The benefits of grape seed extract in neurological disorders and brain aging

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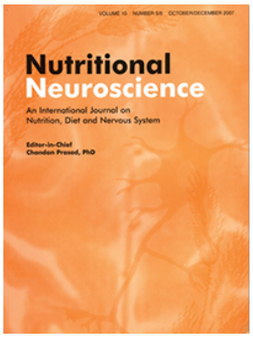

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REVIEW

The benefits of grape seed extract in neurological disorders and brain aging

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ABSTRACT

Common neurological disorders, including neurodegenerative diseases, stroke, epilepsy, autism and psychiatric disorders, affect many people worldwide and threaten their lives and health by inducing movement disorders, behavioral disorders, or a combination of both. Oxidative stress and neuroinflammation play a central role in neuronal damage and neurological diseases induction and progression. In addition, protein homeostasis (proteostasis) impairment occurs in many neurodegenerative diseases, which plays a critical role in the progression of the pathology. Grape seed contains several flavonoids and non-flavonoids and exerts potent antioxidant and anti-inflammatory effects. In addition, polyphenols and flavanols can maintain cellular proteostasis. Since impaired proteostasis is closely involved in all amyloid diseases, particularly neurodegenerative diseases, grape seeds extract can be a valuable therapeutic agent. Therefore, this review discusses the protective and therapeutic mechanisms of grape seed against neurological disorders and, in the end, links GSE to microRNAs as future therapeutic developments.

KEYWORDS

Grape seed; gallic acid; proanthocyanidins; brain ageing; autism spectrum disorder; cerebral ischemia; epilepsy; microRNAs; neurodegeneration

Highlights

- Gallic acid of grape seed reduces amyloid fibril formation by 49% and reduces Aβ levels in the brain.
- Grape seed extract decreases alpha-synuclein aggregation (hallmark of Parkinson's disease) in brain.
- Grape seed extract inhibits polyglutamine aggregation and increases motor coordination and extend lifespan in animals with Huntington's disease.
- Grape seed exerts protective effects against autism through inhibition of cerebellar Purkinje cells degeneration.
- Grape seed procyanidin extract could influence microRNAs activity and protect cells against cerebral ischemia.

Introduction

Neurological disorders affect many people's health every year, creating complications and impairing life quality. Neurodegeneration, stroke, epilepsy, autism and psychiatric disorders such as depression, anxiety and schizophrenia may present with symptoms like movement disorders, behavioral disorders, or a combination of both [1–3]. These daily life problems impose considerable financial pressure on healthcare providers more than patients. For example, it has been estimated that only in the United States, the costs of the healthcare system for Alzheimer's disease (AD) in 2018 were about 277 billion US dollars [4]. Therefore, finding appropriate, low-risk and low-cost treatments, especially in prevention, is one of the medical priorities. Given that oxidative stress and neuroinflammation play fundamental roles in developing and progressing neurological diseases, particularly in neurodegenerative diseases [1,3,5,6], it is necessary to pay special attention to antioxidant and anti-inflammatory agents in preventing and treating neurological diseases. In addition, as microRNAs (miRs) have been demonstrated to play fundamental roles in several biological (normal physiological and pathophysiological) processes [7–10] and due to the relationship between grape seed and microRNAs, it can be considered a suitable therapeutic agent.

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The grape seed extract (GSE) is a well-known source of potent antioxidant and anti-inflammatory agents with several therapeutic effects [11–14]. Due to the flavonoids and non-flavonoids content of GSE, it has a preventive potential on both the development and progression of neurological diseases and can be beneficial for neural cells coping with environmentally originating dangers [13–15]. The current review discusses the therapeutic effects of this extract against common neurological disorders, both from the contents and its connection with regulatory RNA pathways, to present new insight into prevention and possible perspective for therapeutics development.

Grape seed

Based on the differences in structure and activity, grape polyphenolics are categorized into two classes: flavonoids and non-flavonoids [16,17,18]. Notable protective and beneficial flavonoids in the grape seed are proanthocyanidins, anthocyanins, procyanidins, and flavan-3-ols [19]. In addition to flavonoids, the grape seed contains many other phenolic compounds including, phenolic acids, carotenoids, stilbenes, tannins, and catechins [20].

Grape seed contains 8%–20% of oil [21] containing different saturated and non-saturated fatty acids, including linolenic, linoleic, oleic, palmitic, arachidonic and stearic acids [22]. Linoleic acid is the most abundant (65%) fatty acid found in grape seeds. However, 85–90% of the fatty acids in grape seed oil are polyunsaturated fatty acids (PUFA) [23], which benefit human health.

In addition, some antioxidant vitamins such as vitamins C and E (tocopherols and tocotrienols) are present in grape seed [24], which significantly increases the antioxidant properties of grape seed. The grape seed oil has been shown to have a great content of vitamin E (average: 27 mg per 100 g of oil), which is higher than that of olive and soybean oils [23].

GSE antioxidant activities are exerted directly by scavenging reactive oxygen species (ROS), inhibiting lipid oxidation, and chelating redox-active transition metals, such as copper and iron [25]. As previous studies showed, grape seed has a higher antioxidant property than other parts of grapes, such as skin, leaves and wine [26]. This high antioxidant capacity is related to the high catechin content, epicatechin, gallic acid, procyanidins, and proanthocyanidins in grape seed [26].

