Received: 11 September 2024 | Accepted: 18 November 2024

DOI: 10.1002/ame2.12525

REVIEW

Polyphenols as Wnt/β-catenin pathway modulators: A promising strategy in clinical neurodegeneration

Biswajit Kumar Utpal[1] | Sajib Chandra Roy[2] | Mehrukh Zehravi[3] | Sherouk Hussein Sweilam[4,5] | A. Dinesh Raja[6] | M. Akiful Haque[7] | Chandan Nayak[8] | Senthilkumar Balakrishnan[9] | Laliteshwar Pratap Singh[10] | Saswati Panigrahi[11] | Mohammed Ali Alshehri[12] | Safia Obaidur Rab[13] | Najmus Sakib Minhaj[2] | Talha Bin Emran[1]

[1]Department of Pharmacy, Faculty of Health and Life Sciences, Daffodil International University, Dhaka, Bangladesh

[2]Department of Pharmacy, Faculty of Pharmacy, University of Dhaka, Dhaka, Bangladesh

[3]Department of Clinical Pharmacy, College of Dentistry and Pharmacy, Buraydah Private Colleges, Buraydah, Saudi Arabia

[4]Department of Pharmacognosy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

[5]Department of Pharmacognosy, Faculty of Pharmacy, Egyptian Russian University, Cairo, Egypt

[6]Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, India

[7]Department of Pharmaceutical Analysis, School of Pharmacy, Anurag University, Hyderabad, India

[8]Department of Pharmaceutics, School of Pharmacy, Arka Jain University, Jharkhand, India

[9]Department of Pharmaceutics, JKKMMRF-Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Namakkal, India

[10]Department of Pharmaceutical Chemistry, Narayan Institute of Pharmacy, Gopal Narayan Singh University, Sasaram, India

[11]Department of Pharmaceutical Chemistry, St. John Institute of Pharmacy and Research, Vevoor, Palghar, India

[12]Department of Biology, Faculty of Science, University of Tabuk, Tabuk, Saudi Arabia

[13]Department of Clinical Laboratory Sciences, College of Applied Medical Science, King Khalid University, Abha, Saudi Arabia

Correspondence
Biswajit Kumar Utpal, Department of Pharmacy, Faculty of Health and Life Sciences, Daffodil International University, Dhaka 1207, Bangladesh.
Email: utpalpharmacy17@gmail.com

Mehrukh Zehravi, Department of Clinical Pharmacy, College of Dentistry and Pharmacy, Buraydah Private Colleges, Buraydah 51418, Saudi Arabia.
Email: mahrukh.zehravi@hotmail.com

Abstract

Polyphenols, a diverse group of naturally occurring compounds found in plants, have garnered significant attention for their potential therapeutic properties in treating neurodegenerative diseases (NDs). The Wnt/β-catenin (WβC) signaling pathway, a crucial player in neurogenesis, neuronal survival, and synaptic plasticity, is involved in several cellular mechanisms related to NDs. Dysregulation of this pathway is a hallmark in the development of various NDs. This study explores multiple polyphenolic compounds, such as flavonoids, stilbenes, lignans, and phenolic acids, and their potential to protect the nervous system. It provides a comprehensive analysis of their effects on the WβC pathway, elucidating their modes of action. The study highlights the dual function of polyphenols in regulating and protecting the nervous system, providing reassurance about the research benefits. This review

Biswajit Kumar Utpal, Sajib Chandra Roy, and Mehrukh Zehravi have contributed equally to this work.

provides a comprehensive analysis of the results obtained from both in vitro studies and in vivo research, shedding light on how these substances influence the various components of the pathway. The focus is mainly on the molecular mechanisms that allow polyphenols to reduce oxidative stress, inflammation, and apoptotic processes, ultimately improving the function and survival of neurons. This study aims to offer a thorough understanding of the potential of polyphenols in targeting the WβC signaling pathway, which could lead to the development of innovative therapeutic options for NDs.

KEYWORDS
neurodegenerative diseases, neurological diseases, polyphenols, Wnt/β-catenin pathway

1 | INTRODUCTION

Neurological diseases are an increasing concern globally in this century. Abnormalities of the autonomic nervous system, the brain, the muscles, the cranial nerves, the peripheral nerves, the spinal cord, the nerve roots, and the neuromuscular junctions (NMJ) are all included in the category of neurological diseases affecting both the central and the peripheral nervous systems.[1] These conditions include epilepsy, multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), and other forms of dementia; cerebrovascular diseases such as brain tumors and stroke; neuro-infections; traumatic disorders that result from head injuries; and neurological diseases that are caused by malnutrition.[2,3] In general, neurological diseases can be broken down into two categories: neurological injuries and neurodegenerative diseases (NDs), with the latter being the more common of the two.[4] These abnormalities cause a gradual and continual loss of brain cells, which ultimately results in neurodegeneration.[5,6] Despite thorough research, there is still a lack of effective medicines that can end or reverse the progression of many diseases. An area of research that shows promise is focusing on specific cellular pathways involved in developing NDs. One such system that has received substantial consideration is the Wnt/β-catenin (WβC) signaling pathway.[7] The WβC signaling system is a crucial mechanism that controls multiple aspects of cellular functions, such as development, differentiation, proliferation, and survival.[8] Within the central nervous system (CNS), this route plays a vital role in the production of new neurons, the ability of synapses to change and adapt, and the maintenance of neurons.[9] Signaling disruption is becoming more widely acknowledged as a shared characteristic in developing several NDs. Abnormal signaling can result in decreased neuronal function, heightened susceptibility to oxidative stress (OS), and enhanced inflammatory responses, all of which contribute to the advancement of NDs.[9] In AD, aberrant Wnt signaling is associated with amyloid-β (Aβ) plaque formation and tau hyperphosphorylation, leading to cognitive decline.[9] In PD, impaired Wnt signaling affects dopaminergic neuron survival,[10] whereas in MS, it influences oligodendrocyte progenitor cell differentiation and myelination, exacerbating disease pathology.[11] Huntington's disease (HD) also involves altered Wnt signaling, contributing to neuronal degeneration.[12] Additionally, after acute neural injuries like stroke or traumatic brain injury,[8] Wnt signaling plays a role in repair and regeneration.[9] Targeting the WβC pathway using therapeutic interventions, including natural compounds like polyphenols, offers the potential for treating these conditions. Still, precise modulation is essential to avoid adverse effects due to the pathway's involvement in diverse physiological functions.[8,13] More study is needed to develop tailored therapeutics that maximize the beneficial effects of WβC signaling, providing diverse secondary metabolites with novel pharmacophores. Only 1% of over 250 000 higher plants have been thoroughly studied for their medicinal use.[14] According to the World Health Organization, three-fourths of the global population relies on plant-based drugs for essential medical treatment. These phytochemicals, found in herbs, spices, and foods, can have synergistic, additive, or antagonistic effects on human health.[15] Polyphenols are a diverse group of naturally occurring compounds that may be abundant in various plant-based foods, including tea, wine, and fruits and vegetables.[16] They have been demonstrated to exhibit a wide range of biological activities, including neuroprotective, anti-inflammatory, and antioxidant properties.[16,17] According to a recent study, polyphenols can prevent the WβC signaling pathway, which can be used as a therapy method for neurological diseases.[18] It has been discovered that polyphenols like epigallocatechin-3-gallate (EGCG) and resveratrol can alter the WβC signaling pathway in AD, therefore lowering the toxicity of Aβ and the hyperphosphorylation of tau.[19] In PD, polyphenols may protect dopaminergic neurons by enhancing WβC signaling, thereby improving motor function.[19,20] In MS, these compounds can promote remyelination by influencing the differentiation of oligodendrocyte progenitor cells.[21] HD also benefits from polyphenol-induced modulation of Wnt signaling, which can help mitigate neuronal degeneration.[22] Furthermore, polyphenols have demonstrated their potential to enhance the involvement of the WβC pathway in the neuronal repair and regeneration process after acute traumas such as stroke and traumatic brain injury.[18] Polyphenols have a significant therapeutic potential; nevertheless, there are still problems regarding their bioavailability and the efficient transport of polyphenols to the brain.[23] To overcome these

challenges and improve the effectiveness of polyphenol-based therapies for neurological conditions, researchers are looking at the possibility of using advances in nanotechnology and drug delivery systems. Therefore, the connection of polyphenols and the WβC signaling pathway is a very intriguing and compelling field of research that holds significant implications for developing innovative treatment options for neurological diseases.[18]

This study aims to comprehensively analyze previous research on polyphenols and their impact on the WβC signaling pathway in connection to NDs. By examining the molecular mechanisms, therapeutic possibilities, and barriers linked to polyphenol-based therapies, we aim to emphasize both the potential and constraints of this approach. Furthermore, we will review developments in drug delivery strategies that increase polyphenols' effectiveness and open the door to novel therapies for NDs.

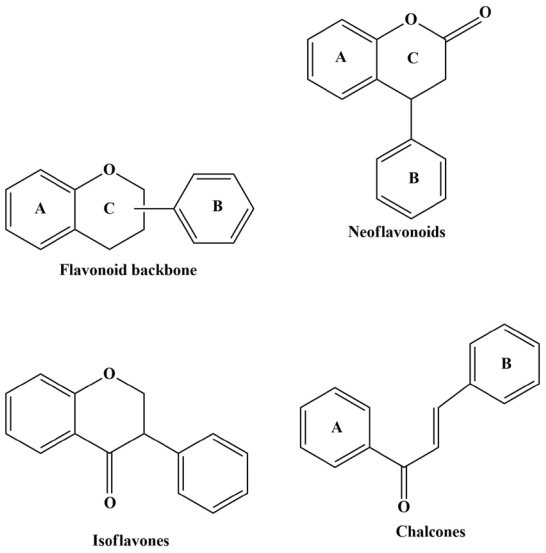

FIGURE 1 Chemical structure of flavonoid, neoflavonoid, isoflavonoid, and chalcone backbone.

2 | CHEMISTRY OF POLYPHENOLS

Phenolic compounds, often known as phenolics, are distinguished by their aromatic ring structures with at least one hydroxyl group. The complexity of these substances can vary greatly, spanning from essential molecules to intricate polymers with substantial molecular weights.[24] The categorization of phenolics is a subject of considerable discussion; however, the prevailing approach divides them into two primary categories: flavonoids and nonflavonoid polyphenols. Scientific literature frequently employs this categorization to arrange and investigate these substances.[25] Flavonoids have a structural backbone consisting of C6–C3–C6, with two phenolic C6 units known as ring A and ring B. Flavonoids can be classified into several subgroups based on the variability of the core C3 unit, also known as ring C. The subgroups consist of flavan-3-ols, flavonols, flavones, flavanones, and anthocyanins.[26] The distinct arrangement and hydroxylation pattern of these rings lead to the extensive range of flavonoids in the natural world. Most flavonoids typically have ring B connected to the C2 location of ring C. Nevertheless, certain flavonoids, including isoflavones and neoflavonoids, exhibit a linkage between ring B and the C3 and C4 locations of ring C, respectively.[26] Flavonoids in plants are predominantly present as glycosides, meaning they are attached to sugar molecules rather than as free aglycones, which are the fundamental structures of flavonoids.[27] The process of glycosylation has an impact on the solubility, stability, and bioavailability of these substances. The biological functions of flavonoids, such as their ability to act as antioxidants, reduce inflammation, and inhibit the growth of microorganisms, are determined by their unique structural characteristics and patterns of glycosylation.[28] The activities mentioned are essential for the function of flavonoids in plant defense mechanisms and their potential health advantages when included in the human diet.[29]

Conversely, nonflavonoid polyphenols comprise many chemicals, including phenolic acids, stilbenes, and lignans. Furthermore, these molecules have noteworthy biological properties and play a role in the general health advantages linked to diets abundant in polyphenols. Phenolic acids, recognized for their antioxidant qualities, are present in several foods.[30] Stilbenes, like resveratrol, are present in grapes and berries and are being studied for their ability to slow down the aging process and prevent diseases.[31] Lignans (Figure 1), found in seeds, whole grains, and vegetables, are recognized for their ability to protect against specific types of cancer and cardiovascular diseases.[32]

Flavones consist of two benzene rings connected by a heterocyclic pyrone ring, forming its basic chemical structure. Luteolin and apigenin are the primary flavones commonly found in food, usually in the form of glycosides. Flavones and their 3-hydroxy derivatives, known as flavonols, make up the most significant subgroup of polyphenols.[33] This subgroup includes compounds such as glycosides, methoxides, and other acylated products in all three rings. Quercetin and kaempferol, the most common flavonol aglycones, have a wide range of glycosidic combinations.[34] Quercetin has at least 279 recognized combinations, whereas kaempferol has 347 identified combinations. Flavanones and their 3-hydroxy derivatives, commonly called flavanonols or dihydroflavonols, have been significantly identified over the past 15 years.[35] Certain flavanones (Figure 2) exhibit distinct substitution patterns, including prenylated, furanoflavanones, pyranoflavanones, and benzylated flavanones. As a result, a wide range of substituted derivatives can be found within this class. Taxifolin, a flavanonol, is present mainly in citrus fruits and is widely recognized.[35]

Flavanols (Figure 3), sometimes called flavan-3-ols or generally known as catechins, have unique structural features when compared to the majority of flavonoids. Flavanols, unlike other flavonoids, do not have a double bond between carbon 2 and carbon 3, and they also do not have a carbonyl group at carbon 4 in ring C.[36] The structural organization of flavanols, in conjunction with hydroxylation at carbon 3, enables the molecule to have two chiral centers, forming four possible diastereoisomers as a consequence.[37] The isomer with a *trans* configuration is called catechin, whereas that with a

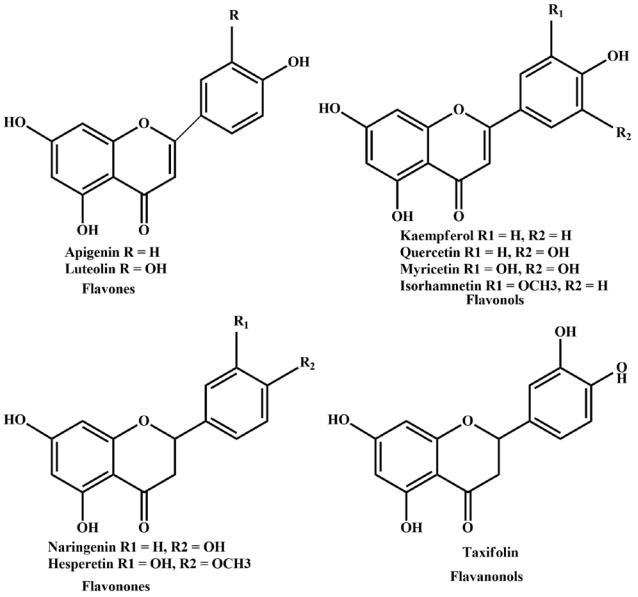

FIGURE 2 Chemical structure of flavones, flavonoids, flavanones, and flavonols.

cis configuration is called epicatechin.[38] Each configuration comprises four stereoisomers: (±)-catechin and (±)-epicatechin. Both (+)-catechin and (−)-epicatechin are significant isomers that may be found in various plants consumed. The peels of grapes, apples, and blueberries are particularly rich in flavanols, which may be abundant in different fruits.[39] The monomeric flavanols, especially catechin and epicatechin, and their derivatives, such as gallocatechins, are the significant flavonoids that may be found in tea leaves and cacao beans (chocolate).[40] The polymers known as proanthocyanidins can be formed by combining catechin and epicatechin. Through the process of acid-catalyzed cleavage of the polymeric chains, these polymers have the potential to produce anthocyanidins.[36,37,39]

Anthocyanidins are the primary pigments responsible for the intense red, blue, and purple hues in vegetable flower petals, fruits, and some types of grains, such as black rice.[41] In plants, anthocyanidins are most often found in glycosidic molecules called anthocyanins. Cyanidin, pelargonidin, and delphinidin are the most prevalent anthocyanidins.[42] There are also more than 20 unique anthocyanidins, bringing the total number of anthocyanidins to 31 different variants. Surprisingly, almost 90% of anthocyanins originate from cyanidin, delphinidin, and pelargonidin, together with their methylation variations.[43] More than 500 anthocyanins have been discovered, characterized by differences in hydroxylation, methoxylation patterns on the B ring, and glycosylation with various sugar units.[44] In addition, xanthones (Figure 4), a different group of polyphenolic chemicals, are known for their remarkable stability and have a dibenzo-γ-pyrone structure.[45] These compounds, known as xanthone, xanthene-9-one, or dibenzo-γ-pyrone, have gained significant attention from the food and pharmaceutical industries because of their chemical structures, which enable interactions with different drug targets. As a result, they have potential in drug development efforts.[46,47]

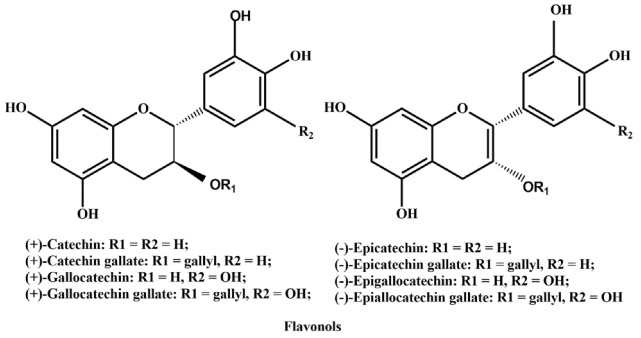

FIGURE 3 Chemical structure of different flavonols.

