Antioxidant Activities of Caffeic Acid and Its Related Hydroxycinnamic Acid Compounds

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Hydroxycinnamic acid compounds are an important source of antioxidants due to their ubiquitous occurrence in the plant kingdom and their characteristic activities. In this study, we compared the antioxidative and free radical scavenging activities of caffeic acid (CA), caffeic acid phenethyl ester (CAPE), ferulic acid (FA), ferulic acid phenethyl ester (FAPE), rosmarinic acid (RA), and chlorogenic acid (CHA) with those of α-tocopherol and BHT. In the Rancimat test, the addition of test compounds in lard significantly extended the induction time of lipid oxidation, and the activities in decreasing order were CA $\sim$ α-tocopherol > CAPE $\sim$ RA > CHA $\gg$ BHT > FA $\sim$ FAPE. When the lipid substrate was changed to corn oil, the effectiveness of antioxidants on the induction time was obviously decreased, and the potency order of antioxidants was changed to RA > CA $\sim$ CAPE $\sim$ CHA > α-tocopherol > BHT; FA and FAPE had no significant antioxidative effect in the corn oil system. The 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) scavenging activity of the test compounds was RA $\gg$ CAPE > CA > CHA > α-tocopherol > FA > FAPE > BHT. The effect on retarding oil-in-water emulsion oxidation was BHT > CA > CAPE > RA > FA > CHA > α-tocopherol > FAPE, and the incubation times to reach an absorbance of 0.4 by the ferric thiocyanate method were 14.4, 11.4, 8.6, 7.3, 6.4, 4.6, 4.2, and 2.8 days, respectively, with the value of the control around 1.3 days.

INTRODUCTION

Hydroxycinnamic acid compounds are widely distributed in the plant kingdom. They usually exist as esters of organic acid or glycosides or are bound to protein and other cell wall polymers. Only a small number of them exist as free acids in nature (Herrmann, 1989, 1992, 1993). The occurrence of such compounds in food significantly affects stability, color, flavor, nutritional value, and other food qualities. Hydroxycinnamic acid compounds also process some biological activities (Chan et al., 1986; Huang et al., 1988; Nardini et al., 1995; Laranjinha et al., 1996; Chen, J. H., et al., 1996).

Lipid oxidation is an old but still very important topic in food stability and in human health. Many studies have been carried out to search for and to develop antioxidants having a natural origin. The potential of using hydoxycinnamic acid compounds as natural antioxidants has drawn more attention due to their ubiquitous occurrence in nature. In this work, we have investigated the antioxidative and free radical scavenging properties of six natural hydroxycinnamic acid compounds and compared their activities with those of two widespread typical food antioxidants, tocopherol and BHT. The models we have used were pure lipid oxidation (Rancimat method), oil-in-water emulsion oxidation, and the stable free radical scavenging model. The six hydroxycinnamic acid compounds we studied were caffeic acid (CA), caffeic acid phenethyl ester (CAPE), ferulic acid (FA), ferulic acid phenethyl ester (FAPE), rosmarinic acid (RA), and chlorogenic acid (CHA). Their structures are shown in Figure 1.

Caffeic acid is the most predominant phenolic acid in sunflower seeds (Leung et al., 1981) and greatly affects the solubility of plant protein (Mieth et al., 1992). Chlorogenic acid and caffeic acid were found in potatoes, and their concentrations in the peel are higher than the concentrations in the flesh inside of the potatoes (Rodriguez de Sotillo et al., 1994). These phenolic compounds are responsible for enzymatic browning and act as antioxidants in potatoes (Hayase et al., 1984). It is well-known that chlorogenic acid makes up 5–10% of the weight of coffee beans (Smith, 1985) and plays a significant role in coffee color and aroma formation (Baltes, 1976). Ferulic acid occurs widely in grain foods and vegetables (Graf, 1992; Rybka et al., 1993), and it is one of the major antioxidant constituents in beer (Maillard et al., 1995). The occurrence of ferulic acid in orange juice is responsible for the off-flavor formation during storage (Peleg et al., 1992). In rosemary and sage, two of the most important spices in meat processing, rosmarinic acid is one of the principle antioxidative constituents (Cuvelier et al., 1996). Phenethyl esters of caffeic acid and ferulic acid exist in honeybee propolis, a folk medicine used as an anti-inflammatory agent for centuries. These lipophilic hydroxycinnamic acid esters were found to possess significant biological activities (Grunberger et al., 1988; Sud'ina et al., 1993; Rao et al., 1995; Chen, J. H., et al., 1996).

