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Research Article

Antioxidant activity of polyphenols and permissible values of glyphosate in artisanal wines from the Pisco Routes of the Ica Valley, Peru

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Abstract

The major production of artisanal and industrial wines is elaborate in the Ica Valley, Peru. The objective was to evaluate the antioxidant activity of polyphenols and permissible values of glyphosate in artisanal wines from the Pisco Routes of the Ica Valley, Peru. Samples: six coded artisanal wines and two commercial brands as references (60088 and 60089). Total polyphenol content (TPC) was found between 107.90 ± 0.30 (60091) and 234.73 ± 0.61 mg GAE/100 mL (60084); total flavonoid content (TFC) was between 9.70 ± 0.30 (60091) and 16.83 ± 0.25 mg QE/100 mL (60084). Antioxidant activity: DPPH between 34.9 ± 0.44 (60091) and 55.6 ± 0.30 mM TEAC/100 mL (60085). FRAP between 42.50 ± 0.36 (60091) and 117.3 ± 0.44 (60085). Correlation relationship: TPC/DPPH (mM TEAC/100 mL) for 60086 (r = 0.7302, R^2 = 0.5332), 60091 (r = 0.8029, R^2 = 0.6447), 60085 (r = -0.9820, R^2 = 0.9643), and for the reference 60089 (r = -0.9960, R^2 = 0.9932). TPC/FRAP (mM TEAC/100 mL) for 60086 (r = 0.8096, R^2 = 0.6554); reference 60088 presents an inverse and strong correlation with a 100% relationship at a linear level of both variables. TFC/DPPH for 60085 (r = -1.0, R^2 = 1.0), 60084 (r = -0.9934, R^2 = 0.9868), and 60090 (r = 0.9586, R^2 = 0.9190). TFC/FRAP for 60087 (r = -0.9798, R^2 = 0.9601) and 60090 (r = 0.9750, R^2 = 0.9506) is higher compared to the reference wines 60088 and 60089. It is concluded that the samples of artisanal wines have the same antioxidant activity that would be due to their polyphenolic and flavonoid compounds, and the glyphosate content is below the maximum permissible limit values (0.1 mg/L).

Keywords

polyphenols, flavonoids, glyphosate, antioxidant activity, artisanal wines

Introduction

Vitis vinifera L. (vine) is a perennial plant that belongs to the Vitaceae family that is cultivated in the coastal areas of Lima, Arequipa, Moquegua, Tacna, and on the Pisco-ICA route, Peru, for its high nutritional value and as raw material (berry or grape) for the production of wines (Cáceres et al. 2017; Bardales et al. 2022; Alvarado et al. 2023a; Surco et al. 2023).

Wine is the product of the fermentation of grape must and catalyzed by yeast; it contains water, ethanol (range: 10–13%), bioactive compounds such as esters, organic acids (citric, fumaric, lactic, malic, oxalic acid, succinic, and tartaric) that determine the pH, pectin, stilbenes (trans and cis-resveratrol), cinnamates, phenolic acids, such as vanillic acid (catechin metabolite), caffeic, and gallic acid (Román et al. 2019); Flavonoids such as flavonols (quercetin), flavan-3-ols (catechin, epicatechin), flavan-3,4-diols or leucoanthocyanins, polymeric procyanidins (condensed tannins), and anthocyanins (responsible for the red and purple colors) have also been characterized; The content of polyphenolic compounds is 10 times higher in red wines than in white wine (Waterhouse 2002; Lorenzo et al. 2005).

Among the most important polyphenolic compounds in wine is trans-resveratrol (3,4',5-trihydroxy-trans-stilbene), which is found at a concentration of 0.53-1.49 mg/L (Rocchetti et al. 2021); this polyphenol, after being absorbed in the intestinal mucosa, is biotransformed in the liver through phase I and II (Chow et al. 2010). By sulfoconjugation, sulfotransferase 1A1 (SULT1A1) transfers a sulfate group from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to the 3-position of trans-resveratrol, forming the metabolite trans-resveratrol-3-O-sulfate (Miksits et al. 2005; Chow et al. 2010); Likewise, by glucuronidation, the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) transfers a glucuronic group from UDP-α-D-glucuronic acid (UDPGA) to the 3-position of trans-resveratrol to form trans-resveratrol-3-O-β-glucuronide; conjugated metabolites are eliminated through urine (Guthrie et al. 2017). Through phase I oxidation, trans-resveratrol is converted into the active metabolite piceatannol (3,4,3',5'-tetrahydroxy-trans-stilbene); this process is generated by the action of the enzyme CYP1B1; subsequently, piceatannol is conjugated by UGT1A1, forming piceatannol-3-O-β-glucuronide (Guthrie et al. 2017).

