


# Chapter 13


## The Role of Polyphenols and Bioactive Compounds for Combating Neurodegenerative Diseases

**P. Jayashree**

 <https://orcid.org/0009-0008-6957-9256>


*Vels Institute of Science, Technology, and Advanced Studies, India*

**S. S. Meenambiga**

 <https://orcid.org/0000-0002-5445-525X>

*Vels Institute of Science, Technology, and Advanced Studies, India*

**Hanishka Pothiraj**

 <https://orcid.org/0009-0002-5692-0386>

*Vels Institute of Science, Technology, and Advanced Studies, India*

### ABSTRACT

*Neurodegenerative illnesses afflict hundreds of millions of people globally, resulting in significant healthcare expenses. Conventional treatments have hardly an effect on the disease, which at most are symptomatic, and recent studies have found, that the action of polyphenols and bioactive molecules are beneficial against the disease progression and also in maintaining cognitive function. These phytochemicals abundant in fruits, vegetables, herbs and medicinal plants exhibit a range of beneficial effects which could lead to the transformation of the concept of neuroprotection. Polyphenols such as flavonoids, phenolic acids, and tannins, have gained significant attention due to their potential in antioxidant and anti-inflammatory properties. It can therefore modulate specific signalling pathways implicated in autophagy, amyloid clearance and synaptic plasticity thus, could be potentially beneficial in the treatment of pathologies such Alzheimer's, Parkinson's and Huntington's diseases.*

DOI: 10.4018/979-8-3373-4139-2.ch013

## INTRODUCTION

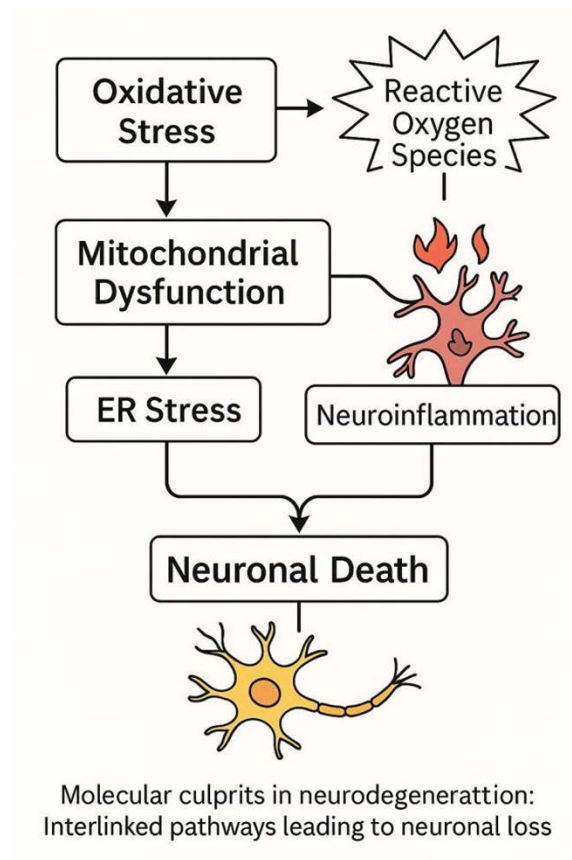
Neurodegenerative diseases, which include Alzheimer's, Parkinson's and Huntington's disease, are serious health problems worldwide, and involve complex, multicausal disorders causing oxidative stress, neuroinflammation and disturbance of mitochondrial function and of proteostasis leading to progressive neuronal loss and cognitive decline (Bhullar and Rupasinghe 2013) (Grabska-Kobyłeczka, Szpakowski et al., 2023). The few pharmacological therapies that are currently available only provide temporary symptomatic relief as well as side effects and they are not effective at modifying the progression of the disease. This highlights the importance for new therapeutic approaches (Renaud and Martinoli 2019). Polyphenols, one of the bioactive compounds of plant-based diet and other drugs obtained from such diet have become the agents of choice in fighting oxidative stress and inflammation in neurodegenerative disease, such as Alzheimer's Disease (Uddin et al., 2020). They hit multiple cellular pathways such as Nrf2, MAPK, JAK/STAT and Wnt/ $\beta$ -catenin and are able to produce anti-oxidant, anti-inflammatory actions as well as to enhance neuronal survival and synaptic plasticity (Kooshki et al., 2023). Polyphenol-rich diets are associated with lower risk for neurodegenerative disorders and decreased cognitive decline when compared with other plant extracts (Yan, Guo et al., 2022). Bioactive substances such as alkaloids and terpenoids have some potential: that of modulating neurotransmission, preventing tau protein aggregation, and fostering cognitive resilience. This chapter intends to link, through analysis of the mechanisms of actions and therapeutic relevance, the basic level of knowledge with the applied level of knowledge, thereby emphasizing the potential of such natural compounds for use in the development of novel dietary and pharmacologic therapeutic options for neurodegenerative disorders (Higham, Hidalgo et al., 2019).

## MOLECULAR MECHANISMS UNDERLYING NEURODEGENERATION

Neurodegeneration is impelled via molecular mechanisms that interact sophisticatedly, disturbing neuronal survival plus function. Anomalies within protein equilibrium stand as pivotal to these mechanisms, notably by way of diminished autophagy, which elicits the accretion of misshapen proteins and deleterious clusters within neurons (Esmaili, Yarjanli et al., 2022). Mitochondrial impairment constitutes another vital determinant because it obstructs energy synthesis, elevates reactive oxygen species (ROS) creation, and engenders oxidative pressure, all of which harm and eradicate neurons (Esteras, Rohrer et al., 2017). Aberrations within mitochondrial DNA coupled with its dynamism additionally strengthen oxidative strain which elevates cellular impairment within maladies such as Alzheimer's and Parkinson's (Moradi Vastegani, Nasrolahi et al., 2023). As dysregulated proteins aggregate in the ER, cellular stress responses inducing apoptosis or necroptosis are provoked, therefore endoplasmic reticulum (ER) stress is additionally consequential, as a programmed type of cell demise noticed in maladies like multiple sclerosis (Picon, Jayaraman et al., 2021). Microglia and astrocytes that are activated instigate neuroinflammation. Genetic factors such as TREM2 variants regulate microglial activation and neurodegeneration magnitude since it emits pro-inflammatory cytokines which aggravate neurodegeneration (Leyns, Ulrich et al., 2017). MicroRNAs are dysregulated which additionally disrupts gene expression networks because they affect neural and immune pathways as they contribute to disease progression across various neurodegenerative disorders (Jużwik, Drake et al., 2019). Multi-omics approaches reveal that genetic along with epigenetic factors, inclusive of rare and common variants, interact among environmental influences to mold disease susceptibility with progression. These linked molecular pathways

impair autophagy as well as induce mitochondrial and ER stress. They oxidatively impair likewise, incite neurons, modulate genetics, constitute the etiology of neurodegenerative disease, and furnish targets therapeutically (Ellwardt & Zipp 2014).

*Figure 1. Molecular mechanisms underlying neurodegeneration*



## Protein Misfolding and Aggregation

The misfolding and clumping of specific molecules signals several brain diseases. For example, amyloid-beta and tau indicate Alzheimer's,  $\alpha$ -synuclein points to Parkinson's, and TDP-43 suggests amyotrophic lateral sclerosis (Tsoi, Quan et al., 2023). These proteins have intrinsically disordered regions that let them to adopt abnormal conformations and aggregates. This causes disruption in cell functioning and neuronal death. A phenomenon called liquid-liquid phase separation happens when proteins bunches up spontaneously on their own into highly dynamic condensates that has recently been implicated in triggering the pathogenic aggregation of proteins and formation of inclusion bodies in neurons (Zbinden et al., 2020). Mutations, post- translational modifications, and truncations further enhance the aggregation propensity of these proteins, exacerbating disease progression.

## Impaired Proteostasis and Axonal Transport

Protein homeostasis, or simply proteostasis, refers to the cellular process proteins to maintain proper concentration, conformation, localization, and degradation of proteins that helps ensure their correct function. Neurons require these protein balance to stay healthy. As we get older, our body's ability to maintain this balance declines. This leads to the accumulation of toxic clumps of protein aggregates (Tan et al., 2019). The system that keeps proteins in check includes two main parts: ubiquitin-proteasome system and autophagy-lysosome pathway.

Defects with axonal transport are thought to be an early sign of many brain diseases. This movement is crucial for moving cell parts, proteins, and chemical signals along the neuron (Guo et al., 2020). When genes are mutated, it links axonal transport defects into neurodegeneration. These transport problems often interact alongside other pathological issues, like protein aggregation and mitochondrial dysfunction.

## Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is a common trait among neurodegenerative diseases that cause nerve cells to break down. These leads to defective energy production and increased reactive oxygen species (ROS) production which is harmful (Tan et al., 2019). This oxidative stress then damages cellular elements like fats, proteins, and DNA causing nerve cells to injure and die. Damage to mitochondria is linked to other cellular processes including protein aggregation and axonal transport along nerve fibres. These factors make brain cell breakdown worse in a vicious cycle.

## Dysregulation of Cellular Stress Responses

Neurons respond to stressors through adaptive signalling pathways, including the integrated stress response (ISR). These stressors are, at times, protective mechanisms, but the prolonged enhancement of phosphorylation of eukaryotic initiation factor  $2\alpha$  (eIF2 $\alpha$ ) results in exacerbated neurodegeneration due to global translation inhibition, neuroinflammation, and increased cell death. It means the ISR serves several roles: transient ISR activation acts as a protective one, chronic ISR activation can induce pathological characteristics such as memory loss, protein aggregation, and a neurodegenerative phenotype (Bond et al., 2020).

## Role of microRNAs and Genetic Factors

Regulators of gene expression post-transcription includes a group of small, non-coding RNAs called MicroRNAs (miRNAs). Previously unrecognized aspects of neurodegeneration are now discovered to involve miRNAs (Juźwik et al., 2019). Dysregulation of certain miRNAs affects both neural and immune systems pathways and thus drives disease progression in several neurodegenerative conditions. Genetic mutations such as those in presenilin's and amyloid precursor protein (APP) in familial Alzheimer's further acknowledge the molecular pathways that bring about the onset and progression of the disease (Maire et al., 2020; Ratan et al., 2023). Environmental and lifestyle factors, in combination to a genetic susceptibility, determines the risk and course of neurodegenerative disorders (Liu et al., 2023).

