

Original article

## Correlation between anti-glycation effect and total polyphenol content in wine

Takaaki Tanabe<sup>1)</sup>, Shinichi Sugiura<sup>2)</sup>, Daisuke Teranishi<sup>1)</sup>

1) Mottox Inc., Osaka, Japan

2) Center for Clinical Pharmacy Education and Research, Faculty of Pharmacy, Doshisha Women's College of Liberal Arts, Kyoto, Japan

### Abstract

Wine has the ability to inhibit the formation of advanced glycation end products (AGEs), an attractive health function for daily glycative stress management. On the other hand, the alcohol content of wine limits its intake, even in the absence of alcohol intolerance or underlying diseases that are adversely affected by alcohol consumption. Therefore, to enable selection of wines with stronger anti-glycation effects, we evaluated the anti-glycation effects of 277 wines and examined how wine color, grape variety, producing country, and vinification method affected the anti-glycation effects of the wines. In parallel with the evaluation of anti-glycation activity, the total polyphenol content in terms of gallic acid was also determined. The results showed that there was a strong correlation between the inhibition ratio of fluorescence AGE formation and total polyphenol content in wine at various concentrations ( $R^2 = 0.736 \sim 0.863$ ). Red wine was significantly higher in terms of total polyphenol content, but there was no significant difference between orange and red wines in terms of  $IC_{50}$ , a measure of AGE formation inhibition. On the other hand, there was no significant difference in total polyphenol content between white wine and rosé wine, but rosé wine showed a significantly lower value in  $IC_{50}$ . Analysis by grape variety showed that wines made from Saperavi generally had significantly higher total polyphenol content than other varieties, while wines made from Pinot Noir/Pinot Nero and Rkatsiteli tended to have significantly lower total polyphenol content. However, there were no significant differences in  $IC_{50}$  among grape varieties. These suggest that while total polyphenol content is a major contributor to the anti-glycation effect of wine, other factors may also contribute.

**KEY WORDS:** advanced glycation end products (AGEs), wine, anti-glycation, total polyphenol content

### Introduction

Countermeasures against glycative stress, a risk factor for aging and related diseases, have garnered attention recently<sup>1-3)</sup>. Glycation reactions in foods, called Maillard reactions, are non-enzymatic chemical reactions between reducing sugars such as glucose and proteins (amino acids), and it is believed that similar reactions occur daily in the body. Glycated proteins undergo glycation reaction intermediates, mainly carbonyl compounds, to form and accumulate advanced glycation end products (AGEs), which are generally characterized by their resistance to degradation and gradual accumulation in the body. Glycative stress, such as protein denaturation and the formation and accumulation of AGEs, is known to be involved not only in the aging process but also in aging-related diseases (*e.g.*, diabetes and its complications, atherosclerosis, osteoporosis, cancer, and Alzheimer's disease)<sup>4)</sup>. Strategies to counteract this glycative stress (anti-glycation) include suppression of AGE formation, blood glucose control, degradation and elimination of AGEs, and suppression of

inflammatory reactions caused by AGEs. The anti-glycation effects of common foods and beverages have been studied, including herbal teas<sup>5)</sup>, fruits<sup>6)</sup>, vegetables<sup>7,8)</sup>, spices<sup>9)</sup>, yogurt<sup>10)</sup>, and Japanese sake (seishu)<sup>11)</sup>.

Various health functions have been reported for wine, including antioxidant and anti-inflammatory effects as typified by the French Paradox<sup>12)</sup>. These functions are thought to be mainly due to the abundant phenolic compounds and polyphenols contained in wine<sup>13-16)</sup>. In addition, trace components such as potassium, organic acids, and amino acids are also thought to contribute to health functions. In 2023, Sugiura *et al.* demonstrated anti-glycation effects of wines as a new health function<sup>17)</sup>. According to their report, all 15 wines (6 white wines and 9 red wines) that were verified showed AGE formation inhibitory effects. In particular, red wine showed stronger action than aminoguanidine<sup>18,19)</sup>, a known inhibitor of AGE formation, and it was found that the action was maintained to some extent even after dilution. Furthermore, through clinical studies, it was suggested that drinking red wine with a strong inhibitory effect on AGE

Contact Address: Daisuke Teranishi  
Mottox Inc.

1-6-20 Kosaka-Hommachi, Higashi-Osaka-shi, Osaka, 577-0802 Japan

TEL: +81-6-6723-3131 FAX: +81-6-6723-3140

e-mail: d\_teranishi@motttox.co.jp

Co-authors: Tanabe T, t\_tanabe@motttox.co.jp; Sugiura S, ssugiura@dwc.doshisha.ac.jp

Glycative Stress Research 2024; 11 (4): 151-167

(c) Society for Glycative Stress Research

formation may reduce AGEs in the blood.

Wine drinking has been popular throughout the world for centuries. Epidemiological and clinical evidence suggests that wine in moderate contents has positive effects on health<sup>20</sup>. However, because wine contains alcohol, there are limits to the content consumed, even in the absence of alcohol intolerance or underlying diseases that are adversely affected by alcohol consumption. In fact, excessive drinking has been reported to promote glycation<sup>4</sup>. Therefore, it is recommended to select wines that are more potent inhibitors of AGE formation so that they can be effective even when consumed in small amounts. The objective of this study was to evaluate the AGE formation inhibitory effect of 277 wines with various combinations of wine color, grape variety, producing country, and vinification method, and to clarify the trend. Concurrently, the total polyphenol content was measured and its correlation with the inhibition of AGE formation in wine was discussed.

## Methods

### Samples and reagents

The wines used were 277 brands (56 white wines, 10 rosé wines, 16 orange wines, and 195 red wines) from 21 countries imported by Mottox Inc. (Osaka). Each wine was prepared in a 5-fold, 25-fold, 50-fold, and 100-fold diluted state in addition to the undiluted state. For dilution, a 13.5% ethanol solution was used. Human serum albumin was purchased from Sigma-Aldrich (St. Louis, MO), Folin-Ciocalteu's phenol reagent (FC phenol reagent, 2 N) and gallic acid from Merck Ltd. (Tokyo), and all other reagents from Fujifilm Wako Pure Chemicals Co. (Osaka).

### Determination of total polyphenol content

As previously reported<sup>21</sup>, total polyphenol content was determined for each wine using the FC method. The FC phenol reagent was diluted 2-fold with distilled water in advance. Add 100 g of sodium carbonate to 500 mL of distilled water and dissolve by boiling, and cooled at room temperature and filtered after 1 day. 0.25 g of dried gallic acid was dissolved in 5 mL of ethanol in a 50 mL female flask and diluted with water to make a stock solution of 5 g/L gallic acid. Using this stock solution, standard solutions of 0, 50, 100, 150, 250, 350, 450, and 600 mg/L of gallic acid were prepared. The sample wines were red wine diluted 10-fold, orange wine diluted 5-fold, rosé wine diluted 2-fold, and undiluted white wine.

In a micro tube, take 790 µL of distilled water, add 10 µL of the standard solution of gallic acid or sample wine, and mix thoroughly. 50 µL of FC reagent was added and mixed thoroughly. Then, within 30 seconds to 8 minutes, add 150 µL of sodium carbonate solution and mix thoroughly. The solution is allowed to stand at 20 °C for 2 hours, then 200 µL is transferred to a clear microplate and the absorbance at 750 nm is measured with a microplate reader Infinite 200 PRO (Tecan Japan Co., Ltd., Kanagawa). A calibration curve was prepared by plotting the absorbance at 750 nm against the concentration of a standard solution of gallic acid, and the total phenolic content of the wine in terms of gallic acid

was calculated from the absorbance at 750 nm for the sample wine and the dilution factor.

### Evaluation of fluorescence AGE formation inhibitory effect

The human serum albumin (HSA)-glucose glycation model<sup>22</sup> was used to evaluate the anti-glycation effect by measuring fluorescence AGE formation. Solution preparation was performed in deep-well plates using an automated pipetting system Freedom EVO 100 (Tecan Japan Co., Ltd., Kanagawa). 500 µL of 0.1 mol/L phosphate buffer (PBS, pH 7.4), 200 µL of 40 mg/mL HSA solution, and 100 µL of 2.0 mol/L glucose solution, and 100 µL of various concentrations of wine were used. Distilled water was then added to bring the total volume to 1.0 mL (Solution A). At the same time, a solution of distilled water was incubated as a blank for each reaction instead of the glucose solution (Solution B). Instead of adding wine, 100 µL of 13.5% aqueous ethanol solution was added to reach the same alcoholic strength as the wine, and distilled water was added to make a total volume of 1.0 mL and incubated (Solution C). Meanwhile, a solution with distilled water instead of glucose solution was incubated as a blank when no wine was added (solution D).

After each solution was adjusted, it was incubated at 60 °C for 40 hours. After the reaction, 200 µL of the solution was transferred to a black microplate and the fluorescence intensity (*FI*) derived from AGEs was measured using a microplate reader Infinite 200 Pro at an excitation wavelength of 360 nm and fluorescence wavelength 430 nm. The inhibition ratio of fluorescence AGE formation in wine (%) was calculated by the following equation.

$$\text{Inhibition of AGE formation (\%)} \\ = [1 - (FI_A - FI_B) / (FI_C - FI_D)] \times 100$$

A calibration curve was created based on the inhibition ratio of fluorescence AGE formation at five concentrations (0.1%, 0.02%, 0.004%, 0.002%, and 0.001%), and the half maximal inhibitory concentration ( $IC_{50}$ ) was calculated from the total polyphenol content of each wine.

### Statistical analysis

Comparisons of total polyphenol content and  $IC_{50}$  with wine color, grape variety, and producing country were evaluated using Tukey's multiple comparison test. All statistical analyses were performed using EZR version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama)<sup>23</sup>. Statistical significance was defined as a *p* value < 0.05.

## Results

### Total polyphenol content

The total polyphenol content of each wine is shown in **Table 1**. Values ranged from 198 mg/L to 4,910 mg/L in terms of gallic acid. The mean values of total polyphenol content for each wine color are also shown in **Fig. 1**. The total polyphenol content of white wines was  $282 \pm 50.6$  mg/L and that of rosé wines was  $290 \pm 80.2$  mg/L, but the difference

was not significant. The total polyphenol content was significantly higher in red wine ( $2,770 \pm 643$  mg/L), orange wine ( $1,240 \pm 500$  mg/L), and rosé wine  $\approx$  white wine, in that order. In order to consider varietal differences between red and orange wines, single varietal wines were defined as those containing at least 75% of one grape variety. The each pair of Garnacha and Grenache, Pinot Noir and Pinot Nero, Primitivo and Zinfandel, and Syrah and Shiraz are synonyms, and therefore considered to be the same variety. The total polyphenol content per variety for red and orange wines with at least three samples of a single variety (18 varieties) is shown in [Fig. 2](#). The total polyphenol content of wines made from Saperavi was  $4,540 \pm 511$  mg/L, significantly higher than the other 13 varieties except Aglianico ( $3,270 \pm 614$  mg/L) and Montepulciano ( $3,430 \pm 590$  mg/L) and Tannat ( $3,220 \pm 126$  mg/L) ( $p < 0.05$ ). The total polyphenol content of wines made from Pinot Noir / Pinot Nero was  $2,190 \pm 362$  mg/L and was significantly lower than that of Aglianico, Cabernet Sauvignon ( $2,760 \pm 463$  mg/L), Merlot ( $3,220 \pm 126$  mg/L), Montepulciano, Primitivo/Zinfandel ( $3,080 \pm 543$  mg/L), and Saperavi ( $p < 0.05$ ). The total polyphenol content of wines made from Rkatsiteli were  $1,650 \pm 390$  mg/L, significantly lower than those of Aglianico, Monastrell ( $2,930 \pm 200$  mg/L), Montepulciano, Primitivo/Zinfandel, Saperavi and Tannat ( $p < 0.05$ ). No significant differences in total polyphenol content were found among these other varieties. The mean total polyphenol content per producing country for red and orange wines with at least three samples (12 countries) are shown in [Fig. 3](#). The total polyphenol content of Italian wines ( $3,000 \pm 601$  mg/L) was significantly higher than that of South African ( $2,310 \pm 394$  mg/L) and New Zealand ( $2,050 \pm 432$  mg/L) wines ( $p < 0.05$ ). There were no significant differences in total polyphenol content among the other producing countries.

### Inhibitory effect on fluorescence AGE formation

[Fig. 4](#) shows the results of the plot of total polyphenol content versus fluorescence AGE formation inhibition at each concentration for the 277 wines. All wines showed inhibition of AGE formation: 46.1%  $\sim$  98.5% for undiluted wines, 12.7%  $\sim$  83.2% for 5-fold dilution, 6.51%  $\sim$  70.7% for 25-fold dilution, 5.15%  $\sim$  65.6% for 50-fold dilution, and 4.74%  $\sim$  61.2% for 100-fold dilution. At all concentrations, there was a high correlation between the total polyphenol content and the inhibition ratio of AGE formation. This correlation was higher for the 25-fold dilution ( $R^2 = 0.863$ ), 50-fold dilution ( $R^2 = 0.811$ ), 5-fold dilution ( $R^2 = 0.767$ ), undiluted wines ( $R^2 = 0.756$ ), and 100-fold dilution ( $R^2 = 0.736$ ).