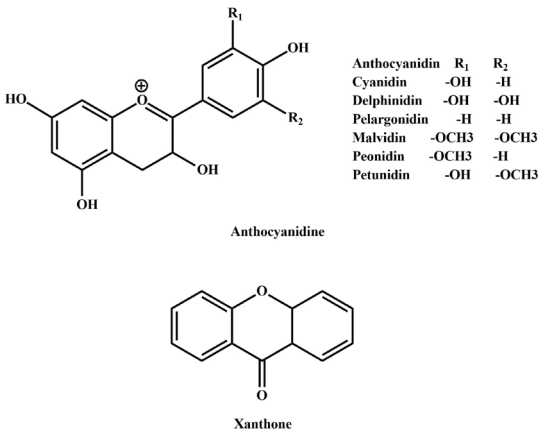

FIGURE 4 Chemical structure of anthocyanidine and xanthone.

Other nonflavonoid polyphenols that can be present in the diet, in addition to phenolic acids, flavonoids, and phenolic amides, have significant consequences for the health of humans. On the one hand, ellagic acid and its derivatives are frequently discovered in berries like strawberries and raspberries, as well as in the skins of many kinds of tree nuts.[48] Resveratrol, on the other hand, may be found in significant quantities in grapes and red wine. Resveratrol (Figure 5), $C_{14}H_{12}O_3$, is classified as a stilbenoid molecule with a relatively small molecular weight. 3,5,4′-Trihydroxystilbene, or resveratrol, is a polyphenolic antioxidant compound of two phenol rings linked by a styrene double bond.[49] Curcumin, obtained from turmeric, is a notable polyphenol known for its potent antioxidant capabilities. Curcumin, known as diferuloylmethane, is a symmetrical molecule with the IUPAC (International Union of Pure and Applied Chemistry) name (1*E*,6*E*). The compound is named 1,7-*bis*(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, and its chemical formula is $C_{21}H_{20}O_6$. Specifically, the structure comprises two aromatic ring systems that include *o*-methoxy phenolic groups. These ring systems are linked by a seven-carbon linker that consists of an α,β-unsaturated β-diketone moiety.[50,51] In addition, it is essential to point out that rosmarinic acid, which is a compound that is composed of two molecules of caffeic acid, and ellagic acid, which is a compound that is composed of two molecules of gallic acid, are polyphenols that are of particular importance. Both gallic acid and ellagic acid may be found in their

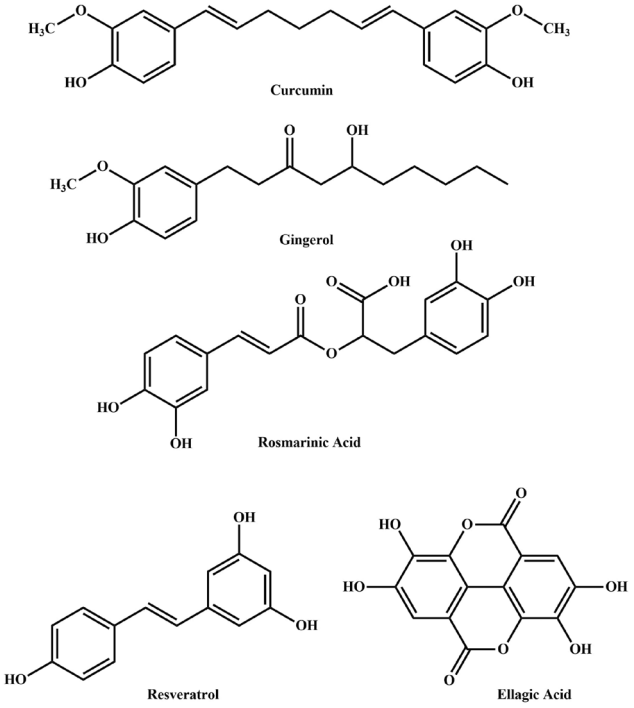

FIGURE 5 Chemical structure of nonflavonoid polyphenols.

free forms; however, they can also be found in various plants in the form of glucose esters, classified as hydrolyzable tannins.[52–55] Given their potential antinutritive characteristics, this review will not delve into a thorough study of these substances.

3 | WBC SIGNALING PATHWAY TARGET

In both invertebrates and vertebrates, Wnts—glycoproteins with abundant cysteine—activate receptor-mediated signal transduction. The signaling cascades associated with Wnt may be classified into two primary pathways: the β-catenin dependent canonical pathway and the β-catenin independent noncanonical pathway. A crucial function is carried out by the frizzled family of seven-pass transmembrane receptors in most WβC signaling cascades.[56] There are two basic classes of Wnt proteins, referred to as the Wnt1 class and the Wnt5a class, respectively. Regarding signal transmission, the Wnt5a group of proteins often utilizes routes that do not need the presence of β-catenin. The Wnt1-like proteins, on the contrary, are responsible for activating the canonical β-catenin-dependent pathway through their interaction with the Fzd and LRP5/6 co-receptor structures.[57]

The WβC signaling pathway is one of the most thoroughly researched of all the WβC signaling pathways. At least 6 of the 19 Wnt proteins initiate this signaling pathway, namely Wnt1, 2, 3, 3a, 8, 8b. In the majority of cases, the function of this pathway is primarily controlled by the cytoplasmic β-catenin concentration.[58] Low levels of β-catenin in the cytoplasm are common, and it is accomplished by continuously breaking it down through the ubiquitin–proteasome pathway. The breakdown process is controlled by a multiprotein complex consisting of axin, adenomatous polyposis coli (APC), glycogen synthase kinase-3β (GSK-3β), and casein kinase 1α (CK1α).[12] The ubiquitin–proteasome pathway comprises many crucial enzymes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3). CK1α and GSK-3β promote the breakdown of β-catenin by phosphorylating particular amino-terminal residues.[59] GSK-3β phosphorylates Ser33, Ser37, and Thr41, whereas CK1α phosphorylates Ser45. The phosphorylation events serve as a signal for β-catenin to be recognized by the β-transducin repeat-containing protein (β-TrCP), which is part of the E3 ubiquitin ligase complex.[12,57] This recognition leads to the destruction of β-catenin by the 26S proteasome complex.[8] The extracellular cysteine-rich domain of the Fzd receptor family and LRP5 or LRP6 interacts with Wnt proteins, which are glycoproteins released and bind with these proteins.[60] This connection activates the classical WβC signaling pathway, resulting in the phenomenon described. After the formation of a complex between the Wnt molecule and the Fzd/LRP5/6 receptor, an LRP-Wnt-Fz complex is formed due to the binding of three molecules. This arrangement stimulates the addition of a phosphate group to the cytoplasmic disheveled (Dvl) protein. It hinders the functions of GSK-3β and CK1α by capturing them at the scaffolding protein axin.[61] Due to this inhibition, adding a phosphate group to β-catenin is impeded, leading to the accumulation of β-catenin in the cytoplasm that has not been phosphorylated. The absence of phosphorylation in β-catenin results in its inability to be identified by β-TrCP, preventing its destruction and allowing it to enter the nucleus. When β-catenin is present in the nucleus, it forms a complex with the transcriptional factor TCF, also known as the T-cell factor.[62] In the absence of β-catenin, the transcription factor TCF, in conjunction with Groucho, a co-repressor, forms a complex with Groucho to inhibit transcriptional activity. The relationship between TCF and Groucho encourages the activation of downstream target genes, such as *c-myc* and *cyclin D1*, whereas β-catenin is responsible for interrupting this contact. This process occurs when they work together in conjunction with TCF and many other transcriptional cofactors, such as CREB-binding protein.[63] The importance of the WβC signaling system in many cellular activities is emphasized by these connections and regulatory mechanisms.[64]

When the LRP5/6 and Fzd receptors interact with Dickkopf (DKK1) and soluble frizzled-related protein (sFRP), respectively, they prevent the formation of the LRP-Wnt-Fz complex, thus impeding WβC signaling.[8] Synapses are affected both directly and indirectly by the reduction in Wnt signaling, which lowers the survival rate of microglia. Synapses are directly affected by the changes in Wnt signaling. Studies have shown that the canonical WβC antagonist DKK1 is elevated in the brains of people who have AD as well as in mice that have been modeled to have AD.[65] As a result of DKK1's binding to LRP5/6 co-receptors, frizzled and LRP5/6 cannot recognize Wnt proteins, which leads to a suppression of Wnt signaling. Consequently, individuals who suffer from AD exhibit increased levels of GSK-3β

activity and decreased levels of cytoplasmic β-catenin as a consequence of the inhibitory impact exhibited by DKK1.[66]

The WβC signaling system is vital in forming the blood–brain barrier (BBB) and developing blood vessels in the brain during embryonic development. From a clinical perspective, specific genetic variants in LRP6 are linked to a higher likelihood of experiencing an ischemic stroke.[67] Persons who have recently had a blockage of blood flow to the brain also exhibit elevated levels of DKK1 in their blood plasma, compared to persons in good condition. Elevated levels of DKK1 in cerebral ischemia (CI) exacerbate the disease by improving GSK-3β action and impeding the canonical WβC pathway.[61] Elevated levels of DKK1 are detected in individuals with AD, PD, and CI.[68] High DKK1 expression in PD is linked with better GSK-3β action and diminished WβC signaling. Moreover, there is a connection between LRRK2 and Parkin mutations and the dysregulation of WβC signaling. WβC signaling controls a range of biological activities, such as the growth and upkeep of midbrain dopaminergic (mDA) neurons.[69] Because neuronal degeneration initiates PD, regenerative medicine primarily studies them as a potential treatment. Regarding the maintenance, protection, and regeneration of nigrostriatal dopaminergic neurons, the WβC signaling pathway, working with glial cells, plays a vital role. Considering this information, this particular signaling route is essential in facilitating an all-encompassing program for restoring neurological function in PD.[70] Downregulation of the WβC pathway, which leads to a reduction in the transcription of Wnt prosurvival genes, is one of the essential features of HD. As a result, this ultimately increases apoptosis. A disruption in the breakdown of β-catenin is caused by the WβC canonical pathway, making HD progression more severe.[71] Research has found that there is a peculiar cytoplasmic accumulation of phosphorylated β-catenin. This phosphorylated β-catenin cannot travel to the nucleus and activate the transcription of target genes. In addition to participating in other signaling pathways, the WβC signaling pathway is essential in oligodendrocyte development and remyelination. Many studies have revealed that Wnt molecules can inhibit the oligodendrocyte development process.[72] The protein known as Wnt3a, which belongs to the WβC signaling family, has been associated with the development of cancer and other processes involved in cell proliferation and determining their destiny during the early stages of development (Figure 6). Several methods can potentially impact the progression of MS, which may lead to consequences.[73]

In summary, the WβC pathway governs various neuronal processes in the CNS, such as differentiation, synapse formation, neurogenesis, and neuroprotection. Synaptic plasticity is crucial for cognitive tasks, including learning and memory. Its decline is connected with cognitive impairments in NDs like AD.[64,71] Wnt proteins play a role in promoting the development of synapses and regulating neurotransmission, both before and after the synapse. Recent evidence suggests that WβC signaling is vital for the progress of mDA neurons and new neuron generation in the adult hippocampus. The deregulation of this pathway is involved in the development of NDs. Within a healthy CNS, the WβC signaling pathway is a sensor of the surroundings, ensuring a delicate equilibrium between cell survival and cell death.[59,65] When Wnt signaling is inhibited, β-catenin undergoes phosphorylation and degradation, which stops the transcription of genes responsible for promoting neuron survival. The Wnt target genes implicated in neurogenesis, neuron survival, maintenance, and plasticity comprise CCND1, NeuroD1, survivin, Mmp9, CACNA1G, NEUROGENIN 1, NURR1, and brain-derived neurotrophic factor (BDNF). These genes have essential responsibilities in the functioning of neurons, which are necessary for the overall health and functioning of the CNS.[58]

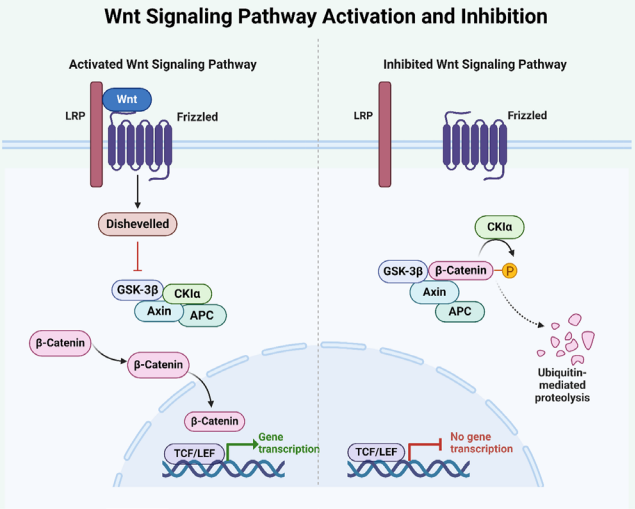

FIGURE 6 Schematic diagram showing the Wnt/β-catenin signaling pathway. Without Wnt ligands, β-catenin is degraded by a destruction complex composed of axin, APC, and GSK-3β, preventing nuclear entry and gene transcription. When Wnt binds to the frizzled receptor and co-receptor LRP5/6, the destruction complex is inhibited, allowing β-catenin to accumulate, translocate to the nucleus, and activate Wnt target genes through interaction with TCF/LEF. These genes regulate essential processes such as cell proliferation and neuronal development. Dysregulation of this pathway is linked to diseases like cancer and Alzheimer's. APC, adenomatous polyposis coli; GSK-3β, glycogen synthase kinase-3β; LRP5/6, low-density lipoprotein receptor-related protein 5/6; TCF/LEF, T-cell factor/lymphoid enhancer factor; Wnt, wingless-related integration site. Biorender.com program.

