academicJournals

Vol. 10(27), pp. 402-408, 17 July, 2016
DOI: 10.5897/JMPR2016.6100
Article Number: 26D5A2059544
ISSN 1996-0875

http://www.academicjournals.org/JMPR

Journal of Medicinal Plants Research

Full Length Research Paper

Cytotoxic effect and antioxidant activity of Andean berry (*Vaccinium meridionale Sw*) wine

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Received 16 March, 2016; Accepted 30 June, 2016

***Vaccinium meridonale* Sw or Andean berry has antioxidant properties due to its high content of polyphenols, as anthocyanins and phenolic acids. Polyphenols have been associated with the prevention of chronic and cardiovascular diseases. In the last years, alcoholic drinks have been studied for their composition and health benefits. By this, the aim of this research was to obtain three types of alcoholic beverages from Andean berry, which have different treatments. The methods used to obtain the beverages were macerated fruit machine (MAC), preheating of the fruit (CAL) and by combining both of them (MIX). The antioxidant activity was evaluated by FRAP, DPPH, ORAC methods and anthocyanins and total phenols were measured. Finally, the antiproliferative effect was evaluated on a colon cancer cell line (SW480). Findings suggest that ethanol content of final products is not altered by treatment of unfermented Andean berry juice (must). The alcohol concentrations for MAC, CAL and MIX drinks were 90±1.7, 89±3.6 and 94±4.1 g/L, respectively. The results showed that CAL and MIX methods favor the extraction of secondary metabolites and consequently increase the antioxidant activity. The fermentation process affected the antioxidant power and total phenolic content in beverages CAL and MIX. However, no significant changes in these parameters were observed in the MAC drink. These beverages can eventually reduce the cancer cell viability between 15.1 (20 µg/L) and 37.2% (200 µg/mL). Thus, it was concluded that MIX treatment has higher antioxidant power and it could reduce the cancer cell viability.**

Key words: Fermented beverage, Andean berry, antioxidant activity, antiproliferative activity, alcoholic beverage.

INTRODUCTION

The *Vaccinium meridonale Sw* known commonly as “mortiño” or Andean berry belongs to the Ericaceae family with small berries from red to purple color, which are valuable for its antioxidant activity and high

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polyphenols content. Andean berry have been reported to have 329.0 ± 28.0 mg eq cyanidin 3 glucoside/ 100 g FW of anthocyanin, 758.6 ± 62.3 mg eq galic acid/ 100 g FW of total phenols, which show antioxidant power; DPPH (2404 ± 120 TEAC), ABTS (8694 ± 435 TEAC) and FRAP (581 ± 29 de AEAC) (Montoya et al., 2012). The antioxidant activities of phenolic compounds are mainly contributed to their redox properties, allowing them to act as reducing agents, hydrogen donors and single oxygen quenchers (Ljevar et al., 2016).

A diet rich in antioxidant might prevent different some non-communicable chronic diseases such as cancer, cardiovascular and neurodegenerative diseases (Wiczkowski et al., 2014; Pace et al., 2014). A big number of studies suggest that wine consumption might reduce the risk of heart attack, and give anti-inflamatory, anti-carcinogenic, anti-viral, anti-bacterial effects (King et al., 2006; Apostolidou et al., 2015). Nevertheless, the antioxidant value from foods can be lost easily according to the food treatment.

An alternative to preserve the antioxidant value of Andean berry is the alcoholic beverage production. Different authors suggest that after a fermentation process, the antioxidant value of fruit still remains in wine and can be preserved during long periods of time (Rai and Anu Appaiah, 2014). However, different maceration methods can affect the antioxidant power in wine. The most common methods of maceration are: 1- Mechanical maceration, 2- fruit preheating, 3- enzymatic hydrolysis and 4- fruit filtration under pressure (Duarte et al., 2010; Ahmed, 2011; Ubeda et al., 2013).

