Review

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Review

Alzheimer's Disease: Molecular Mechanisms of the Disease and Involved Factors — A Comprehensive Narrative Review

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. Its hallmarks are extracellular amyloid-beta (Aβ) plaques and intracellular hyperphosphorylated tau forming neurofibrillary tangles, leading to synaptic dysfunction and neuronal loss. Despite extensive research, the mechanisms driving these proteinopathies and the contribution of genetic, molecular, and environmental factors remain unclear. Objective: This review summarizes the molecular mechanisms underlying AD and the factors influencing its onset and progression. Methods: A narrative review of peer-reviewed studies from PubMed, Scopus, and Web of Science was conducted. Relevant articles on neuropathology, molecular pathways, genetic susceptibility, oxidative stress, mitochondrial dysfunction, neuroinflammation, and metabolic and lifestyle risk factors were analyzed. Results: AD is marked by Aβ accumulation and tau pathology, causing synaptic and neuronal loss. Key mechanisms include abnormal amyloid precursor protein processing, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and calcium dysregulation. Genetic variants (APP, PSEN1, PSEN2, APOE ε4) increase risk, while aging, cardiovascular disease, diabetes, and lifestyle factors further influence disease onset and progression. Conclusion: AD arises from complex interactions among molecular and environmental factors. Understanding these pathways is essential for developing preventive strategies and effective therapies, with personalized approaches offering future promise.

Keywords: Alzheimer's disease; inflammation; risk gene mutation; microglial over-activation; oxidative stress; diets

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Introduction

1.1. Background

Alzheimer's disease (AD) is one of the most prevalent chronic, progressive, and irreversible neurodegenerative disorders, characterized by a gradual decline in learning and memory, language and speech abilities, and motor function [1–4]. The pathological hallmarks of AD include the extracellular accumulation of amyloid-beta (Aβ) peptides and intracellular aggregation of hyperphosphorylated tau proteins forming neurofibrillary tangles (NFTs) [5–9]. These pathological changes result either from excessive production or impaired clearance of these proteins and typically begin several years before the appearance of clinical manifestations [7]. In addition to amyloid and tau pathology, neuroinflammation and oxidative stress (OS) are central contributors to disease progression, leading to plaque formation, synaptic loss, neuronal degeneration, and ultimately neuronal death [6,10–12].

AD is the most common cause of dementia, accounting for approximately 60–80% of cases worldwide [7,12,13]. The disease usually begins with mild cognitive impairment and nutritional disturbances and progresses to severe disability, multiorgan complications, and death [14]. Globally, AD is the fifth leading cause of death, typically occurring 4–8 years after diagnosis, and remains the leading cause of dementia [5,15]. Early-onset AD (EOAD), which develops before 65 years of age, is predominantly familial and accounts for less than 5% of cases [16–19]. In contrast, late-onset AD (LOAD), which represents more than 95% of cases, is largely sporadic and arises from complex interactions between genetic susceptibility and environmental factors [20–22].

Limited understanding of the multifactorial mechanisms underlying AD has hindered the development of effective disease-modifying therapies [23]. Although several drugs have been developed based on the amyloid hypothesis, most provide only symptomatic relief and do not significantly alter disease progression [24–27]. Therefore, comprehensive evaluation of disease mechanisms, identification of research gaps, and clarification of inconsistent findings are essential for developing effective preventive and therapeutic strategies. This review aims to discuss the mechanisms and contributing factors involved in the development and progression of AD.

2. Stages of AD

The staging of AD is determined by disease severity and the specific brain regions affected [27]. Amyloid deposition typically begins in the neocortex during the preclinical stage. Neuropathological changes may start 15–20 years before clinical symptoms become evident [7]. Disease progression ranges from an asymptomatic pathological phase to symptomatic stages characterized by cognitive decline, organ dysfunction, and eventual failure. Broadly, patients progress from normal cognitive function (preclinical stage) to subtle impairments and then to overt dementia [13].

2.1. Preclinical Stage

The preclinical stage is characterized by the accumulation of Aβ in the brain, which may precede clinical dementia by 15 to 20 years [7,27]. During this phase, individuals remain cognitively normal despite ongoing pathological changes [22,28]. Biomarkers include early histopathological alterations and elevated levels of Aβ, total tau (T-tau), phosphorylated tau (P-tau), and inflammatory cytokines [24,28]. This prolonged and silent phase underscores the importance of biomarker-based early detection strategies [23,25].

2.2. Clinical Stage

The clinical stage is marked by progressive accumulation of misfolded proteins and neuronal degeneration, leading to cognitive and functional impairment. This stage is subdivided according to severity.

2.2.1. Prodromal Stage

The prodromal stage corresponds to mild cognitive impairment (MCI), during which individuals experience subtle memory deficits, reduced attention, and difficulty concentrating, while still maintaining independence in daily activities [8,27,28]. Disease duration and progression are influenced by age, sex, and the presence of the APOE ε4 allele [28]. Cerebrospinal fluid biomarkers and amyloid PET imaging are often positive during this stage [27].

2.2.2. AD Dementia Stage

The dementia stage is characterized by marked impairment in memory, thinking, social functioning, and independence [27]. It includes mild, moderate, and severe phases. In the mild stage, individuals retain partial independence but experience noticeable memory loss, misplacement of objects, missed appointments, and word-finding difficulties [27].

In the moderate stage, cognitive deficits intensify, and patients may forget significant aspects of their personal history [24]. In the severe stage, profound memory loss is accompanied by impaired communication, visuospatial dysfunction, motor impairment, and loss of reflexes, as summarized in Table 1 [13,24].

Table 1. Stages and Manifestations of AD.

Stage		Manifestations	Citation
Preclinical	One	No memory loss, but PET imaging or CSF analysis identified amyloidosis in the entorhinal region and hippocampus. It is an asymptomatic phase and lasts for about 6–10 years before progressing to the clinical stages. Age, sex, Apo E status, and other factors determine the duration of this stage	[7,22,27,28]
	Two	In this stage, amyloidosis occurs in the entorhinal region, and the hippocampus is associated with forgetting names and misplacing objects. It is AD with **VMML**	[7,8,22]
Clinical Prodromal	Three	Amyloidosis spreads to more areas in the brain, including the temporal, frontal, and parietal cortices, cerebrovascular problems, increasing forgetfulness, loss of concentration, decreased work performance, getting lost, and difficulty in finding the right words for objects or places. It is **AD with MCI**	[8,22,27]
Dementia	Four	Significant impairment in individual, social, and occupational functioning, loss of independence to perform activities. Amyloidosis spreads to more areas of the brain, causing cerebrovascular problems**,** concentration difficulties, and forgetting recent events. It is **AD with MD**.	[7,27]
Mild	Five	In this stage, amyloidosis spreads to the entire cortex, including sensory, motor, and other brain areas. Cerebrovascular problems and major memory deficiencies are also observed. Needing assistance, forgetting details like address or phone number, not knowing the time, and inability to know places are also manifested. **It is AD with MSD**	[27]
	Six	Neuritic plaques and NFTs are severely accumulated in the entire brain area. Forgetting names/family members, recent events, urine incontinence, difficulty in speaking and eating, anxiety, depression, and delusions are common. **It is AD with SD**	[24]
Sever	Seven	The problem is getting more severe, characterized by the inability to speak or walk. Loss of motor skills (apraxia), perception (agnosia), and bladder reflex. It is nearing death and **is AD with VSD**	[13,24]

