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Improvements in antioxidant status after agraz consumption was associated to reductions in cardiovascular risk factors in women with metabolic syndrome

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ABSTRACT

In this study were evaluated the effects of the chronic consumption of agraz (*Vaccinium meridionale*) on antioxidant status and oxidative stress markers in 40 women with metabolic syndrome (MetS) (47.2 ± 9.4 years) through a double-blind, crossover design study, in which participants consumed daily agraz or placebo during 4 weeks, separated by a 4-wk washout period. At the end of each intervention period, endogenous antioxidant enzymes activity, serum total antioxidant capacity (TAC) (ferric reducing ability of plasma [FRAP]; Oxygen Radical Absorbance Capacity [ORAC] and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) [ABTS]), and oxidative stress markers (Oxo-2'-deoxyguanosine (8-OHdG) and F2-isoprostane) were determined. Women who increased endogenous antioxidant enzymes activity and serum TAC after agraz consumption, compared to placebo, significantly reduced oxidative stress markers, total cholesterol, LDL-cholesterol (LDL-c) levels, and waist circumference, demonstrating beneficial effects in the group of women in whom antioxidant parameters increased after agraz consumption, evidencing an individual variability in response to the beverage consumed.

Mejoras en el estado antioxidante después del consumo de agraz se asociaron con reducciones en factores de riesgo cardiovascular en mujeres con síndrome metabólico

RESUMEN

En este estudio se evaluaron los efectos del consumo crónico de agraz (*Vaccinium meridionale*) sobre el estado antioxidante y los marcadores de estrés oxidativo en 40 mujeres con síndrome metabólico (SM) (47,2 ± 9,4 años) mediante un estudio de diseño cruzado, doble ciego, en el que los participantes consumieron diariamente agraz o placebo durante 4 semanas, separados por un período de lavado de 4 semanas. Al final de cada período de intervención se midió la actividad de las enzimas antioxidantes endógenas, la capacidad antioxidante total en suero (capacidad reductora férrica del plasma [FRAP]; la capacidad de absorción de radicales de oxígeno [ORAC] y 2,2'-azino-bis (3-etilbenzotiazolina) -Ácido 6-sulfónico) [ABTS]) y marcadores de estrés oxidativo (Oxo-2'-desoxiguanosina (8-OHdG) y F2-isoprostano). Las mujeres que aumentaron la actividad de las enzimas antioxidantes endógenas y la capacidad antioxidante total sérica después del consumo de agraz, en comparación con el placebo, redujeron significativamente los marcadores de estrés oxidativo, el colesterol total, los niveles de colesterol LDL (c-LDL) y el perímetro abdominal, demostrando efectos benéficos en el grupo de mujeres que aumentaron los parámetros antioxidantes luego del consumo de agraz, evidenciando una variabilidad individual en respuesta a la bebida consumida.

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Andean berry; antioxidant enzymes; oxidative stress; total antioxidant capacity; *vaccinium meridionale*; superoxide dismutase; catalase; glutathione peroxidase

PALABRAS CLAVE

Baya de los Andes; enzimas antioxidantes; estrés oxidativo; capacidad antioxidante total; *Vaccinium meridionale*; Superóxido dismutasa; catalasa; glutatión peroxidasa

1. Introduction

People with metabolic syndrome (MetS) have an increased risk to develop cardiovascular diseases (CVD), which represent the leading cause of mortality in the world (Roth et al., 2017). This syndrome is defined by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATPIII) as the presence of three or more cardiovascular risk factors (CVRF) including high waist circumference, high blood pressure, elevated levels of fasting blood triglycerides (TG) and glucose levels, and low high-density lipoprotein cholesterol (HDL-c) levels (Alberti et al., 2009).

In addition to these CVRF, people with MetS also presents oxidative stress (Bhutia et al., 2018), which has been defined

as an unbalance between the generation of oxidative species and the antioxidant status, in favor of the oxidative species (Betteridge, 2000). In this sense, compared with people without MetS, people with MetS have higher lipoperoxidation and oxidative DNA damage (Bhutia et al., 2018), and a reduced endogenous antioxidant enzymes activity such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) (Sabir et al., 2016). In addition, total antioxidant capacity (TAC)-defined as the “global antioxidant efficiency mirroring the multiple aspects of redox interactions” (Serafini & Del Rio, 2004, p. 106)-, is significantly reduced as the components of MetS increase (Bakhtiari et al., 2017). All these alterations on the antioxidant status are significantly related to CVRF (Brunelli et al., 2017).

Contrarily, it has been demonstrated that an antioxidant-rich diet like increased fruit and vegetables consumption has beneficial effects on the reduction of CVD risk (Kim et al., 2016) associated with increases in blood TAC (Nälsén et al., 2006), endogenous antioxidant enzyme activity (Shiraseb et al., 2015) and reduction of lipids, insulin resistance, inflammation (Kim et al., 2016), and hypertension (Villaverde et al., 2019), among other CVRF. These beneficial effects have been related to bioactive compounds such as polyphenols, a group of secondary metabolites of plants, and common antioxidants in a great variety of foods (Pérez-Jiménez et al., 2010). In this sense, dietary polyphenol intake has shown to reduce the prevalence of MetS components (Zujko et al., 2018).

