Heliyon 7 (2021) e06185

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Aquatic exercise associated or not with grape juice consumption-modulated oxidative parameters in Parkinson disease patients: A randomized intervention study

Grazielle S. De Oliveira [a], Gislaine S. Pinheiro [a], Isabel C.T. Proença [b,d], Amanda Blembeel [b], Marcela Z. Casal [c], Daniela Pochmann [b], Leonardo Tartaruga [c], Flavia G. Martinez [c], Alex Sander Araújo [d], Viviane Elsner [a,b,d], Caroline Dani [a,b,*]

[a] Curso de Fisioterapia do Centro Universitário Metodista-IPA, Porto Alegre, RS, Brazil
[b] Programa de Pós-Graduação em Biociências e Reabilitação, Centro Universitário Metodista-IPA, Porto Alegre, RS, Brazil
[c] Laboratório de Pesquisa do Exercício, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[d] Programa de Pós-Graduação em Ciências Biológicas: Fisiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

ARTICLE INFO

Keywords:
Grape juice
Aquatic exercise
Oxidative stress
Cognition

ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder with significant motor disabilities and cognitive decline. Importantly, the imbalance of oxidative stress is related to PD physiopathology and progression. This study aimed to evaluate the impact of grape juice consumption associated with an aquatic exercise protocol on oxidative stress parameters and cognitive function in individuals with PD. The participants were randomized into two groups: grape juice group (GJG) and control group (CG) and were submitted to 4 weeks of an aquatic intervention (twice a week, approximately 60 minutes/session). The GJG also consumed 400 ml of grape juice per day (integral and conventional) during this period. Cognitive function was assessed by the Montreal Cognitive Assessment (MoCa) questionnaire. For the analysis of oxidative stress markers, specifically lipid oxidative damage (TBARS), proteins (Carbonil), acid uric and the activity of antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase), blood collection were done before and after intervention. No changes were observed in cognitive function after intervention in both groups. Regarding biomarkers, a reduction of antioxidant enzymes, thiobarbituric acid reactive substances (TBARS) and uric acid was observed in both groups. However, only the GJG showed a significant reduction on protein oxidation levels after intervention. In conclusion, the consumption of grape juice associated with an aquatic exercise protocol might be consider an effective alternative to reduce the oxidative damage in PD, reinforcing the importance of this intervention in promoting beneficial impact in this population.

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders that impact the substantia nigra and striatum in the basal ganglia, causing motor and non-motor symptoms [1, 2, 3]. In this context, impairment in cognitive function is usually observed in these individuals [1], typically affecting memory, attention, executive as well as visual-spatial abilities [4].

A growing body of evidence has been highlighting that the imbalance on oxidative stress markers plays a pivotal role in PD physiopathology, contributing to the dopaminergic neurons death in the midbrain [5, 6, 7]. On the other hand, several experimental studies demonstrated that exercise is a potential therapeutic strategy able to modulate these markers [8] and attenuates cognitive deficits [9]. It was reported that the neuroprotective effects of exercise may be correlated to the maintenance of redox balance [10]through increasing the activity of antioxidant enzymes and oxidative damage repair enzymes [11].

In this sense, we recently showed that an aquatic exercise program (during 30 days, twice a week, 60 min each session) induced important changes in several oxidative stress markers in peripheral blood from PD patients [12]. These findings support the idea that this exercise modality might be consider an interesting therapeutic strategy for PD individuals

* Corresponding author.
E-mail address: carolinedani@yahoo.com.br (C. Dani).

https://doi.org/10.1016/j.heliyon.2021.e06185
Received 3 June 2020; Received in revised form 26 June 2020; Accepted 29 January 2021

due the physical proprieties of the water and the safe conditions offered by the aquatic environment allow us to move more efficiently while reducing the fear of falling [13, 14]. In fact, PD individuals who underwent aquatic therapy showed better improvement in many outcome measures compared to traditional land-based protocols [14], reinforcing the effectiveness of this exercise modality.

Interestingly, it has been pointed out that an appropriated diet also seems to be an important alternative to prevent and improve motor and non motor impairments in PD. In this context, natural plant antioxidants have been shown to mediate the oxidative stress-induced effects in PD, which have gained considerable attention in vitro and in vivo [15]. However, clinical trials with polyphenols and food rich in these compounds are scare, which is restricting the potential use of these compounds as an alternative treatment for PD [15].

Phenolic compounds as antioxidant agents have been highlighted as important tools for the treatment of this disorder and are found in vegetables, fruits, chocolates, tea, coffee, wine, grape juice, and vinegar at different levels [16, 17]. Grape juice (GJ) also contains high levels of polyphenol compounds such as flavonoids and nonflavonoids [18] and its consumption is able to improve endothelial function, increase antioxidant capacity, reduce plasma protein oxidation and decrease platelet aggregation [19]. Some studies also reported that GJ could be an important source of prevention to neurodegenerative diseases reducing the oxidative stress [20, 21, 22]. Furthermore, its consumption can reverse cognitive and motor deficits in aging [23, 24] and modulated important neurotrophins, such as BNDF [25]. Specifically regarding PD, experimental data showed that GJ combined with treadmill exercise could improve motor behaviour, decreasing the rotations [26].

An important review published [15] proposed that natural plant antioxidants, including the grape juice [26], have been shown to mediate the oxidative stress-induced effects in PD, which has gained considerable attention in both in vitro [27] and in vivo studies [28].

Experimental studies showed that grape and its derivates could be useful against oxidative damage in the brain due to the presence of phenolic compounds [20, 21, 29, 30]. Also, our group showed that the grape juice could be an important choice to improve the antioxidant profile and memory/cognition evaluation in older women [31, 32, 33]. Preclinical findings have supported the potential of polyphenols in providing neuroprotection against oxidative stress-induced toxicity in PD [26, 34]. However, clinical trials regarding the potential use of polyphenols as an alternative treatment for PD.

Recently we observed that GJ with exercise could be important to improve the oxidative stress profile and functionality in elderly woman [31, 32]. However, Therefore, this study aimed to evaluate the impact of an aquatic exercise protocol with or without GJ consumption in the cognitive performance and oxidative stress modulation in PD patients.

2. Materials and methods

2.1. Ethical considerations

This study was approved by the Ethics Research Committee of Centro Universitário Metodista-IPA (no. 3.190. 828) and also was registered by ReBEC clinical trial (RBR-2c4xxb) [35]. An informed consent was provided and signed before the protocol began and the investigation was in full compliance with the Helsinki Declaration. All methods were performed following the relevant guidelines and regulations. Written informed consent was obtained from all participants before data collection [35].

2.2. Study population

Individuals who met the following criteria were included: people diagnosed with idiopathic PD, 1 to 3 on the Hoehn &Yahr (H&Y) scale and physically inactive for at least one month. They should be on regular drug treatment and have the ability to understand verbal instructions to perform tests and intervention [35].

Exclusion criteria were determined as having a cognitive impairment (MEEM $\leq$24), deep brain stimulation surgery (DBS), history of vertigo, surgeries in lower limbs during the last year, use of prostheses in the lower limbs, severe heart diseases or other associated neurological diseases [35].

2.3. Study design

This study was a randomized controlled clinical study. Sample size was calculated by G.Power Software. To calculate the sample size it was considered the effect size (1.3), two tails, alpha error probability (0.05) and power (0.8), resulting in a size of 10 each group. The effect size was calculated from the average and standard deviation showed at a similar study published at literature [36].

