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Revisión / Review

Pharmacotherapeutic potential of *Vitis vinifera* (grape) in age-related neurological diseases

[Potencial farmacoterapéutico de *Vitis vinifera* (uva) en enfermedades neurológicas asociadas a la edad]

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Abstract: Age-related neurological disorders (ANDs), including neurodegenerative diseases, are complex illnesses with an increasing risk with advancing years. The central nervous system's neuropathological conditions, including oxidative stress, neuroinflammation, and protein misfolding, are what define ANDs. Due to the rise in age-dependent prevalence, efforts have been made to combat ANDs. *Vitis vinifera* has a long history of usage to treat a variety of illness symptoms. Because multiple ligand sites may be targeted, *Vitis vinifera* components can be employed to treat ANDs. This is demonstrated by the link between the structure and action of these compounds. This review demonstrates that *Vitis vinifera* and its constituents, including flavonoids, phenolic compounds, stilbenoids and aromatic acids, are effective at reducing the neurological symptoms and pathological conditions of ANDs. This is done by acting as an antioxidant and anti-inflammatory. The active Vitis vinifera ingredients have therapeutic effects on ANDs, as this review explains.

Keywords: Pharmacotherapeutic; Neurological diseases; Neurodegenerative diseases; Review; *Vitis vinífera*

Resumen: Las enfermedades neurológicas asociadas a la edad (AND, por su sigla en inglés) incluyendo las enfermedades neurodegenerativas, son enfermedades complejas con un riesgo creciente con la edad. Las condiciones neuropatológicas del sistema nervioso central, que incluyen el estrés oxidativo, la neuro inflamación, y el plegado erróneo de proteínas, son lo que define las AND. Debido al aumento en la prevalencia dependiente de la edad, se han hecho esfuerzos para combatir las AND. Vitis vinifera tiene una larga historia de uso para el tratamiento de síntomas. Puesto que puede hacer objetivo a muchos sitios ligando, los componentes de *Vitis vinifera* se pueden utilizar para tratar AND. Esto se demuestra por el vínculo entre la estructura y la acción de estos compuestos. Esta revisión demuestra que la *Vitis vinifera* y sus constituyentes, incluídos los flavonoides, componentes fenólicos, estilbenoides, y ácidos aromáticos, son efectivos para reducir los síntomas neurológicos y las condiciones patológicas de AND. Esto se produce por su acción como antioxidante y antiinflamatorio. Los ingredientes activos de Vitis vinifera tienen efectos terapéuticos en AND, y esta revisión lo explica

Palabras clave: Farmacoterapia; Enfermedades neurológicas; Enfermedades neurodegenerativas; Revisión; *Vitis vinifera*

INTRODUCTION

Increased life expectancy is associated with an increase in the average age of the population and a higher prevalence of age-related diseases (Calapai *et al*., 2017). According to recent studies, the aging process begins with microscopic changes at the molecular levels. These changes include telomere destruction, mutation accumulation, and epigenetic changes that lead to genomic inconsistency. These defects increase over time and cause morphological and functional changes in the structure of the brain such as progressive reduction of neurons, excessive inflammation, decreased levels of neurotransmitters, and loss of vascular integrity leading to microbleeds and infarction (Kowalska *et al*., 2017). Aging is the major risk factor for neurological diseases because compared to other organs, the brain is more susceptible to the aging process (Wyss-Coray, 2016). The brain is the most important target organ in uncontrollable stress conditions due to its high oxidative metabolism. High levels of cortisol cause the destruction of brain neurons, accelerate neurodegenerative processes, reduce growth hormone, and lead to oxidative stress by releasing pro-inflammatory cytokines. 50 to 60% of the lipids that make up the brain are unsaturated, which makes the brain more prone to lipoperoxidation and the formation of secondary compounds such as isoprostanes, acrolein, and malondialdehyde. Lipoperoxidation changes can lead to cell dysfunction and brain cell death. It can also alter the structure of proteins, leading to neurodegenerative disease. On the other hand, in these conditions, the concentration of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase are low (Pazos-Tomas *et al*., 2020). Age-related neurological diseases (ANDs) are defined as a group of multifactorial diseases with common pathological aspects such as oxidative stress, loss of neurons, abnormal protein accumulation in the central nervous system, and neuroinflammation (Buendia *et al*., 2016).Various methods have been proposed to support healthy aging (Fuhrman *et al*., 2005). There is no definitive cure for ANDs, and there are only a few approved drugs to treat this disease but not for prevention (Bhullar & Rupasinghe, 2013).

Various investigations have shown that natural antioxidants might prevent the overproduction of free radicals. Hence, these nature-derived components might control the onset of the disease and prevent the exacerbation of many diseases that are related to redox-derived stressors and oxidative stress, such as aging, basically by suppressing the oxidative process (Bjørklund *et al*., 2018).

Grape (*Vitis vinifera* L.) is known as one of the oldest plants that have high nutritional and medicinal value and is used as a herbal medicine in many diseases (Ardid-Ruiz *et al*., 2020). Grapes are used in traditional medicine due to their high nutritional value and large amounts of polyphenols, organic acids, minerals, and vitamins (Ibrahim Fouad & Zaki Rizk, 2019). The positive effects of *Vitis vinifera* on health are mainly due to the amounts of phenols. The highest amount of phenol is in the seed of this fruit. The phenols in the seeds are catechin, gallic acid, and epicatechin, while myricetin and ellagic acid are located in the skin of the grape. *Vitis vinifera* is known for its high amounts of polyphenols and antioxidants, which have anti-cancer effects, anti-inflammatory properties, nootropic activity, and antimicrobial and anti-viral activities. These components also can inhibit peroxidation activities which are induced by UV radiation (Lakshmi *et al*., 2014). These activities have been examined *in vivo* and *in vitro* in humans and animals (Natarajan *et al*., 2017). According to the positive effects of *Vitis vinifera*, many drugs are being developed to treat or prevent many diseases, including neurodegenerative diseases (Wang *et al*., 2012).

There is a lack of such an approach about the role of *Vitis vinifera* in neurological disorders. Hence, in the recent review, we aimed to assess the pharmacotherapeutic potential of Vitis vinifera (grape) in age-related neurological diseases.

METHOD

In order to compile this paper, we searched the internet for relevant studies on the pharmacotherapeutic potential of grape in age-related neurological disorders (ANDs). To discover relevant publications up to September 2022, we searched Google Scholar, PubMed, and Scopus. We applied appropriate search tactics and Mesh keywords for each database.

Our search strategy on PubMed is shown below: ((((((((((((grape[Title/Abstract]) OR (*Vitis vinifera* l.[Title/Abstract]))) AND (oxidative stress[Title/Abstract])) OR (parkinson's[Title/Abstract])) OR (multiple

sclerosis[Title/Abstract])) OR (migraine[Title/Abstract])) OR (alzhiemer's[Title/Abstract])) OR (stroke[Title/Abstract])) OR (neuroinflammation[Title/Abstract])) OR (brain tumor[Title/Abstract])) OR (epilepsy[Title/Abstract])) OR (dementia[Title/Abstract])) OR (apoptosis[Title/Abstract]).

After choosing all of the studies on the impact of grapes on ANDs, we eliminated the redundant ones and limited some of them by reading the abstracts. oAfter manually checking and controlling all references, we looked up any missing articles in the references of the articles we had already discovered.

Alzheimer's disease

Alzheimer's disease is a central nervous system neurodegenerative condition that is linked to aging and is characterized by selective neuronal loss. The accumulation of senile plaques in the brains of Alzheimer's patients is thought to be caused by excessive β-amyloid (Aβ). ROS are produced by Aβ. Enhancing or potentiating endogenous oxidative defense capability by dietary or pharmaceutical consumption of antioxidants is one potential strategy for preventing the cellular damage brought on by oxidative stress. Resveratrol, a polyphenolic phytoalexin present in grape seeds and skin, is regarded as one of the chemicals that might help prevent neurological disorders like AD. The studies of Li *et al*. (2004), looked at the potential protective benefits of Oligonol, Oligonol is a polyphenol derived from lychee fruit that is produced by an oligomerization process that converts high-molecular-weight polyphenol polymers into low-molecular-weight oligomers. It contains catechin-type monomers and oligomers of proanthocyanidins.

Received message. Oligonol is a polyphenol derived from lychee fruit that is produced by an oligomerization process that converts high-molecular-weight polyphenol polymers into low-molecular-weight oligomers. It contains catechin-type monomers and oligomers of proanthocyanidins. a polyphenolic preparation rich in oligomers and obtained from grape seed extracts, on apoptotic cell death brought on by Aβ in cultured pheochromocytoma (PC12) cells. In conclusion, Oligonol and grape seed polyphenol prevented Aβ from inducing oxidative stress, which led to apoptosis in Rat PC12 cells (Li *et al*., 2004). It is difficult to determine the pathophysiology of AD, which makes it difficult to treat. AD is defined by interactions between several associated biological and pathologic pathways, including hereditary and environmental variables, age, education, and lifestyle. The major characteristics of AD are intracellular abnormal buildup of hyperphosphorylated Tau tangles and extracellular aggregation of A plaques. Plaques and neurofibrillary tangle density are associated with high inflammatory pathway activation, mitochondrial dysfunction, energy depletion, etc. All these events cause synapse loss and neuronal death, which ultimately show up in patients as gradual neurocognitive impairment, linguistic changes, and a persistent decline in a person's capacity to carry out daily tasks. The production of amyloid plaques and neurofibrillary tangles, AD-induced oxidative stress, neuro inflammatory, and synaptic dysfunction are all examples of the pathophysiology that grape-derived polyphenols have been demonstrated to influence in this review by El Gaamouch *et al*. (2021). *In vitro*, grape seed extracts disrupt the formation of misfolded A-peptide aggregates and prevent their buildup. According to preclinical research, grape polyphenols reduce Aβ-mediated neuropathology by preventing Aβ from being produced, boosting Aβ clearance, and preventing Aβ from oligomerizing. Grape polyphenols work as powerful antioxidants and anti-inflammatory agents that protect against inflammation and increase the brain's resistance to AD and associated dementia (El Gaamouch *et al*., 2021). Cell counting kit 8 and lactate dehydrogenase tests were used in the research by Lian *et al*. (2016), to assess the effects of grape seed proanthocyanidin on PC12 cell viability. This study showed that therapy with grape seed proanthocyanidin reduces the formation or aggregation of amyloid precursor protein (APP), lowers the buildup of neurotoxic Aβ, and stops the deposition of hyperphosphorylated tau. In vivo preclinical research and *in vitro* biochemical studies' findings indicated that grape seed proanthocyanidin treatment could influence AD through two, non-exclusive mechanisms: i) Boost antioxidant activity, ii) downregulation of oxidative stress-induced Aβ buildup caused by caspase 3 (Lian *et al*., 2016).

Memory loss is a typical symptom of the group of cognitive illnesses known as dementia.

Alzheimer's disease is connected to 60–80 percent of dementia cases (Alzheimer's Association, 2019). Alzheimer's disease is a fatal neurological condition that progresses over time. The main risk factor for Alzheimer's disease is aging (Ferri *et al*., 2005).

Maviz is a unique variety of raisins with limited production. These raisins are naturally sun-dried which helps give the product its natural sweetness, taste and texture. They are large dried berries of black grapes and are more powerful and complete in terms of properties than raisins and green grapes. They are also known as black raisins. The antioxidant and radical-scavenging ability of Maviz extracts as well as their anti-Alzheimer activity were assessed in the study by Bakhtiyari *et al*. (2017). Male Wistar rats were injected with a dosage of 5 μL of beta Amyloid peptidesbe 1-42 (Aβ) solution (10 ng/μL) in the frontal brain to test the anti-Alzheimer properties of Maviz extracts. Beta Amyloid peptides 1-42 (Aβ) were not administered to the control group; instead, sterile phosphate-buffered saline was given. Rats were separated into four treatment groups and given ethanolic extracts of Maviz fruit and seed at dosages of 300 mg/kg and 350 mg/kg, respectively, and aqueous extracts of Maviz fruit and seed at doses of 150 mg/kg and 50 mg/kg, respectively. This therapy was given eight days after injection. One group received simply standard saline treatment. Morris water maze tests and passive avoidance tests were used to examine behavioral changes in rats. Radical scavenging activity was examined using 2,2-diphenyl-1-picrylhydrazyl, and the activities of superoxide dismutase and catalase were measured in three rats from each group. The findings of this investigation suggest that the Maviz seed ethanolic extract contains the greatest concentrations of phenolic components and the strongest radical scavenging properties. The most effective defense against beta Amyloid peptides 1-42 injection, however, is provided by Maviz fruit extracts (ethanolic and aqueous), which also have anti-Alzheimer effects. According to studies, the anti-Alzheimer properties of Maviz are attributed to the fruit's high concentrations of 5-hydroxymethylfurfural and 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (Bakhtiyari *et al*., 2017).