Vaccinium meridionale also called agraz, is an important source of polyphenols (total phenol content between 609 ± 31 mg to 758.6 ± 62.3 Gallic Acid equivalents/100 g fresh fruit), specially anthocyanins, with a high TAC (Garzón et al., 2010; Gaviria et al., 2009). In 2018, a study conducted with rats evaluating the effects of this fruit in ischemia-reperfusion, demonstrated that agraz significantly improved systolic and diastolic function and antioxidant capacity, increased SOD and CAT activity and reduced lipid peroxidation (Shen et al., 2018). Given these characteristics, agraz has generated great interest for its potential effects on human health. Currently, there is very limited information in humans about the effects of agraz on endogenous antioxidant enzymes activity, serum TAC and its relationship with CVRF. Therefore, we aimed to evaluate the effects of the chronic consumption of agraz on antioxidant and oxidative stress markers in women with CVRF, i.e. with MetS.

2. Methods

2.1. Study population

In this study, 40 women from Medellín- Colombia, between 25 and 60 years old and with MetS, according to the NCEP ATP-III, were included (Alberti et al., 2009). MetS was defined as having three or more of the following risk factors: waist circumference ≥ 88 cm; triglycerides ≥ 150 mg/dL; HDL-c < 50 mg/dL; blood pressure $\geq 130/\geq 85$ mmHg, and fasting plasma glucose ≥ 100 mg/dL. Exclusion criteria included the presence of kidney disease, heart disease, diabetes; having TG ≥ 500 mg/dL, fasting plasma glucose ≥ 126 mg/dL, low-density lipoprotein cholesterol (LDL-c) ≥ 190 mg/dL, blood pressure $\geq 140/90$ mm Hg; smoking; taking anti-inflammatory, lipid-lowering, hypoglycemic, and anti-hypertensive medications; being pregnant or planning to become pregnant; consuming supplements or nutraceuticals and the intake of more than 20 g alcohol per day. This study was conducted according to the Declaration of Helsinki and it was approved by the Human Bioethics Committee of the Sede de Investigación Universitaria, University of Antioquia (Act No. 15-35-558-02). Written informed consent was obtained from all subjects.

2.2. Dosage information

Agraz fruits were bought in the east of Antioquia (Colombia), and processed in a food laboratory from the University of Antioquia to produce a lyophilized product to preserve its bioactive compounds. The daily dose of the agraz beverage

was prepared with 7.38 g of lyophilized product dissolved in 200 mL of pure water, which was equivalent to the total phenols present in 200 g of fresh agraz fruit (1,027.9 mg Gallic Acid equivalents in 200 mL). The placebo was designed by food engineers from the University of Antioquia using food-grade ingredients to simulate organoleptic and physicochemical characteristics of the agraz beverage, but lacking polyphenols. The daily dose of placebo was also 200 mL. Microbiologic and physicochemical characterization of the agraz and placebo beverages have been described previously (Quintero-Quiroz et al., 2019).

2.3. Study design

This was a double-blind, placebo-controlled, crossover design study. The method used for the beverage assignment was the alternating quasi-randomization allocation method, in which, one subject received the placebo, and the next received the agraz beverage, and so on. The total duration of the study was 12 weeks: four weeks of agraz or placebo consumption, 4 weeks of washout, and finally 4 weeks of the alternate treatment (Figure 1). During the study, women were asked to avoid consumption of polyphenol-rich foods, such as grapes, wine, green tea, other berries, among others. To verify the daily consumption of the beverage in each intervention period and the abstinence of polyphenol-rich foods, a questionnaire was used (Barona et al., 2012). Adherence less than 70% was considered a criterium to withdraw a volunteer from the study. Likewise, participants were asked to keep their usual physical activity and diet throughout the study. To verify compliance with this criteria, physical activity was monitored through a seven-day physical activity record at the baseline and end of each intervention period. In addition, diet was also evaluated using a modified food frequency questionnaire (FFQ) designed and validated previously in the University of Antioquia (Álvarez Monsalve & González Zapata, 2011). This FFQ included nine different food groups and 143 foods, allowing to determine the kilocalories and macronutrients consumed in the last month; it was completed at baseline and end of each intervention period.

2.4. Sample size

The sample size was estimated with the software Epidat (version 3.1), based on the results of a previous research with similar protocol, in which a sample size of 40 subjects was considered adequate to provide sufficient statistical power to detect a statistically significant difference in systolic blood pressure (one of MetS parameters) (Barona et al., 2012). Considering an expected mean difference of 6 mmHg after four weeks of polyphenol-rich beverage consumption, compared to placebo, with 95% confidence, and a minimum power of 80%, the software yielded a minimum necessary size of 40 subjects.

