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Smoking and the increased risk of Alzheimer's disease

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Abstract:

Cigarette smoking has been proven to be a significant risk factor for pathological changes associated with aging and Alzheimer's disease (AD). It is the primary cause of cognitive impairment worldwide and is classed as a neurological condition. AD is characterized by the extracellular aggregation of amyloid (Aβ) plaques and the intracellular development of neurofibrillary tangles in the cortical and marginal areas of the human brain. Individuals with AD will have memory loss in addition to growing neurocognitive impairment. To determine if smoking can have an influence on the development of AD, the effects of smoking on the brain must be examined. Several researchers have already examined the decline in cigarette smoking and recognized it as a significant risk factor for AD. On the other hand, additional study has established that there is no correlation between cigarette smoking and the development of AD. Inconsistencies in the variables and experimental techniques were discovered in several of these investigations. For example, the kind of AD detected in individuals varied: whereas one trial demonstrated the development of late-onset AD, another experiment indicated non-late-onset AD. As a result, additional experiments with more precise control of variables and consistent techniques are required. This review aims to investigate the pathological alterations that smoking causes in the human brain, with a particular emphasis on findings indicating that late-onset AD is a result of cigarette smoking. Additionally, this study aimed to elucidate the several processes through which smoking may raise the risk of AD.

Keywords: Alzheimer's disease, APP proteins, Aβ plaques, cigarette smoking, epidemiology, oxidative stress

Introduction

It has been established that smoking contributes to the development of neurological illnesses, such as Alzheimer's disease (AD) and dementia (1, 2). In addition, it has been linked to both an increased and a decreased risk of AD (1). According to one study, late-onset AD (beginning beyond the age of 65) accounts for more than 90% of all AD cases. Additionally, it is predicted that roughly 35 million individuals globally suffer with AD, a figure that is expected to almost quadruple by 2030 as the conditions of human lifestyle improve (3, 4). Cigarette smoking may increase amyloid pathology, according to the findings of an animal model of AD (5). Other research has indicated that detecting amyloid-beta 42 levels in cerebrospinal fluid (CSF) may give diagnostic specificity for AD, with human studies indicating a clear relationship between elevated CSF amyloid-beta 42 levels and moderate cognitive impairment associated with AD (6). It will be the emphasis of this review to examine the evidence that smoking can cause late-onset AD, as well as a complete examination of the several processes by which smoking may cause the disease.

Aβ plaques and AD:

Aβ plaques begin in the basal, temporal, and orbitofrontal neocortex areas of the brain before spreading to the hippocampus, amygdala, diencephalon, and basal ganglia (7, 8). Amyloid

pathogenesis begins with a shift in the breakdown of APP, an integral protein on the plasma membrane, by β-secretases (BACE1) and γ-secretases, resulting in insoluble Aβ fibrils (9, 10). A then oligomerizes, diffuses into synaptic clefts, and degrades synaptic connections (9). It polymerizes as a result, creating plaques of insoluble amyloid fibrils (11-13). As a result of this polymerization, kinases are activated, resulting in hyperphosphorylation of the microtubule-associated protein and subsequent polymerization into insoluble NFTs (14, 15). Microglia are recruited to surround plaques and tangles that form as a result of the formation of plaques and tangles (8, 14, 16). This stimulates microglia and triggers a local inflammatory response, both of which result in neurotoxicity (15, 17).

APP proteins in AD:

APP is a member of a protein family that also includes mammalian amyloid precursor-like proteins, which are APLP1 and APLP2, as well as Drosophila Amyloid antecedent protein-like proteins, or APPL (6, 13, 18). It is a transmembrane protein containing extracellular domains that are required for optimal cell membrane function (19, 20). By differential enzyme cleavage, APP forms amyloidogenic fragments in a sick state (21). While the physiological activities of APP are unknown at the time, scientists have discovered that it is capable of controlling growth and motility of cells (16, 22, 23). All of this is linked to the release of soluble ectodomains after proper APP cleavage in transiently transfected cell lines (13, 19).