It has been shown that the biotransformation of trans-resveratrol into piceatannol is important, since it inhibits certain proteins of cancer-inducing pathways (Hsieh et al. 2012). One of the molecular pathways that induce cancer is PI3K/AKT/mTOR, described in Fig. 1A: The process begins when protein kinase D1 (PDK1) activates by phosphorylation the rapamycin-insensitive complex type C2 (mTORC2) and the serine/threonine protein kinase 1 (AKT1) that is linked to phosphatidylinositol-3,4,5-triphosphate (PIP3) of the membrane; at the same time, mTORC2 and phosphatidylinositol-3-kinase type C3 (PI3K-C3) phosphorylate AKT1. Active AKT1 induces the expression of glycogen synthase kinase 3 (GSK3), Fox transcription factor 1 (FOXO1), 3 (FOXO3), and 4 (FOXO4) (Hsieh et al. 2012; Aldecoa and Avila 2021). Likewise, a higher concentration of mTORC2 is expressed, the same one that activates the P-4E-BP1 protein that is involved in the development of prostate cancer (Hsieh et al. 2012). Meanwhile, GSK3 is involved in colon, liver, pancreas, and ovarian cancer; FOXO1 induces alveolar rhabdomyosarcoma (pediatric skeletal muscle tumor), and FOXO3 and FOXO4 induce the development of leukemia (Slany 2009; Meyer et al. 2018). Additionally, by overexpression of CYP1B1 in various tumors, the PI3K/AKT1/MTOR2 and tyrosine kinase pathways are activated (Murray et al. 2001; Li et al. 2017).

In Fig. 1B, it is proposed that trans-resveratrol and its metabolite piceatannol inhibit AKT1 and mTORC2, decreasing the development of cancer cells (Hsieh et al. 2012).

It has also been reported that 17β-estradiol is biotransformed into 4-hydroxyestradiol by the action of the *CYP1B1*3* allelic variant (rs1056836, Leu432Val) that is overexpressed in breast epithelial cell cancer and other types of cancer (Tang et al. 2000; Tsuchiya et al. 2004); In other studies, the genes *CYP2E1*, *CYP1A1*, and *CYP1A2* are described as being associated with a higher risk of cancer (Sánchez-Siles et al. 2020; Alvarado et al. 2021a; Alvarado et al. 2021b). In this sense, it has been proposed that resveratrol and its metabolite piceatannol inhibit the expression and activity of CYP1B1 (Chen et al. 2004), CYP2E1 (Wu et al. 2013), CYP1A1, and CYP1A2 (Chang et al. 2007).

On the other hand, to ensure annual production of good-quality berries, herbicides are used to control various weeds in the vineyards (Reineke and Thiéry 2016; Pertot et al. 2017). Additionally, fungicides are used to combat *Botrytis cinerea* Pers.; fungi are responsible for the decomposition of the grapevine cluster (Fedele et al. 2020). Among the main herbicides used in vineyards is glyphosate, made up of a molecule of phosphonomethyl and glycine (N-phosphonomethylglycine); this weak organic acid inhibits 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS) of the shikimate pathway in plants, preventing the synthesis of phenylalanine, tyrosine, and tryptophan (Takano and Dayan 2020). Likewise, it is important to know that the residual effect of glyphosate is greater than five years (Van Bruggen et al. 2018); therefore, they accumulate in the berries of the vine and are detected in red and white wines (Heap and Duke 2018).