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common form of dementia, affecting more than 36 million people worldwide [27]. In addition to memory loss, neuropsychiatric symptoms, visual-spatial skills impairment, loss of language function, inability to calculate, delusions, and depression occur in these patients [13,28]. Pathologically, the main feature of AD is an increase in amyloid-beta (Aβ) as well as hyperphosphorylation and aggregation of tau protein in the brain [4,29]. The aggregation of Aβ occurs because of impaired protein homeostasis (proteostasis) and is associated with forming the neuritic plaques, which are hallmarks of AD [30,31]. Normal proteostasis regulates proteins' biogenesis, folding, and degradation and is necessary to maintain cellular metabolic function [31]. It has been shown that the accumulation of insoluble Aβ induces the aggregation of peptides forming amyloid fibrils in the brain, which leads to impairment in synaptic structures and functions.

In addition to tau aggregation, various changes occur in the brain of AD patients. For instance, acetylcholine decreases in the brain, increasing inflammation [22]. Neuroinflammation is also induced in AD brain due to tau aggregation. It has been shown that tau aggregation induces astrocytes and microglia hyperactivation, resulting in astrocytosis and microgliosis, closely associated with inflammation [32]. On the other hand, inflammation and oxidative stress, particularly Mitochondria-associated oxidative stress, play a critical role in AD onset [32,33]. Thus, since GSE contains several antioxidant agents, including vitamin C, vitamin E, procyanidins, proanthocyanidins, it can be expected to have an inhibitory effect against AD onset and progression [5].

GSE administration decreases the level of malondialdehyde (MDA) and increases the level of glutathione (GSH) and superoxide dismutase (SOD). This extract can also prevent the loss of AKT and ERK activities in the hippocampus and cerebral cortex [34], indicating that GSE can ameliorate the impairment of hippocampal synaptic plasticity induced by oxidative stress and rescue cognition deficits AD (Table 1). Also, grape seed procyanidins could disrupt the lipid peroxidation chain and protect neurons by activating Akt phosphorylation [35]. They can also attenuate oxidative stress by activating nuclear erythroid-related factor 2 (Nrf2), nuclear factor-kappa B (NF-κB), and mitogen-activated protein kinase (MAPK) signaling cascades (Figure 1) [12,29,36]. Additionally, GSE could suppress mitochondria-associated oxidative stress. It has been shown that this extract inhibits mitochondrial permeability transition pore (mPTP) opening via increasing phosphorylated glycogen synthase kinase 3β (p-GSK-3β) binds to adenine nucleotide translocator (ANT), which results in a decrease in the formation of the complex ANT-cyclophilin D (CypD) [37].

Besides anti-oxidative effects, grape seed has been shown to have potent anti-inflammatory effects. Polyphenol extracts, abundantly found in GSE, prevent the release of proinflammatory mediators, including 5-lipoxygenase (5-LOX) (Figure 1) [38–40]. GSE also prevents the induction of neuroinflammation by preventing a decrease in acetylcholine levels in the Alzheimer's brain [22].

Another neuroprotective effect of grape seed is through Sirtuin 1 (SIRT1) and cAMP response element-binding protein (CREB) modulation. GSE-derived procyanidins have been demonstrated to regulate ERK phosphorylation, increase CREB-mediated gene expression, and modulate SIRT1/CREB signaling (Figure 1) [4]. SIRT1 protein is located in the cytoplasm and nucleus of mammalian cells and can act as an anti-ageing protein. Moreover, CREB protein, a transcription regulator in neurons, plays a crucial role in neurogenesis and cognition performance. SIRT1/CREB signaling is disrupted in the AD brain [4].

As mentioned, amyloid fibril formation is a hallmark of AD. Gallic acid of GSE has been found to reduce amyloid fibril formation by 49% and reduce Aβ levels in the brain [41]. According to the studies, reduced and carboxymethylated form of the milk protein, kappa-casein (RCM-k-CN), forms amyloid fibrils [42,43] and it has been reported that GSE prevents mature fibrils formation from RCM-k-CN [42]. A previous study found that gallic acid is the most active component of GSE at inhibiting k-CN fibril formation [41]. GSE inhibits around 97% of the Aβ (1–42) peptide aggregation [30]. GSE administration decreases Aβ*56 levels in the brain [44]. Since this Aβ oligomer has been shown to induce cognition dysfunction, GSE can be a valuable agent against AD.

It should be noted that GSE does not change the levels of amyloid-β protein precursor, monomeric Aβ, or other Aβ oligomers [44], which indicates this extract has safe and affordable intervention against AD by maintaining proteostasis. Therefore, clinical trials on AD treatment and even prevention can be suggested for this supplement. Figure 1 shows the possible therapeutic pathways of GSE against AD.

Parkinson's disease

Parkinson's disease (PD) is an age-related disorder and the second most common neurodegenerative disease in the world, which is characterized by severe degeneration of dopaminergic neurons in substantia nigra pars compacta (SNpc) [1,6]. Like AD, PD is closely related to oxidative damage. Mitochondrial dysfunction has been shown to have a critical role in PD onset and progression [1]. In PD brain, levels of Dynamin-1-like protein (Drp-1) and mitochondrial fission 1 (Fis-1), mitochondrial fission markers, are increased (Figure 1). Conversely, levels of mitofusin 1,2 (Mfn-1,2) and optic atrophy-1 (Opa-1) that are key factors for mitochondrial fusion are decreased [1]. This imbalance in mitochondrial fission/fusion depletes adenosine triphosphate (ATP) [45]. Due to the high demand of dopaminergic neurons for energy, it eventually leads to the death of these neurons.

Pathogenesis of PD is closely associated with impaired proteostasis. The alpha-synuclein aggregation is critical in inducing mitochondrial dysfunction in PD by disrupting mitochondrial dynamics via Drp1 mislocalization [46]. In addition, aggregation of this protein results in several types of other dysfunctions such as synaptic dysfunction, axonal transportation disruption, calcium homeostasis impairment, which lead to Parkinson's symptoms [1,2,47].

