

## Review

# The role of hydrogen therapy in Alzheimer's disease management: Insights into mechanisms, administration routes, and future challenges

Jiaxuan He<sup>a,1</sup>, Fan Liu<sup>a,1</sup>, Ting Xu<sup>a,1</sup>, Jiahui Ma<sup>a</sup>, Haiyang Yu<sup>a</sup>, Jing Zhao<sup>a</sup>, Yanyan Xie<sup>b</sup>, Li Luo<sup>c</sup>, Qinsi Yang<sup>d</sup>, Ting Lou<sup>e,\*</sup>, Luqing He<sup>f,\*</sup>, Da Sun<sup>a,\*</sup>

<sup>a</sup> Institute of Life Sciences & Biomedical Collaborative Innovation Center of Zhejiang Province, Wenzhou University, Wenzhou 325035, China

<sup>b</sup> The Affiliated Kangning Hospital of Wenzhou Medical University, Wenzhou 325000, China

<sup>c</sup> Dongguan Hospital, Southern Medical University, Dongguan 523059, China

<sup>d</sup> Wenzhou Institute, University of Chinese Academy of Sciences, Wenzhou 325000, China

<sup>e</sup> Yiwu Center for Disease Control and Prevention, Yiwu 322000, China

<sup>f</sup> Department of Science and Education, the Third People's Hospital Health Care Group of Cixi, Ningbo 315300, China



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## ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder predominantly affecting the elderly. While conventional pharmacological therapies remain the primary treatment for AD, their efficacy is limited effectiveness and often associated with significant side effects. This underscores the urgent need to explore alternative, non-pharmacological interventions. Oxidative stress has been identified as a central player in AD pathology, influencing various aspects including amyloid-beta metabolism, tau phosphorylation, autophagy, neuro-inflammation, mitochondrial dysfunction, and synaptic dysfunction. Among the emerging non-drug approaches, hydrogen therapy has garnered attention for its potential in mitigating these pathological conditions. This review provides a comprehensively overview of the therapeutic potential of hydrogen in AD. We delve into its mechanisms of action, administration routes, and discuss the current challenges and future prospects, with the aim of providing valuable insights to facilitate the clinical application of hydrogen-based therapies in AD management.

## 1. Introduction

The global demographic shift towards an aging population has magnified the health challenges faced by the elderly, with neurodegenerative diseases, particularly Alzheimer's disease (AD), emerging as a paramount concern [1]. Currently, AD afflicts approximately 55 million individuals worldwide, affected by AD, and this number is on an

alarming rise [2]. The World Health Organization has reported that every three seconds, a new AD case is diagnosed, and projections suggest that by 2030, the affected population will surpass 78 million, potentially tripling by 2050 [3]. This burgeoning prevalence underscores AD as a looming public health crisis, amplifying the socio-economic burden on communities and families [4].

The therapeutic for AD predominantly comprises pharmacological

**Abbreviations:** AD, Alzheimer's disease; Keap1, Kelch-like ECH associated protein-1; ARE, Antioxidant response element; SOD1, Superoxide dismutase 1; CAT, Catalase enzymes; TAC cycle, Tricarboxylic acid cycle; NMDA, N-methyl-D-aspartate; AChEIs, Acetylcholinesterase inhibitors; IL-1 $\alpha$ , Interleukin-1 $\alpha$ ; IL-1 $\beta$ , Interleukin-1 $\beta$ ; TNF- $\alpha$ , Tumor necrosis factor- $\alpha$ ; ABAD, A $\beta$ -binding alcohol dehydrogenase; CYP D, Cyclophilin D; GSK3, Glycogen synthase kinase 3; CDK5, Cyclin-dependent kinase 5; GSK3 $\beta$ , Glycogen synthase kinase-3 $\beta$ ; AMPK, Adenosine 5'-monophosphate (amp)-activated protein kinase; Nrf2, Nuclear factor-carotenoid 2-p45-derived factor; BDNF, Brain-derived neurotrophic factor; ER, Estrogen receptor; PKC, Protein kinase C; SAE, Sepsis-associated encephalopathy; DNMT1, DNA methyltransferases 1; DNMT3A, DNA methyltransferases 3; ICH, Intracerebral hemorrhage; TBI, Traumatic brain injury; CSF, Granulocyte colony-stimulating factor; NO, Nitric oxide; ROS, Reactive oxygen species; 3  $\times$  Tg, Triple transgenic; NFT, Neurofibrillary tangles; A $\beta$ , Amyloid  $\beta$ ; 4-HNE, 4-Hydroxynonenal; GFAP, Glial fibrillary acidic protein; ADAS-Cog, The Alzheimer disease assessment scale-cognitive subscale; BACE1, Beta-secretase 1; APP, Amyloid precursor protein; CIP2A, Cancerous inhibitor of protein phosphatase; PP2A, Protein phosphatase 2A; ATP, Adenosine triphosphate; HRW, Hydrogen-rich water; PdH, Palladium hydride; SAPP $\beta$ , Soluble peptide app $\beta$ ; PD, Parkinson's disease; UPDRS, Unified-Parkinson disease rating scale; APOE4, Apolipoprotein E-4; Sirt1, Sirtuin 1; FOXO3a, Forkhead box O3a; CNS, Central nervous system; BDNF, brain-derived neurotrophic factor.

\* Corresponding authors.

E-mail addresses: [louting22@163.com](mailto:louting22@163.com) (T. Lou), [helq619@163.com](mailto:helq619@163.com) (L. He), [sunday@wzu.edu.cn](mailto:sunday@wzu.edu.cn) (D. Sun).

<sup>1</sup> These authors contributed equally to this work.

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and non-pharmacological interventions. Conventional pharmacological treatments mainly involve acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, have demonstrated efficacy. However, they are not curative, and a significant proportion of patients experience adverse reactions, with nearly one-third being intolerant to AChEIs [5]. This therapeutic limitation has propelled research towards non-pharmacological alternatives, which aim to decelerate disease progression and preserve cognitive function [6].

A pivotal link has been established between amyloid  $\beta$  ( $A\beta$ ) peptides and oxidative stress [7], where  $A\beta$  peptides induce oxidative stress, leading to mitochondrial dysfunction and a surge in reactive oxygen species (ROS) production [8]. In turn, oxidants and oxidation products produced under oxidative stress can increase the expression of Amyloid precursor protein (APP), leading to the accumulation of  $A\beta$  [9,10] and the cycle continues to aggravate the condition. While antioxidants have been proposed as potential therapeutic agents against oxidative damage, their clinical efficacy has been inconsistent [11]. Notably, some antioxidant supplements have shown limited impact in preventing diseases like cancer, myocardial infarction, and atherosclerosis, and in certain instance, even elevated mortality rates [12,13]. Therefore, in the process of developing effective antioxidants to prevent oxidative stress-related diseases, it is very important to understand their side effects. In this

case, the ideal antioxidant molecule is expected to alleviate excessive oxidative stress without disrupting redox homeostasis. In other words, the ideal molecule should not reduce the signaling molecule. Such as  $H_2O_2$  but should effectively reduce  $\cdot OH$  and other strong oxidants. Based on existing experiments, we have come to the current conclusion that the ideal antioxidant may be  $H_2$ .

