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SYSTEMATIC REVIEW ARTICLE

The Role of High Mobility Group Box 1 (HMGB1) in Neurodegeneration: A Systematic Review

Fathimath Zaha Ikram[1], Alina Arulsamy[2], Thaarvena Retinasamy[2] and Mohd. Farooq Shaikh[2,*]

[1]*Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Selangor, Malaysia;* [2]*Neuropharmacology Research Laboratory, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Selangor, Malaysia*

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Abstract: ***Background*:** High mobility group box 1 (HMGB1) protein is a damage-associated molecular pattern (DAMP) that plays an important role in the repair and regeneration of tissue injury. It also acts as a pro-inflammatory cytokine through the activation of toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (RAGE), to elicit the neuroinflammatory response. HMGB1 may aggravate several cellular responses, which may lead to pathological inflammation and cellular death. Thus, there have been a considerable amount of research into the pathological role of HMGB1 in diseases. However, whether the mechanism of action of HMGB1 is similar in all neurodegenerative disease pathology remains to be determined.

***Objective*:** Therefore, this systematic review aimed to critically evaluate and elucidate the role of HMGB1 in the pathology of neurodegeneration based on the available literature.

***Methods*:** A comprehensive literature search was performed on four databases; EMBASE, PubMed, Scopus, and CINAHL Plus.

***Results*:** A total of 85 articles were selected for critical appraisal, after subjecting to the inclusion and exclusion criteria in this study. The selected articles revealed that HMGB1 levels were found elevated in most neurodegeneration except in Huntington's disease and Spinocerebellar ataxia, where the levels were found decreased. This review also showcased that HMGB1 may act on distinctive pathways to elicit its pathological response leading to the various neurodegeneration processes/diseases.

***Conclusion*:** While there have been promising findings in HMGB1 intervention research, further studies may still be required before any HMGB1 intervention may be recommended as a therapeutic target for neurodegenerative diseases.

Keywords: Neurodegenerative disease, externally induced neurodegeneration, RAGE/TLR4, nuclear factor-κB (NFκB) pathway, TNF-α, therapeutic strategies, high mobility group box 1 (HMGB1).

1. INTRODUCTION

High mobility group box 1 (HMGB1) protein is a non-histone chromosomal protein with high electrophoretic mobility. The HMGB family comprised of three nuclear proteins; HMGB1 (HMG1), HMGB2 (HMG2), and HMGB3 (HMG4 or HMG2b). The HMGB1 protein is made of 215 amino acids in full length and consists of 80 amino acids per domain, primarily named as "HMG boxes A and B". Each box domain exerts a different effect, independently; Box A domain exerts an anti-inflammatory effect, while Box B domain may be more involved in pro-inflammatory effects [1]. HMGB1 is widely distributed in mammalian tissue cells and may be found in high levels in the neonatal livers, lymphoid tissues, thymus, and testis.

The HMGB1 protein is a DNA binding protein, which is highly involved in the regulation of gene transcription and the maintenance of the nucleosome structure, by bending the DNA and promoting the binding of other proteins [2, 3].

HMGB1 also acts as a damage-associated molecular pattern (DAMP) that plays a role in the repair and regeneration of tissue injury [4].

HMGB1 may also act as a pro-inflammatory cytokine, whereby it may activate the inflammatory receptors; toll-like receptor 4 (TLR4) and receptor for advanced glycation end products (RAGE) [5], thereby eliciting an inflammatory response. This omnipresent protein may be secreted actively by stressed cells or released passively by necrotic tissues, and may aggravate a range of cellular responses, often leading to pathological responses when the secretion levels are high and prolonged [6] Various pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1α may be induced by HMGB1, which leads to

*Address correspondence to this author at the Neuropharmacology Research Laboratory, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Selangor, Malaysia; Tel/Fax: +60 3 5514 4483; E-mail: farooq.shaikh@monash.edu

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chronic inflammation [7]. Chronic inflammation, especially in the central nervous system, may pathologically contribute towards the development of neurological disorders such as neurodegenerative diseases [8, 9].

Neurodegenerative disease is defined by the progressive loss of neurons, in terms of structure and/or function, in the central nervous system, which leads to various functional neurological deficits, governed by the affecting brain area/region [10]. Neurodegenerative disease may be classified according to their principal molecular abnormalities, their anatomical distribution in the brain like frontotemporal degenerations, as well as by their primary clinical presentations like parkinsonism [11]. Examples of neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis and amyotrophic lateral sclerosis (ALS). Given the growing ageing population especially in developed countries, the prevalence of neurodegenerative diseases is expected to rise as well [12], as aging is a common risk factor shared among various neurodegenerative disease [13]. In fact, some predict that one in every 10 individuals aged above 65 years old may already be diagnosed with AD [13]. Thus, urging researchers to hasten their search for an effective cure/treatment for each neurodegenerative diseases, given that the quality of life of the affected individuals drastically reduces as the disease progresses.

The onset of neurodegeneration of these diseases, sometimes referred to as protein abnormalities, may precede its clinical manifestations years prior, which provides a challenge towards its treatment and prevention [10]. These neurodegeneration abnormalities include tauopathies, α-synucleinopathies, amyloidosis, and the hyperphosphorylation of the TAR DNA-binding protein 43 (TDP-43) [11]. While the etiology of these protein abnormalities may still be unclear, as both genetic and environmental factors may play a role in them, targeting neuroinflammation has become the front runner for therapeutic or intervention strategies against neurodegenerative disease [10]. Neuroinflammation may be a double-edged sword [14], but chronic neuroinflammation has been seen as a precursor or aggravator to many protein abnormalities due to its contribution in protein misfolding [15-17]. Neuroinflammation may also cause other pathologies such as the release of neurotoxic mediators leading to excitotoxicity and oxidative stress, which may lead to progressive neuronal death or loss of function [18].

Considering that HMGB1 contributes to the pathogenesis of many inflammatory mediated diseases, including diabetes, sepsis, chronic pain, atherosclerosis, heart disease, and governs their downstream inflammatory pathways [7], the literature surrounding its involvement in neuroinflammation and neurodegenerative diseases have also shown to be ample. However, HMGB1 may govern different pathological pathways in different neurodegenerative diseases. Thus, this systematic review aims to critically evaluate the available literature regarding the distinct role of HMGB1 in the various pathological pathways of neurodegeneration /neurodegenerative diseases in hopes to elucidate its potential as a therapeutic/intervention target for the many types of neurodegenerations that have been burdening millions of people worldwide.

2. METHODOLOGY

2.1. Literature Search

The systematic literature search was carried out to retrieve all available literature in regards to HMGB1 and neurodegeneration as of April 2021. Four databases; EMBASE, PubMed, Scopus, and CINAHL Plus were utilized for the literature search. The search terms ["HMGB1" OR "High mobility group box-1" OR "High mobility group box 1" OR "High mobility group B1"] and ["Neurodegeneration" OR "Nerve degeneration" OR "Alzheimer disease" OR "Parkinson disease" OR "Amyotrophic Lateral Sclerosis" OR "Multiple Sclerosis" OR "Huntington" OR "Chronic Traumatic Encephalopathy"] were used in these databases. On all databases, the Boolean operator "AND" was utilized to link the search terms together. All searches were performed based on their title, abstract and keywords. The articles were initially screened through their titles and abstracts, after which the screening of relevant articles was performed *via* full text.

2.2. Literature Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used to conduct the literature selection [19]. The following inclusion criteria were applied during the selection process; 1) peer-reviewed original research articles investigating the role of HMGB1 in neurodegeneration, and 2) articles with full text available. The exclusion criteria during the selection process included; 1) articles labelled as editorials, symposiums, conference papers, commentaries, book chapters, case reports, systematic reviews and reviews, 2) duplicated articles, 3) articles not in the English language, and 4) articles not focusing their investigation on HMGB1 in relation to neurodegeneration.

2.3. Quality Appraisal

Different tools were used to assess the quality of the selected relevant articles. The Quality Assessment Tool for Quantitative Studies by the Effective Public Health Practice Project (EPHPP) [20] (Table **S1**) was used to evaluate clinical studies (excluding postmortem samples). While the Systematic Review Centre for Laboratory animal Experimentation Risk of Bias (SYRCLE RoB tool) [21] (Table **S2**) was used to assess the quality and risk of bias of preclinical animal studies. Quality appraisal of cell-based studies could not be performed, as currently there are no appropriate tools available for assessing the quality of preclinical *in vitro* studies.

3. RESULTS

The initial literature search retrieved a total of 1233 articles collectively from the four databases: 243 from PubMed, 506 from EMBASE, 15 from CINAHL Plus, and 469 from Scopus. Based on the inclusion and exclusion criteria, 642 duplicated articles were removed. The remaining 591 articles were screened in accordance with the PRISMA guidelines (Fig. **1**). A total of 383 articles were then excluded, as they were not original research articles, not available in full text or not in the English language. The remaining 208 records were screened for relevance to the aim of this systematic review; the role of HMGB1 in neurodegeneration/ neurodegenerative disease. One hundred and twenty-three articles

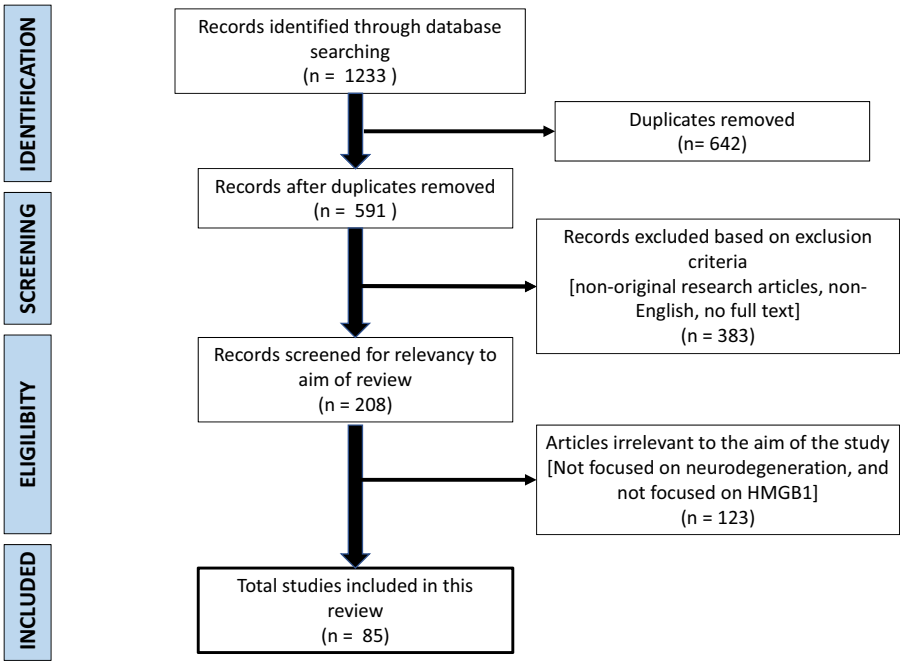

Fig. (1). Prisma flowchart.

were found irrelevant to aim of this review and thus were excluded; not involving HMGB1 or neurodegenerative diseases/neurodegeneration. Therefore, the final 85 articles were chosen for critical appraisal in this systematic literature review (Fig. **1**). These studies were further categorized into different neurodegenerative diseases/neurodegeneration as well as subdivided into clinical and preclinical studies within each category. Tables were utilized to present the significant findings from these articles.