The impact of dietary polyphenols from curcumin or grape seed extract on genomic instability events in a transgenic mice model for AD was evaluated in the study by Thomas *et al*. (2009). In order to do this, DNA damage was examined using the absolute telomere length assay on olfactory bulb tissue and buccal mucosa, as well as the micronucleus assay on erythrocytes and buccal mucosa. According to the study's findings, mice fed with micro-encapsulated grape seed extract plus curcumin saw a 10-fold reduction in buccal micronucleus frequency compared to the control group, whereas mice treated with grape seed extract experienced a 7-fold reduction. Additionally, mice treated with micro-encapsulated grape seed extract showed a striking reduction in polychromatic erythrocyte micronucleus frequency as compared to the control group. Contrarily, there was no appreciable reduction in the incidence of erythrocyte micronuclei in mice given grape seed extract plus curcumin. Mice treated with curcumin, micro-encapsulated grape seed extract, and grape seed extract showed a non-significant increase in buccal cell telomere length. In mice treated with curcumin, there was a negligible increase in telomere length in the olfactory bulb compared to the control group. The findings of this study show that substances containing polyphenols may have a significant influence in genomic instability in transgenic mice used to study Alzheimer's disease (Thomas e*t al*., 2009).

In the research by Dal-Pan *et al*. (2017), the benefits of a polyphenol-rich fruit extract on an animal model of Alzheimer's disease were assessed for their ability to improve cognition without altering neuropathology. The mice employed in this investigation were 12-month-old triple-transgenic and non-transgenic models of Alzheimer's disease (15 - 20 mice in each group). Three groups of triple-transgenic mice were used to study the disease: the control group had a normal diet; the two other groups received a dosage of 500 mg/kg of polyphenolic extract from blueberries and grapes and 2500 mg/kg of polyphenolic extract from the same sources. Three groups of non-transgenic mice were created: those who consumed a regular diet, those who received a dosage of 500 mg/kg of polyphenolic extract from blueberries and grapes, and those who received a dose of 2500 mg/kg of polyphenolic extract from the same fruits. All mice were slaughtered at the age of 16 months after the animals were given a cognitive examination after three months. The findings of this study show that both non-transgenic and triple-transgenic mice models of Alzheimer's disease

improved on cognitive tests after receiving a three-month therapy with polyphenolic extract from blueberries and grapes. Both groups of mice did not experience a decline in cognitive ability thanks to polyphenolic extract from blueberries and grapes. Although this benefit was more pronounced and dose-dependent in triple-transgenic mice that received blueberry and grape polyphenolic extract as food. Amyloid β plaques and neurofibrillary tangles are two of the neuropathological symptoms of Alzheimer's disease (Tremblay *et al*., 2007; Nelson *et al*., 2012; Montine *et al.*, 2016). The findings demonstrate that the neuropathological indicators of Alzheimer's disease in the mouse brain were unaffected by polyphenolic extract from blueberries and grapes. Additionally, the energy, synaptic, and inflammatory metabolism in the triple-transgenic mouse model of Alzheimer's disease was unaffected by the polyphenolic extract from blueberries and grapes. According to a plasma examination of mice, mice given polyphenolic extract from blueberries and grapes have metabolites like catechin and epicatechin in their blood.

The enhancement of mouse memory performance is directly correlated with the concentrations of 2-hydroxybenzoic acid, dihydroxyphenyl valerolactone, and hydroxyphenylpropionic acid. Triple-transgenic mouse models of Alzheimer's disease had blood concentrations of some metabolites that were higher than those of non-transgenic mice, including 2-hydroxybenzoic acid, catechins glucuronide, and methyl catechins glucuronide, while others, including hydroxyphenylvaleric acid, were lower.

The conclusion is that polyphenols can influence behavior through their metabolites. Brain derived neurotrophic factor has been investigated as a potential therapy for neurodegenerative diseases like Alzheimer's disease for a number of years, however it cannot pass the blood-brain barrier (Kazim *et al*., 2014). On the other side, it has been shown that people with Alzheimer's disease have altered levels of brain derived neurotrophic factor in their brains (Shin *et al.*, 2014). The concentration of brain-derived neurotrophic factor reached acceptable levels after treatment with polyphenolic extract from blueberries and grapes, and the cognitive activities of mice were enhanced (Dal-Pan *et al*., 2017).

The potential benefits of grape seed polyphenol extract on memory impairments caused by chronic cerebral hypoperfusion in rats were assessed in the study by Chen *et al*. (2017). One of the primary causes of Alzheimer's disease and vascular dementia is chronic cerebral hypoperfusion. By permanently and bilaterally occluding the common carotid artery, memory impairment brought on by chronic cerebral hypoperfusion was replicated in rats to study the effects of grape seed polyphenol extract. To assess mice's memory, the Morris water maze test was performed. By testing the levels of acetylcholine, acetylcholinesterase, and choline, cholinergic function was assessed. To assess oxidative stress, the activities of catalase, malonic dialdehyde, glutathione peroxidase, and superoxide dismutase were assessed. According to the study's findings, memory deficits in rats that were given grape seed polyphenol extract for a month might be reduced. Additionally, the results of this study show that feeding rats a grape seed polyphenol extract improves cholinergic neuronal function and reduces oxidative stress in the hippocampus of chronic cerebral hypoperfusion rat models. According to the results of this study, grape seed polyphenol extract may enhance memory by lowering oxidative stress and cholinergic dysfunction (Chen *et al*., 2017).

The anti-dementia effects and mechanism of grape peel extracts on imitative dementia rat models were evaluated in the study by MS et al. $NaNO_2$, D-galactose, Piracetam Tablets, and physiological saline solution were intraperitoneally injected into healthy male Wistar rats to imitate dementia. Mice were injected with low, medium, and high doses of grape peel extract. According to the study's findings, grape peel extracts can considerably enhance learning and memory abilities. Nitric oxide synthase, superoxide dismutase, and catalase enzyme activity in rat brain are all enhanced by grape peel extracts. On the other hand, grape peel extracts stop the acetylcholinesterase and malondialdehyde enzymes from working. It can lessen the expression of beta-amyloid- and beta-APP-positive immunoreactive neurocytes in the cerebral cortex and hippocampus (Long *et al*., 2006).

A study by Rapaka *et al*. (2019), assessed *Vitis Vinifera*'s anti-neuroprotective Alzheimer's properties. Aluminum chloride was administered to Sprague-Dawley rats for 8 weeks, and the toxin impact of aluminum resulted in a decline in the animals' capacity for memory and learning in the Morris water maze test. Following that, *Vitis vinifera*

was given for 16 weeks at doses of 250 mg/kg and 500 mg/kg. *Vitis vinifera* altered the expression of the APP and Tau genes, lowered the production of amyloid plaques and Tau tangles, and decreased inflammation, oxidative stress, and cholinergic activities. According to this study, *Vitis vinifera* may be an excellent option for treating AD (Rapaka *et al*., 2019).

In another study, it was found that the polysaccharide from *Vitis vinifera* L. (VTP) significantly affects the production of TNF-a, IL6 and IL1b, as well as the expression of the phosphorylated NF-κBp65 protein. Donezepil and VTP (a daily serving of 80 grams of whole grape powder for six months) were administered to rats with AD after amyloid-β25-35 injection. Learning and memory were improved, and the harmful effects of amyloid-β25-35 were diminished. Levels of phosphorylation, gene and protein expression, and RNA levels of NF-κBp65 and IκB-α were also altered (Ma *et al*., 2018).

In their work, Russo *et al*. (2003), set out to see if the combination of micronutrients in black grape skin could shield human umbilical vein endothelial cells (HUVECs) against the toxicity of 25-35 h-amyloid peptide or serum from Alzheimer's patients. Human umbilical vein endothelial cells were created using a combination of human umbilical cords from healthy women who had healthy babies at term. The medium was replaced every three days while the cultures were kept for 12 days at 37°C in an environment that was humidified with 95% air and 5% CO_2. Serum from aged healthy persons or patients with Alzheimer's disease was used to treat the cells, and serum-free medium was used for the final medium change. Results from the COMET experiment was analyzed to determine DNA fragmentation, mitochondrial complex activity, reactive oxygen species (ROS) production, malonyl dialdehyde (MDA) levels, and lactic dehydrogenase (LDH) release to determine cytoplasmic membrane breakdown. The experiments' findings indicate that black grape skin extract reduces the production of ROS, protects cellular membranes from oxidative damage, and prevents DNA breakage. When treating AD disease, this natural chemical may be used to halt the progression of pathology (Russo *et al*., 2003).

The goal of studies by Wang *et al*. (2010), was to assess the physicochemical properties of grape seed derived polyphenolic extract (GSPE) in spontaneous tau aggregation as well as the *in vivo* efficacy of GSPE in preventing tau-mediated neuropathology in mouse models of AD-type tauopathy.

To evaluate the preventive efficacy of GSPE in tau-mediated neuropathology, TMHT mice were given 200 mg/kg/day of GSPE beginning at 3 months old, prior to the onset of mutant tau-mediated neurodegeneration, and continued for two months. Mice were sacrificed with their heads severed following anesthesia. Brains that had been harvested and hemisected were used. One hemisphere was washed, fixed with 4% paraformaldehyde, and paraffin embedded for histological study. One hemisphere was promptly frozen, ground in liquid nitrogen, and maintained at 80°C for biochemical investigation (Wang *et al*., 2010).

According to the research, oral administration of grape seed-derived polyphenolic extract (GSPE) significantly reduced the development of tau neuropathology in TMHT mice, a model for Alzheimer's disease. This was achieved by mechanisms including lessened activation of the brain's extracellular signal-receptor kinase 1/2. GSPE inhibits tau aggregation *in vitro*, tau neuropathology in the THMT animal model of tauopathy, and tau neuropathology *in vivo* in addition to reducing tau hyperphosphorylation (Wang *et al*., 2010).

In a study by Wang *et al*. (2008), the potential use of grape seed polyphenolic extract (GSPE), a highly pure and thoroughly described water-soluble polyphenolic preparation from the seeds of *Vitis vinifera*, as a nutraceutical substitute for moderate red wine consumption to slow cognitive decline associated with AD is looked at. Adult female Tg2576 mice, which showed a more robust plaque neuropathology and a lower death rate than the male Tg2576 animals, were separated into the GSPE treatment group and the water control group. For feeding, mice got 200 mg/kg/d of GSPE in their water. Drinking solutions were changed every three days. The mice were sedated for five months with the general anesthetics ketamine HCl and xylazine before being beheaded (Wang *et al*., 2008).

The results show that GSPE decreases Abeta peptide oligomerization in vitro, indicating that grape seed-derived polyphenolics may be efficient Alzheimer's disease preventative or therapeutic agents. By preventing Abeta peptide oligomerization, GPSE therapy lessens amyloid-related cognitive impairments in Tg2576 mice and reduces brain

amyloid neuropathology (Wang *et al*., 2008).

The misfolding and eventual buildup of tau proteins, which appear to be related to microtubule structures, can result in paired helical filaments and tangle neurofibers, which can contribute to Alzheimer's disease (AD).

The ultrastructural changes of paired helical filaments derived from autopsied brains of AD patients by grape seed-originated polyphenol extract (GSPE) were examined in the study by Ksiezak-Reding et al. because it has recently been demonstrated that GSPE has a decreasing effect on the pathologic collection of tau in rodent models. The architectures of paired helical filaments were altered by GSPE, which also increased the width of the filaments and partially destroyed them. Tau consistency was also diminished. Additionally, GSPE had an impact on the immunogold assay; it might really change the way antibodies behaved in different areas of the body. Since the length of tau polypeptides and their phospho-epitope components remained intact, the benefits of GSPE have not been associated with a breakdown of covalent bonds; rather, the study suggests that GSPE may have impacts on proline dominated portions of tau. Considering the methods described, the authors suggest GSPE as a viable AD therapy (Wang *et al*., 2010, Ksiezak-Reding *et al*., 2012).

