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Modifying the diet and gut microbiota to prevent and manage neurodegenerative diseases

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Abstract: The global prevalence of Alzheimer’s disease and Parkinson’s disease is steadily increasing due to the aging population. The lack of effective drugs against these neurodegenerative disorders makes it imperative to identify new strategies for their prevention and treatment. Recent studies have revealed that harnessing the power of the gut microbiota through modification of diet may be a valuable approach for reducing the risk, modulating the symptoms, and ameliorating the pathophysiological aspects of neurodegenerative diseases. Consuming specific dietary components can alter the prevalence of bacterial communities within the gut to a healthy enterotype, which can influence the production of beneficial metabolites by microbiota. This article focuses on several dietary components, which have been demonstrated to affect the gut microbiota–brain axis and therefore could lead to attenuation of specific pathological processes in neurodegenerative diseases. Published evidence indicates that fermented foods, including kefir, and foods that are high in bioactive polyphenols and complex carbohydrates, such as grapes, pomegranates, and seaweed, may be effective at reducing neuroinflammation, oxidative stress, neurotransmitter dysfunction, and neuronal death associated with Alzheimer’s and Parkinson’s diseases. Even though experimental evidence supporting the protective properties of the above dietary components in these diseases is emerging, it is evident that further human clinical studies are required to conclusively establish the benefits of any suggested dietary interventions. The translational potential of such research is illustrated by the clinical success of the recently developed Alzheimer’s

drug, GV-971, which is a seaweed derivative that works by modulating the gut microbiota–brain axis.

Keywords: grapes; gut–brain axis; kefir; microbiome; pomegranate; seaweed.

Introduction

Due to the rapidly aging worldwide population, the prevalence of neurodegenerative diseases has gradually increased over the past few decades reaching epidemic levels (Brayne and Miller 2017; Milo and Kahana 2010). Although many advances have been made to understand the complex mechanisms underlying their pathogenesis, neurodegenerative disorders such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) remain incurable (Brayne and Miller 2017; Dorsey et al. 2007; Ferri et al. 2005; Scheltens et al. 2021). Therefore, identifying novel approaches to prevent the onset, ameliorate symptoms, and delay the progression of AD and PD is imperative to improve the quality of life in elderly populations.

Recent evidence indicates that the gut microbiota can significantly affect the overall health of humans. Diet modifications, such as limiting meat and dairy consumption and increasing the intake of fruits and vegetables, as well as fermented foods, have been shown to shift the gut microbiota to a healthy enterotype and reduce the risk of major chronic diseases such as cancer, cardiovascular disease, and type II diabetes mellitus (Schulze et al. 2018; Wastyk et al. 2021). Research efforts investigating the impact of diet on the gut microbiota have been made possible by advanced sequencing technologies which identify various communities of bacteria residing in the gut of healthy individuals and subjects affected by various diseases. A meta-analysis of sequencing data obtained from various gut bacterial studies of healthy individuals reveals several trends; regardless of ethnicity and geographical location, healthy gut microbiota have the highest abundance of the phyla Firmicutes and Bacteroidetes. The phyla Actinobacteria and Proteobacteria are also found in great abundance. Actinobacteria, specifically Bifidobacterium, are often found in probiotics and play an important role in maintaining a healthy gut. Although Actinobacteria contribute significantly to a

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healthy gut microbiota, they are less abundant than Firmicutes and Bacteroidetes. Following Actinobacteria, Proteobacteria are the next most prevalent phylum of bacteria in the healthy gut microbiota (Mobeen et al. 2018).

While there is an abundance of studies linking diet and gut microbiota to the etiology of nonintestinal diseases, limited information is available about the effects of diet on the gut microbiota–brain axis throughout the progression of neurodegenerative disorders (Anand et al. 2015; Jalilpiran et al. 2020; Ley et al. 2014); however, signaling between the gut and the brain has been shown to play an active role in the pathogenesis of these diseases (Sampson et al. 2016). Gut microbiota composition and decreased microbial diversity have been linked to AD and PD etiology (Kesika et al. 2021; Yemula et al. 2021). The purpose of this article is to illustrate the potential of several foods to modify the risk, progression, and severity of neurodegenerative diseases. The ability of these foods to modulate the composition and metabolic activity of gut bacterial communities or to be converted into bioactive compounds by metabolic processes of gut microbes is discussed. This article focuses on studies that are pertinent to the link between a number of bioactive dietary compounds, gut microbiota, and neurodegenerative diseases and is limited to discussing AD and PD.

Although AD and PD have differing etiologies and disease mechanisms, they display several overlapping symptoms and pathophysiological features. AD is characterized by the deposition of neurotoxic amyloid-beta ($A\beta$) and tau protein aggregates in the brain, whereas clinically, patients present with progressive dementia due to cortical and hippocampal atrophy (Kowalski and Mulak 2019; Scheltens et al. 2021). The hallmark features of PD include the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the development of Lewy bodies consisting of α -synuclein. Clinically, PD patients present with motor symptoms, such as tremors and bradykinesia, and nonmotor symptoms, including gastrointestinal and olfactory dysfunctions, which often emerge prior to the onset of motor disturbances (Smith and Parr-Brownlie 2019). A shared pathophysiological feature of both AD and PD is chronic neuroinflammation, which results from adverse activation of the neuroimmune system (Bjelobaba et al. 2017; Kowalski and Mulak 2019; Wang et al. 2015b). When microglia, the resident immune cells of the brain, become chronically activated by stimuli such as the disease-associated $A\beta$ or α -synuclein, they secrete an abundance of inflammatory mediators and neurotoxins that promote neurodegeneration (Hoenen et al. 2016; Mandrekar-Colucci and Landreth 2010). Apoptosis of

neurons caused by the buildup of neurotoxins leads to impairments in memory, cognition, and motor function (Han et al. 2017; Yasuda et al. 2013). Another hallmark common to AD and PD is mitochondrial dysfunction, which is associated with damage to mitochondrial DNA (mtDNA) and increased oxidative stress within neurons, resulting in metabolic dysregulation and altered neurotransmitter production (Cenini et al. 2019).

AD and PD are multifaceted neurological disorders, making them challenging to diagnose and treat (DeMaagd and Philip 2015; DeTure and Dickson 2019). The blood–brain barrier (BBB) represents an additional obstacle for developing effective therapies because it is poorly penetrated by most drugs. Furthermore, most of the drugs currently used to relieve symptoms of these diseases cause an abundance of unwanted effects at therapeutic doses, such as gastrointestinal symptoms, dizziness, and fatigue (He et al. 2018; Szeto and Lewis 2016). Therefore, until a disease-modifying treatment option becomes available, identifying new nonpharmacological interventions that can be used for disease prevention and management of symptoms is critical. This article covers four dietary components that have been found to modulate both clinical manifestations and specific pathophysiological features of AD and PD. Altering the diet to include grapes, pomegranates, kefir, and seaweed may be an effective dietary approach to prevent and modulate the progression of these neurodegenerative diseases.

Methods

Studies published between 1997 and 2022 are cited in this article, with more than half of these articles appearing during the last five years. The initial search was performed within Ovid Medline, PubMed, and Google Scholar databases using the following keywords: Alzheimer's disease, neuroinflammation, diet, microbiota, microbiome, Parkinson's disease, neurodegenerative disease, gut–brain axis, gut, microglia, astrocytes, and glia. Abstracts of the retrieved research articles were screened, and full versions of the relevant articles were acquired. Furthermore, pertinent articles were identified by reviewing the reference lists of cited publications.

Grape products

The health benefits of consuming grapes and grape products have been an area of interest in health science research for many decades. Grape products have protective effects against coronary heart disease, cancer, and type 2 diabetes mellitus (Rasines-Perea and Teissedre 2017;

Singh et al. 2015). These benefits are believed to be a result of the high concentration of antioxidant and anti-inflammatory polyphenols found in the seeds, skin, and pulp of the fruit (Nuttall et al. 1998).

Bioactive compounds and metabolites

Animal studies have demonstrated that gut microbiota are key metabolizers of various grape polyphenols. For example, the coadministration of antibiotics with a grape-derived bioactive dietary polyphenol preparation consisting of grape seed polyphenol extract, concord grape juice, and resveratrol significantly reduces the plasma concentration of phenolic products in mice (Frolinger et al. 2019). Catechin and epicatechin are two major grape polyphenols that are extensively fermented by gut microbes, forming highly bioactive and bioavailable metabolites (Carry et al. 2018). Specific gut bacteria, such as *Bacteroides ovatus* in the phylum Bacteroidetes, are responsible for producing 3-hydroxybenzoic acid (3-HBA) and 3-(3'-hydroxyphenyl) propionic acid (3-HPPA) by metabolizing grape catechins and epicatechins (Ho et al. 2019; Zhao et al. 2019). Oral administration of grape seed-derived polyphenol extract for 11 days increases the concentration of 3-HBA and 3-HPPA in rat brain tissue, indicating that these metabolites can cross the BBB. The same microbiota-derived metabolites interfere with the assembly of A β peptides into neurotoxic aggregates and inhibit the formation of α -synuclein fibrils *in vitro*, demonstrating their potential to act as neuroprotective agents (Ho et al. 2019; Wang et al. 2015a). The formation of A β plaques and α -synuclein fibrils in the brain are pathophysiological features of AD and PD, respectively. Because 3-HBA and 3-HPPA cross the BBB, altering the diet to include grape products and to facilitate the growth of specific gut bacteria, which produce these metabolites, could inhibit the formation of pathological protein structures in the brain (Ho et al. 2019; Pridridge 2009).

Whole grape products

Whole grape products have been shown to modulate the human gut microbiota. For example, the daily consumption of whole grape powder for 4 weeks increases the alpha diversity index of the gut microbiome and alters the abundance of specific bacteria such that the relative abundance of the phylum Verrucomicrobia and the genera *Akkermansia*, *Flavonifractor*, and *Lachnospiraceae* increases, whereas that of the genera *Bifidobacterium* and *Dialister* decreases (Yang et al. 2021). However, only limited studies have been

conducted to investigate whether the consumption of grape products benefits individuals diagnosed with possible or probable AD or PD, and the data obtained by these studies are often contradictory (Vislocky and Fernandez 2010). A mouse model of stress is characterized by elevated brain mRNA levels of the proinflammatory cytokines interleukin (IL)-6 and tumour necrosis factor α (TNF- α). The pretreatment of animals with a polyphenol-enriched grape juice for 5 days prior to the induction of stress causes the return of IL-6 and TNF- α mRNA levels to those seen in unstressed animals. The expression of NADPH oxidase 2 and heme oxygenase 1 genes that are upregulated in oxidative stress are also reduced to near-normal levels in stressed animals treated with grape juice, indicating a beneficial effect of this treatment on the oxidative stress response (Bobadilla et al. 2021). Alleviating oxidative stress in the brain could decrease the death of dopaminergic neurons (He et al. 2020), as well as inhibit the misfolding of A β and α -synuclein (Abramov et al. 2020).

Human research demonstrates that the consumption of whole grape products improves cognition. A study involving elderly persons with mild cognitive impairment reveals that the daily consumption of grape powder preserves brain metabolic activity. Participants who consume the grape formulation show no significant decline in brain metabolism, whereas subjects who are given a placebo display a significantly reduced metabolic activity in the left superior posterolateral temporal cortex and right posterior cingulate cortex (Lee et al. 2017). Similarly, another study indicates that elderly adults who consume red wine daily have improved cognitive performance with benefits increasing in a dose-dependent manner up to 75–100 ml of wine per day, when compared to individuals who do not drink wine (Nurk et al. 2009).

Grape seed extract

Concentrated grape seed extracts provide a possible means of achieving more potent effects when compared to the whole fruit. In a scopolamine-induced rat model of AD, pretreatment and cotreatment with grape seed oil positively affect spatial memory and brain acetylcholine levels, suggesting its neuroprotective activity. Learning and memory of rats administering grape seed oil have improved by 20%, according to the Morris water maze test (Berahmand et al. 2020). Protective effects of the grape seed extract are also observed in an *in vitro* rotenone-induced model of PD. Rotenone reduces the viability of human SH-SY5Y-derived neuronal cells by 60% and upregulates the production of intracellular reactive oxygen species (ROS) in these cells.

Treatment with liposomes containing a grape seed and skin extract after rotenone administration rescues the neuronal cell viability and reduces the intracellular ROS production to control levels (Marino et al. 2021). Similar benefits are observed in a 6-hydroxydopamine (6-OHDA) animal model of PD (Ben Youssef et al. 2021). The intraperitoneal administration of a grape seed and skin extract before 6-OHDA insult increases the survival of dopaminergic neurons in the SNpc by 50% and results in a complete rescue of the motor function of mice evaluated using the open-field test. The accompanying *in vitro* investigations identify reduced neuronal apoptosis through inhibition of the caspase-3 pathway, downregulation of the proinflammatory nuclear factor (NF) κ B signaling, and decreased ROS production by dopaminergic neurons as the candidate mechanisms responsible for the beneficial effects of this extract (Ben Youssef et al. 2021). Thus, grape seed extract exhibits several distinct neuroprotective properties.

