Vitis vinífera: An Alternative for the Prevention of Neurodegenerative Diseases

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Abstract: To present a systematic review of published studies in databases such as PUBLMED, REDALYC, SCIELO, DIALNET, SCOPUS, EBSCO and CONRICYT related to the role-played by the components present in the vegetable oil of grape seed (Vitis vinífera) and the prevention or delay in the onset or progression of neurodegenerative diseases. The analysis of the research revealed that neurodegenerative diseases causes alterations in consciousness or in the nervous system leading to severe damage in neuronal cells, these pathologies are considered gradual and progressive. Various syndromes manifest the degenerative diseases of the nervous system; in some of them the predominant symptom is the progressive dementia. Among the components of the diet that in numerous epidemiological studies have shown an inverse association are vitamins, minerals, carotenoids, polyunsaturated fatty acids and polyphenols, the latter being the ones addressed in this document. There is an important evidence that a nutritional support based on polyunsaturated fatty acids and antioxidants can be applied to subjects with a history of neurodegenerative conditions in order to act as neuroprotectors. This requires the determination of the nutritional benefits of these nutrients or of nutraceuticals for the health of this group of patients.

Key words: neurodegenerative diseases, Vitis vinífera, nutritional components

1 Introduction

The reactive oxygen species (ROS) and free radicals originated in biological systems are capable of oxidizing cellular proteins, nucleic acids, and lipids leading to premature aging, mutagenesis and carcinogenesis. Food vegetable products provide a wide variety of active compounds called secondary metabolites, which have antioxidant, antitumor activity, and immunostimulatory properties; the deterioration of cells in the human body can occur due to the lipid peroxidation present in aerobic cells, between the interaction of free radicals and polyunsaturated fatty acids, however, it is not the only factor that intervenes. The Vine seeds (Vitis vinífera L.) have been studied due to their active properties that contain the phenolic compounds, flavonoids, and phenolic acids. Presented substances in the seeds have a variety of biological effects: antioxidants, captures of free radical, anti-inflammatory, antihypertensive, antimutagenic, antineoplastic, antiviral, antibacterial, antiulcer stomach, anti-tumor, healing, anti-hyperglycemic, cardioprotection, anti-hepatoxic or anti eye cataract, and sunscreens; these properties are related to the reactivity of the phenol group and have been tested in vitro, in vivo, in animals and in humans. The phenolic components presented in Vitis vinífera are organic substances with functions of both as immunological defense, and as protection against reactive oxygen species, since they have in their structure one or more aromatic rings which they manage to sequester the free radicals presented its antioxidant activity depends on the number and location of the hydroxyl groups contained in its structure.

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Grape seed oil contains E vitamin (tocopherols), phenolic compounds, and fatty acids; antioxidants are acting in the prevention of aging, heart disease, and cancer since they prevent reactive oxygen species (ROS) cause damage in to DNA and oxidative reactions carried out by free radicals. According to the analyzes made on the grape seed, it has been determined that linoleic acid (omega-6) is present in the 62.81%, 65.34% for conventional and organic oil, in addition, to other fatty acids such as palmitic acid (C16: 0), palmitoleic (C16: 1), stearic (C18: 0), oleic (C18); the content of alpha-tocopherol, delta-tocopherol and gamma-tocopherol have values above the FAO/WHO table (2015), both for organic and conventional oils.

2 Neurodegenerative diseases

Neurodegenerative conditions induce alterations in consciousness or in the nervous system that cause severe damage to neuronal cells, these pathologies are considered gradual and progressive; degenerative diseases of the nervous system are manifested by various syndromes and in some of them the predominant symptom is progressive dementia. Now at day, neurodegenerative diseases are classified based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), within this are Parkinson’s Disease (PD), Alzheimer’s Disease (AD), Huntington’s Disease (HD), Dementia and Amyotrophic Lateral Sclerosis (ALS). All these pathologies have a multifactorial etiology, mainly environmental, of aging, and family history, where the genes involved in each condition have been reported (see Table 1); this genetic origin is related to several involved mechanisms, of interaction between genes and molecular pathways.

Parkinson’s disease (PD) is the most common form of dementia with the highest prevalence in the world after Alzheimer’s disease; PD is a neurodegenerative disease characterized by its slow development and manifested around 60 to 85 years old, there are early cases, before 50 years, there are even reports of cases of extreme peculiarity, very early onset, whose appearance oscillates at approximately 20 years. The cardinal signs of PD are akinesia, tremor at rest, stiffness, increased muscle tension and resistance to movement and instability of the posture due to loss of balance, which leads to frequent falls, some other symptoms may occur as bradykinesia and dysarthria. Alzheimer’s disease (AD) is clinically characterized as a cause of dementia present in senior people, patients may present anxiety and depression. It is a disease whose pathogenesis is complex because it can occur in an inherited way, or in an environmental way as a result of multifactorial aging process. The AD is a neurodegeneration characterized by protein deposits to the neurons, which is the accumulation of amyloid peptide surrounded by degenerated nerve endings, as well as intracellular neurofibrillar alterations due to phosphorylation in the “tau” cytoskeletal protein. This accumulation of proteins occurs intracellularly in the “tau” for formed protein and the extracellular accumulation is β-amyloid, both leading to the degradation of neurofibrillar tangles and amyloid plaques, causing inflammation and dysfunction of brain cells. In addition, oxidative stress in neurodegenerative diseases has been widely described from the reduction of the defense mechanism in the formation of radicals free oxygen in a physiological way derived from mitochondrial respiration, immune response and the reduction of inflammatory processes associated with aging.

For to genetic causes, mutations in the genes of presenilins 1 and 2 have been described in the gene that codes for the β-amyloid precursor protein, and in the apoE gene. Other risk factors are the presence of head trauma, exposition to chemical compounds, atherosclerosis, osteoarthritis and depression. Huntington’s disease (HD) is a neurodegenerative disorder that has a characteristic that affects neuroanatomic and neurophysiological to the language, from the moment it is caused by the destruction of a specific subpopulation of gâbergic neurons of the caudate nucleus, this process of progressive cell death results in an alteration of motor control and various behavioral and intellectual deficits, which can lead to chronic depression, irritability and aggressiveness. Genetically speaking, HD is due to an anormal expansion of the CAG triplet in the sequence of the HTT gene which becomes pathogenic when 34 repetitions are exceeded and a direct correlation between the length of the repeated segment and the precocity manifests the disorder. Dementia refers to the severe damage of intellectual functions, dementia disorders are caused by abnormal pathological processes (of a genetic or vascular nature, among others). They can affect both young people and the elderly, the course of dementia in young people usually leads to a much faster cognitive decline even in weeks in contrast to the decline presented in the elderly, which can last for years. An essential characteristic of Dementia consists in the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive impairments: aphasia, apraxia, agnosia or an impaired ability to perform.

