Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.36488

Resveratrol as a Neuroprotective Bridge from Blue Zone Longevity to Alzheimer's Prevention

Ruitong Liu

Portsmouth Abbey School, Portsmouth, USA
emily_liu@portsmouthabbey.org

Abstract. Alzheimer's disease is the most common type of dementia among older adults in ageing populations, and the pathological changes that occur before symptoms appear are too extensive; therefore, the focus of research has shifted from late-stage treatment to prevention. This paper investigates whether the low chronic-disease burden in Blue Zone populations can serve as a starting point for prevention-oriented research on neurodegeneration and, as a mechanistic case study, uses resveratrol. First, the literature on the Blue Zone has been evaluated as an observational, hypothesis-generating system rather than a controlled natural experiment, and the proposed path connecting peripheral inflammatory burden to central nervous system immune activity has been set up hypothetically. Next, the neuroinflammatory cascade of Alzheimer's disease is presented, including amyloid-beta and tau pathology, nuclear factor kappa B signalling, cytokine release and oxidative stress, as well as a self-amplifying feedback mechanism among these factors. Resveratrol is a known Sirtuin 1 activator that suppresses various harmful factors, such as the accumulation of amyloid and tau phosphorylation, glial cell activation, reduced antioxidant capacity, impaired insulin signalling, mitochondrial dysfunction, and so on. Although human trials have shown that resveratrol can reach the central nervous system and alter some biomarkers, there have been no corresponding cognitive benefits; instead, an unexplained decrease in brain volume and severe bioavailability limitations have occurred. Resveratrol is thus best understood as a typical representative of the all-around prevention system rather than as the cause of Blue Zone longevity or an independent treatment.

Keywords: Blue Zones, resveratrol, Alzheimer's disease, neuroinflammation, SIRT1

1. Introduction

Neurodegenerative diseases, as a whole, pose a significant threat to public health around the world today, and among them, Alzheimer's disease (AD) accounts for a large proportion of cases in older adults, making up about 60%-70% of dementia cases in this age group [1]. Global deaths from AD have more than doubled since about 1990, rising to around 1.62 million by 2019 [2], and an estimated 416 million people are currently living across the AD continuum [3]. The cost is also very high. The United States had healthcare and long-term care costs of $360 billion in 2024 alone, and they are expected to reach around $1 trillion by 2050 [4]. Chronic neuroinflammation has also been linked to other neurodegenerative diseases, and thus, inflammatory dysregulation may be a general

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DOI: 10.54254/2753-8818/2026.36488

susceptibility of the aging brain rather than a characteristic of Alzheimer's disease alone [5]. AD is also a highly urgent object for prevention-oriented research due to its large scale and extended preclinical period. Its pathological changes can accumulate silently for about ten years before any clinical symptoms appear, so by the time of diagnosis, the underlying disease process may have already progressed considerably [6].

In addition to the above mechanistic evidence, the good health and long life of the people in Blue Zones also provide an excellent epidemiological starting point for preventive research. These geographically and culturally distinct groups have longer lifespans and lower incidences of some chronic diseases than expected for the general population in the country [7]. It cannot be concluded that the lower inflammation or other reasons in the diet are the causes. At the same time, they have also raised a problem of whether the lifestyle pattern associated with a lower systemic inflammatory burden can offer neuroprotection, and whether some food components may help explain this link. First, Blue Zones have been studied as an epidemiological system, and now a path linking systemic inflammation to brain immune function has been proposed. Next, it shows the neuroinflammatory cascade in Alzheimer's disease, uses resveratrol as a mechanistic example linking dietary exposure to this path, and presents preclinical and clinical data as well as the main limitations that currently restrict its therapeutic application.

2. Blue Zones as an observational framework

The five most famous Blue Zones are Okinawa in Japan, Loma Linda in the United States, Ikaria in Greece, Barbagia in Italy, and Nicoya in Costa Rica. These geographically and culturally distinct groups have been shown to have a relatively high proportion of long-lived residents and lower incidences of chronic diseases such as cardiovascular disease, cancer and cognitive impairment [7]. However, these observations should not be considered strong evidence of causation by a shared set of behaviours leading to a longer life or reduced disease risk. These areas have different cultures and diets, migration patterns, healthcare access, social structures, and genetic backgrounds. The way to confirm a person's age or sickness and select subjects may differ by area. The above factors may confound comparisons and therefore make differences difficult to attribute to lifestyle. Therefore, Blue Zones are better viewed as an observational system for hypothesis generation rather than a controlled natural experiment to determine whether lifestyle affects inflammation and longevity.