[Table 1](#) shows the  $IC_{50}$  calculated from the calibration curve obtained from the inhibition rate of fluorescence AGE formation at each concentration and the total polyphenol content. Values ranged from  $1.24$   $\mu$ g/mL to  $99.0$   $\mu$ g/mL. The mean  $IC_{50}$  for each wine color is shown in [Fig. 5](#). The  $IC_{50}$  for orange wine was  $8.67 \pm 2.76$   $\mu$ g/mL and for red wine was  $9.85 \pm 4.09$   $\mu$ g/mL, but there was no significant difference in  $IC_{50}$ . The  $IC_{50}$  values were significantly lower in the following order: orange wine  $\approx$  red wine, rose wine ( $30.7 \pm 13.7$   $\mu$ g/mL), and white wine ( $41.3 \pm 16.1$   $\mu$ g/mL). The mean  $IC_{50}$  for each grape variety is shown in [Fig. 6](#), and there was no significant difference in  $IC_{50}$  among the varieties. The mean  $IC_{50}$  for

each producing country is shown in [Fig. 7](#). The  $IC_{50}$  for wines from Georgia was  $4.98 \pm 2.28$   $\mu$ g/mL, which was significantly lower than for wines from France ( $10.7 \pm 4.76$   $\mu$ g/mL) and South Africa ( $13.2 \pm 2.09$   $\mu$ g/mL) and Australia ( $11.6 \pm 4.66$   $\mu$ g/mL,  $p < 0.05$ ). Also, wines from Italy ( $8.48 \pm 3.44$   $\mu$ g/mL) and the U.S.A. ( $7.61 \pm 1.63$   $\mu$ g/mL) had significantly lower  $IC_{50}$  values than those from South Africa ( $p < 0.05$ ). No significant differences in  $IC_{50}$  were found between the other producing countries.

## Discussion

### Wine color

The color of wine is determined by how the black or white grapes used as raw material are vinified. White wines are fermented exclusively from the juice obtained from crushed and pressed white grapes, and thus their color will be almost identical to that of the juice. On the other hand, most red wines are fermented from crushed black grapes and undergo a process called “maceration” to extract pigments and components from the skins and seeds. The grapes are then pressed and moved to the maturation process. Most black grapes, like white grapes, have clear pulp and do not develop the color of red wine simply by pressing, but a characteristic color is achieved by maceration. In orange wine, white grapes are macerated and fermented in the same way as in the red wine process to extract pigments and components from the white grapes and achieve an orange-like color. As with red wine, the pigments and components are extracted differently depending on the length of maceration, fermentation temperature, and grape variety, with orange wines ranging from yellow to orange to amber (mainly found in Georgia). Rosé wine can be produced through various methods. The “direct pressing method” involves pressing black grapes like white grapes, resulting in a pale pink juice that is fermented. The “maceration method” involves briefly macerating black grapes, same as red wine production, and stopping the process when the desired color and flavor are achieved. In some regions, rosé can also be produced by blending white and red wines. Additionally, rosé wines may be vinified using a mix of black and white grapes, either with the direct pressing method or the maceration method, contributing to the wide range of rosé colors. All of this indicates that the differences in total polyphenol content for each wine color shown in [Fig. 1](#) are a direct reflection of the differences in production methods, *i.e.*, color. The fact that there was no significant difference in total polyphenol content between rosé and white wines was also due to the rosé wine production method. The direct pressing method is the same process as for white wine, and even if the maceration method is used, it is a far shorter maceration period and fermentation at lower temperatures than for red wine or orange wine, and therefore does not extract as many phenolic compounds. In the case of orange wines, the duration of maceration and temperature can be adjusted more flexibly than with red wines, resulting in a wider range of total polyphenol content. Furthermore, the differences in the type and content of phenolic compounds between white and black grapes are likely to be reflected in the significantly higher total polyphenol content in red wines.

Table 1. Total polyphenol content and anti-glycation activity of 277 wines

ID	Color	Winery/Winemaker	Product	Grape varieties	Country	Region	Designation of Origin	Vintage	Alc/vol (%)	Total polyphenol content (µg/mL)
1	White	Chateau Lamothe Vincent	Chateau Lamothe Vincent Blanc	Sauvignon Blanc 87%/Semillon 13%	France	Bordeaux	A.O.C. Bordeaux	2020	12.5	248
2	White	Domaines Paul Mas	Les Tannes en Occitanie Chardonnay	Chardonnay 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	13.5	283
3	White	Domaines Paul Mas	Les Tannes en Occitanie Sauvignon Blanc	Sauvignon Blanc 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	12.5	212
4	White	Domaines Paul Mas	La Forge Estate Unwooded Chardonnay	Chardonnay 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	13.5	273
5	White	Domaines Paul Mas	La Forge Estate Chardonnay	Chardonnay 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	13.5	261
6	White	Domaines Paul Mas	La Forge Estate Sauvignon Blanc	Sauvignon Blanc 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	12	217
7	White	Domaines Paul Mas	La Forge Estate Viognier	Viognier 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	13.5	279
8	White	Domaines Paul Mas	La Forge Estate Gewurztraminer	Gewurztraminer 100%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2022	13.5	264
9	White	Champagne Beaumont des Crayeres	Grande Reserve Brut	Meunier 60%/Chardonnay 25%/Pinot Noir 15%	France	Champagne	A.O.C. Champagne	NV	12.5	228
10	White	TERRE E BORGHI	Piemonte Chardonnay	Chardonnay 100%	Italy	Piemonte	Piemonte D.O.C.	2021	12	210
11	White	Casa Vinicola SARTORI SPA	Soave Classico	Garganega 90%/Trebiano 10%	Italy	Veneto	Soave D.O.C.	2021	12	210
12	White	Terre Cevico Soc. Coop. Agricola	Terre Cevico Albana di Romagna Secco	Albana 100%	Italy	Emilia Romagna	Romagna Albana D.O.C.G.	2021	12.5	351
13	White	Terre Cevico Soc. Coop. Agricola	Austo Chardonnay	Chardonnay 100%	Italy	Emilia Romagna	Vino	2021	13	331
14	White	Mastroberardino Societa' Agricola Srl	Lacryma Christi del Vesuvio Bianco	Coda di Volpe 100%	Italy	Campania	Lacryma Christi del Vesuvio D.O.C.	2022	12.5	208
15	White	Azienda Agricola Conti Zecca	Donna Marzia Chardonnay Barrique	Chardonnay 85%/Malvasia Bianca 15%	Italy	Puglia	Salento I.G.P.	2021	12.5	259
16	White	Cantina e Oleificio Sociale	Domodo Chardonnay	Chardonnay 100%	Italy	Puglia	Puglia I.G.P.	2020	12	309
17	White	Cantina e Oleificio Sociale	Domodo Pinot Grigio	Pinot Grigio 100%	Italy	Puglia	Puglia I.G.P.	2021	12	305
18	White	Feudo Arancio	Pinot Grigio	Pinot Grigio 100%	Italy	Sicilia	Sicilia D.O.C.	2021	13	288
19	White	Feudo Arancio	Grillo	Grillo 100%	Italy	Sicilia	Sicilia D.O.C.	2021	13	296
20	White	Cantine Aurora	ERA Grillo	Grillo 100%	Italy	Sicilia	Sicilia D.O.C.	2021	12.5	270
21	White	Cantine Europa	Roceno Grillo Sicilia D.O.C.	Grillo 100%	Italy	Sicilia	Sicilia D.O.C.	2021	12.5	277
22	White	De Haan Altes	El Convertido Verdejo	Verdejo 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	12	399
23	White	De Haan Altes	El Convertido Sauvignon Blanc	Sauvignon Blanc 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	12	402
24	White	Domino de Punctum	Lobelia Chardonnay	Chardonnay 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	13	225
25	White	Real Compania de Vinos	Reales Vinedos Blanco	Macabeo 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2020	12.5	291
26	White	Baica Vinos y Vinedos	Antonita Puntelos Baica Tempranillo Blanco	Tempranillo Blanco 100%	Spain	La Rioja	Rioja D.O.C.a.	2021	12.5	254
27	White	Casa Relvas	Atlantico Branco Reserva	Antao Vaz 50%/Verdelho 40%/Viognier 10%	Portugal	Alentejano	Vinho Regional Alentejano	2021	12.5	295
28	White	Hattingley Valley	Hattingley Valley Classic Reserve Brut	Chardonnay 47%/Pinot Noir 32%/Meunier 19%/Pinot Noir Precoce 2%	U.K.	England	P.D.O. English	NV	12	251
29	White	Weingut Schloss Gobelburg	Domaene Gobelburg Gruner Veltliner	Gruener Veltliner 100%	Austria	Niederosterreich	Kamptal D.A.C.	2022	12.5	252
30	White	Chateau Derezla	Tokaji Furmint Dry White	Furmint 87%/Sarga Muskotaly 13%	Hungary	Tokaj	D.H.C. Tokaji	2021	12	300
31	White	Vile Budureasca	Vine in Flames Fetesca Regala	Fetesca Regala 100%	Romania	Muntenia	D.O.C. Dealu Mare	2020	13.5	321
32	White	Vile Budureasca	Vine in Flames Chardonnay	Chardonnay 100%	Romania	Muntenia	D.O.C. Dealu Mare	2021	13.5	414
33	White	Spier Wines	Spier Chardonnay	Chardonnay 100%	South Africa	Western Cape	W.O. Western Cape	2022	13.5	304
34	White	Spier Wines	Spier Sauvignon Blanc	Sauvignon Blanc 90%/Semillon 10%	South Africa	Western Cape	W.O. Western Cape	2022	13.5	237
35	White	The Fair Valley Wine Company	Fairvalley Chenin Blanc	Chenn Blanc 100%	South Africa	Western Cape	W.O. Coastal Region	2021	13.5	45.2
36	White	MAN Vintners	Okha Chardonnay	Chardonnay 100%	South Africa	Western Cape	W.O. Western Cape	2021	13.5	330
37	White	MAN Vintners	Okha Chenin Blanc	Chenin Blanc 100%	South Africa	Western Cape	W.O. Western Cape	2022	13.5	278
38	White	Boutinot Ltd.	Cape Heights Chenin Blanc	Chenin Blanc 100%	South Africa	Western Cape	W.O. Western Cape	2022	12	281
39	White	Boutinot Ltd.	Cape Heights Viognier	Viognier 100%	South Africa	Western Cape	W.O. Western Cape	2020	12.5	273
40	White	Ironstone Vineyards	Stone Valley Chardonnay	Chardonnay mainly	U.S.A.	California	California	2019	13.5	305
41	White	Ironstone Vineyards	Ironstone Chardonnay	Chardonnay mainly	U.S.A.	California	Lodi A.V.A.	2021	14.5	331
42	White	Delicato Family Vineyards	1924 Scotch Barrel Chardonnay	Chardonnay mainly	U.S.A.	California	California	2019	13.5	340
43	White	Vina Marchigue	Panel Chardonnay Reserva Especial	Chardonnay 100%	Chile	Central Valley	Curico Valley D.O.	2021	13.5	258
44	White	Vina del Pedregal S.A	Aves del sur Chardonnay Reserva	Chardonnay 100%	Chile	Central Valley	D.O. Loncomilla Valley	2021	13.5	405
45	White	Vina del Pedregal S.A	Aves del sur Sauvignon Blanc Reserva	Sauvignon Blanc 100%	Chile	Central Valley	D.O. Loncomilla Valley	2018	13.5	262

