

Butylated caffeic acid: An efficient novel antioxidant

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SUMMARY: A novel antioxidant, butylated caffeic acid (BCA) was rationally designed by adding a *tert*-butyl group to caffeic acid, which was synthesized at a high yield (36.2%) from 2-methoxy-4-methylphenol (**1**) by a four-step reaction including Friedel-Crafts alkylation, bromine oxidation, ether bond hydrolysis and Knoevenagel condensation. Its antioxidant capacity was much stronger than common commercial antioxidant *tert*-butyl hydroquinone (TBHQ) and its mother compound, caffeic acid, in both rancimat and deep frying tests. When investigated *via* the DPPH method, the antioxidant capacity of BCA was almost equal to TBHQ, but lower than caffeic acid. BCA could be a potentially strong antioxidant, especially for food processing at high temperatures such as deep frying and baking.

KEYWORDS: *Antioxidant capacity; Butylated caffeic acid; Deep frying*

RESUMEN: *Ácido cafeico butilado: un nuevo y eficaz antioxidante.* Se diseñó razonadamente un nuevo antioxidante, el ácido cafeico butilado (BCA) mediante la adición de un grupo *terc*-butilo al ácido cafeico, que se sintetizó con un alto rendimiento (36,2%) a partir de 2-metoxi-4-metilfenol, reacción de Friedel-Crafts, oxidación de bromo, hidrólisis del enlace éter y condensación de Knoevenagel. Su capacidad antioxidante fué mucho más fuerte que la del antioxidante comercial mas común el *terc*-butil hidroquinona (TBHQ) y la de su compuesto madre el ácido cafeico, tanto en rancimat como en pruebas de fritura. Cuando se investigó mediante el método DPPH, la capacidad antioxidante de BCA fue casi igual a TBHQ, pero menor que la del ácido cafeico. BCA podría ser un fuerte antioxidante potencial, especialmente para el procesamiento de alimentos a alta temperatura, tales como freír y hornear.

PALABRAS CLAVE: *Ácido cafeico butilado; Capacidad antioxidante; Fritura*

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1. INTRODUCTION

As widely known, dietary lipids are highly acceptable by consumers because of the palatability, typical smell and taste of their products. They play an important role in food nutrition and flavor during processing. Meanwhile, the exposure of lipids to air triggers their autoxidation, giving rise to rancid odors and flavors, with the decomposition of nutritional components (flavors, essential amino acids, fat-soluble vitamins, etc.), formation of secondary oxidation products and reduction in food safety. Lipid oxidation is one of the main causes of food quality deterioration, with the production of aldehydes, ketones, alcohols, hydrocarbons, volatile organic acids, and epoxy compounds. With an adequate understanding of how this oxidative degradation actually takes place in fats and oils, it has been determined that the autoxidation of unsaturated fatty acids occurs *via* a free radical chain reaction, including initiation, propagation, and termination.

Currently, with the brief background on how oxidation takes place in lipids, many efforts such as biological, physical, and chemical methods have been made to reduce oxidation (Akoh and Min, 2008). The best method, however, is still the addition of strong antioxidants to prevent the deterioration of lipids (Chen and Ho, 1995; Rojas and Brewer, 2007).

Among the commercial antioxidants, TBHQ is frequently applied during deep frying due to its low price and effective antioxidant capacity (Shahidi *et al.*, 1992). TBHQ, an aromatic organic phenol, is chemically synthesized. It is a derivative of hydroquinone, substituted with a *tert*-butyl group, and has good solubility in lipids (Emerton and Choi, 2008). The maximum level of TBHQ allowed in a finished product like frozen fish stored for 14 weeks is 120 mg/kg (Hsieh and Regenstein, 1991). The addition of TBHQ in lipids does not cause discoloration even when iron is present, and does not change the flavor or odor of the material. In addition, TBHQ is effective at early storage times in lengthening the induction period before oxidation is initiated, though it is not effective for baked food applications (Emerton and Choi, 2008; Hsieh and Regenstein, 1992).

