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Molecular Mechanism of Promotion, Progression and Possible Therapies of Alzheimer's Disease

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Abstract:

Objective: Alzheimer's disease (AD) is the common neurodegenerative disorder in the world, and intracellular neurofibrillary tangles and extracellular amyloid-beta (Aβ) protein deposits correspond to the most important pathological hallmarks of the disease. The current study is particularly concerned with molecular mechanisms underneath the promotion of AD. There is no cure reported for AD, although the therapeutic treatments mainly improve the symptoms of the disease. Consequently, an early and appropriate diagnosis is crucial to slow the evolution of the disease. The purpose of Tau and Aβ levels in the blood and cerebrospinal fluid (CSF) are generally used for the diagnosis of AD. Several medical equipment are also used to verify the diagnosis including the medical history, mental status tests, and evaluations of the brain construction with neuroimaging techniques. Molecular genetics is proved to be a precious tool to recognize the molecular origin of AD. Although several commercial drugs are available which reduce the severity of this dreadful disease but none of them is safe as they produce side effects.

Conclusion: Current review highlights the role of natural compounds on AD promotion and progression.

Keywords: Alzheimer's disease, Amyloid-beta protein, Cerebrospinal fluid, Therapeutic, Brain

Introduction: Alzheimer disease (AD) is neurodegenerative disarray that is considered by build-up of β-amyloid (Aβ) and tau proteins, progressive atrophy, and cognitive refuse. AD is clinically considered by the progressive loss of memory, cognitive functions and behavioural changes. Vascular invective begins energy of molecular trialprime to neurodegeneration, cognitive injury and dementia in AD. The cellular and molecular mechanisms in cerebral blood vessels and the pathophysiological procedures direct to cerebral blood run dysregulation, interruption of the neurovascular unit (NVU) and the blood-brain barrier (BBB) which all may donate to the arrival and progression of dementia and AD.

AD is the fourth-largest cause of death for people over 65 years of age. Dementia of AD is the commonest type of dementia; the other two forms are vascular dementia (VaD) and mixed dementia [1]. VaD is one of

the most ordinary causes of dementia after AD, causing around 15% of cases. But, unlike AD, there are no qualified treatments for VaD.

Recent investigations have shown that cell non-autonomous mechanisms are also vital for the pathogenesis of neurodegeneration with intracellular filamentous inclusions. The intercellular transfer of inclusions prepared of tau, α-synuclein, huntingtin and superoxide dismutase 1, has been established, instructive the reality of mechanisms significant of those by which prions reach through the nervous system [2].

Currently, the remedy of AD is aimed at recovering both, cognitive and behavioural symptoms. In anticipation of the newly available drugs for the treatment of AD are cholinesterase inhibitors, which have limited success because these drugs improve cognitive functions only in mild dementia and cannot stop the process of neurodegeneration. Besides drugs of this category show gastrointestinal side effects. As the cells of central and peripheral nervous system cannot regenerate, newer strategies are aimed at preserving the surviving neurons by preventing their degeneration. N-methyl-D-aspartate (NMDA) receptor-mediated glutamate excitotoxicity plays a major role in Aβ-induced neuronal death. Therefore, it was thought that NMDA receptors could be a promising target for preventing the sequence of AD. All the compounds synthesized originally in this class showed toxicity mainly because of their high similarity for NMDA receptors. Memantine (1-amino adamantane derivative), an NMDA-receptor antagonist was reported to be effective in therapy of AD. Memantine is also reported to have valuable property in other CNS disorders such as Parkinsonism (PD), stroke, epilepsy, CNS trauma, amyotrophic lateral sclerosis (ALS), drug addiction and chronic pain [1]. Neuroimaging methods are important tools for assessing and monitoring pathological brain changes associated with progressive neurodegenerative conditions [3].