The participants who met the inclusion criteria were randomized into an intervention group (aquatic exercise program + grape juice consumption, ACQ-EXE + GJ) or control group (aquatic exercise program, without grape juice, ACQ-EXE) by a researcher who did not participate in the collections, through the website randomization.com [35]. The evaluation of cognitive function and anthropometric variables as well blood collection for oxidative stress measurement was done before and after intervention. All assessments as well the intervention were conducted on the "on" state of medication (after 1–2 hs of medicine intake) [35].

The aquatic exercise program occurred twice a week, lasting one hour each session, totalling 8 sessions during 30 days. According to the literature, grape juice consumption during 30 days is able to reduce oxidative stress parameters in peripheral blood in elderly ones [33]. During the intervention period, ACQ-EXE + GJ also drunk the juice, consuming 400 ml/daily. This grape juice amount was in accordance to the literature [31, 33]. It was recommended for ACQ-EXE group to avoid grape derivates, grape juice, and wine. A Food Frequency Questionnaires (FFQ) was answering by all the participants.

2.4. Aquatic exercise program

The AQC-EXE + GJ and AQC-EXE groups underwent an aquatic physical training program, carried out in the indoor swimming pool (depth 1.95 m, length 25 m, mean water temperature 31 °C) of Universidade Federal do Rio Grande do Sul (UFRGS), according to the literature [35]. The training intensity was controlled using Borg's subjective feeling of effort scale [37].

2.5. Research tools

2.5.1. Grape juice

Grape juice was elaborated with Vitis labrusca sp. (var. Bordo and Isabel) from Garibaldi winery (Garibaldi, RS, Brazil), from 2018 harvest. The grape juice was packed in tetra pack (200 mL). The phenolic compounds content was analysed according to the following tests.

2.5.2. Phenolic compounds analysis

Folin-Ciocalteau reagent was used for the quantification of the phenolic compounds. Phenolic concentration was estimated by correlating the absorbance of the samples to a standard curve made with gallic acid, and the result was expressed as milligrams of gallic acid equivalents/gram extract (mg EAG/L of grape juice) [38].

We quantified the total flavonoids according the literature (MORESCO et al., 2014). The concentration of flavonoids was estimated by correlating the absorbance of the samples to a standard curve performed with quercetin, in which the results were expressed as milligram equivalents of quercetin/gram extract (mg EQuerc/L of grape juice) [38]. The phenolic compounds isolated was performed by HPLC, with each standard (gallic acid, epigallocatechin, catechin, epicatechin, epigallocatechin gallate, rutin, ferulic acid, and resveratrol) [38]. The results were expressed as milligrams/L of grape juice.

2.5.3. Anthropometric evaluation

The evaluation of body composition was performed according to the recommendations of the International Society for the Advancement of Cineanthropometry (ISAK) to characterize the participants [39].

2.5.4. Cognitive function analysis

The cognition was evaluated by The Montreal Cognitive Assessment (MoCA), a screening tool developed to detect cognitive impairment by assessing various domains of cognition including attention, executive function, memory, language, visuospatial skills, conceptualization, calculation, and orientation. It is a simple paper-and-pencil test that takes only approximately 10 min to complete. The maximum MoCA score is 30, and total scores of less than 26 points may be indicative of cognitive impairment (Julayanont et al., 2015).

2.5.5. Sample preparation and oxidative stress measurement

For the levels of lipid peroxidation, we used the test to evaluate the reactive substances to thiobarbituric acid (TBARS) [40]. The TBARS was determined by absorbance at 535 nm (SP-2200 Spectrophotometer, Bioespectro Curitiba, Brazil). The results were expressed in nmol/mg protein.

Oxidative damage to proteins was measured by determining the carbonyl groups and is based on the reaction with dinitrophenylhydrazine (DNPH), according to Levine et al. (1990). The results were expressed in nmol/mg protein [41].

The non-enzymatic sulfhydryl technique determined defenses. This assay is based on the reduction of 5,5′-dithiol-bis (2-nitrobenzoic acid) (DTNB) by thiol groups, generating a yellow compound (TNB)The sulfhydryl content is inversely correlated to oxidative protein damage. The results were expressed in nmol/mg protein [42].

The activity of superoxide dismutase (SOD) was determined spectrophotometrically by measuring the inhibition of adrenochrome formation rate [43]. The results were expressed as U SOD/mg of protein. The assay for assessing the activity of catalase (CAT) was performed according to the method described by Aebi (1984) the results were expressed as U CAT/mg protein [44].

2.6. Statistical analysis

All collected data were analyzed in SPSS® software version 22.0 for Windows®. The normality was verified using the Shapiro-Wilk test. Data on sample characterization and body composition were described as mean ± standard deviation (SD). To evaluate the primary outcomes of the study, a GEE (generalized estimation equation) with gamma distribution was performed. Results were expressed as mean ± standard error (SE). Also, the mean percentage (%) of the difference between the pre and post times was presented. The % differences were analyzed by t-test or Mann-Whitney. The correlation between variables was analyzed by the Person or Spearman test. $p < 0.05$ was considered a significance level.

3. Results

Twenty-four participants were included in this research, although, due health problems, six dropped out and did not participate of the aquatic program meets. In the end, a total of eighteen participants finished the intervention and maintained a minimum of 70% frequency in the aquatic exercise program. The flow diagram, according to the Consolidated Standards of Reporting Trials (CONSORT), is depicted in Figure 1. About the grape juice composition, the phenolic compounds profile is showing in Table 1.

According to Hoehn & Yahr Scale, the majority of the participants in both groups were stage 2.5, at least. In this stage, 88.82% from ACQ-EXE and 80% at ACQ-EXE + GJ, without statistical differences ($p = 0.445$). About the UPDRS score, no statistical difference between the groups was observed ($p = 0.590$), ACQ-EXE (14.88 ± 5.46), and ACQ-EXE + GJ (16.5 ± 7.10).

Regarding anthropometric measurements (body mass, BMI, Waist, hip, and calf circumferences), no difference between the groups and the moments were found. All the measures are shown in Table 2. Similarly, no significant change in cognitive performance was found between pre- and post-intervention in both groups, according to the results of the MoCa questionnaire, as shown in Table 3.

The results about oxidative stress markers are shown in Table 4 and Figure 2. Considering the factors, isolated or associated, the aquatic exercise (time effect) was the most important factor in reducing the thiobarbituric acid reactive substances (TBARS), before (0.79 ± 0.20) vs after (0.317 ± 0.04) ($p < 0.05$). We didn't observe the differences between the groups (Figure 2A). However, the carbonyl levels significantly decreased only in the GJ group before (63.08 ± 6.80) vs after (55.91 ± 5.03), while at the ACQ-EXE group, we observed an increase in this parameter before (43.68 ± 6.48) vs after (59.08 ± 3.73) ($p < 0.05$) (Table 4). We observed a statistically difference between the groups, the grape juice aquatic exercise showed the most significantly reduce (Figure 2B).