Buettner listed nine shared lifestyle practices in the popular Blue Zone literature, referred to as the "Power 9", which include patterns of daily movement, a plant-based diet, stress reduction, a purposeful life and social connections [8]. Power 9 is descriptive and not a unified intervention tested in a controlled environment. At present, no data show that all of the nine practices, alone or together, reduce systemic inflammation. Research outside the Blue Zone framework has also shown that some of the individual components are biologically plausible. Chronic psychological stress can activate the nuclear factor kappa B (NF-κB) pathway to promote systemic inflammation, increase the expression of pro-inflammatory genes such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), and it is associated with elevated levels of these cytokines [9]. Mindfulness-based practices may also affect the immune system and inflammation [10], and plant-centered, polyphenol-rich diets have been associated with lower levels of pro-inflammatory markers in the blood, such as IL-6 and C-reactive protein (CRP) [11]. In addition, multidomain interventions that integrate diet, exercise and cognitive exercise, all of which broadly resemble the Blue Zone lifestyle profile, have also demonstrated a certain slowing of cognitive decline in randomised trials [12]. As these studies have not directly tested the Power 9 or Blue Zone populations, they only provide plausible reasons for certain lifestyle mechanisms and do not validate the entire framework.

DOI: 10.54254/2753-8818/2026.36488

Another distinction is also relevant to the resveratrol-specific case study mentioned later in this review. The Mediterranean Blue Zones (Ikaria and Barbagia) have a long-standing tradition of moderately consuming red wine in a cultural context [13]. Red wine is a food source of resveratrol [14], but the amount obtained from moderate dietary intake is much lower than the pharmacological doses used in the clinical trial mentioned later in this review [15, 16]. Alcohol carries health risks at a low level of consumption as well [17]. Resveratrol in red wine is thus employed only to provide a subject for investigation in a mechanistic case study and should not be regarded as a proposal for preventing Alzheimer's disease through alcohol consumption.

3. A proposed pathway from systemic to neural

The epidemiology does not explain the reasons for the Blue Zone pattern. Any path connecting the lifestyle practices in Blue Zones to reduced neuroinflammation remains speculative as it links two separate bodies of evidence rather than presenting a directly demonstrated causal chain. Peripheral inflammatory mediators such as IL-6 and TNF-α are now known to affect central nervous system (CNS) immune regulation and microglial priming [18]. Based on the model above, a reduced peripheral inflammatory burden over an extended period of time may also decrease basal neuroinflammation and thus limit factors that promote neurodegeneration. This model has not shown that Blue Zone lifestyles reduce AD risk through inflammation. Therefore, research is being conducted to explore the neuroinflammatory pathomechanisms of Alzheimer's disease.

4. Alzheimer's disease and the neuroinflammatory cascade

Dementia is a syndrome of acquired cognitive decline in several areas that is severe enough to interfere with daily life [19], and Alzheimer's disease is the most common cause of this. AD is defined pathologically as an extracellular accumulation of amyloid-beta (Aβ) plaques and intracellular formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein [20]. Similar NF-κB-mediated inflammatory processes have also been found in other neurodegenerative diseases [21], so the mechanisms presented below may not be exclusive to AD. Given its high incidence and the quantity of available resveratrol data, this paper will study AD.

The amyloid cascade hypothesis proposes that abnormal proteolytic cleavage of amyloid precursor protein (APP) by β- and γ-secretase enzymes produces amyloid-beta 42 (Aβ42) peptides that are prone to oligomerisation and fibrillar aggregation, and soluble oligomeric forms have now been identified as the most synaptotoxic type [22]. Tau is also abnormally hyperphosphorylated, detaches from microtubules, and forms NFTs. Accumulation of Aβ is believed to act upstream to seed tau pathology [23], and tau spread contributes to synaptic dysfunction and loss [24]. Biomarker evidence indicates that Aβ deposition precedes detectable tau pathology and neurodegeneration by more than a decade [25], showing that the disease is biologically advanced long before clinical signs occur.

Among the many paths in the larger neuroinflammatory network, one is NF-κB, a transcription factor that regulates many inflammatory genes but does not operate independently. Aβ oligomers can activate microglia through receptors such as Toll-like receptor 4 (TLR4), trigger NF-κB nuclear translocation and the subsequent production of pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-6 and TNF-α [26], and reactive astrocytes further increase the release of these cytokines [27]. Oxidative damage takes place at the same time. Activated microglia produce reactive oxygen species (ROS), Aβ itself impairs mitochondrial function, and the antioxidant system of nuclear

DOI: 10.54254/2753-8818/2026.36488

factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and glutathione (GSH) is reduced in neurodegenerative diseases [28].