In a different study conducted by Siahmard *et al*. (2012), male rats were given injections of streptozocin in both lateral ventricles of the brain to cause AD by causing a biochemical and oxidative imbalance, and then were given diluted grape extract to examine the association between *Vitis vinifera* juice consumption and AD. The passive avoidance test data showed that AD rat models had their memory and learning abilities reduced, while AD rat models that drank red grape juice had their memory and learning abilities improved. Consequently, it is advised to employ *Vitis vinifera* in the future to prevent the progression of AD (Siahmard *et al*., 2012).

The loss of memory and cognition is thought to be a result of aluminum exposure, one of the major pathogenic causes of Alzheimer's disease. showed that *V. vinifera* could exert significant favorable effects on biochemical variables and limit the mRNA expression of tau and amyloid precursor protein, hence introducing neuroprotective effects on rat models of AD (Rapaka *et al*., 2019).

Another study by Ma *et al*. (2018), showed that VTP (a daily serving of 80 grams of whole grape powder for six months) suppressed the expression of IL-1B, IL-6, and TNF-α as well as decreased levels of NF-κBp65, p-IκB-α, IκB-α, and NF-κBp65 and IκB-α mRNA in addition to improving memory and learning function in rat models. Because of its anti-inflammatory properties, the results above point to VTP as a potential treatment drug for AD (Ma *et al*., 2018) (Figure No. 1).

Epilepsy

The neuroprotective and anticonvulsant effects of organic and conventional purple grape juices on seizures in Wistar rats caused by pentylenetetrazole were examined in an article in a study by Dalpicolli Rodrigues *et al*. (2012) (PTZ). They also assessed the behavioral alterations and polyphenolic properties of the mice given grape juice. For 17 days, they administered saline and regular or natural grape juice to these animals. On the 18th day, they continued the treatment for 30 minutes following exposure. After receiving PTZ, individuals were evaluated for any potential convulsions. Research has demonstrated that polyphenols including resveratrol (97), (-)-epigallocatechingallate (95), flavan-3-ol derivatives (96), and 6-methylflavanone (94), are GABA receptor regulators. Grape fruit juice contains a lot of these antioxidants (Dani *et al*., 2007). Resveratrol and flavan-3-ol derivatives are present in both grape juices, however neither was able to prevent the seizures brought on by PTZ (as measured by using tonic-clonic seizure time, overall seizure time, range of seizure and number of seizures achieving degree 5 on). This result can be explained by the fact that grape juice contains fewer polyphenols than those that have been shown to be effective at binding to GABA receptors (96, 97). PTZ has the potential to increase oxidative damage to lipids and proteins (Obay *et al*., 2008; Nazıroğlu *et al*., 2009; Silva *et al*., 2009). All brain tissue is damaged, which results in epilepsy. Organic grape juice, in contrast to regular grape juice, lowers SOD and CAT activity (which is the PTZ mechanism). According to prior research on the use of isopolgel (101), ghrelin (100), and erdosteine (102), all in the treatment of rats. These studies demonstrate that grape juice, whether regular or natural, has identical neuroprotective properties, making it safe for usage in epilepsy patients.

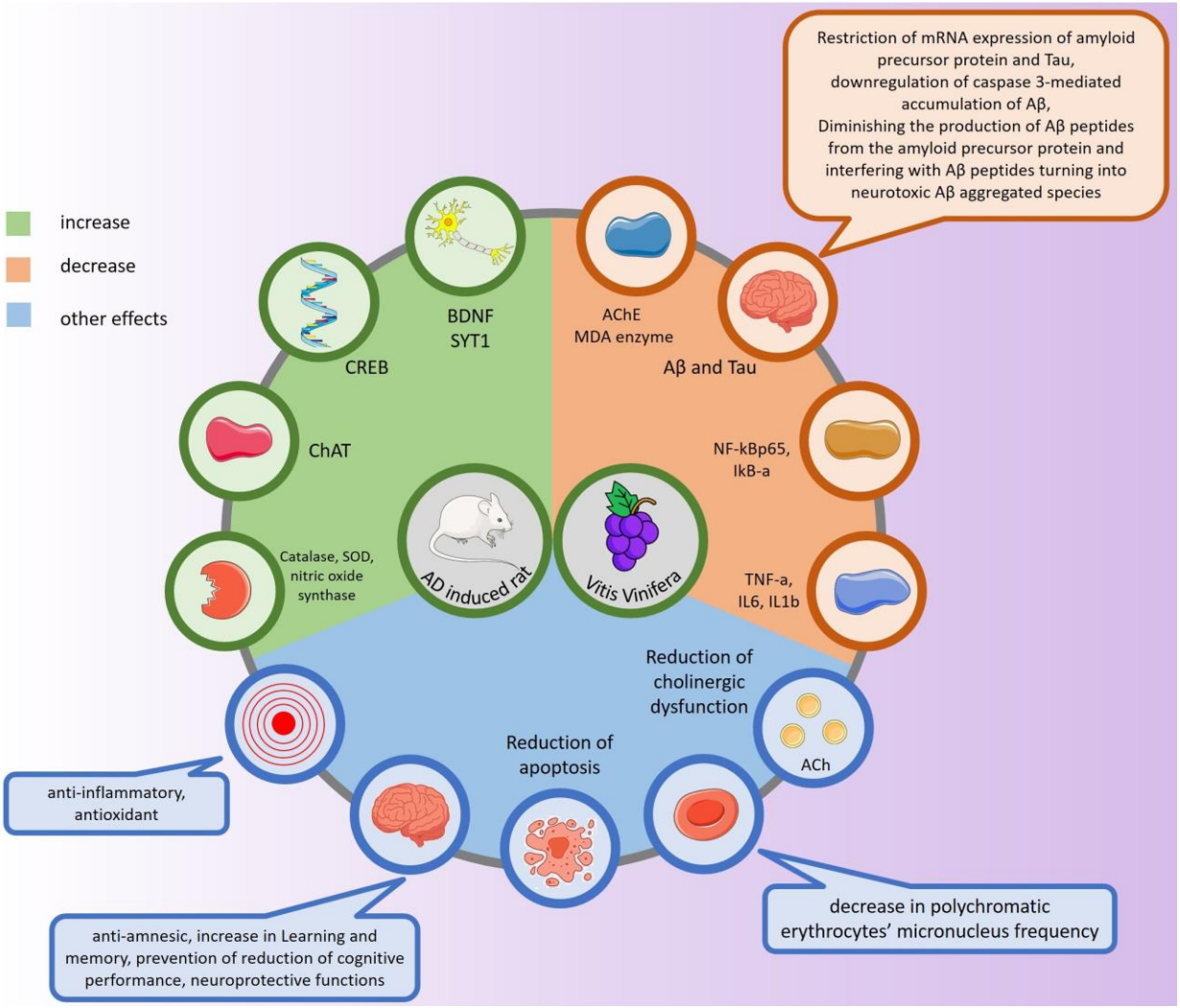

Figure No. 1
A summary of effects of *Vitis vinifera* in AD-induced rats/mice; AChE: acetylcholinesterase; MDA: malondialdehyde; Aβ: Amyloid beta; NF-kB: Nuclear factor kappa B; TNF: tumor necrosis factor; IL: interleukin; ACh: acetylcholine; SOD: superoxide dismutase; ChAT: choline acetyltransferase; CREB: cAMP-response element binding protein; BDNF: Brain-derived neurotrophic factor; SYT1: Synaptotagmin-1

Parkinson's disease (PD)

The prevalence of Parkinson's disease (PD), the second most prevalent neurodegenerative condition, is approximately 1-2% in the elderly (Gazewood *et al*., 2013). Parkinson's disease is characterized by rigidity, bradykinesia, resting tremor, and postural instability (Blochberger & Jones, 2011). In the substantia nigra, PD is correlated with a gradual loss of neurons. (Van Kampen *et al*., 2003). The most significant risk factor for PD is aging, and those over 60 are more likely to develop the condition (Rodriguez *et al*., 2015). Polyphenol-containing substances are regarded as antioxidant agents that are crucial in the treatment of Parkinson's disease (PD). Tea, coffee, fruits, vegetables, chocolates, grape juice, and vinegar all contain polyphenolic components. High levels of polyphenols, including flavonoids and non-flavonoids, can be found in grape juice. Various grape juice concentrations have reportedly been shown to significantly improve

aging-related cognitive and mobility problems (Eshraghi-Jazi *et al*., 2012).

Red wine (*Vitis vinifera*) consumed in addition to other medications, such as monoamine oxidase inhibitors or dopamine agonists, may have a higher therapeutic impact. Red wine (*Vitis vinifera*), which is examined for its curative and supplemental uses in PD. Natural polyphenol resveratrol is found in *Vitis vinifera* species and is well-known for its anti-inflammatory and antioxidant properties. By inhibiting nuclear transcriptional factors, resveratrol reduces the activation of immune cells as well as the production and release of inflammatory proteins. Resveratrol dose-dependently protects dopamine neurons from lipopolysaccharide (LPS)-induced neurotoxicity with exceptional neuroprotection. Resveratrol defends neurotransmitters from LPS harm by preventing microglia from becoming activated and the production of pro-inflammatory molecules. Additionally, resveratrol reduces the activation of intracellular mitogen-activated protein kinases (MAPKs), NF-κB pathways, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Resveratrol's anti-inflammatory effects allow it to sustain neurons and lessen neuronal degeneration in regions crucial to dopamine action. Additionally, by maintaining intracellular antioxidant state, resveratrol reduced oxidative stress and motor impairment in a PD rat model, indicating a neuroprotective effect (Morgan *et al*., 2017). The impact of exercise and grape juice on epigenetic regulation and functional results in PD was evaluated in the study by De Oliveria *et al*. (2020). Patients with idiopathic PD who had not engaged in physical activity within the previous month and who scored between 1 and 3 on the Hoehn & Yahr (H & Y) scale were included in the study and split into two groups for this reason. The intervention was carried out with aquatic exercise (AQ) twice a week for 60 minutes in the first group (n=9), and 400 mL of grape juice (GJ) was given to the second group (n=10) in addition to the daily aquatic exercise (AQ+GJ). Following a 4-week period, patients' mobility (as measured by the Timed Up and Go, or TUG), functional capacity (6-min walk test, or 6MWT), risk of falling (as measured by the Berg Balance Scale, or BBS), brain-derived neurotrophic factor (BDNF), and overall histone H4 concentration in their blood were all assessed. Patients with Parkinson's disease who routinely engaged in water workouts for four weeks saw improvements in their functional capacity and mobility. Previous research suggests that decreasing brain-derived neurotrophic factor levels in the substantia nigra may cause dopaminergic neurons to die, worsening patients' mobility problems and neurodegeneration (Howells *et al*., 2000; Huang *et al*., 2019). On the other side, enhanced transcriptional activity and gene expression are linked to histone acetylation. While deacetylation of histones is linked to transcriptional inhibition (Bannister & Kouzarides, 2011). The findings of this study demonstrate that aquatic activities boost brain-derived neurotrophic factor levels and histone H4 acetylation in Parkinson's patients. The findings of De Oliveira *et al*. (2020), studies's revealed that grape juice has no significant effects in improving motor outcomes in PD and that there is no difference between the two experimental groups, despite previous experimental studies showing the neuroprotective effects of grapes in various parts of the brain that are involved in PD, such as the substantia nigra and striatum (Dani *et al*., 2008; De Oliveira *et al*., 2020). In a rotenone model of Parkinson's disease, amurensin G promotes autophagy and lessens cellular toxicity, according to a study by Ryu *et al*. (2013). titled "Amurensin G induces autophagy and reduces cellular toxicity" (PD). In response to amurensin G treatment, GFP-LC3 was expressed punctately in the cytoplasm. Amurensin G pretreatment of human SH-SY5Y cells in a Parkinson's disease model reduced the rotenone-induced toxicity. Amurensin G decreased apoptosis and stopped apoptosis from being induced by rotenone because it caused G2/M cell cycle arrest. The autophagy regulator beclin1 was also suppressed, rendering amurensin G ineffective. Cellular toxicity is decreased by amurensin G-induced autophagy (Ryu *et al*., 2013).