In Table 4, we observed a significant difference between before and after aquatic activity, for all parameters. We didn't observe a difference between the groups (Figures 2C, D e E). According to Table 4, a significant reduction on Catalase enzymes (CAT), before (53.02 ± 3.78) vs after (12.18 ± 1.37), glutathione peroxidase (GPX), before (144.23 ± 15.90) vs after (47.94 ± 4.54), superoxide dismutase (SOD)before (14.14 ± 0.94) vs after (7.62 ± 1.30) was reported after intervention in both groups ($p < 0.05$) (Table 4 and Figure 2). In addition to the reduction of reactive species and damage to lipids, after the intervention, both groups demonstrated a significant reduction of uric acid after the intervention, as shown in Figure 3. We observed an important correlation between all the parameters, showing that there is a relation between the oxidative damage, antioxidant defense, and influence at cognitive function (Table 5). Before the intervention we observed a positive correlation between lipid and protein oxidation, also between CAT activity and cognition. After the intervention we observed statistically correlation between lipid peroxidation and protein oxidation with the antioxidant enzymes activities, showing that there is an important relation with oxidative stress damage and the antioxidant defense.

4. Discussion

The present study was the first randomized control trial demonstrating the effect of grape juice consumption and aquatic exercise program on cognitive function and oxidative stress profile in PD patients. Our results showed that the grape juice consumption could be an important diet choice to reduce the oxidative protein damage, and also, the aquatic exercise program improved the cognition performance and the antioxidant profile in this population.

Our anthropometric data could be related to the literature reporting that the identification of dietary and lifestyle variables associated with the development of PD may offer pathogenetic clues and prevention opportunities [45].In a population-based prospective cohort study, 26, 173 participants in the EPIC–Greece cohort showed an inverse association was found between polyunsaturated fat intake and tobacco smoking and incident PD [45]. In addition, some studies are showing that food rich in phenolic compounds could be an important choice to regulate the anthropometric profile. In this sense, a randomized clinical trial conducted with obese subjects that consumed white wine and purple grape juice, found that both groups presented reduced weight and waist circumference [46]. A recent study with Brazilian white grape juice also found that moderate consumption had a positive impact on reducing weight and abdominal fat, which is directly associated with cardiovascular disease [47]. However, it is important to note that these studies were performed with healthy participants and without exercise activity,

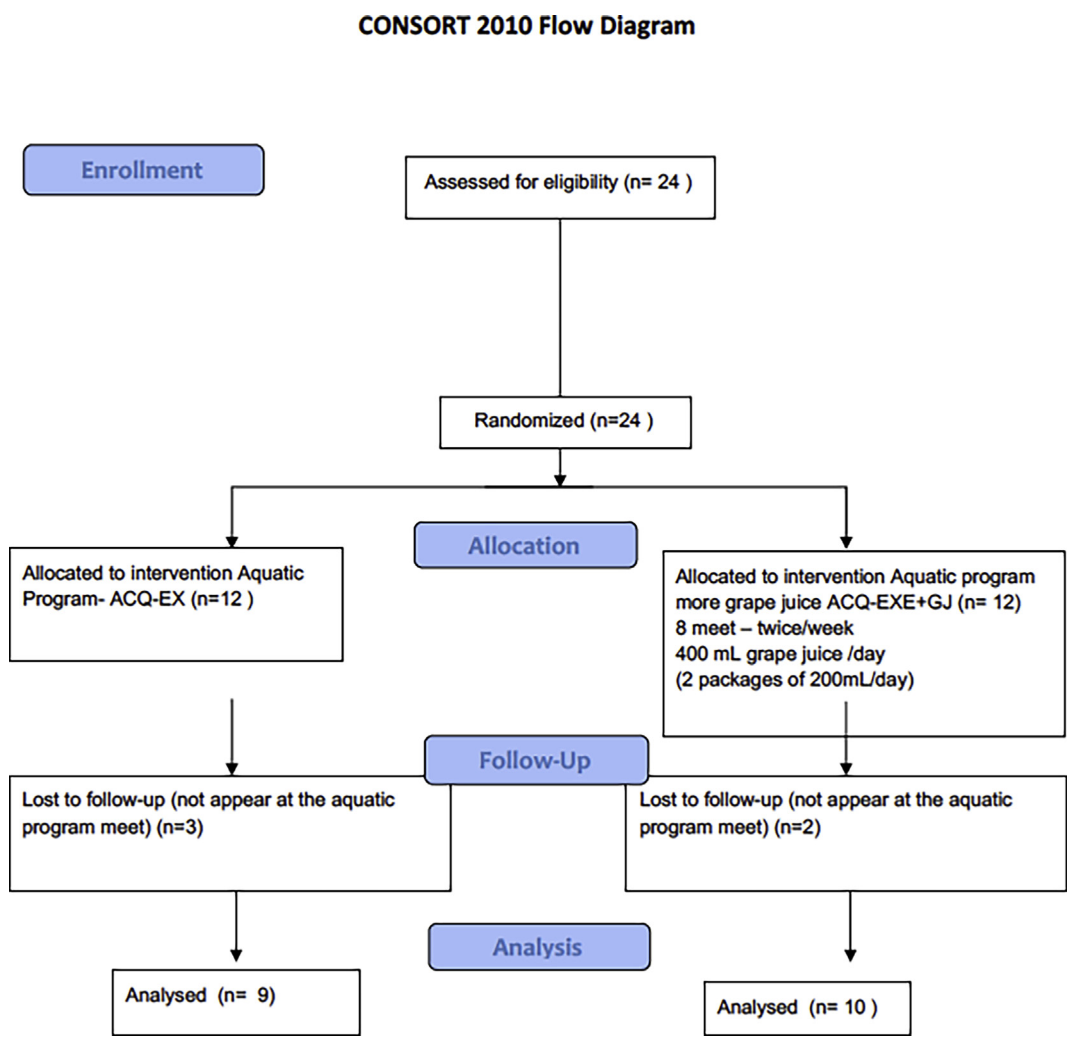

Figure 1. Consort flow diagram.

different from our study, where we designed with PD participants submitted to an aquatic exercise program for 30 days.

Phenolic compounds are essential to the vinery health, enological characteristics, and mainly to human health. The compound's content is different according to cultivar and to "terroir" characteristics, such as climate, soil, and cultivar differences. In our study, we observed that our grape juice is an important source of phenolic compounds, similar to observed by other studies with Brazilian cultivars [48]. These authors showed similar results compared to the current study at total phenolics (GAE mg L−1) 2015.00b ± 21.79, and both showed lower results than organic grape juices (3378.33a ±50.08). About isolated phenolic compounds, we observed that our grape juice showed higher levels of gallic acid compared to another study with conventional (11.51 mg/L) and organic grape juice (16.96 mg/L) [48]. However, catechin and epicatechin levels were much lower than another study at another study, but the resveratrol content (2.24 mg/L) [48] was similar to our result (1.9 mg/L).

PD is a progressive neurodegenerative disease with the advance of the disease, a cognitive decline is expected [49]. Cognitive impairment in PD patients affects the initial phase of learning, but this impairment can be contained through exercises with double tasks, associating motor training with visual and auditory stimuli, proposing two tasks that require attention [50, 51]. However, in this study, the cognitive assessment was performed using the MoCA questionnaire and showed no significant difference between the pre and post-intervention in both groups. Differently, another research with Sardinian folk showed that a dance program (two sessions/week, 90-min/class, for 12 weeks) increased MoCA score and therefore ameliorated cognition function in PD patients,

Table 1. Total phenolic, total flavonoids, and quantification of main anthocyanidins were analyzed in the grape juice.

Phenolic compounds	Values (MED±SD)
Total phenolic compounds (mg EAG/L)	2.187 ± 13.85
Total flavonoids compounds (mg EQuerc/L)	388.66 ± 1.52
Phenolic compounds identification (mg/L)	
Gallic acid	24.6 ± 0.2
Epigallocatechin	0.2 ± 0.01
Catechin	0.4 ± 0.01
Epicatechin	1.76 ± 0.05
Epigallocatechin gallate	1.80 ± 0.01
Hesperidin	2.53 ± 0.05
Ferulic acid	11.73 ± 0.15
Naringin	0.33 ± 0.05
Resveratrol	1.9 ± 0.01

MED – median; SD: standard deviation.

