NEUROPROTECTIVE AGENT RESVERATROL IN MANAGING OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a multifaceted neurodegenerative disorder characterized by memory loss, brain mass reduction, and the presence of Amyloid β plaques. Oxidative stress, mitochondrial dysfunction, and inflammation are all associated with this disease, and their interconnectivity in causing the development is still being investigated. The accumulation of reactive oxygen and nitrogen species from lipid peroxidation and macromolecule oxidation is thought to be responsible for oxidative stress's effects. The mitochondrial cascade hypothesis suggests that amyloid beta plaques form due to the loss of mitochondrial function. This leads to abnormal expression of machinery involved with the amyloid precursor protein (APP) and contributes to the pathology of Alzheimer's disease. Amyloid β accumulation harms synapses and impairs neuronal transmission, causing neuronal pathway deterioration. Recent studies indicate that resveratrol, a polyphenol compound found in several plant species and fruits, may have therapeutic potential in treating Alzheimer's disease by reducing oxidative stress and plaque pathology. Resveratrol is thought to inhibit serval inflammatory and other neurotoxic pathways that serve to cause apoptosis and neuronal communication blockage in the CNS. However, additional research is necessary to fully comprehend the benefits of resveratrol and other polyphenols for Alzheimer's disease treatment.

Keywords: *Alzheimer's Disease, Amyloid β, Amyloid precursor protein, Oxidative stress, Neurofibrillary tangles, Resveratrol, Tau Protein*

INTRODUCTION

Alzheimer's Disease (AD) is a progressive neurogenerative disorder characterized by dementia and cognitive decline. As of 2021, an estimated 6.7 million Americans over the age of 65 have Alzheimer's dementia (Rajan et al., 2021). The disease was first classified by a clinical psychiatrist and neuroanatomist named Alois Alzheimer in 1906 (Alzheimer, 1906). In the almost 120 years since its classification, little has been accomplished in the search for an effective treatment for this detrimental neurological disease. This review aims to compile and organize the current body of knowledge surrounding Alzheimer's disease and investigate the current research surrounding a possible treatment option in a stilbenoid known as resveratrol found in several plant species. Examining the evidence and data gathered on this topic is essential to establish fundamental knowledge of the disease and guide future research to establish a firm body of knowledge.

The review will specifically investigate several factors contributing to disease progression in AD, including mitochondrial dysfunction, imbalance of metal ions contributing to amyloid-beta (Aβ) plaque formation, and the hyperphosphorylation

of tau causing neurofibrillary tangles. These pathways, integral to AD progression, are closely tied to oxidative stress, stemming from an imbalance where oxidants surpass antioxidants (Bai et al., 2022; Huang et al., 2016). Oxidative stress damages neuronal cells and contributes to cell senescence and the degeneration of brain tissue, thus contributing to AD pathology (Liguori et al., 2022). Moreover, reactive oxygen species (ROS), primarily from mitochondrial dysfunction, cause oxidative stress and are related to forming Aβ plaques (Ionescu-Tucker & Cotman, 2021).

Due to the need to develop new treatments for neurodegenerative diseases, naturally occurring antioxidants are beginning to receive increased attention as a primary treatment option (Habtemariam, 2019; Zhang et al., 2017). Among the most prevalent antioxidant candidates is resveratrol, a stilbenoid polyphenol compound in various plant species and fruits, such as grapes and blueberries (He and Yan, 2013; Tsai et al., 2017). Studies have shown that resveratrol presents neuroprotective actions in experimental models of AD (Caruana et al., 2016). Thus, Resveratrol may be a promising therapeutic approach in reversing oxidative stress and treating AD.

This review will focus primarily on the studies and information available concerning Aβ plaque formation, neurofibrillary tangles (NFTs), oxidative stress, and resveratrol. The role of oxidative stress in the progression of AD is explored through the mitochondrial cascade hypothesis, epigenetic changes, the free radical theory of aging, impaired neurotransmission, and the contribution of metallic ions to plaque formation. Aβ plaques and their impact on AD are investigated through the polymerization of amyloid beta into plaques, the influence of microglial cells on AD, and the neurotoxic effects of Aβ. Additionally, Aβ associated oxidative stress and the potential use of resveratrol's antioxidant properties to treat oxidative stress are reviewed. Antioxidants have promising potential for diseases such as AD because they have unique abilities to scavenge free radicals, reduce inflammation, and reduce overall oxidative stress. This review is limited to oxidative stress and its relationship with Alzheimer's disease, resveratrol, and amyloid beta. There are many other hypotheses for the causes of AD unrelated to oxidative stress, but these will not be included in this study. Other potential medical uses for resveratrol and possible treatments for Alzheimer's disease are also outside the scope of this review.

