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## **Dietary soybean isoflavones in Alzheimer's disease prevention**

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## **ABSTRACT**

Soybean isoflavone (SIF) is a type of polyphenol present extensively in legumes. Because of its unique chemical construction and the physiological activity of the phenolic hydroxyl group, SIF exhibits strong antioxidant activity in antioxidant and nonantioxidant enzyme systems. Genistein is the major isoflavone in soy foods, accounting for more than 50% of the isoflavone content. The health effects of soybean dietary isoflavones on humans have gained increased attention. Recent studies have suggested that SIF may alleviate neurodegenerative diseases such as Alzheimer's disease (AD). Despite the comprehensive research on AD, effective treatments for AD are yet to be established. The early diagnosis and prevention of mild cognitive impairment (MCI) have become crucial for delaying AD development. Several dietary polyphenols have exerted cognitive effects on AD, and the appropriate intake of dietary SIF helps reduce the risk of AD. This study reviews the possible mechanisms of AD pathogenesis and their relationships with SIF intake; the results provide useful insights for AD prevention in the future.

**Key Words: Alzheimer's disease, soybean isoflavone, dietary, cognitive impairment, prevention**

## **INTRODUCTION**

With increase in human longevity and world population, Alzheimer's disease (AD) has become a major threat to the health and quality of life of elderly people. The prevalence of AD has increased over the years.<sup>1</sup> In 2010, World Health Organization (WHO) reported that 35.6 million patients were afflicted by dementia worldwide.<sup>2</sup> With an anticipated doubling of the number of patients with AD every 20 years, the total number is estimated to be 65.7–115.4 million by 2050. The percentage varies from 4.19% to 8.5% across countries, with an incidence of 4.15% in China.<sup>3</sup> AD and other types of dementia are by far the leading chronic disease that needs for care (dependence) among older people globally. AD does shorten the lives of those affected, but its greatest impact is on quality of life, both for AD patients, and for their family and carers, thus contributing to a huge economic impact.<sup>4</sup> According to World Alzheimer Report 2015,<sup>5</sup> the total estimated worldwide cost of dementia has been US \$818 billion, an enormous sum similar to the Gross Domestic Product (GDP) of countries like Netherlands. However, nearly 94% of people living with AD are from low and middle income countries and cared for at home, where health and care systems often provide limited support. Since low and middle income countries have fewer economic resources and professional

personnel to meet the needs of health and social care for their rapidly growing older populations, AD has become one of the biggest global public health concerns and social care challenges that requires urgent solutions and remedies today and in the future.<sup>6</sup>

Epidemiological and animal studies have demonstrated that phytochemicals and other plant extracts promote brain development and maintain brain function. Furthermore, blue berry extracts rich in anthocyanin and ginkgo biloba extracts enhance the cognitive function of old animals.<sup>7</sup> In addition, resveratrol can hinder cytotoxicity and  $\beta$ -amyloid ( $A\beta$ )-induced apoptosis, protect the neurons, and prevent memory impairment.<sup>8</sup> Therefore, phytochemicals present in natural foods might delay the onset of neurodegenerative diseases by improving memory and cognitive functions.<sup>9</sup> The use of phytochemicals, including SIF, resveratrol, and tea polyphenols, has recently been extensively studied for AD therapy and prevention. Supplementary resveratrol has been reported to improve the memory performance and functional connectivity of the hippocampus in healthy overweight older adults,<sup>10</sup> and epigallocatechin gallate exerts protective effects against  $A\beta$ -induced neuronal apoptosis by reactive oxygen species (ROS) scavenging.<sup>11</sup> Similar to phytoestrogens in terms of structure, SIF has antioxidant, antiapoptotic, and anti-inflammatory effects on AD.

SIF, the most common form of phytoestrogens that bind to estrogen receptors (ERs), have a common diphenolic structure. The three effective forms of SIF, namely Gen, Dai, and Gly, are naturally present in soybean and nonfermented soyfoods, primarily in their  $\beta$ -glycoside forms.<sup>12</sup> Notably, the naturally occurring antioxidant compound Gen is present in high concentrations in soybean and is the most active form of SIF. Increasing evidence reveals that SIF plays a major role in the prevention of cancer, heart diseases, osteoporosis, and cognitive dysfunction.<sup>13</sup> Furthermore, the function of SIF in the central nervous system has recently received considerable attention.

In addition, the beneficial effects of SIF on neurotoxicity and cognitive function are being increasingly elucidated.

