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ORIGINAL ARTICLE

Neuroprotective Properties of Plant-Based Secondary Metabolites: Molecular Insights into Therapeutics

S Dulary[1], B Durga[2]*

1 Registered Research Scholar in Biochemistry, Meenakshi Academy of Higher Education and Research (MAHER), Chennai, Tamil Nadu, India
2 Professor & Vice Principal, Meenakshi College of Allied Health Sciences(MCAHS), Meenakshi Academy of Higher Education and Research(MAHER), Chennai,Tamilnadu, India

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* **Corresponding author**.

viceprincipal@maherfahs.ac.in

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Abstract

Objectives: To explore the neuroprotective potential of secondary metabolites in mitigating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, that focuses on their interaction with molecular targets and mechanisms involved in neuroprotection. **Methods:** This review synthesizes the current research literature on the pathophysiology of neurodegenerative diseases, emphasizing key mechanisms such as oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity, and protein aggregation. It further examines how naturally occurring secondary metabolites from plants, fungi, and microorganisms influence these pathological pathways to exert neuroprotective effects. Data were systematically searched in PubMed, Google Scholar, and Embase for articles published in English between 2019 and 2025. Keywords included "neuroinflammation", "secondary metabolites", "oxidative stress", "amyloid aggregation", and "neuroprotection". Screening was performed according to PRISMA guidelines. Out of 150 peer reviewed studies, 35 qualitative articles were examined in which plant flavonoids and polyphenols in models of neurodegenerative (in vitro) diseases were included. Non-English or irrelevant articles, articles about other topics, in vivo studies without in vitro data, and studies that were not making full publications available were excluded. Molecular targets of metabolites or secondary metabolites, mechanistic pathways (i.e., antioxidant, anti-inflammatory, anti-apoptotic), organelle-specific effects, bioavailability, and blood-brain barrier permeability parameters were evaluated. **Findings:** Some secondary metabolites (naringenin, hesperidin, quercetin, anthocyanins) have strong neuroprotective ability and one study cited improved neuronal survival rates of 40-60% and decreased inflammatory markers. The key outcome of this review is identifying these compounds as the most promising ones based on the best potency and diverse mechanism of actions, specifically because they regulate oxidative stress, neuroinflammation and protein aggregation. Major bottlenecks are low bioavailability, low blood-brain penetration, and no long-term safety data. Future area of focus should include in vivo validation studies, pharmacokinetics, target identification, in vitro and in vivo assessment,

and combinational or nanotechnology-based approaches; with a long-term goal of conducting well-designed clinical trials for neurodegenerative diseases. **Novelty:** In contrast to prior reviews that generally consider antioxidants and anti-inflammatory actions, this review identifies naringenin, hesperidin, baicalein, and ferulic acid as the most promising neuroprotective compounds overall. By comparing the effects of these compounds in in vitro neurodegenerative models, this review highlights their relative potency, efficacy and their underlying molecular mechanisms of action. Such an approach also closes a literature gap and provides a framework for transitioning these neuroprotective candidates to clinical utility through in vivo testing, pharmacokinetics, and clinical translational studies that may lead to novel therapeutic strategies.
Keywords: Neuroinflammation; Secondary metabolites; Oxidative stress; Amyloid aggregation; Polyphenols; Flavonoids

1 Introduction

Neurodegenerative diseases are chronic progressive diseases which cause slow degeneration of neuronal structure and functions leading to death. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), and Amyotrophic Lateral Sclerosis (ALS), are all neurodegenerative diseases. These disorders are characterized by overlapping characteristics such as cognitive impairment, memory impairment, motor impairment, deposition of pathological misfolded protein, and neuronal loss[(1)]. To date, although decades have passed since it was initially discovered, there have been few (even no) genuine (effective) treatment interventions in terms of the multifactoriality of neurodegeneration, such as oxidative stress, mitochondrial dysfunction, inability to clear abnormal protein aggregation, excitotoxicity, and persistent neuroinflammation[(2)]. The effects of polyphenols in nerve cells are known to be reduced by the oxidative properties of polyphenols, which have been shown to have a role in the neuroinflammatory process, and has been shown to modulate the signaling pathways of inflammation, apoptosis and neuroprotection, and has been implicated in the normal functioning of the blood-brain barrier. Therefore, the author and his colleagues, under Molecular Mechanisms in Neurodegeneration, have investigated dietary consumption of polyphenols, including fruits and vegetables, in promoting healthy brain as well as its role in the prevention and management of neurodegenerative disease[(3)].