Cigarette smoking and brain aging:

Tobacco use has been found as a significant risk factor for age-related pathological changes and AD (2, 24). Because smoking can affect other cellular functions, such as the motor-based trafficking system, we measured the levels of acetylated-tubulin in the blood, which can reduce kinesin-1 binding affinity (25). According to one study, smokers exhibited lower acetylated tubulin levels (26-28). Acetylated-tubulin immunoreactivity was considerably reduced in the CA1 and CA3 sections of the hippocampus in the smoking group (29-31). Following a quantitative study of Western blot data, researchers discovered that the smoking group's level of acetylated tubulin was only 0.59±0.03 times higher than that of the control group (32). This change inβ - tubulin acetylation levels might indicate a faulty cellular transport mechanism. Because acetylated tubulin levels varied, smoking could have additional effects on the transport system within cells (27). It has been demonstrated that the degree of phosphorylation affects tau's affinity for microtubules (MTs) and, as a result, the integrity of the cytoskeleton (33). Additionally, it was discovered by the presence of tau phosphorylation sites found in many of the mouse hippocampus (29, 34). Smoking had no influence on overall tau levels, as determined by Western blots using a pan-tau (K9JA) antibody (35, 36). Western blots were utilized to detect tau phosphorylation at the four phosphorylation sites using phosphorylation-dependent and site-specific tau antibodies (17). Furthermore, smoking increased tau phosphorylation by approximately 3 folds at Tyr231, Tyr205, and Ser404 (25, 37, 38). The data, however, reveal that there is no statistically significant difference in the levels of phosphorylated tau at Ser396 between those who smoke and those who do not (17).

Role of cigarette smoking and risk of AD:

Numerous variables contribute to the development of AD, but the most powerful and often duplicated risk factors are age and the APOE 4 allele, which is handed down from generation to generation (39). Between the ages of 60 and 90, the chance of developing AD increases by 50% every five years, and the risk increases by 3–5 times for those with one copy of the APOE 4 allele, and by a whopping 12 times for individuals with two copies (i.e., homozygotes for the APOE 4 allele) (40, 41). When paired with other genetic and changeable environmental risk factors, age and APOE genotype may exacerbate the pathophysiology and risk of AD (39, 42). Numerous studies have been undertaken in recent years to discover risk factors for AD that may be adjusted or treated in order to decrease their frequency during the asymptomatic preclinical period, resulting in a considerable reduction in the number of people with the condition (40, 43). There is, however, considerable dispute over the strength of the association between AD and suspected risk factors for the illness that can be modified (7).

APP processing was altered by passive cigarette smoking:

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AD is associated with an increase in tau phosphorylation and synaptic activity (26). As a result, more degenerative alterations associated with AD were identified in the test subjects (37). The researchers observed that APP levels had grown but that its expression had remained the same (44). Throughout AD, both β-secretase and γ -secretase alter the enzymatic cleavage of APP, resulting in increased synthesis of sAPP and, finally, Aβ peptide (13, 19, 45). Test rats who smoked cigarettes had higher amounts of the neurotransmitter sAPP in their hippocampus than those that did not (17, 46). The smoking group conveyed considerably greater levels of Aβ, particularly in the CA3 area (29, 31). The control group had little to no Aβ staining in CA3, but the smoking group had Aβ accumulating in the cell body (8, 29). Despite the fact that the control group had a greater baseline level of Aβ in the dentate gyrus than the smoking group, the smoking group experienced an increase in Aβ staining (47). Tobacco use appears to alter the process of APP and redirect it to the amyloidogenic pathway, resulting in an increase in Aβ peptide synthesis.

Oxidative stress a major mechanism for cigarette smoke in neurodegenerative effects:

Tobacco smokers had significantly greater levels of oxidative stress indicators and significantly lower amounts of antioxidants, anti-oxidative enzymes, or both (48, 49). The term "systemic oxidative stress" refers to the way cigarette smoke affects various organs (50). A previous study found that both smokers and AD patients have elevated free radical damage levels in their cerebral cortex (49, 51). Additionally, another recent research established the effect of oxidative stress by demonstrating that Vitamin E can protect against the rise in acetylcholinesterase activity and lipid peroxidation caused by cigarette smoke in rat brains (52). Using a paradigm, the researchers demonstrated the presence of oxidative stress in the hippocampus of cigarette-exposed rats (52). Antibodies specific for 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-hydroxyguanosine (8-OHg) were used to assess the presence of oxidative stress (8-OHG) (53, 54). When reactive free radicals oxidize guanine in DNA and RNA, 8-OHdG and 8-OHG are formed (53, 54). 8-OHG and 8-OhdG levels in susceptible neurons of AD patients are raised, and the amount of eight-OHG in their CSF is significantly connected with disease duration (53, 54). Early in the course of neurodegenerative disorders, synaptic degradation occurs (53, 54). Synaptic loss, on the other hand, has been seen in both healthy persons and AD patients (55). These proteins are required for appropriate synaptic function (55, 56). Synaptophysin, the most abundant protein in synaptic vesicles, is used to specify the amount of functional synapses (25). Synaptophysin works in conjunction with other synaptic proteins, most notably synaptobrevin, to regulate synaptic vesicle exocytosis and hence neurotransmitter release (55). Another presynaptic protein that is involved in the control of neurotransmitter release is known as Synapsin-1 (9). Synapsin-1 modulates synaptic vesicle release by modulating its phosphorylation state (57). Cigarette smoking lowered the expression of two synaptic degeneration markers, synapsin-1 and synaptophysin (24, 58, 59). Additionally, drebrin, a protein found in dendritic spines, is becoming more abundant. Actin filaments comprise the dendritic spine's basic cytoskeletal structure (33). Drebrin binds to actin and interferes with its interaction with myosin, resulting in diminished actomyosin contractile force and spine retraction (51). It has been proven that drebrin overexpression alters the spine's morphology, and an increase in drebrin expression may interfere with normal synaptic activity due to the intimate relationship between spine shape and synaptic plasticity (60). Drebrin expression is changed in persons with AD and moderate cognitive impairment (47, 60). Drebrin expression was increased in cognitively impaired elderly rats, but not in elderly rats with normal cognition, according to the study (60). More drebrin is thought to hinder the remodeling of spine structure that happens during periods of high activity (60). This may result in a tightening of the synapses' structure, rendering them less malleable (33). Thus, synaptophysin, synapsin-1, and drebrin findings indicate that chronic cigarette smoking results in synaptic alterations linked with aging and cognitive decline (2, 61).