4 | TARGETING WBC SIGNALING PATHWAY BY POLYPHENOL

4.1 | Alzheimer's disease

AD is an ND that slowly worsens over time and primarily affects people who are in their later years. It is the most prevalent cause of dementia, which is marked by changes in behavior and personality, as well as a deterioration in cognitive function and memory loss. The formation of amyloid plaques (Aβ) and tau tangles in the brain is a hallmark of the disease, which causes a disruption in the communication between neurons and ultimately results in the death of those neurons.[74] For the past 25 years, Alzheimer's drug discovery

has been driven by the amyloid hypothesis. Nevertheless, no anti-Aβ medication has succeeded in any of the clinical trials. Therefore, to address the pressing need for novel tailored therapeutics, current research is moving toward discovering medicines that can target various processes linked to the progression of AD.[75,76] The WβC signaling pathway is crucial for cell functions like proliferation, migration, and differentiation, with Wnt proteins governing adult stem cells in mammals. Its disruption is linked to AD development.[77] Over a decade ago, researchers proposed a strong link between AD and impairments in the WβC signaling pathway.[77,78] In AD, the WβC signaling pathway is disrupted in various ways, including a decrease in β-catenin in the brains of AD patients with presenilin-1 (PS1) mutations and an increase in Dkk1 in AD brains and transgenic AD models.[79] The overexpression of Dkk1 is associated with cognitive deficiencies, synaptic disintegration, and reduced synaptic proteins.[80] On the contrary, knocking down Dkk1 may prevent neuronal death and tau phosphorylation caused by Aβ, and an antibody directed against Dkk1 can prevent synaptic loss caused by Aβ. A new susceptibility factor called clusterin has recently been discovered for late-onset AD. Inhibition of clusterin protects against the neurotoxicity of antibodies and prevents the induction of Dkk1 by antibodies.[81] Increased c-Jun activity results from Dkk1's ability to inhibit the canonical WβC pathway while simultaneously activating the noncanonical Wnt/JNK signaling cascade. These findings reveal that the clusterin/Dkk1/Wnt/JNK pathway activated by antibodies may be responsible for the neurotoxicity of antibodies. The aberrant phosphorylation of tau protein, which produces intra-neuronal neurofibrillary tangles, is one characteristic that distinguishes AD.[82] In vitro, tau is phosphorylated by several kinases, but the most important in vivo include CDK 5, microtubule affinity-regulating kinase, extracellular signal-related kinase 2, and GSK-3β. Increased GSK-3β activity is observed in cultured neurons after Aβ treatment, and active GSK-3β is present in AD brains, associated with decreased β-catenin levels and increased tau hyperphosphorylation.[82,83] GSK-3β transgenic mice exhibit neurodegeneration and spatial learning deficits.[84] Phosphorylated tau prevents apoptosis by maintaining β-catenin levels, as increased phosphorylated tau correlates with increased nuclear β-catenin, and β-catenin knockdown negates tau's antiapoptotic effects.[85] This indicates that β-catenin plays a protective role in AD. There is a neuroprotective effect of the Wnt signaling pathway against the toxicity of Aβ. By inhibiting the decrease in β-catenin and neurotoxicity caused by Aβ in cultured hippocampus neurons, Wnt-3a plays a crucial role.[86] Wnt-3a's protective effect is mediated by the Fz1 receptor, with Fz1 overexpression enhancing cell survival and Fz1 knockdown reducing Wnt-3a's neuroprotective effect.[87] In an AD mouse model, GSK-3β inhibitor lithium activates WβC signaling; increases β-catenin; inhibits GSK-3β; and reduces memory impairment, Aβ aggregates, oligomers, and astrogliosis.[88] Therefore, poor canonical WβC signaling may contribute to neurodegeneration found in AD, and stimulating this pathway may be a potential treatment method.[89]

Polyphenol treatment is a widely used and effective strategy for the management of AD. Various polyphenols, including curcumin, honokiol, quercetin, resveratrol, fisetin, EGCG, and oleuropein, have shown promise in AD treatment.[20] Honokiol is an anti-inflammatory agent that reduces cytokine production in glial cells and modulates peroxisome proliferator-activated receptor gamma (PPARγ) levels, nuclear factor kappa B (NF-κB) activities, reactive oxygen species (ROS) production, and apoptosis.[90,91] Curcumin inhibits Aβ aggregation, lowers mitochondrial membrane potential, increases Bcl-2 expression, and reduces Cyt-c, AChE, and Bax expression in brain cells.[92] Quercetin helps diminish ROS production, persuading AMP-activated protein kinase (AMPK), restoring ATP synthesis, and reducing Aβ accumulation.[93] Research indicates that polyphenols, including curcumin, can target the WβC signaling pathway in AD. Curcumin has been exposed to enhance β-catenin mRNA and protein levels, induce cyclin D1, and activate the WβC signaling pathway by inhibiting GSK-3 and γ-secretase. On the contrary, GSK-3 plays a neuroprotective role by phosphorylating and inactivating various transcription factors and signaling pathways.[94] Additionally, curcumin influences neurogenesis by targeting the WβC pathway, leading to the overexpression of proliferation-related genes (*reelin*, *nestin*, *Pax6*) and differentiation-related genes (*neuroligin*, *NeuroD1 neuregulin*, *neurogenin*, *Stat3*). Moreover, small-interfering RNA-mediated genetic WβC pathway inhibition has linked curcumin to Wnt inhibition.[95] Another study demonstrated that curcumin has antiamyloidogenic properties, showing potential in AD treatment. In a rat model where Aβ peptide was injected, curcumin mitigated learning deficits, reduced the activation of astrocytes and microglial cells, and stabilized the AKT/GSK-3 pathways and BDNF expression. Curcumin-lipid core nanoparticles (CURCUMIN-LNC) were even more effective, requiring 20 times lower doses than curcumin alone to achieve protective effects against Aβ-induced signaling disturbances (Table 1).[96] Curcumin also protected neuroblastoma SH-SY5Y cells from mitochondrial dysfunction induced by Aβ, reducing OS and suppressing apoptosis-related proteins such as Bax, caspase-3, and cytochrome C.[97] Additionally, curcumin reduced the production of Aβ by inhibiting GSK-3β-induced activation of PS1, a key component in γ-secretase activity essential for Aβ production.[98] Curcumin also activates the WβC pathway by suppressing GSK-3β, and increasing β-catenin and cyclin D levels, particularly in the nucleus (Figure 7).[95]

In an in vivo study, significant behavioral, histological, and biochemical alterations were identified in mice with AD induced by aluminum chloride ($AlCl_3$). These changes mainly involved OS, inflammation, Wnt/GSK-3β/β-catenin signaling, endoplasmic reticulum (ER) stress, autophagy, and apoptosis. The delivery of aluminum chloride ($AlCl_3$) caused OS, as indicated by increased levels of malondialdehyde and decreased expression of cellular antioxidants (Nrf2, HO-1, SOD, and TAC). aluminum chloride ($AlCl_3$) caused an increase in the expression of inflammatory biomarkers (TNF-α [tumor necrosis factor alpha] and IL-1β) and GSK-3β, resulting in an increase in tau phosphorylation, a decrease in BDNF production, and a downregulation of the WβC pathway. These modifications affected the behavioral and histological changes identified in the AD model produced by aluminum chloride

($AlCl_3$). The administration of EGCG resulted in significant improvement in all evaluated parameters. The cocoa–nutraceutical combination mitigated the unfavorable adverse effects caused by AD by regulating interconnected pathophysiological pathways, including inflammation, antioxidant responses, GSK-3β-Wnt/β-catenin signaling, endoplasmic reticulum (ER) stress, and apoptosis.[99] In another experimental model, high-fat (HF) diet-induced metabolic stress in SAMP8 mice resulted in impaired cognitive abilities, increased OS, and mitochondrial dysfunction, including changes in organelle dynamics. Notably, the HF diet also affected the WβC pathway in the hippocampus. Resveratrol, known for its antioxidant properties, mitigated some HF-induced alterations by reducing OS, restoring mitochondrial biogenesis, and decreasing neurodegenerative markers like tau hyperphosphorylation. Additionally, resveratrol's activation of the WβC pathway highlights its neuroprotective role.[100] These data show that resveratrol may have therapeutic promise for reducing cognitive decline in aging and NDs, which implies that resveratrol may have such potential. In contrast, a study on PC12 cells revealed that honokiol possesses neuroprotective properties, protecting against the neurotoxicity caused by Aβ1-42 in these cells. The inhibition of mitochondrial apoptosis and OS appears to be the mechanism by which this neuroprotection is mediated, at least in part. The study's results showed that honokiol may reduce levels of β-catenin protein and block the activation of GSK-3β. These features make honokiol a promising candidate for treating AD (Table 1).[101] In summary, polyphenols act as modulators of the WβC pathway by restoring its proper function in AD. By inhibiting GSK-3β, promoting β-catenin accumulation, and enhancing the activation of neuroprotective genes, polyphenols help reduce Aβ and tau pathology, combat OS, and improve synaptic plasticity and neurogenesis. These combined actions suggest that polyphenols may offer therapeutic potential for mitigating the progression of AD through WβC pathway modulation.

4.2 | Parkinson's disease

PD, the second most common age-related ND after AD, affects mobility. The disorder is characterized by the slow disintegration of mDA neurons in the substantia nigra pars compacta, leading to decreased dopamine levels and aberrant α-synuclein accumulation.[102] The gradual depletion of dopamine leads to motor symptoms, including rigidity, tremor, bradykinesia, and postural instability. The exact molecular pathways responsible for the initiation of PD are not yet fully understood. However, it has been observed that OS and inflammation, which are linked to mitochondrial dysfunction and apoptosis, are present in the brains of individuals with PD.[56] Till now, there is no therapy available that can influence the progression of PD.[103] The primary approach to treatment involves replacing dopamine through the administration of levodopa or dopamine agonists.[104] However, these medicines only temporarily relieve symptoms and might have adverse effects such as reduced effectiveness and dyskinesias. A comprehensive understanding of the molecular pathways that cause the onset and progression of PD is essential to identify novel molecular targets for the advancement of more efficient therapy approaches.[105]

The WβC signaling system significantly impacts PD by controlling multiple cellular processes related to the survival, development, and maintenance of mDA neurons.[106] Wnt proteins, released glycoproteins, attach to cell surface receptors like the Fzd receptors and LRP5/6. The WβC pathway is activated when Wnt ligands, such as Wnt1 and Wnt3a, bind to certain receptors, initiating a signaling cascade.[107] The binding of certain molecules forms a receptor complex that hinders the function of GSK-3β. This occurs by attracting Dvl proteins and other substances, leading to cytoplasmic β-catenin's stability. In the absence of WβC signaling, β-catenin undergoes phosphorylation by GSK-3β and CK1α inside a destruction complex that consists of axin and APC.[108] Phosphorylation of β-catenin serves as a signal for ubiquitination and subsequent proteasomal destruction. However, activating WβC signaling inhibits phosphorylation, allowing the accumulation of β-catenin, and allows to enter the nucleus. Wnt target genes are activated by β-catenin's interactions with TCF/LEF transcription factors in the nucleus. These genes are essential for cell survival, proliferation, and differentiation.[109] The WβC pathway is critical to the survival and function of mDA neurons, which are increasingly reduced in PD. Synapse development and maintenance affect neuronal transmission and plasticity via this signaling system. It also protects the BBB, which is impaired in PD and other NDs.[107,108]

Disruptions in the WβC pathway are often associated with PD development, as they are vital in pathogenic processes. The canonical WβC antagonist DKK1 is elevated in PD, suppressing WβC signaling. DKK1 interacts with LRP5/6, inhibiting the assembly of the Wnt receptor complex, which leads to heightened GSK-3β activity and reduced levels of β-catenin.[110] In addition, mutations in genes such as LRRK2 and Parkin, linked to familial PD, can interfere with controlling the WβC pathway, exacerbating the deterioration of mDA neurons. Considering these specific functions, directing therapeutic efforts toward the WβC pathway can be effective in treating PD.[111] Increasing Wnt signaling can promote the survival of neurons, the formation of new neurons, and the ability of synapses to change and adapt. Compounds with the ability to encourage the WβC signaling pathway or hinder its antagonists, such as DKK1, could potentially provide neuroprotective benefits in PD.[112] Comprehending and controlling this system could, therefore, offer novel treatment approaches for treating and potentially reducing the advancement of PD. Similar to AD, various polyphenols are considered beneficial for PD patients.[113] Curcumin, for example, protects dopaminergic neurons by reducing OS-induced damage, removing α-synuclein, regulating apoptosis, and decreasing inducible nitric oxide synthase levels.[114] Other polyphenols, such as honokiol, quercetin, and fisetin, also show potential benefits. A few studies have targeted the WβC signaling pathway using polyphenols in PD. Research indicates that curcumin reduces OS-induced injury in PD mice by regulating Wnt-related factors (cyclin D1, Wnt3a, c-myc, and β-catenin), glutathione

TABLE 1 Pharmacological studies of polyphenols acting on the Wnt/β-catenin pathway in neurodegenerative diseases.

Diseases	Compounds	In vitro/ in vivo models	Study model	Dose/ concentration	Target molecule	Mechanism	Reference
Alzheimer's disease	Curcumin	In vitro	PC12 cell	0.5 μM	GSK-3β	TCF/LEF and cyclinD1 promoter activities were elevated, GSK-3β levels were lowered, and β-catenin nuclear translocation was improved.	[94]
	Curcumin	In vitro	APPswe-transfected SY5Y cells	5.0 μmol/L	GSK-3β	Increasing cyclin D1	[95]
	Curcumin	In vivo	Mice	20 mg	β-Catenin	Curcumin internalization to the subventricular zone and hippocampus increased; reduced axin 1–2, APC, DKK1, Wif-1, and GSK-3β; and increased Wnt3, LRP5, and LEF.	[94]
	Curcumin	In vivo	Rat	50 mg/kg/day	Akt/ GSK-3β	It effectively reduces behavioral impairments, neuroinflammation, tau hyperphosphorylation, and cell signaling abnormalities caused by Aβ.	[96]
	Curcumin	In vitro	Human neuroblastoma SH-SY5Y cells	20 mM	GSK-3β	Curcumin pretreatment reduces total and phospho-Ser9 GSK-3 expression (pSer9-GSK-3) and rescues neurons against Aβ-induced mitochondrial metabolic deficit and aberrant OS. Curcumin's protection against Aβ-induced mitochondrial dysfunction involves inhibiting GSK-3 activity.	[97]
	Resveratrol	In vivo	Rat	15 mg/kg	GSK-3β	Enhancing depression-like behavior by downregulating p-GSK-3β and upregulating p-β-catenin expression.	[118]
	Resveratrol	In vivo	subclinical hypothyroidismat model	15 mg/kg	β-Catenin	Enhancing the frequency and distance of raising sucrose preference by activating the WβC signaling pathway.	[119]
	Resveratrol	In vivo	SAMP8 model	160 mg/kg	β-Catenin	Enhancing cognitive impairment and lowering IL-6 and TNF-α through β-catenin activation.	[100]
	Honokiol	In vitro	PC12 cell	5 and 10 μM	GSK-3β and β-catenin	Honokiol's neuroprotective qualities may be associated with the inhibition of GSK-3β activation and the reduction in β-catenin protein levels.	[101]
	Quercetin	In vivo	Swiss mice	1.6 pmol	GSK-3β	Potentiation of Wnt/β-catenin signaling to prevent neurodegeneration.	[120]
	Cyanidin	In vitro	PC12 cell	90 and 10 μg/ mL	GSK-3β and β-catenin	Cyanidin dramatically increased Wnt3a, β-catenin, and NeuroD1 mRNA expression while decreasing WIF1 and DKK1 expression.	[121]
	Morin	In vitro	Human neuroblastoma SH-SY5Y cells	10 μM	GSK-3β	Inhibited GSK-3β activity and blocked GSK-3β-induced tau phosphorylation.	[122]
	Osthole	In vitro	Neural stem cells	5 and 10 μM	GSK-3β and β-catenin	Inhibition of GSK-3β and increase in β-catenin expression.	[123]
	Salvianolic acid B	In vitro	Induced pluripotent stem cells	10 μM	GSK-3β	GSK-3β inactivation, AKT phosphorylation, and increased cyclin D expression.	[124]
	Apigenin	In vivo	Rat	50 mg/kg	GSK-3β	Protects against amyloid-β 25–35 by reducing GSK-3β expression, reducing tau protein hyperphosphorylation, and regulating BACE1 expression.	[125]
	Epigallocatechin-3-gallate	In vivo	Rat	10 mg/kg	GSK-3β	By modulating GSK-3β-Wnt/β-catenin signaling, endoplasmic reticulum ER stress, and apoptosis.	[99]