In the past few years, the neuroprotective effect of secondary metabolites, including polyphenols and flavonoids, or bioactive plant-derived compounds, is prioritized in its special interest. Polyphenols that consist of phenolic groups above one have high antioxidant and anti-inflammatory properties. The biggest subclass of polyphenols is the flavonoids which have been significantly studied and researched in their ability to influence cell signaling pathways, inhibit apoptotic cell death and prevent protein aggregation, becoming potential agents to interfere with the neurodegenerative diseases[(4)].

Likewise, a wide range of plant compounds known as Flavonoids are capable of mitigating neuronal damage through many pathways including anti-oxidative stress, decreased inflammatory effects and lowered programmed cell death commonly referred to as apoptosis. Endoplasmic Reticulum preserves the cellular homeostasis, and the flavonoids lessen the ER stress and, therefore, guard the neurons against destruction[(5)]. Therefore, different significant functions of naturally found secondary metabolites, particularly organic chemicals like polyphenols and flavonoids found in plants, provide valuable outcomes in relation to neurodegeneration in human beings[(6)].

Earlier reviews have also provided ample emphasis on the general antioxidant and anti-inflammatory properties of these compounds, although were generally small scale in scope and did not include recent in vitro and molecular evidence, especially of specific signaling pathways, particular organelles like mitochondria and the endoplasmic reticulum, and novel metabolites. Moreover, many of the studies conducted previously lacked such systematic treatment and have omitted the study of therapeutic levels, delivery by the blood-brain barrier, and specific cell line models used. Regardless of all neuro protective effects of secondary metobolites relative potency, efficacy and safety models of neurodegenerative diseases in-vitro and in-vivo are studies that should be conducted to discover the compound potent neuroprotective activity that can be used in designing strategies to NDs.

To fill this gap, successful comparing of the neuroprotective properties of Naringenin, Ferulic acid, Baicalein and Hesperidin in In vitro models of the neurodegenerative diseases is conducted. Testing of potency and efficacy of these compounds would help prevent or reduce neurodegeneration. Models that recapitulate pathophysiology of neurodegenerative diseases have to be used to examine the molecular pathways involved in the neuroprotective activity of either of the compounds.

The present review is a systematic gathering and synthesis of over 150 recent articles, which were downloaded to PRISMA (Preferred Reporting Items to Systematic Reviews and Meta-Analyses) guideline, through the databases of PubMed (90 articles), Google Scholar (40 articles), and Embase (20 articles). This review is particularly concerned with current advances in secondary

metabolite molecular mechanisms of neuroprotection, including their roles in ER stress response, mitochondrial homeostasis, neuroinflammation and neuronal apoptosis.

In addition to these, the paper of the review also mentions promising preclinical data of such new compounds as Naringenin, Baicalein, Ferulic acid, Limonin, and Hesperidin. Not only will the results provide a current synthesis of the available body of knowledge but also signify uninvestigated avenues of therapeutic opportunities and research, thereby creating the justification behind the detailed and focused review in this developing area of neurotherapeutics.

1.1 Research Contributions:

The current review provides a recent and up-to-date summary of over 150 articles, highlighting the molecular mechanisms by which polyphenols and flavonoids can regulate neurodegenerative mechanisms. It absorbs recent innovations on lesser-known metabolites and organelle-specific activities, which represents a systematic review by using the PRISMA model.

1.2 Research Gaps:

The literature reviews that have taken place have broadly discussed the general antioxidant or anti-inflammatory activity of plant secondary metabolites. They, however, failed to harness more recent in vitro molecular studies, overlooked the difficulties of directing agents to the blood-brain barrier, and seldom used new bioactive substances with growing prominence.

1.3 Questions:

This review attempts to address the following research questions:

What is the best neuroprotective pathway of the primary neurodegenerative diseases of Alzheimer, Huntington and Parkinson by secondary metabolites, in particular polyphenols and flavonoids?

Which molecular processes and organelle-specific mechanisms (e.g. oxidative stress, neuroinflammation, mitochondrial dysfunction, protein aggregation) would mediate these neuroprotective effects of these metabolites?