The antioxidant capacity of TBHQ, however, decreases after a while because of the following reasons: It is absorbed by fried products; it evaporates under high temperature due to its low molecular weight (Hwang *et al.*, 2013). Other disadvantages include being questioned for possible negative side-effects in humans (Van Esch, 1986).

As a natural antioxidant, caffeic acid (*3,4-dihydroxycinnamic acid*) has been studied in many reports. It is among the major hydroxycinnamic acids present in wine. It shows not only a good biological activity with known antiviral, anti-inflammatory, anticancer properties and heart protecting effects, but also an efficient antioxidant capacity *in vitro*, which has

also been utilized extensively as a potent antioxidant (Gülçin, 2006). However, caffeic acid exhibits poor solubility in oils due to its carboxyl group, which decreases its fat-solubility in practice.

It is highly desirable to develop a new antioxidant of better lipid solubility than caffeic acid with antioxidant capacity as strong as BCA (butylated caffeic acid, or systematic nomination: (*E*)-3-(3-(*tert*-butyl)-4,5-dihydroxyphenyl) acrylic acid), which could be utilized for food preservation. This study is aimed at investigating the structural modification of caffeic acid *via* its alkylation and examining its antioxidant activity in food processing.

The modification of structures such as polyphenolic compounds increases their solubility in oils, and speeds up the leaving out of *ortho*-hydrogen, thereby, improving antioxidant capacity in oils (Huang *et al.*, 2014; Zhang *et al.*, 2004). Hence, structural modification is a convenient and efficient method that can be employed to improve the solubility of caffeic acid in oils by adding long-chain alkanes or the *tert*-butyl group at the *ortho*-aromatic ring, without decreasing phenol hydrogens.

Considering the steric hindrance effect and lipid solubility, the influence of the *tert*-butyl group is better than long-chain alkanes. At first, the *tert*-butyl group was added to the *ortho*-aromatic ring directly through Friedel-Crafts alkylation reaction from caffeic acid, although it proved abortive after a series of experimental condition alterations such as material ratio, temperature, the pattern of material addition and solvents. It could be that the density of electrons in benzene decreased because of the location-based effects of the acrylic acid group. Therefore, two main steps were devised: the *tert*-butyl group was added to the main body of benzene without location-based effects and then it was conjugated by the group of acrylic acid.

2. MATERIALS AND METHODS

2.1. Materials

Lard was rendered in the laboratory and stored at -18 °C for use. Commercial soybean oil was purchased from Wilmar International Limited (Shanghai, China). Potatoes were purchased from a local market. Other chemicals were obtained from Sinopharm Chemical Reagent Co. Ltd. The solvents employed were of AR grade.

All of the reactions were monitored by thin-layer chromatography (TLC) performed on silica gel GF₂₅₄ (homemade). Ultraviolet (UV) spectra were recorded with a UV-2450 spectroscopic instrument (Shimadzu Corp, Kyoto, Japan). The quartz cell was used as a vessel. The protection factors for antioxidants were measured by the rancimat method (Metrohm, Shanghai, China). All NMR experiments were conducted on a Bruker Avance 500 MHz spectrometer

(Bern, Switzerland) operating at 500.1 MHz for ^1H and 125.8 MHz for ^{13}C , respectively. Chemical shifts were reported in ppm using TMS as internal standard. The single-crystal structure analysis was performed using X-ray diffraction on a Bruker Smart Apex II diffractometer (Germany) at 296K, μ (Cu/K α)=0.108 mm $^{-1}$, Dcalc =1.354 mg/m 3 , 5584 reflections were measured, 1935 were unique (Rint=0.0147). The structure was dissolved with SheLXS a structure solution program using Direct methods and refined with SheLXL refinement package using least squares minimization (Zhou *et al.*, 2016).

The samples were examined in duplicate. Pearson's correlation test and t test were conducted using Origin 8 (Origin Lab, MA, United States). Reported data show standard deviation below 5%. Statistical significance has p values always below 0.05.