Due to the previous mentioned, this study proposes the following objectives (i) to produce three types of alcoholic beverages from Andean berry, with three different maceration methods; preheating, mechanical maceration and a combination of both, (ii) to measure the antioxidant activity and (iii) to determinate anti-proliferative activity.

MATERIALS AND METHODS

Fruits

Andean berry (*V. meridionale Sw*) were harvested in Santa Elena village, located in the rural area of Medellin city, at 2600 m.a.s.l, with an average temperature of 14.5°C and relative humidity of 89%. This material had a voucher number ILS 14050070.

Treatment of must

Must were prepared adding 1 kg of fruit and 1 L of water according to modified methods proposed by of Solieri and Giudici (2008) and Ferreira et al. (2009). To obtain the beverages three different methods were used, macerated fruit machine (MAC), preheating of the fruit (CAL) at 80°C during 15 min and a combination of both of them (MIX).

Yeast and inoculation

The yeast was prepared according to the procedure described by Coronel (2008) with some modifications. *Saccharomyces cerevisae* (Pasteur Red Star), 0.4 g of yeast per 100 mL of beverage was used. It was activated in water at 37°C during 10 min.

Antioxidant activity

DPPH method

Radical scavenging activity against the stable radical DPPH was measured using the methods proposed by Brand-Williams et al. (1995), with certain modifications. The method is based on the reaction of 10 mL of sample with 990 mL of DPPH solution for 30 min at room temperature. The absorbance decrease, associated with a reduction in the DPPH concentration, was measured at 517 nm. The results were expressed in trolox equivalents antioxidant capacity (TEAC).

FRAP assay

The antioxidant capacity of wine was estimated according to the procedure described by Benzie and Strain (1996), with some modifications. This method is based on the increase of absorbance due to the formation of 2, 4, 6-tripyridil-s-triazine (TPTZ)-Fe (II) in the presence of reducing agents. A volume of 50 µl of extract was mixed with 950 µl FRAP reagent previously dissolved in acetate buffer (pH 3.6). The absorbance increase was measured at 590 nm. The FRAP values were expressed as AEAC (ascorbic acid equivalent antioxidant capacity: mg ascorbic acid per L) using an ascorbic acid standard curve.

Oxygen radical absorbance capacity (ORAC) assay

The ORAC Essay was determined using the following methodology: 3 mL were prepared with 21 µl of 10 µM fluorescein solution, 2899 µl of 75 µM phosphate buffer (pH 7.4), 50 µl of 600 mM 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH) and 30 µl of extract. Fluorescence was recorded on a Perkin Elmer LS45 spectrofluorometer with a thermostated multicell. The ORAC value µmol Trolox/L was calculated by using the following equation:

$$\mathrm{ORAC} = \frac{(\mathrm{AUC} - \mathrm{AUC}^{0})}{(\mathrm{AUC}_{\mathrm{Trolox}} - \mathrm{AUC}^{0})} \mathrm{f}[\mathrm{Trolox}] \quad (1)$$

Where AUC is THE area under THE curve FOR sample CONTROL (AUC°), and trolox reference (AUC_{Trolox}) (Zapata et al., 2013).

Phenolic content

Total anthocyanins

Anthocyanins were determined by pH differencial method. The absorbance was measured at 530 nm and 700 nm in buffers of 1 and 4.5 pH. The expression A = [(A530 – A700) pH1.0 – (A530 – A700) pH 4.5] was used for calculating anthocyanins. Their value was expressed as Cianidine-3-glucoside/L (Zambrano-Moreno et al., 2015).

Total phenols

The total phenolic content was determined according to the adapted Folin–Ciocalteu method (Singleton and Rossi, 1965). The extracts (50 µl) were mixed with 125 µl of Folin–Ciocalteu reagent and 400 µl of sodium carbonate solution (7.1% p/v), and the

Table 1. Ethanol concentration, yield and productivity of Andean berry wine.

