REVIEW PAPER

Mechanistic Insights Into Neurodegenerative Disorders With Emphasis On The Neuroprotective Effects Of *Abresham* And *Ustukhuddus*

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ABSTRACT

Neurodegenerative disorders are progressive and multifactorial diseases characterized by neuronal loss, synaptic dysfunction and cognitive and motor impairment. Major pathogenic mechanisms include abnormal protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity and disruption of brain barrier systems. Current pharmacological therapies primarily offer symptomatic relief and fail to halt disease progression, highlighting the need for multi-target neuroprotective strategies. Traditional Unani medicine provides a holistic framework for neurological health, emphasizing restoration of cerebral balance and systemic homeostasis. Abresham (Bombyx mori silk) and Ustukhuddus (Lavandula stoechas) are well-established Unani drugs traditionally used for neurological and neuropsychiatric disorders. Emerging analytical and preclinical evidence demonstrates that Abresham exerts neuroprotective effects through antioxidant, anti-inflammatory, mitochondrial-stabilizing, and neuromodulatory actions mediated by silk proteins such as fibroin and sericin. Ustukhuddus exhibits neuroprotection via modulation of GABAergic and cholinergic neurotransmission, suppression of neuroinflammation, and reduction of oxidative stress, largely attributed to its volatile oils and phenolic constituents. This review integrates contemporary mechanistic insights into neurodegeneration with traditional Unani knowledge to highlight the therapeutic potential of Abresham and Ustukhuddus as promising multi-target neuroprotective agents.

Keywords: Neurodegenerative Disorders, Abresham, Ustukhuddus, Systemic Homeostasis.

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INTRODUCTION

Neurological and neurodegenerative disorders (NDs) constitute one of the most pressing and rapidly expanding global health challenges of the 21st century [1,2]. These disorders are characterized by the progressive and often irreversible loss of neuronal structure and function, ultimately leading to cognitive, motor, sensory, and behavioral impairments [3]. Major neurodegenerative and neurological conditions including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), stroke, epilepsy, depression, and anxiety collectively contribute to substantial morbidity, mortality, and socioeconomic burden worldwide [4–6]. The deliberate degeneration of neurons and synaptic networks that underpins these disorders underscores the urgent need for therapeutic strategies that extend beyond symptomatic relief to preserve neuronal integrity and slow or halt disease progression [7].

Neurodegenerative disorders typically manifest later in life and are associated with a gradual loss of neurons and synaptic connectivity in specific brain regions, resulting in disease-specific clinical phenotypes [8,9]. In AD, early neuronal degeneration occurs in the hippocampus, a region essential for declarative and episodic memory, leading to progressive cognitive decline [10,11]. In PD, classical motor symptoms such as tremor, bradykinesia, and postural instability become clinically evident only

after the loss of approximately 70–80% of dopaminergic neurons in the substantia nigra [12,13]. MS, in contrast, is primarily an immune-mediated disorder in which activated microglia and immune cells attack myelin sheaths, causing demyelination, impaired neuronal signal conduction, and diverse neuropsychiatric manifestations [14,15]. Diagnosis of NDs relies on clinical assessment supported by neuroimaging techniques such as magnetic resonance imaging (MRI), with disease severity closely correlating with the extent of neuronal loss [16].

The global burden of neurodegenerative disorders continues to rise at an alarming rate. In 2019, neurological disorders affected approximately 349.2 million individuals and accounted for nearly 10 million deaths worldwide, ranking second in global disease prevalence [17,18]. AD represents the most significant contributor and is currently recognized as one of the leading causes of death globally, with more than 55 million individuals suffering from dementia nearly 60% of whom reside in low- and middle-income countries [19,20]. Similarly, the global prevalence of PD exceeded 8.5 million cases in 2019, with a marked increase in disability-adjusted life years over the past two decades [21]. MS affects more than 1.8 million individuals worldwide, while ALS and HD, though rarer, are associated with high mortality rates and profound disability [22–24]. Aging, genetic predisposition, environmental exposure, and lifestyle factors collectively contribute to the increasing incidence of these disorders [25].

At the molecular and cellular levels, neurodegeneration is a multifactorial process involving oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, impaired protein homeostasis, dysregulated apoptotic signalling and synaptic failure [26,27]. Despite significant advances in understanding these pathogenic mechanisms, currently approved pharmacotherapies largely offer symptomatic relief and fail to modify disease progression [28]. Therapeutic efficacy is further compromised by challenges such as poor blood–brain barrier penetration, long-term adverse effects, drug resistance and reduced patient compliance, resulting in suboptimal clinical outcomes [29,30].

These limitations have prompted growing interest in multi-target and integrative therapeutic approaches, including traditional medical systems that emphasize holistic disease management. Unani medicine conceptualizes neurological health through the functional integrity of Dimagh (brain) and Asab (nervous system), regulated by the balance of Mizaj (temperament), Akhlat (humors) and Tabiyat (self-regulatory power of the body) [1,3]. Numerous Unani drugs and formulations are traditionally prescribed for cognitive impairment, epilepsy, anxiety, melancholia, paralysis and age-related neurological decline [4,6].