46	White	Vina del Pedregal S.A	Aves del sur Gewurztraminer Reserva	Gewurztraminer 100%	Chile	Central Valley	D.O. Loncomilla Valley	2021	14	309	23.7
47	White	V.E.S.A	Gamma Organic Chardonnay Reserva	Chardonnay mainly	Chile	Aconcagua	Casablanca Valley D.O.	2022	13.5	256	29.7
48	White	V.E.S.A	Gamma Organic Sauvignon Blanc Reserva	Sauvignon Blanc mainly	Chile	Aconcagua	Casablanca Valley D.O.	2021	12.5	230	25.8
49	White	V.E.S.A	Gamma Organic Gewurztraminer Reserva	Gewurztraminer mainly	Chile	Central Valley	Rapel Valley D.O.	2021	13	266	63.5
50	White	Bodegas Callia	Callia Chardonnay - Torrontes	Chardonnay 60%/Torrontes 40%	Argentina	San Juan		2022	13	207	27.9
51	White	Berton Vineyards Pty Ltd	Metal Classic Chardonnay	Chardonnay 100%	Australia	South Australia	South Eastern Australia G.I.	2021	13.5	341	38.6
52	White	Berton Vineyards Pty Ltd	Metal Sauvignon Blanc	Sauvignon Blanc 100%	Australia	South Australia	Padthaway G.I.	2022	12.5	288	32.2
53	White	Logan Wines	Apple Tree Flat Chardonnay	Chardonnay 100%	Australia	New South Wales	Central Ranges G.I.	2021	12.5	262	64.1
54	White	Boatshed Bay	Boatshed Bay Marlborough Sauvignon Blanc	Sauvignon Blanc 100%	New Zealand	South Island	Marlborough G.I.	2022	12.5	234	22.4
55	White	Boatshed Bay	Boatshed Bay Pinot Gris	Pinot Gris 100%	New Zealand		Marlborough G.I.	2021	13.5	268	41.6
56	White	Katsunuma Jozo	KOSHU TERROIR SELECTION IWAI	Koshu 100%	Japan	Yamanashi	G.I. Yamanashi	2022	11.5	348	24.8
57	Rose	Chateau de Segries	Tavel Rose	Grenache 50%/Cinsaut 30%/Clarette 10%/Syrah 10%	France	Cotes du Rhone	A.O.C. Tavel	2021	14.5	512	13.3
58	Rose	Domaines Paul Mas	Claude Val Rose	Grenache 50%/Cinsaut 30%/Syrah 20%	France	Languedoc & Roussillon	I.G.P. Pay d'Oc	2021	12.5	247	28.3
59	Rose	Casa Vinicola SARTORI SPA	Villa Mura Pinot Grigio Blush	Pinot Grigio 100%	Italy	Veneto	Delle Venezie D.O.C.	2021	12	263	28.0
60	Rose	Feudo Arancio	Rosato	Nero d'Avola 100%	Italy	Sicilia	Terre Siciliane I.G.T.	2021	12	247	28.5
61	Rose	Cantine Europa	Roceno Rosato Di Nerello Mascalese Terre Siciliane I.G.P.	Nerello Mascalese 100%	Italy	Sicilia	Terre Siciliane I.G.P.	2021	12	290	17.0
62	Rose	De Haan Altes	El Conventido Tempranillo Rose	Tempranillo 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	11.5	319	26.8
63	Rose	Cooperativa Agraria Santa Quitéria	Higuera Rosa	Syrah 100%	Spain	Castilla La Mancha	Almansa D.O.	2021	12.5	293	56.6
64	Rose	Baica Vinos y Vinedos	Antonita Puntuelos Baica Garnacha Rosado	Garnacha 100%	Spain	La Rioja	Rioja D.O.C.a.	2021	13.5	274	43.4
65	Rose	Vina Valdivieso	Valdivieso Brut Rose	Chardonnay/Pinot Noir	Chile	Central Valley		NV	12	198	16.2
66	Rose	Logan Wines	Apple Tree Flat Rose	Merlot 45%/Shiraz 37%/Tempranillo 18%	Australia	New South Wales	Central Ranges G.I.	2019	13	256	48.7
67	Orange	Maison Marius Bielle	BAZOOKA	Sauvignon Blanc/Semillon/Muscadelle (Blend ratios are not disclosed.)	France	Bordeaux	Vin de France	2022	13.5	1430	6.95
68	Orange	DOMAINE DE LA PINTÉ	SavOr	Savagnin 100%	France	Jura	Vin de France	2022	13	1340	8.59
69	Orange	Primostic s.r.l.	Ribolla Gialla Riserva	Ribolla Gialla 100%	Italy	Friuli Venezia Giulia	Collio D.O.C.	2019	13.5	1330	6.69
70	Orange	Primostic s.r.l.	Pinot Grigio Orange Wine	Pinot Grigio 100%	Italy	Friuli Venezia Giulia	Collio D.O.C.	2020	14	1170	7.20
71	Orange	Azienda Agricola Conti Zecca	CALAVENTO ORANGE	Malvasia Bianca 100%	Italy	Puglia	Salento I.G.T.	2021	12.5	740	8.42
72	Orange	Domino de Punctum	20000 Leguas	Chardonnay 34%/Viognier 33%/Viura 33%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	12.5	915	16.7
73	Orange	Bodegas Jimenez-Landi	Vino Naranja	Garnacha 50%/Malvar 50%	Spain	Castilla La Mancha		2022	14	1320	7.46
74	Orange	Bodegas Azul y Garanza	Naturalza Salvaje Garnacha Blanca	Garnacha Blanca 100%	Spain	Navarra	Vino	2022	13	950	6.89
75	Orange	Casa Relvas	Art Terra Curtimenta	Antao Vaz 50%/Arinto 45%/Viognier 5%	Portugal	Alentejano	Vinho Regional Alentejano	2021	12.5	480	10.6
76	Orange	Sant'Or Winery	Sant'Or Roditis Amphora Aging Skin Contact	Roditis 100%	Greece	Peloponnese	P.G.I. Achaia	2022	12.5	1770	6.53
77	Orange	Vaziani Winery	Makashvili Wine Cellar Rkatsiteli	Rkatsiteli 100%	Georgia	Kakheti		2020	13	1340	5.96
78	Orange	Qvevri Wine Cellar	Rkatsiteli Qvevri	Rkatsiteli 100%	Georgia	Kakheti		2021	13	1410	6.32
79	Orange	Shalauri Wine Cellars	Rkatsiteli	Rkatsiteli 100%	Georgia	Kakheti		2019	12	2200	8.10
80	Orange	Shalauri Wine Cellars	Mtsvane	Mtsvane 100%	Georgia	Kakheti		2020	12.5	2180	8.47
81	Orange	Logan Wines	Clementine Pinot Gris	Pinot Gris 100%	Australia	New South Wales	Central Ranges G.I.	2022	12	610	11.3
82	Orange	Vintelofer	Park Wine White	Gewurztraminer 100%	Australia	South Australia	Adelaide Hills G.I.	2022	12	610	12.7
83	Red	Chateau Roquebrune	Chateau Roquebrune	Cabernet Sauvignon 100%	France	Bordeaux	A.O.C. Bordeaux	2018	13.5	2940	9.93
84	Red	Chateau Couronneau	Chateau Couronneau Rouge	Merlot 100%	France	Bordeaux	A.O.C. Bordeaux Supérieur	2021	14	3680	4.40
85	Red	Chateau Poupille	Chateau Poupille	Merlot 100%	France	Bordeaux	A.O.C. Castillon Cotes de Bordeaux	2018	13.5	3080	9.95
86	Red	Chateau Poupille	Poupille	Merlot 100%	France	Bordeaux	A.O.C. Castillon Cotes de Bordeaux	2017	14.5	3070	7.42
87	Red	Maison Marius Bielle	BRUT(ES)	Merlot 100%	France	Bordeaux	A.O.C. Lalande de Pomerol	2021	13	3150	8.17
88	Red	Chateau Bel Air Lagrave	Chateau Bel Air Lagrave	Cabernet Sauvignon 60%/Merlot 35%/Petit Verdot 5%	France	Bordeaux	A.O.C. Moulis	1988	12.5	2880	16.4
89	Red	Chateau Cos d'Estournel	Les Pagodes de Cos	Cabernet Sauvignon 55%/Merlot 36%/Cabernet Franc 5%/Petit Verdot 4%	France	Bordeaux	A.O.C. St-Estephe	2019	13.5	2550	14.2
90	Red	Chateau Croizet Bages	Chateau Croizet Bages	Cabernet Sauvignon 66%/Merlot 34%	France	Bordeaux	A.O.C. Pauillac	2019	14.5	3260	14.0

Inhibition of AGE Formation in Wine and Polyphenols

91	Red	Chateau Croizet Bages	Chateau Croizet Bages	Cabernet Sauvignon 70%/Merlot 27%/Cabernet Franc 3%	France	Bordeaux	A.O.C.Pauillac	2008	13	2720	21.1
92	Red	Chateau Leoville Las Cases	Le Petit Lion du Marquis de Las Cases	Cabernet Sauvignon 46%/Merlot 43%/Cabernet Franc 11%	France	Bordeaux	A.O.C.St-Julien	2019	13.5	2800	9.42
93	Red	Chateau d'Issan	Blason d'Issan	Merlot 60%/Cabernet Sauvignon 40%	France	Bordeaux	A.O.C.Margaux	2019	13.5	2830	9.83
94	Red	Chateau d'Issan	Chateau d'Issan	Cabernet Sauvignon 70%/Merlot 30%	France	Bordeaux	A.O.C.Margaux	2019	13.5	2640	11.8
95	Red	Chateau Haut Bailly	Haut Bailly II	Merlot 60%/Cabernet Sauvignon 40%	France	Bordeaux	A.O.C.Pessac-Leognan	2019	14	2960	9.05
96	Red	Chateau Valandraud	Virginie de Valandraud	Merlot 70%/Cabernet Franc 20%/Cabernet Sauvignon 10%	France	Bordeaux	A.O.C.St-Emilion	2019	14.5	3130	7.24
97	Red	Francois Thienpont	Les Filloottes	Merlot 85%/Cabernet Franc 15%	France	Bordeaux	A.O.C.Pomerol	2019	14.5	3760	6.23
98	Red	Couvent des Visitandines	Bourgogne Pinot Noir	Pinot Noir 100%	France	Bourgogne	A.O.C.Bourgogne	2020	12.5	2570	8.97
99	Red	Clos du Moulin Aux Moines	Bourgogne Clos de la Perriere Red	Pinot Noir 100%	France	Bourgogne	A.O.C.Bourgogne	2020	12.5	2180	14.9
100	Red	Clos du Moulin Aux Moines	Pommard Village	Pinot Noir 100%	France	Bourgogne	A.O.C.Pommard	2020	13	2700	12.4
101	Red	Paul Beaudet	Beaujolais	Gamay 100%	France	Bourgogne	A.O.P.Beaujolais	2020	13	2790	6.43
102	Red	Paul Beaudet	Beaujolais-Villages	Gamay 100%	France	Bourgogne	A.O.P.Beaujolais-Villages	2020	13	3310	5.62
103	Red	Pierre Marie Chermette	Beaujolais Nouveau Les Griottes Par Avion	Gamay 100%	France	Bourgogne	A.O.P.Beaujolais	2023	13	1690	10.3
104	Red	Chateau des Maladrets	Beaujolais-Villages Nouveau Par Avion	Gamay 100%	France	Bourgogne	A.O.C.Beaujolais-Villages	2023	12.5	2620	7.85
105	Red	Domaine Marc Delienne	Fleurie Greta Carbo	Gamay 100%	France	Bourgogne	A.O.C.Fleurie	2019	13.5	1500	11.7
106	Red	Domaines Paul Jaboulet Aine	Crozes Hermitage Domaine de Thalabert Rouge	Syrah 100%	France	Cotes du Rhone	A.O.C.Croze Hermitage	2020	14	2550	9.79
107	Red	Domaines Paul Jaboulet Aine	Hermitage La Maison Bleue Rouge	Syrah 100%	France	Cotes du Rhone	A.O.C.Hermitage	2020	15.5	2370	8.80
108	Red	Vignobles & Compagnie	Cotes du Rhone Rouge "Grande Reserve"	Grenache 80%/Syrah 20%	France	Cotes du Rhone	A.O.C.Cotes du Rhone	2020	14	2410	17.1
109	Red	SCA Les Vignerons d'Estezargues	Sy... Cotes du Rhone Village Signargue	Syrah 90%/Grenache 10%	France	Cotes du Rhone	A.O.P.Cotes du Rhone Village	2019	14.5	3220	9.03
110	Red	Domaines Paul Mas	Les Tannes en Occitanie Cabernet Sauvignon	Cabernet Sauvignon 100%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2021	14	2700	4.70
111	Red	Domaines Paul Mas	Les Tannes en Occitanie Merlot	Merlot 100%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2020	14	2590	5.71
112	Red	Domaines Paul Mas	Les Tannes en Occitanie Pinot Noir	Pinot Noir 100%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2021	13	2120	7.92
113	Red	Domaines Paul Mas	La Forge Estate Cabernet Sauvignon	Cabernet Sauvignon 100%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2021	14	2700	6.72
114	Red	Domaines Paul Mas	La Forge Estate Merlot	Merlot 100%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2020	14	2740	6.04
115	Red	Domaines Paul Mas	La Forge Estate Pinot Noir	Pinot Noir 100%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2021	13.5	2240	9.78
116	Red	Domaines Paul Mas	La Forge Estate Syrah-Vioignier	Syrah 84%/Vioignier 16%	France	Languedoc & Roussillon	I.G.P.Pay d'Oc	2021	13.5	2590	10.0
117	Red	FONTAINE DES GRIVES	L'Envol Rouge Vin de France	Merlot 100%	France	Sud-Ouest	Vin de France	2021	12	813	17.4
118	Red	FONTAINE DES GRIVES	Les Sentin/Ailes Rouge Vin de France	Merlot 100%	France	Sud-Ouest	Vin de France	2020	14.5	2220	19.9
119	Red	Le Cedre Diffusion	Chateau Haut Monplaisir Tradition Cahors	Malbec 100%	France	Sud-Ouest	A.O.C.Cahors	2019	13	3400	20.4
120	Red	Famille Laplace	Aramis Rouge	Tannat 75%/Syrah 25%	France	Sud-Ouest	Vin de France	NV	13.5	3060	17.1
121	Red	Famille Laplace	Les 2 Vaches Rouges	Tannat 100%	France	Sud-Ouest	Vin de France	NV	13.5	3250	21.0
122	Red	Chateau d'Aydie	Ode d'Aydie Madiran	Tannat 100%	France	Sud-Ouest	A.O.P.Madiran	2017	14	3400	5.90
123	Red	Chateau d'Aydie	Chateau d'Aydie Madiran	Tannat 100%	France	Sud-Ouest	A.O.P.Madiran	2017	14.5	3150	4.02
124	Red	TERRE E BORGHI	Barbera d'Asti	Barbera 100%	Italy	Piemonte	Barbera d'Asti D.O.C.G.	2021	13	2110	10.4
125	Red	TERRE E BORGHI	Langhe Nebbiolo	Nebbiolo 100%	Italy	Piemonte	Langhe D.O.C.	2020	13.5	2270	10.4
126	Red	Ca del Baio	BRIC DEL BAIO Langhe DOC Nebbiolo	Nebbiolo 100%	Italy	Piemonte	Langhe D.O.C.	2021	14.5	2670	4.10
127	Red	Casa Vinicola Nicoletto	Langhe Nebbiolo	Nebbiolo 100%	Italy	Piemonte	Langhe D.O.C.	2008	13	2770	10.0
128	Red	Azienda Agricola Deltetto S.S.	Roero Rosso Gorrini	Nebbiolo 100%	Italy	Piemonte	Roero D.O.C.G.	2019	14	2740	4.75
129	Red	Cantine San Silvestro	Barbaresco Magno	Nebbiolo 100%	Italy	Piemonte	Barbaresco D.O.C.G.	2020	14	2530	7.15
130	Red	Cantine San Silvestro	Barolo Patres	Nebbiolo 100%	Italy	Piemonte	Barolo D.O.C.G.	2019	14	3260	4.79
131	Red	Casa Vinicola SARTORI SPA	Villa Mura Pinot Nero	Pinot Nero 100%	Italy	Veneto	Trevezze I.G.T.	2019	13	2240	10.1
132	Red	Casa Vinicola SARTORI SPA	Cabernet Sauvignon Organic	Cabernet Sauvignon 100%	Italy	Veneto	Vino	NV	12	2110	11.8
133	Red	Le Ville di Antiane Srl	Amarone della Valpolicella	Corvina 65%/Covivone 20%/Rondinella 15%	Italy	Veneto	Amarone della Valpolicella D.O.C.G.	2019	15	2840	4.21
134	Red	Tenuta Sant'Antonio	Sant' Antonio Amarone della Valpolicella	Corvina 70%/Rondinella 20%/Croatina 5%/Osceleta 5%	Italy	Veneto	Amarone della Valpolicella D.O.C.G.	2018	15	3030	3.79
135	Red	Medici Ermate & Figli s.r.l.	Quercioni Reggiano Lambrusco Secco	Lambrusco Salamino/Lambrusco Marani	Italy	Emilia Romagna	Reggiano D.O.C.	NV	11	3090	5.90
136	Red	Medici Ermate & Figli s.r.l.	Concerto Lambrusco Reggiano Secco	Lambrusco Salamino 100%	Italy	Emilia Romagna	Reggiano D.O.C.	2022	11.5	1640	11.0