The most prevalent element of MTs is tubulin (27). Acetylation of β-tubulin is required for axonal transit, as demonstrated on stable MTs (27). If β-tubulin is acetylated, the cargo-transporting motor protein Kinesin-1 will be able to associate with MTs (25-27). In AD patients, acetylated-tubulin levels are lower in neurons with neurofibrillary tangles (28). Cigarette

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smokers possessed around 40% less acetylated tubulin than nonsmokers, implying axonal transport impairment (61). To validate this argument, a more functional research may be necessary (62). Reduced acetylated-tubulin levels may suggest fewer stable or mature MTs, as well as alterations in the cell's transportation system (61). Tau is a membrane-associated protein that is necessary for vesicle formation, stability, and trafficking (24, 61). Due to the reduced affinity of hyperphosphorylated tau proteins for MTs, they are more prone to form paired-helical filament structures and aggregate to form neurofibrillary tangles (63). As a result, Cigarette smoke exposure resulted in hyperphosphorylation of tau at Thr 231, Thr 205, and Ser 404, respectively (26, 61). Thus, tau's usual activities may be compromised, resulting in a drop in acetylated-tubulin, implying a loss of microtubule integrity (61).

Nicotine administration to transgenic AD mice on a regular basis has been shown to exacerbate tau pathology (64, 65). Tau phosphorylation is regulated by GSK3, CDK5, ERK1/2, JNK, and PP2A kinases and phosphatases (15, 65). It was revealed that p-ERK1/2 and p-JNK levels were increased in the hippocampuses of smokers (24, 57, 62). Numerous components of tobacco smoke are highly reactive oxidants (66). For example, nicotine has been demonstrated to generate reactive oxygen species in mesencephalic neurons of rats (ROS) (20, 67). Because the smoking group had a greater concentration of 8-OHG during the experiment, oxidative stress may have acted as a catalyst for JNK and ERK, both of which phosphorylated tau proteins (68). By altering APP processing, oxidative stress can contribute to the pathogenesis of AD. It has been demonstrated in vitro that it can alter β- and y-secretases and increase Aβ production via a JNK-dependent mechanism (49, 66). According to current research, Aβ's immunoreactivity is increased in smokers' brain slices (69). Toxicology plays an important part in the course of AD; the peptide has the potential to cause synapses to deteriorate and axonal transport to be disrupted (69). Cigarette smoking-induced Aβ is almost certainly responsible for a portion of the observed reduction in acetylated tubulin and synaptic alterations (24).

Cognitive and neurodegenerative impact from cigarette smoking:

The researchers discovered evidence that smoking has a detrimental effect on the neurobiology and function of the brain in people who have no history of clinically significant psychiatric or medical conditions, such as schizophrenia or alcohol/substance use disorders, as well as those who have a history of mild traumatic brain injury (70). These findings are particularly significant for smokers, as the neurobiological and cognitive abnormalities observed in these individuals closely resemble many of the neuropathological and cognitive abnormalities observed in the recently suggested "preclinical" phases of AD (2). The majority of the research is devoted to the consequences of smoking on the human body in those over the age of 65 (54). Apart from cerebrovascular risk factors for stroke, little study has been conducted on the long-term effects of smoking on the brain and its functioning, particularly in middle-age people and young adults (61, 71).

