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PRINCIPAL PHENOLIC PHYTOCHEMICALS IN FRENCH SYRAH AND GRENACHE RHONE WINES AND THEIR ANTIOXIDANT ACTIVITY IN INHIBITING OXIDATION OF HUMAN LOW DENSITY LIPOPROTEINS

PRINCIPAUX COMPOSÉS PHÉNOLIQUES DES CÉPAGES FRANÇAIS SYRAH ET GRENACHE ET LEUR ACTIVITÉ ANTIOXYDANTE DANS L'INHIBITION D'OXYDATION DES LIPOPROTÉINES BASSE DENSITÉ

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Abstract : Wine contains natural plant phenolic antioxidants that may protect circulating lipoproteins from oxidative damage . By inhibition of the copper-catalyzed oxidation of LDL we determined the activity of thirteen rhône coast wines exclusively from Syrah and Grenache varieties. About 50 p. cent of the wines were made with a long maceration process. Major monomeric phenolic compounds and procyanidin dimers were analyzed in each sample by HPLC and correlated with relative LDL antioxidant activity. Correlations obtained can be grouped in 3 classes: catechin (r = 0.75), procyanidins, B1, B2, B3 (r = 0.43-0.55), malvidin-3-glucoside and cyanidin (r = 0.43), gallic acid, myrecitin, rutin (r = 0.2-0.4). On the same basis total phenol contents of wines gave a correlation with LDL antioxidant activity of r = 0.72. Comparison, at the same total phenol concentration, with different red California wines shows that antioxidant activity of French Syrah and Grenache range between that of Merlot (56-65 p. cent) and Cabernet Sauvignon (37-45 p.cent). In contrast Syrah wines made with a short extraction process gave lower inhibition of LDL oxidation of 16 p. cent which is less than white California wines averaging 36 p. cent. Activity of each wine phenolic compound can play a role in protecting LDL against oxidation.

Résumé : Le vin contient des composés phénoliques antioxydants naturels issus de la baie de raisin qui protégeraient les lipoprotéines circulantes de dommages oxydatifs. Par inhibition *in vitro* de l'oxydation catalysée par le cuivre des LDL (Lipoprotéines à basse densité), nous avons déterminé l'activité de 13 vins des Côtes du Rhône provenant exclusivement des cépages Syrah et Grenache. Près de 50 p. cent des vins étaient issus d'une élaboration avec un procédé de longue macération. Les composés phénoliques monomériques majeurs ainsi que différentes procyanidines dimères ont été analysés pour chaque échantillon par HPLC et corrélés avec l'activité antioxydante relative exercée sur les LDL. Les corrélations obtenues peuvent être groupées en 3 classes: catéchine (r = 0,75), procyanidines B1, B2, B3 (r = 0,43-0,55), malvidine-3-glucoside et cyanidine (r = 0,43), acide gallique, myrécitine, rutine (r = 0,2-0,4). Sur la même base, les composés phénoliques totaux des vins donnèrent une corrélation avec l'activité antioxydante sur les LDL de r = 0,72. La comparaison avec différents vins californiens rouges et blancs montre que les activités antioxydantes des cépages Syrah et Grenache provenant de France sont comprises entre celles du Merlot (56-65 p. cent) et du Cabernet Sauvignon (37-45 p. cent). En contraste pour une même concentration de composés phénoliques totaux, les vins de Syrah issus de procédé d'extraction court donne des inhibitions d'oxydation des LDL plus faibles de 16 p. cent ce qui est inférieur aux résultats obtenus pour les vins blancs californiens dont la moyenne se situe à 36 p. cent. L'activité de chaque composé phénolique du vin peut jouer un rôle dans la protection contre l'oxydation des LDL.