What are the existing shortcomings of extrapolation of drug candidates in in vitro systems to clinical relevance and what would future methods, including nanocarrier drug delivery, combination therapy, and in vivo validation, do to mitigate these shortcomings?

2 Review Methodology

The systematic review has been done in line with PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) guidelines wherein the search of the literatures was performed on sites such as PubMed, Google scholar and Embase with publications that were published since January 2019. A set of keywords such as neurodegenerative diseases, neuroinflammation, secondary metabolites, amyloid accumulation, oxidative stress, and mitochondrial dysfunction with the help of Boolean operators, such as AND and OR, were applied to receive refined results helping to ensure inclusion of the relevant studies.

At the first round of screening, the duplication of articles was detected and eliminated, leaving a rare collection of 100 articles. After evaluating the abstract and the titles, 25 articles were filtered out as those which were not directly related to the topic assigned to students. Another 35 articles were filtered out following a thorough content analysis since it did not concern in vitro researches with polyphenols and flavonoids. The final selection of 35 articles was excessively reviewed after several screening sessions and factors like peer review status, relevance to the AI field, and academic focus were taken into account to include in this review.

Hence, the selection process for this review article is highly rigorous, enabling a qualitative analysis of the subjective topic. The selected articles are of good quality and have been critically evaluated on different parameters such as cell types used in models of neurodegeneration, the conditions used in experiments, specific polyphenol/flavonoid subclasses investigated, and the cellular/molecular targets affected. The studies specifically investigated the neurodegenerative activity of endogenous polyphenols/flavonoids with reproducible outcomes supporting them. Figure 1 provides an overall idea of the screening methodology and the systematic process by which the articles have been chosen.

Therefore, the choice of this review article is very strict, which allows conducting a qualitative study of the subjective topic. The quality of the selected articles is high, and they have been critically discussed based on the various parameters like the cell types employed in models of neurodegeneration, the conditions employed in the experiments, the polyphenol/flavonoid subclass studied, and the cellular/molecular targets studied. In particular, the neurodegenerative activity of endogenous

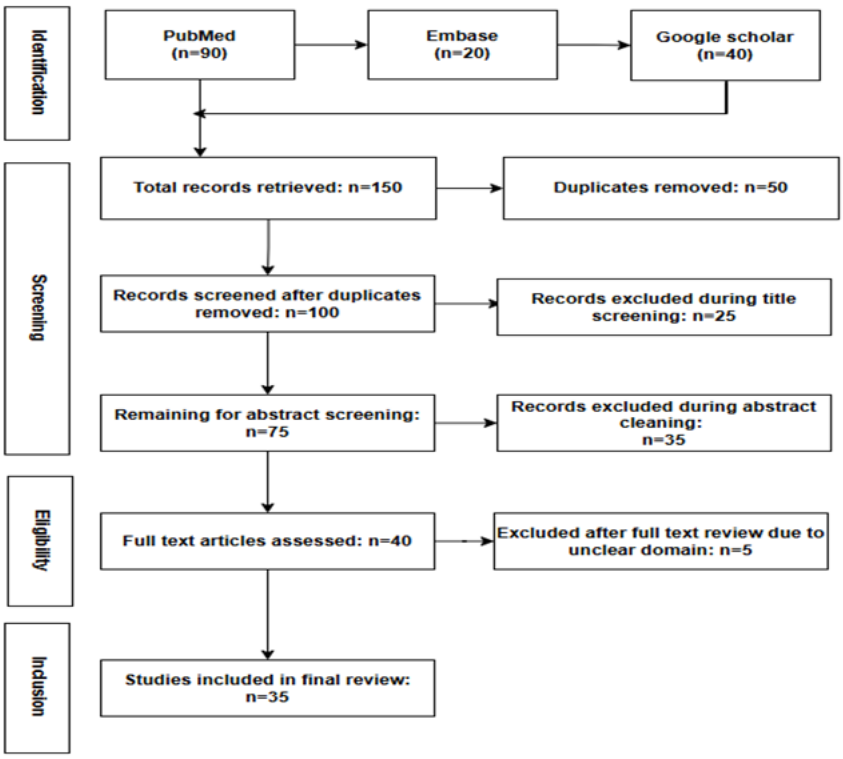

Fig 1. Methodology for screening the literature

polyphenols/flavonoids using reproducible outcomes in support was investigated in the studies. Table 1 gives a general concept of the screening methodology and systematic process on which the articles have been selected.

