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Unlocking Neuroprotection: How β-Sitosterol Modulates Cellular Signalling to Combat Neurodegeneration?

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Abstract

Background: Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and related syndromes represent a growing global health burden with current therapies largely limited to symptomatic relief rather than disease modification. By 2025, increasing evidence indicates that mono-target pharmacological approaches fail to address the interconnected cellular dysfunctions underlying neurodegeneration, including oxidative stress, mitochondrial failure, chronic neuroinflammation, impaired autophagy and synaptic disintegration.

Objective: This review aims to critically evaluate β-sitosterol as a multi-target neuroprotective phytosterol and elucidate its role in modulating key cellular signalling pathways involved in neurodegenerative progression.

Methods: Recent experimental and translational studies were systematically analysed to assess the molecular mechanisms through which β-sitosterol regulates neuronal and glial signalling networks with emphasis on antioxidant defence, inflammatory modulation, mitochondrial stabilization and proteostasis control.

Results: β-Sitosterol demonstrates pleiotropic neuroprotective actions through activation of Nrf2-ARE signalling, suppression of NF-κB-mediated neuroinflammation, modulation of PI3K/Akt/GSK-3β survival pathways and restoration of AMPK-mTOR-regulated autophagy. Its structural similarity to cholesterol further enables regulation of membrane lipid rafts, synaptic integrity and calcium homeostasis, collectively enhancing neuronal resilience across multiple neurodegenerative models.

Conclusion: β-Sitosterol emerges as a promising disease-modifying neuroprotective agent capable of restoring cellular signalling balance rather than targeting isolated pathological endpoints, supporting its potential role in next-generation neurotherapeutic strategies.

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1. Introduction

Despite major advances in neuroscience and molecular medicine, neurodegenerative disorders remain among the most challenging diseases to prevent or treat effectively. Aging of population, metabolic dysregulation and chronic neuroinflammatory stress contribute to the persistent increase of such conditions like Alzheimer disease (AD), Parkinson disease (PD) and related neuro degeneration syndromes throughout the world in general. Despite the existence of a number of such pharmacological compounds that are already clinically used, the majority of treatments are symptomatic but not disease-modifying and provide few long-lasting neuroprotective effects [1]. By the year 2025, it has become clearer that mono-target therapeutic modalities are not able to respond to the multiple layered dysfunctions of cells underlying progressive neuronal degeneration. This understanding has transformed research emphasis to multi-target signalling-based interventions that can restore cellular homeostasis and not just the suppression of individual pathological characteristics. In this dynamic therapeutic environment, neuroprotective compounds have been demonstrated to be beneficial and bioactive phytosterols, especially, β-sitosterol have

gone further to emerge as promising therapeutic agents [2]. β-sitosterol is traditionally known as an anti-inflammatory and cholesterol lowering agent in peripheral tissues but now this compound is attracting interest on its central nervous system (CNS) action. Recent support of lipidomic and membrane biology has shown that sterol like molecules is able to regulate the neuronal membrane architecture, receptor clustering and intracellular signal cascades involved in neuronal survival. In comparison with traditional neuroprotective agents that operate subsequent to damage incurring irreversible harm, β-sitosterol seems to regulate early stress responses in cells and therefore should be viewed as a disease-modifying agent in contrast to a symptomatic adjunct [3].

Neurodegeneration is no longer considered as a disorder of neurons but as a failure at the systems level which brings in the involvement of neurons, glial cells, mitochondrial networks and proteostasis machinery. Interaction Oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, impaired autophagy and synaptic disintegration are interplaying factors that enhance neuronal loss. The processes are related to each other by tight regulation signalling pathways that include PI3K/Akt, AMPK mTOR, NF-κB and Nrf2 and that together decide the fate of neurons in stress. Drugs that can mediate a combination of more than one signalling axis have therefore become of growing interest in modern neuropharmacology with β-sitosterol having been shown to mediate multiple of them and implying a wider neuroprotective profile than single target therapies. The developing experimental data has shown that β-sitosterol has antioxidant effects acting through the promotion of endogenous defence mechanisms, stabilization of mitochondrial activity and suppression of CNS pro-inflammatory events signalling [4, 5]. Moreover, it is structurally similar to cholesterol and thus it can be incorporated into neuronal membranes affecting lipid raft dynamics and synaptic signalling ability. The properties are especially applicable when it comes to neurodegenerative diseases in which membrane destabilization and synaptic impairment cause neuronal death to occur. β-sitosterol consists of an exceptional category of neuroactive phytochemicals by acting in the area crossing membrane biology and intracellular signalling, capable of involved disease paths at an early stage [6].

The concept of neuroprotection has broadened by 2025 beyond the principle of neuronal survival, with the additional aspects of neuronal synaptic integrity, the mechanisms by which the manners in which the nervous systems respond to glial signals, neural metabolic flexibility. In its regard, the β-sitosterol is consistent with the new paradigms of network resilience as opposed to isolated molecular targets. The review will be a systematic study of the molecular pathways of action of β-sitosterol in cellular signalling pathways that alter neurodegeneration, including its effects in controlling oxidative stress, neuroinflammation, mitochondrial protections and proteostasis. The incidences of such mechanisms are required to analyse the transnationality of β-sitosterol as a multi-target neuroprotective agent in future generation of neurodegenerative disease therapeutics [7, 8].