Key words : cardioheartdisease (CHD), LDL oxidation, wine, phenolic compounds, antioxidants, Syrah, Grenache, varieties, maceration
Mots clés : maladie cardiovasculaire, oxydation des LDL, vin, composés phénoliques, antioxydants, Syrah, Grenache, cépages, macération

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INTRODUCTION

Epidemiological studies conducted during the last twenty years have shown that coronary heart diseases are less prevalent in countries consuming a regular and moderate consumption of wine (St-LÉGER and *al.*, 1979 ; FREIDMAN and KIMBALL, 1986 ; W.H.O., 1989 ; KLATSKY and AMSTRONG, 1992). The so-called French paradox, advanced by RENAUD and De LORGERIL (1992), is based on the lower mortality rates from cardio-heart diseases (CHD) in France than those in United States or the United Kingdom with similar saturated fat intake. RENAUD perceived that this result may be related in part to regular consumption of wine. Different compounds present in wine may also explain the proposal health benefit of wine. Alcohol is know to increase HDL levels and reduce atherogenic LDL (GAZIANO et *al.*, 1993), and reduce platelet aggregation (RENAUD et *al.*, 1984). However the studies of FRIEDMAN and KIMBALL (1986) showed that beer and wine reduce CHD risks more than alcohol for non-smokers. Furthermore, the reduction in heart disease is difficult to explain simply by taking into account the effects of alcohol, and little attention has been given to the potentially beneficial effects of non-alcoholic wine components.

In the same time, considerable interest in natural antioxidants from plant sources has been generated. Diets high in fruits and vegetables have also been associated with lower chronic disease rates CHD and cancer (BAILEY and WILLIAMS, 1994), and several studies have implicated consumption of phenolic antioxidants such as vitamin E in food products, which correlate with reduced heart disease (RIMM et *al.*, 1993).

Polyunsaturated fatty acids occur as a major part of the low-density lipoproteins in blood and oxidation of these lipids components in low-density lipoproteins may play a role in atherosclerosis (STEINBERG et *al.*, 1989 ; ESTERBAUER et *al.*, 1992). With a continue high level of oxidized lipids, blood vessels damage reaction process continues and can lead to generation of foam cells and plaque, the symptoms of atherosclerosis. In addition, *in vitro* studies show that oxidation of human LDL can be inhibited by physiological levels of vitamins C and E (JIALAL et *al.*, 1990), and certain flavonoids (De WHALLEY et *al.*, 1990). Thus, the hypothesis was advanced that potent antioxidative phenolics in wine can prevent oxidation of LDL and explain the French paradox. Thus, the inhibition of human LDL was demonstrated by the addition of the mixture of polyphenols from wine (FRANKEL et *al.*, 1993). Red wine diluted 1000-fold inhibited the *in vitro* oxidation of human LDL significantly more than α-tocopherol. Other effects of red wines include inhibition of chronic inflammation, and thrombotic tendencies (KINSELLA et *al.*, 1993).

In the present study we evaluated the antioxidant activities of 13 French Rhône red wines made from two specific varieties : Syrah and Grenache in inhibiting human LDL oxidation *in vitro*. This antioxidant activity was related to the principal phenolic compounds analyzed by HPLC and compared with previous results for 20 California wines.

MATERIALS AND METHODS

I — WINES

The different types of red wines obtained from different wineries in the Rhône Valley and the Rhône coast are listed in table I, by variety, for 3 geographical delimited zones.

TABLE I

Syrah and grenache Rhône coast wines classified by geographical areas evaluated for antioxidant properties

Wines*	Types	Vintage
South Rhône coast Grenache		
1G	Villedieu	1989
2G	Villedieu	1990
3G	Villedieu	1991
4G	Villedieu	1992
North Rhône coast Syrah		
5S	Hermitage	1990
6S	Hermitage	1991
7S	Hermitage	1992
8S	Hermitage	1993
South Rhône coast Syrah		
9S	Villedieu	1988
10S	St-Apollinaire	1989
11S	St-Apollinaire	1990
12S	Puyméras	1990
13S	Villedieu	1991
14S	Villedieu	1993

*Wine numbers - G = Grenache - S = Syrah

II — ANTIOXIDANT ASSAY

The same procedure was used as before and was based on the inhibition of copper catalyzed oxidation of freshly prepared human LDL from the plasma of three normolipidemic volunteers (FRANKEL et *al.*, 1993). For each evaluation of wines, the results of duplicate analyses were expressed as percent inhibition (FRANKEL et *al.*,1995).