SEARCH METHODS

In conducting this review of Alzheimer's disease, it was vital to identify a clear and focused question to answer to direct the review (Bramer et al., 2018). However, searching for articles on resveratrol's role in AD pathways would leave out many supporting details. Therefore, it was essential to identify key concepts that help to address different elements of the question so that a complete picture of the idea can be painted (Bramer et al., 2018). In the case of this review, it was fundamental to describe several pathological elements and pathways associated with AD before explaining how resveratrol could mitigate these pathologies and control these markers. Additionally, the PubMed database served as a pivotal resource for gathering essential information. The search methodology aimed to ensure the inclusion of relevant studies and clinical trials and primarily focused on primary research articles. It is crucial to use primary sources to ensure that the information presented in this review was based on recent studies and that the information collected was backed by reliable scientific data (Bramer et al., 2018).

Additionally, several strategies were used to gather relevant research. These strategies included keyword selection, inclusion and exclusion criteria, date range filtering, and publication type filtering. Keyword selection was used to narrow down the search results for each section of the review to aid in collecting a more focused scope of information (Bramer et al., 2018). Inclusion and exclusion criteria ensured the review stayed faithful to its aim. The inclusion criteria for this review included studies that were experimental publications and primary sources of information. The exclusion criteria for this review excluded review papers, meta-analyses, and other forms of secondary sources of information. It is crucial to evaluate initial search results intently because relevant papers will be cited and cited by other relevant sources (Bramer et al., 2018). With so much information, theories, and history available for this disease, it was essential to vet the selected articles to ensure that they were relevant to the aim of this review.

The PubMed database was chosen as the primary database used in this review due to its broad overview of existing literature in disease pathology and its extraordinarily comprehensive database of biomedical topics. Boolean search operators were used to ensure a precise yet comprehensive collection of studies across several key topics according to the criteria previously described. The Boolean search terms included the following: For general Alzheimer's disease and resveratrol: ("Alzheimer's disease" OR "Alzheimer disease" OR "AD") AND ("Resveratrol" OR "polyphenols" OR "stilbenes"); for tau pathology: ("Tau hyperphosphorylation" OR "Tau protein" OR "Tau pathology") AND ("neurofibrillary tangles" OR "NFTs" OR "paired helical filaments"); for resveratrol and oxidative stress in AD: ("Resveratrol" AND "oxidative stress" OR "antioxidant" OR "free radical scavenger") AND ("Alzheimer's disease and Antioxidants" OR "Alzheimer disease Inflammatory Treatment" OR "AD Treatments"); and for oxidative stress mechanisms in AD: ("Oxidative stress" OR "ROS" OR "reactive oxygen species" OR "mitochondrial dysfunction") AND ("Oxidative Stress in Alzheimer's disease" OR "AD pathology" OR "AD and Oxidative Stress"). Additional terms targeting study types were used to focus the search on primary research articles: ("primary study," OR "original research," OR "experimental study"). This Boolean structure helped capture studies relevant to AD pathology, tau-related neurofibrillary tangles, oxidative stress, and resveratrol's potential mitigating effects while excluding less pertinent sources.

The date range filtering was as follows: ("2014/01/01"[Date - Publication]: "2024/01/01"[Date - Publication]), ensuring the review presents recent findings. This range allowed for exceptions only if a source marked a historically significant discovery, contributing a foundational understanding. Additional terms targeting study types were used to focus the search on primary research articles ("primary study," OR "original research," OR "experimental study"). Inclusion criteria focused on experimental studies and primary sources, while exclusion criteria filtered out secondary sources such as review papers and meta-analyses (Bramer et al., 2018). This review article employs these search methods in the PubMed database to present an up-to-date knowledge of AD.