Resveratrol

Resveratrol is another health-promoting grape polyphenol, which has been suggested to be protective against obesity, type II diabetes, and cardiovascular disease (Pannu and Bhatnagar 2019; Springer and Moco 2019). This polyphenol is found in highest concentrations in the seeds and skin of grapes (Li et al. 2006). Resveratrol is a small and lipophilic molecule, which allows it to pass through the BBB (Turner et al. 2015) and makes it suitable for targeting CNS pathologies.

Modulation of gut microbiota

Resveratrol is rapidly broken down in the gut, blood, and peripheral tissues and is dependent on gut microbiota for increasing its bioavailability and therapeutic effectiveness (Chaplin et al. 2018). *Bifidobacterium infantis* and *Lactobacillus acidophilus*, of the phyla Actinobacteria and Firmicutes, respectively, are two gut bacteria that can form resveratrol by metabolizing its precursors, such as piceid found in grape juice (Basholli-Salih et al. 2016; Theilmann et al. 2017). In addition, gut bacteria hydrolyze glucuronate and sulfate conjugates of resveratrol back to unconjugated resveratrol, facilitating its enterohepatic circulation and increased bioavailability (Pannu and Bhatnagar 2019; Springer and Moco 2019).

The bioactivity of resveratrol is well-established; however, its metabolites are also responsible for many of the beneficial effects of this polyphenol. For example, *in*

vitro fermentation of fecal bacteria with resveratrol-3-*O*-sulfate, a major metabolite of resveratrol, facilitates the growth of *Lactobacillus reuteri* and *Lactobacillus intestinalis*. Furthermore, resveratrol-3-*O*-sulfate improves intestinal barrier integrity in lipopolysaccharide (LPS)-treated Caco-2 cells, a model of the intestinal epithelial barrier, as shown by upregulated mRNA expression of tight junction proteins such as occludin, zonula occludens (ZO)-1, claudin-1, and claudin-4 (Zhang et al. 2021). Animal studies have demonstrated that this metabolite, as well as another major product of resveratrol metabolism, *trans*-resveratrol-3-*O*-glucuronide, is found in the brain less than 1 h after oral administration of resveratrol, confirming that these compounds can cross the BBB (Menet et al. 2017). Resveratrol metabolites also display some of the same biological activities as resveratrol including anticancer and antiestrogenic effects (Aires et al. 2013; Ruotolo et al. 2013); thus, administering resveratrol and increasing its metabolism by gut microbiota could have protective effects on brain functions.

Effects on short-chain fatty acids

Animal studies of cardiovascular disease, obesity, and insulin resistance have shown that the consumption of resveratrol can modify the gut microbiota by decreasing the abundance of pathogenic bacteria and increasing the abundance of short-chain fatty acid (SCFA)-producing bacteria. Due to its ability to modulate the composition of the gut microbiota, resveratrol demonstrates beneficial effects on body weight and metabolism (Bird et al. 2017; Zhou et al. 2019). SCFAs have also received attention for their anti-inflammatory and antioxidant effects in the brain. A recent study identifies that SCFAs produced by gut bacteria regulate select microglia functions *in vitro*, such as inhibiting the immune-induced production of proinflammatory mediators TNF- α , IL-1 β , and monocyte chemoattractant protein (MCP)-1, and decrease the production of cytotoxic ROS by human monocytic THP-1 cells and myelomonocytic HL-60 cells, respectively, used as models of human microglia. Selective SCFAs also inhibit the phagocytic activity of THP-1 microglia-like cells (Wenzel et al. 2020). The SCFAs produced in the gut can be detected in serum and can pass through the BBB, making them a candidate of neuroprotective agents (Bachmann et al. 1979; Cummings et al. 1987; Dalile et al. 2019). Therefore, increasing the abundance of SCFA-producing bacteria may be one of the mechanisms leading to attenuated inflammatory and oxidative stress responses after consumption of resveratrol-containing foods.

Candidate mechanisms of action

Advances have been made to understand the mechanisms through which resveratrol achieves its broad spectrum of beneficial effects. The accumulation of abnormal protein aggregates and injured mitochondria in the brains of AD and PD patients is a widely recognized pathological feature of these diseases. Oxidative stress caused by injured mitochondria can initiate the production of misfolded proteins, including A β and α -synuclein, which promote inflammation in the brains of AD and PD patients leading to neurodegeneration. Therefore, enhancing the clearance of injured mitochondria and anomalous proteins may mitigate the pathological features of these diseases (Lezi and Swerdlow 2012; Sweeney et al. 2017; Wu et al. 2011). Resveratrol induces neuronal autophagy through the activation of adenosine monophosphate (AMP)-activated protein kinase/sirtuin-1 (AMPK/SIRT1). Studies establish that the activation of this pathway leads to the clearance of injured mitochondria and misfolded proteins including A β and α -synuclein, identifying a potential mechanism through which resveratrol may reduce neuroinflammation in AD and PD (Li et al. 2018; Wu et al. 2011).

Peroxisome-proliferator-activated receptor gamma coactivator (PGC)-1 α is a transcription coactivator that is involved in mitochondrial biogenesis and energy metabolism. The downregulation of brain PGC-1 α levels has been reported in AD and PD and is associated with mitochondria and synapse dysfunction, oxidative stress, and cell damage (Shin et al. 2011; Sweeney et al. 2017). The expression of PGC-1 α can be induced by resveratrol indirectly through the AMPK/SIRT1 pathway. For example, culturing PD patient-derived fibroblasts with resveratrol rescues mitochondrial function through activation of the AMPK/SIRT1/PGC-1 α pathway. Resveratrol also increases the mRNA expression of several PGC-1 α gene targets, including mitochondrial transcription factor A, and cytochrome *c*, resulting in improved oxidative phosphorylation capacity of mitochondria and reduced ROS production (Ferretta et al. 2014). Furthermore, Katsouri et al. (2016) demonstrate that the increasing human PGC-1 α expression in transgenic AD mouse models reduces A β deposition and improves memory and cognitive functions. Results from the novel object recognition test show that transgenic AD mice, which also overexpress PGC-1 α , spend approximately 25% more time exploring new objects compared to familiar objects; meanwhile, control animals expressing lower PGC-1 α levels explore novel objects 4% more than familiar objects. This indicates that upregulation of PGC-1 α is one of the mechanisms through which resveratrol may ameliorate AD pathology (Katsouri et al. 2016).

In mouse models of accelerated aging, resveratrol restores cognitive and neuromuscular functions to levels comparable with those seen in aging-resistant mice. Compared to untreated animals, mice that are administered resveratrol by intragastric gavage score approximately two to four times better in the Morris water maze test for learning and memory and the tightrope test for neuromuscular coordination and sensorimotor capacity. These effects are associated with increased antioxidant activity in the whole-brain homogenates, including upregulated superoxide dismutase mRNA and enzymatic activity, increased glutathione peroxidase (GSH-Px) activity, and decreased malondialdehyde (MDA), a product of lipid peroxidation. In addition, the percentage of mtDNA deletions is reduced, indicating that resveratrol protects mitochondria from DNA damage inflicted by oxidative stress (Liu et al. 2012). Although aging and neurodegenerative disease are two different processes, senescence-accelerated mouse models can offer important insights into the contribution of oxidative and inflammatory stress to the degeneration of mitochondria and decline in cognitive functions in older adults living with AD and PD (Heng et al. 2017).

Resveratrol may also act by modulating the expression of proteins that regulate apoptotic processes involved in AD and PD. A study using rat PC12 neuronal cells shows treatment with the parkinsonian toxin 1-methyl-4-phenylpyridinium ion (MPP⁺) results in oxidative stress, cell death, and an associated increase in the ratio of proapoptotic B-cell lymphoma (Bcl)-2-associated X protein (Bax) to anti-apoptotic Bcl-2 protein. The pretreatment of neuronal cells with resveratrol before the addition of MPP⁺ significantly increases their survival rate and restores the Bax to Bcl-2 protein ratio to control levels. Resveratrol also inhibits the cytosol to nucleus translocation of apoptosis-inducing factor and the release of apoptosis-inducing cytochrome *c* from mitochondria (Bournival et al. 2009).

Some of the neuroprotective effects of resveratrol could be mediated by its interaction with astrocytes, which support a broad range of neuronal functions (Linnerbauer et al. 2020). When added to rat neuron–astrocyte cocultures, resveratrol increases the number of dopaminergic neurons and neurites and upregulates dopamine uptake. Since these beneficial effects are not observed in neuron monocultures or neuron–microglia cocultures, they could be due to astrocytes releasing neurotrophic factors including brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). When resveratrol is coadministered to the cell culture with anti-BDNF and anti-GDNF antibodies, the protective effects are no longer observed (Zhang et al. 2012). Altered dopamine

metabolism and decreased neurotrophin levels are associated with the progression of PD (Masato et al. 2019; Sampaio et al. 2017); therefore, resveratrol could be used to correct these abnormalities.

Resveratrol may also decrease microglia-mediated neurotoxicity. When murine BV-2 microglia are pretreated with resveratrol prior to immune stimulation with the bacterial endotoxin LPS, they secrete lower levels of inflammatory mediators, including IL-6, IL-1 receptor antagonist (IL-1ra), IL-27, macrophage colony-stimulating factor, MCP-1, MCP-5, and TNF- α compared to cells exposed to LPS only. These protective effects of resveratrol are due to the inhibition of toll-like receptor (TLR)4/TIR-domain-containing adaptor-inducing interferon- β leading to attenuated NF κ B activity (Capiralla et al. 2012). TLR4, when stimulated by A β or other endogenous damage-associated molecular patterns, mediates inflammatory responses throughout the brain, and its overactivation has been associated with neuroinflammation in neurodegenerative diseases such as AD and PD (Leitner et al. 2019). Capiralla et al. (2012) further demonstrate that the pretreatment of the RAW 264.7 macrophages with resveratrol inhibits the fibrillar A β -triggered activation of signal transducer and activator of transcription (STAT)1 and STAT3, phosphorylation of NF κ B inhibitor alpha (I κ B α), and TNF- α and IL-6 secretion. Another study shows that pretreatment with resveratrol prior to rotenone administration attenuates murine BV-2 microglia activation. Resveratrol inhibits the rotenone-induced production of ROS, MDA, IL-6, IL-1 β , and TNF- α (Sun et al. 2021). The neuroprotective effects of resveratrol are also confirmed in the amyloid precursor protein (APP)/presenilin 1 (PS1) mouse model of AD. Oral administration of resveratrol for 15 weeks before the onset of amyloidosis leads to smaller A β plaques and less microglial activation compared to mice fed a diet not supplemented with resveratrol (Capiralla et al. 2012). Reducing microglia-mediated neuroinflammation and the deposition of A β plaques, along with decreasing oxidative damage and modifying apoptotic and neurotoxic processes, have been suggested as potential therapeutic strategies in AD and PD (He et al. 2020; Wang et al. 2015b).

Human clinical studies

The beneficial effects of resveratrol in the periphery are well-established; however, whether resveratrol is protective against neurodegenerative diseases remains unclear. Even though animal and *in vitro* studies indicate neuroprotective effects of resveratrol in AD and PD models (Meng et al. 2020), very limited human clinical studies have been performed, providing only preliminary evidence for its

effectiveness in modulating neurodegenerative diseases (Moussa et al. 2017; Turner et al. 2015).

Clinical trials indicate that resveratrol improves the biomarkers of AD and decreases neuroinflammation in patients living with mild to moderate AD (Moussa et al. 2017; Turner et al. 2015). Oral administration of resveratrol for 52 weeks stabilizes the decline in plasma and cerebrospinal fluid (CSF) A β 40 compared to the placebo group (Turner et al. 2015). Moussa et al. (2017) report a similar stabilizing effect for CSF A β 40 as well as A β 42 following the administration of resveratrol for the same time period. Since the decreased plasma and CSF levels of A β 40 and A β 42 are associated with cognitive decline in AD (Seppälä et al. 2010), the altered A β trajectories indicate that resveratrol treatment may slow the progression of the disease process (Moussa et al. 2017). Furthermore, the treatment with resveratrol significantly reduces CSF levels of matrix metalloproteinase 9, an indicator of BBB damage that is associated with neuroinflammation. This observation indicates that resveratrol may improve the BBB integrity and limit the influx of inflammatory mediators into the brain (Fourati et al. 2020). The neuroprotective effects of grape products discussed in this section are summarized in Table 1.

Pomegranate products

Pomegranate products have beneficial clinical effects in diverse human pathologies including cancer, diabetes, obesity, and cardiovascular disease (Banihani et al. 2014; Bassiri-Jahromi 2018; Eghbali et al. 2021; Hosseini et al. 2016). A high content of bioactive polyphenols in pomegranate products is suggested to be responsible for their favorable effects in these peripheral diseases (Al-Harbi et al. 2021; Fourati et al. 2020); however, only few experimental and clinical studies have explored the neuroprotective effects of pomegranate products in neurodegenerative disease (DaSilva et al. 2019).

Modulation of gut microbiota

Consumption of pomegranates has been shown to support gut microbiota richness in rodents due to the prebiotic functions of polyphenols in the pomegranate fruit (Sorrenti et al. 2019); however, Mosele et al. (2015) demonstrate that the daily consumption of pomegranate juice by healthy volunteers does not alter the human fecal bacteria community significantly, but rather changes the abundance of specific bacterial metabolites present in the collected

Table 1: Potentially protective biological activity of grape products in neurodegenerative diseases.