About to Amyotrophic Lateral Sclerosis (ALS), is a degenerative disease of motor neurons, it is characterized by a loss of capacity and motor activity, the main cause is the degeneration of neurons, ranging from damage to upper motor neurons in gray nuclei and cerebral cortex and inferior in the gray columns of the spinal cord and brain stem. Some pathological features include thickening of the proximal area of motor axons due to abnormal cross-linking and
Table 1  Genes associated to neurodegenerative diseases and drug treatment.

| DISEASE | GENE | LOCUS | PROTEIN | TREATMENT |
|---------|------|-------|---------|-----------|
| Parkinson’s disease (Pd) | LRRK2 | PARK8 12p11.2-q13.1 | Dardarin | LEVODOPA |
| Autosomal Dominant | | | | Monoamine Oxidase B Inhibitors |
| | SNCA | PARK1/PARK4 4q21-q23 | α-sinucleina (SNCA) | |
| | VPS35 | PARK17 | Complejo retromer | |
| | | | VPS35 | |
| | PARKINA | 6q25.2-q27 | Parkin | |
| Parkinson’s disease (PD) | PINK1 | 1p36 | PTEN | DOPAMINE AGONISTS |
| Autosomal Recessive | | | | Bromocriptine |
| | | | | Pergolidine |
| | | | | Cabergoline |
| | | | | Apomorphine |
| | | | | Ropinirole |
| | | | | Pramipexole |
| | | | | Rotigotine |
| | | | | Catecol O Methyltransferase Inhibidores |
| | | | | Tolcapone |
| | | | | ANTICHOLINERGICS |
| | DJ1 | 1p36.12 | Protein deglycase | |
| | | | DJ1 | |
| | | | | ATP13A2 | 1p36.13 | ATPasa type 13p2 |
| | | | | | | Biperiden |
| | | | | | | Procyclidine |
| | | | | | | Trihexyphenidyl |
| | DNAJC6 | 1p31.3 | DNAJ / HSP40 | |
| | | | | | | Tolcapone |
| | | | | | | ANTICHOLINERGICS |
| | | | | | | ATP13A2 | 1p36.13 | ATPasa type 13p2 | Biperiden |
| | | | | | | Procyclidine |
| | | | | | | Trihexyphenidyl |
| | | | | | | DNAJC6 | 1p31.3 | DNAJ / HSP40 | Tolcapone |
| | | | | | | ANTICHOLINERGICS |
| | | | | | | DNAJC6 | 1p31.3 | DNAJ / HSP40 | Tolcapone |
| Parkinson’s disease (PD) | ATP13A2 | 1p36.13 | ATPasa type 13p2 |
| Complex genetic forms (autosomal recessive inheritance) | | | | |
| | FBX07 | 22q12 | F-box | |
| | SYNJ1 | 21q22.11 | phosphoinositide phosphatase | |
| | PLA2G6 | 22q13.1 | Phospholipase A2 (PLA2) group VI | |
| Genomic Location | Gene | Description |
|------------------|------|-------------|
| 1p31.3 | DNAJC6 | DNAJ/HSP40 |
| 15q22.2 | VPS13C | VPS13C |
| 1q42.13 | PSEN2 | Présénille 2 |
| 21q21.3 | Aβ (APP) | Amyloid precursor protein (APP) |
| 17q21.31 | TAU | Tau |
| 9q21.32 | UBQLN1 | Ubiquitin |
| 6p22.2 | The sortilin-related receptor one (SORL1) | VPS10 y VLDL |
| 19q13.32 | ApoE2 | Apolipoprotein 2 |
| 19q13.32 | ApoE3 | Apolipoprotein 3 |
| 19q13.32 | ApoE4 | Apolipoprotein 4 |
| 4p16.3 | HTT | Huntingtine |

**Cholinesterase Inhibitors**
- Tacrine
- Donepezil, Rivastigmine, Galantamine y Memantina

**Enfermedad de Huntington (EH)**
- Huntington disease
- Modified Dopamine drugs
  - Tetrabenazine
  - clozapine
  - Medications that modify glutamate
  - Amantadine
  - Riluzone

**Alzheimer’s Disease (AD)**
- Autosomal Dominant
  - PSEN1 14q24.2 Présénille 1
  - PSEN2 1q42.13 Présénille 2
  - Aβ (APP) 21q21.3 Amyloid precursor protein (APP)

**Table 1 Continued.**
Table 1  Continued.

| Dementia and Amyotrophic Lateral Sclerosis |  |  |  |
| --- | --- | --- | --- |
| **EPHA4** | 2q36.1 | A4 de EPH receptor |  |
| CHGB | 20p13.3 | Protein tyrosine suldation |  |
| Cromogranin |  |  |  |
| KIFAP3 | 1q24.2 | protein-associated kinesin 3 |  |
| SMN | 5q13 | SMN |  |
| ALS2 | 2q33.1 | Alsina |  |
| SETX | 9q34.13 | Senataxin |  |
| VCP | 9p13.3 | Valosin containing |  |
| TARDBP | 1p36.2 | TAR DNA-binding protein 43 (TDP-43) |  |
| VAPB | 20q13 | VAMP protein associated with B y C |  |
| UBQLN2 | Xp11 | Ubiquilin 2 |  |
| DAO | 12q22 | D-aminoacid oxidase |  |
| SETX | 9q34.13 | Senataxin |  |
| CHMP2B | 3p11 | Charged multivesicular body protein 2B |  |
| ANG | 14q112 | angiogenin |  |
| OPTN | 10p13 | optineurin |  |