TABLE 1 (Continued)

Diseases	Compounds	In vitro/ in vivo models	Study model	Dose/ concentration	Target molecule	Mechanism	Reference
Parkinson's disease	Curcumin	In vivo	Rat	10 and 15 μmol/L	Wnt3a, b-catenin	Lowering malondialdehyde and increasing the levels of c-myc, cyclin D1, superoxide dismutase, glutathione peroxidase, dopamine transporter, and tyrosine hydroxylase.	[115]
	Curcumin	In vivo	Wistar rat	20 mg/kg	Wnt-β, β-catenin	Inhibiting WβC pathway	[126]
	Resveratrol	In vivo	Wistar rat	20 mg/kg	Wnt-β	Demonstrated neuroprotective effects in PD mice by regulating WβC.	[116]
	Apigenin	In vivo	Rat model	10 and 20 mg/kg	Wnt-β, β-catenin	Reduced inflammation	[127]
Stroke	Resveratrol	In vitro	Organotypic hippocampal culture	10, 25, and 50 mM	Akt/ GSK-3β	Akt and ERK1/2 were phosphorylated/activated, whereas GSK-3β was phosphorylated/ inactivated.	[128]
	Morin	In vivo	Male Wistar rat	30 mg/kg	Wnt-β, β-catenin	Improved functional outcomes and increased angiogenic factors via the WβC signaling and Ang1/Tie-2 pathway.	[129]
	Quercetin	In vivo	Rat	25 μmol	Wnt-β, β-catenin	Diminished cerebral edema and BBB permeability and enhanced BBB functionality.	[130]
	Kaempferol	In vivo	Male C57BL/6 mice	30 mg/kg	β-Catenin	Promoted O-GlcNAcylation of β-catenin to activate the Wnt/β-catenin pathway.	[131]
	Baicalin	In vivo	Male S–D	30 mg/kg	GSK-3β, β-catenin	It substantially stimulated the nuclear translocation of β-catenin and its phosphorylation of GSK-3β.	[132]
Huntington's disease	Quercetin	In vitro	Neural stem cell population	10 mM	GSK	Abrogates this NSC population while preserving neuron.	[133]
	Quercetin	In vivo	Female Wistar rats	25 mg/kg	Akt/ GSK-3β	Act against OS, mitochondrial dysfunctions, and neurobehavioral deficits.	[134]
Multiple sclerosis	Curcumin	In vivo	Male albino Wistar rats	60 mg/kg	Akt/ GSK-3β	Protection against neuronal degeneration.	[135]
	Resveratrol	In vivo	Female SJL/J mice	10 mg/kg	–	During optic neuritis, an inflammatory optic nerve lesion that occurs in MS, neuronal loss was prevented.	[136]
	Baicalin	In vivo	Healthy male SD rat	5 and 10 mg/kg	β-Catenin, Wnt5b, Wnt3a	Significant downregulation of active β-catenin, Wnt5b, and Wnt3a proteins.	[137]
Amyotrophic lateral sclerosis	Resveratrol	In vivo	Mice	25 mg/kg	–	Increase motor performance and longevity in this model of ALS.	[138]

Abbreviations: ALS, amyotrophic lateral sclerosis; APC, adenomatous polyposis coli; BBB, blood–brain barrier; GSK-3β, glycogen synthase kinase-3β; IL-6, interleukin 6; LEF, lymphoid enhancer factor; NSC, neural stem cell; OS, oxidative stress; SD, Sprague–Dawley; TCF, T-cell factor; TNF-α, tumor necrosis factor alpha; WβC, Wnt/β-catenin.

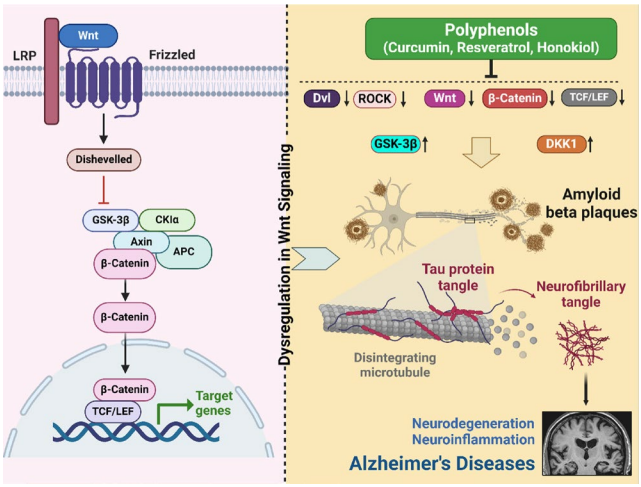

FIGURE 7 Schematic representation of the mechanism of action of polyphenols in Alzheimer's disease (AD) through modulation of the WβC signaling pathway. Dysregulation of this pathway triggers an increase in Wnt, ROCK, β-catenin, and Dvl levels, while reducing GSK-3β and DKK1, and contributing to the formation of amyloid-β plaques and neurofibrillary tangles—hallmarks of AD. Polyphenols counteract this dysregulation, helping restore balance in the WβC pathway and prevent AD progression. DKK1, Dickkopf-1; Dvl, disheveled; GSK-3β, glycogen synthase kinase-3β; ROCK, rho-associated protein kinase; WβC, Wnt/ β-catenin. program (https://biorender.com/.

peroxidase, malondialdehyde, superoxide dismutase, and mitochondrial membrane potential (Figure 8).[115]

Resveratrol was shown to reduce the neurotoxicity of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine on dopaminergic neurons in SNpc, preserving their function and allowing for striatal dopamine absorption. Resveratrol dramatically reduced MPP + -induced toxicity in SH-SY5Y neurons. Resveratrol dramatically increased Wnt1, p-Ser9-GSK-3β, and β-catenin levels in SNpc of PD animals and SH-SY5Y cells. Resveratrol primarily regulates the WβC signaling pathway, providing neuroprotective benefits in the PD model.[116] Quercetin has been found to enhance cognitive impairment in PD induced by 6-hydroxydopamine (6-OHDA) treatment. Additionally, it diminishes the depletion of striatal dopamine and enhances the presence of OS indicators. Quercetin, when taken by mouth, effectively reduces the loss of dopamine in the striatum, improves behavioral impairments, and slows down the degradation of the nigrostriatal system. In a rat model using 6-OHDA, the quercetin glycoside rutin partially alleviates motor impairments. This improvement is associated with a moderate yet considerable increase in dopamine and GSH levels in the brain's striatum. In general, quercetin has demonstrated potential advantages in the treatment of PD and cholinergic insufficiency.[117] Finally, polyphenols provide neuroprotective benefits in PD by modulating the WβC signaling pathway at both molecular and cellular levels. These compounds counteract OS, inflammation, and neuronal death—key factors in PD progression. At the molecular level, polyphenols inhibit GSK-3β, a negative regulator of Wnt signaling, stabilizing β-catenin and promoting its nuclear translocation. This activation of Wnt target genes enhances neuronal survival and neurogenesis. At the cellular level, polyphenols reduce oxidative damage and inflammation, protecting dopaminergic neurons from degeneration and ultimately slowing PD progression.

4.3 | Stroke

In the event of a stroke, the WβC pathway plays a significant role, and its involvement may be broken down into two distinct phases: the initial phase of injury and the subsequent phase of healing. The WβC signaling pathway is started during the acute phase in response to ischemia injury. This activation may be a protective mechanism, enhancing cell survival and suppressing apoptosis in the penumbra.[139] Enhancing the signaling pathway between Wnt and β-catenin during this phase can offer neuroprotection by maintaining the stability of β-catenin and encouraging the production of survival genes. In the recovery phase, the WβC pathway plays a crucial role in neurogenesis, angiogenesis, and synaptic plasticity, all crucial for functional recovery after a stroke.[140] In addition to assisting in developing new blood vessels, this route facilitates the repair and regeneration of injured brain tissue. The therapeutic approach of targeting the WβC system for stroke treatment holds great potential, but it also presents several obstacles. Current research endeavors are centered around identifying specific compounds or delivery mechanisms that can efficiently target the WβC pathway in stroke settings. Resveratrol exhibits neuroprotective effects in various models of neural injury and disease. In an in vitro ischemia model using oxygen–glucose deprivation of hippocampal samples, resveratrol induced phosphorylation of GSK-3β, AKT, and ERK1/2, with its neuroprotective effects being suppressed by the PI3K inhibitors but not MEK inhibitors.[128] Resveratrol also activates AMP-activated protein kinase (AMPK) to enhance insulin signaling and effects inhibited by the AMP-activated protein kinase (AMPK) inhibitors.[141] In a model of CI, resveratrol demonstrated antioxidant properties and scavenged free radicals, implicating GSK-3β and CREB in its neuroprotective mechanisms.[142] Lipid core nanocapsules improved the neuroprotective efficacy of resveratrol in rats administered with Aβ, by modulating JNK and GSK-3 signaling pathways.[143] Dietary resveratrol supplementation increased phosphorylation of GSK-3β and levels of neuroprotective proteins debrin and transthyretin.[144] After traumatic brain injury, resveratrol protected astrocytes by inhibiting apoptotic and autophagic cell death by suppressing ROS-mediated GSK-3β activation. Additionally, in a rat model of brain ischemia reperfusion, resveratrol reduced DJ-1 protein levels and activated the PI3K/AKT pathway, which suppressed GSK-3β activity, contributing to its neuroprotective effects.[145] In another study, reperfusion therapy after CI frequently results in reperfusion injury, which is induced by brain edema and disruption of the BBB in male rats. Global CI was induced by blocking both carotid arteries simultaneously and lowering blood pressure. Their findings demonstrated that quercetin effectively decreased cerebral edema and leakage of the BBB, while also enhancing the function of the BBB. Quercetin can potentially enhance the expression of ZO-1, claudin-5, β-catenin,

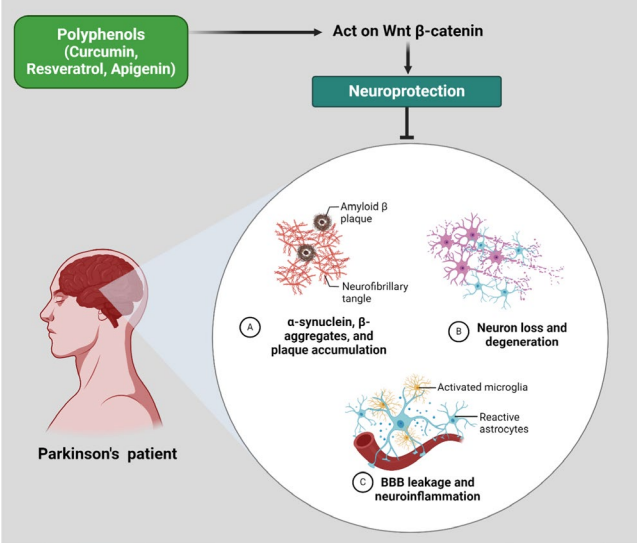

FIGURE 8 Schematic representation of polyphenol-mediated modulation of WβC signaling in PD. The progression of PD is marked by the downregulation of WβC signaling, driven by multiple pathological factors, including reduced neurotrophic factor levels, astrocyte-induced OS, and microglia-mediated inflammation. Additional contributors, such as the antagonistic effects of GSK-3β, DKK1, SFRPs, and neurotoxins, exacerbate the disruption of WβC signaling, ultimately leading to neurodegeneration. Polyphenols are proposed to counteract these harmful mechanisms, offering neuroprotective potential by restoring WβC pathway activity. DKK1, Dickkopf-related protein 1; GSK-3β, glycogen synthase kinase-3β; SFRPs, secreted frizzled-related proteins; PD, Parkinson's disease; WβC, Wnt/β-catenin.

and LEF1, while reducing the expression of MMP-9, GSK-3β, and axin. Furthermore, the presence of DKK1 can nullify the benefits of quercetin. Therefore, quercetin can ameliorate BBB dysfunction after global cerebral ischemia/reperfusion (I/R) in rats. This effect is likely due to the stimulation of the canonical WβC signaling pathway.[130] On the contrary, through the Ang1/Tie-2 route and the WβC signaling pathway, 20 mg/kg of morin effectively increased angiogenic factors in the rat model, resulting in improved functional outcomes.[129] Another study showed that EGCG promoted the breakdown of intracellular β-catenin, which reduced β-catenin response transcription induced by Wnt3a-conditioned medium. This impact was not seen for oncogenic versions of β-catenin, but EGCG did cause N-terminal phosphorylation at the Ser33/37 residues and consequent promotion of its destruction. There was no change in the β-catenin breakdown induced by EGCG when GSK-3β was pharmacologically inhibited or depleted. Protein phosphatase 2A expression and activity were unaffected by EGCG.[146] A study examined kaempferol's effects on infarction volume and neurological function in the middle cerebral artery (MCAO) animal model. The oxygen and glucose deprivation (OGD)/reoxygenation (R) brain stem cell paradigm examined kaempferol's effects on cell survival, migration, and apoptosis. Kaempferol decreased brain infarction and neurological impairment after middle cerebral artery (MCAO) chronic cerebral hypoperfusion. Kaempferol prevented OGD/R-treated NSC death and enhanced cell migration. Furthermore, OGD/R decreased *O*-GlcNAcylation and β-catenin *O*-GlcNAcylation, impacting the WβC pathway, whereas Kaempferol restored the effect. Inactivating the WβC pathway decreased NSCs' physiologic functions mediated by kaempferol. Kaempferol prevented cerebral infarction through NSC migration, viability, and apoptosis prevention. Kaempferol mechanically stimulated the WβC pathway by enhancing β-catenin *O*-GlcNAcylation. Kaempferol may reduce stroke.[131] Baicalin polarized microglia as anti-inflammatory and suppressed pro-inflammatory cytokines in another chronic cerebral hypoperfusion rat model. Baicalin therapy dramatically increased GSK-3β phosphorylation, β-catenin expression, and nuclear translocation. Baicalin simultaneously decreased nuclear nuclear factor kappa B (NF-κB) expression. Baicalin may improve cognitive impairment in chronic cerebral hypoperfusion -induced vascular dementia rats by promoting myelination and reducing inflammation, possibly activating WβC, and decreasing nuclear factor kappa B (NF-κB In summary, polyphenols modulate the WβC pathway in stroke by stabilizing β-catenin, inhibiting GSK-3β, reducing inflammation, and mitigating OS. These actions improve neuronal survival, reduce brain damage, and enhance poststroke recovery. This makes polyphenols promising candidates for therapeutic strategies aimed at neuroprotection and rehabilitation in stroke patients. However, further clinical studies are needed to validate these findings and translate them into effective treatments.