ApoE: Apolipoprotein E; CSF: Cerebrospinal fluid; MCI: Mild cognitive impairment; MD: Moderate dementia; MSD: Moderately severe dementia; NFTs: Neurofibrillary tangles; PET: Positron emission tomography; SD: Severe dementia; VMML: Very mild memory loss; VSD: Very severe dementia.

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3. Magnitude and Burden of AD

The global prevalence of AD is rising and represents a major public health concern [30,31]. Currently, an estimated 50–55 million individuals worldwide live with AD or related dementias, and this number is expected to double within the next two decades [15,23,32–34]. Approximately 10 million new cases are diagnosed annually [35]. In the United States, 6.08 million individuals were living with AD in 2017, and projections estimate this number will reach 15 million by 2060 [36]. Globally, more than 75% of cases remain undiagnosed, particularly in low- and middle-income countries [15]. In Africa, 2.76 million people aged 50 years and older were living with dementia in 2010, with the highest proportion in Sub-Saharan Africa [37]. In Ethiopia, 8,316 deaths were attributed to AD and dementia in 2016 [38].

The socioeconomic burden of AD increases with disease severity [39]. Annual per capita costs range from US$468.28 in mild AD to US$171,283.80 in severe AD [39]. In the United States, the annual cost of care was US$28,078 in 2016 and is projected to reach US$1.4 trillion [40]. Globally, the economic burden is expected to reach US$4.7 trillion in 2030, US$8.5 trillion in 2040, and US$16.9 trillion in 2050, with 65% of the burden occurring in low- and middle-income countries [39].

4. Alzheimer's Disease Risk Factors

Although Aβ plaques and NFTs define AD pathology, multiple modifiable and non-modifiable risk factors contribute to disease development [6,17]. Aging, genetic susceptibility, environmental exposures, blood–brain barrier (BBB) dysfunction, traumatic brain injury, vascular disorders, chronic diseases, inflammation, oxidative stress, sleep disturbances, impaired autophagy, anxiety, stress, unhealthy lifestyle, dietary habits, and physical inactivity are among the major contributors [17,42–51].

Aging is associated with increased histone deacetylase activity, reduced synaptic density, diminished astrocytic support, decreased melatonin secretion, increased oxidative stress, and heightened inflammation, all of which increase vulnerability to AD [53–55]. Environmental factors such as air pollution, heavy metals, pesticides, smoking, obesity, chronic stress, infection, and sedentary behavior further elevate risk [17,18,42]. Importantly, the combined effects of these factors often exceed their individual contributions [6,17].

5. Diagnosis of AD

Early diagnosis is crucial for initiating appropriate management and slowing disease progression [56,57]. Diagnosis relies on combined clinical evaluation, imaging techniques, and neurochemical biomarker analysis.

5.1. Imaging Techniques

Neuroanatomical changes are detectable 10–20 years before clinical symptoms emerge [34,58]. Non-invasive imaging modalities such as magnetic resonance imaging (MRI), optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) are used to detect Aβ deposition and structural brain alterations [59]. Retinal Aβ accumulation and thinning of the retinal nerve fiber layer can also be detected using OCT [59].

5.2. Clinical Manifestations

Structural and functional brain changes result in progressive cognitive impairment, language deficits, behavioral changes, and motor dysfunction [5,26]. Cortical thinning, ventricular enlargement, and regional brain atrophy are key diagnostic features [56,58,60,61]. Early Aβ deposition occurs in the frontal, parietal, and temporal lobes, including the hippocampus and entorhinal cortex [56,62], and later spreads to additional regions such as the basal ganglia and

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brainstem [63]. Common clinical manifestations include memory loss, difficulty performing daily tasks, depression, irritability, aggression, social withdrawal, and sleep disturbances [14,20,25].

5.3. Neurochemical Analysis

Biomarker analysis enables early detection before symptom onset [57]. Elevated pro-inflammatory cytokines (IL-1, IL-6, TNF-α, NF-κB) and reduced anti-inflammatory cytokines (IL-4, IL-10) are commonly observed [46,64,65]. CSF and serum levels of Aβ42, Aβ40, T-tau, P-tau, oxidative stress markers, and neurotransmitters support diagnosis and disease monitoring [66]. Combined clinical, imaging, and laboratory assessments improve diagnostic accuracy [6,67].

Amyloid-β and Tau Accumulation

Amyloidosis refers to the accumulation of amyloid-β (Aβ) in tissues [70]. In Alzheimer's disease (AD), Aβ accumulates in the brain parenchyma and cerebral vessels [71]. Extracellular insoluble Aβ plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau are the pathological hallmarks of AD [5,8,72]. Aβ plaques, derived from amyloid precursor protein (APP), typically form earlier than NFTs [15]. APP, encoded on chromosome 21 (21q21.2–3), is a membrane protein involved in neurogenesis, neuroprotection, and synaptic plasticity [72,73]. Mutations in APP enhance amyloidogenic processing and are linked to early-onset AD (EOAD) [74].

In the amyloidogenic pathway, APP is cleaved by β-secretase (BACE1), generating soluble APPβ and C-terminal fragment β (C99), which is subsequently cleaved by γ-secretase to produce Aβ peptides (mainly Aβ40 and Aβ42) and AICD. Aβ42 is more aggregation-prone and strongly associated with plaque formation [22,75,82]. In contrast, the non-amyloidogenic pathway involves α-secretase cleavage within the Aβ region, producing neuroprotective sAPPα [75–79].

PSEN-1 (chromosome 14q24.2) and PSEN-2 (chromosome 1q42.1) encode presenilin proteins, essential γ-secretase subunits [80]. Mutations in these genes increase Aβ production and are strongly associated with EOAD [6,23,75,78]. APP gene duplication, as seen in Down syndrome, further accelerates Aβ accumulation [85,86].

