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REVIEW

Linkage of circadian rhythm disruptions with Alzheimer's disease and therapeutic interventions

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Abstract Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and pathological brain changes. While aging is the primary risk factor, circadian rhythm disruption (CRD) is increasingly recognized as a central driver of AD pathology. CRD exacerbates oxidative stress, systemic inflammation, and gut microbiome dysbiosis, impairing sleep-wake cycles, disrupting metabolic homeostasis, and promoting neuroinflammation, ultimately accelerating disease progression. Oxidative stress, a key factor in neuronal damage, is both a cause and consequence of circadian misalignment, while mitochondrial dysfunction further amplifies oxidative damage, impairing synaptic function and cognitive stability. Additionally, gut microbiome dysbiosis contributes to neuroinflammatory processes, worsening neurodegeneration. Given these complex interactions, this review aims to elucidate the role of CRD in AD pathology and explore potential therapeutic interventions targeting circadian dysfunction. Specifically, it examines the efficacy of time-restricted feeding (TRF), a dietary strategy that aligns food intake with circadian rhythms. TRF has shown promise in restoring circadian function, reducing oxidative stress, improving mitochondrial health, and promoting gut microbiome diversity. By addressing CRD, TRF may offer a novel approach to mitigating AD pathologies. This review also identifies current research gaps and future directions for developing circadian-based interventions in AD prevention and treatment.

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1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide, characterized by progressive cognitive decline and hallmark brain pathologies, including amyloid-beta (aβ) plaques and neurofibrillary tangles (NFT)[1]. The etiology of AD is complex, involving genetic, environmental, and behavioral factors. It is well known that circadian dysregulation aggregates AD pathology[2]. For example, studies in animal models and humans demonstrate that circadian disruptions increase the production and delay the clearance of aβ-42. Moreover, animal studies showed that circadian misalignment exacerbates tau phosphorylation known marker for AD pathology. Furthermore, circadian dysregulation triggers neuroinflammation and promotes dysbiosis and oxidative stress, suggesting the involvement of AD risk factors[3]. There is no direct evidence suggesting knock-out/mutation of core clock genes leads to AD; however, variants based on studies from animal models and human circadian genes have been implicated in AD risk based on GWAS data[4,5]. Furthermore, chronic sleep disorders in humans linked with circadian misalignment possess higher AD risks, including more accumulation of aβ-42 and phospho-Tau[6,7]. Circadian dysregulation, when combined with other risk factors for Alzheimer's disease, plays a significant role in driving the disease's pathology. However, there is no definitive evidence to suggest that it alone is enough to cause the disease, making its role more complex and contributing to the worsening of the disease's progression. The relationship between circadian rhythms and AD appears to be bidirectional; disruptions in circadian rhythms can worsen AD pathology, and AD can further disrupt circadian rhythms[8]. Circadian rhythms are driven by core clock genes like, Circadian Locomotor Output Cycles Kaput (*Clock*), Brain and Muscle ARNT-Like 1 (*Bmal1*), Period (*Per*), and Cryptochrome (*Cry*), which regulate several physiological processes, including sleep-wake cycles, feeding behavior, digestion, and gut motility, which in turn impact the composition and functionality of gut microbiota[9], immune responses, and antioxidant defenses[10]. In AD, CRD misaligns the sleep-wake cycles and gut microbiome, worsens oxidative stress, and impairs aβ clearance, which creates a feedback loop and accelerates disease progression[3]. The relationship between circadian rhythms and gut microbiomes is also complex and bidirectional, often characterized as an "egg and chicken" paradigm, where both components regulate and are regulated by one another. More mechanistic-based studies are much need to establish this, and this review might be a triggering factor for conducting these studies.

Gut microbiomes show diurnal oscillations to optimize nutrient absorption, immune modulation, and metabolite production[9]. Recent studies highlight gut microbiota and circadian rhythm alterations in AD progression, but their exact relationship remains unexplored[11]. Evidence from the co-housing of wild-type mice with AD mice experiment showed dysbiosis and cognitive deficits after three months[12]. The gut microbiome is also highly sensitive to dietary changes and feeding times[13]. *Firmicutes* are higher during the fed state, and *Bacteroidetes* and *Verrucomicrobia* peaked during fasting times[14]. This bidirectional regulation suggests that neither the gut microbiome nor the circadian rhythms can be considered strictly "primary"; instead, their relationship, through the gut−brain axis, forms a complex feedback loop that is critical for maintaining host metabolic and neuroimmune homeostasis. In AD, disruption of the gut−brain axis contributes to neuroinflammation, oxidative stress, and metabolic dysregulation, further aggravating the disease[15]. The emerging interventions, including dietary changes and probiotics, offer the potential for reducing these pathological factors, suggesting that restoring gut health could slow AD progression[16]. For instance, *Akkermansia muciniphila*, a gut bacterium, plays a key role in modulating neuroinflammatory pathways central to AD[17]. This evidence supports the intricate relationship between circadian rhythms, gut microbiomes, and oxidative stress in AD pathology.

Recent findings have suggested that oxidative stress exacerbates AD progression, which is tightly linked to CRD and gut dysbiosis, with mitochondrial dysfunction[18], increasing aβ and tau accumulation[19]. Oxidative stress occurs when an imbalance between antioxidant defenses and reactive oxygen species (ROS) changes, which can induce neuronal damage and dysfunction[20]. This leads to synaptic dysfunction, accelerating neuronal loss, and promoting cognitive decline[21]. Together, these interconnected pathways emphasize the pivotal role of oxidative stress in AD's pathophysiology. Therapeutic strategies to mitigate oxidative stress have shown promise in altering disease trajectories. Dietary polyphenols, known for their antioxidant properties, and compounds like nicotinamide mononucleotide have been explored for their neuroprotective effects, modulating disease pathways and improving neuronal survival[22]. Since oxidative stress is an effector and lacks a specific cause or targeted approach for the treatment, limited biomarkers and limitations like a blood−brain barrier (BBB) and the short half-life of the drug make it difficult to use for AD therapy. The melatonin hormone, beyond its well-known role in sleep regulation, has been shown to influence gut microbiome composition and reduce oxidative stress[23], further illustrating the link between circadian health and gut microbiome. In experimental models, melatonin treatment increased beneficial bacterial populations, reduced systemic inflammation, and improved cognitive outcomes by enhancing gut health[24]. These findings suggest that circadian realignment and reshaping of gut microbiomes potentially mitigate key drivers of AD progression.

Interventions like time-restricted feeding/eating (TRF/E, known as TRE in humans), where food consumption is limited to a particular time in a day followed by fasting for the rest of clock time, have emerged as a promising intervention to restore circadian function[25]. Studies indicate that TRF not only reduces oxidative stress by enhancing mitochondrial function but also promotes a healthier gut microbiome by increasing microbial diversity and beneficial species such as *A. muciniphila*[26]. This helps reduce neuroinflammation by targeting key pathways, including the nucleotide-binding oligomerization domain-like signaling pathway, which belongs to a family of intracellular pattern recognition receptors that combat neurodegeneration and age-related cognitive decline[27].

While research has explored these factors individually, there is a lack of comprehensive understanding of how they are intricate and contribute collectively to the pathophysiology of AD. Particularly, there remains a need to synthesize the evidence on how these lifestyles and genetic factors are interrelated and how they may be targeted simultaneously to slow disease progression. By exploring these relationships, this review aims to provide a holistic understanding of the underlying mechanisms linking circadian rhythms, gut health, oxidative stress, and metabolic health to AD. This integrative approach may identify novel therapeutic strategies that address the multifaceted nature of AD, providing the way for additional personalized and comprehensive treatment options.

2. Circadian rhythms and regulation

Circadian rhythms are governed by the suprachiasmatic nucleus (SCN) found in the hypothalamus, which coordinates the release of melatonin and other neurohormonal signals that regulate sleep-wake cycles, metabolism, and cognitive functions[28]. At the molecular level, circadian rhythms are driven by a feedback loop involving core clock genes such as *Bmal1*, *Clock*, *Per*, and *Cry* (Fig. 1). These genes work in concert to regulate the expression of clock-controlled genes (CCGs) that influence various physiological processes, including sleep-wake cycles[29]. The positive regulators of CCGs, BMAL1, and CLOCK, form a transcriptional complex to induce the expression of their negative regulators, *Per* and *Cry* genes[30]. Once the PER and CRY accumulate, they move to the nucleus and repress their activity dose-dependently by inhibiting the BMAL1:CLOCK transcription complex[30]. BMAL1 and CLOCK proteins are stable or have a slow turnover rate to start a new cycle compared to PER and CRY, which undergo proteolytic degradation during the 24-h cycle[31]. Through this negative feedback loop of PER:CRY proteins BMAL1:CLOCK sustains a 24-h cycle of clock gene expression that governs the timing of sleep and wakefulness[32]. Events like irregular light exposure, shift work, or genetic mutations in core clock genes can lead to circadian rhythm sleep-wake disorders[33] (Fig. 1).

2.1. *Circadian rhythm sleep-wake disorders and their impact on AD*

Disruptions in circadian rhythms and sleep-wake cycles, such as fragmented sleep and insomnia, are preceded by AD pathology, suggested as a potential early symptom or risk factor for AD[6]. Microtubule-associated protein tau (MAPT), aβ, levels, and other metabolic by-products like lactate fluctuate diurnally in the brain, peaking during wakefulness and decreasing during sleep, this fluctuation is linked to the glymphatic system's efficiency[7]. Glymphatic system refers to the synergistic function of both astrocytes and lymphatic system, where astrocytic water channel aquaporin-4 (AQP4) supports the cerebrospinal fluid-interstitial fluid exchange in the brain and supports aβ clearance[7]. Chronic circadian misalignment leads to increased aβ production, which in turn promotes the degradation of clock proteins like BMAL1, CREB-binding protein (CBP), and PER1, thereby accelerating plaque formation and reducing clearance[34]. In AD patients, arrhythmic *Bmal1* methylation correlates with abnormal tau phosphorylation, night wakeup, and decreased cognitive functions[35].

Meta-analysis and community-based, cohort longitudinal studies with many participants revealed that shift workers, particularly those working during the night times, were more prone to dementia and AD[36,37]. Recent research highlights a bidirectional relationship between the disruption of sleep and circadian rhythms to the pathogenesis and progression of AD. A 15-year longitudinal study with 1401 older adults (median age: 81.8 years, IQR: 76.3−85.7 years, both genders) revealed a bidirectional link between circadian dysregulation and Alzheimer's progression[38]. Familial Natural Short Sleepers are associated with mutations in DEC2 (P384R) and NPSR1 (Y206H), genes regulating sleep duration and circadian rhythms. These mutations promote efficient sleep with reduced duration and no cognitive decline. In Alzheimer's mouse models, DEC2-P384R; 5XFAD and female Npsr1-Y206H; 5XFAD mice exhibited reduced tau pathology in the hippocampus and significantly fewer amyloid plaques at six months, suggesting enhancing sleep quality