Among these, Abresham (Bombyx mori silk) and Ustukhuddus (Lavandula stoechas) hold a prominent place in Unani therapeutics. Abresham is traditionally described as a cardiac and cerebral tonic used in nervous debility, anxiety and neuropsychiatric disorders [7,9]. Modern studies suggest that silk-derived proteins such as fibroin and sericin possess antioxidant, anti-inflammatory, and cytoprotective properties, indicating potential neuroprotective relevance [10–12]. Similarly, Lavandula stoechas has been widely used for epilepsy, headache, memory disorders, anxiety, and depression, with phytochemical investigations revealing essential oils, flavonoids, and phenolic compounds that exhibit antioxidant, neuro-modulatory, and anti-inflammatory activities [13–16].

The integration of advanced analytical techniques with preclinical pharmacological evaluation is essential for validating traditional neuroprotective agents. Analytical methods enable the identification, quantification and standardization of bioactive constituents, while in vitro and in vivo models provide mechanistic insights, safety profiling, and translational relevance [17–20]. Such integrative strategies are particularly important for polycomponent traditional drugs, where synergistic interactions significantly contribute to therapeutic efficacy [21–23].

In light of the escalating global burden of neurodegenerative disorders and the limitations of existing therapies, a comprehensive and evidence-based evaluation of traditional neuroprotective agents is both timely and necessary [24–26]. This review aims to systematically analyze the available analytical and preclinical evidence supporting the neuroprotective potential of Abresham and Ustukhuddus, elucidate their mechanistic pathways, and identify key research gaps to facilitate clinical translation [27–30]. By bridging traditional Unani wisdom with contemporary neuropharmacological science, this work seeks to contribute to the development of safe, effective, and multi-target therapeutic strategies for neurodegenerative disorders.

Major Types of Neurodegenerative Disorders (NDs)

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder that affects the central nervous system (CNS), including the brain and spinal cord (Figure 1). MS is characterized by an abnormal immune response in which the immune system mistakenly attacks myelin, the protective covering surrounding nerve fibers [31,32]. This immune-mediated attack results in inflammation, demyelination, and subsequent damage to

underlying neurons, thereby disrupting the normal propagation of electrical impulses along neural pathways.

The clinical manifestations of MS vary widely and may include fatigue, impaired mobility, sensory disturbances such as numbness or tingling, muscle weakness, coordination deficits, visual disturbances including blurred or double vision, and cognitive impairments affecting memory and concentration [33].

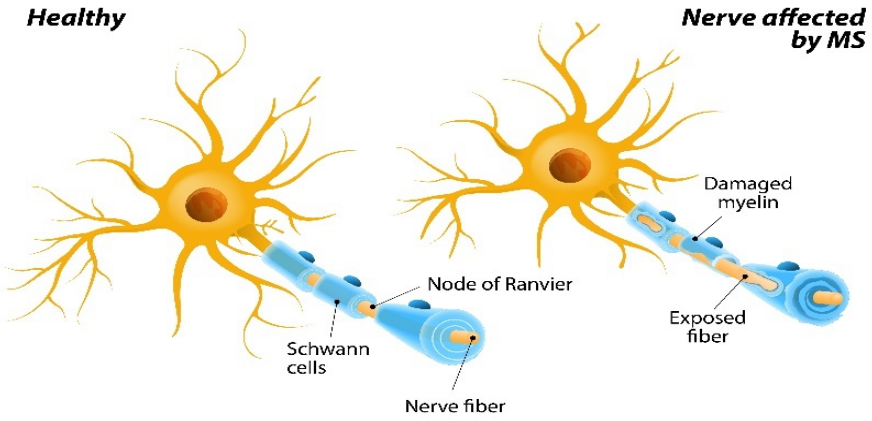

Figure 1: Multiple Sclerosis

MS is broadly classified into three main forms. Relapsing–remitting MS (RRMS) is characterized by episodic relapses followed by periods of partial or complete recovery. Primary progressive MS (PPMS) presents with a continuous progression of neurological disability from disease onset, without distinct relapses or remissions. Secondary progressive MS (SPMS) initially manifests as RRMS but later evolves into a steadily progressive form with worsening symptoms and disability [34]. Although the precise etiology of MS remains unclear, it is widely believed to result from a complex interaction between genetic susceptibility and environmental factors. Identified risk factors include certain viral infections, vitamin D deficiency, and smoking [35].

The diagnosis of MS remains challenging due to the absence of a single definitive diagnostic test. Neurologists typically rely on a combination of clinical evaluation, neurological examination, magnetic resonance imaging (MRI), and, in some cases, cerebrospinal fluid analysis to establish a diagnosis [36]. Currently, there is no definitive cure for MS; however, several therapeutic strategies aim to manage symptoms, modify disease progression, and improve overall quality of life. These approaches include pharmacological interventions, rehabilitative therapies, and lifestyle modifications. Disease progression varies significantly among individuals, with some patients experiencing mild symptoms and prolonged remission, while others exhibit a more aggressive and disabling course. Ongoing research focuses on elucidating disease mechanisms, developing novel therapeutic strategies, and improving patient outcomes [37]. Advances in immunotherapy and disease-modifying treatments have further expanded management options for MS [38]. Commonly used drugs include beta-interferons, copolymer 1 and immunosuppressive agents such as mitoxantrone and natalizumab.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that primarily affects the brain, leading to gradual deterioration of memory, cognitive functions, and behavioral patterns. It represents the most common cause of dementia in the elderly population [32]. First described by Dr. Alois Alzheimer in 1906, AD is characterized by the accumulation of abnormal protein aggregates in the brain, notably beta-amyloid plaques and neurofibrillary tau tangles [39]. These pathological deposits interfere with synaptic communication between neurons, ultimately resulting in neuronal death and progressive brain atrophy [40].

