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INHIBITION OF LIPID PEROXIDATION AND RADICAL SCAVENGING ACTIVITY OF SYNTHESIZED CURCUMIN AND BISDEMETHOXYCURCUMIN IN FOOD SYSTEMS

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ABSTRACT

In this study, curcumin and bisdemethoxycurcumin (BDMC) were synthesized using a patented procedure and tested *in vitro* for inhibition of lipid peroxidation and for radical scavenging activities. At the same 0.14 mM concentration, the order of the inhibitory effect on lipid peroxidation was 2,6-di-tert-butyl-4-methylphenol (BHT) > curcumin > BDMC (97% > 89.7% > 73.4%, respectively). Curcumin also showed activities in scavenging hydrogen peroxide and DPPH radicals stronger than BDMC due to the presence of two methoxy groups in the curcumin molecule. However, BDMC showed higher $ABTS^{\bullet+}$ cationic radical scavenging activity. Curcumin was then chosen to be used and tested for antioxidant effects in two food systems. At the same molar concentration, curcumin is about 25% less effective than BHT in inhibiting crude fish oil peroxidation. Starch films containing curcumin showed DPPH scavenging activities lower than those of free curcumin due to the protecting effect of gelatinized starch and the slow release of curcumin from the film.

1. Introduction

Lipid oxidation is one of the major problems in the food industry because it produces substances that deteriorate product quality and adversely affect the colour and nutrition of lipid-containing products. Moreover, the oxidation of cell membrane lipids is very destructive to human health (Shahidi and Zhong 2010). Among the methods for controlling lipid oxidation, the use of antioxidants is effective, convenient and economical. Antioxidants are also used for health promotion due to their ability to protect the body against oxidative stresses and damages. Traditional antioxidants in the food industry, such as BHA (butylated hydroxyanisole) or BHT (2,6-di-tert-butyl-4-methylphenol), have been used since the 1940s. However, recent studies showed that they may cause adverse effects on human health and the environment (Leclercq, Arcella, and Turrini 2000; Yang et al. 2018; Wang et al. 2019; Ito, Fukushima, and Tsuda 1985).

Curcumin and other curcuminoids isolated from turmeric are classified as multipotent antioxidants, because besides antioxidant activity, these compounds have shown antibacterial, antiviral, anti-inflammatory, antitumor, and many other helpful biological activities (Amalraj et al. 2017). The *in vivo* and *in vitro* properties of curcumin have been tested on several systems. Curcumin was proved to have anti-inflammatory, antioxidant properties and many other therapeutic effects (Hewlings and Kalman 2017).

Compared with curcumin, bisdemethoxycurcumin (BDMC) is less

abundant in turmeric and thus was less extensively investigated. Moreover, few studies compared the biological activities of these two curcuminoids in the same conditions (Jayaprakasha, Rao, and Sakariah 2006; Venkatesan and Rao 2000). However, the demand for BDMC production is increasing due to the discovery of its new biological and pharmaceutical activities (Ramezani, Hatamipour, and Sahebkar 2018; Kim, Park, and Kim 2001; Jin et al. 2020). This demand and the difficulties in isolating BDMC from turmeric remind the importance of the synthetic approach.

In this study, both curcumin and BDMC were synthesized by a patented procedure and tested for antioxidant and radical scavenging activities *in vitro*. After a comparison of the *in vitro* results, curcumin was chosen to be used and tested for antioxidant effects in two food systems (crude fish oil and starch film).

2. Materials and methods

2.1.Materials

Tributyl borate, n-butylamine, vanillin, 4-hydroxybenzaldehyde, 2,4-pentanedione, boric oxide, isopropanol, absolute ethanol, sodium dihydrogenphosphate (NaH_2PO_4), glycerol were purchased from Xilong Scientific (China); linoleic acid, iron(II) sulfate heptahydrate ($FeSO_4.7H_2O$), potassium thiocyanate (KSCN), hydrogen peroxide (H_2O_2), 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid (ABTS), 35% hydrochloric acid (HCl), ammonium persulfate ($(NH_4)_2S_2O_8$) from MilliporeSigma (USA). Yellowtail fish and corn starch were purchased from a local supermarket in Ho Chi Minh City.