Smoking and Cognitive Impairment Among Persons:

Previous study has demonstrated that former smokers and nonsmokers exhibit no significant difference in cognitive ability (72). On the other hand, some studies have established a link between smoking and cognitive ability, demonstrating that former smokers outperform nonsmokers (73). After correcting for factors such as age, education, diabetes, hypertension, stroke, and heart disease, a prospective research of older Taiwanese respondents discovered that former smokers had a lower rate of cognitive impairment than nonsmokers (73). On the other hand, some research have found that ex-smokers are more likely to experience cognitive impairment (65). Although the exact mechanisms by which smoking causes dementia are unknown, it is thought that smoking has an influence on the cardiovascular system and oxidative stress, both of which can raise the risk of developing AD (72). Smoking increases the risk of hypertension by causing damage to the cardiovascular system, implying that smoking is yet another risk factor for hypertension (24, 73, 74). According to cerebrovascular pathology and AD pathology, hypertension is associated with an elevated risk of AD and dementia (75, 76).

Another possible explanation for smoking's detrimental effect on cognitive function is oxidative

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stresss (66). Tobacco use promotes oxidative stress, which causes blood vessel cells to die, arteries to shrink, and cerebral blood flow to decrease. As a result, reduced cerebral perfusion may result in cognitive impairment (24). New research suggests that oxidative stress can contribute to the genesis and development of AD (24). A second mechanism through which smoking may impair cognitive function is through lifestyle factors (66). Cigarette smoking has been linked to increased alcohol use, an increased BMI, and a lack of physical activity, all of which are risk factors for cognitive impairment (63, 72). Nonphysiological variables may contribute to the association between cigarette smoking and cognitive decline (66). According to population-based research, the relationship between socioeconomic status (SES) and smoking practices is inverse, with individuals with lower SES being more likely to become smokers (77). Numerous studies have established that socioeconomic variables contributed to the development of AD (77, 78). As a result, the link between smoking and poor socioeconomic position may help explain why smokers are more likely to experience cognitive impairment (77). By contrast, nicotine has been associated with possible biological anti-dementia properties (77). Nicotine has been shown to improve short-term cognitive performance and decrease amyloid plaque formation (66). It stimulates cognitive and memory-related brain receptors (66). Another factor affecting the link between cigarette smoking and cognitive decline is that smokers die younger than nonsmokers, resulting in a survivorship bias (72). As a result, only a tiny percentage of smokers reach the ages at which dementia symptoms frequently develop (43, 79). As a consequence, lower dementia rates among smokers may be attributable to factors other than smoking's protective properties, and smokers' death may be due to causes other than dementia (1, 79). A recent study examined whether the association between smoking and cognition is exacerbated by smokers' early death (80). After adjusting for criteria such as smoking history, socioeconomic position, and marital status, they revealed that men and women who were current smokers died at a greater rate than those who had never smoked (73, 77). On the other hand, a research analysis discovered contradictory conclusions about the effects of smoking and the chance of developing AD (80). Despite the fact that pharmacological studies support a plausible biological mechanism, this investigation found no evidence to support prior epidemiological results regarding smoking's protective effect against AD (79, 80).

Conclusion :

Cigarette smoking is a well-documented cause of premature aging. Use of tobacco reduces life expectancy and raises the chance of heart disease, cancer, and respiratory issues, among other health problems. While both smokers and non-smokers exposed to cigarette smoke have been linked to AD, the chemical mechanism behind this phenomenon is still unclear. Numerous studies have demonstrated that continuous smoking can accelerate brain aging by altering the synaptic proteins, which results in pre-AD neuropathology. Therefore, the consequence of smoking on distinct types of AD must be further researched; finding apolipoprotein E and other suspected genetic markers for AD will assist in characterizing the condition and its interplay with environmental variables such as smoking. This research may contribute to the theoretical underpinnings of a cure.

References:

1. Niu H, Qu Y, Li Z, Wang R, Li L, Li M, et al. Smoking and risk for Alzheimer disease: A meta-analysis based on both case-control and cohort study. The Journal of Nervous and Mental Disease. 2018;206(9):680-5.
2. Durazzo TC, Meyerhoff DJ, Yoder KK. Cigarette smoking is associated with cortical thinning in anterior frontal regions, insula and regions showing atrophy in early Alzheimer's Disease. Drug and alcohol dependence. 2018;192:277-84.
3. Maia MA, Sousa E. BACE-1 and γ-secretase as therapeutic targets for Alzheimer's disease. Pharmaceuticals. 2019;12(1):41.
4. Schaduangrat N, Prachayasittikul V, Choomwattana S, Wongchitrat P, Phopin K, Suwanjang W, et al. Multidisciplinary approaches for targeting the secretase protein family as a therapeutic route for Alzheimer's disease.

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Medicinal Research Reviews. 2019;39(5):1730-78.

