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Extracellular matrix, amyloid fibrils and infections. Is there a new approach to combat amyloidosis?

Anna Lia Asti
https://orcid.org/0000-0002-5511-1272
University of Bologna
https://ror.org/01111rn36
Corresponding author: annalia.asti@unibo.it

Eva Negri
https://orcid.org/0000-0002-5511-1272
University of Bologna
https://ror.org/01111rn36

Stefania Preda
https://orcid.org/0000-0002-5511-1272
University of Pavia
https://ror.org/00s6t1f81

Linia Patel
https://orcid.org/0000-0002-5511-1272
University of Milan
https://ror.org/00wjc7c48

Carla Colombani
https://orcid.org/0000-0002-5511-1272
University of Milan
https://ror.org/00wjc7c48

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ABSTRACT

Recent studies suggest that amyloid is an ancient, highly conserved effector molecule of innate immunity. This set ofiology model characterises amyloid deposition as an innate, chronic immune response that normally protects against microbial infection in the brain. Nonetheless, the fact that the amyloid is functionless remains widely held, despite evidence that the human Aß sequence is conserved across most vertebrate species, up to at least 400 million years. Growing amyloid fibrils capture, agglutinate, and finally entrap microbes in a resistant network of amyloid. Glycosaminoglycans (GAGs), which are major components of the extracellular matrix (ECM), are carbohydrate polymers. They are usually attached to ECM proteins to form proteoglycans and appear to enhance amyloid fibril formation. In general, GAGs are thought to facilitate amyloid fibril formation and stabilise amyloid aggregates. The antimicrobial protection hypothesis reveals how an increased brain microbial burden may directly exacerbate fibril deposition, inflammation and neurodegenerative disease progression, such as Alzheimer's disease. Actually, therapeutics are severely limited, and no interventions are available to reverse the course of these diseases.

Introduction

A key player in the pathogenesis of Amyloidosis and Alzheimer's disease (AD) is the amyloid peptide, which can aggregate into fibrils that constitute the main component of amyloid plaques. Recent data have shown that amyloid fibril formation not only results in toxic aggregates but

also provides biologically functional molecules; such amyloids have been identified on the surface of fungi and bacteria [1]. The amyloid fibril ultrastructure is characterised by fibres 7–12 nm in diameter and of indeterminate length, since fibril assembly is associated with a β-sheet conformation, as observed by X-ray diffraction [2], which describes patterns with a high content of antiparallel cross-β pleated sheets as the secondary molecular structure. These fibrils are different in the various pathologies, but exhibit several common physicochemical features: fibrillar morphology, predominantly β-sheet secondary structure, affinity for binding thioflavin S, apple-green birefringence on Congo Red, very high stability, and protease-resistance [2]; Transmission Electron Microscopy (TEM) of the fibrils revealed a superficial twist and two protofibrils [3] (Figure 1). The causative agents of these highly complex diseases, which are often the result of multiple genetic and environmental factors, remain unknown, and the molecular basis underlying their pathogenesis has yet to be fully clarified [4]. Data from the literature indicate that bacterial endotoxins may be involved in the inflammatory and pathological processes associated with amyloidosis and Alzheimer's disease (AD). Amyloidosis is a diverse group of diseases that have in common the extracellular deposition of fibrils composed of a protein, the amyloid fibrils [5]. The long-term effects of persistent or lifelong repeated infections may differ across hosts, depending on their general health, pharmacological treatments, genetic background (Apolipoprotein E, APOE 4, enhances the expression of inflammatory mediators [6]), and concurrent diseases. The incidence increases with age and has rare, genetic, autosomal-dominant hereditary forms. Improved diagnostic tools have shown that amyloidosis is common in older populations [7]; for example, AA amyloidosis is the most common form in developing countries and can complicate longstanding infections, while AL amyloidosis affects men more than women and has the highest incidence and an estimated prevalence of 30,000 to 45,000 cases in the US and European Union. In a population autopsy study of people experiencing heart failure (8), wild-type transthyretin (wtTTR) was found in 19%, while ATTR was found in 13% of people [8]. Cardiac amyloidosis is considered a rare disease, but improvements in imaging techniques have enabled recognition that some patients previously diagnosed with other diseases were affected by cardiac amyloidosis; the two main forms are AL and ATTR amyloidosis.

Amyloid-β (Aβ) protein is the major component of senile plaques in Alzheimer's disease (AD) patients; bacterial endotoxin may also promote the production or aggregation of Aβ, [9] Tau, and α-synuclein to give different neurodegenerative diseases. Aβ is an ancient, conserved effector molecule of innate immunity, an antimicrobial peptide (AMP) [10]. Physiologically produced and circulating Aβ may serve these functions because it may initially be beneficial at the beginning of an infection, as an AMP helps contain the original pathogen [11]. Persistent sub-acute CNS infection may drive chronic activation of the innate immune system, and the resulting AD pathology may be mediated by a response of the innate immune system to a perceived infection [9].

Neuroinflammation is a key process that helps protect the brain from pathogens; prolonged inflammation can lead to pathological states such as Parkinson's disease (PD), Alzheimer's disease (AD), and other neurodegenerative disorders [12,13]. In addition, periodontal polybacterial disorders, primarily caused by Gram-negative bacteria [14], may play a role. The infectious agents involved in the pathogenesis of AD are also linked to atherosclerosis, cardio- and cerebrovascular disorders, chronic lung diseases, inflammatory bowel diseases, and various neurological and neuropsychiatric disorders [15]. Epidemiological studies have confirmed these data [16]. Treatments offer only minimal relief of symptoms; therapeutic efforts have focused on developing drugs that can suppress the inflammatory response.

This Review aims to investigate the relationship between the extracellular matrix (ECM), amyloid protein, infections and consequent diseases. Lipopolysaccharide (LPS) promotes *A*β aggregation [9]. At the same time, Glycosaminoglycans (GAGs) may exert a pathogenic and/or stabilising role during fibrillogenesis *in vivo*, and Heparan sulphate (HS) proteoglycans appear to represent the major GAG-containing components involved. It remains to be determined to what extent the ECM contributes to the formation and maintenance of amyloid fibrils *in vivo*.