2.2. General synthesis of BCA

The compounds **2-4** were prepared according to earlier methods (Saiz-Poseu *et al.*, 2012; Wang *et al.*, 2006) with slight modifications (Scheme 1).

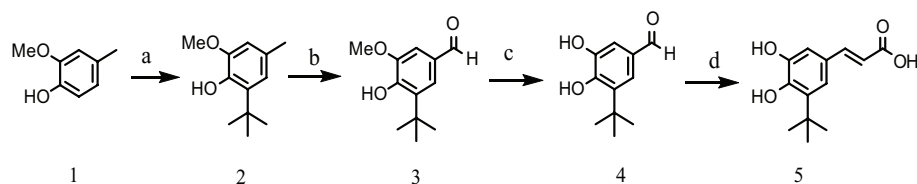
Preparation of 2-(tert-butyl)-6-methoxy-4-methylphenol (2): 7.80 mL of 2-methoxy-4-methylphenol (**1**) (61.7 mmol, 1 equiv) were added to 85% phosphoric acid (19 ml) and *tert*-butanol (30 ml, 328.4 mmol, 5.32 equiv) at 90 °C. After stirring for 7 hours, and concentrated to remove most of the *tert*-butanol under reduced pressure, ethyl acetate (100 mL) and water (10 mL) were added. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude products were purified with flash chromatography (petroleum ether:ethyl acetate= 20:0.5) to yield **2**, a light, colorless oil (8.50 g, 71%). ^1H NMR (500MHz, CDCl₃, ppm) δ 1.49 (s, 9H), 2.37 (s, 3H), 3.93 (s, 3H), 5.91(s, 1H), 6.67 (s, 1H), 6.78(d, J=0.35Hz, 2H). ^{13}C NMR (125.8 MHz, CDCl₃, ppm) δ 21.53, 29.56, 34.67, 56.14, 109.423, 127.92, 135.24, 142.01, 146.55.

Preparation of 3-(tert-butyl)-4-hydroxy-5-methoxybenzaldehyde (3): 3.00 g of compound **2** (15.5 mmol, 1 equiv) were added to *tert*-butanol (35 mL), stirred at 0 °C, then liquid bromine (2.5 ml, 48.7 mmol, 3.14 equiv) was added drop-wise, under nitrogen atmosphere for 20 minutes, while keeping the solution pink. After the addition, the mixture was stirred at room temperature for 1h, quenched by 50 ml H₂O and

then partitioned with 50 ml ethyl acetate. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude products were purified with flash chromatography (petroleum ether: ethyl ether=13:1) to yield **3**, a light, yellow solid (2.6 g, 80%), ^1H NMR (500MHz, CDCl₃, ppm) δ 1.44 (s, 9H), 3.97 (s, 3H), 6.64(s, 1H), 7.34 (d, J=1.65Hz, 1H), 7.47(d, J=1.65Hz, 2H). 9.84 (s, 1H). ^{13}C NMR (125.8 MHz, CDCl₃, ppm) δ 29.14, 34.70, 56.33, 106.79, 125.34, 128.30, 135.65, 147.25, 150.41, 191.52.

Preparation of 3-(tert-butyl)-4,5-dihydroxybenzaldehyde (4): 2.00 g of compound **3** (9.6 mmol, 1 equiv) were dissolved in CHCl₃ (20 mL), and stirred at 0 °C. After, AlCl₃ (1.79 g, 13.5 mmol, 1.4 equiv) was added in batches and then pyridine (3.4 mL, 42.3 mmol, 4.4 equiv) was added drop-wise. The mixture was refluxed for 24 h, cooled down to 0 °C and washed with 10% HCl (60 mL x 3) until the aqueous phase became light blue. It was then was partitioned with 150 ml ethyl acetate. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude products were purified with flash chromatography (petroleum ether: ethyl ether=4:1) to yield **4**, a white powder (1.4 g, 75%), ^1H NMR (500 MHz, acetone-d₆, ppm) δ 1.46 (s, 9H), 7.31(d, J=1.8Hz, 1H), 7.44 (d, J=1.8Hz, 1H), 9.78 (s, H). ^{13}C NMR (125.8 MHz, acetone-d₆, ppm) δ 28.71, 34.44, 111.56, 122.79, 128.48, 135.96, 144.99, 150.48, 190.80.