Study type	Model	Treatment	Main findings	Reference
<i>In vitro</i>	Rotenone-treated human SH-SY5Y-derived neurons	Rotenone (100 μ M) for 24 h, followed by liposomes containing a grape seed and skin extract (400 μ g/ml) for 48 h	Treatment with liposomes rescues neuronal cell viability Reduces intracellular ROS production	Marino et al. (2021)
	6-OHDA-treated primary murine midbrain dopaminergic neurons	Grape seed and skin extract (500 or 1000 μ g/ml) for 6 h prior to 6-OHDA insult	Reduces apoptosis through inhibition of the caspase-3 pathway, downregulation of the proinflammatory NF κ B signaling pathway, and lowering of ROS production by dopaminergic neurons	Ben Youssef et al. (2021)
	LPS-treated Caco-2 cell model of intestinal epithelial barrier	Resveratrol-3-O-sulfate (100 μ M)	Improves intestinal barrier integrity as measured by upregulated mRNA expression of occludin, ZO-1, claudin-1, and claudin-4	Zhang et al. (2021)
	PD patient-derived fibroblasts	Resveratrol (25 μ M) for 24 or 48 h	Rescues mitochondrial function through AMPK/SIRT1/PGC-1 α pathway Increases gene expression of TFAM and cytochrome <i>c</i> leading to improved mitochondrial oxidative phosphorylation capacity and reduced ROS production	Ferretta et al. (2014)
	MPP+ treated rat PC12 neuronal cell model of PD	Pretreatment with resveratrol (0.1 μ M) 3 h prior to MPP+	Increases survival rate of neurons Normalizes Bax to Bcl-2 protein ratio Inhibits cytosol to nucleus translocation of AIF and reduces release of apoptosis-inducing cytochrome <i>c</i> from mitochondria	Bournival et al. (2009)
	Rotenone-treated murine BV-2 microglia	Pretreatment with resveratrol (50 μ M) 1 h prior to rotenone	Inhibits rotenone-induced production of ROS, MDA, IL-6, IL-1 β , and TNF- α	Sun et al. (2021)
	Mouse model of stress by immobilization	Oral pretreatment for 5 days with 200 μ l polyphenol-enriched grape juice prior to stress	Reduces mRNA levels of proinflammatory mediators IL-6 and TNF- α to those observed in unstressed animals Normalizes indicators of oxidative stress (NOX2 and HMOX-1)	Bobadilla et al. (2021)
Animal	Scopolamine mouse model of AD	Pretreatment and cotreatment with grape seed oil (2 mg/kg) daily for 10 days	Improves spatial memory, as tested by Morris water maze Increases brain levels of acetylcholine	Berahmand et al. (2020)
	6-OHDA mouse model of PD	Grape seed and skin extract administered intraperitoneally prior to 6-OHDA insult	Improves survival of dopaminergic neurons in SNpc Enhances motor function as demonstrated by open-field test	Ben Youssef et al. (2021)
	Senescence-accelerated mouse model of aging	Daily oral administration of resveratrol (25–100 mg/kg) for 8 weeks	Restores cognitive functions to levels seen in aging-resistant mice Increases antioxidant activity as measured by upregulated SOD mRNA and enzymatic activity, increased GSH-Px activity, and decreased MDA Protects from oxidative stress-induced mitochondrial DNA damage as indicated by lower percentage of mtDNA deletions	Liu et al. (2012)
	APP/PS1 mouse model of AD	Diet supplemented with 0.35% resveratrol for 15 weeks prior to the onset of amyloidosis	Smaller A β plaques Less reactive microglia	Capiralla et al. (2012)
	Human clinical trials	Elderly persons with mild cognitive impairment	Consumption of 36 g grape powder in 240 ml (8 ounces) water twice per day for 6 months	Preserves metabolic activity in the left superior posterolateral temporal cortex and right posterior cingulate cortex
Patients with mild to moderate AD		Daily consumption of resveratrol (0.5–2 g) for 52 weeks	Stabilizes the decline in plasma and CSF A β 40 levels	Turner et al. (2015)

Table 1: (continued)

Study type	Model	Treatment	Main findings	Reference
	Patients with mild to moderate AD	Daily consumption of resveratrol (0.5–2 g) for 52 weeks	Stabilizes the decline in CSF A β 40 and A β 42 levels	Moussa et al. (2017)

6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; AIF, apoptosis-inducing factor; AMPK/SIRT1, AMP-activated protein kinase/sirtuin-1; APP, amyloid precursor protein; A β , amyloid beta; Bax, Bcl-2-associated X protein; Bcl, B-cell lymphoma; CSF, cerebrospinal fluid; GSH, glutathione; HMOX-1, heme oxygenase 1; IL, interleukin; LPS, lipopolysaccharide; MDA, malondialdehyde; MPP⁺, 1-methyl-4-phenylpyridinium ion; mtDNA, mitochondrial DNA; NF, nuclear factor; NOX2, NADPH oxidase 2; PD, Parkinson's disease; PGC, peroxisome-proliferator-activated receptor gamma coactivator; PS1, presenilin 1; ROS, reactive oxygen species; Px, peroxidase; SNpc, substantia nigra pars compacta; SOD, superoxide dismutase; TFAM, mitochondrial transcription factor A; and TNF- α , tumor necrosis factor α .

samples (Mosele et al. 2015). An *in vitro* study modeling the human gut microbiota finds that adding pomegranate powder to microbe cultures beneficially alters the microbiota metabolism to increase the production of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and a subset of SCFAs including acetate and propionate (Farag et al. 2020). The downregulation of GABA is implicated in the pathophysiology of motor and nonmotor symptoms of PD (Murrueta-Goyena et al. 2019), and as mentioned previously, SCFAs have anti-inflammatory activity in the CNS; therefore, modulating the gut microbiota by consuming pomegranates may have neuroprotective and anti-neuroinflammatory effects.

Indole-3-propionic acid

When pomegranate juice is consumed, the gut microbiota increases the production of the SCFA indole-3-propionic acid (IPA), which is accompanied by an increase in plasma IPA concentrations (Henning et al. 2019). IPA is known for its protective effects in the periphery as well as in the brain (Hwang et al. 2009; Zhao et al. 2019). A study using a rodent model of ischemia reveals that the consumption of IPA leads to higher neuron survival rates in the hippocampus compared to control animals. The potent antioxidant activity of IPA is believed to be responsible for these effects because decreased lipid peroxidation can be detected in hippocampal homogenates as reduced levels of 4-hydroxy-2-nonenal (Hwang et al. 2009). Although ischemia has a different etiology than AD and PD, it promotes AD-like neurodegeneration, as shown by the overexpression of APP, neuroinflammation, and neuronal loss (Pluta et al. 2018). Therefore, models of ischemia can offer valuable insights into the neuroprotective effects of pomegranate against neurodegenerative disease. IPA has also been shown to be protective against the neurotoxic effects of A β . For example, *in vitro* experiments demonstrate that rat embryonic day 18

primary hippocampal neurons and SK-N-SH human neuroblastoma cells are protected against A β toxicity when cotreated with IPA. Further experimentation establishes that IPA decreases A β -induced lipid peroxidation in rat PC12 neuronal cells (Chyan et al. 1999).

Urolithin A

Urolithin A is another bacterial metabolite, which is produced from the ellagitannins found in pomegranate. It has been shown to have neuroprotective effects both *in vivo* and *in vitro*. A study using APP/PS1 transgenic AD model mice demonstrates that a daily oral administration of urolithin A improves learning and memory in some cases, restoring the parameters measured by the Morris water maze test to values that are close to those obtained by wild-type animals consuming a placebo diet (Gong et al. 2019). Upon examination of the brain tissue, enhanced hippocampal neurogenesis can be observed. In the cortex and hippocampal region, there is significantly less amyloid plaque deposition and fewer activated glial cells. Furthermore, urolithin A-treated animals have lower levels of the inflammatory mediators TNF- α and IL-1 β in both the cortex and the hippocampus. Gong et al. (2019) propose that these neuroprotective effects of urolithin A are mediated by the AMPK/NF κ B and AMPK/p38 mitogen-activated protein kinase (MAPK) pathways due to the significant increase in phosphorylated (p)-AMPK and a decrease in p-p65NF κ B, p-p38MAPK, β -site APP cleaving enzyme 1 (BACE1), and APP in the cortex and hippocampus (Gong et al. 2019).

Urolithin A may also exert neuroprotective effects in PD. A study using rotenone-induced rat model of PD demonstrates that the consumption of pomegranate juice for 11 days protects the animals from developing motor defects by approximately 80%, as shown by postural instability tests. Urolithin A is able to cross the BBB

following oral administration because its presence can be detected in brain homogenates by ultraperformance liquid chromatography coupled with electrospray ionization tandem quadrupole time-of-flight mass spectrometry. Compared to untreated animals, there is significantly less neurodegeneration in the substantia nigra of rats treated with urolithin A, accompanied by a significant reduction in the ratio of α -synuclein oligomers to monomers in the midbrain indicating diminished aggregation of α -synuclein. The antioxidant activity of urolithin A could also partially contribute to the neuroprotective effects observed in this study since further analysis of brain tissue shows a significant decrease in lipid peroxidation, as shown by the reduced levels of MDA. An increased activity of the antioxidant GSH system is also demonstrated by upregulated levels of GSH, catalase, GSH-Px, and glutathione S-transferase. Furthermore, the expression of mitochondrial aldehyde dehydrogenase 2, an enzyme that detoxifies cytotoxic aldehydes and protects against oxidative stress, is also increased (Kujawska et al. 2020). Liu et al. (2022) identify the benefits of urolithin A treatment in a 6-OHDA mouse model of PD. Compared to animals not treated with urolithin A, C57BL/6J mice that are administered urolithin A by intraperitoneal injection for 7 days prior to 6-OHDA insult display increased survival of dopaminergic neurons in the nigrostriatal system and enhanced motor function, as demonstrated by 1.6–2.75-fold improvement in various motor function tests including the pole, suspension, rotarod, and apomorphine-induced rotation tests (Liu et al. 2022). The presence of neuroprotective compounds such as IPA and urolithin A in pomegranate products, including juice, combined with their ability to favorably alter the metabolite profile of gut microbiota, could make these foods beneficial in neurodegenerative pathologies.

Human clinical studies

Consumption of pomegranate products has promising beneficial effects on cognitive parameters in humans. A study involving healthy middle-aged and older adults reveals that the consumption of pomegranate juice helps preserve memory function. According to the Brief Visuospatial Memory Test-Revised, subjects consuming a placebo beverage experience a significant decline in test scores over a 12-month study period, whereas in the group of individuals regularly drinking pomegranate juice, there is a slight increase in the scores, albeit insignificant (Siddarth et al. 2020). Buschke Selective Reminding Test of

verbal memory shows a significant 25% increase in the consistent long-term retrieval score in older adults with memory complaints who consume pomegranate juice for 28 days. No increase in this test score is observed in the placebo group. Functional magnetic resonance imaging demonstrates that subjects consuming pomegranate juice also display increased activity in the basal ganglia, thalamus, left inferior frontal gyrus, left middle frontal gyrus, left inferior temporal gyrus, left and right occipital lobes, left and right fusiform gyrus, and the parahippocampal regions (Bookheimer et al. 2013). These beneficial effects should be considered when designing neuroprotective dietary interventions because memory impairment and decreased brain activity are symptoms of AD, and to a lesser extent to PD.

Supplementation with pomegranate has also aided in neuropsychological improvement following ischemic stroke. Stroke patients who consume pomegranate polyphenol pills display significant improvement on The Repeatable Battery for the Assessment of Neuropsychological Status, especially in the visuospatial/constructional and language subsections (Bellone et al. 2019). Ischemic stroke is a major risk factor of AD (Vijayan and Reddy 2016); thus, enhancing cognitive functions following cerebrovascular events could assist in the prevention of neurodegenerative diseases. The neuroprotective effects of pomegranate products discussed in this section are summarized in Table 2.

Kefir

Kefir is a fermented probiotic milk product traditionally made from kefir grains containing yeasts in combination with lactic acid and acetic acid bacteria. The exact microbial composition of kefir varies depending on the origin of the grains, fermentation process, culture methods, and maintenance (Prado et al. 2015). The consumption of traditionally made kefir has been shown to promote healthy gut microbiota communities and alleviate the symptoms of peripheral inflammatory conditions including inflammatory bowel disease and allergies (Curciarello et al. 2021; Kim et al. 2019; Takata et al. 2015; Yilmaz et al. 2019). Reduced biomarkers of peripheral inflammation, such as erythrocyte sedimentation rate and blood levels of C-reactive protein (CRP), have been reported in patients with Crohn's disease after consumption of kefir for 4 weeks (Yilmaz et al. 2019). The potential of kefir to beneficially modulate the gut microbiota–brain axis in neurodegenerative diseases is an emerging topic that has been discussed in a recent review by Pereira et al. (2021).

Table 2: Potentially protective biological activity of pomegranate in neurodegenerative diseases.