The APOE gene on chromosome 19q13.32 is the strongest genetic risk factor for late-onset AD (LOAD) [6,17,88]. APOE has three isoforms: APOE2, APOE3, and APOE4 [89]. APOE4 increases Aβ and tau accumulation, neuroinflammation, oxidative stress (OS), and synaptic dysfunction [23,77,88,91], whereas APOE2 promotes Aβ clearance and exerts neuroprotective effects [90–92]. Elevated cholesterol enhances γ-secretase activity and amyloidogenesis [93,96]. APOE polymorphisms, therefore, serve as important genetic biomarkers in LOAD [94].

Tau proteins stabilize microtubules, supporting neuronal structure and transport [99]. However, Aβ accumulation, ROS, mitochondrial dysfunction, calcium dysregulation, and kinase activation (GSK3β, Cdk5) induce tau hyperphosphorylation and NFT formation [67,100]. These aggregates disrupt microtubules and impair synaptic function [34]. Mutations in the MAPT gene (chromosome 17q21) increase tau deposition and familial AD risk [75,101].

Environmental factors such as diet, chronic stress, infection, smoking, and metabolic disorders interact with AD risk genes, promoting plaque and tangle accumulation, glial activation, oxidative stress, and neurodegeneration [6,11,99]. Major AD-related genes include BACE1, APP, PSEN-1, PSEN-2, MAPT, and APOE.

6.2. Neuroinflammation and Microglia Over-Activation

Beyond plaques and tangles, neuroinflammation is a central feature of AD [67]. Astrocytes and microglia normally maintain homeostasis and defend against injury [5,63,102–105]. However, chronic activation transforms microglia from resting (M0) to pro-inflammatory (M1) phenotypes, releasing cytokines that exacerbate pathology [33] (**Figure 1**).

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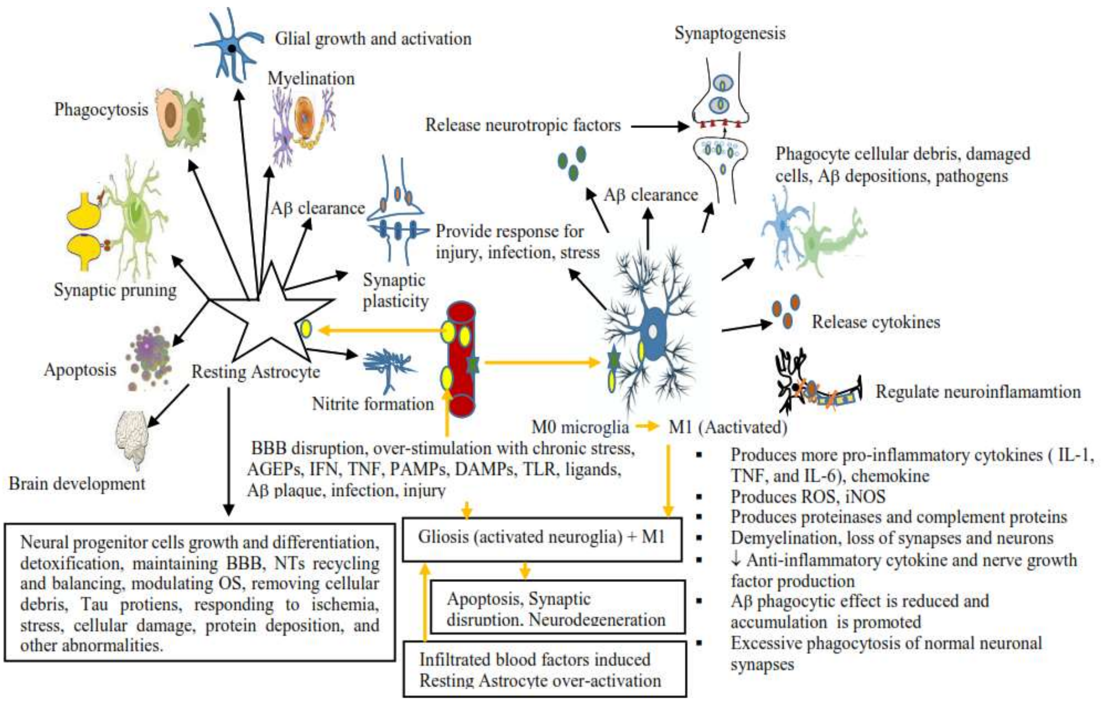

Figure 1. Normal Functions of Neuroglia and Their Roles in the Pathogenesis of AD. The yellow lines indicate that BBB disruption and other conditions induced by neuroglia over-activation cause AD-like pathologies. Aβ: Amyloid beta, AD: Alzheimer's disease, AGEPs: Advanced glycation end products, DAMPs: Damage-associated molecular pattern, IL: Interleukin, INF: Interferon, PAMPs: Pathogen-associated molecular pattern, TLR: Toll-like receptor, TNF: Tumor necrosis factor.

BBB disruption permits infiltration of peripheral cytokines and immune cells, amplifying glial activation and promoting Aβ deposition [33,106]. Although early microglial activation facilitates Aβ clearance, sustained inflammation impairs phagocytosis and enhances plaque and NFT formation [82,108] in such a way that there is bidirectional relationship between Aβ accumulation and neuroinflammation (**Figure 2**).

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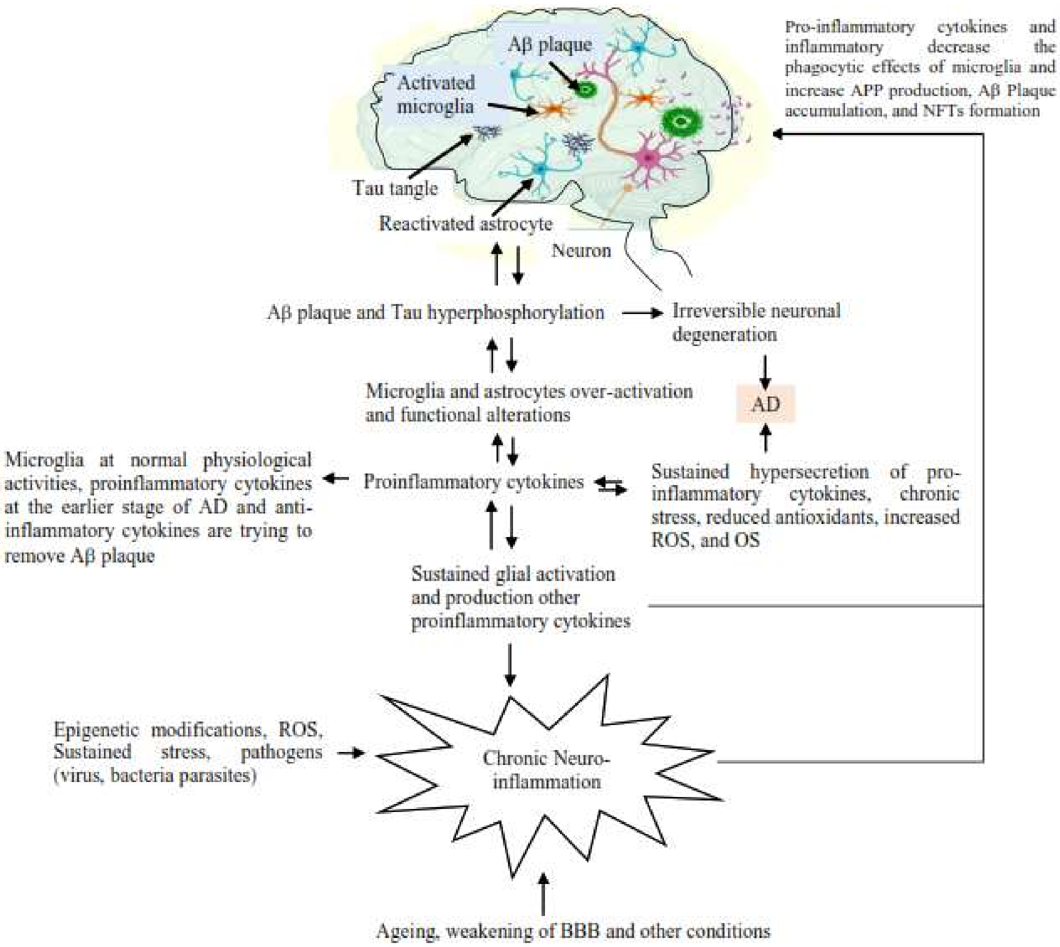