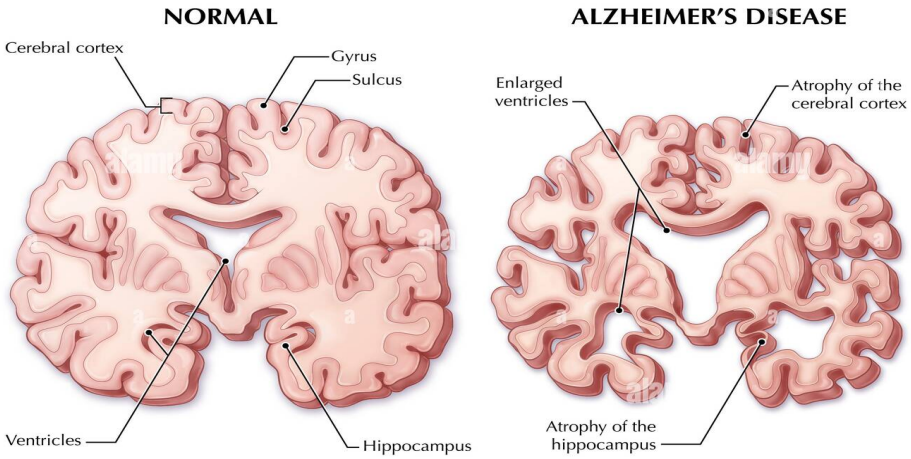

Figure 2: Progressive Neurodegeneration in Alzheimer's Disease

Clinically, AD presents with memory impairment, cognitive decline, behavioural changes and reduced functional abilities. Diagnosis typically involves a comprehensive assessment of medical history, neuropsychological testing, and exclusion of alternative causes of cognitive impairment. In certain cases, advanced neuroimaging techniques and cerebrospinal fluid analysis are employed to support diagnosis. AD is commonly categorized into three stages mild (early), moderate (middle) and severe (late) each defined by specific symptom severity and levels of functional impairment [40].

Although there is currently no curative treatment for AD, pharmacological agents such as cholinesterase inhibitors and memantine are used to alleviate symptoms and slow cognitive deterioration. Adjunctive therapeutic interventions, including occupational therapy and cognitive training, may also provide symptomatic benefits [41]. Current research efforts are directed toward understanding the underlying pathophysiology of AD and developing disease-modifying therapies. Increased awareness and early diagnosis have been shown to improve quality of life for patients and caregivers alike. AD places a substantial emotional, physical, and economic burden on caregivers, underscoring the importance of support systems, education and access to healthcare resources. Early medical consultation enables timely intervention and better disease management.

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurological disorder primarily characterized by a decline in motor function. The disease arises from the gradual degeneration of dopamine-producing neurons, particularly within the substantia nigra region of the brain [41]. Dopamine plays a crucial role in coordinating voluntary muscle movements and maintaining motor control [42,32]. While the exact cause of PD remains unclear, both genetic predisposition and environmental exposures are believed to contribute to disease onset.

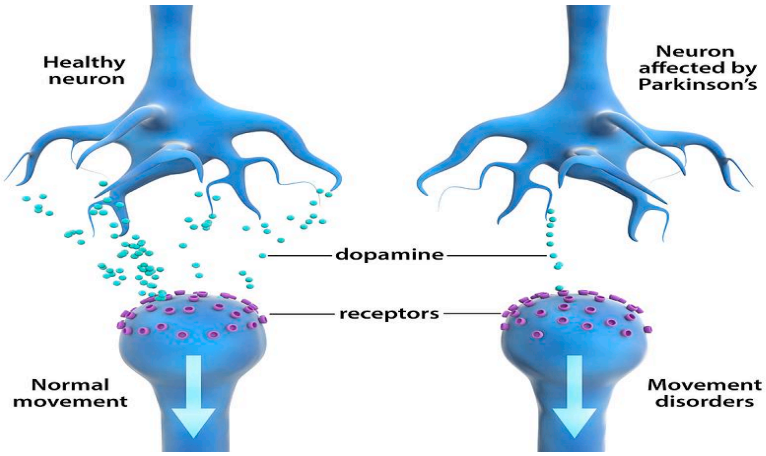

Figure 3: Progressive Neurodegeneration in Parkinson's Disease

The cardinal motor symptoms of PD include tremors, bradykinesia, muscle rigidity, and postural instability [43]. Diagnosis is largely clinical, based on symptom presentation and medical history, as no definitive diagnostic biomarker currently exists. Neurological examinations and imaging studies may be utilized to exclude other neurological disorders [44]. Levodopa, a dopamine precursor, remains the cornerstone of PD treatment for managing motor symptoms. Additional medications, including dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors, are frequently prescribed to enhance therapeutic efficacy [45].