Study type	Model	Treatment	Main findings	Reference
<i>In vitro</i>	The simplified human intestinal microbiota (SIHUMix)	Pomegranate extract (0.5 or 5 mg/ml) for 24 h	Alters gut microbiota metabolism including increased production of GABA and SCFAs	Farag et al. (2020)
	Rat E-18 primary hippocampal neurons and SK-N-SH human neuroblastoma cells	Cotreatment with IPA (1–100 μ M) and A β (1 μ M) for 24 h	Protects against A β toxicity as seen by increased neuronal cell viability	Chyan et al. (1999)
	Rat PC12 neuronal cells	Cotreatment with IPA (1–100 μ M) and A β (10 μ M)	Inhibits A β -induced lipid peroxidation	Chyan et al. (1999)
Animal	Transient forebrain ischemia in Mongolian gerbils	Daily oral administration of IPA (10 mg/kg) for 15 days prior to ischemic insult	Increases neuron survival rate and decreases lipid peroxidation in the hippocampus	Hwang et al. (2009)
	APP/PS1 transgenic mouse model of AD	Daily oral administration of urolithin A (300 mg/kg) for 14 days	Improves spatial learning and memory Enhances hippocampal neurogenesis Decreases amyloid plaque deposition, reduces reactive glial cells, and lowers concentrations of TNF- α and IL-1 β in cortex and hippocampus Increases <i>p</i> -AMPK and decreases <i>p</i> -p65NF κ B, <i>p</i> -p38MAPK, BACE1, and APP in cortex and hippocampus	Gong et al. (2019)
	Rotenone-induced rat model of PD	Daily oral administration of sixfold concentrated pomegranate juice (500 mg/kg) for 10 days prior to rotenone injection followed by 35 days treatment with pomegranate juice and rotenone	Reduces neurodegeneration in substantia nigra Decreases ratio of α -synuclein oligomers to monomers demonstrating diminished aggregation of α -synuclein Reduces lipid peroxidation as indicated by lowered MDA levels Upregulates antioxidant systems as measured by increased levels of catalase, GSH, GSH-Px, and GSH-S-transferase Increases expression of mitochondrial aldehyde dehydrogenase 2 indicating improved protection against oxidative stress	Kujawska et al. (2020)
	6-OHDA mouse model of PD	Daily intraperitoneal injection of urolithin A (10 mg/kg) for 7 days prior to 6-OHDA	Increases survival of dopaminergic neurons in the nigrostriatal system Improves motor function measured by the pole, suspension, rotarod, and apomorphine-induced rotation tests	Liu et al. (2022)
Human clinical trials	Healthy middle-aged and older adults	Daily consumption of 240 ml (8 ounces) pomegranate juice for 12 months	Preserves visual memory function over a 12-month period as measured by significantly better BVMT-R learning scores compared to the placebo group	Siddarth et al. (2020)
	Nondemented older adults with self-reported memory complaints	Daily consumption of 240 ml (8 ounces) pomegranate juice for 28 days	Improves verbal and visual memory functions as demonstrated by cognitive testing and fMRI Increases brain activity in the basal ganglia, thalamus, left inferior frontal gyrus, left middle frontal gyrus, left inferior temporal gyrus, left and right occipital lobes, left and right fusiform gyrus, and the parahippocampal regions	Bookheimer et al. (2013)

Table 2: (continued)

Study type	Model	Treatment	Main findings	Reference
	Ischemic stroke patients	Consumption of 1 g pomegranate polyphenol pill (equivalent to 240 ml juice) twice daily, starting 2 weeks after stroke	Improves neuropsychological functions as measured by increased RBANS score, especially in visuospatial/constructional and language domains	Bellone et al. (2019)

6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; APP, amyloid precursor protein; A β , amyloid β ; BACE1, β -site APP cleaving enzyme 1; BVMT-R, Brief Visuospatial Memory Test-Revised; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; GSH, glutathione; IL, interleukin; IPA, indole-3-propionic acid; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NF, nuclear factor; p, phosphorylated; PD, Parkinson's disease; PS1, presenilin 1; Px, peroxidase; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; SCFA, short-chain fatty acid; and TNF- α , tumor necrosis factor α .

Modulation of gut microbiota

Interestingly, clinical studies evaluating the benefits of consuming commercially produced probiotics in various health conditions often report no significant improvement or contradictory evidence (McFarland 2021; Suez et al. 2019). Yet, clinical trials that utilize traditional kefir, made with kefir grains, have consistently detected favorable outcomes for diverse pathologies, such as type II diabetes mellitus, osteoporosis, and obesity (Ostadrhimi et al. 2015; Pražnikar et al. 2020; Tu et al. 2015). The effectiveness of traditionally made kefir is believed to be due to the survival of the yeasts and bacteria found in the grains, which better resist the harsh environment of the gut compared to other traditional probiotic species such as *Saccharomyces cerevisiae* (Kim et al. 2019).

Efforts have been made to understand the underlying mechanisms through which kefir elicits its beneficial effects. A recent study has aimed to identify how kefir engages the gut microbiota–brain axis to modulate neurological functions. It demonstrates that the oral administration of kefir containing *Lactococcus lactis*, *Lactobacillus kefirifaciens*, *Pseudomonas spp.*, and *Bifidobacterium breve* for 3 weeks reduces the repetitive behavior assessed by the marble burying test by approximately 30% and ameliorates deficits in the reward-seeking behavior induced by milk consumption, whereas other parameters studied, including anxiety-like and depressive-like behaviors, are not affected. This improvement in neurological functions is accompanied by decreased peripheral inflammation, as shown by reduced circulating levels of neutrophils, lower concentration of chemokine C-X-C motif ligand 1, higher concentration of the anti-inflammatory cytokine IL-10, and increased circulating levels of regulatory T cells (van de Wouw et al. 2020). Supplementing the diet with kefir also modulates mouse

gut bacterial communities, which significantly correlates with positive changes in behavioral and immunological parameters. In addition, kefir consumption increases the overall bacterial diversity throughout the gut. Specifically, there is an increase in the prevalence of *L. reuteri*, *Eubacterium plexicaudatum*, *Bifidobacterium pseudolongum*, *Parabacteroides goldsteinii*, *Bacteroides intestinalis*, *Anaerotruncus* unclassified, and *Alistipes* unclassified. Furthermore, the prevalence of *Lachnospiraceae* bacterium 3_1_46FAA, *Cutibacterium acnes*, *Bacillus amyloliquefaciens*, and *Candidatus* Arthromitus is decreased. The lower prevalence of *Ca. Arthromitus* is correlated with the observed increase in circulating regulatory T cells, whereas the higher abundance of *B. pseudolongum* is correlated with the observed decrease in circulating neutrophils. Interestingly, none of the bacterial species present in the kefir beverage colonize the gut of the mice (van de Wouw et al. 2020). A study using the germ-free transgenic mouse model of PD has demonstrated that gut bacteria are necessary for the progression of α -synuclein-mediated brain pathology, which indicates that modulating the gut microbiota may have protective effect in PD (Sampson et al. 2016).

Alterations in the gut microbiota are also associated with changes in neurotransmitter production within the gut of the mice. Most notably, the increased prevalence of *B. pseudolongum* and *L. reuteri* positively correlates with an increased capacity of the microbiota to produce glutamate and GABA (van de Wouw et al. 2020). Altered neurotransmission, resulting from disrupted neurotransmitter production and regulation throughout the body, is a key feature of neurodegenerative diseases, including AD and PD; therefore, this study offers important insights into how gut microbiota may be able to modulate neurotransmitter production throughout the progression of neurodegenerative

disease, and how fermented foods, like kefir, could be used to beneficially adjust this modulation (Kaur et al. 2019; O’Gorman Tuura et al. 2018).

Kefir minimizes risk factors of neurodegenerative diseases

Although kefir is well-known for its anti-inflammatory and antiallergic effects in the periphery (Yilmaz et al. 2019), its consumption can also reduce certain risk factors of neurodegenerative diseases including oxidative stress and hypertension. Aging, the most considerable risk factor for neurodegenerative diseases (Lin and Beal 2006), is associated with oxidative stress, which also directly contributes to the pathogenesis of AD and PD (Chen and Zhong 2014; Raza et al. 2019). An *in vivo* study using aged mice reveals that treatment with Probiotics Fermentation Technology (PFT), a novel kefir grain product containing *Lactobacillus kefir* P-IF, *L. kefir* P-B1, *Kazachstania turicensis*, *Kazachstania unisporea*, and *Kluyveromyces marxianus*, reverses age-associated oxidative stress. After 6 weeks of supplementing the diet with PFT, oxygen radical formation is inhibited, GSH and total antioxidant capacity is increased, whereas nitric oxide and MDA levels are reduced demonstrating a reversal of age-associated oxidative changes back to the levels comparable to young, untreated mice (Ghoneum et al. 2020).

Increasing evidence links midlife systolic hypertension to magnified risk of AD, suggesting that high blood pressure may be a contributing factor to the development of this neurodegenerative disease (Lennon et al. 2019). In the spontaneously hypertensive rat model, oral supplementation with kefir for 9 weeks significantly attenuates mean arterial pressure. The same study also describes improved morphology of the intestinal barrier and a reduction of the proinflammatory cytokines TNF- α and IL-6 in the hypothalamic paraventricular nucleus and rostral ventrolateral medulla, areas of the brain directly involved in the pathogenesis of hypertension (de Almeida Silva et al. 2020).

Kefir modulates symptoms of neurodegenerative diseases

In addition to reducing select risk factors of neurodegenerative diseases, consuming kefir has recently been shown to also modulate disease symptoms. A study using a fly model of AD finds that supplementing the feed with kefir made from grains containing *L. kefir* *kefir*, *L. kefir*,

Acetobacter fabarum, *L. lactis*, and Rickettsiales improves the neurodegenerative phenotype of the flies, as shown by a 1.6-fold higher survival rate and a two-fold improvement in the climbing ability as well as reduced severity of vacuolar lesions in the brain (Batista et al. 2021). Beneficial effects of kefir on AD symptoms have also been reported in human studies. Patients with suspected AD who consume kefir for 90 days display a significant improvement in cognitive functions and parameters: a 66% and 62% increase in immediate and late memory test scores, respectively; a 100% increase in the Similarity and Cookie Theft Picture test scores, which are representative of the visual-spatial and abstraction abilities, respectively; an approximate 25–30% improvement in the Boston and Verbal Fluency tests, which examine executive and language functions; and a 28% increase in the Mini-Mental State Examination (MMSE) score. These improvements are accompanied by a significant reduction in the serum levels of proinflammatory cytokines TNF- α , IL-12p70, and IL-8. Kefir supplementation also supports mitochondrial function, as shown by the increased mitochondrial membrane potential and reduced intracellular ROS levels in erythrocytes collected from the study subjects. The kefir beverage used in this study is inoculated with kefir grains that contain *Acetobacter aceti*, *Acetobacter sp.*, *Lactobacillus delbrueckii*, *Lactobacillus fermentum*, *Lactobacillus fructivorans*, *Enterococcus faecium*, *Leuconostoc spp.*, *L. kefir* *kefir*, *Candida famata*, and *Candida krusei* (Ton et al. 2020). Other studies demonstrate the beneficial effects of similar probiotic supplementation in modulating neurocognitive outcomes. For example, consuming milk containing *L. acidophilus*, *L. fermentum*, *Lactobacillus casei*, and *Bifidobacterium bifidum* for 12 weeks results in significantly enhanced cognitive functions in AD patients, as shown by a 28% improvement in their MMSE scores, which contrasts the 5% decline in MMSE scores observed in the control group. In addition, this fermented beverage has favorable effects on insulin metabolism and serum levels of triglycerides, MDA, and CRP, indicating improved energy metabolism and decreased oxidative stress and inflammation (Akbari et al. 2016). The neuroprotective effects of kefir discussed in this section are summarized in Table 3.

Seaweed

Seaweed is a popular food traditionally consumed in East Asia that has gained attention for its wide range of associated health benefits including lowered blood pressure, improved blood lipid profiles, and reduced risk of stroke. Regular consumption of seaweed may also have anticancer,

Table 3: Potentially protective biological activity of kefir in neurodegenerative diseases.