3.1. Overview of Selected Studies

The selected studies included in this review comprised of 27 clinical studies and 65 preclinical studies of which 47 articles were animal studies. Among these, 7 articles were a combination of both clinical and preclinical studies. The 85 articles investigating the role of HMGB1 in neurodegenerative diseases that were included in this review were segregated into 9 categories; 17 articles were on Alzheimer's disease (Table **1**), 12 articles were on Parkinson's disease (Table **2**), 5 articles were on Huntington disease (Table **3**), 11 articles were on amyotrophic lateral sclerosis (Table **4**), 23 articles of multiple sclerosis (Table **5**), 2 articles were on spinocerebellar ataxia (Table **6**), 3 articles were on neuromyelitis optica (Table **7**), 5 articles of retinal neurodegeneration (Table **8**) and 10 articles that were on externally induced neurodegeneration (Table **9**). The 3 articles on neuromyelitis optica disease (Table **7**) were also included in the table on multiple sclerosis (Table **5**), as these three studies involved the study of HMGB1 in both diseases. However, the significant findings were discussed as relevant to their respective neurodegenerative disease within each table.

The majority of the studies were of prospective cohort studies investigating either or a combination of the HMGB1 levels, the pathological role of HMGB1, and the therapeutic potential of HMGB1 antagonist/agonist in patients with neurodegenerative diseases. Quality assessment using the EPHPP tool revealed that the clinical studies were mostly of strong quality and unbiased (Supplementary File 1), as the sample sizes were within statistical power with no/minimal missing data and most of the samples had a low drop-out/withdrawal rate.

Collectively, the clinical studies recruited patients or volunteers between the ages of 30-60 years old. Only one study involving Alzheimer's disease patients, however, had a recruitment age between 60 and 90 years old [22]. In addition, the majority of the studies were skewed towards female patients during recruitment, suggesting men were underrepresented in the sample size of clinical studies. Unfortunately, other demographic factors, such as ethnicity, were not uniformly represented across the clinical studies, and therefore were not reported in this review.

Unlike the clinical studies, preclinical research was observed to be predominating the selected studies in this review, with 65 studies in total. Most of the studies (47 articles) had utilized a mice or rodent model, that varied in sample strain (C57Bl/6, FAD, Sprague Dawley, Wistar), age (adult and aged groups) and gender (males/females only or a combination) within each neurodegenerative disease/neurodegeneration. In contrast to the samples in the clinical studies, the preclinical animal studies were mainly of the male gender. The other 18 preclinical studies were mainly primary cultures or *in vitro* cells. The preclinical studies also investigated the HMGB1 levels, their pathological role and therapeutic potential in relation to neurodegeneration. The SYRCLE RoB quality analysis tool showed that the preclinical studies were of mostly unbiased quality (Supplementary File **2**), as the sample sizes were within statistical power and were free from selective reporting of results. Figure (**2**) illustrates the overall pathological role of HMGB1 in the neurodegenerative pathology.

Table 1. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Alzheimer's disease.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical	Patients with MCI (12), AD (12) and controls (12) 60-88 years	MCI (1F, 11M), AD (4F, 8M), controls (10F, 1M)	→ Serum HMGB1 were significantly upregulated in AD patients	[22]
Clinical Postmortem	Advanced stage of AD (3) 70, 81, and 87 years old Control (1) 29 years old	AD (3F), Control (1M)	→ Overexpression of HMGB1 was found in the protein extracts of AD brains compared to control brain.	[23]
Clinical Postmortem/ Preclinical	Primary culture microglia and frontal cortex AD tissue	NA	→ Extracellular HMGB1 may act as a chaperone for Aβ and decrease the microglial Aβ clearance by intervening with the degradation of Aβ40 and internalization of Aβ42 by microglia → Extracellular HMGB1 may also interact with RAGE and TLR4 that were involved in microglial Aβ phagocytosis	[24]
Clinical Postmortem/ Preclinical	Microglia culture and AD post-mortem brains	NA	→ The full length of HMG1 had bound to Aβ42, which regulated the formation of their oligomers and aggregates, but did not reduce their level → HMGB1 was found upregulated in AD brain → HMG1 immunoreactivity was found colocalized with Aβ immunoreactivity that has association with microglia	[25]
Clinical Postmortem/ Preclinical	Htau (3) and wildtype (WT) BALB/c mice (2) Brain samples from FTLD (4), AD (4), and age-matched controls (4)	NA	→ Tau oligomers colocalized with HMGB1 protein in the FTLD and AD brain tissues, as well as in aged mouse cortical tissue → HMGB1 levels were significantly elevated in the FTLD and AD brain tissues → HMGB1 was found to translocate out of the nuclei into the cytoplasm during inflammatory signalling	[26]
Preclinical	5xFAD mice (NA) 1, 3, 6, and 12 months	Males	→ Extracellular HMGB1 release mediated neurite degeneration, initiated with TLR4-myristoylated alanine-rich C-kinase substrate (MARCKS) → HMGB1 triggering MARCKS phosphorylation that was sustained throughout the course of AD → HMGB1 increment may be treated with anti-HMGB1 monoclonal antibody (anti-HMGB1 mAb) to prevent neurite degeneration, cognitive impairment, beta-amyloid aggregation, and Alzheimer's onset even post Aβ aggregation.	[27]
Preclinical	C57BL/6 mice (60) 9 months and 18 months	Males	→ Glycyrrhizin oral pre-treatment inhibited HMGB1 expression, which inhibit spatial memory deficits → Glycyrrhizin pre-treatment also reduced the production of pro-inflammatory cytokines and Alzheimer's related pathologies (Tau phosphorylation and Aβ aggregation)	[28]
Preclinical	Human brain microvascular endothelial cells (HBMVECs)	NA	→ Extracellular levels of HMGB1 were increased due to hypoxia/reoxygenation conditions, which is regulated by Sirt1 → HMGB1 inhibition significantly reduced the activation of the JNK pathway, thereby neuronal death → HMGB1 neutralization significantly inhibited Aβ production caused by hypoxia/reoxygenation conditions	[29]

(Table 1) contd….

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Preclinical	Transgenic (Tg) (32) and wild-type (WT) (30) mice of the TgCRND8 line 8 to 32 weeks	Male	→ HMGB1 may be pro neurogenic and may promote neural differentiation *via* NF-κB signalling pathway and RAGE activation, respectively, which was a similar effect elicited by Aβ oligomers → HMGB1 showed no effect on astrogliogenesis, oligodendrogenesis, or cell survival	[30]
Preclinical	Primary hippocampal neurons	NA	→ Aβ25–35 treatment resulted in a higher expression of RAGE and TLR4-NF-κB receptors as well as HMGB1 protein in the hippocampal neuronal cells.	[31]
Preclinical	Sprague Dawley rats (NA) 7 weeks	Male	→ Levels and binding rates of HMGB1 in Aβ1-42 entorhinal cortex was significantly elevated compared to sham controls → Levels and binding rates of HMGB1 reduced in Aβ1-42 treated with soluble RAGE secreting mesenchymal stem cells, which acts as a decoy to prevent HMGB1 activation of RAGE receptors	[32]
Preclinical	PS1 and PS/APP mice (NA) 12 month Wistar rats (NA) 280g	Male	→ HMGB1 immunoreactivity was observed in the senile plaques, where levels of HMGB1 protein were found to be increased in AD brains → Injection of HMGB1 with Aβ42 blocked the clearance of Aβ42 from the ipsilateral rat hippocampus → Extracellular HMGB1 was also observed to increase the Aβ42-induced neurodegeneration → HMGB1 augmented the Aβ mediated neurotoxicity and stabilized the formation of Aβ monomer, when the microglial phagocytosis was impeded	[33]
Preclinical	3×Tg-AD mice (12) 5 months	Female	→ Cognitive impairment in 3xTg-AD mice was improved by intracerebroventricular injection of recombinant HMGB1 → Recombinant HMGB1 decreased intracellular Aβ level and promoted neurogenesis	[34]
Preclinical	BALB/c male mice (20) 6 weeks	Male	→Elevated HMGB1 levels were found in brain tissue and Aβ25-35-treated PC12 cells of AD mice which may contribute to the memory deficits	[35]
Preclinical	ICR mice (100) 23-25g	Male	→ Inhibition of glial mediated neuroinflammation *via* the HMGB-1/RAGE/NF-κB signalling pathway may alleviate memory dysfunction post Aβ25-35 intoxication	[36]
Preclinical	APP/PS1 (Tg) mice (48) and C57BL/6J mice (12) months	NA	→ Increased Aβ and extracellular HMGB1 levels induced memory impairment *via* binding to TLR4 and RAGE → Blocking the TLR4/2-MyD88 signalling pathway in reactive microglia may reduce HMGB1 expression, which may reduce Aβ plaques and improve learning and memory	[37]
Preclinical	p35 knockout, transgenic and wild type mice as well as combinations of them (7-10) 5 months	Male and female	→ The p35/Tg2576 (KO/Tg) mice model of AD demonstrated synaptic dysfunction and enhanced neuronal cell death, which is associated with activated microglial infiltration and increased expression of HMGB1 → Microglial infiltration in the dentate gyrus (DG) and CA1 region upregulated the HMGB1 secretion, which when combined with Aβ enhanced neuronal apoptosis	[38]

Note: NA, not available; AD, Alzheimer's disease; MCI, mild cognitive impairment; F, female; M, male; HMGB1, high mobility group box 1; TLR4, toll like receptor 4; Aβ, amyloid *beta*; JNK, c-Jun N-terminal kinase; RAGE, receptor for advanced glycation end products; NF-κB, Nuclear factor *kappa* B; MyD88, Myeloid differentiation factor 88; HMG1, high mobility group 1; FTLD, frontal-temporal lobe dementia; KO, knockout, CA1, hippocampal *cornu ammonis* region 1.

Table 2. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Parkinson's disease.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical	PD (120) and healthy volunteers (100). 65-67 years	PD (70M, 50F), Control (57M, 43F)	→ Serum levels of HMGB1 and TLR4 protein were found to be significantly increased in PD patients compared with that in healthy controls → Increased expression of both HMGB1 and TLR4 in PD patients → Activation of the NF-κB pathway and TNF-α level were positively correlated with high expression of the HMGB1/TLR4 axis	[39]
Clinical Postmortem/ Preclinical	Human nigral tissue (6 PD and 5 C), 79-80 years; CSF and serum (75 PD, 47 C), 61-64 years; C57Bl/6J mice (~42), NA	NA	→ Increased serum and CSF HMGB1 levels and increased HMGB1 proteins in substantia nigra of PD patients → HMGB1 led to microglial activation and increased gliosis in substantia nigra pars compacta, contributing to PD progression → HMGB1 neutralizing antibodies and glycyrrhizin may prevent and impede dopaminergic cell death through the reduction of RAGE and TNFα levels	[40]
Preclinical	C57BL/6N (125), 8–10 weeks	Male	→ Oxymatrine inhibited neuroinflammation and elicited a neuroprotective effect on the dopaminergic neurons *via* the suppression of the HMGB1/TLR4/NF-κB signalling pathway	[41]
Preclinical	Mesencephalic neuron–glia or neuron-enriched cultures	NA	→ Microglial Mac-1 interaction with HMGB1 may mediate the dopaminergic neurodegeneration through its mediation of persistent neuroinflammation → HMGB1 induces membrane translocation of $p47^{phox}$ in the microglia	[42]
Preclinical	Human neuroblastoma cells (SH-SY5Y)	NA	→ Overexpression of HMGB1 led to cytosol translocation and interaction with α-synuclein → HMGB1 may increase α-synuclein expression through its affinity for Beclin1, which in turn causes autophagy dysfunction and leads to overexpression of HMGB1 (a vicious cycle)	[43]
Preclinical	Human neuroblastoma cells (SH-SY5Y)	NA	→ Neurotoxicant PQ, commonly found in PD, increased the HMGB1 levels significantly, which subsequently caused translocation of HMGB1 from nucleus to cytoplasm and into the extracellular environment → Neutralizing/knocking out HMGB1 prevented PQ-induced neurotoxic effects and reduced the expression of RAGE and cell death → Levels of RAS, P38, and NF-κB P65 protein, as well as TNFα and IL-6 were all suppressed by knockout of HMGB1 → HMGB1 neuronal death induced by PQ neurotoxicity may act *via* RAGE-P38-NF-κB signalling pathways	[44]
Preclinical	Male C57Bl/6 mice (32), 8 weeks	Male	→ HMGB1 expression increased acutely after MPTP treatment and returned back to basal level → HMGB1 released from reactive astrocytes may affect the maintenance of dopaminergic neuronal function *via* the modulation of tyrosine hydroxylase (TH) expression → RAGE was induced in acute MPTP and co-localised with TH-positive neurons in the substantia nigra pars compacta region	[45]

(Table 2) contd….