This study reviewed the cognitive effects of SIF on AD and summarized the potential mechanisms of AD prevention, thus facilitating the exploration of targeted drug therapies.

### ***AD development and influencing factors***

An understanding of the pathological mechanism of AD is a prerequisite for establishing effective preventive and treatment strategies. The present hypotheses, such as genetic mutations (APP, ApoE, and tau),  $A\beta$  toxicity, the abnormal modification of the tau protein (cell skeleton structure modification), oxidative stress, inflammation, dysregulation of metal

metabolism, and damage to the vascular system and synapses in the brain, may be involved in AD development.<sup>14</sup> A $\beta$  toxicity has been widely accepted as the most possible mechanism because A $\beta$  is considered the major constituent of the senile plaques (SPs) observed in the brains of patients with AD, which are toxic to the neurons. A $\beta$  accumulation results from the inadequate secretion of  $\alpha$ ,  $\beta$ , and  $\gamma$  secretory enzymes, leading to the abnormal hydrolysis of the A $\beta$  precursor. The A $\beta$  protein in the extracellular compartment of the neurons is present mainly as A $\beta$ 1-40 and A $\beta$ 1-42. Despite its low yield, A $\beta$ 1-42 is easily aggregated and subsequently deposited, leading to a diffused SP.<sup>15</sup> Another characteristic of AD is the aggregation of highly phosphorylated proteins and the subsequent formation of neurofibrillary tangles (NFTs). Moreover, different mechanisms may partially contribute to AD pathogenesis. Huang and Mucke (2012) have summarized the recent views of the pathological mechanisms of AD.<sup>16</sup>

Controllable and noncontrollable factors contribute to the onset and development of AD. The noncontrollable factors include age and various chronic metabolic disorders, such as diabetes, hyperlipidemia, and the degeneration of the brain vascular system. The incidence of AD doubles every 5 years in the elderly people older than 65 years.<sup>17</sup> The degeneration of the brain vascular system may directly impair the memory function area, such as the pituitary gland, and cause A $\beta$  deposition.<sup>18</sup> The mechanism may be associated with apoptosis and neuronal death. However, a consensus on the relationship between plasma lipid alterations and cognitive impairment or AD development is yet to be established.<sup>19</sup> Hyperlipidemia was also considered as a risk factor for AD; however, other studies have not observed this relationship.<sup>20</sup> This discrepancy in results may be due to the differences in age, education level, and experimental conditions of the study participants.

The controllable factors include environmental and dietary influences. A healthy life style,<sup>21</sup> such as engaging in adequate exercise and social interactions and consuming balanced foods, helps maintain cognitive function and reduces the risk of AD.<sup>22</sup> Our previous study demonstrated that increased sea food intake, appropriate exercise, reading, and watching TV can protect against MCI.<sup>23</sup> Furthermore, dietary nutrients are involved in the onset and development of AD. The abundant intake of vegetables and fruits can promote antioxidant defenses and reduce oxidative injuries of the brain tissues and neurons in patients with AD,<sup>24</sup> indicating that plant phytochemicals, such as resveratrol, tea polyphenols, curcumin, and SIF, exert beneficial effects by improving brain development and maintaining brain function. Similarly, antioxidant compounds and polyunsaturated fatty acids attenuate aging and delay the regression of cognitive function, thus preventing AD onset.<sup>25</sup> There has been increasing

evidence from numerous studies suggesting that alternative dietary pathways such as dietary diversity may impact on cognitive function and the model to follow seems to be the so-called Mediterranean diet (MeDi). The dietary pattern of MeDi is characterized by abundant plant food intake in the form of vegetables, fruits, breads, other forms of cereals, beans, potatoes, nuts and seeds; fruit as the typical dessert; dairy products as cheese and yogurt; olive oil as the main source of monounsaturated fatty acids (MUFA); low-to-moderate consumption of fish resting with the proximity of the sea; fewer than four eggs consumed per week; a low-to-moderate consumption of poultry; relatively low intakes of red meat and moderate consumption of wine normally during meals.<sup>26</sup> Observational studies already suggested that diversity of foods or nutrients that take part in the MeDi (i.e., fish, rich in unsaturated fatty acids (UFA), antioxidants, such as vitamin E, carotenes; vitamin B12, folates, flavonoids and moderate alcohol) may have protective effects against dementia.<sup>27</sup>