Others

- Donepezil
- Coenzyme Q10
- Minocycline
- Nabilone
- Riluzole
- Edaravone
| Gene     | Chromosome | Description                                                                 |
|----------|------------|-----------------------------------------------------------------------------|
| PFN1     | 17p13      | Profilin 1                                                                  |
| TUBA4A   | 2q35       | Tubulin alpha 4a                                                            |
| UNC13A   | 19p13      | Unc 13 homolog A                                                            |
| FIG4     | 6q21       | SAC                                                                         |
| ELP3     | 8p21.1     | elongation protein 3 homolog                                                |
| NEFH     | 22q12.2    | TAR DNA-binding protein 43 (TDP-43)                                          |
| SIGMAR1  | 9p13.3     | Receptor intracellular no opioid sigma1                                     |
| C21orf2  | 15q24      | -                                                                           |
| CHRNA3   | 15q24      | -                                                                           |
| CHRNA4   | 20q1       | -                                                                           |
| CHRNA4   | 15q24      | -                                                                           |
| ERBB4    | 2q34       | Tyrosine kinase receptor ERB-B2                                              |
| DCTN1    | 2p13       | dynactin-1                                                                  |
| C19orf12 | 9q12       | Mitochondrial membrane protein-associated neurodegeneration (MPAN)           |
| SPG11    | 15q21.1    | Spatacsin protein                                                           |
| PRPH     | 12q13      | Intermediate filament cytoskeleton protein type III                          |
| NTE      | 19p13      | -                                                                           |
| PON1-3   | 7q21       | Paraoxonase                                                                 |
| SS18L1   | 20q13.3    | CREST                                                                       |
disorientation of neurofilaments cytoplasmic neuronal inclusions similar to Lewy bodies, fragmentation of the Golgi apparatus, as well as Wallerian axonal degeneration.

The pharmacological treatments available for neurodegenerative diseases are symptomatic and do not alter the course or progression of the disease; they also produce adverse reactions in patients, having a limited scope; therefore, it is necessary to develop alternative therapies for the treatment and reduction of the progress of these diseases.

### 3 Neuroprotection and *Vitis vinifera*

The brain has a high oxidative metabolism that becomes the main target organ when it is affected in the state of uncontrolled stress, the high concentration of cortisol not only lead to damage the brain cells, but also accelerate neurodegenerative disorders of the brain, decreasing growth factors, causing the release of proinflammatory cytokines that leads to the presence of oxidative stress. Between 50-60% of the lipids that make up the brain are unsaturated fatty acids that make it susceptible to lipoperoxidation and the formation of secondary compounds such as acrolein, malondialdehyde and isoprostanes. The formation of lipoperoxidation can cause cell dysfunction and the death of neurons, this oxidation causes alterations in the protein structures favoring the development of neurodegenerative diseases, it also has a low concentration of antioxidant enzymes, such as: superoxide dismutase, catalase, and glutathione peroxidase. The production of reactive oxygen species (ROS) by cells of the central nervous system (CNS), occurs through microglia cells considered as CNS macrophages for their ability to remove waste substances and damaged structures, when are activated they release ROS as O$_2^-$ and H$_2$O$_2$ as well as a whole series of cytokines, the latter can induce the microglia to release more ROS or produce the expression of the enzyme inducible nitric oxide synthase (iNOS), which produces reactive species derived from nitrogen (nitric oxide) and reactive oxygen species.

The oxidative stress of Alzheimer’s disease significantly increases the levels of Malondialdehyde (MDA), as the lipids contained in the brain oxidize, mainly polyunsaturated fatty acids, being more susceptible to oxidative cell damage due to the high level of oxygen consumption and the postmitotic neurons and form lipid peroxides, the latter are unstable and decompose forming carbonyl compounds, and contribute to the formation of MDA.

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**Table 1** Continued.

| Gene   | Chromosome | Description               |
|--------|------------|---------------------------|
| ALS3   | 18q21      | ALS3                      |
| ALS6-21| 6p25       | Fused in sarcoma          |
| ALS-FTD| 16p12      | -                         |
| MATR3  | 5q31.2     | Matrin 3                  |
| ATXN2  | 12q24      | Ataxin 2                  |
| SQSTM1 | 5q35       | P62                       |
| HNRNPA2B1 | 7p15     | hnRNP s                   |
| HNRNPA1 | 12q13      | HnRNP DNAJC6              |
| ALS7   | 20p13      | -                         |
| CHCHD10| 22q11      | Mitochondrial protein     |
| FUS    | 16p11.2    | RNA binding protein       |

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Table 2  Relationship between Vitis vinifera and neuroprotection.

| DISEASE                  | REPORT                                                                 | MODEL               | EFFECT                                                                                                                | AUTHOR                  |
|-------------------------|------------------------------------------------------------------------|---------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------|
| Neuroprotection         | Grape Seed Extract Acting on Astrocytes Reveals Neuronal Protection Against Oxidative Stress via Interleukin-6-mediated Mechanisms. | Animal model. Wistar rats | Grape seed extract prevents the death of hippocampal neurons in culture in oxidative stress induced by H₂O₂ by increasing the production of IL 6 in astrocytes and mRNAs. | Fujishita, K. et al., 2009 |
| Parkinson’s disease (PD)| Grape extract protects mitochondria from oxidative damage and improves locomotor dysfunction and prolongs shelf life in a Drosophila model of Parkinson’s disease. | Animal model. Sprague-Dawle rats | They made a botanical formulation called Regrapex-R, that it is a combination composed of an extract of whole grape (Vitis vinifera) and Polygonum cuspidatum. A potent antioxidant activity was obtained with free radical elimination, protects mitochondria from oxidative damage, and is an effective agent to improve the loss of locomotor function in a Drosophila model for Parkinson’s disease. One gram of Regrapex-R contains 100 mg of resveratrol complex (trans-resveratrol and its glycosides), 10 mg of emodin complex (emodin and emodin glycosides), 450 mg of polyphenols and 12 mg of anthocyanins. | Long et al., 2009 |
| Alzheimer’s Disease (AD)| A New Specific BACE-1 Inhibitor from the Stem bark Extract of Vitis vinifera. | in vitro FRET test | They isolated a new resveratrol dimer, (+) vitisinol E, which has inhibitory activity on BACE-1 (excision enzyme of beta site APP 1) in vitro, from Vitis vinifera stem bark extract (Vitaceae) along with four oligomers of resveratrol (+) - vitisinol, (+) - ε-viniferin, (+) - ampelopsin A, (+) - vitisin A and (+) -viticin B. The inhibition of BACE-1 is important in the treatment of for Alzheimer’s, since β-secretase in neurons is essential for the production of beta amyloid. | Choi et al., 2009 |
| Neuroprotection         | Phenolic content of grapevine leaves (Vitis labrusca var. Bordo) and its neuroprotective effect against peroxide damage. | In vitro model | Phenolic compounds and antioxidant activity of organic and conventional grape leaf extracts prepared from V. labrusca (var. Board) in brain tissues (in vitro model) were evaluated. The administration of V. vinifera extract (400 mg / kg, p.o., 45 d) could protect the brain from the neurotoxicity of aluminum (100 mg / kg, p.o., 45 d). The organic leaf extract showed approximately 10 times more resveratrol than the conventional one. Both extracts were able to reduce the damage to lipids and proteins induced by hydrogen peroxide in the rats’ brains. Protein damage was reduced with organic leaf extract in the cortex, hippocampus and cerebellum. Conventional leaf extracts reduced carbonyl protein only in the cortex. | Dani et al., 2010 |
| Neuroprotection and epilepsy | Neuroprotective and anticonvulsant effects of organic and conventional purple grape juices | Animal model. Wistar rats | Conventional and organic purple grape juices (10 μL / g, 17 d), rich in polyphenols in Wintsa rats were evaluated against pentylenetetrazole-induced damage (seizure drug); it was found that both | Rodrigues et al., 2012 |
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Table 2