REVIEW OF LITERATURE

Alzheimer's disease is characterized by several pathogenic markers that contribute to neurodegeneration and cognitive decline. However, this review examines only the most prevalent pathologies discussed in current literature and resveratrol and the compounds' role in mitigating these pathologies. The review will first discuss the most prevalent pathogenic marker, amyloid beta peptides, and how they contribute to AD through plaque formation, oxidative stress, and microglial dysfunction. Then, this review will discuss the role of tau proteins in neurodegeneration through the formation of neurofibrillary tangles due to the hyperphosphorylation of tau. Next, the review will examine how tau, Aβ, and other factors such as metals and mitochondrial dysfunction contribute to ROS production, oxidative stress, and, ultimately, oxidative damage that leads to neuron cell death and apoptosis. Finally, this review will discuss resveratrol's ability to mitigate oxidative stress, amyloid pathology, tau pathology, and other factors contributing to disease progression.

AMYLOID BETA PROTEINS AND AD

The primary pathogenic marker and event associated with AD is the aggregation of amyloid peptides forming large extracellular masses called plaques (Gomes et al., 2018). β-amyloid (Aβ) peptides come in two forms, with lengths of either 40 or 42 amino acids, labeled as Aβ1-40 and Aβ1-42, respectively. Both these variants result from improper cleavage of the amyloid precursor protein (APP), a transmembrane glycoprotein (Rukmangadachar & Bollu, 2022). APP is present in most cells throughout the body; however, it is more prevalent throughout the plasma membrane of neurons than in other somatic cells. In healthy individuals, APP cleaves through the non-amyloidogenic pathway (O'Brien & Wong, 2011). This pathway involves two enzymes where alpha-secretase cleaves the protein on the extracellular domain, producing sAPPα, and gamma-secretase cleaves at the intracellular domain, turning the remaining peptide chain into a p3, and an amyloid precursor protein intracellular domain (AICD) molecule (O'Brien & Wong, 2011). However, in an individual with AD, a different pathway called the amyloidogenic pathway is active (Rukmangadachar & Bollu, 2022), in which APP is cleaved by the action

of beta and gamma-secretase. Beta-secretase's enzyme cleavage site creates the N terminal end, and the gamma-secretase enzyme's cleavage site creates the C terminal end of the Aβ peptide (Haass & Selkoe, 2007; Vassar et al., 1999). These Aβ peptides then aggregate to form β-pleated sheets in the extracellular matrix with the help of select metallic ions, producing aggregates of Aβ oligomers and forming large bodies of neurotoxic plaques (Chignon et al., 2018). The Aβ plaques develop first in the basal, temporal, and orbitofrontal regions of the brain and then progress throughout the brain inwards, entering the diencephalon, basal ganglion, and even reaching the cerebellum and brain stem in the most severe cases of AD (Tiwari et al., 2019).

Aβ is a critical initiator of AD and functions to produce several neurotoxic effects in a patient's brain through several forms of oxidative stress. A significant pathway of Aβ induced oxidative stress involves the overstimulation of microglial cells. Microglial cells are the resident phagocytes of the central nervous system (CNS), which are responsible for the overall maintenance of the CNS through pathogen defense, neural tissue repair, and the removal of cellular debris (Yao et al., 2015). Microglial cells will generally phagocytize Aβ oligomers and small aggregate plaques; however, in significant accumulations of Aβ peptides, microglial cells become static, leading to apoptosis (Hansen et al., 2017). In addition to these apoptotic and static effects, Aβ fibrils have been shown to induce over-activation of microglial cells, causing the over-secretion of proinflammatory mediators and ROS, resulting in further neuronal damage (Gomes et al., 2018). Aβ fibrils also deactivate the microglial cells through interactions with the microglial cell surface receptor TREM2 (Hansen et al., 2017).

Interactions with Aβ fibrils cause the microglial cells to congregate around the Aβ plaque to reduce toxicity and prevent the aggregation of additional Aβ oligomers to the plaque. However, this interaction deactivates the microglial cells from performing their normal immune functions (Hansen et al., 2017). Although the microglial cells make several attempts to remove Aβ peptides and prevent further aggregation of these oligomers, the microglial cells do more damage to the neurons and prevent themselves from fighting the Aβ further. This allows the Aβ peptides to aggregate out of control after deactivation. Thus, the aggregation of Aβ fibrils to form plaques is detrimental to neuronal functions and causes several neurotoxic effects that contribute to the pathogenesis of AD, resulting in the severe neurological symptoms of AD.