2.5. Anthropometrics, blood pressure, blood and 24-hour urine collection

Waist circumference and blood pressure were determined as previously reported (Marín-Echeverri et al., 2018). Venous blood was obtained after 12 h of overnight fasting using serum separator (yellow-topped) tubes. Then, samples were

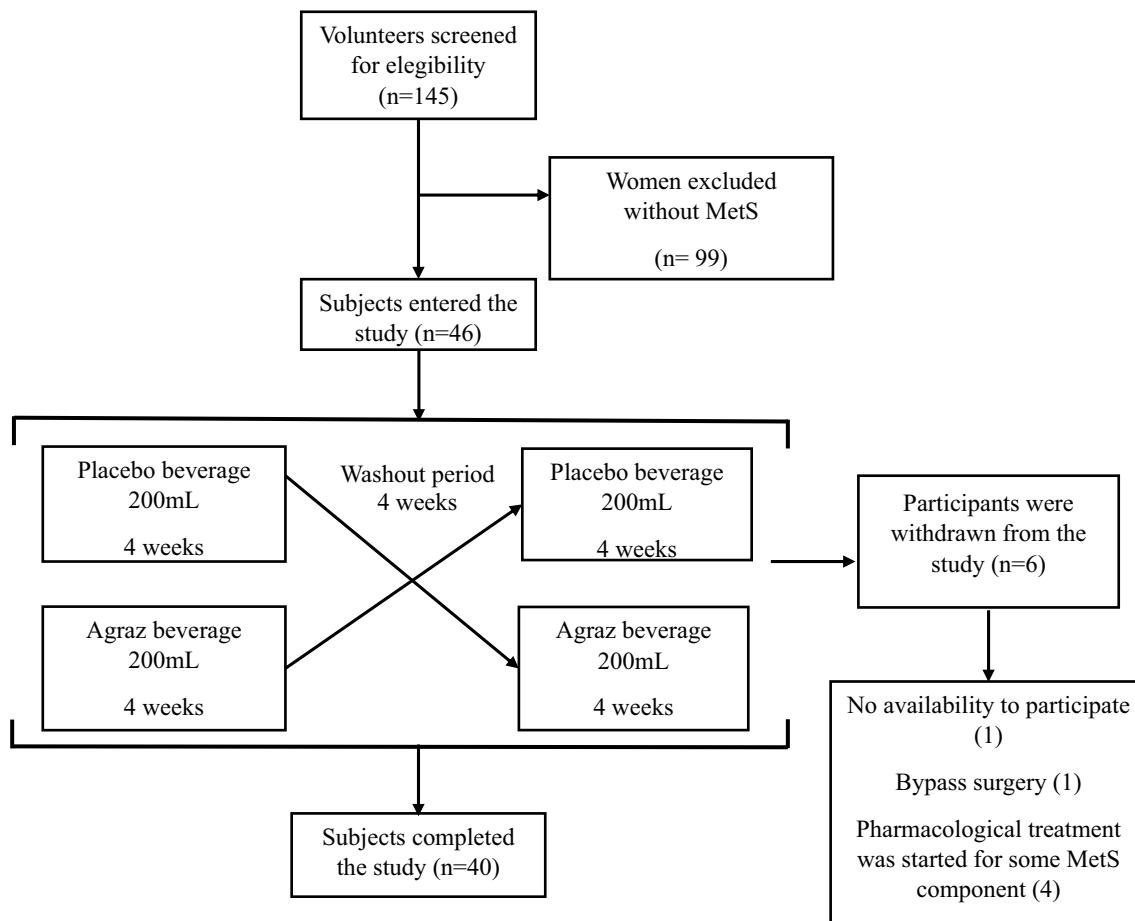


Figure 1. Study protocol.

Figura 1. Protocolo del estudio.

centrifuged at $2000 \times g$ for 10 min, the serum was separated and stored at -70°C . The participants were provided with a clean container and asked to collect the urine during 24 hours, discarding the first urine in the morning, starting with the second urine and ending when the 24 hours of collection were completed. Participants kept the container with the urine at 4°C during the collection period. Urine samples were stored at -70°C . Urinary creatinine was determined in the 24-h urine sample to normalize the values of urinary F2-isoprostanes and 8-OHdG, and the results were expressed as ng/mg creatinine.

2.6. Endogenous antioxidant enzymes activity

The endogenous antioxidant enzymes activity was determined at the end of each intervention period. The activity of SOD was determined with the commercial OxiSelect™ kit Superoxide Dismutase Activity Assay (Cell Biolabs, Inc, CA, San Diego, USA), following manufacturer's instructions. Results were expressed in U/mL. Likewise, CAT activity was measured using the OxiSelect™ Catalase Activity Assay Kit (Cell Biolabs, Inc, CA, San Diego, USA) following manufacturer's instructions. Results were also expressed in U/mL. Finally, GPx activity was determined with the Glutathione Peroxidase Assay Kit (Cayman Chemical, MI, USA), following manufacturer's instructions. Results were expressed in nmol/min/mL.

