REVIEW ARTICLE

Protective Effects of Polydatin Against Dementia-Related Disorders

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Abstract: Dementia is a collection of symptoms affecting a person's cognition. Dementia is debilitating, and therefore, finding an effective treatment is of utmost importance. Resveratrol, which exhibits neuroprotective effects, has low bioavailability. However, its glucoside polydatin is more bioavailable. Here, the evidence that supports the protective role of polydatin against dementia-related diseases such as Alzheimer's disease, vascular dementia, alcohol-related dementia, and Lewy body dementias is presented. The beneficial effects of polydatin from a mechanistic perspective are specifically emphasized in this review. Future directions in this area of research are also discussed.

1. INTRODUCTION

Dementia is a group of symptoms affecting memory, thinking, and reasoning skills. It is now no longer being perceived as a normal part of the aging process. Data from the World Health Organization (WHO) indicated that dementia affected 47 million people globally in 2015 [1]. WHO also predicted that the figure will further increase to 75 million in the next 10 years. Dementia has a deleterious impact on aging societies and their families. Thus, finding an effective treatment to halt the progression of dementia is crucial.

Dementia can occur due to a variety of possible diseases including Alzheimer's disease (AD). It has been demonstrated that the polyphenolic stilbene resveratrol, a potent sirtuin 1 (SIRT1) activator, can exert neuroprotection in several models of AD [2]. A recent clinical trial has shown that resveratrol is relatively safe, and can alter AD biomarker trajectories [3]. Besides, it can also maintain the blood-brain barrier (BBB) integrity in an experimental AD model [4]. Nevertheless, the bioavailability of resveratrol is low due to extensive hepatic metabolism and rapid renal elimination [5]. Thus, the issue of low bioavailability of resveratrol warrants the attention to explore newer compounds such as its analog polydatin.

Polydatin, also known as piceid, is a glucoside form of resveratrol. It differs from resveratrol by the substitution of a hydroxyl group for a glucose unit [6]. The chemical structures of polydatin and resveratrol are shown in Fig. **1**.

Wang *et al.* (2015) have shown that polydatin and resveratrol could mutually be converted *in vivo* [7]. Although polydatin can retain the biological properties of resveratrol, it is less susceptible to enzymatic oxidation [8]. In support of this notion, Wang *et al.* further demonstrated that the concentration of polydatin in rat serum was always higher (~3–5 times) than resveratrol after the animals were orally administered with either polydatin or resveratrol at 200 mg/kg [7].

The cellular mechanisms of polydatin in various tissues and organs have been thoroughly reviewed by Du *et al.* (2013) [9]. The potential protein targets of polydatin have also been identified [10]. It is supposed that polydatin can cross the BBB as it protects brain damage from cerebral ischemia when administered intravenously [11]. Moreover, orally administered polydatin could reduce rotenone-induced neurodegeneration in the substantia nigra [12]. The ability of polydatin to cross the BBB is essential in combating brain disorders. In comparison to its counterpart resveratrol, the literature on the protective role of polydatin against dementia-related diseases is relatively scarce. This paper is aimed to review the protective potential and modes of action of polydatin against dementia-related disorders. Fig. **2** depicts an overview of this paper. The future perspectives of polydatin research in relation to these diseases will also be discussed.

2. ALZHEIMER'S DISEASE

AD is a neurodegenerative disorder and accounts for about two-third of the overall cases of dementia [13]. The progression of the disease is accompanied by the gradual impairment of memory and cognitive function. A major hallmark feature of AD is the accumulation of senile plaques

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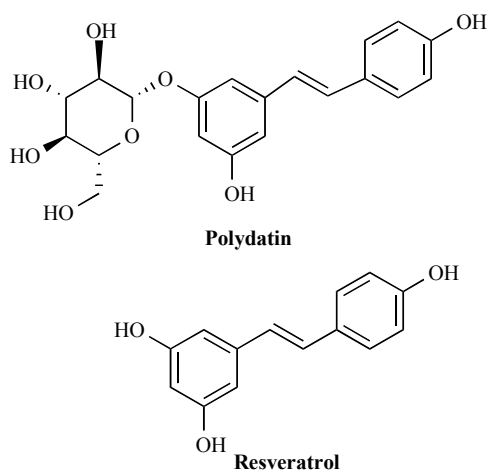
Fig. (1). Structures of polydatin and resveratrol.