2. Neurodegeneration Associated Cellular Dysregulation and Therapeutic Gaps

Neurodegenerative diseases are commonly known to be disorders of converging cellular failures instead of single pathway diseases by the year 2025. The resultant effect of the collective action of oxidative stress, mitochondrial dysfunction, chronic neuroinflammation and destruction of protein quality control systems is progressive neuronal loss. The processes change over years and gradually overwhelmed the compensatory mechanisms and resulted in the irreversible synaptic and neuronal damage. The current modes of therapy which are primarily aimed at changing neurotransmitter levels or alleviating symptoms do not break such upstream pathological mechanisms. This has resulted in persistence of the disease process despite clinical interventions, thus creating a priori the pressing need to develop therapies that will have the ability to attack the core cellular processes [9].

Biological heterogeneity in the disease processes of regions of the brain and cell types is one of the major obstacles to neurodegeneration therapy. The response of neurons, astrocytes, microglia and oligodendrocytes to stress signals is different but they interrelate to determine disease pathways. Ineffective communication between these cells increases the pathological signalling particularly in cases where initially localised cell damage would result in wide spread damage of the neural networks. Also, numerous neurodegenerative processes proceed concurrently and cause overlapping and reinforcing loops of injury. As an illustration, the oxidative stress aggravates the mitochondrial dysfunction thereby facilitating the neuroinflammatory activity and misfolding of proteins [10]. It is due to this interconnectedness that there has always been a lack of clinical efficacy of mono target drugs.

The other significant therapeutic gap is the time the intervention. Neurodegenerative disorders are commonly diagnosed when significant neuronal damages have already taken place and therefore neuroprotective treatments will not be effective in diseases diagnosed at an advanced stage. Molecular changes right at the beginning of the disease including redox imbalance, bioenergetic stress in mitochondrion and dysfunctioning autophagy, happen multiple years before clear clinical symptoms show up. Treatments that are capable of normalizing these anomalies of early cellular anticipation can thus have exceptionally greater disease-limiting prospects. This discovery has overcome the focus of research to agents that regulate signalling pathways that drive cellular resilience and changes to stress instead of late-stage pathological phenotypes [11, 12].

In this context, pleiotropic signalling compounds that are produced naturally, such as β-sitosterol have become the focus again. β-sitosterol is a compound that stimulates several cellular pathways that are associated with neurodegeneration. The underlying pathophysiological mechanisms that underlie the neuronal susceptibility need to be comprehended to contextualize the neuroprotective property of beta-sitosterol and other multi-target agents. The next subsections explore the main cellular functions behind neurodegenerative pathology and the weaknesses of the existing treatment approaches. Moreover, new systems neuroscience models highlight that neurodegeneration is an outcome of systems

signs of failure of adaptive signalling networks but not of single events of neurological toxicity. The resistance to metabolic stress and environmental toxins in the long run, together with the molecular drift of cells, gradually diminish the buffering capacity of cells [13]. The cumulative nature of these insults causes neuronal signalling to change to maladaptive states that involve chronic stress kinase activation and loss of trophic support. Notably, in the initial phases these transitions can be reversed which also implies a rather important therapeutic time frame in which intervention can occur. Thus, contemporary neuroprotective approaches are taking an increased goal of supporting intrinsic resilience pathways that uphold cellular homeostasis when exposed to chronic stress as opposed to addressing end-stage pathological outcomes [14].

2.1. Oxidative Stress, Mitochondrial Dysfunction and Redox Collapse

One of the primary causes of neurodegeneration is oxidative stress which occurs due to the disruption of the balance between the production of reactive oxygen species (ROS) and the mechanisms of endogenous antioxidants. Deficiency in antioxidative defence mechanisms due to their high metabolic rates and large lipid content in neurons and low regenerative abilities make neurons especially vulnerable to oxidative damage. Overproduction of ROS destroys lipids, proteins and nucleic acids of cells, eventually exerting adverse effects on the neuron viability. Oxidative stress is not simply a consequence of neuronal injury in neurodegenerative disease but it is a participant in the disease process as well as disease initiation and progression [15, 16]. Mitochondria are a critical part of the process as they are the primary source and the primary target of ROS. The mitochondrial dysfunction contributes to the hampered oxidative phosphorylation, low ATP generation and higher electron leakage contributing to the multiplication of ROS. This forms a vicious energy depletion and oxidative destruction cycle. Mitochondrial disturbances such as the disturbance of fission-fusion balance and dysfunctional mitophagy increase neuronal susceptibility. Notably, calcium buffering capacity is also impaired by the mitochondrial dysfunction and thus it adds to the excitotoxic signalling and synaptic failure [17].

Although symptoms of oxidative stress have been widely implemented in neurodegeneration, antioxidant treatment has demonstrated low clinical efficacy. To a great extent, this failure indicates the failure of traditional antioxidants to access pertinent intracellular reduces or alter the pathways of regulation higher. Neuroprotective use of SODs should be mediated by repair of endogenous redox signalling systems but not random scavenging of free radicals. Drugs that can regulate transcriptional regulators of antioxidant defines like Nrf2 and stabilize mitochondrial activity are thus gaining more interest in modern neurotherapeutic studies. The more recent data suggests that oxidative stress changes neuronal lipid composition affecting the fluidity of the membranes and receptor arrangements [18]. Degradation of polyunsaturated fatty acids by peroxidation inhibits the fusion process of the synaptic vesicles and also reduces the release of neurotransmitters in the synapses hence affecting the synaptic plasticity in an impaired way. The respiratory chain dysfunction further increases further since oxidative damage in mitochondrial DNA leads to persistent bioenergetic deficits. Furthermore, the redox imbalance disrupts calcium-dependent signalling pathways that are important in neuronal survival. These results support the idea that there is not just damaging by oxidative stress but a dynamic restructuring of neuronal signalling space which drives the importance of the interventions designed to stabilize redox-controlled cell-to-cell communication [19].