| Disease/Neuropathology | Description | Model/Condition | Treatment/Intervention | Outcome/Effect | Reference |
|------------------------|-------------|-----------------|-------------------------|----------------|-----------|
| Alzheimer's Disease (AD) | Dietary resveratrol prevents Alzheimer's markers and increases life span in SAMP8. | Animal model SAMP8 rats | The administration of resveratrol (1 g / kg, 2 months) to SAMP8 mice, a model of Alzheimer's disease demonstrated a positive effect on the extension of the half and maximum life of memory and neurodegenerative markers in mice related to age, improving cognitive impairment, by increasing the lifespan of animals and activating AMPK pathways and survival pathways, such as SIRT1 in vivo; It also has a neuroprotective role, reducing amyloid load and reducing tau hyperphosphorylation. | Porquet et al., 2013 |
| Aluminum induced neuroprotection | Neuroprotective role of hydroalcoholic extract of Vitis vinifera against aluminium-induced oxidative stress in rat brain. | Animal model. Sprague-Dawley rats | In this study, V. vinifera hydroalcoholic extract was administered through diet (400 mg / kg, p.o., 45 d) to rats induced to aluminium-induced neurotoxicity 100 mg / kg, p.o., 45 d). The administration with V. vinifera and Al caused a significant improvement in short-term memory, cognition, anxiety, locomotion and muscular activity. Al exposure led to a significant decrease in the activity of acetylcholine in the brain, increase in serum glucose Acetylcholine affects human memory and cognitive function by dramatically decreasing the activity of acetylcholine transferase in the cortex and hippocampus of Alzheimer's patients. | Lakshmi et al., 2014 |
| Alzheimer's Disease (AD) and Neuroprotection | Viniphenol A, a Complex Resveratrol Hexamer from Vitis vinifera Stalks: Structural Elucidation and Protective Effects against Amyloid-β-Induced Toxicity in PC12 Cells. | PC12 cell cultivation | New minor stilbenes were determined from Vitis vinifera stems, through purification and by centrifugal partition chromatography. Viniphenol A (1–20 μM), a hexamer of resveratrol, showed protective effects against β-amyloid-induced toxicity in PC12 cell cultures. | Papastamoulis et al., 2014 |
| Peripheral neuropathy | Functional and Morphological Effects of Grape Seed Proanthocyanidins on Peripheral Neuropathy in Rats with Type 2 Diabetes Mellitus. | Animal model. Sprague-Dawley rats | They examined the effect of grape seed proanthocyanidins on functional and morphological abnormalities in the peripheral nerves of rats with type 2 diabetes mellitus. 500 mg / kg were administered in rats induced with diabetes; abnormal peripheral nerve functions and tissues were improved. impaired nerves in the spinal cord; In addition, this dose showed an inhibitory effect on Ca2 + overload in the sciatic nerves. GSP grape seed proanthocyanidins can prevent early functional and morphological abnormalities in the peripheral nerves of rats with type 2 diabetes mellitus. | Ding et al., 2014 |
In multiple epidemiological studies the benefits of the antioxidant activity of grape juice have been reported in relation to the reduction of oxidative stress, inflammations, and the protection of diseases such as cancer, cardiovascular diseases, and dermal disorders. In many of them is emphasized that proanthocyanidins are powerful antioxidants that mediate many biological activities, such as anti-inflammatory, anti-diabetic, cardiovascular protections, anti-cancer, antiviral activities, and play a role in immunomodulation.

The vegetable oil from *Vitis vinifera* has organic acids, mainly malic acid, oxalic acid and tartaric acid; and polyphenolic compounds that have a classification in six subgroups among which we can find: flavonols, flavones, isoflavones, anthocyanins, flavanones and flavanols, highlighting mainly the so-called flavan-3-oles, particularly catechin and epicatechin, these are associated with inhibition of arterial thrombosis, anti-inflammatory activity, reduction of total cholesterol and lipoprotein low density *in vivo* as part of its antioxidant capacity. In addition, the oil contains resveratrol, it is known that resveratrol inhibits the nuclear factor κB, involved in the toxicity of β-amyloid which is responsible for generating Alzheimer’s disease. This same compound has proven to have a repressor of the

| Table 2 | Continued. |
| --- | --- |
| **Neuroprotection** | Protective mechanism of grape seed oil on carbon tetrachloride-induced brain damage in γ-irradiated rats. |
| Animal model. | Wistar female rats. |
| **Neuroprotection** | Protective activity of grape juice in rat brain, mainly malic acid, oxalic acid and tartaric acid. |
| Animal model. | Wistar rats. |
| **Alzheimer’s Disease (AD)** | Resveratrol and Solid Lipid Nanoparticles for the Treatment of Alzheimer’s Disease. |
| Animal model. | Nanoparticles |
| **Alzheimer’s Disease (AD)** | Vitis vinifera acts as anti-Alzheimer’s agent by modulating biochemical parameters implicated in cognition and memory. |
| Animal model. | Sprague-Dawley rats |
| **Alzheimer’s Disease (AD)** | The beneficial effects of V. vinifera grape seed oil on carbon tetrachloride-induced neurotoxicity in rats irradiated with gamma rays were studied. The administration of (0.87 g / ml) has neuroprotective effects against oxidative stress, reducing levels of malondialdehyde and nitric oxide, xanthine oxidase, iNOS and proinflammatory cytokines such as TNF-α, IL-6 and TGF-β1; and increasing antioxidant levels. |
| | Ismail et al., 2015 |
| **Alzheimer’s Disease (AD)** | In this study, the effects of organic and conventional grape juice on neurotrophic factor modulation (BDNF) and astrocytic marker protein (S100B) on the hippocampus and the frontal cortex of Wistar rats were analyzed; the animals that received organic and conventional grape juice showed, in the frontal cortex, an elevated level of BDNF in relation to the saline group. Grape juices are capable of modulating an important marker in brain tissue and could be an important factor in preventing brain diseases. |
| | Dani et al., 2017 |
| **Alzheimer’s Disease (AD)** | They evaluated the grape extracts (skin and seed), in inhibiting the aggregation of Aβ. They showed that solid lipid nanoparticles (SLN) functionalized with an antibody, the transferrin receptor monoclonal antibody (OX26 mAb), can function as a possible carrier for transporting the extract to the brain. Experiments with human brain-type endothelial cells show that the cellular uptake of OX26 SLNs is substantially more efficient than that of normal SLNs and SLNs functionalized with a nonspecific antibody. |
| | Loureiro et al., 2017 |
| **Alzheimer’s Disease (AD)** | Vitis vinifera activity was evaluated in Alzheimer-induced rats exposed to aluminum. The expression of amylloid protein and Tau were evaluated by PCR analysis. A neuroprotection was obtained by modifying the biochemical parameters; in addition to the inhibition the mRNA expression of the amyloid and tau precursor protein. |
| | Rapaka et al., 2018 |
p53 gene, thus preventing neuronal apoptosis and its oxidative damage, there is evidence that treatments with resveratrol decreases brain damage caused by ischemia, hemorrhages, seizures and epilepsy, thus serving as an alternative to the treatment and prevention of neurodegenerative conditions such as Alzheimer’s disease, Parkinson and Huntington. Bazán in 2016, showed that *Vitis vinifera* oil contains as a major component omega-6, functioning as well as a platelet antiaggregant preventing thrombotic diseases or strokes.