5. Voytyuk I, De Strooper B, Chávez-Gutiérrez L. Modulation of γ-and β-secretases as early prevention against Alzheimer's disease. Biological psychiatry. 2018;83(4):320-7.
6. Begcevic I, Brinc D, Brown M, Martinez-Morillo E, Goldhardt O, Grimmer T, et al. Brain-related proteins as potential CSF biomarkers of Alzheimer's disease: A targeted mass spectrometry approach. Journal of proteomics. 2018;182:12-20.
7. Frigerio CS, Wolfs L, Fattorelli N, Thrupp N, Voytyuk I, Schmidt I, et al. The major risk factors for Alzheimer's disease: age, sex, and genes modulate the microglia response to Aβ plaques. Cell reports. 2019;27(4):1293-306.
8. He Z, Guo JL, McBride JD, Narasimhan S, Kim H, Changolkar L, et al. Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. Nature medicine. 2018;24(1):29-38.
9. Maesako M, Zoltowska KM, Berezovska O. Synapsin 1 promotes Aβ generation via BACE1 modulation. PLoS One. 2019;14(12):e0226368.
10. Qiao A, Li J, Hu Y, Wang J, Zhao Z. Reduction BACE1 expression via suppressing NF-κB mediated signaling by Tamibarotene in a mouse model of Alzheimer's disease. IBRO Neuroscience Reports. 2021;10:153-60.
11. Schelle J, Wegenast-Braun BM, Fritschi SK, Kaeser SA, Jährling N, Eicke D, et al. Early Aβ reduction prevents progression of cerebral amyloid angiopathy. Annals of neurology. 2019;86(4):561-71.
12. Reiss AB, Arain HA, Stecker MM, Siegart NM, Kasselman LJ. Amyloid toxicity in Alzheimer's disease. Reviews in the Neurosciences. 2018;29(6):613-27.
13. Urban AS, Pavlov KV, Kamynina AV, Okhrimenko IS, Arseniev AS, Bocharov EV. Structural Studies Providing Insights into Production and Conformational Behavior of Amyloid-β Peptide Associated with Alzheimer's Disease Development. Molecules. 2021;26(10):2897.
14. Drummond E, Nayak S, Pires G, Ueberheide B, Wisniewski T. Isolation of amyloid plaques and neurofibrillary tangles from archived Alzheimer's disease tissue using laser-capture microdissection for downstream proteomics. Laser Capture Microdissection: Springer; 2018. p. 319-34.
15. Rad SK, Arya A, Karimian H, Madhavan P, Rizwan F, Koshy S, et al. Mechanism involved in insulin resistance via accumulation of β-amyloid and neurofibrillary tangles: Link between type 2 diabetes and Alzheimer's disease. Drug design, development and therapy. 2018;12:3999.
16. Cai H-Y, Yang J-T, Wang Z-J, Zhang J, Yang W, Wu M-N, et al. Lixisenatide reduces amyloid plaques, neurofibrillary tangles and neuroinflammation in an APP/PS1/tau mouse model of Alzheimer's disease. Biochemical and biophysical research communications. 2018;495(1):1034-40.
17. Furcila D, Domínguez-Álvaro M, DeFelipe J, Alonso-Nanclares L. Subregional density of neurons, neurofibrillary tangles and amyloid plaques in the hippocampus of patients with Alzheimer's disease. Frontiers in neuroanatomy. 2019;13:99.
18. Cha HJ, Shen J, Kang J. Regulation of gene expression by the APP family in the adult cerebral cortex. Scientific reports. 2022;12(1):1-9.
19. Steiner H, Fukumori A, Tagami S, Okochi M. Making the final cut: pathogenic amyloid-β peptide generation by γ-secretase. Cell Stress. 2018;2(11):292.
20. Bamford RA, Widagdo J, Takamura N, Eve M, Anggono V, Oguro-Ando A. The interaction between contactin and amyloid precursor protein and its role in Alzheimer's disease. Neuroscience. 2020;424:184-202.
21. Alam S, Piazzesi A, Abd El Fatah M, Raucamp M, van Echten-Deckert G. Neurodegeneration caused by S1P-lyase deficiency involves calcium-dependent tau pathology and abnormal histone acetylation. Cells. 2020;9(10):2189.

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22. Yin Q, Ji X, Lv R, Pei J-J, Du Y, Shen C, et al. Targetting exosomes as a new biomarker and therapeutic approach for Alzheimer's disease. Clinical interventions in aging. 2020;15:195.

23. Kim Y, Kim Y. L-histidine and L-carnosine exert anti-brain aging effects in D-galactose-induced aged neuronal cells. Nutrition Research and Practice. 2020;14(3):188-202.

24. Wu P, Li W, Cai X, Yan H, Chen M, Alzheimer's Disease Neuroimaging I. Associations of cigarette smoking with memory decline and neurodegeneration among cognitively normal older individuals. Neuroscience Letters. 2020;714:134563.