ECM and GAGs in amyloid fibril formation

ECM provides a three-dimensional (3D) structure that regulates cell-cell adhesion and signals that direct cellular processes leading to tissue development [6]. ECM proteins are large and multifunctional molecules; they are composed of many domains that frequently are repeated within the same molecules or show phylogenetic links to domains in other proteins. ECM proteins evolved with the emergence of multicellular organisms approximately 700 million years ago, and many of them have been surprisingly well preserved throughout evolution [17]. The components of ECM are produced intracellularly by resident cells and secreted into the ECM via exocytosis; once secreted, they aggregate with the existing matrix. Cells attach to the ECM through integrin receptors, and engagement of these receptors initiates multiple intracellular signalling cascades that regulate cell survival, proliferation, and differentiation [17]. The ECM can influence cell shape, proliferation, motility, differentiation, growth factor responsiveness, and gene expression. The composition of ECM fibronectin and laminin determines which integrin receptors are involved in binding and impacts the signalling that leads to tissue formation [18]. Continuous cross-talk between cells and the surrounding matrix directs critical processes in tissue development and the maintenance of the cellular phenotype. The transformation from the compact form to the extended fibrillar form of fibronectin, a highly regulated process termed fibrillogenesis, requires the application of mechanical forces generated by cells [16,17].

ECM molecules influence β-amyloid precursor protein (APP) biogenesis, including the generation of amyloidogenic fragments containing the Aβ peptide. APP can bind to various molecules in the cellular environment, such as ECM components, laminin, and HS proteoglycans [18]. Interactions with the extracellular environment may result in proteolytic cleavage and binding to matrix components such as GAGs and collagen, which serve as scaffolds and facilitate aggregation and fibril buildup. These effects could be due to a direct regulation of APP expression by ECM signalling molecules and/or to a modulation of APP processing by the ECM-related cytoskeletal [19]. In general, GAGs are thought to facilitate amyloid fibril formation and stabilise the amyloid aggregates [20].

GAGs can both promote misfolding of polypeptides into pro-amyloidogenic intermediates rich in β-sheets and act as a structural template for self-assembly; they can also enhance lateral aggregation of small fibrils, conferring insolubility and protection from proteolysis. GAGs could even play a protective role by converting proteotoxic soluble oligomers into less toxic amyloid fibrils and related cross-β-sheet aggregates. Proteins containing exposed clusters of basic residues may undergo amyloid-like aggregation in the presence of GAGs [20]. Ultrastructural association of GAG-positive staining with amyloid is well established, and colocalization with different types of amyloid fibrils has been described; they may exert a pathogenic and/or stabilising role during fibrillogenesis *in vivo*.

Because multicellularity evolved independently in different multicellular lineages, the composition of ECM varies between multicellular structures; the different types of proteoglycans found within the ECM are HS, chondroitin sulfates (CS), keratan sulfates (KS) [18].

Many cell types contribute to the development of the various ECM types found across a wide range of tissues, such as fibroblasts, the most common cell type in connective tissue ECM. Although some ECM components appear to be ubiquitous in amyloid, other components are limited to specific pathological scenarios [21].

Infection and inflammatory triggers

The reactive, soluble ECM proteoglycans, via competitive inhibition, are very effective at preventing bacterial binding to membrane proteoglycans; soluble proteoglycans act as nonspecific anti-adherence factors, blocking bacterial access to host cells. It is well established that all these processes are implicated in amyloidosis and AD, suggesting that bacteria or bacterial debris may be among several factors that trigger the cascade of events leading to chronic inflammation and amyloid deposition [22]. Many studies have reported alterations in the expression profiles of ECM proteins in early-onset AD [18].

Bacterial peptidoglycan has a variety of biological actions in mammals [23]; it is an inflammatory

cytokine inducer, activates the complement classic pathway, affects vascular permeability, generates nitric oxide (NO), induces proteoglycan synthesis and apoptosis, and is amyloidogenic. Bacteria possess high-affinity receptors to bind proteoglycans, and the degree of their virulence depends on their ability to bind sulphated proteoglycans; joints with cartilage degeneration may show fibrillation as an indication of proteoglycan loss [21]. The burden of infectious agents has been linked to the development of amyloidosis and AD in sporadic cases. In AD, this appears to be substantially due to microglial activation [23], long-lasting inflammation, neuronal alterations, oxidative stress, and amyloid-beta accumulation, as well as to a direct effect of infectious agents [10].

For example, chronic spirochaetal infection can cause slowly progressive dementia, cortical atrophy and amyloid deposition in the atrophic form of general paresis [22]; there is a statistically significant association between various types of spirochetes, including the periodontal pathogens *Treponemas* and *Borrelia burgdorferi*, *Chlamydophila pneumoniae*, *Herpes simplex* virus type-1 (HSV-1) IgM levels and AD. It has been observed that Gram-negative bacteria and their endotoxin (LPS) are involved in intestinal dysbiosis in amyloid fibril formation [9]. The outcome of infection is determined by genetic predisposition, the virulence and biology of the infecting agent, and various environmental factors [10]. The question remains open as to whether the increased accumulation of GAGs in amyloid plaques may be due to a parallel response, together with ß-amyloid, to an unknown amyloidogenic stimulus, most likely inflammation [22], or to secondary deposition of unusual proteins.

Inflammatory responses to HIV infection

It has been postulated that inflammatory responses to HIV infection of the brain parenchyma can promote overproduction and accumulation of APP. The observed increase in APP may be due to cytokine production by microglia and astrocytes, secondary to their activation by a generalised inflammatory response against the virus in the brain [24]. The incidence of amyloid deposition is increased in the era of highly active antiretroviral therapy (HAART), despite reductions in viral burden, decreased inflammatory markers, and decreased morbidity related to HIV infection; this is most pronounced in older patients and may be mediated by inhibition of the insulin-degrading enzyme [24].

Previous studies reported that levels of Aβ deposited in the brain correlate with brain HIV viral load; however, other studies found no correlation between cognitive deficits and Aβ levels [25]. The observation of low Aβ1–42 levels in patients with Tuberculous meningitis (TBM) is of potential interest. It should be interpreted in the context of the recent discovery of a possible antimicrobial role (AMP) of amyloid-beta (10) and of a hypothetical infectious "trigger" for AD.

It has been shown that α-synuclein [26] and Aβ fibrils are associated with neurological diseases and enhance HIV-1 entry and replication in human T cells, macrophages, and microglia. In addition, findings show that HIV-1 and brain amyloids may engage in a detrimental interplay that accelerates the development of neurological disorders [26].

Amyloid classification

The hallmark of amyloidosis is the extracellular deposits of amyloid fibrils (**Figures 1** and **2**) in virtually any organ, accompanied by cellular degeneration and organ failure. The diagnosis of amyloidosis requires histopathologic identification of an amyloid deposit in the affected tissue [27]. After staining histological sections with Congo red, the amyloid deposits show apple green birefringence under the polarised light microscope. Misfolded proteins are degraded intracellularly in proteasomes or extracellularly by macrophages [28].