2.7. Serum total antioxidant capacity (TAC)

Serum TAC was determined at the end of each intervention periods, using different methods:

ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)] was determined using a modified method described by Re et al. (1999) Briefly, ABTS cation radical (ABTS $^{\bullet+}$) was generated with ABTS 7 mM and potassium persulfate 2,45 mM, incubating by 12–16 hours at room temperature. Then, ABTS was dissolved in PBS 5 mM pH 7.4 (to obtain an absorbance of $0.70 (\pm 0.02)$ at 734 nm at room temperature). This method was processed in 96-well microplate, in which 250 μL of ABTS solution was mixed with 2.5 μL of serum or Trolox standards (concentration 0–2000 μM) by triplicate. After 5 minutes' incubation at room temperature, the absorbance was measured at 734 nm using a microplate reader (Multiskan Go, Thermo Scientific, MA, Walthamcity, USA). Concentrations were determined using the standard curve and results were expressed in terms of μmol Trolox equivalents (TE)/mL.

The ferric reducing ability of plasma (FRAP) was measured using a modified method of Benzie and Strain (1996) in which FRAP reagent was prepared with 25 mL of 0.3 M acetate buffer-pH 3.6, 2.5 mL of TPTZ (2,4,6-tri-pyridyl-s-triazine) 10 mM and 2.5 mL of ferric chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) 20 mM. In a 96-well microplate, 10 μL of serum diluted 1:3 with H_2O , Trolox standards (concentration 0–400 μM) or reagent blank was mixed with 300 μL of freshly prepared FRAP warmed at 37°C . The plate was incubated at

37°C for 8 minutes and absorbances were measured at 593 nm using a microplate reader (Multiskan Go, Thermo Scientific, MA, Walthamcity, USA). All reactions were processed in triplicate. Results were expressed in terms of $\mu\text{mol TE/mL}$.

ORAC (Oxygen Radical Absorbance Capacity) was determined using a modified method of Ou et al. (2001) in which radical AAPH (2,2'-Azobis(2-amidinopropane) dihydrochloride) generates a peroxy radical, which oxidizes fluorescein, losing its fluorescence. In presence of serum antioxidants, the loss of fluorescence decreases. Serum samples were diluted 1:400 using phosphate buffer (pH 7.3) and Trolox was used as a standard (concentration 0–100 μM). The kinetics of oxidative degradation of fluorescein was determined using the differences in areas under the curves (AUC) at the excitation and emission wavelength of 485 and 520 nm, respectively. Results were expressed in $\mu\text{mol TE/mL}$ and were obtained using the following formula

$$\frac{\mu\text{molTE}}{\text{mLsample}} = \frac{\mu\text{mol (of the curve)} * \text{DF} * 1\text{L}}{L * 1000\text{mL}}$$

DF: Dilution factor

2.8. Oxidative stress markers

Oxidative stress markers were determined at the end of each intervention period. 8-Oxo-2'-deoxyguanosine (8-OHdG) and F2-isoprostane levels were determined in 24-hour urine, using the commercial kit 8-hydroxy 2 deoxyguanosine ELISA Kit (Abcam, Cambridge, MA, USA) and OxiSelect™ 8-iso-prostaglandin F2 ELISA kit (Cell Biolabs, Inc., San Diego, CA, USA), respectively, following manufacturer's instructions. Results were expressed in terms of ng/mg creatinine.

2.9. Statistical analysis

To evaluate data distribution, Shapiro Wilk test was used. Variables with non-normal distribution were log-transformed and verified again with Shapiro Wilk test. Data are presented as mean and standard deviation (SD). To determine the differences between the results obtained at the end of each intervention period, a paired T-test was implemented. In addition, changes after agraz consumption compared to placebo were calculated subtracting the

results obtained after agraz consumption minus those obtained after placebo consumption. Thus, it was possible to determine increases or reductions in each variable, and to determine the association of the changes among variables through one-way ANCOVA, with adherence as a covariate. All analyses were done using SPSS version 21 for Windows (SPSS, IBM Corporation, 2012). Differences with a value of $p < .05$ were considered significant.

3. Results

Forty women with MetS (47.2 ± 9.4 years old) were included in this study. The baseline metabolic syndrome characteristics for these women have been previously reported (Espinosa-Moncada et al., 2018). There were no statistical differences regarding these clinical parameters between the baseline data of each consumption period ($p > .05$) (Espinosa-Moncada et al., 2018). Adherence was around 95%, indicating an adequate intake of each beverage (placebo and agraz) and abstinence from polyphenol-rich foods. In addition, no statistical differences were found in diet (kilocalories and macronutrients intake) and physical activity during the whole study ($p \geq 0.05$).

There were no statistical differences in endogenous antioxidants enzymes and serum TAC measured by ABTS, FRAP and ORAC, after 4 weeks of consuming agraz compared to placebo ($p < .05$) (Table 1).

Regarding oxidative stress markers, we previously had reported a significant reduction in 8-OHdG of -0.27 ± 0.72 ng/mg creatinine after agraz consumption compared to placebo ($p = .041$) (Espinosa-Moncada et al., 2018). However, no changes were found in F2-isoprostanes in this group of women.