Recent AD treatments are all sign-relieving agents and closely rely on the use of acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine and galantamine). AChE inhibitors slow down the deprivation of the neurotransmitter acetylcholine, thus raising its bioavailability. A new approved AD treatment aims to decrease glutamate excitotoxicity which act as a non-competitive NMDA receptor antagonist to decrease glutamate-mediated neurotoxicity [4]. Blood vessels in the brain convey critical nutrients and eliminate metabolic waste products from the CNS [5].

Regular aerobic exercise, meditation, use of anti-inflammatory agents, use of estrogen by female and awareness reduce the risk of AD [6,7,8]. Topical work, both clinical and experimental, indicates that many neurodegenerative disorders frequently exhibit a corresponding metabolic dysfunction which may intensify neurological symptoms. It stands to reason accordingly that metabolic pathways may themselves contain able beneficial targets for central neurodegeneration (ND). Recent indication for metabolic dysregulation in AD, Huntington's disease, and PD discusses numerous potential mechanisms that may underlie the potential relationships between metabolic dysfunction and etiology of nervous system deterioration. We also emphasize some major signalling pathways concerned in the link between marginal metabolism and the CNS that are latent targets for upcoming therapies. It is possible that in the near future, therapeutics with combinatorial neuroprotective and eumetabolic performance may acquire higher efficacies compared to take away pluripotent remedies [9]. Each year an approximate 42 million people worldwide bear a mild traumatic brain injury (MTBI) or concussion. Other cruel traumatic brain injury (TBI) is a well-

recognized risk aspect for array of neurodegenerative diseases with AD, PD and ALS. The role of MTBI in hazard of PD or ALS is less well conventional. Rhythmic MTBI and cyclic sub-concussive head trauma have been linked to bigger risk for a range of ND including chronic traumatic encephalopathy (CTE). CTE is a single neurodegenerative tauopathy first described in boxers but more just described in a range of contact sport athletes, military veterans, and civilians showing to cyclic MTBI. Studies of repetitive MTBI and CTE have been limited by referral prejudice, lack of agreement clinical criteria for CTE, challenges of quantifying MTBI disclosure, and prospective for difficult. The occurrence of CTE is indefinite and the amount of MTBI or sub-concussive strain contact required to create CTE is imprecise. The epidemiology of MTBI, post-TBI dementia, PD, and CTE while prominence procedural challenges and vital budding instructs to investigate in this field [10]. Oxidative stress and mitochondrial dysfunctions have also been widely reported in patients with AD.

2. Causes of AD: The genetic structure of an entity also take part in considerable role in early and late – onset AD. Consequently, aging is one of the main factors for AD. Other factors also boost the risk of AD such as cardiovascular and cerebrovascular disease, depression, traumatic head injury, family history of dementia, smoking, presence of APOE-e4 allele, and higher parental age. Three main genes are involved in early onset AD: amyloid precursor protein (APP), presenilin 1(PSEN1), and presenilin 2 (PSEN2). The apolipoprotein E (APOE) E4 allele has been found to be a main risk factor for late-onset Alzheimer disease (LOAD). In addition, several other genes have been found that might be probable risk factors for AD, including clusterin (CLU), complement receptor 1(CR1), phosphatidylinositol binding clathrin assembly protein (PICALM) and sortilin-related receptor (SORLI), triggering receptor expressed on myeloid cells 2 (TREM2) and cluster of differentiation 33 (CD33). Recognition of new AD related genes is significant for better thoughtful of the pathological mechanisms leading to neurodegeneration [11].

3. Risk Factors: There are many associated risk factors for AD like alcohol utilization, revelation to environmental pollutants and heavy metals and other disease states in body.

a) Alcohol consumption is found to be strongly connected with general cognitive problems [12].

b) Exposure to various heavy metals may begin and uphold neurological dysfunctions and guide to AD.