All forms of amyloid contain the pentraxin glycoprotein amyloid P-component (AP), which is directly bound to the protein fibrils [29]. Serum amyloid-P component (SAP) contributes to the stabilisation of amyloid and proteoglycans in their role in fibrillization. SAP is an uncommon amyloid signature protein in animal amyloidosis, although it is frequently detected in human amyloidosis [20]. In fact, SAP colocalises with primate amyloid but is not detected in canine or feline amyloidosis. ApoE is yet another extrafibrillar component detected in all amyloids subjected to study. It has

been proposed that ApoE acts as a "molecular chaperone," possibly serving as a prerequisite for fibrillogenesis [29]. For classification, the capital letter A for amyloid is followed by the protein designation [30]. At present, 36 proteins are known to be amyloidogenic; 10 of these are significant in veterinary medicine [30].

Amyloid-ß (Aß)

Amyloid-ß (Aß) protein fragment (**Figures 1** and **2**) is the major component of senile plaques found in the brains of patients with AD. This peptide is cleaved from a larger protein, the amyloid-ß protein precursor (AßPP), which is a ubiquitously expressed transmembrane glycoprotein [31]. Amyloid results from abnormal folding of proteins, which are deposited as fibrils (**Figures 1** and **2**) in extracellular tissues and disrupt normal function. Major secreted forms of APP are generated by proteolytic cleavage at the cell surface, then enter the extracellular space, and are eventually incorporated into the ECM; the biological functions of Aß peptide could be regulated by complexing with ECM molecules. Abnormalities in any ECM component or its integrin receptor could underlie some of the alterations observed in AD [32]. Authors reported that ECM components alter APP content and COOH-terminal fragments containing the Aß peptide levels in both fibroblasts and neuronal cells [33].

Multiple physiological roles for Aβ have been proposed, including regulation of cholesterol transport, protection against oxidative stress, and activation of key kinases [33]. Aβ is the most studied form of senile amyloidosis.

The neurofibrillary tangle (NFT) is an intracellular form of amyloid, whereas all other types of amyloidosis are extracellular. The Aβ form of amyloid is associated with cerebral amyloid angiopathy in AD in humans and with vascular deposits (CAA) in the canine brain, mimicking human AD pathology and cognitive impairment [20]. The study by Bowery [34] demonstrated the neurodegenerative effects of tetanus toxin in rats, and a growing body of literature suggests that CNS infections may act as cofactors in the development of neurodegenerative diseases [35]. In fact, chronic infusion of LPS, the outer cell wall component of Gram-negative bacteria (**Figure 3**), into the fourth ventricle of rats reproduces many of the inflammatory and pathological features observed in the brains of AD patients. Aß has the capacity to associate with lipid bilayers of bacterial cell membranes (**Figure 3**) and to exert antimicro-

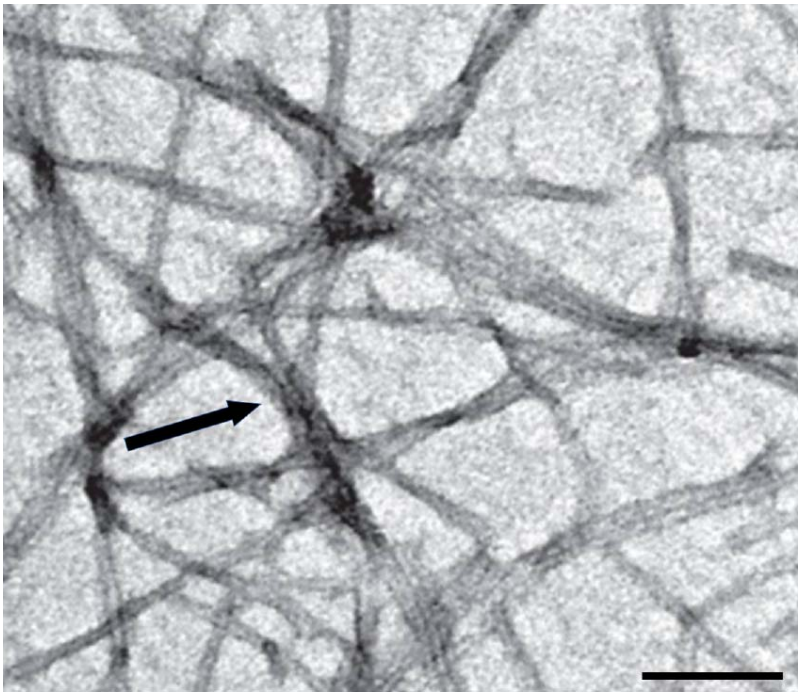

Figure 1. Transmission Electron Microscopy (TEM). The picture shows amyloid fibrils with the classical β-sheet structure (arrow) and of indeterminate length. Bar = 1 µm.

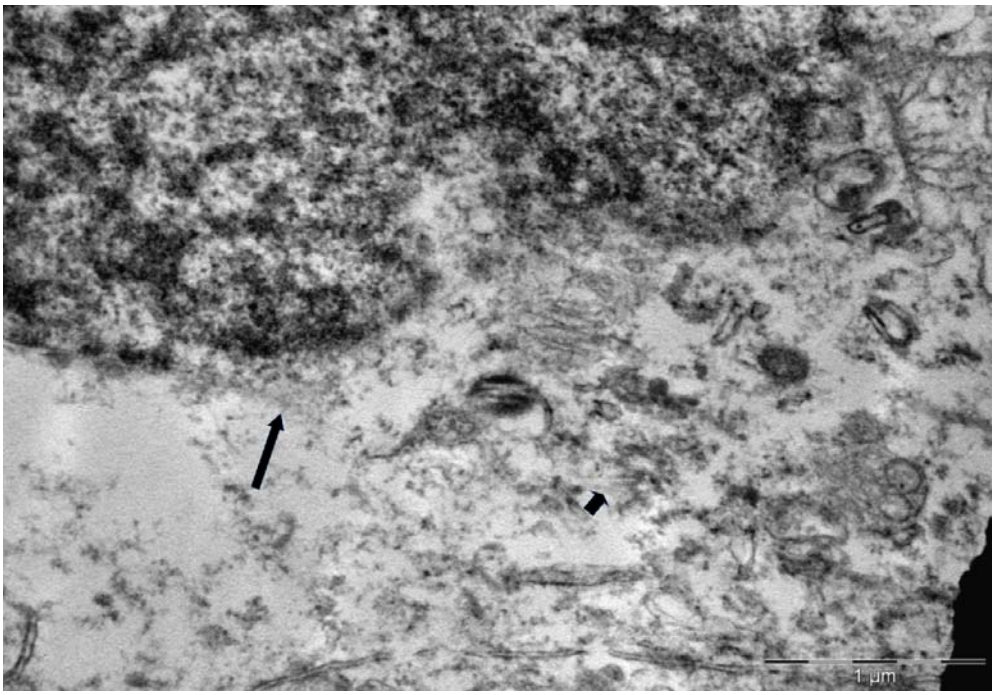

Figure 2. Transmission electron microscopy (TEM). The picture shows SH-SY5Y cells co-incubated with Aβ1–42. Fibrils are detectable near the nucleus (arrow) and in the cell cytoplasm (arrowhead); scattered fibrils are also visible. Bar = 1 µm.