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Preclinical	C57BL/6 mice (150), 10 weeks	Male	→ Rosmarinic acid treatment inhibited NF-κB nuclear translocation of HMGB1, suppressed activation of the HMGB1/TLR4 signalling pathway and increased TH positive cells in the substantia nigra → Rosmarinic acid treatment improved motor function in PD mice and reduced accumulation of α-synuclein and its effects on neuroinflammation → Rosmarinic acid treatment reduced expression of HMGB1, TLR4 and MyD88	[46]
Preclinical	Sprague–Dawley rats (101) 200-250g	Female	→ Anti-HMGB1 mAb protected TH-positive dopaminergic neurons in substantia nigra and striatum, reduced motor deficits, blocked the translocation of HMGB1 into cytoplasm, inhibited the increase in HMGB1, as well as stabilized BBB through its anti-inflammatory effects in a 6-OHDA PD model	[47]
Preclinical	Human neuroblastoma cells (SH-SY5Y)	NA	→ Endogenous intracellular HMGB1 was found to promote the degradation of α-synuclein by autophagy in a neuroblastoma cell line → Two HMGB1 activation pathways were suggested; the Atg 5-dependent autophagy-initiation pathway and the Beclin 1-dependent autophagy-initiation pathway	[48]
Preclinical	C57BL/6J mice (16), 8–10 weeks	Male	→ HMGB1A significantly inhibited the microglia activation and inhibited T cell infiltration in the substantia nigra → HMGB1A inhibited the differentiation of T cells into Th17, which causes neuronal death through IL-17 production in the substantia nigra → HMGB1A also relieved the inhibition of CD200-CD200R signalling, which protected MPP^+ mediated neuronal damage	[49]
Preclinical	Peptide/protein isolation	NA	→ HMGB1 specifically binds to aggregated α-synuclein in Lewy bodies isolated from the rat brain → α-synuclein aggregates may conceal the transcriptional cofactor of HMGB1which contributes to the neurodegenerative process	[50]

Note: NA, not available; PD, Parkinson's disease; F, female; M, male; HMGB1, high mobility group box 1; TLR4, toll like receptor 4; RAGE, receptor for advanced glycation end products; NF-κB, Nuclear factor *kappa* B; MyD88, Myeloid differentiation factor 88; IL-17, interleukin 17; MPP^+, 1-methyl-4-phenylpyridinium; Th17, T helped 17 cell; Atg-5, Autophagy-related protein 5; BBB, blood brain barrier; TH, Tyrosine hydroxylase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; IL-6, interleukin 6; TNFα, tumor necrosis factor alpha; CSF, cerebrospinal fluid; PQ, paraquat.

3.1.1. Alzheimer's Disease

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease. It is primarily characterized by the accumulation of amyloid-β (Aβ) plaques surrounding neuronal cells and the aggregation of neurofibrillary tangles (NFTs) within the neurons resulting in hyperphosphorylated tau proteins, both of which may lead to disruptions in neuronal communication and subsequent neuronal death [107]. Based on (Table **1**), clinical studies on HMGB1 in relation to AD were scarce, with only one article investigating serum levels of HMGB1 biomarker. This article had a mixture of male and female subjects, but the role of gender on HMGB1 was not discussed. Among the preclinical AD studies, only two articles utilized female animals, with 7 articles utilizing the male rodents, but none discussed the role of gender in the context of HMGB1 and neurodegeneration. In terms of HMGB1 expression, (Table **1**) showed that there was only one clinical article showing that HMGB1 levels were significantly increased in the serum samples of aged AD patients compared to healthy controls and even MCI patients. Three clinical articles showed that the HMGB1 protein was significantly upregulated in the AD brain tissue compared to controls. In support, the elevation of HMGB1 protein was also found in the brain tissue of AD animal models. As for HMGB1 pathology, the main pathology discussed in majority of the articles was the interaction of HMGB1 with TLR4, RAGE, MARCKS and NFκB (Table **1**). The preclinical studies also showed that HMGB1 may interact with amyloid in the microglia, preventing its clearance from the brain. In contrast, one preclinical study showed that HMGB1 had no significant effect on other glial cells, astrogliogenesis and oligodendrogenesis. In the preclinical AD models, HMGB1 was shown to translocate from the nucleus to the cytoplasm. This translocation was associated with increases in pro-inflammatory cytokine release. In terms of HMGB1's therapeutic potential, several preclinical articles suggested that anti-HMGB1 or HMGB1 inhibition had prevented neurite degeneration, amyloid-β aggregation, pro-inflammatory cytokine release, tau phosphorylation and neuronal death. Besides that, anti-HMGB1 or HMGB1 inhibition has also improved cognitive impairment

Table 3. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Huntington's disease.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Preclinical	R6 transgenic mice (ranged) Different ages (weeks to months old)	NA	→ R6/1 mice (HD model) showed 2- to 3- fold higher levels of HMGB1 in the cerebellum (stable CAG repeat) than in the striatum (unstable CAG repeat) → HMGB1 helps stabilization of cerebellar functions through further activation of APE1 and FEN1 → HMGB1 is a cofactor for base excision repair (BER)	[51]
Preclinical	Gene Data: UPR-KEGG-GO (265), UPR-Interactions (281), UPR-Literature (2048)	NA	→ HMGB1 gene may link the unfolded protein response activated by misfolding protein to the loss of neurons in HD → HMGB1 protein may act like a chaperone to prevent protein aggregation	[52]
Preclinical	WT mouse striatal STHdhQ7/Q7 cells, TruHD-Q21Q18 and TruHD-Q43Q17 fibroblast cells	NA	→ Huntingtin interacts with HMGB1 as a whole but not its individual boxes (A and B) → HMGB1 interaction with huntingtin was exacerbated under oxidative stress due to ROS → HMGB1 may facilitate nuclear entry of Huntingtin	[53]
Preclinical	Human neuroblastoma cells (SHSY5Y), human embryonic kidney epithelial cells (HEK293), hamster lung fibroblasts (O23), mouse embryonic fibroblast (MEF) NIH3T3 cells, and hmgb1−/− MEF cells	NA	→ Extracellular HMGB1 exhibited chaperone-like activity to reduce protein aggregation but at optimal concentrations → HMGB1 restored the cell viability after aggregation-induced toxicity → HMGB1 also inhibited the formation of aggregates and toxicity caused by expanded polyglutamine (poly Q) → Exogenous recombinant HMGB1 may reduce intracellular mutant Huntingtin protein (mHtt) aggregates, but overexpression of HMGB1 may aggravate the formation of mHtt aggregates	[54]
Preclinical	Primary neuron culture, Purkinje cells, Hela cells and transgenic Drosophila	NA	→ Reduction of HMGB1/2 expression in the nucleus promotes neuronal dysfunction and death in polyQ pathologies → HMGB1/2 may ameliorate neuronal death and improve neuronal viability *in vitro* and *in vivo*, by reverting the transcriptional repression and genotoxic stress signals induced by mutant polyQ proteins (mHtt) → HMGB1/2 reduction was observed prior to neuronal death	[55]

Note: NA, not available; HD, Huntington's disease; HMGB1 or 2, high mobility group box 1 or 2; APE1, Apurinic/apyrimidinic endonuclease 1; FEN1, Flap structure-specific endonuclease 1; ROS, reactive oxygen species.

in AD animal models. One study showed that soluble RAGE may act as a decoy for HMGB1 binding, thereby preventing the activation of cellular RAGE receptors (Table **1**). Interestingly, one study suggested that recombinant HMGB1 decreased the amyloid-β level and promoted neurogenesis in an AD transgenic mice model.

3.1.2. Parkinson's Disease

Parkinson's disease (PD) is a common age-related neurological disorder, with the basic pathological feature of the loss of substantia nigra and striatum dopaminergic neurons, accumulation of α-synuclein and the clinical manifestations of resting tremor, bradykinesia, muscle rigidity, and abnormal posture and pace [108]. Based on Table **2**, two clinical studies investigated the HMGB1 serums levels in aged PD patients, with one of them investigating HMGB1 levels in CSF and brain tissue as well. Among the 6 preclinical studies, only one study utilized female Sprague Dawley rats, while the remaining 5 articles unanimously utilized male C57Bl/6 mice, however, none of the articles discussed the role of gender in relation to HMGB1. In terms of HMGB1 expression, HMGB1 was significantly elevated in the serum, CSF and brain tissue of PD patients when compared to healthy controls. Similarly, in the preclinical models, HMGB1 expression was found to be significantly increased in the brain tissues of PD animal models (Table **2**). As for pathology, HMGB1 was shown to predominantly interact with the TLR4/RAGE/NFκB pathway, but none of the PD studies showed the interaction of all three pathways within a single model. In addition, the pro-inflammatory cytokine