Compared to traditional antioxidants, hydrogen-based therapy is a promising non-pharmacological approach, has shown potential as an antioxidant in preventive and therapeutic applications [14]. By selectively reducing the most cytotoxic hydroxyl radical in ROS, hydrogen can effectively protect cells. The inhalation of hydrogen gas significantly inhibits the effects of oxidative stress on brain injury, thus hydrogen can be utilized as an effective antioxidant therapy. Owing to its excellent ability to rapidly diffuse across membranes, it is capable of reaching sites of stress and reacting with cytotoxic ROS, thus protecting cells against oxidative damage [15]. Considering hydrogen's dispersible lipid solubility and characteristics, it is possible to use hydrogen therapeutically in a variety of ways. Inhalation of low concentration hydrogen can protect the spinal cord [16], heart [17], liver [18], lung [19] and intestine [20] from ischemia-reperfusion injury, Arthritis symptoms were relieved after drinking hydrogen-rich water [21]. Intravenous injection of hydrogen saline has shown good efficacy in models of acute



**Fig. 1.** Therapeutic potential of hydrogen in mitigating AD pathology. (A) Key pathological hallmarks of AD: neuronal inflammation, autophagy dysfunction,  $\beta$ -amyloid plaques accumulation, mitochondrial dysfunction, tau protein abnormalities, and synaptic impairments; (B) Diverse administration routes of hydrogen therapy: inhalation, ingestion of hydrogen-rich water, direct injection, and targeted delivery using nanomaterials.

pancreatitis [22], hemorrhagic shock [23] and acute hearing loss [24]. In a rat model, hydrogen-containing peritoneal dialysate was found to be effective in preventing peritoneal dialysis-related peritoneal fibrosis [25].

In this review, we delve into hydrogen's role as a natural antioxidant, elucidating its multifaceted mechanisms in targeting AD-associated pathways. We aim to provide a comprehensive overview of hydrogen-based therapeutic strategies for AD, exploring their mechanisms of action, administration routes, and highlighting the current challenges and future prospects. Our overarching goal is to furnish valuable insights that can catalyze the clinical translation of hydrogen-based interventions for AD (Fig. 1).

## 2. Oxidative stress plays an pivotal role in the progression of AD

Oxidative stress, characterized by an imbalance between the production of free radicals and the body's ability to counteract their harmful effects, has been identified as a significant contributor to the pathogenesis of AD [10]. Elevated oxidative stress levels have been documented in both AD mouse models and human AD tissues, suggesting a strong association between free radical generation and plaque formation [26]. This oxidative milieu is believed to precede AD pathology, influencing A $\beta$  deposition, neurofibrillary tangles (NFTs) formation, vascular abnormalities, and cognitive deterioration. Notably, even before the manifestation of senile plaques and NFTs, a marked decrease in antioxidants like glutathione and vitamin E, coupled with increased lipid peroxidation, has been observed in triple transgenic AD mouse model [27]. Furthermore, oxidative stress is implicated in amplifying tau hyperphosphorylation in neurons, with specific amino acids like methionine enhancing oxidative activity in the A $\beta$  sequence [28]. As the brain ages, given its high oxygen consumption and limited antioxidant defenses, is particularly vulnerable to oxidative stress [29]. When the accumulation of ROS surpasses the body's antioxidant defenses, it can inflict damage on cellular macromolecules, disrupt cell functions, induce the release of pro-apoptotic proteins from mitochondria, and ultimately lead to neuronal apoptosis in the central nervous system [30].

### 2.1. Neuroinflammation

Neuroinflammation is a hallmark of AD and is characterized by the chronic activation of glial cells, primarily astrocytes and microglia, in the brain [31]. Under physiological conditions, microglia exist in a quiescent state, playing a pivotal role in maintaining brain homeostasis [32]. However, in the AD environment, stimuli such as A $\beta$  and ROS activate microglia, leading to the release of proinflammatory cytokines including interleukin-1 $\alpha$  (IL-1 $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [33]. This microglial activation further instigates the activation of other neuroimmune cells, notably astrocytes, initiating an innate immune response that culminates in a cascade of proinflammatory events [34].

Activated microglia, besides promoting the synthesis of cathepsin B, contribute to neuronal dysfunction and exacerbate neuroinflammatory state, further complicating the AD pathology [35]. Concurrently, astrocytes, the primary immune cells in the brain, are also activated [31,36–40]. Recent studies suggest that while activated astrocytes possess neuroprotective properties and can inhibit A $\beta$  aggregation, they also promote ROS release and inflammatory cytokines secretion [41], thereby AD progression.

### 2.2. Imbalance of metal ion homeostasis

Metal ions, specifically copper, iron, and zinc, are pivotal for maintaining physiology healthy, serving as essential elements for cellular functions and homeostasis [42]. However, the imbalance of these metal ions, whether in excess or deficiency, can disrupt mitochondrial

homeostasis. This disruption can lead to alterations membrane integrity and interfere with mitochondrial functions, such as the tricarboxylic acid cycle (TCA cycle), oxidative phosphorylation, and glutathione metabolism [43–45]. Such mitochondrial dysfunction amplify oxidative stress and hasten neuronal apoptosis, both of which are key processes in the pathogenesis of AD [46]. Recent studies have highlighted the active roles of iron and copper in regulating core functions of the central nervous system (CNS), encompassing myelin phospholipids generation, neurotransmitters synthesis, synaptic signal conduction, and O $_2$  transport [47,48]. These operations are mainly achieved through the structural and catalytic modulation of protein channels, enzymes, and receptors [49]. While the redox properties of copper and iron are indispensable for many biological processes, they also serve as sources of ROS. Elevated ROS levels can expedite neurodegenerative changes by promoting protein oxidation, accumulation, and misfolding, particularly of protein like  $\alpha$ -Synuclein [50]. Additionally, ROS can induce lipid deterioration, transforming lipids into lipid peroxides, which are detrimental to neuronal cells and are pivotal contributors to iron-dependent cell death, known as ferroptosis [51].

Given the intricate relationship between metal ion homeostasis and AD, a deeper understanding of this balance can offer invaluable insights into AD's pathogenesis. Moreover, it can pave the way for the development of innovative therapeutic strategies targeting metal ion imbalances in AD.

### 2.3. Mitochondrial dysfunction

Mitochondria, often termed the cellular powerhouses, are central to myriad essential physiological processes. Their pivotal role in energy production and cellular homeostasis makes them susceptible to dysfunctions that can have profound implications for cellular health [52]. Recent research accentuated the integral role of mitochondrial dysfunction in the pathogenesis of AD [53,54], with evidence suggesting its onset even in the early stages of the disease.

A $\beta$  peptide, Tau protein, and ROS, all hallmark players in AD, have been shown to induce mitochondrial dysfunction through multifaceted mechanisms. For instance, A $\beta$ -binding alcohol dehydrogenase (ABAD) exacerbates A $\beta$ -mediated mitochondrial stress, culminating in neuronal stress and subsequent cognitive impairment [55,56]. A $\beta$  accumulation has also been linked to mitochondrial Ca $^{2+}$  overload, a precursor to neuronal apoptosis [57,58]. Furthermore, interactions between A $\beta$  and cyclophilin D (Cyp D) can instigate the opening of the mitochondrial permeability transition pore, leading to mitochondrial swelling, compromised membrane integrity, and abnormal axonal mitochondria transport, all of which contribute to neuronal death [59].

Concurrently, Tau protein, especially when aggregated or hyperphosphorylated, can disrupt mitochondrial distribution, impairing synaptic function in neurons, suggesting an early role of mitochondrial dysfunction in AD pathogenesis [60–64]. Such mitochondrial dysfunctions are often accompanied by a cascade of pathophysiological events, including metabolic downturns, Ca $^{2+}$  homeostasis disruptions, elevated ROS production, lipid peroxidation, and apoptosis observed in AD brains [59,65–70].

The delicate balance between ROS and the antioxidant system, when disrupted, can precipitate oxidative stress [71], impairing glucose metabolism and leading to the loss of the ionic gradient [72]. Such disruptions can impede adenosine triphosphate (ATP) production [73], affecting the generation and propagation of action potentials. Elevated intracellular Ca $^{2+}$  levels can activate Ca $^{2+}$  dependent endonuclease, phospholipase, and protease, releasing cytochrome C and apoptosis-inducing factors, culminating in neuronal apoptosis [74]. This excess intracellular Ca $^{2+}$  can also compromise of microtubule assembly, impede mitochondria and neurotransmitter vesicle transport, deplete presynaptic energy terminals, and diminish neurotransmission, ultimately leading to synaptic dysfunction, neuronal death, and cognitive deficits [73]. Understanding the intricacies of mitochondrial



dysfunction in AD offers a promising avenue for therapeutic interventions and drug development, as highlighted in recent studies.