4.4 | Huntington's disease

HD is a hereditary, advancing neurological condition distinguished by mental, cognitive, and motor deficiencies. The main etiology of HD is genetic abnormalities occurring in the Huntington gene located on chromosome 4.[147] These mutations result in profound neurodegeneration in certain brain regions, including the thalamus, amygdala, insula, globus pallidus, and striatum. This prevalent neurodegeneration leads to a variety of symptoms, such as difficulties with speech, walking, and swallowing in the early stages, and stiffness, slow movement, and inability to move in the later stages.[148] Initially, cognitive deficits impact the regions underneath the cerebral cortex and then advance to a more widespread cognitive dysfunction caused by the shrinking of both the cerebral cortex and the regions beneath it.[149] Psychiatric symptoms, such as lack of interest, moodiness, and loss of touch with reality, are prevalent and differ greatly across individuals due to genetic variations. Aggression, psychosis, and sleep difficulties are prevalent among HD patients, with respective prevalence rates of 13%, 7%, and 13%.[150]

HD is linked to lower levels of β-catenin and decreased TCF-mediated transcription, especially in striatal cells with the huntingtin knock-in mutation. HD has exhibited inhibition of the WβC signaling pathway due to GSK-3β phosphorylation.[151] However, the decreased β-catenin levels in HD are mostly a result of post-transcriptional modifications rather than proteasomal degradation

driven by GSK-3β. High levels of miR-124, which maintain β-catenin, have been detected in HD. The β-catenin levels in HD have been shown to fluctuate across various models, including knock-in mice, Drosophila, and postmortem samples from HD patients, as indicated by research.[152] In individuals, HD neuronal cells derived from induced pluripotent stem cells (iPSC) exhibit a significant disruption of the β-catenin complex while exhibiting elevated expression of transcription factor 3 and frizzled transcripts. Furthermore, there is an increase in the expression of *CCND1*, a gene targeted by the WβC signaling pathway. Furthermore, microvascular cells obtained from iPSCs of patients diagnosed with HD exhibited increased expression of Wnt ligands, effectors, and downstream targets.[153] Blocking WβC signaling has been demonstrated to effectively prevent the development of angiogenic deficiencies and BBB disruption in HD. In contrast to other NDs, suppressing WβC signaling seems to positively affect HD.[154] Recent studies suggest that blocking WβC signaling, both in laboratory settings (in vitro) and in living organisms (in vivo), can alleviate symptoms of HD. However, it is uncertain if pharmaceutical inhibition can provide similar advantages to individuals with HD. Further investigations should examine this route as a possible treatment target for HD. At the level of 50 mM that is employed in HD, quercetin acts on the population of neural stem cells (NSC). It can effectively abrogate this NSC population while still sparing neuronal cells.[133] In summary, polyphenols hold potential as modulators of the WβC pathway, offering a promising therapeutic approach to combat the neurodegeneration observed in HD.

4.5 | Multiple sclerosis

MS is a persistent and serious disease that involves inflammation and autoimmunity. It is defined by the loss of myelin, a protective covering, in the white matter of the CNS. Chronic inflammation is responsible for the degeneration of the protective layer surrounding nerve fibers in the brain and spinal cord, ultimately resulting in the death of nerve cells and a steady reduction in neurological capacities.[155] Microglia and Th17 cells are important contributors to the process, as they release pro-inflammatory mediators that play a role in demyelination. TCF-1, a transcription factor involved in the WβC signaling pathway, functions as an epigenetic regulator that detrimentally influences the process of Th17 development.[156] Research has demonstrated that removing TCF-1 increases the expression of the interleukin-17 gene and promotes the development of Th17 cells. This effect has been observed in experimental autoimmune encephalomyelitis (EAE), a model used to study MS.[157] Within the context of EAE, the absence of LRP5, LRP6, or β-catenin leads to heightened production of pro-inflammatory cytokines and the polarization of Th1 and Th17 cells, ultimately worsening the disease's severity.[158] Nevertheless, the concentrations of WNT3a and β-catenin are notably increased in the pain regions of the spinal cord, suggesting a multifaceted function of these molecules in the pathogenesis of MS.[159] The WβC signaling pathway serves as an initial pathogenic indicator for diagnosing MS. Disruption of WβC signaling increases the permeability of the BBB and facilitates the entry of neutrophils. It is the WβC signaling pathway that plays a crucial role in maintaining the strength and effectiveness of the BBB. It does this by modulating the activity of endothelial cells and tight junction proteins.[160] Recent research suggests that WβC signaling is elevated in CNS endothelial cells during MS, resulting in the breakdown of endothelial cells, increased infiltration of CD4+ T cells, and demyelination. Previous research has demonstrated that suppressing WβC signaling at the genetic level before disease onset can worsen these pathological outcomes. Conversely, reactivating WβC signaling can partially improve endothelial function and hinder infiltration in MS.[161] Resveratrol has been shown to reduce the loss of neurons in female SJL/J mice that were suffering from optic neuritis. Optic neuritis is an inflammatory optic nerve lesion associated with MS. Resveratrol was administered at 10 mg/kg.[136]

4.6 | Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is an ND defined by the deterioration of motor neurons, resulting in a gradual loss of muscle strength and eventual paralysis. The source of ALS is still unknown and involves several disease-causing mechanisms. Around 5%–10% of ALS cases are hereditary, and the remaining 90%–95% occur randomly. During the past 30 years, researchers have discovered more than 25 mutated genes that play a role in the development of ALS. These genes contribute to inflammation, glutamate accumulation, and calcium-level imbalances. The prevalence of ALS is increasing, presenting a substantial worldwide health challenge.[162] Various therapies are employed to control the condition. Mexiletine, levetiracetam, baclofen, gabapentin, and tizanidine are utilized for the treatment of painful spasms, whereas botulinum toxin, atropine, amitriptyline, hyoscyamine, and glycopyrrolate are employed to manage sialorrhea.[163] Pharmacological substances such as difluoroquinolone, riluzole, and edaravone provide alleviation from symptoms in ALS. Notwithstanding these alternatives, there is still a demand for disease-modifying treatments that are truly effective. The WβC signaling system, vital in neural development, neurogenesis, synaptic integrity, and plasticity, is excessively active in ALS transgenic mice. Nevertheless, whether this excessive activation is advantageous or detrimental is yet to be determined. WβC pathways that do not involve β-catenin, such as Wnt/Ca2+ and Wnt/PCP, control Ca^{2+} levels by regulating the release of Ca^{2+} from the ER.[164] Activation of these pathways affects the destiny and movement of cells, leading to neurodegeneration. Astrocytes, microglia, and oligodendrocytes are essential for maintaining a stable internal environment in the brain and contribute to the development of ALS. The cells within ALS patients exhibit elevated amounts of WβC signaling and activation of β-catenin.[165] Disruption of these pathways can result in the deterioration of motor neurons, the activation of astrocytes, the presence of pro-inflammatory microglia, and the impairment of oligodendrocyte function. Oligodendrocytes in ALS exhibit both regenerative and harmful effects. Although older

oligodendrocytes can restore the structure of myelin, regenerated oligodendrocytes frequently exhibit delayed maturation and poor myelin repair. Inhibiting GSK-3β, which increases WβC signaling, has a positive impact on existing oligodendrocytes but has a detrimental effect on regenerating ones. Additional investigation is required to clarify these pathways.[166]

The NMJ is essential for motor function as it connects skeletal muscle with spinal cord motor neurons. ALS causes paralysis and neuromuscular problems due to the separation of the NMJ.[167] Acetylcholine and acetylcholine receptors (AChR) play a crucial role in maintaining the structure and functioning of the NMJ. Wnt proteins, including Wnt4 and Wnt11, play a crucial role in synapse formation by promoting the development of postsynaptic structures, such as AChR clusters, and facilitating the growth of motor axons. On the contrary, Wnt3a hinders the clustering of AChR, which negatively affects motor function. The establishment of the NMJ in mammals is facilitated by the WβC and Wnt/PCP signaling pathways, which involve the participation of Wnt4 and Wnt11.[168] Early detection of NMJ and skeletal muscle abnormalities could mitigate motor problems in ALS by enabling timely intervention. Activation of WβC plays a role in causing the loss of nerve function in neurons and impairing the functioning of glial cells. Suppressing WβC signaling, in addition to using muscle-specific kinase agonists and activating low-density lipoprotein receptor-related protein 4, could perhaps provide therapeutic advantages for ALS. However, further investigation is required to comprehend the interaction between WβC signaling and the advancement of ALS (Figure 9).[169]

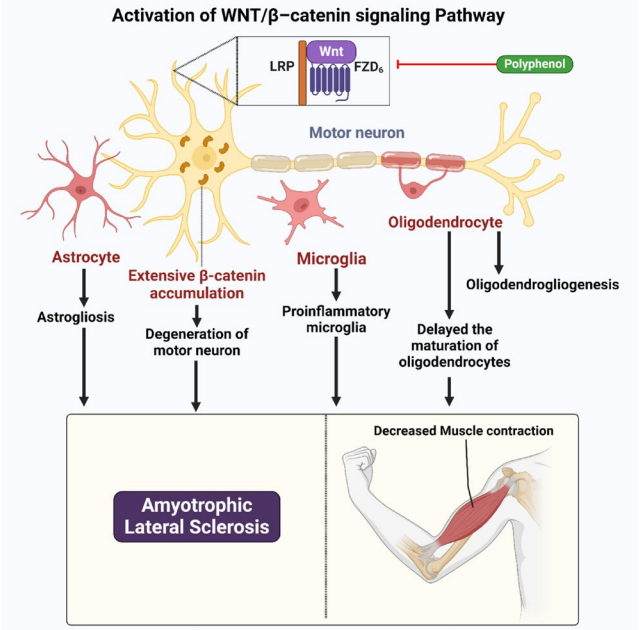

FIGURE 9 Illustration representing the action of polyphenol on the ALS (amyotrophic lateral sclerosis). The development of ALS is influenced by WβC signaling and the β-catenin protein. In ALS, the substantial buildup of β-catenin in motor neurons leads to deterioration. The activation of WβC signaling influences astrogliosis in ALS. The activation of WβC signaling facilitates the transition of microglia to a pro-inflammatory state. Delaying the maturation of regenerated oligodendrocytes is caused by activation of WβC signaling. Activation of WβC signaling encourages the restoration of the degenerative myelin structure and oligodendrogliogenesis in the existing oligodendrocytes. Polyphenols prevent ALS through their action on the WβC signaling pathway. WβC, Wnt/β-catenin. program (https://biorender.com/.

5 | RESTORING WBC SIGNALING

Neurological diseases, categorized by the dysregulation of multiple pathogenic pathways, frequently result in a considerable decrease in the signaling of WβC. The restoration of WβC signaling is a technique with great potential for producing innovative medicines to treat neurological diseases. This is because this route is vital to ensure the brain remains healthy. Not only is WβC signaling responsible for regulating cell survival, synaptic plasticity, neurogenesis, and the integrity and function of the BBB, but it is also responsible for a wide variety of other biological processes.[7] In the adult hippocampus, for instance, WβC signaling is vital for preserving synaptic integrity. The loss of synapses, synaptic plasticity, and long-term memory is frequently related to the overexpression of DKK1, an antagonist of the WβC pathway. In AD, reactivating the WβC pathway has demonstrated the capacity to reverse memory and synapse loss. This is especially true in the scenario of disease.[170] The restoration of WβC signaling in the brains of people who suffer from NDs, such as PD and AD, has the potential to facilitate a wide variety of neuronal processes often interfered with in these situations.[171] The treatments now available for NDs generally focus on alleviating symptoms rather than delivering curative solutions. This highlights the critical need for therapies that target the processes responsible for the disease process. Considering this, the WβC signaling pathway is an intriguing potential therapeutic target. The research findings have shown that several components of the WβC pathway, including GSK-3β, β-catenin, APC, TCF7L2, and FZD3, have been linked to schizophrenia. This further emphasizes the extensive significance of WβC signaling in the field of neurological health.[172]

Restoring the WβC signaling pathway balance is crucial for developing new treatments for NDs, aiming to reestablish equilibrium between Wnt-OFF and Wnt-ON states. This will ensure that WβC signaling is neither overly activated nor under-restored. It is possible that this well-balanced strategy could reduce the dangers that are associated with abnormal Wnt activation, such as the development of tumors, while simultaneously maximizing the neuroprotective and regenerative capabilities of the pathway. Therefore, the targeting of the WβC pathway presents a viable avenue for the production of medicines that are curative for NDs. Future therapeutics could address the underlying causes of these diseases by concentrating on the restoration and careful control of WβC signaling. This would result in more effective and long-lasting improvements for patients. To implement these discoveries into therapeutic practice, it will be

essential to continue studying the particular processes and effects of WβC signaling in various NDs.

6 | CHALLENGES IN TARGETING THE WBC SIGNALING PATHWAY

Targeting the Wnt-β signaling pathway for neurological diseases remains challenging due to its complexity. The WβC signaling network, with 19 Wnt ligands, 10 frizzled receptors, and 7 protein families, governs vital biological processes like embryogenesis and tissue regeneration. Disrupting WβC signaling can lead to tumor proliferation NDs, and metabolic irregularities.[173] Safety considerations further complicate the development of therapeutic drugs targeting the WβC pathway. Only a limited number of artificial small compounds have advanced to the stage of clinical trials, and among them, the porcupine inhibitor LGK974 has shown notable harmful consequences. For instance, clinical trials investigating LGK974 demonstrated its potential to induce the depletion of the intestinal epithelium, highlighting the delicate balance necessary for regulating this system. Multiple endeavors have been made to enhance the activation of WβC signaling as a therapeutic approach for disorders, including osteoporosis and neurological diseases. However, these endeavors are dangerous, as abnormal stimulation of WβC signaling might stimulate cancer development. This underscores the urgent need for safe and effective therapeutic interventions for WβC signaling. An additional key hurdle is the problem of selectivity and specificity when targeting the WβC signaling pathway. The components of the route frequently possess multifunctional functions and participate in diverse biological processes.[9] For example, GSK-3, a crucial enzyme involved in WβC signaling, also phosphorylates more than 100 distinct substances, contributing to glycogen production, inflammatory processes, and the stability of microtubules. Targeting this kinase could have extensive and unanticipated impacts due to its vast range of regulatory roles. Moreover, GSK-3β is involved in various diseases, including cancer, AD, and fibrosis, as well as metabolic disorders, including diabetes and inflammatory diseases.[174] Wnt5a, usually related to noncanonical signaling, can activate β-catenin and function canonically.[175] On the contrary, Wnt11, which is typically connected with noncanonical signaling, has been discovered to define dorsal axis development in Xenopus through a canonical pathway that involves β-catenin. The complex interplay and interconnection between different functions and pathways within the WβC signaling network pose significant challenges in selectively targeting individual proteins for therapeutic interventions without impacting other essential activities.[176] The complexity, safety concerns, and challenge of obtaining selectivity and specificity all highlight the significant obstacles in developing effective and safe WβC signaling therapies for neurological diseases. Although there has been notable progress in comprehending the WβC pathway, using this information in clinical settings is still tricky and challenging because of inherent obstacles.

7 | CONCLUSION AND FUTURE PERSPECTIVES

Polyphenols, including curcumin, resveratrol, apigenin, morin, and cyanidin, have gained recognition as promising agents for targeting the WβC signaling pathways in various NDs such as AD, PD, HD, stroke, MS, and ALS. These compounds exhibit a broad range of actions, modulating the WβC signaling pathway and providing neuroprotection through their anti-inflammatory, antioxidant, and antiapoptotic properties. Preclinical studies have consistently demonstrated the significant ability of polyphenols to influence the WβC pathway, which is critical in the pathogenesis of NDs. For instance, curcumin has been shown to reduce amyloid plaque formation and tau hyperphosphorylation in AD models. At the same time, resveratrol has been found to enhance neuronal survival and synaptic plasticity through WβC modulation. Similarly, apigenin, morin, and cyanidin exert neuroprotective effects by targeting fundamental molecular mechanisms within the WβC pathway. Given the potential therapeutic advantages of these polyphenols, targeting the WβC signaling pathway represents a viable strategy for treating and managing NDs. Their ability to cross the BBB and exert effects within the CNS further highlights their promise as neurotherapeutics.