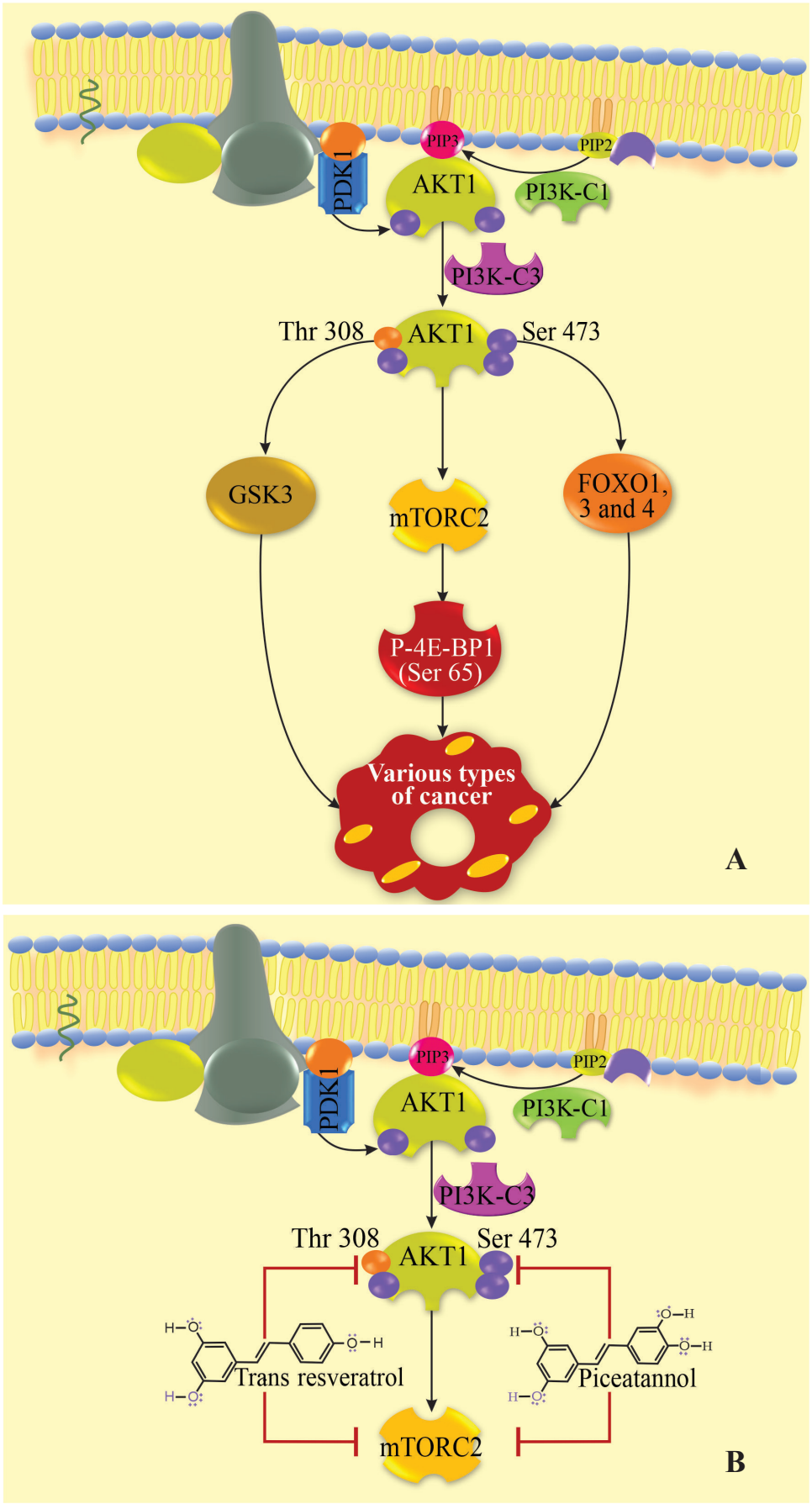

Figure 1. PI3K/AKT/mTOR molecular pathway that induces cancer and proposed inhibition of AKT1/mTORC2 by trans-resveratrol and piceatannol.

Based on this background, the SciELO, PubMed-NCBI, and ScienceDirect databases were searched for published studies on polyphenolic compounds and glyphosate content in artisanal wines made in Peru. It was evident that these studies are scarce; in this sense, it is justified to carry out research on the topic, mainly for three reasons: first, to know the total content of polyphenols and flavonoids and their association with antioxidant activity *in vitro*; second, to identify the presence of glyphosate and whether these are within the maximum residue levels (MRL) in the wines that are made in the Artisanal Wine Cellars compared to two types of industrially produced wines from the Ica Valley; third, the findings obtained could be part of the scientific evidence for health and agricultural authorities to supervise the use of glyphosate in the cultivation of *Vitis vinifera* L. Therefore, the objective was to evaluate the antioxidant activity of polyphenols and permissible values of glyphosate in artisanal wines from the Pisco Routes of the Ica Valley, Peru.

Materials and methods

Reagents and standards

The chemical reagents and chemical solutions used were reagent grade, and the standards were of high purity: HPLC grade water, acetonitrile (Merck), 99% purity formic acid, ethanol, and methanol (Beaker Brand, USA); sodium acetate, acetic acid, hydrochloric acid, sodium carbonate, ferric trichloride, and Folin Ciocalteu reagent from the Merck brand (Germany); gallic acid, Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2'-azino-bis-(ammonium 3-ethyl benzothiazolin-6-sulfonate) brand Sigma-Aldrich (USA), and glyphosate 99.9% Lot number 229ACBE265 (Lab. Instruments, Italy).

Samples

Eight samples of wines from various brands were acquired that are available in the wineries of the Pisco Routes located in the Ica Valley, Peru. Two samples (60088 and 60089) were obtained from Industrial Wine Cellars. Six samples were obtained from Artisanal Wine Cellars (homemade): Two samples (60084 and 60085) were obtained from the Pueblo Nuevo district (14°07'38"S, 75°42'21"W/ -14.1270907, -75.7059197), two (60086 and 60087) from the San Juan Bautista district (14°00'4"S, 75°44'06"W/ -14.0112703, -75.7350876), and two (60090 and 60091) from the Subtanjalla district (14°01'06"S, 75°45'30"W/ -14.0184263, -75.7583885). All samples were assigned a unique identification code (60084-60091) for double-blind analysis.

Total polyphenol content

A calibration curve of the gallic acid standard (Sigma-Aldrich) was prepared in a range of 1–7.5 µg/mL, and the Folin-Ciocalteu reagent was diluted with ultrapure water in a ratio of 1:2. 0.10 mL of wine (diluted 1:5 in distilled water) and 0.5 mL of Folin-Ciocalteu reagent (Merck) were mixed, homogenized, and allowed to react for 5 min, taken to an ultrasound bath for 5 min, then 1.4 mL of 20% sodium carbonate solution (Na_2CO_3) was added, the mixture was homogenized in Vortex for 1 min, and allowed to react for 90 min protected from light and at laboratory temperature. The absorbance of the blank (distilled water) and the samples was recorded at 760 nm in a spectrophotometer (Spectrophotometer Peak Instrumental, model C-7100, USA). The analysis was performed in triplicate, and the total polyphenolic content was expressed in mg of gallic acid (mg GAE)/100 mL of wine (Ramos-Escudero et al. 2012; Alvarado et al. 2023b; Hu et al. 2023; Alvarado et al. 2024). The total polyphenol content was calculated with equation (1) as follows:

$$\text{TPC (mg GAE/100 mL)} = (\text{Absorbance-Intercept})/\text{Slope} \quad (1)$$

Total flavonoid content

A quercetin calibration curve of 50–500 µg/mL was previously prepared.

In a 5 mL tube, 0.2 mL of wine and 1 mL of deionized water were added. After mixing, 0.075 mL of 5% sodium nitrite ($NaNO_2$) was added, homogenized, and allowed to react.