2.2. Methods

2.2.1.Synthesis of curcumin and BDMC

Curcumin was synthesized following a procedure adapted from a patent with some modifications (Krackov and Bellis 1997). Boron oxide (4.66 g; 67.9 mmol) and 2,4-pentanedione (7.3 mL; 70.1 mmol) were placed into a 100 mL round-bottomed flask under constant magnetic stirring. After 15 min, tributyl borate (27.3 mL; 140 mmol), isopropanol solvent (10 mL) and vanillin (21.3 g; 140 mmol) were subsequently added after every 5 min. The mixture was heated to 60 ^oC and kept for 5 min. The reaction was triggered by slow drop-wise addition of *n*-butylamine (2.13 g; 29.1 mmol) into the reaction mixture for 1 h. After 3 h, the reaction mixture was poured into 1 L of 5% aqueous acetic acid solution at 60 ^oC to hydrolyse the curcuminoid-boron oxide complex. The product appeared to be a viscous liquid oil but turned to a red-orange solid after 2 h of continuous stirring. The solid product was filtered and recrystallized 2 times in 75% aqueous ethanol, and then dried at 70 ^oC for 2 h.

To synthesize BDMC, the same procedure was conducted, but vanillin was replaced by 4-hydroxybenzaldehyde (17.1 g; 140 mmol).

2.2.2.Characterization of curcumin and BDMC

The synthesized curcumin and BDMC were dissolved separately in absolute ethanol and scanned from 320 to 1100 nm using a UV-vis spectrophotometer (UH5300, Hitachi, Japan). Their melting points were determined by using an MP55 Melting Point System (Mettler Toledo, USA).

2.2.3.Inhibition of linoleic acid peroxidation assay

The ferric thiocyanate method was used to determine the lipid peroxidation inhibition by curcumin and BDMC (Jayaprakasha, Singh, and Sakariah 2001). Solutions of each curcuminoid with different concentrations (10 - 50µg/mL) in 2.5 mL of a phosphate buffer (0.04 M; pH 7.0) were added to 2.5 mL of an aqueous emulsion of linoleic acid. Each 5 mL of the linoleic emulsion contained 15µL of Tween-20 and 15µL of linoleic acid in the phosphate buffer (0.04 M; pH 7.0). The emulsion with curcuminoid was incubated at 37 ^oC in the dark. After predetermined internals of time, 0.1 mL of the sample was mixed with distilled water (9.7 mL), KSCN solution (0.1mL; 30%) and fresh 20 mM $FeSO_4$ in 3.5% HCl solution (0.1 mL). After

exactly 5 min of incubation in the dark, the absorbance of the solution was measured at 500 nm. The same procedure was conducted for the control sample, which was the linoleic emulsion mixed with an equivalent amount of the phosphate buffer instead of the curcuminoid solution.

Inhibition percentage of curcuminoid on lipid peroxidation was calculated as followed:

$$Peroxidation\ inhibition(\%) = (1 - \frac{A_C}{A_o}) \times 100 \quad (1)$$

where A_C is the absorbance of the sample containing curcuminoid after reacting with ferric thiocyanate reagent when the absorbance of the control reached maximum; A_o is the maximum absorbance of the control after reacting with ferric thiocyanate reagent.

2.2.4.Hydrogen peroxide scavenging activity

Hydrogen peroxide scavenging activity was conducted according to a published study (Ruch, Cheng, and Klaunig 1989). Each curcuminoid solution (15 µg/mL; 3.4mL) in phosphate buffer (0.1 M; pH 7.4) was added to a H_2O_2 solution (43 mM; 0.6 mL). After 1 h of incubation in the dark, the absorbance at 230 nm of the mixed solution was measured. The control was the 43 mM H_2O_2 solution.

The H_2O_2 scavenging activity was calculated as followed:

$$H_2O_2\ scavenging(\%) = (1 - \frac{A_C}{A_o}) \times 100 \quad (2)$$

where A_C is the absorbance of the H_2O_2 solution containing curcuminoid; A_o is the absorbance of the H_2O_2 control sample (without curcuminoids).

2.2.5.DPPH radical scavenging capacity assay

DPPH scavenging activities of the curcuminoids were evaluated according to a published method (Ak and Gülçin 2008). An ethanolic solution of DPPH (0.1 mM; 1 mL) was added to an ethanolic solution of a curcuminoid (10 - 50µg/mL). After 30 min of incubation in the dark, the absorbance at 517 nm of the solution was measured.