Treatment	Ethanol (g/L)	Yield (Yp/s) g/g	Productivity (P) g/day L
MAC	90 ± 1.7[a]	0.36 ± 0.01[a]	5.04 ± 0.09[a]
MIX	94 ± 4.1[a]	0.38 ± 0.02[a]	5.28 ± 0.23[b]
CAL	89 ± 3.6[a]	0.36 ± 0.01[a]	4.94 ± 0.20[a]

Values are mean ± SD (n=4), value not sharing common alphabets for the same attribute are significantly different (P<0.05).

resulting solution was brought to a final volume of 1000 µl. The mixture was stirred and stored at room temperature for 30 min in the dark. The absorbance was measured at 760 nm against a control sample. Aqueous solutions of gallic acid were used to build a calibration curve. The results were expressed as gallic acid equivalents (GAE)/L (Zapata et al., 2013).

Hydroxycinnamic acids determination by HPLC–DAD

Hydroxycinnamic acids were analyzed by direct injection of previously filtered samples through a 0.45 Rm pore-size nylon filter, in a HPLC–DAD using a Shimadzu LC- 20AD/T HPLC equipped with a SPD-6AUV detector (Kyoto, Japan) and a Pinacle (II) C18 column (5 Rm) 250 × 4.6 mm (Restek©, Bellefonte, USA) with an auto injector and a photodiode array detector (PDA). Chlorogenic, caffeic, ferulic and p-coumaric. Acids were adopted as the standard for identification and quantification of hydroxycinnamic acids at 320 nm. The mobile phase was a sample of 10 RL of a mixture of acetonitrile, acidified water (phosphoric acid at pH = 2.5) (40:60) v/v, supplied at a rate of 0.8 mL/min (Kelebek et al., 2009).

Cell culture

SW480 cells were obtained from the European Collection of Animal Cell Culture (ECACC, Salisbury, UK). They were cultured according to a procedure previously described (Maldonado et al., 2014). Cells were cultured in 75 cm^2 Falcon tubes with modified eagle´s medium (Dulbecco), supplemented with 25 mM glucose, 2 mM L-glutamine, 10% inactivated horse serum (heated at 56°C), 100 U/mL penicillin, 100 µg/mL streptomycin, and 1% non-essential amino acids.

Incubations were carried out at 37°C in a humidified atmosphere with 5% of CO_2. The culture medium was replaced every 48 h. For all experiments, horse serum was reduced to 3%, and the medium was supplemented with 10 µg/mL insulin, 5 µg/mL transferrin and 5 ng/mL selenium (ITS defined medium). Cells were exposed during 24 h after seeding, to different concentration of fermented beverage which etanol was eliminated through rotative evaporation at 30°C under vacuum.

Sulforhodamina B (SRB) assay

The effect of extracts on growth cells were studied by using the SRB assay according to Gossé et al. (2005), a colorimetric assay based on staining of total cellular protein from cells with SRB dye. 3000 viable cells from each cell line were exposed to extracts during 24 h after being seeded and incubated for different times. Control cells were treated with 0.1% dimethyl sulphoxide (DMSO). Culture media was replaced every 48 h. The cell culture growing was stopped by the addition of trichloroacetic acid (50% v/v), and cell proteins were determined by staining with 0.4% (w/v) SRB (Sigma-Aldrich, United States).

The relationship between cell number (protein content/well) and absorbance is linear from 0 to 2×10^5 cells per well. All experiments were performed in triplicate. The concentration able to kill 50% of cells (IC_{50}) was calculated using GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA). The absorbance of control group (non-treated cells) was considered as 100% viability. The percent inhibition was calculated using the following equation:

$$\% \text{ Inhibition} = [1 - (OD_t / OD_c)] \times 100$$

Where OD_t is the optical density (OD) of treated cells, and OD_c is the control (non-treated cells).

Statistical analysis

The variables were characterized in terms of the extraction temperature, using the Statgraphics Centurion XVI statistical software. Analysis of variance (ANOVA) was conducted to each variable with a significance level of 5%.