Study type	Model	Treatment	Main findings	Reference
Animal	Aged (10-month-old) Swiss albino mice	Daily oral administration of PFT (2 mg/kg) for 6 weeks	Reverses age-associated oxidative changes as demonstrated by inhibited oxygen radical formation Reduces NO and MDA levels Increases GSH, total antioxidant capacity, and antihydroxyl radical content	Ghoneum et al. (2020)
	Eight-week-old spontaneously hypertensive rats	Daily oral administration of kefir (0.3 ml/100 g) made from kefir grains for 9 weeks	Decreases mean arterial pressure Improves intestinal barrier morphology Reduces TNF- α and IL-6 levels in hypothalamic paraventricular nucleus and rostral ventrolateral medulla	de Almeida Silva et al. (2020)
	<i>Drosophila melanogaster</i> model of AD	Kefir mixed with food	Improves neurodegenerative phenotype as demonstrated by enhanced survival rate and climbing ability of flies as well as reduced severity of vacuolar lesions in the brain	Batista et al. (2021)
	Eight-week-old C57BL/6J mice	Daily oral administration of kefir (0.2 ml) containing <i>L. lactis</i> , <i>L. kefirifaciens</i> , <i>P. spp.</i> , and <i>B. breve</i> for 3 weeks	Improves repetitive and reward-seeking behavior as well as enhances contextual learning and memory Decreases peripheral inflammation as measured by reduced circulating levels of neutrophils, lower concentration of CXCL1, higher concentration of IL-10, and increased circulating regulatory T cells Increases prevalence of <i>L. reuteri</i> , <i>E. plexicaudatum</i> , <i>B. pseudolongum</i> , <i>P. goldsteinii</i> , <i>B. intestinalis</i> , <i>Anaerotruncus</i> unclassified, and <i>Alistipes</i> unclassified in the gut Decreases prevalence of <i>L. bacterium</i> 3_1_46FAA, <i>C. acnes</i> , <i>B. amyloliquefaciens</i> , and <i>Ca. Arthromitus</i> in the gut	van de Wouwe et al. (2020)
Human clinical trials	Humans with suspected AD	Daily oral administration of kefir (2 ml/kg) containing <i>A. aceti</i> , <i>A. sp.</i> , <i>L. delbrueckii</i> , <i>L. fermentum</i> , <i>L. fructivorans</i> , <i>E. faecium</i> , <i>Leuconostoc</i> spp., <i>L. kefirifaciens</i> , <i>Ca. famata</i> , and <i>Ca. krusei</i> for 90 days	Improves memory, visual-spatial, abstraction, executive, language, constructive, and attentive abilities Reduces serum levels of TNF- α , IL-12p70, and IL-8 Enhances mitochondrial function as measured by increased mitochondrial membrane potential and reduced intracellular ROS in erythrocytes	Ton et al. (2020)
	Humans with suspected AD	Daily oral administration of probiotic milk (200 ml) containing <i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i> , and <i>L. fermentum</i> for 12 weeks	Increases cognitive function as demonstrated by improved MMSE scores, which contrasts the decline of such scores in the control group Enhances energy metabolism as demonstrated by improved insulin metabolism and serum levels of triglycerides Decreases oxidative stress and inflammation as measured by lowered MDA and CRP levels	Akbari et al. (2016)

AD, Alzheimer's disease; CRP, C-reactive protein; CXCL, CXC motif ligand; GSH, glutathione; IL, interleukin; MDA, malondialdehyde; MMSE, Mini-Mental State Examination; NO, nitric oxide; PFT, probiotics fermentation technology; ROS, reactive oxygen species; and TNF- α , tumor necrosis factor α .

antiviral, antidiabetic, and anti-inflammatory effects (Brown et al. 2014). Epidemiological data show that, when compared to Western societies, East Asian countries have lower incidences of a range of chronic illnesses, including neurodegenerative diseases, coronary heart disease, and stroke. However, over the past few decades, as East Asian cultures have veered away from traditional foods and embraced more Westernized diets, the prevalence of some of these chronic diseases has grown significantly (Iso 2011; Kim et al. 2009; Ni et al. 2018). Dietary patterns containing seaweed have also been linked to improved brain health and have, therefore, been studied for their potential to prevent AD and PD, as well as to slow down their progression (Hannan et al. 2020; Pereira and Valado 2021).

Modulation of gut microbiota metabolism

It is reported that AD patients have elevated levels of circulating phenylalanine, isoleucine, and the pro-inflammatory type 1 T helper (Th1) cells (Larsson and Markus 2017; Wang et al. 2019; Wissmann et al. 2013). Furthermore, culturing murine Th1 cells with phenylalanine and isoleucine promotes their proliferation (Wang et al. 2019). Peripheral immune cell infiltration into the brain is one of the proposed mechanisms that contributes to neuroinflammation in neurodegenerative diseases (Sommer et al. 2017; Wang et al. 2019). In AD, damage to neurons correlates with the increased entry of peripheral leukocytes across the BBB, which results in activation of CNS immune cells, promoting further infiltration of effector T cells into the brain (Burgaletto et al. 2020). Therefore, converting the gut microbiota to an enterotype that reduces the production of phenylalanine and isoleucine leading to decreased proliferation of peripheral effector Th1 cells may be one of the mechanisms by which seaweed and its constituents, such as sodium oligomannate, slow the progression of AD. Other studies have also reported amino acid level changes in the serum of PD patients. Figura et al. (2018) analyzed the serum amino acid profiles of patients with PD and reported that, when compared to individuals with shorter disease duration, subjects with more advanced PD have lower serum levels of alanine, arginine, and phenylalanine, but increased concentrations of threonine (Figura et al. 2018). A more recent systematic review and meta-analysis indicates that PD patients exhibit decreased serum levels of aspartate, serine, tryptophan, and lysine, but elevated serum proline and homocysteine concentrations compared to age- and sex-matched healthy controls (Jiménez-Jiménez et al.

2021). Due to these inconsistent findings, additional studies investigating changes in amino acid metabolism throughout the progression of AD and PD pathologies are warranted; nonetheless, the consumption of seaweed has emerged as a dietary intervention that can mitigate this dysregulated amino acid metabolism.

Phlorotannin

The neuroprotective effects of seaweed may be due to its rich content of various bioactive polyphenols such as phlorotannin. It is present in brown algae and demonstrates neuroprotective effects against A β -induced cytotoxicity *in vitro*. A study investigating the neuroprotective activity of various fractions of extracts from *Ecklonia radiata*, a brown alga, reports that, of the six fractions tested, the one containing the highest concentration of phlorotannin shows the strongest antiaggregative effect against A β _{1–42}, as well as the greatest antiapoptotic activity in preventing A β _{1–42}-induced cell death. The phlorotannin-containing fraction inhibits over 90% of A β _{1–42} aggregate formation. Treatment with A β _{1–42} causes apoptosis of 20% of rat PC12 neuronal cells, whereas concomitant exposure to the phlorotannin fraction lowers this rate nearly three-fold (Alghazwi et al. 2020). Reducing the aggregation of A β and its neurotoxicity has been proposed as a therapeutic strategy in AD (Szeto and Lewis 2016).

Polymannuronic acid

Seaweed also contains an abundance of carbohydrates with bioactive properties. Polymannuronic acid is a polysaccharide component of alginate found in the cell walls of brown seaweed. An *in vivo* study using the C57BL/6J mouse model of PD reports that, when compared to untreated animals, mice fed with polymannuronic acid daily for 4 weeks prior to injection with 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) display improved motor function compared to the control animals (Dong et al. 2020). This effect is attributed to a significantly higher survival rate of tyrosine hydroxylase immunoreactive (TH-IR) neurons in the SNpc. Treatment of PD mice with polymannuronic acid suppresses the mRNA expression of the pro-inflammatory cytokines TNF- α and IL-6 in the colon and SNpc, but increases the mRNA expression of occludin and ZO-1, which are tight junction-associated proteins essential for maintenance of blood–brain and intestinal barriers. Therefore, the

neuroprotective effects of polymannuronic acid are likely mediated by attenuating inflammation in the gut, brain, and systemic circulation, as well as by enhancing the integrity of the BBB and intestinal barrier (Dong et al. 2020). A recent study using the same mouse model of PD demonstrates that the oral administration of polymannuronic acid for 4 weeks prior to MPTP insult protects against loss of dopaminergic neurons, enhances motor function, and improves neurotransmitter levels in the striatum. Compared to untreated PD mice, those that consume polymannuronic acid have significantly more TH-IR neurons in the SNpc, approximately 30% quicker descent time in the pole test indicating improved motor function, and increased striatal levels of serotonin and its main metabolite, 5-hydroxyindole acetic acid (Du et al. 2021). A different study using the N2a-sw murine cell model of AD finds that a 24 h treatment with unsaturated mannuronate oligosaccharide, a depolymerized derivative of polymannuronic acid, leads to significantly reduced $A\beta_{1-42}$

production and deposition. This is caused by the downregulation of APP and BACE1, which are proteins essential for the amyloidogenic pathway contributing to AD pathogenesis (Bi et al. 2021).

Sodium oligomannate

Sodium oligomannate is another carbohydrate found in brown algae that has been used to develop an anti-AD drug, GV-971. This drug modulates the gut microbiota to decrease neuroinflammation, as observed in the 5XFAD transgenic and APP/PS1 mouse models of AD. The oral administration of GV-971 once a day for 3 months significantly improved the cognitive functions of APP/PS1 mice, as shown by improvements in various spatial learning and memory performance scores in the Morris water maze test, which in some cases reach levels comparable to those seen in wild-type animals. Compared to untreated mice, GV-971

Table 4: Potentially protective biological activity of seaweed in neurodegenerative diseases.

Study type	Model	Treatment	Main findings	Reference
<i>In vitro</i>	Rat PC12 neuronal cell model of AD	Phlorotannin extracted from <i>Ecklonia radiata</i> for 48 h	Inhibits <i>in vitro</i> $A\beta_{1-42}$ aggregation by 90% Reduces $A\beta_{1-42}$ -induced apoptosis threefold	Alghazwi et al. (2020)
	Murine N2a-sw neuronal cell model of AD	Unsaturated mannuronate oligosaccharide (1 mg/ml) for 24 h	Decreases $A\beta_{1-42}$ production as measured by downregulated APP and BACE1 expression	Bi et al. (2021)
Animal	MPTP-induced C57BL/6j mouse model of PD	Oral administration of polymannuronic acid (30 mg/kg) for 4 weeks	Improves motor functions as measured by increased survival of TH-IR neurons in SNpc Exhibits anti-inflammatory effect in CNS as measured by suppressed IL-6 and TNF- α mRNA expression Enhances integrity of BBB and intestinal barrier as demonstrated by increased expression of occludin and ZO-1	Dong et al. (2020)
	MPTP-induced C57BL/6j mouse model of PD	Oral administration of polymannuronic acid (30 mg/kg) for 4 weeks prior to MPTP	Increases survival of TH-IR neurons in the SNpc Improves motor function in pole test Increases striatal levels of serotonin and its metabolite 5-hydroxyindole acetic acid	Du et al. (2021)
	5XFAD transgenic mouse model of AD	Oral administration of GV-971 (100 mg/kg) for 1 month	Normalizes fecal and blood phenylalanine and isoleucine concentrations Decreases Th1 cells, reactive microglia, $A\beta$ plaque deposition, and tau phosphorylation in the brain	Wang et al. (2019)
	APP/PS1 mouse model of AD	Oral administration of GV-971 (50 or 100 mg/kg) for 3 months	Improves cognitive functions as measured by enhanced spatial learning and memory performance	Wang et al. (2019)
Human clinical trials	Phase III clinical trial of patients with mild to moderate AD	Oral administration of GV-971 (450 mg) twice a day for 36 weeks	Improves ADAS-Cog12 score compared to baseline and patients who took a placebo	Xiao et al. (2021)

AD, Alzheimer's disease; ADAS-Cog12, Alzheimer's Disease Assessment Scale; APP, amyloid precursor protein; $A\beta$, amyloid β ; BACE1, β -site APP cleaving enzyme 1; BBB, blood-brain barrier; CNS, central nervous system; IL, interleukin; MPTP, 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine; PD, Parkinson's disease; PS1, presenilin 1; SNpc, substantia nigra pars compacta; Th1, type 1 T helper; TNF- α , tumor necrosis factor α ; and ZO, zonula occludens.

administration also alters the composition of gut microbiota communities, inhibits infiltration of peripheral Th1 cells in the brain, reduces microglial activation, modifies brain cytokine levels, and decreases A β plaque deposition and tau phosphorylation in the brains of APP/PS1 AD mice. To determine the possible mechanisms through which GV-971 inhibits neuroinflammation, fecal metabolome analyses of wild-type, untreated APP/PS1 and GV-971-treated APP/PS1 AD mice have been conducted, which reveal significant alterations in amino acid metabolism, specifically within the phenylalanine- and isoleucine-related pathways. Fecal and blood concentrations of phenylalanine and isoleucine are substantially elevated in untreated AD mice compared to those in wild-type mice, and GV-971 administration significantly reduces the concentrations of these amino acids to levels similar to those of wild-type mice. In addition, the fecal matter has been transplanted from GV-971-treated AD mice to untreated wild-type mice, which are subsequently intraventricularly administered aggregated A β . A decrease in Th1 cells in the brain of recipient mice is observed, demonstrating that the feces of GV-971-treated AD mice effectively substitute oral administration of GV-971. Coadministration of antibiotics abolishes these effects, further demonstrating that the therapeutic actions of GV-971 are achieved mainly through alteration of the gut microbiota (Wang et al. 2019).

Human clinical studies

GV-971 has recently been shown by a phase III clinical trial to significantly improve cognition in patients with mild to moderate AD. This is demonstrated by a statistically significant -2.15 point difference between the treatment and placebo groups in change from the baseline after 36 weeks of treatment according to the 12-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog12). The drug–placebo difference in ADAS-Cog12 scores increases with duration of treatment and severity of cognitive decline. Although additional research is required to identify the GV-971 mechanisms of action, this trial demonstrates improvement in clinical scores, whereas nonclinical studies provide evidence of disease-modifying mechanistic actions of GV-971 illustrating the potential of this drug to ameliorate symptoms and slow the progression of AD (Xiao et al. 2021). Notably, GV-971 has already been approved for clinical use in China to improve cognitive function in mild to moderate AD (Ettcheto et al. 2021). The neuroprotective effects of seaweed discussed in this section are summarized in Table 4.

