*Review Article*

The Role of Minocycline in Alzheimer’s Disease: Acetylcholinesterase Inhibition and Neuroprotective Mechanisms



**ABSTRACT**

|  |
| --- |
| Minocycline, a semisynthetic tetracycline antibiotic, has garnered attention for its potential therapeutic effects on Alzheimer’s disease (AD). It has been extensively studied for its potential neuroprotective effects beyond its antimicrobial properties. This review explores the pharmacological mechanisms, therapeutic applications, and clinical trials of minocycline, with a particular focus on its role in neurodegenerative diseases such as AD. Acetylcholinesterase (AChE) is the enzyme responsible for the breakdown of acetylcholine in the synaptic cleft, and its inhibition is a key therapeutic target in AD treatment. By inhibiting AChE, minocycline increases acetylcholine levels in the brain, which may improve cognitive function and mitigate neurodegenerative processes. The study concluded that minocycline is a promising therapeutic agent for the treatment of AD. As this condition is affecting more people worldwide, minocycline could lead to effective and timely treatment for people suffering from this disease. |

*Keywords: Monocycline,* Alzheimer’s disease, Acetylcholinesterase, tetracycline antibiotic

**1. INTRODUCTION**

Alzheimer's disease (AD) is the leading cause of dementia and has rapidly become among the most expensive, deadly, and burdensome diseases of the 21st century (1). Currently, the disease affects over 50 million people worldwide, which is expected to triple by 2050 and increase economic and social costs at that time (2). In fact, the U.S. alone faces an estimated $1.2 trillion burden by 2050. Despite global efforts, including the commitment of the G8 Dementia Summit in 2013 to find a cure or disease-modifying therapy by 2025, effective treatments remain elusive, with current medications offering symptomatic benefits and doing little to stop disease advancement (2, 3).

Alzheimer's disease is a neurodegenerative disorder characterized by progressive cognitive decline, memory loss, and functional disability (4) [65]. The pathological etiology of the disease involves the accumulation of β-amyloid plaques and tau tangles; both factors are related to disrupted communication between neurons and contribute to the synaptic and neuronal loss (5). Although the exact etiology of AD is still unknown, growing evidence has gradually shifted the focus from targeting Aβ alone to investigating neuroinflammatory mechanisms, oxidative stress, and cholinergic dysfunction (5). The rapidly increasing global burden of AD has created an urgent need for the identification of novel targets that address not only symptoms but also underlying disease mechanisms [66].

AD is a complex and multifactorial pathology, but two great hypotheses have dominated the field: the cholinergic hypothesis and the amyloid hypothesis [67]. Described for the first time by the German psychiatrist Alois Alzheimer, this disease features neuritic plaques and neurofibrillary tangles caused by the medial temporal lobe and neocortical deposition of Aβ peptides (4). According to Breijyeh and Karaman (2020), neuropathological changes could be separated into two: positive lesions, which were characterized by deposition of abnormal protein accumulation, and negative lesions, marked by brain atrophy and synaptic loss (6).

The most familiar hallmark of AD pathology is the presence of senile plaques, which are extracellular Aβ deposits with dense cores that disrupt neuronal communication. The enzymes that catalyze the development of Aβ peptides from amyloid precursor protein (APP) are β-secretase and γ-secretase (7). The second hallmark of AD is the presence of neurofibrillary tangles (NFTs), which are intracellular aggregates of hyperphosphorylated tau protein. These tangles have been reported to meddle with the normal functioning of cytoskeletal microtubules, thereby causing cytoskeletal collapse, axonal damage, and neuron death (8).

Among the earliest manifestations of AD are synaptic losses, primarily in the neocortex and limbic system, which are crucial regions for memory and learning (9). Synaptic failure, caused by the loss of dendritic spines, axonal dystrophy, and mitochondrial dysfunction, contributes to the cognitive decline seen in AD patients (10). Also, it is mediated by the processes of neuroinflammation, oxidative stress, and cholinergic dysfunction, thereby exacerbating neurodegeneration (10).

Though not completely understood, research has highlighted two primary pathological targets: cholinergic dysfunction and the accumulation of amyloid beta (11). The cholinergic hypothesis involves impaired synthesis of acetylcholine and reduced cholinergic neurotransmission (12). Acetylcholine (ACh) is a major neurotransmitter necessary for learning, memory, and attention, and its decline in AD leads to significant cognitive impairment. ACh is synthesized by the enzyme choline acetyltransferase (ChAT); a loss in its activity has been associated with AD pathophysiology. This is reflected in the degeneration of cholinergic neurons, particularly those in the basal forebrain (13).

It has been suggested that Aβ oligomers cause cholinergic-based synaptic loss and subsequent neurotoxicity and inflammation that ultimately results in cellular death (14,59). Furthermore, progressive tau kinase-induced mitochondrial and endoplasmic reticulum damage results in synaptic loss, hindered metabolism, and cytotoxicity of neural cells (15). Moreover, in vivo experimental studies indicate that the presence of Aβ inhibits choline uptake, and since ACh release is blocked, cognitive impairment among AD patients occurs. Fortunately, such abnormalities do not cause cholinergic neuronal death to worsen (13). Additionally, marked reductions in nicotinic and muscarinic ACh receptors on terminals were observed in AD brains, which had a significant negative impact on cholinergic signaling (13).

Despite intense research and hundreds of clinical trials, effective treatments against AD have yet to be discovered. Several hundred such trials had been conducted with promising drugs, but the results needed to have clinically significant improvements. The reason for this failure possibly depends on the fact that the pathogenesis of AD is associated with multiple biochemical pathways (at least 25). Hence, treatment targets most of these pathways simultaneously, and even drugs with potential efficacy are unlikely to succeed when administered alone (16, 5). In general, there are two classes of drugs used to treat AD: cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists. They are developed to enhance the functions of the brain through increasing cholinergic signaling or reducing the glutamate-induced excitotoxicity that leads to refined cognitive functioning. Still, these treatments have poor efficacy and are quite expensive (6).