Table 4. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Amyotrophic Lateral Sclerosis disease.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical	sporadic ALS (53), familial ALS (8), healthy controls (40), 60-61 years	sporadic ALS (34M, 19 F), familial ALS (4M, 4F), healthy controls (23M, 17F)	→ Serum autoantibodies against HMGB1 was found significantly higher in ALS patients compared to AD, PD and healthy controls, potential use as a biomarker for ALS → HMGB1 autoantibodies was also significantly increased in female subjects as compared to males	[56]
Clinical Post-mortem	Control (6), ALS thoracic SC tissue samples (5), 63.6 years	Male and Female	→ HMGB1 expression was highly increased in the ALS thoracic spinal cord (SC) compared to controls and was co-expressed with RAGE → RAGE expression was also increased in ALS SC tissues	[57]
Clinical Post-mortem	Post-mortem sporadic ALS (12) 59.5 years Controls (6) 64.5 years	ALS (8M, 4F), control (4M, 2F)	→ Upregulation of TLR2, TLR4 and HMGB1 expression in sALS brains and spinal cord → TLR2 was expressed in activated microglia cells in gray and white matter of SC, while TLR4 was expressed in glial and neuronal cells as well as in motor neurons → RAGE was expressed in astrocytes, microglia and motor neurons in ALS SC, but without any significant changes in overall expression → HMGB1 receptor was expressed in both nuclear and cytoplasm of motor neurons, activated microglia and reactive astrocyte in ALS SC	[58]
Preclinical	Transgenic $SOD1^{G93A}$ mice C57BL/6J (12-13), 35 days	Female	→ Intraperitoneal injection of anti-HMGB1 2G7 antibody treatment showed transient improvement in early motor deficits, but no effect on survival time → Anti-HMGB1 2G7 antibody treatment only reduced TNFα and C5aR1 receptors but did not affect microglia and astrocytes	[59]
Preclinical	$SOD1^{G93A}$ transgenic mice (6), control non-transgenic (6), 8-21 weeks	Female	→ Increased HMGB1 expression in the nucleus of active glial cells during symptomatic stages → No significant HMGB1 expression in the presymptomatic mice group → Progressive reduction in HMGB1 immunopositive motor neurons as the disease progress	[60]
Preclinical	Wobbler (56) and control (30) mice, 5 months	NA	→ Wobbler mice showed motor neuron degeneration like in ALS, which may be initiated by HMGB1-TLR4-NFκB pathway → HMGB1 is highly expressed in microglia and astrocytes during disease progression → HMGB1 localizing in SC microglia and astrocytes were down-regulated with selective glucocorticoid receptor modulator $CORT^{113176}$ treatment	[61]
Preclinical	Primary astrocyte culture from $SOD1^{WT}$ and $SOD1^{G93A}$ transgenic mice, NA	NA	→ Significant translocation of HMGB1 to the cytoplasm in the ALS motor neuron cells → Exogenous disulfide HMGB1 increased the production of neurotrophic factors GDNF and BDNF in healthy SC astrocytes but not $SOD1^{G93A}$ cells, *via* TLR/RAGE signalling	[62]
Preclinical	Primary astrocyte culture from transgenic mSOD1 mice 7 days, 4-6 weeks, 12-14 weeks	Male and Female	→ Gene expression of HMGB1 was increased, increases in NF-kB expression, increased release of HMGB1 protein into extracellular milieu in mSOD1 astrocytes and motor neuron loss in the cortical tissue at the symptomatic stage	[63]
Preclinical	Transgenic $SOD1^{G93A}$ mice C57BL/6J (24) 30-175 days Transgenic TDP-43^{Q331K} mice C57BL/6J (12) 4-5 weeks and 16 months	Female	→ HMGB1 and RAGE were upregulated in the spinal cord and skeletal muscle in all ALS models. → Lack of RAGE signalling in $SOD1^{G93A}$ mice exerts a protective effect on survival and function of motor neurons, reduction in denervation markers in skeletal muscle, improved motor performance and slowed disease progression	[64]

(Table 4) contd….

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Preclinical	Transgenic hSOD1^{G93A} and WT mice (72) 30-175 days	Female	→ TLR4 and HMGB1 upregulation in the lumbar SC astrocyte and microglia of hSOD1^{G93A} mice → Moderate improvement in hind-limb grip strength and extended survival in hSOD1^{G93A} mice with TLR4 gene deletion	[65]
Preclinical	Transgenic SOD1^{G93A} mice C57BL/6J (60) 4–6 and 12–14 weeks	Male and Female	→ Pre-symptomatic stage showed no changes in HMGB1 but down-regulated inflammatory markers → Symptomatic stage showed elevated HMGB1 and upregulation of inflammatory markers and signalling pathways (NF-κB)	[66]

Note: NA, not available; ALS, Amyotrophic Lateral Sclerosis; sALS, sporadic ALS; F, female; M, male; HMGB1, high mobility group box 1; TLR2 or 4, toll like receptor 2 or 4; RAGE, receptor for advanced glycation end products; NF-κB, Nuclear factor *kappa* B; TNFα, tumor necrosis factor alpha; SC, spinal cord; mSOD1, mutant superoxide dismutase 1; GDNF, glial cell line-derived neurotrophic factor; BDNF, brain-derived neurotrophic factor; AD, Alzheimer's disease; PD, Parkinson's disease; C5aR1, complement component 5a receptor 1

Table 5. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Multiple Sclerosis disease.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical	MS (45) and Control (7), 39.4 - 45.5 years MS (34) and NIC (30), 33.5-44 years	NA MS (10M, 24F), Control (3M, 27F)	→ HMGB1, RAGE, TLR2, and TLR4 were upregulated in expression in active lesions of MS but were at normal levels in inactive lesions of MS → HMGB1 was detected in MS CSF and in the cytoplasm of macrophages and microglia of MS lesions, where activated microglia resulted in a positive loop towards HMGB1 translocation	[67]
Clinical	MS (102), Controls (113) 35.29 years	MS (17.6% M and 82.4% F) and controls (24.8% M and 75.2% F)	→ Single nucleotide polymorphisms in HMGB1 were not associated with risk towards MS in regards to genotype and allele frequencies.	[68]
Clinical	MS (165), Controls (31), 37.1-40.1 years	MS (54M, 111F), Control (11M, 20F)	→ HMGB1 was significantly elevated by 4.5-fold times in plasma of MS patients compared to control → HMGB1 levels were higher in MS patients with greater lesion affected regions → MS patients with higher EDSS had higher HMGB1 levels	[69]
Clinical	IFNβ-RRMS (30), untreated RRMS (30), Controls (30) 43-51 years	IFNβ-RR-MS (12M, 18F), Untreated RR-MS (10M, 20F), Control (11M, 19F)	→ HMGB1 was significantly elevated in the serum of RRMS compared to controls by 31% → IFN-β treatment in RRMS patients decreased HMGB1 levels in serum	[70]
Clinical	MS (28), Controls (30), Years	NA	→ Lower levels of soluble RAGE in MS CSF compared to controls → No significant changes in HMGB1 expression in the CSF or plasma of MS	[71]
Clinical	RRMS (84), Controls (70) 34 years	RRMS (24M, 60F), Control (20M, 50F)	→ No significant difference in HMGB1 mRNA expression in RRMS compared to controls → TLR4 expression was significantly lower in RRMS compared to control → No changes in the expression of immune markers or HMGB-1 with IFN-β treatment in RRMS	[72]
Clinical	Control (29), MS (57), 40-43 years	Control (16M, 13F), MS (26M, 31F)	→ A significant increase in HMGB1 mRNA expression and HMGB1 protein levels in MS compared to controls → HMGB1 levels and expression differed between the types of MS, with highest in RRMS patients	[73]
Clinical	SPMS (38), PPMS (35), Controls (42), 53-58 years	SPMS (13M, 25F), PPMS (12M, 23F) Control (18M, 24F)	→ HMGB1 levels were found not significantly different between the groups, but pro-inflammatory cytokines (TNFα and IL-8) were found increased in PPMS compared to SPMS and controls	[74]

(Table 5) contd….

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical	MS (96), Control (34), 44.7 years	MS (23M, 73F), Control (10M, 24F)	→ HMGB1 serum levels were higher in MS than controls → HMGB1 serum levels were reduced in DMD-treated MS	[75]
Clinical	RRMS (17) 46 years	5M, 12F	→ Fingolimod treatment reduced serum HMGB1 levels, reduced serum RAGE ligands, increased soluble RAGE and endogenous secretary RAGE, and reduced disability in RRMS patients	[76]
Clinical	NMO (22), MS (18), 35.5 years Controls (14), 50 years	NMO (6M, 16F). MS (7M, 11F), Controls (6M, 8F)	→ HMGB1 was lower in the CSF of MS compared to NMO → No correlation between HMGB1 and clinical activity of MS noted	[77]
Clinical	NMO (29), MS (20) 41.7 years	NMO (1M, 28F), MS (4M, 16F)	→ Plasma levels of HMGB1 may help identify NMO from MS during the early stages of disease → HMGB1 pathology may be more correlated to NMO than MS	[78]
Clinical	MS (178), Controls (31), 38.1-40.6 years	MS (53M, 125F), Control (11M, 20F)	→ HMGB1 plasma levels were significantly higher in MS than controls	[79]
Clinical	NMO (42), 51.5 years MS (30), 33.2 years ONNDs control (30), 59.1 years	NMO (3M, 39F), MS (9M, 21F), ONNDs controls (19M, 11F)	→ HMGB1 was increased in the serum and CSF of MS, but was only increased in the CSF of NMO, suggesting peripheral HMGB1 circulation in MS → HMGB1 was significantly elevated in MS compared with ONNDs	[80]
Clinical Postmortem/ Preclinical	MS post-mortem tissue iPSC, NPC and OPC cultures	NA	→ PPMS NPC treated with rapamycin abrogated HMGB1 secretion → Extracellular release of HMGB1 by senescent NPC, altered the gene expression and impaired the maturation of OPC, similar to HMGB1 secretion by progenitor cells in PPMS lesions →HMGB1 suppressed oligodendrocyte differentiation	[81]
Preclinical	Wistar rats (20), 8–10 weeks	Female	→ Matrine (MAT) treatment inhibited HMGB1 and its downstream molecules (TLR4, MyD88) expression, inhibited the activation of NF-κB and reduced demyelination → MAT also significantly reduced HMGB1 and TLR4 protein and mRNA expression in astrocytes and microglia of the spinal cord	[82]
Preclinical	Dark Agouti rats (15), 2-4 months	Female	→ Ethyl pyruvate reduced the mRNA and protein expression of HMGB1 and induced its cytosolic translocation within the CNS, may treat MS	[83]
Preclinical	C57BL/6 mice (20), 8–10 weeks and SD rats (15), 6–8 weeks	Female	→ HMGB1 levels correlated with the disease severity of EAE model, and neutralizing HMGB1 through TNT (Titania nanotubes) treatment protected against demyelination	[84]
Preclinical	SJL/J (15) and C57BL/6 mice (25), 6-8 weeks	NA	→ Elevated HMGB1 in the EAE mice serum correlated with motor deficits, but did not correlate with a severity of clinical disease → Cytoplasmic HMGB1 and expression of RAGE, TLR4 was found in active lesions in EAE spinal cord → HMGB1 neutralizing antibodies (in chronic and relapsing-remitting EAE) administered at disease remission inhibited infiltration of CD45+ inflammatory cells, CD3+ and CD4+ T cells, thereby possibly preventing neurodegeneration	[85]
Preclinical	C57BL/6 mice (NA), 5-6 weeks age	Female	→ Glycyrrhizin treatment in EAE inhibited total and extracellular HMGB1 release, which exerts a protective effect against clinical symptoms, inflammation, and demyelination post EAE → Glycyrrhizin decreased HMGB1 expression in astrocytes and microglia, and reduced in the release from neurons after TNFα stimulation → Glycyrrhizin therapeutic effects on HMGB1 expression and release did not last till late stages of EAE disease progression	[86]

(Table 5) contd….