However, one of the aspects to consider in the ingestion of *Vitis vinifera* is its assimilation in the organism, mainly because resveratrol is rapidly metabolized (less than 2h) in the liver and intestinal epithelial cells in glucuronic acid conjugates and of the phenolic sulfate group that are then eliminated, because resveratrol has a low bioavailability that limits its biological and pharmacological benefits, the whole process that this compound has to go through the blood brain barrier to reach the brain where it is It has demonstrated its neuroprotective effects. Therefore, methods with greater assimilation in the organism, of this compound, have been developed in recent years through nanotechnology as described by Loureiro, In which they developed a targeted therapeutic system for intravenous administration of resveratrol and extracts of Seed and grape skin using solid lipid nanoparticles by crossing the blood-brain barrier in an *in vitro* model, demonstrating that the synthesized nanoparticles are capable of encapsulating the extracts and can be functionalized to cross the barrier.

Studies have been conducted in animals and *in vitro* models with promising results of the use of *Vitis vinifera* as shown in Table 2, for example, in the study conducted by Boraí et al., it was shown that polyphenol-based treatment has a beneficial therapeutic effect against the neurobehavioral and neurochemical changes associated with Alzheimer’s dementia, through regression in the neurodegenerative characteristics of dementia from Alzheimer in the rat model intoxicated with Al, induced by AlCl₃ by reducing brain damage and improving functional outcome, in the Behavioral T maze test and confirmed by kíte testing and histopathological investigations. Also, Ma and collaborators in animal models observed that the polyphenols of the flavones of *Vitis vinifera*, can promote synaptic plasticity and indirectly affect the expression of cholinergic neurotransmitters, which can be a mechanism of *Vitis vinifera* protection in rats with Alzheimer’s disease by improving protein expression of p-CREB, BDNF and SYT1 in hippocampus rat, depending on the dose.

In the study conducted by Li and collaborators reported that the selected grape seed polyphenol extract can adequately interferes with the assembly of tau peptide in neurotoxic aggregates, in addition to a significantly slowing of the development of Alzheimer’s tau neuropathology in the mouse model brain TMHT of AD through mechanisms associated with the attenuation of the signal kinase 1/2 of the extracellular signal receptor in the brain. Also, they reported in previous studies of *in vitro* physical biochemistry and *in vivo* preclinical studies where grape seed polyphenol extract interfering with tau fibrillation and attenuate tau phosphorylation mediated by ERK1/2 in Thr181 and Ser396/400/404. Therefore they suggest that grape seed polyphenol extract is highly tolerated in rodents and humans, being bioavailable in the brain.

### 4 Final considerations

As final considerations, we can say that today the main sources of polyunsaturated fatty acids of the omega-3 type could act as antioxidants are cold-water fish, however, environmental conditions have caused a decrease in the recommendation of the consumption; together with the adoption of lifestyles characterized by high consumption of tobacco, presence of heavy metals in food and beverages, alcohol, and sedentary lifestyle, has caused an increase in the diseases that now, we consider public health problems. This has led to look for new alternatives, the most viable is the consumption of vegetable origin oils present in a greater availability to the population, and at lower cost, in addition to the fact that among their nutritional properties they are free -cholesterol, trans-type fats, and not interact with other nutrients. The consumption of grape seed oil can be considered as a prevention and treatment option in neurodegenerative or cardiovascular diseases, the mechanism of action, tissue specificity, administration dose, and duration of this treatment has not yet been understood, it is an objective that should be proposed in the medium term, in view of this, they require a greater number of investigations that significantly could determine the nutritional benefits of these nutrients, or of nutraceutical foods for the health of the population.

### Conflicts of Interest

The authors declare no conflict of interest.

### References

1. Gomez, C.; Bermejo, L.; Loria V. Importance of a balanced omega 6/omega 3 ratio for the maintenance of health. Nutritional recommendations. *Nutr. Hosp.* 26, 323-329 (2011).