Given such deficiencies in current AD therapies, drug repurposing has thus become an attractive alternative in pursuit of cost-effective and timely solutions (17). Drug repurposing is a drug development process that detects new therapeutic potential for previously approved drugs (18). That reduces time and expenses in drug development. Successful examples include ketoconazole, repurposed for Cushing's syndrome (19), and topiramate an anti-epileptic, now used for obesity treatment (20).

While originally developed as a broad-spectrum antibiotic, minocycline, in recent years, has been widely reported for repurposing into the treatment of various non-infectious diseases, including cancer and neuroinflammatory disorders (21). Its ability to cross the blood-brain barrier makes minocycline particularly valuable in the treatment of neurological ailments such as AD (22, 60). Minocycline possesses anti-inflammatory, antioxidant, and anti-apoptotic properties, aside from its antimicrobial mode of action, which is highly instrumental in its neuroprotective functions (21).

Minocycline has been repurposed for conditions like cancer due to its ability to affect cellular processes, like inhibition of the epithelial-mesenchymal transition (EMT), one of the main hallmarks of cancer. According to Yang et al. (2022), in colorectal cancer cells, minocycline inhibits this transition phase and metastasis via binding and inactivating the LYN kinase, leading to suppression of STAT3 activity (23). Moreover, minocycline has anti-inflammatory properties, which may position it for the treatment of chronic inflammatory disorders by modulating the production of pro-inflammatory cytokines and thus reducing systemic inflammation (24). Therefore, minocycline has been pointed out as an anti-inflammatory drug capable of targeting these pathways, positioning minocycline as a versatile therapeutic agent in the treatment of neurodegenerative diseases like AD, in which inflammation and oxidative stress have been pointed out as major contributors to disease progression (22).

Furthermore, extensive minocycline studies have been conducted, focusing on its neuroprotective properties, especially action against inflammation within the brain. Neuroinflammation plays a crucial role in the pathogenesis and progression of neurodegenerative diseases, including AD (25, 60). The primary immune cells of the brain, microglia, upon activation, secrete pro-inflammatory cytokines, including TNF-α and IL-1β (26), into the milieu, which mediates neuronal damage and impairs cognition in AD (25). It has been observed that minocycline exerts an inhibitory action on microglial activation and, in fact, inhibits the release of such deleterious cytokines, thereby weakening inflammation in the brain (27, 59).

Preclinical studies have shown that minocycline suppresses neuroinflammatory responses in stress-induced neurodegeneration models. In a chronic unpredictable mild stress (CUMS) model, minocycline treatment (50 mg/kg) reduced microglial activation, normalized pro-inflammatory cytokine levels, and improved mitochondrial function, ultimately protecting neurons in the medial prefrontal cortex and hippocampus from stress-induced damage. This was accompanied by reduced anxiety-like behavior in treated mice (25, 28). Moreover, minocycline reduces the activation of c-Jun N-terminal kinase, JNK-an enzyme that plays a pivotal role within an inflammatory cascade-which contributes to preventing Aβ deposition and tau phosphorylation, two central features of AD pathology (29).

Minocycline decreases neurodegenerative pathways because it acts as an antioxidant agent. Oxidative stress generated through the overproduction of reactive oxygen species (ROS) is one of the important causes of neuronal damage in AD. Minocycline helps in scavenging free radicals and upregulates antioxidant enzymes like superoxide dismutase and catalase that protect neurons from oxidative damage (30). In addition, minocycline has also been reported to stabilize mitochondrial function, thus sustaining energy homeostasis in neurons and ultimately inhibiting apoptosis induced through mitochondrial dysfunction (24). These collective actions make minocycline a very promising agent in the prevention of neurodegeneration in AD (24, 61).

Both clinical and preclinical studies have begun to unearth the benefits of minocycline in AD. In preclinical models, minocycline has shown efficacy in decreasing Aβ accumulation and enhancing cognitive outcomes. For instance, in rodent models of AD, treatment with minocycline was able to dampen the behavioral deficits associated with Aβ toxicity and reduce neuroinflammation, preventing further deterioration in cognition, as shown by Mehta and Banerjee (2019) (31). This was further established in a similar study where minocycline was able to reduce both oxidative stress and inflammation in diabetic rats, establishing neuroprotection for a wide variety of neurodegenerative conditions (32, 59, 64).

The clinical benefits of minocycline have also been researched in human studies. Thus, a Phase II clinical trial of minocycline treatment in patients with mild AD revealed a non-statistically significant trend toward cognitive improvement (3). In addition, the study underlined that future studies will be required to determine an optimal dosage and duration of treatment that will maximize the therapeutic efficacy of Minocycline in AD. Hence, the combination of anti-inflammatory and neuroprotective properties of Minocycline represents a new therapeutic direction for AD patients in cases where traditional methods of treatment could not affect underlying disease mechanisms (3).

This review specifically aims to examine the relationship between minocycline and acetylcholinesterase via exploration of the cholinergic mechanism of the disease pathology. Thus, a recent study by Hosein et al. (2023) comparing minocycline activity to scopolamine, an agent that blocks ACh receptors, discovered that minocycline could have the potential to modulate acetylcholinesterase, which is a catalytic enzyme for the hydrolysis of acetylcholine in the brain (33). Based on that study, minocycline shows potential in treatment concerning the modulation of AChE activity, which is a key factor in the cognitive impairment associated with AD. Acetylcholine is recognized as a neurotransmitter that plays major roles in various cognitive functions, including learning and memory, whose deficiency is widely known as a symptom of AD (33). Therefore, minocycline can inhibit AChE to increase the levels of acetylcholine in the brain, thereby managing cognitive functions in AD patients (34).