PD progression is gradual and highly variable across individuals. Advanced stages may involve impairments in speech, swallowing, and cognitive function. In addition to motor symptoms, PD is associated with a range of non-motor manifestations, including sleep disturbances, mood disorders, and cognitive decline [46]. Regular physical activity, particularly exercises targeting balance and flexibility, has been shown to improve symptom control and overall well-being. Ongoing research aims to elucidate PD pathogenesis and develop more effective disease-modifying therapies. Heightened awareness and early diagnosis are critical for optimal disease management [47]. Early intervention has been shown to significantly enhance quality of life in PD patients [48].

Major Molecular Mechanisms Involved in Neurodegenerative Disorders (NDs)

Neurodegeneration is a complex and progressive phenomenon characterized by the gradual loss of structure and function of specific neuronal populations in the brain, a process that is frequently associated with aging [49]. During neurodegeneration, certain proteins fail to maintain their normal functional conformation, leading to their accumulation and aggregation in distinct regions of the brain [50]. In addition to abnormal protein behavior, neurodegeneration is accompanied by several pathological events, including chronic inflammation, impaired energy metabolism, and DNA damage. Over time, the cumulative effect of these disturbances intensifies, ultimately resulting in neuronal death [51]. Neuronal loss may occur through different mechanisms, such as programmed cell death or structural disintegration. The following sections comprehensively discuss the primary molecular mechanisms underlying neurodegeneration, while Figure 4 illustrates the key pathogenic pathways involved in neurodegenerative disorders.

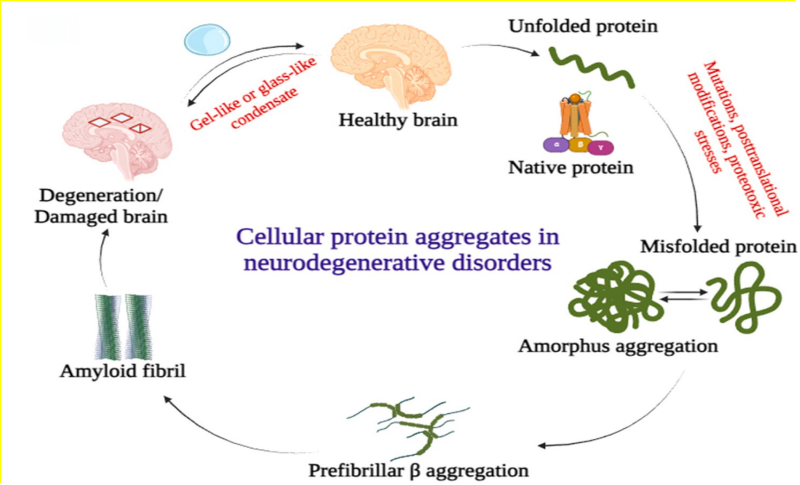

Figure 4: Cellular Protein Aggregation Linked to Neurodegeneration

Abnormal Protein Misfolding and Aggregation

The accumulation and aggregation of misfolded proteins are hallmark features of many neurodegenerative diseases and are widely regarded as central contributors to disease pathogenesis [52,53]. Protein aggregation arises when incorrectly folded proteins interact abnormally with one another through specific domains, leading to the formation of insoluble complexes [54]. This process often initiates from a small misfolded seed that triggers a cascade of conformational changes in surrounding proteins, converting them into toxic species. Typically, misfolded proteins assemble into β-sheet–rich structures as oligomeric intermediates form during early aggregation stages [52]. These aggregates may accumulate either intracellularly or extracellularly, forming inclusions that are characteristic of different neurodegenerative disorders (Figure 4).

Distinct neurodegenerative diseases are associated with unique protein aggregates. For example, Alzheimer's disease (AD) is characterized by extracellular β-amyloid (Aβ) plaques and intracellular aggregates of hyperphosphorylated tau protein [55]. Parkinson's disease (PD) and Huntington's disease (HD) also involve tau protein abnormalities, while PD and related synucleinopathies are marked by pathological inclusions of α-synuclein. In contrast, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia are commonly associated with aggregates of TAR DNA-binding protein 43 (TDP-43) [56–58]. Amyloid fibrils are large, insoluble structures that assemble into amyloid plaques, whereas amyloid oligomers are smaller, water-soluble species capable of diffusing throughout the brain.

The accumulation of Aβ exerts profound pathological effects, including the excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as the activation of inflammatory pathways, thereby creating a self-perpetuating toxic cycle [59]. These processes disrupt mitochondrial function and impair cognitive processes, ultimately promoting neurodegeneration. To counteract protein misfolding, neurons rely on intricate protein quality-control systems that maintain proteostasis. Molecular chaperones facilitate correct protein folding and promote the degradation of aberrant proteins before they accumulate and exert toxic effects [60]. Given the critical role of these mechanisms in neuronal survival, understanding their regulation during neurodegeneration is of significant therapeutic interest.

Oxidative Stress in Neurodegenerative Disorders

Oxidative stress is now globally recognized as a major contributor to biochemical and biomolecular alterations that underlie neurodegenerative diseases, including AD, multiple sclerosis (MS), ALS, HD, and PD [61–63]. While physiological levels of ROS and RNS play essential roles in neuronal signalling, synaptic plasticity and memory formation, excessive production of these reactive species leads to cellular damage [64–66]. Elevated ROS and RNS levels can damage critical cellular components such as DNA, proteins, and lipids, inducing oxidative stress and triggering neuronal death. Oxidative stress arises when antioxidant defense systems become insufficient or when ROS/RNS production exceeds normal physiological limits. Thus, maintaining a precise balance between oxidants and antioxidants is essential for neuronal integrity and function.