Figure 2. Multidirectional Linkage between Aβ Plaque, NFTs Formation, and Neuroglia Over-activation in Chronic Neuro-inflammation and AD Development. Aβ: Amyloid beta, AD: Alzheimer's disease, APP: Amyloid precursor protein, BBB: Blood-brain barrier, NFTs: Neurofibrillary tangles, OS: Oxidative stress, ROS: Reactive oxygen species, Tau: Tubulin-associated Unit.

Calcium dysregulation further amplifies inflammatory cascades by activating calcineurin and promoting cytokine release [66,110]. Microglial receptors TREM2 and CX3CR1 regulate phagocytosis of Aβ and tau (**Figure 3**). Wild-type TREM2 supports microglial survival, migration, and anti-inflammatory polarization [112–114], whereas TREM2 mutations impair Aβ clearance and increase AD risk [111,118,124]. Alterations in CX3CL1/CX3CR1 signaling similarly aggravate amyloid and tau pathology [125]. Neuroinflammation is therefore both an early and progressive contributor to AD [33,126].

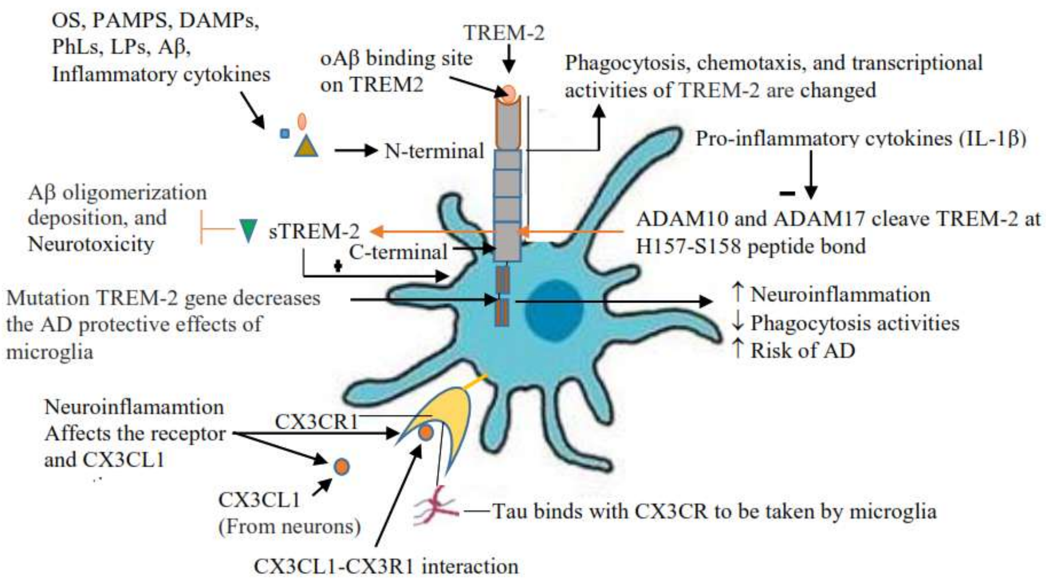

Figure 3. Roles of TREM2 and CX3CR1 in the Aβ and Tau Proteins Phagocytosis Effects of Microglia.AD: Alzheimer's disease, ADAM 17: a disintegrin metalloprotease 17, ADAM10: a disintegrin metalloprotease 10, BACE1: β-site APP cleaving enzyme 1, CX3CR1: Chemokine (C-X3-C motif) receptor 1, DAMPs: Damaged associated molecular patterns, IL: Interleukin, LPs: Lipopolysaccharides, oAβ: Oligomeized amyloid beta, OS: oxidative stress, PAMPs: Pathogen associated molecular patterns, sTREM-2: Soluble triggering receptor expressed on myeloid cells 2, TREM-2: Triggering receptor expressed on myeloid cells 2.

6.3. Oxidative Stress

Oxidative stress (OS), resulting from an imbalance between ROS and antioxidants, precedes and promotes amyloid and tau pathology [129]. Aβ induces ROS production through mitochondrial dysfunction, NADPH oxidase activation, and NMDA receptor overstimulation [99,128]. Conversely, OS enhances β-secretase activity, cholesterol accumulation, inflammatory signaling, and amyloidogenic APP processing [21,130].

Chronic stress activates the HPA axis, elevating cortisol, reducing neurogenesis, shrinking hippocampal volume, and promoting Aβ and tau pathology [17,127,133,134]. Mitochondrial impairment and cytochrome oxidase dysfunction further increase ROS [5,78,135]. OS therefore contributes to both initiation and progression of AD (**Figure 4**).