TAU PROTEINS AND NEUROFIBRILLARY TANGLES

Tau proteins bind to and stabilize axonal microtubules in neurons and are vital in regulating axonal growth and transport. Post-translational phosphorylation plays a vital role in regulating tau proteins to bind microtubules. Thus, the conformation of tau is highly sensitive to both over-phosphorylation and under-phosphorylation. In AD, hyperphosphorylation of tau changes its conformation from soluble to insoluble, leading to neurofibrillary tangles (NFTs) due to the aggregation of tau proteins (Gao et al., 2018). Additionally, there is a strong correlation between DNA damage and the accumulation of tau in the nucleus, which shows that Tau aggregation and misfolding that produces these NFTs are likely the result of oxidative damage caused by ROS (Denechaud et al., 2022).

Current research supports the idea that the polymerization of Aβ fibrils into plaques causes the production of NFTs by activating several MAP kinase pathways that lead to hyperphosphorylation of tau proteins (Gong & Iqbal, 2008). Hyperphosphorylation of Tau has toxic effects on the protein, contributing to neuronal cell death in AD. However, this toxicity is only present with current hyperphosphorylation, and if the phosphorylation returns to normal levels, then tau proteins return to a normal nontoxic state (Gong & Iqbal, 2008). NFTs are straight and fibrous patches of insoluble proteins inside the neuronal cytoplasm, which act to interfere with neuronal communication and signal processing capabilities, ultimately activating the apoptotic pathway and leading to neuronal death (Miao et al., 2019). Additionally, research shows that Tau hyperphosphorylation is not uniformly present within the cortex or even in clusters in the cortex (Denechaud et al., 2022). Neurons with cytoplasm containing hyperphosphorylated Tau are present next to neurons in which their cytoplasm is devoid of phosphorylated tau, showing that within the same region, very different stages of Tau pathology may coexist, illustrating that disease progression could be independent for each neuron or pathway in the brain or that the

state of Tau phosphorylation is constantly fluctuating (Denechaud et al., 2022).

Hyperphosphorylated Tau appears to be involved in reactivating the cell cycle, and there is a significant accumulation of nuclear tau during the reactivated S phase (Denechaud et al., 2022). By better understanding the interactions between Tau phosphorylation and the neuron cell cycle, it might be possible to formulate a treatment using Tau proteins already present in the patient's CNS.

OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

Oxidative stress is a destructive process involved in the pathogenesis of AD, caused by pro-oxidants that exceed the level of antioxidants present (Bai et al., 2022). Oxidative stress in AD patients is generally the result of inflammatory pathways and mitochondrial dysfunction linked to other pathology associated with AD (Griñán-Ferré et al., 2018). The activation of microglia inflammatory pathways and mitochondrial dysfunction are generally a result of Aβ aggregation that enhances the production of reactive oxygen species (ROS) in the CNS (Cieślik et al., 2019). A unique phospholipid synthesized in the inner mitochondrial membrane known as cardiolipin is essential for mitochondrial membrane stability and overall metabolism (Paradies et al., 2019). However, cardiolipin is exceptionally prone to oxidation, which causes electron transport chain dysfunction and the release of proapoptotic proteins, causing an increase in ROS production (Singh et al., 2019). ROS in the brain induces the production of Aβ fibrils and aggregation, increasing levels of oxidative stress for the neurons even further (Gomes et al., 2018). Illustrating a cyclic process where Aβ peptides induce oxidative stress, and the oxidative stress amplifies the production of the amyloid fibrils, both components increasing the production of the other as the disease progresses (Bai et al., 2022).

Most ROS are produced in the mitochondria due to the oxidation of metabolites in the electron transport chain (Dunn et al., 2015). ROS production increases when the function of a highly conserved mitochondrial control mechanism is impaired. When ROS are present in high concentrations in neural tissue, the APP gene is abnormally expressed, contributing to forming Aβ plaques (Bai et al., 2022; Ionescu-Tucker & Cotman, 2021). The predisposition to early-onset Alzheimer's in individuals with Down Syndrome, who possess an extra copy of chromosome 21, where the APP gene resides, underscores the role of abnormal APP expression in AD development (Cheignon et al., 2018). Additionally, Aβ peptides have been shown to interfere with mitochondrial membrane potential, decrease the activity of electron transport complex two, and disrupt the mitochondrial structure, causing several membrane deformities (Cieślik et al., 2019). Thus, Aβ accumulation contributes to forming plaques, which are thought to contribute significantly to oxidative stress in AD patients' brains (Bai et al., 2022). Oxidative stress is detrimental and often irreversible due to its capability to cause epigenetic changes (Ionescu-Tucker & Cotman, 2021). Epigenetic changes can result in altered function in a variety of normal CNS proteins, contributing to neurodegeneration and increased rates of amyloid-beta plaque formation through changes to chromatin through H3K9 methylation (Ionescu-Tucker & Cotman, 2021; Myung et al., 2008).