Additionally, a study conducted by Amirahmadi et al. (2022) also demonstrated that Minocycline reduces neuroinflammatory markers such as TNF-α, IL-1β, and IL-6, hence further supporting the dual action of minocycline in reducing inflammation and enhancing cholinergic neurotransmission (35). Moreover, minocycline increased the cholinergic receptor M1 levels that are important for the communication of acetylcholine-mediated signal transmission and showed that it has multiple ways of modulating cholinergic function (35,62).

However, the exact mechanism of inhibiting AChE by minocycline is not fully understood, and this area needs further research. Anti-inflammatory effects were suggested for minocycline in some other studies indirectly to inhibit AChE by alleviating oxidative stress and neuroinflammation, which themselves are well-known accelerating factors for AChE activity (36). Furthermore, combining AChE inhibition with the effects of minocycline in reducing Aβ deposition and stabilizing mitochondrial function may afford a general therapeutic approach to several critical features of AD pathology (37).

Whereas these initial studies have indeed been promising, confirmation regarding the role of minocycline as an AChE inhibitor in more extensive trials, as well as thorough elucidation of its mechanisms of action for AD, are needed. Because of its multifaceted effects on inflammation, oxidative stress, and neuronal health, minocycline has gained prominence as a new and promising treatment strategy against AD (38, 36). Additionally, literature on how minocycline affects AChE is further discussed in relation to its broader implications within the pathophysiology of Alzheimer's disease in this review.

**2. Mechanisms of Action of Minocycline**

It is a second-generation tetracycline antibiotic, which has gained researcher attention not only for its antimicrobial properties but also for its anti-inflammatory, neuroprotective, and immunomodulatory effects. Also, it is an antibiotic recognized in psychiatry for its pleiotropic anti-inflammatory and neuroprotective potential (39)

**2.1 Antibacterial Mechanism**

Minocycline’s primary mechanism of action as an antibiotic involves the inhibition of bacterial protein synthesis. It binds to the 30S ribosomal subunit, obstructing the attachment of aminoacyl-tRNA to the mRNA-ribosome complex. This prevents the addition of new amino acids to the growing peptide chain, thereby inhibiting bacterial growth (40). This bacteriostatic action is crucial in treating various bacterial infections (58, 63)

**2.2 Anti-inflammatory Properties**

Clinical studies have demonstrated that minocycline possesses significant anti-inflammatory properties. One such study by Garrido-Mesa et al. (2013) showed that minocycline inhibits the activity of matrix metalloproteinases (MMPs), enzymes involved in the degradation of extracellular matrix components (24, 62). By inhibiting MMPs, minocycline reduces tissue destruction and inflammation, which is beneficial in conditions like rheumatoid arthritis and periodontitis.

Moreover, minocycline has been shown to suppress the activation of microglia, the resident immune cells in the central nervous system (CNS). Microglial activation is a hallmark of neuroinflammation, which is associated with various neurodegenerative diseases. In a clinical trial involving patients with multiple sclerosis, minocycline was found to reduce microglial activation and subsequent neuroinflammation (41).

Additionally, a study by Schmidt et al. (2021) explored minocycline’s effects on the microbiota-immune axis following spinal cord injury (42). The researchers found that minocycline administration normalized the suppression of cytokines/chemokines induced by spinal cord injury, highlighting its systemic anti-inflammatory effects (42). [This study also noted that minocycline attenuated microglial activation, further supporting its role in reducing neuroinflammation](https://link.springer.com/article/10.1007/s10787-022-01071-2) (42).

**2.3 Neuroprotective Effects**

Minocycline’s neuroprotective effects are attributed to its ability to inhibit apoptosis (programmed cell death) and reduce oxidative stress. Clinical research by Zhu et al. (2002) demonstrated that minocycline inhibits the release of cytochrome c from mitochondria, a key step in the apoptotic pathway (43). By preventing cytochrome c release, minocycline reduces the activation of caspases, which are enzymes that execute apoptosis (43). Additionally, minocycline has been shown to scavenge reactive oxygen species (ROS), thereby reducing oxidative stress and neuronal damage. This antioxidant property is particularly beneficial in conditions such as stroke and traumatic brain injury, where oxidative stress plays a critical role in neuronal injury (44).

**2.4 Immunomodulatory Actions**

Minocycline modulates the immune response by affecting the function of various immune cells. Clinical studies have demonstrated that minocycline inhibits the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), by macrophages and microglia (45). This cytokine inhibition contributes to the anti-inflammatory effects of minocycline (45). Furthermore, minocycline has been shown to enhance the regulatory functions of T cells, which are crucial for maintaining immune homeostasis and preventing autoimmune responses. In a study by Chen et al. (2000), minocycline was found to promote regulatory T cell activity, thereby helping to modulate the immune response and reduce inflammation (46).

#### **2.5 Reduction of Oxidative Stress**

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, plays a critical role in the pathogenesis of various neurodegenerative diseases. Minocycline has been reported to exert antioxidative effects, thereby reducing oxidative stress. In the same study by Amirahmadi et al. (2022), minocycline treatment led to a significant decrease in malondialdehyde levels, a marker of lipid peroxidation, and an increase in total thiol levels and superoxide dismutase activity (35).