Relative percent inhibition calculated by multiplying the values of percent inhibition at 10 µM total phenol by taking the highest value as 100 p. cent (figures 1, 2 and 3).

III — TOTAL PHENOLS CONTENT

Total phenols were analyzed by the Folin-Ciocalteu method (SINGLETON and ROSSI, 1965), calibrating against gallic acid standards, and expressing the results as GAE.

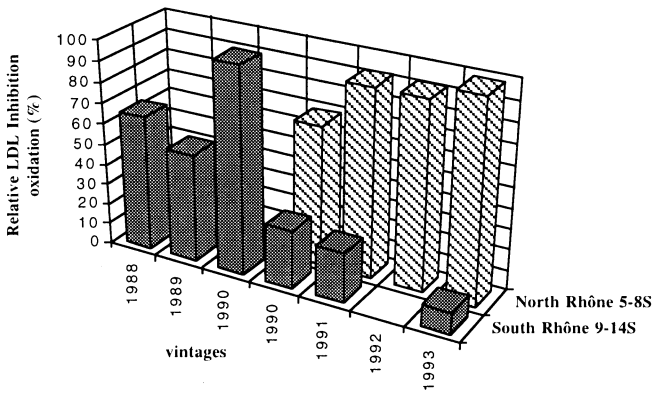


Fig. 1 — Relative LDL inhibition oxidation for Syrah wine vintages

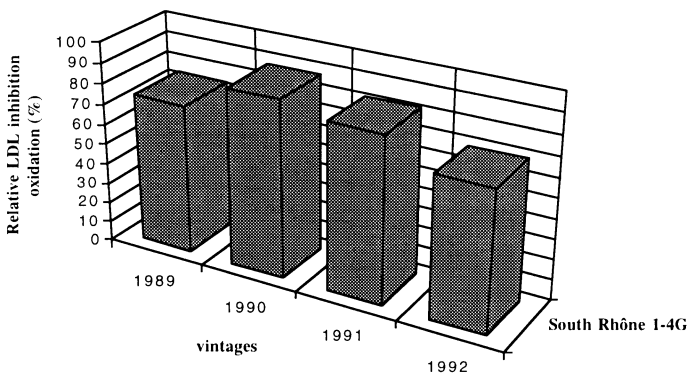


Fig. 2 — Relative LDL inhibition oxidation for Grenache wine vintages

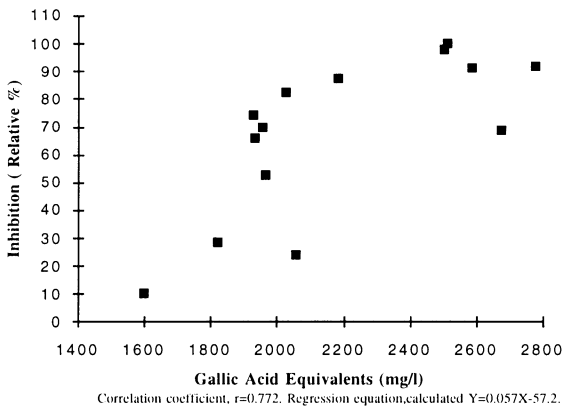


Fig. 3 — Relative percent inhibition of LDL oxidation by wines vs total phenol content as gallic acid equivalents