In a study published by Long *et al*. (2009), it was examined how to increase lifespan, improve locomotor performance, and protect mitochondria from oxidative damage in a drosophila model of Parkinson's disease. Regrapex-R was found to contain significant antioxidant activity by mixing a whole grape extract with polygonum cuspidatum, and it was further demonstrated to protect mitochondria from oxidative damage (Long *et al*., 2009). Al-Okbi *et al*. (2022), claim that it may lengthen life expectancy as well as offer protection against neurodegenerative diseases. This work examines the interactions between iron status, the immune system,

specifically inflammatory cytokines, brain divalent metal transporter 1 (DMT1), and dopamine receptor D1 (DRD1) in a rat model of Parkinson's disease (PD). The data show that an increase in cytokines in PD is connected to iron deficient anemia. Reduced DRD1 levels, altered immune system, including cytokines, and increased brain DMT1 are some of the causes of Parkinson's disease. Modulation of the immune system, oxidative stress, iron status, inflammation, DMT1, and DRD1 were found to have neuroprotective effects (Al-Okbi *et al*., 2022).

Grape skin extract (GSE), a byproduct of the production of red wine, was added to the regular diet of a *Drosophila melanogaster* model of Parkinson's disease to study the consequences. GSE consumption allowed PINK1 mutant flies to live longer, improve indirect flight muscle health and function, and reverse aberrant mitochondrial morphology. Biochemical and genetic studies revealed a correlation between the beneficial effects of GSE and mitophagy activation. Resveratrol alone cannot account for GSE's positive impact on mitophagy activation; GSE may also enhance autophagy activation, maintain mitochondrial function, and guard against Parkinson's disease (PD) pathogenesis (Wu *et al*., 2018).

Eshraghi-Jazi *et al*. (2012), investigated the effects of red grape juice (400 mg of grape seed extract capsules three times per day for a total daily dose of 1200 mg), exercise, and their combination on the progression of Parkinson's disease in rats. This study revealed that there was a substantial difference in the number of rotations between the PD group and the Sham group. Following the study, both PD-GJ and PD-GJ-Ex groups reduced the number of rotations in both groups. Rotations were found to be slightly improved by exercise alone. There is proof that GJ decreases rotation in Parkinson's disease-affected rats because of antioxidant medications (Eshraghi-Jazi *et al*., 2012). Wu et al. evaluated the reducing capacity, ferrous chelating activity, and anti-auto-oxidation capability of the grape seed proanthocyanidin extract (GSPE) (dose of 100 mg/kg body weight per day for seven consecutive days via oral gavage). GSPE showed cytoprotective properties against 6-OHDA-induced cellular damage over the course of a 24-hour incubation period, independent of NOS activity. This protective effect of GSPE may be facilitated by its capacity to chelate iron, which may enable it to scavenge free radicals and so lessen 6-OHDA autooxidation. In a cell culture setting, GSPE and NOSI offer additional or synergistic protection. More *in vivo* characterisation is needed for GSPE's use in the prevention of Parkinson's disease (Wu *et al*., 2010).

Varadharajan (2021), investigated in silico the neuroprotective efficiency of grape seed extract against Parkinson's disease. Hydrogen bonds are preferred to hydrophobic contacts in docking tests with ethanolic extract of grape seed, which showed that volatile components can bind to both the C-terminal and N-terminal regions of Alpha-synuclein. Additionally, hydrogen bonds were created, and the compounds' N-terminal Val40, Lys43, and Lys45 commonly engaged in hydrophobic interactions. Among the substances examined, the molecule Dasycarpidan-1-methanol, acetate (ester) demonstrated the highest affinity for binding, penetration of the Blood-Brain Barrier, druglike qualities, and lead like features (Varadharajan, 2021). The extract from grape seeds and skin contains a variety of polyphenolic chemicals (Charradi *et al*., 2012). Extracts from grape seeds and skin exhibit anti-inflammatory, anti-mutagenic, anti-carcinogenic, and anti-apoptotic effects (Ramassamy, 2006; Sharma & Katiyar, 2010; Uchino *et al*., 2010; Park *et al*., 2012). Regarding midbrain dopaminergic neurons, Youssef *et al*. (2021), concentrated on the neuroprotective effects of grape seed and skin extract both *in vivo* and *in vitro*.

Three groups were created for the earlier model: the control group, 6-hydroxydopamine-only, and 6-hydroxydopamine plus grape seed and skin extract (250 mg/kg body weight of the mice). They were divided into 4 groups and used midbrain dopaminergic cell culture for the later model: i) a control group, ii) a treatment with 6-hydroxydopamine at a concentration of 50 M, iii) a treatment with the same amount of 6-hydroxydopamine plus extra grape seed and skin extract at a concentration of 500 g/mL, iv) and a treatment with the same amount of 6-hydroxydopamine plus grape seed and skin extract at a concentration of 1000 g/mL were all possible treatments. Grape seed and skin extract protects dopaminergic neurons, according to the *in vitro* model's findings. Tyrosine hydroxylase-positive cells and Microtubule-associated protein 2 positive cells are protected from death by grape seed and skin extracts. Cleaved caspase-3 is one of the variables used to gauge cell death. In comparison to the 6-

hydroxydopamine-treated group, the amount of cleaved caspase-3 was lower in the grape seed and skin extract groups. Reactive oxygen species can be produced more frequently because of 6-hydroxydopamine toxicity. The Nuclear factor kappa B pathway might become activated at higher levels of reactive oxygen species. The generation of these compounds is reduced by grape seed and skin extract, which inactivates the nuclear factor kappa B pathway. Results of an *in vivo* model demonstrated that grape seed and skin extract preserves the motor activity that 6-hydroxydopamine had damaged (Youssef *et al*., 2021) (Figure No. 2).

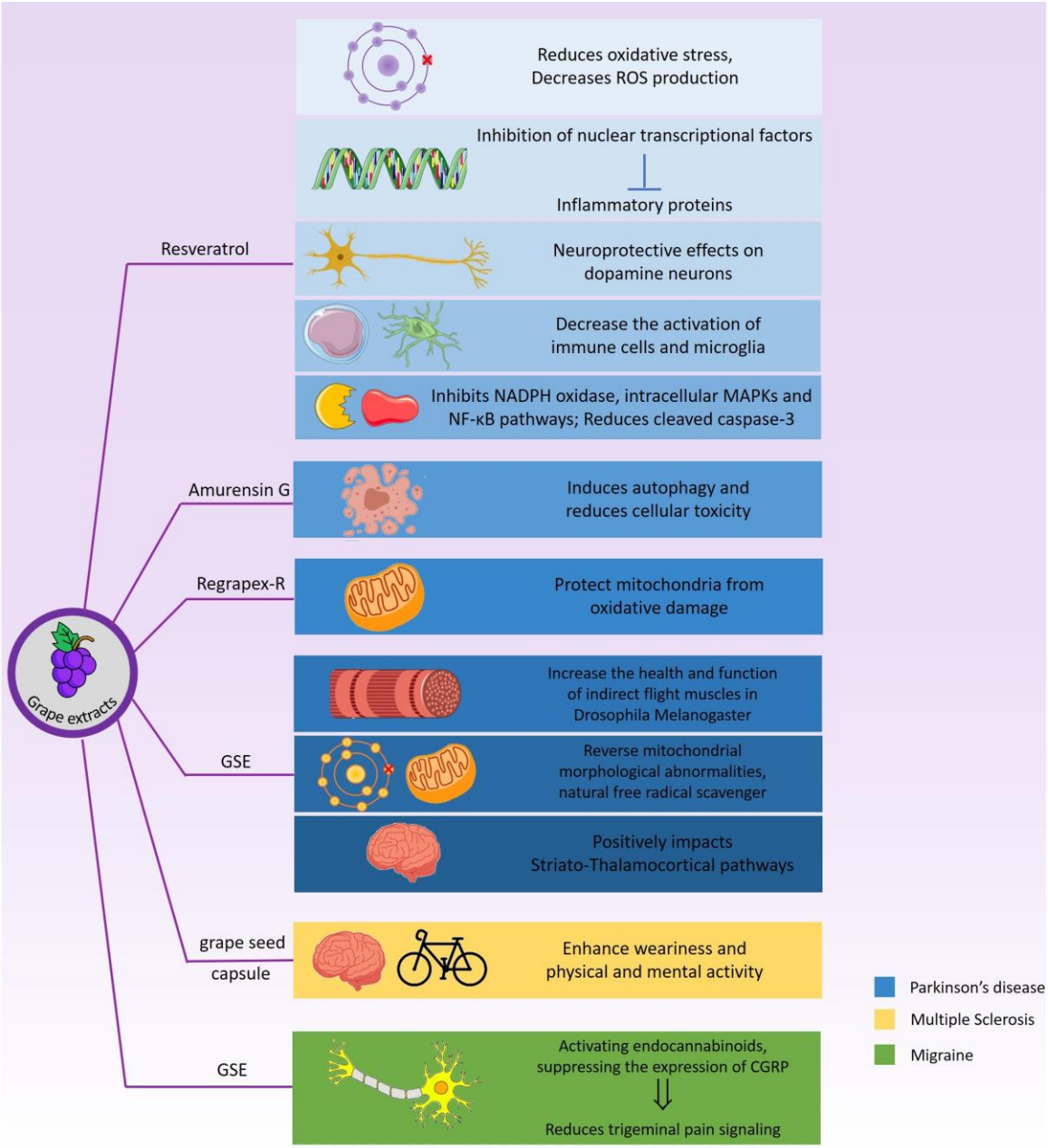

Figure No. 2
A summary of effects of grape extracts on Parkinson's disease (blue), Multiple Sclerosis (yellow) and Migraine (green); ROS: Reactive Oxygen Species; MAPK: Mitogen-activated protein kinase

Multiple Sclerosis (MS)

In a study, Siahpoosh et al. investigated the impact of grape seeds on MS patients' quality of life. The use of grape seed capsules by MS patients had a substantial impact on both their physical and emotional health, according to the study's findings. Several currently available MS drugs lessen the possibility of relapses, the severity of the sickness, and the disease's development. Aside from their negative side effects, these medications don't have much of an effect on symptom relief, performance enhancement, or quality of life enhancement. Grape seed can be used as a supplement to increase patients' fatigue and physical and mental activity because it has no notable side effects and works well at increasing patients' physical and mental activity (Siahpoosh *et al*., 2018) (Figure No. 2).

Migraine

Woodman *et al*. (2022), further investigated how GSE inhibits mechanical nociception in a preclinical model of episodic migraine. In an injury-free paradigm of migraine-like pain, GSE supplementation decreases trigeminal pain signals by activating endocannabinoids and inhibiting the production of CGRP centrally. GSE may therefore be helpful as an additional migraine therapy (Woodman *et al*., 2022). The authors of a study by Slavin et al. called their investigation Using spice and grape pomace extracts to affect migraine-related indicators in vitro. Following treatment with grape pomace and ginger (0.2 mg equivalent of ginger per mL), a statistically significant decrease in CGRP generation was seen (1.0 mg equivalent per mL). The control vehicle's release of CGRP decreased by 22% and 87%, respectively. In PC12 cells treated with ginger extracts, there was a marginal decrease in calcium influx. It might have been unable to detect an impact due to the solubility of turmeric extracts. Future research on migraines may reveal that grape pomace and ginger extracts have anti-inflammatory qualities (Slavin *et al*., 2015) (Figure No. 2).

Stroke

The most significant public health illnesses are stroke, which can be fatal or severely disabling. Stroke incidence has been attempted to be decreased in patients in a variety of ways, but none of them have been significantly successful, leading to an increase in patients. One method of controlling this neurological condition is prevention in high-risk populations. Ischemic stroke is the most common type and is characterized by a broad range of factors that can cause edema, necrosis, apoptosis, and autophagy, including inflammation, oxidative stress, and the formation of free radicals. In their study, Kadri *et al*. (2020), used *in-vitro* and *in-vivo* models to examine grape seed powder (GSP potential)'s to prevent stroke. The cells used to assess the *in vitro* curative and protective effects of GSP against oxygen-glucose deprivation (OGD) were primary neuron-astrocyte cultures. GSP was used as a curative drug after stroke occurrence in a murine I/R model for in vivo consideration. Tests on behavior and images of the dentate gyrus' ultrastructure in the hippocampus were conducted. GSP altered cytokine and BDNF expression, protected against cell death, and enhanced behavioral outcomes (Kadri *et al*., 2020).