## POLYPHENOLS: CLASSIFICATION, SOURCES, AND BIOAVAILABILITY

### Classification of Polyphenols:

Polyphenols are a heterogeneous class of naturally occurring phytochemicals extensively found in plants, playing a role in colouration, flavour, and defence against infections. They are structurally defined by the presence of many phenol units. Polyphenols are categorically divided into flavonoids, phenolic acids, lignans, and stilbenes, according to their chemical structure and the quantity of phenolic rings.

**Flavonoids:** Flavonoids constitute the most common class of polyphenols, accounting for more than 60% of total dietary polyphenols. Their basic structure consists of two aromatic rings (A and B) connected by a three-carbon bridge, resulting in a closed pyran ring (C ring). Flavonoids are categorised into:

**Flavanols**, such as quercetin and kaempferol, are present in onions, kale, and broccoli. **Flavones**, such as apigenin and luteolin, are prevalent in parsley and celery. **Flavanones**, such as hesperidin and naringenin, are prevalent in citrus fruits. **Flavanols**, such as catechins and epicatechins, are prevalent in tea, chocolate, and grapes. **Anthocyanins**, such as cyanidin and delphinidin, are responsible for the red, blue, and purple hues in berries and red cabbage. **Isoflavones**, such as genistein and daidzein, are mostly located in soybeans and legumes.

### Phenolic Acids

Phenolic acids are categorised into two subtypes:

Hydroxybenzoic acids, such as gallic acid and protocatechuic acid, are present in tea, berries, and nuts. Hydroxycinnamic acids (e.g., caffeic acid, ferulic acid, chlorogenic acid) are prevalent in coffee, whole grains, and specific fruits. Phenolic acids have an essential part in antioxidant activity and are implicated in the modulation of inflammatory pathways.

### Stilbenes

Stilbenes are less prevalent in the plant kingdom. Resveratrol is the most extensively researched chemical, predominantly located in grapes, red wine, and peanuts. Stilbenes have attracted interest for their possible cardioprotective, anticancer, and neuroprotective properties.

### Lignans

Lignans are polyphenolic chemicals present in seeds, particularly flaxseeds, as well as in grains and vegetables. Prominent examples encompass secoisolariciresinol and matairesinol. Lignans in humans are transformed into enterolignans, which demonstrate oestrogenic and antioxidant properties.

### Additional Polyphenols

This group comprises tannins (both hydrolysable and condensed) and curcuminoids (including curcumin). Tannins, present in tea and wine, are recognised for their astringent flavour and antibacterial

characteristics. Curcuminoids, chiefly derived from turmeric, are acknowledged for their anti-inflammatory and antioxidant properties.

Polyphenols have several health advantages, encompassing antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and anticancer properties. Their bioavailability and metabolism are contingent upon the dietary matrix, gut flora, and host variables.

## **SOURCES OF POLYPHENOLS**

Polyphenols are abundantly found in the plant kingdom and are prevalent in numerous foods, playing an essential part in the human diet. Their sources can be defined roughly depending to the elementary dietary kinds.

### **1. Vegetables and Fruits**

Fruits provide the most frequent dietary source of polyphenols. Berries, including blueberries, strawberries, raspberries, and blackberries, are significantly rich in anthocyanins, flavonols, and phenolic acids. Apples, grapes, cherries, and citrus fruits exhibit significant amounts of flavanols, flavanones, and phenolic acids. Vegetables such as onions, spinach, broccoli, kale, and artichokes contain flavonoids, including flavonols (quercetin and kaempferol) and phenolic acids (chlorogenic and caffeic acids) (Manach et al., 2004).

### **2. Libations**

Beverages high in polyphenols significantly contribute to daily polyphenol consumption. Tea, particularly green and black types, is abundant in catechins and theaflavins. Coffee is a prominent source of chlorogenic acid, a principal hydroxycinnamic acid. Red wine contains resveratrol, flavonols, and tannins as a result of the fermentation of grape skins. Cocoa-based beverages are abundant in flavanols, chiefly catechins (Pandey & Rizvi, 2009).

### **3. Nuts, Seeds, and Pulses**

Walnuts, almonds, and hazelnuts possess a variety of polyphenols, notably ellagic acid and proanthocyanidins. Flaxseeds and sesame seeds are superior suppliers of lignans. Legumes, such as soybeans, are abundant in isoflavones, including genistein and daidzein.

### **4. Entire Grains and Cereals**

Whole grains, such as oats, wheat, and rye, are rich in phenolic acids, including ferulic acid and p-coumaric acid. The outer layers (bran) are notably abundant in bound phenolic chemicals, which enhance the antioxidant activity of cereals.

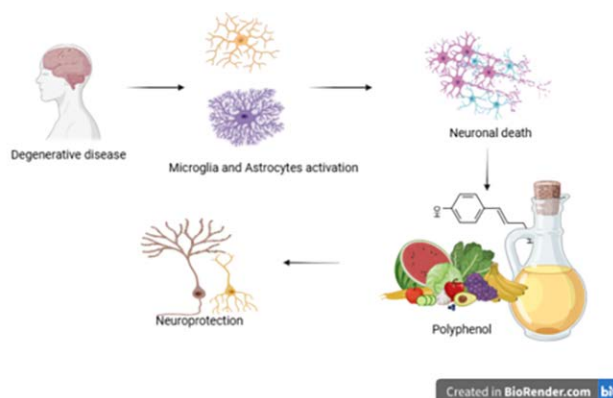
## 5. Botanicals, Seasonings, and Oils

Herbs and spices, including cloves, oregano, thyme, cinnamon, and turmeric, are rich in polyphenols, particularly flavonoids and curcuminoids. Extra virgin olive oil contains secoiridoids and phenolic alcohols, such as hydroxytyrosol.

## 6. Additional Sources

Dark chocolate, originating from cocoa, is plentiful in flavanols, particularly epicatechin. Processed foods that include berries, teas, or cocoa may provide polyphenols, however processing can influence their levels. Integrating a variety of polyphenol-rich foods into the diet is linked to many positive health effects, including decreased risks of chronic diseases attributed to their antioxidant and anti-inflammatory properties (Pérez-Jiménez et al., 2010).

Figure 2. Bioactive polyphenols and neurodegeneration



## BIOAVAILABILITY OF POLYPHENOLS

The bioavailability of polyphenols indicates the quantity of consumed polyphenols that are absorbed and utilized by the body to produce biological effects. Although prevalent in plant-based meals, polyphenols typically demonstrate low and inconsistent bioavailability owing to their intricate chemical structures and interactions in the digestive system (Scalbert & Williamson 2000). Polyphenols are found in foods in multiple forms, such as glycosides, esters, and polymers, which exhibit limited absorption in the small intestine. Intestinal enzymes or gut microbes frequently require enzymatic hydrolysis to liberate aglycone molecules for subsequent absorption. Upon absorption, polyphenols undergo significant phase II metabolism (glucuronidation, sulfation, and methylation) in the intestinal wall and liver, resulting in metabolites that circulate in the bloodstream (Manach et al., 2005).

## Factors affecting polyphenol bioavailability comprise:

**Chemical structure:** Monomeric forms like catechins and isoflavones are better absorbed than polymeric proanthocyanidins and tannins. **Food matrix:** The presence of fats can enhance the absorption of lipophilic polyphenols. **Gut microbiota:** Microbial fermentation in the colon converts unabsorbed polyphenols into bioactive metabolites. **Individual variability:** Genetics, age, health status, and microbiota composition significantly affect polyphenol metabolism.

Polyphenol metabolites may preserve or even enhance biological activity relative to their parent molecules, so contributing to antioxidant, anti-inflammatory, and cardioprotective properties. Enhancing polyphenol bioavailability is a current research priority, employing techniques such as nanoencapsulation, emulsions, and co-administration with absorption enhancers (Del Rio, Costa et al., 2010).

## NEUROPROTECTIVE MECHANISMS OF POLYPHENOLS

Polyphenols protect neurons through several ways that address the main causes of neurodegeneration. They act by scavenging reactive oxygen and nitrogen molecules, which lowers oxidative stress — a big factor in neuronal damage and in diseases like Alzheimer's and Parkinson's (Di Meo et al., 2020, Uddin et al., 2020). These plant-based compounds also chelate metal ions limiting the formation of more harmful free radicals and shielding nerve cell structures (Naoi et al., 2019). Beyond their antioxidant properties, they alter crucial cell signalling pathways, such as those associated with inflammation and cell death such as the NF- $\kappa$ B and Wnt/ $\beta$ -catenin pathways which reduces neuroinflammation and promotes neuronal survival (Al Mamun et al., 2024). They boost the expression of neurotrophic factors and interaction with surface receptors, which supports nerve growth, flexibility, and cognitive function (Arias-Sánchez et al., 2023). In the mitochondrial level, polyphenols helps maintain mitochondrial function and integrity by regulating mitochondrial biogenesis, dynamics, and apoptosis (Campos-Esparza et al., 2009). This is the key supply of energy for nerve cells and helps them resist cell death. Also, polyphenols can modulate neuro-transmitter systems by helping them bring back balance in nerve signals and supports brain health (Rebas et al., 2020). Their ability to cross the blood-brain barrier and safety makes polyphenols suitable for both to prevent and to help treat neurodegenerative diseases alongside other methods (Silva & Pogačnik 2020).

### Neuroprotective Mechanisms of Polyphenols

Progressive neuronal loss driven by oxidative stress, chronic inflammation, mitochondrial dysfunction, protein misfolding, and apoptosis is a hallmark of neurodegenerative illnesses like HD, PD, and AD. Many studies have looked at the neuroprotective effects of polyphenols, a broad class of phytochemicals present in many foods including fruits, vegetables, tea, coffee, and wine. Slowing neuronal degeneration and enhancing brain health are considerably aided by their complex mechanisms.