Table 1 summarizes the roles of diverse heavy metals in causing neuronal abnormalities. Many metals ions in living system regulate proper proteins folding, thus any disturbance in its concentration causes grave pathological problems such as ND. Due to disparity of Fe, Zn, Cu ions concentration the oxidative stress and misfolding of proteins also increases which ultimately leads to neurodegeneration and also act as responsible factor for whole brain damage [13].

c) Down's syndrome: Down syndrome arises in individuals carrying an extra copy of chromosome 21 and is associated with a greatly increased risk of early-onset AD. It is thought that this risk is conferred by the presence of three copies of the gene encoding Alzheimer β-APP [14].

d) Role of benzodiazepines: The short-term effects of benzodiazepines on memory are well recognized and are assumed in the long term. There are numerous studies reported so far concerning benzodiazepine use and the risk of dementia disorders [15].

Benzodiazepines can decrease BACE-1 and γ-secretase activity and slow down the accumulation of Aβ oligomers in the brain. Since astrocytes located in the area of amyloid plaques could have gamma aminobutyric acid (GABA)-secreting activity, patients with pre-dementia lesions could be at amplified risk of presenting with more obvious damaging cognitive effects of benzodiazepines. After all, due to the neural compensation and cognitive reserve concepts, some subjects could manage with initial lesions by developing different networks. By lowering the brain activation level, benzodiazepines could limit this capacity [15].

4. Symptoms of AD: Depending upon the degree of cognitive impairment, AD has 3 steps (1) Preclinical or mild (2) Moderate and (3) Late stage. Each stage has different symptoms. As in preclinical stage most patients suffer from long term memory loss even though they do not show other AD symptoms. Later, this is followed by language disorder and impairment of visuospatial skills (APOE genotype is associated). In case of mid stage, the patients show neuropsychiatric symptoms like social withdrawal, agitation, psychosis, wandering, apathy, and disinhibition. Symptoms like Dyspraxia, sleep disturbance, olfactory dysfunctions and extrapyramidal motor signs such as akathisia (A rating scale for drug-induced akathisia), dystonia, parkinsonia occurs in late stage of AD [16,17,18].

5. Promotion and Progression of AD

Early onset AD: Incident of familial Alzheimer's disease (FAD) represents the marginal (5%–10%) of all AD cases. Familial early onset Alzheimer's disease (EOAD) can be characterized by the Mendelian inheritance pattern; but, EOAD patients have also been reported without any family history (termed sporadic EOAD). Three genes are measured as the chief risk factors for EOAD: APP, PSEN1, and PSEN2. Mutations in these genes might result in change of amyloid beta (Aβ) production, primary apoptosis of the neurons and dementia [19,20,21,22].

Late-onset AD: Detection of SNP-SNP interface played an important role in better perceptive genetic basis of LOAD [23]. The APOE gene, situated on chromosome 19, is a main genetic risk factor for LOAD, and its importance has been validated from population studies. ApoE protein is the major cholesterol carrier in the brain, which can be involved in neuronal maintenance and repair. ApoE binds to several receptors on the cell surface, which are involved in lipid delivery and transport, glucose metabolism, neuronal signalling, and mitochondrial function. Usually, ApoE binds to Aβ peptide and play a role in its clearance [24].

In the past decade, the centre of attention of drug discovery and development labours has shifted toward DMTs for AD; that is, treatments whose aspire is to concern the causal disease process by impacting one or more of the many brain changes quality of AD. These treatments could slow the development of the disease or hold-up its onset [25].

BIN1 appearance levels are amplified in human brain and are associated with later disease onset and shorter disease duration in AD patients [26,27]. Extensive confirmation indicates that many trials contribute to AD succession, together with oxidative stress, tenderness, and transformed cholesterol metabolism. The brain's high lipid content makes it mainly exposed to oxidative species, with the subsequent improvement of lipid peroxidation and cholesterol oxidation, and the consequent formation of