The three groups of I/R, GSP + I/R, and sham control groups without I/R each had 32 male Wistar rats. The generated supernatant, which contained phenolic compounds after dissolving GSP in a solution of 10% ethanol (v/v), was used in this study. The main phenolic components of GSP included epicatechin, catechin, gallic acid, and quercetin. Male Wistar rats had their carotid arteries cut open and clamped for 30 minutes. Furthermore, reperfusion was performed on the I/R and GSP+I/R halves of the rat population. Rats were given betadine and amoxicillin (50 mg/kg) after the operation to prevent infection, and they also received daily intraperitoneal infusion of either a high dosage of 2.5 (g/kg bw) GSP or 10% ethanol for 15 days following the injury. On day 15 after the injury, a behavioral investigation was conducted. Using primary neuron-astrocyte cocultures, in-vitro investigation of the preventive and therapeutic effects of GSP on oxygen-glucose deprivation (OGD) was carried out. Following GSP treatment, expression levels of brain-derived neurotrophic factor (BDNF), anti-inflammatory genes (TGF-α, IL-10), and pro-inflammatory genes (TNFβ-, IL-6), as well as both, were returned to normal levels. Furthermore, rats given GSP showed dose-dependent increases in cell viability. In addition to protecting brain cells from post-ischemic death, GSP also significantly increased rats' behavioral scores and memory. This improvement may point to the benefits of GSP in preventing I/R changes in brain regions important in memory processing, such as the

hippocampal dentate gyrus. In conclusion, high-dose GSP has been shown to have both a therapeutic and protective impact in stroke, with no toxicity. Memory loss and other cognitive abilities are disrupted by Alzheimer's disease (AD), a progressive neurological condition. This disease has neuropathological features include brain atrophy, senile plaques, and neurofibrillary tangles. Hong *et al*. (2021), investigated the ability of *Vitis vinifera*'s ampelopsin A ,which it was administered orally to the mice at doses of 25 mg/kg and 50 mg/kg body weight, to prevent memory loss (anti-amnesic potential) brought on by the injection of scopolamine in mice (Hong *et al*., 2021).

The third ventricle of the brains of C57BL/6 mice was treated with 10 ng/L ampelopsin A three times per week for a month to achieve this. Ampelopsin A was administered to mice after they received scopolamine (0.8 mg/kg, i.p.). Through its effects on hippocampus synaptic plasticity, the cholinergic antagonist scopolamine has demonstrated that it hinders memory and learning development (Shinoe *et al*., 2005; Fernandez de Sevilla *et al*., 2021).

The evaluation of cholinergic system activity and the expression of the CREB/BDNF signaling in the hippocampus allowed researchers to study the effects of ampelopsin A at the molecular level. The common grapevine, *Vitis vinifera*, is a major source of stilbenoids, notably monomeric resveratrol and ampelopsin A. These two stilbenoids have potent anti-amyloidogenic properties (Zga *et al*., 2009).

Cognitive and memory function are severely compromised by the inhibition of neurotrophic factor (BDNF) and brain-derived cAMP response element-binding protein (CREB). Therefore, after ampelopsin A administration to the central nervous system, elevated BDNF and CREB signaling pathways had neurocognitive and neuroprotective effects on intrinsic neuronal excitability and behaviors. Additionally, as shown in the research of hippocampi, ampelopsin A reversed the cholinergic deficiencies and molecular signal cascades via BDNF/CREB pathways. As a consequence, enhanced BDNF/CREB-related signaling was partially responsible for the neurocognitive and neuroprotective effects of chronic ampelopsin A administration (orally to mice at a dose of 50 mg/kg body weight) to the central nervous system on intrinsic neuronal excitability and behaviors (Amidfar *et al*., 2020).

In a study conducted by Wang *et al*. (2005), the death of cells in Mongolian gerbils was ischemic in brain cells. DNA fragmentation, oxidative stress, and activation of glial cells were the causes of delayed neuronal death in the CA1 area of the hippocampal brain. Because grapes contain polyphenols that can shield the brain from ischemia and its repercussions, adding grape powder to gerbils' food had a protective effect on their neurons (Wang *et al*., 2005). In a different study conducted by the same researcher, the effects of oral doses on ischemia and reperfusion in gerbils were assessed. They examined the effects of grape polyphenol extract (GPE) before and after ischemia. They came to the conclusion that early therapies have considerable therapeutic benefits and that oral GPE diet has neuroprotective effects (Wang *et al*., 2009a).

Rats exposed to hypoxia were tested for brain injury by Feng *et al*. (2005), using changes in the right hemisphere's weight. The amounts of thiobarbituric acid and 8-isoprostaglandin F2 in the brain were decreased by grape seed extract, and lipid peroxidation was repressed. Additionally, it improved the brain's hippocampus, cortex, and thalamus scores. The antioxidant impact of a *Vitis amurensis* stem and leaf extract on ischemic brain injury was assessed. By being taken orally, *V. amurensis* reduced edema, infarct, neuronal death, glutathione depletion, and lipid peroxidation. Administration of *V. amurenesis* prevented the emergence of MAPKs, COX-2, and pro-apoptotic proteins. Ampelopsin A, trans-E-viniferin, Y-2-viniferin, and *V. amurensis* all prevented glutamate-induced neuronal death as well as alterations in apoptosis-related proteins and calcium elevation. In conclusion, the anti-apoptotic properties of this natural substance prevent neurodegeneration in ischemia and stroke (Kim *et al*., 2012).

In another study, the ability of three plants - *Vitis amurensis*, *Aralia cordata*, and *Glycyrrhizae radix* (SSB) - to prevent stroke and brain damage brought on by ischemia was assessed. To do this, rats were given ischemia, and glutamate was given to cultivated cortical cells, killing them. Orally given SSB reduced brain infarction, edema, and the emergence of behavioral issues. Additionally, it stopped the death of neurons brought on by glutamate, increased Ca, and ROS production. As a

result of SSB's anti-excitotoxic activity, which also has neuroprotective effects, ischemia can be treated (Choo *et al*., 2016).

In the recent research (Tu *et al*., 2019), the neuroprotective potential of grape seed proanthocyanidin extract (GSPE) was examined by pretreating animals with brain damage to assess its neuroprotective potential. Damage to the brain and improvements in behavioral traits were found. GSPE can prevent the production of Bax and cleaved Caspase-3, which lowers the amount of brain cell apoptosis. In a study conducted by Kadri *et al*. (2019), it was shown that large dosages of grape seed extract can lessen the effects of I/R on problems including hippocampal dentate gyrus region inflammation, ionogram dyshomeostasis, and, of course, changes to the brain's ultrastructure and proteome. 84 of the 108 proteins that were changed by the GSE pretreatment were protected, as were inflammatory indicators like CD56 or CD68 and a calcium burst in the hippocampus.

Dementia and radiation brain injury

The late effects of radiation treatment continue to have a considerable influence on patients' quality of life, especially in youngsters, even though it has greatly improved patient survival in several cancer types. After radiation-induced brain damage, cognitive impairment, including learning and memory difficulties connected to the hippocampus area, can emerge and proceed to dementia (Turnquist *et al*., 2020).

In a study by Xiao & Liu (2016), it was discovered that grape seed proanthocyanidin extract rescued rats against learning impairments caused by brain radiation exposure (GSPE). Each of the four groups—the control, model, high, and low dosage GSPE groups - contained 120 male Wistar rats. The expression of phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) and growth associated protein-43 (GAP-43) was detected in the hippocampus using immunohistochemistry, and the levels of malonaldehyde (MDA) and superoxide dismutase (SOD), respectively, were determined using the thiobarbituric acid method (TBA). When compared to the model group, the GSPE groups' findings showed reduced levels of morphological damage to nerve cells and increased ERK1/2 activation. The results suggest that GSPE (50 mg/kg of body weight of GSPE daily for 2 weeks which was administered orally through a feeding tube) protects against learning deficiencies caused by radiation damage to the brain, which are linked to increased ERK1/2 activity and GAP-43 expression (Xiao & Liu, 2016) (Figure No. 3).

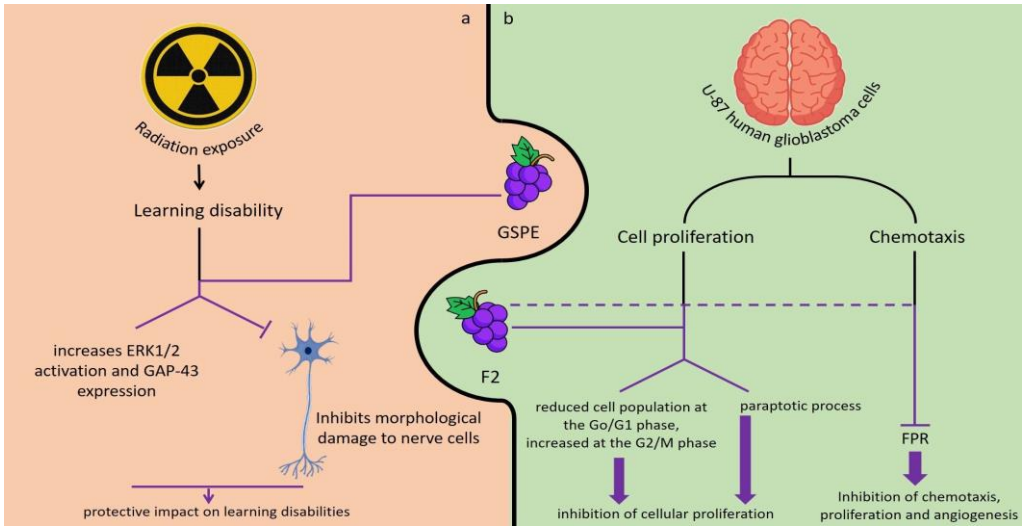

Figure No. 3

A summary of impacts of grape extracts on (a) brain of rats following radiation exposure, and (b) U-87 human glioblastoma cells; ERK: extracellular signal-regulated kinase; GAP-43: growth associated protein 43; FPR: Formyl peptide receptor; GSPE: grape seed proanthocyanidin extract; F2: oligomer procyanidins

Neuroinflammation

The illness advances more quickly due to neuroinflammation (Heneka & O'Banion, 2007) According to the results of blood and brain samples, image analysis, and statistical analysis, consuming grape seed extract over an extended period of time did not cause any liver damage or a discernible change in body weight. Blood and brain amyloid-beta peptide levels are reduced by grape seed extract by 33% and 44%, respectively. Mice given grape seed extract had notable decreases in microgliosis. However, there was no discernible decline in the amount of astrogliosis. When activated, macrophages and microglia release cytokines that are the major source of inflammation in the brains of people with Alzheimer's disease. The plasma concentration of these cytokines was reduced by the grape seed extract (Wang *et al*., 2009b). In relation to microglia, the research by Liu *et al*. (2022), concentrated on how grape seed proanthocyanidins affected neuroinflammation through polarizing microglia. The activation of microglia is the primary mechanism of neuroinflammation (Block & Hong, 2005; Uriarte Huarte *et al*., 2021). The phenotypes of microglia are pro- and anti-inflammatory (Kigerl *et al*., 2009). Grape seeds are the finest source of proanthocyanidins. (Cerbaro *et al*., 2020; Liu *et al.*, (2022); Sintara *et al*., 2020; Morissette *et al*., 2020). For this investigation, the researchers cultured microglia cells, pretreated them for 6 hours with various doses of grape seed proanthocyanidins (3.125, 6.25, 12.5, and 25 μM), and then treated them for 24 hours with lipopolysaccharide. Consequently, they discovered that cells were not harmful at concentrations lower than 25 μM. The release of pro-inflammatory mediators is stimulated by lipopolysaccharide, which also increases pro-inflammatory microglia polarization. In addition to reducing the quantity of NO generated following LPS treatment and promoting anti-inflammatory plolarizapolarization, grape seed proanthocyanidins also inhibit pro-inflammatory polarization (Liu *et al*., 2022). In the research by Tikhonova et al., they looked at how grape polyphenols affected Parkinson's disease mice's neuroinflammation. For this, they divided the mice into two categories. the first group consisted of Parkinson-free mice. Parkinson was used to induce Parkinson in the latter group, and each group was divided into those who consumed or did not consume grape polyphenol concentrate (at a concentration of 1.5 mL/kg/day). Then, they conducted behavioral assessments (open field and passive avoidance). After data analysis, scientists discovered that giving grape polyphenol to Parkinson's mice considerably lengthened their lives. In the passive avoidance test, this group of mice shown improved reconsolidation of memories and decreased memory extinction. As anticipated, Parkinson's mice that were not receiving therapy had greater horizontal movement than other groups (Unger *et al*., 2006; Paumier *et al*., 2013; Farrell *et al*., 2014). In the frontal and dentate gyrus of the hippocampus region, immunohistochemical data revealed a significant reduction in levels of α-synuclein, Ionized Calcium-Binding Adaptor Molecule 1, and Cluster of Differentiation 54. Grape polyphenol therapy for an extended period of time had no discernible effects (Tikhonova *et al*., 2020). Wang *et al*. (2009b), examined the effects of grape seed extract on inflammation in Alzheimer's disease mice in a different investigation. They created an experiment with three groups for this purpose: a control group, a polyphenol group, and a curcumin group. We solely concentrate on grape seed extract-derived polyphenols. The experiment started with mice that were 3 months old and lasted for 9 months. A total of 592.5 mg/g dry weight of polyphenol was present. As is well known, cerebral amyloid angiopathy, reactive microgliosis and astrogliosis, amyloid-beta peptide, and neurofibrillary tangles are the primary causes of Alzheimer's disease (Thomas & Fenech, 2007).