2.2. Neuroinflammation and Glial-Driven Signalling Toxicity

The role of chronic neuroinflammation has now been considered a major cause of neurodegenerative disease progression. Although acute inflammatory reactions can be beneficial, the pro-inflammatory cytokine, chemokine and pro-inflammatory reactive nitrogen species release by the continuous activation of microglia and astrocytes can aggravate neuronal damage. This de-stimulated inflammatory condition interferes with synaptic homeostasis, changes the neuronal excitability and speeds up neurodegenerative cascades. Microglial cells are the main immune keepers of CNS that is quick responsive to the pathological stimuli of protein aggregations and degenerated neurons [20]. Microglia in neurodegenerative diseases tend to develop a pro-inflammatory phenotype as in which they are continuously activated through the NF-κB, MAPK and inflammasome pathways. Astrocytes respond to this, in their turn entrapping into the reactive transformation of the organs, dedicating themselves to the functions of neurotrophic support and partaking in inflammatory signalling. The two way communication of the microglia and the astrocytes create a feed forward loop that perpetuates neuroinflammation despite no longer sustaining injury [21].

The requirements of multiple and redundant inflammatory signalling networks in the brain have been shown to be under responsive to the current anti-inflammatory therapies that are directed to single pathways or cytokines. Besides, absolute inhibition of neuroinflammation can hamper obligatory immune check and mentation processes. The focus of therapeutic methods should hence focus on restoring the balance of the inflammatory responses, but not completely down, to zero. The agents that will be able to regulate the glial signalling and facilitate the transition to neuroprotective phenotypes have become a promising path in disease modifying intervention [22]. In addition to the release of cytokines, chronic glial response changes metabolic coupling between neurons and astrocytes to disturb lactate shuttling and energy provision to synapses. Long-term inflammatory signalling changes the synaptic pruning processes as well and results in the unsuitable removal of functional synapses. The molecules produced by microglia as inflammatory factors may interfere with neurogenesis as well as suppress synaptic restoration, impairing recovery. Also, chronic inflammation increases susceptibility to a secondary insult, including oxidative stress and excitotoxicity. Such complex interactions place neuroinflammation at the forefront as the cause and contributor of electro degradation and require that therapeutic modulation be performed softly and piece rate [23].

2.3. Protein Misfolding, Autophagy Failure and Proteostasis Breakdown

The common characteristics of most of the neurodegenerative disorders are protein misfolding and aggregation such as the AD, the PD and others. Accumulation of misfolded protein like amyloid-β, tau and α-synuclein interferes with cellular homeostasis, disrupts synaptic activity and causes neurotoxic

signalling pathways. These aggregates do not only inhibit the functioning of neurons but also glial inflammatory responses which increase disease progression.

Proteostasis under physiological conditions is ensured with the coordinated action of the ubiquitin-proteasomes and autophagy-lysosomes. In neurodegeneration, there is progressive impairment of clearance mechanisms resulting in the buildup of toxic protein species [24, 25]. In particular, autophagic dysfunction is a harmful condition because neurons are very dependent on it, autophagy to get rid of degraded organelles and long-lived proteins. Disruption of autophagic flux leads to stress on the cell, mitochondrial malfunction and augmentation. apoptotic susceptibility. The protein aggregation driving force has been mainly the target of therapeutic interventions, production or improving clearance of the individual pathological proteins. However, such interventions have not had uniform clinical results with emphasis on wider interventions, policies leading to restoration of global proteostasis. Regulation of upstream autophagy regulators as the AMPK-mTOR axis provides, is a more comprehensive way to treat the aspect of proteostasis failure. Agents that have the capability of reactivating autophagic pathways but maintain cellular viability may has extended neuroprotective effects than in common neurodegenerative conditions [26]. Recent research indicates that neuronal stress signalling is also impaired by the disruption of autophagy as well permitting the damage of mitochondria and oxidation of proteins to accumulate. This accumulation increases cells sensitivity to inflammatory and oxidative injuries. Defective lysosomal function also reduces the ability to degrade thus causing congestion inside the cells altered trafficking. Notably, autophagy overlaps synaptic maintenance as it is impaired, clearance mechanisms have undesirable effects on plasticity and synaptic protein turnover. These insights highlight proteostasis as a clearance mechanism but an important ionic controller of neuronal. plasticity which strengthens the field of its application in neurodegenerative disease [27].

3. B-Sitosterol: Molecular Pharmacology and Neuroactive Properties

β-Sitosterol is a plant phytosterol structurally similar to cholesterol designed to include an ethyl group at the C24 position which gives it a specific biological behaviour. Although its anti-inflammatory and lipid lowering effects in the peripheral tissues have historically been examined, the scope of its applicability is currently increasingly abundant in the central nervous system. The recent developments in the sterol biology and membrane signalling have shown that phytosterols are not biologically neutral in the neural tissue but instead they are involved in cellular homeostasis regulation. β-sitosterol has become a prospective neuroprotective molecule based on its ability to regulate oxidative balance, inflammatory signalling, mitochondrial stability and proteostasis networks [28].