Sud'ina et al. (1993) have studied the inhibitory effect of caffeic acid phenethyl ester on the superoxide generated by stimulated neutrophiles. Cuvelier et al. (1992) have compared the antioxidative efficiency of some phenolic acids, including caffeic acid, ferulic acid, rosmarinic acid, chlorogenic acid, and BHT.

The objectives of this work are to investigate the antioxidative potency of these hydroxycinnamic acid compounds and to try to elucidate the relationship between their activities and chemical structures.

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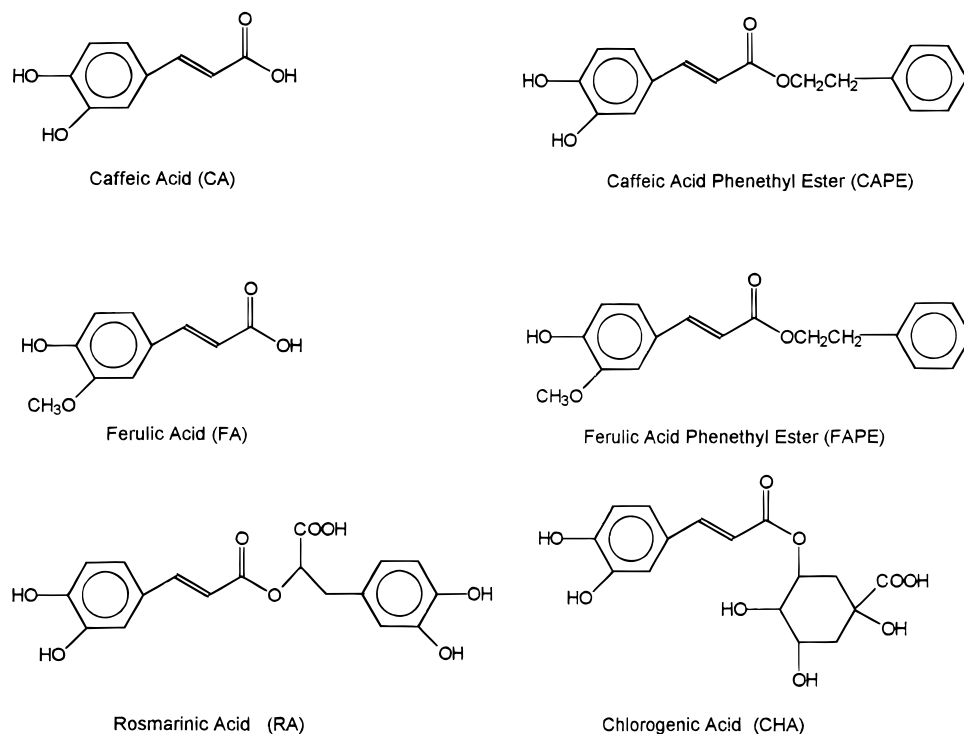
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Figure 1. Structures of some hydroxycinnamic acid compounds.

MATERIALS AND METHODS

Materials. Caffeic acid, ferulic acid, phenethyl alcohol, chlorogenic acid, dicyclohexylcarbodiimide (DCC), silica gel (130−230 mesh), the thin layer plate (250 μm thickness, 2−50 μm particle size), and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Aldrich Chemical Co. (Milwaukee, WI). All organic solvents and corn oil stripped of natural antioxidants were obtained from Fisher Scientific (Springfield, NJ). Rosmarinic acid was purchased from Extrasynthese (Genay, France). α-Tocopherol and Triton X-100 were obtained from Sigma Chemical Co. (St. Louis, MO). Pure lard (pork fat) was a kind gift from Oscar Food Ingredients (Milwaukee, WI).

Preparation of CAPE and FAPE. CAPE was synthesized using the method described by J. H. Chen et al. (1996), and FAPE was prepared using a similar method. Ferulic acid (1.9 g, 10 mmol) and phenethyl alcohol (6.0 g, 50 mmol) were dissolved in 25 mL of tetrahydrofuran; dicyclohexylcarbodiimide (DCC) (3.6 g, 20 mmol) was then added. After stirring at room temperature for 10 h, 18 μL of distilled water was added to the reaction mixture and stirred for 10 min to react with excess DCC. After filtration to remove solid white urea, the filtrate was evaporated in a vacuum rotary evaporator at 50 °C to obtain a brown viscous solution. The solution was loaded onto a preequilibrated silica gel column (130−230 mesh, 38 × 400 mm) and eluted with increasing gradient solvents (100% of petroleum ether to 25% ethyl acetate in petroleum ether). The fractions containing FAPE were pooled, concentrated, and then purified with a silica gel column one more time under the same conditions described above. White solid FAPE (1.4 g) was obtained, and the yield of this reaction was around 40%. This compound was analyzed by mass spectroscopy, which showed a molecular ion at m/z 298 (C$_{18}$H$_{18}$O$_4$) and major fragment peaks at m/z 194 (base peak), 177, 145, 89, and 77.