2. Ballesteros, F.; Sejas, M.; Herbas, A.; Carpenter, I. Sindrome metabólico y su relación con ácidos grasos omega-3. *Rev. Boliv. Quím.* 24, 58-63 (2007).
3) Benítez, P.; Burgos, R.; Calvo, S.; Gómez, C.; Royo M. Nutrición, salud y alimentos funcionales. Universidad Nacional de Educación a distancia; 383(2011).
4) Alonso Merchán, V. Síndrome metabólico y riesgo de enfermedad cardiovascular. Acta Med. Colomb. 30, 150-154 (2005).
5) Natarajan, S.B.; Hwang, J.W.; Kim, Y.S.; Kim, E.K.; Park, P.J. Ocular promoting activity of grape polyphenols-A review. Environ. Toxicol. Pharmacol. 50, 83-90 (2017).
6) Rincón, M.; Valenzuela, R.; Valenzuela, A. Stearidonic acid: an omega-3 fatty acid from plant origin with great potential in health and nutrition. Rev. Chil. Nutr. 42, 297-300 (2015).
7) Carrasco, F.; Galgani, J.; Reyes, M. Insulin resistance syndrome: Diagnosis and management. Rev. Med. Clin. CONDES 24, 827-837 (2017).
8) Ferrer, J.; Granell, L.; Muñoz, A.; Sánchez, C. Consumo de frutos secos y aceites vegetales en personas con diabetes mellitus tipo 1. Nutr. Hosp. 31, 2641-2647 (2015).
9) Costa, J.R.; Amorim, M.; Vilas-Boas, A.; Tonon, R.V.; Cabral, L.M.C.; Pastrana, L.; Pintado, M. Impact of in vitro gastrointestinal digestion on the chemical composition, bioactive properties, and cytotoxicity of Vitis vinifera L. Cv. Syrah grape pomace extract. Food. Funct. 10, 1856-1869 (2019).
10) Ribeiro, C.C.D.; Silva, R.M.; Campanholo, V.M.L.P.; Ribeiro, D.A.; Ribeiro Piaotti, A.P.; Forones, N.M. Effects of grape juice in superoxide dismutase and catalase in colorectal cancer carcinogenesis induced by azone-methane. Asian Pac. J. Cancer Prev. 19, 2839-2844 (2018).
11) Kuhn, P.; Kalariva, H.M.; Poulev, A.; Ribnicky, D.M.; Jaja-Chimedza, A.; Roopchand, D.E.; Raskin, I. Grape polyphenols reduce gut-localized reactive oxygen species associated with the development of metabolic syndrome in mice. Plos One 13 (10), e0198716 (2018).
12) Navarrete, E.; Prospéro, O.; Hudson, R.; Guevara, R. Enfermedades neurodegenerativas que cursan con demencia. Gac. Méd. Méx. 136 (6), 189-200 (2000).
13) American Psychiatric Association. Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM–5). 5th ed. Médica Panamericana (2016).
14) Hurtado, F.; Cardenas, M.A.; Cardenas, F.; León, L.A. La enfermedad de Parkinson: Etiología, Tratamientos y Factores preventivos. Universitas Psychologica 15 (5), 1-26 (2016).
15) Poewe, W.; Seppi, K.; Tanner, C.M.; Halliday, G.; Brundin, P.; Volkman, J.; Schrag A.E.; Lang, A.E. Parkinson disease. Nat. Rev. Dis. Primers 23(3), 17013 (2017).
16) Cárdenas, G.; Décot, M.A.; Martínez, H.; Martínez, L.; Esmer, M. Genetics of Parkinson’s disease: A review of recent findings. Medicina Universitaria 13(51), 96-100 (2011).
17) Koros, C.; Simitsi, A.; y Stefanis, L. Genetics of Parkinson’s disease: Genotype–phenotype correlations. Inter. Rev. Neurobiol. 132, 197-231 (2017).
18) Gutiérrez, D.; Yescas, P.; López, M.; Boll, M. Factores genéticos de la demencia en la enfermedad de Parkinson (EP). Gac. Med. Mex. 151, 110-118 (2015).
19) Tarakad, A.; Jankovic, J. Diagnosis and management of Parkinson’s disease. Semin. Neurol. 37 (2), 118-126 (2017).
20) Jankovic, J.; Poewe, W. Therapies in Parkinson’s disease. Curr. Opin. Neurol. 25, 433-447 (2012).
21) Gazewood, J.D.; Richards, D.R.; Clebak, K. Parkinson disease: an update. Am. Fam. Physician. 87 (4), 267-273 (2013).
22) Guerreiro, R.; Hardy, J. Genetics of Alzheimer’s disease. Neurotherapeutics 11, 732-737 (2014).
23) Waring, S.; Rosenberg, N. Genome-wide association studies in Alzheimer disease. Arch. Neurol. 65, 329-334 (2008).
24) Setó-Salvia, N.; Clarimón, J. Genética en la enfermedad de Alzheimer. Rev. Neurol. 50 (6), 360-364 (2010).
25) Kim, H.G.; Oh, M.S. Herbal medicines for the prevention and treatment of Alzheimer’s disease. Curr. Pharm. Des. 18, 57-75 (2012).
26) Nopoulos, P. Huntington disease: A single-gene degenerative disorder of the striatum. Dialogues Clin. Neurosci. 18, 91-98 (2016).
27) Rodríguez, J.; Díaz, Y.; Rodríguez, Y.; Rodríguez, Y.; Núñez, E. Actualización en enfermedad de Huntington. CCM 17, 546-557 (2013).
28) Armstrong, M.; Miyasaki, J. Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 79, 597-603 (2012).
29) Van, M.A.; Hardiman, O.; Chio, A.; Al, A.; Pasterkamp, R.J.; Veldink, J.H.; Van, L.H. Amyotrophic lateral sclerosis. Lancet 390, 2084-2098 (2017).
30) Ghassemi, M.; Brown, R.H. Genetics of amyotrophic lateral sclerosis. Cold. Spring. Harb. Perspect. Med. 8 (5), a024125 (2017).
31) Willis, A.W. Parkinson disease in the elderly adult. Mo. Med. 110 (5), 406-410 (2013).
32) Schapira, A.H. Recent developments in biomarkers in Parkinson disease, Curr. Opin. Neurol. 26, 395-400 (2013).
33) Mayeux, R. Epidemiology of neurodegeneration. Annu. Rev. Neurosci. 26, 81-104 (2003).
34) Bartels, A.L.; Leenders, K.L. Parkinson’s disease: The syndrome, the pathogenesis and pathophysiology. Cortex 45, 915-921 (2009).
Vitis vinífera: An Alternative for the Prevention of Neurodegenerative Diseases

35) Pagano, G.; Ferrara, N.; Brooks, D.J.; Pavese, N. Age at onset and Parkinson disease phenotype. *Neurology* **86**, 1400-1407 (2016).

36) Yokel, R.A. The toxicology of aluminum in the brain: A review. *Neurotoxicology* **21**, 813-828 (2000).

37) Suay, L.; Ballester, F. Revisión de los estudios sobre exposición al aluminio y enfermedad de alzheimer. *Rev. Esp. Salud. Public* **76**, 645-658 (2002).

38) Banegas, J. Enfermedad de alzheimer. *BUN Synapsis* **2**(2), 4-10 (2007).

39) Richard, T.; Poupard, P.; Nassra, M.; Papastamoulis, Y.; Iglesias, M.L.; Krisa, S.; Waffo-Teguo, P.; Merillon, J.M.; Monti, J.P. Protective effect of α-viniferin on β-amyloid peptide aggregation investigated by electrospray ionization mass spectrometry. *Bioorga. Med. Chem.* **19**, 3152-3155 (2011).