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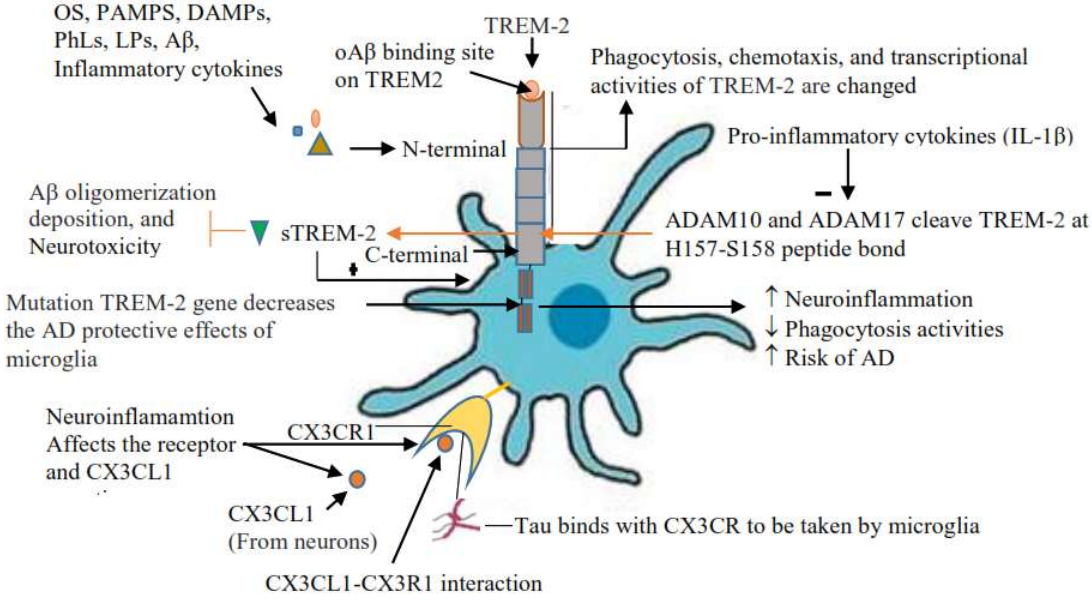

Figure 4. Roles of Oxidative Stress in the AD Pathogenesis. Oxidative stress uses different mechanisms in the Aβ and NFTs formation, which causes AD. AD: Alzheimer's disease, Aβ: Amyloid beta, APP: Amyloid precursor protein, CU: Copper, Fe: Iron, NFTs: neurofibrillary tangles, Tau: Tubulin associated unit, UV: ultraviolet, and Zn: Zinc.

6.4. Neurochemical Imbalance

Neurotransmitter imbalance underlies cognitive and behavioral symptoms in AD [136].

6.4.1. Dopamine

Dopaminergic projections from the VTA decline early in AD, contributing to cognitive and motivational deficits [64,138]. Receptor loss in the hippocampus correlates with symptom severity [54,139].

6.4.2. Serotonin

Reduced serotonin and receptor density (5HT1A, 5HT2A) are associated with aggression, depression, and cognitive decline [19,54,126]. Tau pathology in serotonergic nuclei exacerbates neuronal loss.

6.4.3. Acetylcholine

Cholinergic deficits are central to AD. Reduced acetylcholine (ACh), ChAT, and nicotinic receptors impair learning and memory, while increased acetylcholinesterase promotes Aβ aggregation [54,100,142]. ACh enhances Aβ phagocytosis via α7-nAChR [76,141].

6.4.4. GABA

Reduced GABA levels and receptor degradation contribute to agitation and cognitive impairment [54,70,143].

6.4.5. Glutamate

Glutamate dysregulation leads to NMDA receptor overactivation, calcium influx, excitotoxicity, and neuronal loss [147–155]. As summarized in **Figure 5**, astrocytic uptake increases synaptic glutamate, promoting hyperactivity and seizure susceptibility [150,157].

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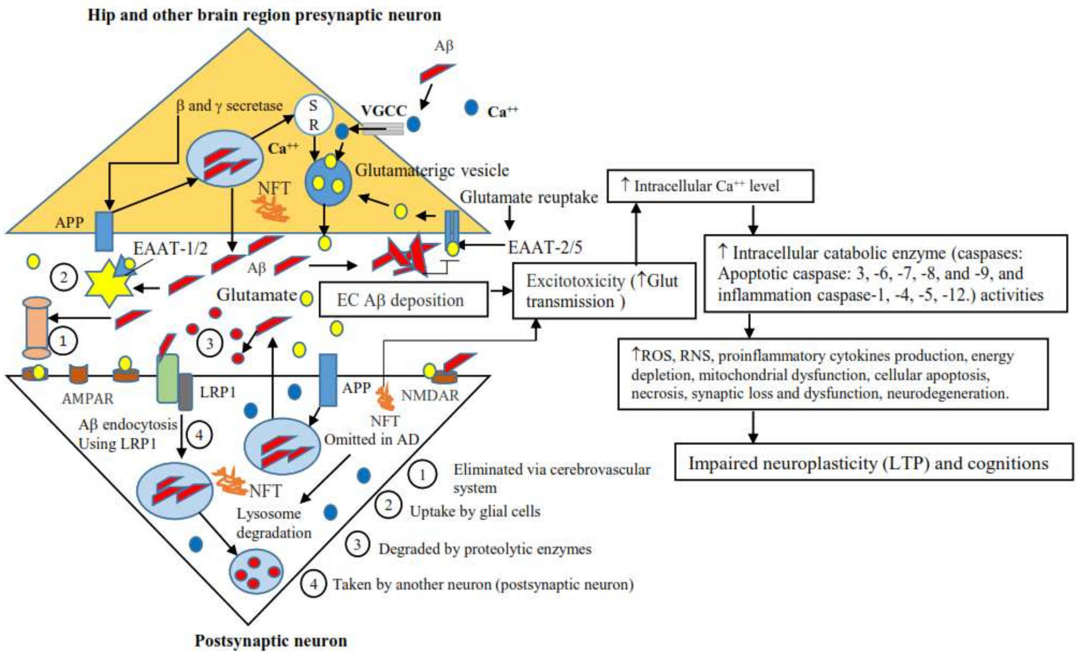

Figure 5. Neuronal hyperactivity-induced neuroplasticity and cognition Impairments. Aβ: Amyloid beta, AD: Alzheimer's disease, AMPAR:α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, APP: Amyloid precursor protein, EAAT: Excitatory amino acid transporters, EC: Extracellular, Glut: Glutamate, Hip: Hippocampus, LRP1: Low-density lipoprotein receptor-related protein 1, LTP: Long-term potentiation, NFT: neurofibrillary tangle, NMDAR: N-methyl- D-Aspartate receptor, RNS: Reactive nitrogen species, ROS: Reactive oxygen species, VGCC: Voltage-gated calcium channel.

6.4.6. Noradrenalin

Degeneration of locus coeruleus neurons reduces noradrenergic modulation of neuroinflammation and BBB integrity [19].

6.4.7. Melatonin

Melatonin exerts antioxidant, anti-inflammatory, and anti-amyloidogenic effects, reducing Aβ and tau pathology [52,162–165].

6.4.8. Cortisol

Elevated cortisol correlates with hippocampal atrophy, cognitive decline, and impaired feedback regulation [168–172].

