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Protective effects of equimolar mixtures of monomer and dimer of dehydrozingerone with α-tocopherol and/or ascorbyl palmitate during bulk lipid autoxidation

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ABSTRACT

Protective effects of recently synthesised dehydrozingerone, M_1OH (which is one half of the molecule of curcumin) and dimer of dehydrozingerone, $D_1(OH)_2$, as individual compounds (1 mM) and as equimolar binary (1:1) and ternary (1:1:1) mixtures with α-tocopherol (TOH) and/or ascorbyl palmitate (AscPH), were studied during bulk lipid autoxidation at 80 °C. The highest oxidation stability of lipid substrate, in the presence of individual compounds, was found for TOH, followed by $D_1(OH)_2$ and M_1OH, determined from the main kinetic parameters (antioxidant efficiency, reactivity and capacity). AscPH did not show any protective effect. Synergism was obtained for the binary mixtures of (TOH + AscPH) [42.4%], (M_1OH + TOH) [32.4%] and (M_1OH + AscPH) [35.6%] and for the ternary mixture of (M_1OH + TOH + AscPH) [28.7%]. Different protective effects observed were explained on the basis (of results) of TOH regeneration and its content determined by HPLC. These antioxidant binary and ternary mixtures can be used as functional components of foods with health-promoting effects.

1. Introduction

Antioxidants are the principal ingredients that protect food quality by preventing oxidative deterioration of lipids. Phenolic compounds are very efficient in preventing lipid autoxidation; however, only some of them are currently permissible by law as food antioxidants (Shahidi, 1999). There is a growing interest in natural and natural-like antioxidants, mostly related to the lower toxic effects of these compounds (Koehn & Carter, 2005; Marchiani, Rozzo, Fadda, Delogu, & Ruzza, in press; Nahlala, Moyo, & Van Staden, 2010; Sharma, 2011). Recent research has attempted to identify the functional components of foods that provide health-promoting or disease-combating effects (Bors et al., 2002; Kancheva, 2011, Chapter 1).

Curcumin or diferuloylmethane, derived from the rhizome of *Curcuma longa*, responsible for the yellow colour of the spice turmeric, manifests a wide spectrum of biological activities and excellent free radical-scavenging activity (Aggarwal & Harikumar, 2009; Chen, Deng, Zhou, Yang, & Liu, 2006; Marchiani et al., 2013). Unfortunately, curcumin has low solubility in aqueous and physiological solutions and undergoes rapid degradation into ferulic acid (FA), vanillin (Va) and dehydrozingerone (a half molecule of curcumin, M_1OH) (Fig. 1) (Wang et al., 1997). Curcumin metabolites are 4-substituted 2-methoxy phenols, a large class of naturally occurring phenols to which hydroxycinnamic acids belong. The latter are major components of the primary cell wall of cereals and other plants (Galasso, Kovac, Modelli, Ottavini, & Pichierri, 2008). Dehydrodimers of ferulic acid (5,5′-disubstituted biphenols) (Callipo et al., 2010) manifest higher antioxidant activity and often they are less toxic than is the corresponding phenolic monomer (Garcia-Conesa, Wilson, Plumb, Ralph, & Williamson, 1999; Fujisawa, Atsumi, Murakami, & Kadoma, 2005).

New recently synthesised C_2-symmetry hydroxylated biphenyl [$D_1(OH)_2$] and the corresponding monomer, dehydrozingerone (M_1OH) (Marchiani et al., 2013; Pisano et al., 2010), were selected for this study. Biphenyl $D_1(OH)_2$ exhibited (both *in vitro* and *in vivo*) significantly reduced tumour growth in malignant melanoma and it partially inhibited the aggregation process of alpha-synuclein, involved, as misfolded protein, in Parkinson's disease. In both pathologies, oxidative stress plays an important role; thus,