Conclusions

Specific dietary components may ameliorate or prevent the onset of neurodegenerative diseases either by modifying the gut microbiota composition to a healthier enterotype or by utilizing the metabolic activity of gut microbiota to produce bioactive molecules that target neurodegenerative processes and pathology. Although numerous studies link diet with health, whether overall or CNS, there is a significant knowledge gap related to the effects of diet and specific dietary components on neurodegenerative diseases that are mediated through the alteration of gut microbiota composition and activity (Bianchi et al. 2021; Micha et al. 2017). This article illustrates the neurological benefits of increased intake of grapes, pomegranate, kefir, and seaweed (see Tables 1–4 for summary). It can be concluded that consuming foods that are either fermented or rich in bioactive polyphenols and complex carbohydrates may aid in the prevention of AD and PD and amelioration of disease progression. Combining dietary interventions with pharmacological agents is another promising therapeutic strategy that has to be explored in the future (Scheltens et al. 2021). Although further human clinical studies are needed to ascertain the benefits observed in animal and *in vitro* studies, the aforementioned dietary components have been found to modulate the gut microbiota–brain axis and to show potential as non-pharmacological interventions for the management of AD and PD.

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References

- Abramov, A.Y., Potapova, E.V., Dremin, V.V., and Dunaev, A.V. (2020). Interaction of oxidative stress and misfolded proteins in the mechanism of neurodegeneration. *Life* 10: 101.
- Aires, V., Limagne, E., Cotte, A.K., Latruffe, N., Ghiringhelli, F., and Delmas, D. (2013). Resveratrol metabolites inhibit human

- metastatic colon cancer cells progression and synergize with chemotherapeutic drugs to induce cell death. *Mol. Nutr. Food Res.* 57: 1170–1181.
- Akbari, E., Asemi, Z., Kakhaki, R.D., Bahmani, F., Kouchaki, E., Tamtaji, O.R., Hamidi, G.A., and Salami, M. (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Front. Aging Neurosci.* 8: 256.
- Alghazwi, M., Charoensiddhi, S., Smid, S., and Zhang, W. (2020). Impact of *Ecklonia radiata* extracts on the neuroprotective activities against amyloid beta ($A\beta_{1-42}$) toxicity and aggregation. *J. Funct. Foods* 68: 103893.
- Al-Harbi, S.A., Abdulrahman, A.O., Zamzami, M.A., and Khan, M.I. (2021). Urolithins: the gut based polyphenol metabolites of ellagitannins in cancer prevention, a review. *Front. Nutr.* 8: 647582.
- Anand, S.S., Hawkes, C., de Souza, R.J., Mente, A., Dehghan, M., Nugent, R., Zulyniak, M.A., Weis, T., Bernstein, A.M., Krauss, R.M., et al. (2015). Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the world heart federation. *J. Am. Coll. Cardiol.* 66: 1590–1614.
- Bachmann, C., Colombo, J.P., and Berüter, J. (1979). Short chain fatty acids in plasma and brain: quantitative determination by gas chromatography. *Clin. Chim. Acta* 92: 153–159.
- Banihani, S.A., Makahleh, S.M., El-Akawi, Z., Al-Fashtaki, R.A., Khabour, O.F., Gharibeh, M.Y., Saadah, N.A., Al-Hashimi, F.H., and Al-Khasieb, N.J. (2014). Fresh pomegranate juice ameliorates insulin resistance, enhances β -cell function, and decreases fasting serum glucose in type 2 diabetic patients. *Nutr. Res.* 34: 862–867.
- Basholli-Salihi, M., Schuster, R., Mulla, D., Praznik, W., Viernstein, H., and Mueller, M. (2016). Bioconversion of piceid to resveratrol by selected probiotic cell extracts. *Bioproc. Biosyst. Eng.* 39: 1879–1885.
- Bassiri-Jahromi, S. (2018). *Punica granatum* (pomegranate) activity in health promotion and cancer prevention. *Onco Rev.* 12: 345.
- Batista, L.L., Malta, S.M., Guerra Silva, H.C., Borges, L.D.F., Rocha, L.O., da Silva, J.R., Rodrigues, T.S., Venturini, G., Padilha, K., da Costa Pereira, A., et al. (2021). Kefir metabolites in a fly model for Alzheimer's disease. *Sci. Rep.* 11: 11262.
- Bellone, J.A., Murray, J.R., Jorge, P., Fogel, T.G., Kim, M., Wallace, D.R., and Hartman, R.E. (2019). Pomegranate supplementation improves cognitive and functional recovery following ischemic stroke: a randomized trial. *Nutr. Neurosci.* 22: 738–743.
- Ben Youssef, S., Brisson, G., Doucet-Beaupré, H., Castonguay, A.M., Gora, C., Amri, M., and Lévesque, M. (2021). Neuroprotective benefits of grape seed and skin extract in a mouse model of Parkinson's disease. *Nutr. Neurosci.* 24: 197–211.
- Berahmand, F., Anoush, G., Hosseini, M.J., and Anoush, M. (2020). Grape seed oil as a natural therapy in male rats with Alzheimer's diseases. *Adv. Pharmaceut. Bull.* 10: 430–436.
- Bi, D., Yao, L., Lin, Z., Chi, L., Li, H., Xu, H., Du, X., Liu, Q., Hu, Z., Lu, J., et al. (2021). Unsaturated mannuronate oligosaccharide ameliorates β -amyloid pathology through autophagy in Alzheimer's disease cell models. *Carbohydr. Polym.* 251: 117124.
- Bianchi, V.E., Herrera, P.F., and Laura, R. (2021). Effect of nutrition on neurodegenerative diseases. A systematic review. *Nutr. Neurosci.* 24: 810–834.
- Bird, J.K., Raederstorff, D., Weber, P., and Steinert, R.E. (2017). Cardiovascular and antiobesity effects of resveratrol mediated through the gut microbiota. *Adv. Nutr.* 8: 839–849.
- Bjelobaba, I., Savic, D., and Lavrnja, I. (2017). Multiple sclerosis and neuroinflammation: the overview of current and prospective therapies. *Curr. Pharmaceut. Des.* 23: 693–730.
- Bobadilla, M., Hernández, C., Ayala, M., Alonso, I., Iglesias, A., García-Sanmartín, J., Mirpuri, E., Barriobero, J.I., and Martínez, A. (2021). A grape juice supplemented with natural grape extracts is well accepted by consumers and reduces brain oxidative stress. *Antioxidants* 10: 677.
- Bookheimer, S.Y., Renner, B.A., Ekstrom, A., Li, Z., Henning, S.M., Brown, J.A., Jones, M., Moody, T., and Small, G.W. (2013). Pomegranate juice augments memory and fMRI activity in middle-aged and older adults with mild memory complaints. *J. Evidence-Based Complementary Altern. Med.* 2013: 946298.
- Bournival, J., Quessy, P., and Martinoli, M.G. (2009). Protective effects of resveratrol and quercetin against MPP⁺-induced oxidative stress act by modulating markers of apoptotic death in dopaminergic neurons. *Cell. Mol. Neurobiol.* 29: 1169–1180.
- Brayne, C. and Miller, B. (2017). Dementia and aging populations—a global priority for contextualized research and health policy. *PLoS Med.* 14: e1002275.
- Brown, E.M., Allsopp, P.J., Magee, P.J., Gill, C.I.R., Nitecki, S., Strain, C.R., and McSorley, E.M. (2014). Seaweed and human health. *Nutr. Rev.* 72: 205–216.
- Burgaletto, C., Munafò, A., di Benedetto, G., de Francisci, C., Caraci, F., di Mauro, R., Bucolo, C., Bernardini, R., and Cantarella, G. (2020). The immune system on the TRAIL of Alzheimer's disease. *J. Neuroinflammation* 17: 298.
- Capiralla, H., Vingtdoux, V., Zhao, H., Sankowski, R., Al-Abed, Y., Davies, P., and Marambaud, P. (2012). Resveratrol mitigates lipopolysaccharide- and $A\beta$ -mediated microglial inflammation by inhibiting the TLR4/NF- κ B/STAT signaling cascade. *J. Neurochem.* 120: 461–472.
- Carry, E., Zhao, D., Mogno, I., Faith, J., Ho, L., Villani, T., Patel, H., Pasinetti, G.M., Simon, J.E., and Wu, Q. (2018). Targeted analysis of microbial-generated phenolic acid metabolites derived from grape flavanols by gas chromatography-triple quadrupole mass spectrometry. *J. Pharm. Biomed. Anal.* 159: 374–383.
- Cenini, G., Lloret, A., and Cascella, R. (2019). Oxidative stress in neurodegenerative diseases: from a mitochondrial point of view. *Oxid. Med. Cell. Longev.* 2019: 2105607.
- Chaplin, A., Carpené, C., and Mercader, J. (2018). Resveratrol, metabolic syndrome, and gut microbiota. *Nutrients* 10: 1–29.
- Chen, Z. and Zhong, C. (2014). Oxidative stress in Alzheimer's disease. *Neurosci. Bull.* 30: 271–281.
- Chyan, Y.J., Poeggeler, B., Omar, R.A., Chain, D.G., Frangione, B., Ghiso, J., and Pappolla, M.A. (1999). Potent neuroprotective properties against the Alzheimer β -amyloid by an endogenous melatonin-related indole structure, indole-3-propionic acid. *J. Biol. Chem.* 274: 21937–21942.
- Cummings, J.H., Pomare, E.W., Branch, W.J., Naylor, C.P., and Macfarlane, G.T. (1987). Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* 28: 1221–1227.
- Curciarello, R., Canziani, K.E., Salto, I., Barbiera Romero, E., Rocca, A., Doldan, I., Peton, E., Brayer, S., Sambuelli, A.M., Goncalves, S., et al. (2021). Probiotic lactobacilli isolated from kefir promote down-regulation of inflammatory lamina propria t cells from patients with active IBD. *Front. Pharmacol.* 12: 594.