#### 2.4. Tau hypothesis

Tau protein, a microtubule-associated protein, is instrumental in stabilizing microtubule structures, thereby facilitating efficient axonal transport [75]. A hallmark pathological feature of AD is the formation of intracellular NFTs, primarily composed of hyperphosphorylated Tau (p-Tau). This hyperphosphorylation is instigated by aberrant kinases and phosphatases activities and intriguingly, such accumulations have been observed even before the clinical onset of AD [76,77].

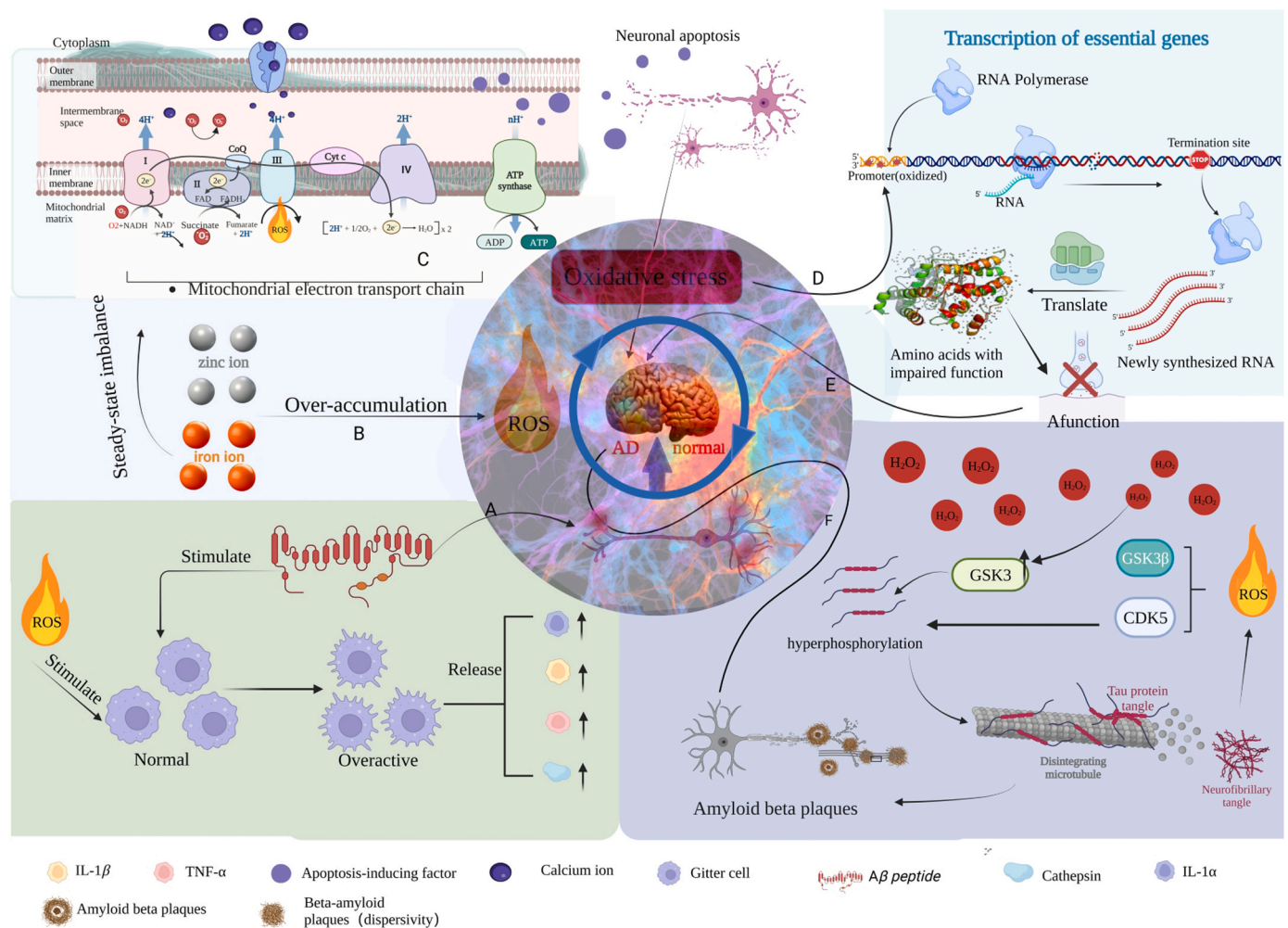
Recent insights have revealed that oxidative stress can directly modulate the activity of specific protein kinases, notably glycogen synthase kinase-3 (GSK3) [78]. For instance, embryonic kidney 293/Tau cells exposed to  $H_2O_2$ , exhibit hyperphosphorylation at specific sites, such as Ser396, Ser404, and Tr231, attributed to amplified GSK3 activity [79]. Under pathological scenarios, ROS-induced disturbances in Tau's normal function lead to its interaction with kinases like cyclin dependent protein kinase-5 (CDK5) and glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ). This results in Tau hyperphosphorylation which in turn diminishes its affinity for microtubules, promoting their depolymerization and

perturbing neural signaling [80–82].

Furthermore, chronic oxidative stress has been shown to amplify tau phosphorylation in M17 neuroblasts, which is implicated in axonal lesions in vivo [83]. During tauopathies, oxidative stress can induce neuronal cell-cycle anomalies and JNK-mediated apoptosis. Concurrently, Tau hyperphosphorylation, microtubules disruption, and tau accumulation can foster ROS generation, further intensifying the pathogenesis of AD [80,84]. Given the intricate interplay between Tau protein, oxidative stress, and AD, understanding the Tau hypothesis in depth can offer novel therapeutic avenues and insights into disease progression.

#### 2.5. Oxidative DNA damage

Oxidative DNA damage stands as a pivotal factor in the pathogenesis of AD. While AD is primarily characterized by cognitive dysfunction diminished executive functions, oxidative DNA damage can impair gene transcription, affect promoter function, and induce mutations in pivotal genes [85]. Such damage can have profound implications on synaptic function, given the intricate involvement of over 1000 proteins in synaptic transmission, which is further exacerbated by the massive synaptic loss observed in both AD and Lewy body disease [86,87].



**Fig. 2.** The process mechanism of ROS oxidative stress and neuroinflammation caused by various factors and finally leading to AD. (A) Stimulation of A $\beta$  and ROS triggers a microglial immune response that culminates in neuroinflammation and neuronal upset, accelerating the development of Alzheimer's Disease (AD); (B) An imbalance in zinc and iron levels destabilizes mitochondria, resulting in oxidative stress, neuronal apoptosis, and an exacerbation of AD; (C) Mitochondrial dysfunction intensifies neuronal stress, leading to cognitive impairment and further progression of AD; (D-E) Oxidative damage to DNA hampers gene transcription processes, provoking critical gene mutations and consequently amplifying cognitive deficits; (F) The expression of GSK3, induced by free  $H_2O_2$ , disrupts nerve signal transmission, thereby playing a role in the progression of AD.



Recent advances have elucidated the intricate relationship between oxidative DNA damage and AD. For instance, histone deacetylase HDAC1 has been identified to modulate OGG1-initiated oxidative DNA damage repair in the aging brain and AD [88]. Additionally, the role of the cocaine amphetamine regulated transcript (CART) in counteracting oxidative stress and DNA damage in APP/PS1 mice, a widely recognized animal model of AD, has been highlighted [89].