Despite these encouraging findings, significant challenges remain before these preclinical results can be translated into clinical applications. One of the main hurdles is the bioavailability and stability of polyphenols, which limit their therapeutic efficacy. Advanced drug delivery technologies, such as nanoparticles and liposomes, could improve the bioavailability of polyphenols, allowing more targeted delivery to the brain and enhancing their therapeutic potential. Future research is essential to elucidate further the molecular mechanisms through which polyphenols regulate the WβC pathway in NDs. Moreover, large-scale clinical trials are crucial to confirm the safety and efficacy of these compounds in human populations. Combining polyphenols with existing pharmaceutical treatments may also yield synergistic effects, enhancing therapeutic outcomes. In addition, personalized medicine approaches, which consider individual patients' genetic and molecular profiles, could optimize the efficacy of polyphenol-based therapies and minimize adverse effects. In conclusion, polyphenols targeting the WβC signaling pathway have substantial potential for developing novel therapeutic strategies for NDs. Future efforts should focus on overcoming challenges related to bioavailability and stability, conducting comprehensive clinical trials, and exploring personalized treatment options. With continued research and innovation, polyphenols could become a key component in managing and treating NDs, offering patients improved outcomes and quality of life.

AUTHOR CONTRIBUTIONS

Biswajit Kumar Utpal: Conceptualization; data curation; formal analysis; investigation; supervision; validation; visualization; writing – original draft; writing – review and editing. **Sajib Chandra Roy:** Data curation; resources; validation; visualization; writing – original draft; writing – review and editing. **Mehrukh Zehravi:**

Conceptualization; data curation; formal analysis; investigation; resources; supervision; validation; writing – original draft; writing – review and editing. **A. Dinesh Raja:** Data curation; resources; validation; visualization; writing – original draft; writing – review and editing. **M. Akiful Haque:** Data curation; investigation; validation; visualization; writing – original draft; writing – review and editing. **Chandan Nayak:** Formal analysis; investigation; validation; visualization; writing – review and editing. **B. Senthilkumar:** Formal analysis; investigation; visualization; writing – review and editing. **Laliteshwar Pratap Singh:** Data curation; formal analysis; resources; visualization; writing – review and editing. **Saswati Panigrahi:** Data curation; formal analysis; resources; visualization; writing – review and editing. **Safia Obaidur Rab:** Formal analysis; funding acquisition; investigation; validation; visualization; writing – review and editing. **Najmus Sakib Minhaj:** Data curation; validation; visualization; writing – review and editing. **Talha Bin Emran:** Conceptualization; data curation; investigation; project administration; supervision; validation; visualization; writing – review and editing. **Sherouk Hussein Sweilam:** Data curation; formal analysis; investigation; visualization; writing – original draft; writing – review and editing. **Mohammed Ali Alshehri:** Formal analysis; validation; visualization; writing – review and editing.

ACKNOWLEDGMENTS

The authors are thankful to their own institutions and to the Deanship of Research and Graduate Studies, King Khalid University, Abha, Saudi Arabia, for financially supporting this work through the Large Research Group Project under Grant no. R.G.P.2/509/45.

FUNDING INFORMATION

This research received no external funding.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICAL STATEMENT

Not applicable.

CONSENT

Not applicable.

ORCID

Biswajit Kumar Utpal https://orcid.org/0009-0000-4946-0006

REFERENCES

1. Borsook D. Neurological diseases and pain. *Brain*. 2012;135(2):320-344.
2. Momin EN, Mohyeldin A, Zaidi HA, Vela G, Quiñones-Hinojosa A. Mesenchymal stem cells: new approaches for the treatment of neurological diseases. *Curr Stem Cell Res Ther*. 2010;5(4):326-344. doi:10.2174/157488810793351631
3. Leinenga G, Langton C, Nisbet R, Götz J. Ultrasound treatment of neurological diseases-current and emerging applications. *Nat Rev Neurol*. 2016;12(3):161-174.
4. Rosenberg GA. Neurological diseases in relation to the blood-brain barrier. *J Cereb Blood Flow Metab*. 2012;32(7):1139-1151. doi:10.1038/jcbfm.2011.197
5. Kumar GP, Anilakumar KR, Naveen S. Phytochemicals having neuroprotective properties from dietary sources and medicinal herbs. *Pharm J*. 2015;7(1):1-17. doi:10.5530/pj.2015.7.1
6. Saxena S. Role of medicinal plants in neurodegenerative diseases. *J Int Med Sci Acad*. 2015;28(4):218-221. doi:10.1007/s40898-017-0004-7
7. Gao J, Liao Y, Qiu M, Shen W. Wnt/β-catenin signaling in neural stem cell homeostasis and neurological diseases. *Neuroscientist*. 2021;27(1):58-72. doi:10.1177/1073858420914509
8. Mo Z, Zeng Z, Liu Y, Zeng L, Fang J, Ma Y. Activation of Wnt/Beta-catenin signaling pathway as a promising therapeutic candidate for cerebral ischemia/reperfusion injury. *Front Pharmacol*. 2022;13:914537. doi:10.3389/fphar.2022.914537
9. Huang P, Yan R, Zhang X, Wang L, Ke X, Qu Y. Activating Wnt/β-catenin signaling pathway for disease therapy: challenges and opportunities. *Pharmacol Ther*. 2019;196:79-90. doi:10.1016/j.pharmthera.2018.11.008
10. Vallée A, Vallée JN, Lecarpentier Y. Parkinson's disease: potential actions of lithium by targeting the WNT/B-catenin pathway, oxidative stress, inflammation and glutamatergic pathway. *Cells*. 2021;10(2):1-16. doi:10.3390/cells10020230
11. Lengfeld JE, Lutz SE, Smith JR, et al. Endothelial Wnt/β-catenin signaling reduces immune cell infiltration in multiple sclerosis. *Proc Natl Acad Sci USA*. 2017;114(7):E1168-E1177. doi:10.1073/pnas.1609905114
12. Libro R, Bramanti P, Mazzon E. The role of the Wnt canonical signaling in neurodegenerative diseases. *Life Sci*. 2016;158:78-88. doi:10.1016/j.lfs.2016.06.024
13. Ramakrishna K, Nalla LV, Naresh D, et al. WNT-β catenin signaling as a potential therapeutic target for neurodegenerative diseases: current status and future perspective. *Diseases*. 2023;11(3):89. doi:10.3390/diseases11030089
14. Das R, Mitra S, Tareq AM, et al. Medicinal plants used against hepatic disorders in Bangladesh: a comprehensive review. *J Ethnopharmacol*. 2022;282:114588. doi:10.1016/j.jep.2021.114588
15. Petlevski R, Hadžija M, Slijepčevič M, Juretič D. Effect of "antidiabetis" herbal preparation on serum glucose and fructosamine in NOD mice. *J Ethnopharmacol*. 2001;75(2–3):181-184. doi:10.1016/S0378-8741(01)00177-5
16. Bhullar KS, Rupasinghe HPV. Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. *Oxid Med Cell Longev*. 2013;2013:1-18. doi:10.1155/2013/891748
17. Shi R, Gao D, Stoika R, Liu K, Sik A, Jin M. Potential implications of polyphenolic compounds in neurodegenerative diseases. *Crit Rev Food Sci Nutr*. 2022;64:5491-5514. doi:10.1080/10408398.2022.2155106
18. Moradi SZ, Jalili F, Farhadian N, et al. Polyphenols and neurodegenerative diseases: focus on neuronal regeneration. *Crit Rev Food Sci Nutr*. 2022;62(13):3421-3436. doi:10.1080/10408398.2020.1865870
19. Fukutomi R, Ohishi T, Koyama Y, Pervin M, Nakamura Y, Isemura M. Beneficial effects of epigallocatechin-3-o-gallate, chlorogenic acid, resveratrol, and curcumin on neurodegenerative diseases. *Molecules*. 2021;26(2):415. doi:10.3390/molecules26020415
20. Maleki Dana P, Sadoughi F, Mansournia MA, Mirzaei H, Asemi Z, Yousefi B. Targeting Wnt signaling pathway by polyphenols: implication for aging and age-related diseases. *Biogerontology*. 2021;22(5):479-494. doi:10.1007/s10522-021-09934-x
21. Theodosis-Nobelos P, Rekka EA. The multiple sclerosis modulatory potential of natural multi-targeting antioxidants. *Molecules*. 2022;27(23):8402. doi:10.3390/molecules27238402

22. Akter R, Rahman H, Behl T, et al. Prospective role of polyphenolic compounds in the treatment of neurodegenerative diseases. *CNS Neurol Disord Drug Targets*. 2021;20(5):430-450. doi:10.2174/1871527320666210218084444
23. Mignet N, Seguin J, Chabot GG. Bioavailability of polyphenol liposomes: a challenge ahead. *Pharmaceutics*. 2013;5(3):457-471. doi:10.3390/pharmaceutics5030457
24. El Gharras H. Polyphenols: food sources, properties and applications—a review. *Int J Food Sci Technol*. 2009;44(12):2512-2518. doi:10.1111/j.1365-2621.2009.02077.x
25. Kabera JN, Semana E, Mussa AR, He X. Plant secondary metabolites: biosynthesis, classification, function and pharmacological properties. *J Pharm Pharmacol*. 2014;2:377-392.
26. Corcoran MP, McKay DL, Blumberg JB. Flavonoid basics: chemistry, sources, mechanisms of action, and safety. *J Nutr Gerontol Geriatr*. 2012;31(3):176-189. doi:10.1080/21551197.2012.698219
27. Kelly EH, Dennis JB, Anthony RT. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. *J Nutr Biochem*. 2002;13:572-584.
28. Tsao R, Mccallum J. Chemistry of flavonoids. In: de la Rosa LA, Alvarez-Parrilla E, González-Aguilar GA, eds. *Fruit and Vegetable Phytochemicals: Chemistry, Nutritional Value, and Stability*. John Wiley & Sons, Ltd; 2009:131-153. doi:10.1002/9780813809397.ch5
29. Shashank K, Abhay KP. Chemistry and biological activities of flavonoids: an overview. *Sci World J*. 2013;58(4):145-148.
30. Jia X, Yang D, Xie H, Jiang Y, Wei X. Non-flavonoid phenolics from Averrhoa carambola fresh fruit. *J Funct Foods*. 2017;32:419-425. doi:10.1016/j.jff.2017.03.025
31. Chou YC, Ho CT, Pan MH. Stilbenes: chemistry and molecular mechanisms of anti-obesity. *Curr Pharmacol Rep*. 2018;4(3):202-209. doi:10.1007/s40495-018-0134-5
32. Pecyna P, Wargula J, Murias M, Kucinska M. More than resveratrol: new insights into stilbene-based compounds. *Biomol Ther*. 2020;10(8):1-40. doi:10.3390/biom10081111
33. Singh M, Kaur M, Silakari O. Flavones: an important scaffold for medicinal chemistry. *Eur J Med Chem*. 2014;84:206-239. doi:10.1016/j.ejmech.2014.07.013
34. Leonte D, Ungureanu D, Zaharia V. Flavones and related compounds: synthesis and biological activity. *Molecules*. 2023;28(18):6528. doi:10.3390/molecules28186528
35. Khan MK, Rakotomanomana N, Loonis M, Dangles O. Chemical synthesis of citrus flavanone glucuronides. *J Agric Food Chem*. 2010;58(14):8437-8443. doi:10.1021/jf1010403
36. Luo Y, Jian Y, Liu Y, Jiang S, Muhammad D, Wang W. Flavanols from nature: a phytochemistry and biological activity review. *Molecules*. 2022;27(3):719. doi:10.3390/molecules27030719
37. Andrés-Lacueva C, Medina-Remon A, Llorach R, et al. Phenolic compounds: chemistry and occurrence in fruits and vegetables. In: de la Rosa LA, Alvarez-Parrilla E, González-Aguilar GA, eds. *Fruit and Vegetable Phytochemicals: Chemistry, Nutritional Value, and Stability*. John Wiley & Sons, Ltd; 2009:53-88. doi:10.1002/9780813809397.ch2
38. Tsao R, Yang R, Young JC, Zhu H. Polyphenolic profiles in eight apple cultivars using high-performance liquid chromatography (HPLC). *J Agric Food Chem*. 2003;51(21):6347-6353. doi:10.1021/jf0346298
39. Mendoza-Wilson AM, Glossman-Mitnik D. Theoretical study of the molecular properties and chemical reactivity of (+)-catechin and (−)-epicatechin related to their antioxidant ability. *J Mol Struct Theo Chem*. 2006;761(1–3):97-106. doi:10.1016/j.theochem.2006.01.001
40. Si W, Gong J, Tsao R, Kalab M, Yang R, Yin Y. Bioassay-guided purification and identification of antimicrobial components in Chinese green tea extract. *J Chromatogr A*. 2006;1125(2):204-210. doi:10.1016/j.chroma.2006.05.061
41. Jordheim M. Basic anthocyanin chemistry and dietary sources. *Anthocyanins Heal Dis*. 2013;1:13-90. doi:10.1201/b15554-3
42. Smeriglio A, Barreca D, Bellocco E, Trombetta D. Chemistry, pharmacology and health benefits of Anthocyanins. *Phyther Res*. 2016;30:1265-1286. doi:10.1002/ptr.5642
43. Andersen ØM, Jordheim M. The anthocyanins. *Flavonoids: Chemistry, Biochemistry and Applications*. CRC Press; 2006.
44. McCallum JL, Yang R, Young JC, Strommer JN, Tsao R. Improved high performance liquid chromatographic separation of anthocyanin compounds from grapes using a novel mixed-mode ion-exchange reversed-phase column. *J Chromatogr A*. 2007;1148(1):38-45. doi:10.1016/j.chroma.2007.02.088
45. Negi JS, Bisht VK, Singh P, Rawat MSM, Joshi GP. Naturally occurring Xanthones: chemistry and biology. *J Appl Chem*. 2013;2013:1-9. doi:10.1155/2013/621459
46. Li G, Thomas S, Johnson JJ. Polyphenols from the mangosteen (*Garcinia mangostana*) fruit for breast and prostate cancer. *Front Pharmacol*. 2013;4:80. doi:10.3389/fphar.2013.00080
47. Orozco FG, Failla ML. Biological activities and bioavailability of Mangosteen Xanthones: A critical review of the current evidence. *Nutrients*. 2013;5:3163-3183.
48. Miranda J, Lasa A, Aguirre L, Fernandez-Quintela A, Milton I, Portillo MP. Potential application of non-flavonoid phenolics in diabetes: Antiinflammatory effects. *Curr Med Chem*. 2015;22(1):112-131.
49. Franciosoa A, Mastromarino P, Masci A, d'Erme M, Mosca L. Chemistry, stability and bioavailability of resveratrol. *Med Chem (Los Angeles)*. 2014;10(3):237-245. doi:10.2174/15734064113096660053
50. Bairwa K, Grover J, Kania M, Jachak SM. Recent developments in chemistry and biology of curcumin analogues. *RSC Adv*. 2014;4(27):13946-13978. doi:10.1039/c4ra00227j
51. Jitoe-Masuda A, Fujimoto A, Masuda T. Curcumin: from chemistry to chemistry-based functions. *Curr Pharm Des*. 2013;19(11):2084-2092. doi:10.2174/138161213805289246
52. Esatbeyoglu T, Huebbe P, Ernst IMA, Chin D, Wagner AE, Rimbach G. Curcumin-from molecule to biological function. *Angew Chem Int Ed*. 2012;51(22):5308-5332. doi:10.1002/anie.201107724
53. Gupta SC, Prasad S, Kim JH, et al. Multitargeting by curcumin as revealed by molecular interaction studies. *Nat Prod Rep*. 2011;28(12):1937-1955. doi:10.1039/c1np00051a
54. Indira PK. Chemical and structural features influencing the biological activity of curcumin. *Curr Pharm Des*. 2013;19(11):2093-2100. doi:10.2174/138161213805289228
55. Priyadarsini KI. Photophysics, photochemistry and photobiology of curcumin: studies from organic solutions, bio-mimetics and living cells. *J Photochem Photobiol C: Photochem Rev*. 2009;10(2):81-95. doi:10.1016/j.jphotochemrev.2009.05.001
56. van Amerongen R, Nusse R. Towards an integrated view of Wnt signaling in development. *Development*. 2009;136(19):3205-3214. doi:10.1242/dev.033910
57. Clevers H, Nusse R. Wnt/β-catenin signaling and disease. *Cell*. 2012;149(6):1192-1205.
58. Ferrari GVD, Kaykas A, Kohn AD, Moon RT. WNT and [beta]-catenin signalling: diseases and therapies. *Nat Rev Genet*. 2004;5(9):691-708.
59. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. *Cell*. 2017;169(6):985-999. doi:10.1016/j.cell.2017.05.016
60. Berwick DC, Harvey K. The importance of Wnt signalling for neurodegeneration in Parkinson's disease. *Biochem Soc Trans*. 2012;40(5):1123-1128. doi:10.1042/BST20120122
61. Serafino A, Sferrazza G, Colini Baldeschi A, et al. Developing drugs that target the Wnt pathway: recent approaches in cancer and neurodegenerative diseases. *Expert Opin Drug Discov*. 2017;12(2):169-186. doi:10.1080/17460441.2017.1271321