137	Red	Terre Ceviso Soc. Coop. Agricola	Austo Merlot Rubicone IGT	Merlot 100%	Italy	Emilia Romagna	Rubicone I.G.T.	2020	14	3910	5.29
138	Red	Terre Ceviso Soc. Coop. Agricola	Merlot Rubicone IGP Biologico	Merlot 100%	Italy	Emilia Romagna	Rubicone I.G.P.	2021	14	2850	8.83
139	Red	Azienda Agricola F.lli Grati	Rosso di Toscana CAVALIERE	Sangiovese 90%/Caniolo 7%/Colorino 3%	Italy	Toscana	Toscana I.G.T.	2018	13	2690	12.2
140	Red	Azienda Agricola F.lli Grati	Chianti CAVALIERE	Sangiovese 90%/Caniolo 7%/Colorino 3%	Italy	Toscana	Chianti D.O.C.G.	2020	12.5	2710	11.7
141	Red	Azienda Agricola F.lli Grati	Chianti Rufina VILLA DI VETRICE	Sangiovese 90%/Caniolo 7%/Colorino 3%	Italy	Toscana	Chianti D.O.C.G.	2018	13.5	2640	9.60
142	Red	Castelli del Grevepesa SCA	Clemente Sette Chianti Classico	Sangiovese 100%	Italy	Toscana	Chianti Classico Rufina	2019	14	2910	11.5
143	Red	Castelli del Grevepesa SCA	Clemente Sette Chianti Classico Riserva	Sangiovese 100%	Italy	Toscana	Chianti Classico Rufina	2018	14	2950	10.9
144	Red	Castelli Martinuzzi Societa Agricola S.S.	Rosso di Montalcino	Sangiovese 100%	Italy	Toscana	Rosso di Montalcino D.O.C.	2021	15	2270	12.7
145	Red	Castelli Martinuzzi Societa Agricola S.S.	Brunello di Montalcino	Sangiovese 100%	Italy	Toscana	Brunello di Montalcino D.O.C.G.	2017	14.5	3000	8.60
146	Red	Azienda Agricola Le Macchiole	Le Macchiole Bolgheri Rosso	Merlot 50%/Syrah 20%/Cabernet Franc 15%/Cabernet Sauvignon 15%	Italy	Toscana	Bolgheri D.O.C.	2020	14	2970	8.56
147	Red	Cantina Goretti	Montefalco Sagrantino	Sagrantino 100%	Italy	Umbria	Montefalco Sagrantino D.O.C.G.	2017	15.5	4030	2.18
148	Red	Cantine Aurora	ERA Montepulciano d'Abruzzo	Montepulciano 100%	Italy	Abruzzo	Montepulciano d'Abruzzo D.O.C.	2020	13	2850	8.66
149	Red	Cantina e Oleificio Sociale	Domodo Montepulciano d'Abruzzo	Montepulciano 100%	Italy	Abruzzo	Montepulciano d'Abruzzo D.O.P.	2020	13	4240	10.2
150	Red	Caldora s.r.l.	Caldora YUME Montepulciano d'Abruzzo	Montepulciano 100%	Italy	Abruzzo	Montepulciano d'Abruzzo D.O.C.	2020	13.5	3200	7.86
151	Red	Cantina Diomede	Canace	Nero di Troia(Uva di Troia)85%/Aglanico 15%	Italy	Puglia	Puglia I.G.P.	2019	13.5	3460	3.72
152	Red	Torrevento s.r.l.	Vento Rosso N (Nero di Troia IGT)	Nero di Troia (Uva di Troia) 100%	Italy	Puglia	Puglia I.G.T.	2020	13	3920	6.44
153	Red	Torrevento s.r.l.	Vento Rosso P (Primitivo IGT)	Primitivo 100%	Italy	Puglia	Puglia I.G.T.	2021	13	3770	7.25
154	Red	Azienda Agricola Conti Zecca	Donna Marzia Primitivo Barrique	Primitivo 85%/Negroamaro 15%	Italy	Puglia	Salento I.G.P.	2020	14	2430	14.6
155	Red	Azienda Agricola Conti Zecca	Passione oro appassimento	Primitivo 100%	Italy	Puglia	Salento I.G.P.	2019	14	2740	11.3
156	Red	Azienda Agricola Conti Zecca	Donna Marzia Aglianico	Aglianico 85%/Cabernet Sauvignon 15%	Italy	Puglia	Salento I.G.P.	2021	14	2310	11.7
157	Red	Azienda Agricola Conti Zecca	Donna Marzia Negroamaro	Negroamaro 85%/Cabernet Sauvignon 15%	Italy	Puglia	Salento I.G.P.	2021	14	2270	12.1
158	Red	Azienda Agricola Conti Zecca	Donna Marzia Cabernet Sauvignon Barrique	Cabernet Sauvignon 85%/Negroamaro 15%	Italy	Puglia	Salento I.G.P.	2019	14	2940	15.2
159	Red	Azienda Agricola Conti Zecca	Donna Marzia Merlot Barrique	Merlot 85%/Cabernet Sauvignon 15%	Italy	Puglia	Salento I.G.P.	2021	14.5	1930	16.5
160	Red	San Marzano vini S.p.A.	Il Pumo Primitivo	Primitivo 100%	Italy	Puglia	Salento I.G.P.	2021	13.5	3570	4.50
161	Red	San Marzano vini S.p.A.	Il Pumo Negroamaro	Negroamaro 100%	Italy	Puglia	Salento I.G.P.	2021	13.5	3650	4.17
162	Red	San Marzano vini S.p.A.	M Merlot	Merlot 100%	Italy	Puglia	Salento I.G.P.	2020	14.5	4100	5.39
163	Red	San Marzano vini S.p.A.	Collezione 50	Negroamaro 50%/Primitivo 50%	Italy	Puglia	Vino	NV	14.5	4000	7.37
164	Red	San Marzano vini S.p.A.	Talo Primitivo di Manduria	Primitivo 100%	Italy	Puglia	Primitivo di Manduria D.O.P.	2021	14	3880	8.10
165	Red	Cantina Diomede	Basilium Terre dei Portali Aglianico del Vulture	Aglianico 100%	Italy	Basilicata	Aglianico del Vulture D.O.C.	2020	13.5	3830	1.60
166	Red	Casa Vinicola D'Angelo	Aglianico del Vulture	Aglianico 100%	Italy	Basilicata	Aglianico del Vulture D.O.C.	2019	13.5	4060	1.24
167	Red	Mastroberardino Societa' Agricola Srl	Mastro Rosso Campania IGT	Aglianico 80%/Piedrosso 20%	Italy	Campania	Campania I.G.T.	2022	12.5	2720	15.6
168	Red	Mastroberardino Societa' Agricola Srl	Redimore Irpinia Aglianico	Aglianico 100%	Italy	Campania	Irpinia D.O.C.	2020	13.5	2830	8.72
169	Red	Mastroberardino Societa' Agricola Srl	Taurasi Radici	Aglianico 100%	Italy	Campania	Taurasi D.O.C.G.	2017	13.5	3800	6.47
170	Red	Mastroberardino Societa' Agricola Srl	Taurasi Radici Riserva	Aglianico 100%	Italy	Campania	Taurasi D.O.C.G.	2015	13.5	3370	9.09
171	Red	Mastroberardino Societa' Agricola Srl	Laeryma Christi del Vesuvio Rosso	Piedrosso 100%	Italy	Campania	Laeryma Christi del Vesuvio D.O.C.	2022	12.5	3160	12.9
172	Red	Cantine Aurora	ERA Sangiovese	Sangiovese 100%	Italy	Marche	Marche I.G.T.	2020	13	2670	8.87
173	Red	Cantine Aurora	ERA Syrah	Syrah 100%	Italy	Sicilia	Terre Siciliane I.G.T.	2020	13	2730	7.87
174	Red	Cantine Europa	Roceo Nerello Mascalese Terre Siciliane I.G.P.	Nerello Mascalese 100%	Italy	Sicilia	Terre Siciliane I.G.P.	2021	13	2480	7.15
175	Red	Cantine Europa	Roceo Nero d'Avola Sicilia D.O.C.	Nero d'Avola 100%	Italy	Sicilia	Sicilia D.O.C.	2021	13	2560	8.89
176	Red	Passopisciaro Srl - Societa' Agricola	Passorosso	Nerello Mascalese 100%	Italy	Sicilia	Erna Rosso D.O.C.	2020	15	3030	4.41
177	Red	Feudo Arancio	Sangiovese	Sangiovese 100%	Italy	Sicilia	Terre Siciliane I.G.T.	2021	13.5	2810	10.1
178	Red	Feudo Arancio	Cabernet Sauvignon	Cabernet Sauvignon 100%	Italy	Sicilia	Sicilia D.O.C.	2020	13.5	3227	7.88
179	Red	Feudo Arancio	Syrah	Syrah 100%	Italy	Sicilia	Sicilia D.O.C.	2020	13.5	3050	9.14
180	Red	Feudo Arancio	Nero d'Avola	Nero d'Avola 100%	Italy	Sicilia	Sicilia D.O.C.	2020	13	2970	9.77
181	Red	Feudo Arancio	HEDONIS RISERVA	Nero d'Avola 100%	Italy	Sicilia	Sicilia D.O.C.	2015	14	3320	7.13
182	Red	De Haan Altes	El Convertido Syrah	Syrah 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	13	2650	8.34
183	Red	De Haan Altes	El Convertido Tempranillo	Tempranillo 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	13	2590	10.1
184	Red	Dominio de Punctum	Lobelia Tempranillo	Tempranillo 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	13.5	2360	13.9
185	Red	Dominio de Punctum	Lobelia Cabernet Sauvignon	Cabernet Sauvignon 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	13.5	3240	10.6