The brain is particularly vulnerable to oxidative stress due to its high oxygen consumption, abundance of polyunsaturated fatty acids and transition metals, and relatively low concentrations of antioxidant molecules such as glutathione [67,68]. Mitochondria represent the

primary intracellular source of ROS generation [69]. During oxygen metabolism, superoxide anions (O_2^-) are produced, which serve as precursors for several highly reactive species, including hydrogen peroxide, hydroxyl radicals, hypochlorous acid, and hydroperoxyl radicals [70].

Within mitochondria, manganese superoxide dismutase converts superoxide into hydrogen peroxide, which can subsequently generate highly reactive hydroxyl radicals through the Fenton reaction [71]. This reaction is accelerated in the presence of transition metals such as iron and copper. Hydroxyl radicals may also be generated via the Haber–Weiss reaction, which involves interactions between superoxide anions and hydrogen peroxide [72].

ROS generation also occurs in peroxisomes during metabolic processes involved in energy production, resulting in the formation of hydrogen peroxide [69,73]. Under normal conditions, catalase effectively regulates hydrogen peroxide levels. Another significant source of ROS is NADPH oxidase (NOX), an enzyme complex that produces superoxide and hydrogen peroxide. NOX enzymes are expressed in microglia, neurons, and astrocytes [74].

The neurovascular unit, composed of neurons, glial cells, and blood vessels, plays a critical role in maintaining brain homeostasis [75]. Accumulating evidence indicates that NOX enzymes are implicated in the pathogenesis of several neurodegenerative disorders, including AD, PD, and HD. Moreover, conditions such as AD and PD are associated with increased activity of xanthine oxidase, further amplifying oxidative damage [76]. ROS and RNS can induce structural modifications in DNA, proteins, and lipids through oxidative and nitrosylation reactions.

In AD patients, extensive oxidative damage has been observed in brain tissues, affecting proteins, nucleic acids, and lipids [59]. Similarly, PD is characterized by elevated levels of oxidative stress biomarkers, including 8-hydroxy-2-deoxyguanosine, 4-hydroxy-2-nonenal (indicative of lipid peroxidation), protein carbonyls, and 3-nitrotyrosine, reflecting protein damage [77]. These oxidative alterations severely impair neuronal function and contribute to the progression of neurodegenerative disorders.

Neuroinflammation and Microglial Activation

Inflammation represents a fundamental defense response of the body against infection, injury, toxins, and other harmful stimuli [78]. Neuroinflammation refers specifically to inflammatory processes occurring within the central nervous system (CNS) and involves complex interactions among multiple cell types [79]. Microglia and astrocytes are the principal mediators of inflammatory responses in the brain [80].

Under physiological conditions, microglia contribute to brain homeostasis by performing essential functions such as debris clearance, synaptic remodeling, pathogen detection, and removal of misfolded proteins [78]. During the early stages of AD, microglia can exert neuroprotective effects by facilitating the clearance of Aβ aggregates [81]. Activated microglia also support astrocyte proliferation, promoting neuronal repair and protection.

Astrocytes undergo marked structural and biochemical changes in response to brain injury, including hypertrophy, increased expression of intermediate filaments, enhanced proliferation, and migration [82,83]. While neuroinflammation initially serves a protective role, chronic or excessive inflammatory responses can be detrimental. Aging, metabolic disorders, and viral infections may promote sustained neuroinflammation, leading to progressive neuronal damage.

A central regulator of neuroinflammation is Nuclear Factor Kappa B (NF-κB), a transcription factor that governs the expression of genes involved in inflammation, apoptosis, cell survival, and neuronal development [78,84]. Activation of NF-κB in microglia leads to increased production of pro-inflammatory mediators, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), interleukins (IL-6 and IL-1), and ROS [85]. These mechanisms are critically involved in the pathophysiology of several neurodegenerative diseases. Overall, neuroinflammation is recognized as a major driving force in disorders such as MS, PD, AD, HD, and ALS, highlighting the importance of targeting inflammatory pathways to prevent or slow neurodegeneration [86].

Mitochondrial Dysfunction in Neurodegenerative Disorders

The brain plays a vital role in regulating essential physiological functions and therefore has exceptionally high energy demands, which are met primarily through oxygen-dependent processes. Approximately 20% of the body's total oxygen consumption is utilized by the brain. A major energy-consuming component is the Na^+/K^+-ATPase, which is essential for maintaining neuronal excitability and signal transmission [87]. Neuronal energy requirements are largely fulfilled through oxidative phosphorylation, which generates adenosine triphosphate (ATP). It is estimated that neurons consume nearly 4.7 billion ATP molecules per second [88,89].

Beyond energy production, mitochondria are involved in critical neuronal processes, including calcium signaling, synaptic transmission, and the regulation of cell survival and apoptosis [90,91]. Mitochondrial health is maintained through dynamic processes such as

biogenesis, fission, fusion, and mitophagy, which collectively ensure the removal of damaged mitochondria and preservation of cellular integrity [59].