Table 1: Cellular dysfunctions targeted by β-sitosterol [29-35]

Pathological Process	Key Molecular Events in Neurodegeneration	β-Sitosterol Modulatory Action	Neuroprotective Outcome
Oxidative Stress	Excess ROS generation, lipid peroxidation, reduced glutathione (GSH), mitochondrial DNA damage	Activates Nrf2–ARE signalling, enhances SOD, CAT, GPx expression	Reduced oxidative injury, preserved neuronal redox balance
Mitochondrial dysfunction	Loss of mitochondrial membrane potential (ΔΨm), ATP depletion, cytochrome-c release	Stabilizes mitochondrial membranes, improves oxidative phosphorylation efficiency	Prevention of intrinsic apoptosis and energy failure
Neuroinflammation	Microglial M1 polarization, elevated TNF-α, IL-1β, IL-6, COX-2 induction	Suppresses NF-κB and STAT3 signalling, promotes M2 microglial phenotype	Attenuation of chronic neuroinflammatory damage
Protein misfolding and aggregation	Accumulation of Aβ plaques, α-synuclein fibrils, hyperphosphorylated tau	Enhances autophagy and proteostasis via AMPK–mTOR inhibition	Reduced toxic protein burden
Impaired autophagic flux	Lysosomal dysfunction, reduced LC3-II turnover, p62 accumulation	Restores autophagic clearance pathways	Improved neuronal survival and homeostasis
Apoptotic signalling	Bax upregulation, caspase-3 activation, neuronal cell death	Activates PI3K/Akt, suppresses Bax/Bcl-2 imbalance	Inhibition of programmed neuronal loss
Synaptic dysfunction	Loss of synaptic proteins (PSD-95, synaptophysin), Ca^{2+} dysregulation	Stabilizes membrane lipid rafts and calcium homeostasis	Preservation of synaptic plasticity and cognition
Cholesterol dyshomeostasis	Altered lipid raft composition, disrupted neurotransmitter receptor clustering	Mimics cholesterol structure, modulates membrane fluidity	Improved receptor signalling and synaptic integrity

In contrast to classical neuroprotective drugs that have a specific enzyme or receptor as the target, β-sitosterol have a pleiotropic action acting in various cellular compartments. This is due to its lipophilic nature and downstream effects to cytosolic and nuclear signalling pathways. This multi-level interaction is consistent with the modern concept of neurodegeneration as a systems-level condition that is caused by the interchanges maladaptation of molecular interactions. Notably, β-sitosterol has also been found to analogously exert an effect on adaptive stress responses instead of countering end stage pathology. There is current pharmacological interest in β-sitosterol because it has a good safety profile and a high dietary exposure. However, in contrast to most synthetic neuroprotective agents, β-sitosterol has been shown to have low systemic toxicity which renders it an appealing choice in long term intervention of chronic neurodegenerative diseases. Its translational biomodulator impact can thus only be assessed by comprehending its molecular pharmacology [36, 37].

3.1. Chemical Structure, Brain Bioavailability and Membrane Dynamics

Structurally, β-sitosterol is very similar to cholesterol and is able to conform to lipid bi-layer and affect the organization of membranes. Membranes of neurons are abundant in cholesterol-dependent microdomains, also known as lipid

rafts that provide a platform on which receptors cluster and in intracellular signals. A change in the composition of the membrane sterols can greatly influence the synaptic transmission, receptor sensitivity and efficiency in signalling. After binding into these microdomains, β-sitosterol can either regulate membrane fluidity and stabilize synaptic architecture during stress [38]. It is historical that the bioavailability of the brain has been the cause of the lack of interest in phytosterols as neuroactive agents. Nonetheless, recent evidence involves β-sitosterol being capable of penetrating the blood brain barrier to an appreciable degree especially with conditions of heightened permeability of aging and neurodegenerative pathology [39]. There is also possible distribution in the neural tissue by means of transport mechanisms that involve sterol binding proteins. Even though concentrations in the brain are smaller than periphery concentrations, relatively a small accumulation will have great biological impact as it can be amplified by signalling cascades. Membrane associated actions of β-sitosterol extend beyond structural stabilization. The effects of β-sitosterol on calcium signalling, synaptic plasticity and neuronal excitability may be indirectly through the action of influencing the cholesterol dependent receptor systems such as glutamatergic and neurotrophic receptors. All these membrane-based effects put β-sitosterol as a modulator of early pre-synaptic dysfunction, one of the main events before neuronal loss in most neurodegenerative disorders [40].

3.2. Antioxidant and Mitochondrial Signalling Modulation

The antioxidant activity of β-sitosterol is potent and achieved not directly by the scavenging effect of the free radical but by modulating the endogenous defensive processes of the cells. Among its most vivid ones is activation of redox sensitive transcription factors like nuclear factor erythroid 2-related factor 2. Nrf2 activation results in the upregulation of antioxidant enzymes, such as superoxide dismutase, catalase and heme oxygenase-1 and enhances resilience to oxidative stress by the intrinsic cellular capability. On a mitochondrial scale, β-sitosterol has been reported to maintain membrane potential, lessen the formation of excessive amounts of ROS and enhance bioenergetic efficiency. Its effects are especially indicated in neurons when dysfunction of the mitochondria is immediately converted to synaptic failure and apoptosis [41]. By stabilizing mitochondrial dynamics and promoting efficient oxidative phosphorylation, β-sitosterol helps maintain ATP availability required for synaptic transmission and neuronal maintenance. Notably, also the area of mitochondrial protection overlaps with the area of calcium homeostasis. Oversaturation of calcium influx which is commonly seen in neurodegenerative diseases attenuates mitochondrial stress and activates apoptotic pathways. β-Sitosterol mediated regulation of mitochondrial signalling may hence contribute to lower excitotoxicity and better neuronal survival. These mitochondrial actions bring to the fore the effect of β-sitosterol as a cellular energy balance controller and not as a mere antioxidant [42].