in the brain [14]. Senile plaques are aggregates of amyloid-β (Aβ) protein found abundantly in the brain of patients with advanced AD [15]. The aggregation of proteins, in general, can produce higher-order supramolecular structures including fibrillar forms [16]. Aβ fibrils are typical cross β-sheets that are aligned perpendicularly to the axis of the fibril [16]. Thus, discovering agents that can halt or reverse the Aβ fibrillization could potentially treat AD.

Although the mechanistic insights of resveratrol in AD have extensively been reviewed [2, 3, 17-19], the comparative literature of its role with other stilbenes including polydatin is still lacking. Rivière *et al.* (2007, 2010) compared the inhibitory effect of stilbenes, including polydatin and resveratrol, on the formation of Aβ fibrils in an *in vitro* cell-free system [6, 20]. Curcumin was selected as a positive control in their studies because this polyphenol has been reported to possess a potent anti-amyloidogenic effect [21]. Among all the stilbene compounds tested, at the equimolar concentration of 10 μM, the effectiveness of polydatin and resveratrol in inhibiting Aβ fibril formation was ~20% greater than that of the curcumin control group [20]. Rivière *et al.* also found that polydatin is equally effective as resveratrol in inhibiting Aβ fibril formation with the IC_{50} value ranging from 4.7 to 6.0 μM [6, 20]. Other stilbene derivatives such as astringine, piceatannol, viniferin, and resveratrol diglucoside could also inhibit Aβ polymerization but the effect was weaker than the curcumin control [20]. In a different study using HPLC and electron microscopy, Rivière *et al.* also demonstrated in another *in vitro* cell-free study that polydatin could destabilize Aβ oligomers and fibrils, and convert these macromolecules to non-neurotoxic monomers [22]. The authors proposed that the mechanism of this destabilization could be a dynamic interaction between polydatin and Aβ, which could open the hydrophobic zipper, and shift the reversible equilibrium ''random coil↔β-sheet'' to the disordered structure. Table **1** summarizes the pharmacological effects of polydatin on dementia-related disorders.

The accumulation of Aβ plaques precedes other pathological changes and causes degeneration of neurons. The degeneration of cholinergic forebrain neurons is regarded as the most prominent among the neurons in AD [23]. A reduc-

tion in the number of nicotinic acetylcholine receptors (nAChRs) has also been demonstrated in AD [24]. Treatment with the nAChR agonist such as nicotine can augment attention and cognitive functions in normal humans and animals [25]. Thus, nAChRs may be crucial therapeutic targets for AD treatment. A study by Xiao *et al.* has shown that $Aβ_{1-42}$ (5 μM) could downregulate the expression of α3 and α7 nAChRs in the human neuroblastoma SY-SY5Y cell line [26]. On the other hand, polydatin (0.1 mg/mL) could upregulate the expression of α3 and α7 nAChRs, and reverse $Aβ_{1-42}$-induced downregulation of α3 and α7 nAChRs [26]. Recently, resveratrol has also been demonstrated to inhibit Aβ aggregation and cognitive decline in transgenic AD mice *via* upregulating the expression of α7 nAChRs in the brain [27]. Although muscarinic acetylcholine receptors (mAChRs) are also affected in AD [24], the role of polydatin and resveratrol in this receptor subtype is unclear.

Another main culprit of AD is hyperphosphorylation of tau protein [14]. This leads to the formation of neurofibrillary tangles, another pathological marker of AD. Resveratrol can alleviate tau hyperphosphorylation [28, 29]. Despite this important finding, the role of polydatin in preventing tau hyperphosphorylation is poorly understood.

3. VASCULAR DEMENTIA

Vascular dementia (VaD) is the second most common cause of dementia, accounting for ~15% of cases [30]. The disease can lower the quality of life (QOL) of patients and their caregivers. VaD is caused by a variety of vascular disorders that affect the brain such as cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage [31]. It has also been reported that 25-30% of ischemic stroke survivors develop VaD [32]. The protection of cerebrovascular disease by polydatin has been extensively reviewed by Tang *et al.* (2019) [11].