### ***Effect of SIF on AD prevention***

AD is among the most common dementia disorders and has complex medical and social consequences. The initiating molecular event is unknown, and its pathophysiology is highly complex. However, free radical injury appears to be a fundamental process contributing to neuronal death. Increasing evidence supports the role of oxidative damage in AD pathogenesis. Several studies have demonstrated significantly increased lipid peroxidation and protein, DNA, and RNA oxidation in the vulnerable regions of the brain of patients with late-stage AD. Various compounds with antioxidant ability that attenuated A $\beta$ -induced oxidative stress have been reported to inhibit the formation and extension of  $\beta$ -amyloid fibrils.<sup>28</sup> SIF represents a series of polyphenolic compounds, and Gen is the main bioactive form. SIF protects neurons and prevents nervous system degeneration through antioxidation, anti-inflammation, and cell signaling pathways.<sup>29-32</sup> Daily SIF supplementation (116 mg) in adult males for 12 weeks has been reported to enhance their spatial memory ability.<sup>33</sup> In addition, SIF supplementation in old (menopausal) women for 6 months has improved their cognitive, attention, and planning abilities, particularly non-language-related memory.<sup>34</sup> Similar improvements were observed in 36 (menopausal) women aged 50–65 years supplemented with SIF for 12 weeks.<sup>35</sup> In addition, an animal study revealed that dietary SIF supplementation increased the plasma SIF concentrations and improved the learning, memory, and anxiety abilities. Furthermore, the spatial learning ability was improved in the rats fed with SIF diet for 16 weeks.<sup>36</sup> In addition, our group has investigated that SIF can protect the learning memory area from injury induced by continuous injections of A $\beta$ 1-40 and A $\beta$ 1-42 in

rats. These studies indicate that SIF supplementation improves cognitive function in patients or animals with AD by exerting antioxidative and antiapoptotic effects, playing an anti-inflammatory injury role, and protecting the brain vascular system. The multiple dimensions of SIF for the etiology of AD are presented in Figure 1.

### **Antioxidative effect of SIF on AD**

A $\beta$  deposition can cause ROS production in the brain tissues of patients with AD, leading to oxidative damage.<sup>37</sup> The levels of oxidative stress products, such as lipid peroxide malonic dialdehyde (MDA), and DNA oxidation products, such as 8-hydroxy deoxyguanosine (8-OHdG), in the brain are higher in patients with AD than in those without AD.<sup>38</sup> This result was further confirmed by the significant increase in MDA levels and reduction activity. However, SIF has many physiological functions, and some of its beneficial effects have been attributed to antioxidant properties. SIF contains multiple phenolic hydroxyls that react with free radicals as a hydrogen donor, thus inhibiting lipid peroxidation and thereby reducing peroxidation and increasing the activity of antioxidant enzymes in human body.<sup>39</sup> Several studies have explored the antioxidant effects of SIF. SIF can not only prevent DNA oxidative damage through free radical scavenging but also improve the activities of antioxidant enzymes in human body.<sup>40</sup> Furthermore, uric acid (UA) is the final product of purine metabolism and a water-soluble antioxidant capable of reducing cellular oxidation by inhibiting nitrite-mediated nitrification and oxidative damage caused by iron-dependent ascorbate oxidation.<sup>41</sup> In line with this, higher UA levels have been reported to be neuroprotective and associated with slower progression of AD.<sup>42</sup> Soy foods consumption contributes to the amount of dietary purine intake and thus increased serum UA levels.<sup>43</sup>

Animal studies have shown that SIF alone or in combination with folic acid (FA) can significantly improve the total antioxidant capacity and glutathione (GSH) and GSH-peroxidase (Px) levels in the serum and brain tissues of pregnant rats. They may suppress neural tube defects by inhibiting the peroxide reaction.<sup>44</sup> The hypothesis was also confirmed in the male Wistar rats model,<sup>45</sup> in which Gen reduced A $\beta$ 1-42-induced damage and 8-OHdG levels, increased the level of 8-oxoguanine DNA glycosylase, and ultimately improved the redox state.<sup>46</sup> In addition, SIF increased the GSH/glutathione disulfide (GSSG) ratio and the expression of GSH-Px and manganese superoxide dismutase (MnSOD) in the brain tissues and mitochondria. In addition, SIF can reverse nuclear factor E2-related factor 2 (Nrf2) decline and A $\beta$ -induced downstream protein heme oxygenase-1 (HO-1) expression in the brain tissue, demonstrating the antioxidant effects of SIF.<sup>47</sup> Furthermore, SIF can significantly

improve the antioxidative ability of the AD model mice induced by D-galactose, promoting nerve cell growth and improving brain function.<sup>48</sup> The antioxidative effects of SIF have also been confirmed by in vitro studies. Gen alone or in combination with FA can reverse cell vitality decline and ROS elevation caused by A $\beta$ 25-35 in the cerebral cortex nerve cells.<sup>49</sup> Gen can significantly reduce thiobarbituric acid reaction products induced by iron and increase SOD vitality activity.