Evaluation of the Inhibitory Effect on Lipid Oxidation by the Rancimat Method. Pure lard (pork fat) or stripped corn oil was used as the lipid substrate to evaluate the lipid oxidation inhibition activity of six hydroxycinnamic acid compounds, α-tocopherol, and BHT. A Metrohm 679 Rancimat instrument (Herisan, Switzerland) was used in this experiment. Two micromoles (50 μL of a 40 mM methanol solution) of the above compounds was mixed with 2.5 g of lipid in different glass cylinders. The oxidation experiments were carried out at 110 °C, and air was blowing through the samples during the experiment at 20 mL/min. The same amount of methanol was added to the control of pure lipid, and methanol in glass cylinders was flushed out in the first 30 min without linking the receiving electrochemical cell. All tests were run in triplicate and averaged.

Scavenging Effect on DPPH Radicals. This experimental procedure was adapted from Chen et al. (1994). In an ethanol solution of DPPH radical (final concentration was 1.0 × 10^{-4} M), test compounds were added, and their concentrations were 20 μM. The reaction mixtures were shaken vigorously and then kept in the dark for 30 min. The absorbance of the resulting solutions was measured in 1 cm cuvettes using a Milton Roy 301 spectrophotometer at 517 nm against blank, which was without DPPH. All tests were run in triplicate and averaged.

Antioxidative Activity in Oil-in-Water Emulsion. In 4 mL of the oil-in-water emulsion (3% corn oil with 0.3% Triton X-100, emulsified by vortex at high speed for 1 min), test compounds were added until their final concentrations were 150 μM. The mixed emulsion was put in an 8 mL vial with a Teflon cap. The oxidation was carried out at 60 °C and the mixture continuously shaken at 250 rpm in a controlled environment incubator shaker (New Brunswick Scientific Co., Inc., Edison, NJ).

The oxidation of corn oil was monitored by the ferric thiocyanate method described in the paper of H. M. Chen et al. (1996). In a glass tube containing 75% ethanol (2.35 mL), 30% ammonium thiocyanate (50 μL), and a 20 mM ferrous chloride solution in 3.5% HCl (50 μL), 50 μL of the reaction mixture was added. After 3 min, the absorbance of the colored solution was measured at 500 nm in a 1 cm cuvette with a Milton Roy 301 spectrophotometer. All tests were run in triplicate and averaged.

RESULTS AND DISCUSSION

Evaluation of the Antioxidative Activity Using the Rancimat Method. The Rancimat method is commonly used to evaluate the antioxidative potency of various antioxidants (Chen et al., 1995), and it is based on the increase of electrical conductivity in receiving flasks due to the formation of small molecules from lipid oxidation.

As shown in Table 1, the addition of test compounds in lard significantly extended the induction time of lipid

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Table 1. Induction Time of Lipid Oxidation Measured by the Rancimat Method

compound[a]	induction time for lard (h) (SD)[b]	antioxidant index for lard[c]	induction time for corn oil (h) (SD)[b]	antioxidant index for corn oil[c]
control	2.12 (0.14)[c]	1.00	2.03 (0.06)[c']	1.00
caffeic acid	23.7 (1.4)[d]	11.1	5.11 (0.22)[d']	2.51
caffeic acid phenethyl ester	20.9 (0.9)[e]	9.86	4.89 (0.09)[d',e']	2.41
ferulic acid	4.28 (0.25)[f]	2.01	2.16 (0.06)[c']	1.06
ferulic acid phenethyl ester	4.24 (0.15)[f]	2.00	2.05 (0.10)[c']	1.01
rosmarinic acid	20.7 (0.5)[e]	9.76	6.02 (0.27)[f']	2.97
chlorogenic acid	16.6 (1.0)[g]	7.83	4.74 (0.28)[e']	2.33
α-tocopherol	23.5 (0.3)[d]	11.1	3.91 (0.21)[g']	1.93
BHT	5.88 (0.34)[h]	2.77	3.49 (0.18)[h']	1.72

[a] The concentration of added compounds was 2 μmol in 2.5 g of oil. [b] Each value is the mean of triplicate measurements, and SD means standard derivation of measurement. Values within a column with different letters are significantly different at $P < 0.05$. The substrate was pure lard (pork fat) or corn oil stripped of nature antioxidants. [c] Antioxidant index is defined as the induction time of lipid oxidation with antioxidant over the induction time of control.