Furthermore, the activation of cycle checkpoint protein kinase 1 (Chk1) due to DNA damage has been found to foster tau and APP hyperphosphorylation, leading to cognitive dysfunction in AD through the CIP2A/PP2A signaling pathway [90]. This discovery underscores the potential therapeutic efficacy of Chk1 inhibitors in AD. Moreover, defects in DNA repair leading to NAD<sup>+</sup> depletion, impaired mitophagy, accumulation of damaged mitochondria, metabolic dysregulation, and energy exhaustion have been observed in both accelerated aging diseases and AD [91]. This suggests a shared mechanism between DNA repair and NAD<sup>+</sup> metabolism in neurodegenerative processes.

In light of these findings, delving deeper into the role of oxidative DNA damage in AD and identifying potential therapeutic strategies targeting this pathway could pave the way for innovative treatment of this debilitating disease.

### 3. Biomedical functions of hydrogen

Hydrogen, a colorless and odorless gas, is the lightest mass and the smallest molecular weight of any element. It is composed of a single electron and proton, has a low solubility at room temperature under atmospheric pressure, and it exhibits highly biocompatible [92]. Hydrogen's biomedical significance was first recognized in 1975 when it was found to be effective in treating skin tumors in albino mice [93]. In 2007, its selective antioxidant properties were discovered [15]. Since then, hydrogen's therapeutic potential has been explored in various medical fields. It has shown promise in the treatment and amelioration of neurodegenerative diseases, cardiovascular disease, metabolic syndrome, and diabetes [94,95], acute soft-tissue injuries and skin lesions [96,97], kidney disease, inflammatory diseases [98] and even cancer [99].

Recent studies have highlighted hydrogen's role as a key intracellular signaling molecule [100]. It has been found to ameliorate neurodegenerative diseases primarily through anti-inflammatory, anti-oxidative stress, anti-apoptosis, and modulation of autophagy and hormonal signaling pathways [93,101–103]. The unique properties of hydrogen, including its ability to rapidly diffuse across membranes, make it a promising therapeutic agent.

#### 3.1. Suppressing inflammation levels

It has been reported that an inflammatory response in the brain tissue of Alzheimer's patients can cause oxidative stress [104] and cell apoptosis [105] which may lead to mitochondrial dysfunction [106,107].

Hydrogen has been shown to mitigate the amount of ROS released from mitochondria, thereby reducing mitochondrial DNA peroxidation and inhibiting the expression of NOD-like receptor thermal protein domain associated protein 3 (NLRP3), caspase-1, and IL-1 $\beta$  to alleviate inflammation [108–110]. Concurrently, hydrogen may also convert free radicals ( $\cdot$ OH) to water molecules through the retraction reaction [111,112], eliminating ROS produced by mitochondria under lipopolysaccharide stimulation. This process inhibits mitochondrial ROS-mediated NLRP3 de-ubiquitination, revealing a potential mechanism by which hydrogen suppresses the activation of NLRP3 production induced by mitochondrial reactive oxygen [113]. These natural anti-inflammatory and antioxidant effects of hydrogen have been suggested to be potentially beneficial in the treatment of AD [114].

Meanwhile, hydrogen can regulate microglial polarization via the mammalian target of rapamycin (mTOR) signaling pathway, thereby

reducing sepsis-induced neuroinflammation [115]. Through the activation of Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), hydrogen-rich saline has been demonstrated to promote the differentiation of M2-type microglia, and prevention of neuronal damage and apoptosis [116].

Beyond that, recent studies have shown that hydrogen can also exert neuroprotective effects by reducing oxidative stress and apoptosis in neuroblastoma cells [117–120]. These findings further underscore the potential of hydrogen as a therapeutic agent in the management of AD. And these mechanisms collectively contribute to the reduction of inflammation and prevention of neuronal damage and apoptosis [107].

#### 3.2. Regulation of energy metabolism

In AD, the balance between oxidative phosphorylation and aerobic glycolysis of glucose, crucial for maintaining the brain's energy supply, is disrupted. This leads to decreased energy metabolism, contributing to cognitive decline and memory deficits [121]. Such an energy deficit is underscored by the diminished activity of critical enzymes, notably the pyruvate dehydrogenase complex, leading to compromised electron transport chains and a subsequent decrease in ATP production [122].

Recent studies have illuminated the potential of hydrogen in mitigating these metabolic challenges. Hydrogen has demonstrated its capability to attenuate oxidative stress and curtail mitochondrial damage, thereby bolstering ATP synthesis and fortifying the electron transport chain within mitochondria [123–127]. This not only shields neurons from potential damage but also augments cognitive functionality [128].

Moreover, hydrogen can modulate the dynamics of metabolic energy pathways. For instance, hydrogen has been identified to curtail the release of ROS from mitochondria, thereby diminishing mitochondrial DNA peroxidation and suppressing the expression of pivotal inflammatory mediators [129]. In essence, the multifaceted role of hydrogen in regulating energy metabolism, combined with its potent antioxidant attributes, positions it as a promising therapeutic candidate in the arsenal against AD.

#### 3.3. Reduce oxidative stress levels

##### 3.3.1. Activation of antioxidant pathways

A $\beta$  peptide, a primary contributor to AD [130], is linked with the overproduction of ROS [131]. This ROS surge, instigated by A $\beta$ , intensifies mitochondrial dysfunction and propels cell apoptosis [5,123]. This suggests that antioxidant therapy may effectively prevent ROS-related AD. Recent advancements in research have spotlighted the therapeutic potential of hydrogen-rich water (HRW) in combating oxidative stress-induced diseases. HRW exhibits a remarkable ability to neutralize excess ROS, thereby attenuating oxidative damage. This mechanism not only diminishes cell death instigated by A $\beta$  but also decelerates the progression of AD [132]. For instance, HRW has been demonstrated to counteract A $\beta$ -induced mitochondrial potential loss and oxidative stress by activating AMPK and amplifying the downstream antioxidant response of forkhead box O3a (FOXO3) [132].

Furthermore, HRW plays a pivotal role in bolstering the brain's antioxidant defense system. It elevates the levels of intracellular antioxidant enzymes, notably superoxide dismutase 1 (SOD1) and catalase (CAT), thereby serving as a neuroprotective agent that diminishes the risk and progression of AD [133–136]. A recent study also emphasized the role of HRW in ameliorating neuropathological impairments in an AD mouse model, particularly by attenuating neuroinflammation [137]. In conclusion, the multifaceted role of HRW in activating antioxidant pathways and its subsequent neuroprotective effects offer promising avenues for therapeutic interventions in AD.