3.3. Neuroinflammatory Suppression and Glial Reprogramming

In addition to its antioxidant properties, β-sitosterol has strong anti-inflammatory activity in the CNS. One of the characteristic neurodegenerative pathological events is chronic activation of inflammatory signalling pathways like the NF-κB and STAT3 which lead to reduced expression of pro inflammatory cytokines (TNF-α, IL-1β and IL-6). β-Sitosterol has been demonstrated to suppress these pathways. This inhibition lowers the neurotoxic environment that promotes the destruction of the neurons. The microglial cells are specifically concerned with sterol-based signalling modulation [43]. β-Sitosterol also seems to induce phenotypic modification of pro-inflammatory, neurotoxic, microglial cells to a more restorative, neuroprotective type. This reprogramming undergoes by attenuating the inflammatory amplification but without miscellaneous immune surveillance abilities. This effect can also extend to astrocytes and this group of cells can be recovered in terms of the restoration of metabolic and trophic signalling to neurons due to less inflammatory activation [44]. The selective effect of β-Sitosterol on restoring the balance of glial signalling instead of causing a generalised anti-inflammatory effect is a vital benefit over the traditional anti-inflammatory agents. Through the upstream signalling regulators, β-Sitosterol enhances a balanced inflammatory response that enables neuronal regeneration and synapse maintenance. This effect on neurons and glial cells forms the basis of its possible use as a holistic neuroprotective agent which may prevent both inherent neuronal susceptibility and external inflammatory stressors [45].

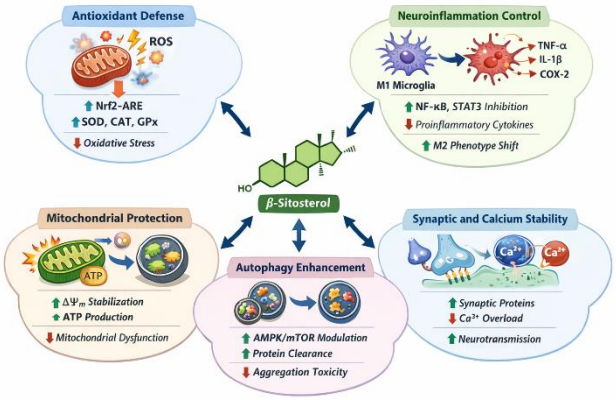

Fig 1: β-Sitosterol-driven neuroprotective signalling network

4. B-Sitosterol Mediated Neuroprotective Signaling Networks

Neuroprotection is coming to be more conceptualised as a product of a co-ordinated modulation within interconnected signalling networks and not a product of specific pathway inhibition. Complex crosstalk of metabolic, inflammatory and proteostatic signalling axes of neuronal survival, synaptic maintenance and adaptive responses to stresses dictate the behaviour of neurons in pathological settings.

β-sitosterol represents one such network-based mode of action, as it intersects a number of intracellular pathways which together determine neuronal survival, adaptive response to stresses under pathological conditions. β-sitosterol also does not work as a direct agonist or antagonist as it acts as a signalling modulator, it fine tunes the pathway activity and replenishes cellular equilibrium [46, 47].

Table 2: Neuroprotective signalling pathways modulated by β-Sitosterol [48-55]

Signalling Pathway	Pathological Dysregulation in Neurodegeneration	β-Sitosterol–Mediated Modulation	Functional Neuroprotective Outcome
Nrf2-ARE antioxidant pathway	Suppressed Nrf2 nuclear translocation, reduced antioxidant enzyme expression	Promotes Nrf2 activation and ARE binding; upregulates SOD, CAT, HO-1, GPx	Enhanced cellular antioxidant defense, reduced oxidative neuronal damage
NF-κB inflammatory signalling	Chronic NF-κB activation driving TNF-α, IL-1β, IL-6 overproduction	Inhibits IκBα degradation and p65 nuclear translocation	Attenuation of neuroinflammation and cytokine-mediated neurotoxicity
PI3K/Akt/GSK-3β survival axis	Reduced Akt phosphorylation, hyperactivation of GSK-3β leading to tau pathology	Activates Akt and inhibits GSK-3β phosphorylation	Prevention of neuronal apoptosis and reduced tau hyperphosphorylation
AMPK-mTOR autophagy pathway	mTOR hyperactivation suppressing autophagic clearance	Activates AMPK and downregulates mTOR signalling	Restoration of autophagy and clearance of misfolded proteins
MAPK (p38/JNK/ERK) signalling	Stress-induced p38 and JNK overactivation promoting neuronal death	Select selectively suppresses stress-activated MAPKs	Reduced stress-mediated apoptosis and inflammation
Caspase-dependent apoptotic cascade	Elevated caspase-3, caspase-9 activation leading to neuronal loss	Downregulates caspase activation via mitochondrial stabilization	Inhibition of intrinsic apoptosis
Calcium signalling pathways	Intracellular Ca^{2+} overload causing excitotoxicity	Stabilizes membrane channels and Ca^{2+} homeostasis	Protection against excitotoxic neuronal injury
Cholesterol/lipid raft signalling	Altered membrane microdomains affecting receptor clustering	Modulates lipid raft composition due to sterol mimicry	Improved synaptic receptor signalling and plasticity
Neurotrophic signalling (BDNF/TrkB)	Reduced neurotrophic support in aging and neurodegeneration	Indirect enhancement of neurotrophic signalling	Improved synaptic maintenance and cognitive resilience