end products, mostly 4-hydroxynonenal and oxysterols, correspondingly from the two processes. The chronic provocative trial observed in the AD brain includes activation of microglia and astrocytes, jointly with development of inciting molecule and free radical release. Beside with glial cells, neurons themselves have been found to contribute to neuroinflammation in the AD brain, by portion as sources of inflammatory intermediaries. Oxidative stress is warmly associated with neuroinflammation, and a nasty circle has been found to connect oxidative stress and inflammation in AD. At the side of oxidative stress and inflammation, transformed cholesterol metabolism and hypercholesterolemia also extensively donate to neuronal damage and to evolution of AD. Rising indication is now consolidating the hypothesis that oxidized cholesterol is the driving force after the development of AD, and that oxysterols are the link connecting the disease to altered cholesterol metabolism in the brain and hypercholesterolemia; this is because of the capacity of oxysterols, unlike cholesterol, to cross the BBB. The key role of oxysterols in AD pathogenesis has been powerfully supported by investigations indicating their participation in modulating neuroinflammation, Aβ accumulation, and cell death [28].

Inflammatory and immune responses have a major role in its growth and progression. A number of the genetic loci connected with AD risk enclose genes with known roles in inflammation, the complement system and the immune response in general (ABCA7, CLU, CRI, MS4A4E/MS4A6A, CD33, EPHA1, HLA-DRB5, HLA-DRB1, INPP5D, MEF2C and TREM2). Pathway analysis of GWAS data have celebrated the immune response as important in AD, an incorporated network analysis of genome and transcriptome data recognized the immune and microglia module for AD, and TYROBP as the driver gene for this module [29,30].

Patients with ND often accept psychiatric diagnoses either because their ND has a psychiatric prodrome or because neuropsychiatric symptoms of the ND are misguided for those of a major psychiatric disorder. Both patterns are seen in AD, which has a poorly understood relationship with depression [31]. Depression or apathy in patients with amnestic-MCI increases the risk of continuing to AD. Apathy, but not depression, predicts which patients with amnestic-MCI will progress to AD. Thus, apathy has a vital impact on amnestic-MCI and should be considered a mixed psychiatric disturbance related to ongoing AD neurodegeneration [32].

Since last decade, homocysteine has been regarded as a sign of cardiovascular disease and an exact risk factor for many other diseases. Homocysteine is biosynthesized from methionine through multiple steps and then goes through one of the two major metabolic pathways: remethylation and transsulfuration. Hyperhomocysteinemia is a state in which too much homocysteine is present in the body. The main cause of hyperhomocysteinemia is a dysfunction of enzymes and cofactors associated with the process of homocysteine biosynthesis. Previous causes include profligately methionine intake, certain diseases and side effects of some drugs. Hyperhomocysteinemia is a trigger for many diseases, such as atherosclerosis, congestive heart failure, age-related macular degeneration, AD and hearing loss. There are many studies showing a constructive relationship between homocysteine level and various symptoms [33].

The role of ApoE on chromosome 19 has been frequently defined. Defensive factors consist of ApoE-2 genotype, history of estrogen replacement therapy in postmenopausal women, higher educational level, and

history of use of nonsteroidal anti-inflammatory agents. The most proximal brain events connected with the clinical expression of dementia are progressive neuronal dysfunction and loss of neurons in specific regions of the brain [34].

The role of pesticides in alterations experiential in cognitive functions and AD has been suggested based on epidemiological studies, but the mechanisms have been poorly explored [35]. Pesticides are known neurotoxins. Most pesticides share a number of qualities, such as the capacity to bring on oxidative stress, mitochondrial dysfunction, α-synuclein fibrillization and neuronal loss [36].

In Etiology of AD, involvement of Aβ plaque accumulation and oxidative stress in the brain has important roles. Numerous nanoparticles such as titanium dioxide, silica dioxide, silver and zinc oxide have been experimentally using for treatment of ND. There has been a vast attention on grouping of antioxidant bioactive compounds such as selenium (Se) and flavonoids with the oxidant nanoparticles in AD [37].