RESULTS

Ethanol concentration, yield and productivity of fermented Andean berry beverages are reported in Table 1. The differences in ethanol concentration and yield were not statistically significant ($p < 0.05$) in fermented beverage.

Antioxidant activity and phenolic compounds of must and fermented beverages of Andean berry (wine)

Three treatments (MAC, CAL and MIX) for getting musts were carried out. They were analyzed by DPPH, FRAP and ORAC techniques in order to measure antioxidant power. Totals phenols and anthocyanins were also quantified. Results for the above treatments showed statistical differences and they are represented in Figure 1. Results suggest that heated treatments MIX and CAL increased the extraction of phenolic metabolites and the antioxidant power. On the contrary, CAL treatment did not produce the same effect and results were lower. MIX and CAL did not show any significant differences between them, regarding to antioxidant activity and phenolic compounds.

Fermented beverages were also analyzed by using the same techniques. CAL and MIX fermented treatments presented higher values in DPPH, total phenols and

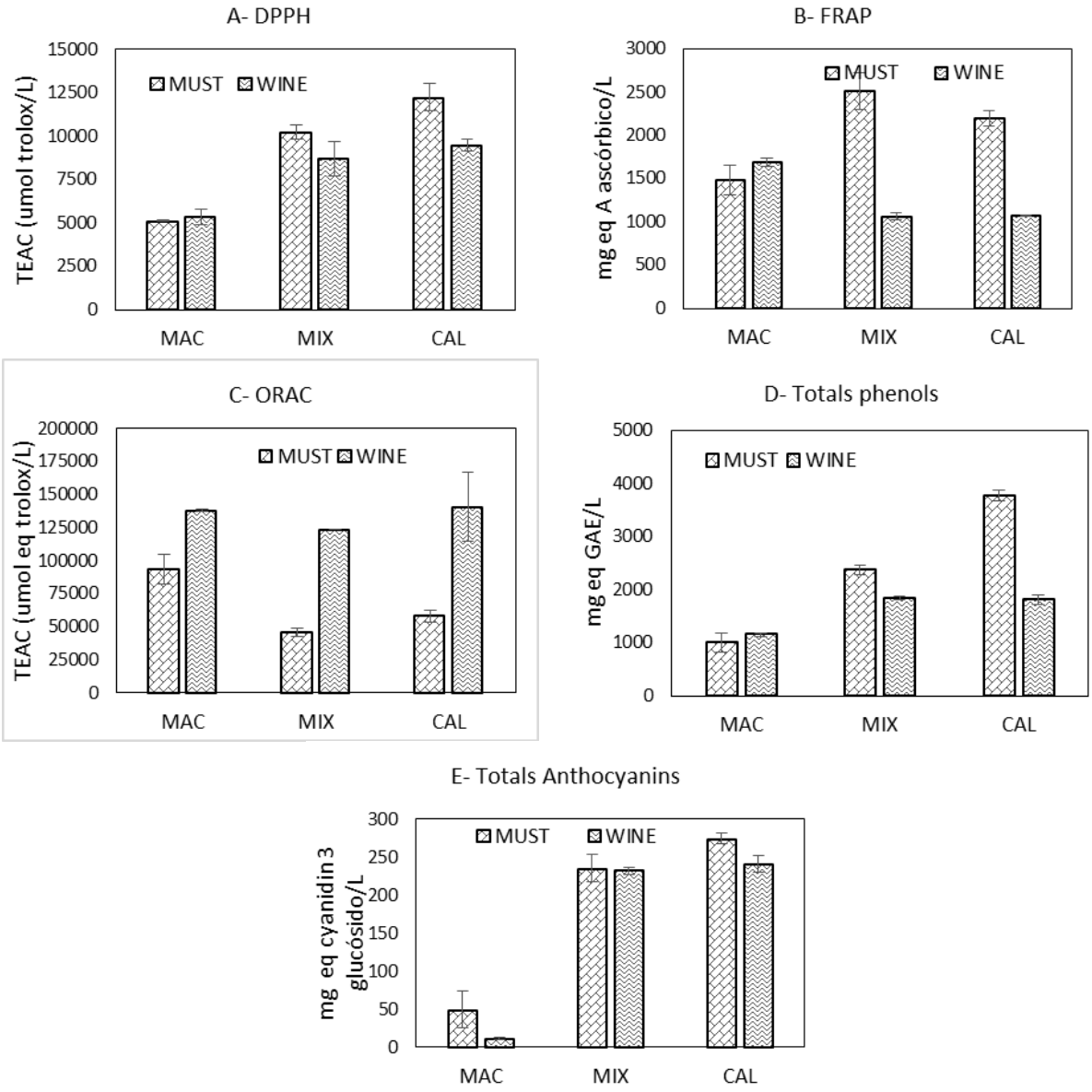

Figure 1. Comparison of antioxidant activity A) DPPH, B) FRAP y C) ORAC, and secondary metabolites content D) Total phenols and E) Total anthocyanins of must and fermented beverages from Andean berry.

anthocyanins assays. While MAC fermented treatment showed higher values in the FRAP assay. Oxygen radical absorbance capacity (ORAC) assay did not exhibit significant statistical differences between the three fermented treatments.

The must and its fermented beverages were compared. Findings indicate that the fermentation process contributed to decrease the totals phenols and the antioxidant activity which was measured by FRAP and DPPH for MIX and CAL treatments.

According to the anthocyanins, they were preserved in the same treatments after the fermentation process (CAL, MAC, MIX). However, the antioxidant activity measured by ORAC increased for the three treatments. Finally, MAC treatment preserved totals phenols content and the antioxidant power, this last one was measured by FRAP and DPPH. Hydroxycinnamic acid results are reported in Table 2. MAC, MIX and CAL treatments showed a higher value in chlorogenic acid, p-coumaric acid and ferulic acid respectively.

Antiproliferative activity of CAL fermented beverages

The pharmaceutical function of fermented beverages was tested. The effect of fermented beverages on SW480 cell