Interestingly, GSE restores brain proteostasis and decreases alpha-synuclein aggregation in the brain [48]. Grape phenols have been shown to decrease alpha-synuclein aggregation in the frontal cortex and reduce the expression of neuroinflammatory markers such as ionized calcium-binding adapter molecule 1 (IBA1) and CD54 (Figure 1), leading to alleviation of non-motor symptoms [48]. It has also been reported that GSE decreases ROS, inflammation, and apoptosis in the substantia nigra of the midbrain and efficiently protects dopaminergic neurons against 6-hydroxydopamine (6-OHDA) and improves motor functions (Figure 1, Table 1) [14].

The mitochondrial protective effects of GSE have been reported in previous studies. It is found that the mitochondrial DNA content and the expression of mitochondrial biogenesis factors are increased by GSE administration. Studies also reported that GSE and resveratrol activate the expression of PGC-1α, silent mating type information regulation 2 homolog 1 (SIRT1) and AMP-activated protein kinase (AMPK) and could prevent mitochondrial dysfunction [49,50]. As the studies show, GSE has a solid potential to attenuate PD symptoms by protecting different brain parts. For instance, it has been demonstrated that treatment of PD rats with GSE influences powers of frequency bands in the thalamic ventral anterior (VA) nucleus and could improve post-lesion motor dysfunctions [51].

Huntington's disease

Huntington's disease (HD) is a severe neurodegenerative disorder with a mean age of onset around 30 years and a mean prevalence of 5.5 cases per 100,000

Table 1. The neuroprotective effects of grape seed extract in vitro and in vivo.

Chemical composition	Experimental model	Major effect	Target disease (preventive)	Reference
Polyphenols (proanthocyanidin)	– PC12 cell line – APP/PS-1 double transgenic mice	*In vitro* experiment: – Alleviation of Aβ25-35 cytotoxicity and LDH leakage ratio – ↓ Apoptosis – ↑ MMP *In vivo* experiment: – Improvement in cognition and spatial memory ability – Alleviation of amyloid plaques in the hippocampus – Improvement in pathology of APP and tau protein – ↓ PS-1 mRNA expression level	AD	[12]
-	– Midbrain dopaminergic cell line – Adult male CD1 mice	*In vitro* experiment: – Protection of dopamine neurons against 6-OHDA toxicity; – ↓ Apoptosis (↓ cleaved caspase-3 activity) – ↓ ROS production – ↓ Inflammation (↓ phospho-NF-κB p65 activation) *In vivo* experiment: – Protection against neuronal loss and motor deficits – SOD1 expression level in the lesions	PD	[13]
Polyphenols	– PC12 cell line – Q93httexon1 drosophila – R6/2 mice	*In vitro* experiment: – ↓ PolyQ aggregation – ↓ Protein oxidation *In vivo* experiment: – Improvement in lifespan (drosophila and mice) – Protection against motor skill decay (mice)	HD	[14]
–	– AD male rat	– Improvement in cognition and spatial learning memory function – Protection against the cholinergic system – ↑ Brain acetylcholine level – ↓ Neuronal necrosis (↑ cell viability) and hippocampus tissue degeneration	AD	[20]
Polyphenols (resveratrol)-loaded NPs	– Stock solutions of Aβ peptide	– ↓ Aβ1-42 fibrillation and aggregation	AD	[31]
Polyphenols (proanthocyanidin)	– Sporadic AD rat	– Improvement in cognitive deficits and hippocampal LTP – ↓ MDA level – ↑ SOD and GSH levels – Protection against loss of AKT and ERK activities in the hippocampus and cerebral cortex	AD	[34]
Polyphenols (proanthocyanidin)	– Primary mouse cortical neurons – Sporadic AD mice	*In vitro* experiment: – ↓ Neuronal apoptosis – Improvement of mitochondrial dysfunction (↑ MMP, ATP, and CcO activities) – ↑ phosphorylation of PI3K-Akt-GSK-3β (Ser9) pathway *In vivo* experiment: – Improvement in cognitive function – ↓ Aβ production and tau phosphorylation – ↓ Neuronal loss and apoptotic cell death in the cerebral cortex and hippocampus tissue – ↓ Mitochondrial oxidative stress and mPTP opening (↑ phosphorylation of PI3K-Akt-GSK-3β pathway) in the cerebral cortex and hippocampus tissue	AD	[37]
Phenolics (gallic acid)	– PC12 cell line	– Inhibition of κ-CN fibril formation – ↓ Aβ aggregation	AD	[41]
Polyphenols	– Tg2576 transgenic mice	*In vitro* experiment: – ↓ Aβ56 brain level	AD	[44]

(*Continued*)

Table 1. Continued.