Glioblastoma

The most prevalent and aggressive primary central nervous system cancer, with a median survival of 15 months, is glioblastoma multiform (GBM). There have been several studies on genetic and environmental variables in GBM, although the majority are sporadic. GBM is often discovered later in life, with a median diagnostic age of 64. The incidence rises with age, peaks between the ages of 75 and 84, and then declines after 85 (Thakkar *et al*., 2014). The biological activity of glioblastoma cells was examined in the research by Zhang *et al*. (2010), using oligomer procyanidins (F2, degree of polymerization 2-15), a natural fraction derived from grape seeds. About 60–70% of the total proanthocyanidin content of grapes is found in the seeds. Monomeric, dimeric, trimeric, tetrameric, and

various oligomeric proanthocyanidin bioflavonoids are present in grape seed proanthocyanidins extract. It is well acknowledged that the greatest physiologically active component of grape seed extract is the oligomer proanthocyanidins. The oligomer proanthocyanidins F2 obtained from grape seeds containing flavan-3-ol monomer units (catechins) connected mostly by acid-labile 48 and, in some cases, by 46 bonds were reported to improve rat brain's ability to remove OH and shield mouse brain from ethanol-induced oxidative DNA damage. In several mechanisms, F2 caused the suppression of U-87 cell human glioblastoma growth. The cell population first changed during the Go/G1 phase and then returned to normal at the G2/M phase. In addition, the cells may go through a phase known as paraptosis, which is distinguished from either apoptosis or necrosis by the rounding of the cells and significant cytoplasmic vacuolation. In summary, these investigations showed for the first time that F2 not only prevented U-87 glioblastoma from proliferating, but also perhaps prevented it from moving, which suggested that tumor cell growth was also prevented. Additionally, F2 decreased the expression of the Formyl peptide receptor (FPR), which is crucial for glioma cell chemotaxis, proliferation, and angiogenesis in addition to promoting tumor growth (Zhang *et al*., 2009; Zhang *et al.*, 2010) (Figure No. 3)

CONCLUSION

Our research establishes the efficacy of grape seed extract against neurological disorders associated with aging in general as well as against Parkinson's, MS, migraines, Alzheimer's, apoplexy, brain tumors, epilepsy, and dementia.

By inhibiting the production of Bci-2 and Bax, it has protective properties against apoplexy by reducing oxidative damage and the associated Apoptosis. Its antioxidant and antiapoptotic properties may play a role in the structural process (Kong *et al*., 2017). It reduces apoptosis in Parkinson's disease by inhibiting Caspase 3, obstructing cellular signaling controlled by inflammatory NF-kB, and reducing the formation of ROS (Youssef *et al*., 2021). Antioxidant, anti-inflammatory, anti-amyloidogenic, and neuromodulator properties are how it combats Alzheimer's disease (Ibrahim Fouad & Zaki Rizk, 2019). It guards against peroxidation in MS and suppresses dangerous free radicals like superoxide and hydroxyl. Catalase, Superoxide Reductase, and Peroxidase are three more enzymes that it regulates. It raises anti-inflammatory cytokines useful in the recovery stage of the illness, such as IL-10, IL-4, and TGF-Beta (Transforming growth factor beta), and reduces inflammatory cytokines like Alpha-TNF, Interferon Gamma, and Interleukin 1 and 6 which cause inflammations in MS patients (Siahpoosh *et al*., 2018). Its method for causing alterations in the STN and likely higher brain areas involved in reacting to stress and pain transmission in migraines is to stimulate the generation of physiologically accessible metabolites that pass the blood-nerve barrier (Woodman *et al*., 2022). Through the use of enzymes (Superoxide dismutase and Catalase) and non-enzymes (Sulfhydryl protein) in the brain tissues, it works to defend against lipid and protein oxidative damages, reduce nitric oxide, and boost antioxidant defenses in cases of epilepsy (Rodrigues *et al*., 2012). In solid tumors, it inhibits cell division, triggers apoptosis, and stops the cell cycle. To stop the spread of solid tumors, it could be a novel and practical therapy method (El-Din *et al*., 2019). To comprehend its impacts on people, clinical trial studies should be conducted as well as more *in vivo* and *in vitro* research that aims to find more processes.

REFERENCES

Al-Okbi SY, Mabrok HB, Al-Siedy ESK, Mohamed RS, Ramadan AA. 2022. Iron status, immune system, and expression of brain divalent metal transporter 1 and dopamine receptors D1 interrelationship in Parkinson's disease and the role of grape seed and green coffee bean extracts and quercetin in mitigating the disease in rats. **J Herbmed Pharmacol** 11: 63 - 74. **https://doi.org/10.34172/jhp.2022.07**

Amidfar M, de Oliveira J, Kucharska E, Budni J, Kim YK. 2020. The role of CREB and BDNF in neurobiology and treatment of Alzheimer's disease. **Life Sci** 257: 118020. **https://doi.org/10.1016/j.lfs.2020.118020**

Ardid-Ruiz A, Harazin A, Barna L, Walter FR, Bladé C, Suárez M, Deli MA, Aragonès G. 2020. The effects of *Vitis vinifera* L. phenolic compounds on a blood-brain barrier culture model: Expression of leptin receptors and protection against cytokine-induced damage. **J Ethnopharmacol** 247: 112253.

https://doi.org/10.1016/j.jep.2019.112253
Alzheimer's Association. 2019. 2019 Alzheimer's disease facts and figures. **Alzheimers Dement** 15: 321 – 387.
Bakhtiyari E, Ahmadian-Attari MM, Salehi P, Khallaghi B, Dargahi L, Mohamed Z, Kamalinejad M, Ahmadiani A. 2017. Non-polyphenolic compounds of a specific kind of dried grape (Maviz) inhibit memory impairments induced by beta-amyloid peptide. **Nutr Neurosci** 20: 469 - 477. **https://doi.org/10.1080/1028415X.2016.1183986**
Bannister AJ, Kouzarides T. 2011. Regulation of chromatin by histone modifications. **Cell Res** 21: 381 - 395. **https://doi.org/10.1038/cr.2011.22**
Bhullar KS, Rupasinghe HPV. 2013. Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. **Oxid Med Cell Longev** 2013: 891748. **https://doi.org/10.1155/2013/891748**
Bjørklund G, Dadar M, Martins N, Chirumbolo S, Goh BH, Smetanina K, Lysiuk R. 2018. Brief challenges on medicinal plants: An eye-opening look at ageing-related disorders. Basic Clin Pharmacol Toxicol 122: 539 - 558. **https://doi.org/10.1111/bcpt.12972**
Blochberger A, Jones S. 2011. Clinical focus-Parkinson's disease-clinical features and diagnosis. **Clin Pharmacist** 3: 361.
Block ML, Hong JS. 2005. Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism. Prog Neurobiol 76: 77 - 98. **https://doi.org/10.1016/j.pneurobio.2005.06.004**
Buendia I., Michalska P, Navarro E, Gameiro I, Egea J, Leon R. 2016. Nrf2–ARE pathway: an emerging target against oxidative stress and neuroinflammation in neurodegenerative diseases. **Pharmacol Ther** 157: 84 - 104. **https://doi.org/10.1016/j.pharmthera.2015.11.003**
Calapai G, Bonina F, Bonina A, Rizza L, Mannucci C, Arcoraci V, Laganà G, Alibrandi A, Pollicino C, Inferrera S, Alecci U. 2017. A randomized, double-blinded, clinical trial on effects of a *Vitis vinifera* extract on cognitive function in healthy older adults. **Front Pharmacol** 8: 776. **https://doi.org/10.3389/fphar.2017.007768**
Cerbaro AF, Rodrigues VSB, Rigotti M, Branco CS, Rech G, de Oliveira DL, Salvador M. 2020. Grape seed proanthocyanidins improves mitochondrial function and reduces oxidative stress through an increase in sirtuin 3 expression in EA. hy926 cells in high glucose condition. **Mol Biol Rep** 47: 3319 - 3330. **https://doi.org/10.1007/s11033-020-05401-x**
Charradi K, Elkahoui S, Karkouch I, Limam F, Hassine FB, Aouani E. 2012. Grape seed and skin extract prevents high-fat diet-induced brain lipotoxicity in rat. **Neurochem Res** 37: 2004 - 2013. **https://doi.org/10.1007/s11064-012-0821-2**
Chen C, Zheng Y, Wu T, Wu C, Cheng X. 2017. Oral administration of grape seed polyphenol extract restores memory deficits in chronic cerebral hypoperfusion rats. **Behav Pharmacol** 28: 207 - 213. **https://doi.org/10.1097/FBP.0000000000000276**
Choo HR, Jang JY, Song KS, Seong YH. 2016. Protective effect of an ethanol extract mixture of *Vitis amurensis*, *Aralia cordata*, and *Glycyrrhizae radix* against ischemia-induced brain injury in rats and excitotoxicity in cultured neurons. **J Biomed Transl Res** 17: 13 - 19. **https://doi.org/10.12729/jbtr.2016.17.1.013**
Dal-Pan A, Dudonne S, Bourassa P, Bourdoulous M, Tremblay C, Desjardins Y, Calon F. 2017. Cognitive-enhancing effects of a polyphenols-rich extract from fruits without changes in neuropathology in an animal model of Alzheimer's disease. **J Alzheimers Dis** 55:115 - 135. **https://doi.org/10.3233/JAD-160281**
Dani C, Oliboni L, Vanderlinde R, Bonatto D, Salvador M, Henriques J. 2007. Phenolic content and antioxidant activities of white and purple juices manufactured with organically-or conventionally-produced grapes. **Food Chem Toxicol** 45: 2574 - 2580. **https://doi.org/10.1016/j.fct.2007.06.022**
Dani C, Pasquali MAB, Oliveira MR, Umezu FM, Salvador M, Henriques JAP, Moreira JFC. 2008. Protective effects of purple grape juice on carbon tetrachloride-induced oxidative stress in brains of adult Wistar rats. **J Med Food** 11: 55 - 61. **https://doi.org/10.1089/jmf.2007.505**
De Oliveira GS, Iraci L, Pinheiro GS, Casal MZ, Haas AN, Pochmann D, Martinez FG, Elsner V, Dani C. 2020. Effect of exercise and grape juice on epigenetic modulation and functional outcomes in PD: A randomized clinical trial. **Physiol Behav** 227: 113135. **https://doi.org/10.1016/j.physbeh.2020.113135**

El-Din NKB, Ali DA, El-Magd RFA. 2019. Grape seeds and skin induce tumor growth inhibition via G1-phase arrest and apoptosis in mice inoculated with Ehrlich ascites carcinoma. **Nutrition** 58: 100 - 109. **https://doi.org/10.1016/j.nut.2018.06.018**

El Gaamouch F, Liu K, Lin HY, Wu C, Wang J. 2021. Development of grape polyphenols as multi-targeting strategies for Alzheimer's disease. **Neurochem Int** 147:105046. **https://doi.org/10.1016/j.neuint.2021.10504**

Eshraghi-Jazi F, Alaei H, Azizi-Malekabadi H, Gharavi-Naini M, Pilehvarian A. 2012. The effect of red grape juice and exercise, and their combination on parkinson's disease in rats. **Avicenna J Phytomed** 2: 90 - 96.