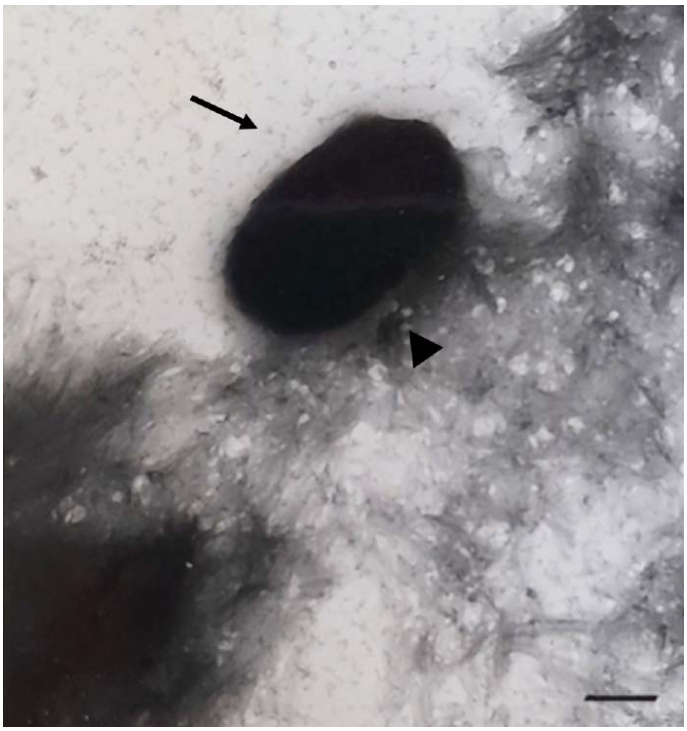

Figure 3. Transmission electron microscopy (TEM). The picture shows the interaction between an Aβ fragment and a viable, intact bacterium, *Escherichia coli* (arrow). The capacity to associate with lipid bilayers is considered a defining feature of AMPs, and these peptides usually enhance their antimicrobial activity by permeabilising membranes. Few short irregular filaments are closely in contact with the bacterial wall (arrowhead); in the background, scattered filaments. The image was obtained using the negative-stain technique. Bar = 500 nm.

bial activity by membrane permeabilisation and alterations in calcium homeostasis [10]. An infectious origin of AD is consistent with recent observations showing that Aß belongs to the group of AMPs [10], potent, broad-spectrum bactericides targeting Gram-negative and Gram-positive bacteria, enveloped viruses, fungi, and protozoans. Aβ in mice and rats differs from human Aβ by three amino acids and does not form amyloid deposits in their brains [36].

Secondary amyloidosis (AA)

The precursor protein serum amyloid A protein (SAA) is an acute-phase protein synthesised in the liver in response to cytokines. The function of SAA in inflammation has not been fully determined, but it is known that SAA binds to high-density lipoprotein (HDL), which subsequently binds endotoxin [37]. Although hepatocytes mainly synthesise acute-phase SAA, extrahepatic SAA expression and production have been reported in several species, including humans and animals. The efficiency with which SAA is converted into amyloids, or the rate at which amyloid deposits are turned over within tissues, may differ from patient to patient. However, neither mechanism has been elucidated [38]. Although for reasons that are not known, amyloidosis occurs only in a small proportion of patients with chronic inflammatory disorders, the most frequent underlying disorder is inflammatory arthritis [38].

The role of ECM in amyloidogenesis has been analysed *in vitro*, with an increase in the formation of β-sheet structure of SAA protein being associated with binding to HS [8]; biochemical methods can detect an increase of HS or CS/DS, in laminin and collagen type IV in amyloid fibrils in the human AA [39].

Previous biochemical studies demonstrated total GAG amounts ranging from 3 to 15 times higher in AL amyloid fibrils than in AA amyloid fibrils. The present finding of relatively weak immunoreactivity for GAGs in AA-type deposits is thus consistent with reports in the literature, in which the immunoreactivity for laminin and collagen type IV is much stronger than that for HS or CS [39].

Experimental studies have shown that SAA can be transmitted orally [40]; horizontal transmission between animals has been reported, with amyloid protein deposition associated with a chronic inflammatory condition [41]. The precursor proteins in amyloid fibrils may be amyloidogenic mutants, as in some familial amyloidosis, whereas other precursors are normal wild-type proteins [42]. Several studies on experimentally induced amyloidosis performed in domestic ducks [41], hamsters [42], rabbits [43], mice [44] and pig [30] have shown that different bacteria, following repeated inoculations, may produce histologic amyloidotic changes in spleen, liver, and kidney that resemble the chronic lesions seen in man [13], and that are probably due to the continuous septic conditions.

Reducing inflammation can help reduce amyloid precursor levels. The standard treatment aims to resolve the underlying inflammatory conditions, such as rheumatoid arthritis and chronic infections [38]. Treatment was undertaken to suppress the underlying inflammatory disease and reduce SAA concentration as much as possible.

AL-amyloid protein

AL is generated following overproduction of immunoglobulin light chains (LCs) associated with immunocyte dyscrasia. In this form of amyloidosis, plasma cells produce excessive quantities of LCs that are resistant to complete enzymatic degradation and are susceptible to forming insoluble fibrils.

The AL form of amyloid can contain complete LCS, the NH_2-terminus portion or both. Immunoglobulin-secreting cells, B lymphocytes, and plasma cells are associated with the deposition of AL-amyloid [45]. In humans, AL is the most common form of systemic amyloidosis; the pathogenesis of some systemic amyloidosis, such as AL and wild-type β2 microglobulin amyloidosis, involves increased plasma concentrations of the parent protein [46,47].

The disease is progressive and, accordingly, early diagnosis is vital to prevent irreversible organ damage, of which cardiac damage and renal damage predominate.