Chemical composition	Experimental model	Major effect	Target disease (preventive)	Reference
		In vivo experiment: – Improvement in cognitive function		
Polyphenols	– C57BL/6 mice – Transgenic PD mice	– ↑ Lifespan – Improvement in memory reconsolidation and memory loss – ↓ α-synuclein accumulation – ↓ IBA1 (microglial marker) and CD54 (inflammatory marker) expression levels in the frontal cortex and hippocampus	PD	[49]
–	– PD rat	– Protection neurons against 6-OHDA toxicity – Reinforcement of thalamic electrical power – Improvement in post-lesion motor dysfunctions – Modulation of direct and indirect striato-thalamo-cortical pathways	PD	[51]
–	– Wistar female rat and male offspring	– ↓ CAT, SOD, and GSH-Px levels in the cerebellum – Protection against VPA toxicity (↑ oxidative stress, ↓ Purkinje cell density, neuronal cell death, astrocytes hyperactivation, and cerebellar gliosis)	ASD	[55]
Polyphenols (proanthocyanidin)	– Epileptic rat	– Improvement in hippocampal dysfunction and cognitive decline; – ↓ MDA level – ↓ ROS production – ↑ GSH activity – ↓ Expression of pro-apoptotic proteins (Cyt c, caspase-9 and caspase-3) – Protection against damage to CA1 pyramidal neurons – ↓ *M*itochondria oxidative stress and dysfunction	Seizure	[61]
Polyphenols (epicatechin, catechin, gallic acid, and quercetin)	– Primary rat brain (neuron-astrocyte) cells – Mice I/R	*In vitro* experiment: – Protection against OGD-induced toxicity; – Sustained cell viability – Modulation of cytokines (TNF-α, IL-6, TGF-β1, and IL-10) and BDNF expression *In vivo* experiment: – Improvement in behavioral outcomes – Protection of hippocampus against I/R injury-induced alterations (↓ autophagic vacuoles)	Ischemic stroke	[71]
Total phenolics, non-flavonoids, and total flavonoids	– Male Wistar rat I/R	– Protection of hippocampus against I/R-disturbed proteome – Protection of the brain against I/R-induced ion dyshomeostasis, inflammatory biomarkers (CD56 or CD68), and Ca^{2+} burst in the hippocampus	Ischemic stroke	[72]
Polyphenols (proanthocyanidin)	Sprague-Dawley rat	– Protection of hippocampus against iron overload-induced oxidative stress – ↓ Neuronal apoptosis; – *I*mprovement in divalent mineral element (Fe^{2+}, Zn^{2+}, Mg^{2+}, and Ca^{2+}) imbalances – ↓ MDA level – Upregulation of GSH-Px, SOD, and CAT – Regulation of Fas, Bax, and Bcl-2 (apoptotic) genes expression	Neurodegenerative disorders (ageing, AD, PD, etc.)	[76]
Polyphenols (proanthocyanidin)	– C57BL/6 mice	– ↓ Neuronal apoptosis; – ↓ ER stress and inflammation – Inhibition of ERK/GRP78/caspase-12 signaling pathway at the protein level	Ischemic stroke	[77]
Polyphenols	– Naive mice	– ↑ Antidepressant efficacy via the autoregulatory feedback loop (VGF(TLQP-62)/BDNF/TrkB)	Depression-like behaviors (induced by chronic variable stress)	[78]
Polyphenols	– Male albino rats of Wistar strain (young and aged rats)	– Protection of the CNS against ROS – Improvement in memory performance; – ↓ ROS production (aged rats)	Ageing	[83]

(*Continued*)

Table 1. Continued.

Chemical composition	Experimental model	Major effect	Target disease (preventive)	Reference
		– ↓ PCO and thiol levels (aged rats) – ↓ Protein oxidation (aged rats)		
Polyphenols (proanthocyanidin)	– Female Wistar rats (two groups of age)	– Improvement in cognitive abilities – ↓ OS-related LF accumulation In the hippocampus; – ↓ blood glucose – ↓ Lipid peroxidation – ↓ H2O2 level – ↑ *P*-SH content	Ageing	[86]
–	– Aged mice	– Attenuation in cognitive decline – Alleviation of hippocampal neurogenesis and synaptogenesis – ↓ DNs production	Ageing	[87]

Abbreviations: PC, pheochromocytoma; APP, amyloid precursor protein; PS-1, presenilin-1; Aβ, amyloid-beta; LDH, lactate dehydrogenase; MMP, mitochondrial membrane potential; AD, Alzheimer's disease; 6-OHDA, 6-hydroxydopamine; ROS, reactive oxygen species; NF-κB, nuclear factor-kappa B; SOD1, superoxide dismutase; PD, Parkinson's disease; PolyQ, polyglutamine; NPs, nanoparticles; LTP, long-term potentiation; MDA, malondialdehyde; GSH, glutathione; ERK, extracellular signal-regulated kinase; ATP, adenosine triphosphate; CcO, cytochrome c oxidase; PI3 K, phosphatidylinositol 3-kinase; GSK-3β, glycogen synthase kinase 3β; mPTP, mitochondrial permeability transition pore; κ-CN, kappa-casein; *IBA1*, ionized calcium binding adaptor molecule 1; *CD54*, Cluster of Differentiation 54; *CAT*, catalase; GSH-Px, glutathione peroxidase; *VPA*, Valproic Acid; ASD, Autism Spectrum Disorder; Cyt c, cytochrome *c*; I/R, ischemia/reperfusion; OGD, oxygen-glucose-deprivation; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; TGF-β1, transforming growth factor beta 1; BDNF, brain derived neurotrophic factor; Ca^{2+}, calcium **(2+)**; Fe^{2+}, iron **(2+)**; Zn^{2+}, zinc **(2+)**; Mg^{2+}, magnesium **(2+)**; Bax, Bcl-2 Associated X; Bcl-2, B-cell lymphoma 2; TrkB, tropomyosin receptor kinase B; CNS, central nervous system; PCO, *protein carbonyl*; *OS*, oxidative stress; LF, lipofuscin; *H2O2*, hydrogen peroxide; *P*-SH, protein sulphydryl; *DNs, dark neurons*.

people globally, characterized by a combination of cognitive, psychiatric, and motor symptoms [52]. HD is due to increased copies of CAG repeats in exon 1 of the *HTT* gene, encoding the huntingtin protein [52]. This mutation leads to a huntingtin protein with an abnormal length of polyglutamine repeats [53]. An increase in polyglutamine repeats in the huntingtin is the hallmark of HD.

