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Pilot project. Resveratrol intake by physical active and sedentary older adult women and blood pressure

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ABSTRACT

Objective: Although the use of resveratrol is widespread, there is a lack of studies concerning its use in older adults who practice regular physical activity. The present study aimed to evaluate how resveratrol influenced anthropometric parameters, heart measures, blood analytes in women participants, aged 60 to 80 years old, distributed in four groups consisting of those who regularly exercise or not, and those who were under resveratrol treatment or not. The older adult women exercised in a Community Center.

Methods: A prospective, comparative clinical pilot study was carried out based on convenience non-probability sampling. Resveratrol 300 mg/daily/60 days was orally-administered to 43 participants that were regularly accompanied and checked for anthropometrical parameters, heart measures, blood analytes, leukogram, and plaquetogram indices.

Results: The effect of resveratrol and exercise was not significant in most of the parameters evaluated in the study. Nonetheless, both systolic ($p = 0.0120$) and diastolic ($p = 0.0241$) blood pressures (BP) were elevated in sedentary older adult women in comparison with older women that regularly exercised. However, they remained within the normal BP range considered for the age. Mean corpuscular volume (MCH; $p = 0.0198$) and red blood cell distribution width (RDW; $p < 0.0001$) were improved in the groups receiving resveratrol and exercises compared to the sedentary group receiving resveratrol. The sedentary group receiving resveratrol showed diminished segmented cells ($p = 0.0459$), basophils ($p < 0.0001$), and lymphocytes ($p < 0.0001$).

Conclusions: Present findings showed that resveratrol consumption for sedentary older women could lead to dysregulated blood pressure. Although resveratrol consumption is indicated to treat inflammation, its use must be discussed with a health professional and not be inadvertently self-administered due to significant alterations in blood pressure in older adult women, primarily if not related to exercise practice.

1. Introduction

The consumption of resveratrol is being propagated due to its antioxidative and anti-inflammatory effects, claiming to improve neurocognition (Bastianetto et al., 2015), to work as an adjuvant in cancer treatment, and as a preventive nutritional supplement (Park and Pezzuto, 2015), also to prevent aging and promotes longevity (Tomé-Carneiro et al., 2013). Despite possible benefits, the rampant consumption of the stilbene may lead to some unpredictable direction, particularly if taken without medical advice.

Resveratrol is a stilbene polyphenol found in wine grapes (*Vitis vinifera*), red wines, peanuts (*Arachis hypogea*), and roots of various plant species including *Polygonum cuspidatum* and rhubarb (*Rheum rhapontiicum*). Resveratrol was first noticed in science due to its intimate relation to the "French paradox" (Renaud and Lorgeril, 1992), where the incidence of cardiovascular diseases was lower in the French despite their high consumption of fat, richly present in their cuisine, maybe because of the substantial red wine consumption.

According to the World Health Organization (WHO), older adults are 60 years old or older people living in developing countries, or 65 years old or older people living in developed countries (World Health Organization, n.d.-a). According to the WHO, by 2050, the number of older adults in the world is estimated to reach two billion people, 80 % of whom will live in developing countries. Brazil was estimated to be the

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fifth country in the absolute numbers of older adults by 2015, behind countries like China, India, the United States of America, and Indonesia (World Health Organization, n.d.-b).

The adoption of the concepts related to improving the quality of life at an advanced age has been incorporated into the public health system policies to develop continuous and preventive strategies to achieve a quality of life for older adults (Hootman et al., 2012). The adoption of a regular physical activity practice is one of the factors known to improve the quality of life in older adults. It increases the general physical rate, improves health indicators, and stimulates social living (Garatachea et al., 2015).

Although several clinical studies are being done with resveratrol, only a few are dedicated to assessing its action on anthropometric parameters, heart measurements, and serum biochemical parameters of older adults (Olesen et al., 2014). Notwithstanding, studies focusing on the groups who practice regular physical activity are scarce. Considering that the continuous practice of physical activity ameliorates the natural physical decline that emerges with aging (Kaliman et al., 2011), the consumption of natural compound resveratrol, an anti-inflammatory drug, can be an adjuvant to improving the quality of life associated with the regular practice of sports.