62. Glass DA, Bialek P, Ahn JD, et al. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. *Dev Cell*. 2005;8(5):751-764. doi:10.1016/j.devcel.2005.02.017
63. Willert K, Jones KA. Wnt signaling: is the party in the nucleus? *Genes Dev*. 2006;20(11):1394-1404. doi:10.1101/gad.1424006
64. Niehrs C. The complex world of WNT receptor signalling. *Nat Rev Mol Cell Biol*. 2012;13(12):767-779. doi:10.1038/nrm3470
65. Harrison-Uy SJ, Pleasure SJ. Wnt signaling and forebrain development. *Cold Spring Harb Perspect Biol*. 2012;4(7):1-11. doi:10.1101/cshperspect.a008094
66. Bin JY, Gao Q, Tan XX, et al. Lithium alleviates blood-brain barrier breakdown after cerebral ischemia and reperfusion by upregulating endothelial Wnt/β-catenin signaling in mice. *Neuropharmacology*. 2021;186:186. doi:10.1016/j.neuropharm.2021.108474
67. Arenas E. Wnt signaling in midbrain dopaminergic neuron development and regenerative medicine for Parkinson's disease. *J Mol Cell Biol*. 2014;6:42-53.
68. Marchetti B. Wnt/β-catenin signaling pathway governs a full program for dopaminergic neuron survival, neurorescue and regeneration in the MPTP mouse model of Parkinson's disease. *Int J Mol Sci*. 2018;19(12):3743. doi:10.3390/ijms19123743
69. Salinas PC. Wnt signaling in the vertebrate central nervous system: from axon guidance to synaptic function. *Cold Spring Harb Perspect Biol*. 2012;4(2):a008003. doi:10.1101/cshperspect.a008003
70. Godin JD, Poizat G, Hickey MA, Maschat F, Humbert S. Mutant huntingtin-impaired degradation of β-catenin causes neurotoxicity in Huntington's disease. *EMBO J*. 2010;29(14):2433-2445. doi:10.1038/emboj.2010.117
71. Jia L, Piña-Crespo J, Li Y. Restoring Wnt/β-catenin signaling is a promising therapeutic strategy for Alzheimer's disease. *Mol Brain*. 2019;12(1):104. doi:10.1186/s13041-019-0525-5
72. Anand AA, Khan M, Monica V, Kar D. The molecular basis of Wnt/β-catenin signaling pathways in neurodegenerative diseases. *Int J Cell Biol*. 2023;2023. doi:10.1155/2023/9296092
73. McLeod F, Salinas PC. Wnt proteins as modulators of synaptic plasticity. *Curr Opin Neurobiol*. 2018;53:90-95. doi:10.1016/j.conb.2018.06.003
74. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8(6):595-608. doi:10.15252/emmm.201606210
75. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. *Cell*. 2019;179(2):312-339. doi:10.1016/j.cell.2019.09.001
76. Futch HS, Croft CL, Truong VQ, Krause EG, Golde TE. Targeting psychologic stress signaling pathways in Alzheimer's disease. *Mol Neurodegener*. 2017;12(1):49. doi:10.1186/s13024-017-0190-z
77. Inestrosa NC, Varela-Nallar L. Wnt signaling in the nervous system and in Alzheimer's disease. *J Mol Cell Biol*. 2014;6(1):64-74. doi:10.1093/jmcb/mjt051
78. De Ferrari GV, Chacón MA, Barría MI, et al. Activation of Wnt signaling rescues neurodegeneration and behavioral impairments induced by β-amyloid fibrils. *Mol Psychiatry*. 2003;8(2):195-208. doi:10.1038/sj.mp.4001208
79. Rosi MC, Luccarini I, Grossi C, et al. Increased Dickkopf-1 expression in transgenic mouse models of neurodegenerative disease. *J Neurochem*. 2010;112(6):1539-1551. doi:10.1111/j.1471-4159.2009.06566.x
80. Purro SA, Dickins EM, Salinas PC. The secreted Wnt antagonist dickkopf-1 is required for amyloid β-mediated synaptic loss. *J Neurosci*. 2012;32(10):3492-3498. doi:10.1523/JNEUROSCI.4562-11.2012
81. Kuwabara T, Hsieh J, Muotri A, et al. Wnt-mediated activation of NeuroD1 and retro-elements during adult neurogenesis. *Nat Neurosci*. 2009;12(9):1097-1105. doi:10.1038/nn.2360
82. Bertram L, Tanzi RE. Genomic mechanisms in Alzheimer's disease. *Brain Pathology*. 2020;130(5):966-967.
83. Hooper C, Killick R, Lovestone S. The GSK3 hypothesis of Alzheimer's disease. *J Neurochem*. 2008;104(6):1433-1439. doi:10.1111/j.1471-4159.2007.05194.x
84. Hernández F, Borrell J, Guaza C, Avila J, Lucas JJ. Spatial learning deficit in transgenic mice that conditionally over-express GSK-3β in the brain but do not form tau filaments. *J Neurochem*. 2002;83(6):1529-1533. doi:10.1046/j.1471-4159.2002.01269.x
85. Li HL, Wang HH, Liu SJ, et al. Phosphorylation of tau antagonizes apoptosis by stabilizing β-catenin, a mechanism involved in Alzheimer's nerodegeneration. *Proc Natl Acad Sci USA*. 2007;104(9):3591-3596. doi:10.1073/pnas.0609303104
86. Alvarez AR, Godoy JA, Mullendorff K, Olivares GH, Bronfman M, Inestrosa NC. Wnt-3a overcomes β-amyloid toxicity in rat hippocampal neurons. *Exp Cell Res*. 2004;297(1):186-196. doi:10.1016/j.yexcr.2004.02.028
87. Chacón MA, Varela-Nallar L, Inestrosa NC. Frizzled-1 is involved in the neuroprotective effect of Wnt3a against Aβ oligomers. *J Cell Physiol*. 2008;217(1):215-227. doi:10.1002/jcp.21497
88. Toledo EM, Inestrosa NC. Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1ΔE9 mouse model of Alzheimer's disease. *Mol Psychiatry*. 2010;15(3):272-285. doi:10.1038/mp.2009.72
89. Inestrosa NC, Montecinos-Oliva C, Fuenzalida M. Wnt signaling: Role in Alzheimer disease and schizophrenia. *J Neuroimmune Pharmacol*. 2012;7(4):788-807.
90. Wang JY, Wang X, Wang XJ, et al. Curcumin inhibits the growth via Wnt/γ-catenin pathway in non-small-cell lung cancer cells. *Eur Rev Med Pharmacol Sci*. 2018;22(21):7492-7499. doi:10.26355/eurrev-201811-16290
91. Wang M, Li Y, Ni C, Song G. Honokiol attenuates Oligomeric amyloid β 1-42 -induced Alzheimer's disease in mice through attenuating mitochondrial apoptosis and inhibiting the nuclear factor kappa-B signaling pathway. *Cell Physiol Biochem*. 2017;43(1):69-81. doi:10.1159/000480320
92. Voulgaropoulou SD, van Amelsvoort TAMJ, Prickaerts J, Vingerhoets C. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Res*. 2019;1725:1725. doi:10.1016/j.brainres.2019.146476
93. Khan H, Ullah H, Aschner M, Cheang WS, Akkol EK. Neuroprotective effects of quercetin in alzheimer's disease. *Biomol Ther*. 2020;10(1):59. doi:10.3390/biom10010059
94. Tiwari SK, Agarwal S, Seth B, et al. Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/β-catenin pathway. *ACS Nano*. 2014;8(1):76-103. doi:10.1021/nn405077y
95. Zhang X, Yin WK, Shi XD, Li Y. Curcumin activates Wnt/β-catenin signaling pathway through inhibiting the activity of GSK-3β in APPswe transfected SY5Y cells. *Eur J Pharm Sci*. 2011;42(5):540-546. doi:10.1016/j.ejps.2011.02.009
96. Hoppe JB, Coradini K, Frozza RL, et al. Free and nanoencapsulated curcumin suppress β-amyloid-induced cognitive impairments in rats: involvement of BDNF and Akt/GSK-3β signaling pathway. *Neurobiol Learn Mem*. 2013;106:134-144. doi:10.1016/j.nlm.2013.08.001
97. Huang HC, Xu K. Curcumin-mediated neuroprotection against amyloid-β-induced mitochondrial dysfunction involves the inhibition of GSK-3β. *J Alzheimers Dis*. 2012;32(4):981-996. doi:10.3233/JAD-2012-120688
98. Zhang X, Zhang H, Si L, Li Y. Curcumin mediates presenilin-1 activity to reduce β-amyloid production in a model of Alzheimer's disease. *Pharmacol Rep*. 2011;63(5):1101-1108. doi:10.1016/s1734-1140(11)70629-6
99. Abu-Elfotuh K, Tolba AMA, Hussein FH, et al. Anti-Alzheimer activity of combinations of cocoa with Vinpocetine or other

nutraceuticals in rat model: modulation of Wnt3/β-catenin/GSK-3β/Nrf2/HO-1 and PERK/CHOP/Bcl-2 pathways. *Pharmaceutics*. 2023;15(8):2063. doi:10.3390/pharmaceutics15082063
100. Palomera-Avalos V, Griñán-Ferré C, Puigoriol-Illamola D, et al. Resveratrol protects SAMP8 brain under metabolic stress: focus on mitochondrial function and Wnt pathway. *Mol Neurobiol*. 2017;54(3):1661-1676. doi:10.1007/s12035-016-9770-0
101. Xian YF, Ip SP, Mao QQ, Lin ZX. Neuroprotective effects of honokiol against beta-amyloid-induced neurotoxicity via GSK-3β and β-catenin signaling pathway in PC12 cells. *Neurochem Int*. 2016;97:8-14. doi:10.1016/j.neuint.2016.04.014
102. Gasser T. Molecular pathogenesis of Parkinson disease: insights from genetic studies. *Expert Rev Mol Med*. 2009;11:11. doi:10.1017/S1462399409001148
103. De A. Wnt/Ca2+ signaling pathway: a brief overview. *Acta Biochim Biophys Sin Shanghai*. 2011;43(10):745-756.
104. Mikels AJ, Nusse R. Purified Wnt5a protein activates or inhibits β-catenin-TCF signaling depending on receptor context. *PLoS Biol*. 2006;4(4):570-582. doi:10.1371/journal.pbio.0040115
105. Zhang L, Yang X, Yang S, Zhang J. The Wnt/β-catenin signaling pathway in the adult neurogenesis. *Eur J Neurosci*. 2011;33(1):1-8. doi:10.1111/j.1460-9568.2010.7483.x
106. Caricasole A, Copani A, Caraci F, et al. Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain. *J Neurosci*. 2004;24(26):6021-6027.
107. Kriks S, Shim JW, Piao J, et al. Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson's disease. *Nature*. 2011;480(7378):547-551. doi:10.1038/nature10648
108. L'Episcopo F, Tirolo C, Testa N, et al. Plasticity of subventricular zone neuroprogenitors in MPTP (1-Methyl-4-Phenyl-1,2,3,6-Tetra hydropyridine) mouse model of Parkinson'S disease involves cross talk between inflammatory and Wnt/β-catenin signaling pathways: functional consequences for neuropr. *J Neurosci*. 2012;32(6):2062-2085. doi:10.1523/JNEUROSCI.5259-11.2012
109. L'Episcopo F, Serapide MF, Tirolo C, et al. A Wnt1 regulated Frizzled-1/β-catenin signaling pathway as a candidate regulatory circuit controlling mesencephalic dopaminergic neuron-astrocyte crosstalk: Therapeutical relevance for neuron survival and neuroprotection. *Mol Neurodegener*. 2011;6(1):49. doi:10.1186/1750-1326-6-49
110. Jankovic J, Chen S, Le WD. The role of Nurr1 in the development of dopaminergic neurons and Parkinson's disease. *Prog Neurobiol*. 2005;77(1–2):128-138. doi:10.1016/j.pneurobio.2005.09.001
111. Sleiman PMA, Healy DG, Muqit MMK, et al. Characterisation of a novel NR4A2 mutation in Parkinson's disease brain. *Neurosci Lett*. 2009;457(2):75-79. doi:10.1016/j.neulet.2009.03.021
112. Kwok JBJ, Hallupp M, Loy CT, et al. GSK3B polymorphisms alter transcription and splicing in Parkinson's disease. *Ann Neurol*. 2005;58(6):829-839. doi:10.1002/ana.20691
113. Bhat A, Mahalakshmi AM, Ray B, et al. Benefits of curcumin in brain disorders. *Biofactors*. 2019;45(5):666-689. doi:10.1002/biof.1533
114. Mursaleen L, Somavarapu S, Zariwala MG. Deferoxamine and curcumin loaded Nanocarriers protect against rotenone-induced neurotoxicity. *J Parkinsons Dis*. 2020;10(1):99-111. doi:10.3233/JPD-191754
115. Wang YL, Ju B, Zhang YZ, et al. Protective effect of curcumin against oxidative stress-induced injury in rats with Parkinson's disease through the Wnt/β-catenin signaling pathway. *Cell Physiol Biochem*. 2017;43(6):2226-2241. doi:10.1159/000484302
116. Dong Y, Wang Z, Yan Z, Wu C, Yang T, Qiu H. Neuroprotective effects of resveratrol on a mouse model of Parkinson's disease via the Wnt/Beta-catenin signaling pathway. *Indian J Pharm Sci*. 2022;84(4):959-968. doi:10.36468/pharmaceutical-sciences.990
117. Haleagrahara N, Siew CJ, Ponnusamy K. Effect of quercetin and desferrioxamine on 6-hydroxydopamine (6-OHDA) induced neurotoxicity in striatum of rats. *J Toxicol Sci*. 2013;38(1):25-33. doi:10.2131/jts.38.25
118. Meng W, Jiang Y, Ma J. Is the prognostic significance of O6-methylguanine-DNA methyltransferase promoter methylation equally important in glioblastomas of patients from different continents? A systematic review with meta-analysis. *Cancer Manag Res*. 2017;9:411-425. doi:10.2147/CMAR.S140447
119. Ge JF, Xu YY, Qin G, Cheng JQ, Chen FH. Resveratrol ameliorates the anxiety- and depression-like behavior of subclinical hypothyroidism rat: possible involvement of the HPT axis, HPA axis, and Wnt/β-catenin pathway. *Front Endocrinol (Lausanne)*. 2016;7:44. doi:10.3389/fendo.2016.00044
120. Predes D, Maia LA, Matias I, et al. The Flavonol Quercitrin hinders GSK3 activity and potentiates the Wnt/β-catenin signaling pathway. *Int J Mol Sci*. 2022;23(20):12078. doi:10.3390/ijms232012078
121. Suresh S, Vellapandian C. Cyanidin ameliorates Bisphenol A-induced Alzheimer's disease pathology by restoring Wnt/β-catenin signaling Cascade: an in vitro study. *Mol Neurobiol*. 2024;61(4):2064-2080. doi:10.1007/s12035-023-03672-6
122. Gong EJ, Park HR, Kim ME, et al. Morin attenuates tau hyperphosphorylation by inhibiting GSK3β. *Neurobiol Dis*. 2011;44(2):223-230. doi:10.1016/j.nbd.2011.07.005
123. Yao Y, Gao Z, Liang W, et al. Osthole promotes neuronal differentiation and inhibits apoptosis via Wnt/β-catenin signaling in an Alzheimer's disease model. *Toxicol Appl Pharmacol*. 2015;289(3):474-481. doi:10.1016/j.taap.2015.10.013
124. Shu T, Liu C, Pang M, et al. Salvianolic acid B promotes neural differentiation of induced pluripotent stem cells via PI3K/AKT/GSK3β/β-catenin pathway. *Neurosci Lett*. 2018;671:154-160. doi:10.1016/j.neulet.2018.02.007
125. Alsadat AM, Nikbakht F, Hossein Nia H, et al. GSK-3β as a target for apigenin-induced neuroprotection against Aβ 25–35 in a rat model of Alzheimer's disease. *Neuropeptides*. 2021;90:102200. doi:10.1016/j.npep.2021.102200
126. Tiwari SK, Agarwal S, Tripathi A, Chaturvedi RK. Bisphenol-A mediated inhibition of hippocampal neurogenesis attenuated by curcumin via canonical Wnt pathway. *Mol Neurobiol*. 2016;53(5):3010-3029. doi:10.1007/s12035-015-9197-z
127. Anusha C, Sumathi T, Joseph LD. Protective role of apigenin on rotenone induced rat model of Parkinson's disease: suppression of neuroinflammation and oxidative stress mediated apoptosis. *Chem Biol Interact*. 2017;269:67-79. doi:10.1016/j.cbi.2017.03.016
128. Zamin LL, Dillenburg-Pilla P, Argenta-Comiran R, et al. Protective effect of resveratrol against oxygen-glucose deprivation in organotypic hippocampal slice cultures: involvement of PI3-K pathway. *Neurobiol Dis*. 2006;24(1):170-182. doi:10.1016/j.nbd.2006.06.002
129. Khamchai S, Chumboatong W, Hata J, Tocharus C, Suksamrarn A, Tocharus J. Morin attenuated cerebral ischemia/reperfusion injury through promoting angiogenesis mediated by Angiopoietin-1-Tie-2 Axis and Wnt/β-catenin pathway. *Neurotox Res*. 2022;40(1):14-25. doi:10.1007/s12640-021-00470-7
130. Jin Z, Ke J, Guo P, Wang Y, Wu H. Quercetin improves blood-brain barrier dysfunction in rats with cerebral ischemia reperfusion via Wnt signaling pathway. *Am J Transl Res*. 2019;11(8):4683-4695.
131. Zhang S, Jiao H. Kaempferol regulates apoptosis and migration of neural stem cells to attenuate cerebral infarction by O-GlcNAcylation of β-catenin. *Open Life Sci*. 2024;19(1):20220829. doi:10.1515/biol-2022-0829
132. Xiao Y, Guan T, Yang X, et al. Baicalin facilitates remyelination and suppresses neuroinflammation in rats with chronic cerebral hypoperfusion by activating Wnt/β-catenin and inhibiting