**3. Evidence from Preclinical and Clinical Studies on Minocycline’s Impact on Neurodegeneration, Cognitive Improvement, and Neuroinflammation**

* 1. **Preclinical Studies**

Preclinical studies have demonstrated that minocycline can reduce neurodegeneration and improve cognitive functions in animal models. For instance, a study by Amirahmadi et al. (2022) showed that minocycline attenuated cholinergic dysfunction and neuroinflammation-mediated cognitive impairment in a scopolamine-induced Alzheimer’s rat model (35). [The treatment improved memory dysfunction by restoring acetylcholinesterase (AChE) and cholinergic receptor M1 (ChRM1) levels, balancing oxidant/antioxidant levels, and inhibiting inflammatory responses](https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-022-01310-1) (35).

Another study by Zhan et al. (2024) highlighted minocycline’s effectiveness in inhibiting NLRP3 activation and ameliorating neuroinflammation in a chronic cerebral hypoperfusion model. [The treatment mitigated neuroinflammation and improved cognitive functions by inhibiting the activation of the NLRP3 inflammasome](https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-022-01310-1) (47).

**3.2 Clinical Studies**

Clinical studies have also provided evidence supporting minocycline’s neuroprotective effects. A study by Celorrio et al. (2022) investigated the long-term efficacy of minocycline in traumatic brain injury (TBI) patients (48). [The study found that a short course of minocycline reduced hippocampal neurodegeneration, preserved white matter myelination, and improved fear memory performance six months post-injury](https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-022-01310-1) (48). The multifaceted mechanisms of action of minocycline have led to its investigation in various clinical settings. For instance, its neuroprotective and anti-inflammatory properties have been explored in the treatment of neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease (48). Clinical trials have shown that minocycline can slow disease progression and improve neurological function in these conditions (49, 24).

In addition, minocycline’s immunomodulatory effects have been studied in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Clinical research has demonstrated that minocycline can reduce disease activity and improve clinical outcomes in these patients (50).

Additionally, the same study mentioned earlier by Schmidt et al. (2021) explored minocycline’s impact on spinal cord injury (SCI) patients (42). The results indicated that minocycline had a profound effect on microbiota diversity and composition, which was paralleled by the normalization of SCI-induced cytokine/chemokine suppression. [This normalization was associated with decreased anxiety-like behavior and attenuated microglial activation](https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-022-01310-1) (42).

#### **4 Therapeutic Applications for AD and Other Neurodegenerative Disorders**

Minocycline has been investigated for its potential benefits in various neurological conditions:

* 1. **Alzheimer’s Disease**

Minocycline’s ability to inhibit acetylcholinesterase (AChE) and reduce neuroinflammation makes it a candidate for AD treatment. However, clinical trials have shown mixed results regarding its efficacy in slowing cognitive decline (51).

* 1. **Parkinson’s Disease**

Studies suggest that minocycline may protect dopaminergic neurons and improve motor function in a Parkinson’s disease model (52).

* 1. **Multiple Sclerosis**

Minocycline has demonstrated potential in reducing lesion formation and delaying disease progression in multiple sclerosis (53).

#### **5. Discussion**

This review explores the potential of minocycline as a therapeutic agent for Alzheimer’s disease pathology through its inhibitory effects on AChE and its neuroprotective properties.Β-amyloid is believed to affect cholinergic neurotransmission and to cause a reduction in the choline uptake and a release of ACh (54) (see Fig 1).

Fig. 1: Pathological role of Aβ aggregate (54)

A diagram of a cell cycle

Description automatically generated

#### Research has shown that Minocycline, a brand-new broad-spectrum tetracyclic antibiotic, has neuroprotective effects such as antiapoptosis and anti-inflammation, and it plays a brain-protective role in various neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (38,59).

#### Preclinical evidence has shown that minocycline suppresses neuroinflammatory responses in various models of neurodegeneration. Using a model of CUMS-induced neuroinflammation in mice, for instance, it was shown that treatment with minocycline protects against stress-induced alterations in neuronal functioning. CUMS, a model for stress-induced emotional disorders such as anxiety, leads to neuroinflammation mediated by activated microglia, which also impairs mitochondrial function and disrupts medial prefrontal cortex-hippocampus connectivity. Intraperitoneal minocycline, 50 mg/kg for 7 consecutive days in the third week of CUMS exposure, hampered these neuroinflammatory responses by reducing the levels of pro-inflammatory cytokines, raising the expression of neuroprotective molecules, and protecting the neurons from stress-induced injury. Therefore, according to behavioral tests, including novelty-suppressed feeding and contextual anxiety tests, minocycline decreased anxiety-like behavior in CUMS-exposed mice (25) (Fig, 2).

#### Fig. 2: Minocycline prevents CUMS-induced anxiety-like phenotypes in mice (25)

#### figure 1

#### Additionally, scopolamine is an antagonist for acetylcholine receptors. It creates defects in memory through elevation of the activity of AChE, thereby diminishing ACh levels. In the model of scopolamine-induced amnesia, minocycline effectively lowered the increased AChE activity, thus restoring ACh levels and showing improvement in cognitive function. Further, the antioxidant properties of minocycline reduced the oxidative stress well known to be an aggravating factor in AChE overactivity. These two modes of action, AChE inhibition and antioxidant defense, form the basis for minocycline use in treating neurodegenerative diseases like AD (33). While AChEI do not significantly improve cognitive function or appear to halt the course of AD, they may instead lower overall mortality and delay the rate at which cognitive deterioration advances over an extended period (55,61).