Intense exercise contributes to the imbalance between reactive oxygen species (ROS) production and antioxidant defenses, resulting in oxidative stress. Resveratrol is associated with improvements in mitochondrial function and biogenesis and the protection against cardiovascular disease, cancer, cholesterol, and type II diabetes. Physical exercise provides resistance against oxidative stress, damage, and cell death of skeletal muscle cells (Baur and Sinclair, 2006; Lagouge et al., 2006). One of the benefits of resveratrol intake includes the direct elimination of ROS (Stojanovic et al., 2001), the inhibition of xanthine oxidase (Jia et al., 2008)' and the activation of intracellular pathways that improve metabolism and induce mitochondrial biogenesis (Baur and Sinclair, 2006). Although a substantial amount of studies related to resveratrol use are available in the literature, not much has been established so as the compound can be used as adjuvant therapy, particularly related to old individuals.

Based on the limited amount of information regarding the use of resveratrol by older adults who regularly - or not - practice exercise, a prospective comparative study based on convenience and non-probability sampling was conducted to prospect for alterations in anthropometrical parameters, heart measures, blood analytes, leukogram, and plaquetogram indices.

2. Material and methods

2.1. Participants

A total of 43 female participants aged between 60 and 80 years old were included in the pilot study in early 2017. The participants were enrolled at a sports Community Center in the City of São Paulo, signed an informed consent form, and received a copy of the document. The number of participants was defined based on previous works (Jambassi Filho et al., 2020; Ferreira et al., 2015). Participants underwent anamnesis, physical examination, and anthropometry examinations before the experiment's beginning and again at the end of the treatment period, which spanned from April to July 2017.

2.2. Inclusion and exclusion criteria

The present study was performed with older adult women who exercised or not. Participants were enrolled in the study if they (a) were women over 60 years old or older at enrolment; (b) regularly attended moderate-intensity physical activities, here considered as three times a week, for 30 min; (c) were sedentary – to be considered a reference group; (d) showed interest in participating in the experiment; (e) showed the ability to comprehend and understand the procedures that will be performed; (f) had good memory (or valuable resources to remember) and autonomy, which were evaluated during the anamnesis by the physician; (g) showed the ease of communication and familiarity with the terms to be adopted; (h) were not under chronic severe inflammatory diseases requiring the constant intake of anti-inflammatory drugs.

The exclusion criteria were (a) being an eventual practitioner of physical activity, which are those exercising two or fewer times in the week; (c) having problems with decreased coagulation; (d) under thrombolytic medication or taking acetylsalicylic acid; (e) suffering from myocardial infarction; (f) cardiovascular diseases requiring the ingestion of non-steroidal anti-inflammatory drugs, such as acetylsalicylic acid; (g) a stroke patient who is under treatment with thrombolytics; (h) a patient taking warfarin or any medicines that cause bleeding.

2.3. Resveratrol and placebo

Resveratrol (Forn Fagron lot17A17B050013849, made in 01/31/2016, val. 10/03/2018, Shanghai, China) was encapsulated in gelatine capsule size 1 shells which were large enough to support the daily dose of 300 mg each. The placebo also consisted of identical gelatine capsules containing 300 mg of starch instead of resveratrol. The capsules were produced and dispensed in an amount sufficient for the 60 days of treatment (Farmácia Amaranthus, São Paulo, Brazil). The medicines were individually prepared to be distributed to each group of participants. To establish a single-blind trial, capsules of the same colour but different shades identified both groups, containing or not resveratrol. The medicines were dispensed to the participants, who received them according to sortition made by dice, where odd numbers represented the placebo groups and even numbers represented the resveratrol groups. Sortition was performed by an independent third party supporting the principal researcher of the study during the first anamnesis.