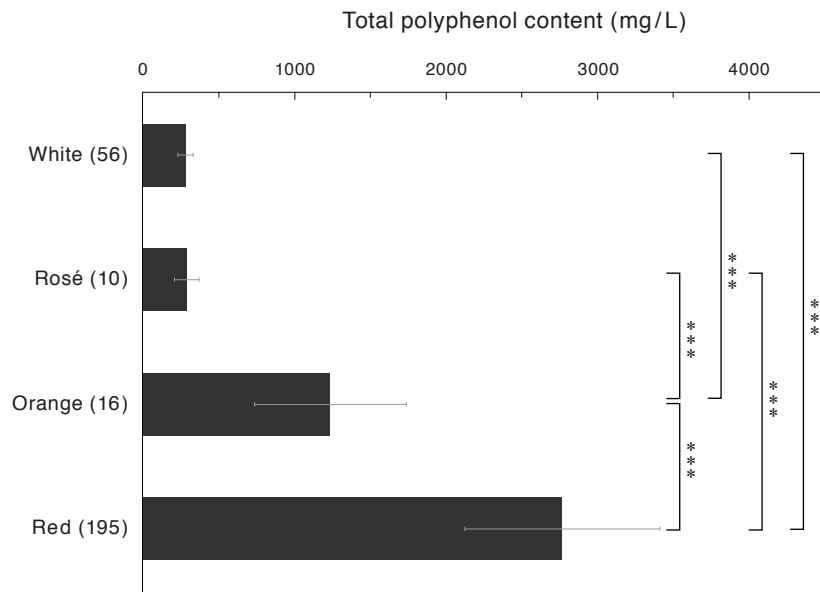
Inhibition of AGE Formation in Wine and Polyphenols

186	Red	Real Compania de Vinos	Reales Vinedos Cabernet Sauvignon	Cabernet Sauvignon 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2019	13.5	2950	9.08
187	Red	Bodegas Abai	Abai Merlot	Merlot 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2020	14	3750	3.75
188	Red	Bodegas Abai	Abai Garnacha	Garnacha 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2021	13.5	3110	4.25
189	Red	Vinos de Arganza	Seculo Mencia Roble	Mencia 100%	Spain	Castilla y Leon	Vino de la tierra de Castilla y Leon	2020	13.5	2540	12.5
190	Red	Baica Vinos y Vinedos	Antonita Pnuelos Baica Tempranillo	Tempranillo 100%	Spain	La Rioja	Rioja D.O.C.a.	2021	13.5	1890	12.2
191	Red	Eguren Ugarte	Ugarte Rioja	Tempranillo 80%/Garnacha Tinta 20%	Spain	La Rioja	Rioja D.O.C.a.	2020	14	2860	8.32
192	Red	Eguren Ugarte	Ugarte Crianza	Tempranillo 80%/Garnacha Tinta 20%	Spain	La Rioja	Rioja D.O.C.a.	2019	14.5	3070	9.72
193	Red	Eguren Ugarte	Ugarte Reserva	Tempranillo 95%/Garciano 5%	Spain	La Rioja	Rioja D.O.C.a.	2015	14.5	2980	11.8
194	Red	Bodegas Azul y Garanza	Naturalaza Salvaje Garnacha	Garnacha 100%	Spain	Navarra	Navarra D.O.	2021	13	2330	12.0
195	Red	Barahonda	Barahonda Crianza	Monastrell 75%/Syrah 15%/Petit Verdot 10%	Spain	Murcia	Yecla D.O.	2019	14.5	3140	7.35
196	Red	Barahonda	Barahonda Monastrell	Monastrell 100%	Spain	Murcia	Yecla D.O.	2021	14.5	3120	7.75
197	Red	Barahonda	Barahonda Barrica	Monastrell 75%/Syrah 25%	Spain	Murcia	Yecla D.O.	2019	14.5	2950	8.13
198	Red	Barahonda	Carro Organic	Monastrell 100%	Spain	Murcia	Yecla D.O.	2021	14	2830	10.7
199	Red	Bodegas y Vinedos Ponce	Depaula	Monastrell 100%	Spain	Castilla La Mancha	Manchuela D.O.	2022	12.5	2600	8.89
200	Red	Bodegas y Vinedos Ponce	Clos Lojen	Bobal 100%	Spain	Castilla La Mancha	Manchuela D.O.	2021	12.5	2660	14.2
201	Red	Bodegas y Vinedos Ponce	La Estrecha	Bobal 100%	Spain	Castilla La Mancha	Manchuela D.O.	2021	12.5	2020	14.4
202	Red	Bodegas Eguren	Mercedes Eguren Cabernet Sauvignon	Cabernet Sauvignon 100%	Spain	Castilla La Mancha	Vino de la Tierra de Castilla	2020	14	2710	8.21
203	Red	Bodegas Jimenez-Landi	Pielago	Garnacha 100%	Spain	Castilla La Mancha	Mentrida D.O.	2020	14.5	2930	22.6
204	Red	Cooperativa Agraria Santa Quiteria	Higuera Tinto	Garnacha Tintorela 100%	Spain	Castilla La Mancha	Almansa D.O.	2020	13.5	2820	8.90
205	Red	Cooperativa Agraria Santa Quiteria	Tintorba Ecologico Seleccion	Garnacha Tintorela 100%	Spain	Castilla La Mancha	Almansa D.O.	2019	13	2720	11.4
206	Red	Casa Relvas	Atlantico Tinto Reserva	Alicante Bouschet 50%/Aragonéz 20%/Cabernet Sauvignon 20%/Touriga Nacional 10%	Portugal	Alentejano	Vinho Regional Alentejano	2020	14	2710	8.06
207	Red	Luis Duarte Vinhos	Rapariga da Quinta Tinto Reserva	Alicante Bouschet 52%/Aragonéz 31%/Touriga Nacional 17%	Portugal	Alentejano	Vinho Regional Alentejano	2020	14.5	3040	4.85
208	Red	Weinkeller Kloster	Klostor Pinot Noir Pfalz	Pinot Noir 100%	Germany	Pfalz	Qualitätswein	2021	13	1780	11.2
209	Red	Vile Budureasca	Vine in Flames Cabernet Sauvignon	Cabernet Sauvignon 100%	Romania	Muntenia	D.O.C.Dealu Mare	2019	14.5	2840	11.1
210	Red	Vile Budureasca	Vine in Flames Pinot Noir	Pinot Noir 100%	Romania	Muntenia	D.O.C.Dealu Mare	2019	14	2440	8.86
211	Red	Vile Budureasca	Premium Feteasca Neagra	Feteasca Neagra 100%	Romania	Muntenia	D.O.C.Dealu Mare	2019	14.5	2520	4.79
212	Red	Borovitz Winery	Collection Cabernet Sauvignon	Cabernet Sauvignon 100%	Bulgaria	Danube Plain	P.G.I.Danube Plain	2018	12.5	1390	12.6
213	Red	Borovitz Winery	Collection Gamza	Gamza 100%	Bulgaria	Danube Plain	P.G.I.Danube Plain	2018	12.5	1080	16.6
214	Red	Sant'Or Winery	Sant'Or Agiortitiko	Agiortitiko 100%	Greece	Peloponnese	P.G.I.Peloponnese	2020	13.5	3180	7.87
215	Red	Sant'Or Winery	Sant'Or Krasis	Mavrodafni 100%	Greece	Peloponnese	P.G.I.Achaia	2020	13	2730	10.1
216	Red	Kir-Yianni	Kali Riza	Xynomavro 100%	Greece	Northern Greece	P.D.O.Amyndeon	2019	13.5	3250	8.85
217	Red	Kir-Yianni	Rannista	Xynomavro 100%	Greece	Northern Greece	P.D.O.Naoussa	2019	14	3470	7.23
218	Red	Shalauri Wine Cellars	Saperavi	Saperavi 100%	Georgia	Kakheti		2017	13.5	4900	1.49
219	Red	Vaziani Winery	Makashvili Wine Cellar Saperavi	Saperavi 100%	Georgia	Kakheti		2019	12.5	3820	5.52
220	Red	Papari Valley	3 Qvevri Terraces Saperavi No.16	Saperavi 100%	Georgia	Kakheti		2022	16.5	4910	2.50
221	Red	Zorah Wines	Karasi	Areni Noir 100%	Armenia	Vayots Dzor		2018	13.5	1500	11.6
222	Red	Tzora Vineyards	Judean Hills	Syrah 25%/Cabernet Sauvignon 25%/Merlot 25%/Petit Verdot 25%	Israel	Judean Hills		2019	14.5	3680	8.65
223	Red	Spier Wines	Spier Cabernet Sauvignon	Cabernet Sauvignon 85%/Cabernet Franc 15%	South Africa	Western Cape	W.O. Western Cape	2021	14	2660	17.3
224	Red	The Fair Valley Wine Company	Fairvalley Pinotage	Pinotage 100%	South Africa	Western Cape	W.O. Coastal Region	2020	13.5	2980	11.9
225	Red	MAN Vintners	Okha Cabernet Sauvignon	Cabernet Sauvignon mainly	South Africa	Western Cape	W.O. Western Cape	2020	13.5	2480	15.9
226	Red	MAN Vintners	Okha Pinotage	Pinotage mainly	South Africa	Western Cape	W.O. Western Cape	2021	13.5	2430	13.1
227	Red	Boutinot Ltd.	Cape Heights Cabernet Sauvignon	Cabernet Sauvignon 100%	South Africa	Western Cape	W.O. Western Cape	2019	14	2290	13.4
228	Red	Boutinot Ltd.	Cape Heights Shiraz	Shiraz 100%	South Africa	Western Cape	W.O. Western Cape	2020	14	2330	10.0
229	Red	Elgin Ridge	282 Pinot Noir	Pinot Noir 100%	South Africa	Western Cape	W.O. Elgin	2020	12	1840	13.5
230	Red	Newton Johnson Wines	Newton Johnson Walker Bay Pinot Noir	Pinot Noir 100%	South Africa	Western Cape	W.O. Walker Bay	2021	13.5	1830	11.9
231	Red	Newton Johnson Wines	Newton Johnson Family Vineyards Pinot Noir	Pinot Noir 100%	South Africa	Western Cape	W.O. Upper Hemel-en-Aarde Valley	2021	13	1670	10.7
232	Red	Stark-Conde Wines	The Press Club Cabernet Sauvignon	Cabernet Sauvignon 85%/Cabernet Franc 7%/Petit Verdot 5%/Petite Syrah 3%	South Africa	Western Cape	W.O. Coastal Region	2020	14	2590	13.7