In addition, Gen inhibits iron-induced lipid peroxidation in the cerebral cortex nerve cells,<sup>50</sup> reduces ROS generation, and increases MMPS, the GSH/GSSG ratio, and Nrf2 and HO-1 expression in PC12 cells.<sup>51</sup> Moreover, the astrocyte (C6 cell line) and cerebral vascular endothelial (bEND.3) cell lines supplemented with Gen have exhibited increased antioxidant activity, thus protecting cell structure integrity and function.<sup>52, 53</sup>

### **Antiapoptotic effect of SIF on AD**

Oxidative stress-induced cellular apoptosis is the main characteristic of early AD, and mitochondria play a key role in the generation and survival of nerve cells.<sup>54</sup> SIF protect nerve cells by upregulating the antiapoptotic genes and downregulating the proapoptotic genes.<sup>46</sup> Gen alone or in combination with FA downregulates caspase-3 and Bax and upregulates Bcl-2, exhibiting antiapoptotic effects.<sup>55</sup> However, the underlying molecular mechanism remains unclear. Gen may compete with the neurovirulence of A $\beta$ 25-35, exerting neuroprotective effects.<sup>51</sup> Moreover, Gen alone or in combination with FA improves the mobility of the nerve cell membrane and alleviates nerve cell DNA injury and mitochondria swelling, thus resulting in the reduction of ROS and Ca<sup>2+</sup> and inhibition of apoptosis ultimately. Similarly, FA in combination with SIF was the principal factor for preventing neural tube deformity.<sup>56</sup> SIF enhanced the in vivo antioxidant ability, and the protective effects of FA resulted in the decreased incidence of deformity.

Therefore, A $\beta$ 25-35 and A $\beta$ 1-42 could mediate the oxidative stress injury in the brain tissues and neurons of rats. SIF inhibits the oxidative injury of tissues, cells, or mitochondria and exerts neuroprotective effects, particularly in the brain tissues, cerebral cortical neurons, neurons, and astrocytes. The main mechanisms include the decreased accumulation of ROS, maintaining the balance of the GSH/GSSG oxidation–reduction system, MnSOD upregulation, the inhibition of mtDNA oxidative damage, and the upregulation of the related metabolic enzymes of mitochondria. In addition, it includes the antiapoptosis induced by oxidative damage and antioxidative damage induced by A $\beta$ 25-35.

### **Anti-inflammatory injury role of SIF in AD**

Inflammatory injuries represent another main pathological mechanism of AD and other neurodegenerative diseases.<sup>51</sup> Within the A $\beta$ -deposited and adjacent areas, strong inflammation is localized. Furthermore, inflammatory factors such as NO, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , complement proteins, and other cytokines are upregulated,<sup>57</sup> which leads to NFT production, cell death, or the accelerated apoptosis of neuron cells. A $\beta$  induces inflammation in the brain through microglial activation. Notably, patients with AD have an elevated expression of toll-like receptor 2 (TRL2) and TRL4 in the brain.<sup>58</sup> Fukata et al. have demonstrated that TLR promotes inflammation by microglia and TRL4 can trigger NF- $\kappa$ B signaling.<sup>59</sup> Therefore, TRL4/NF- $\kappa$ B plays an important role in the A $\beta$ -mediated inflammation. Various studies have elucidated the effectors, pathways, and mechanisms of the anti-inflammatory effects of SIF. Long-term users of nonsteroidal anti-inflammatory drug (NSAID) for rheumatoid arthritis treatment had a decreased risk of AD compared with their age-matched controls.<sup>60</sup> In clinical trials, the anti-inflammatory drug indometacin improved cognitive damage in mild or moderate injury,<sup>61</sup> suggesting that anti-inflammatory drug treatments can effectively prevent or alleviate AD pathogenesis.