IV — HPLC ANALYSIS OF MAJOR PHENOLICS

Phenolic compounds (gallic acid, caffeic acid, catechin, epicatechin, sinapic acid, rutin, malvidin-3-glucoside, quercitin) were purchased from Aldrich (Milwaukee, U.S.A.) and Sigma (St-Louis, U.S.A.). Cyanidin was provided by Vernon L. Singleton (University California, Davis), procyanidins dimers B1, B2, B3, B4 were extracted as described by TEISSEDRE et *al.* (1995). Separation and quantification of these compounds was carried out by modification of a previously reported HPLC method (LAMUELA-RAVENTOS and WATERHOUSE, 1994). A Hewlett-Packard (Santa-Clara, CA, U.S.A.) Model 1090 with three low pressure pumps and a diode array UV visible detector coupled to an HP Chem. Station was used for solvent delivery system and detection. A Novapack C18 column, 3.9 x 150 mm, 4 mm particle size, from Waters/Millipore thermostated at 40°C was used as the stationary phases with a flow of 0.5 ml/min. The solvents used for the separation were : solvent A = 30 mM dichloroacetic acid adjusted to pH 1.5 with sulphuric acid ; solvent B = methanol (HPLC grade). The solvent system consisted of increasing the percent of MeOH in solvent A from 0 at the start to 10 at 7 min, 12.3 at 19 min., 25 at 27.5 min., 39.5 at 42 min, 50.5 at 48 min, 70 at 53 min, 80 at 55 min with a 3 min hold. The detection was at 280 nm, 313 nm, 520 nm, 620 nm. The retention time of each compound is shown in table II.

RESULTS

It is well known by enologists that total phenol content in wine is directly related with the grape variety, vineyard location, growing factors in the vineyards,

winemaking techniques and aging process. The concentrations of total phenol as determined by the Folin-Ciocalteu method varied from 1601 to 2774 mg/l GAE, averaging 2243 mg/l GAE for the Syrah wines and from 1931 to 2185, averaging 2025 mg/l GAE for the Grenache wines (table III). These levels are in agreement with a previous work showing that Syrah had the highest total phenol (TEISSEDRE and WATERHOUSE, 1995 a, b).The total phenol concentrations vary more for the Syrah than for the Grenache varieties, and especially for the south Rhône Syrah variety.

The relative inhibition of LDL varied from 10 to 100 p. cent with the south Rhône Syrah wine (figure 1). In fact, the different samples chosen in this area come from wineries which do not use the same extraction parameters : the wines 12S, 13S, 14S were made by a very short extraction process. In contrast, the wines 9S, 10S, 11S, were made by a longer extraction process. Thus, the north Rhône Syrah wines (made by the same winery, by a long extraction process) produced an inhibition of LDL oxidation increasing from 68.5 to 98 p. cent with the vintages (figure 1). These results can be compared with the three older vintages of the south Rhône area wines.

For the south Rhône Grenache wines (figure 2), the inhibition of oxidation of LDL ranged between 69.5 and 87.6 p. cent. These wines come from the same winery which uses a long maceration process. The antioxidant activity observed seems to be independent of the vintage. The variations observed in inhibition of LDL oxidation for different varieties can also be explained by other factors than the extraction process during winemaking. First, a difference in the grapes phenolic concentration bound to the maturity which is not exactly the same each year. Second, some possible oxidation of phenolics compounds during the storage. However, the same maximum level in the inhibition of LDL oxidation is found for the different varieties.

The composition of major monomeric phenolic constituents is summarized in table III. Catechin concentrations are very closed for Syrah and Grenache wines which average respectively : 137 mg/l and 141 mg/l. The average level of epicatechin is found lower than for catechin for the two variety wines : 90 mg/l for Syrah wines and only 52 mg/l for the Grenache wines. However for the 1993 Syrah vintages, the catechin and epicatechin levels were nearly equal.