DPPH scavenging activity was calculated as followed:

$$DPPH\ scavenging(\%) = (1 - \frac{A_C}{A_o}) \times 100 \quad (3)$$

where A_C is the absorbance of the DPPH solution containing curcuminoid; A_o is the absorbance of the DPPH control sample (without curcuminoids).

2.2.6.ABTS$^{\bullet+}$ cationic radical scavenging activity

The cationic radical scavenging activity was determined according to an improved decolourization method (Re et al. 1999). $ABTS^{\bullet+}$ was generated by mixing an aqueous ABTS solution (2 mM; 5 mL) with an ammonium persulfate solution (2 mM $(NH_4)_2S_2O_8$; 5 mL) and subsequent incubation in the dark for 4 h at room temperature. The $ABTS^{\bullet+}$ solution was then diluted to an absorbance of 0.750 ± 0.025 at 734 nm in a phosphate buffer (0.1 M; pH 7.4). After that, 2.9 mL of the diluted $ABTS^{\bullet+}$ was added to 0.1 mL of ethanolic solution of curcuminoid (10-50 µg/mL). The absorbance at 734 nm was measured after 30 min. The $ABTS^{\bullet+}$ scavenging ability was calculated as followed:

$$ABTS^{\bullet+}\ scavenging\ (\%) = (1 - \frac{A_C}{A_o}) \times 100 \quad (4)$$

where A_C is the absorbance of the $ABTS^{\bullet+}$ solution containing curcuminoid; A_o is the absorbance of the $ABTS^{\bullet+}$ control sample (without curcuminoids).

2.2.7.Testing of oxidation inhibition on fish oil

Crude fish oil was extracted and purified from yellowtail catfish fat according to a procedure described elsewhere (List 2009). An ethanolic solution of curcumin was added into 10 mL of the oil at different concentrations (1.0 – 5.0 µg/mL). After thorough mixing, the oil was poured into a Petri dish and kept in a drying oven for 24 h at 60 ^oC to accelerate the oil oxidation (Pan et al. 2007). After this oxidation period, the oil was testest for peroxide content by the ferric thiocyanate described above.

2.2.8.Starch films incorporated with curcumin and DPPH scavenging test

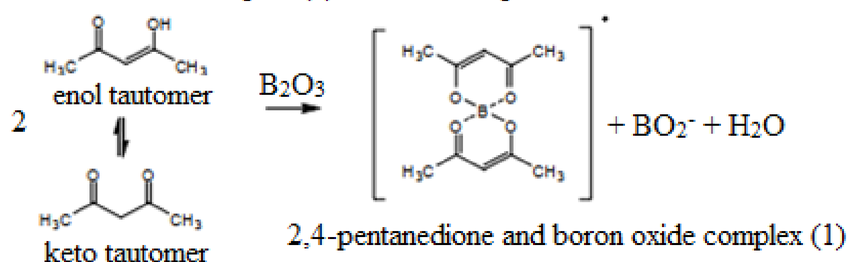
To incorporate curcumin into starch films, a procedure adapted from another study was used (Nawab et al. 2017). Corn starch (2 g) was suspended in 40 mL of distilled water. An ethanolic curcumin solution was added to the suspension to reach a predetermined curcumin/starch mass ratio (0-5%). Glycerol (0.6 g) as a plasticizer was then added and the mixture was heated under stirring at 90 °C for 30 min. After that, the mixture was poured into a Petri dish and left for drying at room temperature for 48 h.

To evaluate the antioxidant activity of the composite film, 25 mg of the film was dissolved in 3 mL of distilled water at 55 °C (Moradi et al. 2012). The radical scavenging activity of the starch – curcumin suspension was determined by the DPPH method. The suspension (0.5 mL) was added to 2.5mL of 0.6 mM DPPH ethanolic solution. After 30 min of incubation in the dark, the absorbance at 517 nm of the mixture was measured. The control of this test was a starch film without curcumin (Bitencourt et al. 2014).