The free radical theory of aging also called the oxidative stress theory of aging, hypothesizes that loss in tissue and organ function seen in old age is due to an accumulation of oxidative stress (Liguori et al., 2022). Tissues in younger populations regenerate through methods of cell proliferation; this loss of function in older populations is due to progressive hindrances in the processes of cell proliferation (Liguori et al., 2022). The free radical theory of aging hypothesizes that this loss of function is due to free radical oxidation of cellular DNA, producing more and more dysfunctional and mutated versions of the tissues throughout the life span (Liguori et al., 2022). As discussed, oxidative damage is detrimental to a wide variety of tissues and, over time, can cause the breakdown of macromolecules like lipids, DNA, and proteins (Liguori et al., 2022). Neurons are especially susceptible to oxidative stress as they are locked into G0 of the cell cycle and non-dividing and exposed to high calcium levels, leading to mitochondrial damage (Grimm & Eckert, 2017). It is also important to note that because they are non-dividing, neurons will not produce dysfunctional copies but will become dysfunctional themself as the structures and proteins produced from the cellular DNA are improperly produced (Liguori et al., 2022).

After oxidative stress causes amyloid beta production accumulation to form neural plaques, it is hypothesized that amyloid beta can affect the synapses and damage neuron transmission (Kashyap

et al., 2019). Tests of neuronal pathway decay in transgenic mice initially show little adverse effects, likely due to the brain's ability to use alternate pathways to accomplish essential functions (Kashyap et al., 2019). However, as the disease progresses in transgenic mice, several essential pathways and their observed functionality become defective at approximately 120 days from the onset of Aβ accumulation (Kashyap et al., 2019). As more and more pathways are interrupted by amyloid plaques, the options for propagating a viable synapse to perform the desired function decrease exponentially.

Several metals may also affect how oxidative stress is related to AD. Certain metals can act as antioxidants but are also responsible for the accumulation of amyloid beta peptides to form oligomers and the accumulation of oligomers for amyloid β plaques (Citation needed). Metallic ions such as zinc, copper, and iron are involved in cell signaling pathways in the CNS and affect the conformation proteins such as Tau and Aβ (Singh et al., 2019). Moreover, Aβ peptides in the presence of metal ions induce the production of ROS within the CNS by various redox reactions (Cheignon et al., 2018). Zinc accumulation has explicitly been associated with cognitive and memory processes in the brain. When zinc binds to amyloid β, it creates an incredibly toxic and dysfunctional protein version that increases oxidative stress output (Singh et al., 2019).

Oxidative stress is a multifactorial pathological marker linked to AD through several pathways, such as mitochondrial dysfunction, amyloid beta accumulation, and metal interactions. While a growing body of evidence supports oxidative stress's role in AD, the exact mechanisms underlying this relationship are still being explored because there is just so much that is unknown. The development of effective treatments for Alzheimer's disease may require a better understanding of how oxidative stress and other factors interact to cause neurodegeneration. Further research is needed to fully understand the mechanisms involved in this complex disease and identify potential targets for intervention and prevention.

RESVERATROL AND OXIDATIVE STRESS

Resveratrol is a polyphenol compound derived from grapes, berries, red wine, peanuts, and other fruits and nuts (Farkhondeh et al., 2020). The compound has gained considerable attention as a potential therapeutic agent for Alzheimer's Disease (AD). The neuroprotective mechanisms of resveratrol in AD have been subject to numerous studies intending to explain the underlying processes and cellular pathways. One of the main neuroprotective effects of resveratrol is its ability to reduce inflammation (Gomes et al., 2018). Several studies have shown that resveratrol can modulate the expression of pro-inflammatory cytokines, such as interleukin-1β, tumor necrosis factor-α, and nitric oxide, which are all involved in the pathogenesis of AD (Gomes et al., 2018). Furthermore, in vitro and in vivo studies have demonstrated that resveratrol can block the activation of NF-κB and MAPK pathways, which regulate inflammation and apoptosis in AD (Gomes et al., 2018). In addition to its anti-inflammatory properties, resveratrol has been shown to act as an antioxidant and could be used to combat oxidative stress.