25. Guo B, Huang Y, Gao Q, Zhou Q. Stabilization of microtubules improves cognitive functions and axonal transport of mitochondria in Alzheimer's disease model mice. Neurobiology of Aging. 2020;96:223-32.

26. Guha S, Johnson GVW, Nehrke K. The crosstalk between pathological tau phosphorylation and mitochondrial dysfunction as a key to understanding and treating Alzheimer's disease. Molecular Neurobiology. 2020;57(12):5103-20.

27. Barbier P, Zejneli O, Martinho M, Lasorsa A, Belle V, Smet-Nocca C, et al. Role of tau as a microtubule-associated protein: structural and functional aspects. Frontiers in aging neuroscience. 2019:204.

28. Biswas S, Kalil K. The microtubule-associated protein tau mediates the organization of microtubules and their dynamic exploration of actin-rich lamellipodia and filopodia of cortical growth cones. Journal of Neuroscience. 2018;38(2):291-307.

29. Ułamek-Kozioł M, Czuczwar SJ, Kocki J, Januszewski S, Bogucki J, Bogucka-Kocka A, et al. Dysregulation of autophagy, mitophagy, and apoptosis genes in the CA3 region of the hippocampus in the ischemic model of Alzheimer's disease in the rat. Journal of Alzheimer's Disease. 2019;72(4):1279-86.

30. Maiti P, Paladugu L, Dunbar GL. Solid lipid curcumin particles provide greater anti-amyloid, anti-inflammatory and neuroprotective effects than curcumin in the 5xFAD mouse model of Alzheimer's disease. BMC neuroscience. 2018;19(1):1-18.

31. Pluta R, Ułamek-Kozioł M, Kocki J, Bogucki J, Januszewski S, Bogucka-Kocka A, et al. Expression of the tau protein and amyloid protein precursor processing genes in the CA3 area of the hippocampus in the ischemic model of Alzheimer's disease in the rat. Molecular Neurobiology. 2020;57(2):1281-90.

32. Pchitskaya EI, Zhemkov VA, Bezprozvanny IB. Dynamic microtubules in Alzheimer's disease: association with dendritic spine pathology. Biochemistry (Moscow). 2018;83(9):1068-74.

33. Yamazaki H, Sasagawa Y, Yamamoto H, Bito H, Shirao T. CaMKIIβ is localized in dendritic spines as both drebrin-dependent and drebrin-independent pools. Journal of neurochemistry. 2018;146(2):145-59.

34. Li C, Liu W, Li X, Zhang Z, Qi H, Liu S, et al. The novel GLP-1/GIP analogue DA5-CH reduces tau phosphorylation and normalizes theta rhythm in the icv. STZ rat model of AD. Brain and Behavior. 2020;10(3):e01505.

35. Das R, Balmik AA, Chinnathambi S. Phagocytosis of full-length Tau oligomers by Actin-remodeling of activated microglia. Journal of neuroinflammation. 2020;17(1):1-15.

36. Gibbons GS, Banks RA, Kim B, Changolkar L, Riddle DM, Leight SN, et al. Detection of Alzheimer disease (AD)-specific tau pathology in AD and nonAD tauopathies by immunohistochemistry with novel conformation-selective tau antibodies. Journal of Neuropathology & Experimental Neurology. 2018;77(3):216-28.

37. Barthélemy NR, Mallipeddi N, Moiseyev P, Sato C, Bateman RJ. Tau phosphorylation rates measured by mass spectrometry differ in the intracellular brain vs. extracellular cerebrospinal fluid compartments and are differentially affected by Alzheimer's disease. Frontiers in aging neuroscience. 2019;11:121.

38. Hettmann T, Gillies SD, Kleinschmidt M, Piechotta A, Makioka K, Lemere CA, et al. Development of the clinical candidate PBD-C06, a humanized pGlu3-Aβ-specific antibody against

Volume 5, Issue 2; March-April 2022; Page No 801-810

Alzheimer's disease with reduced complement activation. Scientific reports. 2020;10(1):1-13.