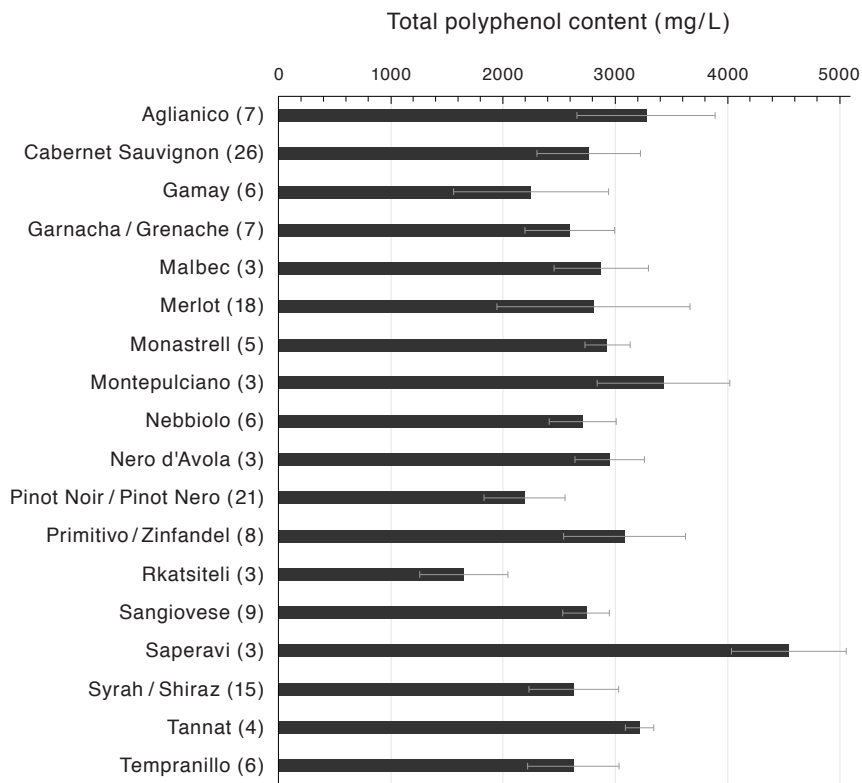
233	Red	Ironstone Vineyards	Stone Valley Cabernet Sauvignon	Cabernet Sauvignon mainly	U.S.A.	California	California	2018	13.5	2251	9.49
234	Red	Delicato Family Vineyards	Gnarly Head Cabernet Sauvignon	Cabernet Sauvignon mainly	U.S.A.	California	California	2020	13.5	2430	8.95
235	Red	Ironstone Vineyards	Ironstone Zinfandel	Zinfandel mainly	U.S.A.	California	Lodi A.V.A.	2020	14.5	2590	6.65
236	Red	Ironstone Vineyards	Ironstone Petite Syrah	Petite Syrah mainly	U.S.A.	California	Lodi A.V.A.	2019	14.5	3580	3.71
237	Red	Ironstone Vineyards	Ironstone Cabernet Franc	Cabernet Franc mainly	U.S.A.	California	Lodi A.V.A.	2020	14.5	2570	7.49
238	Red	Delicato Family Vineyards	Gnarly Head Pinot Noir	Pinot Noir mainly	U.S.A.	California	California	2020	13.5	2410	6.15
239	Red	Delicato Family Vineyards	Gnarly Head Old Vine Zinfandel	Zinfandel mainly	U.S.A.	California	Lodi A.V.A.	2020	14.5	2610	8.14
240	Red	Delicato Family Vineyards	1924 Bourbon Aged Double Black Cabernet Sauvignon	Cabernet Sauvignon mainly	U.S.A.	California	Lodi A.V.A.	2020	15	3290	6.85
241	Red	Delicato Family Vineyards	1924 Double Black Red Blend	Zinfandel mainly	U.S.A.	California	Lodi A.V.A.	2020	14.5	3050	7.33
242	Red	Cooper Mountain Vineyards	Pinot Noir Willamette Valley	Pinot Noir 100%	U.S.A.	Oregon	Willamette Valley A.V.A.	2019	13.5	2520	9.86
243	Red	Fior di Sole	Four Star Napa Valley Cabernet Sauvignon	Cabernet Sauvignon 100%	U.S.A.	California	Napa Valley A.V.A.	2020	13.9	2510	9.15
244	Red	Star Lane Vineyard	Cabernet Sauvignon Happy Canyon of Santa Barbara	Cabernet Sauvignon 78%/Petit Verdot 9%/Cabernet Franc 7%/Malbec 6%	U.S.A.	California	Happy Canyon of Santa Barbara A.V.A.	2018	14.2	2710	7.56
245	Red	Vina Marchigie	Panul Carmenere	Carmenere 100%	Chile	Central Valley	Colchagua Valley D.O.	2021	13.5	2550	15.2
246	Red	Vina Marchigie	Panul Carmenere Reserva Especial	Carmenere 100%	Chile	Central Valley	Colchagua Valley D.O.	2019	13.5	2430	11.1
247	Red	Vina Marchigie	Panul Cabernet Sauvignon Reserva Especial	Cabernet Sauvignon 100%	Chile	Central Valley	Colchagua Valley D.O.	2021	14	2850	10.1
248	Red	Vina Marchigie	Panul Pinot Noir Reserva Especial	Pinot Noir 100%	Chile	Central Valley	Colchagua Valley D.O.	2021	14	2520	9.74
249	Red	Vina del Pedregal S.A	Aves del sur Cabernet Sauvignon Reserva	Cabernet Sauvignon 100%	Chile	Central Valley	D.O. Loncomilla Valley	2017	14.5	3160	18.8
250	Red	Vina del Pedregal S.A	Aves del sur Merlot Reserva	Merlot 100%	Chile	Central Valley	D.O. Loncomilla Valley	2018	14.5	2680	17.9
251	Red	Vina del Pedregal S.A	Aves del sur Syrah Reserva	Syrah 100%	Chile	Central Valley	D.O. Loncomilla Valley	2018	14.5	2710	15.1
252	Red	V.E.S.A	Gamma Organic Cabernet Sauvignon Reserva	Cabernet Sauvignon mainly	Chile	Central Valley	Central Valley D.O.	2021	13.5	2920	6.14
253	Red	V.E.S.A	Gamma Organic Pinot Noir Reserva	Pinot Noir mainly	Chile	Central Valley	Central Valley D.O.	2021	13.5	2580	6.12
254	Red	V.E.S.A	Gamma Organic Syrah Reserva	Syrah mainly	Chile	Central Valley	Central Valley D.O.	2021	14	2480	7.37
255	Red	Vina Valdivieso	Single Vineyard Maipo Valley Cabernet Sauvignon	Cabernet Sauvignon 100%	Chile	Central Valley	Maipo Valley D.O.	2018	14.5	2740	4.50
256	Red	Vina Valdivieso	Single Vineyard Sagrada Familia Merlot	Merlot 100%	Chile	Central Valley	Sagrada Familia D.O.	2019	14	2450	7.55
257	Red	Altos Las Hormigas	La Danza Malbec	Malbec 100%	Argentina	Mendoza	Mendoza	2020	13.5	2850	9.55
258	Red	Bodegas Callia	Callia Malbec	Malbec 100%	Argentina	San Juan	San Juan	2021	13	2370	11.3
259	Red	Alpamanta Estate Wines	Alpamanta Brea Pet Nat Ctrolla Grande	Criolla Grande 100%	Argentina	Mendoza	Mendoza	2022	12.5	1390	15.9
260	Red	Berton Vineyards Pty Ltd	Metal Cabernet Sauvignon	Cabernet Sauvignon mainly	Australia	South Australia	South Eastern Australia G.I.	2021	14	3380	8.18
261	Red	Berton Vineyards Pty Ltd	Metal Durif	Durif mainly	Australia	New South Wales	Riverina G.I.	2021	14	3280	9.70
262	Red	Berton Vineyards Pty Ltd	Metal The Black Shiraz	Shiraz mainly	Australia	South Australia	South Eastern Australia G.I.	2021	14.5	2950	19.0
263	Red	Denton View Hill Vineyard	Denton Shed Pinot Noir	Pinot Noir 100%	Australia	Victoria	Yarra Valley G.I.	2021	13.5	1730	13.4
264	Red	Future Perfect Wines	Future Perfect Pinot Noir	Pinot Noir 100%	Australia	Tasmania	Tasmania G.I.	2021	12.2	1510	12.2
265	Red	Schwarz Wine Company Pty Ltd	Meta Grenache	Grenache 100%	Australia	South Australia	Barossa Valley	2022	14	1840	11.8
266	Red	Grant Burge	COONAWARRA INK Cabernet Sauvignon	Cabernet Sauvignon mainly	Australia	South Australia	Coonawarra G.I.	2020	14.5	3800	2.72
267	Red	Grant Burge	BAROSSA INK Shiraz	Shiraz mainly	Australia	South Australia	Barossa Valley G.I.	2020	14.5	3140	9.80
268	Red	Shaw + Smith	Shiraz	Shiraz 100%	Australia	South Australia	Adelaide Hills G.I.	2020	14	2260	8.85
269	Red	Logan Wines	Apple Tree Flat Shiraz	Shiraz 100%	Australia	New South Wales	Central Ranges G.I.	2021	13	2840	20.3
270	Red	Logan Wines	Apple Tree Flat Merlot	Merlot 100%	Australia	New South Wales	Central Ranges G.I.	2021	13.5	2410	12.0
271	Red	Boatshed Bay	Boatshed Bay Marlborough Pinot Noir	Pinot Noir 100%	New Zealand	South Island	Marlborough G.I.	2020	13.5	2050	12.3
272	Red	Seresin Estate Limited	Seresin Estate Leah Pinot Noir	Pinot Noir 100%	New Zealand	South Island	Marlborough G.I.	2022	13	2370	9.97
273	Red	Te Kairanga	TK Pinot Noir	Pinot Noir 100%	New Zealand	North Island	Martinborough G.I.	2021	13.5	1930	14.6
274	Red	Mount Edward	Ted Pinot Noir	Pinot Noir 100%	New Zealand	South Island	Central Otago G.I.	2021	14	2800	13.9
275	Red	Mount Edward	Mount Edward Gamay	Gamay 100%	New Zealand	South Island	Central Otago G.I.	2022	12.5	1590	11.8
276	Red	Sam Harrop	Cedalion Syrah	Syrah 100%	New Zealand	North Island	Waikato Island G.I.	2020	13.5	1570	9.09
277	Red	Shinshu Takayama Winery	ANTO TAKAYAMAMURA MERLOT	Merlot 100%	Japan	Nagano	Nagano	2022	12	1330	10.7

Total polyphenol content shown as gallic acid equivalents.  $IC_{50}$ : 50% inhibitory concentration. Mean of three independent experiments for each sample shown.



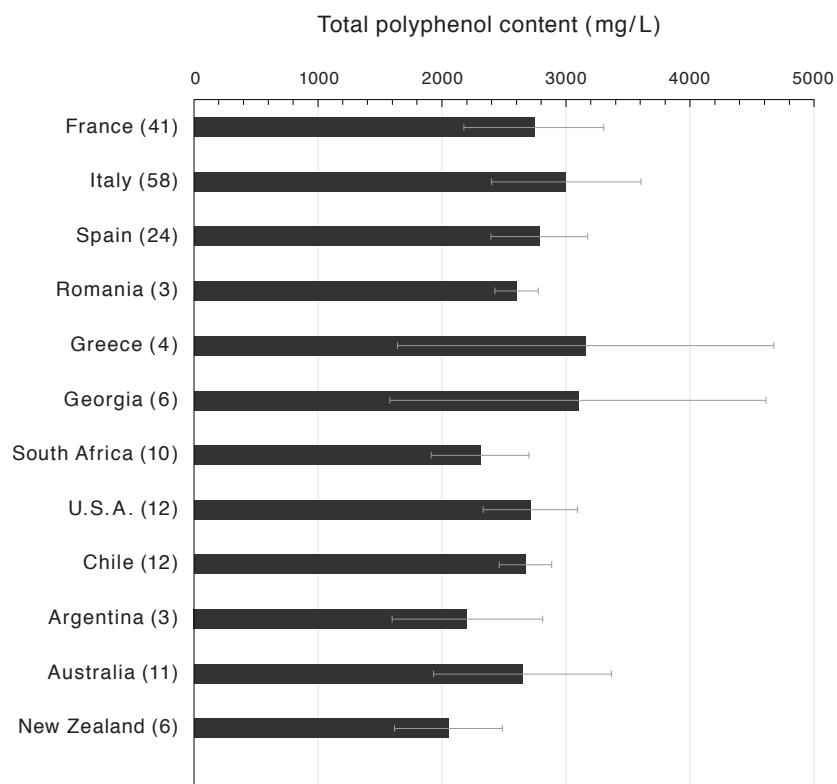
**Fig.1. Differences in total polyphenol content between wine colors.**

All data were shown as the mean  $\pm$  standard deviation. \*\*\* $p < 0.001$ , Tukey test.