VaD model can be induced experimentally by four-vessel occlusion (4-VO) method in which both vertebral arteries and common carotid arteries are occluded. As indicated by the Morris water maze test, rats with 4-VO showed severe cognitive deficits [33]. The 4-VO rats orally treated with polydatin (50 mg/kg) showed significant cognitive improvement on day 4 with the escape latency reduced by half [33]. Biochemical assays indicated that polydatin reduced the level of malondialdehyde and increased the catalase and superoxide dismutase activities [33]. Polydatin could also alleviate oxygen-glucose deprivation-induced injuries in cultured rat's cortical neurons [33]. Furthermore, Sun *et al.* (2014) showed that polydatin attenuated cognitive impairment in rats with hypoxic-ischemic brain injury *via* upregulating brain-derived neurotrophic factor [34]. Overall, these findings suggest that the therapeutic potential of polydatin against VaD is partly due to its neuroprotective and antioxidant effects.

Risk factors for VaD include diabetes, hypertension, and metabolic syndrome. There are various animal models of VaD including the ones that mimic its risk factors [35]. Mechanisms implicated in the pathogenesis of VaD may include mitochondrial, endothelial, and BBB dysfunctions, as well as inflammation [35]. For instance, resveratrol has
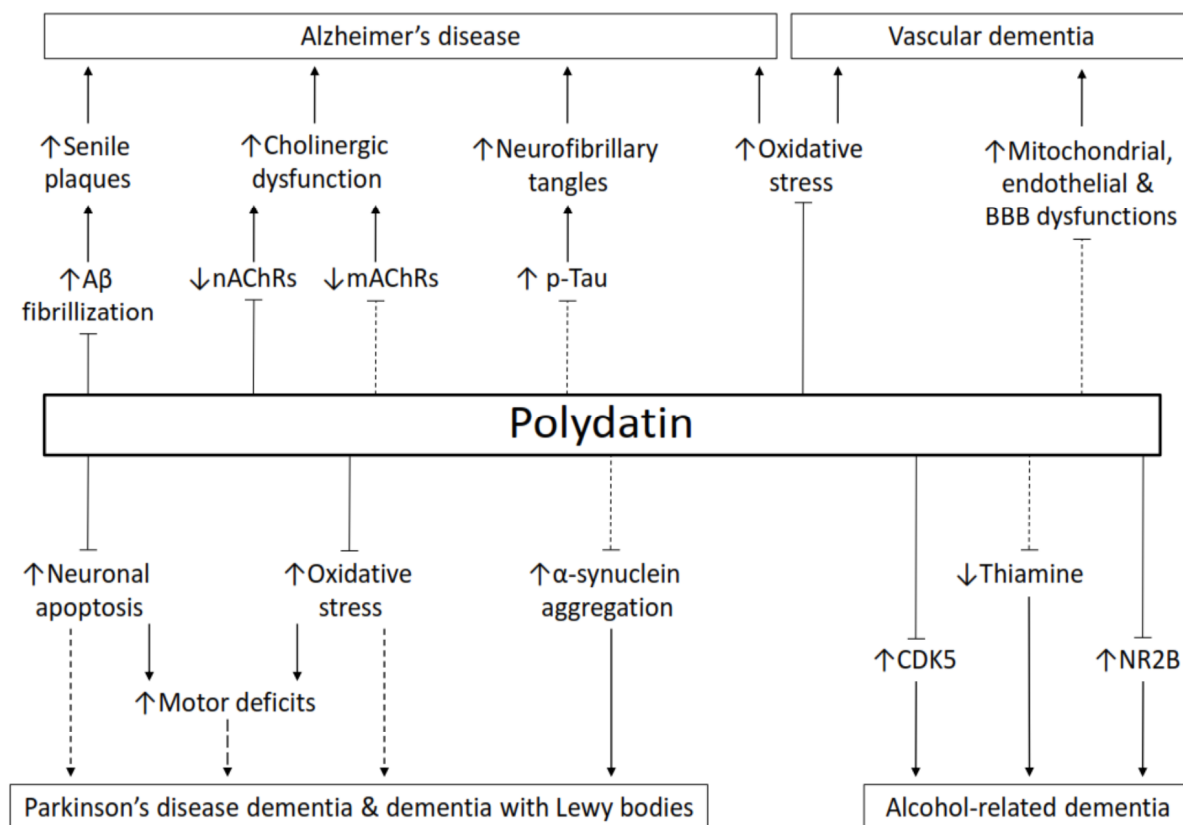
Fig. (2). The protective role of polydatin against dementia-relating disorders. The lines with an arrowhead indicate facilitation. The lines with a blocked end indicate inhibition. The dashed lines indicate the hypothetical pathways that might be regulated by polydatin. Aβ, amyloid-β; CDK5, cyclin-dependent kinase 5; mAChRs, muscarinic acetylcholine receptors; nAChRs, nicotinic acetylcholine receptors; NR2B, NMDA receptor 2B subunit; p-tau, phosphorylated tau. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