After 5 min, 0.075 mL of 10% aluminum chloride ($AlCl_3$) was added, mixed, and allowed to react. After 5 min, 0.5 mL of 1 M sodium hydroxide (NaOH) was added. It was homogenized and allowed to rest for 5 min.

The absorbance of the samples and the blank was recorded at 510 nm using a spectrophotometer (Spectrophotometer Peak Instrumental, model C-7100, USA).

The analysis was performed in triplicate, and the total flavonoid content was expressed in mg of quercetin (mg QE/100 mL) of wine (Ramos-Escudero et al. 2012; Surco et al. 2023).

The total flavonoid content was calculated with equation (2) as follows:

$$\text{TFC (mg QE/100 mL)} = (\text{Absorbance-Intercept})/\text{Slope} \quad (2)$$

Determination of antioxidant activity by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay

To carry out the antioxidant activity, the DPPH reagent mixture was prepared; 9.5 mL of DPPH methanolic solution (0.130 mM) was mixed with 5 mL of aqueous acetate buffer (100 mM, pH 5.5). To perform the Trolox calibration curve, pre-established dilutions were prepared (0.0315, 0.0625, 0.125, 0.250, 0.500, and 0.750 mM; pH adjusted to 7.0); a standard solution of 400 µM of Trolox was used as a positive control; methanol (analytical grade, beaker) was used as a blank. Several 3 mL tubes were identified, and then a mixture was made as follows: To an amount of 0.10 mL of wine, 0.29 mL of DPPH reagent was added. The reaction mixture was allowed to stand for 2 hours protected

from light and at laboratory temperature. The absorbance of the samples and the blank (methanol) was measured at 517 nm in a spectrophotometer (Spectrophotometer Peak Instrumental, model C-7100 USA). The analysis was performed in triplicate, and the mean DPPH activity for each sample was expressed as mM Trolox equivalent (TEAC)/100 mL of wine ± standard deviation (Alvarado et al. 2023b; Hu et al. 2023). The antioxidant activity of DPPH was calculated using equation (3) as follows:

$$\text{DPPH (mM TEAC/100 mL)} = \text{(Absorbance-Intercept)/Slope} \quad (3)$$

Determination of antioxidant activity using the ferric reducing antioxidant power (FRAP) assay

The FRAP reagent mixture was prepared each time the experiment was performed and allowed to incubate at 37 °C before use.

5 mL of 10 mM TPTZ (2,4,6-tripyridyl-s-triazine) (dissolved in 40 mM HCl), 5 mL of 20 mM aqueous ferric chloride solution ($FeCl_3.6H_2O$), and 50 mL of buffer were mixed with aqueous acetate (300 mM, pH 3.6) in a ratio of 1:1:10. The Trolox standard solution was prepared at preset concentrations (0.0312, 0.0625, 0.125, 0.250, 0.500, and 1.00 mM) to produce a calibration curve; a 400 mM Trolox standard solution was used as a positive control. For the analysis, 0.02 mL of wine was mixed with 0.80 mL of FRAP reagent and allowed to react for 30 min under protection from light. The absorbance was measured at 593 nm in a spectrophotometer (Spectrophotometer Peak Instrumental, model C-7100 USA). The analysis was performed in triplicate, and the mean FRAP activity for each sample was expressed as mM Trolox/100 mL wine ± standard deviation (Hu et al. 2023). FRAP antioxidant activity was calculated using equation (4) as follows:

$$\text{FRAP (mM TEAC/100 mL)} = \text{(Absorbance-Intercept)/Slope} \quad (4)$$

Direct determination of glyphosate

The wine samples were spiked with known concentrations of glyphosate, and a calibration curve was configured. Filtered wine samples (0.22 µm syringe) were directly injected (15 µL) into an LC column using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) system (PerkinElmer QSight 210 MD Screening System UHPLC Pump A) that was used in triple quadrupole mode operating in multiple reaction monitoring (MRM) mode. The flow rate was set at 0.5 mL/min, and the injection volume was 15 µL.

LC conditions were: Acquity UPLC HSS C18 column (particle size 1.8 µm, 2.1 × 100 mm); Mobile Phase (Solvent A: 1% formic acid; Solvent B: Acetonitrile). Gradient Conditions: 3 min of 95% A/5% B mobile phase followed by 3 min of wash with acetonitrile; equilibrate for 7 min with initial conditions. The MS parameters were ion source (ESI negative mode), electro spray/V-5000, source temp 450 °C, HSID temp 320 °C, dry gas 100, nebulizer, and gas 100. The limit of detection (LOD) and limit of quantification (LOQ) were determined to be 0.005 mg/kg and 0.010 mg/kg, respectively (Liao et al. 2022; Pérez-Mayán et al. 2022).

Statistical analysis

Data were expressed as mean ± standard deviation (SD), 95% confidence interval (95% CI), Pearson correlation coefficient, and analysis of variance were calculated, and p-values less than 0.05 were considered statistically significant. GraphPad Prism Statistical Software version 10.1.2 was used. for Windows.