In animal experiments, SIF reduced the concentrations of IL-1 $\beta$ , TNF-r, and iNOS and reversed A $\beta$ 1-42-mediated inflammation involved in LR2, FPR Myd88, and IKK.<sup>62</sup> Gen inhibited TNF-induced inflammation in the endothelial cells of C57BL/6 mice.<sup>63</sup> Our previous study demonstrated that A $\beta$ 1-42 increased the levels of IL-1 $\beta$  and TNF- $\alpha$  in serum and upregulated the NF- $\kappa$ B signaling genes and proteins, which led to inflammatory injuries in the brain and loss of learning and memory abilities in rats.<sup>47</sup> However, SIF treatment can reduce the levels of IL-1 $\beta$  and TNF- $\alpha$  and alleviate A $\beta$ -induced inflammatory injuries.<sup>64</sup> Moreover, SIF attenuated the gene and protein upregulation of the A $\beta$ 1-42-induced pro-inflammatory factors, namely IL-1 $\beta$  and NOS.<sup>65</sup> Apelt and Schliebs (2001)<sup>66</sup> used transgenic mice and observed an enhanced expression of IL-1 $\beta$ , IL-10, and TNF- $\alpha$  in the A $\beta$ -accumulated regions with a high number of stimulated microglia. These results indicated an inflammatory status in the brain regions with large amount of A $\beta$  deposits, which may trigger the protective responses of anti-inflammatory mechanisms. Furthermore, SIF intervention can suppress the gene expression and protein production of IL-10.<sup>67</sup>

In addition, the protective effect of SIF against A $\beta$ -mediated inflammatory damage has been demonstrated in BV2-microglial cells and C6 glial cells.<sup>67</sup> Zhou et al (2014)<sup>68</sup> and Yu et al (2013)<sup>69</sup> have confirmed the anti-inflammatory damage role of SIF in neuron cells. Gen

suppressed A $\beta$ 25-35-mediated apoptosis in C6 glial cells by attenuating TNF- $\alpha$  and IL-1 $\beta$  release and downregulating TLR4 and NF- $\kappa$ B expression.<sup>30</sup> Studies have revealed that Gen protects against A $\beta$ 25-35-mediated inflammatory damage by modulating NF- $\kappa$ B signaling in C6 glial cells.<sup>70,71</sup> In summary, SIF downregulates inflammatory factors, including IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and TGF- $\beta$ , complement proteins, and other immunogens, and consequently protects the brain and neuron cells and prevents the onset of AD by controlling NF- $\kappa$ B signaling.

### **Protective effects of SIF on the brain vascular system and AD**

Recently, microvascular pathogenesis was reported in the brain of patients with AD and exhibited a close relationship with cognitive impairment. Vascular endothelial damage is the early sign of neurodegeneration.<sup>72</sup> A systematic analysis revealed that multiple juices (strawberry or grape) protect the vascular system by mediating endothelial growth factors.<sup>73</sup> Furthermore, some dietary components such as n-3 polyunsaturated fatty acids and polyphenolic compounds in plant foods exhibited similar effects.<sup>74</sup> Studies in humans, animals, and cultured cells have confirmed that SIF exerts its protective effects against endothelial damage through antioxidant defenses, anti-inflammation, and the alteration of signaling modulators and vascular factors. SIF inhibited apoptosis in human vascular endothelial cells with ox-LDL-mediated in vitro oxidative injuries.<sup>75</sup> Moreover, a study suggested that a high SIF intake might upregulate circulating blood vascular endothelial growth factor (VEGF) and NO levels and downregulate von Willebrand factor (vWF), thus protecting against vascular endothelial damage and preventing neuronal regression.<sup>70</sup>

Our previous studies have revealed that SIF enhances endothelial progenitor cell numbers and proliferation.<sup>76</sup> SIF at a concentration of 80 mg/kg can effectively block A $\beta$ -induced endothelial oxidative damage. Moreover, SIF can downregulate the production of calmodulin (CAM) and vascular attachment molecules in the main artery of rats. In addition to its antioxidant function, SIF can elevate plasma VEGF concentrations by reducing plasma ET-1 (impairing learning memory ability) and brain MMP-9 levels. Daleprane et al (2012) reported that polyphenolic compounds can upregulate inflammatory cytokines, PDGF, and VEGF, protecting against vascular endothelial cell damage.<sup>77</sup> In addition, Andrade et al. investigated the protective effects of SIF with regard to cell attachment and confirmed that SIF downregulates CAM production.<sup>78</sup> In addition, Gen exerted protective effects against LDL-induced endothelial injuries.<sup>79,80</sup> Previously, we have demonstrated that Gen counteracts A $\beta$ 25-35-induced ROS stimulation, nitrotyrosine nitration, and GSH depletion in endothelial

cells.<sup>53</sup> By controlling the brain A $\beta$  status and transport and inhibiting Nrf2, GCLC, and PI3K expression, Gen plays an important role in brain vascular damage protection.<sup>81</sup>