Table 2. Participants' characteristics and Anthropometric parameters in PD patients before and after aquatic exercise with or without grape juice.

		ACQ-EXE (n = 09)	ACQ-EXE + GJ (n = 10)	p	P group	P time	P interaction
Gender (female/male)		1(11.1%)/8(88.9%)	1 (10%)/9 (90%)	0.937			
Age (years)		65.5 ± 2.16	68.33 ± 0.413	0.551			
Body mass (kg)	Before	81.71 ± 3.72	76.97 ± 3.21		0.328	0.874	0.927
	After	81.68 ± 3.71	76.90 ± 3.17				
BMI (kg/m^2)	Before	27.07 ± 0.88	25.70 ± 1.34		0.386	0.820	0.854
	After	27.06 ± 0.06	25.60 ± 1.28				
WC (cm)	Before	100.11 ± 3.25	98.66 ± 2.27		0.822	0.341	0.942
	After	99.44 ± 2.77	97.37 ± 2.53				
HC (cm)	Before	103.00 ± 1.58	100.20 ± 1.98		0.625	0.672	0.092
	After	100.94 ± 2.01	101.43 ± 2.65				
CC (cm)	Before	37.66 ± 0.89	35.11 ± 0.96		0.058	0.278	0.403
	After	37.60 ± 0.99	34.71 ± 1.20				

BMI: Body mass index. WC: waist circumference. HC: Hip circumference; CC: Calf circumference. Data are presented as mean ± standard deviation (numeric data) or relative frequency (categorical data). The comparison between groups was performed using the Student t-test for independent data or chi-square test ($p < 0.05$). Comparison between before and after, considering the groups, were analyzed by GEE, with Sidak's post-test.

Table 3. Cognition evaluation through the Montreal Cognitive Assessment (MoCA) at PD submitted to an aquatic exercise program with or without grape juice.

Parameter	Before Mean ± SE	After Mean ± SE	%	Effect factor	(p-value)	
				Group	Time	Interaction
ACQ-EX	25.11 ± 0.65	23.12 ± 2.21	-7.92%	0.32	0.61	0.23
ACQ-EX + GJ	25.22 ± 0.95	26.11 ± 1.08	3.52%			

ACQ-EX: aquatic exercise; GJ: grape juice; SD: standard deviation; Avg: average. * Indicates a significant difference ($p < 0.05$) concerning pre and post times; Comparison, according to GEE, $p < 0.05$ was considered as a significant value. Difference: negative values indicate a decrease in the post-; positive values indicate an increase in post-.

suggesting that intervention time could be an important factor to improve the cognition in this population.

Recent studies suggest a beneficial role for polyphenols about cognition [52, 53]. These results are explained by evidence of many potential mechanisms, including, the relation gut microbiota [54], modulation of neuroinflammation [55], improved cerebrovascular function [56], and others. Studies with Concord grape juice suggested a positive impact on cognition following short term supplementation, 6–9 ml/kg per day following 12-week supplementation in improvements to California Verbal Learning Test (CVLT) list acquisition in older adults with mild cognitive impairment [23]. According to the literature a similar dosing schedule (range 355–621 ml/day) led to reduced CVLT recognition memory errors and increased activation in the right superior parietal cortex and right middle frontal cortex following 16-week supplementation [57]. There were also many interaction effects with the study phase indicating the important effect of grape juice. Specify, consumption of grape juice in arm 1 was associated with enduring benefits to verbal recall, executive function, and driving ability in the second arm of

Table 4. Indicators of oxidative damage and antioxidant enzymes activity pre and post-match simulation submitted to Aquatic exercise (ACQ-EX), with or without grape juice (GJ).

Parameters	Before Mean ± SE	After Mean ± SE	Effect factor	(p-valor)	
			Group	Time	Interaction
TBARS (nmol/mg)					
ACQ-EX	0.90 ± 0.31	0.30 ± 0.07	0.78	0.000*	0.375
ACQ-EX + GJ	0.70 ± 0.27	0.33 ± 0.04			
CARBONIL (nmol/mg)					
ACQ-EX	43.68 ± 6.48	59.08 ± 3.73*	0.245	0.116	0.000
ACQ-EX + GJ	63.08 ± 5.83	55.91 ± 5.03*			
CAT					
ACQ-EX	55.08 ± 6.09	11.85 ± 1.78*	0.92	0.00*	0.000
ACQ-EX + GJ	51.03 ± 4.61	12.51 ± 2.11*			
GPX					
ACQ-EX	119.69 ± 15.11	46.30 ± 6.52*	0.17	0.00*	0.000
ACQ-EX + GJ	173.81 ± 31.70	49.64 ± 6.31*			
SOD					
ACQ-EX	14.63 ± 0.77	5.98 ± 0.99*	0.26	0.00*	0.000
ACQ-EX + GJ	13.66 ± 1.67	9.70 ± 2.89*			

ACQ-EX: aquatic exercise; GJ: grape juice; SE: standard error. * Indicates a significant difference ($p < 0.05$) about pre and post times; Comparison, according to GEE, $p < 0.05$ was considered as a significant value.