Results and discussion

The total content of polyphenols (TPC), total flavonoids (TFC), and antioxidant activity of the wines produced by Artisanal Wineries of the Pisco Routes of the Ica Valley were estimated, and additionally, two samples of commercial wines (60088 and 60089) of industrial origin were analyzed, which were used as reference samples (Table 1). TPC was quantified in mg gallic acid equivalents (GAE)/100 mL and TFC in mg quercetin equivalents (QE)/100 mL of wine. Samples 60084 and 60087 present high TPC values and are close to the reference 60089, while the TFC is higher compared to the reference sample 60089.

While the potential antioxidant activity of the wine samples was determined by two *in vitro* methods. Antioxidant activity was observed by the DPPH method, with the minimum value being 34.9 ± 0.44 mM TEAC/100 mL in sample 60091. This effect would be due to the transfer of a hydrogen ion (H^+) from wine polyphenols to the free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH).

Antioxidant activity has also been observed by the FRAP method; in this case, the polyphenolic compounds of wine have the ability to transfer an electron to the FRAP radical (SET), reducing the ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+}), which is visualized by turning the color of the solution to intense blue. For the two *in vitro* antioxidant methods, a calibration curve was carried out with the Trolox standard, and with this, the antioxidant activity was established as Trolox equivalent (mM TEAC/100 mL of wine sample).

Pearson correlation coefficient analysis was applied to find the statistical relationship between the variables of polyphenolic/flavonoid compounds and antioxidant activity (Table 2).

To interpret the results of the Pearson correlation coefficient, whether negative or positive, it was based on the study by Hazra and Gogtay (2016), which considers poor correlation when the values are <0.30, moderate if the values are between 0.30 and 0.50, good when the range is 0.50–0.70, and strong if the values are >0.70.

The analysis of the content ratio of total polyphenols (TPC: mg GAE/100 mg) and DPPH (mM TEAC/100 mL) shows a strong and positive correlation with its corresponding coefficient of determination (R^2) for sample

Table 1. Estimation of the content of polyphenols, total flavonoids, and antioxidant activity of wines from the Pisco Routes of the Ica Valley.

Wine sample code	Assay and statistics							
	TPC*	TFC**	DPPH$^{\Theta}$	ANOVA		FRAP$^{\Theta}$	ANOVA	
	Mean ± SD	Mean ± SD	Mean ± SD(mM TEAC/100 mL)	DPPH/ TPCp-Value ($p < 0.05$)	DPPH/TFC p-Value ($p < 0.05$)	Mean ± SD (mM TEAC/100 mL)	FRAP/TPC p-Value ($p < 0.05$)	FRAP/TFC p-Value ($p < 0.05$)
60084	234.73 ± 0.61	16.83 ± 0.25	52.8 ± 0.20	1.03×10^{-10}	4.25×10^{-9}	90.9 ± 1.15	4.53×10^{-9}	4.32×10^{-8}
60085	207.47 ± 0.31	16.50 ± 0.10	55.6 ± 0.30	4.21×10^{-11}	2.85×10^{-9}	117.3 ± 0.44	8.09×10^{-10}	2.58×10^{-10}
60086	134.93 ± 0.55	10.40 ± 0.36	47.4 ± 0.36	2.13×10^{-9}	2.40×10^{-8}	48.5 ± 0.32	1.97×10^{-9}	1.71×10^{-8}
60087	210.23 ± 0.91	13.63 ± 0.38	54.4 ± 0.35	1.01×10^{-9}	1.71×10^{-8}	78.5 ± 0.31	1.85×10^{-9}	2.11×10^{-9}
60090	119.60 ± 0.50	10.23 ± 0.32	49.4 ± 0.38	4.23×10^{-9}	1.72×10^{-8}	53.47 ± 0.40	5.95×10^{-9}	1.35×10^{-8}
60091	107.90 ± 0.30	9.70 ± 0.30	34.9 ± 0.44	1.84×10^{-9}	1.29×10^{-7}	42.50 ± 0.36	1.76×10^{-9}	2.78×10^{-8}
60088	345.30 ± 0.26	18.30 ± 0.26	56.5 ± 0.30	2.45×10^{-12}	4.08×10^{-5}	171.4 ± 0.26	1.42×10^{-11}	1.86×10^{-7}
60089	237.40 ± 0.70	15.80 ± 0.17	92.5 ± 0.35	5.69×10^{-10}	4.52×10^{-10}	118.6 ± 0.20	9.40×10^{-10}	2.92×10^{-11}

TPC: total polyphenol content (mg GAE/100 mL); TFC: total flavonoid content (mg QE/100 mL); TEAC: mg equivalent to 1 mM Trolox/100 mL; Reference compounds: *gallic acid, **quercetin, $^{\Theta}$ Trolox; ANOVA: one-way analysis of variance. Samples of reference wines (60088 and 60089) from industrial manufacture.

Table 2. Relationship of the content of polyphenols and total flavonoids with the antioxidant activity of wines by the DPPH and FRAP methods.