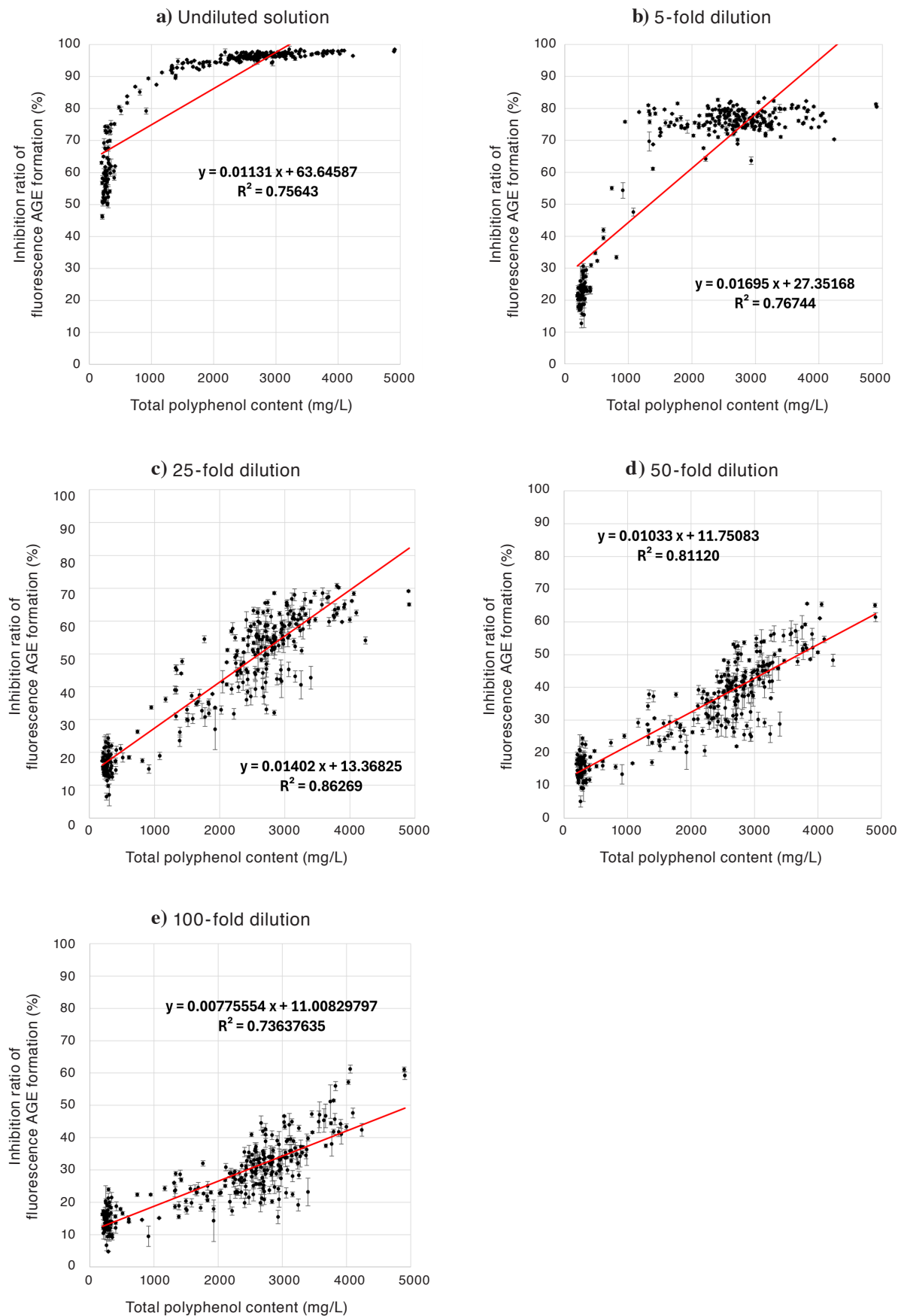
**Fig.2. Differences in total polyphenol content between grape varieties.**

All data were shown as the mean  $\pm$  standard deviation.



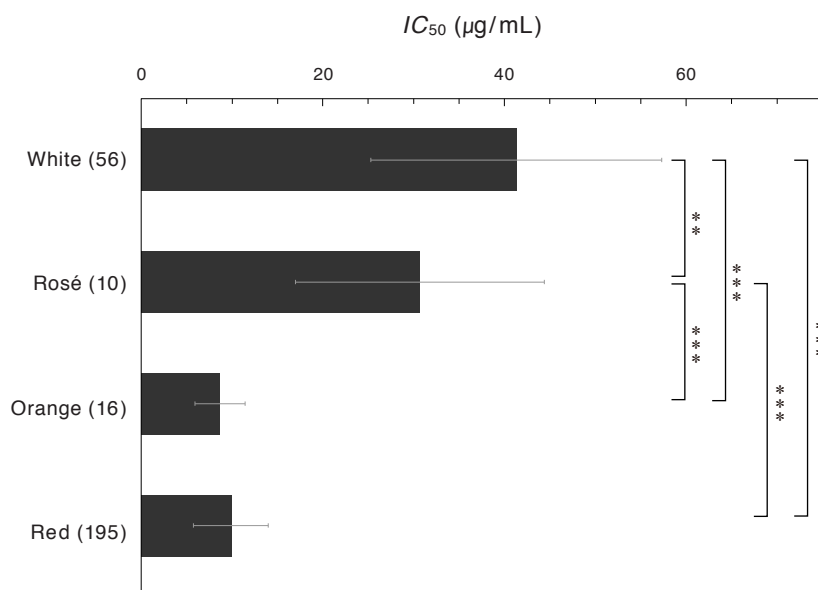
**Fig.3. Differences in total polyphenol content between wine-producing countries.**  
All data were shown as the mean  $\pm$  standard deviation.

Inhibition of AGE Formation in Wine and Polyphenols



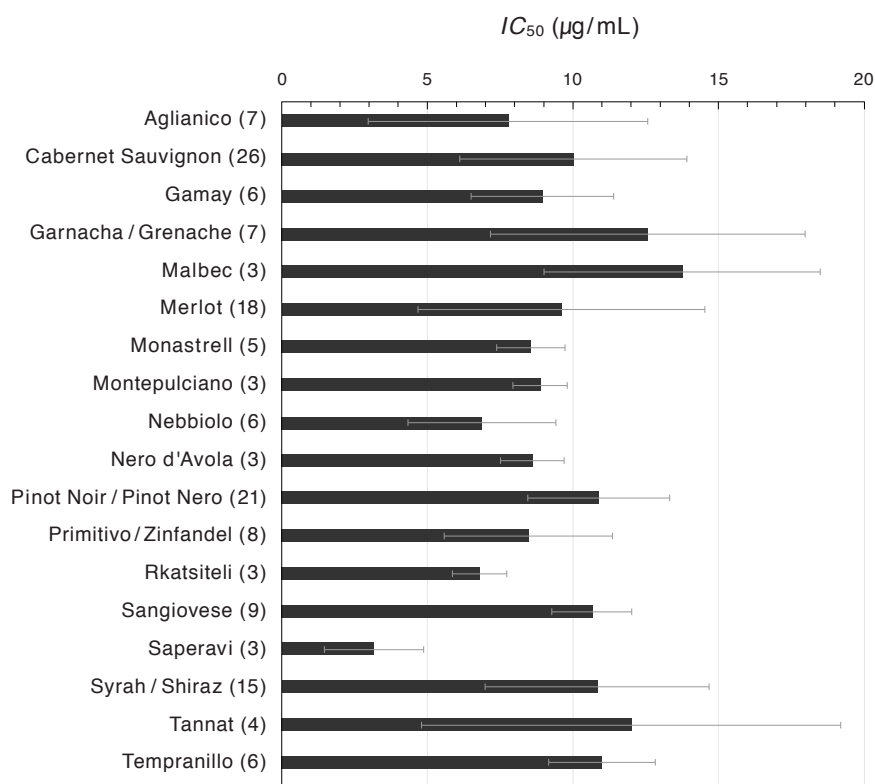
**Fig. 4. Linear relationship between inhibition ratio of fluorescence AGE formation and total polyphenol content of wine.**

All data were shown as the mean  $\pm$  standard deviation from three independent experiments. AGE, advanced glycation end products.



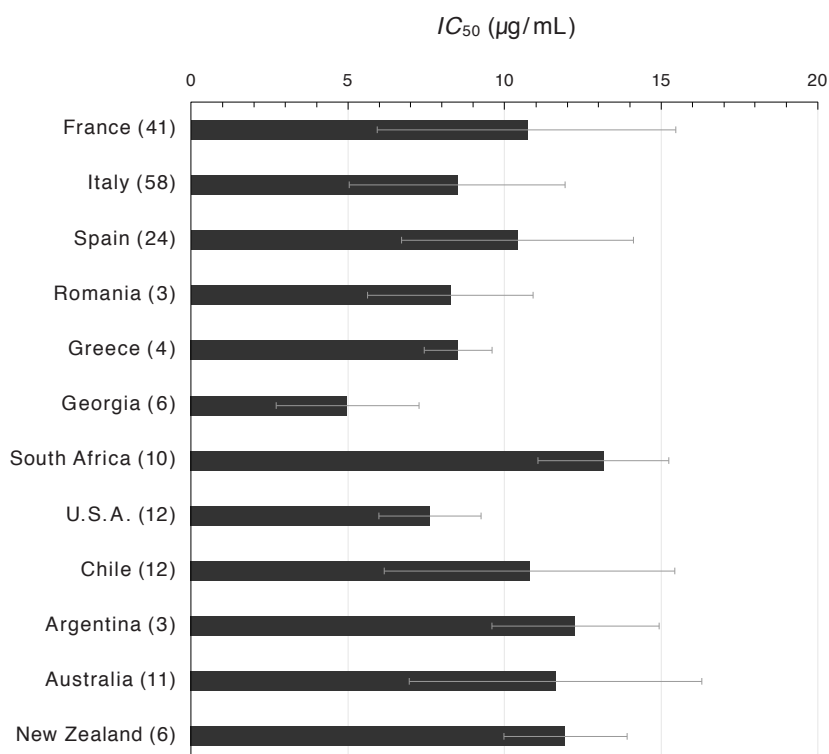
**Fig. 5. Differences in  $IC_{50}$  between wine colors.**

All data were shown as the mean  $\pm$  standard deviation. \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , Tukey test.  $IC_{50}$ , half maximal inhibitory concentration.



**Fig. 6. Differences in  $IC_{50}$  between grape varieties.**

All data were shown as the mean  $\pm$  standard deviation. There was no significant difference in  $IC_{50}$  between grape varieties.  $IC_{50}$ , half maximal inhibitory concentration.



**Fig. 7. Differences in  $IC_{50}$  between wine-producing countries.**

All data were shown as the mean  $\pm$  standard deviation.  $IC_{50}$ , half maximal inhibitory concentration.

On the other hand, there was a significant difference in  $IC_{50}$  between white wine and rosé wine, and no significant difference between orange wine and red wine (Fig. 5). As shown in Fig. 4, there is a strong correlation between the rate of inhibition of AGE formation and the total polyphenol content, while Fig. 5 indicates that factors other than total polyphenol content are also involved in the inhibition of AGE formation. Although there is no significant difference in total polyphenol content between white wine and rosé wine, it is possible that phenolic compounds derived from black grapes are involved in the AGE formation inhibitory effect. For example, resveratrol, a type of polyphenol, has been reported to be higher in rosé wine than in white wine<sup>24</sup>. Therefore, it is possible that not only the total polyphenol content, but also specific phenolic compounds and polyphenols are involved in the inhibition of AGE formation.

It is also known that DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activity, one of the indicators of antioxidant activity, is highly correlated with total polyphenol content. On the other hand, a tendency for rosé wine to have stronger DPPH radical activity than white wine has also been reported<sup>25</sup>. Even if the total polyphenol content is similar, rosé wine, which has stronger free radical scavenging capacity, is thought to suppress the generation of a large amount of free radicals in the early stages of the glycation reaction, leading to inhibition of AGE formation. The difference and relationship between oxidation and glycation reactions remain unknown, and further research is needed.

In addition, the total polyphenol content differs nearly 10-fold between white and red wines, but the  $IC_{50}$  difference is about 4-fold, suggesting that white wine has components other than total polyphenol content that contribute to the inhibition of AGE formation. Tartaric acid, malic acid, and citric acid are major organic acids constituting wine, and tartaric acid and citric acid are known to have chelating effects. The presence of transition metal ions is said to be related to the AGE formation, and citric acid has been demonstrated to inhibit the formation of two types of AGEs in the lens protein<sup>26</sup>. It is thought that citric acid chelates metal ions, thereby preventing autoxidation of reducing sugars and Amadori products and inhibiting the AGE formation. In addition, terpenoid compounds that characterize the aroma of some white wines in particular are also known to inhibit AGE formation<sup>27</sup>.

#### Grape varieties

With respect to total polyphenol content, wines vinified from Saperavi were significantly higher than many other varieties, while wines vinified from Pinot Noir and Rkatsiteli were significantly lower (Fig. 2). Saperavi is a “Teinturier” grape variety, which means that even the pulp and juice are red, and it is known to contain more phenolic compounds than other grapes<sup>28</sup>. Thus, red wines made from Saperavi have relatively high total polyphenol content.

On the other hand, as shown in Fig. 6, there was no

significant difference in  $IC_{50}$  between the varieties. This may be due to the fact that factors other than total polyphenol content are involved in the inhibition of AGE formation, similar to the discussion regarding wine color. For example, resveratrol, a type of polyphenol known as a dietary supplement, is known to have various anti-glycation effects<sup>29</sup>. Pinot Noir has a thin skin and is susceptible to fungal diseases, and as a phytochemical, it produces a large amount of resveratrol, which has anti-fungal activity, in its skin<sup>30</sup>. Therefore, it is known that it may contain higher concentrations of resveratrol than Cabernet Sauvignon, which generally produces wines with higher total polyphenol content than Pinot Noir. Thus, even if the total polyphenol content is relatively low, certain phenolic compounds and polyphenols may contribute to the inhibition of AGE formation. Indeed, it has been reported that the addition of various phenolic compounds and polyphenols to a glycation model resulted in widely different rates of inhibition of AGE formation<sup>31</sup>. Although not included in the current study, it is known that even anti-fungus resistant grapes such as the piwi variety (Pilzwiderstandsfähige Rebsorten) contain relatively high levels of resveratrol, which may also be expected to inhibit AGE formation<sup>32</sup>.