Farrell KF, Krishnamachari S, Villanueva E, Lou H, Alerte TN, Peet E, Drolet RE, Perez RG. 2014. Non-motor parkinsonian pathology in aging A53T α-synuclein mice is associated with progressive synucleinopathy and altered enzymatic function. **J Neurochem** 128: 536 - 546. **https://doi.org/10.1111/jnc.12481**

Feng Y, Liu YM, Fratkins JD, Leblanc MH. 2005. Grape seed extract suppresses lipid peroxidation and reduces hypoxic ischemic brain injury in neonatal rats. **Brain Res Bull** 66: 120 - 127. **https://doi.org/10.1016/j.brainresbull.2005.04.006**

Fernandez de Sevilla D, Nuñez A, Buño W. 2021. Muscarinic receptors, from synaptic plasticity to its role in network activity. **Neuroscience** 456: 60 - 70. **https://doi.org/10.1016/j.neuroscience.2020.04.005**

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. 2005. Global prevalence of dementia: a Delphi consensus study. **Lancet** 366: 2112 - 2117. **https://doi.org/10.1016/S0140-6736(05)67889-0**

Fuhrman B, Volkova N, Coleman R, Aviram M. 2005. Grape powder polyphenols attenuate atherosclerosis development in apolipoprotein E deficient (E0) mice and reduce macrophage atherogenicity. **J Nutr** 135: 722 - 728. **https://doi.org/10.1093/jn/135.4.722**

Gazewood JD, Richards DR, Clebak KD. 2013. Parkinson's disease: an update. **Am Fam Physician** 87: 267 - 273.

Heneka MT, O'Banion MK. 2007. Inflammatory processes in Alzheimer's disease. **J Neuroimmunol** 184: 69 - 91. **https://doi.org/10.1016/j.jneuroim.2006.11.017**

Hong Y, Choi YH, Han YE, Oh SJ, Lee A, Lee B, Magnan R, Ryu SY, Choi CW, Kim MS. 2021. Central administration of ampelopsin A isolated from *Vitis vinifera* ameliorates cognitive and memory function in a scopolamine-induced dementia model. **Antioxidants** 10: 835. **https://doi.org/10.3390/antiox100608**

Howells DW, Porritt MJ, Wong JY, Bachelor PE, Kalnins R, Hughes AJ, Donnan DA. 2000. Reduced BNDF mRN expression in the Parkinson's disease substantia nigra. **Exp Neurol** 166: 127 - 135. **https://doi.org/10.1006/exnr.2000.7483**

Huang Y, Huang C, Yun W. 2019. Peripheral BNDF/TrkB protein expression is decreased in Parkinson's disease but not in essential tremor. **J Clin Neurosci** 63: 176 - 181. **https://doi.org/10.1016/j.jocn.2019.01.017**

Ibrahim Fouad G, Zaki Rizk M. 2019. Possible neuromodulating role of different grape (*Vitis vinifera* L.) derived polyphenols against Alzheimer's dementia: treatment and mechanisms. **Bull Natl Res Cent** 43: 108. **https://doi.org/10.1186/s42269-019-0149-z**

Kadri S, El Ayed M, Cosette P, Jouenne T, Elkhaoui S, Zekri S, Limam F, Aouani E, Mokni M. 2019. Neuroprotective effect of grape seed extract on brain ischemia: a proteomic approach. **Metab Brain Dis** 34: 889 - 907. **https://doi.org/10.1007/s11011-019-00396-2**

Kadri S, El Ayed M, Limam F, Aouani E, Mokni M. 2020. Preventive and curative effects of grape seed powder on stroke using *in vitro* and *in vivo* models of cerebral ischemia/reperfusion. **Biomed Pharmacother** 125: 109990. **https://doi.org/10.1016/j.biopha.2020.109990**

Kazim SF, Blanchard J, Dai CL, Tung YC, Laferla FM, Iqbal IG, Iqbal K. 2014. Disease modifying effect of chronic oral treatment with a neurotrophic peptidergic compound in a triple transgenic mouse model of Alzheimer's disease. **Neurobiol Dis** 71: 110 - 130. **https://doi.org/10.1016/j.nbd.2014.07.001**

Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG. 2009. Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. **J Neurosci** 29: 13435 - 13444. **https://doi.org/10.1523/JNEUROSCI.3257-09.2009**

Kim JY, Jeong HY, Lee HK, Kim S, Hwang BY, Bae K, Seong YH. 2012. Neuroprotection of the leaf and stem of *Vitis amurensis* and their active compounds against ischemic brain damage in rats and excitotoxicity in

cultured neurons. **Phytomedicine** 19: 150 - 159. **https://doi.org/10.1016/j.phymed.2011.06.015**

Kong X, Guan J, Gong S, Wang R. 2017. Neuroprotective effects of grape seed procyanidin extract on ischemia-reperfusion brain injury. **Chin Med Sci J** 32: 92 - 99. **https://doi.org/10.24920/J1001-9294.2017.020**

Kowalska M, Owecki M, Prendecki M, Wize K, Nowakowska J, Kozubski W, Lianeri M, Dorszewska J. 2017. **Aging and neurological diseases**. In: Dorszewska J, Kozubski W. (Ed), Senescence - Physiology or Pathology, Intech Open Sciences. **https://doi.org/10.5772/intechopen.69499**

Ksiezak-Reding H, Ho L, Santa-Maria I, Diaz-Ruiz C, Wang J, Pasinetti GM. 2012. Ultrastructural alterations of Alzheimer's disease paired helical filaments by grape seed-derived polyphenols. **Neurobiol Aging** 33: 1427 - 1439. **https://doi.org/10.1016/j.neurobiolaging.2010.11.006**

Lakshmi B, Sudhakar M, Anisha MJN. 2014. Neuroprotective role of hydroalcoholic extract of *Vitis vinifera* against aluminium-induced oxidative stress in rat brain. **Neurotoxicology** 41: 73 - 79. **https://doi.org/10.1016/j.neuro.2014.01.003**

Li MH, Jang JH, Sun B, Surh YJ. 2004. Protective effects of oligomers of grape seed polyphenols against β-amyloid-induced oxidative cell death. **Ann N Y Acad Sci** 1030: 317 - 329. **https://doi.org/10.1196/annals.1329.040**

Lian Q, Nie Y, Zhang X, Tan B, Cao H, Chen W, Gao W, Chen J, Liang Z, Lai H, Huang S, Xu Y, Jiang W, Huang P. 2016. Effects of grape seed proanthocyanidin on Alzheimer's disease *in vitro* and *in vivo*. **Exp Ther Med** 12: 1681 - 1692. **https://doi.org/10.3892/etm.2016.3530**

Liu W, Ma ZJ, Liu MQ, Kang JH, Chen HW, Lin AX, Wang ZH, Guo XD, Wang YD, Liu YT, Kang XW. 2022. Grape seed proanthocyanidins attenuate LPS-induced neuroinflammation through microglia polarization regulation via TLR4/MyD88/NF-κB signaling pathway in BV2 cells. **SSRN** 3991808. **https://doi.org/10.2139/ssrn.4091202**

Long J, Gao H, Sun L, Liu J, Zhao-Wilson X. 2009. Grape extract protects mitochondria from oxidative damage and improves locomotor dysfunction and extends lifespan in a Drosophila Parkinson's disease model. **Rejuvenation Res** 12: 321 - 331. **https://doi.org/10.1089/rej.2009.0877**

Long M, Hong Y, Zhou XH, Yang Y. 2006. Anti-dementia effects of grape peel extracts experiment study. **Wei Sheng Yan Jiu** 35: 300 - 303.

Ma L, Wang X, Li Y, Xiao H, Yuan F. 2018. Effect of polysaccharides from *Vitis vinifera* L. on NF-κB/IκB-α signal pathway and inflammatory factors in Alzheimer's model rats. **Biotechnol Biotechnol Equipment** 32: 1012 - 1020. **https://doi.org/10.1080/13102818.2018.1464948**

Montine TJ, Monsell SE, Beach TG, Bigio EH, Bu Y, Cairns NJ, Frosch M, Henriksen J, Kofler J, Kukull WA, Lee EB, Nelson PT, Schantz AM, Schneider JA, Sonnen JA, Trojanowski JQ, Vinters HV, Zhou XH, Hymanl BT. 2016. Multisite assessment of NIA-AA guidelines for the neuropathologic evaluation of Alzheimer's disease. **Alzheimers Dement** 12: 164 - 169. **https://doi.org/10.1016/j.jalz.2015.07.492**

Morgan LA, Grundmann O. 2017. Preclinical and potential application of common western herbal supplements as complementary treatment in Parkinson's disease. **J Diet Suppl** 14: 453 - 466. **https://doi.org/10.1080/19390211.2016.1263710**

Morissette A, Kropp C, Songpadith JP, Junges Moreira R, Costa J, Mariné-Casadó R, Pilon G, Varin TV, Dudonné S, Boutekrabt L, St-Pierre P, Levy E, Roy D, Desjardins Y, Raymond F, Houde VP, Marette A. 2020. Blueberry proanthocyanidins and anthocyanins improve metabolic health through a gut microbiota-dependent mechanism in diet-induced obese mice. **Am J Physiol Endocrinol Metab** 318: E965 - E980. **https://doi.org/10.1152/ajpendo.00560.2019**

Natarajan SB, Hwang JW, Kim YS, Kim EK, Park PJ. 2017. Ocular promoting activity of grape polyphenols. A review. **Environ Toxicol Pharmacol** 50: 83 - 90. **https://doi.org/10.1016/j.etap.2016.12.004**

Nazıroğlu M, Kutluhan S, Uğuz AC, Çelik Ö, Bal R, Butterworth PJ. 2009. Topiramate and vitamin E modulate the electroencephalographic records, brain microsomal and blood antioxidant redox system in pentylentetrazol-induced seizure of rats. **J Membr Biol** 229: 131 - 140. **https://doi.org/10.1007/s00232-009-9177-1**

Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Del Tredici K, Duyckaerts C, Frosch MP, Haroutunian V, Hof PR, Hulette CM, Hyman BT, Iwatsubo T, Jellinger KA, Jicha GA, Kövari E, Kukull WA, Leverenz JB, Love S, Mackenzie IR, Mann DM, Masliah E, McKee AC,

Montine TJ, Morris JC, Schneider JA, Sonnen JA, Thal DR, Trojanowski JQ, Troncoso JC, Wisniewski T, Woltjer RL, Beach TG. 2012. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. **J Neuropathol Exp Neurol** 71: 362 - 381. **https://doi.org/10.1097/NEN.0b013e31825018f7**

Obay BD, Taşdemir E, Tümer C, Bilgin HM, Atmaca M. 2008. Dose dependent effects of ghrelin on pentylenetetrazole-induced oxidative stress in a rat seizure model. **Peptides** 29: 448 - 455. **https://doi.org/10.1016/j.peptides.2007.11.020**

Park JS, Park MK, Oh HJ, Woo YJ, Lim MA, Lee JH, Ju JH, Jung YO, Lee ZH, Park SH, Kim HY, Cho ML, Min JK. 2012. Grape-seed proanthocyanidin extract as suppressors of bone destruction in inflammatory autoimmune arthritis. **Plos One** 7: e51377. **https://doi.org/10.1371/journal.pone.0051377**

Paumier KL, Rizzo SJS, Berger Z, Chen Y, Gonzales C, Kaftan E, Li L, Lotarski S, Monaghan M, Shen W, Stolyar P, Vasilyev D, Zaleska M, Hirst WD, Dunlop J. 2013. Behavioral characterization of A53T mice reveals early and late stage deficits related to Parkinson's disease. **Plos One** 8: e70274. **https://doi.org/10.1371/journal.pone.0070274**

Pazos-Tomas CC, Cruz-Venegas A, Pérez-Santiago AD, Sánchez-Medina MA, Matías-Pérez D, García-Montalvo IAJ. 2020. *Vitis vinifera*: An alternative for the prevention of neurodegenerative diseases. **J Oleo Sci** 69: 1147 - 1161. **https://doi.org/10.5650/jos.ess20109**

Ramassamy C. 2006. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets. **Eur J Pharmacol** 545: 51 - 64. **https://doi.org/10.1016/j.ejphar.2006.06.025**

Rapaka D, Bitra VR, Vishala TC, Akula A. 2019. *Vitis vinifera* acts as anti-Alzheimer's agent by modulating biochemical parameters implicated in cognition and memory. **J Ayurveda Integr Med** 10: 241 - 247. **https://doi.org/10.1016/j.jaim.2017.06.013**

Rodrigues AD, Scheffel TB, Scola G, Santos MTD, Fank B, de Freitas SCV, Dani C, Vanderlinde R, Henriques JAP, Coitinho AS, Salvador M. 2012. Neuroprotective and anticonvulsant effects of organic and conventional purple grape juices on seizures in Wistar rats induced by pentylenetetrazole. **Neurochem Int** 60: 799 - 805. **https://doi.org/10.1016/j.neuint.2012.01.009**