Wine sample code	TPC and DPPH Relation		Correlation	TPC and FRAP Relation		Correlation	TFC and DPPH Relation		Correlation	TFC and FRAP Relation		Correlation
	r	R^2		r	R^2		r	R^2		r	R^2	
60084	-0.3273	0.1071	Moderate	-0.1889	0.0357	Poor	-0.9934	0.9868	Strong	0.9176	0.8421	Strong
60085	-0.9820	0.9643	Strong	0.0751	0.0056	Poor	-1.0	1.0	Strong	-0.1147	0.0132	Poor
60086	0.7302	0.5332	Strong	0.8096	0.6554	Strong	0.8462	0.7160	Strong	0.9059	0.8207	Strong
60087	-0.4603	0.2118	Moderate	-0.9499	0.9024	Strong	-0.8399	0.7054	Strong	-0.9798	0.9601	Strong
60090	-0.7924	0.9932	Strong	-0.9897	0.9796	Strong	0.9586	0.9190	Strong	0.9750	0.9506	Strong
60091	0.8029	0.6447	Strong	-0.2773	0.0769	Poor	0.8029	0.6447	Strong	-0.2773	0.0769	Poor
60088	-0.9450	0.8929	Strong	-1.0	1.0	Strong	-0.8990	0.8082	Strong	-0.7061	0.4986	Strong
60089	-0.9960	0.9932	Strong	-0.5	0.2500	Moderate	0.8219	0.6757	Strong	0.0000	0.0	Null

r: correlation; R^2: coefficient of determination. Samples of reference wines (60088 and 60089) from industrial manufacture.

60086 (r = 0.7302, R^2 = 0.5332) and sample 60091 (r = 0.8029, R^2 = 0.6447), indicating that there is a 53.32% and 64.47% relationship at a linear level of both variables of wines 60086 and 60091, respectively. This positive correlation means that increasing the quantity of polyphenols increases antioxidant activity.

An inverse and strong correlation is also observed for sample 60085 (r=-0.9820, R^2=0.9643) and for reference wine 60089 (r = -0.9960, R^2 = 0.9932); that is, there is a 96.43% relationship at the linear level of both variables. This relationship indicates that, as the concentration of total polyphenol increases, antioxidant activity decreases. This phenomenon suggests that at high concentrations of polyphenols, the functional groups that neutralize free radicals are saturated, reducing the overall efficiency of antioxidant activity; in some cases, flavonoids become pro-oxidants, negatively affecting antioxidant activity (Waterhouse et al. 2016); the other factor would be the formation of a complex between the polyphenols and the proline, fructose, and glucose residues of the wine, decreasing the bioavailability of the polyphenol and reducing its antioxidant activity (Ignat et al. 2011). At the same time, the statistical analysis shows that, as antioxidant activity increases, the polyphenol content decreases. This is generated when some polyphenols are oxidized into secondary compounds that could contribute to antioxidant activity in the short term, but also flavonols, flavan-3-ols, and condensed tannins contribute to maintaining antioxidant activity even when the most important polyphenols decrease (Cheynier et al. 2016).

By the other *in vitro* method, a strong and positive correlation was also observed between TPC and FRAP (mM TEAC/100 mL) for sample 60086 (r = 0.8096 and R^2 = 0.6554); while the reference wine sample 60088 presents an inverse and strong correlation with a 100% relationship at a linear level of both variables, which suggests that, as flavonoids increase, antioxidant activity decreases, and vice versa. Likewise, a strong inverse correlation was found for sample 60085 (r = -1.0; R^2 = 1.0) and 60084 (r = -0.9934, R^2 = 0.9868) after relating the TFC (mg QE/100 mL) to the DPPH assay, being greater compared to the reference 60088. A strong and positive correlation was observed (r = 0.9586, R^2 = 0.9190) for sample 60090, indicating a 91.90% relationship at a linear level of both variables; that is, increasing the quantity of flavonoids also increases the antioxidant activity. While the antioxidant activity of flavonoids by the FRAP method experienced an inverse and strong correlation for sample 60087 (r = -0.9798, R^2 =

0.9601) and a positive and strong correlation for sample 60090 ($r = 0.9750$, $R^2 = 0.9506$), being higher compared to the reference wines 60088 and 60089.

These results indicate the potential antioxidant activity of artisanal wines, which would be due to their polyphenolic compounds (sample 60086) and flavonoids (60085 and 60090). In previous studies it has been reported that the antioxidant activity of wines is due to their polyphenolic compounds, which supports the findings in the present study. In two recent studies, they attribute resveratrol from red wine as the phenolic compound responsible for the antioxidant activity (Şöhretoğlu et al. 2022; Lalani et al. 2023). Regarding the benefits of phenolic compounds in wine, they can increase HDL cholesterol levels and decrease platelet aggregation (de Gaetano et al. 2002; Huxley and Neil 2003; Arranz et al. 2012). Likewise, resveratrol and piceatannol have been shown to inhibit tyrosine kinase and AKT1/mTORC2, suppressing tumor growth (Potter et al. 2002; Ruparelia et al. 2024). Additionally, resveratrol could have a synergistic effect with cisplatin, doxorubicin, docetaxel, and paclitaxel in the treatment of breast cancer (Behroozaghdam et al. 2022).

In the present study, the antioxidant activity of the wines from the Ica Valley has been demonstrated, but it is also relevant for public health to know the levels of insecticides and pesticides that could be concentrated in the wines. Hence the interest in studying the concentration levels of glyphosate in wines produced by artisanal wineries of the Pisco Routes. Glyphosate was found below the maximum residue levels (MRL) (Table 3). Upon statistical analysis, it was verified that the coefficient of variation is less than 30% (3.39–24.74%), indicating that the glyphosate concentration of the samples is relatively homogeneous; therefore, the meaning is representative. These results are consistent with the 95% confidence interval given that their values are closer to zero. While the means of glyphosate values in the wines produced by artisanal wineries and industrial wineries are statistically significant with a probability ($p\text{-value} < \alpha = 0.05$) that the mean glyphosate values of each wine sample do not exceed MRL values of 0.1 mg/L (0.1 ppm) (Lapierre et al. 2024).

