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# WNT/β CATENIN PATHWAY MODULATORS IN SYNAPTIC REMODELING- PROMISING THERAPEUTIC AGENTS FOR ALZHEIMER'S DISEASE

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## ABSTRACT

Alzheimer's disease (AD) is a chronic neurological condition that primarily affects elderly people and gradually impairs memory and other cognitive abilities. It is characterized by aggregation of senile plaques, hyper phosphorylated tau protein, irreversible loss of neurons and synaptic insufficiency. It has been founded that Wnt Signalling inhibition can hasten the onset and progression of AD neuropathology and memory loss. So Wnt signaling is a well-known system that plays important functions in controlling neural development, synaptic transmission, and plasticity. As Wnt modulators Wnt proteins, Oxoglutarate dehydrogenase-like (OGDHL), certain statins like simvastatin, and some naturally occurring compounds such as curcumin, cannabidiol, and ginkolide b are examples of medications that have recently exhibited Wnt/β-targeting activity. Emerging evidences suggests that sigma 1 receptor agonists like fluoxetine and citalopram may also be effective novel therapeutics for the treatment of Alzheimer's disease. This review summarizes the contribution of the Wnt signaling system to AD pathogenesis by focusing on the possible therapeutic implications of Wnt modulators in brain synaptic remodeling.

**Keywords: Alzheimer's disease, Aβ precursor protein, Sigma 1 receptor, Synaptic remodeling**

## INTRODUCTION

Synapses comprises the core information transfer unit of the central nervous system and functions of brain relies on regulation of fundamental mechanisms of synaptogenesis, neurogenesis, maintenance of synaptic plasticity and accurate inception of synaptic linkages progression. So Synaptic dysfunction causally related with early appearing of neurological diseases such as bipolar disorder, obsessive compulsive disorder, delirium, schizophrenia and late degenerative disorders such as Alzheimer's, Parkinson's disease, Huntington's diseases. Hebbian mechanisms of Long term potentiation (LTP) and long term depression are the key factors of learning and memory via remodeling of synaptic complexes **[1]**.

Alzheimer's disease is a chronic neurodegenerative disease mostly in elderly people leads to progressive impairment of memory and other cognitive functions of brain. It is characterized by aggregation of senile plaques, hyper phosphorylated tau protein, irreversible loss of neurons and synaptic insufficiency **[2]**. According to world Alzheimer's report, approximately 50 million people worldwide suffer from AD and this number is estimated to increase to >139million by 2050(world Alzheimer's report,2021).However it is an incurable disease, no effective treatments are available to stop the progression of Alzheimer's disease. Only symptomatic relief is possible **[3]**. AD can be late onset (LOAD) and sporadic (SAD) or early-onset (EOAD) and familial (FAD). Familial Alzheimer's is rare, inherited and occurs by the mutations in the genes Aβ precursor protein (APP) and presenilin genes(PSEN1, PSEN2). Sporadic type is common in individuals over the age of 65%. It is a complex combination of environmental and genetic, viral and other factors. Among the three isoforms of Apolipoprotein E (APOE), APOE 4 is the main risk factor of SAD. To explain the pathophysiology of AD, Extracellular accumulation of β Amyloid and intracellular accumulation of Neurofibrillary tangles are considered as the main neurological hallmarks **[4]**.

### Amyloid cascade hypothesis

Aβ precursor protein (APP) is a 695 amino acid membrane protein which modulates neurite outgrowth, cell growth and survival, neuronal development, and axonal transport .APP produces C-terminal fragments by the hydrolysis of α-, β-, γ-, and η-secretases via three pathways. This - α secretase can cleave APP at residue L688, which is located in the middle of the A domain, resulting in soluble APP alpha (sAPP) and a cell-membrane-bound C-terminal fragment 83. (CTF83). CTF83 is synthesised and cleaved by γ -secretase to produce APP intracellular domain (AICD)

and a small p3 fragment. AICD has nuclear signalling functions, and sAPP has several neuroprotective properties. The second pathway is the amyloidogenic pathological pathway in which APP is cleaved to CTF-β by β-secretase and then different lengths of Aβ peptides, including Aβ42 by γ-secretase which leads to aggregation and plaque formation will disrupt synapses, and initiate cascade of toxic events, which ultimately leading to neuronal loss and death. The third pathway is the regulated under physiological conditions by η-secretase **[5]**.