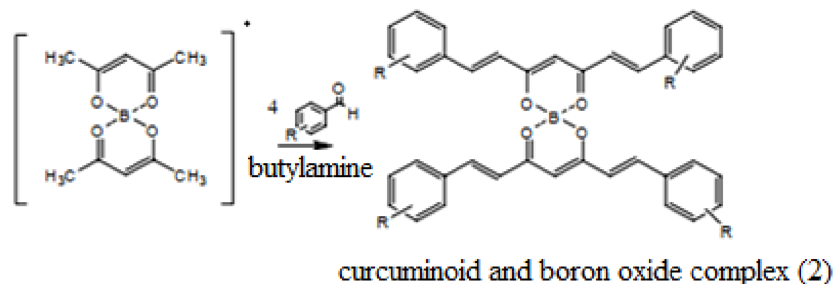
3. Results and discussions

3.1. The curcuminoids synthesis

Step 1. Formation of complex (1) between 2,4-pentanedione and boron oxide



Step 2. Condensation between the complex (1) and benzaldehyde derivative to form the complex (2)



Step 3. Acidic hydrolysis of the complex (2) to form curcuminoid

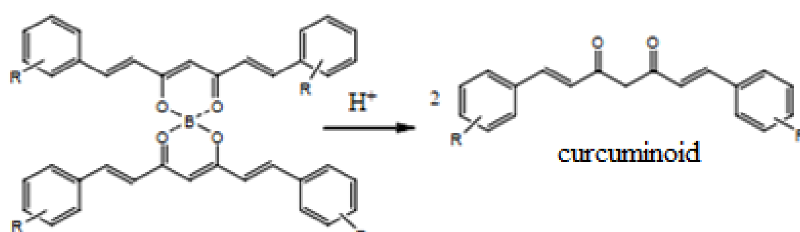


Figure 1. Mechanism of the synthesis of curcuminoids.

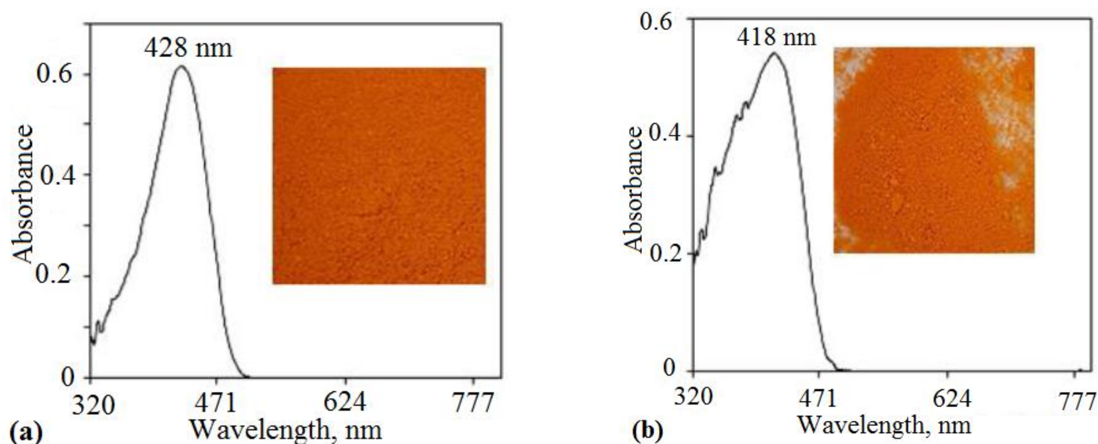


Figure 2. UV-vis spectra and the appearance of synthesized curcumin (a) and BDMC (b).

The first step in the synthesis of curcuminoids (Figure 1) is the formation of the complex (1) between 2,4-pentanedione and boron oxide to prevent the Knoevenagel reaction of the methylene group in the 2,4-pentanedione molecule. In the second step, aldol condensations between this complex (1) and a benzaldehyde derivative (vanillin for curcumin or 4-hydroxybenzaldehyde for BDMC) take place twice in the presence of n-butylamine catalyst to form the complex (2). The third step is the acidic hydrolysis of the complex (3) to produce the free curcuminoid (Handler et al. 2007).

The synthesized curcumin was a red-orange powder (melting point 179 °C – 182 °C) with a maximum absorbance at 428 nm in 95% ethanol (Figure 2a). Meanwhile, the synthesized BDMC was orange-yellow powder (melting point 215 – 220 °C) with a maximum absorbance at 418 nm in 95% ethanol (Figure 2b). These physicochemical properties of curcumin and BDMC are in accordance with the literature values. The range of melting points indicates that the synthesized compounds were of high purity (Péret-Almeida et al. 2005).

