Taxifolin for Amyloid-β-associated Neurodegenerative Diseases

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Amyloid-β (Aβ) has been closely implicated in the pathogenesis of cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD), the major causes of dementia. Thus, Aβ could be a target for the treatment of these diseases, for which, currently, there are no established effective treatments. Taxifolin is a bioactive catechol-type flavonoid present in various plants, such as herbs, and it exhibits pleiotropic effects including anti-oxidant and anti-glycation activities.

cerebral amyloid angiopathy | Alzheimer's disease | amyloid-β fibril formation | taxifolin

1. Therapeutic Potentials of Taxifolin for Cerebral Amyloid Angiopathy and Alzheimer's Disease

1.1. Therapeutic Effects of Taxifolin on Cerebral Amyloid Angiopathy

Despite studies demonstrating pathological roles of Aβ in CAA, no effective treatments for CAA have been established. However, accumulating evidence has suggested the emerging effectiveness of taxifolin as a potential agent in the prevention and treatment of Aβ-associated cognitive dysfunction. Historically, oxidative stress has been reportedly closely implicated in the pathogenesis of age-related cognitive dysfunction, because the rate of oxidative metabolism is higher in the central nervous system than that in other tissues, and oxidative damage in the brain progresses with aging [1]. Furthermore, Aβ is also involved in the production of reactive oxygen species and causes neuronal dysfunction [2]. Therefore, dietary intervention with antioxidants has been expected to alleviate oxidative damage in the brain [1], thereby leading to reduced risk of cognitive dysfunction. Based on this possibility, extensive studies extracted a diverse array of compounds from various plants, characterized them, and addressed the potential neuroprotective effects of various antioxidants. During the course of these researches, taxifolin, a bioactive constituent of various plants, including onions, milk thistle, French maritime bark, and Douglas fir bark [3] [4], was found and has become a topic of a great interest as a potential novel therapeutic target. Its biochemical and safety profiles have already been established [5][6]. Taxifolin is known to possess multiple pharmacological actions, such as anti-oxidation, advanced glycation end products (AGE) formation suppression, and mitochondrial protection, and has received increasing attention because of its potential efficacy in the treatment of various diseases including malignancies, cardiovascular diseases, chronic hepatitis, hyperlipidemia, and neurocognitive disorders [7].

We have recently addressed the potential therapeutic effects of taxifolin using in vitro and in vivo approaches and provided the first evidence delineating the novel beneficial effects of taxifolin on CAA [7]. The thioflavin T fluorescence assay and transmission electron microscopy imaging performed by us revealed that the addition of taxifolin to an $A\beta_{40}$ solution significantly inhibited the aggregation of $A\beta_{40}$ in vitro, indicating a novel suppressive effect of taxifolin on $A\beta_{40}$ fibril formation [7]. Furthermore, we investigated the inhibitory effects of taxifolin on $A\beta_{40}$ fibril formation in vivo using a mouse model of CAA, which expresses the human *APP* gene with Swedish/Dutch/Iowa triple mutations [7][8]. Quantitative analyses using filter trap assay and enzyme-linked immunosorbent assay showed that the cerebral levels of Aβ oligomers were decreased in the taxifolin group mice, which were fed taxifolin-containing chow, compared with the control group mice, which were fed standard chow. Therefore, these findings indicate that orally administered taxifolin has a novel preventive effect on $A\beta_{40}$ fibril formation in the brains of CAA model mice [7].

Experiments to assess spatial learning and reference memory revealed that taxifolin significantly suppressed cognitive impairment in these mice compared with controls. As expected from taxifolin's inhibitory effects on $A\beta_{40}$ fibril formation, immunohistochemical analysis showed that it reduced the cerebrovascular accumulation of $A\beta_{40}$ in CAA model mice compared with controls. Furthermore, laser speckle flowmetry indicated that taxifolin significantly restored the reduced cerebral blood flow in CAA model mice. Notably, in conjunction with the reduced cerebral Aβ oligomer levels and improved cerebral blood flow, blood $A\beta_{40}$ levels were elevated in the taxifolin group mice compared with controls, suggesting that taxifolin facilitated the clearance of $A\beta_{40}$ from the brain into systemic circulation; this would lead to a neuroprotective effect, contributing to cognitive impairment prevention [7].