Table 2. Scavenging Effects of Antioxidants on the 2,2-Diphenyl-1-picrylhydrazyl Radical[a]

compound	absorbance at 517 nm[b] (SD)[c]	inhibition percentage (SD)
control	1.159 (0.005)	–
caffeic acid	0.576 (0.028)	51.5 (2.44)
caffeic acid phenethyl ester	0.509 (0.014)	57.5 (1.24)
ferulic acid	0.879 (0.012)	24.8 (1.06)
ferulic acid phenethyl ester	1.018 (0.011)	12.5 (0.97)
rosmarinic acid	0.191 (0.016)	85.6 (1.41)
chlorogenic acid	0.749 (0.035)	36.3 (3.00)
α-tocopherol	0.791 (0.004)	32.5 (0.35)
BHT	1.052 (0.012)	8.9 (1.06)

[a] The concentration of DPPH ethanolic solution was 1.0×10^{-4} M. [b] The concentration of compounds was 20 μM. [c] Each value is the mean of triplicate measurements, and SD means standard derivation of measurements. All values within a column are significantly different at $p < 0.05$.

oxidation, and the effects in decreasing order were caffeic acid ~ α-tocopherol > caffeic acid phenethyl ester ~ rosmarinic acid > chlorogenic acid ≫ BHT > ferulic acid ~ ferulic acid phenethyl ester. When the lipid substrate was changed to corn oil, the retarding effect of antioxidants on the induction time was obviously decreased, and the potency order of antioxidants was changed to rosmarinic acid > caffeic acid ~ caffeic acid phenethyl ester ~ chlorogenic acid > α-tocopherol > BHT > ferulic acid ~ ferulic acid phenethyl ester. The addition of ferulic acid and its phenethyl ester in corn oil has no significant antioxidative effect.

Scavenging Effect on DPPH Radicals. Free radical scavenging is generally the accepted mechanism for antioxidants inhibiting lipid oxidation. The model of scavenging stable DPPH free radicals can be used to evaluate the antioxidative activities in a relatively short time (Brand-Williams et al., 1995) compared to other methods. The effect of antioxidants on DPPH radical scavenging was thought to be due to their hydrogen-donating ability (Blois, 1958).

As shown in Table 2, the scavenging activity order of the test compounds was rosmarinic acid ≫ caffeic acid phenethyl ester > caffeic acid > chlorogenic acid > α-tocopherol > ferulic acid > ferulic acid phenethyl ester > BHT.

Antioxidative Effect in Oil-in-Water Emulsion. In real food systems, lipids usually exist in the emulsion form instead of in the bulk form. The antioxidative activity in an emulsion is hard to evaluate because of the partition phenomena between hydrophilic and hydrophobic phases and the complex interfacial affinities between air−oil and oil−water interfaces involved. Some researchers have studied the different degrees of effectiveness of hydrophilic and hydrophobic antioxidants in bulk oil or emulsion testing systems (Frankel

et al., 1994, 1996; Frankel and Huang, 1996; Hopia et al., 1996; Huang et al., 1996a,b; Schwarz et al., 1996). They observed that the hydrophilic antioxidants showed greater antioxidative potency than hydrophobic ones in bulk oil, while hydrophobic antioxidants showed greater activities than hydrophilic antioxidants in emulsion.