In summary, SIF/Gen protects against vascular and neuronal tissue damages in the brain. The plausible mechanisms include reduction in vWF (endothelial damaging factor) levels; increase in NO (vessel-relaxing factor) and VEGF (antiendothelial injury factor) levels; activation of Nrf2/ARE signaling; regulation of the downstream production of antioxidant enzymes  $\gamma$ -GCS, HO-1, and others; maintenance of the redox status of endothelial cells; and enhancement of the total cellular antioxidant defenses.

### **Relationship between SIF and nerve synapse development**

In patients with early AD, cortical and hippocampal neural synaptic density reduction and synaptic missing can occur with disease progression, which is closely associated with the degree of cognitive impairment.<sup>82</sup> Synaptic missing is the basic characteristic of AD and decreased synaptophysin expression in the brain of patients with AD.<sup>83</sup> A $\beta$  production and glial cell proliferation can be accompanied by decreased PSD-95 levels in postsynaptic density.<sup>84</sup>

The effects of SIF on learning and memory impairment have been previously investigated in the A $\beta$ 1-42 artificial injury rat model of memory by our research group.<sup>85</sup> The results revealed that SIF can resist A $\beta$ 1-42-mediated nerve pathological changes in the synaptic structure and reverse the downregulation of synaptophysin in the rat brain synaptic molecules PSD-95 and NMDA receptors (NR1 and NR2B) and CAM-CAMKII-CREB signaling pathway disorders. Further investigation revealed that SIF can modulate the synaptic plasticity-associated proteins, such as NMDA receptors, and the CaM/CaMKII/CREB/BDNF signaling pathway to reduce A $\beta$ -induced rat neural synaptic damage.<sup>31</sup> Moreover, Gen inhibited voltage-gated Ca $^{2+}$  flow and suppressed hippocampal synaptosome by potassium chloride, demonstrating the protective effect of SIF on synapse-associated proteins.<sup>86</sup> In the A $\beta$ 25-35-mediated synaptic nerve cell damage model, Gen antagonized synaptic marker synaptophysin and PSD-95 downregulation, inhibited Ca $^{2+}$  overload, reversed the CAM-CAMKII-CREB signaling pathway disorders, and protected the sudden touch-related proteins.<sup>87</sup> Altogether, SIF exerts neuroprotective effects in synaptic function and structural plasticity by maintaining an intact synaptic structure and regulating the expression of synaptic markers, synaptic plasticity-associated proteins (NMDA, CAMKII, CREB, and BDNF), and related signal transduction factors.

### **Estrogen-like effect of SIF on AD**

An epidemiological study revealed that estrogen is related to AD.<sup>88</sup> In postmenopausal women, the decline in estrogen levels increased the incidence of AD.<sup>89</sup> Moreover, a meta-analysis demonstrated that estrogen replacement therapy reduces the risk of AD (odds ratio = 0.66, 95% confidence interval = 0.53–0.2), suggesting that estrogen prevents cognitive impairment.<sup>90</sup> However, both the Women Estrogen-Stroke Study and Women's Health Initiative study revealed that estrogen did not play a protective role and increased the incidence of stroke and dementia.<sup>91</sup>

SIF is considered as a natural phytoestrogen because of its structural similarity with estradiol, which can bind to ERs to exhibit estrogen-like effects. SIF protects the brain tissues and nerve cells mainly by exerting estrogen-like effects through ERs. In a double-blind parallel study, SIF (60 mg/d) supplementation in postmenopausal women for 12 weeks significantly improved their cognitive functions in terms of picture recalling, attention sustenance, and task planning.<sup>92</sup> In addition, dietary supplementation with SIF (110 mg/d) had favorable effects on cognitive function, particularly verbal memory.<sup>34</sup> A double-blind 2.5-year trial in 350 postmenopausal women revealed that SIF (91 mg) uptake did not affect their cognitive function but improved their visual memory ability.<sup>93</sup> Moreover, a safety assessment study reported that SIF improved cognitive function in terms of visual spatial memory and verbal fluency, and a daily SIF intake of 100 mg is considered safe.<sup>94</sup> An *in vivo* study showed that SIF-fed rats ran faster than controls in the maze test, indicating that SIF improves the cognitive function of rats.<sup>95</sup> Although several studies have investigated the effects of SIF in patients with AD, their actual role remains controversial.