Additionally, resveratrol has been demonstrated to scavenge free radicals, reduce oxidative stress, and inhibit lipid peroxidation (Gomes et al., 2018). These properties are hoped to be beneficial in combating pathogenic markers of AD, as oxidative stress and lipid peroxidation are thought to play a critical role in the pathogenesis of the disease (Gomes et al., 2018). Furthermore, evidence shows that resveratrol can increase the expression of several neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Gomes et al., 2018). These neurotrophic factors are essential in promoting neuronal survival and neuroplasticity and may also help to protect against the neurodegeneration associated with AD. Furthermore, evidence shows that resveratrol can interact with several neuronal signaling pathways, including the PI3K/Akt and AMPK pathways (Gomes et al., 2018). Stimulation of these pathways is likely crucial in the potential treatment of AD, as it can lead to controlled phosphorylation of tau protein, as well as supporting neuroprotection and improved cognitive function in AD patients (Gomes et al., 2018).

Dr. Yadav and fellow researchers have recently studied resveratrol as a therapeutic agent for the treatment of vascular dementia, which is a kind of dementia caused by decreased blood flow to the brain. Resveratrol is a neuronal expression of Nrf2 and HO-1 that mitigates oxidative damage (Yadav

et al., 2018). Additionally, administering resveratrol to rats with vascular dementia significantly decreased ROS production in several areas of the brain by about 1/3 overall (Yadav et al., 2018). With a decreased ROS production, resveratrol also reduced amyloid-mediated neurotoxicity by manipulating AMPK-dependent pathways responsible for the hyperphosphorylation of tau proteins that form NFTs (Yadav et al., 2018). The administration of resveratrol to the rats also reduced lipid peroxidation in the brain by about 40% and protein carbonyl levels by about 50%. It was even able to decrease mitochondrial ROS production through the SOD pathway by 50% (Yadav et al., 2018). However, resveratrol was shown to downregulate HIF-1-alpha, a protein subunit essential to anti-inflammatory pathways, which could serve to hinder treatment for AD. However, ways to combat this issue are being explored, and it is possible to overcome this challenge by supplementing it with other forms of medication.

The Nrf2 protein is critical for controlling inflammatory responses, oxidative stress, and several synthesis pathways, such as protein, carbohydrates, and lipids (Farkhondeh et al., 2020). Additionally, Nrf2 is essential in maintaining cell homeostasis and seems to play a considerable role in inhibiting the progression of several pathological conditions, such as vascular dementia, AD, and Parkinson's disease (Farkhondeh et al., 2020). Resveratrol activates and upregulates the transcription of Nrf2 through the disassociation of Keap-1 from Nrft2, serving to increase the translocation of Nrf2 into the nucleus and suppress inhibitory signaling pathways to upregulate transcription (Farkhondeh et al., 2020) greatly. This protein is exceptionally neuroprotective and illustrates one of the many positive effects resveratrol would have on an AD patient's brain chemistry.

Yao et al. (2015) investigated the effects of resveratrol on the proliferation of microglia induced by oligomeric amyloid-beta (oAβ), which is a crucial aspect of microglial activation following brain damage. The study shows that oAβ induced the proliferation of microglia. This effect was markedly inhibited by resveratrol, suggesting that the anti-inflammatory effect of resveratrol may contribute to the inhibition of microglial proliferation. Furthermore, resveratrol inhibited the oAβ-induced mRNA and protein expression of the gp91phox and p47phox NADPH oxidase subunits, decreasing ROS production. In combating ROS released from mitochondria, looking for ways to maintain mitochondrial membrane potential and stability while terminating the produced free radicals is essential.

The article by Yu et al. (2018) examines the effects of two natural compounds, resveratrol and morin, on the insoluble tau protein in tau transgenic mice. To investigate the effects of these compounds on insoluble tau protein, resveratrol, and morin were administered to Tau transgenic mice (Yu et al., 2018). Both resveratrol and morin reduced the levels of NFTs caused by insoluble tau proteins in the transgenic mice. However, mice that received the resveratrol treatment had significantly decreased levels of the insoluble tau proteins (Yu et al., 2018).