6.4.9. Quinolinic Acid

The kynurenine pathway shifts toward neurotoxic metabolites such as quinolinic acid (QA), promoting NMDA-mediated excitotoxicity and tau phosphorylation [175–178]. Reduced serotonin and melatonin further exacerbate pathology (**Figure 6**).

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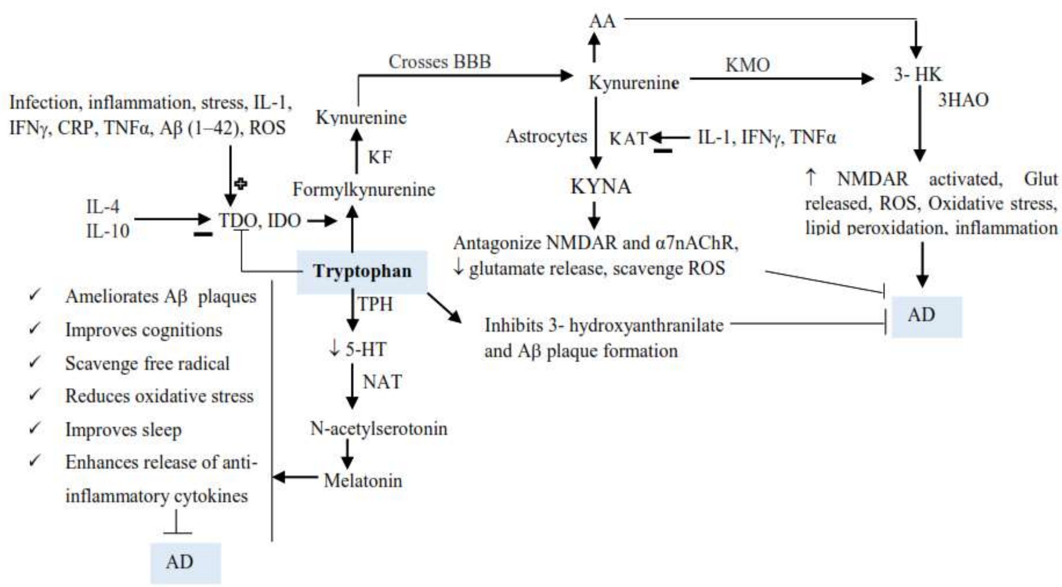

Figure 6. Roles of the Kynurenine pathway and its metabolites in the development of Alzheimer's disease. Tryptophan conversion to serotonin and then to melatonin, and production of KYNA from astrocytes, prevent AD development. AA: Anthranilic acid, Aβ: Amyloid beta, AD: Alzheimer's disease, CRP: C-reactive protein, Glut: Glutamate, 3-HK: 3-Hydroxykynurenine, 5-HT: 5-Hydroxy tryptophan, HAO: 3-hydroxy anthranilate 3, 4-dioxygenase, IDO: Indoleamine 2, 3-dioxygenase, IFNγ: Interphone, IL: Interleukins, KAT: Kynurenine Aminotransferase, KF: Kynurenin formylase, KMO: Kynurenine 3-monooxygenase, KYNA: Kynurenine Acid, NAT: N-acetyltransferase, NMDR: N-methylene D-aspartate receptor, ROS: Reactive oxygen species, TDO: Tryptophan 2, 3-dioxygenase, TNFα: Tumor necrosis factor-alpha, and TPH: Tryptophan hydroxylase.

Table 2. summarizes major neurotransmitter alterations in AD.

Neurotransmitter	Alteration	Citation
Acetylcholine	Decreased	[70,100,138]
Dopamine	decreased	[126,129,138,139]
Cortisol	Increased	[167,168,170]
Glutamate	Increased	[70]
GABA	Decreased	[70,138]
Tryptophan	Decreased	[179]
Neurotoxin kynurenine pathway metabolites	Increased	[175,179,181]
Brain cholesterol level	Increased	[93,179]
Melatonin, serotonin, and noradrenaline	Decreased	[19,126,129,157]

6.5. Roles of Diets in the Pathogenesis and Progression of AD

Diet is a major modifiable risk factor [184]. Diets high in saturated fats, sugar, cholesterol, TMAO, and homocysteine increase neuroinflammation, OS, tau phosphorylation, and Aβ aggregation [184–189]. Elevated cholesterol and APOE4 impair cholesterol transport and enhance amyloidogenesis [92,193].

Conversely, Mediterranean-style diets rich in antioxidants, omega-3 fatty acids, vitamins, and fiber reduce inflammation and OS [3,46,194–198]. Dietary components exert epigenetic effects on AD-related genes [6,199,200]. Mechanisms are illustrated in Figure 7.

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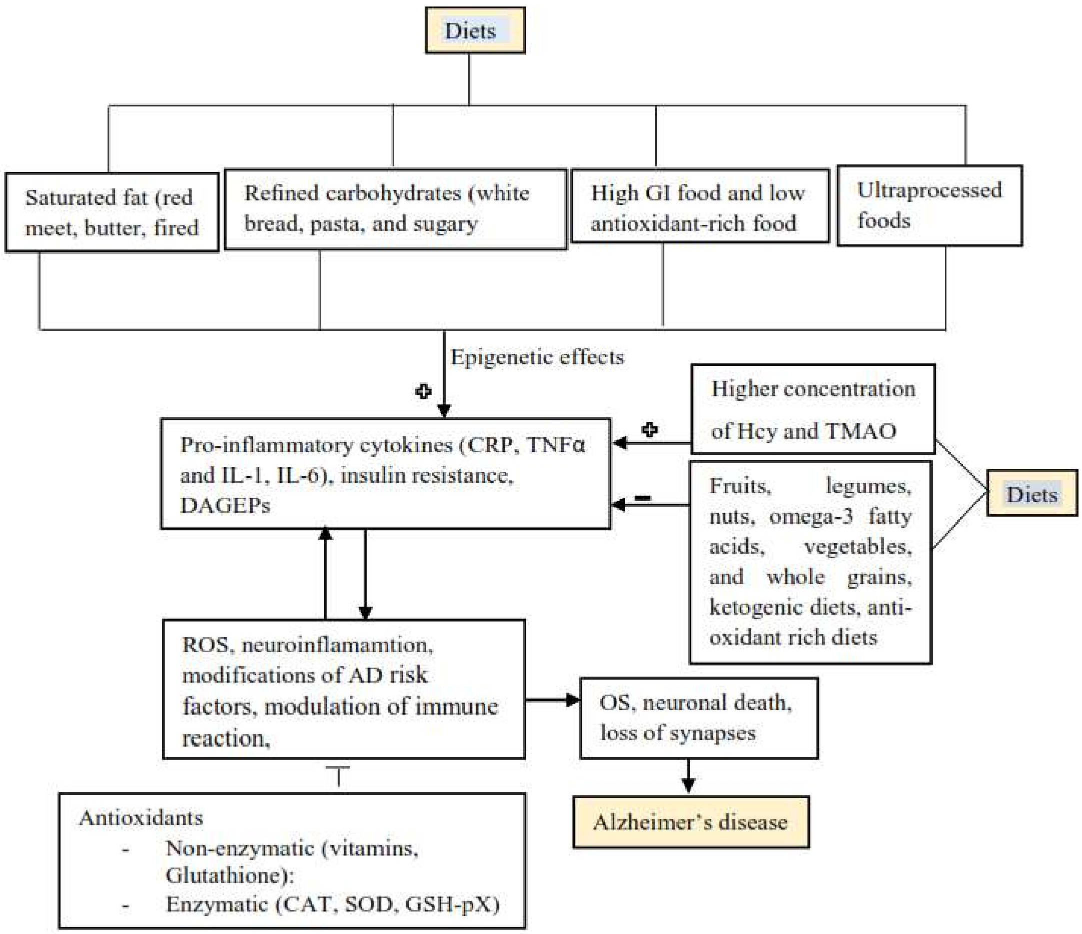