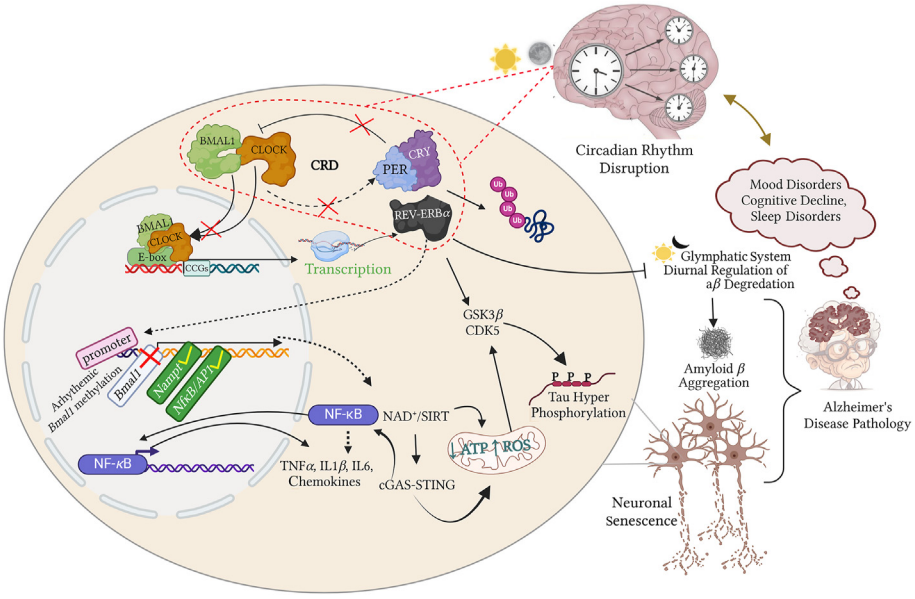

Figure 1 How circadian rhythm disruption endorses Alzheimer's disease pathology. Circadian rhythm disruption (CRD) derails core clock proteins (BMAL1, CLOCK, PER, CRY) function and misaligns clock-controlled genes (CCGs) expression. Which in turn disturbs the glymphatic system and amyloid beta clearance. Rev-Erbα, a *Bmal1* negative regulator, increases neuroinflammation through NF-κB, regulates cytokines (IL1β, TNFα, IL6), and chemokine release. The NAMPT−NAD$^+$/SIRT axis increases ROS, disturbs mitochondrial stability, and releases mtDNA, which further activates cGAS−STING signaling. Excessive reactive oxygen species (ROS) promote tau hyperphosphorylation through GSK3β and CDK5 tau kinases. Excessive ROS, mitochondrial damage, and inflammation contribute to neuronal senescence and aggravate AD pathogenesis. AD, in turn, impacts the sleep-wake cycle, mood disorder, and cognitive function and leads to disruption of circadian rhythms (https://BioRender.com/r74v731).

may protect against neurodegeneration in AD[39]. Another FNSS mutation, Adrb1-A187V, alters β1-adrenergic receptor signaling in brain regions responsible for sleep regulation, reduces tau pathology, and improves random eye moment (REM) sleep in a mouse model of tauopathy[40]. A double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of trazodone (50 mg, administered daily at 10:00 P.M.) for improving sleep disturbances in 30 community-dwelling patients with AD. Over a 2-week treatment period, trazodone significantly enhanced sleep, with participants sleeping an additional 42.5 min per night and increasing nighttime sleep percentage by 8.5% compared to the placebo group[41,42]. This highlights the significance of circadian rhythms and the quality of sleep in AD pathology.

2.2. *Circadian rhythm disruption and oxidative stress in AD*

Disrupted sleep further amplifies oxidative stress by impairing the brain's antioxidant defense mechanisms[43]. ROS levels are normally regulated by circadian control of metabolic processes, including (nicotinamide adenine dinucleotide) NAD^+ metabolism, which is involved in mitochondrial function and oxidative stress regulation[44]. Since the BMAL1/CLOCK complex controls the nicotinamide phosphoribosyl transferase (NAMPT)−NAD^+/SIRT axis through histone acetyltransferase and transcription factor functions[45], CRD further weakens mitochondrial efficiency and increases ROS production. The oxidative environment fosters tau hyperphosphorylation by activating kinases such as glycogen synthase kinase-3β (GSK-3β)[46], and cyclin-dependent kinase (CDK5)[47], both of which play crucial roles in tau pathology and neurofibrillary tangle formation (Fig. 1). In addition to oxidative stress, NAD^+ deficiency contributes to mitochondrial damage by creating pseudohypoxia conditions[48], and releases mtDNA into the cytosol. Cyclic GMP−AMP synthase (cGAS) binds to mtDNA and further activates an endoplasmic reticulum resident membrane protein, *i.e.*, stimulator of interferon genes (STING) dependent pathway (Fig. 1) which contributes to neuroinflammation by activating type-1 interferon (IFN)[49]. Type 1 IFN induces NF-κB−TNF-α, IL-6, IL-1β which further activates senescence-associated secretory phenotype protein (SASP) to induce cellular senescence in AD[50].

2.3. *Circadian rhythm and neuroinflammation*

Neuroinflammation and CRD are deeply intertwined in the pathogenesis of AD. A key molecular link between CRD and neuroinflammation is the NF-κB signaling pathway. Normally, core clock genes like *Bmal1* and *Clock* suppress nuclear factor-kappa B (NF-κB) activity through their regulation of HPA−CRH (hypothalamus-pituitary-adrenal−corticotropin-releasing hormone)−ACTH (adrenocorticotropic hormone) release and glucocorticoid synthesis[51]. The CRD in AD leads to an over-activation of NF-κB, resulting in the chronic release of pro-inflammatory cytokines such as interleukin-1β, interleukin-6 (IL-1β, IL-6), and tumor necrosis factor-α (TNF-α)[52], which further accelerates aβ deposition, tau hyperphosphorylation, and neuronal death. This creates a feedback loop that drives both neuroinflammation and AD progression. In addition, glucocorticoid synthesis regulates inflammation by inhibiting the NF-κB and activator protein-1 (AP-1)[53]. Glucocorticoid synthesis suppresses NF-κB and activating protein-1 (AP-1) by increasing the inhibitory-κB (IκB) and interfering with AP-1 binding to DNA[53].

Glucocorticoids also control the expression of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes involved in eicosanoid-like prostaglandins and leukotrienes biosynthesis[54]. Enzymes like COX, LOX, leukotriene B4 receptor 1 (BLT1), and cysteinyl leukotriene receptor 1 (CysLT1)[55], exhibit diurnal variations in their expression and activity[56], leading to excessive activation of BLT1 and CysLT1 receptors, intensifying the inflammatory response, which further contributes to impaired aβ clearance in AD[57]. Other lipid mediators like 'lipoxins' and 'resolvins' are involved in resolving inflammation, tissue repair, and clearing of aβ by enhancing the phagocytic activity of microglia[58]. Lipoxin A4 (LXA4)−LOX pathway, follows circadian rhythms, with higher levels during the rest phase to counteract inflammatory processes and promote tissue healing[59]. Lipoxin receptors (ALX/FPR2) are also regulated by circadian genes, further aggravating AD pathology[60]. Circadian proteins PER/CRY1 promote the acetylation of glucocorticoid receptors (GR) at multiple lysine residues by facilitating the recruitment of CBP/p300 (a histone acetyltransferase) and preventing their binding to glucocorticoid response elements (GRE)[51]. Moreover, the circadian clock proteins BMAL1 and Reverse-Erb-α (REV-ERBα) play critical roles in modulating microglial activity by suppressing their activation during the rest period through suppressing NF-κB activity (Fig. 1), histone modification, and controlling the metabolic shift towards glycolysis (Warburg effect)[61]. CRD exacerbates oxidative stress, neuroinflammation, and accumulation of aβ and tau proteins, thereby accelerating neurodegeneration, which in turn disturbs sleep and circadian rhythms[9]. Therapeutically, advanced treatments for circadian rhythms sleep-wake cycle disorders often involve light therapy, timed melatonin administration, and behavioral adjustments to realign the sleep-wake cycle with environmental cues[62]. This section delves into intricate molecular pathways linking circadian rhythms to AD, the limitations of the recent studies on CRD−AD relation and discusses emerging therapeutic strategies that help restore circadian alignment and mitigate disease progression.

2.4. *Chronobiology and therapeutic implications for AD*

Chronotherapy offers promising insights into circadian disruptions in AD. It involves aligning treatments with the body's circadian cycles to optimize drug efficacy and reduce side effects. Chronotherapies, such as TRF, light therapy, or pharmacological agents, could restore circadian synchronization and potentially mitigate the cognitive decline in AD. To examine the neuroprotective effects of verapamil (VRP) administered at different time points. 40 male albino mice (8−10 weeks old, 30−35 g) were treated with LPS and divided into four groups: normal control, LPS control, and VRP-treated (morning or evening administration). VRP improved behavior, restored brain architecture, reduced phospho tau, decreased neuroinflammation markers (CD11b, CD68, TNF-α, IL-6, IL-1β), and intracellular calcium ions and increased mitochondrial function, calcium/calmodulin-dependent protein kinase II (CAMKII) isoforms, protein kinase A (PKA), cyclic AMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF), with morning VRP showing superior results[63] (Table 1[63-69]).

In a sporadic AD, Sprague−Dawley rat model using intracerebroventricular aβ42 infusion and pinealectomy, chronic melatonin supplementation (50 mg/kg, intraperitoneally) over 40 days improved spatial memory and normalized aβ42 levels and γ-secretase activity (Table 1) in the brain[64]. Recent studies have demonstrated that melatonin directly binds to and inhibits the activity of death-associated protein kinase 1 (DAPK1) in AD,

Table 1 Therapeutic approaches studied to restore circadian rhythms including time-restricted feeding and their implication in Alzheimer's disease outcome discussed in this review.

Target	Model	Study	Outcome
Verapamil chronotherapy study[63]	Male albino (VRP-treated morning/evening)	Investigated neuroprotective effects of verapamil (VRP)	Morning VRP administration reduces tau phosphorylation, intracellular Ca^{2+}, neuroinflammation markers, and mitochondrial function
Melatonin supplementation study[64]	Sporadic AD rat model (intracerebroventricular aβ1−42 infusion and pinealectomy)	Chronic melatonin supplementation (50 mg/kg, intraperitoneally) over 40 days	Spatial memory improved, aβ42 levels normalized, and γ-secretase activity reduced
Melatonin binds to DAPK1[65]	Animal and human AD models	Impact of melatonin on DAPK1 and its downstream effects on tau pathology	Melatonin inhibited DAPK1 activity and reduced tau protein accumulation
Restricted feeding and circadian misalignment[66]	8−12-week-old C57BL/6 mice	High-light regimes (700 lx active phase, 150 lx rest phase) for realignment over 7 days	Circadian realignment restored baseline levels of metabolic functions
TRF on cognitive function[67]	APP23 transgenic AD mouse model	6-month TRF (6:18 feeding and fasting) to examine cognitive performance and circadian rhythm restoration	Improved cognitive performance, reduced amyloid plaque load, and restored circadian rhythms
TRF on circadian realignment and cognitive function[68]	APP/PS1 transgenic mouse model of AD	TRF is limited to the active dark phase	Improved circadian clock gene expression reduced aβ deposition and restored cognitive function
TRF[69]	14 healthy subjects	14-h TRF intervention over 30 days to measure amyloid-β deposition and BDNF levels	Reduced aβ deposition and increased BDNF, neuroplasticity, learning, and memory

leading to reduced tau protein accumulation and phosphorylation while promoting synaptic growth and microtubule assembly[65]. This suggests that reduced melatonin levels in AD contribute to circadian misalignment and poor sleep quality much earlier than AD symptoms.

2.5. *Limitations on the role of circadian rhythms with AD*

While models such as FNSS mutations (DEC2-P384R, NPSR1-Y206H, Adrb1-A187V) in mouse systems have provided valuable insights, they may not fully capture the complexity of human circadian physiology and AD pathology due to species-specific differences in metabolism, sleep architecture, and gene regulation. Moreover, many findings linking circadian disruption with AD biomarkers like aβ and tau accumulation are based on associative data, raising questions about whether circadian disturbances are a contributing factor or a consequence of disease progression. Human observational studies, while informative, cannot often fully control confounding variables such as medication use and comorbid conditions, making causal inference challenging. Therapeutic strategies, including light therapy and melatonin administration, have shown promise but remain limited by inconsistencies in treatment parameters such as duration, intensity, and individual chronotype variations, which affect reproducibility and standardization across studies. Mechanistically, while core clock genes (*Bmal1*, *Clock*, *Per*, and *Cry*) and pathways like NF-κB and the glymphatic system have been explored, their direct mechanistic roles in AD progression remain incompletely validated in both preclinical and clinical contexts. Additionally, the influence of biological sex and hormonal variations on circadian regulation and AD pathology has not been thoroughly examined, despite evidence suggesting sex-specific differences in circadian responses and disease susceptibility in some models.