2.3.1. Resveratrol dose preamble

The establishment of the resveratrol dosage of 300 mg/day was adopted in the present study. The participants' age was based on multiple studies, despite how controversial the experimental designs were among themselves, revealing the absence of a standardized protocol related to resveratrol intake, mainly referring to older adult women.

Some studies have been carried out with resveratrol administration with doses spanning from 300 mg (Wong et al., 2016a) to 500 mg (Bedada et al., 2016; Turner et al., 2015), or doses as high as 5 g per day (Yiu et al., 2015) without referencing safety. Concerning the resveratrol daily intake period, some studies adopted 12 weeks (Chow et al., 2014),. In comparison, others adopted a period as long as 52 weeks of resveratrol administration (Turner et al., 2015), again, without referring to the safety of drug use. A study with 30 men (12 participants) and women (18 participants) was conducted for 12 weeks of 500 mg/day resveratrol intake. Among other conclusions, they verified that resveratrol intake did not diminish cardiovascular risk (Alway et al., 2017) as expected due to its antioxidant activity. The participants' age range is quite broad in several studies, ranging from 40 to 80 years old (Bedada et al., 2016) or 49 to 78 years old (Wong et al., 2016b). In the present study, participants are between 60 and 80 years old (mean 66.4 $\pm$ 1.013 years old, life-expectancy to women 76 years old), which is a narrow age span compared to other studies.

Because the participants are older adults and consequently present a high possibility of decreased metabolic activity (Amarya et al., 2014), the dosage of resveratrol intake must be carefully chosen. For that reason, the dose of 300 mg daily for 60 days, although lower than the doses usually tested in adults, was adopted in the present study. According to current findings, the resveratrol intake protocol used in the present study induced alterations in the blood pressure and in some of the blood cell parameters of older adult women.

2.4. Clinical studies

The study followed the ethics principles suggested by the Universidade Paulista Ethics Committee, guided by the current standards from SISNEP/MCTI, and was conducted under approval number CEP/CAAE 61528216.1.0000.5512/08.06.2017.

2.5. Clinical evaluation and support during the study

At enrolment (day 1), participants underwent the first clinical evaluation that included acquiring personal data and anamnesis, anthropometric data acquisition such as weight, BMI, waist circumference, systolic and diastolic pressure, and heart rate. The serum levels of glycemia, uric acid, triglycerides, and total cholesterol were accessed. A red series considering erythrocytes, hematocrits, MCV, HCM, CHCM, and RDW, and a white series considering leucocytes, segmented, eosinophils, basophils, lymphocytes, and monocytes were also assessed. After this, the participants started resveratrol intake for 60 days. On day 60, participants underwent the last clinical evaluation, and the parameters were assessed one last time. The participants underwent a weekly personal physical examination to evaluate their well-being during the study, particularly regarding possible symptoms related to resveratrol intake. The baseline characteristics of the participants at enrolment (day 1) were obtained and are presented in Table 1.

2.6. Experimental design

The experimental design of the present study followed the established norms for a pilot prospective, comparative clinical study based on convenience, non-probability sampling. The test was conducted with older adult women that practice or not physical exercises. Resveratrol and the placebo were prepared so that the participant could not identify them. A third person packed gelatine capsules, was not involved in the research, did not have direct contact with the administrator or any participants, and identified the medicine packs with sequential numbering. After sortition, the total amount of gelatine capsules stipulated for a 60-day treatment was dispensed to the participant. The medicine pack number ID was annotated in the participant file.

The participants were separated into four groups: (a) the control group: sedentary participants (named sEsR; n = 12); (b) sedentary and resveratrol group (named sEcR; n = 11); (c) the group practicing physical activity (named cEsR; n = 10); and (d) physical activity practitioners and resveratrol (named cEcR; n = 10). The blood samples were taken at baseline (one day before treatment initiation) and the end of the 60-day treatment (one day after treatment end). The baseline data obtained from the weight, body mass index, waist circumference, blood pressure, heart rate, blood cholesterol, fasting glucose, uric acid, triglycerides, total cholesterol and ferritin, hemogram, leukogram, and plaquetogram were compared to the same parameters evaluated after 60 days of treatment. The raw data is presented in the supplementary material.