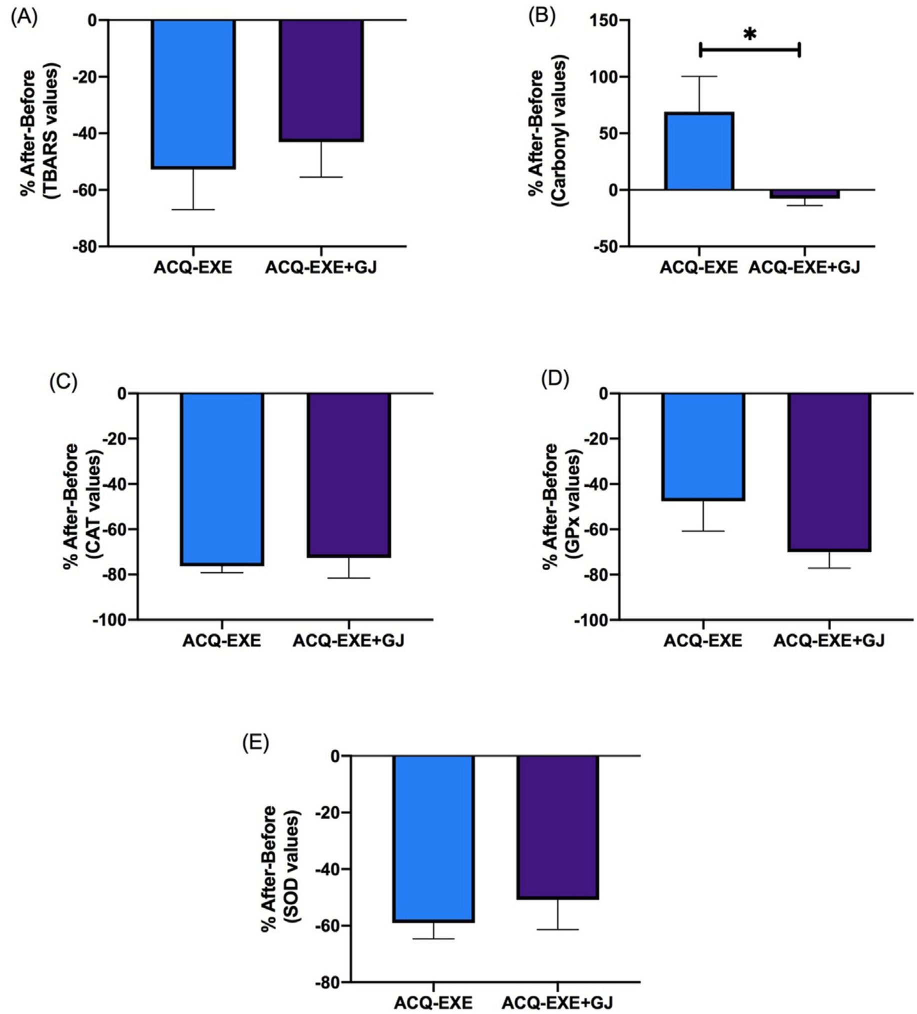

Figure 2. Effects of an aquatic exercise program with or without grape juice consumption on indicators oxidative stress (A and B) and antioxidant enzyme activities (C, D e E). Data are expressed as mean ± SE. * indicates significant difference ($p < 0.05$) between pre and post times; the differences were evaluated by t-test).

the study when placebo was consumed [58]. However, we didn't observe differences between the moments and the groups in cognition after 30 days. Considering that the studies cited above were designed in 16 and 12-weeks, a possible explanation for our results is that longer periods of grape juice consumption are necessary to change cognition.

To date, this is the first evidence to show the effect of grape juice with aquatic exercise on oxidative stress profile in PD. we observed that the consumption of grape juice reduced the protein oxidation damage (Carbonyl levels). Corroborating our findings, healthy older adults who received 400 mL/day of purple grape for thirty days presented significant reduction in the levels of oxidative damage to proteins [33], but with a significant increase at superoxide dismutase activity, different from our study. This divergence could be partially explained because in the research conducted by Da Costa (2015) the participants were submitted only to the consumption of grape juice without the practice of physical exercise [33].

We observed that the exercise program was very important to modulate the lipid peroxidation (TBARS) and all antioxidant enzyme activities. The exercise reduced all these parameters, and we didn't observe the grape juice influence in theses parameters (TBARS and SOD, CAT, and GPX activities). Recently, we found that PD patients submitted to an aquatic exercise program showed a significant increase in TBARS levels comparing the basal period with the first section [12]. We also showed a reduction in CAT activity immediately after and 30 days after the first session compared with the before time, similar to this study.

It has been pointed out that the regular exercise practice could promote beneficial adaptations in PD patients, reducing the free radical production and increasing antioxidant defense [59, 60]. However, this is not a consensus, since there are studies where only low-to-moderate exercise intensities could promote antioxidant adaptations against adverse ROS effects, and the high intensity could induce deleterious effects [59, 61]. In other research, it was described that a supervised exercise training performed twice weekly for 8 weeks, consisting of three sets each of the leg press, leg curl, and calf press, showed that this kind of exercise did not altered lipid peroxidation (MDA levels) and antioxidant activities (GPX and SOD activities) in PD patients [62]. According to these authors, longer-term exercise intervention trials are needed to determine the relationship between subject oxidant status and functional/clinical parameters. In this progressive disease, regular exercise may simply serve the function of slightly maintaining or improving a subject's oxidant status and help to worsen oxidant status with the progression of the disease [62].

In our study, we found a reduction of antioxidant enzymes of first-line superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) reduction could be explained because we also have a reduction in TBARS levels, in this sense, theses enzymes probably during the aquatic training acted to prevent the oxidative damage provoke by the exercise. In the literature, physical exercise can induce free radicals increases, but it contributes to the signaling of antioxidant activity [63].

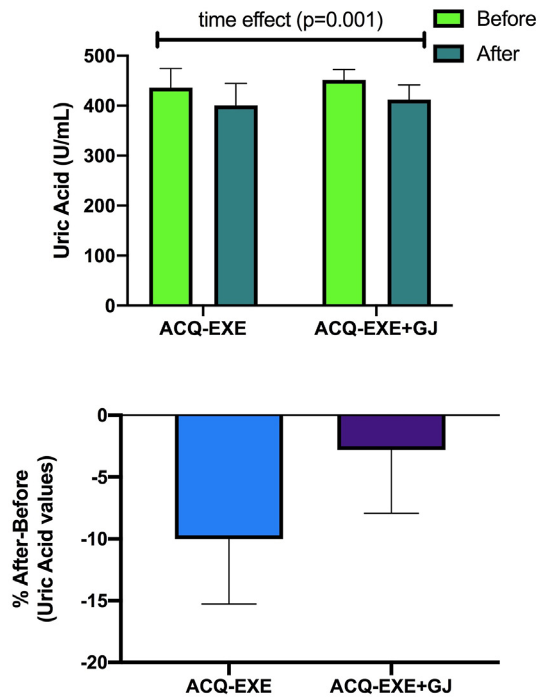

Figure 3. Effects of an aquatic exercise program with or without grape juice consumption on uric acid, before and after (A), and the difference (before and after) (B). Data are expressed as mean ± SE. * indicates significant difference ($p < 0.05$) between pre and post times; the differences were evaluated by t-test).

In a PD rat model, the authors showed that the total number of rotations decreased after grape juice intake, probably due to increasing the activities of antioxidant enzymes and affecting neuronal parameters [26]. Therefore, richer content of phenolic compounds and higher amounts of resveratrol and anthocyanins should be able to treat PD in rats, probably due to different mechanisms, mainly the oxidative stress modulation.

Caffeine and urate are both purines and well-established inverse risk factors linked to reduced PD risk and both possess neuroprotective properties via adenosine receptor antagonist and antioxidant actions, respectively [64]. In a recent study, a strong inverse association was also observed in plasma urate levels and caffeine consumption, highlighting the robustness of caffeine intake and urate as factors inversely associated with idiopathic PD [65]. In accordance, we also observed a reduction in uric acid levels after the exercise program, without differences with grape juice consumption. Similar to our results, it was demonstrated a significant reduction in exercise group serum uric acid level over control in hypertension [66]. The authors concluded that in moderate-intensity and continuous conditions, the serum uric acid showed lower values, comparing to control groups. Altogether, these results led us to infer that exercise is able to modulate this marker in different populations such as hypertension and PD.

Table 5. Correlations between the parameters.

Parameters	R	p
Before intervention for both group		
TBARS x Carbonyl	0.574	0.025*
CAT x MoCA	0.543	0.037*
After intervention for both groups		
Carbonyl x GPx	0.635	0.015*
After intervention for ACQ-EXE group		
Carbonyl x CAT	0.714	0.047*
Carbonyl x GPx	0.714	0.047*
TBARS x SOD	0.811	0.027*
TBARS x GPX	0.404	0.033*
After intervention for ACQ-EXE + GJ group		
Carbonyl x CAT	0.829	0.042*
Uric Acid x MoCA	-0.975	0.005*

*$p < 0.05$ according to the Spearman correlation test. TBARS: reactive substances to thiobarbituric acid. CAT: catalase activity; SOD: superoxide dismutase activity. GPX: glutathione peroxidase activity. MoCA: Montreal Cognitive Assessment.