3. Circadian rhythm role in influencing gut microbiota and AD pathology

The circadian clock and microbiome are intricately linked. When the clock is disrupted, gut bacteria lose their natural rhythms, leading to metabolic dysregulation, immune dysfunction, and potentially contributing to AD (Fig. 2) progression[70]. Emerging evidence shows the gut microbiome's influence on neuroinflammation, oxidative stress, aβ accumulation, and cognitive decline. The gut microbiome influences AD pathology by modulating the aβ aggregation and tau hyperphosphorylation through the gut−brain axis[71]. Certain bacteria, such as *Escherichia coli* and *Salmonella*, produce amyloid-like proteins (*e.g.*, Curli) which activate the gut−brain axis through toll-like receptors 2 (TLR2) in gut epithelium and vagus nerve stimulation through PGP 9.5, a neuroendocrine/enteroendocrine marker[72]. In 2022, Das et al. brought crucial evidence to support this hypothesis that they have discovered increased bacterial amyloid beta burden much before the development of aβ pathology in the brain using Tg2756 AD mouse model[72]. In contrast, in *Caenorhabditis elegans* AD model, *Bacillus subtilis* exhibited significant neuronal and behavioral protective effects. It showed delayed aging and neuronal decline in wild-type strain N2 compared to worms colonized with non-probiotic *E. coli* OP50. In transgenic strains (CL2120 and GMC101), *B. subtilis* alleviated aβ-induced paralysis and protected CL2355 worms from behavioral impairments and aging. These benefits were attributed to quorum-sensing peptide production and gut-associated biofilm formation[73]. In this study, they discovered bacterial *csgA* and *csgB* genes, which encode the major and minor subunits of curli amyloid fibrils in *E. coli*, significantly promoting neurodegeneration[74]. Further experiments demonstrated that curli fibrils can be cross-seed with host proteins, leading to protein aggregation and neuronal damage[74]. By

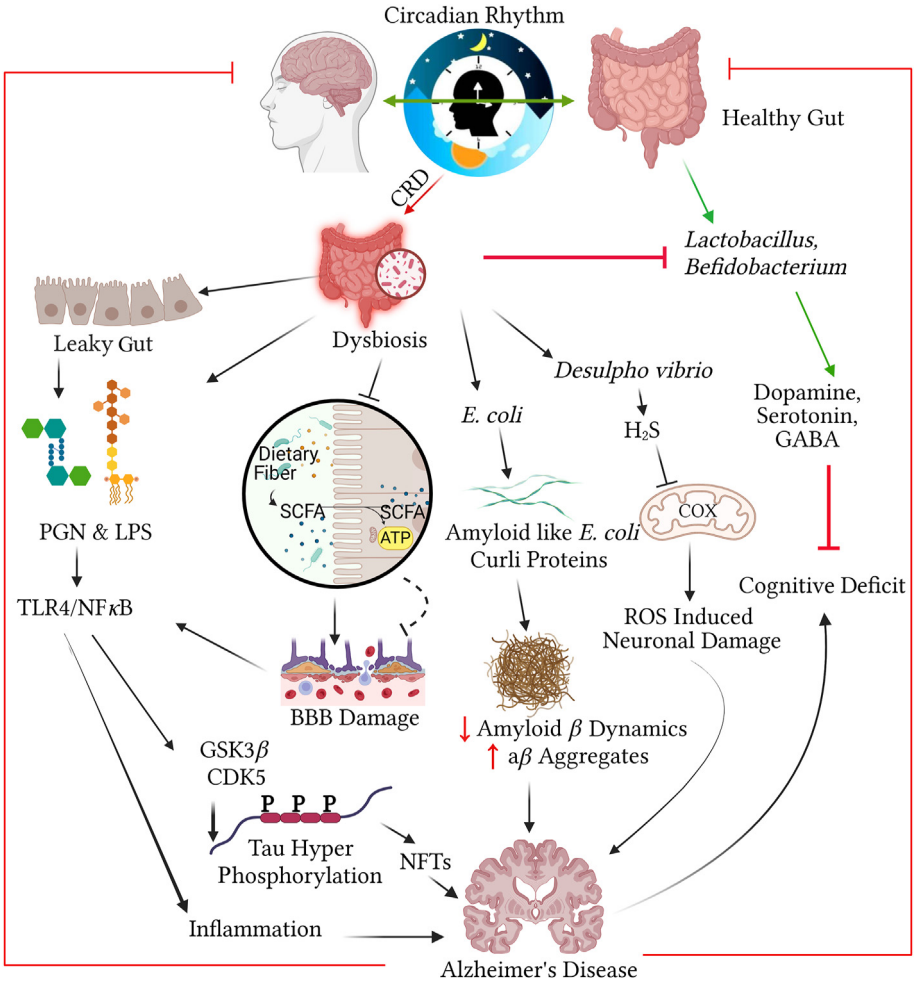

Figure 2 The bidirectional relationship between circadian rhythms and gut microbiome. How dysbiosis and healthy gut impact AD pathology and circadian rhythms. Circadian rhythm disruption disturbs gut−brain communication. It contributes to gut dysbiosis. Increased harmful bacteria like *E. coli* and *Desulpho vibrio* disturb mitochondrial integrity and aβ dynamics by H_2S and Curli proteins. Dysbiosis also reduces dopamine, serotonin, and GABA and induces cognitive deficits, promotes reactive oxygen species (ROS) and aβ aggregation, reduces short-chain fatty acids (SCFA) and increases gut leakage. This, in turn, leads to the release of LPS, and peptidoglycans (PGN) into the blood circulation and binds to toll-like receptors (TLRs) on the blood−brain barrier's (BBB) endothelial cells and damages BBB integrity. BBB damage activates NF-κB and releases proinflammatory cytokines, activates tau kinases (GSK3β, CDK5) that hyperphosphorylate tau and form neurofibrillary tangles (NFTs). Accumulation of aβ, NFT and increased neuroinflammation propagates AD pathology. They further disturb gut-to-brain communication and circadian rhythms (https://BioRender.com/q15n319).

exploring these findings, we have discussed the intricate molecular pathways linking gut dysbiosis to AD and evaluated the potential of microbiome-based therapies, including probiotics, prebiotics, and symbiotics in the context of AD.

The gut−brain axis is a complex, bidirectional communication network between the gastrointestinal tract (GI) and the CNS, involving neural, endocrine, immune, and metabolic pathways that connect the enteric nervous system (ENS) with the CNS[75]. Disruption of the gut−brain axis through dysbiosis amplifies neuroinflammation and oxidative stress, the two key drivers of AD progression[76]. The gut microbiome modulates the gut−brain axis by producing metabolites like serotonin, Gama amino butyric acid (GABA), and SCFAs (*e.g.*, butyrate, acetate, propionate), produced by *Lactobacillus* and *Bifidobacterium*[77], suppress neuroinflammation by reducing IL-6, IL-1β, and TNF-α secretion and maintain BBB integrity by regulating CD14, upregulating low-density lipoprotein receptor-related protein 1, and free fatty acid receptor 3 (FFAR3)[78] in BBB endothelial cells, which prevents harmful molecules from entering the brain[79]. Dysbiosis results in a reduction of SCFA production from dietary fibers, impairing BBB integrity by limiting the expression of tight junction proteins such as occludin, claudin-5, and annexin A1[80] and triggering neuroinflammatory cascades through COX2, PGE2, inducible nitric oxide synthase, and nitric oxide[81]. LPS activates TLR4 and triggers neuroinflammatory responses by enhancing the production of TNF-α, IL-1β, and IL-6 (Fig. 2) through the NF-κB pathway[82]. This creates a pro-inflammatory environment that promotes neurodegeneration and AD pathology.

3.1. *Impact of dysbiosis-induced neuroinflammation in AD*

In AD patients, poor eating habits, aging, and CRD lead to an imbalance or disruption in the composition of gut microbiome and gut dysbiosis which increases intestinal permeability, often known

as "leaky gut", and allows bacterial components such as LPS and peptidoglycans (PGNs) to enter the systemic circulation and reach the brain[83] (Fig. 2). LPS-induced activation of TLR4/NF-κB signaling triggers microglial activation and innate immune responses *via* the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. This activates caspase-1-mediated pyroptosis, releasing pro-inflammatory cytokines like IL-1β and IL-18, which damage surrounding cells and neuronal synapses, amplifying synaptic loss and dysfunction[84].

The pro-inflammatory environment further activates kinases like GSK-3β and CDK5. These kinases drive the phosphorylation of tau, leading to the destabilization of microtubules and the formation of NFTs[85]. Conversely, a healthy gut microbiome promotes the production of neurotrophic factors, such as BDNF, through the serotonergic (5-HT1A) receptor-CREB-BDNF pathway, which is essential for neuronal survival, synaptic plasticity, and cognitive function (Fig. 2)[78]. Colonization of pathogenic bacteria, such as *Porphyromonas gingivalis*, in the gut produces 'gingipains', a cysteine protease that contributes to aβ accumulation and tau hyperphosphorylation and exacerbates neuroinflammation through activation of TLR2 and TLR9[86]. Moreover, the increased prevalence of Enterobacteriaceae, *Desulfovibrio*, *Anaerococcus*, *and Providencia* contributes to the depletion of *Bifidobacterium* and *Lactobacillus*, worsening chronic neuroinflammation and synaptic dysfunction in AD patients[87,88]. Intragastric administration of *Clostridium butyricum* for four weeks improved cognition in APP/PS1 mice by reducing aβ deposition, microglial activation, and proinflammatory cytokines (TNF-α, IL-1β), restored gut microbiome balance and butyrate levels (Table 2[89-103]). Butyrate also inhibits NF-κB/p65 phosphorylation in aβ-exposed BV2 microglia, reducing CD11b and COX-2 expression[89].

3.2. Gut microbiome linkage with oxidative stress and AD

The depletion of SCFA-producing bacteria like *Lactobacillus* and *Bifidobacterium* compromises the production of essential antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase 1 (GPx1) in AD patients[104]. Pathogenic bacteria like *Desulfovibrio* produce H_2S and cause damage to the intestinal barrier through decreasing thiosulphate sulfotransferase, which degrades H_2S[105], leads to intestinal mucosa damage (leaky gut), and releases the H_2S and other toxins into systemic circulation[106]. H_2S modulates the activity of vascular endothelial growth factor (VEGF), angiogenin-1 (Ang-1) protein, and metalloproteinase-9 and increases the endothelial cell permeability[107]. Once H_2S crosses the BBB it impairs mitochondrial respiration by inhibiting cytochrome *c* oxidase, thereby amplifying ROS production (Fig. 2) and exacerbating oxidative stress[78]. SCFAs, particularly butyrate, play a critical role in mitigating oxidative stress by enhancing mitochondrial bioenergetics and preventing the activation of ROS-producing pathways like c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK)[92]. This modulation of mitochondrial function reduces oxidative damage to neurons, preventing the aggregation of aβ and hyperphosphorylated tau proteins[76]. The gut microbiome increases SCFA production like butyrate, which enhances intestinal barrier function through AMP-activated protein kinase (AMPK) signaling[91], enhances antioxidant defenses[92], and reduces inflammation by increasing IL-10, TGF-β, and reducing IL-2 (Table 2)[90]. In the 3 × Tg-AD mouse model, age-related decline in butyrate-producing gut bacteria was linked to AD progression. Reduced butyrate synthesis *via* the acetyl-CoA pathway decreased histone acetylation (H3K9/K14-Ac) in hippocampal neurons, leading to oxidative stress, tau hyperphosphorylation, memory deficits, and neuromuscular dysfunction. Early (at 6 months of age) oral tributyrin administration preserved gut bacteria, histone acetylation, and reduced oxidative stress associated with AD pathogenesis[108].