Figure 7. Roles of Diets and their Mechanisms in AD Development. Diets affect oxidative stress and inflammatory responses, ROS production, and finally affect Tau hyperphosphorylation, amyloid-beta accumulation, and neuronal deaths though they modify the effects of AD risk genes and other conditions. CAT: Catalase, CRP: C-reactive protein, DAGEPs: Dietary advanced end products, GSH-pX: Glutathione peroxidase, IL: Interleukin, OS: Oxidative stress, ROS: Reactive oxygen species, SOD: Superoxide dismutase and TNF: Tumor necrosis factor.

Honey, produced by Apis mellifera [203], contains sugars, phenolics, flavonoids, vitamins, and bioactive compounds with antioxidant and anti-inflammatory properties [53,204]. Honey reduces Aβ accumulation, tau phosphorylation, neuroinflammation, OS, and acetylcholinesterase activity while enhancing antioxidant gene expression via Nrf2 [64,208–211]. Its mechanisms are summarized in **Figure 8**.

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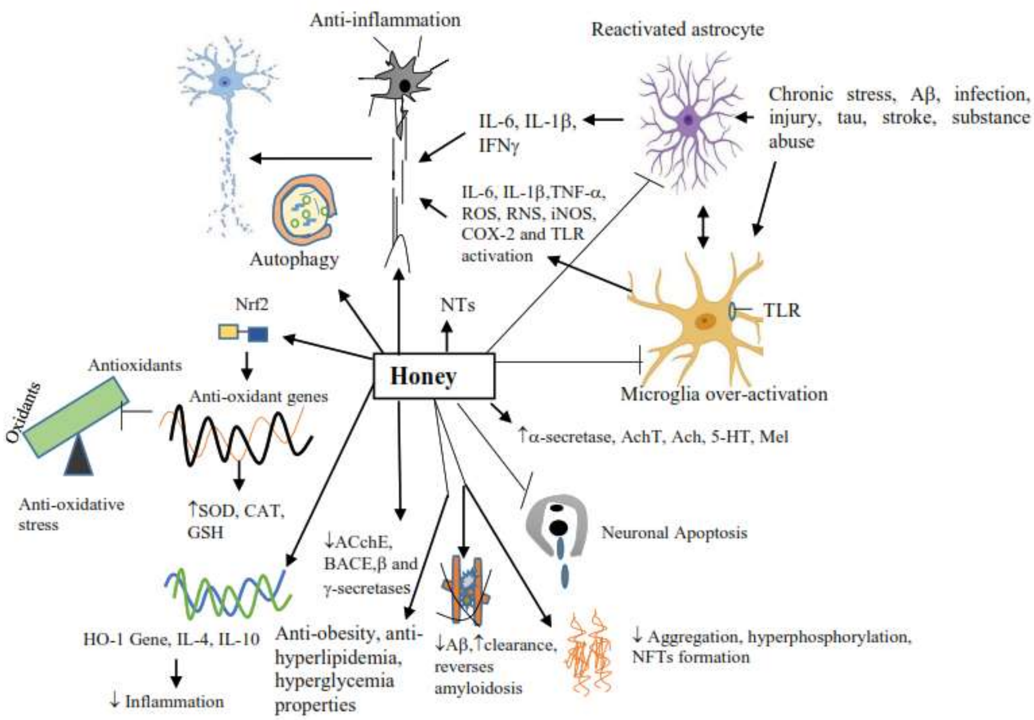

Figure 8. Mechanism of Actions of Honey in AD Development and Progression. Honey uses its different effects on conditions involved in the pathogenesis of AD. AChE: Acetylcholinesterase, Aβ: amyloid beta, BACE1: β-site APP cleaving enzyme, CAT: Catalase, COX-2: Cyclooxygenase-2, 5-HT; Five hydroxyl tryptophan, GSH: Glutathione, HO-1: Heme oxygenase-1, IL: Interleukin, INFγ: Interferon-gamma, L-DOPA: L-3,4-dihydroxyphenylalanine, MD: mitochondrial dysfunction, Mel: melatonin, Nrf2: Nuclear factor erythroid 2-related factor 2, NTs: Neruotransmetters, ROS: reactive oxygen species, SOD: superoxide dismutase, Tau: Tubulin associated unit, TLR: Toll-like receptor, and Vit: Vitamin.

Interactions between honey, cannabinoids, orexin, and histamine pathways further modulate inflammation and sleep-related Aβ clearance [213–228]. Although findings are sometimes contradictory, honey demonstrates potential as a complementary strategy in AD prevention.

6. Conclusion

Aβ plaques and NFTs result from genetic mutations, epigenetic changes, neuroinflammation, oxidative stress, chronic stress, infection, unhealthy diets, and neurotransmitter imbalance (Figure 9). Aβ40 and Aβ42 are key plaque components formed through β- and γ-secretase cleavage of APP. Neurotransmitter dysregulation contributes significantly to cognitive decline. Diets rich in antioxidants and anti-inflammatory compounds, including honey, may delay disease progression.