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Preclinical	C57BL/6 mice (NA), 5-7 weeks	Female	→ Nuclear expression of HMGB1 observed in astrocytes, microglia and neurons of spinal cord → Elevated extracellular HMGB1 was observed in the spinal cord homogenate, CSF, and sera in different stages of EAE disease, similar to MS, with the peak at onset and a decrease in CSF from pre-onset to remission stage → Blocking HMGB1 delayed disease onset time and attenuated disease severity	[87]
Preclinical	C57BL/6 mice (24), 10 weeks	Female	→ Recombinant thrombomodulin (rTM) suppressed HMGB1 upregulation in plasma and IL-17 production →rTM also decreased invasion of inflammatory cells and demyelination by suppressing the release of HMGB1 from nuclei to cytoplasm around lesions in EAE	[88]
Preclinical	C57BL/6 mice (28), NA	NA	→ Anti-HMGB1 monoclonal antibodies alleviated inflammation in the CNS and significantly improved clinical severity and prevented demyelination effects of EAE → Complete loss of nuclear HMGB1 immunoreactivity in EAE suggesting translocation for inflammatory action	[89]

Note: NA, not available; MS, Multiple Sclerosis; F, female; M, male; HMGB1, high mobility group box 1; TLR2 or 4, toll like receptor 2 or 4; RAGE, receptor for advanced glycation end products; NF-κB, Nuclear factor *kappa* B; TNFα, tumor necrosis factor alpha; SC, spinal cord; DMD, disease modifying drugs; EAE, experimental autoimmune encephalomyelitis; CNS, central nervous system; CSF, cerebrospinal fluid; IL-17, interleukin 17; CD, Cluster of differentiation; SD, Sprague-Dawley; MyD88, Myeloid differentiation factor 88; mRNA, messenger ribonucleic acid; iPSC, Induced pluripotent stem cells; NPC, Neural progenitor cells; OPC, Oligodendrocyte progenitor cells; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; NMO, Neuromyelitis optica; ONNDs, other non-inflammatory neurological disorders; SPMS, Secondary progressive MS; IFN-β, interferon Beta; NIC, noninflammatory control; EDSS, Expanded Disability Status Scale.

Table 6. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Spinocerebellar ataxia disease.

Type of Study	Subject, sample size (n), and mean age group	Gender	Significant findings related to HMGB1	References
Preclinical	Mutant Atxn1-KI mice (12), 5 and 25 weeks	Male	→ AAV induced HMGB1 exerted a therapeutic effect on motor outcomes and SCA1 pathology even after the onset of symptoms in SCA1 model → HMGB1 was bound to damage mitochondrial DNA and enhanced its repair → HMGB1 reduction and inhibition by mutant Atxn in SCA1 model increased mitochondrial DNA damage	[90]
Preclinical	HEK-293T cells and SH-SY5Y cells	NA	→ Overexpression of HMGB1 reduced mutant TBP aggregation in cells, which is often expressed in SCA → Mutant TBP sequestered HMGB1 into polyQ aggregates, thereby reducing soluble functional HMGB1 levels and may led to a reduction in nuclear *HSPA5* expression → Reduced cytoplasmic HMGB1 may decrease autophagy activation, which worsens SCA17 pathology	[91]

Note: NA, not available; SCA, Spinocerebellar ataxia; HMGB1, high mobility group box 1; polyQ, Polyglutamine; AAV, Adeno-Associated Virus; DNA, deoxyribonucleic acid; Atxn, Ataxin; TBP, TATA-binding protein; *HSPA5*, Heat Shock Protein Family A (Hsp70) Member 5.

TNFα levels were also positively correlated with the increases in HMGB1 in the PD model. The selected articles also showed that HMGB1 had a greater interaction with the microglia in the substantia nigra, which may have propagated the dopaminergic degeneration in that area. One study showed that HMGB1 may be released from astrocytes in PD models and may cause dopaminergic degeneration *via* modulation of the tyrosine hydroxylase (TH) expression. Interestingly, only two studies showed the interaction of HMGB1 with a-synuclein accumulation. There were also two studies that revealed that HMGB1 may promote PD pathology *via* the Beclin 1-autophagy pathway. In terms of HMGB1 therapeutic potential in PD, two studies showed that HMGB1 inhibitor or HMGB1 neutralizing antibody prevented dopaminergic cell death *via* the reduction of RAGE and/or TNFa expression levels. Similarly, other preclinical studies also showed that suppression or inhibition of the HMGB1/TLR4/NFκB pathway may prevent dopaminergic cell death as well as improve motor outcomes and reduce the a-synuclein accumulation in PD models.

Table 7. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Neuromyelitis Optica disease.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical	NMO (22), MS (18), 35.5 years Controls (14) 50 years	NMO (6M, 16F). MS (7M, 11F), Controls (6M, 8F)	→ HMGB1 was higher in the CSF of NMO patients than in MS patients and the control group → HMGB1 increase correlated with the elevation of IL-6 and IL-17 in the CSF	[77]
Clinical	NMO (29), MS (20) 41.7 years	NMO (1M, 28F), MS (4M, 16F)	→ HMGB1 was significantly higher in the plasma of NMO patients than in MS patients, which correlated with levels of disability and recurrence of disease → Plasma HMGB1 was significantly higher in APQ4-positive than APQ4-negative patients → HMGB1 increase may have an association with IFN-γ in NMO patients → Plasma HMGB1 could identify NMO from MS during the early stages	[78]
Clinical	NMO (42), 51.5 years MS (30), 33.2 years ONNDs control (30) 59.1 years	NMO (3M, 39F), MS (9M, 21F), ONNDs controls (19M, 11F)	→ HMGB1 was increased in the CSF of NMO patients compared to MS patients and ONNDs control → HMGB1 increases positively correlated with increases in CSF cell counts, inflammation levels (IL-6 and GFAP) and BBB disruption (protein levels and QAlb) → HMGB1 levels were higher in APQ4-positive than APQ4-negative patients but not statistically different	[80]

Note: NMO, Neuromyelitis Optica; HMGB1, high mobility group box 1; MS, multiple sclerosis; APQ4, Aquaporin-4; IL-6, interleukin 6; IL-17, interleukin 17;CSF, cerebrospinal fluid; ONNDs, other non-inflammatory neurological disorders; IFN-γ, Interferon gamma; GFAP, glial fibrillary acidic protein; M, male; F, female; QAlb, CSF/serum albumin ratio; BBB, blood brain barrier.

3.1.3. Huntington's Disease

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disorder. Some of the characteristic symptoms include loss of motor control, cognitive decline, and behavioural abnormalities. HD is caused by an expansion of polyglutamines (polyQ) in the huntingtin (HTT) protein that leads to the production of a defective huntingtin protein, which misfolds and accumulates within neurons, thus forming aggerates that affect normal cellular function [109]. Based on Table **3**, there were no clinical studies performed on HD disease in relation to HMGB1. Among the 5 preclinical studies, only one study utilized an animal HD model, while the majority of the investigations were performed in cell cultures. Since the preclinical animal study did not disclose the gender of their sample, no gender variability in HMGB1 was investigated in HD. In terms of HMGB1 expression levels, HD transgenic mice showed increased levels of HMGB1 expression in the cerebellum and striatum, where the former had 2-3 folds higher expression. However, in terms of HMGB1 pathology, HMGB1 appears to be neuroprotective against HD disease. Two studies showed that HMGB1 protein may prevent the aggregation of protein and neuronal death, possibly through its interaction with polyQ protein. One study noticed that HMGB1 acted like a chaperone for the protein aggregates but only at optimal HMGB1 expression levels, where an overexpression of HMGB1 resulted in increased aggregation of misfolded proteins. Another study suggested that HMGB1 may elicit its neuroprotective role *via* activation of the APE1 and FEN1 pathways. There were no studies available that investigated the effects of HMGB1 as a therapeutic potential for HD disease.

3.1.4. Amyotrophic Lateral Sclerosis Disease

Amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's disease is a devastating neurodegenerative disease involving rapid degeneration of large pyramidal neurons mostly in the primary motor cortex, motor neurons in the brainstem, and anterior horns of the spinal cord. There is a lack of effective disease-modifying treatment for ALS due to a poor understanding of its underlying molecular mechanisms. The multifaceted pathophysiology of ALS involves a complex interplay of environmental and genetic factors. Common genetic mutations involve mutations in the chromosome 9 open reading frame 72 (C9orf72) in 40%, TAR DNA-binding protein 43 (TDP-43) in 20%, superoxide dismutase 1 (SOD1) genes in 1-5%, fused in sarcoma (FUS) in 1-5% as well, thereby allowing transgenic ALS preclinical models to be created based on these genes. Based on Table **4**, among the three clinical studies, only one study looked into the HMGB1 levels in the serum of ALS patients, while the other two articles looked at the HMGB1 expression levels in the brain and spinal cord. Interestingly, majority of the preclinical ALS studies utilized the female SOD1 transgenic mice, with one study utilizing the female TDP-43 transgenic mice and only two studies utilized male SOD1 transgenic mice together with female SOD1 transgenic mice. Nevertheless, none of the preclinical studies investigated the role of gender in relation to HMGB1 in ALS models. In contrast, one clinical study investigated the gender differences in HMGB1 expression. In terms of HMGB1 expression levels, the clinical study showed that HMGB1 was significantly elevated in the serum of ALS patients compared to healthy controls, with female subjects expressing higher levels than male counterparts. Similarly, HMGB1 protein expression

Table 8. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in Retinal Neurodegeneration.

Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Clinical/ Preclinical	Diabetic (46), 53.9 years Controls (34), 47.8 years SD rats (24), 8-9 weeks	Diabetic, (35M, 11F) Control, (23M, 11F) Male rats	→ HMGB1 mediated the reduction of BDNF levels in serum of diabetic patients → HMGB1 inhibitor attenuated the diabetes-induced increases in HMGB1 and decreases in BDNF in the animal retina → HMGB1 significantly decreased the synaptic vesicle proteins and significantly increased the activated cleaved caspase-3 in retina in diabetes and HMGB1 administered control animals → Soluble RAGE and ICAM-1 levels were upregulated in serum of diabetic patients	[92]
Preclinical	PKD-2-247 (PKD) rats (NA), SD rats (NA), 1 and 3 months	NA	→ Increased expression of HMGB1 and amyloid-β in the ganglion cell layer around superficial vessel network, which correlated with astrocyte activation	[93]
Preclinical	Retinal photoreceptor-derived cell line (661W) C57BL/6 mice (42), 6–8 weeks	Male	→ HMGB1 was released and regulated by 661W cells and retinal explants of animals under elevated pressure → RAGE, TLR2 and TLR4 was also increased in 661W cells and retinal explants of animals under elevated pressure → Exogenous recombinant HMGB1 promoted cytokine release, pro-apoptotic factor release and drove the pro-inflammatory pathways *via* RAGE and TLR2 in 661W cells and retinal explants	[94]
Preclinical	C57BL/6 mice (11) and HMGB1ΔRod transgenic mice (6), weeks	NA	→ HMGB1 was expressed higher in cones than rods of naive mice retina → HMGB1 upregulated in the rods after retinal detachment, but progressively decreased, causing degradation of rods → Retinal detachment increased HMGB1 in rods, and its translocation into cytoplasm and then into extracellular space → After retinal detachment, loss of rods and reduction in the thickness of the outer nuclear layer were significantly increased in the HMGB1ΔRod retinas as compared to the control	[95]
Preclinical	SD rats (NA), 7–8 weeks	Male	→ Inhibition/inactivation of NF-kB as well as its reduced phosphorylation, reduced HMGB1-induced and NMDA-induced neuronal injury and retinal degeneration	[96]

Note: NA, not available; F, female; M, male; HMGB1, high mobility group box 1; TLR2 or 4, toll like receptor 2 or 4; RAGE, receptor for advanced glycation end products; NF-κB, Nuclear factor *kappa* B; BDNF, brain-derived neurotrophic factor; ICAM-1, Intercellular adhesion molecule-1; NMDA, N-Methyl-D-aspartate; SD, Sprague-Dawley.

was also increased in the ALS thoracic spinal cord tissue and in the ALS brain. Increased expression of HMGB1 was also found in the preclinical models of ALS, mainly in the glial cells. Two studies showed that HMGB1 expression changes in a bell shape according to the disease progression stage, where HMGB1 was only found elevated together with other pro-inflammatory cytokines, during the symptomatic stage of ALS. In terms of HMGB1 pathology, HMGB1 was shown to propagate into motor neuron degeneration *via* the activation of the glial or motor neuron TLR2 or TLR4/NFκB pathways and/or TLR/RAGE pathways during the symptomatic stages (Table **4**). In terms of HMGB1 therapeutic potential, one study concluded that anti-HMGB1 may elicit improvements in early ALS motor function deficits *via* reductions in pro-inflammatory cytokines. While two studies showed that the lack/deletion of RAGE or TLR4 gene may also elicit improvements in motor response in ALS preclinical models, regardless of HMGB1 levels.