NF-κB signaling. *Behav Brain Res*. 2023;442:442. doi:10.1016/j.bbr.2023.114301

133. Xie Y, Zhang J, Lin Y, et al. Aberrant development corrected in adult-onset Huntington's disease iPSC-derived neuronal cultures via WNT signaling modulation. *Stem Cell Reports*. 2020;14:406-419.
134. Sandhir R, Mehrotra A. Quercetin supplementation is effective in improving mitochondrial dysfunctions induced by 3-nitropropionic acid: implications in Huntington's disease. *Biochim Biophys Acta Mol basis Dis*. 2013;1832(3):421-430. doi:10.1016/j.bbadis.2012.11.018
135. Hsu CH, Cheng AL. The molecular targets and therapeutic uses of curcumin in health and disease. *Adv Exp Med Biol*. 2007;595:471-480.
136. Shindler KS, Ventura E, Dutt M, Elliott P, Fitzgerald DC, Rostami A. Oral resveratrol reduces neuronal damage in a model of multiple sclerosis. *J Neuro Ophthalmol*. 2010;30(4):328-339. doi:10.1097/WNO.0b013e3181f7f833
137. Jugait S, Areti A, Nellaiappan K, et al. Neuroprotective effect of Baicalein against Oxaliplatin-induced peripheral neuropathy: impact on oxidative stress, neuro-inflammation and WNT/β-catenin signaling. *Mol Neurobiol*. 2022;59(7):4334-4350. doi:10.1007/s12035-022-02858-8
138. Markert CD, Kim E, Gifondorwa DJ, Childers MK, Milligan CE. A single-dose resveratrol treatment in a mouse model of amyotrophic lateral sclerosis. *J Med Food*. 2010;13(5):1081-1085. doi:10.1089/jmf.2009.0243
139. Menet R, Lecordier S, ElAli A. Wnt pathway: an emerging player in vascular and traumatic mediated brain injuries. *Front Physiol*. 2020;11:11. doi:10.3389/fphys.2020.565667
140. Page S, Al-Ahmad A. Determining the effect of the WNT/b-catenin pathway on the ischemic blood-brain barrier using induced pluripotent stem cells. *FASEB J*. 2018;32:32(S1). doi:10.1096/fasebj.2018.32.1_supplement.40.6
141. Patel MI, Gupta A, Dey CS. Potentiation of neuronal insulin signaling and glucose uptake by resveratrol: the involvement of AMPK. *Pharmacol Rep*. 2011;63(5):1162-1168. doi:10.1016/S1734-1140(11)70635-1
142. Simão F, Matté A, Pagnussat AS, Netto CA, Salbego CG. Resveratrol prevents CA1 neurons against ischemic injury by parallel modulation of both GSK-3β and CREB through PI3-K/Akt pathways. *Eur J Neurosci*. 2012;36(7):2899-2905. doi:10.1111/j.1460-9568.2012.08229.x
143. Frozza RL, Bernardi A, Hoppe JB, et al. Neuroprotective effects of resveratrol against Aβ administration in rats are improved by lipid-core nanocapsules. *Mol Neurobiol*. 2013;47(3):1066-1080. doi:10.1007/s12035-013-8401-2
144. Varamini B, Sikalidis AK, Bradford KL. Resveratrol increases cerebral glycogen synthase kinase phosphorylation as well as protein levels of drebrin and transthyretin in mice: an exploratory study. *Int J Food Sci Nutr*. 2014;65(1):89-96. doi:10.3109/09637486.2013.832171
145. Abdel-Aleem GA, Khaleel EF, Mostafa DG, Elberier LK. Neuroprotective effect of resveratrol against brain ischemia reperfusion injury in rats entails reduction of DJ-1 protein expression and activation of PI3K/Akt/GSK3b survival pathway. *Arch Physiol Biochem*. 2016;122(4):200-213. doi:10.1080/13813455.2016.1182190
146. Oh S, Gwak J, Park S, Yang CS. Green tea polyphenol EGCG suppresses Wnt/β-catenin signaling by promoting GSK-3β- and PP2A-independent β-catenin phosphorylation/degradation. *Biofactors*. 2014;40(6):586-595. doi:10.1002/biof.1185
147. Rai SN, Singh BK, Rathore AS, et al. Quality control in Huntington's disease: a therapeutic target. *Neurotox Res*. 2019;36(3):612-626. doi:10.1007/s12640-019-00087-x
148. Medina A, Mahjoub Y, Shaver L, Pringsheim T. Prevalence and incidence of Huntington's disease: an updated systematic review and meta-analysis. *Mov Disord*. 2022;37(12):2327-2335. doi:10.1002/mds.29228
149. Starkstein SE, Brandt J, Bylsma F, Peyser C, Folstein M, Folstein SE. Neuropsychological correlates of brain atrophy in Huntington's disease: a magnetic resonance imaging study. *Neuroradiology*. 1992;34(6):487-489. doi:10.1007/BF00598956
150. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington disease. *Neuropsychiatry Neuropsychol Behav Neurol*. 2001;14(4):219-226.
151. Mason SL, Barker RA. Advancing pharmacotherapy for treating Huntingtons disease: A review of the existing literature. *Expert Opin Pharmacother*. 2016;17(1):41-52.
152. Ghatak S, Raha S. Micro RNA-214 contributes to proteasome independent downregulation of beta catenin in Huntington's disease knock-in striatal cell model STHdhQ111/Q111. *Biochem Biophys Res Commun*. 2015;459(3):509-514. doi:10.1016/j.bbrc.2015.02.137
153. Liu T, Im W, Mook-Jung I, Kim M. MicroRNA-124 slows down the progression of huntington's disease by promoting neurogenesis in the striatum. *Neural Regen Res*. 2015;10(5):786-791. doi:10.4103/1673-5374.156978
154. Lim RG, Quan C, Reyes-Ortiz AM, et al. Huntington's disease iPSC-derived brain microvascular endothelial cells reveal WNT-mediated Angiogenic and blood-brain barrier deficits. *Cell Rep*. 2017;19(7):1365-1377. doi:10.1016/j.celrep.2017.04.021
155. McLeod JG. Multiple sclerosis–A review. *Aust NZ J Med*. 1982;12(4):302-308. doi:10.1111/j.1445-5994.1982.tb03818.x
156. Balasa R, Barcutean L, Balasa A, Motataianu A, Roman-Filip C, Manu D. The action of TH17 cells on blood brain barrier in multiple sclerosis and experimental autoimmune encephalomyelitis. *Hum Immunol*. 2020;81(5):237-243. doi:10.1016/j.humimm.2020.02.009
157. Suryawanshi A, Manoharan I, Hong Y, et al. Canonical Wnt signaling in dendritic cells regulates Th1/Th17 responses and suppresses autoimmune neuroinflammation. *J Immunol*. 2015;194(7):3295-3304. doi:10.4049/jimmunol.1402691
158. Fancy SPJ, Baranzini SE, Zhao C, et al. Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. *Genes Dev*. 2009;23(13):1571-1585. doi:10.1101/gad.1806309
159. Xie C, Li Z, Zhang GX, Guan Y. Wnt signaling in remyelination in multiple sclerosis: friend or foe? *Mol Neurobiol*. 2014;49(3):1117-1125. doi:10.1007/s12035-013-8584-6
160. Ortiz GG, Pacheco-Moisés FP, Macías-Islas MÁ, et al. Role of the blood-brain barrier in multiple sclerosis. *Arch Med Res*. 2014;45(8):687-697. doi:10.1016/j.arcmed.2014.11.013
161. Tran KA, Zhang X, Predescu D, et al. Endothelial β-catenin signaling is required for maintaining adult blood-brain barrier integrity and central nervous system homeostasis. *Circulation*. 2016;133(2):177-186. doi:10.1161/CIRCULATIONAHA.115.015982
162. Kernich CA. Amyotrophic lateral sclerosis. *Neurologist*. 2000;6(4):243-244. doi:10.1097/00127893-200006040-00007
163. Pehar M, Harlan BA, Killoy KM, Vargas MR. Role and therapeutic potential of astrocytes in amyotrophic lateral sclerosis. *Curr Pharm Des*. 2018;23(33):5010-5021. doi:10.2174/1381612823666170622095802
164. Inestrosa NC, Varela-Nallar L. Wnt signalling in neuronal differentiation and development. *Cell Tissue Res*. 2015;359(1):215-223. doi:10.1007/s00441-014-1996-4
165. González-Fernández C, Mancuso R, Del Valle J, Navarro X, Rodríguez FJ. Wnt signaling alteration in the spinal cord of amyotrophic lateral sclerosis transgenic mice: special focus on Frizzled-5 cellular expression pattern. *PLoS One*. 2016;11(5):e0155867. doi:10.1371/journal.pone.0155867

166. Yu L, Guan Y, Wu X, et al. Wnt signaling is altered by spinal cord neuronal dysfunction in amyotrophic lateral sclerosis transgenic mice. *Neurochem Res*. 2013;38(9):1904-1913. doi:10.1007/s11064-013-1096-y
167. Yang W, Leystra-Lantz C, Strong MJ. Upregulation of GSK3β expression in frontal and temporal cortex in ALS with cognitive impairment (ALSci). *Brain Res*. 2008;1196:131-139. doi:10.1016/j.brainres.2007.12.031
168. Nonneman A, Robberecht W, Van Den Bosch L. The role of oligodendroglial dysfunction in amyotrophic lateral sclerosis. *Neurodegener Dis Manag*. 2014;4(3):223-239. doi:10.2217/nmt.14.21
169. Verma S, Khurana S, Vats A, et al. Neuromuscular junction dysfunction in amyotrophic lateral sclerosis. *Mol Neurobiol*. 2022;59(3):1502-1527. doi:10.1007/s12035-021-02658-6
170. Serafino A, Giovannini D, Rossi S, Cozzolino M. Targeting the Wnt/β-catenin pathway in neurodegenerative diseases: recent approaches and current challenges. *Expert Opin Drug Discov*. 2020;15(7):803-822. doi:10.1080/17460441.2020.1746266
171. Marchetti B, Tirolo C, L'Episcopo F, et al. Parkinson's disease, aging and adult neurogenesis: Wnt/β-catenin signalling as the key to unlock the mystery of endogenous brain repair. *Aging Cell*. 2020;19(3):e13101. doi:10.1111/acel.13101
172. AH L. Wnt/β-catenin and its diverse physiological cell signaling pathways in neurodegenerative and neuropsychiatric disorders. *J Neuroimmune Pharmacol*. 2012;7(4):725-730.
173. Xiao J. Phytochemicals in medicine and food. *Phytochem Rev*. 2015;14(3):317-320. doi:10.1007/s11101-015-9407-3
174. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther*. 2015;148:114-131. doi:10.1016/j.pharmthera.2014.11.016
175. Park CH, Chang JY, Hahm ER, Park S, Kim HK, Yang CH. Quercetin, a potent inhibitor against β-catenin/Tcf signaling in SW480 colon cancer cells. *Biochem Biophys Res Commun*. 2005;328(1):227-234. doi:10.1016/j.bbrc.2004.12.151
176. Tao Q, Yokota C, Puck H, et al. Maternal Wnt11 activates the canonical Wnt signaling pathway required for axis formation in Xenopus embryos. *Cell*. 2005;120(6):857-871. doi:10.1016/j.cell.2005.01.013

How to cite this article: Utpal BK, Roy SC, Zehravi M, et al. Polyphenols as Wnt/β-catenin pathway modulators: A promising strategy in clinical neurodegeneration. *Anim Models Exp Med*. 2025;8:266-286. doi:10.1002/ame2.12525