Gallic acid was the third most abundant monomeric phenolic compound determined. This compound generally increases during wine aging by hydrolysis of tannins (ARCHIER, 1992). The average levels of gallic acid are similar for the two varieties : 63 mg/l in Syrah wines and 65 mg/l in the Grenache wines. Caffeic acid varied from 5 to 18 mg/l in Syrah wines and from 8 to 12 mg/l in Grenache wines. Like other free phenolic acids, this last compound found in grapes as ester combinations increases during winemaking and aging by a slow alkaline hydrolysis (RIBÉREAU-GAYON et *al.*, 1976). Malvidin-3-glucoside which belongs to the anthocyanin family was found in high amounts for the two varieties especially for recent vintages (6 to 140 mg/l). In effect, this molecule represents a major proportion of the anthocyanins in grapes and red young wines (DOURNEL, 1985). A second anthocyanin analysed cyanidin exists in traces (0 to 5 mg/l) and disappears completely in older vintages. This is not surprising because this compound is one of the more easily oxidized anthocyanin, which can produce during aging to protocatechic acid, taxifoline and catechine (GALVIN, 1993).

We found also smaller amounts of the flavonols rutin (2 to 13 mg/l), myrecitin (2 to 18 mg/l) and quercetin (0 to 18 mg/l). These green and yellow antioxidant pigments are generally in skins of red grapes in the monoglucoside form. During the fermentation, they are easily hydrolysed and we find again the 3 aglycons in free state.

TABLE II

Average value of analytical HPLC retention time Rt

Compound	Rt min
Gallic acid	4.13
Procyanidin B3	9.11
Procyanidin B1	10.10
Catechin	10.51
Procyanidin B4	11.11
Caffeic acid	12.12
Procyanidin B2	13.79
Epicatechin	17.71
Sinapic acid	28.24
Cyanidin	30.47
Rutin	34.93
Malvidin-3-glucoside	35.31
Myrecitin	36.08
Quercitin	41.64

Procyanidins levels found in the Grenache and Syrah wines averaged respectively 115 and 127 mg/l for the dimer B1, 50 and 72 mg/l for the dimer B2, 34 and 37 mg/l for the dimer B3, 169 and 174 mg/l for the dimer B4. These levels followed the same pattern established in other studies (BOURZEIX et *al.*, 1986 ; RICARDO Da SILVA, 1992 ; LAMUELA-RAVENTOS and WATERHOUSE, 1994). These compounds previously isolated and identified in grapes (WEINGES and PIRETTI, 1971 ; LEA and *al.*, 1979) are dimeric forms of catechin and epicatechin with a 4->8 binding between the monomeric forms. Procyanidin and catechin solution during maceration and fermentation of grapes is favoured at higher : temperature, alcohol concentrations and maceration time (SINGLETON and DRAPER, 1964 ; ROMEYER, 1984). Table III shows larger amount of these compounds for youngest vintages of the south Rhône Grenache and the north Rhône Syrah, as well as for the south Rhône Syrah wines of the 1990 vintage.

A correlation coefficient of $r = 0.72$ ($p < 0.001$) was found between relative inhibition of LDL oxidation and total phenol content in gallic acid equivalents (figure 3). Concentrations of individual phenolic constituents were correlated with the LDL antioxidant activity. The best r value was found for catechin : 0.75 ($p < 0.05$), followed by anthocyanins : cyanidin and malvidin-3-glucoside, procyanidin B1, B2, B3 with $r = 0.42\text{-}0.55$ ($p < 0.05$). A third group : gallic acid, myrecitin, rutin showed a lower correlation of 0.2-0.4 ($p < 0.1$). A fourth group constituted by quercitin and caffeic acid gave the lowest correlation between, $r = 0.2\text{-}0.3$ ($p < 0.15$). These results indicate that the phenolic compounds found in wines at different levels are active in protecting LDL from oxidation.