3.1.5. Multiple Sclerosis Disease

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disorder of the central nervous system (CNS) that can lead to progressive neuro-axonal degeneration. About 80-85% of MS patients may experience relapsing-remitting MS (RRMS), with 15-20% of patients experiencing primary progressive MS (PPMS). Bowel/bladder and pyramidal tract dysregulation, optic nerve dysfunction, diplopia, ataxia, and disruption of sensation in the limbs are common symptoms

Table 9. Study characteristics and significant findings of selected articles investigating the role of HMGB1 in externally induced neurodegeneration.

External Etiology	Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
LPS-induced	Preclinical	Mixed primary glial cells BALB/c mice (52), 6-10 weeks	Male	→ LPS induction increased mRNA expression and translocation of HMGB1 and TLR4, as well as increased expression of NF-κB, which were all attenuated by Andrographolide → Andrographolide treatment also reduced LPS-induced increases in reactive astrocytes and active microglial markers, as well as the neurodegenerative stimuli released by activated microglia (nitrite and iNOS) → LPS also induced synaptic loss of function, amyloidogenesis and BACE production, which leads to neurodegenerative-like memory impairment, that was rescued by Andrographolide through HMGB1-TLR4-NFκB inhibition	[97]
HMGB1- induced	Preclinical	Mixed primary glial cells BALB/c mice (91), 8-10 weeks	Male	→ Administration of HMGB1 and suppression of CXC Receptor 7 resulted in cognitive impairment due to HMGB1-CXC Ligand 12 complex formation which upregulated immune cell infiltration → CXCR7 agonist downregulated HMGB1-CXCL12 complex formation and maintained BBB integrity, inhibited HMGB1-induced reactive microglia and reactive astrocyte, thereby possibly attenuating progressive neurodegeneration	[98]
Hypoxia-induced	Preclinical	Mixed primary glial cells BALB/c mice (65), 6-10 weeks	Male	→ Mac-1 (microglial) when coupled with HMGB1 led to working memory loss and neurodegeneration → Intranasal Mac-1 siRNA (Mac-1 suppression) delivery managed to switch the microglia phenotype (M1 to M2), reduce inflammatory mediators (TLR4, CD-14, NFκB), reduce HMGB1, increase neuronal viability and halt hypoxia-induced working memory loss → Hypoxia leads to upregulation of CXCL10 in neurons and CXCR3 in microglia, which was counteracted by Mac-1 suppression, thereby preventing dendritic loss	[99]
Sepsis-induced	Preclinical	Wistar rats (36), 60 days	Male	→ Sepsis elevated all cytokines in the brain at 24 hours after induction which decreased with time, except TNFα, which increased after 15 days → TLR4 and GFAP levels were only altered after 30 days post sepsis, indicated late activation of microglia and astrocytes, which may contribute to late RAGE upregulation and subsequent tau phosphorylation and Aβ accumulation, which was prevented by RAGE inhibition → HMGB1 levels increase 15 and 30 days after sepsis induction and then decreased	[100]
Intracerebral haemorrhage-induced	Preclinical	C57BL/6 mice ICH (388), Sham (66), 12 months	Male and Female	→ ICH induced necrotic and apoptotic cells at 72 hours post-ICH, which correlated with increases in HMGB1 released from necrotic cells → Epicatechin reduced ICH iron-induced cell death, promoted Nrf2 nuclear accumulation, and reduced oxidative brain damage, possibly through the downregulation of HMGB1	[101]

(Table 9) contd….

External Etiology	Type of Study	Subject, Sample Size (n), and Mean Age Group	Gender	Significant Findings Related to HMGB1	References
Ischaemic-induced	Preclinical	Neural cell culture C57 mice (NA), 25-30g	Male	→ Brain ischemia increased the expression of HMGB1 in neurons and astrocytes, released HMGB1 from neural cells, which activated glia, worsened excitotoxicity and neuronal death → Exogenous HMGB1 increased post-ischemia excitotoxicity and neuronal death → Exogenous HMGB1 contributes to neurodegeneration *via* increased transcription of iNOS and IL-1β	[102]
Mitochondrial dysfunction-induced	Preclinical	SD rats (NA), 280–300g Primary striatal cultures	NA	→ 3-nitropropionic acid (3-NP) triggered autophagy and apoptosis, which was exacerbated by exogenous HMGB1, which may contribute to cell death and neurodegeneration *via* JNK pathway → HMGB1 knockdown or blockade, inhibited or reduced 3NP induced LC3-II activation, SQSTMI degradation, autophagy signalling and striatal death	[103]
Ethanol-induced	Preclinical	Hippocampal-entorhinal cortical slice cultures	NA	→ Poly [ADP-ribose] polymerase (PARP) initiated the neuroinflammatory and neurodegenerative pathways post binge-ethanol → PARP upregulated PLA2 which increased ARA-cyclooxygenase and HMGB1, thereby increasing ROS and subsequently contributing to neurodegeneration post binge-ethanol	[104]
Ethanol-induced	Preclinical/ Clinical	Hippocampal-entorhinal cortical slice cultures, SH-SY5Y and BV2 cells, Post-mortem human hippocampal tissue	NA	→ Ethanol increased TLR7 expression, induced the release of HMGB1 and let-7b from microglia-derived microvesicles, which increased the binding of let-7b with HMGB1, thereby promoting neurodegeneration → HMGB1-let-7b binding increased TLR7 expression in neurons as well → HMGB inhibition prevented TLR7 mediated neurotoxicity and alcohol withdrawal toxicity may be mediated by HMGB1-TLR7	[105]
Ethanol-induced	Preclinical	C57BL/6 mice (NA), 8 weeks	Male	→ Ethanol potentiated Poly I:C induction of proinflammatory cytokines *via* NF-κB activation, as well as increased the expression of HMGB1 and TLR3 in the brain → Ethanol and Poly I:C increased levels of superoxide, NOX, caspase-3, neurodegenerative markers and cell death markers	[106]

Note: NA, not available; F, female; M, male; HMGB1, high mobility group box 1; TLR, toll like receptor; RAGE, receptor for advanced glycation end products; NF-κB, Nuclear factor *kappa* B; SD, Sprague-Dawley; Poly I:C, Polyinosine-polycytidylic acid; NOX, NADPH oxidase; NADPH, Nicotinamide adenine dinucleotide phosphate; let-7b, lethal-7b; ROS, reactive oxygen species; ARA, arachidonic acid; PLA2, Phospholipase A2; LC3-II, autophagosomes marker; JNK, c-Jun N-terminal kinases; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; iNOS, inducible nitric oxide synthase; BACE, Beta-secretase; ICH, intracerebral haemorrhage; TNFα, tumor necrosis factor alpha; GFAP, Glial Fibrillary Acidic Protein; SQSTMI, Sequestosome-1; IL-1β, interleukin 1 Beta; Nrf2, nuclear factor erythroid 2–related factor 2.

in MS. Based on Table **5**, majority of the HMGB1 studies in MS disease were clinical studies. Most studies included MS patients and healthy controls, while 2 clinical studies investigated HMGB1 levels in different types of MS and 4 clinical studies also included patients of different diseases (NMO and non-inflammatory neurological disorders). Most of the clinical studies recruited more female MS patients than their male counterpart. This was also reflected in the preclinical studies where female animals were predominantly utilized. Three different animal strains were used in the preclinical MS studies, which were adult Wistar rats, adult Dark Agouti rats and adult C57Bl/6 mice. In terms of HMGB1 expression levels, significantly elevated levels of HMGB1 were found in the serum, plasma, CSF, microglia and lesions of MS patients, when compared to healthy controls. One study suggested differences in HMGB1 expression levels between the different types of MS, where RRMS had the highest expression levels. In contrast, another study showed that there were no changes in expression levels between the types of MS. Similar to the clinical studies, HMGB1 was also found elevated in the serum, CSF and tissue homogenates of MS animal models. Some clinical studies successfully displayed HMGB1 as a biomarker that may be used to identify neuromyelitis optica (NMO) from MS, due to the differences in

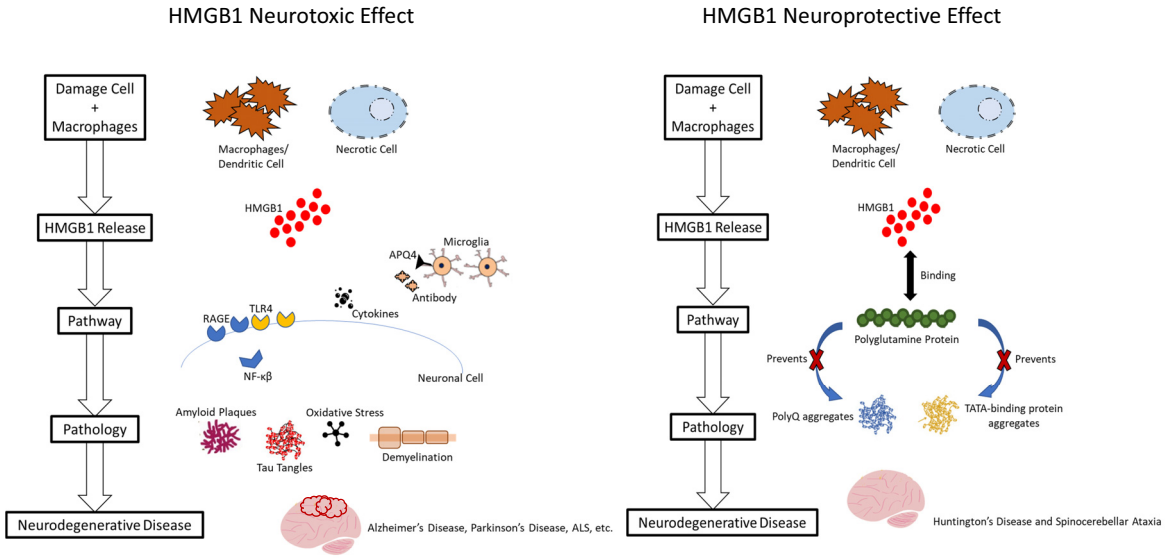

Fig. (2). Overview of the role of HMGB1 in the pathophysiology of neurodegenerative diseases. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

expression. In terms of HMGB1 pathology, the clinical studies showed that TLR2, TLR4 and RAGE levels were also equally elevated with HMGB1 levels, suggesting that their pathways may be involved in HMGB1 pathology. Similarly, TLR4 and RAGE was also the suggested pathways in preclinical MS models, with the addition of the NFκB and MyD88 pathway. One study indicated that HMGB1 suppressed oligodendrocyte differentiation, while another study suggested the HMGB1-guided infiltration of T cells, both of which may contribute to the neurodegenerative phenomenon (demyelination of neurons) seen in MS neuronal cells. In terms of HMGB1 therapeutic potential, one clinical study suggest that IFN-B treatment decreases the HMGB1 levels in the serum, but another showed no effects, though neither showcased whether this improved MS conditions. Interestingly, Fingolimod treatment in MS patients managed to not only reduce the HMGB1 and RAGE ligand levels but also decrease the disability scores by the MS patients, suggesting improvement of the disease. In the preclinical studies, MAT treatment, ethyl pyruvate, TNT treatment, Glycyrrhizin treatment, Recombinant thrombomodulin, anti-HMGB1 and HMGB1 neutralising antibodies, all showed reduction in HMGB1 levels, reduced pro-inflammatory cytokines, inhibition of the NFκB pathway and decreased the demyelination process in MS neurons. Although the study with the Glycyrrhizin treatment showed that its therapeutic effects on HMGB1 were only acute.