Caspase proteins are proteases that operate as one of the central components of the apoptotic cell pathway, and specifically, Caspase-3 is a protease essential in practically every mode of the apoptotic pathway (Su et al., 2001). Caspase-3 is generally found only as an inactive precursor protein in minimal quantities contained in somatic cells cytoplasm but becomes enzymatically active through cleavage of the precursor protein when apoptosis is initiated (Su et al., 2001). Kong et al. (2019) evaluated the effects of resveratrol on levels of antioxidant enzymes and the activity of Caspase 3. Treatment with resveratrol served to upregulate levels of antioxidant enzymes significantly and additionally appeared to decrease levels of activated Caspase-3 in cells afflicted with oxidative stress. In addition, treatment with resveratrol significantly increased the expression of the estrogen receptor ERα, suggesting that resveratrol may also modulate the effects of estrogen in AD (Kong et al., 2019). Resveratrol reliably modulates the activity of antioxidant and anti-inflammatory pathways while preventing apoptosis. Further research is needed to determine the efficacy of resveratrol for treating AD in humans and further investigate the molecular mechanisms by which it works. Regulation of apoptotic pathways in neurodegenerative diseases is essential to treatment, as neurons are locked in a non-dividing state, unable to repair large-scale tissue damage, so preserving every cell possible will lead to better outcomes in a patient's recovery.

The complex nature of resveratrol's neuroprotective mechanisms highlights its potential as

a promising therapeutic agent for treating AD. However, further research is needed to determine the optimal treatment dosage and duration and to fully elucidate the exact mechanisms by which resveratrol exerts its neuroprotective effects. Overall, resveratrol represents a promising avenue for future research and development of potential treatments for AD (Su et al., 2001).

DISCUSSION AND RECOMMENDATIONS

The review provides a comprehensive overview of the critical pathogenic markers associated with AD and examines the potential therapeutic role of resveratrol in mitigating the effects of AD. The primary pathogenic markers discussed include Aβ peptides, tau proteins, oxidative stress, and their intricate interplay that serves to produce the incredible severity of AD.

AMYLOID BETA PROTEINS AND AD:

The aggregation of Aβ peptides leading to the formation of plaques is a central event in AD pathology (Gomes et al., 2018). This review highlights the cascade of events initiated by the amyloidogenic pathway, involving beta and gamma-secretase cleavage of amyloid precursor protein (APP). The resulting Aβ peptides aggregate into neurotoxic plaques, particularly in regions such as the brain's basal, temporal, and orbitofrontal areas (Cheignon et al., 2018; Tiwari et al., 2019). The neurotoxic effects of Aβ are underscored by its impact on microglial cells, inducing overstimulation, apoptosis, and proinflammatory mediator secretion. Aβ fibrils further deactivate microglial cells, increasing neuronal damage (Hansen et al., 2017). This understanding of Aβ pathology sets the stage for exploring the proposed AD treatment, resveratrol. It is unclear whether oxidative stress is the cause of Aβ or if Aβ is the cause of oxidative stress. However, both likely influence each other. More research is needed to be specific.

TAU PROTEINS AND NEUROFIBRILLARY TANGLES

The review elucidates the role of tau proteins in AD, emphasizing hyperphosphorylation as a critical event leading to the formation of NFTs. The connection between Aβ fibril polymerization and the activation of MAP kinase pathways, contributing to tau hyperphosphorylation, provides a link between two of the primary pathogenic markers associated with AD (Denechaud et al., 2022; Gao et al., 2018). These NFTs interfere with neuronal signal transduction and signal processing and contribute severely to activating the apoptotic pathway in affected neurons (Miao et al., 2019). Additionally, the heterogeneity of tau pathology within the cortex raises intriguing questions about disease progression and potential therapeutic targets related to tau phosphorylation. However, this presents several challenges as multiple pathways must be addressed at once beyond the MAP kinase pathway for a treatment to be effective.

OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

The discussion on oxidative stress in AD emphasizes its multifactorial nature, involving inflammatory pathways, mitochondrial dysfunction, and the role of specific molecules like cardiolipin (Cieślik et al., 2019; Griñán-Ferré et al., 2018; Singh et al., 2019). The cyclic relationship between Aβ peptides and ROS production in mitochondria complicates the understanding of oxidative stress in AD (Bai et al., 2022). Additionally, the free radical theory of aging contributes to oxidative stress and possible gene mutations that lead to AD pathogenesis, linking oxidative stress to the age-related decline in tissue function, which is particularly relevant to neurodegenerative diseases like AD, primarily affecting the elderly population (Liguori et al., 2022). Most importantly, oxidative stress produces inflammation through several different mechanisms, and the overarching effect of the inflammation is neuronal cell death (Kashyap et al., 2019). Although all these separate pathways contribute to oxidative stress, which culminates into inflammation and neuronal cell death and should be researched more in the search for reliable treatment options, it is also possible that positive strides in AD treatment could be made in discovering methods to reduce overall inflammation.

