biol Sex Differences* 2020; 11:1-18. doi: https://doi.org/10.1186/s13293-020-0283-1
231. Noguchi-Shinohara M, Ono K, Hamaguchi T, Nagai T, Kobayashi S, Komatsu J, Samuraki-Yokohama M, *et al*. Safety and efficacy of Melissa officinalis extract containing rosmarinic acid in the prevention of Alzheimer's disease progression. *Sci Rep* 2020;10(1):1-0. doi: 10.1038/s41598-020-73729-2
232. Frohlich J, Chaldakov GN, Vinciguerra M. Cardio- and neurometabolic adipobiology. Consequences and implications for therapy. *Int J Mol Sci* 2021; 22:4137. doi: 10.3390/ijms22084137
233. Yanev S, Aloe L, Fiore F, Chaldakov GN. Neurotrophic and metabotrophic potential of nerve growth factor and brain-derived neurotrophic factor: Linking cardiometabolic and neuropsychiatric diseases. *World J Pharmacol* 2013; 2: 92-99. doi:10.5497/wjp.v2.i4.92