### Antioxidant Defense Mechanism:

When there is an accumulation of reactive nitrogen species (RNS) and reactive oxygen species (ROS), it damages the DNA, proteins, and lipids of neurons, a process known as neurodegeneration. They di-

rectly scavenging free radicals, polyphenols greatly enhance antioxidant activity, by Preventing Fenton reactions by chlorating redox-active metals such as iron and copper, Enhancing the activity of natural antioxidant enzymes made by the body, including SOD, CAT, and GPx. Furthermore, polyphenols promote cellular defense mechanisms against oxidative damage and activate the Nrf2/ARE pathway, which in turn enhances the transcription of phase II detoxifying enzymes (Scalbert et al., 2005).

### **Anti-Inflammatory Mechanism:**

The production and release of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) that worsen neuronal injury is caused by activated microglia and astrocytes in chronic neuroinflammation. On one-way polyphenols reduce inflammation is by blocking NF- $\kappa$ B signalling, which is a crucial transcription factor in this process. Another way is by lowering levels of pro-inflammatory mediators such as COX-2 and iNOS, Reduced activation of microglia through modulation of pathways involving Toll-like receptors and To prevent immune-mediated damage to nerve cells, polyphenols inhibit neuroinflammation (Tang & Le, 2016).

### **Mitochondrial Protection:**

Mitochondrial inability leads to reduced ATP synthesis and elevated ROS production, which contribute to neuronal death. Polyphenols maintain mitochondrial integrity by stabilising mitochondrial membranes. Augmenting mitochondrial biogenesis through the activation of PGC-1 $\alpha$  (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) and Enhancing ATP synthesis and diminishing mitochondrial oxidative stress. This protection guarantees the preservation of neuronal energy metabolism essential for appropriate synaptic function.

### **Modulation of Cell Survival Pathways:**

Polyphenols modify neuronal survival and death by influencing many cell signalling pathways:

- PI3K/Akt Pathway: Prevents apoptosis and increases neuronal survival.
- MPK Pathways (ERK, JNK, p38): Control reactions to survival cues, inflammation, and oxidative stress.
- Nrf2/ARE Pathway: Promotes the expression of cytoprotective genes.

Polyphenols preserve cellular homeostasis and shield neurones against apoptosis by means of these pathways.

**Inhibition of Protein Aggregation:** Neurodegenerative diseases often involve the aggregation of misfolded proteins, such as Amyloid-beta plaques in AD, Alpha-synuclein aggregates in PD. Polyphenols like epigallocatechin gallate (EGCG) and resveratrol have demonstrated the ability to: Inhibit protein aggregation, Disaggregate preformed fibrils and Reduce oligomer-induced neurotoxicity. This prevents synaptic dysfunction and neuronal loss caused by toxic protein aggregates.

## **ENHANCEMENT OF NEUROTROPHIC SUPPORT AND SYNAPTIC PLASTICITY:**

Neurotrophins like brain-derived neurotrophic factor (BDNF) are critical for synaptic plasticity, neuronal survival, and cognitive functions. Polyphenols enhance BDNF expression, promoting: Neurogenesis, Synaptic plasticity and Cognitive performance. By supporting neuronal repair and connectivity, polyphenols contribute to cognitive resilience against degenerative processes.

## **Metal Ion Chelation:**

Oxidative damage occurs when metal ion homeostasis is disturbed in the brain. Zinc, iron, and copper are neurotoxic, although certain polyphenols mitigate this effect by acting as natural metal chelators. This effect reduces the neurotoxicity associated with protein Pathy by preventing the aggregation of amyloid-beta and alpha-synuclein, which can be caused by metals.

Polyphenols exhibit promising neuroprotective actions via antioxidant, anti-inflammatory, anti-apoptotic, and anti-aggregation mechanisms. Their ability to modulate multiple pathological processes simultaneously highlights their potential as therapeutic agents in managing neurodegenerative diseases.

## **Modulation of Mitochondrial Function and Apoptosis:**

Polyphenols, which usually targets mitochondria, plays a neuroprotective role due to damaged mitochondria presence in the neurons during neurodegenerative diseases. Understanding their mechanism of action is important as helps to prevent free oxygen and nitrogen radicals, antioxidant gene expression induction and pro- and anti-apoptotic protein regulation (Naoiet al., 2019). Polyphenols also mediate mitochondrial biogenesis, dynamics (fission and fusion), and autophagic degradation into optimal quality and quantity of mitochondria. Moreover, they antagonize membrane potential stabilisation and apoptotic factor release triggered by these stimulants and attenuate cell death in neurons in vitro (Campos-Esparza et al., 2009).

## **Regulation of Neuroinflammation and Cell Signaling Pathways:**

Polyphenols contribute to modifying signal transduction pathways that are implicated in neuroinflammation and neuronal survival besides acting as antioxidants. These polyphenols stop the stimulants enclosing pro-inflammatory mediators like NF- $\kappa$ B pathway and the production of cytokines fostering neurodegeneration (Silva & Pogačnik 2020; Al Mamun et al., 2024). Additionally, polyphenol-induced signaling of the neurotropic factors also contributes to neuronal growth, plasticity and cognitive functions (Arias-Sánchez et al., 2023). Polyphenols exert their influence over pathways such as the Wnt/ $\beta$ -catenin and neurotransmitter systems with the action of sustain neuronal health and perhaps retard the pathology found in neurodegenerative diseases (Rebas, Rzajew et al., 2020). These pleiotropic effects, combined with their capacity to cross the blood-brain barrier and low toxicity profiles, render polyphenols promising agents for neuroprotection. Molecular Mechanisms Underlying Neurodegeneration have shown in Table 1.

*Table 1. Molecular mechanisms underlying neurodegeneration*

S. No.	Mechanism	Key Features	Associated Diseases	Reference
1	Protein Misfolding & Aggregation	Abnormal accumulation of misfolded proteins like $\alpha$ -synuclein, tau, A $\beta$	Alzheimer's, Parkinson's, Huntington's	Soto & Pritzkow, 2018
2	Oxidative Stress	Excessive ROS production damages lipids, proteins, and DNA	ALS, Parkinson's, Alzheimer's	Wang et al., 2014
3	Mitochondrial Dysfunction	Impaired ATP production, increased ROS, calcium imbalance	Parkinson's, Huntington's, ALS	Booth et al., 2017
4	Excitotoxicity	Overactivation of glutamate receptors causes Ca <sup>2+</sup> influx and neuronal death	ALS, Huntington's, Alzheimer's	Wang et al., 2019
5	Neuroinflammation	Chronic activation of microglia and astrocytes releasing cytokines	Alzheimer's, Parkinson's, MS	Heneka et al., 2015
6	Impaired Proteostasis	Dysfunction in ubiquitin-proteasome and autophagy-lysosome pathways	Alzheimer's, Parkinson's	Hegde, 2010
7	DNA Damage & Repair Defects	Accumulation of mutations and impaired repair mechanisms	ALS, Ataxias	Madabhushi et al., 2014
8	Axonal Transport Defects	Disruption of microtubule-based transport of organelles and proteins	ALS, Huntington's	Millecamps & Julien, 2013
9	Loss of Synaptic Integrity	Synaptic dysfunction and degeneration before neuron loss	Alzheimer's, Parkinson's	Palop & Mucke, 2010
10	Epigenetic Dysregulation	Aberrant methylation, histone modification affecting gene expression	Alzheimer's, Huntington's	De Jager et al., 2014

## PRINCIPAL CELLULAR SIGNALLING PATHWAYS INVOLVED

Numerous cellular signalling mechanisms modulate neuroinflammation, influencing glial activation and neuronal well-being:

### Nuclear Factor-kappa B (NF- $\kappa$ B) Signalling Pathway

Immune responses, inflammation, cell proliferation, and survival are all crucially regulated by the Nuclear Factor-kappa B (NF- $\kappa$ B) signalling system. Inhibitor proteins (I $\kappa$ Bs) keep NF- $\kappa$ B transcription factors in the cytoplasm when cells are at rest. When the I $\kappa$ B kinase (IKK) complex is stimulated by signals like cytokines, infections, or stress, I $\kappa$ Bs are phosphorylated and degraded. This facilitates the translocation of NF- $\kappa$ B dimers, primarily made up of p65 and p50 subunits, into the nucleus, where they stimulate the transcription of target genes related to cell survival, inflammation, and immunological control.

Because pro-inflammatory genes are spontaneously and persistently activated, dysregulated NF- $\kappa$ B signalling plays a role in cancer, autoimmune illnesses, and chronic inflammatory diseases. NF- $\kappa$ B is a prospective therapeutic target in conditions including rheumatoid arthritis and some kinds of cancer because of its essential involvement in inflammation and immunity (Zhang et al., 2017).

## Mitogen-Activated Protein Kinase (MAPK) Routes

Mitogen-Activated Protein Kinase (MAPK) pathways are essential signalling cascades that control cellular functions such as proliferation, differentiation, inflammation, and death. The three principal MAPK pathways are ERK (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase), and p38 MAPK (Kyriakis & Avruch 2012). These cascades are generally initiated by growth factors, cytokines, or stressors. Following activation, MAPKs phosphorylate several transcription factors and proteins, hence regulating gene expression and cellular responses. The dysregulation of MAPK signalling is associated with cancer, inflammatory illnesses, and neurological disorders, rendering these pathways relevant therapeutic targets (Huddleston, 2011).