40) Loureiro, J.; Andrade, S.; Duarte, A.; Neves, A.; Queiroz, J.; Nunes, C.; Sevin, E.; Fenart, L.; Gossellet, F.; Coelho, M.A.; Pereira, M.C. Resveratrol and grape extract-loaded solid lipid nanoparticles for the treatment of Alzheimer’s disease. *Molecules* **22**(2), E277 (2017).

41) Lee, J.; Torosyan, N.; Silverman, D. Examining the impact of grape consumption on brain metabolism and cognitive function in patients with mild decline in cognition: A double-blinded placebo controlled pilot study. *Exp. Gerontol.* **87**, 121-128 (2017).

42) Miu, A.C.; Benga, O. Aluminum and Alzheimer’s disease: A new look. *J. Alzheimers. Dis.* **10**, 179-201 (2006).

43) Coon, K.D.; Myers, A.J.; DW, C.; Webster, J.A.; Pearson, J.V.; Lince, D.H.; Zismann, V.L.; Beach, T.G.; Leung, D.; Bryden, L.; Halperin, R.F.; Marlowe, L; Kal-cek, M.; Walker, D.G.; Ravid, R.; Heward, C.B.; Rogers, J.; Papassotriopoulos, A.; Reiman, E.M.; Hardy, J.; Stephon, D.A. A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer’s disease. *J. Clin. Psychiatry.* **68**, 613-618 (2007).

44) Guo, Z.; Cupples, L.A.; Kurz, A.; Auerbach, S.H.; Volicher, L.; Chui, H.; Green, A.D.; Sadovnick, R.; Duara, C.; DeCarli, C.; Johnson, K.; Go, R.C.; Growdon, J.H.; Haines, J.L.; Kukull, W.A.; Farrer, L.A. Head injury and the risk of AD in the MIRAGE study. *Neurology* **54**, 1316-1323 (2000).

45) Calderón, L.; Reed, W.; Maronpot, R.R.; Henriquez, C.; Delgado-Chávez, R.; Calderón, A.; Dragustinovis, I.; Franco-Lira, M.; Aragon-Flores, M.; Solt, A.; Altenburg, M.; Torres-Jardón, R.; Swenberg, J. Brain inflammation and Alzheimer’s-like pathology in individuals exposed to severe air pollution. *Toxicologic. Pathol.* **32**, 650-658 (2004).

46) Tyas, S.L.; Manfreda, J.; Strain, L.A.; Montgomery, P.R. Risk factors for Alzheimer’s disease: A population-based, longitudinal study in Manitoba, Canada. *Int. J. Epidemiol.* **30**, 590-597 (2001).

47) Benítez, A. Enfermedad de Huntington: fundamentos moleculares e implicaciones para una caracterización de los mecanismos neuronales responsables del procesamiento lingüístico. *Rev. Neurol.* **48**(2), 75-84 (2009).

48) Gatchel, J.R.; Zoghbi, H.Y. Diseases of unstable repeat expansion: Mechanisms and common principles. *Nat. Rev. Genet.* **6**(10), 743-755 (2005).

49) Brusilow, W.S. Is Huntington’s a glutamine storage disease? *Neuroscientist* **12**(4), 300-304 (2006).

50) Esparza-Pérez, A.M. La demencia: diagnóstico y evaluación. *Rev. Esp. Méd. Quir.* **10**, 6-13 (2005).

51) Poveda, A. Clasificación etiopatogénica de la demencia. En Alberca, R. Y López-Pousa, S. Enfermedad de Alzheimer y otras demencias. *España: Panameri- cana* 81 (1998).

52) American Psychiatric Association. DSM-I V. Manual Diagnóstico y estadístico de los trastornos mentales (Masson Washington, D. C.) (2000).

53) Nixon, S.J. Alzheimer’s disease and vascular dementia. In neuropsychology for clinical practice. Etiology, assessment and treatment of common neurological disorders. APA. 65-105 (1996).

54) Marin, J. Esclerosis lateral amiotrófica: una actual-ización. *Rev. Mex. Neuroci.* **10**(4), 281-286 (2009).

55) Rowland, L.P. What’s in A name? Amyotrophic lateral sclerosis, motor neuron disease and allelic heterogeneity. *Ann. Neurol.* **43**, 691-694 (1998).

56) Cluskey, S.; Ramsden, D.B. Mechanisms of degeneration in amyotrophic lateral sclerosis. *J. Clin. Pathol. Mol.* **54**, 386-392 (2001).

57) Hamilton, J.A.; Hillard, C.J.; Spector, A.A.; Watkins, P.A. Brain uptake and utilization of fatty acids, lipids and lipoproteins: application to neurological disorders. *J. Mol. Neurosci.* **33**, 2-11 (2007).

58) Barnham, K.J.; Masters, C.L.; Bush, A. Neurodegenerative diseases and oxidative stress. *Nat. Rev. Drug. Discov.* **3**, 205-214 (2004).

59) Mayne, S.T. Antioxidant nutrients and chronic disease: Use of biomarkers of exposure and oxidative stress status in epidemiologic research. *J. Nutr.* **133**, 933S-940 (2003).

60) Denns, K.K.; Go, Y.M.; Jones, D.P. Redox systems biology of nutrition and oxidative stress. *J. Nutr.* **149**, 553-565 (2019).

61) Fernández, J.; Hu, X.; Ryan Smith, M.; Go, Y.M.; Jones, D.P. Selenium at the redox interface of the genome, metabolome and exposome. *Free Radic. Biol. Med.* **127**, 215-227 (2018).

62) Jones, D.P. Radical-free biology of oxidative stress. *Am. J. Physiol. Cell. Physiol.* **295**, C849-868 (2008).

63) Sies, H. Hydrogen peroxide as a central redox signal-
ing molecule in physiological oxidative stress: oxidative stress. Redox Biology. 11, 613-619 (2017).

64) Go, Y.M.; Jones, D.P. Redox theory of aging: Implications for health and disease. Clini. Sci. 131, 1669-1688 (2017).

65) Deepthi, R.; Veera, R.; Jayarami, M.; Annapurna, A. Calcium regulation and Alzheimer’s disease. Asian Pac. J. Trop. Dis. 4, S513-S518 (2014).

66) Burin, V.; Falcão, L.; Gonzaga, L.; Fett, R.; Rosier, J.; Bordignon-Luiz, M.T. Colour, phenolic content and antioxidant activity of grape juice. Ciên. Tecnol. Aliment. 30, 1027-1032 (2010).