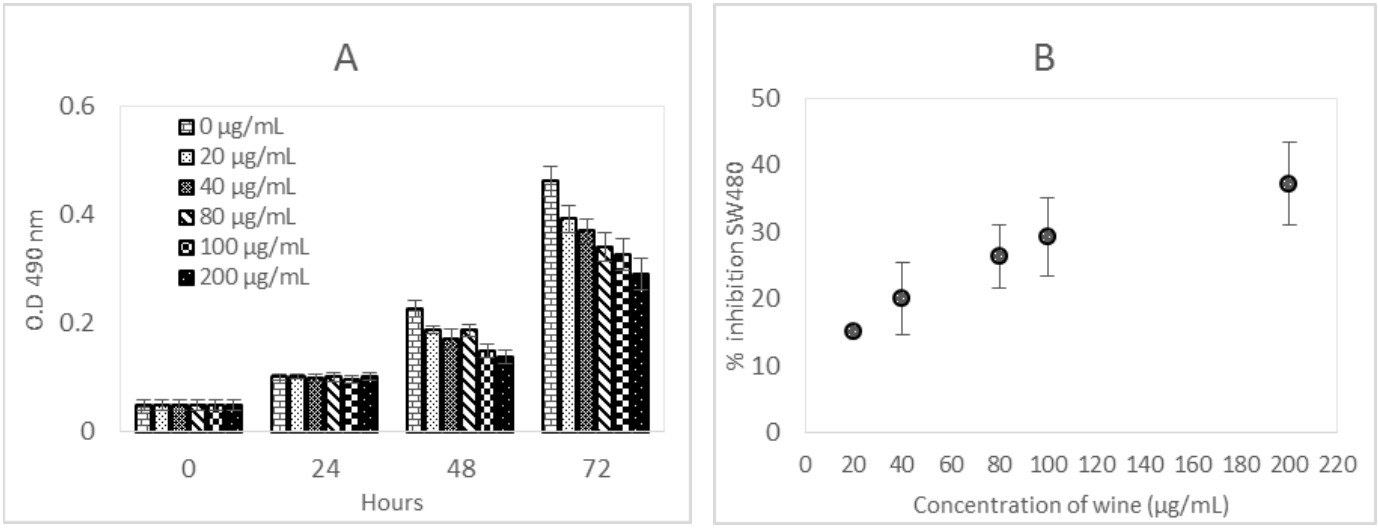

Figure 2. A) Effect of dealcoholized Andean berry wine on SW480 cell growth. B) % Inhibition vs concentration of dealcoholized wine.

Table 2. Hydroxycinnamic acid in fermented beverages of Andean berry.

Tratamiento	Chlorogenic acid (mg/L)	P-Coumaric acid (mg/L)	Ferulic acid (mg/L)
MAC	3.21 ± 0.29[a]	0.00 ± 0.00[a]	0.00 ± 0.00[a]
MIX	1.10 ± 0.03[b]	2.36 ± 0.12[b]	0.00 ± 0.00[a]
CAL	0.47 ± 0.06[c]	0.21 ± 0.00[c]	2.67 ± 0.03[b]

Values are mean ± SD (n=4), value not sharing common alphabets for the same attribute are significantly different (P<0.05).

growth is represented in Figure 2A as OD of cell proteins at 490 nm treated or not with the extract at different concentrations (0 to 200 µg/mL). The OD of SW480 cell protein was reduced 37.3% at 200 µg/mL (Figure 2B). The inhibitory effect on cell viability on SW480 increased significantly ($p < 0.05$) as concentration increased from 20 to 200 µg/mL. The IC_{50} value calculated from the non-linear regression between percent of inhibition and logarithm concentration was found SW480: IC_{50} = 139.1 µg/mL.

DISCUSSION

Results suggest that by using this methodology is not possible to obtain industrial yields. Experimental yield can vary from 90 – 95% of theoretical yield. However, in the industry, this yield can vary between 87 and 93% (Vasquez and Dacosta, 2007). In this assay we obtained 70.5% (MAC and CAL) and 74.5% (MIX) of yield. This lower value might be caused by yeast using glucose to produce other metabolites or adapting to the substratum.

Heating treatments presented better results over mechanical treatment due to the high temperature. This aided the extraction of phenolic compounds thanks to the solubility effect of metabolites and diffusion rate of these compounds in solution. According to Suteerapataranon et al. (2009), the solubility and diffusion coefficient increase when temperature increase. Moreover, thermal treatment may concentrate the compounds of fruits by evaporation (López de Lerma and Peinado, 2011; Torija et al., 2003). Other authors also report that after pasteurization reducing sugar, soluble solids, acidity and flavonoids might be increased (Nurgel et al., 2002; Ferreira et al., 2009).

MAC treatment presented a lower value of antioxidant activity. It suggests that the medium may be oxidized by polyphenol oxidase enzyme. The mechanical maceration increases the area of contact of oxygen which improves enzymatic action. As the opposite, the enzyme is inhibited by heating in CAL and MIX treatments.

Our results are similar to those reported by Porgali et al. (2012), according to the analysis of red wines antioxidant activity. This author reported a value of 1836 ± 40.5 mg GAE eq/L for Karpat wine and 3466 ± 54.4 mg GAE eq/L for Buzbag wine in totals phenols. Besides, Granato et al. (2010) reported a range of 1041.63 – 1958.78 mg GAE/L for Brazilian red wines. And Baroni et al. (2012), reported values of 3.6 ± 2.8 mg/L ferulic acid for Cabernet Sauvignon wine, 4.1 ± 2.7 mg/L for Malbec

and 2.9 ± 3.2 mg/L for Shyrah. Additionally, this author reported a Coumaric acid value of 4.5 ± 1.2, 7.3 ± 2.1 and 5.7 ± 5.2 mg/L for Cabernet Sauvignon, Malbec and Shyrah wine respectively.