The LC protein, unlike most proteins, does not adopt an α-helical conformation; instead, it misfolds into a β-pleated sheet. An increase in serum levels of free LCs (FLCs) precedes the development of AL amyloidosis by many years. This

insoluble protein deposits in tissues and interferes with organ function [48]; AL amyloidosis progresses much more rapidly than other forms of amyloidosis. Symptoms depend on the organ involvement, ranging from heart failure with preserved ejection fraction, nephrotic syndrome, organomegaly to peripheral neuropathies and unspecific symptoms such as fatigue, asthenia and body weight loss [39].

Alterations also involve intrinsic components of the ECM such as matrisome proteins, proteoglycans and GAGs, enzymes and constituents of the basal lamina. In early disease stages, ECM changes allow the organ to adapt to pathological stimuli, but eventually become detrimental and contribute to the pathogenesis of heart failure [39].

Amyloid fibrils are interlocked with physiological fibrous matrix proteins and alter the properties of the ECM in an unconventional manner [49].

Several lines of evidence indicate that the intrinsic proteolytic activity of the ECM is intensified in amyloid-affected organs, independent of cell-mediated inflammation [39].

Indeed, growing evidence shows that specific ECM components, such as collagen and HSPGs, which are consistently increased in amyloid-positive tissues, can modulate protein misfolding and promote fibrillogenesis.

In the literature, only a few studies report correlations between infections and AL amyloidosis. HIV antigens act like superantigens and stimulate B cell proliferation, determining immunoglobulin production; on the other hand, HIV infection causes CD4+ T cell depletion, which induces immunodeficiency. Immunoglobulins can misfold and accumulate as amyloid fibrils, leading to amyloidosis; moreover, some studies have correlated monoclonal proliferation of plasma cells with HIV [50].

Transthyretin (ATTR) and wild type (wtATTR)

TTR is a plasma transport protein, mainly produced in the liver, that carries the thyroid hormone thyroxine and the retinol-binding protein bound to retinol in plasma and cerebrospinal fluid. Plasma TTR is also negatively affected by the acute-phase response, which is often associated with malnutrition. Amyloid TTR (ATTR) is among the most common forms of amyloidosis in human pathology and was previously known as “senile systemic amyloidosis” because the amyloid fibrils are mainly observed in elderly patients. The underlying mechanism for TTR instability is TTR gene mutations that destabilise the TTR structure and are associated with hereditary forms of ATTR amyloidosis [52], as well as the non-genetic form, wild-type (wtTTR) [52].

ATTR fibrils can accumulate in multiple organs and systems, including the heart, kidneys, and peripheral nervous system; patients with the hereditary form may present with polyneuropathy or cardiomyopathy [51].

The diagnosis is made by specialised genetic tests, nerve conduction study and advanced cardiac imaging [52]. It is crucial to identify the initial symptoms because ATTR is a debilitating disease. Myocardial inflammation is present in approximately one-third of all patients with ATTR-CM (amyloid cardiomyopathy). ATTR-CM [53,54] is characterised by increased inflammation and an imbalance in ECM homeostasis, with ECM degradation prevailing over synthesis. ECM homeostasis depends on the equilibrium between protein degradation and synthesis, respectively mediated by Matrix Metalloproteinases (MMPs) and their inhibitors (TIMPs). The ECM remodelling biomarkers [52] increased as ECM degradation prevailed over ECM synthesis. These changes create a complex environment in which amyloid deposition likely initiates inflammation and ECM remodelling, which then feed on each other to form a vicious cycle [52].

Activation of the innate immune system may be the primary inflammatory response in ATTR-CM, whereas the adaptive immune system may play only a subordinate role [53].

Tau

Tau protein is an important protein that stabilises the cytoskeleton of neurons. It belongs to the microtubule-associated protein family and can effectively stabilise microtubules. The normal function of Tau is essential for neuronal transport and synaptic structure, but if the process occurs abnormally, Tau becomes hyperphosphorylated (p-tau). P-tau aggregates very easily and forms neurofibrillary tangles inside neurons, caus-

ing neuronal death. The mechanism underlying tau hyperphosphorylation remains unknown, but Aβ142 is also involved [56]. In human AD, the most prevalent tauopathy, it is histologically characterised by neurofibrillary tangles (NFTs), fibrillar aggregates of tau in cerebral neurons [55]. In pathological conditions, collectively known as tauopathies, tau loses its affinity for microtubules, becomes hyperphosphorylated, and aggregates into oligomers, fibrils, and neurofibrillary tangles (NFT) [55]. This implies that tau is exposed to an extracellular environment where different proteases and ECM components could affect its ability to propagate pathology. In diseased states, matrix remodelling can paradoxically contribute to the further spread of tau pathology. Recent advances also point to a significant role for the adaptive immune system in shaping tauopathy progression. Hyperphosphorylated tau may be the consequence of an antiviral mechanism intended to protect the brain from infections, in which tau serves as a host defence protein in the innate immune system of the brain. The possibility that AD aetiology is associated with viruses, bacteria, fungi, and parasites has been postulated over the past three decades [56].

α-Synuclein

α-Synuclein is a protein that, during normal ageing and in pathological conditions, tends to aggregate into fibrillar structures, a process closely associated with neurodegenerative phenomena. It is associated with mitochondrial dysfunction, and high levels of this protein compromise mitochondrial function; the pathogenic mechanisms of this interaction remain unclear. Neuronal inclusions composed of misfolded α-synuclein protein, known as Lewy bodies, are the characteristic lesions of PD in humans [57].

A classic Lewy body is a spherical mass with an eosinophilic cytoplasmic inclusion, a dense nucleus surrounded by a radial fibrillar halo of 10 nm, the main structural component of which is α-synuclein [57]. Animal models have been developed for preclinical research on screening novel disease-modifying therapies; in fact, intracerebral injections of α-synuclein extracted from human patient brains have suggested its "prion-like nature." Over the past decade, evidence has accumulated implicating the ECM in neurodegeneration and PD specifically (58). The brain is relatively poor in fibrous proteins such as collagen but rich in proteoglycans that contain negatively charged GAG side chains that sequester cations and water [58].

Of the few studies that have specifically assessed the ECM in PD, alterations in MMPs and basement membrane proteins are among the most frequent findings.

GAGs are localised to Lewy bodies in PD and inhibit proteases that degrade alpha-synuclein. Moreover, the internalisation of alpha-synuclein fibrils into neuroblastoma and oligodendrocyte-like cells depends on HS. Other findings emphasise the potential protective effects of heparin in synucleinopathies [58].