Beyond its role in inflammation and oxidative stress, gut microbiota affects neurotransmitter synthesis, such as serotonin, dopamine, and GABA (Fig. 2). Neurotransmitters are vital for synaptic plasticity, memory, and cognitive resilience, and were found to be decreased in the postmortem AD patients[109]. The reduction of *Lactobacillus* also limits the production of tryptophan, a precursor for serotonin and dopamine, which leads to mood disorders and further contributes to cognitive deterioration[110]. Experiments with GC and CC Swiss Webster breeding mice were found to be resistant to restoring neurotransmitter balance through normal gut flora at later ages, exacerbating cognitive decline, and impairing neuronal communication[111]. Lifestyle changes, diet, exercise, and medication contribute to age-related decline in microbial diversity, further compounding these effects and adding a critical dimension to the understanding of AD pathogenesis.

3.3. Therapeutic potential of probiotics and prebiotics in AD

Probiotics comes from the Greek word 'probiotika' which means for life, invented by Ferdinand Vergin in 1954[112]. Stillwell and Lilly, in 1965 described the probiotics as microbes that support the growth of other microbes[113]. Given the critical influence of gut microbiota on AD progression, microbiome-targeted therapies offer significant promise. Supplementation with *Bifidobacterium breve* MCC1274 in wild-type mice reduced Alzheimer's-related pathologies by decreasing soluble hippocampal aβ1−42, presenilin 1 protein, phosphorylated tau levels, and enhanced synaptic protein expression[93]. Oral treatment of *Lactobacillus lactis* engineered to deliver human p62 protein in a 3 × Tg-AD, 8-week mouse model for two months increased brain p62 expression, improved memory, reduced aβ, inflammation, and oxidative stress, and enhanced protein clearance *via* the ubiquitin−proteasome system and autophagy[94]. *Bifidobacterium lactis* Probio-M8 was administered for 45 days to a 4-month-old APP/PS1 transgenic B6C3F1 mice reduced brain aβ plaques, improved cognitive performance in Y-maze and novel object recognition tests, and alleviated gut dysbiosis by enhancing bacterial diversity and beneficial microbial composition (Table 2)[95]. A 12-week randomized, double-blind, placebo-controlled trial with 90 patients (aged 50−90) with mild to moderate AD evaluated the effects of *Lacticaseibacillus rhamnosus* HA-114 and *Bifidobacterium longum* R0175 (7.5×10^9 CFU/capsule). Both probiotics reduced oxidative stress markers (MDA, 8OHdG) and inflammatory cytokines (TNF-α, IL-6) while increasing GSH and IL-10 levels. Additionally, quality of life and physical activity improved, with no significant differences observed between the probiotic strains[114]. In a study on 6-month-old C57BL/6 and App^{NL-G-F} AD mice, an 8-week administration of the probiotic mixture VSL#3 (1.29×10^9 CFU/day) reduced aβ aggregation and brain damage while improving memory, cognitive function (c-Fos expression), and serum SCFA levels. These effects were observed after four months, highlighting the therapeutic potential of probiotics in AD models[97]. A 12-week randomized, double-blind, active-controlled trial investigated the effects of a multi-strain probiotic supplement

Table 2 Therapeutic approaches studied to restore gut microbiome including time-restricted feeding and their implication in Alzheimer's disease outcome discussed in this review.

Target	Model	Study	Outcome
Clostridium butyricum[89]	APP/PS1 AD mouse model	Evaluated the effects of *C. butyricum* on cognition, aβ deposition, microglial activation, and gut microbiota balance	Improved cognition, reduced aβ deposition, neuroinflammation, restored gut microbiome, and inhibited NF-κB/p65
SCFA and intestinal barrier function[90-92]	Animal and cell lines	Investigated the role of butyrate in enhancing intestinal barrier function, reducing oxidative stress, and inflammation	Butyrate improved intestinal barrier integrity, enhanced antioxidant defenses, and reduced inflammation
Bifidobacterium breve MCC1274[93]	Wild-type mice	Supplementation with *B. breve* MCC1274 to evaluate AD-related pathologies	Reduced hippocampal aβ42, presenilin 1 protein, phosphorylated tau, and increased synaptic protein expression
Lactobacillus lactis with p62 transgene[94]	3xTg-AD mouse model	Supplemented for 2 months to examine protein clearance, inflammation, and cognitive outcomes	Increased p62 expression, improved memory, reduced aβ, inflammation, oxidative stress, and enhanced protein clearance
Bifidobacterium lactis Probio-M8[95]	APP/PS1 transgenic mice	Administered to study its effects on cognition, aβ plaques, and gut microbiota	Reduced aβ plaques, improved cognitive performance, and alleviated gut dysbiosis
TUDCA study[96]	92-year-old female AD patients	Long-term tauroursodeoxycholic acid (TUDCA) treatment was examined to analyze gut microbiota changes	Increased *Firmicutes* and *Proteobacteria*, decreased *Enterobacteriaceae*
VSL#3 probiotic mixture[97]	C57BL/6 and *AppNL-G-F* AD mice	Studied for cognitive and molecular outcomes	Reduced aβ aggregation, improved memory/cognitive function, and serum SCFA levels
Selenium-probiotic co-supplementation[98]	AD patients	To evaluate cognitive and metabolic health outcomes	Improved MMSE scores, reduced inflammation and oxidative stress, and improved metabolic health
Synbiotics in AD mice[99]	ddY mice with aβ-induced AD	To examine cognitive and molecular outcomes	Reduced aβ accumulation, tau pathology, neuroinflammation, improved cognitive performance
Triphala with probiotics[100]	Humanized transgenic *Drosophila melanogaster* AD model	Supplementation of Triphala (polyphenol-rich prebiotic) with probiotics for 30 days	Improved motility, restored climbing ability, reduced aβ accumulation, and oxidative stress
Fecal microbiota transplantation (FMT)[101]	APP/PS1 transgenic mice treated with FMT from healthy mice	To examine its effects on aβ, tau pathology, cognitive function, and neuroinflammation	Reduced aβ plaques, tau phosphorylation, and neuroinflammation
TRF on gut microbiome[102]	Aged male hybrid rats (8−21 months old)	TRF (1 meal/day) with ketogenic or standard diets tested for cognition and gut microbiota effects	Improved cognitive performance and enhanced gut microbiota composition
HLCD and TRE study[103]	96 overweight or obese adults (mean age 36 years)	12-week isocaloric-restricted feeding trial comparing healthy low-carbohydrate diet (HLCD), TRE, and control	HLCD reduced fat mass, while TRE improved cardiometabolic markers and increased beneficial gut bacteria

(*B. longum* subsp. *infantis BLI-02*, *B. breve Bv-889*, *B. animalis* subsp. *lactis CP-9*, *B. bifidum VDD088*, and *Lactobacillus plantarum PL-02*) on 40 AD patients aged 50−90 years. The treatment group received 1×10^{10} CFU/day, while the control group received 5×10^{7} CFU/day. After 12 weeks, the probiotic group showed a 36% increase in serum BDNF, cognitive improvement, SOD levels, reduced IL-1β, and oxidative stress markers[115] (Table 2).

Prebiotics are non-digestible/non-viable food components that confer health benefits on host-associated modulation of microbiota[116], for example, inulin and fructooligosaccharides (FOS), fermented by *Bifidobacterium* and *Lactobacillus* species and release lactate and acetate, which were used as a substrate by *Eubacterium hallii* and *Anaerostipes caccae* in the gut and produce SCFAs like butyrate[117]. Through cross-feeding interaction, prebiotics support the growth of beneficial bacteria, enhancing antioxidant defenses to protect intestinal integrity and gut health[118]. Prebiotics through SCFA strengthen the gut barrier, butyrate is an energy source for colonocytes and helps intestinal integrity, reducing systemic inflammation and preventing the translocation of harmful bacterial metabolites into the bloodstream[119]. A study on a 92-year-old female Alzheimer's patient receiving long-term tauroursodeoxycholic acid (TUDCA) treatment revealed significant gut microbiota changes using next-

generation sequencing. TUDCA (Table 2) increased *Firmicutes* and *Proteobacteria*, reduced *Bacteroidetes*, decreased Enterobacteriaceae (22.93%−0.55%), and increased *Ruminococcaceae* (5.8%−13.73%). These changes were linked to increased bile acid influx[96]. A 12-week randomized, double-blind trial with 79 Alzheimer's patients assessed the effects of selenium and probiotic co-supplementation (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*). The combination improved mini-mental status examination (MMSE) scores (+1.5) more than selenium alone (+0.5) or placebo (−0.2). Inflammation and oxidative stress markers decreased while metabolic health improved, including lower insulin, HOMA-IR, triglycerides, and LDL cholesterol. Pro-inflammatory TNF-α expression was downregulated, while PPAR-γ and LDLR expressions increased. These results suggest that selenium-probiotic supplementation enhances cognition, reduces inflammation, and improves metabolic health in AD patients[98].

Synbiotics are a combination of probiotics that contain live microorganisms like *Lactobacillus* spp, *Bifidobacterium* spp, and *Saccharomyces boulardii* and prebiotics like Inulin, Fructooligosaccharides (FOS), Galactooligosaccharides (GOS), also known as non-digestible food fiber which offer a synergistic approach that optimizes gut microbial composition and provides comprehensive neuroprotection[120]. Early studies indicate that synbiotics can improve cognitive function[121], administration of *B. breve A1* (1×10^9 cells in 0.2 mL) and sodium acetate (150 mmol/L) in drinking water from 2 days before intracerebroventricular (ICV) injection of aβ protein effectively reduced aβ accumulation, mitigated tau pathology, and suppressed neuroinflammation in 10-week-old male ddY (Deutschland, Denken, Yoken) AD mice after 6 days (Table 2). Cognitive improvements were observed, with significant restoration in Y-maze alternation behavior, and passive avoidance test latency times[99]. Supplementation of Triphala (a polyphenol-rich prebiotic) with probiotics *Lactobacillus plantarum NCIMB 8826*, *Lactobacillus fermentum NCIMB 5221*, *and Bifidobacterium longum* subsp. *infantis NCIMB 702255* to humanized transgenic *Drosophila melanogaster* AD model over 30 days. The treatment significantly improved motility, restoring climbing ability to near-normal levels and increasing median survival by 75% compared to 40% in controls (Table 2). It also reduced aβ accumulation, lowered acetylcholinesterase activity, and mitigated oxidative stress[100].

Advanced research is exploring fecal microbiota transplantation (FMT) and personalized microbiome-based therapies as potential treatments for AD. Studies support that co-housing wild-type mice with 5xFAD AD transgenic mice for three months resulted in AD-exposed WT mice that developed cognitive impairments, increased hippocampal aβ40 and aβ42 levels, pTau at S202/T205 and S262, and gut microbiota dysbiosis. Gut microbiome analysis revealed a reduction in butyrate-producing bacteria, such as *Faecalibaculum* and *Ruminiclostridium-1*, and significantly lower fecal butyrate levels (Table 2)[12]. APP/PS1 transgenic mice treated with FMT from healthy mice for 4 weeks showed shorter escape latencies in the Morris water maze and higher discrimination indices in the object recognition test. FMT reduced aβ40, aβ42, and amyloid plaques in the cortex and hippocampus, decreased tau phosphorylation at threonine 231, and increased synaptic markers PSD-95 and synapsin I. It also reduced neuroinflammation markers COX-2 and CD11b, by modulating gut microbiota[101]. These findings (Table 2) underscore the transmissible nature of gut microbiome dysbiosis and its critical role in propagating Alzheimer's-like pathology and cognitive deficits *via* the gut−brain axis. Also, supporting gut microbiomes alone or in conjunction with CRD could contribute to AD pathology.