GSE has been shown to have the potential to inhibit polyglutamine aggregation *in vitro* [12]. Its administration could increase motor coordination and extend lifespan in animals with HD [12] (Table 1). Therefore, GSE seems a potential preventative and therapeutic agent against HD, worthy of investigation.

Autism

Autism spectrum disorder (ASD) is defined by the presence of social communication and interaction impairments, along with restricted and repetitive behaviors, including motor movements and insistence on sameness [54]. The pieces of evidence showed that the cerebellum of autism patients incorporates some morphological and ultrastructural changes, including a decrease in the Purkinje cell number, a reduction in nuclear size, and the degeneration of cytoplasmic organelles [55].

Oxidative stress and inflammation are closely involved in ASD and play a critical role in developing this disorder [56,57]. Alterations in the activities of antioxidant enzymes, including SOD, glutathione peroxidase, catalase, and oxidative markers such as MDA, have been demonstrated in ASD [57,58]. Also, increased cytokine levels, including IL-1β, IL-6, IL-8, IL-17, IL-12p40, and IL-12p70, have been demonstrated in ASD children [58].

GES has been repeatedly shown to reduce oxidative stress markers and protect tissues from inflammatory damage [12,34,36,48]. Recently, it has been shown that GSE modulates Nrf2 activity and alleviates oxidative damage [59]. Nrf2 is an essential key transcription factor responsible for antioxidant defense and inhibits the expression of inflammatory cytokines [60]. Also, GSE has been demonstrated to exert protective effects against these changes and ameliorate autism symptoms [55]. Gallic acid, a major component of grape seed, can facilitate the decrease in the number of cerebellar Purkinje and granular cells in autistic rats [61]. Although only one study cannot confirm that this extract has therapeutic potential against autism, it shows that GSE has protective effects against this disease, and it is better to be considered a possible therapeutic agent. Future

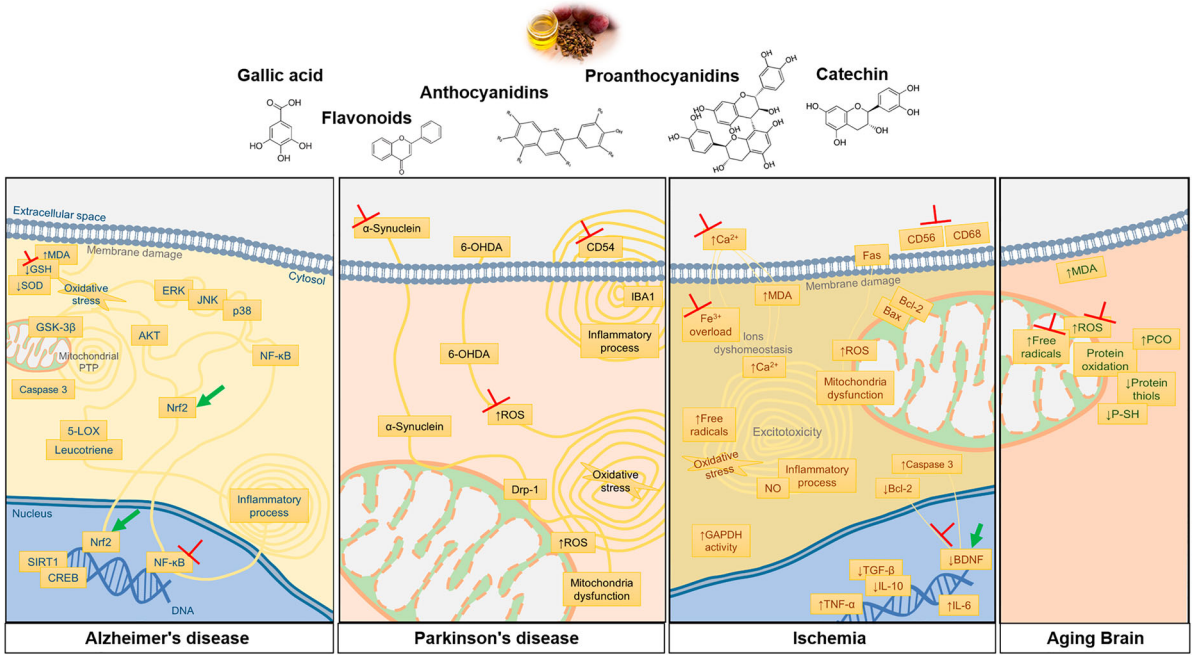

Figure 1. The potential neuroprotective effects of grape seed components. GSE via its bioactive molecules (upper part) can influence some key intercellular signaling pathways, which contribute to the pathogenesis of Alzheimer's disease, Parkinson's disease, ischemia, and ageing brain (down section). GSE enhances the anti-oxidative status, which slows down Alzheimer's processes by removing dysfunctional mitochondria and inflammatory responses. They also reduce inflammation, oxidative stress, ion overloads, and mitochondrial dysfunction, which influence the processes of Parkinson's disease, ischemia, and ageing brain. Green arrows represent up-regulation, and blocked lines (red) symbolize down-regulation.

studies should investigate the effects of GSE on various aspects of autism.

Epilepsy

Epilepsy is a common neurological disease characterized by the recurrence of unprovoked seizures. Although numerous anti-epileptic drugs have been proposed, they merely treat symptoms rather than cure the disease. Several side effects have been reported, which affect the quality of life [62]. Therefore, finding a safe therapeutic for disease can be helpful.