We observed important positive correlations between antioxidant enzyme activities and oxidative damage, showing that the enzymes are increasing in situations where we have more damage than more antioxidant activity, but these results we observed mainly at ACQ-EXE group. According to the literature, the acute physical exercise furthers the increase in the formation of reactive oxygen species (ROS) in the function of the increment on the oxygen intake. However, the exercise modality that we choose in our study generates adaptations able to soften the harmful effects caused by ROS. These adaptations are related to several systems, among which the most important are the enzymatic system, composed by the superoxide dismutase, catalase and glutathione peroxidase [67].

At group ACQ-EXE + GJ, we observed a correlation with serum uric acid and MoCA score. It have been proposed that a moderate and continuous exercise program is associated with a serum uric acid decrease, and this result is related to an improved in the hypertensive patient [66]. Also, in a recent study, the authors demonstrated that the cognitive impairment group showed higher levels of serum uric acid than the control group [68].

Through this research, we conclude that aquatic exercise program is an important alternative for reducing oxidative stress. Specifically, is able to induce a significant reduction in TBARS and SOD, CAT, and GPX enzymes, in addition to reducing uric acid levels in PD patients. Furthermore, grape juice consumption can be an essential ally mainly in reducing protein oxidation levels, indicating that the association of both strategies might promote beneficial effects in this population. In the Figure 4 we summarized the main results from this research (Figure 4).

We recognize as a limitation of this study the short intervention period (30 days) and the reduced number of participants. This number was calculated according to a similar study. Thus, it is recommended that other studies should consider a prolonged intervention period. These findings might contribute to elucidate the cognitive function and exact oxidative stress pathways involved to the aquatic exercise and/or grape juice consumption effects in PD patients. In addition, we believe that our findings will encourage future investigations with a larger sample, which could enable also verify other issues such as the influence of gender on oxidative stress modulation in response of these interventions.

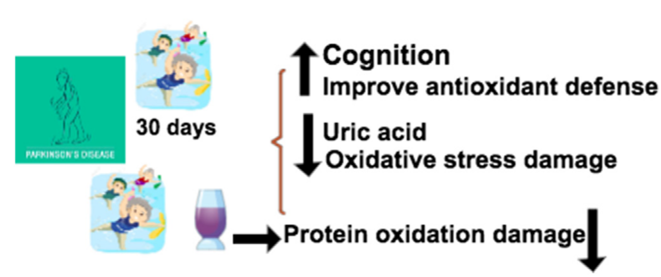

Figure 4. Principal results from two different treatments, aquatic exercise with or without grape juice, in cognition and oxidative stress markers.

Declarations

Author contribution statement

Grazielle S. De Oliveira, Gislaine S. Pinheiro, Viviane Elsner, Caroline Dani: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Isabel C.T. Proença, Amanda Blembeel, Marcela Z. Casal, Daniela Pochmann, Leonardo Tartaruga, Flavia G. Martinez, Alex Sander Araújo: ; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

The clinical trial described in this paper was registered at ReBEC under the registration number RBR-2c4xxb.

Acknowledgements

To CAPES, CNPq, and FAPERGS support.