Interestingly, women who increased SOD activity after agraz consumption ($n = 21$), compared to placebo, significantly reduced oxidative stress markers like 8-OHdG ($p = .022$) and F2-isoprostane ($p = .034$) (Figure 2). Likewise, in those women in whom GPx activity increased after agraz consumption ($n = 18$), compared to placebo, significant reductions in total cholesterol ($p = .023$) and LDL-c ($p = .022$) levels were found (Figure 3). Finally, the increase in serum TAC (determined by ABTS) after 4 weeks of agraz consumption, was significantly associated with waist circumference reduction ($p = .017$) (Figure 4).

Table 1. Antioxidant enzymes activity and serum total antioxidant capacity after 4 weeks of agraz consumption, compared to placebo, in women with metabolic syndrome.

Tabla 1. Actividad de enzimas antioxidantes y capacidad antioxidante sérica total después de 4 semanas de consumo de agraz, comparado con placebo, en mujeres con síndrome metabólico.

Variables	Placebo		Agraz		Δ Change (Agraz-placebo)	Mean \pm SD	p
	n	Mean \pm SD or median (p25-p75)	n	Mean \pm SD or median (p25-p75)			
SOD (U/mL) a	37	228.6 (185.4-266.7)	34	231.4 (196.4-291.7)	14.7 \pm 68.4		0.402
CAT (U/mL) a	37	300.5 (250.6-357.7)	37	296.7 (264-330.6)	7.1 \pm 78.2		0.667
GPx (nmol/min/ml) a	40	84.7 (65.7-148.5)	40	83.5 (59.6-121.2)	-2 (-23.4, 31)		0.670
ABTS (μM Trolox Eq/mL) a	40	2.2 (2.2-2.4)	40	2.3 (2.2-2.3)	0.0 \pm 0.1		0.771
FRAP (μM Trolox Eq/mL) b	40	814.6 \pm 162.5	40	810.2 \pm 176.9	-4.5 \pm 111.3		0.996
ORAC (μM Trolox Eq/mL) b	40	17.3 \pm 4.8	40	17.4 \pm 4.9	0.1 \pm 3.4		0.848

a. T paired or b. Wilcoxon test; * significance $p < 0.05$

a. Prueba T pareada o b. Prueba de Wilcoxon; * significancia $p < 0.05$

Abbreviations: SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; ABTS, 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); FRAP, Ferric reducing ability of plasma; ORAC, Oxygen radical absorbance capacity.

Abreviaciones: SOD, superóxido dismutasa; CAT, catalasa; GPx, glutatión peroxidasa; ABTS, 2, 2'-Azino-bis-(3-etil- benzo-tiazolina-6-acido sulfónico); FRAP, habilidad reductora férrica del plasma; ORAC, capacidad de absorbancia de radicales de oxígeno.

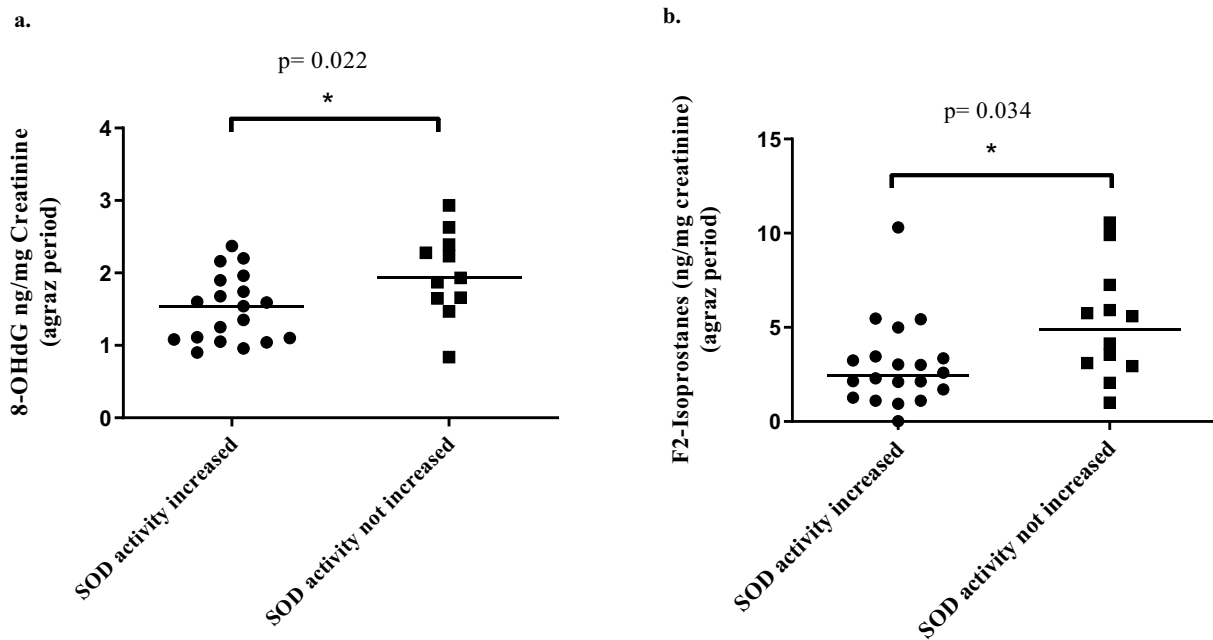


Figure 2. Changes in superoxide dismutase (SOD) activity and effects on oxidative stress markers after 4 weeks of agraz consumption, compared to placebo, in women with metabolic syndrome. (a) Changes in SOD and effects on urinary 8-OHdG. (b) Changes in SOD and effects on 8-isoprostane levels. ANOVA adjusted by adherence. * Significance $p < 0.05$.