The review article uses a systematic approach based on the PRISMA guidelines that imply a systematic review that guarantees the use of a comprehensive and qualitative approach. A preliminary systematic search involved 150 articles on different databases including PubMed (90 articles), Embase (20 articles) and Google Scholar (40 articles). Upon eliminating 50 duplicates, 100 unique records have been further filtered on basis of their title, and 25 records have been eliminated and this is largely because of non-matching of the titles. Therefore, this leads to consideration of 75 records which are further narrowed down on basis of abstract screening thus leaving out 35 records. Accordingly, a complete text analysis of 40 articles is shortlisted, and 5 articles are eliminated as a result of a vague area. In this way, 35 articles have been successfully passed through all necessary requirements that are taken into consideration of the ultimate review. All these parameters are aimed towards attaining the target of examining the high-quality studies concerning different properties of polyphenols and flavonoid compounds and their application in the prevention of neurodegenerative disease in humans. The inclusion criteria will be: (1) Peer-reviewed journal articles, (2) In vitro models of neurodegenerative disease studies, (3) Studies that have used flavonoids and polyphenols of plant origin, (4) English language, and (5) Full-text articles. Exclusion criteria: (1) Reviews or meta-analyses unless they provided critical background information; (2) In vivo or clinical study papers in the absence of complementary in vitro data; (3) In Applicability (e.g. non-therapeutic areas); (4) Non English (in full text); and (5) Non English (in review).

Parameters evaluated in the development of the concept included the specific mechanism (antioxidant, anti-inflammatory, anti-apoptotic, etc.) that induces neuroprotective effects of molecular pathways affected, effects on specific organelles (e.g., endoplasmic reticulum, mitochondria).

One of the serious health conditions particularly in old age is neurodegenerative disease. Therefore, various studies are currently ongoing around the world in a bid to discover an appropriate natural and effective method of fighting neurodegenerative diseases[7]. Flavonoids are a group of plant compounds of a wide range having influence on neurodegenerative diseases. It has features like antioxidant, anti-inflammation and neuroprotection that improve different processes in our body, including oxidative stress reduction, regulation of neuroinflammation, neuronal survival and neurofunction, thus, improving cognitive behaviour[8]. Certain flavonoids were found to reverse behavioral impairments and

lower the indices of oxidative stress. This describes why proper screening techniques should be applied to find possible flavonoid candidates. These findings confirm that flavonoids are a potential source to be used in the treatment of neurodegenerative diseases [9].

Role of sirtuins in the signal transduction of citrus flavonoids, in which it talks of the role of sirtuins, is a part of nicotinamide adenine dinucleotide-dependent deacetylases that occurs in the context of citrus flavonoids. These are reported to have multiple biological activities that include aging, inflammation, regulatory metabolic, anti-cancer, cardio-protective, antioxidant, and neuroprotective effects. In this research, SIRT1 and SIRT6 play the main role as they are involved in the regulation of genetic expression in cellular process, DNA repair, and metabolism. Citrus flavonoids have the capability of regulating SIRT6 on the cellular level and this is associated with numerous health benefits, which indicates the possibility of using citrus flavonoids as a treatment in the diseases involved with sertuin dysfunction. Citrus flavonoids also possess a significant medicinal role because they are able to affect the action of sirtuin and thus afford health and illness treatment [10].

Plant derived flavonoids are also discussed as having a crucial role in the treatment of neurodegenerative diseases and a group of authors investigate this topic as the flavonoids, which have potential to become secondary metabolites, occur in many plants and are therefore significant in the treatment of neurodegenerative diseases. Here we can find the importance of neurons and glial cells (particularly astrocytes and microglia) interaction in the maintenance of central nervous system. Nutrition, homeostasis and neuroprotection are significant to these interactions, but they might ultimately lead to neuroinflammation and neuronal dysfunction when compromised by aging or pathology [11]. The glial role in the central nervous system disorders was the role of astrocytes and microglia in neurodegradation and degeneration in their reactivity with gliosis. This negative outcome of this gliosis also involves the death of nerve cells. All of the potentially beneficial effects seen in this paper are of some flavonoids on nerve cell health in their capacities to induce cell survival and decrease inflammation. [12].