3.4. *Limitation of the current findings with AD*

Despite growing evidence linking the gut microbiome, circadian rhythms, and AD, several limitations hinder their translation into effective therapies. Most studies rely on animal models, such as Tg2756 mice and *Caenorhabditis elegans*, which do not fully replicate human AD pathology due to species differences in gut microbiota composition and immune responses. Additionally, the gut microbiome is highly adapted, and influenced by genetics, diet, age, and medication, making it difficult to establish universal microbiome-based interventions. Variability in sequencing methods and microbiome classification systems further complicates data interpretation. Many studies establish correlations without demonstrating interconnection, leaving uncertainty about whether gut dysbiosis drives AD or results from disease progression. While probiotics, prebiotics, and symbiotics show promise, their effects vary based on strain selection, dosage, and duration, with inconsistent results in clinical trials due to small sample sizes and short intervention periods. FMT has potential, but safety concerns, donor variability, and long-term effects remain unresolved. The complexity of the gut−brain axis, involving immune, metabolic, and neurotransmitter pathways, adds further challenges. The influence of lifestyle factors like diet, sleep, and stress further confounds study outcomes. Standardized methodologies, large-scale longitudinal studies, and well-controlled clinical trials are needed to validate microbiome-targeted therapies and determine their role in slowing AD progression.

4. Oxidative stress and circadian disruption linkage in AD progression

Oxidative stress is a pivotal driver of AD progression and is intricately involved in aβ accumulation, tau hyperphosphorylation, mitochondrial dysfunction, and neuroinflammation[122]. One of the primary mechanisms by which oxidative stress contributes to AD is through its role in aβ pathology. Aggregates of aβ directly impair mitochondrial function by interacting with mitochondrial membranes and proteins, including cytochrome *c* oxidase[123] and mitochondrial permeability transition pore (mPTP)[124]. This interaction leads to enhanced ROS production and reduced ATP synthesis, further compromising neuronal bioenergetics and perpetuating oxidative stress[125]. Moreover, ROS-induced oxidative modifications to lipids and proteins contribute to lipid peroxidation[126] and protein nitration[127], which worsen cellular dysfunction and reinforce aβ toxicity and Tau hyperphosphorylation[128]. These processes form a destructive feedback loop, where increased aβ leads to intensified oxidative damage, mitochondrial failure, and further aβ aggregation.

Oxidative stress also plays a central role in driving tau hyperphosphorylation. ROS activate several tau kinases, including GSK-3β through NADPH oxidase subunits p47 and p67[129], CDK5, and extracellular signal-regulated kinase (ERK) through protein kinase B (PKB)[130] (Fig. 3), which phosphorylate tau at multiple sites, leading to its detachment from microtubules[131]. This detachment destabilizes microtubules, essential for intracellular transport, and promotes the formation of NFTs, a pathological hallmark of AD[132]. In addition to kinase activation, oxidative stress inhibits protein phosphatase 2A (PP2A) (Fig. 3) through JNK, Erk1/2, p38 MAPK, and their upstream

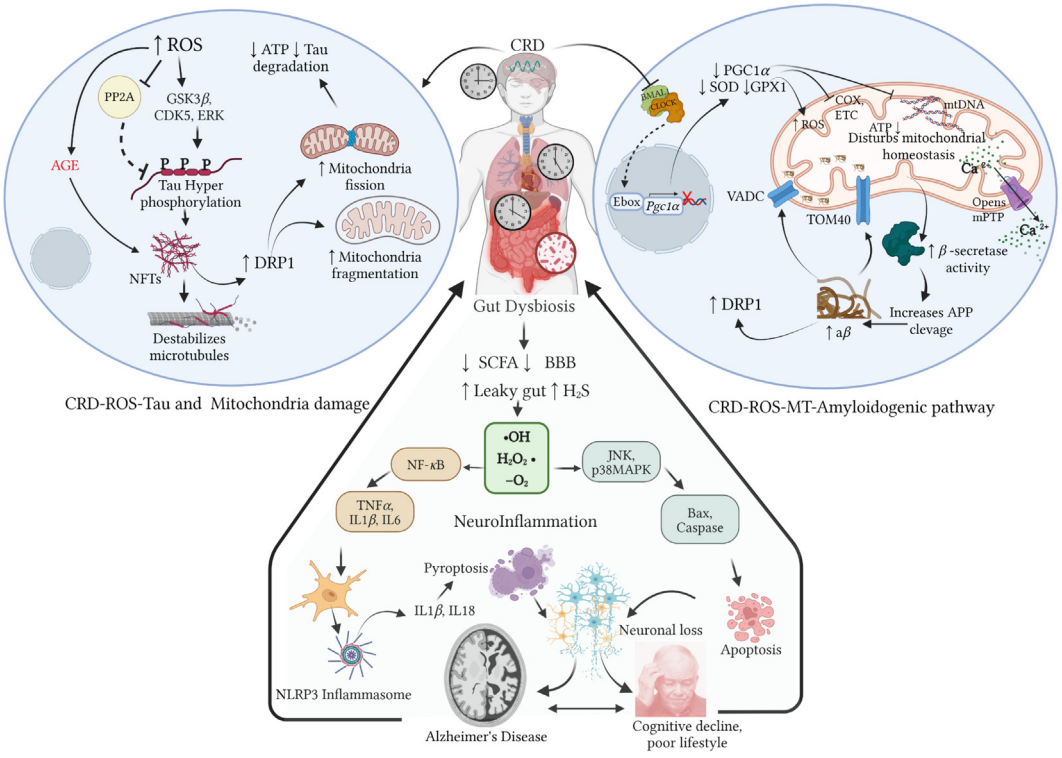

Figure 3 How dysbiosis and circadian rhythms disruption increase the risk of AD progression through oxidative stress, mitochondrial damage, and neuroinflammation. Circadian rhythm disruption affects mitochondrial integrity by decreasing the antioxidant enzymes (SOD, GPx1) and PGC1α expression. This affects the electron transport chain (ETC) and inhibits cytochrome *c* oxidase (COX) and ATP synthesis. PGC1α contributes to mtDNA damage, increases ROS, and disturbs mitochondrial homeostasis by opening mPTP pores. Activation of the BACE1 enzyme further increases aβ42 accumulation and disturbs channel functions of TOM40 and VADC, further increasing ROS. ROS activates tau kinases (CDK5, GSK3β, and ERK), accumulation of advanced glycation end products (AGEs), and inhibition of protein (tau) phosphatase 2A (PP2A), which causes neurofibrillary tangle formation and disturbs microtubule assembly. Tau and aβ activate DRP1, leading to mitochondrial fission and fragmentation. Dysbiosis-induced bacterial metabolites enter the systemic circulation and infiltrate into the brain, which further increases ROS and inflammatory signals. NF-κB activates inflammatory cytokines and induces neuronal death through the microglia−NLRP3−pyroptosis axis. Activation of JNK−MAPK-induced caspase activation and apoptosis, in turn, leads to neuronal/synaptic loss. Mitochondrial homeostasis disturbed by ROS, neuroinflammation, NFTs and aβ accumulation contributes to aggravate AD pathology. AD pathology further increases circadian rhythm disruption and dysbiosis, which leads to a vicious cycle of AD pathology (https://BioRender.com/i23b857).

ASK1, MKK4,1/2 and 3/6 kinases[133], a major tau-dephosphorylating enzyme, by oxidative modification, further promoting sustained tau phosphorylation and tangle formation. Advanced glycation end products (AGEs), which accumulate under oxidative stress conditions, also promote tau aggregation (Fig. 3) through 'receptors for advanced glycation end products' (RAGE)-mediated signaling, further aggravating tau pathology and neuronal toxicity[134]. Chronic neuroinflammation is another major consequence of oxidative stress in AD microglia, the brain's resident immune cells, which are activated in response to oxidative stress, damage-associated molecular patterns (DAMPs), NF-κB, p38 MAPK, and aβ deposition, a vicious cycle. Activated microglia release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which propagate neuroinflammation through NF-κB signaling[135]. This inflammatory response further increases ROS production, exacerbating oxidative damage. The NLRP3 inflammasome, a critical component of innate immunity, is activated in microglia in response to thioredoxin-interacting protein (TXNIP) binding to NLRP3, a component of thioredoxin (TRX) dissociated due to mitochondrial dysfunction and ROS accumulation[136]. NLRP3 activation leads to the secretion of pro-inflammatory mediators like IL-18 and IL-1β, promoting a neurotoxic environment that accelerates synaptic dysfunction and neuronal death through pyroptosis[137], an inflammatory form of programmed cell death (Fig. 3).

4.1. Impact of circadian core complex proteins on mitochondrial function and progression of AD pathology

CRD further compounds mitochondrial stress and AD pathology. BMAL1/CLOCK heterodimer binds to E-box elements on the peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) promoter (Fig. 3), driving transcription[138]. PGC-1α is a master regulator of mitochondrial biogenesis and antioxidant defense by stimulating NRF2, SOD2, and GPx1[139]. Disruption of circadian rhythms, such as sleep deprivation, aging, or shift work, reduces BMAL1/CLOCK expression, impairing PGC-1α activity[138]. Secondary regulators such as REV-ERBα (repressor of *Bmal1*) and retinoic acid-related orphan receptor-α (RORα) (activator of *Bmal1*) also modulate BMAL1 levels, and circadian disruption often results in upregulation of REV-ERBα and downregulation of RORα, further suppressing PGC-1α expression[140].

This reduction in PGC-1α diminishes mitochondrial antioxidant capacity, leading to ROS accumulation, oxidative damage to mtDNA, and impaired activity of complex IV (cytochrome *c* oxidase) within the electron transport chain (ETC). The resulting energy deficits and calcium imbalance caused the opening of the mPTP (Fig. 3), further increasing ROS and oxidative damage[141]. These mitochondrial stressors activate β-secretase (BACE1), enhancing the amyloidogenic cleavage of APP, while the ATP deficit limits aβ clearance by reducing both proteasomal degradation and lysosomal efficiency[141]. Accumulated aβ peptides translocate into mitochondria *via* VDAC1 and TOM40, where they inhibit ETC activity and exacerbate ROS production, establishing a self-perpetuating cycle of mitochondrial dysfunction and aβ toxicity (Fig. 3)[19]. Excessive ROS and mitochondrial dysfunction also activate tau kinases (GSK-3β, CDK5), which hyperphosphorylate tau proteins[46,47]. Hyperphosphorylated tau detaches from microtubules, leading to cytoskeletal destabilization, axonal transport defects, and synaptic dysfunction. CRD also reduces the glymphatic clearance of aβ, worsening its accumulation and neurotoxicity over time[142]. Further, both aβ and pTau upregulate Drp1 (dynamin-related protein 1), promoting excessive mitochondrial fission and fragmentation[143], compounding energy deficits, and synaptic failure.

4.2. *Therapeutic approaches aiming oxidative stress, mitochondria, and inflammation in AD*

Effective therapeutic strategies must target multiple points in this interconnected network to break the cycle of neurodegeneration. Potential interventions like Nrf2 activators such as dimethyl fumarate (DMF), Lanza et al[144]. In 2023 provided proof using Nrf2-RNAi, SH-SY5Y human neuroblastoma cell lines under glucose excess or starvation conditions. They found Nrf2-RNAiabolishing the beneficial effects of DMF, but its benefits in AD condition need to be investigated. Randomized, double-blind, placebo-controlled study of Sulforaphane (NCT04213391) evaluated the efficacy and safety in patients with prodromal to mild AD[145], to enhance endogenous antioxidant defenses and reduce oxidative stress. They found significant upregulation of Nrf2 antioxidant defense. Mitochondrial-targeted antioxidants like MitoQ-treated mice showed improved memory retention compared to untreated 3 × Tg-AD mice as well as reduced brain oxidative stress and synapse loss[146]. Antioxidant SkQ1 showed the efficacy in reducing the signs of AD-like pathology (Table 3) in old OXYS rats by reversing mitochondrial deterioration[147]. At the same time, the antioxidant reduced hippocampal aβ40 and Aβ42 proteins to restore mitochondrial function and reduce ROS production[147]. NLRP3 inflammasome inhibitors, such as CY-09, improve AD pathology and alleviate cognitive impairment in 3 × Tg-AD mice by inhibiting NLRP3 inflammasome activation, reducing neuroinflammation, and protecting against neuronal damage associated with AD progression[148] (Tables 3). MCC950 intervention improved spatial memory and brain histological morphology in SAMP8 mice while reducing amyloid-β deposition in the brain. Additionally, MCC950 inhibited the overexpression of NLRP3, caspase-1, and gasdermin D, key factors involved in pyroptosis, thereby protecting neuronal health[149]. OLT1177 improved the phenotype in APP/PS1 mice by rescuing spatial learning and memory in the Morris water maze test (Table 4). It reduced microglial activation, decreased cortical plaques, and normalized plasma AD metabolic markers, highlighting its potential as a therapeutic agent for AD[150] also being investigated to reduce neuroinflammation and microglial-mediated damage in AD[151].