DISCUSSION

If the varieties of wines are listed according to the inhibition of LDL oxidation the highest value is obtained with California Merlot 60.5 p. cent (figure 4) followed by French Rhône Grenache (54.5 p. cent) and the California petite Sirah (52 p. cent). French Rhône

TABLE III

Inhibition of LDL oxidation and phenolic composition of tested wines*

wines	% inhibition(π) 10 µM GAE	Dilution factor	GAE	Gal	Cat	Caf	Sin	Epicat	Cyan	Malv (mg/l)	Rutin	Myr	Quer	B1	B2	B3	B4	∑B
1G	54.1	22.7	1931	62	122	7.9	4.5	43	0.0	16.4	5.3	6.2	1.8	86	47	33	158	324
2G	56.4	25.7	2187	67	143	9.4	4.4	50	0.0	13.7	5.1	5.9	1.9	107	35	40	173	355
3G	57.3	23.8	2027	68	147	8.9	4.6	52	0.0	41.4	7.7	5.9	4.5	129	57	39	212	437
4G	50.0	23.0	1958	64	151	12.3	2.0	63	0.0	82.4	9.6	4.1	0.0	137	61	26	131	355
5S	36.0	31.5	2675	54	139	7.1	6.2	96	3.2	18.0	8.1	16.0	11.2	107	84	50	203	444
6S	46.4	32.6	2774	79	149	6.4	5.6	76	0.0	42.2	9.5	9.3	2.8	138	86	53	182	459
7S	49.5	30.4	2585	36	161	8.4	3.8	126	0.0	69.0	9.6	4.1	1.4	185	125	31	110	451
8S	55.0	29.5	2504	75	177	4.6	0.8	162	1.2	69.5	10.5	3.3	7.0	152	107	33	165	457
9S	47.7	22.8	1935	65	115	11.9	2.4	71	0.0	6.0	3.3	7.7	4.8	108	56	35	145	344
10S	38.2	23.1	1967	57	122	5.6	2.9	29	0.0	1.9	2.3	1.9	4.0	91	24	39	137	291
11S	55.9	29.5	2510	88	161	17.5	1.8	89	0.0	13.1	3.7	4.7	8.3	179	80	47	250	556
12S	21.8	21.4	1821	68	95	5.9	3.9	39	0.0	17.3	5.1	17.7	18.4	65	25	30	182	302
13S	16.4	24.2	2060	66	140	12.9	4.1	101	4.7	139.6	12.6	6.3	2.6	141	77	27	204	449
14S	10.0	18.8	1601	40	111	17.5	3.0	126	1.2	116.3	12.1	6.4	2.0	106	57	27	160	350
r : correlated antioxidant activity with phenolic concentration			0.718	0.415	0.752	0.271	0.074	0.092	0.426	0.434	0.237	0.309	0.165	0.548	0.455	0.542	0.131	0.277

GAE : gallic acid equivalent - Gal : Gallic acid - Cat : Catechin - Caf : Caffeic acid - Epi : Epicatechin - Sin : Sinapic acid - Cyan : Cyanidin
Malv : Malvidin-3-glucoside - Rut : Rutin - Myr : Myricetin - Quer : Quercitin - B1 : Procyanidin B1 - B2 : Procyanidin B2 - B3 : Procyanidin B3
B4 : Procyanidin B4 - ∑B : B1+B2+B3+B4
*see table I for wine type abbrevations
(π) Inhibition of LDL oxidation at 10 µM GAE (see experimental section)

Syrah made with a long extraction process are similar to the California petite Sirah (47 p. cent). Sirah variety is followed by California Cabernet Sauvignon with 44 p. cent of LDL inhibition of oxidation. The Cabernet Sauvignon ranged between 38 to 55 in percent inhibition. In contrast, French Rhône primor Syrah with short extraction process gave the lowest average result (16 p. cent), which is under the average obtained with the white California wines (36 p. cent). For the white California wine, we distinguished Sauvignon blanc variety with 44.5 p. cent inhibition and Chardonnay (32 p. cent).