**Tau hypothesis.**

Tau protein is a mitochondrial associated protein mainly found in the neuronal axis of the brain. They maintain synaptic function and structural integrity, microtubule stabilization, and cytoplasmic transport function. hyperphoshorylated tau is dissociate from microtubules and aggregated into insoluble PHFs and straight filaments (SFs) that leads to the formation of intra neuronal fibrillar deposits known as Neurofibrillary tangles (NFT) (**Figure 1**). These neurofibrillary tangles can cause neurodegenerative disorders via synaptic dysfunction, neuronal loss and death. When compared to healthy controls, AD patients have four times the amount of abnormal or hyperphosphorylated tau proteins. as well as exhibit increased aggregation effects which have been identified as potential neurotoxins **[6]**.

Tau is regulated by posttranslational modifi cation (PTM), which includes phosphorylat ion, dephosphorylation, acetylation, nitratio n, glycation, ubiquitination, and truncation (proteolytic cleavage) at serine, threonine, and tyrosine residues.Phosphorylation and dephosphorylation are common processes t hat influence the intensity of tau modificati on and are influenced by specific protein ki nases and phosphatases.So, tau's functional properties are directly regulated by post translational modifications [7].

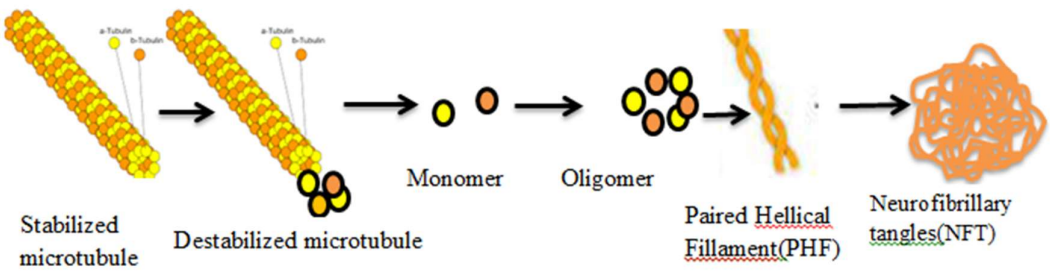



**Figure 1: Conversion of Aβ monomers to oligomers and insoluble neurofibrillary tangles**

**Regulation of Wnt/ β catenin pathway**

Wnt/ β catenin pathway is a prominent evolutionarily conserved pathway have essential role in neurogenesis, synaptic plasticity, also modulate synaptic transmission by acting on both pre and post

synaptically. down regulation of the pathway has emerged as pathogenesis of neurodegenerative disease such PD, AD, and ALS. Wnt are secreted, cysteine rich glycoprotein that initiate receptor mediated signal transduction cascade pathway by act as a ligand.

**In off state**, cytosolic β catenin protein is degraded by the action of axin complex which constituted by glycogen synthase kinase 3 (GSK3), Casein kinase 1(CK1), Scaffolding protein axin, Tumor suppressor adenomatous polyposis coil gene product (APC). It is subsequently phosphorylated by CK1&GSK3.These phosphorylated β catenin is recognized by E3 ubiquitin ligase β-Trcp for proteosomal degradation and Wnt responsive genes are suppressed by the action of DNA bonded T cell factor /lymphoid enhance factor of protein family (TCF-LEF ) and Histone deacetylases (HDAC). So β catenin nuclear translocation is inhibited which leads to inactivity of transcription of Wnt target genes responsible for neuronal survival, integrity (**Figure 2**) **[8]**.