4.3. *Gaps in current clinical trials and drug pipelines*

The latest AD drug pipeline 2024[152] reflects a reduction in new trials compared to 2023[153], with fewer drugs and new chemical entities entering the pipeline 164 trials with 127 drugs active in 2024 compared to 187 trials with 141 drugs in 2023. Most trials focus on disease-modifying therapies targeting aβ, tau, and inflammation, with limited focus on circadian rhythms, gut microbiome, and oxidative stress (Table 4).

Oxidative stress plays a complex role in AD pathology, yet most antioxidant trials have failed due to multiple factors. Late intervention often reduces efficacy, as oxidative damage is already advanced when symptoms appear. Many antioxidants are not targeted specifically to the brain or mitochondria and face challenges crossing the BBB. AD involves multifactorial pathology, including amyloid-β, tau, inflammation, and metabolic dysfunction, with oxidative stress often a downstream effect rather than a

Table 3 Therapeutic approaches studied to mitigate the oxidative stress in Alzheimer's disease discussed in this review.

Target	Model	Study	Outcome
Sulforaphane[145]	AD models	Examined the neuroprotective effects of sulforaphane by activating the Nrf2 pathway	Enhanced endogenous antioxidant defenses and reduced oxidative stress
MitoQ[146]	3xTg-AD models	Evaluated mitochondrial-targeted antioxidant MitoQ to restore mitochondrial function and reduce ROS production	Improved mitochondrial function and reduced ROS production, improved memory
SkQ1[147]	AD models	Examined SkQ1, for its effects on oxidative stress and mitochondrial dysfunction	Reduced mitochondrial oxidative damage and improved mitochondrial function
CY-09[148]	AD models	Tested NLRP3 inflammasome inhibitor CY-09 for its effects on neuroinflammation and microglial-mediated damage	Reduced neuroinflammation and microglial activation
MCC950[149]	SAMP8, AD mouse model	Evaluated the selective NLRP3 inflammasome inhibitor, in reducing inflammation in AD	Reduced pro-inflammatory cytokines, microglial activation, and synaptic damage
OLT1177[150]	AD models	Studied its ability to inhibit NLRP3 inflammasome activation and reduce inflammation	Showed a significant reduction in neuroinflammation and associated neuronal damage

Table 4 The drugs targeting mitochondria, autophagy, inflammation, gut−brain axis/microbiome, memory, and dementia-related pathways that are in clinical trials and approved stages for AD therapy.

Drug name	Primary target	Mechanism of action	Phase of development	Indication
Coenzyme Q10	Mitochondria	Mitochondrial bioenergetics	Phase II	Mitochondrial disorders
MitoQ	Mitochondria	Mitochondrial antioxidant	Phase II	Neurodegeneration
Resveratrol	Inflammation	SIRT1 activator	Phase II	AD, aging
Lactobacillus plantarum	Gut−brain axis	Probiotic, microbiome modulation	Phase II	Cognitive decline
Curcumin	Inflammation	NF-κB inhibitor	Phase II	AD, inflammation
Nicotinamide riboside	Mitochondria	NAD + Booster	Phase II	Cognitive aging
Bacopa Monnieri	Memory	Neuroprotective, antioxidant	Preclinical	Cognitive enhancement
Donepezil	Dementia	Cholinesterase inhibitor	Approved	AD
Rivastigmine	Dementia	Cholinesterase inhibitor	Approved	AD
Galantamine	Dementia	Cholinesterase inhibitor	Approved	AD
Memantine	Dementia	NMDA receptor antagonist	Approved	AD
Eicosatetraenoic acid	Inflammation	Anti-inflammatory, omega-3 fatty acid	Phase II	Neuroinflammation

primary driver. Trials have also suffered from insufficient potency or duration, using suboptimal doses and short treatment periods that do not reflect AD's chronic nature. The selection of antioxidants has been another challenge, as compounds like vitamin E and vitamin C may lack the potency or specificity needed for AD. Biomarker challenges, including unreliable monitoring of oxidative stress reduction, further obscure results. Trial design issues, such as genetic variability, disease stage, comorbidities, dilute potential benefits, and a lack of stratification based on oxidative stress levels, have been consistent issues. Additionally, the body tightly regulated redox balance can lead to compensatory mechanisms, making excessive antioxidant use potentially harmful. Low levels of oxidative stress can also play physiological roles, making its complete suppression counterproductive.

4.4. Future directions for antioxidant research for AD progression

Future research on antioxidants in AD should emphasize early intervention by targeting at-risk populations before oxidative damage becomes significant. Specificity is crucial, with a focus on developing antioxidants capable of penetrating the BBB and targeting mitochondria or other specific oxidative pathways in the brain. Combination therapies should be explored, integrating antioxidants with treatments targeting other pathological aspects such as amyloid-beta and tau accumulation and other approaches like circadian pathways, mitochondrial health, gut−brain axis therapies, TRF, and gut microbiome modulation. Biomarker-driven trials should play a central role, involving patient stratification and consistent monitoring of oxidative stress markers to assess treatment efficacy accurately. Exploring novel compounds, including next-generation antioxidants with catalytic and regenerative properties, could provide more effective solutions. Overall, a refined understanding of oxidative stress and its precise contributions to AD pathology is essential for designing successful therapeutic strategies.

4.5. Oxidative stress and its limitations in AD pathogenesis

Despite extensive research on oxidative stress, mitochondrial dysfunction, and CRD in AD, several critical limitations persist. A major challenge is the bidirectional feedback between oxidative stress and CRD, making it difficult to determine whether these factors drive AD progression or arise as consequences of aβ and tau pathology. Mitochondrial dysfunction is well-recognized in AD, but its role as a primary trigger *versus* a downstream effect remains unclear. Tissue-specific variability in mitochondrial regulators, such as PGC-1α, BMAL1, and CLOCK, further complicates data interpretation, particularly in neurons *versus* astrocytes. Additionally, the link between CRD, mitochondrial impairment, and glymphatic clearance of aβ remains poorly defined, though disruptions in sleep-wake cycles may exacerbate neurodegeneration by impairing this clearance mechanism. While mitochondria-targeted antioxidants like MitoQ and Nrf2 activators have shown promise in preclinical models, their efficacy in human trials is limited due to bioavailability issues and poor blood−brain barrier penetration. Furthermore, short intervention durations, small sample sizes, and inconsistent biomarker assessments reduce reproducibility across studies. Given the complexity of AD, therapies targeting a single mechanism, such as oxidative stress or mitochondrial dysfunction, may be insufficient for clinical impact. Although CRD, oxidative stress, neuroinflammation, and the gut microbiome are promising therapeutic targets, the lack of large-scale, long-term clinical trials and mechanistic clarity limits their immediate translation into effective AD treatments. Future research should prioritize comprehensive validation, biomarker-driven approaches, and personalized interventions to enhance therapeutic efficacy.

5. Time-restricted feeding/eating as a therapeutic strategy in AD

TRF/TRE is a promising non-pharmacological intervention that aligns nutrient intake with the body's circadian rhythms, typically limiting food consumption to a 6- to 12-h window followed by fasting. Unlike traditional intermittent fasting, TRF does not involve caloric restriction, making it more sustainable and accessible for patients[25]. TRF has demonstrated substantial benefits for patients suffering from type 2 diabetes to cancers, in metabolic health, mitochondrial function, and autophagy, all of which are key in reducing oxidative stress and neuroinflammation[154]. By improving circadian alignment, glucose metabolism, and insulin sensitivity, TRF is emerging as a therapeutic strategy for AD by reducing aβ accumulation and cognitive decline[155].

5.1. TRF-mediated circadian regulation in AD

Circadian rhythms regulate key physiological processes such as sleep-wake cycles, hormone secretion, and metabolism, all of

which were commonly disrupted in AD[3]. TRF helps to realign these rhythms by synchronizing eating patterns with the body's internal clocks[156]. TRF promotes circadian clock synchronization between central and peripheral clocks and enhances cognitive function by maintaining glucose metabolism and reducing aβ accumulation[157]. On a molecular level, TRF influences the BMAL1/CLOCK pathway, which governs the expression of CCG involved in glucose metabolism *via* insulin secretion, glucose uptake[158], cellular repair, and protein clearance[159]. BMAL1 and CLOCK proteins form a complex that regulates circadian rhythms by driving the expression of genes such as PER and CRY, which provide feedback to inhibit BMAL1/CLOCK activity, creating a 24-h cycle[160]. TRF helps maintain this feedback loop's balance, ensuring that circadian rhythms remain stable and aligned[161]. TRF (6:18 feeding and fasting) regimen in the APP23 transgenic AD mouse model for six months significantly improved cognitive performance, reduced amyloid plaque load, and decreased neuroinflammation markers such as TNF-α and IL-6. TRF also restored circadian rhythms by normalizing diurnal activity (Table 1) and gene expression patterns related to metabolism and inflammation[67]. TRF-induced activation of SIRT1 also plays a critical role in circadian regulation. SIRT1 interacts with and deacetylates BMAL1, enhancing the stability and function of the BMAL1/CLOCK complex during the fed state[162]. This deacetylation strengthens circadian rhythms by promoting the expression of PER and CRY and helps synchronize peripheral clocks with the central SCN-regulated clock[163]. SIRT1 also influences the rhythmic expression of metabolic and autophagic genes in the brain by activating Forkhead box O3 (FOXO3), a transcription factor that induces autophagy genes like *Lc3, Bnip3*[164], improving the clearance of aβ and maintaining energy homeostasis, both crucial for neuronal health[165]. TRF also impacts the AMPK pathway, a key energy sensor linked to circadian regulation. Activated AMPK modulates the phosphorylation of clock protein CRY1 (Fig. 4), affecting its stability and interactions with other signaling molecules[166]. By destabilizing CRY, AMPK influences the negative feedback loop of the circadian clock, thereby resetting the molecular clock and synchronizing it with metabolic needs. The TRF's regulation of AMPK helps align the energy metabolism with the circadian cycle, reducing disruptions that can contribute to AD pathology. Furthermore, TRF increases REV-ERBα expression during fasting through AMPK-driven CRY degradation and BMAL1 activation (Fig. 4), followed by *Per*, *Cry*, and *Rev-Erbα* gene expression[167] to ensure timely repression and activation of circadian genes like BMAL1, thereby maintaining the circadian cycle[155]. The interaction between REV-ERBα, SIRT1, and AMPK under TRF creates a tightly regulated feedback mechanism that optimizes circadian control of metabolic processes and effectively realigns circadian rhythms enhancing cellular repair, metabolic regulation, and neuronal function. This circadian realignment supports cognitive health and contributes to slowing AD progression.