As shown in Figure 2, the order of oxidation inhibitory activity obtained in the oil-in-water system was dramatically different when compared with the results of the Rancimat test and the DPPH scavenging model. The effect on retarding emulsion oxidation was BHT > caffeic acid > caffeic acid phenethyl ester > rosmarinic acid > ferulic acid > chlorogenic acid > α-tocopherol > ferulic acid phenethyl ester, and the incubation times to reach an absorbance of 0.4 by the ferric thiocyanate method were 14.4, 11.4, 8.6, 7.3, 6.4, 4.6, 4.2, and 2.8 days, respectively, with the value of the control around 1.3 days. This order was consistent with the result of a sensory test, which monitored the generation of rancid odor from oil oxidation during incubation. The interesting phenomenon is that BHT showed the greatest inhibitory effect in this test model, while it was a weak antioxidant in the Rancimat test and the DPPH scavenging models. The activities of caffeic acid and ferulic acid were stronger than those of their corresponding phenethyl esters. These results were not consistent with those of Huang et al. In their experiments, methyl carnosate was more effective than carnosic acid in bulk and emulsified oil, and the difference was greater in the emulsion system.

Discussion. The antioxidative activity of polyphenols is generally ascribed to their hydroxyl groups, but it is not the only factor in determining the potency of their activities. In the case of ferulic acid, there is a single hydroxyl group para-substituted on an aromatic ring which is connected to a highly conjugated side chain. This para substitition allows the phenoxy radical of ferulic acid to be delocalized across the entire molecule and therefore stabilized (Graf, 1992). The ortho substitution with the electron donor methoxy group is also a factor increasing the stability of the phenoxy radical and therefore increases its antioxidative efficiency (Cuvelier et al., 1992; Terao et al., 1993).

The presence of a second hydroxyl group in the ortho or para position is known to increase antioxidative activity due to additional resonance stabilization and *o*-quinone or *p*-quinone formation (Graf, 1992; Cuvelier, 1992; Brand-Willams, 1994). This can be used to explain the fact that antioxidative efficiencies of caffeic acid and its phenethyl ester are greater than those of ferulic acid and FAPE in our three test models, and the strongest DPPH scavenging activity of rosmarinic acid (the dimer of caffeic acid, it possess four hydroxyl groups) among the tested compounds.
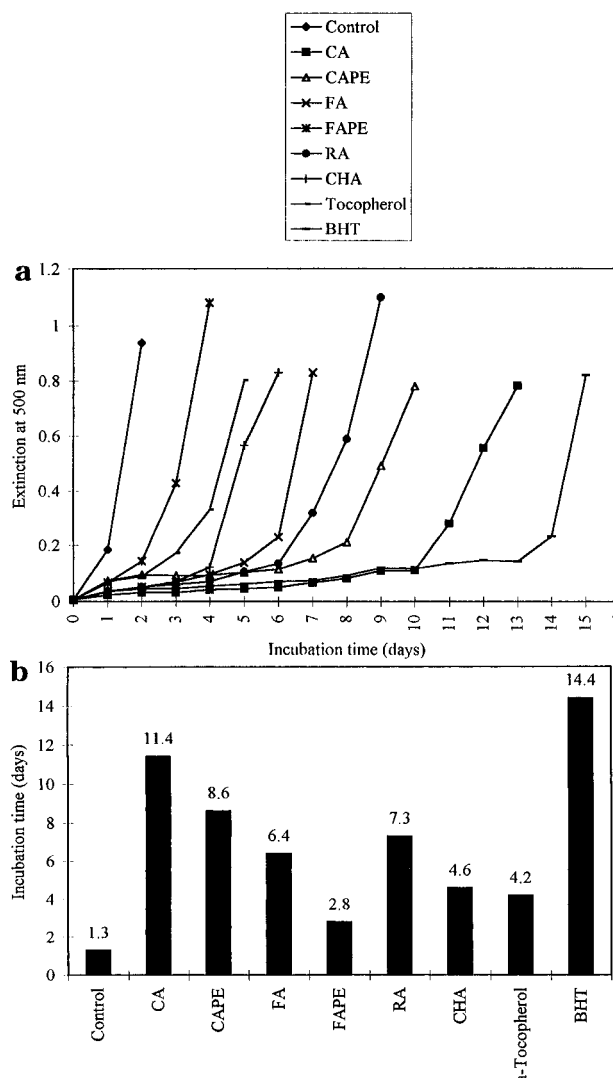
Figure 2. Antioxidative activity in oil-in-water emulsion. In 4 mL of oil-in-water emulsion (3% corn oil with 0.3% Triton X-100), test compounds were added; their final concentration was 150 μM. The oxidation of the mixture was carried out at 60 °C and the mixture continuously shaken at 250 rpm in a controlled environment incubator shaker. The oxidation of corn oil was monitored by the ferric thiocyanate method. In a glass tube containing 75% ethanol (2.35 mL), 30% ammonium thiocyanate (50 μL), and a 20 mM ferrous chloride solution in 3.5% HCl (50 μL), 50 μL of the reaction mixture was added. After 3 min, the absorbance of the colored solution was measured at 500 nm in a 1 cm cuvette with a spectrophotometer. All tests were run in triplicate and averaged: (a) oxidation of oil-in-water emulsion monitored by the ferric thiocyanate method and (b) incubation time of oil-in-water emulsion to reach an absorbance of 0.4 monitored by the ferric thiocyanate method.