Neurodegenerative disorders are distinguished by the imbalance in signalling, pro-death and pro-inflammatory processes prevail over the survival mechanisms. This signalling landscape rebalances with β-sitosterol is what renders the latter neuroprotective. Cellular and preclinical models put forward the evidence that β-sitosterol has the capability to simultaneously promote pro-survival cascade, inhibit stress activated kinases, as well as restore homeostatic feedback loops. Such systems level modulation is especially pertinent considering the redundancy and plasticity of the neuronal signalling networks which routinely circumvent the interventions through single target [56].

4.1. PI3K/Akt/GSK-3β Axis and Neuronal Survival Signalling

Akt pathway is an extensive regulator of neuronal survival, growth and synaptic plasticity. Akt activation is associated with cell survival which suppresses apoptotic factors and improves metabolic efficiency. Dysregulation of this pathway in neurodegenerative disease has been observed to increase neuronal vulnerability to oxidative stress and excitotoxic damage. β-Sitosterol has been reported to increase Akt phosphorylation and thus strengthen the survival signalling of vulnerable neuronal groups. One critical downstream target of Akt is glycogen synthase kinase-3β (GSK-3β), a kinase implicated in tau hyperphosphorylation, synaptic dysfunction and neuronal apoptosis. This modulation is able not only to circumscribe tau pathology but cytoskeletal integrity and synaptic architecture is also stabilized. In addition to its impact on the process of apoptosis, the PI3K/Akt/GSK-3β axis also modulates neurogenesis and synaptic plasticity. Through these actions, the β-sitosterol can play a part in the functional recovery and cognitive resilience, other than actively preventing the cell death. This ability to facilitate survival, as well as plasticity highlights its applicability as an agent modulating disease instead of as one of strictly protective agents [57].

4.2. AMPK-mTOR Autophagy Crosstalk

Autophagy is a vital quality-control process in neurons and helps certain organelles and misfolded proteins to be removed. Autophagic activity depends on the balance between the AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) signalling. The AMPK signalling that is impaired and mTOR hyperactivated in the chronic state of neurodegenerative diseases inhibits autophagic flux, resulting in the piles up of toxic protein aggregate. This signalling axis has been demonstrated to be regulated by β-Sitosterol which stimulates AMPK and alters mTOR. AMPK stimulates energy homeostasis and autophagy activation and regulated mTOR inhibition removes autophagic inhibition. This dual modulation has the effect of the β-sitosterol of restoring the autophagic clearance capacity but not causing excessive catabolic stress. Autophagy restoration has extensive consequences on protein clearance [58]. This process is backed by increased autophagic flux facilitating mitochondrial turnover by mitophagy, reducing oxidative stress and inhibiting mitochondrial inflammatory legendation. These reciprocal advantages are congruent with neurodegenerative pathology of a multifactorial character. Notably, β-sitosterol seems to stimulate a moderate response of autophagy which is not harmful as compared to the negative impacts of the unregulated induction of autophagy. This rational approach offers a contrast to the pharmacological mTOR-blockers which tend to have their therapeutic indexes in the slim [59].

4.3. Synaptic Plasticity, Calcium Homeostasis and Neurotransmission

One of the most predictable and the earliest signs of the development of the neurodegenerative diseases is synaptic dysfunction. Calcium homeostasis disruption, neurotransmitter release and synaptic protein loss, are antecedents of overt neuronal loss and are strongly linked with cognitive impairment, as well as have protective actions at the synaptic level which include stabilizing membrane composition, regulating receptor-associated signalling and inhibiting calcium overload [60]. Overaccumulation of calcium within the cell triggers proteins of degradation, phospholipid degradation and apoptotic pathways which may be regulated by the β-sitosterol mediated control of calcium signalling indirectly by stabilizing membrane bound ion channels and receptors and indirectly by mitochondrial protection which increases calcium buffering capacity. The inhibitory effect of calcium. This multi-pronged regulation of calcium dynamics means that excitotoxic stress ceases and the preservation of the integrity of the synapses [61].

Also, it has been shown that β-sitosterol can have beneficial effects on long term potentiation synaptic proteins and neurotransmission. Preserving synaptic structure and synaptic signalling, β-sitosterol promotes functional neural networks even during pathological states. All these synaptic effects support the idea that neuroprotection should not be confined to cell survival, but rather also should be considered in terms of maintaining neuronal connectivity and processing of information [62].