#### **5.1 Summary of evidence**

#### Several studies have indicated that minocycline may have the ability to inhibit acetylcholinesterase (AChE), an enzyme responsible for the breakdown of acetylcholine in the brain. By inhibiting AChE, minocycline could potentially increase acetylcholine levels in the brain, thereby improving cognitive function in AD patients (35). Both clinical and preclinical studies have begun to establish the benefits of minocycline in the context of AD. In a study conducted by (56) Minocycline has been shown to improve learning and memory in APP/PS1 mice by restricting the activation of the Cdk5/p25 signaling pathway. In another rodent model of AD, minocycline treatment was found to attenuate behavioral deficits associated with Aβ toxicity and reduce neuroinflammation, thus preventing the progression of cognitive decline (53). The study by Cai et al. (2011) also demonstrated its neuroprotective effects across various neurodegenerative conditions by mitigating oxidative stress and inflammation in diabetic rats (33, 58).

#### Minocycline’s clinical benefits have also been explored in human trials. A Phase II clinical trial investigating the effects of minocycline in mild AD patients demonstrated a trend towards cognitive improvement, though the results were not statistically significant (3).

#### **5.2 Limitations**

#### The precise mechanisms by which minocycline inhibits AChE are not yet fully understood, and more research is needed to explore this aspect of its action. Despite many promising preclinical studies, clinal studies are not showing favorable results (51), The MADE (Minocycline in Alzheimer’s Disease Efficacy Trail) findings also indicate that minocycline did not appreciably slow down the development of cognitive and functional impairment in individuals with moderate Alzheimer's disease (3). Additionally, the 400 mg dose of minocycline was found to be poorly tolerated by the patients (51).

#### **5.3 Comparison with other studies**

#### N-methyl-D-aspartate (NMDA) receptor antagonists and cholinesterase inhibitors are the two primary medication groups that are approved for the treatment of AD (57). These drugs aim to improve cognitive function by enhancing cholinergic signaling or reducing glutamate-induced excitotoxicity. Even with this progress in understanding AD’s pathology, these medications only address symptoms without curing the disease; they are also expensive and have limited effectiveness. (6). The combination of minocycline's anti-inflammatory and neuroprotective qualities provides a novel therapeutic option, particularly in cases when conventional therapies are unable to address the underlying disease mechanisms.

#### **6. Conclusion**

#### In conclusion, minocycline is a promising therapeutic agent for the treatment of AD. As this condition is affecting more people worldwide, minocycline could lead to effective and timely treatment for people suffering from this disease. In vitro and animal studies have demonstrated that minocycline can reduce Aβ deposition, inhibit microglial activation, and protect against synaptic loss. Although few clinical trials have shown its potential to improve cognitive outcomes in AD patients, there is a need for further research to confirm its efficacy in human subjects.

#### **6.1 Future Prospects**

#### Investigating Neuroinflammation: Howard et al., (2020) pointed out that although there is good evidence for neuroinflammation in AD, it may be a reaction to pathologic characteristics of the disease rather than an important factor in neurodegeneration, particularly in patients whose AD is mild (3). Therefore, further research can delve into the role of neuroinflammation in different stages of AD to help make better treatment strategies.

#### Since the precise mechanisms by which minocycline inhibits AChE are not yet fully understood, future research can explore this aspect of its action.

#### Dose optimization: Various dose regimes of minocycline can be investigated to find a balance between its efficacy and tolerance. Howard et al., (2020) noted that several animal studies used higher doses (3-7g per day equivalent in humans), in which the 400 mg dose of minocycline was found to be poorly tolerated by the patients (51).

**DISCLAIMER (ARTIFICIAL INTELLIGENCE**)

The author(s) hereby certify that no generative artificial intelligence (AI) tools such as Scalable Language Models (ChatGPT, COPILOT, etc.) or text-to-image generators were utilized in the authoring or editing of the paper.

# References

1. Scheltens P. Alzheimer’s disease. The Lancet [Internet]. 2021 Apr 24;397(10284):1577–90. Available from: https://www.sciencedirect.com/science/article/pii/S0140673620322054

2. Vradenburg G. A pivotal moment in Alzheimer’s disease and dementia: how global unity of purpose and action can beat the disease by 2025. Expert Review of Neurotherapeutics. 2015 Jan 2;15(1):73–82.

3. Howard R, Zubko O, Gray R, Bradley R, Harper E, Kelly L, et al. References [Internet]. Nih.gov. NIHR Journals Library; 2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK556204/#ref1-bib1>

4. De-Paula VJ, Radanovic M, Diniz BS, Forlenza OV. Alzheimer’s Disease. Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease [Internet]. 2012;65:329–52. Available from: <https://pubmed.ncbi.nlm.nih.gov/23225010/>

5. Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. Journal of Central Nervous System Disease [Internet]. 2020 Jan;12(1):117957352090739. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7050025/>

6. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer’s Disease: Causes and Treatment. Molecules [Internet]. 2020 Dec 8;25(24):5789. Available from: <https://www.mdpi.com/1420-3049/25/24/5789>

7. Chen G, Xu T, Yan Y, Zhou Y, Jiang Y, Melcher K, et al. Amyloid beta: structure, Biology and structure-based Therapeutic Development. Acta Pharmacologica Sinica. 2017 Jul 17;38(9):1205–35.

8. Kempf S, Metaxas A. Neurofibrillary Tangles in Alzheimer′s Disease: Elucidation of the Molecular Mechanism by Immunohistochemistry and Tau Protein phospho-proteomics. Neural Regeneration Research. 2016;11(10):1579.

9. John A., Reddy PH. Synaptic basis of Alzheimer’s disease: Focus on synaptic amyloid beta, P-tau and mitochondria. Ageing Research Reviews. 2021 Jan;65:101208.

10. Lleó A, Núñez-Llaves R, Alcolea D, Chiva C, Balateu-Paños D, Colom-Cadena M, et al. Changes in Synaptic Proteins Precede Neurodegeneration Markers in Preclinical Alzheimer’s Disease Cerebrospinal Fluid. Molecular & Cellular Proteomics. 2019 Mar;18(3):546–60.