Figura 2. Cambios en la actividad de la superóxido dismutasa (SOD) y efectos en los marcadores de estrés oxidativo después de 4 semanas de consumo de agraz, comparado con placebo, en mujeres con síndrome metabólico. (a) Cambios en SOD y efectos en 8-OHdG urinario. (b) Cambios en SOD y efectos en los niveles de 8-isoprostanos. ANOVA ajustada por adherencia. * Significancia $p < 0.05$.

Abbreviations: SOD, superoxide dismutase; 8-OHdG, 8-hydroxydeoxyguanosine. Abreviaciones: SOD, superóxido dismutasa; 8-OHdG, 8-hidroxiideoxiguanosina.

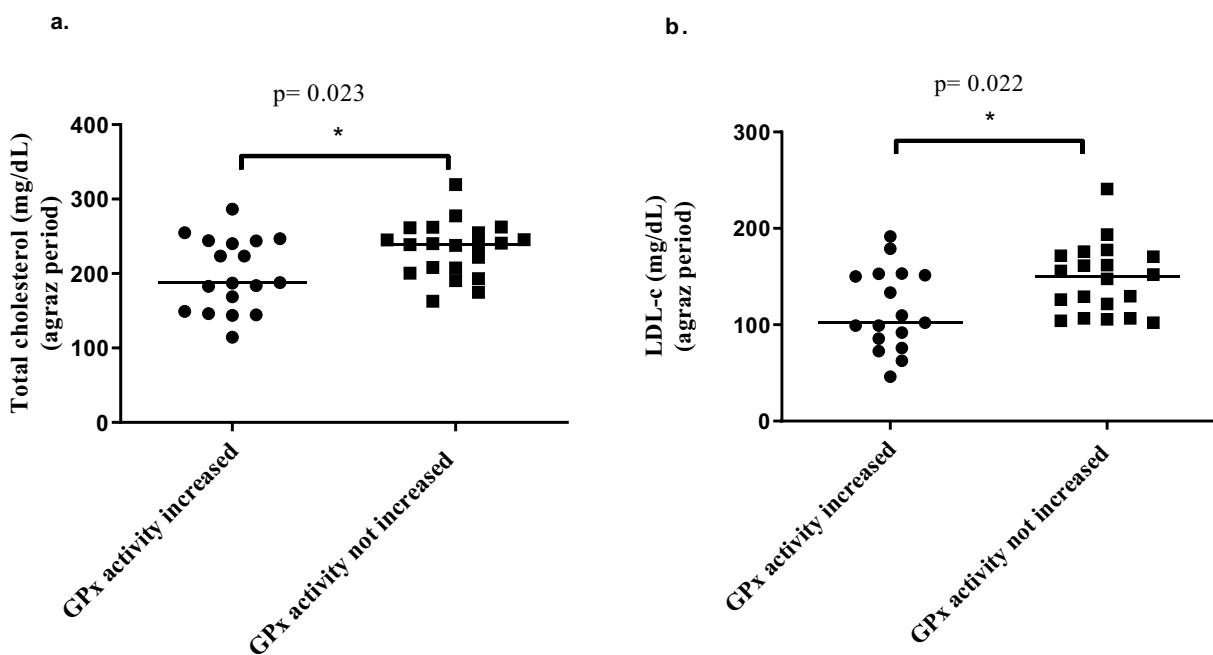


Figure 3. Changes in glutathione peroxidase (GPx) activity and effects on cardio-metabolic risk factors, after 4 weeks of agraz consumption, compared to placebo, in women with metabolic syndrome. Changes in GPx activity and effects on: (a) total cholesterol; (b) low-density lipoprotein cholesterol levels. ANOVA adjusted by adherence. * Significance $p < 0.05$.

Figura 3. Cambios en la actividad de la glutatión peroxidasa (GPx) y efectos en factores de riesgo cardio-metabólico, después de 4 semanas de consumo de agraz, comparado con placebo, en mujeres con síndrome metabólico. Cambios en la actividad de GPx y efectos en: (a) colesterol total; (b) colesterol de las lipoproteínas de baja densidad. ANOVA ajustada por adherencia. * Significancia $p < 0.05$.

Abbreviations: GPx, glutathione peroxidase; LDL-c, low-density lipoprotein cholesterol. Abreviaciones: GPx, glutatión peroxidasa; LDL-c, colesterol de las lipoproteínas de baja densidad.