Two hypotheses have been most studied for AD development. One is related to the overproduction of the Aβ peptide. According to this, neurofibrillary tangles (NFTs) result from the onset of amyloid deposits as Aβ plaques. While the second hypothesis suggests that the hyperphosphorylation of the Tau protein and its subsequent deposition as NFTs is the ultimate reason for the disease. The amyloid flow hypothesis establishes that Aβ aggregation initiates the brain damage leading to memory loss and to AD [38].

Women reportedly make up two-thirds of AD dementia sufferers. Many estimates regarding AD, but, are based on clinical series lacking autopsy confirmation. Within the neuropathologically diagnosed AD cohort, the overall number of women and men did not differ. Men were younger at onset of cognitive symptoms, had shorter disease duration, and more often had different (non-amnestic) clinical presentations. The frequency of autopsy-confirmed AD among women and men stratified by age at death revealed an inverse U-shaped curve in men and a U-shaped curve in women, with both curves having inflections at approximately 70 years of age. Provincial counts of neurofibrillary tangles differed in women and men, especially when examined by age intervals. Men were more often classified as hippocampal sparing AD, whereas limbic predominant AD was more common in women. Men and women did not differ in frequency of MAPT haplotype or APOE genotype [39]. The strongest risk factor for AD is the increasing age [40]. The impact of sex differences on AD risk between women and men, however, has been erratically interpreted [41,42]. A mathematical algorithm based upon compactness and delivery of neurofibrillary tangle counts to classify three neuropathologic subtypes of AD: hippocampal sparing AD, typical AD, limbic predominant AD [43].

6. Mitochondrial dysfunctions in AD: Multiple factors are known to cause mitochondrial dysfunction. These factors include aging, increased free fatty acids, hyperglycemia, polymorphisms and DNA mutations in mitochondrial genome and mutant protein(s) organization with mitochondria. Dysfunctional mitochondria produce reduced ATP, decreased biogenesis, impaired β-oxidation and increased reactive oxygen species. These events may add to diabetes, obesity and insulin conflict at last causing AD in elderly individuals [44].

The brain of patients affiliated with AD present a significant extent of oxidative damage associated with the unusual marked build-up of Aβ and the deposition of neurofibrillary tangles [45]. Growing evidence

suggests an important role played by biometals including iron, zinc and copper in Aβ and neurodegeneration [46].

7. Potential treatment and prevention strategies for AD: Emerging evidence suggests that a low-carbohydrate, high-fat ketogenic diet may help to mitigate the damage associated with these pathologies. The ketogenic diet could improve the effects of impaired glucose metabolism by giving ketones as an additional energy source. In addition, this diet may help to decrease the accumulation of amyloid plaques while reversing Aβ toxicity. Research has begun to identify early fundamental mechanisms in AD that could be targeted by new prevention strategies. Glycation of the ApoE protein leads to impaired carrying of important lipids, including cholesterol, to the brain, resulting in lipid deficiencies that could explain progression to the later pathologies of the disease [47].

7.1 Plasma exchange for AD: Earlier studies have shown that treatment with plasma exchange with therapeutic albumin replacement in AD induced the mobilization of plasma and cerebrospinal fluid Aβ protein. It was associated with an improvement in memory and language functions, as well as the stabilization of brain perfusion, which persisted after treatment discontinuation [48].

7.2 Role of GPR40: G-protein coupled receptor 40 (GPR40) is also known as free fatty acid receptor. It is a typical 7 transmembrane receptor and currently the natural receptor of the saturated or unsaturated long-chain fatty acids. It could trigger the intracellular signalling pathway when associated with the free long-chain fatty acids, thereby controlling physiological function of the cells [49].