## NLRP3 Inflammasome

The NLRP3 inflammasome is a crucial multiprotein complex in innate immunity, tasked with detecting pathogenic microbes and cellular stress. This inflammasome, primarily consisting of the sensor protein NLRP3 (NOD-like receptor family pyrin domain-containing 3), the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and pro-caspase-1, is activated upon the detection of stimuli such as ATP, crystalline substances, or reactive oxygen species. Upon activation, NLRP3 oligomerizes and recruits ASC, subsequently attracting pro-caspase-1, resulting in its activation (Heneka et al., 2014). Active caspase-1 converts pro-inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ) and interleukin-18 (IL-18) into their mature forms, hence enhancing inflammation. Although essential to host defence, dysregulated NLRP3 activation is implicated with chronic inflammatory conditions, including gout, type 2 diabetes, and neurodegenerative illnesses. NLRP3 is an emerging therapeutic target for managing excessive inflammation due to its pathogenic significance (Swanson et al., 2019).

## Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) Pathway

The Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway is an essential signalling mechanism that regulates immunological function, cellular proliferation, differentiation, and survival. This pathway, activated mostly by cytokines and growth factors, facilitates communication from extracellular signals to the nucleus, hence affecting gene expression.

The process initiates when cytokines attach to their designated cell surface receptors, resulting in receptor dimerisation. This facilitates the closeness of related Janus Kinases (JAKs)—a family of non-receptor tyrosine kinases—thereby facilitating their activation by trans-phosphorylation (Shuai & Liu, 2003). Upon activation, JAKs phosphorylate particular tyrosine residues on the receptor's intracellular domain, establishing docking sites for Signal Transducers and Activators of Transcription (STAT) proteins (Villarino et al., 2015). Upon binding to these phosphorylated sites, STATs are phosphorylated by JAKs. Phosphorylated STATs dimerise and translocate to the nucleus, where they bind to specific DNA sequences to regulate the transcription of target genes associated with immunity, inflammation, cell proliferation, and death. The JAK/STAT system is stringently controlled by negative feedback mechanisms, including Suppressors of Cytokine Signalling (SOCS) proteins and protein tyrosine phosphatases, to avert excessive or protracted activation (Banerjee et al., 2017). The dysregulation of this pathway is associated with numerous clinical illnesses, such as autoimmune diseases, malignancies, and inflammatory disor-

ders. The JAK/STAT pathway is a crucial therapeutic target due to its pivotal involvement in immune signalling and disease development. JAK inhibitors, like tofacitinib and ruxolitinib, have been formulated to address illnesses such as rheumatoid arthritis, psoriasis, and certain cancers.(O'Shea & Plenge, 2012).

## PI3K/Akt/mTOR Signalling Pathway

The PI3K/Akt/mTOR signalling system is an essential intracellular cascade that regulates cell growth, proliferation, metabolism, and survival. Activation often initiates when growth hormones or insulin attach to receptor tyrosine kinases (RTKs), resulting in the recruitment and activation of phosphoinositide 3-kinase (PI3K). PI3K phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP2) to produce PIP3, which attracts Akt (protein kinase B) to the plasma membrane (Fruman, Chiu et al., 2017). Akt is triggered by phosphorylation by PDK1 and the mTOR complex 2 (mTORC2). Activated Akt phosphorylates downstream targets that regulate glucose metabolism, protein synthesis, and the prevention of apoptosis (Saxton & Sabatini, 2017). A primary objective is the mechanistic target of rapamycin (mTOR), a serine/threonine kinase that assembles into two separate complexes: mTORC1 and mTORC2. mTORC1 modulates protein synthesis through S6K1 and 4E-BP1, facilitating cellular proliferation. The dysregulation of the PI3K/Akt/mTOR pathway is associated with cancer, diabetes, and neurodegenerative illnesses, positioning it as a significant therapeutic target in oncology and metabolic disorders (Salman et al., 2018). Major Cell Signaling Pathways Regulating Neuroinflammation are shown in Table 2.

Table 2. Major cell signaling pathways regulating neuroinflammation

Pathway	Key Regulators	Effect on Neuro-inflammation	Therapeutic Target Example	Reference
NF- $\kappa$ B	I $\kappa$ B, RelA/p65	Promotes pro-inflammatory cytokines	Curcumin, BAY 11-7082	Liu et al., 2017
MAPK (p38, JNK)	p38 MAPK, ERK1/2, JNK	Promotes glial activation and inflammation	SB203580 (p38 inhibitor)	Kim & Choi, 2010
NLRP3 Inflammasome	NLRP3, Caspase-1	Activates IL-1 $\beta$ , IL-18, pyroptosis	MCC950 (NLRP3 inhibitor)	Swanson et al., 2019
JAK/STAT	JAK1/2, STAT1/3	Cytokine-mediated pro-inflammatory signaling	Tofacitinib (JAK inhibitor)	Villarino et al., 2017
PI3K/Akt/mTOR	PI3K, Akt, mTOR	Anti-inflammatory / pro-survival effects	Rapamycin (mTOR inhibitor)	Huang et al., 2020

## MODULATION STRATEGIES AND THERAPEUTIC APPROACHES

**Pharmacological Inhibitors:** Numerous small molecule inhibitors aimed at NF- $\kappa$ B, MAPK, and JAK/STAT pathways have demonstrated effectiveness in preclinical neuroinflammation models. BAY 11-7082 suppresses NF- $\kappa$ B activation, hence diminishing the generation of pro-inflammatory cytokines by microglia (Zhang et al., 2017). MCC950 specifically suppresses NLRP3 inflammasome activation and mitigates neuroinflammation in Alzheimer's disease models (Heneka et al., 2014).

## **Natural Compounds and Phytochemicals:**

Polyphenols, including curcumin, resveratrol, and quercetin, regulate many signalling pathways, such as NF- $\kappa$ B and MAPK, demonstrating anti-inflammatory and antioxidant properties (Stith et al., 2018). These molecules offer a multitarget strategy with reduced adverse effects relative to manufactured pharmaceuticals.

## **Gene Suppression and RNA-Directed Treatments:**

RNA interference aimed at crucial inflammatory mediators (e.g., NLRP3, NF- $\kappa$ B subunits) has surfaced as a viable approach to mitigate neuroinflammation in experimental models. Nonetheless, clinical translation is constrained by delivery challenges.

## **Modulation of Microbiota:**

Recent research linked gut bacteria with central nervous system inflammation through the gut-brain axis. Modulating the microbiome through prebiotics, probiotics, or dietary treatments can indirectly influence neuroinflammatory signalling pathways (Cryan et al., 2019).

## **Endogenous Cellular Resilience and Alternative Splicing:**

Cyto-protection furthers cell survival and tissue resilience from being injured from reactive oxygen species, inflammation, and other toxic stimuli. Neurons possess self-repair pathways that may assist these cells in living through damage or neurodegeneration. Neuroprotection includes increasing expression of protective proteins, activation of autophagy, as well as modulating stress response pathways for the preservation of neuronal integrity and function (Marmolejo-Martínez-Artesero et al., 2021). Another important process is alternative splicing, which enables the cells to produce different protein variants from a single gene. Alternative splicing in response to environmental changes can give rise to protein variants that favor neuronal survival and adaptation. This thus opens promising means for neuroprotection and provides a therapeutic target for intervention.

## **Neurogenesis, Glial Modulation, and Lifestyle Factors:**

Neuroprotection is perhaps achieved by promoting neurogenesis, the process of generating new neurons, and modifying the activity of other brain cells called glial cells. For instance, stem cell-secreted extracellular vesicles can carry neuroprotective and neurogenic factors to the brain to reduce neuronal injury and to foster memory function (Ma et al., 2020). Another type of CNS cell (glial cells) is astrocytes, that can also acquire neuroprotective phenotypes inhibit harmful inflammation and enhancing neuronal survival under the action of specific molecular switches (Cameron et al., 2024). In addition to that some lifestyle-related factors, such as physical activity, cognitive stimulation, and social engagement, have been demonstrated to exert neuroprotective effects, stimulate neurotrophic signalling and to build cognitive reserve, which reduces the risk of developing dementia in age-related brain disorders.

## Comparison with Existing Pharmacological Approaches

Cholinesterase inhibitors (like donepezil and rivastigmine), NMDA receptor antagonists (like memantine), dopamine precursors (like levodopa), and MAO-B inhibitors (like selegiline) are all traditional drugs used to treat neurodegenerative illnesses. They mostly help with symptoms. These medications usually focus on specific pathways and are often linked to limited success in stopping disease progression. Additionally, negative consequences include stomach problems, trouble sleeping, and motor problems are typical (Cummings et al., 2019). Conversely, polyphenolic chemicals and other bioactive sourced from natural origins offer a multi-targeted treatment framework. These substances affect a number of related processes, including as oxidative stress, neuroinflammation, problems with mitochondria, and proteins that don't fold correctly. For example:

Resveratrol - activates SIRT1 and inhibits NF- $\kappa$ B, which helps fight inflammation and amyloid (Porquet et al., 2014). Curcumin - affects MAPK and JAK/STAT signalling, which helps neurones stay alive and stops inflammatory cascades (Gupta et al., 2013). Epigallocatechin gallate (EGCG) - from green tea stops amyloid-beta from clumping together and helps keep mitochondria healthy (Mandel et al., 2008).

These bioactive exhibit enhanced tolerance and reduced toxicity profiles, rendering them appropriate for prolonged administration and preventive measures. Its capacity to traverse the blood-brain barrier and modulate neurotrophic signalling pathways amplifies its therapeutic significance (Rege et al., 2015). Conventional pharmacological medicines are limited by their restricted mechanisms and side-effect profiles. In contrast, polyphenols provide a systems-level approach that aligns with personalised therapy. (Wang et al., 2020).

## Impact of Lifestyle Variables

Lifestyle factors can profoundly influence neurogenesis by affecting neuroinflammation, oxidative stress, and neurotrophic signalling.