11.A. Armstrong R. Risk Factors for Alzheimer’s Disease. Folia Neuropathologica [Internet]. 2019;57(2):87–105. Available from: <https://www.termedia.pl/Risk-factors-for-Alzheimer-s-disease,20,36928,1,1.html>

12. H. Ferreira-Vieira T, M. Guimaraes I, R. Silva F, M. Ribeiro F. Alzheimer’s disease: Targeting the Cholinergic System. Current Neuropharmacology [Internet]. 2016 Jan 22;14(1):101–15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4787279/>

13. Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer’s disease. Brain [Internet]. 2018 May 29;141(7):1917–33. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6022632/>

14. Paroni G, Bisceglia P, Seripa D. Understanding the Amyloid Hypothesis in Alzheimer’s Disease. Solfrizzi V, editor. Journal of Alzheimer’s Disease [Internet]. 2019 Mar 29;68(2):493–510. Available from: <https://content.iospress.com/articles/journal-of-alzheimers-disease/jad180802>

15. Salvadores N, Gerónimo-Olvera C, Court FA. Axonal Degeneration in AD: The Contribution of Aβ and Tau. Frontiers in Aging Neuroscience. 2020 Oct 15;12.

16. Fessel J. Prevention of Alzheimer’s disease by treating mild cognitive impairment with combinations chosen from eight available drugs. Alzheimer’s & Dementia: Translational Research & Clinical Interventions. 2019;5:780–8.

17.Dotolo S, Marabotti A, Facchiano A, Tagliaferri R. A review on drug repurposing applicable to COVID- Briefings in Bioinformatics. 2021 Mar 22;22(2):726–41.

18. Zhu J, Ma R, Li G. Drug repurposing: Clemastine fumarate and neurodegeneration. Biomedicine & Pharmacotherapy. 2023 Jan 1;157:113904–4.

19. Viecceli C, Mattos ACV, Costa MCB, de Melo RB, Rodrigues T da C, Czepielewski MA. Evaluation of ketoconazole as a treatment for Cushing’s disease in a retrospective cohort. Frontiers in Endocrinology [Internet]. 2022 Oct 7 [cited 2023 Mar 26];13:1017331. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9585352/>

20. Lim F, Bellows BK, Tan S, Aziz Z, Woo JA, Kelly AS, et al. Cost-Effectiveness of Pharmacotherapy for the Treatment of Obesity in Adolescents. JAMA network open [Internet]. 2023 Aug 31 [cited 2023 Oct 13];6(8):e2329178–8. Available from: <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2808942?resultClick=1>

21. Chaves M, Mottin M, Michele Verde-Ramo Soares, Paloma Marinho Jucá, Carolina Horta Andrade, Macedo DS. Tetracyclines, a promise for neuropsychiatric disorders: from adjunctive therapy to the discovery of new targets for rational drug design in psychiatry. Behavioural pharmacology. 2021 Feb 15;32(2&3):123–41.

22. Nazarian S.; Akhondi H. Minocycline [Internet]. 2023. Available from: <https://pubmed.ncbi.nlm.nih.gov/32119406/>

23. Yang L, Yang J, Liu H, Lan J, Xu Y, Wu X, et al. Minocycline binds and inhibits LYN activity to prevent STAT3-meditated metastasis of colorectal cancer. International Journal of Biological Sciences [Internet]. 2022 Mar 21 [cited 2023 Mar 17];18(6):2540–52. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8990469/#:~:text=Through%20direct%20binding%2C%20minocycline%20inhibits>

24. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. British Journal of Pharmacology [Internet]. 2013 Apr 25;169(2):337–52. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651660/>

25. Tabassum S, Afzal Misrani, Huo Q, Ahmed A, Long C, Yang L. Minocycline Ameliorates Chronic Unpredictable Mild Stress-Induced Neuroinflammation and Abnormal mPFC-HIPP Oscillations in Mice. Molecular Neurobiology. 2022 Sep 1;59(11):6874–95.

26. Bernardino Andrea L.  F., Kaushal D., Philipp Mario T. The Antibiotics Doxycycline and Minocycline Inhibit the Inflammatory Responses to the Lyme Disease SpirocheteBorrelia burgdorferi. The Journal of Infectious Diseases [Internet]. 2009 May [cited 2019 May 28];199(9):1379–88. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3697124/>

27. Kobayashi K, Imagama S, Ohgomori T, Hirano K, Uchimura K, Sakamoto K, et al. Minocycline selectively inhibits M1 polarization of microglia. Cell Death & Disease [Internet]. 2013 Mar 1 [cited 2020 Apr 30];4(3):e525–5. Available from: <https://www.nature.com/articles/cddis201354>

28. Yaseen E, Abdullah Z, Zakaria R, Long I. Minocycline protects against lipopolysaccharide-induced glial cells activation and oxidative stress damage in the medial prefrontal cortex (mPFC) of the rat. International Journal of Neuroscience. 2022 Jun 15;134(1):56–65.

29. Forloni G, Colombo L, Girola L, Tagliavini F, Salmona M. Anti-amyloidogenic activity of tetracyclines: studies in vitro. FEBS Letters. 2001 Jan 5;487(3):404–7.

30. Rok J, Rzepka Z, Mateusz Maszczyk, Artur Beberok, & Dorota Wrześniok. Minocycline Impact on Redox Homeostasis of Normal Human Melanocytes HEMn-LP Exposed to UVA Radiation and Hydrogen Peroxide. International Journal of Molecular Sciences [Internet]. 2021 Feb 6 [cited 2024 Sep 13];22(4):1642–2. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7914767/>

31. Mejia ROS, Ona VO, Li M, Friedlander RM. Minocycline Reduces Traumatic Brain Injury-mediated Caspase-1 Activation, Tissue Damage, and Neurological Dysfunction. Neurosurgery. 2001 Jun 1;48(6):1393–401.