7.3 Role of Erythropoietin: Currently available treatments provide some symptomatic relief but fail to modify primary pathological processes that underlie the disease. Erythropoietin (EPO), a hematopoietic growth factor, acts primarily to stimulate erythroid cell production, and is clinically used to treat anaemia. EPO has evolved as a therapeutic agent for neurodegeneration and has improved neurological outcomes and AD pathology in rodents. Conversely, penetration of the BBB and negative hematopoietic effects are the two major challenges for the therapeutic development of EPO for chronic ND like AD. The transferrin receptors at the BBB, which are responsible for transporting transferrin-bound iron from the blood into the brain parenchyma, can be used to shuttle therapeutic molecules across the BBB [50].

In vitro studies demonstrated that some of the molecules processed remarkable inhibitory activity against phosphodiesterase 4D (PDE4D), strong intracellular antioxidant capacity, potent inhibition of metal-induced aggregation of Aβ, and potential BBB permeability [51].

7.4 SiRNA therapy: Gene therapy represents a capable treatment for the AD. Yet, gene delivery to brain lesions through systemic administration remains a big challenge. Researchers have developed a siRNA nanocomplex able to be specifically delivered to the amyloid plaques through surface modification with both CGN peptide for the blood–brain barrier BBB penetration and QSH peptide for *β*-amyloid binding. But, whether the as-designed nanocomplex could indeed improve the gene accumulation in the impaired neuron cells and ameliorate AD-associated symptoms remains unexplored. Nanocomplexes with siRNA against BACE1, the rate-limiting enzyme of A*β* production were prepared as the therapeutic siRNA of AD. The nanocomplexes exhibited high allotment in the A*β* deposits-enriched hippocampus, particularly in the neurons near the amyloid plaques after intravenous administration. In

APP/PS1 transgenic mice, the nanocomplexes down-regulated BACE1 in both mRNA and protein levels, as well as Aβ and amyloid plaques to the level of wild-type mice. Furthermore, the nanocomplexes significantly increased the level of synaptophysin and rescued memory loss of the AD transgenic mice without hematological or histological toxicity [52]. Tauopathies are a heterogeneous group of ND which involve perturbations, phosphorylation or mutations of the neuronal microtubule-binding protein Tau. Tauopathies are characterized by accumulation of hyperphosphorylated Tau leading to the formation of a range of aggregates including macromolecular ensembles such as Paired Helical filaments and NFTs whose morphology characterizes and differentiates these disease states. Why nonphysiological Tau proteins avoid the inspection normal proteostatic mechanisms and finally form these macromolecular assemblies is a central mostly unresolved question of cardinal importance for diagnoses and potential therapeutic interventions. The reaction of the Ubiquitin–Proteasome system, autophagy and the Endoplasmic Reticulum-Unfolded Protein response in Tauopathy models and patients, useful interactions of components of these systems with Tau, as well as the effects of pathological Tau on these systems which eventually lead to Tau aggregation and accumulation are also discussed. These interactions point to potential disease biomarkers and future potential therapeutic targets [53].

7.5 Natural Compounds effective against AD (Table 2)

The therapeutic drugs for AD are predominantly derived from the alkaloids of plant phytochemicals. These drugs, such as galantamine and rivastigmine, attenuate the trash in the cholinergic system but, as the alkaloids occupy the most dangerous end of the phytochemical spectrum (indeed they function as feeding deterrents and poisons to other organisms within the plant itself), they are often associated with unpleasant side effects. In addition, these cholinesterase inhibiting alkaloids target only one system in a disorder, which is typified by multifactorial deficits. The more terpene like as *Ginkgo biloba, Ginseng, Melissa officinalis* (lemon balm) and *Salvia lavandulaefolia* (sage) and phenolic (resveratrol) phytochemicals; arguing that they offer a safer alternative and that, as well as indicating efficacy in cholinesterase inhibition, these phytochemicals are able to target other salient systems such as cerebral blood flow, free radical scavenging, anti-inflammation, inhibition of amyloid-β neurotoxicity, glucoregulation and interaction with other neurotransmitters (such as γ-aminobutyric acid) and signalling pathways [54].