been reported to improve cognition in several animal models of VaD including the 4-VO, bilateral common carotid artery occlusion, and streptozotocin-induced diabetic models by attenuating inflammation, mitochondrial dysfunction, oxidative stress, and apoptosis [36-41]. Therefore, the protective mechanisms of polydatin on other models of VaD should be further explored.

4. LEWY BODY DEMENTIAS

Dementia is common and occurs in 40-70% of Parkinson's disease (PD) patients [42]. Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are accompanied by motor changes including gait disturbances and parkinsonism. PDD and DLB are classified as Lewy body dementias due to the presence of abnormal protein aggregates known as Lewy bodies [43]. The Lewy bodies, consisting of mainly α-synuclein, are found intracellularly inside the neurons in the brainstem, or within the cortex. PDD refers to the cognitive impairment that develops at least a year after the diagnosis of PD [44]. On the other hand, DLB refers to dementia symptoms that develop sooner, or within one year of the onset of motor symptoms [44].

In addition to Lewy pathology, PD is also characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta of the brain [45]. Clinical motor

symptoms of PD include bradykinesia, rigidity, tremor, and postural instability. Prolonged exposure to rotenone (a specific complex 1 inhibitor and a common pesticide) has been demonstrated to cause parkinsonism characteristics in rats. Several studies have reported that rotenone selectively damaged the nigrostriatal dopaminergic neurons. For example, a study by Chen *et al.* (2015) showed a sub-lethal concentration of rotenone (2 mg/kg/day, s.c., 5 weeks) impaired ATP, reduced glutathione, superoxide dismutase, and thioredoxin levels, but increased the level of malondialdehyde in the striatum of rats [12]. Polydatin (40-80 mg/kg), administered orally, could significantly prevent the rotenone-induced biochemical changes and neurodegeneration in the substantia nigra [12]. Similarly, polydatin could also alleviate motor dysfunctions, and exhibit potent antioxidant activity in two other animal models of PD, *i.e.* 6-hydroxydopamine-treated rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice [12].

Treatment with polydatin (25-100 mg/kg/day, i.g.) for 4 weeks also improved motor performance and protected against dopaminergic neurodegeneration of the substantia nigra by suppressing the activation of microglia and the release of pro-inflammatory mediators in a rat model of lipopolysaccharide-induced PD [46]. Polydatin induced similar cellular changes in lipopolysaccharide-treated murine

Table 1.   A summary of the pharmacological effects of polydatin on dementia-relating illnesses.