Table 3. Mean values of glyphosate concentration in artisanal and industrial wines from the Pisco Routes of the Ica Valley.

Sample code	Mean ± SD (mg/L)	VC%	95% CI	p-Value ($p < 0.05$)
60084	0.005 ± 0.0002	3.39	0.004904–0.005296	1.66×10^{-5}
60085	0.008 ± 0.0010	12.50	0.006868–0.009132	3.68×10^{-5}
60086	0.001 ± 0.0003	24.74	0.000840–0.001493	9.01×10^{-6}
60087	0.001 ± 0.0001	10.82	0.000936–0.001197	8.39×10^{-6}
60090	0.015 ± 0.0020	13.33	0.012737–0.017263	2.72×10^{-4}
60091	0.011 ± 0.0015	13.47	0.009605–0.013062	5.92×10^{-4}
60088	0.012 ± 0.0015	12.38	0.010605–014062	5.16×10^{-5}
60089	0.001 ± 0.0001	10.82	0.000936–0.001197	2.72×10^{-4}

SD: standard deviation; VC%: variation coefficient; 95% CI: 95% confidence interval. Samples of reference wines (60088 and 60089) from industrial manufacture.

In a previous study reported by Zoller et al. (2018), the presence of glyphosate has been indicated in wine samples, with concentrations that reached up to 0.0132 mg/L. Meanwhile, Lopez et al. (2020) found levels of 0.01 mg/L in wine and beer; In another study Pérez-Mayán et al. (2022) glyphosate was reported in red and white wines at a concentration of 0.0014 to 0.0314 mg/L. Recently, Lapierre et al. (2024) have found levels of glyphosate in 36 distilled alcoholic beverages below 0.0012 mg/L. In all these studies, the glyphosate values are below the MRL, as found in the present study.

In previous studies, it has been shown that glyphosate increases the risk of endocrine dysfunction, decreasing gametogenesis and androgen synthesis (Defarge et al. 2016; Madani and Carpenter 2022); may increase the risk of Parkinson's disease and autism (Madani and Carpenter 2022; Rojas Avellaneda et al. 2023). On the other hand, Gasnier et al. (2009) report that glyphosate induces oxidative stress, and later Mesnage et al. (2015) indicate that glyphosate can be toxic even below the MRL or cause teratogenic effects, induce cancer risk, and generate hepatotoxicity and renal dysfunction.

Due to this evidence, it is necessary to monitor the use of glyphosate in grapevine crops and determine the MRL of glyphosate in the wines of the Ica Valley to avoid possible diseases due to long-term wine consumption. Fig. 2 represents the chromatograms of the eight wine samples that were analyzed with codes (60084–60091) to avoid any bias of the analyst or researchers. It is observed that the acquisition time of glyphosate is, on average, 2 min in the eight wine samples analyzed.

The main limitation of the present study is having evaluated samples of artisanal wines from three districts despite the fact that they are made in other districts of the Ica Valley; another limitation that can lead to bias is not having quantified and characterized the phenolic and flavonoid compounds present in wines from the samples studied, so the research team is considering evaluating all of this in a future study. Without prejudice to the above and even though there are various studies worldwide on the presence of glyphosate in wine, our research group is the first to explore glyphosate in wines from the Ica Valley, which is the most wine-producing region in Peru. Additionally, we consider that this study is relevant for demonstrating that wines made in a homemade (artisanal) way do not lose their antioxidant activity, and it is additionally evident that the glyphosate content is below the MRL.

Conclusion

It is concluded that the samples of artisanal wines have the same antioxidant activity that would be due to their polyphenolic and flavonoid compounds. It has also been shown that the glyphosate content is below the maximum permissible limit values (0.1 mg/L).

In this sense, its residual effect would have no implication on human health; however, it is important to know the cumulative effect on the human organs of the residents of the Ica Valley who frequently consume these types of wines.