Recent discoveries point to the significance of curcumin, a natural anti-inflammatory agent, in controlling oxidative stress and improving cholinergic function in the brain, even though the mechanisms underlying these actions are strange. We investigated the effects of curcumin in cultures of neuronal cells. Curcumin exert a strong neuroprotective effect in N_2a cells, thus preventing toxicity by oxidative agents H_2O_2 and Fe^{+3}. This is supported by that curcumin control the neurodegenerative effects of both oxidative agents, relieving cells from the loss of neuritogenic processes induced by prooxidants. In addition, curcumin was capable to slow down the tau aggregation curve and disassemble tau pathological oligomeric structures. Curcumin could be a potential compound for prevention of cognitive disorders related with AD [55].

Rutin (quercetin-3-O-rutinoside) is a multifunctional natural flavonoid glycoside with reflective effects on the various cellular functions under pathological conditions. Due to the ability of rutin and its metabolites to cross the BBB, it has also been shown to modify the cognitive and various behavioural symptoms of ND

[56]. Another flavonoid 'Pinocembrin' is a molecule remote from honey and propolis. It has flexible pharmacological and biological manners including antimicrobial, anti-inflammatory, antioxidant, and anticancer activities as well as neuroprotective effects against cerebral ischemic injury [57].

The bromelain (a plant cysteine protease obtained from pineapple stems) has ability to interact *in vitro* with synthetic Aβ42 aggregates in the CSF. This action of bromelain suggests its potential use in the therapy of AD [58].

Ferulic acid (FA) is an antioxidant naturally present in plant cell walls with anti-inflammatory activities and it is able to act as a free radical scavenger [59]. FA has pleiotropic biological activities, including anti-inflammatory and antioxidant properties, suggesting that long-term administration could hold-up the progression of AD. It has been, indeed, reported that the long-term administration of FA to mice protected against learning and memory deficits induced by centrally administered β-amyloid [60]. FA meaningfully attenuated peroxyl radical-induced cell death in hippocampal neuronal cells and reduced, in a dose-response manner, both protein oxidation and lipid peroxidation caused by hydroxyl radicals, which are all consequences of oxidative stress [61]. The effect of FA administration in female transgenic mice, which over express the Swedish mutation of APP together with presenilin 1 (PS1) was deleted in exon 9. It was found that six months of FA treatment significantly condensed the cortical levels of Aβ peptides.

Quercetin is a flavonoid with remarkable pharmacological property and promising therapeutic potential. It is widely spread among plants and found commonly in daily diets primarily in fruits and vegetables. Neuroprotection by quercetin has been reported in some *in vitro* studies. It has been shown to protect neurons from oxidative damage while dropping lipid peroxidation. In accretion to its antioxidant properties, it inhibits the fibril creation of amyloid-β proteins, counteracting cell lyses and inflammatory surge pathways [62].

Catechins are known for antioxidative effects and in conferring protection from neurodegeneration. As mentioned beyond, increased oxidative stress is involved in late-onset neurodegenerative disorders [63].

Baicalein is a natural compound belonging to the class of flavonoids obtained from the Chinese herb *Scutellaria baicalensis*. It was reported that Baicalein inhibits the aggregation of Tau proteins on neurons [64]. Like baicalein, luteolin is also a flavone found in various foods, has defensive and therapeutic value for neurodegenerative diseases with AD. Such effect of luteolin has been linked to its aptitude to reduce neuroinflammation. Luteolin also has other biological functions, including antioxidant activity that may provide added benefit for prevention of AD. The exact mechanisms of inflammatory pathways involved in AD pathogenesis need to be further understood to consume luteolin and many former available anti-inflammatory agents to avoid and treat AD [65].