Morinova and Yanishlieva (1992) have observed the different effects of test temperature on the antioxidative actions of α-tocopherol and ferulic acid in lipid oxidation. They evaluated the efficiency of both antioxidants in lard oxidation at 25, 50, 75, and 100 °C. Their results showed that an increase in temperature in the presence of ferulic acid led to no change in its antioxidative effectiveness, while the antioxidative effectiveness of α-tocopherol increased with temperature. They suggested that the rise in temperature induced changes in the α-tocopherol molecules and then a change in the mechanism of initiation or propagation in lipid oxidation, shown by the participation of antioxidants in a series of reactions involving radicals. It indicated that the results of oxidation stability obtained at a high temperature can be extrapolated to room temperature

only when no change occurs in the mechanism of initiation of radicals in lipids and participation of antioxidants in the reactions of inhibited autoxidation.

Comparing the results of α-tocopherol with those of rosmarinic acid and ferulic acid in our three test models, we can also come to a similar conclusion. The efficiency of α-tocopherol on retarding lard oxidation at 110 °C was obviously greater than that of the other two hydroxycinnamic acids, though this was not the case in the stable free radical scavenging model at room temperature and in the oil-in-water emulsion oxidation model, which was carried out at 60 °C.

Rosmarinic acid, which has four hydroxyl groups, showed the strongest DPPH scavenging potency. Other antioxidants have only one or two hydroxyl groups. Caffeic acid demonstrated the highest inhibition efficiency on lipid oxidation in the Rancimat test. This could be because of the conversion of caffeic acid to other compounds having greater antioxidant activity at higher temperatures, similar to α-tocopherol. Recently, some researchers have reported the generation of novel tetraoxygenated phenylinadan isomers, with impressive antioxidant activity, from the thermal decomposition of caffeic acid (Stadler et al., 1996; Guillot et al., 1996). In our primary experiment, we prepared such isomers and tested their activity using the Rancimat method. Thermal decomposition products of caffeic acid have demonstrated antioxidative activity stronger than that of caffeic acid. During the prolonged high-temperature heating in the Rancimat test, caffeic acid could be decomposed and produce strong antioxidants, with a higher potency than rosmarinic acid even though there are less hydroxyl groups in caffeic acid than in rosmarinic acid.

It is well known that there are more unsaturated fatty acids in vegetable oil (e.g., corn oil) than in animal fat (e.g., lard). Unsaturated fatty acids are more susceptible to oxidation. Although concentration of unsaturated fatty acids in corn oil or pork fat did not significantly affect the induction time of their oxidation in the Rancimat test (control values), the retarding effects of antioxidants on lipid oxidation in the Rancimat test were obviously dependent on the lipid substrate. As shown in our results, the effects were greater in lard than in corn oil.

Chlorogenic acid is the ester of caffeic acid with quinic acid. According to the results of Cuvelier (1992), esterification of caffeic acid by a sugar moiety decreased its antioxidative activity. In our three test models, chlorogenic acid also demonstrated less effective activities than caffeic acid.

The fact that α-tocopherol was a stronger antioxidant than BHT in the Rancimat test, while BHT was the strongest one in the oil-in-water emulsion, is a very interesting phenomenon. It indicated that different initiation and termination mechanisms of lipid oxidation may be involved in those two model systems. The changed forms of antioxidants coexisting in the emulsion system could contribute to the difference. On the other hand, some polyphenols could induce the generation of hydrogen peroxide in an aqueous solution which could promote lipid oxidation (Stadler et al., 1996). Our results indicate that α-tocopherol is effective in inhibiting oxidation of frying oil at high temperatures, while BHT could be an effective inhibitor of food oxidation in aqueous solution or oil-in-water emulsion during storage at relatively low temperatures. Further experiments should address this probability.

Future work should be done to elucidate the activity difference between caffeic acid, ferulic acid, and their

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corresponding phenethyl esters and the reason for the stronger activity of BHT among our test compounds in the oil-in-water emulsion oxidation inhibition.

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