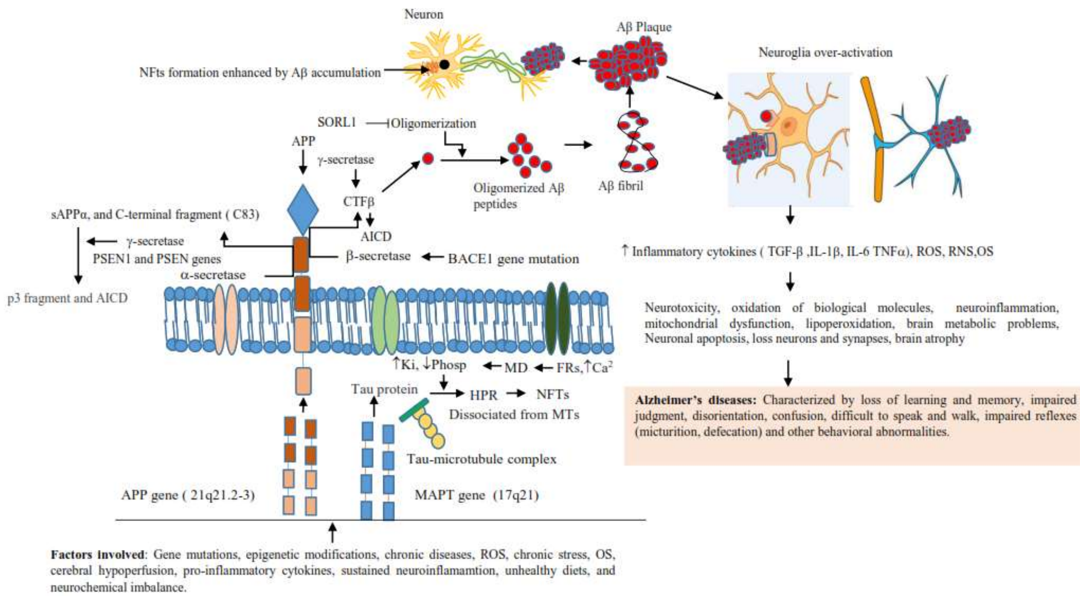

Figure 9. Summary of Amyloid precursor protein processing and amyloid-beta plaque and NFTS formation and factors involved. a disintegrin metalloproteinase 10 (ADAM10), Aβ: Amyloid beta, AICD: AβPP intracellular domain, AD: Alzheimer's disease, APP: Amyloid precursor protein, CTF: C-terminal fragmentβ, FRs: Free radicals, hAPP: Human amyloid precursor protein, HPR: Hyperphosphorylation, IL: Interleukin, Ki: Kinase, MAP1: Microtubule-associated protein-1, MC: Mitochondria, MD: Mitochondrial dysfunction, MTs: Microtubules, NFTs: Neurofibrillary tangles, OLBME: Overloaded biogenic metallic elements, OS: Oxidative stress, Phosp: Phosphatase, PRRs: Pattern recognition receptors, RNS: Reactive nitrogen species, ROS: Reactive oxygen species, sAPPβ: N-terminal soluble APPβ, SORL1: Sortilin-related receptor-one, Tau: Tubulin associated unit, TGF-β: Transforming growth factor-beta, TLRs: Toll-like receptors, TNFα: Tumor necrosis factor-alpha, TREM2: Triggering receptor expressed on myeloid cells.

Generally, unlike previous reviews that primarily focus on amyloid or tau pathology independently, the current review integrates genetic, neurochemical, inflammatory, metabolic, and lifestyle-related contributors into a unified molecular framework. It further highlights the bidirectional interactions among oxidative stress, mitochondrial dysfunction, neurotransmitter imbalance, and dietary factors, providing a comprehensive systems-level perspective of Alzheimer's disease pathogenesis.

7. Future Research Directions

Future investigations should explore genetic and pharmacologic modulation of neurotransmitter receptors, inflammatory cytokines, lipid metabolism, vascular factors, and hormonal regulation. The roles of MAPT, BACE1, ADAM10, APOE, Cdk5, GSK3β, CYP46A1, NFE2L2, SOD, GPX-1, catalase, and HO-1 under chronic stress and dietary influences require deeper evaluation. Identification of early biomarkers in serum, CSF, saliva, urine, ocular fluids, and brain tissue remains essential. The molecular mechanisms through which honey and other dietary components influence gene expression and AD progression also warrant further research.

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Abbreviations

ADAM10/17: a disintegrin metalloproteinase 10/17, AICD: AβPP intracellular domain, Aβ: Amyloid beta, AA: Anthranilic acid, AD: Alzheimer's disease, AGEPs: Advanced glycation end products, Amy: Amygdala, APEO: Apolipoprotein E (Apo-E), APP: Amyloid precursor protein**,** BACE1: β-site APP cleaving enzyme 1, BBB: Blood-brain barrier, CAT: Catalase, CRP: C-reactive protein, CX3CR1: Chemokine (C-X3-C motif) receptor 1, DAGEPs: Dietary advanced glycation end products,DAMPs: Damaged associated molecular patterns, FRs: Free radicals, Glut: Glutamate, GSH-pX: Glutathione peroxidase, HAO: 3-hydroxyanthranilate 3, 4-dioxygenase, hAPP: Human amyloid precursor protein, Hip: hippocampus, 3-HK: 3-Hydroxykynurenine, HPR: Hyperphosphorylation, IDO: Indoleamine 2, 3-dioxygenase, IFNγ: Interferon, IL: Interleukin, Inflame cyto: Inflammatory cytokines , KAT: Kynurenine Aminotransferase, KF: Kynurenin formylase, Ki: Kinase, KMO: Kynurenine 3-monooxygenase, KYNA: Kynurenine Acid, LPs: Lipopolysaccharides, MAP1: Microtubule-associated protein-1, MC: Mitochondria, MD: Mitochondrial dysfunction, MTs: Microtubules , nAchRs : Nicotine acetylcholine receptors, NAT:N-acetyltransferase, NFTs: Neurofibrillary tangles, NMDR: N-methylene D-aspartate receptor, NTs: Neurotransmitters, oAβ: Oligomeized amyloid beta, OLBME: Overloaded biogenic metallic elements, OS: Oxidative stress, PAMPs: Pathogen associated molecular pattern, PFC: Prefrontal cortex, Phosp: Phosphatase, PRRs: Pattern recognition receptors, PSEN-1: Presenilins-1, PSEN-2: Presenilins-2, P-tau: phosphorylated tau, QA: Quinolinic acid, RNS: Reactive nitrogen specious, ROS: Reactive oxygen species, SOD: Superoxide dismutase, sAPPβ: Soluble APP β, SORL1: *sortilin-related receptor*-one,sTREM-2: Soluble triggering receptor expressed on myeloid cells 2, Tau: Tubulin associated unit, TDO: Tryptophan 2, 3-dioxygenase, TGF-β: Transforming growth factor-beta, TLRs: Toll-like receptors, TNFα: tumor necrosis factor-alpha, TPH: Tryptophan hydroxylase, TREM-2: triggering receptor expressed on myeloid cells 2, and T-tau: Total tau protein.

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