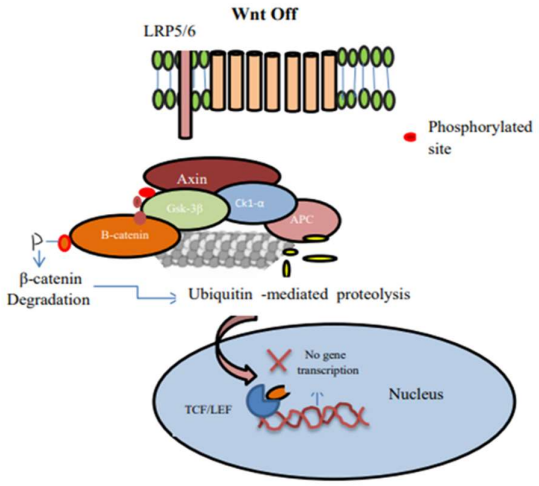



**Figure 2: The canonical Wnt /βcatenin pathway- Off state**

**On state**, Wnt ligands and agonist bind to the Frizzled receptor and Wnt co-receptor lipoprotein receptor related protein 5 LPR5 or LPR6 to trigger the Wnt signaling pathway results in inhibition of GSK3 β induced phosphorylation and proteosomal degradation of β catenin. Stabilized β catenin translocated into nucleus, where it interact with TCF/LEF and activate the expression of wnt target genes involved in neuronal plasticity/survival (**Figure 3)**.

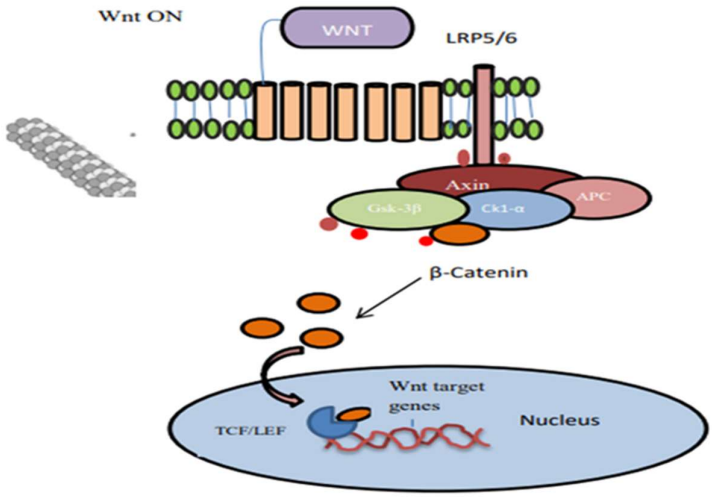



**Figure 3: The canonical Wnt/β catenin pathway –On state**

Regulation of wnt- on and wnf-off state in neuron is balanced by the microglial/ astrocyte component of cns.so, dysregulation of neuron –glia crosstalk may leads to neurodegeneration via reduced neuroprotection, neuronal loss or synaptopathies. Oxidative stress, inflammation, wnt antagonist, neurotoxic agents are act as antagonist of signaling pathway **[9]**.

**Targeting the Wnt proteins in synaptic remodeling**

Wnt modulates synaptic plasticity, transmission and neuronal growth via receptors located in the area of brain. Wnt proteins are categorized into wnt1Wnt1 (including Wnt2, Wnt3, Wnt3a, Wnt8, and Wnt8a), and the Wnt5a (including Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, and Wnt11) classes. The Wnt-1like proteins generally activate the canonical β catenin dependent pathway and Wnt-5a class via β catenin independent non canonical pathway. Wnt7a involved in the formation of active zones which increase the clustering of presynaptic membrane protein synapsin1, synaptophysin, and synaptotagmin, act as a marker for synaptic plasticity and integrity **[10]**. Evidence suggest that Wnt5a has potential role in synaptic structure and its function via inducing denovo dendrite spine formation and enhance density of pre-existent spines, improving efficacy of hippocampal glutamergic synapses. Wnt-3a increases and regulate axonal branching and remodeling in spinal sensory neuron. Studies reveals that both Wnt-7a & Wnt-3a enhance growth cone size and axone branching. During dendritgenesis, Wnt-7b promotes dendrite arborization by increasing length of dendrites and complex branches formation in hippocampal neurons.