Because oxidative stress and mitochondrial dysfunction directly contribute to epileptogenesis, Zhen et al. (2014) investigated the effects of GSE, a potent antioxidant, against pentylenetetrazole. They showed that GSE could ameliorate pentylenetetrazole-induced kindling in rats by inhibiting oxidative damage and protecting the mitochondria in the hippocampus [62].

Epileptogenesis is associated with peripheral inflammation (systemic inflammatory disorders) and central inflammation (in the neuronal tissue), allowing for the breakdown of the blood–brain barrier (BBB) [63,64]. The upregulated inflammatory mediators (such as MMP9 and TLRs) and BBB breakdown cause some morphological synaptic changes in the hippocampus and the development of epilepsy [65–67]. The neurobiology of inflammation in epilepsy would imply the new therapeutic compounds, like GSEs with anti-oxidative and -inflammatory properties (Table 1). Thus, GSE can be considered a novel therapeutic agent for epilepsy.

Ischemia

Ischemic stroke is the most common type of stroke and accounts for approximately 80% of stroke cases [68]. This type of stroke is characterized by various detrimental events, including inflammation, oxidative stress, excitotoxicity, ionic dyshomeostasis, and edema, ultimately leading to cell death [69,70]. In addition, mitochondrial dysfunction has been shown to have an essential role in cell death after ischemia/reperfusion, which is regulated by microRNAs (miRNAs) [71]. On the other hand, a previous study revealed that grape seed procyanidin extract could influence microRNAs activity and protect cells against damage [72]. Therefore, GSE seems to have the potential to modulate mitochondrial dysfunction through microRNAs. Other studies have proved the protective effects of GSE against cerebral ischemia. It has been demonstrated that grape seed improves cell viability, modulates cytokines *in*

vitro, and improves behavioral and motor outcomes in animals with ischemia [72]. GSE prevents the hippocampus from ischemia/reperfusion-induced ultrastructural alterations, ion dyshomeostasis, inflammation, and calcium burst (Figure 1) [73]. In addition, GSE has been shown to correct several glycolytic enzymes such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), pyruvate kinase, enolase, and aldolase that are upregulated in the ischemic brain (Figure 1). GAPDH is involved in ATP synthesis [73,74] and plays a critical role in cell death after ischemia/reperfusion-induced neuronal excitotoxicity [75].

Inhibition of the iron overload toxicity is another GSE protectivity against ischemia (Figure 1). A large amount of iron is released in the ischemic brain and catalyzes more free radicals, which causes more damage [76]. Recently, Yun et al. (2020) has shown that GSE can alleviate neuronal apoptosis after iron overload [77]. They found that GSE administration can counteract the increase in catalase, glutathione peroxidase, and superoxide dismutase activities and decrease B-cell lymphoma 2 (Bcl-2) gene expressions in the iron overload condition (Table 1).

Ischemic stroke is also associated with endoplasmic reticulum (ER) stress-induced apoptosis that proanthocyanidin can attenuate it. Treatment with proanthocyanidin inhibits the expression levels of ER stress-related genes. This compound protects against ischemic stroke by attenuating ER stress-associated neuronal apoptosis through inhibiting glucose-regulated protein 78 (GRP78) and caspase-12 [78].

Psychiatric disorders

Psychiatric disorders are a wide range of disorders, including depression, anxiety, schizophrenia, and bipolar, disrupting individual and social life. According to previous studies, GSE could attenuate anxiety and depression. The grape seed proanthocyanidins ameliorate anxiety-like behavior in animals [79]. Terauchi et al. (2014) reported that GSE could reduce anxiety and depression in middle-aged women [80]. Therefore, it seems that this extract can be considered a valuable antidepressant and anti-anxiety agent. It has been revealed that GSE antidepressant property is exerted via hippocampal VGF [81]. VGF (non-acronymic) is a neuropeptide precursor and has antidepressant efficacy.

GSE has also been shown to have protective effects against stress-induced psychological disorders [82].

Grape seed polyphenols can promote brain health and psychological resilience by reducing peripheral inflammation [83]. Phenolic metabolites also promote psychological resilience by modulating the expression of important synaptic genes, which prevent maladaptive synaptic plasticity induced by environmental stressors [83]. It has been found that polyphenols exert an antistress effect through protein kinase Cα (PKCα) and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways and protect the brain from stress-induced neurological disorders [84]. Naturally derived polyphenols also exert protectivity against stress-induced psychological disorders by regulation of the hypothalamus-pituitary axis and modulation of the microbiota-gut-brain axis [85].

Ageing brain

In old age, oxidative stress is a significant cause of brain damage. Accumulation of oxidative stress causes mitochondrial dysfunction and ultimately leads to cell death [86,87]. Studies indicated an increase in ROS production and a decrease in the activity of antioxidant enzymes in the ageing brain. GSE has been shown to decline ROS production, decrease protein carbonyl (PCO) levels and increase thiols level (Figure 1) [88]. Also, a decrease in lipid peroxidation and hydrogen peroxide level and, conversely, an increase in protein sulphydryl (P-SH) content has been reported in the aged animals' hippocampus GSE administration (Figure 1, Table 1) [89]. The hippocampus homeostasis is essential for cognitive performance because it is closely involved in learning and memory [90,91]. Therefore, GSE can improve cognitive performance in ageing. Other studies proved the beneficial effects of GSE on the hippocampus of aged animals. It has been demonstrated that this extract can increase muscarinic ACh receptor M1 (m1AChR) levels in the hippocampus and improve cognitive performance [92]. In addition, we recently showed that GSE administration to aged rats could increase hippocampal neurogenesis and synaptogenesis [93]. We also found that this extract can decrease hippocampal cell degeneration and improve aged animals' learning and memory performance [93]. Since neurogenesis and synaptogenesis are significantly decreased in an ageing brain, GSE is a potent agent for maintaining cognitive performance by preventing neurogenesis and synaptogenesis.