2.7. Statistical analyses

The statistical analyses were performed using GraphPad Prism version 7.0. The normality was assessed using the Shapiro-Wilk test. The presence of outliers was assessed for each variable by the ROUT Method (aggressivity of Q = 5 %). The homogeneity of the variances was evaluated using Levene's test. The Kruskal-Wallis or the two-way ANOVA tests were run depending on normality, and the significance of the main effect of the sample was investigated using the Dunn's or the Tukey post-tests. The significance level was considered as $\alpha < 0.05$ (Zar, 2010). Data can be accessed in the supplementary material.

3. Results

The study included 43 participants, and the baseline characteristics of the participants at enrolment were (given in mean ± standard error): Mean age of the participants was 66.4 ± 1.013 years old. In contrast, their mean height was 1.575 ± 0.01043 m which means that the participants are slightly taller than the Brazilian average (compared to 1.55 m). The mean weight was 65.05 ± 1.417 kg at the beginning of the study, meaning that the participants were within the weight (compared to the Brazilian average of 62.6 kg). The mean weight at the end of the

Table 1
Baseline and end of experiment characteristics of the total participants enrolled in the study related to the influence of 300 mg/day/60 days resveratrol oral intake and exercise practice in older adult women aged 60 to 80 years old. Shapiro-Wilk test was applied to verify normality, and the one-group *t*-test was done to evaluate the status of the participants in relation to the population; official data were used as theoretical means (IBGE (2021), WHO (2021), and World Bank (2021)). Significance at $\alpha < 0.05$.

Baseline characteristics						
	References*	Mean	SE	t	df	P
Age (years)	76	66.4	1.013	9.469	41	<0.000
Height (m)	1.55	1.575	0.0104	2.363	42	0.0228
Weight (kg)	62.6	65.05	1.417	1.729	42	0.0912
BMI	22 to 27	26.01	0.5539	1.786	41	0.0814
Waist circumference (cm)	88	84.47	1.665	2.123	42	0.0397
WHtR B	0.5	0.5379	0.0118	3.208	42	0.0026
Heart rate (bpm)	70	75.09	1.792	2.842	42	0.0069
SBP (mmHg)	120	126.3	1.665	3.772	42	0.0005
DBP (mmHg)	80	80.47	1.151	0.4043	42	0.6881

End of experiment characteristics						
	References*	Mean	SE	t	df	p
Weight (kg)	62.6	65.1	1.515	2.188	42	0.0343
BMI	22 to 27	26.38	0.6124	1.018	41	0.3147
Waist circumference (cm)	88	85.6	1.783	1.343	42	0.1864
WHtR A	0.5	0.5452	0.0126	3.6	42	0.0008
Heart rate (bpm)	70	76.35	1.903	3.336	42	0.0018
SBP (mmHg)	120	128.6	1.65	5.215	42	<0.0001
DBP (mmHg)	80	84.19	1.421	2.946	42	0.0052

Legend. * = IBGE/WHO/WB parameters used as the theoretical means used in the one group t-test; SE = standard error; inf = inferior; sup = superior; BMI = body mass index; WHtR = waist-to-height ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure.

study was 65.91 ± 1.515 kg. The BMI at the enrolment was 26.01 ± 0.5539 kg/m^2, and at the end was 26.38 ± 0.6124 kg/m^2, compared to 22 to 27 expected to the age of Brazilian Older Adult women. The waist circumference mean was 84.47 ± 1.665 cm at the beginning of the study and was 85.60 ± 1.783 cm observed at the end of the study, as compared to 22 to 27 expected for the age. The waist-to-height ratio (WtHR) obtained from the participants at the enrolment was 0.5379 ± 0.01181 and at the end of the study was 0.5452 ± 0.01256. Heart rate was similar during the study (begin 75.09 ± 1.792 and end 76.35 ± 1.903, compared to 70 bpm), as was the systolic heart rate (begin 126.30 ± 1.665/80.47 ± 1.151 and end 128.60 ± 1.65/84.19 ± 1.421, compared to an average of 120 for the age). Diastolic blood pressure was within normality at the begin (mean 80.47 ± 1.151 mmHg) and at the end (mean 84.19 ± 1.421 mmHg) of the experiment, compared to usual average 80.