TRF, limited to a 6-h feeding window during the active phase, and 18 h of fasting over 3 months significantly improved disruptions in total sleep, wakefulness, agitation, and sleep fragmentation, by enhancing sleep quality and reducing agitation and fragmentation in APP23 transgenic mouse model of AD. In addition to that, TRF also induced nutritional ketosis (β-hydroxybutyrate >0.5 mmol/L) and reduced blood glucose levels compared to ad libitum feeding (ALF) mice[67]. In male *db/db* mice, a diabetic model prone to AD, and wild type controls 8 weeks TRF regimen improved AD pathology. Mice were

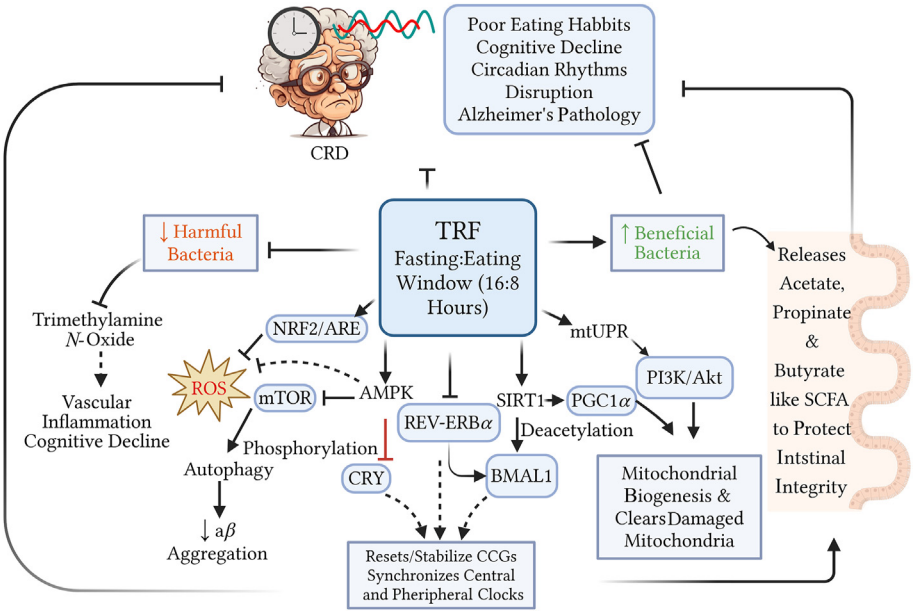

Figure 4 Therapeutic implications of time-restricted feeding (TRF) for resetting the disturbances in circadian rhythms and gut microbiota to control AD progression. TRF promotes autophagy through AMPK activation by inhibiting mTOR, which supports amyloid β clearance. Decreased Rev-ERBα impact on Bmal1 reduces CRY activity. It also activates SIRT1 to induce PGC1α and to promote unfolded protein response mitochondrial biogenesis. TRF further balances the gut microbiome and promotes beneficial bacteria for short-chain fatty acid (SCFA) production, decreasing the harmful bacteria that are responsible for trimethylamine *N*-oxide (TAMO) production and cognitive dysfunction. TRF resets circadian rhythms and synchronizes central and peripheral clocks, which supports a healthy lifestyle to counter AD-associated cognitive decline (https://BioRender.com/d60h309).

subjected to either normal (12:12) or disrupted (6:18) light/dark (LD) cycles, with food provided ad libitum (AL) or restricted to an 8-h window during the active (dark) phase in the TRF group. TRF significantly mitigated cognitive deficits caused by disrupted LD cycles and reduced hyperphosphorylation of tau protein at key sites (Ser396 and Thr231) in the hippocampus. TRF also restored disrupted circadian rhythms by normalizing the expression of key clock genes (*e.g.*, *Per2*, *Rev-erbα*) and improved metabolic health by reducing body weight, lipid accumulation, and liver triglyceride levels. These findings demonstrate that TRF effectively protects against circadian disruption-aggravated AD pathology through circadian and metabolic regulation[168].

5.2. *Impact of TRF and gut microbiome in mitigating AD*

TRF significantly influences gut microbiome composition such as *Bifidobacterium*, *Lactobacillus*, *A. muciniphila*, and *Faecalibacterium prausnitzii*[169]. These beneficial bacteria produce bioactive metabolites, particularly SCFAs like acetate, propionate, and butyrate, which strengthen tight junctions in the gut epithelium, reduce intestinal permeability, and prevent the systemic translocation of harmful endotoxins such as LPS. By limiting the entry of LPS into the bloodstream and modulating the gut microbiome, TRF reduces systemic inflammation, which is linked to the progression of AD. In addition to promoting beneficial bacteria, TRF decreases the populations of harmful bacteria that produce neurotoxic metabolites, such as trimethylamine (TMA), which is converted into trimethylamine *N*-oxide (TMAO). High TMAO levels are associated with vascular inflammation and cognitive decline[170], both of which exacerbate AD pathology (Fig. 4). By resetting gut health through beneficial bacteria, TRF reduces TMAO-producing harmful bacteria, TRF may decrease vascular inflammation and support overall brain function. TRF positively impacts pathways involving the vagus nerve and the HPA axis, which regulate stress responses and neuroinflammation by increasing autonomic response, cortisol, and ghrelin levels[171].

Hence, improving gut flora under TRF directly modulates neuroinflammation and supports cognitive health in AD through these complex pathways. A study involving 10 growing pigs fitted with T-cannulas for proximal colon sampling compared two feeding regimens: Free access with unrestricted feeding and TRF limited to three 1-h slots daily. Over 15 days, colonic digesta samples were collected on Day 16 at 6-h intervals. TRF altered nutrient substrate oscillations (*e.g.*, cellulose and starch), modulated gut microbial rhythmicity, and enhanced microbial interactions, gaining rhythmicity in families such as *Pasteurellaceae*. These results demonstrate TRF's potential to optimize gut health by regulating microbial dynamics and nutrient utilization[172]. A 12-week isocaloric-restricted feeding trial with 96 overweight or obese adults (mean age 36 years), followed by a 28-week follow-up, compared to a healthy low-carbohydrate diet (HLCD), TRE, and a control regimen. HLCD significantly reduced fat mass and altered the gut microbiome. Both interventions increased beneficial gut bacteria (Table 2), including *Parabacteroides distasonis*, *Bacteroides intestinalis*, and *Parabacteroides goldsteinii*[103].

5.3. *Therapeutic impact of TRF on oxidative stress in AD*

TRF offers significant neuroprotective benefits in AD by reducing oxidative stress through the activation of several interconnected molecular pathways. TRF was found to enhance mitochondrial function by upregulating mitochondrial unfolded protein response (mtUPR) and limiting mitochondrial fragmentation by reducing DRP1[7] and stimulating antioxidant defenses, primarily by activating the Nrf2/ARE pathway through AMPK activation and BHB production during fasting[173], which neutralizes ROS, through the transcription of key antioxidant enzymes such as SOD, GPx, and heme oxygenase-1[174]. Recent studies provided substantial evidence for the role of TRF in activating the AMPK pathway[175]. TRF improves mitochondrial efficiency, reduces ROS production, enhances fatty acid oxidation, and promotes mitochondrial biogenesis *via* PGC-1α[176]. TRF also inhibits the mTOR pathway during the non-fed state/fasting period in mice[177], thereby promoting autophagy, a critical process for clearing damaged proteins, organelles, and aβ plaques[67] further reducing oxidative stress. TRF also promotes mtUPR which activates the PI3K/Akt pathway and MAPK/ERK pathway (Fig. 4), ensuring the removal of damaged mitochondria, modulating insulin sensitivity, and cell survival and neuroprotection[178]. Altogether, TRF's ability to activate these interconnected pathways safeguard against ROS-induced oxidative stress, supporting mitochondrial health, and reduces inflammation, which enhances neuronal resilience against stress, making it a promising intervention in mitigating AD progression.

5.4. *TRF-mediated health benefits in AD and therapeutic implications*

AD is often associated with disruptive feeding behaviors, including intake of non-nutritional foods or forgetting to eat altogether. These behaviors are common in mid-to-late-stage AD and are linked to cognitive decline and poor nutritional status[179]. As a result, weight loss and malnutrition become significant problems, further exacerbating the symptoms of AD and accelerating disease progression. A study on aged male Fisher 344 × Brown Norway F1 hybrid rats examined the effects of TRF with ketogenic or standard diets on cognition and gut microbiota. TRF, implemented as one meal per day from 8 to 21 months of age, significantly improved cognitive performance in biconditional association tasks compared to ad libitum feeding (Table 2)[102]. TRF also enhanced gut microbiome composition, increasing beneficial genera like *Allobaculum*, *Intestinimonas*, and *Eubacterium ventriosum*, with distinct beta diversity differences between feeding methods. The ketogenic TRF group showed a lower glucose-ketone index (GKI), indicating enhanced nutritional ketosis. TRF mitigated age-related cognitive decline, demonstrating its potential to improve metabolic and brain health during aging[102]. TRF reduces aβ accumulation and decreases hyperphosphorylated tau proteins through fasting-induced autophagy, also contributing to better memory and behavioral outcomes by reducing inflammation, promoting insulin sensitivity, and BDNF[180]. The study used an APP/PS1 transgenic mouse model of AD to investigate the effects of circadian rhythm restoration through TRF and glucagon-like peptide-1 (GLP-1) treatment over an 8-week period (Table 1). Mice were divided into control, TRF, GLP-1, and combined TRF + GLP-1 groups, with TRF restricting food access to a 10-h window during the active phase. GLP-1 receptor agonist liraglutide was used alongside tools to analyze circadian rhythms, amyloid pathology, and metabolic homeostasis. The results showed that TRF and GLP-1 treatment, particularly in combination, improved circadian clock gene expression (*Bmal1*, *Clock*), reduced aβ deposition, enhanced glucose metabolism, and restored cognitive function, highlighting the therapeutic potential of circadian and metabolic interventions in AD[68]. At the

molecular level, TRF activates the AMPK pathway, which enhances mitochondrial function through AMPK-regulated kinase navel (nua) kinase 1 (NUAK1) (regulates the mitochondria localization in neurons) and brain and retinal angiogenesis-related protein (BRAWNIN, promotes mitochondrial biogenesis) and promotes axon branching[181]. SIRT1, a crucial regulator of circadian rhythms and neuroprotection in the brain by inducing the CCGs through deacetylation, is also activated by TRF. The interplay between SIRT1 and AMPK in regulating autophagy and mitochondrial function provides a strong molecular basis for TRF's cognitive benefits[182]. TRF stimulates neurogenesis, in 8-week-old male C57BL/6 mice by activating neuronal precursor cells through BDNF and neurotropin 3 in the hippocampus, a region critically involved in learning and memory[183]. While human research on TRF and its cognitive benefits is still in the early stages, initial findings are promising. A 14-h TRF intervention conducted over 30 consecutive days in 14 healthy subjects reduced amyloid-β deposition and increased levels of BDNF in the brain and significantly[69] (Table 2) essential for neuroplasticity, learning, and memory. However, larger, long-term randomized controlled trials are needed to confirm these results and determine the broader applicability of TRF as a therapeutic intervention for cognitive decline in AD. Implementing a structured feeding schedule through TRF can help mitigate these maladaptive feeding behaviors by providing consistency and routine.

5.5. *Limitations of TRF research in modulating AD pathology*

Many trials involved small sample sizes, such as the pilot study with 12 participants and the 14-subject TRF intervention, limiting statistical power and generalizability. Short study durations, often ranging from 8 to 12 weeks, make it challenging to assess long-term cognitive and metabolic outcomes. Variability in TRF protocols, including differences in feeding windows and timing (*e.g.*, early *vs.* delayed TRF), further complicates direct comparisons between studies. Additionally, diverse study populations and models, including APP23 and C57BL/6J mice, human participants, and *Drosophila*, create challenges in translating results from animal models to human pathology. Many studies also lacked long-term follow-ups to determine whether observed benefits persisted over time and presented inconsistent use of biomarkers, with some trials focusing on cognitive assessments alone while others included inflammatory and oxidative stress markers like TNF-α and BDNF. Limited control for external factors such as physical activity, diet composition, and sleep patterns introduces potential confounders, while species differences between human and rodent models further limit translational relevance. Some human trials may also be influenced by the placebo effect, especially when using self-reported cognitive assessments without blinding. To strengthen the evidence, base for TRF in AD prevention, future research should involve larger, multi-center trials with standardized TRF protocols, extended intervention periods, comprehensive biomarker profiling, and better control of confounding lifestyle variables.