Disease Model	Beneficial Effects	Type of Exposure	Experimental Unit	Polydatin Concentrations	Description of Effects	Refs.
Alzheimer's disease	Prevention of Aβ aggregation	*In vitro*	Cell-free system	10 μM	Inhibit $A\beta_{25-35}$ polymerization	Rivière *et al.* [6, 20]
		In vitro	Cell-free system	10 μM	Destabilize $A\beta_{25-35}$ fibrils and oligomers	Rivière *et al.* [22]
	Upregulation of nAChRs	*In vitro*	SH-SY5Y cells	0.1 and 0.25 mg/mL for 48 h	Increase α3 and α7 nAChRs, reverse $A\beta_{1-42}$-induced decrease of α3 and α7 nAChRs	Xiao *et al.* [26]
Vascular dementia	Protection against learning and memory impairments	*In vivo*	Adult male Sprague-Dawley rats	12.5-50 mg/kg/day for 30 days; p.o.	Attenuate cognitive deficits, decrease MDA levels, increase CAT and SOD activities	Li *et al.* [33]
		In vivo	Seven-day-old neonatal Sprague-Dawley rats	10 mg/kg/day for 10 days; i.p.	Attenuate cognitive deficits, increase BDNF expression	Sun *et al.* [34]
Alcohol-related dementia	Protection against learning and memory impairments	*In vivo*	Adult male Sprague-Dawley rats	12.5 and 50 mg/kg/day for 30 days; i.g.	Attenuate cognitive deficits	Zhang *et al.* [66]
		In vivo	Rat primary hippocampal neurons	12.5 and 50 mg/kg/day for 30 days; i.g.	Increase cell viability, decrease CDK5 expression and activity	Zhang *et al.* [66]
		In vivo	Alcoholic patients	40 mg (b.i.d.) for 14 days; p.o.	Attenuate cognitive deficits, decrease lipid peroxidation	Pace *et al.* [68]
		In vivo	Rat prefrontal cortex	0.1, 0.2, and 0.4% for 10 days; i.g.; The stock concentration was unreported	Decrease NR2B mRNA expression	Xu *et al.* [76]
Parkinson's disease	Protection against dopaminergic neurodegeneration	*In vitro*	SH-SY5Y cells	10-30 μM for 1h prior to dopamine exposure	Reduce lipid peroxidation, inhibit apoptosis, activate MAPKs	Potdar *et al.* [8]
		In vivo	Adult male Sprague-Dawley rats	20-80 mg/kg/day for 5 weeks; p.o.	Reverse damage in striatal region, increase motor performance	Chen *et al.* [12]
		In vivo	Adult male Wistar rats	25-100 mg/kg/day for 4 weeks; i.g.	Reverse damage in striatal region, increase motor performance, reduce proinflammatory mediators, reduce the activation of NF-κB, increase p-AKT, p-GSK-3β, and Nrf2 levels	Huang *et al.* [46]
		In vitro	BV-2 cells	100-400 μM for 1h	Reduce proinflammatory mediators, reduce the activation of NF-κB, increase p-AKT, p-GSK-3β, and Nrf2 levels	Huang *et al.* [46]
		In vitro	SH-SY5Y cells		Increase cell viability, MMP, and Sirt 1 expression, decrease ROS and DJ1 expression, induce Atg5-mediated autophagy	Bai *et al.* [47]

Abbreviations: Aβ, amyloid-β; BDNF, brain-derived neurotrophic factor; CAT, catalase; CDK5, cyclin-dependent kinase 5; GSK-3β, glycogen synthase kinase-3β; MAPKs, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, mitochondrial membrane potential; nAChRs, NF-κB, nuclear factor-κB; nicotinic acetylcholine receptors; NR2B, NMDA receptor 2B subunit; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; Sirt1, sirtuin 1; SOD, superoxide dismutase.

microglia BV-2 cells by regulating the AKT/GSK3β-Nrf2/NF-κB signaling pathway [46]. In another *in vitro* PD model employing SH-SY5Ycells, the protective effect of polydatin against rotenone-induced toxicity was regulated by Atg5-mediated autophagy [47]. Most studies on the protective role of polydatin in PD have been focused on examining the mechanisms associated with parkinsonian motor deficits. However, cognitive impairment has also been demonstrated in experimental models of PD [48, 49]. Future studies are needed to examine the capability of polydatin in improving cognition in PD models.