Given the limited regenerative capacity of neurons, mitochondrial dysfunction can have severe consequences, leading to neuronal injury and degeneration. Mitochondria generate substantial amounts of ROS due to electron leakage during metabolic processes. Excessive ROS directly damage mitochondrial components, establishing a vicious cycle of oxidative injury [92,93]. ROS can impair iron–sulfur clusters in the electron transport chain, disrupt lipid membranes, and induce damage to mitochondrial DNA and proteins. The mitochondrial inner membrane is particularly susceptible due to its proximity to ROS generation sites [63,66].

Oxidative damage to cellular membranes compromises mitochondrial energy production and disrupts essential cellular functions. Recent studies suggest that damaged mitochondria may initiate inflammatory signaling pathways, further exacerbating neurodegeneration [63,94]. Under stress conditions, mitochondrial DNA can be released extracellularly via vesicle formation, where it acts as a danger-associated molecular pattern, activating immune responses. Numerous studies have demonstrated that mitochondrial abnormalities occur at early stages of neurodegenerative diseases [95,96]. In summary, given the brain's high energy dependence, mitochondrial dysfunction represents a critical contributor to neurodegeneration.

Blood–Brain Barrier (BBB)

The cerebrovascular system includes a highly selective semipermeable interface known as the blood–brain barrier (BBB), which is essential for maintaining CNS homeostasis. Although limited transcellular transport occurs, the adult BBB is primarily composed of capillary endothelial cells connected by adherens junctions and tight junctions, which restrict paracellular diffusion and exhibit minimal pinocytotic activity. Additional cellular components, including pericytes, microglia, and astrocytic end-feet, closely interact with the BBB and contribute to its development and maintenance by regulating endothelial cell migration, proliferation, and vascular architecture [97].

Approximately 20% of the abluminal surface of the BBB is covered by pericytes embedded within the vascular basement membrane. These cells possess contractile proteins that enable them to regulate cerebral blood flow by controlling capillary constriction and dilation. The basement membrane consists of extracellular matrix components produced by endothelial cells and pericytes. Astrocytic end-feet form an extensive network around brain capillaries, enhancing tight junction integrity and preserving BBB structure. Astrocytes also facilitate communication between neurons and endothelial cells, thereby regulating cerebral blood flow in response to neuronal activity. Due to their diverse roles in maintaining CNS homeostasis, synaptic regulation, and neuroprotection, astrocytes are considered key functional units of the CNS. Microglia further contribute to immune surveillance and homeostatic regulation within the brain [98,99]. Exosomes have attracted increasing interest due to their biocompatibility and lipid bilayer structure, which protects their cargo and enables them to traverse biological barriers, including the BBB [100].

Blood–Cerebrospinal Fluid Barrier (B-CSF)

Although disruption of the BBB has long been associated with neurological diseases, impairment of the blood–cerebrospinal fluid (B-CSF) barrier has only recently gained attention. Emerging evidence suggests that the B-CSF barrier plays a significant role in transmitting inflammatory signals from the peripheral circulation to the CNS and contributes to the onset and progression of various neurological disorders [101].

The choroid plexus (CP), located within the lateral, third, and fourth ventricles, consists of a single layer of ciliated epithelial cells supported by connective tissue and fenestrated blood vessels. The CP is responsible for the production and secretion of cerebrospinal fluid (CSF). High vascular permeability allows CP epithelial cells to generate CSF from blood plasma. The continuous transport of sodium, chloride, and bicarbonate ions into the ventricular system through ion channels and co-transporters establishes an osmotic gradient that drives water movement across the B-CSF barrier.

Alzheimer's disease (AD), the most prevalent neurodegenerative disorder, is characterized by progressive cognitive decline, synaptic loss, and dementia. The accumulation of β-amyloid peptides in brain tissue is a central pathological feature of AD. The CP and B-CSF barrier play critical roles in facilitating the clearance of β-amyloid from the brain. Megalin, a multi-ligand endocytic receptor, has been shown to mediate β-amyloid transport from the CSF across the B-CSF barrier, thereby contributing to amyloid clearance [102].

In multiple sclerosis (MS), white matter lesions are characterized by extensive infiltration of T and B lymphocytes, as well as macrophages. The CNS barriers permit immune cell entry into the brain, with the CP serving as a key gateway for lymphocyte migration into the CSF. Notably, $CD4^+$ T-cells regulate immune cell trafficking across the B-CSF barrier through the production of interferon-γ (IFN-γ). This signaling cascade induces the upregulation of adhesion molecules such as VCAM-1 and ICAM-1, facilitating immune cell infiltration [103,104].

Blood–Tumor Barrier (BTB)

The blood–tumor barrier (BTB) forms as a consequence of BBB disruption during tumor progression. Although the BTB exhibits higher permeability than the intact BBB, heterogeneous blood flow and variable permeability limit effective drug accumulation within brain tumors [105]. Key features of the BTB include abnormal pericyte distribution, loss of astrocytic end-feet, disruption of neuronal connectivity, and compromised BBB integrity. These alterations restrict the efficacy of chemotherapeutic agents and contribute to tumor progression in both primary and metastatic brain tumors [106].

The structural complexity of the BTB may prevent therapeutic agents from adequately penetrating the tumor microenvironment. Additionally, irregular permeability within the BTB leads to uneven drug distribution, further limiting treatment effectiveness. Enhancing BTB permeability is therefore critical for improving drug delivery to brain tumors. Differences between the BTB in primary CNS tumors and brain metastases, such as those arising from breast cancer, may help explain variations in permeability. In mouse models of breast cancer brain metastases, vascular density has been reported to be 40–80% lower than that observed in normal brain tissue, highlighting significant alterations in tumor-associated vasculature [107,108].