67) Ismail, E.; Khalil, M.; Al Seif, F.; El-magdoub, F. Biosynthesis of gold nanoparticles using extract of grape (Vitis vinifera) leaves and seeds. PNN 3, 1 (2014).

68) Borai, I.; Ezza, M.; Rizkb, M.; Alyb, H.; El-Sherbinyb, M.; Matloubc, A.; Fouad, G. Therapeutic impact of grape leaves polyphenols on certain biochemical and neurological markers in AlCl3-induced Alzheimer’s disease. Biomed. Pharmacother. 93, 837-851 (2017).

69) López, V.; Soto, M. L.; Vera, G.; Herradón, E.; Desco, M.; Abalo, R. Resveratrol: a polifenol neuroprotector in la dieta mediterránea. Rev. Neurol. 54, 349-356 (2012).

70) Wang, J.; Ferruzzi, M.G.; Ho, L. Brain-targeted proanthocyanidin metabolites for Alzheimer’s disease treatment. Neuro. Sci. 32, 5144-5150 (2012).

71) Neves, A.R.; Lucio, M.; Lima, J.L.; Reis, S. Resveratrol in medical chemistry: A critical review of its pharmacokinetics, drug-delivery, and membrane interactions. Curr. Med. Chem. 19, 1663-1681 (2012).

72) Markus, M.A.; Morris, B.J. Resveratrol in prevention and treatment of common clinical conditions of aging. Clin. Interv. Aging 3, 331-339 (2008).

73) Anekonda, T.S. Resveratrol-A boon for treating Alzheimer’s disease? Brain Res. Rev. 52, 316-326 (2006).

74) Hayden, E.Y.; Yamin, G.; Beroukhim, S.; Chen, B.; Kibalchenko, M.; Jiang, L.; Ho, L.; Wang, J.; Pasinetti, G.M.; Teplov, D.B. Inhibiting amyloid β-protein assembly: Size-activity relationships among grape seed-derived polyphenols. J. Neurochem. 135, 416-430 (2015).

75) Bazán-Salinas, I.L.; Matías-Pérez, D.; Pérez-Campos, E.; Pérez-Campos Mayoral, L.; García-Montalvo, I.A. Reduction of platelet aggregation from ingestion of oleic and linoleic acids found in Vitis vinifera and Arachis hypogaea oils. Am. J. Ther. 23(6), e1315-1319 (2016).

76) Fujishita, K.; Ozawa, T.; Shibata, K.; Tanabe, S.; Sato, Y.; Hisamoto, M.; Koizumi, S. Grape seed extract acting on astrocytes reveals neuronal protection against oxidative stress via Interleukin-6-mediated mechanisms. Cell. Mol. Neurobiol. 29, 1121-1129 (2009).

77) Long, J.; Gao, H.; Sun, L.; Liu, J., Zhao, X. Grape extract protects mitochondria from oxidative damage and improves locomotor dysfunction and extends lifespan in a Drosophila Parkinson’s disease model. Rejuv. Res. 12(5), 321-331 (2009).

78) Choi, Y.; Young, M.; Whan, C.; Cha, M.; Hwan, G.; Young, D.; Yong, S. A new specific BACE-1 inhibitor from the stem bark extract of Vitis vinifera. Planta. Med. 75, 537-540 (2009).

79) Dani, C.; Olbóni, L.; Agostini, F.; Funchal, C.; Serafini, L.; Henriques, J.; Salvador, M. Phenolic content of grapevine leaves (Vitis labrusca var. Bordo) and its neuroprotective effect against peroxide damage. Toxicol in Vitro 24, 148-153 (2010).

80) Rodrigues, A.; Scheffel, T.; Scola, G.; Santos, M.; Fank, B.; de Freitas, S.; Salvador, M. Neuroprotective and anticonvulsant effects of organic and conventional purple grape juices on seizures in Wistar rats induced by pentylentetrazetate. Neurochem. Int. 60, 799-805 (2012).

81) Porquet, D.; Casadesús, G.; Bayod, S.; Vicente, A.; Canudas, A.M.; Vilaplana, J.; del Valle, J. Dietary resveratrol prevents Alzheimer’s markers and increases life span in SAMP8. AGE 35, 1851-1865 (2012).

82) Lakshmi, B.; Sudhakar, M.; Anisha, M. Neuroprotective role of hydroalcoholic extract of Vitis vinifera against aluminium-induced oxidative stress in rat brain. Neurotoxicology 41, 73-79 (2014).

83) Papastamoulios, Y.; Richard, T.; Nassra, M. et al. Vinophenol A, a complex resveratrol hexamer from Vitis vinifera stalks: Structural elucidation and protective effects against amyloidβ-induced toxicity in PC12 cells. J. Nat. Prod. 77, 213-217 (2014).

84) Ding, Y.; Dai, X.; Jiang, Y.; Zhang, Z.; Li, Y. Functional and morphological effects of grape seed proanthocyanidins on peripheral neuropathy in rats with type 2 diabetes mellitus. Phytother. Res. 28, 1082-1087 (2014).

85) Ismail, A.; Moawed, F.; Mohamed, M. Protective mechanism of grape seed oil on carbon tetrachloride-induced brain damage in γ-irradiated rats. J. Photochem. Photobiol. B 153, 317-323 (2015).

86) Dani, C.; Andreazza, A.; Gonçalves, C.; Kapizinski, F.; Henriques, J.; Salvador, M. Grape juice increases the BDNF levels but not alter the S100B levels in hippocampus and frontal cortex from male Wistar Rats. An. Acad. Bras. Cienc. 89, 155-161 (2017).

87) Rapaka, D.; Bitra, V.; Vishala, T.; Akula, A. Vitis vinifera acts as anti-Alzheimer’s agent by modulating biochemical parameters implicated in cognition and memory. J. Ayurveda. Integr. Med. 10(4), 241-247 (2019).

88) Ma, L.; Xiao, H.; Wen, J.; Liu, Z.; He, Y.; Yuan, F. Possible mechanism of Vitis vinifera L. flavones on neu-
rotransmitters, synaptic transmission and related learning and memory in Alzheimer model rats. *Lipids Health Dis.* **17**, 152 (2018).

89) Li, M.H.; Jang, J.H.; Sun, B.; Surh, Y.J. Protective effects of oligomers of grape seed polyphenols against beta-amyloid-induced oxidative cell death. *Ann. N Y Acad. Sci.* **1030**, 317-329 (2004).

90) Bentivegna, S.S.; Whitney, K.M. Subchronic 3-month oral toxicity study of grape seed and grape skin extracts. *Food Chem. Toxicol.* **40**, 1731-1743 (2002).