References

[1] G. Dirnberger, M. Jahanshahi, Executive dysfunction in Parkinson's disease: a review, J. Neuropsychol. 7 (2013) 193–224.
[2] T. Wu, M. Hallett, P. Chan, Motor automaticity in Parkinson's disease, Neurobiol. Dis. 82 (2015) 226–234.
[3] U. Ekman, J. Eriksson, L. Forsgren, S.J. Mo, K. Riklund, L. Nyberg, Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment: a cross-sectional study, Lancet Neurol. 11 (2012) 679–687.
[4] D. Aarsland, K. Bronnick, C. Williams-Gray, D. Weintraub, K. Marder, J. Kulisevsky, D. Burn, P. Barone, J. Pagonabarraga, L. Allcock, G. Santangelo, T. Foltynie, C. Janvin, J.P. Larsen, R.A. Barker, M. Emre, Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis, Neurology 75 (2010) 1062–1069.
[5] G.G. Ortiz, F.P. Pacheco Moisés, M. Mireles-Ramírez, L.J. Flores-Alvarado, H. González-Usigli, V.J. Sánchez-González, A.L. Sánchez-López, L. Sánchez-Romero, E.I. Díaz-Barba, J.F. Santoscoy-Gutiérrez, P. Rivero-Moragrega, Oxidative stress: love and hate history in central nervous system, in: Adv. Protein Chem. Struct. Biol., Academic Press Inc., 2017, pp. 1–31.
[6] O. Hwang, Role of oxidative stress in Parkinson's disease, Exp. Neurobiol. 22 (2013) 11–17.
[7] U.e.A. Warraich, F. Hussain, H.U.R. Kayani, Aging - oxidative stress, antioxidants and computational modeling, Heliyon 6 (2020), e04107.
[8] R.O. da Costa, C.V.J. Gadelha-Filho, A.E.M. da Costa, M.L. Feitosa, D.P. de Araújo, J.D. de Lucena, P.E.A. de Aquino, F.A.V. Lima, K.R.T. Neves, G.S. de Barros Viana, The treadmill exercise protects against dopaminergic neuron loss and brain oxidative stress in parkinsonian rats, Oxid. Med. Cell. Longev. 2017 (2017) 1–10.
[9] A.T.R. Goes, L.C. Souza, C.B. Filho, L. Del Fabbro, M.G. De Gomes, S.P. Boeira, C.R. Jesse, Neuroprotective effects of swimming training in a mouse model of Parkinson's disease induced by 6-hydroxydopamine, Neuroscience 256 (2014) 61–71.
[10] F. Yang, Y. Trolle Lagerros, R. Bellocco, H.-O. Adami, F. Fang, N.L. Pedersen, K. Wirdefeldt, Physical activity and risk of Parkinson's disease in the Swedish national March cohort, Brain 138 (2015) 269–275.
[11] S.C. LaHue, C.L. Comella, C.M. Tanner, The best medicine? The influence of physical activity and inactivity on Parkinson's disease, Mov. Disord. 31 (2016) 1444–1454.
[12] V. Elsner, C. Dani, I.T. Proença, J. Marinho, P. Peccin, I.R.V. da Silva, S. Nique, V. Striebel, D. Pochmann, Aquatic exercise program-modulated oxidative stress markers in patients with Parkinson's disease, Neural Regen. Res. 15 (2020) 2067–2072.
[13] A.R. Plecash, B.R. Leavitt, Aquatherapy for neurodegenerative disorders, J. Huntingtons. Dis. 3 (2014) 5–11.
[14] D. Volpe, M.G. Giantin, R. Maestri, G. Frazzitta, Comparing the effects of hydrotherapy and land-based therapy on balance in patients with Parkinson's disease: a randomized controlled pilot study, Clin. Rehabil. 28 (2014) 1210–1217.
[15] S.L. Hor, S.L. Teoh, W.L. Lim, Plant polyphenols as neuroprotective agents in Parkinson's disease targeting oxidative stress, Curr. Drug Targets 20 (2019).
[16] A. Tresserra-Rimbau, R.M. Lamuela-Raventos, J.J. Moreno, Polyphenols, food and pharma. Current knowledge and directions for future research, Biochem. Pharmacol. 156 (2018) 186–195.
[17] N. Zeghad, E. Ahmed, A. Belkhiri, Y. Vander Heyden, K. Demeyer, Antioxidant activity of Vitis vinifera, Punica granatum, Citrus aurantium and Opuntia ficus indica fruits cultivated in Algeria, Heliyon 5 (2019), e01575.
[18] C. Dani, L.S. Oliboni, R. Vanderlinde, D. Bonatto, M. Salvador, J.A.P. Henriques, Phenolic content and antioxidant activities of white and purple juices manufactured with organically- or conventionally-produced grapes, Food Chem. Toxicol. 45 (2007).
[19] P. Castilla, R. Echarri, A. Dávalos, F. Cerrato, H. Ortega, J.L. Teruel, M.F. Lucas, D. Gómez-Coronado, J. Ortuño, M.A. Lasunción, Concentrated red grape juice exerts antioxidant, hypolipidemic, and antiinflammatory effects in both hemodialysis patients and healthy subjects, Am. J. Clin. Nutr. 84 (2006) 252–262.
[20] A.D. Rodrigues, T.B. Scheffel, G. Scola, M.T.D. Santos, B. Fank, S.C.V. De Freitas, C. Dani, R. Vanderlinde, J.A.P. Henriques, A.S. Coitinho, M. Salvador, Neuroprotective and anticonvulsant effects of organic and conventional purple grape juices on seizures in Wistar rats induced by pentylenetetrazole, Neurochem. Int. 60 (2012).
[21] M.G. Cardozo, N. Medeiros, D. Dos Santos Lacerda, D.C. De Almeida, J.A.P. Henriques, C. Dani, C. Funchal, Effect of chronic treatment with conventional and organic purple grape juices (Vitis labrusca) on rats fed with high-fat diet, Cell. Mol. Neurobiol. 33 (2013) 1123–1133.
[22] C. Dani, D. Bonatto, M. Salvador, M.D. Pereira, J.A.P. Henriques, E. Eleutherio, Antioxidant protection of resveratrol and catechin in Saccharomyces cerevisiae, J. Agric. Food Chem. 56 (2008) 4268–4272.
[23] R. Krikorian, T. a Nash, M.D. Shidler, B. Shukitt-Hale, J. a Joseph, Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment, Br. J. Nutr. 103 (2010) 730–734.
[24] B. Shukitt-Hale, A. Carey, L. Simon, D.A. Mark, J.A. Joseph, Effects of Concord grape juice on cognitive and motor deficits in aging, Nutrition 22 (2006) 295–302.
[25] C. Dani, A.C. Andreazza, C.A. Gonçalves, F. Kapizinski, J.A.P. Henriques, M. Salvador, Grape juice increases the BDNF levels but not alter the S100B levels in hippocampus and frontal cortex from male Wistar Rats, Acad. Bras. Cienc. Ann. Brazilian Acad. Sci. (2017).
[26] F. Eshraghi-Jazi, H. Alaei, H. Azizi-Malekabadi, M. Gharavi-Naini, A. Pilehvarian, Z. Ciahmard, The effect of red grape juice and exercise, and their combination on Parkinson(')s disease in rats, Avicenna J. Phytomedicine. 2 (2012) 90–96. http://www.ncbi.nlm.nih.gov/pubmed/25050236. (Accessed 17 April 2020).
[27] Y. Wu, X. Li, J.X. Zhu, W. Xie, W. Le, Z. Fan, J. Jankovic, T. Pan, Resveratrol-activated AMPK/SIRT1/Autophagy in cellular models of Parkinson's disease, Neurosignals 19 (2011) 163–174.
[28] M.-C. Pardon, C. Joubert, F. Perez-Diaz, Y. Christen, J.-M. Launay, C. Cohen-Salmon, In vivo regulation of cerebral monoamine oxidase activity in senescent controls and chronically stressed mice by long-term treatment with Ginkgo biloba extrac3t (EGb 761), Mech. Ageing Dev. 113 (2000) 157–168.
[29] C. Dani, M.A.B. Pasquali, M.R. Oliveira, F.M. Umezu, M. Salvador, J.A.P. Henriques, J.C.F. Moreira, Protective effects of purple grape juice on carbon tetrachloride-induced oxidative stress in brains of adult Wistar rats, J. Med. Food 11 (2008).
[30] C. Dani, L.S. Oliboni, F.M. Umezu, M.A.B. Pasquali, M. Salvador, J.C.F. Moreira, J.A.P. Henriques, Antioxidant and antigenotoxic activities of purple grape juice-organic and conventional-in adult rats, J. Med. Food 12 (2009).
[31] L. Bassôa, L. Trevizol, I. Fraga, N.C. Martins, F. Variani, D. Pochmann, C. Dani, V.R. Elsner, Grape juice consumption-induced physical functional performance improvement alone or combined with therapeutic exercise in elderly women, Comp. Exerc. Physiol. 15 (2019) 95–104.
[32] V. Rostirola Elsner, L. Trevizol, L. Bassôa, I. Fraga, I. Munhoz, D. Pochmann, C. Dani, Grape juice consumption and/or exercise training-induced neuroplasticity and memory improvement in healthy elderly women, SDRP J. Cell. Mol. Physiol. 2 (2018) 1–10.
[33] P. Cañete da Costa, G. Pires Dorneles, I.R. Vital da Silva, C.L. Pereira de Araujo, G. Pereira Reinaldo, A. Peres, C. Funchal, P. Dal Lago, C. Dani, V. Rostirola Elsner, Chronic purple grape juice consumption induces age-dependent changes on cognitive function in elderly women, J. Syst. Integr. Neurosci. 3 (2017).
[34] Q. Xu, M. Langley, A.G. Kanthasamy, M.B. Reddy, Epigallocatechin gallate has a neurorescue effect in a mouse model of Parkinson disease, J. Nutr. 147 (2017) 1926–1931.
[35] G.S. De Oliveira, L. Iraci, G.S. Pinheiro, M.Z. Casal, A.N. Haas, D. Pochmann, F.G. Martinez, V. Elsner, C. Dani, Effect of exercise and grape juice on epigenetic modulation and functional outcomes in PD: a randomized clinical trial, Physiol. Behav. 227 (2020) 113135.
[36] C. Lavratti, G. Dorneles, D. Pochmann, A. Peres, A. Bard, L. de Lima Schipper, P. Dal Lago, L.C. Wagner, V.R. Elsner, Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia, Physiol. Behav. 168 (2017) 84–90.
[37] C. Foster, J.A. Florhaug, J. Franklin, L. Gottschall, L.A. Hrovatin, S. Parker, P. Doleshal, C. Dodge, A new approach to monitoring exercise training./Une