**Physical Activity:** Aerobic exercise is a highly effective promoter of neurogenesis in the adult hippocampus. It elevates BDNF levels, stimulates NSC growth, and facilitates synaptic plasticity (Van Praag, Fleshner et al., 2014). Exercise modifies glial function by promoting microglial polarisation to the M2 phenotype and diminishing astrocyte reactivity. **Dietary Practices and Nutritional Science:** Diets abundant in polyphenols, omega-3 fatty acids, and antioxidants enhance neurogenesis. Compounds such as curcumin and resveratrol diminish neuroinflammation and oxidative stress, fostering an environment favourable for neural stem cell survival (Gómez-Pinilla 2008). In contrast, diets rich in fat and sugar hinder neurogenesis by exacerbating systemic and central nervous system inflammation. **Cognitive Stimulation:** Environmental enrichment, encompassing cognitive training and learning activities, enhances hippocampus neurogenesis by promoting neurotrophic factor expression and improving synaptic connections. Cognitive engagement also inhibits glial overactivation, preserving homeostasis in the neurogenic niche (Sierra, Encinas et al., 2010). **Sleep and Stress:** Chronic stress and sleep deprivation adversely affect neurogenesis via increasing cortisol levels and facilitating glial-mediated neuroinflammation. In contrast, stress management and sufficient sleep facilitate neurogenic processes.

Neurogenesis is a dynamic process governed by glial cells and affected by lifestyle factors. Regulating glial activation and implementing advantageous lifestyle modifications—such as physical activity, adequate diet, cognitive stimulation, and stress reduction—can cultivate a neurogenic milieu, offering prospects for preventive and therapeutic approaches to neurodegenerative diseases.

## OTHER NEUROACTIVE PHYTOCHEMICALS AND BIOACTIVE MOLECULES

### Classes and Examples of Neuroactive Phytochemicals:

From terpenoids to alkaloids, carotenoids, essential fatty acids, phytosterols, and even some essential oils, an ample variety of substances represent phytochemicals with possible neuroprotective and neuro-modulator activities, derived from plants, fungi, and some animals (Mohd Sairazi and Sirajudeen 2020, Babazadeh, Vahed et al., 2023). Many of these compounds tend to act through a handful of mechanisms—NMDA receptor antagonism, antioxidant power, anti-inflammatory activities, versus reactive oxygen species formation, or apoptotic activation but they can modulate neurotransmitter systems, neurotrophic signaling, and gene expression (Naoi, Inaba-Hasegawa et al., 2017). For instance, they may modulate biosynthesis in serotonin, dopamine, and norepinephrine, paralleled with mood, cognition, and behavior. Some phytochemical activation of Nrf2 signaling-related antioxidant mechanisms in brain cells is exhibited by curcumin, resveratrol, and sulforaphane. These ginsenosides and several flavonoids, work in the help of or by mimicking the action of neurotrophic factors that promote growth and survival of neurons (Bai, Bian et al., 2023).

Neuroactive phytochemicals exhibit structural and functional diversity, often categorised according to their chemical composition and biological functions. The primary categories comprise polyphenols, alkaloids, terpenoids, saponins, sterols, and polysaccharides. Polyphenols: Polyphenols constitute the most extensive category of neuroactive phytochemicals, recognised for their robust antioxidant and anti-inflammatory characteristics. Plant Sources and Therapeutic Applications are shown in Table 3. They are categorised into multiple subgroups: **Flavonoids**

Flavonoids are extensively found in fruits, vegetables, tea, and wine. Quercetin, present in apples, onions, and berries, functions as an antioxidant, regulates cell signaling, suppresses lipid peroxidation, and safeguards neurons from oxidative stress-related damage. Epigallocatechin-3-gallate (EGCG): The predominant catechin in green tea, EGCG safeguards against neuroinflammation, oxidative stress, and amyloid-beta aggregation. Rutin, found in citrus fruits, exhibits neuroprotective properties via its antioxidant capabilities and anti-apoptotic processes. Luteolin, present in celery and green peppers, demonstrates anti-inflammatory and neuroprotective properties through the suppression of pro-inflammatory cytokines. **Phenolic Acids**

Phenolic acids are secondary metabolites present in coffee, fruits, and vegetables. Caffeic acid functions as an antioxidant and mitigates neuroinflammation. Ferulic acid: Demonstrates neuroprotective properties against oxidative stress and safeguards dopaminergic neurones. Rosmarinic acid: Present in rosemary and mint, recognised for its capacity to diminish neuroinflammation and mitigate amyloid-beta toxicity. **Stilbenes**: These compounds possess a 1,2-diphenylethylene core. Resveratrol, present in grapes and red wine, activates SIRT1, demonstrates antioxidant properties, controls neuroinflammation, and diminishes amyloid formation. **Lignans**: Sesamin, present in sesame seeds, possesses antioxidant and anti-inflammatory effects that provide neuroprotection.

**Alkaloids**: Alkaloids are nitrogenous chemicals that exhibit notable pharmacological effects on the central nervous system.

- Huperzine A: Extracted from *Huperzia serrata*, it functions as a reversible acetylcholinesterase inhibitor, enhancing cognitive performance in Alzheimer's disease patients.

- **Berberine:** Present in *Berberis* species, berberine regulates neurotransmitter systems, diminishes neuroinflammation, and demonstrates anti-amyloid properties.

Caffeine, found in coffee and tea, functions as an adenosine receptor antagonist, promoting alertness and maybe diminishing the risk of neurodegenerative disorders.

Nicotine, present in tobacco leaves, activates nicotinic acetylcholine receptors, enhancing attention and memory at low dosages; yet, its medicinal application is contentious due to the risk of addiction.

Arecoline, derived from *Areca catechu*, functions as a muscarinic receptor agonist; nevertheless, its neurotoxic and addictive characteristics constrain its therapeutic applicability.

## Terpenoids

Terpenoids are lipophilic compounds included in essential oils and numerous medicinal botanicals.

**Ginkgolides and Bilobalide:** Extracted from *Ginkgo biloba*, these chemicals demonstrate neuroprotective effects through free radical scavenging, platelet-activating factor reduction, and cerebral blood flow enhancement.

**Curcumin:** A diferuloylmethane derived from turmeric (*Curcuma longa*), curcumin exhibits neuroprotective, anti-inflammatory, antioxidant, and anti-amyloid characteristics. Curcumin also regulates other signalling pathways, including NF- $\kappa$ B and MAPK.

**Cannabidiol (CBD),** derived from *Cannabis sativa*, interacts with CB1 and CB2 receptors, producing anxiolytic, anti-inflammatory, and neuroprotective benefits without inducing euphoric side effects.

**Ginsenosides:** Active saponins found in *Panax ginseng*, including as Rb1 and Rg1, promote neurogenesis, mitigate oxidative stress, and regulate neurotransmitter systems.

## Saponins

Saponins are glycosides possessing soap-like characteristics. **Ginsenosides:** Besides being terpenoids, ginsenosides are categorised as triterpenoid saponins. They improve cognitive function and neuronal viability. **Bacosides,** present in *Bacopa monnieri* (Brahmi), facilitate memory enhancement, mitigate oxidative damage, and stimulate synaptic activity.

## Sterols

Plant sterols exhibit structural similarity to cholesterol and influence brain health.

**Withanolides,** derived from *Withania somnifera* (Ashwagandha), possess anti-inflammatory, antioxidant, and neuroprotective activities. They promote axonal regeneration and synaptic reorganisation.

**$\beta$ -Sitosterol:** Present in nuts and seeds,  $\beta$ -sitosterol regulates membrane fluidity and may safeguard brain membranes from oxidative damage.

## Polysaccharides

Polysaccharides, particularly derived from medicinal fungi, exhibit neuroprotective properties. *Ganoderma lucidum* polysaccharides demonstrate antioxidant and anti-inflammatory properties that

safeguard neurones from oxidative damage. Polysaccharides from *Hericium erinaceus* (Lion's Mane): Facilitate the synthesis of nerve growth factor (NGF), hence enhancing neurogenesis and myelination.

*Table 3. Plant sources and therapeutic applications*

Plant Source	Neuroactive Phytochemicals	Therapeutic Potential	Reference
<i>Ginkgo biloba</i>	Ginkgolides, Bilobalide	AD, cognitive enhancement	Smith & Luo, 2004; Mahadevan & Park, 2008
<i>Curcuma longa</i>	Curcumin	AD, PD, anti-amyloid, anti-inflammatory	Gupta et al., 2013; Small et al., 2018
<i>Camellia sinensis</i>	EGCG, catechins	PD, AD, antioxidant, neuroprotective	Mandel et al., 2008; Panickar, 2013
<i>Vitis vinifera</i>	Resveratrol	AD, PD, anti-amyloid, anti-inflammatory	Sawda et al., 2017; Turner et al., 2015
<i>Bacopa monnieri</i>	Bacosides	Cognitive enhancement, memory support	Calabrese et al., 2008; Kongkeaw et al., 2014
<i>Panax ginseng</i>	Ginsenosides	Memory, neuroprotection, anti-fatigue	Reay et al., 2005; Yuan et al., 2021
<i>Withania somnifera</i>	Withanolides	Cognitive function, neuroprotection	Kulkarni & Dhir, 2008; Tiwari et al., 2014
<i>Cannabis sativa</i>	Cannabidiol (CBD)	Anxiety, neuroprotection, seizure control	Ibeas Bih et al., 2015; Devinsky et al., 2014
<i>Huperzia serrata</i>	Huperzine A	Acetylcholinesterase inhibition in AD	Wang et al., 2006; Zhou et al., 2017
<i>Ganoderma lucidum</i>	Polysaccharides	Antioxidant, neuroprotective	Wachtel-Galor et al., 2011; Xu et al., 2011
<i>Hericium erinaceus</i>	Polysaccharides, hericenones	Neurogenesis, cognitive support	Wong et al., 2016; Nagano et al., 2010

## Obstacles and Constraints

- **Bioavailability:** Numerous phytochemicals, including curcumin and resveratrol, exhibit inadequate absorption, fast metabolism, and restricted brain penetration.
- **Challenges of Standardisation:** The inconsistency in plant extracts and absence of standardised dose impede reproducibility.
- **Safety and Toxicity:** Elevated dosages or prolonged usage may present hazards; extensive safety investigations over the long term are scarce.
- **Regulatory Obstacles:** The majority of neuroactive phytochemicals are categorised as supplements rather than pharmaceuticals, constraining their clinical advancement.