Chronic infections, such as those caused by HSV, can lead to prolonged or recurring inflammatory responses. Even transient infections may trigger αSyn production at their point of entry. Proteins implicated in protein misfolding diseases that can form oligomers and fibrils, such as αSyn, appear to be part of the first line of defence against pathogens, acting as natural AMPs. Infections, whether they penetrate the CNS or not, can induce neuroinflammatory responses that, under certain conditions, can lead to the accumulation and spread of αSyn and ultimately to neurodegeneration [59].

Prion protein

Transmissible spongiform encephalopathies (TSEs), or prion diseases, are a group of rare and fatal neurodegenerative diseases that affect both humans and animals [60]. They may occur as sporadic forms, the most common, as inherited forms associated with mutations within the prion protein gene (PRNP), or as acquired forms due to transmission of an infectious agent. TSEs are characterised by progressive neuronal loss, often accompanied by spongiform brain changes and amyloid fibril deposition. Prion diseases are protein misfolding disorders in which the host-encoded prion protein (PrP) misfolds [61]. The biological functions of proteins are directly dependent on the acquisition of their conformation. PrP may exist as a normal cellular prion protein designated as PrP^{C} and a pathogenic misfolded con-

former designated as PrP^{Sc}. The pathogenesis of prion diseases is associated with the accumulation of aggregates of misfolded PrP^{Sc} conformers. PrP^{Sc} are infectious, naturally transmissible misfolded proteins with neurotoxic properties and cause fatal neurological diseases in humans and a wide range of animal species. Creutzfeldt-Jakob disease (CJD) is a fatal prion disease [62]. The incidence of sporadic CJD is higher among older patients. These diseases can affect humans and animals. The best-known form of TSE is bovine spongiform encephalopathy (BSE), or 'mad cow' disease [62]. International CJD surveillance programs have been active since the emergence, in the mid-1990s, of variant CJD.

Improved detection of CJD with new diagnostic tools, such as magnetic resonance imaging and real-time quaking-induced conversion testing.

ECM plays a critical role in controlling the susceptibility of cultured cells to prion infection. This conclusion is consistent with several lines of evidence linking PrP^{Sc} and PrP^{C} to sulfated GAGs; sulfated GAGs are potent inhibitors of prion propagation in cultured cells and animal models [63].

A range of experimental conditions revealed that PrP^{Sc} is tightly associated with proteins found in the systemic ECM, mostly fibronectin (FN). The interaction of PrP^{Sc} with FN decreased prion infectivity, as determined by the standard scrapie cell assay. Extracellular FN may act as a natural barrier to prion replication, and the ECM composition may be a crucial determinant of prion tropism across different tissues [64].

Aβ protein in AD and α-synuclein in PD are not considered contagious or transmissible between humans; however, experimental transmission of Aβ or α-synuclein aggregates has been achieved in laboratory animal models. The "prion-like" spread of proteins within the CNS has been observed more recently in several non-prion disease-associated proteins, such as Aβ, Tau, and α-synuclein. However, there is no epidemiological evidence for inter-individual transmission of diseases associated with proteins other than PrP [65,66].

Treatment and therapeutic perspectives

Amyloidosis responds poorly to the limited treatment options available; treatments target ECM, inflammation, and amyloid pathways to reduce the precursor protein or promote the clearance of amyloid deposits; once amyloid deposits form, their dissolution is unlikely. Prevention of secondary amyloidosis involves aggressively treating chronic inflammatory disorders to reduce the development of conditions favourable to amyloid deposition. Identifying structure–activity relationships between Aβ and different GAGs, as well as the conditions under which GAG binding occurs, is necessary for successfully developing and evaluating GAG-specific therapeutic interventions [67].

Current pharmacological therapies

Therapies for AD include acetylcholinesterase inhibitors and glutamate receptor antagonists; only four treatment options have been approved in the European Union: donepezil, galantamine, and rivastigmine (acetylcholinesterase inhibitors), and memantine (an N-methyl-D-aspartate receptor antagonist) used to treat moderate to severe dementia in AD [68].

These drugs only have a symptomatic effect; they do not address the cause of the disease, but they alleviate and delay the progression of neuropsychiatric symptoms, offering minimal relief for symptoms [68,69].

However, significant progress has been made in studying the role of neuroinflammation, leading to the development of new therapies targeting this critical pathway. Inflammation plays a central and multifaceted role in disease progression [12]. Consequently, therapeutic efforts have focused on developing drugs that can suppress this inflammatory response. A major issue in this research is identifying new therapeutic compounds that enhance the innate immune system and inhibit Aβ aggregation [70]. Reducing inflammation in AA can directly reduce the amyloid precursor, and the body stops producing fibrils. The standard treatment aims to resolve the underlying inflammatory conditions, such as rheumatoid arthritis and chronic infections. Tocilizumab, an IL-6 inhibitor [71], was associated with a greater reduction in serum AA and a lower rate of progression to end-stage kidney disease.

First-line therapy

For decades, AL was a neglected disease with significant limitations in clinical trial execution. Only in early January 2021 did the U.S. Food and Drug Administration (FDA) recommend the combination of Cyclophosphamide, Bortezomib, Dexamethasone (CyBorD) and Daratumumab as a treatment for AL, based on the results of a randomised, open-label, controlled phase III trial, ANDROMEDA (72). ANDROMEDA compares two groups: CyBorD alone or in combination with subcutaneous daratumumab (Dara-CyBorD) as first-line therapy in patients newly diagnosed with AL [72]. (**Table 1**). The efficacy of CyBorD-Daratumumab is very high, with 78% of patients achieving a significant hematologic response [72]. These therapies have numerous side effects, including cardiotoxicity. This condition requires a dose reduction or treatment suspension.

Bortezomib, a proteasome inhibitor, became the backbone of the treatment regimen and is now used in combination with MDex (BMDex) or Cyclophosphamide and dexamethasone (CyBorD); proteasomes play a role in reducing proteotoxicity and regulating proteins that control cell progression and apoptosis [73] (**Table 1**).

Monoclonal antibody therapy

Immunotherapy for AD targeting Aβ focuses on reducing the toxic effects of Aβ plaques in the brain, which are strongly associated with the cognitive decline seen in AD [74].

Monoclonal antibody therapies, on the other hand, have shown greater promise in targeting Aβ. These therapies are designed to selectively bind to toxic aggregated forms of Aβ, such as plaques and oligomers, thereby reducing their

Table 1. Current treatment for ATTR and AL amyloidosis.