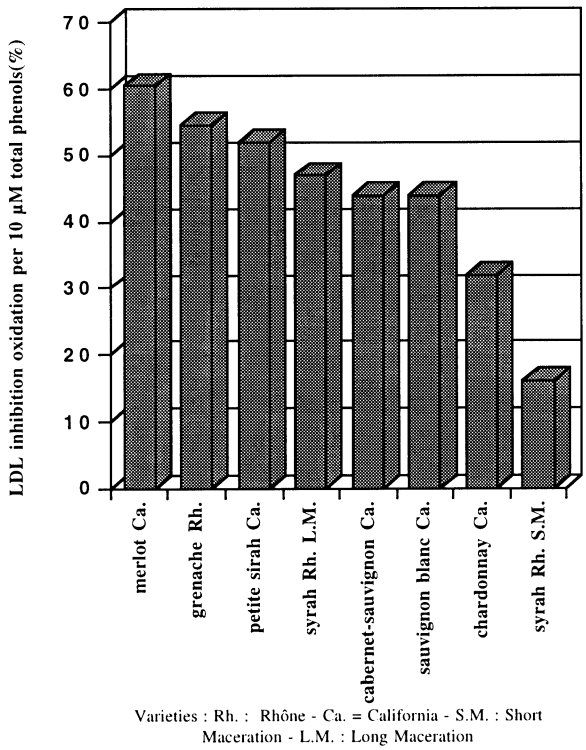


Fig. 4 — LDL inhibition oxidation average for different wine varieties from Rhône Valley and California

Figure 5 compares the averages of LDL inhibition of oxidation calculated for the French red wines tested in this study and California red and white wines of our previous study (FRANKEL and *al.*, 1995). The total red French wines give 42.5 p. cent inhibition for a total phenol content average of 2181 mg/l ; in comparison the total red California wines conduct to 49 p. cent inhibition with a total phenol content average of 2567 mg/l. These results support the thesis that the inhibition of oxidation of the LDL depends of the phenolic concentration of wines, which is directly affected by the wine-making process. The nature of the phenolics play also an important role in the antioxidant activity that they confer to the wines used in this study. Some phenolic compounds are probably more active than others. This study suggests that antioxidant activities of anthocyanins and flavonols (practically absent in white wines) may be less important than for catechins family which is a major source of phenolic of red wines. Structural, physical and chemical properties for each phenolic compound are probably extremely important to explain their antioxidant activities and if each one is absorbed it may prevent LDL oxidation *in vivo*. In a previous work, we found that the antioxidant catechin was absorbed in humans after the consumption of 300 ml red wine which contained 80 mg of free monomeric catechin. Plasma catechin concentrations were substantially above those shown to inhibit the oxidation of LDL *in vitro* (WALZEM and *al.*, 1995). Thus, to prove their possible health influence requires that we pursue *in vitro* and *in vivo* studies on the different antioxidant phenolic compounds found in wines.

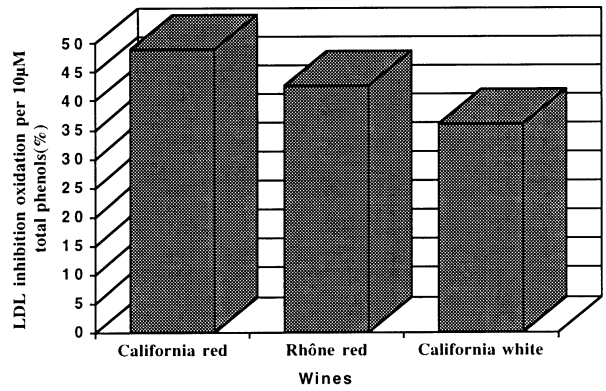


Fig. 5 — LDL inhibition oxidation average for California and Rhône wines

CONCLUSION

Average antioxidant activity levels of the French Rhône Syrah and Grenache wines made with a long maceration process from different vintages tasted in this study produced 50 p. cent in the inhibition of LDL oxidation and ranged between Merlot (60 p. cent) and Cabernet-Sauvignon (44 p. cent), when they are compared with different California wine varieties. In contrast, Rhône Syrah made with a short extraction process conducts to lower antioxidant activity against LDL oxidation than for white California wines.

The nature and concentration of phenolic compounds in the different types of wine are considered to be important to understand their potential health effects.

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