39. Yassine HN, Finch CE. APOE alleles and diet in brain aging and Alzheimer's disease. Frontiers in aging neuroscience. 2020;12:150.
40. Patrick RP. Role of phosphatidylcholine-DHA in preventing APOE4-associated Alzheimer's disease. The FASEB Journal. 2019;33(2):1554-64.
41. Mamun AA, Uddin M, Bashar B, Fahim M, Zaman S, Begum Y, et al. Molecular insight into the therapeutic promise of targeting APOE4 for Alzheimer's disease. Oxidative Medicine and Cellular Longevity. 2020;2020.
42. Offen D, Rabinowitz R, Michaelson D, Ben-Zur T. Towards gene-editing treatment for alzheimer's disease: ApoE4 allele-specific knockout using a CRISPR cas9 variant. Cytotherapy. 2018;20(5):S18.
43. Eid A, Mhatre I, Richardson JR. Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. Pharmacology & therapeutics. 2019;199:173-87.
44. Hung COY, Livesey FJ. Altered γ-secretase processing of APP disrupts lysosome and autophagosome function in monogenic Alzheimer's disease. Cell reports. 2018;25(13):3647-60.
45. Xia W. γ-Secretase and its modulators: Twenty years and beyond. Neuroscience letters. 2019;701:162-9.
46. Zhang P, Kishimoto Y, Grammatikakis I, Gottimukkala K, Cutler RG, Zhang S, et al. Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nature neuroscience. 2019;22(5):719-28.
47. Dombroski TCD, Peixoto-Santos JE, Maciel K, Baqui MMA, Velasco TR, Sakamoto AC, et al. Drebrin expression patterns in patients with refractory temporal lobe epilepsy and hippocampal sclerosis. Epilepsia. 2020;61(8):1581-94.
48. Ali T, Kim T, Rehman SU, Khan MS, Amin FU, Khan M, et al. Natural dietary supplementation of anthocyanins via PI3K/Akt/Nrf2/HO-1 pathways mitigate oxidative stress, neurodegeneration, and memory impairment in a mouse model of Alzheimer's disease. Molecular neurobiology. 2018;55(7):6076-93.
49. Agnihotri A, Aruoma OI. Alzheimer's disease and Parkinson's disease: a nutritional toxicology perspective of the impact of oxidative stress, mitochondrial dysfunction, nutrigenomics and environmental chemicals. Journal of the American College of Nutrition. 2020;39(1):16-27.
50. Mecocci P, Boccardi V, Cecchetti R, Bastiani P, Scamosci M, Ruggiero C, et al. A long journey into aging, brain aging, and Alzheimer's disease following the oxidative stress tracks. Journal of Alzheimer's Disease. 2018;62(3):1319-35.
51. Kreis P, Gallrein C, Rojas-Puente E, Mack TGA, Kroon C, Dinkel V, et al. ATM phosphorylation of the actin-binding protein drebrin controls oxidation stress-resistance in mammalian neurons and C. elegans. Nature communications. 2019;10(1):1-13.
52. Simunkova M, Alwasel SH, Alhazza IM, Jomova K, Kollar V, Rusko M, et al. Management of oxidative stress and other pathologies in Alzheimer's disease. Archives of toxicology. 2019;93(9):2491-513.
53. Syafrita Y, Amir D, Susanti R, Fadhilah I. Relationship of brain-derived neurotrophic factor, malondialdehyde, and 8-Hydroxy 2-Deoxyguanosine with post-ischemic stroke depression. Dementia & Neuropsychologia. 2020;14:41-6.
54. Medhat D, El-Mezayen HA, El-Naggar ME, Farrag AR, Abdelgawad ME, Hussein J, et al. Evaluation of urinary 8-hydroxy-2-deoxyguanosine level in experimental Alzheimer's disease: Impact of carvacrol nanoparticles. Molecular biology reports. 2019;46(4):4517-27.
55. Trujillo-Estrada L, Vanderklish PW, Nguyen MMT, Kuang RR, Nguyen C, Huynh E, et al. SPG302 Reverses Synaptic and Cognitive

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Deficits Without Altering Amyloid or Tau Pathology in a Transgenic Model of Alzheimer's Disease. Neurotherapeutics. 2021:1-16.