5. Disease Specific Implications of B-Sitosterol

Although neurodegenerative disorders have similar cellular and molecular pathophysiology, each distinct disease has its pathological signature and as well as regional vulnerability in the brain. Therefore, it is necessary to assess the therapeutic utility of a neuro protective agent based on disease specific signalling contexts. The accumulating experimental data will indicate that β-sitosterol has neuroprotective properties in a number of neurodegenerative disorders by modulating common upstream pathways but evolves to disease specific marrow drivers [63]. This flexibility improves its approval as a neuroprotective candidate of wide spectrum. The multifactorial nature of neurodegenerative diseases is consistent with the pleiotropic effects of β-sitosterol which includes antioxidant defence, anti-inflammatory regulation, mitochondrial stabilization and proteostasis regulation. Instead of aiming at the active presence of one pathogenic protein, β-sitosterol seems to reduce the cellular stress atmosphere that promotes the development of diseases. Reductions to make in major neurodegenerative disease Disease-specific implications of β-sitosterol along with its potential beneficial impact on disease progression were summarized in the following subsections [64].

5.1. Alzheimer's Disease

AD is a progressive mental disorder which is main linked to extracellular amyloid-β deposition intracellular tau hyperphosphorylation, loss of synapses and sustained neuroinflammation. The early pathogenic events which include oxidative stress and mitochondrial dysfunction are already present and so β-Sitosterol already portrays the disease as a disease modifying intervention than a disease modifying intervention. Experimental results signify that β-Sitosterol has the capacity to mitigate amyloidogenic handling by matching the activity of membrane related secretase and consequently, lowering amyloid-B synthesis [65]. Its effects on lipid rafts formation can vary the localization and activity of the enzymes of amyloid precursor protein processing and it plays a role in reducing plaque burden. Similarly, SK-3β activity reduces tau hyperphosphorylation, addressing another central pathological hallmark of AD. In addition to direct influences on protein pathology, β-sitosterol has strong anti-inflammatory and antioxidant effects in the AD brain. Inhibition of overactivated microglia and redox balance recovery protect the synapses as well as cognitive functioning. All of these effects indicate that β-sitosterol might delay the development of the disease with the stabilization of neuronal and synaptic conditions and not the eradication of the existing pathology [66].

5.2. Parkinson's Disease

The disease being discussed is known as PD and major symptoms include the loss of dopaminergic cells in the substantia nigra and the presence of aggregates of α-synuclein. Mitochondrial dysfunction, oxidative stress and disrupted autophagy rank among the key factors that drive dopaminergic vulnerability as the regulatory impact of β-Sitosterol on all these associated conditions demonstrates its significance in neuroprotection of PD. It has also been demonstrated that β-Sitosterol can improve the resilience of mitochondria and alleviate oxidative stress in dopaminergic cells and maintain cellular energy homeostasis. It's the stimulation of autophagic effects can help to eliminate the misfolded α-synuclein, preventing proteotoxic stress. Overcoming a life-threatening pathological bottleneck in PD progression, β-sitosterol removes autophagic flux restoration. It can also be stated that inflammatory signalling contributes to PD and activated microglia mediate this secondary injury which allows inhibiting the production of pro-inflammatory cytokines by β-sitosterol to provide a more conducive microenvironment to the survival of neurons. Taken together, the above actions indicate that β-sitosterol could be useful as a supplement to current dopaminergic treatments by affecting the upstream pathways of neuronal death [67].

5.3. Other Neurodegenerative and Neuroinflammatory Disorders

The disease being discussed is known as PD and major symptoms include the loss of dopaminergic cells in the substantia nigra and the presence of aggregates of α-synuclein. Mitochondrial dysfunction, oxidative stress and disrupted autophagy rank among the key factors that drive dopaminergic vulnerability as the regulatory impact of β-Sitosterol on all these associated conditions demonstrates its significance in neuroprotection of PD. It has also been demonstrated that β-Sitosterol can improve the resilience of mitochondria and alleviate oxidative stress in dopaminergic cells and maintain cellular energy homeostasis [68]. Its induction of autophagic mechanisms can mediate the clearance of misfolded α-synuclein that lowers the level of proteotoxic stress. Overcoming a life-threatening pathological bottleneck in PD progression, β-sitosterol removes autophagic flux restoration. It can also be stated that inflammatory signalling contributes to PD and activated microglia mediate this secondary injury which allows inhibiting the production of pro-inflammatory cytokines by β-sitosterol to provide a more conducive microenvironment

to the survival of neurons. Taken together, the above actions indicate that β-sitosterol could be useful as a supplement to current dopaminergic treatments by affecting the upstream pathways of neuronal death [69].