Oxidation can destruct vital molecules in cells, which include proteins, lipids, and DNA. It has been demonstrated that the level of oxidation is high in substantia nigra pars compacta compared to other regions of the human brain [50]. Since the substantia nigra is rich in dopaminergic connections, autoxidation of dopamine molecules might also occur in this region. In accordance, dopamine can undergo a non-enzymatic autoxidative reaction to generate reactive oxygen species (ROS) [51]. Excessive formation of ROS can lead to neuronal damage. Moreover, dopamine could induce lipid peroxidation and apoptotic cell death in human neuroblastoma SH-SY5Y cells [8]. However, Potdar *et al.* (2018) reported that polydatin pretreatment (10-30 μM) for 1 h prior to dopamine exposure could inhibit the dopamine-induced loss of BCL-2 in SH-SY5Y cells [8]. BCL-2 is an anti-apoptotic protein, which plays an important role in neurogenesis [52]. In addition, polydatin could also suppress the activity of caspase-3/7, a biomarker of apoptosis [8]. Both apoptosis and oxidative stress are closely linked to AD and PD pathogenesis [14, 45, 53].

Phytochemicals such as resveratrol and curcumin can induce autophagic degradation of α-synuclein in experimental parkinsonism [54, 55]. Resveratrol also suppresses α-synuclein expression and aggregation, oxidative stress, and neuroinflammation [56, 57]. Most importantly, resveratrol also alleviated cognitive and motor deficits in A53T α-synuclein mouse model of PD in a dose-dependent manner [56]. The α-synuclein degradation potential of resveratrol is most likely to be mediated *via* SIRT1 as the SIRT1 inhibitor EX527 could antagonize the protective capability of resveratrol [58]. In a cellular model of PD, Wu *et al.* (2011) reported that both AMP-activated protein kinase and SIRT1 are required for the resveratrol-mediated neuroprotection [59]. A bioinformatic study demonstrated that SIRT1 is a target of microRNA-214 [60]. In agreement with these findings, a different study showed that resveratrol could attenuate the rise in α-synuclein expression in MPTP-induced PD by upregulating the microRNA-214 expression [61]. Despite the strong connection between resveratrol and α-synuclein, the link between polydatin and Lewy pathology has never been established.

5. ALCOHOL-RELATED DEMENTIA

Alcohol-related cognitive and memory impairments can be developed as a result of excessive and prolonged alcohol consumption [62, 63]. For instance, the hippocampus, a brain structure that is associated with learning and memory formation, is susceptible to ethanol-related toxicity and damage.

Studies have shown that hippocampal functions are compromised in animal models [64, 65]. Chronic self-administration of ethanol in rats impaired cognition as quantified using the Morris water maze test [66]. Moreover, acute and chronic alcohol consumption also impairs cognitive skills and abilities in humans [67, 68]. Polydatin could improve cognitive performance in alcoholic patients and rats [66, 68]. Similarly, a study employing Barnes maze task indicated that resveratrol could prevent spatial learning and memory deficits in ethanol-treated mice [69]. In addition, polydatin could also decrease serum lipid peroxidation in alcoholics [68].

Cyclin-dependent kinase 5 (CDK5) is found abundantly in the brain and has been shown to play a crucial role in neuronal function and development [70]. However, dysregulation of CDK5 can result in neurodegeneration [71, 72]. Alcoholic rats also exhibited high levels of CDK5 activity and protein expression [66, 73]. The ethanol might have provoked the brain injury and cognitive impairment by increasing CDK5 activity and protein expression. Polydatin could reduce CDK5 activity and protein expression in the hippocampus of ethanol-treated rats, and ethanol-treated primary hippocampal neuronal cultures [66], suggesting that the neuroprotective ability of polydatin against ethanol-induced neurotoxicity is partly mediated *via* targeting CDK5.

NMDA receptor 2B subunit (NR2B), a constitutive component of the glutamatergic NMDA receptor, plays an important role in dendritogenesis and synaptic plasticity [74]. However, overexpression of NR2B may lead to excitotoxicity. Studies have shown that chronic alcohol exposure can upregulate the expression of the NR2B gene and protein [75]. Thus, alcohol-induced cognitive impairment is partly mediated by altering the expression of NR2B. It has also been reported that the protective effect of polydatin on learning and memory in alcoholic rats is mediated by suppressing NR2B mRNA expression [76]. Nevertheless, whether polydatin might influence the expression of other NMDA receptor subunits such as NR1, remains to be determined.