Preparation of BCA: 1.00 g of 3-(tert-butyl)-4,5-dihydroxybenzaldehyde (**4**) (5.2 mmol, 1 equiv) and malonate (0.54 g) were dissolved in a mixture of benzene (5 ml), pyridine (0.6 ml, 5.2 mmol, 1 equiv) and piperidine (0.06 mL, 0.7 mmol, 0.13 equiv). The solution was stirred at refluxing temperature for 3.5 h, cooled to 25 °C, poured into the mixture of conc. HCl_(aq) and ice water, and then was partitioned with ethyl acetate (20 ml). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude products were purified with flash chromatography (petroleum ether: ethyl ether=3:2) to yield **5** (BCA) (1.04 g, 85%), which was re-crystallized from methanol to afford needle-like light beige crystals, ^1H NMR (500 MHz, acetone-d₆, ppm) δ 1.45 (s, 9H), 6.24 (d, J=15.85Hz, 1H), 7.10(d, J=1.85Hz, 2H), 7.57 (J=15.85Hz, 1H). ^{13}C NMR (125.8 MHz, acetone-d₆, ppm) δ 28.86, 34.41, 111.39, 114.19, 120.16, 125.08, 136.00, 144.79, 147.13, 147.00, 168.07.



SCHEME 1. Reagents and conditions: a) *t*-BuOH, 85% H₃PO₄, 90 °C, 7h, 71%; b) Br₂, *t*-BuOH, rt, 1h, 80%; c) AlCl₃, pyridine, CHCl₃, 75%; d) piperidine, pyridine, 90 °C, 24 h, 85%.

2.3. Deep frying analysis

Commercial soybean oil was purified by silica gel column chromatography to remove its endogenous antioxidants. Different 0.02% (w/w) antioxidants were added to soybean oil samples (500 g) separately and then the oil samples were heated to 180 °C. Fresh potato slices, about 2±0.5 mm thickness, were added at the rate of 20 g/h, fried for 8 minutes, then removed from the oils. Oil samples were tested every 3 h during the frying period until 60 h. Acid values (AV) and Iodine values (IV) were determined for each sample using the International Union of Pure and Applied Chemistry (IUPAC) method (Paquot and Hautfenne, 1987).

The CD values were calculated from the absorbance and the final concentration of the samples (g/100 mL). The results were expressed as conjugated diene (CD) values and computed as follows (Glende and Recknagel, 1994; Zuta *et al.*, 2007):

$$CD = \frac{A}{C} * P$$

Where, A is absorbance of the sample at 233 nm. C is final dilution concentration of the sample (g/100 mL). P is the length of the measuring UV cell (cm).

2.4. Rancimat analysis

The antioxidant capacities of BCA, TBHQ and caffeic acid were measured by the rancimat method (Metrohm, Shanghai, China) at different concentrations in oils. An air flow (20 L/h) was bubbled through the oil heated at different temperatures: 80, 100 and 120 °C. The tests were carried out in duplicate. The protection factors (Pf) were calculated according to the following formula (Silva *et al.*, 2001):

$$Pf = \frac{IP_x}{IP_0}$$

Where, IP_x = the induction period of the sample in the presence of antioxidant.
 IP_0 = the induction period of the sample without antioxidant.