3.2. Inhibition activity toward lipid peroxidation

Lipid oxidation begins with the attack of oxygen on the double bonds the fatty acid fragments to form peroxyls and peroxides (Shahidi and Zhong 2010). The amount of peroxyls and peroxides during the oxidation of linoleic acid is determined in this study by the ferric thiocyanate method. During the analysis, Fe^{2+} ions are oxidized by the peroxides to form Fe^{3+} ions, which in turn react with SCN^- ions to form red complex ions $Fe(SCN)_3$, with a maximum absorbance at 500 nm. Therefore, a higher value of absorbance at 500 nm indicates a higher extent of fatty acid peroxidation (Mihaljević, Katušin-Ražem, and Ražem 1996).

Figures 3a and 3b demonstrate that increasing the concentration of any curcuminoid deceased the extent of lipid peroxidation, and curcumin shows a stronger inhibitory effect. This effect is because the curcuminoids in neutral solutions (pH = 7.0) exist predominantly in the keto form and can act as strong hydrogen donors, thus preventing the formation of radicals participating in the lipid peroxidation process (Subramani et al. 2017).

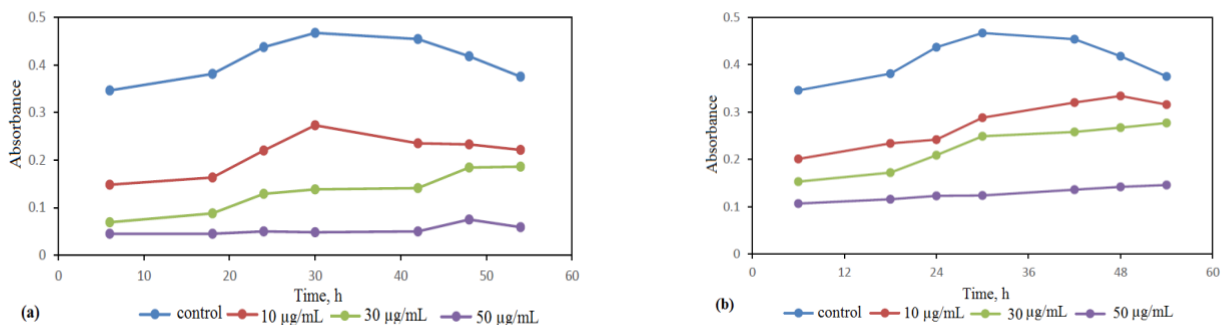


Figure 3. Effects of curcumin (a) and BDMC (b) concentrations on the peroxide levels (expressed in absorbance after reaction with Fe^{2+}/SCN^{-} in ferric thiocyanate assay) of linoleic emulsions.

The relative inhibitory effect of the curcuminoids was compared with that of BHT (butylated hydroxytoluene), a commercial antioxidant widely used in the food industry (Figure 4).

At almost the same molarity, the order of inhibitory effects of the studied compounds was: BHT 0.14 mM > curcumin (50 µg/mL = 0.14 mM) > BDMC (50 µg/mL = 0.16 mM) (97% > 89.7% > 73.4%, respectively). This result indicates that curcuminoids can replace BHT in antioxidant applications with comparable activity. This lower antioxidant activity can be compensated with higher used amounts and the multiple biological activities of the curcuminoids (Jayaprakasha, Rao, and Sakariah 2006).

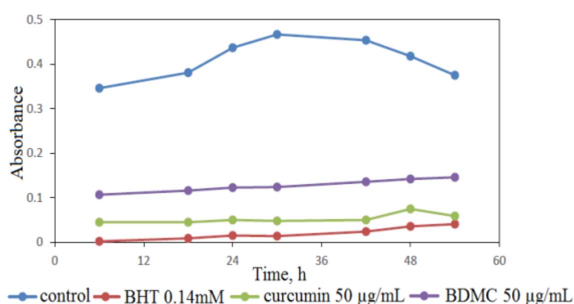


Figure 4. Inhibitory effects of curcumin, BDMC and BHT with similar molarities toward linoleic acid peroxidation.