1.2. Inhibitory Effects of Taxifolin on Amyloid-β_{42} Fibril Formation

Regarding $A\beta_{42}$ fibril formation, which is closely implicated in AD pathogenesis, a previous meticulous study analyzed the effects of taxifolin on $A\beta_{42}$ aggregation and β-sheet formation using wild-type $A\beta_{42}$ or mutant $A\beta_{42}$ carrying substituted amino acids [9]. The results demonstrated a novel mechanism of action of taxifolin in the inhibition of $A\beta_{42}$ aggregation. The mechanism is related to the chemical structure of taxifolin: a catechol-type flavonoid, which possesses 3′,4′-dihydroxyl groups on the B-ring [9]. The catechol structure of taxifolin first autoxidizes and then forms *o*-quinone on the B-ring. This oxidized form, in turn, reacts with $A\beta_{42}$ by targeting Lys16 and/or Lys28 of $A\beta_{42}$, resulting in the production of $A\beta_{42}$–taxifolin adducts. Importantly, Lys16 and Lys28 are located in the intermolecular β-sheet region of $A\beta_{42}$. Therefore, the $A\beta_{42}$–taxifolin adduct formation contributes to the inhibition as well as to the destabilization of $A\beta_{42}$ aggregation, suppressing the elongation phase rather than the nucleation phase in the process of $A\beta_{42}$ fibril formation [9].

1.3. Suppressive Effects of Taxifolin on Neuronal Amyloid-β Production

In addition to the biochemical properties of taxifolin that play a role in suppressing $A\beta_{42}$ fibril formation, it is of importance to discuss the physiological significance of taxifolin in the prevention and/or treatment of cognitive impairment. Sequential cleavage of APP by secretases generates Aβ; the rate-limiting step in this process is the cleavage by β-site secretase enzyme (BACE1) [10][11][12]. As the expression levels and activity of BACE1 are

elevated in the brains of AD patients [13][14], there is a possibility that Aβ production and fibril formation are enhanced in these patients. Several studies have addressed the underlying mechanisms regulating BACE1 gene expression [11][15][16]. $A\beta_{42}$ induces the activation of JAK2 signaling pathway, which then mediates the activation of STAT3 signaling pathway [11]. The elevated STAT3 signaling, in turn, activates NF-κB signaling, which enhances the promoter activity of BACE1, thereby upregulating BACE1 transcription [11][15][16]. These signaling cascades promote amyloidogenesis, leading to neuronal injury and cognitive dysfunction.

To address the physiological significance of taxifolin in the suppression of cognitive decline, a study examined whether taxifolin is involved in attenuating signaling pathways for BACE1 expression using a mouse neuroblastoma N2a Swe cell line [11]. This cell line carries a human *APP* Swedish mutation and, when activated, the cells overexpress the gene, producing Aβ. Biochemical and immunocytochemical analyses revealed that the addition of taxifolin to the in vitro culture of these cells upregulated both the expression and the activity levels of SIRT1 [11], a deacetylase involved in the growth, differentiation, and survival of neurons [17]. Furthermore, the taxifolin-stimulated SIRT1 pathway reduced the activation of STAT3 signaling pathway, thereby downregulating BACE1 expression [11]. Together, these studies suggest novel functions of taxifolin besides the prevention of $A\beta_{42}$ aggregation: taxifolin exhibits suppressive effects on neuronal Aβ production and subsequent Aβ fibril formation through reduction of BACE1 levels by stimulating SIRT1-mediated inhibition of STAT3 signaling pathway. Notably, the authors further demonstrated that cilostazol also exhibits beneficial effects on N2a cells, as observed with taxifolin treatment, by activating the SIRT1 pathway, alleviating the STAT3 pathway, downregulating BACE1 expression, and reducing Aβ production [11]. In particular, their finding that concurrent treatment with taxifolin and cilostazol results in synergistic suppressive effects on Aβ production and on neuronal cell death suggests novel potential therapeutic strategies for CAA as well as AD. In addition, the SIRT1 pathway stimulated by taxifolin and cilostazol might contribute to neurogenesis and cognitive function by potentially upregulating neuroprotective factors such as brain-derived neurotrophic factor [17].