### 3.3.2. Selective reduction of highly cytotoxic hydroxyl radicals and peroxynitrite anion

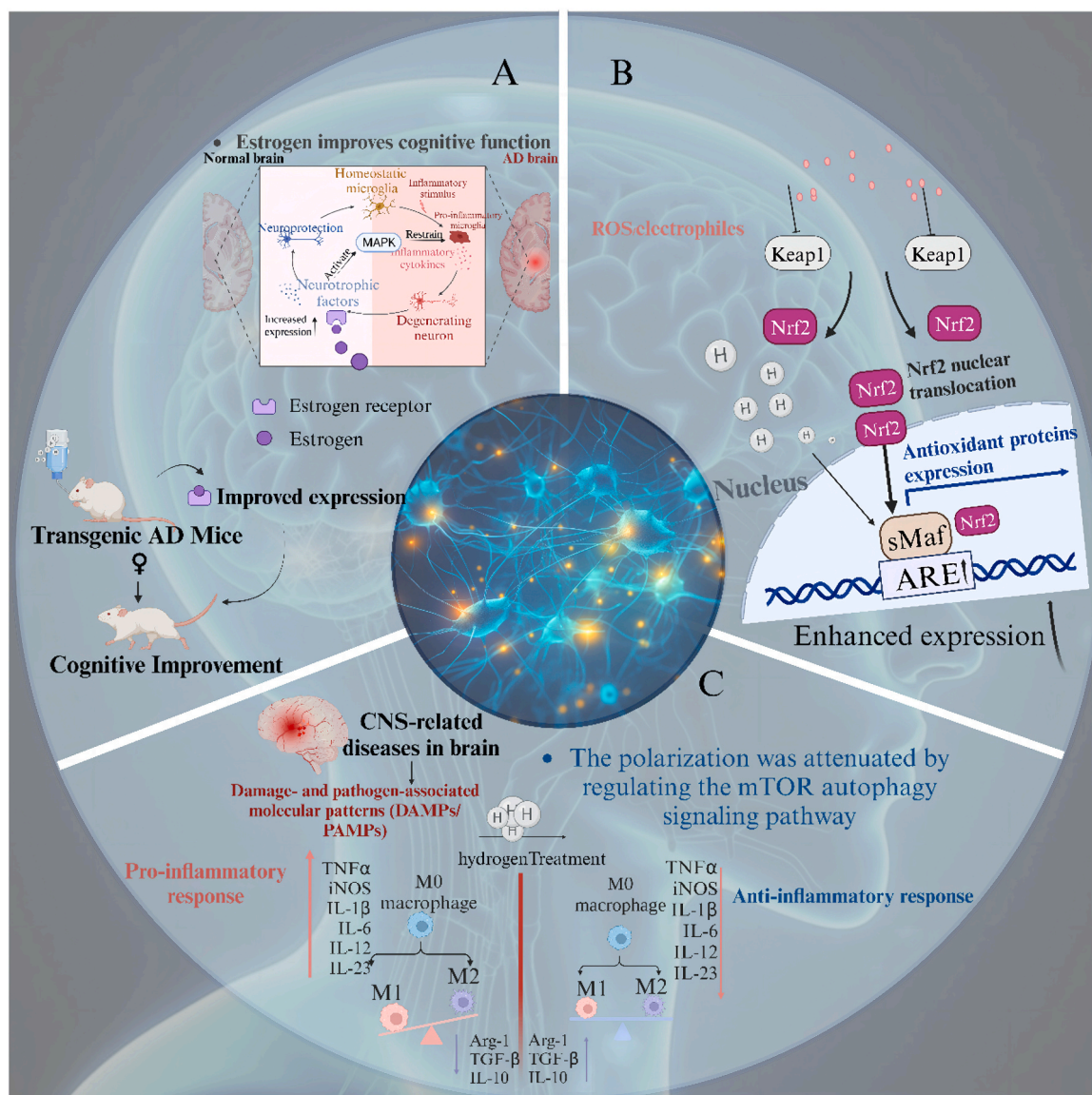
Oxidative stress, resulting from an imbalance between oxidation and antioxidant functions, is a significant contributor to cellular damage, especially in neurodegenerative diseases like AD [138]. This stress is often exacerbated by potent oxidants such as hydroxyl radicals ( $\cdot\text{OH}$ ) and peroxynitrite ( $\text{ONOO}^-$ ), which indiscriminately react with nucleic acids, lipids, and proteins, leading to DNA fragmentation, lipid peroxidation, and protein inactivation [98].

Hydrogen has emerged as a potent therapeutic agent due to its ability to selectively scavenge these harmful radicals. Notably, hydrogen's potential therapeutic effects were first highlighted in 2007 when Ohsawa et al. Demonstrated its selectively reduction- $\cdot\text{OH}$  and  $\text{ONOO}^-$  in cultured cells and its role in reducing the oxidized state of macromolecules involved in non-cell trials [15]. Excessive free radical and ROS production leads to oxidative stress, which causes neuroinflammation and apoptosis, thereby exacerbating the AD process [139]. Hydrogen's selective reduction of  $\cdot\text{OH}$  and  $\text{ONOO}^-$ , has shown promise in protecting the brain against ischemia-reperfusion injury and stroke, suggesting its

potential in reducing the incidence and progression of AD [140]. This protective effect in reducing the incidence and progression of AD offers new therapeutic possibilities.

### 3.3.3. Activation of the cellular endogenous antioxidant system Nrf2

Inflammatory responses in AD can result from dysregulation of oxidative stress signaling pathways [141]. The blood-brain barrier can be destroyed by inflammatory factors, causing central neuroinflammation [142]. The activation of Nrf2 which is an important regulator of antioxidant stress, increases gene expression of phase II detoxifying and antioxidant enzymes, enhancing antioxidant capacity, and thereby reducing oxidative stress and inflammation. Specifically, the Kelch-like ECH associated protein-1 (Keap1)/Nrf2/antioxidant response element (ARE) pathway is at the core of the cellular antioxidant defense system [143]. Under physiological conditions, Keap1 can degrade Nrf2 by ubiquitination. Keap1 is, however, activated when the balance between ROS production and clearance is disrupted, resulting in the blockage of Nrf2 clearance, resulting in excessive accumulation and activation of Nrf2, which then translocates to the nucleus and



**Fig. 3.** Therapeutic role of hydrogen in AD progress. (A) Hydrogen regulates the expression of ER $\beta$  and BDNF, enhancing cognitive function; (B) Hydrogen slows AD progression by activating the cellular endogenous antioxidant system Nrf2; (C) Hydrogen inhibits the overactivation of microglia, promoting an anti-inflammatory response.



regulates anti-oxidative stress genes by targeting ARE [144]. Among them, Nrf2 plays the most active role in the brain when it comes to preventing oxidative stress. As a result, hydrogen promotes cellular response to oxidative stress by activating Nrf2, inhibits the disorder of oxidative stress signaling pathways, and slowing down the development of AD [126].

In addition to the above pathways, hydrogen has also been shown to improve cognitive function in the brains of female transgenic AD mice by regulating the expression of estrogen receptor (ER) and brain-derived neurotrophic factor (BDNF) [145]. Since the ovarian hormones are reduced during menopause, women are more likely to develop AD as a result. By modulating estrogen's effects on brain development and activating mitogen-activated protein kinase and protein kinase C (PKC) signaling pathways, hydrogen may inhibit AD progression and neuronal damage [146].

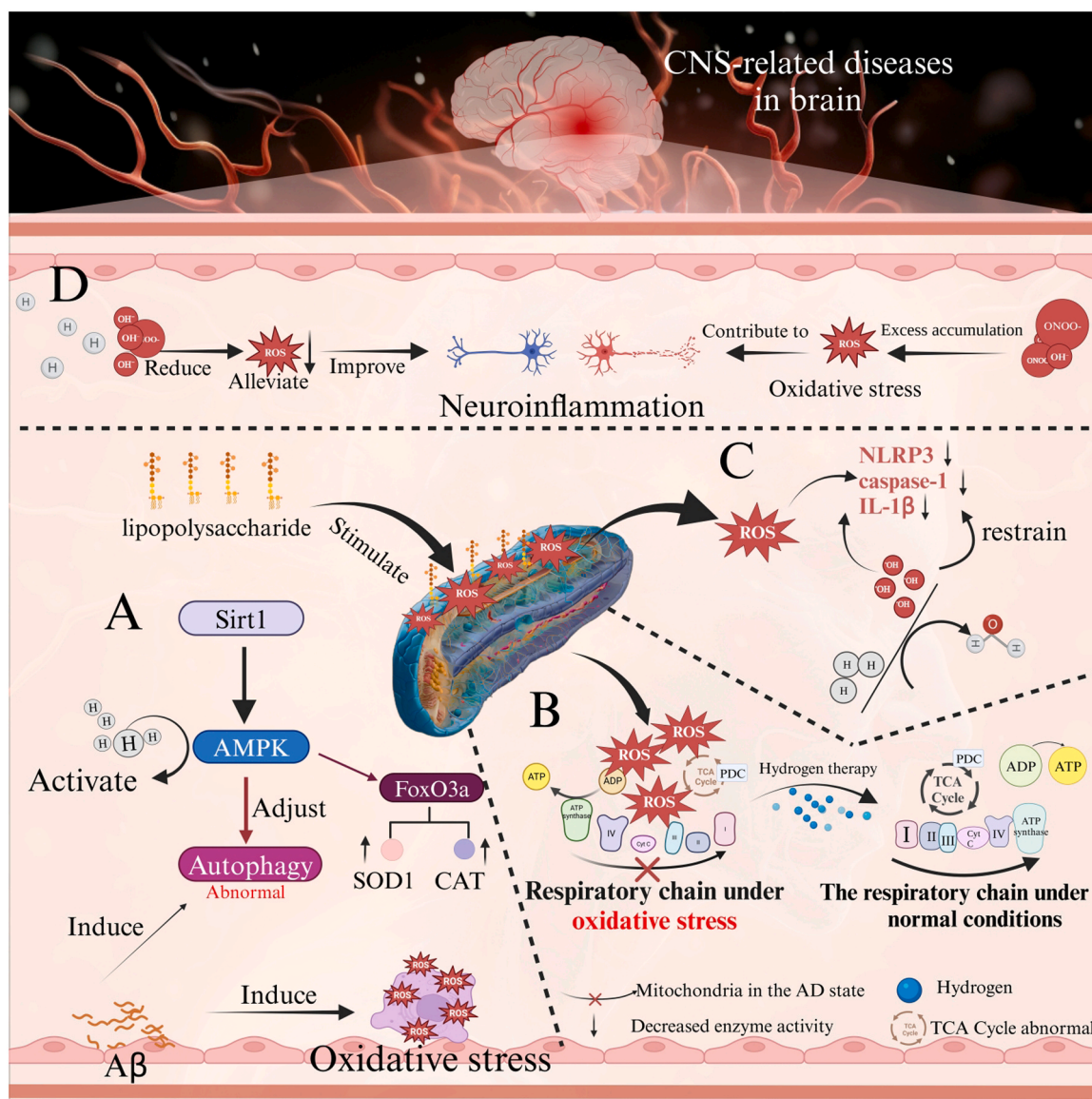
Therefore, molecular hydrogen can synergistically regulate AD