7.6 Inhibitors of AD: The most progressed mechanism-based therapies to date consist of immunological interventions to clear Aβ oligomers and pharmacological drugs to reduce the secretase enzymes that produce Aβ, namely β-site amyloid precursor-cleaving enzyme (BACE) and γ-secretase [66]. The BACE1 is the transmembrane aspartyl protease that cleaves APP at the β-site. The chronological proteolytic cleavage of APP by BACE1 and γ-secretase leads to the construction and release of Aβ peptide in the

brain. Consequently, amyloidogenic secretases are the key therapeutic targets being currently explored for AD-modifying interference. Quite a few studies report that BACE1 inhibitors hold great latent as a potential strategy in declining Aβ brain concentrations, thus preventing the progression of AD [67]. A diversity of aminooxazoline derivatives, including a class of aminooxazoline xanthenes have been reported as BACE1 inhibitors [68,69]. Recent pharmacological therapy for AD includes the cholinesterase inhibitors (ChEIs) donepezil, rivastigmine, and galantamine and the NMDA receptor rival memantine. A number of AChE inhibitors have already been used for clinical treatments. Yet, other than normal situation, AChE is mostly hydrolyzed by BuChE in progressed AD. Explanation for an advanced level of BuChE and decreased level of AChE in the late stage of AD, expansion of careful BuChE inhibitor is of crucial importance [70].

Role of Berberine Derived (Ber-D) inhibitor: A natural product berberine-derived (Ber-D) is a multifunctional inhibitor used in reorganizing celluloversatile toxicity of AD. Ber-D inhibits metal-dependent and -independent Aβ aggregation, which is supported by in silico studies. Ber-D treatment averts mitochondrial dysfunction and related neuronal toxicity fundamental to premature apoptosis. These key multifunctional attributes make Ber-D a potential therapeutic candidate to reorganize multifaceted Aβ toxicity in AD [71]. In recent times, some other natural products like brazilin, luteolin, tanshinone, and apigenin have been evaluated to consider the accent of Aβ toxicity [72]. Mitochondrial dysfunction induced by Aβ is one of the key contributors to versatile toxicity in AD.

8. Conclusion: Current review highlights molecular mechanisms connecting Ca^{2+} disruptions to AD pathology and shows more precise therapeutic agents' target channels on the membranes of intracellular organelles such as the ER, mitochondria, and lysosome which offer new hope for the anticipation and dealing of AD. Till now, therapeutic drugs for AD are largely derived from the alkaloid class of plant phytochemicals. Natural compounds are safe because they don't produce any side effects therefore present study provides research gaps to young minds for attempting therapeutic models against AD, keeping in view the molecular mechanisms and gene mutilations.

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10. Conflict of Interest: There is no conflict of interest between authors.

11. Abbreviations:

AD: Alzheimer disease; ND: neurodegenerative disease; BBB: blood–brain barrier; CNS: Central Nervous System; PD: Parkinson's disease; AchE: acetylcholinesterase; NMDA: N-methyl-D-aspartate; ALS: amyotrophic lateral sclerosis; VaD: Vascular Dementia; CBF: cerebral blood flow; NVU: neurovascular unit; VSMCs: vascular smooth muscle cells; MTBI: mild traumatic brain injury; TBI: traumatic brain injury; CTE: chronic traumatic encephalopathy; APP: amyloid precursor protein; PSEN 1: presenilin 1; PSEN2: presenilin 2; APOE: apolipoprotein; LAOD: late-onset Alzheimer's disease; GWASs: genome-wide association studies; CR1: complement receptor 1; PD: Parkinson's disease; PICALM: phosphatidylinositol binding clathrin assembly protein; SORLI: sortilin-related receptor; TERM2: triggering receptor expressed on myeloid cells 2; CD33; cluster of differentiation 33; FAD: familial

Alzheimer's disease; EOAD: early onset Alzheimer's disease; SNPs: single nucleotide polymorphisms; MCI: mild cognitive impairment; BACE: β-site amyloid precursor-cleaving enzyme; ChEIs: cholinesterase inhibitors; NFTs: neurofibrillary tangles; Aβ: amyloid β; DM: diabetes mellitus; TLR4: Toll-like receptor 4 ; FA: Ferulic acid; RA: Rheumatiod arthritis.

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