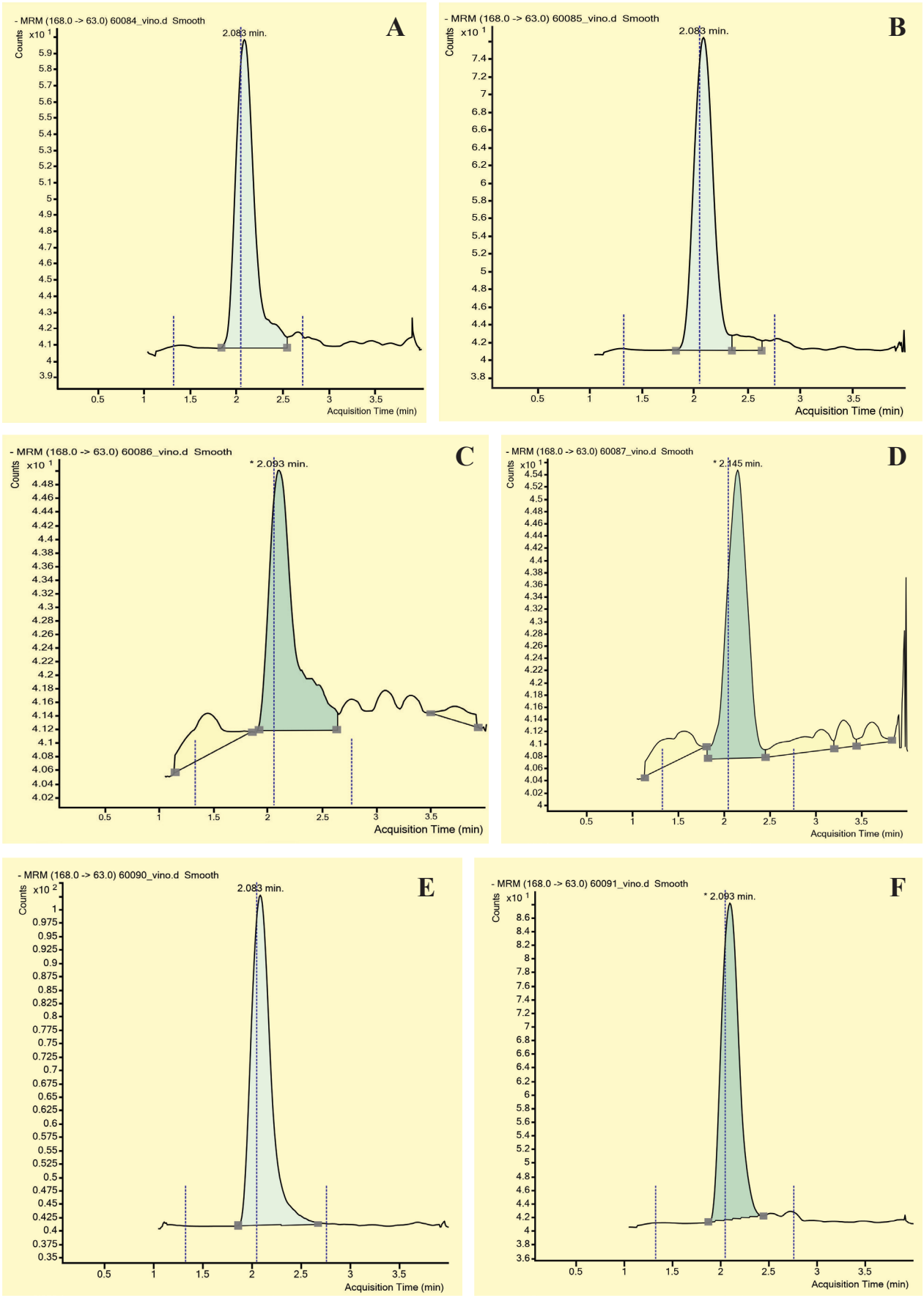

Figure 2. Glyphosate identification chromatograms in wine samples from artisanal wineries. **G, H.** correspond to the chromatograms of the industrial wine samples considered as references in the present study.

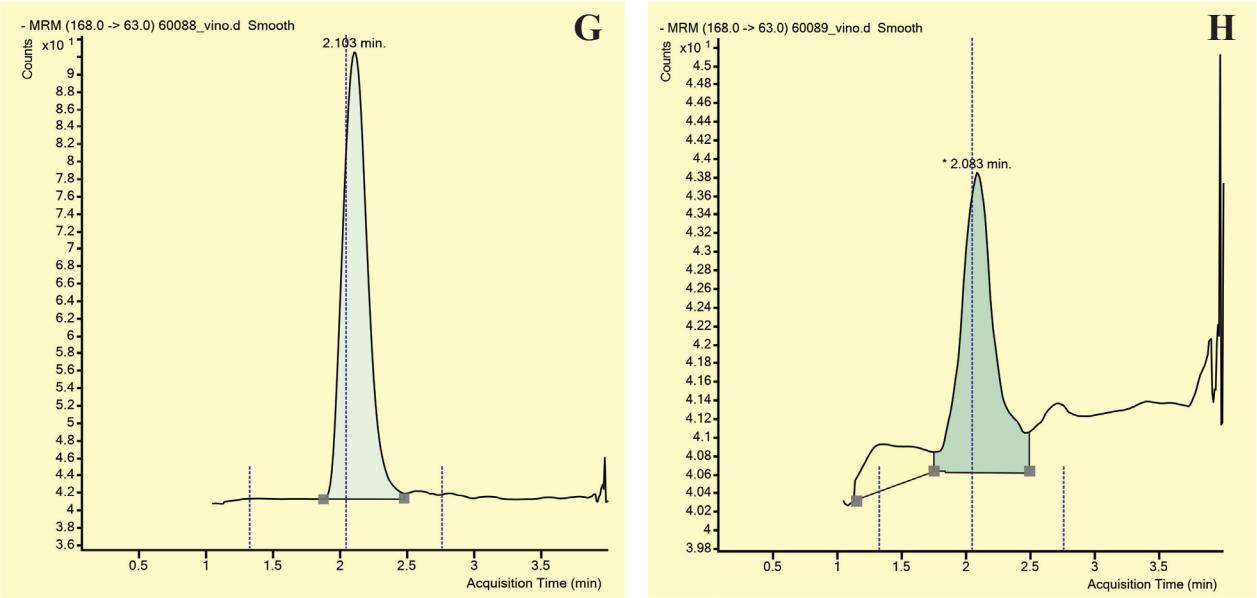

Figure 2. Continued.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability

All of the data that support the findings of this study are available in the main text.

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