2.5. DPPH spectrophotometric assay

A 0.5 mL methanol solution of different antioxidant concentrations was added to a DPPH-methanol solution (3.0 mL, 40 mg/L), and allowed to react for 30 min at 25 °C, then, absorbance at 517 nm was recorded at different time intervals on

a UV visible spectrophotometer. The DPPH concentration in the reaction medium was calculated from the calibrated curve. The radical scavenging activity (%) was calculated according to the following formula (Liu *et al.*, 2014; Piang-Siong *et al.*, 2017):

$$\text{Scavenging activity (\%)} = 1 - \frac{(A_{\text{sample}} - A_{\text{blank}})}{A_{\text{control}}} * 100\%$$

A DPPH solution (3 mL) with methanol (0.5 mL) was used as negative control. A solution (3 mL) with methanol (0.5 mL) with a different concentration of antioxidant was used as a blank. EC_{50} (i.e., efficient concentration of the substance that produces 50% scavenging), obtained for the different antioxidants was calculated by linear regression of plots, where radical scavenging activity (%) was plotted against concentration.

3. RESULTS

3.1. Chemical structure of BCA

The ^1H and ^{13}C chemical shifts of compound BCA agree well with its chemical structure, which is compared with the spectra data for caffeic acid reported in the literature (Jeong *et al.*, 2011).

The single-crystal structure analysis of BCA was performed using X-ray diffraction. The crystal data of BCA presented (Figure 1; Table 1) give the perspective views of this compound together with its atomic labelling system. Thus, it can be confirmed for the absolute configuration of BCA ((*E*)-3-(3-(*tert*-butyl)-4,5-dihydroxyphenyl)acrylic acid).

3.2. Antioxidant capacity in deep frying oil

During the oxidation of lipids containing methylene substituted dienes and polyenes, a shift in the position of the double bond was observed, due to isomerization and conjugated bond formation (conjugated dienes). The percentage changes of CD during frying (Figure 2, A), were as follows: BCA>Caffeic acid>TBHQ>Blank.

No obvious change was observed during the initial 12 hours (Figure 2, B). But, later, the change in AV manifested the capacity of antioxidants as follows: CBA>Caffeic acid>TBHQ>Blank.

When soybean oils were in deep frying at 180 °C, some polyunsaturated fatty acids became conjugated, and some double bonds were destroyed, thus, decreasing iodine values. IV changes at 180 °C (Figure 2, C) increased as follows: BCA>Caffeic acid>TBHQ>Blank.

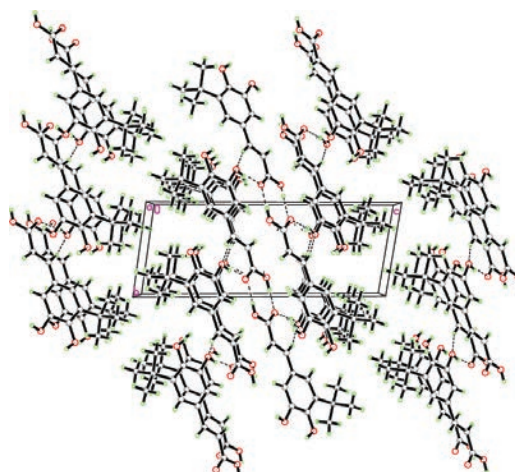
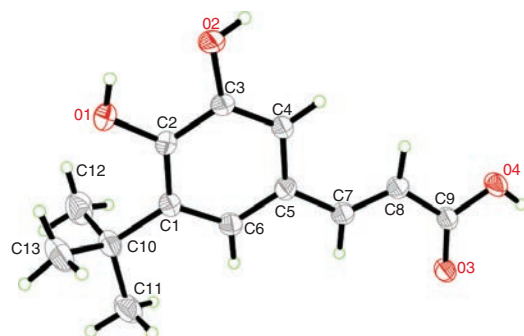


FIGURE 1. Crystal structure diagram of BCA by X-ray diffraction.