56. Hanamura K, Koganezawa N, Kamiyama K, Tanaka N, Oka T, Yamamura M, et al. High-content imaging analysis for detecting the loss of drebrin clusters along dendrites in cultured hippocampal neurons. Journal of Pharmacological and Toxicological Methods. 2019;99:106607.
57. Chang K-W, Zong H-F, Rizvi MY, Ma K-G, Zhai W, Wang M, et al. Modulation of the mapks pathways affects aβ-induced cognitive deficits in alzheimer's disease via activation of α7nachr. Neurobiology of Learning and Memory. 2020;168:107154.
58. Du F, Yu Q, Yan S, Zhang Z, Vangavaragu JR, Chen D, et al. Gain of PITRM1 peptidase in cortical neurons affords protection of mitochondrial and synaptic function in an advanced age mouse model of Alzheimer's disease. Aging cell. 2021;20(5):e13368.
59. Soares Martins T, Trindade D, Vaz M, Campelo I, Almeida M, Trigo G, et al. Diagnostic and therapeutic potential of exosomes in Alzheimer's disease. Journal of Neurochemistry. 2021;156(2):162-81.
60. Chen J, Liu C, Xu M, Zhu J, Xia Z. Upregulation of miR-19b-3p exacerbates chronic stress-induced changes in synaptic plasticity and cognition by targeting Drebrin. Neuropharmacology. 2022:108951.
61. Silva MVF, Loures CdMG, Alves LCV, de Souza LC, Borges KBG, Carvalho MdG. Alzheimer's disease: risk factors and potentially protective measures. Journal of biomedical science. 2019;26(1):1-11.
62. Park JS, Lee J, Jung ES, Kim M-H, Kim IB, Son H, et al. Brain somatic mutations observed in Alzheimer's disease associated with aging and dysregulation of tau phosphorylation. Nature communications. 2019;10(1):1-12.
63. Andrews SJ, Fulton-Howard B, O'Reilly P, Marcora E, Goate AM, collaborators of the Alzheimer's Disease Genetics C, et al. Causal associations between modifiable risk factors and the Alzheimer's phenome. Annals of neurology. 2021;89(1):54-65.
64. Cassidy L, Fernandez F, Johnson JB, Naiker M, Owoola AG, Broszczak DA. Oxidative stress in alzheimer's disease: A review on emergent natural polyphenolic therapeutics. Complementary therapies in medicine. 2020;49:102294.
65. Serrano-Pozo A, Growdon JH. Is Alzheimer's disease risk modifiable? Journal of Alzheimer's Disease. 2019;67(3):795-819.
66. Teixeira JP, de Castro AA, Soares FV, da Cunha EFF, Ramalho TC. Future therapeutic perspectives into the Alzheimer's disease targeting the oxidative stress hypothesis. Molecules. 2019;24(23):4410.
67. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. International journal of nanomedicine. 2019;14:5541.
68. Abou-Elela DH, El-Edel RH, Shalaby AS, Fouaad MA, Sonbol AA. Telomere length and 8-hydroxy-2-deoxyguanosine as markers for early prediction of Alzheimer disease. Indian Journal of Psychiatry. 2020;62(6):678.
69. Leshem G, Richman M, Lisniansky E, Antman-Passig M, Habashi M, Gräslund A, et al. Photoactive chlorin e6 is a multifunctional modulator of amyloid-β aggregation and toxicity via specific interactions with its histidine residues. Chemical science. 2019;10(1):208-17.
70. Ning K, Zhao L, Matloff W, Sun F, Toga AW. Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. Scientific reports. 2020;10(1):1-10.
71. Yu J-T, Xu W, Tan C-C, Andrieu S, Suckling J, Evangelou E, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(11):1201-9.
72. Deal JA, Power MC, Palta P, Alonso A, Schneider ALC, Perryman K, et al. Relationship of cigarette smoking and time of quitting with incident dementia and cognitive decline. Journal

Volume 5, Issue 2; March-April 2022; Page No 801-810

of the American Geriatrics Society. 2020;68(2):337-45.

73. Wang RS, Wang B-L, Huang Y-N, Wan TTH. Synergetic Effect of Physical Activity and Fruit-vegetable Intake on the Decreasing of Cognitive Decline in Older Taiwanese. 2022.

74. Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and Alzheimer's disease: a systematic review and meta-analysis. Journal of Alzheimer's Disease

75. Chornenkyy Y, Wang WX, Wei A, Nelson PT.

    Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline. Brain Pathology. 2019;29(1):3-17.

76. James BD, Bennett DA. Causes and patterns of dementia: an update in the era of redefining Alzheimer's disease. Annual review of public health. 2019;40:65-84.

77. Fornazieri MA, Doty RL, Bezerra TFP, de Rezende Pinna F, Costa FO, Voegels RL, et al. Relationship of socioeconomic status to olfactory function. Physiology & behavior. 2019;198:84-9.

78. Subramaniapillai S, Almey A, Rajah MN, Einstein G. Sex and gender differences in cognitive and brain reserve: Implications for Alzheimer's disease in women. Frontiers in neuroendocrinology. 2021;60:100879.

79. Kuo C-Y, Stachiv I, Nikolai T. Association of late life depression,(non-) modifiable risk and protective factors with dementia and Alzheimer's disease: literature review on current evidences, preventive interventions and possible future trends in prevention and treatment of dementia. International journal of environmental research and public health. 2020;17(20):7475.

80. Johnson AL, Nystrom NC, Piper ME, Cook J, Norton DL, Zuelsdorff M, et al. Cigarette Smoking Status, Cigarette Exposure, and Duration of Abstinence Predicting Incident Dementia and Death: A Multistate Model Approach. Journal of Alzheimer's Disease. 2021;80(3):1013-23.

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