The article offers neuroprotective effects of flavonoids focusing particularly on their importance in mitigating endoplasmic reticulum stress and demonstrates that Endoplasmic reticulum plays a key role in cellular homeostasis regulation. When under stress, the ER will cause deposition of wrongly folded proteins that will cause the unfolded ones, which when not resolved will cause cell death known as apoptosis. The flavonoids alleviate this ER stress and hence protect the neurons. Kaempferol and Quercetin are the two significant mechanisms that are discussed in this article. Kaempferol can be used to curb reducing ER stress-induced apoptosis by inhibiting caspase pathways, but Quercetin is notable due to its effect of targeting UPR and increasing cell survival in a stressful condition. Therefore, the author mentions the possible impact of flavonoids in neuroprotection, in particular, their impact on the endoplasmic reticulum, and preconditions the further development of the effect of flavonoids on treatment mechanisms [13].

Neuroprotective effects Flavonoids, which act via a number of mechanisms, including suppression of oxidative stress, neuroinflammation regulation, promotion of neuronal survival, and alteration of cell survival and apoptotic signaling pathways. Flavonoids are found in various categories, and they are luteolin, quercetin and anthocyanins. In this case, the author highlights that in vivo research is necessary to gain a better insight into pharmacokinetics and risk assessment of flavonoids to use them in clinical practice [14].

Possible actions of flavonoids on cerebellar cells, particularly on their participation in the glyoxalase pathway, are critical in the detoxification of methylglyoxal (MG). In this case, postnatal mice were used to produce cultures of cerebellar neurons, and the cells were cultured under certain conditions in a bid to have a homogenous population with further treatments that were used to determine the role of flavonoids [15]. The other important compound, such as flavonoids, is polyphenols, which possess the capacity to minimize oxidative damage in the neuronal cells. The article explains how polyphenols demonstrate their effects, which are alterations in signaling pathways as an inflammatory, apoptotic, and neuroprotective response, thus, the place of polyphenols in increasing the mechanism of the blood-brain barrier is emphasized. Polyphenols tend to occur in foods such as vegetables, fruits, tea, and red wine that may be included in the diet so that they may be a preventive measure on neurodegenerative diseases. [16].

The in vitro model of neurodegenerative disease is elucidated in detail in which the significance of in vitro models in disease mechanisms, screening of potential drugs and cellular response associated with neurotoxic agents are highlighted. In vitro models are of many different types that include cell lines, primary neuronal cultures, induced pluripotent stem cells, and 3D culture systems [17]. Nevertheless, it is not complex and requires improvement of integrating the types of cells. Therefore, it is proposed that future studies should aim at creating more simulations that are capable of simulating complex interactions with nervous systems. A group of polyphenols termed as Naringin and Naringenin and their efficacy in nervous illnesses. Naringenin and naringin glycosylated are citrus fruits with high concentrations of naringenin. Naringin and Naringenin have antioxidant, anti-inflammatory, and neuroprotective characteristics [18]. These compounds affect various biological pathways such as the regulation of the neurotransmitter system, decrease in oxidative stress, and enhancement of neurotrophic factors which are significant in the survival of neurons and its functionality. Using polyphenols leads to symptom relief and delays the

development of the disease. Naringin and naringenin are new prospective therapeutic agents in management of neurological diseases.[19].

The second study which characterizes polyphenols and their impact in neurodegenerative diseases elicits the possible advantages of polyphenols that are taken through different foods. There are a number of different mechanisms by which polyphenols act as neuroprotectants, including the development of oxidative stress through the neutralization of free radicals, the modulation of inflammatory pathways, the improvement of mitochondrial functions, the survival of neurons, and the effect that gut microbiota has on the health of the brain. The article emphasizes the use of food rich in polyphenols in the diet, which improves brain performance and minimizes the impact of aging[20].