TABLE I. Crystal Data and Structure Refinement for BCA

Empirical formula	C ₁₃ H ₁₆ O ₄
formula weight	236.26
temperature (K)	296(2)
crystal system	triclinic
space group	P-1
a (Å)	6.037(3)
b (Å)	6.357(3)
c (Å)	16.711(9)
v (Å ³)	618.7(6)
z	2
ρ _{calcd} (mg/m ³)	1.268
μ (Mo/Kα)(mm ⁻¹)	0.094
F(000)	252
crystal size (cm ³)	0.23x0.20x0.20
reflections collected/unique	3216 / 2157
R _{int}	0.0118
data/restraints/parameters	2157/0/161
goodness-of-fit on F ²	1.050
R ₁ , wR ₂ [I>2σ(I)]	0.0394, 0.1033
R ₁ , wR ₂ (all data)	0.0498, 0.1149

3.3. Antioxidant capacity using the rancimat method

According to their Pf values (Figure 3), TBHQ, Caffeic acid and BCA showed good antioxidant capacities in the concentration 0.02% at 80, 100, and 120 °C, as follows: BCA>Caffeic acid>TBHQ>Blank.

In different concentrations, 0.01, 0.02, and 0.04% at 100 °C (Figure 4), Pf values changed as follows: BCA>Caffeic acid>TBHQ>Blank. BCA, however, showed a remarkable Pf value (i.e., 79.9) at a concentration of 0.04% at 100 °C.

3.4. Antioxidant capacity using DPPH spectrophotometric assay

The scavenging DPPH radical is widely used to evaluate antioxidant capacity due to its simple, rapid, sensitive and reproducible procedure. In this study, kinetic investigation was performed to estimate the speed of DPPH–Antioxidant reaction. On the other hand, EC₅₀ of TBHQ, caffeic acid and BCA were measured in terms of hydrogen-donating or radical-scavenging capacity.

The EC₅₀ values for the reducing power of TBHQ, Caffeic acid and BCA were 0.1690, 0.1283, and 0.1748 μg/L, respectively. The reducing power decreased as follows:

TBHQ≈BCA>Caffeic acid. The ease of donating hydrogen (Figures 5, A and B) was Caffeic acid>TBHQ≈BCA.

4. DISCUSSION

4.1. Antioxidant capacity of BCA in deep frying oils and rancimat test

In the deep frying oil and rancimat tests, BCA showed stronger antioxidant capacity than TBHQ and caffeic acid (Scheme 2):

1. The influence of the *tert*-butyl group: Increased the grease compatibility and the leaving out of *ortho*-hydrogens on BCA (Huang *et al.*, 2014), at 180 °C.
2. The influence of the acrylic acid group: Enlarged the conjugation system, which provided more stabilized radical resonance to capture more peroxy radicals. It also benefited the intermolecular coupling of BCA to form a large relative molecular mass (Figure 1), with a higher boiling point than TBHQ.

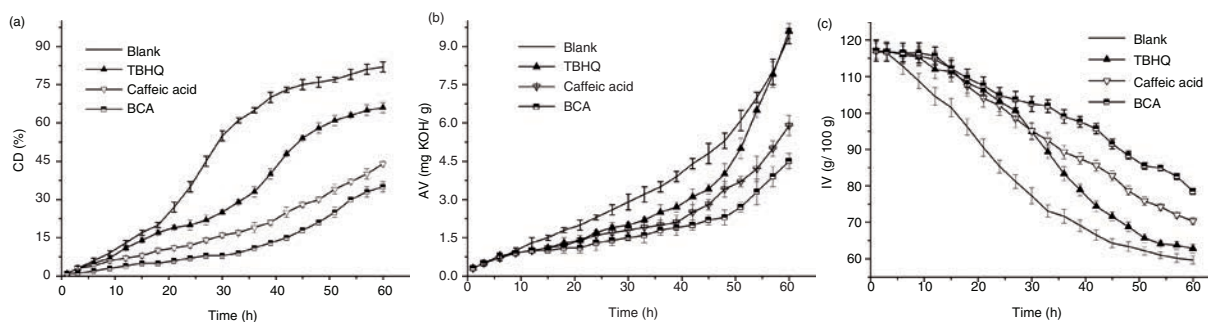


FIGURE 2. Conjugated diene values (CD), Acid values (AV) and Iodine values (IV) of antioxidants during deep frying in soybean oil (average value \pm standard deviation, n=2).