1.4. Potential Therapeutic Effects of Taxifolin on Alzheimer's Disease

Inflammation in the brain has been highly implicated in the pathogenesis of AD through the acceleration of amyloidosis [18] and neuronal cell death [11][19]. Studies have reported that in neurons, the activation of a proinflammatory mediator cytosolic phospholipase A_2 ($cPLA_2$) contributes to age-associated cognitive impairment [20] as well as AD pathogenesis [21][22]. $A\beta_{42}$ can activate $cPLA_2$ [23][24], which is responsible for the main enzymatic process of metabolizing arachidonic acid; this ultimately results in the production of prostaglandin E_2 (PGE_2), which is a neuroinflammatory molecule [4][24][25]. Both $cPLA_2$ and PGE_2 have been reported to cause synapse damage [26].

A recent study has investigated the effects of taxifolin on $cPLA_2$-related inflammatory pathway and Aβ-induced neurotoxicity using the human neuroblastoma SH-SY5Y cell line and mouse primary hippocampal neurons [4]. Biochemical analysis revealed that the in vitro treatment of neurons with $A\beta_{42}$ resulted in elevated levels of both $cPLA_2$ and PGE_2. Furthermore, live cell imaging showed that incubation with $A\beta_{42}$ inhibited the formation of neuronal dendritic filopodia and dendritic spines. In contrast, the addition of taxifolin to these cultures seemed to

combat $A\beta_{42}$-induced neurotoxicity; taxifolin significantly prevented the increase in $cPLA_2$ and PGE_2 levels as well as the inhibition of dendritic filopodia and dendritic spines formation in neurons incubated with $A\beta_{42}$. These data suggest that taxifolin exhibits neuroprotective effects besides its suppressive effects on Aβ production through the downregulation of BACE1 expression [11].

Using a mouse model of AD based on the hippocampal injection of $A\beta_{42}$, the authors further examined the effects of intraperitoneal administration of taxifolin on the levels of cPLA2 and of the synaptic marker post-synaptic density protein-95 (PSD-95) and on cognitive function [4]. In line with the findings of the in vitro experiments, taxifolin suppressed the increase in cPLA2 and PGE2 levels in the hippocampus in $A\beta_{42}$-injected mice. Moreover, $A\beta_{42}$ injection reduced PSD-95 levels in the hippocampus, but taxifolin treatment significantly suppressed these reductions. Furthermore, animal experiments designed to test recognition and spatial memories reported that $A\beta_{42}$-injected mice exhibited deficits in cognitive function, whereas taxifolin treatment improved this cognitive impairment. These results suggest that taxifolin exhibits suppressive effects on cognitive impairment in the preclinical settings of AD, potentially through pleiotropic functions including inhibition of $A\beta_{42}$ fibril formation [9], suppression of $A\beta_{42}$ production [11], and/or alleviation of $A\beta_{42}$-induced neurotoxicity [4].

2. Therapeutic Potentials of Taxifolin for Metabolic Diseases with A High Risk for Neurodegenerative Diseases

2.1. Effects of Taxifolin on Diabetes

Epidemiological studies have reported diabetes to be a high-risk factor for dementia, including AD and vascular dementia [27][28][29]. Potential mechanisms underlying diabetes-related dementia include multifactorial pathways such as Aβ accumulation, neuroinflammation, small vessel infarcts, and neurodegeneration in the brain [27][28][29][30][31]. Accordingly, prevention and treatment of diabetes is critical to reduce the risk of development and progression of dementia.

Detailed findings regarding the effects of taxifolin on diabetes are limited, but a recent study has demonstrated the anti-diabetic effects of taxifolin and its mechanisms of action through in vivo and in silico approaches [32]. The authors used a rat model of diabetes in which pancreatic β-cells were depleted by intraperitoneal injection of alloxan. They found that taxifolin administration via an intragastric route significantly reduced blood glucose levels in the diabetic rats compared with controls (without taxifolin). To elucidate the underlying mechanisms of the hypoglycemic effects of taxifolin, the authors next examined the effects of taxifolin on α-amylase, a carbohydrate-metabolizing enzyme that elevates blood glucose levels; inhibition of α-amylase is effective in the treatment of diabetes [32][33]. Taxifolin treatment significantly reduced serum amylase activity in diabetic rats compared with controls, consistent with its glucose-lowering effects. These studies suggest that taxifolin exhibits hypoglycemic effects through the reduction of α-amylase activity in diabetic rats [32].