This is not a single chain of consequences either. Pro-inflammatory cytokines, such as IL-1β, activate kinases that promote tau hyperphosphorylation, including glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5) [29]. NF-κB activity also promotes the expression of β- and γ-secretase to enhance amyloidogenic APP cleavage and Aβ generation [30]. Together, the above processes form a positive feedback loop that promotes neuroinflammation by Aβ and tau pathology; in turn, both proteinopathies are exacerbated independently of their initial causes.

The above feedback structure is likely why some earlier amyloid-targeting trials did not show significant benefits for cognition [31, 32]. More recently, anti-amyloid therapies such as lecanemab and donanemab have shown a modest slowing of cognitive and functional decline in early AD, but their benefits are still limited and they carry risks of amyloid-related imaging abnormalities [33, 34]. Therefore, additional targets for the next round of research include inflammation. Given that lifestyle factors can affect the degree of inflammation, they are also loosely connected to the Blue Zone pattern mentioned above and thus serve as a model for research on resveratrol.

5. Resveratrol as a mechanistic example

Rather than asking if a single food can provide the protective effect of Blue Zones, this review will use resveratrol as a specific mechanistic case. Resveratrol is a stilbene polyphenol that occurs in grape skins, red wine, berries and some teas [14, 35]. It is relevant because the reported molecular functions overlap with several of the pathways mentioned above, such as inflammatory signals, oxidative stress, amyloid and tau pathology, insulin signalling and mitochondrial dysfunction [36]. This overlap provides biological plausibility but does not show that resveratrol explains Blue Zone longevity or prevents AD in people.

Resveratrol acts as a positive regulator of the Sirtuin 1 (SIRT1) pathway to suppress NF-κB signalling and reduce the expression of pro-inflammatory factors such as TNF-α and matrix metalloproteinase-9 (MMP-9) [15, 26]. Liu and others [37] put forward a model of four pathways for resveratrol action. The above are the pathways: (1) reduce Aβ plaques and NFT deposits; (2) inhibit inflammation and oxidative stress; (3) improve insulin sensitivity and glucose metabolism while promoting mitochondrial and autophagy homeostasis; (4) promote neuroprotection and neurogenesis.

Resveratrol may promote the degradation of Aβ by increasing the level of neprilysin (NEP), an Aβ-degrading enzyme, in a lipopolysaccharide (LPS)-induced mouse model of cognitive impairment [38]. Resveratrol also inhibits aggregation into larger fibrils and thus reduces the extent of aggregation-induced cytotoxicity [39]. Resveratrol also inhibits tau hyperphosphorylation by activating SIRT1 and suppressing the expression of Midline-1 (MID1) [40, 41].

Resveratrol suppresses NF-κB-related inflammatory signals and lowers IL-1β, IL-6, and TNF-α in activated microglial and astrocyte models on the inflammatory and oxidative fronts [26, 42]. It also mitigates astrocyte activation and gliosis [43], while raising GSH levels and reducing oxidative and nitrosative stress in hippocampal astrocytes [42]. Resveratrol reduces TNF-α, IL-1β and IL-6 in LPS-stimulated glial cultures of hippocampal astrocytes, and decreases both prostaglandin E2 (PGE2) production and free-radical generation in primary rat microglia [42, 44]. Together, these results are in line with the same anti-inflammatory hypothesis of the Blue Zone lifestyle more broadly.

Current evidence suggests that resveratrol may also support neuronal survival by improving insulin signaling and mitochondrial biogenesis, via activation of phosphoinositide 3-kinase

DOI: 10.54254/2753-8818/2026.36488

(PI3K)/protein kinase B (AKT) and AMP-activated protein kinase (AMPK) signaling and inhibitory phosphorylation of GSK-3β [37, 42, 45, 46]. The above may protect mitochondria and energy homeostasis in AD brain cells, reduce oxidative stress, and suppress inflammation.

Resveratrol may also promote neuroprotection via SIRT1-dependent pathways to increase the expression of hippocampal brain-derived neurotrophic factor (BDNF) and improve cognitive function in animal models [47], as well as enhance hippocampal neurogenesis in older rats [48]. The above effects may be influenced by the dose, model and physiological conditions, so they should be regarded as examples of biological plausibility rather than confirmed clinical efficacy.

6. Clinical translation

6.1. Clinical evidence

Human evidence of resveratrol is relatively scarce and, thus, more cautious than preclinical studies indicate. Across 17 randomised controlled trials of metabolic and inflammatory disorders, a meta-analysis has found that resveratrol supplementation reduces circulating TNF-α and high-sensitivity C-reactive protein (hs-CRP), but its effect on IL-6 has not reached statistical significance [49]. This shows that resveratrol may have an effect on the body's inflammation in people; however, it does not yet establish a direct therapeutic effect on AD.