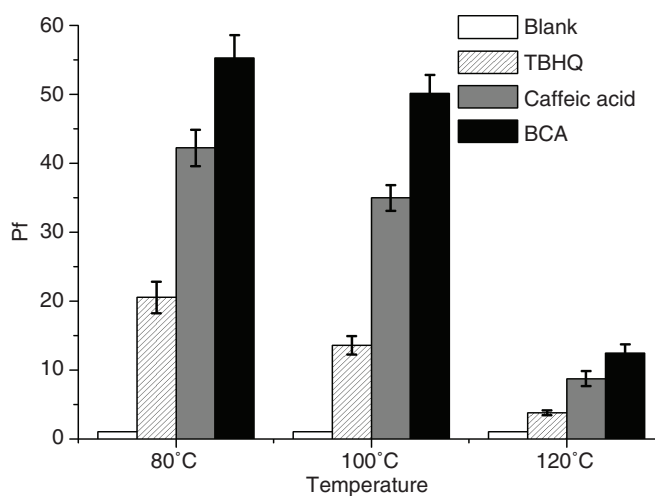


FIGURE 3. Pf values at concentration 0.02% at 80, 100, and 120 °C. (average value \pm standard deviation, n=2). Reported data show standard deviation below 5%. Statistical significance has *p* values always below 0.05.

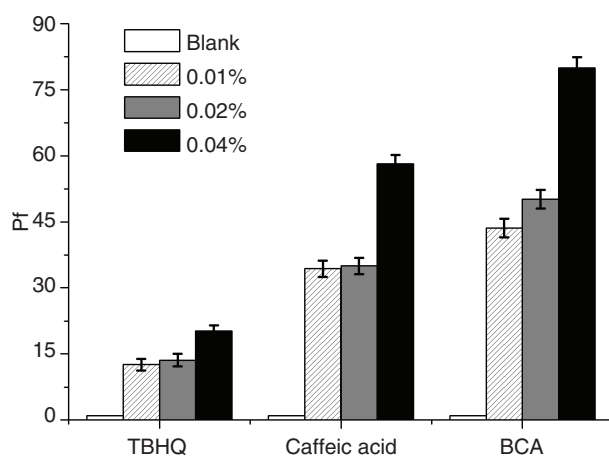


FIGURE 4. Pf values at different concentrations in lard, at 100 °C. (average value \pm standard deviation, n=2). Reported data show standard deviation below 5%. Statistical significance has *p* values always below 0.05.

Hence, BCA lasted longer in deep frying oil compared to TBHQ.

- The influence of the catechol group: Hydrogen bonds in catechol group made the intermediate more stable after one of the phenolic hydroxyl hydrogen atoms left (Baum and Perun, 1962). Meanwhile, some metallic ions were more easily chelated than TBHQ, also by the catechol group of BCA (Cornard and Lapouge, 2006).

4.2. DPPH radical scavenging activity

In the DPPH system, BCA showed approximate antioxidant capacity with TBHQ, and lower capacity compared to caffeic acid:

EC₅₀ values. The steric effect of the *tert*-butyl group hinders free radical DPPH from occupying carbon positions on the benzene ring of BCA. As a result, the