RESVERATROL AND OXIDATIVE STRESS

The introduction of resveratrol as a potential therapeutic agent for AD introduces a novel dimension to the discussion. Resveratrol's neuroprotective effects are attributed to its anti-inflammatory and antioxidant properties (Gomes et al., 2018). The ability of resveratrol to modulate cytokine expression, inhibit NF-κB and MAPK pathways, and scavenge free radicals positions it as a promising candidate for mitigating oxidative stress in AD (Gomes et al., 2018). The compound's impact on

neurotrophic factors and its interaction with signaling pathways such as PI3K/Akt and AMPK further strengthen the rationale for its investigation in AD treatment (Gomes et al., 2018). In Dr. Yadav's studies, resveratrol induced the expression of Nrf2 and HO-1, reducing oxidative stress in rats induced with vascular dementia (Yadav et al., 2018). These rats also demonstrated significant decreases in ROS production, lipid peroxidation, protein carbonyl levels, and amyloid-related toxicity (Yadav et al., 2018). Resveratrol has been studied for some time now, and although it is believed to aid in AD treatment through the mechanisms discussed in this review, resveratrol is no cure. The goal of examining the role of a well-studied, widely available, and naturally occurring compound was to gain a strong understanding of AD pathology and how a compound with broad antioxidant and anti-inflammatory mechanisms affected the progression and pathology of the disease.

RECOMMENDATIONS

Further research is needed to dissect the intricate molecular mechanisms that connect Aβ, tau hyperphosphorylation, and oxidative stress in AD. This is essential to identifying specific targets for drug innervations. It is also crucial to explore different combinations of therapies. As mentioned in this review, AD is multifaceted and would require several pathways to be controlled at one time for the medication to be truly effective. It is possible that this could be achieved through experimenting with different drug combinations that each acts to control and regulate their pathway for the desired effect. Additionally, longitudinal studies on oxidative stress will be beneficial in understanding what factors throughout a person's life contribute to higher or lower levels of oxidative stress.

CONCLUSION

In conclusion, this literature review underscores the complexity of AD and the need for targeted treatments. Oxidative stress plays a vital role in the pathology of Alzheimer's disease (AD) through its involvement in pathways such as mitochondrial dysfunction, amyloid β (Aβ) accumulation, and metal interactions (Cieślik et al., 2019; Gomes et al., 2018; Griñán-Ferré et al., 2018). Aβ peptides induce oxidative stress, amplifying amyloid fibril production and creating a vicious cycle (Gomes et al., 2018). Mitochondrial dysfunction also contributes to AD development by affecting APP gene expression (Rukmangadachar & Bollu, 2022). Additionally, oxidative stress can trigger epigenetic changes, inflammation, and cell senescence, all contributing to neurodegeneration. While the exact mechanisms are still under investigation, the evidence supports oxidative stress as critical in AD pathogenesis (Cieślik et al., 2019; Gomes et al., 2018; Griñán-Ferré et al., 2018; Hansen et al., 2017; Yao et al., 2015).

AD is marked by the aggregation of beta-amyloid peptides into neurotoxic plaques (Rukmangadachar & Bollu, 2022), which impair neuronal function and contribute to the disease's severe neurological symptoms (Tiwari et al., 2019). Microglial cells, responsible for maintaining central nervous system (CNS) health, attempt to clear Aβ oligomers but become over-activated or deactivated in the presence of significant Aβ accumulations, worsening the disease (Hansen et al., 2017). Understanding the complex role of microglial cells in AD may reveal new therapeutic targets.

Tau protein hyperphosphorylation, which leads to neurofibrillary tangles, is another hallmark of AD. Emerging research suggests that Tau hyperphosphorylation varies within the brain and is linked to DNA damage and cell cycle reactivation (Denechaud et al., 2022; Gao et al., 2018). This highlights the complexity of Tau pathology and the need for further study of its role in AD (Miao et al., 2019).

Resveratrol, a polyphenol with anti-inflammatory and antioxidant properties, has shown promise in reducing oxidative damage and improving cognitive function in AD (Yadav et al., 2018). Although not a cure, resveratrol offers a potential therapeutic avenue for slowing AD progression (Gomes et al., 2018). Future research should focus on exploring drug targets that address oxidative stress, Aβ accumulation, and Tau pathology, with longitudinal studies providing insights into these processes over time. While much remains to be discovered, compounds like resveratrol offer promising avenues for further exploration.

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