### Prospective Trajectories

- **Nanotechnology:** Utilisation of nanoparticles, liposomes, and micelles to enhance delivery and bioavailability.
- **Synergistic Formulations:** Integrating several phytochemicals or employing them alongside synthetic medications to augment therapeutic effectiveness.

- Network Pharmacology: Comprehending multi-target effects via systems biology to enhance phytochemical-based therapeutics.

Neuroactive phytochemicals offer promising multi-target treatment strategies for the management of neurodegenerative illnesses and the enhancement of cognitive function. Their natural origin, along with various pharmacological actions including antioxidant, anti-inflammatory, and neurotrophic properties, renders them appealing candidates for neuroprotective methods. Ongoing research aimed at addressing issues such as inadequate bioavailability and standardisation, in conjunction with clinical validations, will ascertain their prospective function in neurotherapeutics (Escartin, Galea et al., 2021).

### **Mechanisms and Therapeutic Potential:**

Plant chemicals that act on the nervous system impact upon more than one pathway associated with brain diseases. These are oxidative cell damage, protein aggregation, mitochondrial dysfunction, and impairment of autophagy (Khan et al., 2020, Limanaqi, Biagioni et al., 2020, Stacchiotti and Corsetti 2020). They can fix mitochondrial balance in cells and help remove misfolded proteins to change inflammatory response. All these slow down neuronal cell death (Naoi, Wu et al., 2019). Some plant extracts and pure compounds can get into the blood-brain barrier to protect neuronal cells in pre-clinical models. This shows better outcomes for diseases like Alzheimer's Parkinson's, and Huntington's (Sánchez-Martínez, Valdés et al., 2022). Provided the very early research looks good but more human studies are needed to prove that they work and determine the best route of administration and safety for use on humans (Khan, Jahan et al., 2020).

### **Synergistic Effects and Multi-Targeted Therapies**

Neuroprotective and promise-altering approaches must have synergistic effects and multi-targeted neuroactive compounds. These methods use combined mechanisms of multiple bioactive agents for better efficacy than single-agent treatments, which commonly involve simultaneous targeting of multiple pathophysiological pathways.

The combination of saikosaponin A and albiflorin showing the synergetic neuroprotective effect against corticosterone-triggered apoptosis and this combination is accomplished via the regulation of metabolic pathways, enhancing of mitochondrial function, decreasing of oxidative stress and inhibition of neuroinflammation. The combination modulates more metabolites and influences metabolic balance and inflammation stronger than the single compounds, thus encouraging multi-target intervention (Li, Hou et al., 2022).

With a similar approach, synergistic neuroprotective effects have been demonstrated with natural products applied in Alzheimer's disease neurodegeneration animal models: docosahexaenoic acid, Ginkgo biloba, D-pinitol, and ursolic acid. The combination benefited survival time and lifespan in animal models, along with significant reductions in amyloid-beta plaque accumulation, and enhanced cognitive performance in animals, outperforming the effects of individual components. These results opens up the possibility of formulating mixtures of either synthetic or bioactive molecules to simultaneously address multiple hallmarks of neurodegeneration (Griñán-Ferré et al., 2021).

These also have been a topic of synergistic benefits when pairing synthetic drugs with natural compounds. For example, neuroprotection from cerebral ischemia/reperfusion injury was best provided by

the simultaneous application of rosuvastatin and resveratrol combinations than either on its own. This is due to the anti-apoptotic, anti-inflammatory, and autophagy-activating synergic actions, showing the benefit of simultaneously attacking several neurodegenerative pathways (Liu, Yang et al., 2018). Beta vulgaris juice and DMSA have a synergistic effect on reducing lead-induced neurotoxicity. They also boost antioxidant and anti-inflammatory responses and help regulate enzymes linked to neurotransmitters (Shaban, Abd El-Kader et al., 2021). Likewise, the combination of phytochemical compounds, such as quercetin, folic acid, with conventional drugs poses the possibility of enhanced antioxidant, anti-inflammatory, and acetylcholinesterase-inhibitory activities. Hence, these combinations could prove suitable as dietary supplements or adjuvant therapies for neurological disorders. Synergistic inhibitory effect on acetylcholinesterase was seen from the combination of Safranin O with quercetin or gallic acid, thus propounding the quest for new multi-targeted anti-neurodegenerative drug treatments (Imededdine et al., 2023).

## Real-World Translational Barriers

Despite promising preclinical studies, numerous challenges in real-world applications hinder the use of polyphenol-based therapeutics and enhanced delivery systems for neurodegenerative illnesses.

**Restricted Clinical Evidence** - The majority of studies on polyphenols are confined to in vitro or animal models. Human trials are scarce, and those that exist often lack sufficient power or standardised outcome measures (Vauzour et al., 2010).

**Bioavailability and Metabolism** - Natural compounds like curcumin and resveratrol demonstrate inadequate absorption, rapid metabolism, and reduced systemic retention, hence influencing dose optimisation and therapeutic reliability (Wang et al., 2020).

**Regulatory Complexity** - Polyphenols occupy a position between nutraceuticals and medicines, complicating the understanding of applicable regulations. Approval processes vary by jurisdiction and sometimes lack defined criteria for safety and efficacy (Patel et al., 2021).

**Manufacturing and Scalability** - Nanocarriers and intelligent delivery systems require sophisticated manufacturing techniques that may not be economically viable or easily scalable for mass production (Kakkar et al., 2019).

**Patient Adherence and Acceptance** - Innovative forms such as microneedle patches or intranasal gels may face resistance due to unfamiliarity, discomfort, or cultural inappropriateness, particularly among elderly individuals.

**Intellectual Property and Commercialisation** - The prevalence of polyphenols in commonly consumed foods complicates patent acquisition and diminishes the business incentives for pharmaceutical companies to spend (Yang et al., 2022).

To overcome these challenges, collaboration across disciplines is essential, alongside the design of robust clinical trials and the formulation of policies that promote innovation while ensuring safety and accessibility.

## Future-Oriented Perspectives on Innovative Delivery Methods

Polyphenols and other bioactive compounds often exhibit restricted therapeutic efficacy due to their poor absorption, rapid degradation, and instability in physiological environments. Innovative delivery

systems are being devised to enhance targeted distribution, regulated release, and penetration of the blood-brain barrier.

Nanotechnology based systems - such as liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles, have shown promise in improving the pharmacokinetics of polyphenols. Curcumin-loaded nanoparticles have demonstrated enhanced brain absorption and neuroprotective benefits in preclinical animal studies (Kakkar et al., 2019).

Hydrogel based - carriers and microneedle patches offer less invasive techniques for prolonged release, particularly for transdermal and intranasal applications. These platforms can circumvent first-pass metabolism and deliver drugs directly to the central nervous system (Patel et al., 2021).

Exosome-mediated - delivery is a study domain that utilises natural vesicles for the safe and targeted transport of bioactive compounds. Researchers have engineered exosomes derived from mesenchymal stem cells capable of transporting resveratrol and other neuroprotective pharmaceuticals across the blood-brain barrier (Yang et al., 2022).

Researchers are exploring “smart delivery systems” capable of releasing therapeutic agents exclusively in diseased tissues in response to variations in pH, temperature, or oxidative stress. These solutions align with the objectives of precision medicine and may reduce off-target effects while enhancing efficacy. As research advances, the integration of these innovative delivery vehicles with polyphenol-based therapeutics may revolutionise treatment approaches for neurodegenerative diseases.

## CHALLENGES

Most neuroactive substances like natural products, peptides, etc., shows an inability to cross the blood-brain barrier efficiently, thus experiencing reduced bioavailability and hence, having limited therapeutic impact in the brain. Many compounds get metabolized rapidly or degraded before they hit their biological targets and their pharmacokinetics and pharmacodynamics in humans remain poorly understood. Though many compounds show promising results at the preclinical stage, few clinical trials have been either inconclusive or show modest results due to varying compound purities, doses, and patient populations. Safety and tolerability concerns arise, as some injections or neuroactive steroids may have levels of neurotoxicity or addictive potential.

## REFERENCES

- Al Mamun, A., Nsiah, N. Y., Hossain, M. A., Islam, M. R., Herrera-Calderon, O., Baghel, M., & Hafez, M. M. (2024). Polyphenols targeting NF- $\kappa$ B pathway in neurological disorders: What we know so far? *International Journal of Biological Sciences*, 20(4), 1332–1355. DOI: 10.7150/ijbs.90982 PMID: 38385077
- Arias-Sánchez, R. A., Saralegui, Y., Hernández-Baltazar, D., & Rovirosa-Hernández, M. J. (2023). Polyphenols and neurodegenerative diseases: Potential effects and mechanisms of neuroprotection. *Molecules (Basel, Switzerland)*, 28(14), 5415. Advance online publication. DOI: 10.3390/molecules28145415 PMID: 37513286
- Babazadeh, A., Ghanbarzadeh, B., & Hamishehkar, H. (2023). Natural bioactive molecules as neuro-medicines for the treatment/prevention of neurodegenerative diseases. *ACS Omega*, 8(4), 3667–3683. DOI: 10.1021/acsomega.2c06098 PMID: 36743024
- Bai, X., Bian, Z., Zhang, M., & Li, J. (2023). Targeting the Nrf2 signaling pathway using phytochemical ingredients: A novel therapeutic road map to combat neurodegenerative diseases. *Phytomedicine*, 109, 154582. Advance online publication. DOI: 10.1016/j.phymed.2022.154582 PMID: 36610130
- Banerjee, S., Biehl, A., Gadina, M., Hasni, S., & Schwartz, D. M. (2017). JAK–STAT signaling as a target for inflammatory and autoimmune diseases: Current and future prospects. *Drugs*, 77(5), 521–546. DOI: 10.1007/s40265-017-0701-9 PMID: 28255960
- Bhullar, K. S., & Rupasinghe, H. P. V. (2013). Polyphenols: Multipotent therapeutic agents in neurodegenerative diseases. *Oxidative Medicine and Cellular Longevity*, 2013, 891748. Advance online publication. DOI: 10.1155/2013/891748 PMID: 23840922
- Bond, S., Driano, J. M., & Costa, A. S. H. (2020). The integrated stress response and phosphorylated eukaryotic initiation factor 2 $\alpha$  in neurodegeneration. *Journal of Neuropathology and Experimental Neurology*, 79(2), 123–143. DOI: 10.1093/jnen/nlz129 PMID: 31913484
- Cameron, E. G., Götz, M., & Goldman, S. A. (2024). A molecular switch for neuroprotective astrocyte reactivity. *Nature*, 626(7999), 574–582. DOI: 10.1038/s41586-023-06935-3 PMID: 38086421
- Campos-Esparza, M. R., Sánchez-Gómez, M. V., & Matute, C. (2009). Molecular mechanisms of neuroprotection by two natural antioxidant polyphenols. *Cell Calcium*, 45(4), 358–368. DOI: 10.1016/j.ceca.2008.12.007 PMID: 19201465
- Cryan, J. F., O’Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., Golubeva, A. V., Guzzetta, K. E., Jaggar, M., Long-Smith, C. M., Lyte, J. M., Martin, J. A., Molinero-Pérez, A., Moloney, G., Morelli, E., Morillas, E., & Dinan, T. G. (2019). The microbiota-gut-brain axis. *Physiological Reviews*, 99(4), 1877–2013. DOI: 10.1152/physrev.00018.2018 PMID: 31460832
- Del Rio, D., Borges, G., & Crozier, A. (2010). Polyphenols and health: What compounds are involved? *Nutrition, Metabolism, and Cardiovascular Diseases*, 20(1), 1–6. DOI: 10.1016/j.numecd.2009.05.015 PMID: 19713090