### **Conclusion**

AD pathogenesis is complex, and SIF can protect the brain tissues and nerve cells by exerting antioxidant, anti-inflammatory, and antiapoptotic effects and by providing vascular endothelial protection to improve synapse function and prevent AD. Additional studies are warranted to investigate the underlying mechanisms of the antiapoptotic and estrogen-like effects of SIF on AD. Furthermore, large-scale population studies and intervention trials must be conducted to provide a highly effective theoretical basis for the prevention and treatment of AD.

At the review level, the methodological difficulty of distinguishing between different dementia outcomes and the dietary associations that needs attention when assessing the findings. Heterogeneity in associations between different dementia outcomes and dietary

effects is related to heterogeneity in research methodology. The methodological difficulties include heterogeneity of study location, dietary evaluations, short follow-up periods and diagnosis of different dementia outcomes such as multi-infarct dementia<sup>96</sup> and diabetes type 3 dementia.<sup>97</sup> Dementia is a typical disease that has a long prodromal period prior to the clinical symptoms. Dietary habits may change for physiological and psychological conditions of different dementia outcomes, it is possible that appetite modifications may occur as a result of different dementia process and the dietary patterns were acquired in later years instead of lifelong. Therefore, it is clear that some challenges face scholars in establishing a conclusive dietary association and providing precise clinical recommendations according to different dementia outcomes.<sup>98</sup>

### **CONFLICT OF INTEREST AND FUNDING DISCLOSURE**

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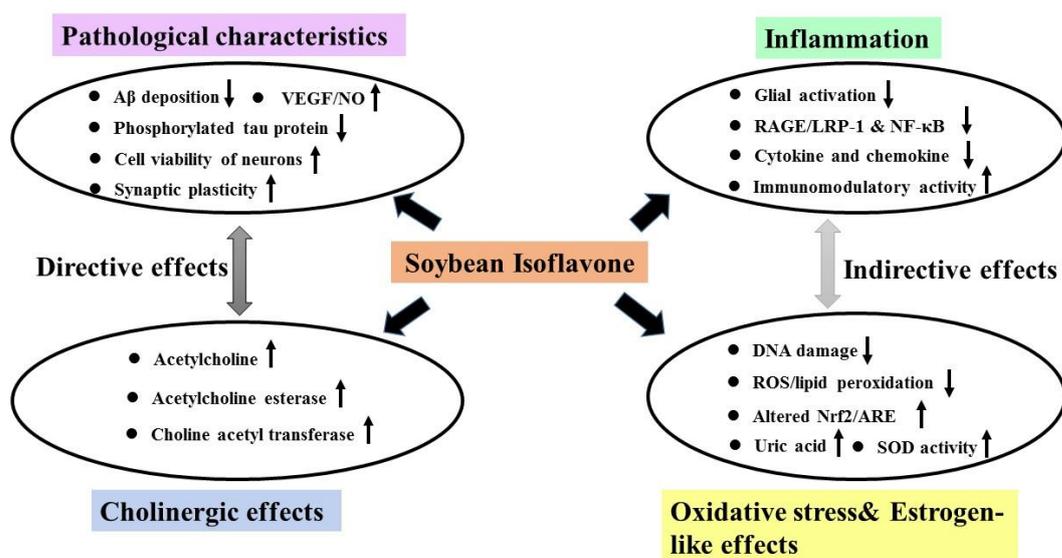
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**Figure 1.** The multiple dimensions of SIF for the etiology of AD. Abbreviations: A $\beta$ :  $\beta$ -amyloid; VEGF: vascular endothelial growth factor; RAGE: receptor for advanced glycation end products; LRP-1: low-density lipoprotein receptor-related protein-1; NF- $\kappa$ B: nuclear factor- $\kappa$ B; ROS: reactive oxygen species; Nrf-2: nuclear factor erythroid 2-related factor 2; ARE: antioxidative responsive element; SOD: superoxide dismutase