32. Cai Z, Zhao Y, Yao S, and Zhao B. Increases in β-amyloid protein in the hippocampus caused by diabetic metabolic disorder are blocked by minocycline through inhibition of NF-κB pathway activation. Pharmacological Reports. 2011 Mar;63(2):381–91.

33. Hosein M., Arezoo Rajabian, Mohsen Parviz, Mahsan Akbarian, Sabiheh Amirahmadi, Farzaneh Vafaee, et al. Minocycline alleviated scopolamine-induced amnesia by regulating antioxidant and cholinergic function. Heliyon. 2023 Feb 1;9(2):e13452–2.

34. Rai P, Brajnandan Kishor, Rakesh Bharatia, Kumar S, Sujeet Kumar Gupta, Sinha A. Synergistic Neuroprotective Potential of Combined Treatment with Vinpocetine and Minocycline Against Streptozotocin and Lipopolysaccharide Induced Memory Impaired Mice. Journal of Pharmaceutical Sciences and Pharmacology. 2017 Jun 1;3(2):124–32.

35. Amirahmadi S, Farimani FD, Akbarian M, Mirzavi F, Eshaghi Ghalibaf MH, Rajabian A, et al. Minocycline attenuates cholinergic dysfunction and neuro-inflammation-mediated cognitive impairment in scopolamine-induced Alzheimer’s rat model. Inflammopharmacology. 2022 Sep 22;30(6):2385–97.

36. Haniyeh Mozafari, Amiri S, Shahram Ejtemaei Mehr, Majid Momeny, Hossein Amini-khoei, Soroush Bijani, et al. Minocycline attenuates depressive-like behaviors in mice treated with the low dose of intracerebroventricular streptozotocin; the role of mitochondrial function and neuroinflammation. Molecular Biology Reports. 2020 Aug 1;47(8):6143–53.

37. Khatoon R, Kaushik P, Parvez S. Mitochondria-Related Apoptosis Regulation by Minocycline: A Study on a Transgenic *Drosophila* Model of Alzheimer’s Disease. ACS Omega. 2022 Jun 1;7(23):19106–12.

38. Budni J, L. Garcez M, de Medeiros J, Cassaro E, Bellettini-Santos T, Mina F, et al. The Anti-Inflammatory Role of Minocycline in Alzheimers Disease. Current Alzheimer Research. 2016 Nov 1;13(12):1319–29.

39. Regen F, N. Le Bret, Hildebrand M, Herzog I, Heuser I, J. Hellmann-Regen. Inhibition of brain retinoic acid catabolism: a mechanism for minocycline’s pleiotropic actions? The World Journal of Biological Psychiatry. 2015 Jun 5;1–7.

40. Chopra I, Roberts M. Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance. Microbiology and Molecular Biology Reviews [Internet]. 2001 Jun 1;65(2):232–60. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC99026/>

41. Casha S, Zygun D, McGowan MD, Bains I, Yong VW, John Hurlbert R. Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. Brain. 2012 Apr;135(4):1224–36.

42. Schmidt EKA, Raposo PJF, Torres-Espin A, Fenrich KK, Fouad K. Beyond the lesion site: minocycline augments inflammation and anxiety-like behavior following SCI in rats through action on the gut microbiota. Journal of Neuroinflammation [Internet]. 2021 Jun 26 [cited 2022 Jan 16] ;18:144. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8234629/>

43. Zhu S, Stavrovskaya IG, Drozda M, Kim BYS, Ona V, Li M, et al. Minocycline inhibits cytochrome c release and delays progression of amyotrophic lateral sclerosis in mice. Nature [Internet]. 2002 May 1 [cited 2023 Mar 2];417(6884):74–8. Available from: <https://www.nature.com/articles/417074a>

44. Plane JM, Shen Y, Pleasure DE, Deng W. Prospects for Minocycline Neuroprotection. Archives of Neurology. 2010 Dec 1;67(12).

45. Nikodemova M, Duncan ID, Watters JJ. Minocycline exerts inhibitory effects on multiple mitogen-activated protein kinases and IκBα degradation in a stimulus-specific manner in microglia. Journal of Neurochemistry. 2006 Jan;96(2):314–23.

46. Chen M, Ona VO, Li M, Ferrante RJ, Fink KB, Zhu S, et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nature Medicine. 2000 Jul;6(7):797–801.

47. Zhan F, Dong Y, Zhou L, Li X, Zhou Z, Xu G. Minocycline alleviates LPS-induced cognitive dysfunction in mice by inhibiting the NLRP3/caspase-1 pathway. Aging. 2024 Feb 6;

48. Celorrio M, Shumilov K, Payne C, Vadivelu S, Friess SH. Acute minocycline administration reduces brain injury and improves long-term functional outcomes after delayed hypoxemia following traumatic brain injury. Acta Neuropathologica Communications. 2022 Jan 28;10(1).

49. Noble W, Garwood CJ, Hanger DP. Minocycline as a potential therapeutic agent in neurodegenerative disorders characterized by protein misfolding. Prion. 2009 Apr;3(2):78–83.

50. Mcevoy T. Minocycline: Rheumatoid Arthritis. Hospital Pharmacy. 2016 Jul;51(7):535–8.

51. Howard R, Zubko O, Bradley R, Harper E, Pank L, O’Brien J, et al. Minocycline at 2 Different Dosages vs Placebo for Patients With Mild Alzheimer Disease. JAMA Neurology. 2020 Feb 1;77(2):164.