Wnt ligands,wnt-3a,7a are able to protect neurons against Aβ toxicity and enhance field excitatory post synaptic potential (FEPSP) in hippocampal neurons. The various toxic effects induced by Aβ, including reduction of β catenin, increase in GSK-3β and impaired neuronal survival are overcome by Wnt-3a protein. The presence of Wnt components in many brain areas, including those that are actively participating in neurogenesis, reveals that wnt pathway not only have structural functions also have involved in sensory processing and superior cognitive functions, so molecular components of the signaling have been proposed as innovative therapeutic targets for neurodegenerative disease such as Alzheimer's via synaptic remodeling **[11]**.

**Sigma 1 Receptor Agonist As Wnt Modulators In AD**

Sigma 1 receptors are endoplasmic reticulum associated, multifunctional, ligand operated molecular chaperone expressed in CNS,liver, muscle, kidney, urinary bladder, immune and reproductive tissues. These intracellular receptors act as pathological agents and target for therapeutic application of neurodegenerative disease. They implicated in neuroprotection, neuroplasticity which have beneficial properties in treatment of cognitive deficit. sigma 1 receptor agonist includes SSRIs as neurosteroids **[12]**.

Fluoxetine (FLX) is one of the SSIRs antidepressant which is also act as a therapeutic sigma 1 receptor agonist. The activation of Wnt/β catenin signaling by fluoxetine via repressing β- amyloid production in Alzheimer's mouse model. Authors demonstrated that fluoxetine treatment would enhance the activity of protein phosphatase type 2A (PP2A) and reduce APP cleavage and A β generation by the activation of Wnt/β catenin signaling. Fluoxetine regulate A β level through APP phosphorylation and BACE1 activity by α secretase pathway, APP could be cleaved within the sequence of Aβ peptide and generate SAPPα fragment. Wnt signaling pathway down regulate the BACE1 and APP protein expresion and in hippocampal brain of fluoxetine treated 3×Tg AD mice. It would be a positive impact for role of sigma 1 receptor agonist in βcatenin pathway **[13]**. Moreover , another sigma1 receptor agonist citalopram alleviates chronic stress induced depression like behaviors in rat by activating GSK3β signaling in dorsal hippocampus. It reveals that increase in wnt/GSK3β signaling by SSRIs as sigma 1 receptor agonist decrease the level of β catenin in the hippocampus, so wnt pathway and sigma 1 receptor agonist could be a well suited target for treatment of cognitive and degenerative disorders **[14]**.

**a) Role in synaptic plasticity**

It is well established that the brain derives neurotropic factor (BDNF) is involved in many neurological functions including proliferation, growth of neuritis and plasticity. Studies found that expression of BDNF in CNS is able to enhanced by fluoxetine. during adolescence, fluoxetine administration upregulate the expression of BDNF in the hippocampus and cortex of 3×TgAD mice and increased synaptic related protein expression. Increase in dendritic spine density in hippocampus and cortex might also contributed to the structural basis of synaptic plasticity and morphological integrity of dendritic spine **[15]**. The fluoxetine treatment potentiating LTP which is associate with increased with increased dendritic spine density.

**b) LPR-5 Mediated Wnt Signaling**

LPR-5 mediated wnt signaling has been implicated in the modulation of dendritic morphogenesis and synaptic function. misregulation of this pathway leads to synaptic dysfunction in neurodegenerative disease in AD **[16]**. oxidative stress induced cell death and tau phosphorylation are reduced via LPR5 mediated wnt signaling.so wnt activity facilitate the expression of proliferative genes and reduce total and active β catenin thereby lower transcription of downstream proliferative genes. On the other hand, LR6 enhance neuronal survival gene expression through Wnt pathway **[17]**.

**c) Statins As Wnt Modulators**

These are drugs commonly used to treat hyperlipidemia are also beneficial in the treatment of neurological disorders. Simvastatin increases Wnt signalling in the adult hippocampus, and Wnt signaling is necessary for statins to improve neuronal specification in differentiating adult neural progenitor cells. simvastatin **(Figure 4)** therapy enhance the number of newborn neurons in the dentate gyrus (DG) via promoting proliferation of intermediate precursor cells (IPCs) in the subgranular zone through the study of numerous stage-specific markers in vivo (SGZ).