Drugs and carriers molecules	Main results	Ref.
	Evidence-based approaches	
Cyclophosphamide, Bortezomib, Dexamethasone (CyBorD) and. Daratumumab FDA approved	Daratumumab is a monoclonal antibody targeting CD38, which reduces the production of amyloid light chains (AL) and appears to prevent their deposition in the extracellular matrix (ECM) along the amyloid pathway. The efficacy of CyBorD–daratumumab is very high, with 78% of patients achieving a significant hematologic response. However, these therapies have numerous side effects, including cardiotoxicity, which may necessitate dose reduction or temporary treatment suspension.	Kastritis E et al., N Engl J Med 2021;385:46–58
TTR Stabilizers Tafamidis (Vyndamax, Vyndaqel) Acoramidis FDA approved	Tafamidis is a small molecule that selectively binds to the thyroxine-binding site of the transthyretin (TTR) tetramer and has been evaluated for the treatment of transthyretin amyloid polyneuropathy. Acoramidis binds to the TTR tetramer with high affinity and selectivity, driven by an optimised network of hydrogen bonds.	Siddiqi OK Amyloid. 2022 29(2):71–78; Dimza M. et al., US Cardiology Review 2025;19:e21.
TTR Silencers Patisiran (Onpattro) and Inotersen (Tegsedi), Vutrisiran (Amvuttra) FDA approved	Patisiran and inotersen are ATTR gene silencers (RNA-silencing agents) that represent exceptional advances in the treatment of hereditary transthyretin-mediated amyloidosis. They degrade TTR mRNA in the liver, reducing the production of TTR. Patisiran showed significant improvement in patients compared with placebo (−6.03 vs. 27.96). Vutrisiran was evaluated in the HELIOS-B trial and demonstrated a lower risk of death.	Iannazzo S. Glob Reg Health Technol Assess. 2021; 12;8:14–21 Dimza M. et al., US Cardiology Review 2025;19:e21.
CRISPR-CAS-9 Nexiguran numerazione (NTLA-2001) (TTR silencer) Phase III study	A CRISPR-Cas9–based therapy, administered as a single intravenous infusion, is designed to be endocytosed by hepatocytes and to introduce a double-stranded DNA break in a specific exon of the TTR gene. This therapy has shown promising results for the treatment of ATTR amyloidosis in early in vitro and in vivo studies.	Mallus MT et al. European Heart Journal Vol.25, Issue Suppl_B, 2023,

Daratumumab hyaluronidase (Dara-CyBorD; Dimethylsulfoxide (DMSO); monoclonal antibody (MoAb); Immunomodulatory drugs (IMiDs); Wild type Transthyretin Amyloid cardiomyopathy (ATTRwt-CM); cyclophosphamide, bortezom ib, and dexamethasone (CyBorD); (wild-type transthyretin amyloid cardiomyopathy, (ATTRwt-CM).

pathological burden without interfering with critical physiological pathways [74] (**Table 2**).

Human Anti-CD38 antibody (Daratumumab) is an IgGκ monoclonal antibody that targets the CD38 antigen expressed on the cell surface of hematopoietic tumours, including multiple myeloma and AL, and exhibits anti-tumour effects [75].

For instance, Aducanumab [76] and other antibodies have shown potential to slow cognitive decline, particularly when administered early in the disease course. Aducanumab (BIIB037) is a human IgG1 monoclonal antibody that specifically binds to the N-terminus of Aβ in its extended conformation. It is designed to target both Aβ aggregates and plaques in FDA-approved/Phase 3 clinical trials [77].

Donanemab (LY3002813) [80] is another monoclonal IgG1 antibody that targets the N-terminal pyroglutamate Aβ epitope, primarily found in deposited Aβ [75]; FDA-approved/Phase 3 clinical trials [78,79].

Lecanemab, a human IgG1 mAb, targets Aβ protofibrils and is designed to enhance microglial-mediated clearance of Aβ. FDA approved in 2023.

Isatuximab, an anti-CD38 mAb, is being studied for the treatment of the plasma cell dyscrasia underlying AL.

Monoclonal antibodies such as Birtamimab and CAEl-101 [75] (**Table 2**) are currently being studied for the removal of amyloid fibrils from the affected organ. Removing the LC deposit will improve the function.

Transthyretin expression silencer

Patisiran and Inotersen (**Table 1**) are TTR gene silencers (80) which represent exceptional advances in the treatment of hereditary transthyretin-mediated (hATTR) [80,81]. Antisense oligonucleotides, such as Inotersen, are complementary to the target mRNA and can block TTR production [80].

Data from the APOLLO-B trial in 2022 demonstrated that Patisiran improved functional capacity, but no significant benefit on all-cause mortality was observed. Vutrisiran, another TTR silencer, was evaluated in the Helios-B trial for patients with ATTT-CM [75,82].

Transthyretin stabiliser drugs

Another approach to treating TTR amyloidosis is to stabilise the TTR protein complex, preventing its dissociation.

Tafamidis, a small molecule that selectively binds to the thyroxine binding site of TTR tetramers, was approved in 2019 by the FDA for the treatment of patients with wt-ATTR and familial ATTR [82,83]; the ATTR-ACT study demonstrated that the reduction in mortality was better in the group treated with early Tafamidis than in the group with a later start (**Table 1**).

Acoramidis is a new TTR stabiliser that binds to TTR tetramers with high affinity and selectivity

Table 2. Monoclonal antibodies (mABs).

Name	Evidence-based approaches	Ref.
Daratumumab	mAb that binds to CD38, approved for the treatment of AL amyloidosis when administered with CyBorD.	Cummings J et al. BioDrugs. 2024 Jan;38(1):5–22. Gupta A et al. Neurol Sci 46, 5607–5619 (2025).
Donanemab	Human IgG1 mAb, targets the N-terminal Aβ epitope. FDA approved in 2023.	Lowe SL. J Prev Alzheimers Dis. 2021;8(4):414–424.
Aducanumab	Human IgG1 mAb, binds to the N-terminus of Aβ FDA approved in 2021.	Cummings J et al. BioDrugs. 2024 Jan;38(1):5–22.
Birtamimab, CAEL-101, and AT-03	Systemic AL amyloidosis designed to neutralize toxic soluble LC aggregates. Currently being studied.	Mallus et al. European Heart Journal. Vol. 25, Issue Suppl_B, 2023.
Isatuximab	An anti-CD38 mAb similar to daratumumab, for the treatment of the plasma cell dyscrasia underlying AL Currently being studied.	Mallus et al. European Heart Journal. Vol. 25, Issue Suppl_B, 2023.
Lecanemab	Human IgG1 mAb, target Aβ protofibrils. FDA approved in 2023.	Walls JS et al. Front Immunol. 2011 8; 2:32.
Amyloid fibril depletion Phase III study	Coramitug (PRX004) is one mAb that has shown safety and tolerability in a phase I trial.	Walls JS et al. Front Immunol. 2011 8; 2:32.

and appears to be effective in the form of polyneuropathy [75]; it is in a Phase III study.