The administration of 300 mg resveratrol per day for 60 days did not cause any significant changes in the parameters accessed in the experiment, besides blood pressure, HCM, eosinophils, segmented, basophils, and lymphocytes.

According to the results (Fig. 1), systolic ($K\text{-}W_{(8,\ 86)} = 23.03$; $p = 0.0017$ blood pressure were lower in the cScR participants before they took resveratrol, in relation to groups sEsR before and after resveratrol intake or sEcR after receiving resveratrol ($p = 0.0305$, $p = 0.0185$, and $p = 0.0120$, respectively). Diastolic blood pressure showed significant differences cScR ($K\text{-}W_{(8,\ 86)} = 16.36$; $p = 0.0221$) between cEcR before receiving resveratrol and sEcR after receiving resveratrol, $p = 0.0241$).

Fig. 1 shows the significant results obtained for some parameters. Regarding red blood cells and their indices, MCH showed significant differences ($K\text{-}W_{(8,\ 86)} = 16.65$; $p = 0.0198$) among groups, and sEcR were lower than cEcR ($p = 0.0472$) before the beginning of the experiments. RDW has also shown statistical differences ($K\text{-}W_{(8,\ 86)} = 43.43$; $p < 0.0001$), and it becomes clear that as exercise and resveratrol are introduced in the analysis as factors, there is an increase in the RDW (red cell distribution volume and width –significances between groups are disposed of in Fig. 1). Concerning the white blood cells, differences were observed for eosinophils ($K\text{-}W_{(8,\ 86)} = 19.36$; $p = 0.0071$), and sEsR was higher than cEsR before the experiments ($p = 0.0500$), while for segmented cells, sEcR after the experiments were higher than cEcR before the experiments ($p = 0.0459$). Basophils were higher in the groups without exercise or resveratrol before the experiments compared to the groups where the participants exercised and took resveratrol (significances disposed of in Fig. 1). Finally, lymphocytes were diminished in the groups that exercised and took resveratrol (significances disposed of in Fig. 1). No statistical differences were observed for the other parameters.

Despite statistical differences were observed, the means were not outside the normal range, according to the reference values adopted in the anthropometric parameters for adults (disposed in Table 1 as reference values) or in the biochemical analyses (erythrocyte: 3.9–5.3 millions/mm^3; haematocrit: 36.0–48.0 %; hemoglobin: 12.0–16.0 g/dl; MCH: 27.0–33.0 pg; MCHC: 32.0–36.0 g/dl; MCV: 80–100 μ^2; RDW: 11.0–14.5 %, leukocyte: 3600–11,000 cells/mm^3; segmented: 1700–8200 cells/mm^3; eosinophil: 20–500 cells/mm^3; basophil: 0–200 cells/mm^3; lymphocyte: 1000–4500 cells/mm^3; monocyte: 100–1000 cells/mm^3; platelets: 140000–400,000 cells/mm^3).

4. Discussion

In order to establish the anthropometric characteristics of the participants, a one-group *t*-test was performed, and data were compared to parameters adopted by WHO (World Health Organization, n.d.-a; World Health Organization, n.d.-b) for low and middle-income countries and by the Brazilian Government/DATASUS (DATASUS, n.d.). The participants are slightly taller than the average. At the beginning of the experiments, participants were within the weight average, BMI within the average for the age. At the end of the experiment, there was weight, WHtR, heart rate, systolic blood pressure and diastolic blood pressure improvements. The following analyses were made to establish the differences among groups considering each participant's initial and final data. The authors understand that the group of participants showed no significant discrepant differences in body constitution (height, weight, BMI) or social aspects as smoking and alcohol use (Pinkhasov et al., 2010) that lead to unprecise data comparison.