through multiple pathways such as anti-inflammatory, anti-oxidative stress, anti-apoptosis and hormone signaling pathways, paving the way for the development and clinical application of hydrogen-based therapeutic strategies for AD.

Hydrogen ameliorates AD by multipath way treatment has been collated in Fig. 3 and Fig. 4.

#### 4. Administration route

Hydrogen's physicochemical properties and biomedical functions have led to the development of various administration methods for both basic research (Table 1) and clinical applications (Table 2). These methods include direct ingestion of gas, hydrogen-rich water, and nanometer hydrogen carrier, etc.



**Fig. 4.** Therapeutic role of hydrogen in AD progress. (A) Hydrogen inhibits the overactivation of microglia, promoting an anti-inflammatory response; (B) Hydrogen regulates the expression of ER $\beta$  and BDNF, enhancing cognitive function; (C) Hydrogen mitigates oxidative stress and neuroinflammation by selectively reducing the production of  $\cdot\text{OH}$  and  $\text{ONOO}^-$ ; (D) Hydrogen mitigates AD progression by reducing oxidative stress, preventing mitochondrial damage, and promoting ATP synthesis and electron transport chain functionality in mitochondria; (E) Hydrogen slows AD progression by activating the cellular endogenous antioxidant system Nrf2; (F) Hydrogen acts as a neuroprotective agent by upregulating the downstream antioxidant response of FOXO3a and reducing A $\beta$ -induced loss of mitochondrial potential and oxidative stress through AMPK in the Sirt1-dependent pathway, thereby reducing brain oxidative stress levels; (G) Hydrogen reduces  $\cdot\text{OH}$  to water molecules, thereby mitigating oxidative stress damage to mitochondria.



**Table 1**

Basic researches on hydrogen therapy for AD.

| Model animal                                                                 | Method of administration                                                                                                                                       | Result of treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Ref.  |
|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Sepsis-associated encephalopathy (SAE) model was established in C57BL/6 mice | 2% H <sub>2</sub> was inhaled for 60 min each time.                                                                                                            | The surveillance period spanning between 6 and 8 days revealed that attenuating DNA methyltransferase 1 (DNMT1) and DNA methyltransferase 3A (DNMT3A) mediated methylation of promoter IV of the brain-derived neurotrophic factor (BDNF) had a protective effect against neuroinflammation instigated by sepsis. This consequential diminution led to an upsurge in BDNF levels, which further ameliorated the cognitive impairments observed in mice affected by sepsis. | [147] |
| Intracerebral hemorrhage (ICH) was induced in rats                           | 3% H <sub>2</sub> was administered by spontaneous inhalation and treated for two hours.                                                                        | It significantly reduced the levels of genes involved in oxidative stress, neuroinflammation, neuronal damage and apoptosis.                                                                                                                                                                                                                                                                                                                                               | [148] |
| Traumatic brain injury (TBI) in rats                                         | Exposure to 2% H <sub>2</sub> for hydrogen treatment lasted from 5 min to 5 h after sham or TBI, respectively.                                                 | Decrease in oxidative products and increase in endogenous antioxidant enzyme activity in brain tissue.                                                                                                                                                                                                                                                                                                                                                                     | [149] |
| C57BL/6 mice were injected with trimethyltin                                 | 3% H <sub>2</sub> was inhaled for 30 min once a day for four weeks                                                                                             | Reduced inflammatory markers such as ROS, Nitric oxide (NO) and Malondialdehyde (MDA) and inflammatory cytokines such as Granulocyte colony-stimulating factor (G-CSF), IL-1, TNF- $\alpha$ .                                                                                                                                                                                                                                                                              | [150] |
| Triple transgenic (3 $\times$ Tg)-AD model mice                              | Continuous drinking concentrations greater than 1.6 ppm. Hydrogen-rich water for seven months                                                                  | Inhibition of A $\beta$ production and deposition in the hippocampus of 3 $\times$ Tg-AD mice, inhibition of tau hyperphosphorylation and NFT formation, inhibition of inflammation and transformation of microglia in the anti-inflammatory direction in 3 $\times$ Tg-AD mice, and improvement of bioenergetics in the mouse brain.                                                                                                                                      | [151] |
| S-D male rats were intraventricular injected with A $\beta$ 5–14             | Intracerebroventricular injection of A $\beta$ 5–14 was followed by hydrogen-rich saline (1 mL/kg, ip, daily) for 42 days.                                     | The hydrogen-rich saline treatment effectively curbed MDA, IL-6, and TNF- $\alpha$ levels, enhanced hippocampal performance in the Morris water maze obstructed by A $\beta$ 1–42, and amplified long-term potentiation (LTP). It concurrently mitigated A $\beta$ 1–42-induced immune reactivation of 4-Hydroxynonenal (4-HNE) and Glial Fibrillary Acidic Protein (GFAP) in the hippocampus.                                                                             | [152] |
| Senescence-accelerated prone mouse 8 (SAMP8) mice                            | Drinking 0.55–0.65 mmol hydrogen-rich water (HRW) for 18 weeks.                                                                                                | Improved cognitive deficits in SAMP8 mice, drinking HRW significantly reduced lipid peroxidation in the brain of SAMP8 mice. The decrease of serotonin in the brain was significantly reduced, and the histopathological changes in hippocampal CA1 and CA3 were inhibited.                                                                                                                                                                                                | [153] |
| Male transgenic DAL101 mice                                                  | Drinking HRW to ensure that the concentration is maintained above 0.6 mM continues from 1 month of age until 18 months of age.                                 | HRW inhibited the decline of learning and memory impairment, reduced oxidative stress in DAL mice, and improved the AD assessment scale–cognitive subscale (ADAS-Cog) scores in tested mice.                                                                                                                                                                                                                                                                               | [109] |
| Female transgenic AD mice                                                    | Intragastric administration of HRW at concentrations greater than 0.6 mmol/L and 0.1 mL/10 g twice daily for 30 days.                                          | Decreased hormone levels, estrogen receptor (ER) $\beta$ , and BDNF expression improve cognitive function in female transgenic AD mice.                                                                                                                                                                                                                                                                                                                                    | [146] |
| 3 $\times$ Tg-AD mouse model                                                 | Stereotactic injection of small palladium hydride (PdH) nanoparticles was performed with coordinates corresponding to the CA2 region of the mouse hippocampus. | The expression of APP, BACE1, and SAPP $\beta$ was proficiently suppressed, thereby curtailing the overproduction of A $\beta$ in Alzheimer's Disease model cells and mice, halting the progression of the disease. The administration of PdH treatment to 3xTg-AD mice markedly improved cognitive deficits, synaptic anomalies, and neuronal mortality.                                                                                                                  | [126] |