Thiamine (vitamin B1) deficiency is associated with neurological deficits exhibited in AD patients [77]. It has been suggested that the deficiency is due to the impairment in the activities of thiamine-dependent enzymes [78]. Chronic alcohol misuse can also lead to thiamine deficiency, which in turn can cause Wernicke-Korsakoff's syndrome, a neuropsychiatric syndrome characterized by severe cognitive impairment [79]. It is still uncertain if polydatin could regulate the activities and expression of thiamine-dependent enzymes such as thiamine monophosphatase, thiamine diphosphatase, and thiamine pyrophosphokinase.

CONCLUSION AND FUTURE PERSPECTIVES

Polydatin may improve cognitive deficits in many other ways other than the ones discussed in this paper such as attenuating neuronal oxidative damage and inflammation. Neuroinflammation and oxidative stress are widely implicated in dementia. For instance, elevated levels of serum inflammatory cytokines have been observed in AD patients [80]. Chronic systemic inflammation is also associated with an increased risk of cerebral microvasculature disease that leads to the development of VaD [81]. Oxidative stress re-

flects an imbalance between free radicals and antioxidants in the body. Free radicals produced by oxidative stress are found in several experimental models of diseases including AD and PD [53]. Polydatin could mitigate neuronal cell death in a rat model of permanent middle cerebral artery occlusion *via* suppressing oxidative stress and neuroinflammation [82]. Studies have shown that polydatin could suppress oxidative stress *via* inhibiting protein kinase C and activating the nuclear factor erythroid 2-related factor 2 (NRF2)/heme oxygenase-1 (HO-1) pathway [83, 84]. A recent study has demonstrated that polydatin attenuated chemotherapy-induced learning and memory impairment by suppressing inflammation, oxidative stress, and apoptosis in rat hippocampus [85].

There is a growing body of evidence that the inflammatory response is mediated by the activated microglia, the resident immune cells of the central nervous system [86]. Microglia activation is a hallmark of brain pathologies such as neurodegeneration in AD and PD. [87, 88]. It has been demonstrated that polydatin could attenuate traumatic spinal cord injury by inhibiting microglial inflammation *via* modulation of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and inducible nitric oxide synthase pathways [89].

Bone morphogenetic proteins (BMPs), a subfamily of the transforming growth factor-β, play an important role in neuron maturation and brain development. Certain BMPs such as BMP-2, BMP-7, and BMP-9 are expressed in the brain [90-92]. In addition, activation of Wnt/β-catenin signaling has been implicated in AD therapy as it attenuates tau hyperphosphorylation and Aβ production [93-95]. It has been reported that the osteogenic-promoting effect of polydatin could be blocked by inhibiting the Wnt/β-catenin and BMP pathways [96].

The role of Aβ and tau protein in the pathogenesis of AD has extensively been studied [14]. These proteins have been identified as the key target of drug development for the treatment of the disease. However, several world-famous large pharmaceutical companies have been retracting from the drug development project mainly because of great difficulty to demonstrate statistically significant benefit of the drugs in improving prognosis of the disease, *i.e.*, to extend the mechanistically beneficial effects observed in the basic study in animal models to the improvement of dementia symptoms at the stage of clinical application. As a natural compound, polydatin could also exhibit instability and low bioavailability issues that may limit its beneficial action. Therefore, new delivery strategies in overcoming these limitations, and increasing therapeutic efficacy of polydatin should further be explored. For instance, the use of bioenhancers as a drug delivery method may benefit patients by promoting the absorption of poorly bioavailable drugs [97]. Additionally, a recent study has reported that the nanoencapsulated polydatin could preserve the characteristics of the free form [98]. Thus, the encapsulation process may also be another promising strategy for delivering polydatin to its therapeutic sites.

While polydatin could be an important nutraceutical agent to treat dementia-related illnesses, the literature on its

protective effects is considerably lacking in comparison to resveratrol. The molecular mechanisms underlying the effects of polydatin in the treatment of dementia remain poorly characterized. Thus, many more studies are required to elucidate the protective mechanisms of polydatin for cognitive impairment before it could be considered for further clinical development in treating dementia.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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