4. Discussion

To the best of our knowledge, this study is the first in evaluating the effect of *V. meridionale* consumption on endogenous antioxidant enzymes activity and to determine

TAC by the methods described, in people at high risk of CVD. We demonstrated that chronic consumption (4 weeks) of agraz, with the daily dose provided in this study, did not

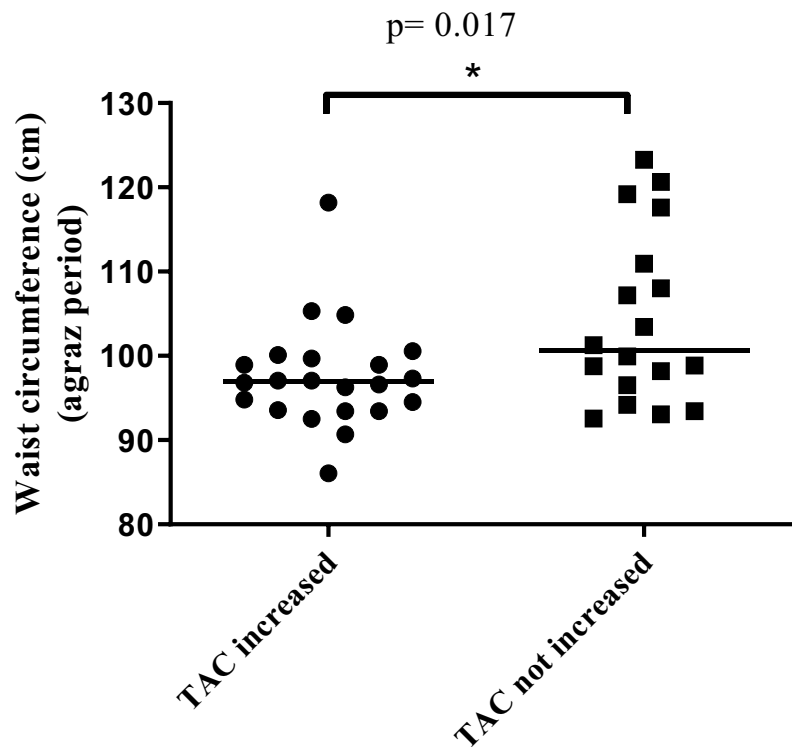


Figure 4. Effects of changes in serum total antioxidant capacity (TAC; measured by ABTS) on waist circumference, after 4 weeks of agraz consumption, compared to placebo, in women with metabolic syndrome. ANOVA adjusted by adherence. *Significance $p < 0.05$.

Figura 4. Efectos de los de los cambios en la capacidad antioxidante total sérica (TAC; medido por ABTS) sobre la circunferencia de cintura, después de 4 semanas de consumo de agraz, comparado con placebo, en mujeres con síndrome metabólico. ANOVA ajustada por adherencia. * Significancia $p < 0.05$.
Abbreviations: TAC, total antioxidant capacity. Abreviaciones: TAC, capacidad antioxidante total.

significantly modify antioxidant enzymes activity when compared to placebo, in this group of women, when analyzed as a whole. Similarly, Riso et al. (2013), did not observe significant changes in endogenous antioxidant enzyme activity in people with CVRF, in a crossover design study, evaluating the effects after 6 weeks of consuming a blueberry drink. Contrarily, studies evaluating the acute and chronic effects of polyphenols rich berries in healthy people, demonstrated beneficial effects with significant increases in the activity of enzymes such as SOD, CAT and GPx, influenced by polyphenols (Kardum et al., 2014; Kuntz et al., 2014; Toaldo et al., 2016). These effects could be explained by the lower levels of oxidative stress (OxS) observed in healthy people versus the higher levels in people with metabolic syndrome (Bhutia et al., 2018; Sabir et al., 2016); given that inactivation of enzymes activity mediated by products generated during oxidation has been reported (Kang, 2013). In fact, we reported a better anti-inflammatory effect after 4 weeks of agraz consumption in women having three MetS parameters in comparison with those with four MetS components (Espinosa-Moncada et al., 2018). Therefore, people included in this study might need strong lifestyle changes for achieving better results.

Interestingly, there was a group of women with increases in the activity of endogenous antioxidant enzymes after agraz consumption, in whom a protective effect was evidenced. Studies with anthocyanins, the main polyphenol present in berries, have shown reductions in OxS levels through significant increases in endogenous antioxidant enzymes activity of CAT, SOD and GPx, and reducing reactive oxygen species (W. Huang et al., 2018; W.-Y. Huang et al., 2018). Although a clear mechanism has not been established, some authors have

indicated that polyphenols and its metabolites, via phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) induce the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), an important transcription factor in the antioxidant response (Hwang et al., 2011; Vari et al., 2011).

In this study, women who increased SOD activity after agraz consumption, compared to placebo, significantly reduced markers of oxidative damage of lipids (F2-isoprostane) and DNA (8-OHdG), indicating a protective effect against oxidative damage of superoxide free radical in this group of people. Likewise, it has been demonstrated a negative correlation between SOD and F2-isoprostanes (Lee et al., 2017) and 8-OHdG (Himmetoglu et al., 2009). The protective effect of SOD could be explained by its biological role catalyzing the dismutation of superoxide radicals to O_2 and H_2O (Bannister et al., 1973), given that superoxide radical (O_2^-) participates in the hydroxyl radical production, a powerful oxidant involved in the oxidative damage of macromolecules such as lipids (Thomson et al., 1990) and DNA (Keyer et al., 1995).