Rodriguez M, Rodriguez-Sabate C, Morales I, Sanchez A, Sabate M. 2015. Parkinson's disease as a result of aging. **Aging Cell** 14: 293 - 308. **https://doi.org/10.1111/acel.12312**

Russo A, Palumbo M, Aliano C, Lempereur L, Scoto G, Renis M. 2003. Red wine micronutrients as protective agents in Alzheimer-like induced insult. **Life Sci** 72: 2369 - 2379. **https://doi.org/10.1016/s0024-3205(03)00123-1**

Ryu HW, Oh WK, Jang IS, Park J. 2013. Amurensin G induces autophagy and attenuates cellular toxicities in a rotenone model of Parkinson's disease. **Biochem Biophys Res Commun** 433: 121 - 126. **https://doi.org/10.1016/j.bbrc.2013.02.053**

Sharma SD, Katiyar SK. 2010. Dietary grape seed proanthocyanidins inhibit UVB-induced cyclooxygenase-2 expression and other inflammatory mediators in UVB-exposed skin and skin tumors of SKH-1 hairless mice. **Pharm Res** 27: 1092 - 1102. **https://doi.org/10.1007/s11095-010-0050-9**

Shin MK, Kim HG, Baek SH, Jung WR, Park DI, Park JS, Jo DG, Kim KL. 2014. Neuropep-1 ameliorates learning and memory deficits in an Alzheimer's disease mouse model, increases brain-derived neurotrophic factor expression in the brain, and causes reduction of amyloid beta plaques. **Neurobiol Aging** 35: 990 - 1001. **https://doi.org/10.1016/j.neurobiolaging.2013.10.091**

Shinoe T, Matsui M, Taketo MM, Manabe T. 2005. Modulation of synaptic plasticity by physiological activation of M1 muscarinic acetylcholine receptors in the mouse hippocampus. **J Neurosci** 25: 11194 - 11200. **https://doi.org/10.1523/JNEUROSCI.2338-05.2005**

Siahmard Z, Alaei H, Reisi P, Pilehvarian AA. 2012. The effect of red grape juice on Alzheimer's disease in rats. **Adv Biomed Res** 1: 63. **https://doi.org/10.4103/2277-9175.100188**

Siahpoosh A, Majdinasab N, Derakhshannezhad N, Khalili HR, Malayeri A. 2018. Effect of grape seed on quality of life in multiple sclerosis patients. **J Contemporary Med Sci** 4: 148 - 152.

Silva MIG, Silva MAG, Neto MRA, Moura BA, de Sousa HL, de Lavor EPH, de Vasconcelos PF, Macêdo DS, de

Sousa DP, Vasconcelos SMM, de Sousa FCF. 2009. Effects of isopulegol on pentylenetetrazol-induced convulsions in mice: possible involvement of GABAergic system and antioxidant activity. **Fitoterapia** 80: 506 - 513. **https://doi.org/10.1016/j.fitote.2009.06.011**

Sintara M, Wang Y, Li L, Liu H, Cunningham DG, Prior RR, Chen P, Chang T, Wu X. 2020. Quantification of cranberry proanthocyanidins by normal-phase high-performance liquid chromatography using relative response factors. **Phytochem Anal** 31: 874 - 883. **https://doi.org/10.1002/pca.2952**

Slavin M, Bourguignon J, Jackson K, Orciga MA. 2015. Influence of spice and grape pomace extracts on migraine-related indicators *in vitro*. **FASEB J** 29: 607 - 615.

Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, Villano JL. 2014. Epidemiologic and molecular prognostic review of glioblastoma. **Cancer Epidemiol Biomarkers Prev** 23: 1985 - 1996. **https://doi.org/10.1158/1055-9965.EPI-14-0275**

Thomas P, Fenech M. 2007. A review of genome mutation and Alzheimer's disease. **Mutagenesis** 22: 15 - 33. **https://doi.org/10.1093/mutage/gel055**

Thomas P, Wang YJ, Zhong JH, Kosaraju S, O'Callaghan NJ, Zhou XF, Fenech M. 2009. Grape seed polyphenols and curcumin reduce genomic instability events in a transgenic mouse model for Alzheimer's disease. **Mutat Res** 661: 25 - 34. **https://doi.org/10.1016/j.mrfmmm.2008.10.016**

Tikhonova MA, Tikhonova NG, Tenditnik MV, Ovsyukova MV, Akopyan AA, Dubrovina NI, Amstislavskaya TG, Khlestkina EK. 2020. Effects of grape polyphenols on the life span and neuroinflammatory alterations related to neurodegenerative parkinson disease-like disturbances in mice. **Molecules** 25: 5339. **https://doi.org/10.3390/molecules2522533**

Tremblay C, Pilote M, Phivilay A, Emond V, Bennett DA, Calon F. 2007. Biochemical characterization of Aβ and tau pathologies in mild cognitive impairment and Alzheimer's disease. **J Alzheimers Dis** 12: 377 - 390. **https://doi.org/10.3233/jad-2007-12411**

Tu X, Wang M, Liu Y, Zhao W, Ren X, Li Y, Liu H, Gu Z, Jia H, Liu J, Li G, Luo L. 2019. Pretreatment of grape seed proanthocyanidin extract exerts neuroprotective effect in murine model of neonatal hypoxic-ischemic brain injury by its antiapoptotic property. **Cell Mol Neurobiol** 39: 953 - 961. **https://doi.org/10.1007/s10571-019-00691-7**

Turnquist C, Harris BT, Harris CC. 2020. Radiation-induced brain injury: current concepts and therapeutic strategies targeting neuroinflammation. **Neurooncol Adv** 2: 057. **https://doi.org/10.1093/noajnl/vdaa057**

Uchino R, Madhyastha R, Madhyastha H, Dhungana S, Nakajima Y, Omura S, Maruyama M. 2010. NFκB-dependent regulation of urokinase plasminogen activator by proanthocyanidin-rich grape seed extract: effect on invasion by prostate cancer cells. **Blood Coagul Fibrinolysis** 21: 528 - 533. **https://doi.org/10.1097/MBC.0b013e32833a9b61**

Unger EL, Eve DJ, Perez XA, Reichenbach DK, Xu Y, Lee MK, Andrews AM. 2006. Locomotor hyperactivity and alterations in dopamine neurotransmission are associated with overexpression of A53T mutant human α-synuclein in mice. **Neurobiol Dis** 21: 431 - 443. **https://doi.org/10.1016/j.nbd.2005.08.005**

Uriarte Huarte O, Richart L, Mittelbronn M, Michelucci A. 2021. Microglia in health and disease: the strength to be diverse and reactive. **Front Cell Neurosci** 15: 660523. **https://doi.org/10.3389/fncel.2021.660523**

Van Kampen J, Robertson H, Hagg T, Drobitch R. 2003. Neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease. **Exp Neurol** 184: 521 - 529. **https://doi.org/10.1016/j.expneurol.2003.08.002**

Varadharajan V. 2021. *In silico* neuroprotective properties of volatile constituents of grape (*Vitis vinifera* L.) seed extract against Parkinson's disease. **Int J Comput Biol Drug Design** 14: 87 - 102.

Wang J, Ferruzzi MG, Ho L, Blount J, Janle EM, Gong B, Pan Y, Gowda GN, Raftery D, Arrieta-Cruz I, Sharma V, Cooper B, Lobo J, Simon JE, Zhang C, Cheng A, Qian X, Ono K, Teplow DB, Pavlides C, Dixon RA, Pasinetti GM. 2012. Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment. **J Neurosci** 32: 5144 - 5150. **https://doi.org/10.1523/JNEUROSCI.6437-11.2012**

Wang J, Ho L, Zhao W, Ono K, Rosensweig C, Chen L, Humala N, Teplow DB, Pasinetti GM. 2008. Grape-derived polyphenolics prevent Aβ oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. **J Neurosci** 28: 6388 - 6392. **https://doi.org/10.1523/JNEUROSCI.0364-08.2008**

Wang J, Santa-Maria I, Ho L, Ksiezak-Reding H, Ono K, Teplow DB, Pasinetti GM. 2010. Grape derived polyphenols attenuate tau neuropathology in a mouse model of Alzheimer's disease. **J Alzheimers Dis** 22: 653 - 661. **https://doi.org/10.3233/JAD-2010-101074**

Wang Q, Simonyi A, Li W, Sisk BA, Miller RL, Macdonald RS, Lubahn DE, Sun GY, Sun AY. 2005. Dietary grape supplement ameliorates cerebral ischemia-induced neuronal death in gerbils. **Mol Nutr Food Res** 49: 443 - 451. **https://doi.org/10.1002/mnfr.200500019**

Wang Q, Sun AY, Simonyi A, Miller DK, Smith RE, Luchtefeld RG, Korthuis RJ, Sun GY. 2009a. Oral administration of grape polyphenol extract ameliorates cerebral ischemia/reperfusion-induced neuronal damage and behavioral deficits in gerbils: comparison of pre-and post-ischemic administration. **J Nutr Biochem** 20: 369 - 377. **https://doi.org/10.1016/j.jnutbio.2008.04.007**

Wang YJ, Thomas P, Zhong JH, Bi FF, Kosaraju S, Pollard A, Fenech M, Zhou XF. 2009b. Consumption of grape seed extract prevents amyloid-β deposition and attenuates inflammation in brain of an Alzheimer's disease mouse. **Neurotox Res** 15: 3 - 14. **https://doi.org/10.1007/s12640-009-9000-x**

Woodman SE, Antonopoulos SR, Durham P. 2022. Inhibition of nociception in a preclinical episodic migraine model by dietary supplementation of grape seed extract involves activation of endocannabinoid receptors. **Front Pain Res** 2. **https://doi.org/10.3389/fpain.2022.809352**

Wu TH, Liao JH, Hsu FL, Wu HR, Shen CK, Yuann JMP, Chen ST. 2010. Grape seed proanthocyanidin extract chelates iron and attenuates the toxic effects of 6-hydroxydopamine: Implications for Parkinson's disease. **J Food Biochem** 34: 244 - 262. **https://doi.org/10.1111/j.1745-4514.2009.00276.x**

Wu Z, Wu A, Dong J, Sigears A, Lu B. 2018. Grape skin extract improves muscle function and extends lifespan of a Drosophila model of Parkinson's disease through activation of mitophagy. **Exp Gerontol** 113: 10 - 17. **https://doi.org/10.1016/j.exger.2018.09.014**

Wyss-Coray TJN. 2016. Ageing, neurodegeneration and brain rejuvenation. **Nature** 539: 180 - 186. **https://doi.org/10.1038/nature20411**

Xiao Y, Liu Y. 2016. Protective effect of Grape seed proanthocyanidin on learning disabilities in a rat model with radiation brain injury. **Chin J Behav Med Brain Sci** 12: 128 - 133.

Youssef SB, Brisson G, Doucet-Beaupré H, Castonguay AM, Gora C, Amri M, Lévesque M. 2021a. Neuroprotective benefits of grape seed and skin extract in a mouse model of Parkinson's disease. **Nutr Neurosci** 24: 197 - 211. **https://doi.org/10.1080/1028415X.2019.1616435**

Zga N, Papastamoulis Y, Toribio A, Richard T, Delaunay JC, Jeandet P, Renault JH, Monti JP, Merillon JM, Waffo-Teguo P. 2009. Preparative purification of antiamyloidogenic stilbenoids from *Vitis vinifera* (Chardonnay) stems by centrifugal partition chromatography. **J Chromatogr B Analyt Technol Biomed Life Sci** 877: 1000 - 1004. **https://doi.org/10.1016/j.jchromb.2009.02.026**

Zhang FJ, Yang JY, Mou YH, Sun BS, Ping YF, Wang JM, Bian XW, Wu CF. 2009. Inhibition of U-87 human glioblastoma cell proliferation and formyl peptide receptor function by oligomer procyanidins (F2) isolated from grape seeds. **Chem Biol Interact** 179: 419 - 429. **https://doi.org/10.1016/j.cbi.2008.12.017**

Zhang FJ, Yang JY, Mou YH, Sun BS, Wang JM, Wu CF. 2010. Oligomer procyanidins from grape seeds induce a paraptosis-like programmed cell death in human glioblastoma U-87 cells. **Pharm Biol** 48: 883 - 890. **https://doi.org/10.3109/13880200903311102**