The neuroprotective properties of Flavonoids, especially hesperidin and quercetin in preclinical (in vitro or in vivo) models of Alzheimer's disease (AD), Parkinson's disease (PD), depression and neurotoxicity are growing in interest. The preclinical data indicate that phenolic compounds facilitate protective effects in various therapeutic responses, including reduction of oxidative stress and ferroptosis, inhibition of monoamine oxidases, stimulation of Nrf2/ARE pathway and stimulation of brain-derived neurotrophic factor (BDNF) production. The compound helps to inhibit amyloid-2 aggregation in AD models; it can induce the survival of dopaminergic cells in PD. Anti-inflammatory effects are mediated by flavonoids which inhibit pro-inflammatory cytokines (TNF- α, IL-1 0) and regulate a number of other regulatory proteins, such as NF-KB and NLRP3 inflammasome. Clinical trials are limited, yet the preclinical data suggests that hesperidin, quercetin and other similar flavonoids are safe and natural therapeutic alternatives in slowing or preventing neurodegeneration as therapeutic entities[21].

The growing population of aged people worldwide will most probably put a strain on the problem of neurodegenerative diseases in the coming decades. The changes of brain homeostasis with age expose individuals to the risk of developing neurodegenerative conditions, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), ischemic injury, and traumatic brain injury (TBI). Poor therapeutic choices have poor efficacy, and this is where alternative and adjuvant mechanisms may be explored. The phenolic compounds, which are the antioxidants of interest, have high antioxidant potential, have the ability to cross the blood- brain barrier (BBB), and have several neuroprotective actions at the molecular level. Research has demonstrated that phenolics (in vitro, in vivo, and smaller clinical trials) have the ability to alleviate oxidative stress, modulatory control of inflammatory pathways, and neuronal damage in neurodegenerative paradigms, which could make them complementary therapeutic agents.[22].

Through autophagy modulation, polyphenols, a particular class of phytochemicals found in a variety of diets, have the potential to treat neurodegenerative disorders. One useful process for cell breakdown and recycling is autophagy. According to this study, polyphenols have the ability to promote autophagy pathways and, as a result, get rid of harmful protein aggregates that lead to neurodegenerative diseases. The study concludes by outlining potential avenues for further research, including examining the bioavailability, individual polyphenols, and the creation of novel formulations to enhance their therapeutic effects[23].

Polyphenols have the ability to raise the activity of antioxidant enzymes, which could lower the risk of neurological and metabolic disorders. The activity is enhanced by polyphenols through mechanisms like inflammation inhibition and signaling pathway modulation. Some polyphenols, such as epigallocatechin gallate (EGCG), may inhibit inflammatory and cell death processes. In this instance, the author makes the point that polyphenols combined with stem cell therapy may improve treatment results. Consequently, it is probable that polyphenols will improve the quantity and differentiation of stem cells, thereby increasing their effectiveness in treating neurodegenerative diseases. The review cites a number of studies that demonstrate the positive effects of polyphenols on stem cells and their potential application in neurodegenerative diseases, indicating growing interest in the relationship between polyphenol-related research and stem cell therapy.

The PI3K/Akt/mTOR signaling pathway—which is made up of phosphoinositide 3-kinase (PI3K), Akt, and the mammalian target of rapamycin (mTOR) is implicated in neurodegenerative illnesses and is essential for controlling important cellular processes like migration, cell division, and apoptosis. When this route is disrupted, a number of neurodegenerative diseases arise. The author talks about a number of phytochemicals that exhibit a potential approach in neurodegeneration, including terpenoids, carotenoids, phenolic compounds, and alkaloids[24].

Hesperidin is a citrus flavonoid that exhibits anti-degenerative disease effects. Hesperidin's ability to neutralize free radicals, reduce oxidative stress, and alter inflammatory pathways makes it a useful neuroprotective substance. Hesperidin's mechanisms of action in controlling the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which is crucial for cellular defenses against oxidative damage, are described in the paper. In order to reduce neuroinflammation, which is one of the main causes of neurodegenerative diseases, this pathway also plays a crucial role in blocking the activation of pro-inflammatory cytokines and signaling pathways.[25].

Numerous flavonoid and polyphenolic substances are compiled in Table 1, which also provides a summary of the total number of in vitro and in vivo research examined and their main conclusions. In both kinds of trials, the majority of these

substances consistently show neuroprotective benefits. Additionally, in the context of neurodegenerative illnesses, combining these substances with the right dosages produces more significant results.