The action of simvastatin on the Wnt pathway is found to be independent of cholesterol and to be mediated by inhibition of isoprenoid biosynthesis **[18]**. These findings imply that statins are beneficial in AD and other neurological disorders bytheactivation of Wnt/β-catenin signaling.

**NATURAL SOURCES AS WNT MODULATORS**

**a) Curcumin**

Curcumin is a dietary polyphenol from Curcuma longa (turmeric) which is commonly used as an herb and spice worldwide. Due to lipophilic nature, it has poor solubility in water or hydrophilic solutions. Studies found that Curcumin nanoparticles enhances neuronal

differentiation by activating the Wnt/-catenin pathway, which is involved in neurogenesis regulation. These nanoparticles improve catenin nuclear translocation, decreased GSK-3 levels, and increased TCF/LEF and cyclin-D1 promoter activity. learning and memory impairments in an amyloid beta-induced rat model of AD-like phenotypes are reversed by these nanoparticles via inducing neurogenesis. according to *in silico* molecular docking studies, Curcumin appears to interact with Wif-1, Dkk, and GSK-3, These findings suggest that curcumin nanoparticles induce adult neurogenesis by activating the canonical Wnt/-catenin pathway, and that they may offer a therapeutic approach to treating neurodegenerative diseases such as Alzheimer's disease by enhancing a brain self-repair mechanism **[19]**. Studies shows that Curcumin may activate the Wnt/-catenin signalling pathway by inhibiting GSK-3 expression and inducing -catenin and CyclinD1 expression, providing a new theory for the treatment of neurodegenerative diseases. **Figure 4(a) [20]**.

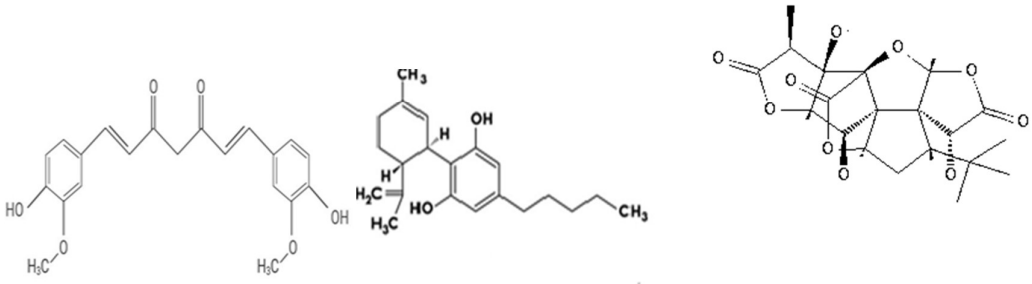
**b) Ginkgolide B**

Ginkgo biloba, a chinese herbal medicine, has been reported to be beneficial to the nervous system and a potential treatment for neurological disorders. Studies discovered that Ginkgo biloba extract (GBE) and one of its main ingredients, ginkgolide B (GB), promoted cell cycle exit and neuronal differentiation in Nuronal stem cells (NSCs )derived from the mouse lateral ventricle's postnatal subventricular zone (SVZ). Furthermore, GB administration increased nuclear -catenin levels and activated the canonical Wnt pathway catenin knockdown prevented the GB has a neurogenic effect, implying that it promotes neuronal differentiation via the Wnt/-catenin pathway. GB activate the pathway through enhancing beta catenin level. Also Stabilization of β-catenin and the activation of the canonical Wnt pathway are due to the inhibition of GSK-3β35. Bilobalide, another component in GBE, has recently been shown to improve phosphorylation and inhibit GSK-3β38**. Figure 4 (b)[21]**.