In the present report, we observed that 300 mg/day/60 days resveratrol consumed by sedentary older adult women elevates blood pressure, as both the systolic and diastolic blood pressure values were improved in the group that did not exercise and received resveratrol, compared to the groups that exercised. Although elevated, it remained within the normal range expected for older adults. According to the American College of Cardiology Foundation, older adults in ages ranging from 65 to 79 years old are expected to show BP of 140/90 mmHg, and unclear what to consider in people aged >80 years old (Aronow et al., 2011). The practice of physical exercise is directly related to improving cardiovascular conditions in all ages, particularly after 60. Nonetheless, some authors stated that the consumption of resveratrol by older adult practitioners of physical exercises could decrease cardiovascular improvement caused by concomitant physical activity (Alway et al., 2017; Gliemann et al., 2013),. Our findings support that resveratrol can interfere with the blood pressure of sedentary old adult women. So, attention may be given to patients within this age.

Resveratrol is a known antioxidant compound, and it was expected to observe some alteration in antioxidant processes within the older adult bodies. Nonetheless, significant differences in MCH and RDW parameters were observed in the groups that exercised and took resveratrol, commonly associated with anemia – one of the leading causes of death among older adults (Lanier et al., 2018), thalassemia, and other blood diseases. No alterations in hemoglobin or ferritin were observed in the present study, although high MCH and RDW were observed in the exercise/resveratrol groups. Again, those parameters differed among the groups but remained within the normal range (Romano et al., 2020).

After the treatments, the white blood cell parameters that resulted in statistically significant differences, eosinophils, segmented cells, basophils, and lymphocytes, were diminished in the exercising and resveratrol groups. It means that exercise and resveratrol somehow contributed to the general condition related to the body's engagement to fight inflammatory processes, which are involved in many disorders that affect older adults and implicate this group's quality of life (Bondy et al., 2021).

Results shown in the present report highlights the urge of focusing in evaluating supplementary food intake by old women, despite they are sports active or sedentary. Although limited to 43 participants, significant outcomes were achieved, and instigate further investigations, especially those related to variations in the time spanning resveratrol intake, resveratrol daily dosage, different kinds and frequency of physical exercise plus resveratrol intake, and expand the study to a larger number of participants, both old females and males.

In the present work, we observed that resveratrol consumption by sedentary older women led to dysregulated blood pressure, despite the use of 300 mg/day/60 days resveratrol can benefit the older individuals, mainly when related to the body's engagement in administrating inflammation processes, leading to a better quality of life. Present findings evidenced that more accurate evaluations regarding the influence of resveratrol intake over blood pressure must be carried out in a wide range of participants. Still, resveratrol consumption must be discussed with a health professional and not be inadvertently self-administered due to its influence on blood pressure in older adult women.