Statistical analysis indicates that there is an influence of pretreatment method of fruit on the antioxidant power of fermented beverage ($P<0.05$). CAL and MIX treatments presented a higher value in antioxidant power. According to this, Granato et al. (2011) and Ubeda et al. (2013) reported that antioxidant activity is affected by different factors such as grapes varieties, different maturities, maceration mechanism, and temperature of maceration.

Rai and Anu Appaiah (2014) demonstrated that totals phenols concentration may increase or decrease during fermentation, depending on process conditions. Other authors reported that free radical scavenger capacity (DPPH), anthocyanins and flavonoids are reduced during fermentation (Pérez-Gregorio et al., 2011). Those findings are similar to the results reported in this study, where DPPH and totals phenols were reduced during fermentation in MAC and CAL treatments.

On the other hand, extreme temperatures can generate labile anthocyanins. In the presence of oxygen, methoxyl, glucosyl and acyl substitutions increase causing a rise in the pH where the maximum thermal stability occurs (Jackman and Smith, 1996). It influences the rate and the mechanism of anthocyanin thermal degradation (Hazdrina et al., 1970).

Dealcoholized fermented beverage of Andean berry was cytotoxic in a dose dependent manner with a maximum effect at 200 µg/mL. This fermented beverage contains a range of biologically active metabolites that showed being a potent anticancer. Anthocyanins might provide a lot of effects such as the reactive oxygen species scavenger capacity, chelate metals, stimulating the expression of enzymes, reducing the formation of oxidative DNA adduct, reducing lipid peroxidation inhibiting toxins and environmental mutagenesis carcinogens, and reducing cell proliferation by modulating the signal transduction pathways (Wang et al., 2000; Wang et al., 2008). Hidroxycinamic acids have been also associated to antiproliferative effect (Yi et al., 2005). Other authors have reported a constantly increased of cytotoxicity up to 61 and 78% at 100 and 200 µg/mL GAE, respectively, after 48 h for lyophilized Trigaio red wine in osteosarcoma cell line (Tedesco et al., 2013; Oliveira et al., 2015).

The IC50 value for this assay was 139.1 µg/mL which according to Criteria of national cancer institute of USA; is considerate active when IC50 value is less than 30 µg/mL in cancer cells lines (Suffnes and Pezzutto, 1990). According to the above mentioned, this beverage shows low cytotoxic activity in spite of high content of total anthocyanins preserved after CAL fermentation beverage. The results obtained here suggest that other phenol compounds different to anthocyanins such as phenolic acids (hydroxycinamic acid, p-coumaric acid) whose concentration was significantly decreased, might be required to induce an important antiproliferative activity. Further analyses will be required to answer this question.

Conclusion

Yield and productivity parameters were independent of fruit macerated treatment. Antioxidant activity and totals phenols were higher in heating treatments (CAL and MIX) due to the temperature which increased the diffusion coefficient of secondary metabolites and inhibiting some oxidative enzymes. During fermentation, antioxidant activity was decreased for CAL and MIX treatments, but for MAC treatment, IT was preserved. The dealcoholized fermented beverage decreased the viability of colon cancer cells. However, according to criteria of national cancer institute of USA, this beverage presents low antiproliferative activity.

Finally, this research suggests that the dealcoholized fermented beverages can become an interesting strategy in cancer chemoprevention tool in secondary prevention of cancer or in adjuvant chemotherapy owing to metabolites contents and antioxidant power.

Conflict of Interests

The authors have not declared any conflict of interests.

ACKNOWLEDGMENT

To the Estrategia de Sostenibilidad 2014 – 2015 de la Universidad de Antioquia.

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