Tafamidis, Acoramidis, and Vutrisiran are the only agents approved by the FDA for the management of ATTR-CM.

Immunomodulatory drugs (IMiDs) [84] are currently used in newly diagnosed patients as well as in salvage therapy in relapsed/refractory patients.

Biomarkers

Earlier disease detection can be achieved with traditional biomarkers such as NT-proBNP and cardiac MRI, as well as novel circulating biomarkers such as the transthyretin aggregate detector (TAD1), and peptide-based nuclear tracers [75]. Studies using positron emission tomography (PET) indicate that the accumulation of Aβ starts 20 years before dementia onset in AD. Different Aβ species can be reliably measured in cerebrospinal fluid (CSF) [85].

Plasma levels of phosphorylated tau protein (p-tau) are closely associated with AD severity and may serve as an important indicator for early diagnosis [86].

CSF biomarkers such as CSF Aβ42, CSF t-tau, and CSF p-tau aid early AD diagnosis, improving diagnostic accuracy and differentiating AD from other dementias [87]. While amyloid PET is more precise, CSF biomarkers are a more accessible and cost-effective alternative. Considering both genetic and immune factors can refine immunotherapy approaches, enhancing the relevance and effectiveness of AD treatments tailored to individual patients [76].

Natural compound: dietary supplements

Selenium (**Table 3**) is a microelement with antioxidant and pro-oxidant properties depending on its concentration [88]. Selenium deficiency leads to many pathological processes and diseases; selenoproteins play an essential role in regulating redox activity and in restoring immune damage caused by oxidative stress. For these properties, selenium has a strong potential to prevent the accumulation of beta-amyloid protein. Low selenium levels throughout life may be associated with neurodegenerative diseases such as AD [88]. Some authors [89] have also reported that selenium nanoparticles can reduce Aβ aggregation by altering the hydrophobic and electrostatic interactions between fibrillar forms of the protein.

Yeast (*Saccharomyces cerevisiae*) is an ideal model for studying human neurodegenerative diseases, because many signalling pathways and proteins associated with neurodegenerative disease are conserved in this microorganism; moreover, these microorganisms enriched with selenium are an effective, safe and natural source of selenium and the most absorbable form of the element [88].

Polyphenols (**Table 3**) are secondary metabolites of plants and are generally involved in defence against ultraviolet radiation or aggression by pathogens.

In the last decade, there has been much interest in the potential health benefits of dietary plant polyphenols as antioxidants. Polyphenol compounds inhibit Aβ aggregation by binding to hydro-

Table 3. Natural treatments and antioxidants for neurodegenerative disease.

Flavonoid rutin polyphenols	The dietary flavonoid rutin can dose-dependently inhibit Aβ42 fibrillization and attenuate toxicity in SH-SY5Y cells. Polyphenolic compounds have inhibitory effects on Aβ aggregation by binding to hydrophobic β-sheet channels through their aromatic structures and disrupting Aβ hydrogen bond formation.	Asti A et al. Natural Product Research 2023, 38(5), 861–866.
Selenium	Selenium is an essential trace element that plays a fundamental role in the antioxidant defense system through its incorporation into selenoproteins such as glutathione peroxidases and thioredoxin reductases. Selenium can increase the levels of interleukins (ILs), which has a beneficial effect on regulating the immune system, inhibit amyloid-β aggregation, and suppress neuroinflammation.	Kieliszek M Sapazhenkava K. Biol. Trace Element Res 2025 203:1251–126.
Antioxidants	Vitamin E, vitamin C, curcumin, melatonin, resveratrol, and α-lipoic acid act to neutralize reactive oxygen species (ROS) and reduce oxidative damage. Curcumin exerts its antioxidant effects by scavenging reactive nitrogen and oxygen species and by regulating antioxidant enzymes. Melatonin exhibits a broad spectrum of neuroprotective effects in Alzheimer's disease (AD), influencing key molecular mechanisms underlying neurodegeneration.	Bilski R., Biomolecules 2015 15 (9), 1345 Asti A et al.

phobic β-sheet channels. They have an aromatic structure and can disrupt Aβ hydrogen bond formation via their hydroxyl groups, acting as electron donors. Regarding prevention, dietary flavonoid Rutin (**Table 3**) can dose-dependently inhibit Aβ42 fibrillization [90] and attenuate toxicity in SH-SY5Y cells. In particular, Rutin nanocrystals are promising natural compounds for protecting neurons from cell death and oxidative stress during PD.

Antioxidants, such as vitamin E, C, curcumin, melatonin, resveratrol, and α-lipoic acid, aim to neutralise ROS and reduce oxidative damage, thereby enhancing neuronal protection (**Table 3**). Vitamin E inhibits hydrogen peroxide production [69]; Curcumin can reduce MDA concentrations, increase antioxidant enzyme and demonstrate its antioxidant properties by scavenging reactive nitrogen and oxygen, regulating enzymes, and chelating metals. Melatonin exhibits a broad spectrum of neuroprotective effects in AD, affecting both the fundamental molecular mechanisms and the functional manifestations of neurodegeneration. Melatonin promotes the non-amyloidogenic pathway by increasing α-secretase expression, leading to the formation of the neuroprotective fragment sAPPα [69].

Conclusions

Whilst the prevailing opinion tends to consider the appearance of amyloids in tissues as the expression of a disturbance in the metabolism of protein substances, it's important to know that controlling long-term inflammation serves to minimise the production of amyloid both in humans and animals. The implications of protein-folding disorders in food-associated hazards must also not be ignored. Early diagnosis is vital and the basis for appropriate, risk-adapted, response-tailored therapy, because the disease, once triggered, progresses rapidly. For future research, it's important to consider that the physiologically produced and circulating β-Amyloid protein (Aβ) may have important functions. In contrast, although Aβ is a key player in AD, it may initially be beneficial at the onset of infection. Acting as an AMP, Aβ helps contain pathogens; host defence peptides such as Aβ not only kill pathogens through their antimicrobial activity but also exhibit high affinity for bacterial LPS and membrane receptors.

However, the specific therapy of patients with advanced amyloidosis remains to be defined; extensive research is needed to identify appropriate targets to provide therapeutic benefits.

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