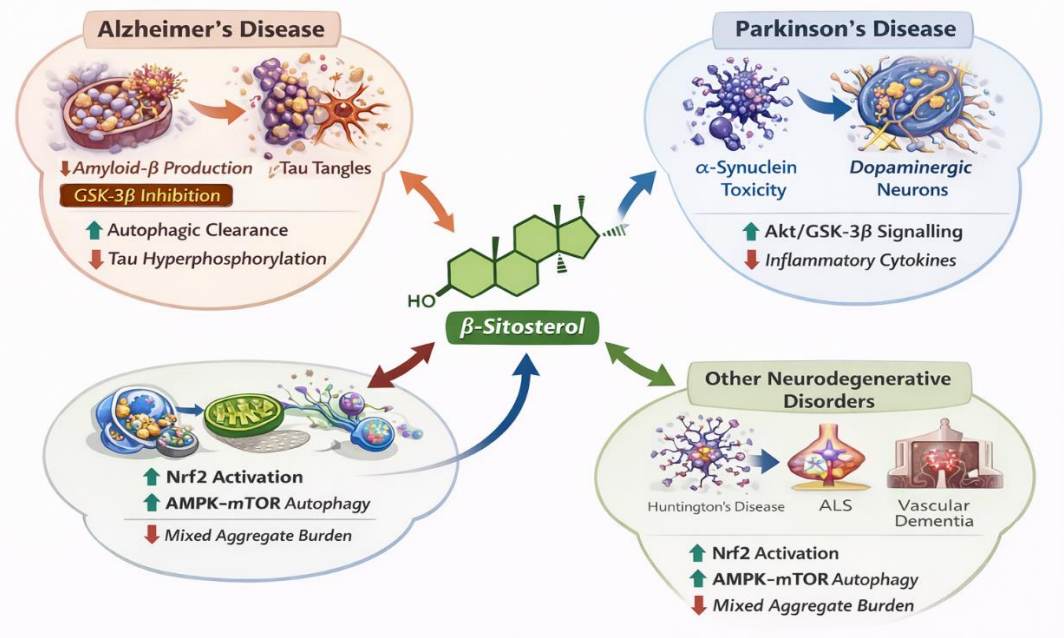

Fig 2: Disease-specific molecular targets of β-sitosterol

6. Translational Challenges and Formulation Strategies

Although there is strong mechanistic evidence to support the neuroprotective property of β-sitosterol a number of challenges at the translational level have to be overcome before it can be included in clinical neurotherapeutics. The fact that its oral bioavailability and brain penetration are rather limited even under physiological conditions is constituted by one of the main limitations. Being a lipophilic sterol, β sitosterol has a limited aqueous solubility and this limits its systemic absorption and repeated access to neural tissue. Such pharmacokinetic barriers require new approaches of formulation to optimise central nervous system exposure [70]. New developments in drug delivery science have provided a new direction of improving bioavailability of phytosterols as well as brain targeting. Lipid-based nanoparticles such as nano emulsions, lipid-based solid lipid nanoparticles and phytosomies have demonstrated the potential to enhance the blood-brain barrier transport of sterol and improve its solubility. These systems can facilitate regulated exercise and prolonged exposure of CNS and maintain the desirable safety profile of β-sitosterol. Also, different methods of intranasal application are under investigation to avoid systemic metabolism and directly reach the brain providing a non-invasive method of neurotherapeutic site. The other translational point of concern is best dosing paradigms and safety in the long term. Neurodegenerative disorders also demand a long-term or long-lasting intervention. Although β-sitosterol is extensively ingested as a dietary supplement, its chronic impact at pharmacological concentrations within the CNS has not been fully elucidated. Strict preclinical investigations on dose-response curve, dose cumulative exposure and possible sterol deposition in neural tissue are necessary to determine safe therapeutic dose ranges [71, 72].

7. Conclusion and Future Perspectives

The changing perception of neurodegeneration as a system disorder has critically changed the approach to neurotherapy by 2025. Modern methods are based on the idea that restoration of cellular resilience, signalling balance and network integrity should be restored rather than an isolated set of pathological characteristics. In this context, β-sitosterol will be the promising multi-target neuroprotective substance able to regulate fundamental pathways of oxidative stress, neuroinflammation, mitochondrial dysfunction, autophagy failure and synaptic degeneration. In contrast to traditional individual drugs that act by a single target, β-sitosterol functions by co-regulation between interrelations of connected signalling pathways and this is in line with the multifactorial types of neurodegenerative diseases. Its ability to enter into neuronal and glial activities, stabilize mitochondrial activity and maintain synaptic organization makes it a potential disease modifying therapy than being a symptomatic one. Notably, its favourable safety profile and natural source also add to its attractiveness as a long-lasting treatment of chronic neurodegenerative diseases.

In the future, pharmacokinetic shortcomings an abridgement of efficacy in clinical trials and incorporation of sophisticated systems of delivery will be essential in establishing the successful translation of β-sitosterol into a neurotherapeutic agent. Formulation science, systems neuroscience and precision pharmacology convergence provides a viable avenue through which β-sitosterol can be developed in experimental models to clinical practice. With deeper and deeper research efforts unravelling the signalling interactions and disease specific effects, β-sitosterol could play a valuable role in the next round of neuroprotective approaches in the future that would involve the delaying or the modulation of the process of neurodegenerative diseases.

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Not Applicable.

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Not Applicable.

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List of Abbreviations
- **AD**: Alzheimer's disease
- **PD**: Parkinson's disease
- **ALS**: Amyotrophic lateral sclerosis
- **ROS**: Reactive oxygen species
- **BBB**: Blood brain barrier
- **Nrf2**: Nuclear factor erythroid 2 related factor 2
- **ARE**: Antioxidant response element
- **NF-Kb**: Nuclear factor kappa-light-chain-enhancer of activated B cells
- **PI3K**: Phosphoinositide 3-kinase
- **Akt**: Protein kinase B
- **GSK-3β**: Glycogen synthase kinase-3 beta
- **AMPK**: AMP-activated protein kinase
- **mTOR**: Mechanistic target of rapamycin
- **MAPK**: Mitogen-activated protein kinase
- **ATP**: Adenosine triphosphate
- **ΔΨm**: Mitochondrial membrane potential
- **BDNF**: Brain-derived neurotrophic factor
- **CNS**: Central nervous system

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