In addition, it is well known that GPx is an enzyme responsible for catalyzing hydrogen peroxide (H_2O_2) reduction to $2H_2O$ mediated by the conversion of reduced glutathione (GSH) to the glutathione oxidized form or glutathione disulfide (GSSG), thus, removing H_2O_2 from the tissues (Mills, 1957). Due to its important role in OxS, the reduced activity of this enzyme has been associated with a higher risk of CVD (Blankenberg et al., 2003). Interestingly, we also found that women with increases in GPx after agraz consumption, compared to placebo, have a significant reduction of CVRF such as total cholesterol and LDL-c.

These results are in accordance with a report by Blankenberg et al. (2003), who demonstrated that people with higher GPx activity have significantly less risk of future cardiovascular events, compared with people with lower GPx activity.

In this study, we determined TAC after agraz and placebo consumption, as a measure to evaluate the antioxidant capacity mediated by both exogenous (dietary) and endogenous antioxidants. It has been reported that anthocyanins (the main polyphenol in *V. meridionale*) have a low bioavailability (Zhong et al., 2017). However, a maximal concentration of its phenolic metabolites in blood between 2 and 30 hours, and a half-life between 0.5 and 96 hours, have been demonstrated after its consumption (De Ferraris et al., 2014). In fact, studies evaluating blood TAC after an acute consumption (during 4 hours) of *Vaccinium* beverages, have shown significant increases in TAC determined by ABTS and ORAC methods, which is associated with increased levels of anthocyanins in blood (Kay & Holub, 2002; Mazza et al., 2002). We did not find significant improvement in TAC after 4 weeks of agraz intake, compared to placebo, in this group of women. Similarly, Karlsen et al. (2010) did not observe increases in TAC determined by the same methods (FRAP, ORAC and ABTS) in a group of 31 subjects with at least one CVRF, after consuming bilberry juice during 4 weeks. Contrarily, Basu et al. (2011), demonstrated that an 8-week intervention with cranberry juice in 31 women with MetS was enough to significantly increase TAC determined by the ABTS method, when compared with the baseline. The intervention period of this last study was double of the time of our study and with a different fruit. Another study demonstrated increases in TAC, measured by the ABTS method, after 2 weeks of consuming an anthocyanin-rich juice, however, these results were obtained in healthy individuals (Kuntz et al., 2014). Our study included women with several CVRF with high levels of OxS, as others have reported (Sabir et al., 2016). Although in this study blood samples were collected after 12 hours of overnight fasting, a period where there could be phenolic metabolites in circulation, it is possible the high levels of OxS in this group of women have not allowed to observe better results. Therefore, further studies exploring higher dosage or an extended duration of the supplementation are warranted.

Interestingly, we found that women who increased TAC determined by ABTS after 4 weeks of agraz consumption ($n = 21$), compared to placebo, had reduced significantly their waist circumference. TAC has been inversely associated with central obesity (Hermsdorff et al., 2011), and recently a significant reduction in waist circumference (4.1%) after 21 days consuming 35 g/day of osmodehydrated agraz in 25 overweight adults was reported (Torres et al., 2018). Although there is not a clear mechanism, anthocyanins like cyanidin 3-glucoside have been shown to ameliorate obesity by upregulating brown adipose tissue mitochondrial function and inducing beige adipocyte phenotypes or "browning" of white fat, increasing so the energy expenditure and improving insulin sensitivity (Matsukawa et al., 2015, 2017). These findings indicate a cardioprotective effect of agraz in those women in whom the level or activity of antioxidant system increased after its consumption, positively impacting central obesity and OxS, two important risk factors for the development of a cardiovascular event.

This study presented some limitations. Although the randomization would be ideal, the method used for the

alternating beverage assignment was used in order to equilibrate the number of participants to begin each period (agraz versus placebo), to reduce bias due to behavioral issues (collective holidays, climate conditions along the year). In addition, the sample size was small, which reduces the possibility to detect associations in the studied variables. In spite of that, the crossover design used in this study has some advantages: a smaller sample size is required in comparison to parallel studies, and patients serve as their own controls, which reduces the influence of confounders.

In conclusion, the chronic consumption (4 weeks) of a daily dose of agraz equivalent to 200 g of fresh fruit, in 40 women with MetS, did not significantly increase serum TAC and endogenous antioxidant enzymes activity in the group as a whole. However, women in whom these antioxidant parameters increased after agraz consumption, several CVRF were improved, such as reductions in lipid and DNA oxidation, total cholesterol, LDL-c and waist circumference, demonstrating a beneficial effect of agraz in this sub-group of women. These results evidence an individual variability that influences the response to agraz consumption, which could be mediated by factors such as intestinal microbioma, food matrices, absorption, genetic variation, among others (Bento-Silva et al., 2020). More studies will be necessary in this regard.

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