Nouvelle approche pour conduire l'entrainement, J. Strength Cond. Res. 15 (2001) 109–115 (Allen Press Publ. Serv. Inc.).
[38] P. Türck, S. Fraga, I. Salvador, C. Campos-Carraro, D. Lacerda, A. Bahr, V. Ortiz, A. Hickmann, M. Koetz, A. Belló-Klein, A. Henriques, F. Agostini, A.S. da Rosa Araujo, Blueberry extract decreases oxidative stress and improves functional parameters in lungs from rats with pulmonary arterial hypertension, Nutrition 70 (2020) 110579.
[39] A. Hurria, H.J. Cohen, M. Extermann, WHO_TRS_854.pdf, J. Geriatr. Oncol. 1 (2010) 40–44. https://linkinghub.elsevier.com/retrieve/pii/S1879406810000068.
[40] E.D. Wills, Mechanisms of Lipid Peroxide Formation in Animal Tissues, 1966. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1265056/pdf/biochemj00754-0162.pdf. (Accessed 29 March 2019).
[41] R.L. Levine, D. Garland, C.N. Oliver, A. Amici, I. Climent, A.-G. Lenz, B.-W. Ahn, S. Shaltiel, E.R. Stadtman, [49] Determination of carbonyl content in oxidatively modified proteins, Methods Enzymol. 186 (1990) 464–478.
[42] C. Dani, K.M. Dias, L. Trevizol, L. Bassôa, I. Fraga, I.C.T. Proença, D. Pochmann, V.R. Elsner, The impact of red grape juice (Vitis labrusca)consumption associated with physical training on oxidative stress, inflammatory and epigenetic modulation in healthy elderly women, Physiol. Behav. 229 (2021) 113215.
[43] J.V. Bannister, L. Calabrese, Assays for Superoxide Dismutase, 2006, pp. 279–312.
[44] H. Aebi, [13] Catalase in vitro, Methods Enzymol. 105 (1984) 121–126.
[45] A. Kyrozis, A. Ghika, P. Stathopoulos, D. Vassilopoulos, D. Trichopoulos, A. Trichopoulou, Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece, Eur. J. Epidemiol. 28 (2013) 67–77.
[46] M. Flechtner-Mors, H.K. Biesalski, C.P. Jenkinson, G. Adler, H.H. Ditschuneit, Effects of moderate consumption of white wine on weight loss in overweight and obese subjects, Int. J. Obes. 28 (2004) 1420–1426.
[47] C. Zuanazzi, P.A. Maccari, S.C. Beninca, C.S. Branco, H. Theodoro, R. Vanderlinde, J. Siviero, M. Salvador, White grape juice increases high-density lipoprotein cholesterol levels and reduces body mass index and abdominal and waist circumference in women, Nutrition 57 (2019) 109–114.
[48] I.M. Toaldo, F.A. Cruz, T.D.L. Alves, J.S. De Gois, D.L.G. Borges, H.P. Cunha, E.L. Da Silva, M.T. Bordignon-Luiz, Bioactive potential of Vitis labrusca L. grape juices from the Southern Region of Brazil: phenolic and elemental composition and effect on lipid peroxidation in healthy subjects, Food Chem. 173 (2015) 527–535.
[49] H. Braak, K. Del Tredici, U. Rüb, R.A.I. De Vos, E.N.H. Jansen Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2003) 197–211.
[50] M.A. de Paraizo, A.L.M. Almeida, L.A. Pires, R.S.A. Abrita, M.H.T. Crivellari, B.D.S. Pereira, N.M. da S. Fernandes, M.G. Bastos, Montreal Cognitive Assessment (MoCA) screening mild cognitive impairment in patients with chronic kidney disease (CKD) pre-dialysis, J. Bras. Nefrol. 38 (2016) 31–41.
[51] G.M. Petzinger, B.E. Fisher, S. McEwen, J.A. Beeler, J.P. Walsh, M.W. Jakowec, Cognitive circuitry in Parkinson's disease, Lancet Neurol. 12 (2013) 716–726.
[52] D.J. Lamport, C. Saunders, L.T. Butler, J.P. Spencer, Fruits, vegetables, 100% juices, and cognitive function, Nutr. Rev. 72 (2014) 774–789.
[53] D.J. Lamport, L. Dye, J.L.D. Wightman, C.L. Lawton, The effects of flavonoid and other polyphenol consumption on cognitive performance: a systematic research review of human experimental and epidemiological studies, Nutr. Aging 1 (2012) 5–25.
[54] M. Gasperotti, S. Passamonti, F. Tramer, D. Masuero, G. Guella, F. Mattivi, U. Vrhovsek, Fate of microbial metabolites of dietary polyphenols in rats: is the brain their target destination? ACS Chem. Neurosci. 6 (2015) 1341–1352.
[55] J.P.E. Spencer, K. Vafeiadou, R.J. Williams, D. Vauzour, Neuroinflammation: modulation by flavonoids and mechanisms of action, in: Mol. Aspects Med., Pergamon, 2012, pp. 83–97.
[56] C. Rendeiro, J.S. Rhodes, J.P.E. Spencer, The mechanisms of action of flavonoids in the brain: direct versus indirect effects, Neurochem. Int. 89 (2015) 126–139.
[57] R. Krikorian, E.L. Boespflug, D.E. Fleck, A.L. Stein, J.D. Wightman, M.D. Shidler, S. Sadat-Hossieny, Concord grape juice supplementation and neurocognitive function in human aging, J. Agric. Food Chem. 60 (2012) 5736–5742.
[58] D.J. Lamport, C.L. Lawton, N. Merat, H. Jamson, K. Myrissa, D. Hofman, H.K. Chadwick, F. Quadt, J.D. Wightman, L. Dye, Concord grape juice, cognitive function, and driving performance: a 12-wk, placebo-controlled, randomized crossover trial in mothers of preteen children, Am. J. Clin. Nutr. 103 (2016) 775–783.
[59] R.S. Monteiro-Junior, T. Cevada, B.R.R. Oliveira, E. Lattari, E.M.M. Portugal, A. Carvalho, A.C. Deslandes, We need to move more: neurobiological hypotheses of physical exercise as a treatment for Parkinson's disease, Med. Hypotheses 85 (2015) 537–541.
[60] Q. Xu, Y. Park, X. Huang, A. Hollenbeck, A. Blair, A. Schatzkin, H. Chen, Physical activities and future risk of Parkinson disease, Neurology 75 (2010) 341–348.
[61] Z. Radak, H.Y. Chung, S. Goto, Exercise and hormesis: oxidative stress-related adaptation for successful aging, Biogerontology 6 (2005) 71–75.
[62] R.J. Bloomer, B.K. Schilling, R.E. Karlage, M.S. Ledoux, R.F. Pfeiffer, J. Callegari, Effect of resistance training on blood oxidative stress in Parkinson disease, Med. Sci. Sports Exerc. 40 (2008) 1385–1389.
[63] M.J. Gomes, P.F. Martinez, L.U. Pagan, R.L. Damatto, M.D.M. Cezar, A.R.R. Lima, K. Okoshi, M.P. Okoshi, Skeletal muscle aging: influence of oxidative stress and physical exercise, Oncotarget 8 (2017) 20428–20440.
[64] M. Morelli, A.R. Carta, A. Kachroo, M.A. Schwarzschild, Pathophysiological roles for purines. Adenosine, caffeine and urate, in: Prog. Brain Res., Elsevier B.V., 2010, pp. 183–208.
[65] R. Bakshi, E.A. Macklin, A.Y. Hung, M.T. Hayes, B.T. Hyman, A.-M. Wills, S.N. Gomperts, J.H. Growdon, A. Ascherio, C.R. Scherzer, M.A. Schwarzschild, Associations of lower caffeine intake and plasma urate levels with idiopathic Parkinson's disease in the harvard biomarkers study, J. Parkinsons Dis. 10 (2020) 505–510.
[66] S. Lamina, G. Okoye, Effects of aerobic exercise training on psychosocial status and serum uric acid in men with essential hypertension: a randomized controlled trial, Ann. Med. Health Sci. Res. 2 (2012) 161.
[67] C.D. Schneider, A.R. de Oliveira, Radicais livres de oxigênio e exercício: Mecanismos de formação e adaptação ao treinamento físico, Rev. Bras. Med. Do Esporte. 10 (2004) 308–318.
[68] L. Wang, X.-M. Zhao, X.-Z. Yuan, F.-Y. Wang, J. Shen, Y. Wang, Association between serum 25-hydroxyvitamin D level and cognitive impairment in patients with white matter lesions: a cross-sectional study, Med. Princ. Pract. (2020).