GSE interplay with regulatory RNAs

MicroRNAs (miRs) are noncoding RNAs, typically with 18–25 nucleotides, and known as critical regulators of gene expression involved in various biological processes, including neurodevelopment, cell maturation, cell differentiation, and cell survival and brain plasticity [7–10]. As master tuners of the cell phenotype, miRNAs

are also closely involved in the induction/prevention of the development and progression of diseases, including neurological disorders [7, 94]. The human genome encodes approximately two thousand functional miRs and each miR can suppress multiple genes by binding to the 3′ untranslated regions of target mRNAs [94]. miRs are expressed in all body tissues and are believed to regulate about 60% of human genes [7,95]. Among all tissues, the miRs expression level is higher in the brain, and 70% of known miRs is expressed in this vital tissue [7,96]. As a single miR could modulate many functionally related genes and a single gene can be targeted by different miRNAs, today they are considered potential targets for developing neuroprotective and therapeutic strategies for neurological disorders.

There is evidence of additional mechanisms of action of grape seed components (Figure 2). miRNA is an epigenetic modifier mediating the post-transcriptional fate of specific mRNAs. Proanthocyanidin extracts have shown the potential to target miRNA expression in the HepG2 human hepatoma cell lines as they could reach the liver at high concentrations [97]. miRNAs seem to act as mediators of proanthocyanidins on cell functionality and metabolism.

Each proanthocyanidin may affect a specific regulatory miRNA due to a complex combination of different molecular structures. For example, miR-30b* is reported as the sole miRNA expressed in response to the two different proanthocyanidin extracts (GSPE and CPE) [98]. In so doing, miR-30b* has the most significant number of validated target mRNAs (Figure 2), such as those transcribed from the genes lipoprotein lipase (*LPL*), glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*), jun proto-oncogene (*JUN*), protein kinase C iota (*PRKCI*), glycogen synthase 1 (*GYS1*), B-cell lymphoma 2 (*BCL2*), transforming growth factor-beta 1 (*TFGB1*), interferon-alpha 1 (*IFNA1*), RELA, I-kappa-B protein kinase B (*IKBKB*), and the like in intracellular pathways. Therefore, lipid and glucose metabolism, insulin signaling, oxidative stress, and inflammation are among the cell functions modulated by GSE [98].

Proanthocyanidins can inhibit intracellular lipid accumulation and, then, macrophage foam cell formation. The reason behind this assumption is that proanthocyanidins down-regulate the mRNA expression of acetyl-CoA acetyltransferase (*ACAT1*) (a gene encoding for major player in intracellular cholesterol esterification) throughout the up-regulation of miR-9 (Figure 2) [99]. Also, suppressing miR-153 expression has been critical for activating Nrf2 signaling (Figure 2) and consequently for oxidant production, oxidative damage, and apoptosis. This would be another example of the specific molecular event of protective effects of GSPE on oxidative stress, which involves Nrf2 and protein kinase B (AKT) systems [100].

miRNAs have emerged as potential molecular targets for targeted therapies, for example, in cancer therapy, so their roles and downstream targets in mediating the properties of GSE are essential to consider. GSEs significantly lessen miR-19a/b expression and cluster host gene, MIR17HG. It leads to up-regulation of the mRNA expression level of tumor suppressor genes, insulin-like growth factor II receptor (IGF-2R) and phosphatase and tensin homolog (PTEN) (Figure 2), the related protein products, and reduced the phosphorylated form of AKT (P-AKT). The antineoplastic properties of GSEs are mediated, among other mechanisms, throughout the modulation of miRNAs, like miR-19a/b and −106b (Figure 2), contributing to the induction of apoptosis and inhibition of cell proliferation, as observed in neoplastic lung cells [101,102]. GSPE significantly down-regulates miR-106b in a variety of neoplastic cells with increased cyclin-dependent kinase inhibitor 1A (*CDKN1A*) mRNA and protein (p21) levels [102].

As regulatory miRNAs could act with their known/unknown downstream targets protecting against neurological disorders, the discussed evidence provides important rationales to determine further GSEs' potential against these disorders via the specific miRNAs.

GSE bioavailability in the brain

Oral bioavailability is the amount of the active constituent of a drug absorbed in the gastrointestinal tract and enters the bloodstream [103]. It is considered a critical pharmacokinetics parameter because poor bioavailability will lead to poor therapeutic results [104]. Oral bioavailability depends on several factors, most of them related to the current status and functionality of the gastrointestinal apparatus (fasting status, gastric emptying rate, availability of dedicated/free transporters) while others are related to the chemical–physical properties of the drug (hydrophobicity, solubility, formulation, interaction with other compounds/drugs) [103,105,106]. Age, gender and gut microbiota complete the frame [107]. Although these aspects are related to drugs, similar variables should be considered in the case of nutritional supplements and dietary components. However, besides oral bioavailability, a central aspect that should be considered is represented by the blood–brain barrier (BBB) permeability to the GSE compounds. Indeed, most of the active compounds in GSE are amphipathic in nature [108]. Therefore, they should be able to cross the BBB freely.