Di Meo, F., Margarucci, S., Galderisi, U., Crispi, S., & Peluso, G. (2020). Bioactive polyphenols and neuromodulation: Molecular mechanisms in neurodegeneration. *International Journal of Molecular Sciences*, *21*(7), 2564. Advance online publication. DOI: 10.3390/ijms21072564 PMID: 32272735

Ellwardt, E., & Zipp, F. (2014). Molecular mechanisms linking neuroinflammation and neurodegeneration in MS. *Experimental Neurology*, *262*(Pt A), 8–17. <https://doi.org/DOI: 10.1016/j.expneurol.2014.02.006>

Escartin, C., Galea, E., Lakatos, A., O’Callaghan, J. P., Petzold, G. C., Serrano-Pozo, A., Steinhäuser, C., Volterra, A., Carmignoto, G., Agarwal, A., Allen, N. J., Araque, A., Barbeito, L., Barzilai, A., Bergles, D. E., Bonvento, G., Butt, A. M., Chen, W.-T., Cohen-Salmon, M., & Verkhratsky, A. (2021). Reactive astrocyte nomenclature, definitions, and future directions. *Nature Neuroscience*, *24*(3), 312–325. DOI: 10.1038/s41593-020-00783-4 PMID: 33589835

Esmaili, Y., Yarjanli, Z., Pakniyat, A., Aghajanzadeh, T., Namdar, A., & Kheiry, F. (2022). Targeting autophagy, oxidative stress, and ER stress for neurodegenerative disease treatment. *Journal of Controlled Release*, *345*, 147–175. DOI: 10.1016/j.jconrel.2022.03.001 PMID: 35248646

Esteras, N., Kundel, F., Amodeo, G. F., Pavlov, E. V., Klenerman, D., & Abramov, A. Y. (2017). Mitochondrial hyperpolarization in iPSC-derived neurons from patients of FTDP-17 with 10+16 MAPT mutation leads to oxidative stress and neurodegeneration. *Redox Biology*, *12*, 410–422. DOI: 10.1016/j.redox.2017.03.008 PMID: 28319892

Fruman, D. A., Chiu, H., Hopkins, B. D., Bagrodia, S., Cantley, L. C., & Abraham, R. T. (2017). The PI3K pathway in human disease. *Cell*, *170*(4), 605–635. DOI: 10.1016/j.cell.2017.07.029 PMID: 28802037

Gómez-Pinilla, F. (2008). Brain foods: The effects of nutrients on brain function. *Nature Reviews. Neuroscience*, *9*(7), 568–578. DOI: 10.1038/nrn2421 PMID: 18568016

Grabska-Kobyłeczka, I., Szpakowski, P., Król, A., & Kobyłeczki, A. (2023). Polyphenols and their impact on the prevention of neurodegenerative diseases and development. *Nutrients*, *15*(15), 3454. Advance online publication. DOI: 10.3390/nu15153454 PMID: 37571391

Griñán-Ferré, C., Corpas, R., Puigoriol-Illamola, D., Palomera-Ávalos, V., Sanfeliu, C., & Pallàs, M. (2021). Synergistic neuroprotective effects of a natural product mixture against AD hallmarks and cognitive decline in *Caenorhabditis elegans* and an SAMP8 mice model. *Nutrients*, *13*(7), 2411. Advance online publication. DOI: 10.3390/nu13072411 PMID: 34371921

Guo, W., Stoklund Dittlau, K., & Van Den Bosch, L. (2020). Axonal transport defects and neurodegeneration: Molecular mechanisms and therapeutic implications. *Seminars in Cell & Developmental Biology*, *99*, 133–150. DOI: 10.1016/j.semcdb.2019.07.010 PMID: 31542222

Heneka, M. T., Kummer, M. P., & Latz, E. (2014). Innate immune activation in neurodegenerative disease. *Nature Reviews. Immunology*, *14*(7), 463–477. DOI: 10.1038/nri3705 PMID: 24962261

Higham, J. P., Hidalgo, A., & Gistelink, M. (2019). Restoration of olfactory memory in *Drosophila* overexpressing human Alzheimer’s disease associated tau by manipulation of L-type Ca<sup>2+</sup> channels. *Frontiers in Cellular Neuroscience*, *13*, 409. Advance online publication. DOI: 10.3389/fncel.2019.00409 PMID: 31551716

Huddleston, J. E. (2011). Metabolic regulation by ERK. *Nature Reviews. Molecular Cell Biology*, 12(9), 546. DOI: 10.1038/nrm3179 PMID: 21860387

Imeddine, K., Yahya, M. F. Z. R., Bouzina, M. A., & Touil, A. (2023). Molecular interactions, binding stability, and synergistic inhibition on acetylcholinesterase activity of safranin O in combination with quercetin and gallic acid: In vitro and in silico study. *Journal of Molecular Structure*, 1286, 135562. Advance online publication. DOI: 10.1016/j.molstruc.2023.135562

Jużwik, C. A., Drake, S. S., Zhang, Y., Paradis-Isler, N., Sylvester, C., Amar-Zifkin, A., Douglas, C., Morquette, B., Moore, C. S., & Fournier, A. E. (2019). microRNA dysregulation in neurodegenerative diseases: A systematic review. *Progress in Neurobiology*, 182, 101664. Advance online publication. DOI: 10.1016/j.pneurobio.2019.101664 PMID: 31356849

Khan, A., Ali, T., Rehman, S. U., Waheed, A., & Kim, M. O. (2020). Neuroprotection: Targeting multiple pathways by naturally occurring phytochemicals. *Biomedicines*, 8(8), 284. Advance online publication. DOI: 10.3390/biomedicines8080284 PMID: 32806490

Kooshki, L., Ghasemi, N., & Azadbakht, M. (2023). The pivotal role of JAK/STAT and IRS/PI3K signaling pathways in neurodegenerative diseases: Mechanistic approaches to polyphenols and alkaloids. *Phytomedicine*, 112, 154686. Advance online publication. DOI: 10.1016/j.phymed.2023.154686 PMID: 36804755

Kyriakis, J. M., & Avruch, J. (2012). Mammalian MAPK signal transduction pathways activated by stress and inflammation: A 10-year update. *Physiological Reviews*, 92(2), 689–737. DOI: 10.1152/physrev.00028.2011 PMID: 22535895

Leyns, C. E. G., Ulrich, J. D., Finn, M. B., Stewart, F. R., Koscal, L. J., Serrano, J. R., Robinson, G. O., Anderson, E., Colonna, M., & Holtzman, D. M. (2017). TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. *Proceedings of the National Academy of Sciences of the United States of America*, 114(43), 11524–11529. DOI: 10.1073/pnas.1710311114 PMID: 29073081

Li, X., Wang, H., Li, J., & Li, Y. (2022). Synergistic neuroprotective effect of saikosaponin A and albiflorin on corticosterone-induced apoptosis in PC12 cells via regulation of metabolic disorders and neuroinflammation. *Molecular Biology Reports*, 49(9), 8801–8813. DOI: 10.1007/s11033-022-07730-5 PMID: 36002654

Limanaqi, F., Biagioni, F., Busceti, C. L., Ryskalin, L., & Fornai, F. (2020). Merging the multi-target effects of phytochemicals in neurodegeneration: From oxidative stress to protein aggregation and inflammation. *Antioxidants*, 9(10), 1022. Advance online publication. DOI: 10.3390/antiox9101022 PMID: 33092300

Liu, J., Zhou, H., Fan, W., & Dong, W. (2023). New insights into molecular mechanisms underlying neurodegenerative disorders. *Journal of Integrative Neuroscience*, 22(3), 58. Advance online publication. DOI: 10.31083/j.jin2203058 PMID: 37258447