#### 4.1. Direct ingestion of gas

Hydrogen gas, as the smallest molecule, is composed of two protons and two electrons. It was once thought to be physiologically inert in mammalian cells. However, this view started to change when the therapeutic effect of hydrogen gas was first demonstrated in a mouse skin squamous cell carcinoma model in 1975 [157]. The toxicity advantage of hydrogen gas is more prominent than other medical gases. Even at high concentrations, hydrogen gas is still non-toxic, and has been widely used in the diving field. Research also shows that inhaling hydrogen gas has no effect on blood pressure and other blood parameters (such as pH, body temperature, etc.), and has no obvious adverse reactions, which is consistent with recent clinical trial results for patients with cerebral infarction and sudden cardiac arrest syndrome [158–162]. Based on current advancements, the inhalation treatment of hydrogen gas is gaining more attention.

As the most convenient and safe way of hydrogen administration, hydrogen itself has promoted the development of hydrogen biomedicine due to its excellent antioxidant properties and outstanding anti-inflammatory performance (Fig. 5).

Hydrogen can be delivered to the lungs via a hydrogen, which can be connected to a ventilator circuit, face mask, or nasal catheter. These method allows for rapid diffusion of hydrogen throughout the body, providing protection against acute oxidative stress without affecting

blood pressure [163].

#### 4.2. Hydrogen-rich water

The therapeutic potential of HRW has garnered significant attention in recent years, particularly in the context of neurodegenerative diseases like AD. Advances in techniques such as electrolysis [167], metal-acid reaction [168], and high-pressure dissolution [169] have facilitated the production and application of HRW.

HRW is produced by dissolving hydrogen in a liquid, offering a convenient and safe alternative to, direct hydrogen inhalation, which necessitates specialized equipment [170]. Due to its high solubility under 0.8 mM conditions, HRW provides a therapeutic concentration equivalent to direct hydrogen inhalation [118].

Recent studies have illuminated the multifaceted benefits of HRW in AD. It has been shown to counteract cognitive decline, mitigate oxidative stress, and foster hippocampal neurogenesis [171]. Such neuro-protective effects are pivotal given the role of oxidative stress in AD pathogenesis [172]. HRW has demonstrated efficacy in alleviating A $\beta$ -induced learning and memory impairment, neuroinflammation, and in modulating inflammatory pathways, particularly through the inhibition of JNK and NF- $\kappa$ B activation [173]. Moreover, drinking HRW may mitigate age-associated cognitive impairments, bolster cognitive ability in carriers of the apolipoprotein E4 genotype, and even extend lifespan

**Table 2**  
Clinical studies on hydrogen therapy for AD.

| Model animal                                                                                                                                               | Method of administration                                                                                                                                           | Result of treatment                                                                                                                                                                                                                                                                                                                                                                                  | Ref   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Three patients with AD                                                                                                                                     | Inhalation of 3% H <sub>2</sub> gas for 6 h twice daily for 1 month.                                                                                               | The average individual change in ADAS-cog was significantly improved after 2 treatments compared with the initial phase, and the treatment significantly improved the integrity of neurons passing through the hippocampus.                                                                                                                                                                          | [155] |
| Eighteen patients with Parkinson's disease (PD)<br>The study was a placebo-controlled, randomized, stratified, double-blind, parallel-group (1:1) approach | H <sub>2</sub> -saturated water was prepared by dissolving 0.8 mM H <sub>2</sub> and drinking 1000 mL daily for 48 weeks. The other groups received placebo water. | Changes in total Unified-PD rating scale scores from baseline to week 8, week 24, week 48, and week 8 were assessed. The primary endpoint of treatment effect in PD patients was the change in total UPDRS score from baseline to week 48. Six of nine participants in the H <sub>2</sub> -water group showed improvement, increasing the UPDRS total score by approximately 5 points over 48 weeks. | [156] |
| Apolipoprotein E4 (APOE4) genotype                                                                                                                         | 300 mL of hydrogen-rich water was consumed daily for one year.                                                                                                     | Significant improvements were seen in the total ADAS-cog score and in the word recall task score, one of the subscores of the ADAS-cog score.                                                                                                                                                                                                                                                        | [154] |

[151,174,175].

Furthermore, a study highlighted the role of HRW in attenuating Aβ-induced cytotoxicity by upregulating the Sirt1-FoxO3a pathway, stimulated by AMP-activated protein kinase in SK-N-MC cells [132]. Another research emphasized the gender-dependent improvement in cognitive function in APP/PS1 mice treated with HRW, without affecting Aβ clearance [139]. The emerging evidence underscores the therapeutic promise of HRW in AD, offering a novel avenue for intervention that targets the oxidative stress and inflammatory pathways central to the disease's progression.

4.3. Nano-carrier

The latest advancements in the nano-delivery system provide strong support for the new applications of traditional drugs in treating many diseases. The representative content of this system is to use nano-carriers to deliver drugs to pathological sites [176]. The nano-carriers involved include liposomes [177], micelle [178], Nanogels [179]. And nano-particles, these have gained widespread use in preclinical research for targeted drug delivery [180]. Traditional methods, such as inhalation or gas loading, may not effectively target the lesion sites, potentially leading to prolonged treatment durations and suboptimal outcomes. This is where nano-carriers, with their superior targeting properties, come into play [181].

Palladium (Pd), a notable excellent nanomaterial, and delivery platform, has demonstrated potential not only in tumors targeting [182]

but also as a robust platform for enhancing the delivery efficiency of biological nano-carriers [183]. Recent breakthroughs have spotlighted Pd hydride (PdH) nanoparticles as high-payload hydrogen carriers. These nanoparticles are capable of in-situ sustained release of bio-reductive hydrogen, marking a significant advancement in the field. PdH nanoparticles can selectively remove highly cytotoxic radicals-OH from AD model cells through self-catalytic release of bio-reductive hydrogen, which can improve mitochondrial dysfunction. Promote cell energy metabolism and inhibit cell apoptosis. The administration of PdH nanoparticles inhibited the overexpression of APP, Beta-secretase 1 (BACE1) and Soluble peptide app (sAPP) thereby reducing the over-production of Aβ in AD model cells and mice and blocking the progression of AD [126]. To be gratified, the integration of nanotechnology into AD therapeutics, particularly through the use of nano-carriers, holds immense promise. By enhancing drug delivery efficiency and targeting capabilities, these systems could revolutionize the treatment landscape for AD and other neurodegenerative disorders.