3.1.6. Spinocerebellar Ataxia Disease

Spinocerebellar ataxia (SCA) involves polyglutamine diseases including SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 caused by the presence of pathological repeat expansions of cytosine-adenine-guanine (CAG) trinucleotide in the mutated genes around the coding region. The cerebellar cortex, inferior olivary nuclei, and dentate nuclei may be affected in SCA disease. In the inferior olivary nuclei, retrograde degeneration of neurons occurs with loss of Purkinje cells [110]. Based on Table **6**, only two preclinical studies had investigated the role of HMGB1 in SCA disease, with only one of them being an animal model. Although the expression levels of HMGB1 have not been investigated, these two studies revealed that HMGB1 may be neuroprotective against SCA. The mutant SCA animal model suggested that increased HMGB1 may result in better motor outcomes as it may repair damage mitochondrial DNA. While the cell culture study showed that HMGB1 may reduce TBP aggregation and increase autophagy activation, thereby improving SCA pathology.

3.1.7. Neuromyelitis Optica Disease

Neuromyelitis Optica disease (NMO) is a demyelinating disease that causes symptoms such as myelitis, optic neuritis leading to vision loss, paraplegia or tetraplegia, sensory impairment, and reduced coordination and strength. Its pathogenesis involves autoantibody production against Aquaporin 4 (AQP4) [78]. Based on Table **7**, all three studies on the role of HMGB1 in NMO disease were of clinical studies. Interestingly, all three studies also involved MS patients, thus those studies on NMO disease only in relation to HMGB1 have not been showcased. Most of the NMO patients were female. All three studies showed that HMGB1 expression was higher in NMO patients than in MS patients, in both the CSF and plasma samples. Increases in HMGB1 correlated with increases in pro-inflammatory cytokines and NMO related disability. Two studies noticed that HMGB1 levels were higher in APQ4 positive NMO patients compared to APQ4 negative NMO patients. One study suggested than IFN-γ may also be associated with HMGB1 increases/pathology in NMO patients, but this was not elaborated further. No studies have been performed on the therapeutic potential of HMGB1 in NMO.

3.1.8. Retinal Neurodegenerative Disease

Retina is part of the CNS evolutionarily structured with complex organisation of over 60 types of cells. Three distinct glial cell types including microglia, astrocytes, and muller cells were found in the mammalian retina with multiple functions, including recycling glutamate, controlling extracellular

homeostasis, and releasing trophic factors along with detection of noxious stimuli and neuroprotection from certain pathologies [111]. Based on Table **8**, there was only one clinical study investigating the role of HMGB1 in retinal degeneration, which involved diabetic patients. There were 5 preclinical studies involved with retinal degeneration and HMGB1, which utilized three different animal strains; SD rats, C57Bl/6 mice and PKD rats, with one study looking at retinal photoreceptor cells. Both clinical and preclinical studies were predominantly of the male gender. In terms of HMGB1 expression levels, HMGB1 was found to be increased in the retinal cells and rods in diabetic patients and in animal models of retinal degeneration. HMGB1 pathology in retinal degeneration involved the RAGE, TLR2 and TLR4 pathways. Although one study suggested that the activation of the NFκB-HMGB1-NMDA pathway may also lead to retinal degeneration. The translocation of HMGB1 into the cytoplasm and extracellular space was also found in animal models of retinal neurodegeneration. Interestingly, HMGB1 inhibitor may promote BDNF release in the retina, thereby improving retinal neurodegeneration.

3.1.9. Externally Induced Neurodegeneration

Several other types of neurodegenerations, or externally induced neurodegeneration have also been associated with HMGB1. These include LPS-induced, HMGB1-induced, mitochondrial dysfunction-induced, intracerebral haemorrhage-induced, hypoxia-induced, ischemia-induced, sepsis-induced and ethanol-induced neurodegeneration. Based on Table **9**, there was only one clinical study that looked at HMGB1 in relation to externally-induced neurodegeneration, which was an ethanol-induced population. The remaining were mostly animal studies involving adult male BALB/c mice, adult or aged male C57Bl/6 mice, adult male Wistar rats or adult SD rats. In terms of HMGB1 expression levels, all models of externally-induced neurodegeneration, increased the HMGB1 levels in the brain, either in the neurons or glial cells. For HMGB1 pathology, each type of externally-induced neurodegeneration showcased a different HMGB1 pathological pathway. The HMGB1-TLR4-NFκB pathway was mainly seen in LPS-induced and hypoxia-induced neurodegeneration. HMGB-induced neurodegeneration involved the HMGB1-CXC pathway, which was also seen in hypoxia-induced neurodegeneration. The hypoxia model also suggested that microglia (Mac-1) interaction with HMGB1 resorted in memory loss. The HMGB1-TLR4-RAGE pathway was seen in the sepsis-induced neurodegeneration. Intracerebral haemorrhage-induced neurodegeneration mainly involved HMGB1 interaction with iron, while ischemia-induced neurodegeneration was based on the increased transcription of iNOS and IL-1b brought upon by HMGB1. Mitochondrial-induced neurodegeneration was based on HMGB1-triggered apoptosis *via* the JNK pathway. Ethanol-induced neurodegeneration involved three different pathways which include HMGB1-TLR7, PARP initiation and Poly I:C activation of the HMGB1-TLR3 pathway.

4. DISCUSSION

Neurodegenerative disease is a progressive long-term ailment that affects millions of people worldwide, and its prevalence may continue to rise given the aging population. Researchers suggest that early detection of neurodegenerative diseases, such as AD, through biomarkers, prior to the onset of clinical presentation of symptoms may provide the best therapeutic window for effective intervention [112, 113]. Biomarkers would not only be able to identify and classify neurodegenerative diseases at the early stages, but may be useful to confirm their clinical diagnosis, perform epidemiological screening, predict the outcome of the diseases as well as to monitor the disease progression and its sensitivity to the treatment strategies [114]. Biomarkers may also serve as targets for therapeutic intervention [115]. Thus, this systematic review aimed to elucidate the role of HMGB1 as a potential and possibly crucial biomarker for neurodegenerative diseases. About 80% of the neurodegenerative diseases and neurodegeneration caused by external etiologies have shown an upregulation of the HMGB1 expression, while only 2 neurodegenerative diseases (HD and SCA) have shown a downregulation of the HMGB1 expression, regardless of whether in the serum, plasma, CSF and tissues. This suggest that HMGB1 may play a dual role in neurodegenerative diseases; pro-inflammatory/neurotoxic and anti-inflammatory/neuroprotective role. However, in multiple sclerosis, contradictory HMGB1 expression has been concluded, where some studies showed no significant increase in HMGB1 expression [67, 71, 72, 74], whereas others showed a significant increase in expression [67, 69, 70, 73, 79]. This contradiction in HMGB1 levels may be related to the stage of the disease progression. For example, in preclinical studies involving EAE, HMGB1 levels were elevated in spinal cord homogenate, CSF, and sera in different stages of the disease, with it peaking at onset and decreasing from pre-onset to remission stage [87]. Thus, the duality in HMGB1's role may be correlated with achieving the optimal expression levels [54] at the different stages of disease progression, as well as the type of HMGB1 pathological pathway interaction at these stages.

4.1. HMGB1, RAGE and TLR4 Interaction

Increasing evidence suggests the involvement of HMGB1 in several disorders of the central nervous system, mainly through the activation of RAGE/TLR4 signalling axes [5]. In support, majority of the studies in this review indicated HMGB1's interaction with the RAGE molecule and TLR4 receptors as the main pathological pathway of neurodegenerative diseases. For example, HMGB1 and RAGE has been associated with the progression of Tau hyperphosphorylation and Aβ aggregations, whereby deletion of either HMGB1 or RAGE could ameliorate both Aβ and Tau pathology in the animal models of AD [28]. A clinical study demonstrated that increases in expression levels of both serum HMGB1 and sRAGE correlated with the Aβ levels in AD patients [22]. Additionally, the activity of soluble thrombomodulin (sTM) antigen, which is a marker of BBB disruption was also observed to be significantly upregulated in the MCI and AD patients [22], suggesting that the increases in serum HMGB1 and sRAGE may have caused leakage of amyloid and oxidative stress proteins from the blood to the brain through the BBB, thereby resulting in neuronal damage.

RAGE may also bind to tau oligomers and initiate the pro-inflammatory signalling *via* the nuclear factor-κB

(NFκB) pathway [116]. The NFκB transcription factor may upregulate the HMGB1 and RAGE expression, which in turn may further induce the production of other cytokines [117]. HMGB1 levels correlated with elevated levels of IL-6 and IL-17 levels in the CSF in addition to elevated IL-17, IFN-γ, and TNF-α levels in the plasma [78]. Tau oligomers may also interact with astrocytes and microglia to further induce inflammation, potentially through the RAGE signalling, as RAGE is expressed on astrocytes and microglia as well [26, 118, 119]. This indicates that HMGB1 may bind to the RAGE receptors on glial cells, triggering the activation of NFκB and other cytokines [34], which results in tau and/or Aβ pathology that further propagates the pathological loop *via* the HMGB-1/RAGE/NFκB signalling pathway. Similarly, increased expression of both HMGB1 and TLR4 in PD patients, coupled with the activation of the NFκB pathway, may bind to the aggregated α-synuclein in Lewy bodies, whereby the α-synuclein levels were positively correlated with high expression of the HMGB1/TLR4 axis [39, 46, 50]. In retinal neurodegenerative pathologies, microglial cell responses have been shown to activate NFkB in response to HMGB1 excitoneurotoxicity in the retina [96, 111], but whether this is through the RAGE pathway was not illustrated in the study. Taken together, the results from the selected studies suggest that the HMGB1/RAGE/TLR4/NFκB pathway and its interaction with neurodegenerative hallmarks may be the most common pathological pathway in which HMGB1 plays a neurotoxic role in neurodegenerative diseases.