- Dalile, B., van Oudenhove, L., Vervliet, B., and Verbeke, K. (2019). The role of short-chain fatty acids in microbiota–gut–brain communication. *Nat. Rev. Gastroenterol. Hepatol.* 16: 461–478.
- DaSilva, N.A., Nahar, P.P., Ma, H., Eid, A., Wei, Z., Meschwitz, S., Zawia, N.H., Slitt, A.L., and Seeram, N.P. (2019). Pomegranate ellagitannin-gut microbial-derived metabolites, urolithins, inhibit neuroinflammation in vitro. *Nutr. Neurosci.* 22: 185–195.
- de Almeida Silva, M., Mowry, F.E., Peaden, S.C., Andrade, T.U., and Biancardi, V.C. (2020). Kefir ameliorates hypertension via gut–brain mechanisms in spontaneously hypertensive rats. *J. Nutr. Biochem.* 77: 108318.
- DeMaagd, G. and Philip, A. (2015). Parkinson's disease and its management: Part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. *Pharmacol. Ther.* 40: 504–532.
- DeTure, M.A. and Dickson, D.W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Mol. Neurodegener.* 14: 32.
- Dong, X.L., Wang, X., Liu, F., Liu, X., Du, Z.R., Li, R.W., Xue, C.H., Wong, K.H., Wong, W.T., Zhao, Q., et al. (2020). Polymannuronic acid prevents dopaminergic neuronal loss via brain-gut-microbiota axis in Parkinson's disease model. *Int. J. Biol. Macromol.* 164: 994–1005.
- Dorsey, E.R., Constantinescu, R., Thompson, J.P., Biglan, K.M., Holloway, R.G., Kieburtz, K., Marshall, F.J., Ravina, B.M., Schifitto, G., Siderowf, A., et al. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 68: 384–386.
- Du, Z., Wang, X., Cao, X., Liu, X., Zhou, S., Zhang, H., Yang, R., Wong, K., Tang, Q., and Dong, X. (2021). Alginate and its two components acted differently against dopaminergic neuronal loss in Parkinson's disease mice model. *Mol. Nutr. Food Res.* 66: e2100739.
- Eghbali, S., Askari, S.F., Avan, R., and Sahebkar, A. (2021). Therapeutic effects of *Punica granatum* (pomegranate): an updated review of clinical trials. *J. Nutr. Metab.* 2021: 1–22.
- Etcheto, M., Busquets, O., Cano, A., Sánchez-Lopez, E., Manzine, P.R., Espinosa-Jimenez, T., Verdager, E., Sureda, F.X., Olloquequi, J., Castro-Torres, R.D., et al. (2021). Pharmacological strategies to improve dendritic spines in Alzheimer's disease. *J. Alzheim. Dis.* 82: S91–S107.
- Farag, M.A., Abdelwareth, A., Sallam, I.E., el Shorbagi, M., Jehmlich, N., Fritz-Wallace, K., Serena Schäpe, S., Rolle-Kampczyk, U., Ehrlich, A., Wessjohann, L.A., et al. (2020). Metabolomics reveals impact of seven functional foods on metabolic pathways in a gut microbiota model. *J. Adv. Res.* 23: 47–59.
- Ferretta, A., Gaballo, A., Tanzarella, P., Piccoli, C., Capitano, N., Nico, B., Annese, T., di Paola, M., Dell'Aquila, C., de Mari, M., et al. (2014). Effect of resveratrol on mitochondrial function: implications in parkin-associated familial Parkinson's disease. *Biochim. Biophys. Acta (BBA) - Mol. Basis Dis.* 1842: 902–915.
- Ferri, C.P., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang, Y., Jorm, A., et al. (2005). Global prevalence of dementia: a Delphi consensus study. *Lancet* 366: 2112–2117.
- Figura, M., Kuśmierska, K., Bucior, E., Szlufik, S., Kozirowski, D., Jamrozik, Z., and Janik, P. (2018). Serum amino acid profile in patients with Parkinson's disease. *PLoS One* 13: e0191670.
- Fourati, M., Smaoui, S., Hlima, H.B., Elhadeif, K., Braïek, O.B., Ennouri, K., Mtibaa, A.C., and Mellouli, L. (2020). Bioactive compounds and pharmacological potential of pomegranate (*Punica granatum*) seeds - a review. *Plant Foods Hum. Nutr.* 75: 477–486.
- Frolinger, T., Sims, S., Smith, C., Wang, J., Cheng, H., Faith, J., Ho, L., Hao, K., and Pasinetti, G.M. (2019). The gut microbiota composition affects dietary polyphenols-mediated cognitive resilience in mice by modulating the bioavailability of phenolic acids. *Sci. Rep.* 9: 1–10.
- Ghoneum, M., Abdulmalek, S., and Pan, D. (2020). Reversal of age-associated oxidative stress in mice by PFT, a novel kefir product. *Int. J. Immunopathol. Pharmacol.* 34: 2058738420950149.
- Gong, Z., Huang, J., Xu, B., Ou, Z., Zhang, L., Lin, X., Ye, X., Kong, X., Long, D., Sun, X., et al. (2019). Urolithin A attenuates memory impairment and neuroinflammation in APP/PS1 mice. *J. Neuroinflammation* 16: 62.
- Han, X.J., Hu, Y.Y., Yang, Z.J., Jiang, L.P., Shi, S.L., Li, Y.R., Guo, M.Y., Wu, H.L., and Wan, Y.Y. (2017). Amyloid β -42 induces neuronal apoptosis by targeting mitochondria. *Mol. Med. Rep.* 16: 4521–4528.
- Hannan, M.A., Dash, R., Haque, M.N., Mohibbullah, M., Sohag, A.A.M., Rahman, M.A., Uddin, M.J., Alam, M., and Moon, I.S. (2020). Neuroprotective potentials of marine algae and their bioactive metabolites: pharmacological insights and therapeutic advances. *Mar. Drugs* 18: 347.
- He, J., Zhu, G., Wang, G., and Zhang, F. (2020). Oxidative stress and neuroinflammation potentiate each other to promote progression of dopamine neurodegeneration. *Oxid. Med. Cell. Longev.* 2020: 6137521.
- He, Q., Liu, J., Liang, J., Liu, X., Li, W., Liu, Z., Ding, Z., and Tuo, D. (2018). Towards improvements for penetrating the blood-brain barrier- Recent progress from a material and pharmaceutical perspective. *Cells* 7: 24.
- Heng, Y., Eggen, B.J.L., Boddeke, E.W.G.M., and Kooistra, S.M. (2017). Mouse models of central nervous system ageing. *Drug Discov. Today Dis. Model.* 25–26: 21–34.
- Henning, S., Yang, J., Lee, R., Huang, J., Small, G., Guo, Y., Heber, D., and Li, Z. (2019). Effect of pomegranate juice consumption on plasma indole propionic acid, a bacterial-derived tryptophan metabolite (P20-003-19). *Curr. Dev. Nutr.* 3: 1761.
- Ho, L., Zhao, D., Ono, K., Ruan, K., Mogno, I., Tsuji, M., Carry, E., Brathwaite, J., Sims, S., Frolinger, T., et al. (2019). Heterogeneity in gut microbiota drive polyphenol metabolism that influences α -synuclein misfolding and toxicity. *J. Nutr. Biochem.* 64: 170–181.
- Hoenen, C., Gustin, A., Birck, C., Kirchmeyer, M., Beaume, N., Felten, P., Grandbarbe, L., Heuschling, P., and Heurtaux, T. (2016). Alpha-synuclein proteins promote pro-inflammatory cascades in microglia: stronger effects of the a53t mutant. *PLoS One* 11: e0162717.
- Hosseini, B., Saedisomeolia, A., Wood, L.G., Yaseri, M., and Tavasoli, S. (2016). Effects of pomegranate extract supplementation on inflammation in overweight and obese individuals: a randomized controlled clinical trial. *Compl. Ther. Clin. Pract.* 22: 44–50.
- Hwang, I.K., Yoo, K.Y., Li, H., Park, O.K., Lee, C.H., Choi, J.H., Jeong, Y.G., Lee, Y.L., Kim, Y.M., Kwon, Y.G., et al. (2009). Indole-3-propionic acid attenuates neuronal damage and oxidative stress in the ischemic hippocampus. *J. Neurosci. Res.* 87: 2126–2137.
- Iso, H. (2011). Lifestyle and cardiovascular disease in Japan. *J. Atherosclerosis Thromb.* 18: 83–88.

- Jalilpiran, Y., Jayedi, A., Djafarian, K., and Shab-Bidar, S. (2020). The Nordic diet and the risk of non-communicable chronic disease and mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Crit. Rev. Food Sci. Nutr.* 23: 1–13.
- Jiménez-Jiménez, F.J., Alonso-Navarro, H., García-Martín, E., and Agúndez, J.A.G. (2021). Cerebrospinal and blood levels of amino acids as potential biomarkers for Parkinson's disease: review and meta-analysis. Response to letter to the editor by Zheng et al. *Eur. J. Neurol.* 28: e13–e14.
- Katsouri, L., Lim, Y.M., Blondrath, K., Eleftheriadou, I., Lombardero, L., Birch, A.M., Mirzaei, N., Irvine, E.E., Mazarakis, N.D., and Sastre, M. (2016). PPAR γ -coactivator-1 α gene transfer reduces neuronal loss and amyloid- β generation by reducing β -secretase in an Alzheimer's disease model. *Proc. Natl. Acad. Sci. U.S.A.* 113: 12292–12297.
- Kaur, S., DasGupta, G., and Singh, S. (2019). Altered neurochemistry in Alzheimer's disease: targeting neurotransmitter receptor mechanisms and therapeutic strategy. *Neurophysiology* 51: 293–309.
- Kesika, P., Suganthy, N., Sivamaruthi, B.S., and Chaiyasut, C. (2021). Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. *Life Sci.* 264: 118627.
- Kim, D.H., Jeong, D., Kim, H., and Seo, K.H. (2019). Modern perspectives on the health benefits of kefir in next generation sequencing era: improvement of the host gut microbiota. *Crit. Rev. Food Sci. Nutr.* 59: 1782–1793.
- Kim, J., Shin, A., Lee, J.S., Youn, S., and Yoo, K.Y. (2009). Dietary factors and breast cancer in Korea: an ecological study. *Breast J.* 15: 683–686.
- Kowalski, K. and Mulak, A. (2019). Brain-gut-microbiota axis in Alzheimer's disease. *J. Neurogastroenterol. Motil.* 25: 48–60.
- Kujawska, M., Jourdes, M., Kurpiak, M., Szulc, M., Szafer, H., Chmielarz, P., Kreiner, G., Krajka-Kuźniak, V., Mikołajczak, P.L., Teissedre, P.L., et al. (2020). Neuroprotective effects of pomegranate juice against Parkinson's disease and presence of ellagitannins-derived metabolite—uroolithin A—in the brain. *Int. J. Mol. Sci.* 21: 202.
- Larsson, S.C. and Markus, H.S. (2017). Branched-chain amino acids and Alzheimer's disease: a Mendelian randomization analysis. *Sci. Rep.* 7: 13604.
- Lee, J., Torosyan, N., and Silverman, D.H. (2017). Examining the impact of grape consumption on brain metabolism and cognitive function in patients with mild decline in cognition: a double-blinded placebo controlled pilot study. *Exp. Gerontol.* 87: 121–128.
- Leitner, G.R., Wenzel, T.J., Marshall, N., Gates, E.J., and Klegeris, A. (2019). Targeting toll-like receptor 4 to modulate neuroinflammation in central nervous system disorders. *Expert Opin. Ther. Targets* 23: 865–882.
- Lennon, M.J., Makkar, S.R., Crawford, J.D., and Sachdev, P.S. (2019). Midlife hypertension and Alzheimer's disease: a Systematic review and meta-analysis. *J. Alzheim. Dis.* 71: 307–316.
- Ley, S.H., Hamdy, O., Mohan, V., and Hu, F.B. (2014). Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet* 383: 1999–2007.
- Lezi, E. and Swerdlow, R.H. (2012). Mitochondria in neurodegeneration. *Adv. Exp. Med. Biol.* 942: 269–286.
- Li, M.Z., Zheng, L.J., Shen, J., Li, X.Y., Zhang, Q., Bai, X., Wang, Q.S., and Ji, J.G. (2018). SIRT1 facilitates amyloid beta peptide degradation by upregulating lysosome number in primary astrocytes. *Neural Regen. Res.* 13: 2005–2013.
- Li, X., Wu, B., Wang, L., and Li, S. (2006). Extractable amounts of trans-resveratrol in seed and berry skin in Vitis evaluated at the germplasm level. *J. Agric. Food Chem.* 54: 8804–8811.
- Lin, M.T. and Beal, M.F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443: 787–795.
- Linnerbauer, M., Wheeler, M.A., and Quintana, F.J. (2020). Astrocyte crosstalk in CNS inflammation. *Neuron* 108: 608–622.
- Liu, G.S., Zhang, Z.S., Yang, B., and He, W. (2012). Resveratrol attenuates oxidative damage and ameliorates cognitive impairment in the brain of senescence-accelerated mice. *Life Sci.* 91: 872–877.
- Liu, J., Jiang, J., Qiu, J., Wang, L., Zhuo, J., Wang, B., Sun, D., Yu, S., and Lou, H. (2022). Urolithin A protects dopaminergic neurons in experimental models of Parkinson's disease by promoting mitochondrial biogenesis through the SIRT1/PGC-1 α signaling pathway. *Food Funct.* 13: 375–385.
- Mandrekar-Colucci, S. and Landreth, G.E. (2010). Microglia and inflammation in Alzheimer's disease. *CNS Neurol. Disord. - Drug Targets* 9: 156–167.
- Marino, A., Battaglini, M., Desii, A., Lavarello, C., Genchi, G., Petretto, A., and Ciofani, G. (2021). Liposomes loaded with polyphenol-rich grape pomace extracts protect from neurodegeneration in a rotenone-based in vitro model of Parkinson's disease. *Biomater. Sci.* 9: 8171–8188.
- Masato, A., Plotegher, N., Boassa, D., and Bubacco, L. (2019). Impaired dopamine metabolism in Parkinson's disease pathogenesis. *Mol. Neurodegener.* 14: 35.
- McFarland, L.V. (2021). Efficacy of single-strain probiotics versus multi-strain mixtures: systematic review of strain and disease specificity. *Dig. Dis. Sci.* 66: 694–704.
- Menet, M.C., Baron, S., Taghi, M., Diestra, R., Dargère, D., Laprévote, O., Nivet-Antoine, V., Beaudeau, J.L., Bédarida, T., and Cottart, C.H. (2017). Distribution of trans-resveratrol and its metabolites after acute or sustained administration in mouse heart, brain, and liver. *Mol. Nutr. Food Res.* 61: 1600686.
- Meng, X., Zhou, J., Zhao, C.N., Gan, R.Y., and Li, H.B. (2020). Health benefits and molecular mechanisms of resveratrol: a narrative review. *Foods* 9: 340.
- Micha, R., Peñalvo, J.L., Cudhea, F., Imamura, F., Rehm, C.D., and Mozaffarian, D. (2017). Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *J. Am. Med. Assoc.* 317: 912–924.
- Milo, R. and Kahana, E. (2010). Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmun. Rev.* 9: A387–A394.
- Mobeen, F., Sharma, V., and Tulika, P. (2018). Enterotype variations of the healthy human gut microbiome in different geographical regions. *Bioinformation* 14: 560–573.
- Mosele, J.I., Gosalbes, M.J., Macià, A., Rubió, L., Vázquez-Castellanos, J.F., Jiménez Hernández, N., Moya, A., Latorre, A., and Motilva, M.J. (2015). Effect of daily intake of pomegranate juice on fecal microbiota and feces metabolites from healthy volunteers. *Mol. Nutr. Food Res.* 59: 1942–1953.
- Moussa, C., Hebron, M., Huang, X., Ahn, J., Rissman, R.A., Aisen, P.S., and Turner, R.S. (2017). Resveratrol regulates neuroinflammation and induces adaptive immunity in Alzheimer's disease. *J. Neuroinflammation* 14: 1–10.