5. Future directions and challenges in hydrogen therapy for AD

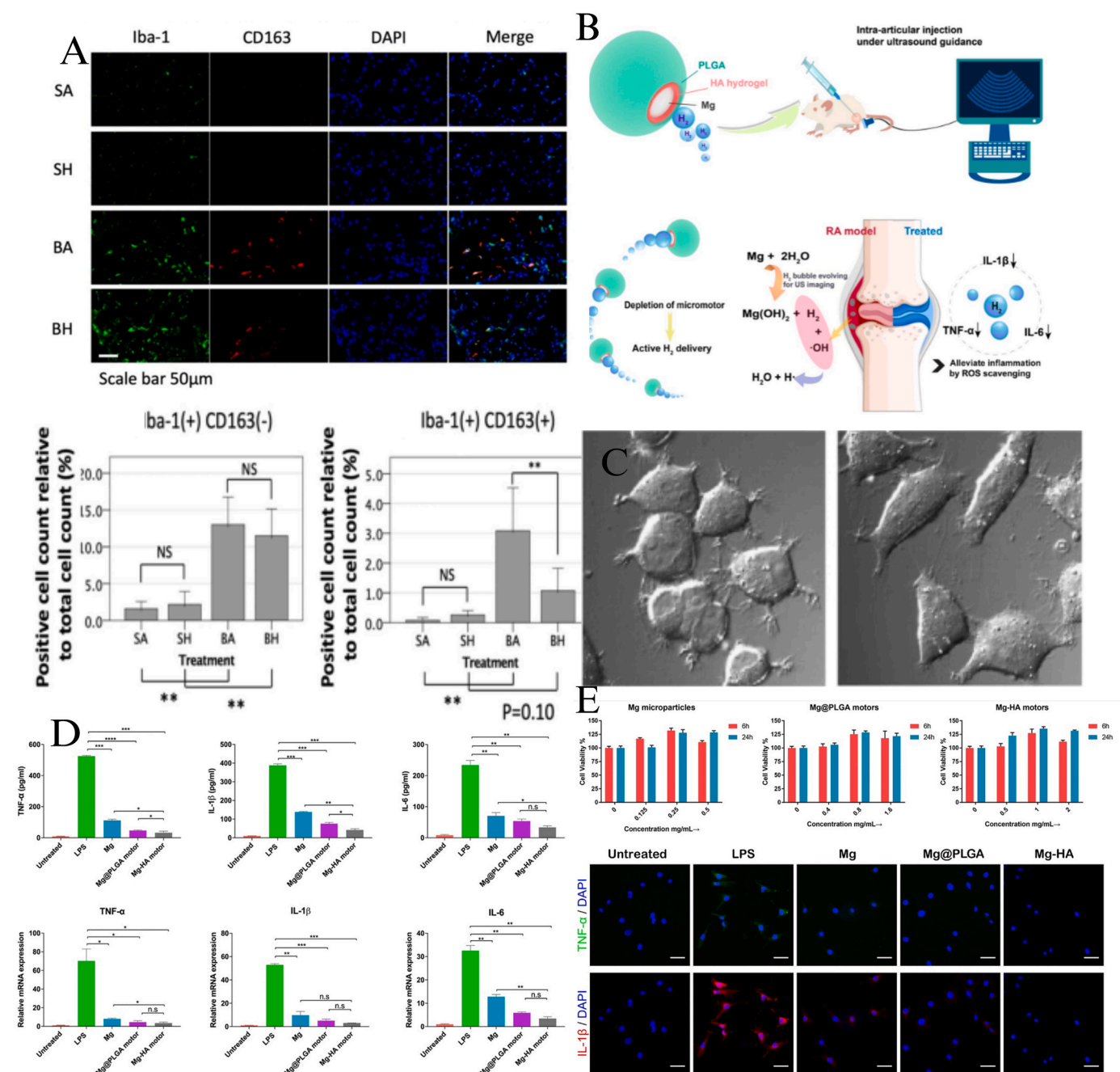
The potential of hydrogen therapy in treating AD is undeniable. However, its widespread application faces has been hindered by several challenges. One of the primary obstacles is the low solubility of hydrogen at ambient temperature and pressure, which restricts the effective dosage that can be introduced into the bloodstream via gas inhalation. Delivering high concentrations of hydrogen in liquid form to specific brain regions, especially across the blood-brain barrier, remains a formidable challenge [147]. Moreover, the long-term biocompatibility of nano-formulations is yet to be ascertained [184]. Addressing these challenges, the following research directions are emerging:

(I) Advancements in administration route: hydrogen eye drop can significantly improve retinal ischemia-reperfusion injury [185] and can also affect cranial nerve lesions [186]. Furthermore, the selection of hydrogen storage materials with a high long-term biocompatibility can enable the continuously in-situ release of highly reduced hydrogen in the brain of AD patients, efficiently crossing the blood-brain barrier to perform their functions.

(II) Sustainable hydrogen production: The need for materials or *microorganisms* capable of sustainably releasing hydrogen at specific locations is increasingly urgent. A study by Chen, H. et al. has synthesized a symbiotic algae-bacterial dressing that develops a sustainable hydrogen production hydrogel for diabetic wound healing [187]. Meanwhile, studies of controlled and sustained release of bioactive compounds have widely utilized hydrogels [188]. Therefore, these studies provide a new idea for the sustained delivery of hydrogen for AD in the future, that is, hydrogels with good biocompatibility can co-carry hydrogen-producing bacteria that can be targeted to the lesion site to play a therapeutic role.

(III) Hydrogen as a diagnostic marker : Hydrogen has been used as a diagnostic marker for many diseases, and respiratory measurements of hydrogen and methane concentrations have been used to diagnose intestinal bacterial overgrowth and thus to diagnose the occurrence of cirrhosis [189], The Europe-wide H<sub>2</sub>-CH<sub>4</sub> breath test indicator diagnosis has been used to provide new insights into the role of symptom assessment in diagnosing carbohydrate (e.g. lactose) intolerance in both adult and child patients, and it is suggested that breath tests for carbohydrate malabsorption require additional validated concurrent symptom assessment to identify carbohydrate intolerance [190]. However, the diagnosis of hydrogen markers for neurodegenerative diseases has not yet emerged, but research based on gut microbes and neurodegenerative diseases has advanced [191], In the future, the diagnosis of hydrogen markers based on hydrogen-producing bacteria will provide a new perspective in the diagnosis and prevention of AD.

These advancements and prospects highlight the potential of hydrogen therapy as a viable treatment for AD, despite the challenges faced. As research progresses, the development of more effective and



**Fig. 5.** The excellent anti-inflammatory and antioxidant experiments of hydrogen and the new perspective of the latest drive hydrogen to remove ROS. (A) After inhaling hydrogen gas for 7 days, a significant decrease in the quantity of Iba-1 positive and cd163 positive cells was observed [164]. Copyright © 2021 BMC; (B) The new Mg-HA hydrogen for its delivery platform [165]. Copyright © 2021 American Chemical Society; (C) When cultured PC12 cells were treated with oxidative stress via antimycin A, (I) cells significantly contracted and elongated short fibers under oxidative stress, (I) when cells were in H<sub>2</sub>, the cell shape remained unchanged [166]. Copyright © 2014 Elsevier; (D-E) The in vitro evaluation of Mg-HA motors showed that hydrogen gas can improve inflammation in MH7A cells after different LPS stimulation, as determined by the quantification of inflammatory cytokines [165]. Copyright © 2021 American Chemical Society.

targeted delivery methods for hydrogen therapy will likely emerge, offering new hope for AD patients.

## 6. Conclusion

Hydrogen-based therapeutic have emerged as a promising avenue in AD treatment, demonstrating potential in modulating the NLRP3 inflammasome, regulating energy metabolism, and safeguarding neuronal health. Notably, the low side-effect profile of hydrogen therapy sets it apart, offering a complementary approach to existing AD interventions. However, while preliminary findings are encouraging,

comprehensive clinical trials are imperative to validate these results and establish robust treatment protocols. As the field advances, hydrogen-based strategies hold the promise of reshaping the therapeutic landscape for AD, offering renewed hope for patients and caregivers.

## CRediT authorship contribution statement

D. Sun, T. Lou, and Q. Yang contributed to the conception of this review. J. He, F. Liu and T. Xu analyzed the literatures and wrote the manuscript. J. Ma, H. Yu, J. Zhao, and Y. Xie completed the figure drawings. D. Sun, J. He, L. Luo and L. He revised the manuscript. All



authors have read and agreed to the published version of the manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.biopha.2023.115807](https://doi.org/10.1016/j.biopha.2023.115807).

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