The two AD-specific trials are more direct but still not conclusive. In the larger Phase 2 trial with 52 weeks and 119 subjects, the high-dose resveratrol was increased gradually from 500 mg once a day to 1000 mg twice a day. Resveratrol was found in both the blood plasma and cerebrospinal fluid (CSF); thus, it could cross the blood-brain barrier, reach the CNS, and generally had good tolerability [16]. Plasma and CSF levels of amyloid-beta 40 (Aβ40) in the placebo group decreased over 52 weeks, but resveratrol treatment did not show this decrease. However, the actual effect of this difference is not known, and it should not be assumed that the disease has progressed slowly. The same trial did not find any change in CSF Aβ42, CSF tau, phosphorylated tau at threonine 181, hippocampal volume or any of the clinical cognitive tests. Resveratrol treatment was also associated with significantly greater whole-brain volume loss, and the authors themselves described this as a paradox; therefore, it became a problem of safety and interpretation [16].

A smaller 52-week trial of 30 people tested 500 mg of resveratrol daily and showed a similar biomarker pattern [15]. Aβ40 levels were relatively unchanged after treatment, and this result was also not clearly indicative of clinical benefit. CSF MMP-9 is a protein that promotes blood-brain barrier disruption and neuroinflammation, and after treatment, it decreased by 46%. Although this result is consistent with a possible biological effect on neuroinflammatory pathways, it does not show restored blood-brain barrier integrity or clinical improvement. A larger brain-volume loss occurred in the resveratrol group again. Similar volume changes have been reported in other amyloid-targeting trials [31, 32, 50], but these comparisons have neither explained nor reduced the finding. The reasons for this have not been determined.

6.2. Limitations and future directions

In short, the above clinical data show that resveratrol has biological activity, is brain-penetrant and relatively safe at high doses, but its therapeutic effect has not been verified. Changes in inflammatory markers or Aβ40 levels do not necessarily lead to measurable cognitive improvement, and both trials were short compared with the actual time course of neurodegenerative changes. A 52-week period may be too short to see any changes in a slow-progressing disease. An extended study

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of the clinical data also reached the same cautious conclusion. Therefore, published evidence does not currently support recommending resveratrol supplementation specifically for the prevention or treatment of AD, although preclinical findings are still promising enough to justify further human trials [51].

Delivery is also a relatively far-reaching problem. Poor oral bioavailability and rapid metabolism limit the clinical effects of resveratrol [52-54]. Doses of around 1 g/day or more have been associated with mild-to-moderate gastrointestinal side effects in most of the subjects, thus limiting further feasible dosing [55]. Therefore, other delivery methods have been explored, such as solid lipid nanoparticles, micelles and liposomes; these nanoparticle carriers have shown improved blood-brain barrier penetration and brain accumulation in preclinical studies [56], but whether they can be translated into effective treatments for humans has yet to be determined.

Finally, the Blue Zone framework imposes an interpretive limit on all the above research. The longevity of these groups is the result of numerous reasons, such as the environment, lifestyle and genetics; diet is only one factor and resveratrol is only one component in the diet. Given the complexity of the web of confounding factors, it is challenging to determine how much each element of this network contributes; thus, specific evidence for resveratrol alone, rather than for polyphenol-rich diets or anti-inflammatory lifestyles in general, has been lacking.

7. Conclusion

Resveratrol is one such biologically plausible example of how a wide-ranging, lifestyle-induced reduction in systemic inflammation, the kind that occurs in the Blue Zone population, may theoretically lead to a lower risk of Alzheimer's disease at the molecular level. Across preclinical models, it affects Aβ and tau pathology, NF-κB-mediated inflammation, antioxidant defence systems, SIRT1-dependent signalling and mitochondrial homeostasis. Human trials further confirm it can enter the CNS and shift selected biomarkers. However, these biological effects have not shown consistent cognitive or disease-modifying advantages, and although the evidence base is relatively promising, it does not currently support strong claims for or against its clinical utility.

Therefore, resveratrol should be regarded as a representative example within the entire system of prevention and not as a single cause for extended life in Blue Zones or an independent treatment for AD. Its strongest current role is as a promising part of a comprehensive system that combines a lower-inflammation, low-risk lifestyle pattern, as first proposed by the Blue Zone population that inspired this review. Future research should focus on improving formulations, providing stronger justifications for dosing, earlier intervention, and extended trials with clinically significant results before its place in the above framework as either an effective add-on or a minor contributor can be reliably determined.

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