Table 1. Overview of Selected Phytochemicals: Chemical Structures, Sources, and Therapeutic Activities

S. No	Secondary Metabolite and its chemical structure	Primary Source	Key Molecular Targets	Neuroprotective Mechanisms
1	**Naringenin**	Grapefruit, Oranges	NF-κB, MAPK, BDNF	• Antioxidant: Reduces oxidative stress. • Anti-inflammatory: Modulates cytokine signalling. • Promotes neurogenesis and plasticity.
2	**Hesperidin**	Citrus fruits	Nrf2, TNF-α, IL-6	• Antioxidant: Activates cellular antioxidant defences. • Anti-inflammatory: Inhibits cytokine release. • Improves cognitive performance.
3	**Quercetin**	Apples, Onions	COX-2, Caspase-3, PI3K/Akt	• Antioxidant: Reduces ROS accumulation. • Anti-inflammatory: Inhibits COX-2 activity. • Enhances neurotrophic factor expression.
4	**Curcumin**	Turmeric	NF-κB, BDNF, SIRT1	• Antioxidant: Scavenges reactive oxygen species. • Anti-inflammatory: Suppresses pro-inflammatory cytokines. • Modulates autophagy and synaptic plasticity.
5	**Anthocyanins**	Berries, Cherries	Nrf2, NF-κB	• Antioxidant: Reduces oxidative injury. • Anti-inflammatory: Regulates NF-κB signaling. • Enhances synaptic connectivity.
6	**Lycopene**	Tomatoes, Red Pepper	NF-κB, mTOR	• Antioxidant: Prevents lipid peroxidation. • Anti-inflammatory: Modulates mTOR and NF-κB pathways. • Protects mitochondrial integrity and neuron survival.
7	**Terpenoids**	Lavender, Mint	MAPK, IL-1β, TNF-α	• Antioxidant: Reduces reactive oxygen and lipid peroxidation. • Anti-inflammatory: Inhibits cytokine release. • Enhances neurogenesis.
8	**Chlorogenic Acid**	Apples	NF-κB, iNOS	• Antioxidant: Prevents neuronal oxidative damage. • Anti-inflammatory: Reduces microglial activation. • Promotes neuroplasticity.
9	**Alkaloids**	Apocynaceae, Solanaceae	NADPH oxidase, Microglia	• Antioxidant: Inhibits ROS-producing enzymes. • Anti-inflammatory: Modulates microglial activity. • Improves mitochondrial function.

3 Conclusion

This systematic review supports the neuroprotective ability of the plant secondary metabolites, particularly polyphenols and flavonoids to delay the neurodegenerative diseases like Alzheimer, Parkinson, and amyotrophic lateral sclerosis. The cause of these differences with other reviews lies in (1) the inclusion of numerous new molecular dimensions, (2) the consideration of organelle-specific processes in mitochondria and the endoplasmic reticulum, and (3) syntheses of possibly under-studied secondary metabolites, but very important. The synthesis utilizes a PRISMA approach to summarize a large body of literature, and to give a solid and comprehensive picture of how these phytochemicals affect some of the large cellular and molecular processes.

Regardless of all preclinical evidence of antioxidant, anti-inflammatory, anti-apoptotic and anti-aggregation effects, translating the effects into applicability in a relevant clinical setting has been and will continue to be a protracted undertaking due to a plethora of barriers including bioavailability, metabolism, absence of dosing standardization, as well as, limited human studies. To counteract these obstacles, scientists will be required to carry out a sequence of subsequent steps in order to bring the promising neuro-protective benefits of the phytochemicals to the administrable dosage in humans. The initial steps will be the identification of phytochemicals that will be the most potent and effective. Having identified these compounds, it is possible to further inform about neuroprotective effects by defining their molecular mechanisms and targets of action, one of which is the action of sirtuins, autophagy mediators, and glyoxalase system.

The next step will be to consider the safety and efficacy of these lead compounds in in vivo physiological models of neurodegenerative diseases. Pharmacodynamics and pharmacokinetics need to be researched in detail, as prospective studies

to support the possible clinical development. Simultaneously, nanocarrier models can be explored to develop new models of delivery to enhance the permeability and stability of BBB. Furthermore, is the other significant research with combination therapy of possible lead compounds to examine the most effective neuroprotective combinations and synergies? Finally, clinical trials will be one of the keys to safety, efficacy, and biomarker responses development and patient responses in the future. Additionally, the identification of targets as well as its validation will also aid these compounds into a translational environment, where approved evidence-based treatment paradigms of neurodegenerative diseases are generated.

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