Grape seed polyphenolic extract bioavailability can be increased by repeated dosing [109]. Some

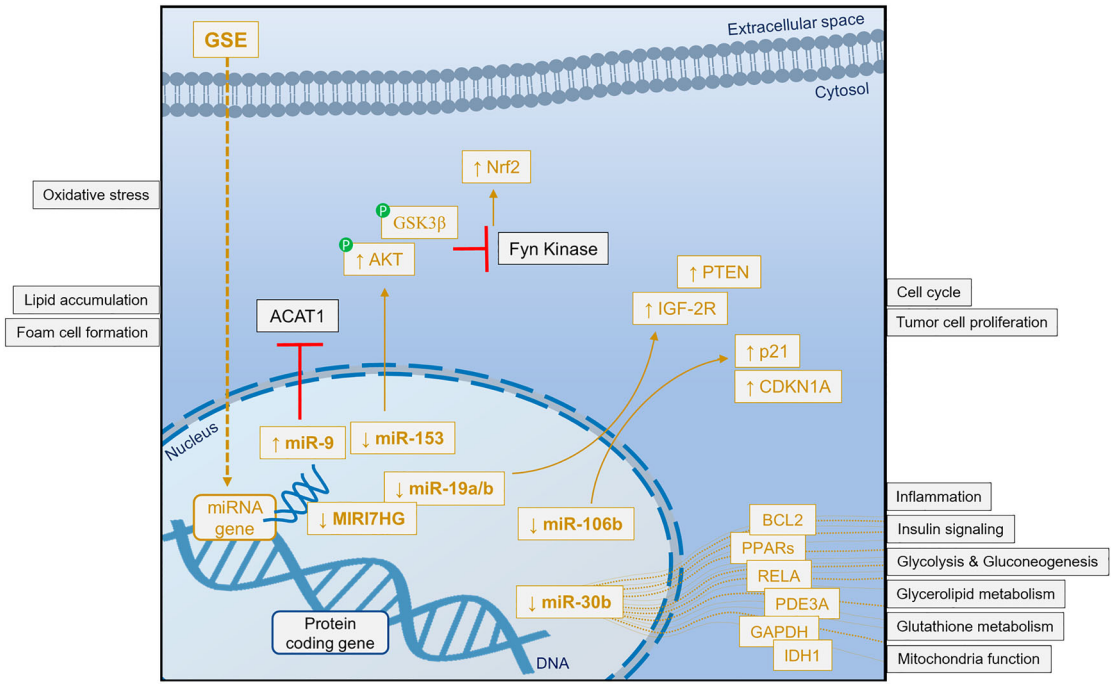

Figure 2. Possible association of regulatory miRNAs with GSE's effects. Schematic conceptual design to reveal the neuroprotective effects of GSE in relationship with different **protein coding** and **miRNA genes**. GSEs strongly modulate the miRNAs expression profile (*miR-9*, *−153*, *−19a/b*, *−106b*, and *−30b*) associated with the miRNA processing machinery altering the responsive coding genes, which in turn affect the main essential processes[93–97]. Alterations in *ACAT1* would influence cholesterol trafficking, which can be mitigated by turning on the *miR-9* gene [94]. Down-regulation of *miR-153* is attributed to the protective mechanism GSE via the AKT/ GSK3β/ Fyn-mediated Nrf2 signaling pathway. Nrf2-mediated cell defense against oxidative stress acts through high phosphorylation of AKT inactivating GSK3β with Ser9 phosphorylation and inhibiting Fyn kinase[95]. GSE significantly down-regulates the host gene (*MIRI7HG*) of *miR-19a/b*, and then upregulates the tumor suppressor genes (*IGF2R* and *PTEN*). The result would be apoptosis and inhibition of tumor cell proliferation mediated by GSE and miR-19a/b. The same result would be regulated by down-regulation of *miR-106b* and up-regulation of *CDKN1A* and p21 expression levels inducing tumoral cell cycle arrest[96,97]. GSE-mediated *miR-30b* down-regulation has a significant function with 480 gene targets [93] affecting inflammatory processes, insulin signaling, metabolic alterations, and mitochondria function.

components such as catechin and epicatechin have been reported that are not detectable in the brain after only a single dose of GSE. Their levels are significantly increased in the brain after repeated daily exposure to the extract [109,110]. This indicates that brain deposition of small molecular weight GSE constituents, including gallic acid, catechin, and epicatechin, is affected by repeated dosing. To have a high bioavailability, GSE should be consumed regularly. Another way to increase the bioavailability of polyphenols is to convert them into phytosomes. In this technique, the polyphenol is chemically reacted with phosphatidylcholine, the major phospholipid of living tissues [104]. The conversion of GSE polyphenols to phytosomes preserves their capacities and improves their delivery to tissues [104].

Conclusions and future perspectives

Research in recent years indicated that GSE's flavonoids and non-saturated fatty acids could reach the central nervous system and showed a preferential bioavailability compared with similar molecules derived from other natural products [109,111]. The interplay of GSE's ingredients with the biological barriers and detailed knowledge of the triggered metabolic pathways can help discover new bioactive agents effective on neurodegeneration and ageing.

Grape seed has a high potential in **preventing** neuronal damage in neurological diseases and brain ageing. It can also delay the onset and progression of these diseases, especially Alzheimer's and Parkinson's diseases, and should be considered a potent protective and therapeutic agent against different neurological disorders (Figure 1). This review indicates the potent protective and therapeutic effects of the GSE, but it should be noted that the present results are related to animal and laboratory studies, and further clinical trials and human-based studies are needed. The authors recommend clinical trials using GSE to supplement patients' standard treatments to understand the

therapeutic effects. In addition, the effects of grape seed on some neurological disorders such as bipolar are unknown. Future studies should investigate grape seed's protective and therapeutic effects on other neurological diseases. In addition, studies on the relationship between microRNAs and GSE therapeutic effects (Figure 2) can open new opportunities to design effective/functional therapeutics.

Data availability statement

All data are included in this published article.

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