Neuroprotective Effects of Abresham (Bombyx mori Silk)

Abresham, commonly known as silk cocoon or silk fiber, is an animal-origin Unani drug obtained from the cocoon of Bombyx mori belonging to the family Bombycidae [109]. In classical Unani literature, Abresham has been extensively described as a potent Muqawwi-e-Dimagh (brain tonic) and Muqawwi-e-Qalb (cardiotonic), indicating its role in strengthening vital organs and faculties [110]. Eminent Unani scholars such as Ibn Sina and Najmul Ghani have highlighted its therapeutic value in neuropsychiatric disorders associated with emotional instability, nervous debility and cognitive weakness [111]. The temperament (Mizaj) of Abresham is described as Hot and Moist (Haar Ratab), usually of mild to moderate degree, which pharmacologically translates into its nourishing and stabilizing influence on nervous tissue, improvement of cerebral circulation, and enhancement of neuronal vitality [112].

Figure 5: Abresham

From a therapeutic perspective, Abresham exhibits multiple actions including Mufarreh (exhilarant), Musakkin-e-Asab (sedative to nerves), and Dafi-e-Tashannuj (anticonvulsant) [113]. Owing to these actions, it has been traditionally prescribed in conditions such as anxiety, melancholia, insomnia, epilepsy, palpitations of neurogenic origin and memory impairment [114]. Abresham is a key constituent of several classical Unani formulations (Figure 5), notably Khamira Abresham Sada, Khamira Abresham Jawahar Wala, Majoon Falasfa and Dawa-ul-Misk Motadil, which are widely used for mental fatigue, stress-related disorders and nervous exhaustion [115]. The usual dose of Abresham powder ranges from 250 to 500 mg, while formulation-specific dosing is followed as per Unani pharmacopeial standards [116].

Biochemically, Abresham is rich in structural and bioactive proteins, primarily fibroin and sericin, which contribute to its therapeutic potential [117]. Sericin, in particular, has been reported to possess antioxidant, anti-inflammatory and cytoprotective properties, while fibroin-derived peptides have demonstrated neurotrophic and membrane-stabilizing effects [118]. The amino acid composition of Abresham is dominated by glycine, alanine, and serine, which are known to play crucial roles

in inhibitory neurotransmission and neuronal homeostasis [119]. In modern scientific terms, the neuroprotective effects of Abresham can be attributed to its ability to reduce oxidative stress, stabilize neuronal membranes, improve mitochondrial function, modulate GABAergic neurotransmission, and attenuate neuroinflammatory pathways, thereby supporting neuronal survival and functional integrity in preclinical models [120].

The neuroprotective potential of Abresham (Bombyx mori silk) is primarily attributed to its unique biochemical composition, which is dominated by high-molecular-weight structural proteins and bioactive peptides that exert multi-level neuroprotective actions [121]. The two principal protein components of silk, fibroin and sericin, play a central role in mediating its protective effects on neuronal tissues. Fibroin is a highly stable, biocompatible protein rich in glycine, alanine, and serine residues, which contribute to its ability to support neuronal membrane integrity and synaptic stability. These amino acids are known to participate in inhibitory neurotransmission and neuromodulation, particularly through glycinergic and GABAergic pathways, thereby reducing neuronal hyperexcitability and excitotoxic damage [122].

Sericin, the second major protein constituent of Abresham, has been extensively reported to possess superoxide dismutase, further strengthening neuronal defense mechanisms [113]. Collectively, these biochemical attributes position Abresham as a neurotrophic and neurostabilizing agent, capable of protecting neurons against oxidative stress, inflammation, excitotoxicity and metabolic dysfunction in preclinical models [114].

Neuroprotective Effects of Ustukhuddus (Lavandula stoechas)

Ustukhuddus, botanically identified as Lavandula stoechas Linn. and belonging to the family Lamiaceae, is one of the most revered plant-based Unani drugs for disorders of the brain and nervous system [115]. potent antioxidant, anti-inflammatory and cytoprotective properties, all of which are critical for neuroprotection [109]. Sericin contains abundant hydroxyl-containing amino acids that effectively scavenge reactive oxygen species (ROS) and reduce lipid peroxidation in neuronal membranes. Since oxidative stress is a key contributor to neurodegenerative processes such as Alzheimer's disease, Parkinson's disease, and ischemic brain injury, the antioxidant action of sericin provides a strong mechanistic basis for the neuroprotective role of Abresham [110]. Additionally, sericin has been shown to modulate inflammatory signaling pathways by downregulating pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukins, thereby attenuating neuroinflammation-induced neuronal damage [111].