3.3. Hydrogen peroxide scavenging ability

It is widely accepted that lipid oxidation is a radical chain reaction with hydrogen peroxide as an important intermediate. Moreover, H_2O_2 is very toxic in vivo and must be rapidly eliminated from the cells (Halliwell, Clement, and Long 2000). The ability of curcuminoids to eliminate H_2O_2 can break the reaction chain of lipid oxidation and protect human health. The H_2O_2 scavenging activities of the curcuminoids and BHT at the same concentration of 15 µg/mL are shown in Table 1, which are similar to the results in another study (Ak and Gülçin 2008). The results indicate that the curcuminoids have H_2O_2 scavenging activity higher than BHT. Although curcumin and BDMC showed no significant difference in H_2O_2 scavenging activities at a confidence level of 95%, these values are significantly different at a confidence level of 90%. Therefore, curcumin is more likely to be more active than BDMC in H_2O_2 scavenging, possibly due to the presence of a methoxy electron-donor group on each benzene ring

Table 1. Hydrogen peroxide scavenging activities (mean ± standard deviation) of the curcuminoid and BHT at the concentration of 15µg/mL.

	Curcumin	BDMC	BHT
H_2O_2 scavenging (%)	27.9 ± 4.1[a]	23.7 ± 3.9[ab]	16.5 ± 3.7[b]

Different letters a and b show statistically different means (p=0.05).

3.4. DPPH• radical scavenging activity

Free radicals play important roles in lipid oxidation and high amounts of radicals adversely affect human health. Lipophilic curcuminoids can scavenge different forms of free radicals, such as reactive oxygen species and reactive nitrogen species, therefore can be considered as chain-breaking antioxidants (Menon and Sudheer 2007). The radical scavenging activities of the curcuminoids and BHT were tested on the DPPH• radical (Figure 5).

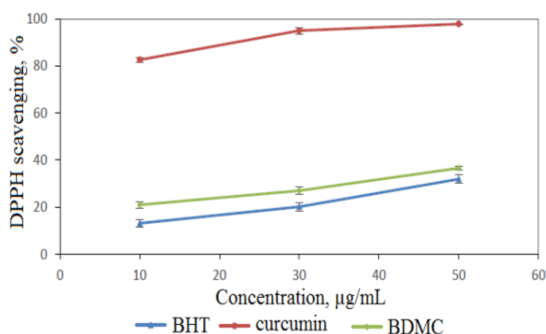


Figure 5. DPPH scavenging activities of BHT, curcumin and BDMC at different concentrations.

The phenolic –OH groups of curcuminoids have been shown to play essential roles in free radical scavenging reactions (Priyadarsini et al. 2003). Therefore, as in the case of H_2O_2 scavenging activity, the methoxy group on the benzene ring of curcumin enhances the stability of the phenoxy radicals formed during the radical scavenging. As a result, curcumin has a DPPH radical scavenging ability significantly higher than BDMC and BHT (Ak and Gülçin 2008).

3.5. ABTS•+ cationic radical scavenging activity

ABTS•+ is the most popular cationic radical used in evaluating antioxidant activities of pure compounds, solutions and beverages. ABTS•+ radicals are water-soluble, and the reactions with ABTS•+ radicals involve electron-transfer, apart from the H-atom transfer in reactions with DPPH radicals (Kaviarasan et al. 2007). In the presence of antioxidants, the coloured ABTS•+ radical cation is reduced to the colourless ABTS molecule. The decolourization extent is related to the antioxidant activity.

The results in Figure 6 show that the ABTS•+ scavenging activities of curcumin, BDMC and BHT are not very different, as in the DPPH scavenging assay.

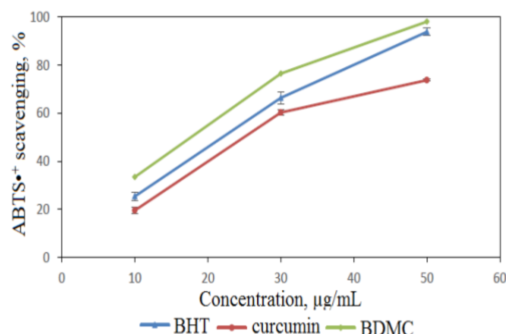


Figure 6. ABTS•+ scavenging activity of BHT, curcumin and BDMC at different concentrations.

In contrast with other types of antioxidant activities, ABTS•+ scavenging activity of curcumin is lower than BDMC, which is in accordance with another study, where synthesized curcuminoids with a methoxy, ethoxy, methyl or tert-butyl group in the ortho-position to the hydroxyl group showed lower ABTS•+ scavenging activity, compared with BDMC (Venkatesan and Rao 2000). This result, which is in contrast with the result in DPPH scavenging activity, can be explained by the fact the ortho-methoxy group forms intramolecular hydrogen bonds with the phenoxyl hydrogen and thus increases its bond dissociation energy (Kajiyama and Ohkatsu 2001).