The authors further addressed the potential direct action of taxifolin on α-amylase with computational and docking studies, comprising ligand–receptor docking studies, free-energy calculations, and molecular dynamics simulations

[32]. In the flexible docking simulations, the authors selected the bioinformatically determined best-docked poses of the taxifolin–α-amylase complex and analyzed the binding modes of taxifolin with α-amylase. The analysis revealed that taxifolin interacts with the residues Trp59, Tyr62, Glu233, and Asp300 present at the active site of α-amylase through a π–π interaction with the benzene rings of Trp59 and Tyr62 and an H-bond interaction with Glu233 and Asp300. In addition, using a molecular mechanics-based scoring method for binding free-energy calculation, the authors showed that van der Waals and nonpolar solvation-free energies also contribute to the binding affinity of taxifolin for α-amylase. Furthermore, the authors examined the dynamic behavior of the taxifolin–α-amylase complex through molecular dynamics simulations, considering the potential effects of solvent, temperature, and pressure on the complex formation, and confirmed the stable conformation of taxifolin at the active site of α-amylase. Accordingly, these in vivo and in silico findings indicate that taxifolin binds to the active site of α-amylase and inhibits its activity, thus leading to improvement of hyperglycemia [32].

2.2. Effects of Taxifolin on Diabetic Nephropathy

Diabetic nephropathy is a serious diabetic complication [34], and chronic kidney diseases (CKDs) are epidemiologically a high-risk factor for dementia [35][36][37]. Reportedly, in a mouse model of CKD, chronic renal dysfunction resulted in elevated oxidative stress levels in the brain, leading to cognitive impairment [38]. Thus, the prevention and improvement of CKDs would contribute to reduce the dementia risk.

Recent studies have reported the novel renal protective effects of taxifolin using a rat model of diabetes, which was developed through pancreatic β-cell depletion with an intraperitoneal streptozotocin injection [34][39]. Taxifolin treatment significantly improved the renal function profiles in diabetic rats compared with controls, in parallel with improved glucose metabolism [34][39]. Consistent with these results, further histological analyses revealed that taxifolin suppressed necrotic cell death in the renal tissue [39] and alleviated renal fibrosis by inhibiting extracellular matrix accumulation and mesangial matrix expansion [34]. Furthermore, biochemical analyses showed that taxifolin reduced the activation of high-glucose-stimulated proinflammatory pathways in rat and human kidney cell lines [34] as well as in renal tissue from diabetic rats [39]. Taxifolin also reduced the levels of reactive oxygen species produced by these kidney cell lines, which were stimulated with high glucose [34]. These findings indicate the potential renal protective effects of taxifolin in diabetic conditions, further supporting its potential beneficial effects on dementia.

2.3. Effects of Taxifolin on Obesity

Obesity has been implicated in the development of dementia in later life [40]; however, a recent study has reported an inverse association between body mass index and dementia incidence [41]. Thus, the potential effect of obesity on dementia incidence remains controversial. Obesity is a high-risk factor for diabetes, cardiovascular diseases, and CKDs [42], which, in turn, are risk factors for dementia [27][28][29][35][36][37][43]. Therefore, improvement in obesity would be beneficial for reducing dementia risk.Recent reports have demonstrated novel roles of taxifolin in improving obesity [44][45]. The authors analyzed the effects of orally administered taxifolin on a rat model of diet-induced obesity (high-fat diet). The taxifolin group showed significant reductions in body weight and serum

cholesterol and triglycerides levels compared with the controls (without taxifolin treatment) [44]. Taxifolin also improved hyperglycemia and insulin resistance as well as oxidative stress levels [45]. Furthermore, it elevated gene expression levels of mitochondrial uncoupling protein-1 and carnitine palmitoyltransferase I, markers for fat oxidation and energy expenditure of the energy-consuming brown adipose tissue [45]. Together, these findings suggest a novel anti-obesity effect of taxifolin, potentially mediated through an improvement of glucose and lipid metabolism as well as of energy homeostasis [44][45], although the mechanistic details underlying these effects remain to be elucidated.

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