- Murueta-Goyena, A., Andikoetxea, A., Gómez-Esteban, J.C., and Gabilondo, I. (2019). Contribution of the GABAergic system to non-motor manifestations in premotor and early stages of Parkinson's disease. *Front. Pharmacol.* 10: 1294.
- Ni, J., Han, F., Yuan, J., Wang, H., Shen, D.C., Xu, Y., and Cui, L.Y. (2018). The discrepancy of neurological diseases between China and western countries in recent two decades. *Chin. Med. J.* 131: 886–891.
- Nurk, E., Refsum, H., Drevon, C.A., Tell, G.S., Nygaard, H.A., Engedal, K., and Smith, A.D. (2009). Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. *J. Nutr.* 139: 120–127.
- Nuttall, S.L., Kendall, M.J., Bombardelli, E., and Morazzoni, P. (1998). An evaluation of the antioxidant activity of a standardized grape seed extract Leucoselect®. *J. Clin. Pharm. Ther.* 23: 385–389.
- O'Gorman Tuura, R.L., Baumann, C.R., and Baumann-Vogel, H. (2018). Beyond dopamine: GABA, glutamate, and the axial symptoms of Parkinson disease. *Front. Neurol.* 9: 806.
- Ostadrahimi, A., Taghizadeh, A., Mobasseri, M., Farrin, N., Payahoo, L., Beyramalipour Gheshlaghi, Z., and Vahedjabbari, M. (2015). Effect of probiotic fermented milk (kefir) on glycemic control and lipid profile in type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Iran. J. Public Health* 44: 228–237.
- Pannu, N. and Bhatnagar, A. (2019). Resveratrol: from enhanced biosynthesis and bioavailability to multitargeting chronic diseases. *Biomed. Pharmacother.* 109: 2237–2251.
- Pardridge, W.M. (2009). Alzheimer's disease drug development and the problem of the blood-brain barrier. *Alzheimer's Dementia* 5: 427–432.
- Pereira, L. and Valado, A. (2021). The seaweed diet in prevention and treatment of the neurodegenerative diseases. *Mar. Drugs* 19: 128.
- Pereira, T., Côco, L., Ton, A., Meyrelles, S., Campos-Toimil, M., Campagnaro, B., and Vasquez, E. (2021). The emerging scenario of the gut-brain axis: the therapeutic actions of the new actor kefir against neurodegenerative diseases. *Antioxidants* 10: 1845.
- Pluta, R., Ulamek-Kozioł, M., Januszewski, S., and Czuczwar, S.J. (2018). From brain ischemia to Alzheimer-like neurodegeneration. *Neuropsychiatry* 8: 1708–1714.
- Prado, M.R., Blandón, L.M., Vandenberghe, L.P.S., Rodrigues, C., Castro, G.R., Thomaz-Soccol, V., and Soccol, C.R. (2015). Milk kefir: composition, microbial cultures, biological activities, and related products. *Front. Microbiol.* 6: 1177.
- Pražnikar, Z.J., Kenig, S., Vardjan, T., Bizjak, M.Č., and Petelin, A. (2020). Effects of kefir or milk supplementation on zonulin in overweight subjects. *J. Dairy Sci.* 103: 3961–3970.
- Rasines-Perea, Z. and Teissedre, P.L. (2017). Grape polyphenols' effects in human cardiovascular diseases and diabetes. *Molecules* 22: 68.
- Raza, C., Anjum, R., and Shakeel, N.U.A. (2019). Parkinson's disease: mechanisms, translational models and management strategies. *Life Sci.* 226: 77–90.
- Ruotolo, R., Calani, L., Fietta, E., Brighenti, F., Crozier, A., Meda, C., Maggi, A., Ottonello, S., and del Rio, D. (2013). Anti-estrogenic activity of a human resveratrol metabolite. *Nutr. Metabol. Cardiovasc. Dis.* 23: 1086–1092.
- Sampaio, T., Savall, A., Gutierrez, M., and Pinton, S. (2017). Neurotrophic factors in Alzheimer's and Parkinson's diseases: implications for pathogenesis and therapy. *Neural Regener. Res.* 12: 549–557.
- Sampson, T.R., Debelius, J.W., Thron, T., Janssen, S., Shastri, G.G., Ilhan, Z.E., Challis, C., Schretter, C.E., Rocha, S., Gradinaru, V., et al. (2016). Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167: 1469–1480.e12.
- Scheltens, P., de Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C.E., Cummings, J., and van der Flier, W.M. (2021). Alzheimer's disease. *Lancet* 397: 1577–1590.
- Schulze, M.B., Martínez-González, M.A., Fung, T.T., Lichtenstein, A.H., and Forouhi, N.G. (2018). Food based dietary patterns and chronic disease prevention. *Br. Med. J.* 361: k2396.
- Seppälä, T.T., Herukka, S.K., Hänninen, T., Tervo, S., Hallikainen, M., Soininen, H., and Pirttilä, T. (2010). Plasma Aβ42 and Aβ40 as markers of cognitive change in follow-up: a prospective, longitudinal, population-based cohort study. *J. Neurol. Neurosurg. Psychiatry* 81: 1123–1127.
- Shin, J.H., Ko, H.S., Kang, H., Lee, Y., Lee, Y.I., Pletinkova, O., Troconso, J.C., Dawson, V.L., and Dawson, T.M. (2011). PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. *Cell* 144: 689–702.
- Siddarth, P., Li, Z., Miller, K.J., Ercoli, L.M., Merrill, D.A., Henning, S.M., Heber, D., and Small, G.W. (2020). Randomized placebo-controlled study of the memory effects of pomegranate juice in middle-aged and older adults. *Am. J. Clin. Nutr.* 111: 170–177.
- Singh, C.K., Liu, X., and Ahmad, N. (2015). Resveratrol, in its natural combination in whole grape, for health promotion and disease management. *Ann. N. Y. Acad. Sci.* 1348: 150–160.
- Smith, L.M. and Parr-Brownlie, L.C. (2019). A neuroscience perspective of the gut theory of Parkinson's disease. *Eur. J. Neurosci.* 49: 817–823.
- Sommer, A., Winner, B., and Prots, I. (2017). The Trojan horse - neuroinflammatory impact of T cells in neurodegenerative diseases. *Mol. Neurodegener.* 12: 78.
- Sorrenti, V., Randazzo, C.L., Caggia, C., Ballistreri, G., Romeo, F.V., Fabroni, S., Timpanaro, N., Raffaele, M., and Vanella, L. (2019). Beneficial effects of pomegranate peel extract and probiotics on pre-adipocyte differentiation. *Front. Microbiol.* 10: 660.
- Springer, M. and Moco, S. (2019). Resveratrol and its human metabolites—effects on metabolic health and obesity. *Nutrients* 11: 1–17.
- Suez, J., Zmora, N., Segal, E., and Elinav, E. (2019). The pros, cons, and many unknowns of probiotics. *Nat. Med.* 25: 716–729.
- Sun, W., Shen, Y., Xiao, H., and Li, H. (2021). Resveratrol attenuates rotenone-induced inflammation and oxidative stress via STAT1 and Nrf2/Keap1/SLC7A11 pathway in a microglia cell line. *Pathol. Res. Pract.* 225: 153576.
- Sweeney, P., Park, H., Baumann, M., Dunlop, J., Frydman, J., Kopito, R., McCampbell, A., Leblanc, G., Venkateswaran, A., Nurmi, A., et al. (2017). Protein misfolding in neurodegenerative diseases: implications and strategies. *Transl. Neurodegener.* 6: 6.
- Szeto, J.Y.Y. and Lewis, S.J.G. (2016). Current treatment options for Alzheimer's disease and Parkinson's disease dementia. *Curr. Neuropharmacol.* 14: 326–338.
- Takata, K., Tomita, T., Okuno, T., Kinoshita, M., Koda, T., Honorat, J.A., Takei, M., Hagihara, K., Sugimoto, T., Mochizuki, H., et al. (2015). Dietary yeasts reduce inflammation in central nerve system via microflora. *Ann. Clin. Transl. Neurol.* 2: 56–66.

- Theilmann, M.C., Goh, Y.J., Nielsen, K.F., Klaenhammer, T.R., Barrangou, R., and Abou Hachem, M. (2017). *Lactobacillus acidophilus* metabolizes dietary plant glucosides and externalizes their bioactive phytochemicals. *mBio* 8: e01421-17.
- Ton, A.M.M., Campagnaro, B.P., Alves, G.A., Aires, R., Côco, L.Z., Arpini, C.M., Guerra e Oliveira, T., Campos-Toimil, M., Meyrelles, S.S., Pereira, T.M.C., et al. (2020). Oxidative stress and dementia in Alzheimer's patients: effects of synbiotic supplementation. *Oxid. Med. Cell. Longev.* 2020: 2638703.
- Tu, M.Y., Chen, H.L., Tung, Y.T., Kao, C.C., Hu, F.C., and Chen, C.M. (2015). Short-term effects of kefir-fermented milk consumption on bone mineral density and bone metabolism in a randomized clinical trial of osteoporotic patients. *PLoS One* 10: e0144231.
- Turner, R.S., Thomas, R.G., Craft, S., van Dyck, C.H., Mintzer, J., Reynolds, B.A., Brewer, J.B., Rissman, R.A., Raman, R., and Aisen, P.S. (2015). A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology* 85: 1383–1391.
- van de Wouw, M., Walsh, A.M., Crispie, F., van Leuven, L., Lyte, J.M., Boehme, M., Clarke, G., Dinan, T.G., Cotter, P.D., and Cryan, J.F. (2020). Distinct actions of the fermented beverage kefir on host behaviour, immunity and microbiome gut-brain modules in the mouse. *Microbiome* 8: 67.
- Vijayan, M. and Reddy, P.H. (2016). Stroke, vascular dementia, and Alzheimer's disease: molecular links. *J. Alzheim. Dis.* 54: 427–443.
- Vislocky, L.M. and Fernandez, M.L. (2010). Biomedical effects of grape products. *Nutr. Rev.* 68: 656–670.
- Wang, D., Ho, L., Faith, J., Ono, K., Janle, E.M., Lachcik, P.J., Cooper, B.R., Jannasch, A.H., D'Arcy, B.R., Williams, B.A., et al. (2015a). Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease β -amyloid oligomerization. *Mol. Nutr. Food Res.* 59: 1025–1040.
- Wang, Q., Liu, Y., and Zhou, J. (2015b). Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl. Neurodegener.* 4: 19.
- Wang, X., Sun, G., Feng, T., Zhang, J., Huang, X., Wang, T., Xie, Z., Chu, X., Yang, J., Wang, H., et al. (2019). Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res.* 29: 787–803.
- Wastyk, H.C., Fragiadakis, G.K., Perelman, D., Dahan, D., Merrill, B.D., Yu, F.B., Topf, M., Gonzalez, C.G., van Treuren, W., Han, S., et al. (2021). Gut-microbiota-targeted diets modulate human immune status. *Cell* 184: 4137–4153.e14.
- Wenzel, T.J., Gates, E.J., Ranger, A.L., and Klegeris, A. (2020). Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. *Mol. Cell. Neurosci.* 105: 103493.
- Wissmann, P., Geisler, S., Leblhuber, F., and Fuchs, D. (2013). Immune activation in patients with Alzheimer's disease is associated with high serum phenylalanine concentrations. *J. Neurol. Sci.* 329: 29–33.
- Wu, Y., Li, X., Zhu, J.X., Xie, W., Le, W., Fan, Z., Jankovic, J., and Pan, T. (2011). Resveratrol-activated AMPK/SIRT1/autophagy in cellular models of Parkinson's disease. *Neurosignals* 19: 163–174.
- Xiao, S., Chan, P., Wang, T., Hong, Z., Wang, S., Kuang, W., He, J., Pan, X., Zhou, Y., Ji, Y., et al. (2021). A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. *Alzheimer's Res. Ther.* 13: 62.
- Yang, J., Kurnia, P., Henning, S.M., Lee, R., Huang, J., Garcia, M.C., Surampudi, V., Heber, D., and Li, Z. (2021). Effect of standardized grape powder consumption on the gut microbiome of healthy subjects: a pilot study. *Nutrients* 13: 3965.
- Yasuda, T., Nakata, Y., and Mochizuki, H. (2013). α -Synuclein and neuronal cell death. *Mol. Neurobiol.* 47: 466–483.
- Yemula, N., Dietrich, C., Dostal, V., and Hornberger, M. (2021). Parkinson's disease and the gut: symptoms, nutrition, and microbiota. *Parkinson's Dis.* 11: 1491–1505.
- Yılmaz, İ., Enver Dolar, M., and Özpınar, H. (2019). Effect of administering kefir on the changes in fecal microbiota and symptoms of inflammatory bowel disease: a randomized controlled trial. *Turk. J. Gastroenterol.* 30: 242–253.
- Zhang, B., Xu, Y., Lv, H., Pang, W., Wang, J., Ma, H., and Wang, S. (2021). Intestinal pharmacokinetics of resveratrol and regulatory effects of resveratrol metabolites on gut barrier and gut microbiota. *Food Chem.* 357: 129532.
- Zhang, F., Wang, Y.Y., Liu, H., Lu, Y.F., Wu, Q., Liu, J., and Shi, J.S. (2012). Resveratrol produces neurotrophic effects on cultured dopaminergic neurons through prompting astroglial BDNF and GDNF release. *J. Evidence-Based Complementary Altern. Med.* 2012: 937605.
- Zhao, Z.H., Xin, F.Z., Xue, Y., Hu, Z., Han, Y., Ma, F., Zhou, D., Liu, X.L., Cui, A., Liu, Z., et al. (2019). Indole-3-propionic acid inhibits gut dysbiosis and endotoxin leakage to attenuate steatohepatitis in rats. *Exp. Mol. Med.* 51: 103.
- Zhou, L., Xiao, X., Zhang, Q., Zheng, J., and Deng, M. (2019). Deciphering the anti-obesity benefits of resveratrol: the "gut microbiota-adipose tissue" axis. *Front. Endocrinol.* 10: 413.