3.6. Applications in some food systems

3.6.1. Inhibition of fish oil oxidation

Fish oil is an industrial product with high nutritional values thanks to the high content of polyunsaturated fatty acids, such as eicosapentaenoic acid (C20:5, EPA), docosapentaenoic acid (C22:5, DPA) and docosahexaenoic acid (C22:6, DHA) (Valenzuela, Sanhueza, and de la Barra 2012). The high contents of these polyunsaturated fatty acids make fish oil sensitive to oxidation with the formation of rancidity products. In this study, due to its higher inhibition activity toward linoleic acid peroxidation, curcumin was chosen as a candidate for BHT alternative to protect fish oils.

Figure 7 shows that at the same concentrations and the same accelerated oxidative conditions, the inhibition effect of BHT is about 25% higher than that of curcumin.

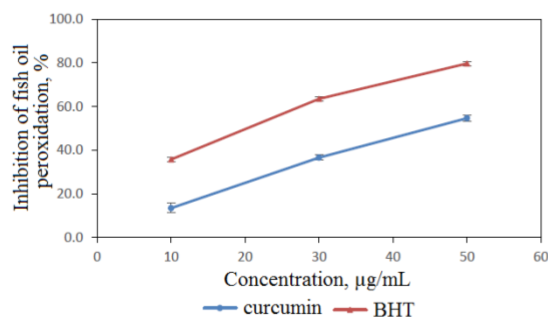


Figure 7. Inhibition of fish oil peroxidation by curcumin and BHT at different concentrations.

Although curcumin is less active than BHT, it can be used with much higher amounts to reach the same inhibiting effect as BHT. From several human studies, curcumin induced no toxicities at dosages up to 8 g/day in phase I clinical trials (Hsieh 2001; Hsu and Cheng 2007). Moreover, using curcumin can impart the oil with many other biological activities, including antibacterial, antiviral, anti-inflammation, anticancer effects of curcumin, which are beneficial to human health (Hewlings and Kalman 2017).

3.6.2. Radical scavenging activity of starch-curcumin composite films

Incorporating curcumin into edible starch films can produce packaging materials and new food with helpful functional properties. Figure 8 shows that increasing the amount of curcumin in the starch films make them more yellow and less transparent. At the studied range of contents, curcumin was uniformly dispersed in the films.

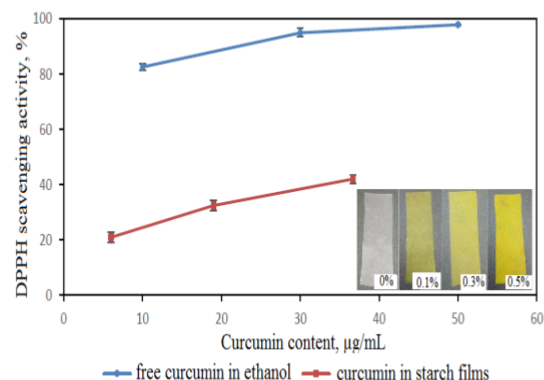


Figure 8. DPPH scavenging ability of free curcumin (blue line) and curcumin in starch films (red line). Inset: the appearance of starch films with different curcumin contents.

The red line in Figure 8 shows that the DPPH scavenging activity of the starch – curcumin films increases with the curcumin content. However, these values were significantly lower than the DPPH scavenging activities of free curcumin. It is because the starch molecules surrounding curcumin were a barrier hindering the diffusion of curcumin and DPPH, thus slow down the reaction rate between these molecules. This means that incorporating curcumin into starch films can protect it from adverse environments. Moreover, this curcumin – starch composite film, if incorporated with flavours, can be used as a multifunctional food or multifunctional packaging material (Mujtaba et al. 2019).

4. Conclusions

Relatively pure curcumin and BDMC were synthesized from 2,4-pentanedione and benzaldehyde derivatives. This synthetic approach is more convenient and environmentally benign than the extraction and

isolation of these compounds from turmeric. Curcumin shows higher antioxidant and radical scavenging activities, but lower activity in ABTS$^{•+}$ scavenging. Curcumin has high potential to replace BHT as an oil antioxidant and to be a multifunctional ingredient in active and intelligent packaging.

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