4.2. HMGB1 and Other Pathological Pathways

HMGB1 may also play a role in neurodegenerative diseases *via* other pathways, some related to the TLR4 and RAGE pathway, while others may not be related. For example, NFkB activation may increase HMGB1-NMDA induced injury in the retinal neurons with ganglion layer cell loss, as NMDA receptors may cause excitotoxicity in neurons through the elevation of intracellular Ca2+, leading to glaucomatous degeneration [96]. Although, the study did show that HMGB1 alone without NFκB activation may delay neuronal cell loss between 3 to 5 days after injecting intravitreal NMDA [96], suggesting that NMDA-NFκB interaction may be more detrimental towards neurodegeneration than HMGB1-NMDA interaction with NFκB. In addition, retinal neurodegeneration studies also indicated the interaction of HMGB1 and TLR2 in the apoptosis pathway in retinal explants [94]. TLR2 and TLR4 involvement with HMGB1 signalling has previously been suggested to differ in different cell lines, releasing varied neuroinflammatory cytokines [120], thereby supporting the HMGB1-TLR2 neurodegenerative signalling in retinal cells, unlike HMGB1-TLR4 signalling in other neurodegenerative diseases. While TLR2 and TLR4 are cell surface receptors, other TLRs such as TLR3 and TLR7 are mainly expressed intracellularly within vesicles [121]. This suggest that ethanol-induced neurodegeneration may be confined in the intracellular space of neuronal cells, affecting neuronal autoimmunity and inducing proinflammatory cytokines, *via* the HMGB1-TLR3 [106] and HMGB1-TLR7 pathways [105].

Beside TLRs, Fujita and colleagues demonstrated that HMGB1 may also play a role in the beta-amyloid peptide aggregation *via* activation of the PKC pathway [27]. They also showed that HMGB1 initiated neurite degeneration *via* TLR4-myristoylated alanine-rich C-kinase substrate (MARCKS) pathway, by triggering MARCKS phosphorylation [27]. MARCKS promotes neurite growth and synaptic plasticity under normal conditions, but when phosphorylated by PKC, it translocates into the cytosol, reducing MARCKS level and initiating the neuroinflammatory and neurodegeneration response [122]. Therefore, HMGB1 may also play a role in neurodegeneration *via* the HMGB1-PKC-MARCKS pathway. Studies on NMO suggested that HMGB1 may also interact with the glial APQ4 membrane protein, promoting edema and cytotoxicity, thereby resulting in neurodegeneration [78, 80]. Thus, the HMGB1-APQ4 pathway may also be another therapeutic avenue for future research, especially if this pathway may also be involved with the pathology of other neurodegenerative diseases.

4.3. HMGB1 and Neurodegenerative Markers

HMGB1 has been found to accumulate extracellularly on Aβ40 plaques in AD brains [24], as well as on senile plaques [33]. The latter study showed that extracellular HMGB1 affects microglial phagocytosis of Aβ40 and Aβ42, thereby blocking the clearance of Aβ42 from the ipsilateral rat hippocampus and augmenting the Aβ mediated neurotoxicity [33]. Extracellular HMGB1 may also act as a chaperone for Aβ which intervenes with the degradation of Aβ40 and stimulates the internalization of Aβ42 by microglia [24]. Thus, inhibition of extracellular HMGB1, may promote Aβ clearance and might serve as a prospective therapeutic approach against AD. Interestingly, in HD disease, extracellular HMGB1 was proposed to act as a chaperone that prevented PolyQ protein aggregation, when at optimal expression levels [54]. This contrasting (neurotoxic/neuroprotective) chaperone-like activity of HMGB1, suggest that the neurodegenerative proteins themselves may play a role in HMGB1's action in neurodegenerative diseases.

Alternatively, some studies have also suggested that HMGB1 expression may increase as a result of the neurodegenerative proteins instead. Elevated HMGB1 levels were observed in PC12 cells after the induction of Aβ25-35, thus indicating that the HMGB1 levels increased due to the Aβ proteins [35]. This also suggest that there may exist a vicious feedback cycle, where increases in HMGB1 may cause increases in neurodegenerative proteins which further propagates the increase in HMGB1 levels, thus causing a progressive neurodegeneration of neurons. This vicious cycle may also exist in lieu with the neuroinflammatory response in neurodegeneration, whereby with the activation of both astrocytes and microglia, HMGB1 will be released and will further accelerate the glia activation *via* the HMGB1/TLR4/NF-κB axis [42]. However, studies have reported that HMGB1 which are released from the reactive astrocytes in the acute period of MPTP intoxication in mice could also affect the maintenance of dopaminergic neuronal function *via* the modulation of tyrosine hydroxylase (TH) expression [45]. Furthermore, previous studies have revealed that overexpressed α-synuclein may bind to HMGB1 and impair its cytosolic translocation as well as block the HMGB1-Beclin1 interaction, which ultimately results in autophagy inhibition [123].

4.4. HMGB1 and Neurodegeneration-Associated Dysfunction

Besides propagating the neurodegenerative pathology, HMGB1 may also contribute to the associated impairments of neurodegenerative diseases. The HMGB1/TLR4/RAGE signalling have also been implicated to contribute to cognitive dysfunctions, outside of the neurodegeneration realm [124]. Thus, it is of no surprise that increases in HMGB1 may also contribute to the cognitive deficits seen in neurodegenerative diseases, possibly acting *via* similar mechanism. It was reported that increased Aβ and extracellular HMGB1 induced memory impairment in AD, *via* binding to TLR4 and RAGE [37]. In support, previous studies have shown that intracerebroventricular (ICV) injection of HMGB1 in WT, $TLR4^{-/-}$, and $RAGE^{-/-}$ mice have been observed to impede learning and memory in non-neurodegenerative disease model *via* similar pathways [125]. Administration of HMGB1 may also cause cognitive impairment by suppressing the CXCR7, which promotes the HMGB1-CXCL12 pathway [98], suggesting a new therapeutic avenue for cognitive-associated neurodegeneration. In addition to that, Mac-1 a microglial marker that is a receptor for HMGB1 may also lead to working memory loss in neurodegenerative disease. Degradation of the Mac-1 receptor downregulated cytoplasmic HMGB1 significantly and retarded the progression of memory loss, suggesting a therapeutic potential by knocking down Mac-1 receptors [99]. Besides cognition, HMGB1 may also affect motor function *via* the RAGE pathway. Mice lacking RAGE signalling had greater survival and better motor function despite the presence of ALS pathology [64].

4.5. Neuroprotective Role of HMGB1

Some studies have suggested that HMGB1 may partly elicit a neuroprotective effect by interacting with the neurodegenerative proteins. HMGB1 interaction with $A\beta_{1-42}$ initiated a potential reparative mechanism by promoting neuronal differentiation of adult hippocampal NPCs by activating the RAGE/NFκB cascade [30, 126], thus demonstrating the proneurogenic potential of HMGB1. Additionally, in PD models, HMGB1 has demonstrated to excel anti-inflammatory effects by inhibiting the activation of microglia and the infiltration of T cells in the substantia nigra [49]. In HD disease models, HMGB1 levels were observed to be reduced in striatal neurons, where they co-localized with mutant huntingtin proteins in nuclear inclusion bodies [53]. Additionally, upregulation of HMGB1 expression levels also enhanced neurite length and ameliorated neuronal death of *in vitro* primary cortical neurons [52, 54]. HMGB1 may also promote neuroprotection by producing brain-derived neurotrophic factors and glial cell line-derived neurotrophic factors [62]. These neuroprotective findings suggest that HMGB1 intervention should not only focus on reducing/inhibiting HMGB1 but also promoting its balance in expression levels.

4.6. HMGB1-related Interventions

This review has elucidated the crucial role of HMGB1 in neurodegenerative diseases, thus, interventions focusing on the HMGB1 molecule may serve as a potential treatment strategy against various neurodegenerative diseases, as well as a preventive strategy for externally-induced neurodegeneration. In support, inhibition of HMGB1 expression or its downstream pathways (RAGE/NFκB), exhibited neuroprotective effects in an animal model of neurodegenerative diseases [27]. Additionally, another study has reported the inhibitory effect of Oxymatrine on the HMGB1/TLR4 and TLR4/NFκB axis, which prevented neuroinflammation and protected the DA neurons in PD mice model [41]. Furthermore, several studies suggested that systemic administration of HMGB1 neutralizing antibodies inhibited the activation of microglial, curbed the secondary neuroinflammation and prevented the dopaminergic cell death in PD models [40, 43, 47]. IFN-β treatment [70], disease-modifying drugs (DMDs) [75] and Fingolimod treatment [76] have shown to effectively reduce HMGB1 levels in MS patients, but only the Fingolimod treatment was associated with improvements in the disease condition. In preclinical studies, HMGB1 antagonist such as quinolizidine alkaloid Matrine (MAT) [82], glycyrrhizin treatment [86], recombinant thrombomodulin (rTM) treatment [88], ethyl pyruvate [83], HMGB1 neutralizing antibodies [85], anti-HMGB1 monoclonal antibodies [89] and administration of Ti-O based nanomaterials [84] have all shown to attenuate the progression of MS-like functional deficits and pathology. This suggest that targeting the HMGB1 pathology may provide an effective treatment against MS that may help to improve the lives of MS patients. For neurodegenerative diseases where a downregulation of HMGB1 propagated the disease, such as HD and SCA, virus-vector mediated HMGB1 or transgenic complementation with HMGB1 have shown to improve the lifespan and motor deficits of mice models [90].

Nevertheless, as of now, most of the HMGB1 interventions have only shown to be effective in MS animal models and patients, with a couple suggesting the protective effects of HMGB1 inhibition in PD animal models. The different pathological pathways in which HMGB1 may interact with, in the different neurodegenerative diseases, might serve as a limitation to the development of effective HMGB1 intervention strategies, especially if the disease has a multifactorial pathological pathway such as AD. Therefore, this suggest that more studies, particularly clinical studies may be needed to understand the beneficial effects, effectivity and potency (dose and duration) of HMGB1 intervention on each neurodegenerative disease. Moreover, the possible interactions of HMGB1 interventions with currently available neurodegenerative treatment strategies may still be elusive, as some treatment strategies targeting the neuroinflammatory pathway may counteract or enhance HMGB1 interventions, as well as *vice versa*.

Thus, this review suggests that there is no specificuniversal strategy of HMGB1 intervention that may benefit all neurodegenerative diseases, but the studies included in this review have indicated that there may be various potential strategies that may prove to be effective with further exploration.

CONCLUSION

Neurodegenerative disease is a devastating progressive CNS disease, which till today has no effective cure or treatment that lessen the burden of its sufferers. This review showed that HMGB1 may act as a precursor molecule that may initiate the various different pathological pathway to-

wards the formation of neurodegenerative proteins/ molecules, thereby leading to progressive neuronal loss in function and structure. HMGB1 may be a crucial biomarker and target for neurodegeneration treatment. This review found that HMGB1 was significantly elevated in a majority of neurodegenerative disease and in neurodegeneration induced by external factors, except in Huntington's disease and Spinocerebellar ataxia. Current research on HMGB1 intervention have shown promising results in reducing/inhibiting HMGB1 as well as promoting it, depending on the type of neurodegeneration, to elicit positive effects on behaviour and pathology. However, further studies may be warranted on these intervention strategies prior to commercialisation. Nevertheless, this review believes that by targeting the HMGB1 biomarker, medicine may be one step closer in eradicating neurodegenerative disease, especially from the growing aging population.

AUTHORS' CONTRIBUTIONS

FZI performed the literature search and selection. FZI, AA and TR performed critical evaluation of articles and prepared the manuscript. AA reviewed and edited the manuscript. MFS conceptualised the idea and reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

PRISMA checklist is available on the publisher's website along with the published article.

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