At the cellular level, Abresham-derived peptides have demonstrated the ability to preserve mitochondrial function, which is essential for neuronal survival and energy metabolism [112]. Mitochondrial dysfunction leads to excessive ROS generation and apoptotic signaling; therefore, the mitochondrial stabilizing effect of silk proteins contributes significantly to their neuroprotective efficacy. Furthermore, trace elements present in Abresham, including zinc and copper, act as cofactors for endogenous antioxidant enzymes such as

Commonly known as French or Spanish lavender, the flowering tops of the plant are used for medicinal purposes. Classical Unani texts refer to Ustukhuddus as "Jaroob-e-Dimagh", meaning the "broom of the brain," emphasizing its unique ability to cleanse the central nervous system of morbid humors, particularly phlegmatic and melancholic derangements that underlie neurological and psychiatric illnesses [116]. Its temperament is described as Hot and Dry (Haar Yabis), generally of second degree, which correlates with its stimulating, resolvent, and detoxifying effects on cerebral functions [117].

Figure 6: Ustukhuddus

Therapeutically, Ustukhuddus exhibits a wide range of actions including Muqawwi-e-Dimagh (brain tonic), Munaffis-e-Balgham (phlegm expellant), Mufarreh (antidepressant), Musakkin-e-Asab (anxiolytic), and Dafi-e-Tashannuj (anticonvulsant) [118]. These actions justify its extensive use in the management of epilepsy, chronic headache, migraine, depression, anxiety, insomnia and memory-related disorders. Ustukhuddus is an important ingredient of several classical Unani formulations (Figure 6) such as Itrifal Ustukhuddus, Majoon Najah, Arq Ustukhuddus, Majoon Baladur and Dawa-ul-Misk, which are prescribed to improve cognitive functions, emotional balance and neurological resilience [119]. The commonly recommended dose ranges from 1-3 g in powdered form or 5-10 g when administered as a decoction, while the essential oil is used in minimal quantities in modern practice [120].

Phytochemically, Ustukhuddus is rich in volatile and non-volatile constituents, including linalool, camphor, 1,8-cineole, flavonoids and phenolic acids, which collectively contribute to its neuropharmacological activity [121]. Modern experimental studies have demonstrated that these compounds exert potent antioxidant, anti-inflammatory, anxiolytic, antidepressant, and anticonvulsant effects. Mechanistically, Ustukhuddus has been shown to modulate GABAergic and cholinergic neurotransmission, reduce oxidative stress-induced neuronal damage, suppress neuroinflammatory mediators and enhance cognitive performance in animal models [122]. These findings provide strong scientific validation to its traditional Unani use as a neuroprotective and neurorestorative agent.

The neuroprotective activity of Ustukhuddus (Lavandula stoechas) is closely associated with its rich phytochemical composition, particularly its volatile constituents and phenolic compounds, which exert diverse pharmacological effects on the central nervous system [109]. Among these, linalool, camphor, and 1,8-cineole are the most prominent bioactive molecules and have been widely investigated for their neuromodulatory and neuroprotective properties. Linalool, a monoterpene alcohol, has demonstrated strong anxiolytic, antidepressant, and anticonvulsant activities, primarily through modulation of GABAA_AA receptors and inhibition of glutamate-mediated excitatory neurotransmission [110]. By reducing neuronal hyperexcitability and calcium influx, linalool effectively protects neurons from excitotoxic injury.

Camphor and 1,8-cineole contribute significantly to the anti-inflammatory and antioxidant actions of Ustukhuddus. These compounds have been shown to inhibit the activation of microglial cells and suppress the release of pro-inflammatory cytokines, thereby reducing neuroinflammation, which is a central pathological feature of many neurodegenerative disorders [111]. Additionally, the flavonoids and phenolic acids present in Ustukhuddus possess strong free-radical scavenging properties, enabling them to neutralize ROS and prevent oxidative damage to neuronal lipids, proteins and DNA [112]. This antioxidant defense mechanism is crucial for maintaining neuronal integrity and cognitive function under pathological conditions.

Experimental studies have further demonstrated that extracts and essential oils of Ustukhuddus enhance cognitive performance and memory retention by modulating cholinergic neurotransmission and increasing cerebral blood flow [113]. The improvement in cholinergic function is particularly relevant in neurodegenerative conditions characterized by acetylcholine deficiency, such as; Alzheimer's disease. Moreover, Ustukhuddus has shown protective effects against seizure-induced neuronal damage in animal models, supporting its traditional Unani use in epilepsy [114]. Through the combined actions of neurotransmitter modulation, oxidative stress reduction and inflammation control, Ustukhuddus acts as a multifunctional

neuroprotective agent with both preventive and therapeutic potential [115–122].

CONCLUSION

Neurodegenerative disorders arise from complex and interconnected molecular pathways involving oxidative stress, protein misfolding, mitochondrial dysfunction, neuroinflammation, and barrier impairment. Single-target pharmacotherapies have shown limited success in modifying disease progression, underscoring the need for integrative and multi-mechanistic approaches. Abresham and Ustukhuddus, two prominent Unani neuroprotective agents, demonstrate complementary mechanisms that address key pathological processes underlying neurodegeneration. Abresham supports neuronal survival by enhancing antioxidant defenses, preserving mitochondrial integrity and stabilizing neuronal membranes, while Ustukhuddus modulates neurotransmitter systems, reduces neuroinflammatory responses and improves cognitive function. Together, these agents align with modern neuropharmacological principles of multi-target intervention. Although preclinical evidence is encouraging, further standardization, mechanistic validation and well-designed clinical studies are required to establish their therapeutic efficacy and translational relevance. Integrating traditional Unani medicine with contemporary neuroscience may facilitate the development of safe, effective and holistic neuroprotective strategies for managing neurodegenerative disorders.

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