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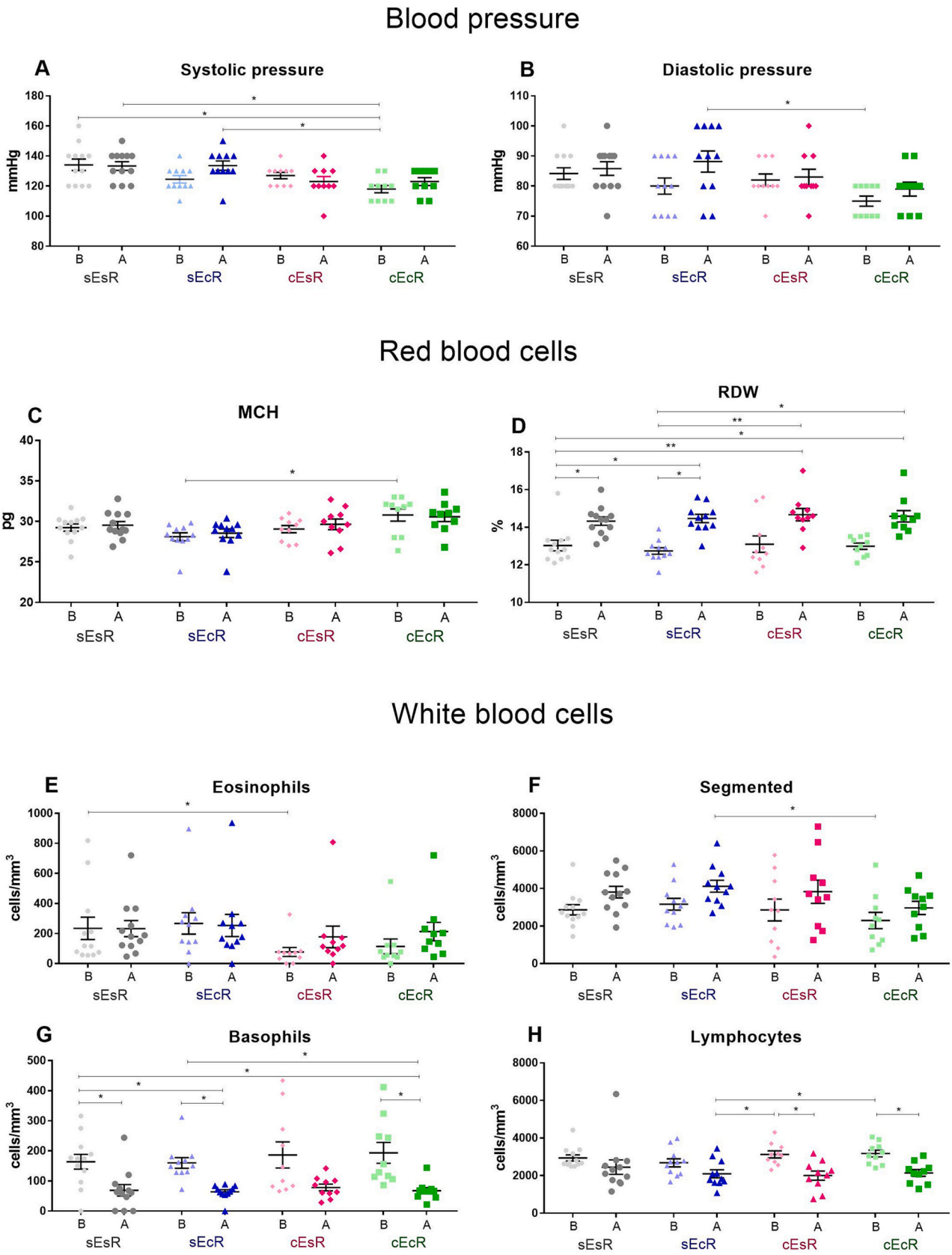

Fig. 1. Statistical differences in parameters observed from sedentary and physically active older adults with and without 300 mg/day/60-day resveratrol intake.

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Credit authorship contribution statement

Ana Lúcia Anauati Nicolau (Sports and Exercise Physician Doctor from São Paulo Municipality working in Community Centers that attends older adults from "Zona Sul" São Paulo) – conducted the clinical approach during her Doctorate in Universidade Paulista Giovani Bravin Peres (Biomedical Professional) – conducted the Statistics Jefferson de Souza Silva (Biomedical Professional) – auxiliar to experimental phase Sandra Heloísa Nunes (Biomedical Professional) – auxiliar to delineate the experiment design Taís Masotti Lorenzetti Fortes (Nurse) - auxiliar to delineate the experiment design Ivana Barbosa Suffredini (Pharmacist) – supervised the work, wrote the manuscript.

All the co-authors have read and approved the present version of the manuscript.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2022.111883.

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