6. Integrating circadian-linked contributing factors to advance AD research

CRD can alter the gut microbiome composition and gut barrier integrity. Reduced BMAL1 activity weakens the expression of tight junction proteins (occludin and claudin-5), compromising gut permeability[80]. This allows endotoxins like LPS to enter circulation, activating TLR4/NF-κB signaling[82], enhancing neuroinflammation, amplifying AD pathology, and modulating CRs. Beneficial bacteria such as *A. muciniphila* and *F. prausnitzii* produce SCFAs like butyrate and propionate, which activate BMAL1 expression and stabilize circadian phases by inhibiting HDACs[163]. Additionally, microbial metabolites like serotonin and melatonin influence central clock regulation in the SCN. CRD impairs mitochondrial antioxidant defense, contributing to oxidative stress. BMAL1 and CLOCK regulate the expression of PGC-1α, a key mitochondrial biogenesis and antioxidant gene[138]. PGC-1α promotes the expression of enzymes such as SOD2 and catalase[139]. Disrupted BMAL1 control reduces PGC-1α, impairing antioxidant capacity and leading to an excess ROS generation[141]. Elevated ROS activates kinases like GSK-3β and CDK5[46], promoting tau hyperphosphorylation while inhibiting PP2A, a tau phosphatase[133]. CRD further reduces mitochondrial efficiency by increasing DRP1 expression, mitochondrial fragmentation, and amplifying oxidative stress-driven neurodegeneration[143].

Dysbiosis, characterized by an imbalance in microbial populations, promotes oxidative stress by increasing pathogenic bacteria like *Desulfovibrio* and *E. coli*. These bacteria produce LPS and H_2S, both of which impair mitochondrial function and amplify ROS production[78]. LPS activates TLR4/NF-κB signaling, enhancing pro-inflammatory cytokine release (IL-1β, IL-6, TNF-α) and promoting neuroinflammation[82]. Curli proteins from *E. coli* also cross-seed with aβ, accelerating its aggregation and oxidative damage[52]. Conversely, SCFA-producing bacteria such as *Lactobacillus* and *Bifidobacterium* reduce oxidative stress by activating the Nrf2 pathway, which upregulates antioxidant enzymes including HO-1, SOD2, and catalase[174]. TRF improves circadian alignment by limiting food intake to a specific window and synchronizing the central (SCN) and peripheral clocks. TRF enhances BMAL1 stability by activating SIRT1, which deacetylates *Bmal1* and stabilizes circadian gene expression[162]. TRF also modulates AMPK activity, which phosphorylates and destabilizes CRY1, resetting the circadian cycle[166]. By realigning circadian rhythms, TRF enhances glymphatic clearance of aβ and tau, reduces metabolic dysfunction, and improves sleep-wake cycles[7].

TRF beneficially reshapes the gut microbiome by increasing SCFA-producing bacteria such as *A. muciniphila*, *Bifidobacterium*, and *Lactobacillus*[87] while reducing pathogenic strains like *Desulfovibrio*[88]. The SCFAs enhance gut barrier integrity by regulating tight junction proteins and reducing systemic inflammation[169]. Butyrate also inhibits HDAC activity and prevents the over activation of NF-κB, reducing pro-inflammatory cytokine release[51]. Strengthened gut barrier integrity reduces LPS leakage, further decreasing systemic inflammation and oxidative stress. TRF reduces oxidative stress by activating the AMPK/Nrf2 pathway, which upregulates antioxidant enzymes (SOD2, GPx, and HO-1) and suppresses the mTOR pathway[177]. This increases autophagy and mitochondrial turnover and reduces ROS production. TRF also enhances mitochondrial health by activating PGC-1α, reducing the ROS production, NFTs and aβ accumulation, which promotes mitochondrial biogenesis and reduces DRP1-mediated mitochondrial fragmentation[184].

6.1. *Unraveling the impact of TRF on the circadian feedback loop in modulating AD pathology*

CRD exacerbates gut dysbiosis by reducing BMAL1 and CLOCK activity, leading to the downregulation of tight junction proteins

such as occludin and claudin-5, which increases gut permeability and allows endotoxins like LPS to enter circulation. This triggers TLR4/NF-κB signaling, promoting neuroinflammation and oxidative stress. CRD also disrupts mitochondrial antioxidant defenses by decreasing PGC-1α expression, impairing enzymes such as SOD2 and catalase, leading to ROS accumulation. Simultaneously, gut dysbiosis results in reduced SCFA production, weakening the gut barrier and amplifying inflammatory signaling through LPS and H_2S release, which further activates the NF-κB pathway and oxidative damage. Oxidative stress drives further CRD by inhibiting BMAL1/CLOCK activity and promoting mitochondrial dysfunction through DRP1 overexpression and impairing mitophagy. TRF helps restore this disrupted balance by enhancing BMAL1 and SIRT1 expression, a key metabolic sensor and NAD^+-dependent deacetylase, not only stabilizes circadian gene expression but also boosts Nrf2 activity, mitigating oxidative stress, promoting mitochondrial health, and reduces inflammation. TRF also improves gut health by promoting SCFA-producing bacteria, which strengthens the gut barrier and reduces systemic inflammation. Furthermore, TRF activates the AMPK/Nrf2 pathway, enhancing mitochondrial antioxidant defenses and reducing ROS accumulation while promoting mitochondrial biogenesis and autophagy, thus lowering oxidative stress and neurodegeneration. These interconnected feedback loops emphasize the importance of targeting circadian rhythms, gut microbiome, oxidative stress, and TRF simultaneously for AD prevention and therapy.

7. Gaps and future directions in AD research

Despite significant advances in AD research, several critical gaps persist, particularly in understanding the interplay between CRD, oxidative stress, and gut microbiota dysbiosis. These factors are often studied in isolation, overlooking the feedback loops that exacerbate neurodegeneration. The molecular mechanisms linking circadian misalignment, mitochondrial dysfunction, oxidative stress, and neuroinflammation remain poorly characterized. For example, the tissue-specific roles of circadian clock proteins (*e.g.*, BMAL1, CLOCK, REV-ERBα) in peripheral organs and their contributions to AD pathology are unclear. Similarly, the diurnal dynamics of gut microbial metabolites, such as SCFA and bile acids, and their effects on central and peripheral clocks are insufficiently understood. Microbial-derived amyloids, LPS, and other bacterial neurotoxins may influence aβ and tau aggregation cross-seeding mechanisms, yet this area remains underexplored. Additionally, the role of the glymphatic system in circadian-regulated aβ clearance and its interactions with neuroinflammation require further investigation. While therapeutic interventions like TRF, probiotics, and melatonin show potential, they lack standardized trial designs, optimized dosages, and strain-specific evaluations, limiting their translational value. Preclinical models such as APP/PS1 mice fail to reflect the metabolic and genetic complexity of human AD, and clinical trials often lack diverse cohorts, extended follow-ups, and representation of underexplored populations. Furthermore, significant lifestyle factors such as sleep deprivation, shift work, and physical inactivity are frequently overlooked, despite their potential impact on circadian health and AD risk.

Addressing these gaps requires integrative approaches that examine the dynamic interplay among CRD, gut microbiome dysbiosis, and oxidative stress while leveraging advanced models, diverse cohorts, and multi-omics techniques. Such efforts will provide a comprehensive understanding of these mechanisms and pave the way for innovative therapeutic strategies to slow or prevent AD progression.

To address critical gaps in AD research, future studies must explore the complex interplay between CRD, oxidative stress, and gut microbiome dysbiosis as interconnected drivers of neurodegeneration. Investigating tissue-specific roles of circadian clock proteins (*e.g.*, BMAL1, REV-ERBα, CLOCK) in the SCN, hippocampus, liver, and intestine is essential. The diurnal dynamics of gut microbial metabolites, such as SCFAs and bile acids, and their downstream effects on peripheral and central clocks require multi-omics profiling to uncover mechanisms linking gut−brain communication to aβ clearance and tau phosphorylation. Therapeutic approaches should include TRF protocols adapted to circadian phenotypes, age, and sex, combined with microbiome-targeted interventions like prebiotics (*e.g.*, inulin, FOS) and probiotics (*e.g.*, *A. muciniphila*, *B. breve*) to enhance microbial diversity, SCFA production, and vagus nerve signaling. Molecular mechanisms underlying microbial amyloid cross-seeding, LPS-induced neuroinflammation, and bacterial neurotoxins in exacerbating aβ and tau pathology must be evaluated using proteomics and gut microbiota transplants in transgenic AD models. Real-time imaging, such as positron emission tomography (PET) tracers, should be employed to assess neuroinflammation and glymphatic clearance dynamics under CRD and gut microbiome-targeted therapies. Mitochondrial dysfunction and oxidative stress remain central to AD pathology, necessitating the development of mitochondrial-targeted antioxidants (*e.g.*, MitoQ) and Nrf2 activators (*e.g.*, Sulforaphane, dimethyl fumarate) to address ROS production and restore mitochondrial homeostasis. Calcium channel blockers (*e.g.*, verapamil) should be tested for their ability to regulate mitochondrial calcium overload and reduce oxidative damage. Neuroimmune modulation, including NLRP3 inflammasome inhibitors (*e.g.*, MCC950) and lipid mediators (resolvins, lipoxins), represents a promising avenue to resolve chronic inflammation and enhance microglial-mediated aβ clearance. Integrated chronotherapy protocols combining TRF, light therapy (*e.g.*, blue light $\sim$480 nm), and pharmacological agents should be developed and personalized using AI-driven tools analyzing real-time biomarker data, including circadian health markers (*e.g.*, BMAL1 expression), gut microbiota metabolites (*e.g.*, SCFA levels), and oxidative stress indicators (*e.g.*, mtDNA damage). Biomarker discovery efforts should also focus on *ApoE* genotype-specific differences and longitudinal tracking of plasma biomarkers such as aβ42/40 ratios and neurofilament light chain (NfL). Preclinical models need to integrate circadian disruptions, gut microbiome alterations, and sex-specific hormonal influences on AD pathology, using systems like *Drosophila*, germ-free mice colonized with human microbiota, and non-human primates. Longitudinal human cohort studies stratified by sex, age, and circadian phenotypes can bridge translational gaps and enhance intervention precision.

Finally, lifestyle interventions combining plant-based diets, physical activity, and circadian alignment therapies should be systematically evaluated for their potential to synergize with pharmaceutical and gut microbiome-targeted therapies. Real-time multi-omics approaches, coupled with systems biology tools like weighted gene co-expression network analysis (WGCNA) and machine learning, can uncover predictive patterns linking CRD, gut microbiome dysbiosis, and oxidative stress to AD progression. By integrating these strategies, future research can generate innovative, personalized interventions that address critical

mechanistic gaps and slow or prevent AD progression while improving patient outcomes.

8. Conclusion and significance

Alzheimer's disease is an extraordinarily complex condition, demanding an equally multifaceted approach to its understanding and treatment. Addressing these critical gaps requires a paradigm shift toward a more integrative and multidisciplinary research framework. Future studies should prioritize simultaneous assessment of circadian rhythms, gut health, oxidative stress, and TRF in both preclinical and human cohorts. Incorporation of personalized interventions targeting multiple biological pathways will improve therapeutic outcomes. The development of non-invasive biomarkers to assess intervention efficacy is essential for tracking disease progression and therapeutic responses in AD without the need for invasive procedures. By expanding mechanistic insights and standardizing intervention protocols, researchers can pave the way for targeted therapies capable of modifying disease progression and improving the quality of life for those affected by AD.

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Author contributions

Initial outline given by Girish C. Melkani and review draft completed by Kishore Madamanchi. Jianhua Zhang and Girish C. Melkani provided final suggestions and corrections.

Conflicts of interest

Authors declared no conflicts of interests.

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