### Producing country

In terms of total polyphenol content, Italy was significantly higher than South Africa and New Zealand. Furthermore, for  $IC_{50}$ , Georgia was lower than France, South Africa, and Australia, and South Africa was significantly higher than Italy and the U.S.A.. However, we believe that it is difficult to make country-by-country comparisons based on this sample size alone. Even within a single country, climatic conditions vary widely, and furthermore, the characteristics of each vintage (rainfall, dryness, etc.) and the grape varieties used need to be considered in a unified manner.

### Other discussion

There are numerous variables in the winemaking process. Natural factors include the characteristics of the grapes themselves, soil, climate, and weather. Further human factors include grape cultivation, vinification, and aging methods, resulting in a variety of wine styles of the same color, same grape variety, and even from the same producing country<sup>33</sup>. In the present study, 277 wines of various styles were evaluated, revealing a high correlation between AGE formation inhibition rate and total polyphenol content. Phenolic compounds and polyphenols, which are abundant in wine, have been shown to have anti-glycation effects<sup>29</sup>. *In vitro* experimental systems such as the present one, where the AGE formation process in food is the background and the reaction time is as long as 40 hours at 60°C, the AGE formation inhibitory effect may be influenced by the inhibition of reactive oxygen species formation by antioxidant action and the trapping action of reactive carbonyl compounds. In contrast, in the body, a more complex factor is added: it may exert various anti-glycation effects, such as inhibiting the interaction between AGEs and RAGE, promoting the expression of glyoxalase 1 (GLO-1), a known anti-glycation enzyme, and inhibiting the accumulation of AGEs.

Although this study evaluated only the inhibition of AGE

formation, there is a possibility that wine drinking may have further anti-glycation effects. More than 90% of wine is composed of water, alcohol, and glycerol, and phenolic compounds, polyphenols, organic acids, and other components are thought to be involved in the inhibition of AGE formation. Wine contains compounds such as amino acids<sup>31</sup>, glutathione<sup>34,35</sup>, eugenol<sup>36</sup>, and melatonin<sup>37-39</sup>, which have been reported to have anti-glycation effects, so it is difficult to say that the inhibition of AGE formation is due solely to phenolic compounds or polyphenols.

Recently, it has been pointed out that the involvement of aldehydes is important for AGE formation *in vivo*<sup>40,41</sup>. In addition to smoking (aldehydes in cigarette smoke) and alcohol consumption (ethanol-derived acetaldehyde), the causes of aldehydes include elevated dicarbonyl compounds secondary to postprandial hyperglycemia (glyoxal, methylglyoxal [MGO], 3-deoxyglucosone) and other carbohydrate-derived aldehydes<sup>42</sup>, and fatty acid-derived aldehydes (malondialdehyde [MDA], acrolein, and MGO)<sup>43</sup>. The reactivity of aldehydes is high, and the rate of AGE formation in cells may be faster than in foods.

Finally, the difference between oxidative stress and glycative stress is discussed. Oxidative reactions are modifications at the molecular level by free radicals and their fellow reactive oxygen species (ROS). The lifetime of free radicals is instantaneous, and oxidation products are formed in a short time. The defense mechanism is equipped with antioxidant enzymes (superoxide dismutase [SOD], peroxidase, and catalase) and a mechanism to produce substances with antioxidant properties (CoQ10 and  $\alpha$ -lipoic acid). On the other hand, glycation reactions are mainly molecular modification by aldehydes. The *in vivo* blood half-life of aldehydes is several minutes to several tens of minutes, which is longer than that of free radicals, and the time required for AGE formation (including carbonylated proteins) may be longer than the time required for oxidation products to be formed. The time required for AGE formation is also shorter *in vivo* than in food or in *in vitro* experimental systems. As defense mechanisms, aldehyde metabolizing enzymes (aldehyde dehydrogenase [ALDH] 1~17, glyceraldehyde triphosphate dehydrogenase [GAPDH], and GLO) are equipped. Polyphenols have both antioxidant and anti-glycation effects (inhibition of AGE formation), but the differences in their mechanisms of action remain unclear. This is an issue for further study.

## Conclusions

As a result of the experiment on 277 wines, it was confirmed that wine has an inhibitory effect on AGE formation, as previously reported. The results showed that the rate of inhibition of AGE formation in wine correlated well with the total polyphenol content. Since wine is an alcoholic beverage, its intake is limited to avoid health hazards. Therefore, it is important to have an index for selecting wines that have strong anti-glycation activity even in small amounts. Since a strong correlation was shown between the total polyphenol content of various wines and the AGE formation inhibition rate, understanding the total polyphenol content may be one of the key points for selecting wines

with strong anti-glycation activity. On the other hand, it was suggested that factors other than total polyphenol content are also intricately involved in the AGE formation inhibitory effect. These results provide valuable insights in viticulture and winemaking to produce wines with stronger anti-glycation activity. We are now undertaking further studies in these directions.

### Conflict of interest

There are no conflicts to declare.

### Research funding

No funding from competitive research funds.

### References

- 1) Yagi M, Yonei Y. Glycative stress and anti-aging: 13. Regulation of glycative stress. 1. Postprandial blood glucose regulation. *Glycative Stress Res.* 2019; 6: 175-180.
- 2) Yagi M, Yonei Y. Glycative stress and anti-aging: 14. Regulation of glycative stress. 2. Inhibition of the AGE production and accumulation. *Glycative Stress Res.* 2019; 6: 212-218.
- 3) Yagi M, Yonei Y. Glycative stress and anti-aging: 15. Regulation of glycative stress. 3. Reduction of AGEs intake from food. *Glycative Stress Res.* 2020; 7: 70-74.
- 4) Rungratanawanich W, Qu Y, Wang X, et al. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. *Exp Mol Med.* 2021; 53: 168-188.
- 5) Hori M, Yagi Y, Nomoto K, et al. Inhibition of advanced glycation end product formation by herbal teas and its relation to anti-skin aging. *Anti-Aging Med.* 2012; 9: 135-148.
- 6) Parengkuan L, Yagi M, Matsushima M, et al. Anti-glycation activity of various fruits. *Anti-Aging Med.* 2013; 10: 70-76.
- 7) Ishioka Y, Yagi M, Ogura M, et al. Antiglycation effect of various vegetables: Inhibition of advanced glycation end product formation in glucose and human serum albumin reaction system. *Glycative Stress Res.* 2015; 2: 22-34.
- 8) Ishioka Y, Yagi M, Ogura M, et al. Polyphenol content of various vegetables: Relationship to antiglycation activity. *Glycative Stress Res.* 2015; 2: 41-51.
- 9) Moniruzzaman M, Takabe W, Yagi M, et al. Formulation of five curry spice mixtures and investigation of their effect on advanced glycation endproduct formation. *Glycative Stress Res.* 2016; 3: 5-14.
- 10) Tanaka Y, Yagi M, Takabe W, et al. Anti-glycative effect of yogurt: Prevention of advanced glycation end product formation. *Glycative Stress Res.* 2017; 4: 25-31.
- 11) Tadasue K, Takabe W, Yagi M, et al. Anti-glycative effect of Japanese sake (seishu): Prevention of advanced glycation end product (AGE) formation. *Glycative Stress Res.* 2017; 4: 80-86.
- 12) Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet.* 1992; 339: 1523-1526.
- 13) Pojer E, Mattivi F, Johnson D, et al. The case for anthocyanin consumption to promote human health: A review. *Compr Rev Food Sci Food Saf.* 2013; 12: 483-508.
- 14) Shahidi F, Ambigaipalan P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects: A review. *J Funct Foods.* 2015; 18: 820-897.
- 15) Akinwumi BC, Bordun K-AM, Anderson HD. Biological activities of stilbenoids. *Int J Mol Sci.* 2018; 19: 792.
- 16) Mutha RE, Tatiya AU, Surana SJ. Flavonoids as natural phenolic compounds and their role in therapeutics: An overview. *Futur J Pharm Sci.* 2021; 7: 25.
- 17) Sugiura S, Iwata Y, Hirano S, et al. Effect of red wine on AGEs in blood. *Glycative Stress Res.* 2023; 10: 164-170.
- 18) Brownlee M, Vlassara H, Kooney A, et al. Aminoguanidine prevents diabetes-induced arterial wall protein crosslinking. *Science.* 1986; 232: 1629-1632.
- 19) Bolton WK, Cattran DC, Williams ME, et al. Randomized trial of an inhibitor of formation of advanced glycation end products in diabetic nephropathy. *Am J Nephrol.* 2004; 24: 32-40.
- 20) Hrelia S, Di Renzo L, Bavaresco L, et al. Moderate wine consumption and health: A narrative review. *Nutrients.* 2023; 15: 175.
- 21) Singleton VL, Rossi JA. Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents. *Am J Enol Vitic.* 1965; 16: 144-158.
- 22) Hori M, Yagi M, Nomoto K, et al. Experimental models for advanced glycation end product formation using albumin, collagen, elastin, keratin and proteoglycan. *Anti-Aging Med.* 2012; 9: 125-134.
- 23) Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant.* 2013; 48: 452-458.
- 24) Romero-Pérez AI, Lamuela-Raventós RM, Waterhouse AL, et al. Levels of cis- and trans-resveratrol and their glucosides in white and rose Vitis vinifera wines from Spain. *J Agric Food Chem.* 1996; 44: 2124-2128.



- 25) Sánchez-Moreno C, Larrauri JA, Saura-Calixto F. Free radical scavenging capacity of selected red, rose and white wines. *J Sci Food Agric*. 1999; 79: 1301-1304.
- 26) Nagai R, Nagai M, Shimasaki S, et al. Citric acid inhibits development of cataracts, proteinuria and ketosis in streptozotocin (type 1) diabetic rats. *Biochem Biophys Res Commun*. 2010; 393: 118-122.
- 27) Vlassopoulos A, Mikrou T, Papantoni A, et al. The Effect of terpenoid compounds on the formation of advanced glycation endproducts (AGEs) in model systems. *Applied Sciences*. 2022; 12: 908.
- 28) Malfeito-Ferreira M, Granja-Soares J, Chandra M, et al. Investigating the influence of vessel shape on spontaneous fermentation in winemaking. *Fermentation*. 2024; 10: 401.
- 29) Yeh WJ, Hsia SM, Lee WH, et al. Polyphenols with antiglycation activity and mechanisms of action: A review of recent findings. *J Food Drug Anal*. 2017; 25: 84-92.
- 30) Sato M. Longevity effects of resveratrol: Recent topics. *J Bre Soc Japan*. 2012; 107: 740-749.
- 31) Sadowska-Bartosz I, Galiniak S, Bartosz G. Kinetics of glycoxidation of bovine serum albumin by glucose, fructose and ribose and its prevention by food components. *Molecules*. 2014; 19: 18828-18849.
- 32) Duley G, Ceci AT, Longo E, et al. Oenological potential of wines produced from disease-resistant grape cultivars. *Compr Rev Food Sci Food Saf*. 2023; 22: 2591-2610.
- 33) Gutiérrez-Escobar R, Aliaño-González MJ, Cantos-Villar E. Wine polyphenol content and its influence on wine quality and properties: A review. *Molecules*. 2021; 26: 718.
- 34) Kritzinger EC, Bauer FF, du Toit WJ. Role of glutathione in winemaking: A review. *J Agric Food Chem*. 2013; 61: 269-277.
- 35) Averill-Bates DA. The antioxidant glutathione. *Vitam Horm*. 2023; 121: 109-141.
- 36) Singh P, Jayaramaiah R, Agawane S, et al. Potential dual role of eugenol in inhibiting advanced glycation end Products in diabetes: Proteomic and mechanistic insights. *Sci Rep*. 2016; 6: 18798.
- 37) Marhuenda J, Villaño D, Arcusa R, et al. Melatonin in wine and beer: Beneficial effects. *Molecules*. 2021; 26: 343.
- 38) Takabe W, Mitsuhashi R, Parengkuan L, et al. Cleaving effect of melatonin on crosslinks in advanced glycation end products. *Glycative Stress Res*. 2016; 3: 38-43.
- 39) Ogura M, Okuda F, Hattori A, et al. Effect of melatonin intake on postprandial blood glucose in the breakfast. *Glycative Stress Res*. 2018; 5: 75-81.
- 40) Yonei Y, Yagi M, Sato K, et al. Glycative stress: Molecular impacts and defense mechanisms. *Glycative Stress Res*. 2023; 10: 145-158.
- 41) Yonei Y, Saito Y, Yagi M, et al. From fatty liver to steatohepatitis: Involvement of aldehydes *Glycative Stress Res*. 2024; 11: 79-93.
- 42) Maessen DE, Hanssen NM, Scheijen JL, et al. Postglucose load plasma  $\alpha$ -dicarbonyl concentrations are increased in individuals with impaired glucose metabolism and type 2 diabetes: The CODAM study. *Diabetes Care*. 2015; 38: 913-920.
- 43) Sato K, Zheng Y, Martin-Morales A, et al. Generation of short chain aldehydes and glyceraldehyde 3-phosphate dehydrogenase (GAPDH). *Glycative Stress Res*. 2022; 9: 129-134.