- Liu, Y., Zhang, Y., Zheng, X., Fang, H., & Li, H. (2018). The synergistic neuroprotective effects of combined rosuvastatin and resveratrol pretreatment against cerebral ischemia/reperfusion injury. *Journal of Stroke and Cerebrovascular Diseases*, 27(6), 1697–1704. DOI: 10.1016/j.jstrokecerebrovasdis.2018.01.033 PMID: 29525080
- Ma, X., Liu, H., Li, J., Wang, Y., Ding, S., Zhang, B., & Wang, R. (2020). ADSCs-derived extracellular vesicles alleviate neuronal damage, promote neurogenesis and rescue memory loss in mice with Alzheimer's disease. *Journal of Controlled Release*, 327, 688–702. DOI: 10.1016/j.jconrel.2020.09.019 PMID: 32931898
- Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition*, 79(5), 727–747. DOI: 10.1093/ajcn/79.5.727 PMID: 15113710
- Manach, C., Williamson, G., Morand, C., Scalbert, A., & Rémésy, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American Journal of Clinical Nutrition*, 81(1), 230S–242S. DOI: 10.1093/ajcn/81.1.230S PMID: 15640486
- Marmolejo-Martínez-Artesero, S., Aparicio, M., & Navarro, A. (2021). Endogenous mechanisms of neuroprotection: To boost or not to be. *Cells*, 10(2), 370. Advance online publication. DOI: 10.3390/cells10020370 PMID: 33578870
- Mohd Sairazi, N. S., & Sirajudeen, K. N. S. (2020). Natural products and their bioactive compounds: Neuroprotective potentials against neurodegenerative diseases. *Evidence-Based Complementary and Alternative Medicine : eCAM*, 2020(1), 6565396. Advance online publication. DOI: 10.1155/2020/6565396 PMID: 32148547
- Moradi Vastegani, S., Nasrolahi, A., Ghaderi, S., Tavassoly, I., & Ghasemi, A. (2023). Mitochondrial dysfunction and Parkinson's disease: Pathogenesis and therapeutic strategies. *Neurochemical Research*, 48(8), 2285–2308. DOI: 10.1007/s11064-023-03904-0 PMID: 36943668
- Naoi, M., Maruyama, W., & Akao, Y. (2017). Neurotrophic function of phytochemicals for neuroprotection in aging and neurodegenerative disorders: Modulation of intracellular signaling and gene expression. *Journal of Neural Transmission (Vienna, Austria)*, 124(12), 1515–1527. DOI: 10.1007/s00702-017-1797-5 PMID: 29030688
- Naoi, M., Wu, Y., Shamoto-Nagai, M., & Maruyama, W. (2019). Mitochondria in neuroprotection by phytochemicals: Bioactive polyphenols modulate mitochondrial apoptosis system, function and structure. *International Journal of Molecular Sciences*, 20(10), 2451. Advance online publication. DOI: 10.3390/ijms20102451 PMID: 31108962
- O'Shea, J. J., & Plenge, R. (2012). JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. *Immunity*, 36(4), 542–550. DOI: 10.1016/j.immuni.2012.03.014 PMID: 22520847
- Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity*, 2(5), 270–278. DOI: 10.4161/oxim.2.5.9498 PMID: 20716914

- Pérez-Jiménez, J., Neveu, V., Vos, F., & Scalbert, A. (2010). Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *European Journal of Clinical Nutrition*, *64*(S3, Suppl 3), S112–S120. DOI: 10.1038/ejcn.2010.221 PMID: 21045839
- Picon, C., Jayaraman, A., Kirkwood, R., Pradeepan, S., Amor, S., & Reynolds, R. (2021). Neuron-specific activation of necroptosis signaling in multiple sclerosis cortical grey matter. *Acta Neuropathologica*, *141*(4), 585–604. DOI: 10.1007/s00401-021-02274-7 PMID: 33569629
- Ratan, Y., Rajput, A., & Sharma, A. (2023). An insight into cellular and molecular mechanisms underlying the pathogenesis of neurodegeneration in Alzheimer's disease. *Biomedicines*, *11*(5), 1398. Advance online publication. DOI: 10.3390/biomedicines11051398 PMID: 37239068
- Rebas, E., Rorbach-Dolata, A., & Piwowar, A. (2020). Neuroprotective polyphenols: A modulatory action on neurotransmitter pathways. *Current Neuropharmacology*, *18*(5), 431–445. DOI: 10.2174/1570159X18666200106155127 PMID: 31903883
- Renaud, J., & Martinoli, M.-G. (2019). Considerations for the use of polyphenols as therapies in neurodegenerative diseases. *International Journal of Molecular Sciences*, *20*(8), 1883. Advance online publication. DOI: 10.3390/ijms20081883 PMID: 30995776
- Salman, A., Koparde, R., & Zand, M. S. (2018). Determining the quantitative principles of T cell response to antigenic disparity in stem cell transplantation. *Frontiers in Immunology*, *9*, 2284. Advance online publication. DOI: 10.3389/fimmu.2018.02284 PMID: 30364159
- Sánchez-Martínez, J. D., Martínez-Gardeazabal, J., & Fernández-Villamarín, M. (2022). Blood–brain barrier permeability study of potential neuroprotective compounds recovered from plants and agri-food by-products. *Frontiers in Nutrition*, *9*, 924596. Advance online publication. DOI: 10.3389/fnut.2022.924596 PMID: 35782945
- Saxton, R. A., & Sabatini, D. M. (2017). mTOR signaling in growth, metabolism, and disease. *Cell*, *168*(6), 960–976. DOI: 10.1016/j.cell.2017.02.004 PMID: 28283069
- Scalbert, A., Johnson, I. T., & Saltmarsh, M. (2005). Polyphenols: Antioxidants and beyond. *The American Journal of Clinical Nutrition*, *81*(1), 215S–217S. DOI: 10.1093/ajcn/81.1.215S PMID: 15640483
- Scalbert, A., & Williamson, G. (2000). Dietary intake and bioavailability of polyphenols. *The Journal of Nutrition*, *130*(8), 2073S–2085S. DOI: 10.1093/jn/130.8.2073S PMID: 10917926
- Shaban, N. Z., Abdelrahman, S. A., & El-Kersh, M. A. (2021). Synergistic protective effect of *Beta vulgaris* with meso-2,3-dimercaptosuccinic acid against lead-induced neurotoxicity in male rats. *Scientific Reports*, *11*(1), 252. Advance online publication. DOI: 10.1038/s41598-020-80669-4 PMID: 33420282
- Shuai, K., & Liu, B. (2003). Regulation of JAK–STAT signalling in the immune system. *Nature Reviews. Immunology*, *3*(11), 900–911. DOI: 10.1038/nri1226 PMID: 14668806
- Sierra, A., Encinas, J. M., Deudero, J. J., Chancey, J. H., Enikolopov, G., Overstreet-Wadiche, L. S., Tsirka, S. E., & Maletic-Savatic, M. (2010). Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, *7*(4), 483–495. DOI: 10.1016/j.stem.2010.08.014 PMID: 20887954

- Silva, R. F., & Pogačnik, L. (2020). Polyphenols from food and natural products: Neuroprotection and safety. *Antioxidants*, 9(1), 61. Advance online publication. DOI: 10.3390/antiox9010061 PMID: 31936711
- Stacchiotti, A., & Corsetti, G. (2020). Natural compounds and autophagy: Allies against neurodegeneration. *Frontiers in Cell and Developmental Biology*, 8, 555409. Advance online publication. DOI: 10.3389/fcell.2020.555409 PMID: 33072744
- Stith, S. S., Diviant, J. P., Brock, C., & Vigil, J. (2018). Patient-reported symptom relief following medical cannabis consumption. *Frontiers in Pharmacology*, 9, 916. Advance online publication. DOI: 10.3389/fphar.2018.00916 PMID: 30210337
- Swanson, K. V., Deng, M., & Ting, J. P.-Y. (2019). The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. *Nature Reviews. Immunology*, 19(8), 477–489. DOI: 10.1038/s41577-019-0165-0 PMID: 31036962
- Tan, S. H., Karri, V., Tay, N. W. R., Chang, K. H., & Wong, K. H. (2019). Emerging pathways to neurodegeneration: Dissecting the critical molecular mechanisms in Alzheimer's disease, Parkinson's disease. *Biomedicine and Pharmacotherapy*, 111, 765–777. DOI: 10.1016/j.biopha.2018.12.101 PMID: 30612001
- Tang, Y., & Le, W. (2016). Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Molecular Neurobiology*, 53(2), 1181–1194. DOI: 10.1007/s12035-014-9070-5 PMID: 25598354
- Tsoi, P. S., Quan, M. D., & Choi, M. L. (2023). Aggregation of disordered proteins associated with neurodegeneration. *International Journal of Molecular Sciences*, 24(4), 3380. Advance online publication. DOI: 10.3390/ijms24043380 PMID: 36834792
- Uddin, M. S., Kabir, M. T., Rahman, M. S., Alim, M. A., Rahman, M. M., & Rauf, A. (2020). Neuroprotective role of polyphenols against oxidative stress-mediated neurodegeneration. *European Journal of Pharmacology*, 886, 173412. Advance online publication. DOI: 10.1016/j.ejphar.2020.173412 PMID: 32771668
- Van Praag, H., Fleshner, M., Schwartz, M. W., & Mattson, M. P. (2014). Exercise, energy intake, glucose homeostasis, and the brain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 34(46), 15139–15149. DOI: 10.1523/JNEUROSCI.2814-14.2014 PMID: 25392482
- Villarino, A. V., Kanno, Y., & O'Shea, J. J. (2015). Mechanisms of Jak/STAT signaling in immunity and disease. *The Journal of Immunology : Official Journal of the American Association of Immunologists*, 194(1), 21–27. DOI: 10.4049/jimmunol.1401867 PMID: 25527793
- Yan, L., Xie, J., & Wang, X. (2022). Dietary plant polyphenols as the potential drugs in neurodegenerative diseases: Current evidence, advances, and opportunities. *Oxidative Medicine and Cellular Longevity*, 2022(1), 5288698. Advance online publication. DOI: 10.1155/2022/5288698 PMID: 35237381
- Zbinden, A., Pérez-Berlanga, M., De Rossi, P., & Polymenidou, M. (2020). Phase separation and neurodegenerative diseases: A disturbance in the force. *Developmental Cell*, 55(1), 45–68. DOI: 10.1016/j.devcel.2020.09.014 PMID: 33049211
- Zhang, Q., Lenardo, M. J., & Baltimore, D. (2017). 30 years of NF- $\kappa$ B: A blossoming of relevance to human pathobiology. *Cell*, 168(1-2), 37–57. DOI: 10.1016/j.cell.2016.12.012 PMID: 28086098