**c) Cannabiodiol**

Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid obtained from Cannabis sativa plant. CBD has been shown to reduce brain damage associated with neurodegeneration. CBD administration leads to decreasing oxidative stress in the mitochondria through Wnt/-catenin signalling pathway activation. CBD enhances hippocampal neurogenesis by inducing the ubiquitination of the APP protein and reduce neuroinflammation via PPAR activation. Studies reveals that CBD may be a promising candidate for Alzheimer's disease therapy because it inhibits oxidative stress and

neuroinflammation via interactions with Wnt/-catenin and PPAR **[22]**. Cannabidiol inhibits the hyperphosphorylation of tau protein in A-stimulated PC12 neuronal cells, which is one of the most prominent hallmarks of Alzheimer's disease **Figure 4(c) [23]**.



Curcumin(a) Ginkgolide b(b) Cannabidiol(c)

**Figure 4: Chemical structures of Natural sources as Wnt modulators**

**OGDHL (Oxoglutarate dehydrogenase-like) As Wnt Modulators**

Oxoglutarate dehydrogenase-like (OGDHL) is related to 2-oxoglutarate dehydrogenase (OGDH), which is one of the rate-limiting components of multiple enzymes in the OGDH complex (OGDHC); the latter is also known as the -ketoglutarate dehydrogenase complex (KGDHC), and its physiological role is associated with glucose oxidation via tricarboxylic acid cycle. 3 × Tg-AD mice model, OGDHL could reduce the learning and memory impairemnts by alleviating Neuroinflammation, decreasing the amyloid plaque load, and reducing tau phosphorylation through increasing Wnt7B via activation of the Wnt/-catenin signalling pathway **[24]**.

**Wnt Pathway In Other Diseases**

Growing evidence suggests that dysregulation of the Wnt/-catenin cascade played a role in the development and progression of some solid tumours and haematological malignancies. An FDA approved anthelmentic agent niclosamide was identified as wnt/β catenin inhibitor with antitumor activity that selectively target ovarian cancer stem cells (CSCs). Furthermore, niclosamide reduced the number of CSCs in basal-like breast cancer by inhibiting the expression of LRP6 and -catenin **[25]**.

Recent studies demonstrated that dysregulation of the Wnt signalling pathways contributes to the occurrence and progression of T2DM by directly influencing pancreatic -cell differentiation and proliferation, as well as insulin secretion and action. The member of

the Wnt family Wnt5a regulates adipogenesis and obesity through the Wnt non-canonical pathway and the Wnt/-catenin canonical pathway by inhibiting the expression of peroxidase proliferation receptor (PPAR) and tumour suppressor gene C/enhancer binding protein (CCAAT/EBP) in adipocytes **[26]**. Resveratrol is a stilbenoid, which is a type of natural phenol, as well as a phytoalexin. TNF- and IL-18 levels were reduced by resveratrol, which are target genes that are strictly downstream of the WNT/-catenin pathway. It also demonstrated significant anti-inflammatory properties by lowering NFkB pathway activation, iNOS and COX-2 expression, and PGE2 levels in the lumbar spinal cord. Furthermore, resveratrol reduced the oxidative stress associated with inflammation and pain, as evidenced by lower lipid peroxidation and higher GSH, SOD, and CAT activities **[27]**.

## CONCLUSION

According to available data, AD is strongly correlated with the wnt signaling pathway, which is crucial for the development of the central nervous system by regulating the synaptic remodeling process. When signaling blockage exists, memory loss and AD neuropathology can both develop and spread more quickly. increasing data suggested that the use of sigma 1 receptor agonists like fluoxetine and citalopram could be act as potential medicines for the treatment of Alzheimer's disease by regulating neural development, synaptic transmission, and plasticity as Wnt signaling modulators. . In addition to Wnt components like Wnt secreted proteins, some natural compounds curcumin, cannabidiol, ginkolide b and synthetic medications statins and Oxoglutarate dehydrogenase-like (OGDHL), may also act as Wnt pathway activators. These modulators may aid in halting the onset of AD through synaptic remodeling. Future studies point to the possibility of treatment alternatives for improving synaptic silence, cognition, and protective effects in AD pathogenesis using Wnt secreted factors and nt modulators.

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