52. Thomas M, Ashizawa T, Jankovic J. Minocycline in Huntington’s disease: A pilot study. Movement Disorders. 2004 Jun;19(6):692–5.

53. Mehta BK, Banerjee S. Minocycline reverses diabetes-associated cognitive impairment in rats. Pharmacological Reports. 2019 Aug;71(4):713–20.

54. Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β-based therapy for Alzheimer’s disease: challenges, successes and future. Signal Transduction and Targeted Therapy [Internet]. 2023 Jun 30;8(1):1–26. Available from: <https://www.nature.com/articles/s41392-023-01484-7>

55. Zuin M, Cherubini A, Volpato S, Ferrucci L, Zuliani G. Acetyl-cholinesterase-inhibitors slow cognitive decline and decrease overall mortality in older patients with dementia. Scientific Reports [Internet]. 2022 Jul 16;12:12214. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9288483/>

56. Zhao Y, Wang C, He W, Cai Z. Ameliorating Alzheimer’s-like pathology by Minocycline via inhibiting Cdk5/p25 signaling. Current Neuropharmacology. 2021 Dec 2;19.

57. Shega JW, Ellner L, Lau DT, Maxwell TL. Cholinesterase Inhibitor and N-Methyl-D-Aspartic Acid Receptor Antagonist Use in Older Adults with End-Stage Dementia: A Survey of Hospice Medical Directors. Journal of Palliative Medicine [Internet]. 2009 Sep [cited 2022 Apr 1];12(9):779–83. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988459/>\

58. Anozie, Ebube Henry, Oluwabusola Oluwakorede Asenuga, James Ponman Sargwak, Emmanuel Chimeh Ezeako, Ifeoma Roseline Nwafor, Yusuf Alhassan, Udoh Joseph Ifeanyi, Eberechukwu Osinachi Azubuike, and Chibuzo Valentine Nwokafor. 2024. “Challenges for Mathematical Modeling of Multidrug-Resistant Tuberculosis in Sub-Saharan Africa”. *Asian Journal of Advanced Research and Reports* 18 (9):90-97. <https://doi.org/10.9734/ajarr/2024/v18i9737>.

59. Egwuatu, Donatus Chigozie, Rachael Olakunmi Ogunye, Peter Chidendu Anene, Yusuf Alhassan, Ifeoma Roseline Nwafor, Joseph Ifeanyi Udoh, Oluwabusola Oluwakorede Asenuga, and Chibuzo Valentine Nwokafor. 2024. “A Review on Conversion of Agricultural Waste to Bioenergy: Processes and Environmental Impacts”. *Biotechnology Journal International* 28 (6):18-34. https://doi.org/10.9734/bji/2024/v28i6746.

60. Asenuga, Oluwabusola Oluwakorede, James Ponman Sargwak, Emmanuel Chimeh Ezeako, Matthew Babalola, Faith Omosigho, Eberechukwu Osinachi Azubuike, and Chibuzo Valentine Nwokafor. 2024. “Genomic Evolution and Dynamics of Drug Resistance in Mycobacterium Tuberculosis across West Africa- A Review”. *Microbiology Research Journal International* 34 (11):120-30. https://doi.org/10.9734/mrji/2024/v34i111504.

61. Ikpa S, Isima P, Nwokafor, C. V., Ekwem O, Udumebraye R, Obasi T, Nwaobia H, Anyanwu A, Agwu C, Anucha C, Chidi P. (2023). Effects of Varied Culture Conditions on Crude Bacitracin Produced By Bacillus Subtilis Isolated from the Soil. Magna Scientia Advanced Biology and Pharmacy. <https://doi.org/10.30574/msabp.2023.8.1.0095>

62. Onwuakor C.E., Ogbulie J.N., Braide W., Ogbulie T.E., Nwokafor C.V., Uchendu C.E.. Optimization of Culture Conditions for Enhanced Bacteriocin Production by Lactococcus lactis MT186647 Using Response Surface Methodology. American Journal of Microbiological Research. Vol. 8, No. 4, 2020, pp 110-116. <https://pubs.sciepub.com/ajmr/8/4/1>

63. Onwuakor Chijioke E., Ogbulie Jude N., Braide Wesley, Ogbulie Tochukwu E., Nwokafor Chibuzo V., Uchendu C.E.. Optimization of Bacteriocin Production by Lactobacillus fermentum Strain COE20 from Fermenting Pentaclethra macrophylla Benth Using Response Surface Methodology. American Journal of Food Science and Technology. Vol. 9, No. 2, 2021, pp 30-37. <https://pubs.sciepub.com/ajfst/9/2/1>

64. Amanze, Emmanuel K., Ogechukwu B. Ochomma, Chukwuma G. Udensi, Chizurum P. Christian, Chioma S. Dike, Joseph C. Okakpu, and Chibuzo V. Nwokafor. 2022. “The Prevalence of Extended Spectrum Beta-Lactamase Producing Uropathogenic Escherichia Coli from Mouau Female Hostel Students”. South Asian Journal of Research in Microbiology 13 (4):24-34. <https://doi.org/10.9734/sajrm/2022/v13i4255>.

65. Kumar, R. Santosh, and Riane Saha. 2022. “An Overview on the Aetiology and Treatment of Alzheimer’s Disease”. *Asian Journal of Medicine and Health* 20 (6):30-39.

66. Tahami Monfared, A. A., Byrnes, M. J., White, L. A., & Zhang, Q. (2022). Alzheimer’s disease: epidemiology and clinical progression. *Neurology and therapy*, *11*(2), 553-569.

67.Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, Holmans PA. New insights into the genetic etiology of Alzheimer’s disease and related dementias. Nature genetics. 2022 Apr;54(4):412-36.