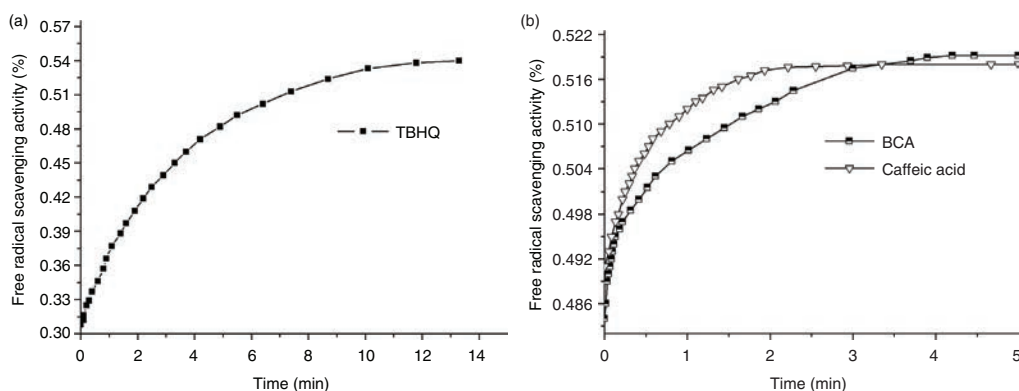
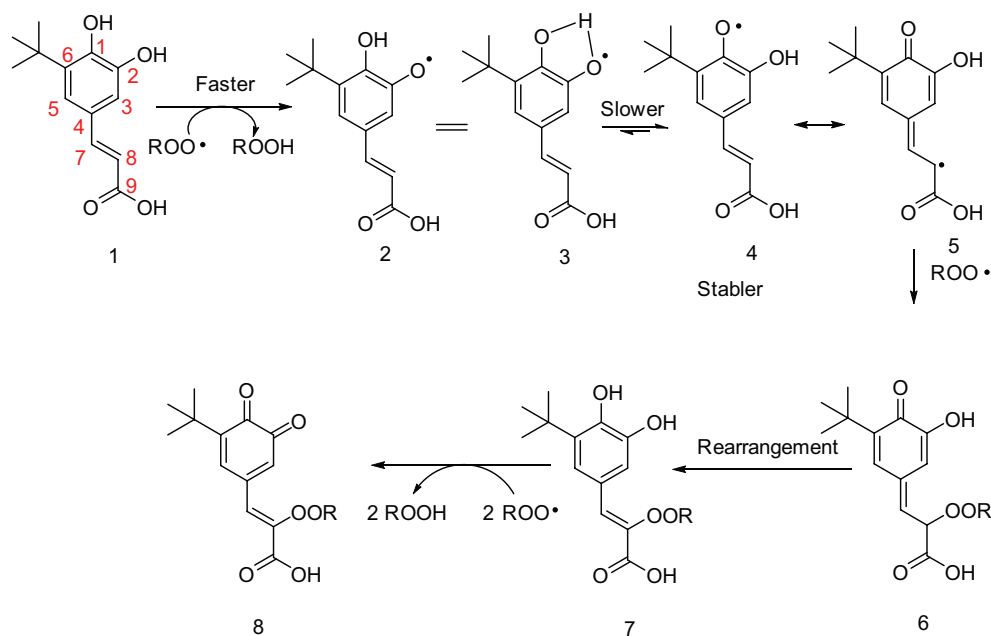


FIGURE 5. Kinetic behavior of TBHQ, caffeic acid and BCA at EC_{50} concentrations in DPPH.



SCHEME 2. Elucidation of the synergistic effects of *ortho*-hydroxy groups on BCA.

free radical scavenging activity of BCA is less than caffeic acid and TBHQ in the DPPH system. However, the synergistic effect of the catechol group benefited the leaving out of hydrogen atoms, and the large conjugated system of the acrylic acid group enabled the stabilized radical resonance to capture more DPPH radicals, thus, making the free radical scavenging activity of BCA similar to TBHQ in the DPPH solution.

Kinetic behavior. The steric effect of the *tert*-butyl group on the BCA caused the second phenol hydrogen in the *ortho-tert*-butyl group to remain after the first one left. The same response was observed for the oxidation of compound **3** to compound **4** without protecting the phenol hydrogen.

5. CONCLUSIONS

The specific structure of BCA was confirmed by X-ray single crystal diffraction, ^1H , and ^{13}C NMR. It had a higher lipophilicity than caffeic acid, and showed superior antioxidant capacity to caffeic acid and TBHQ in deep frying and Rancimat tests, but an almost equal capacity to TBHQ in the DPPH method, suggesting its potential use as an antioxidant in lipophilic conditions. Moreover, the incorporation of the *tert*-butyl group into the caffeic acid molecule may render additional health benefits or possible synergistic effects *in vivo*, which will be further investigated.

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