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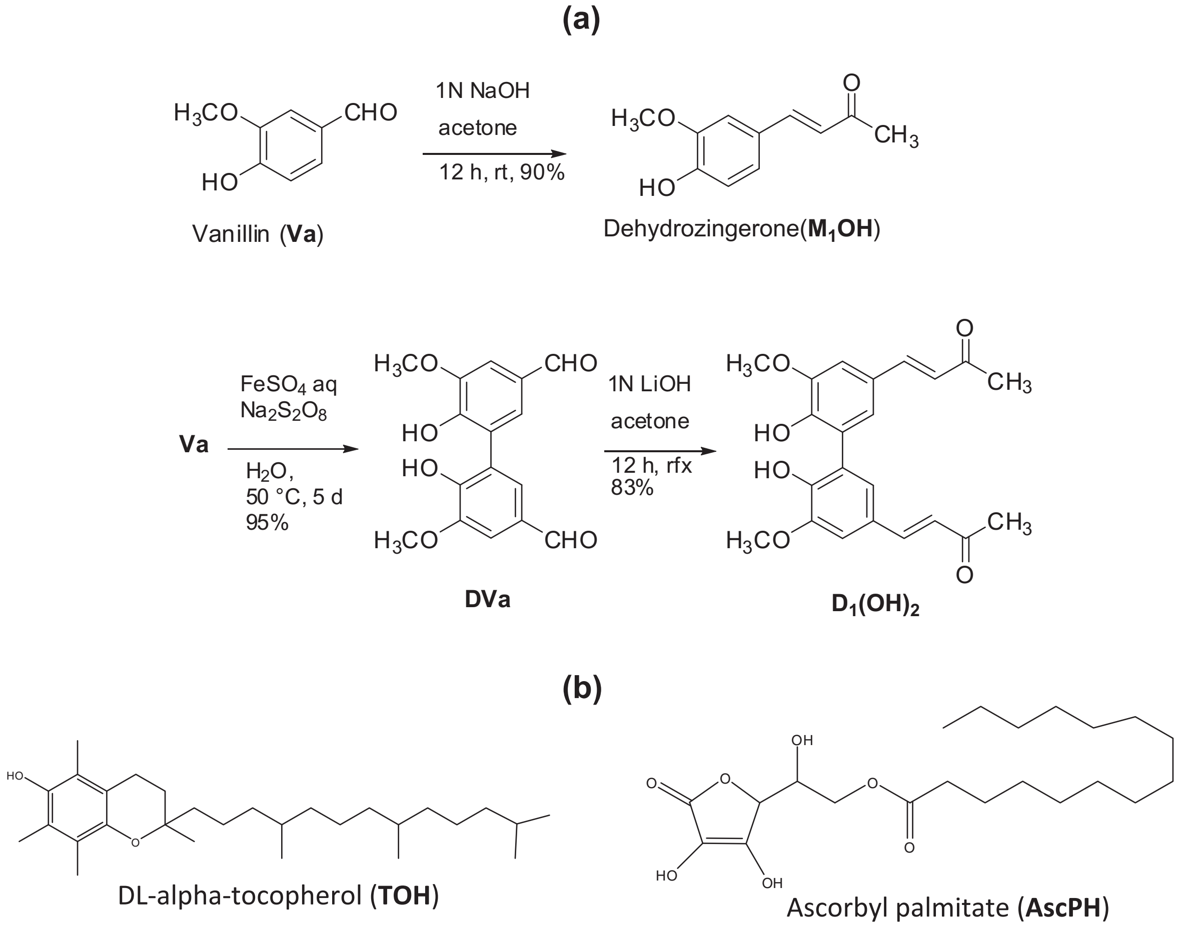

Fig. 1. Scheme of synthesis (a) of dehydrozingerone monomer (M_1OH), dimer of dehydrozingerone [$D_1(OH)_2$] and structures (b) of α-tocopherol (TOH), ascorbyl palmitate (AscPH) and curcumin (curcum).

biphenyl $D_1(OH)_2$ appeared to be a good candidate to control production of radicals.

The protective effects of M_1OH and $D_1(OH)_2$, as chain breaking antioxidants, were tested for individual compounds and also in binary and ternary mixtures with α-tocopherol (TOH) and ascorbyl palmitate (AscPH). The following structural features of M_1OH and $D_1(OH)_2$ make them an interesting scaffold: (a) the presence of an OH group in the benzene ring, which is able to scavenge free radicals by H atom transfer; (b) an electrono-donating *ortho*-methoxy group, increasing ability for H abstraction from an OH-group, i.e. increasing the antioxidant potential; (c) the aliphatic side chain that contains an unsaturated bond able to stabilise the phenoxyl radical. Our previous studies have covered the importance of this unsaturated side chain, especially for its antioxidant activity during bulk phase lipid autoxidation, which could be ascribed to the participation of the double bond in stabilization of the phenoxyl radicals via increased electron delocalization (Kancheva et al., 2013).

This research was focussed on the protective effects of various binary and ternary mixtures of M_1OH, dehydrozingerone and the corresponding dimer $D_1(OH)_2$, with TOH and AscPH. We propose the mechanisms of action, explaining the observed synergism, antagonism and additivism between compounds under study.

2. Materials and methods

2.1. Chemicals

DL-α-tocopherol and ascorbyl palmitate were from E. Merck, Germany. Vanillin (Va), reagents, and solvents (Sigma–Aldrich Chemie GmbH and E. Merck, Germany) were used without further purification. Acetone was freshly distilled over $CaCl_2$.

2.2. Synthesis of C_2-symmetry hydroxylated biphenyl [$D_1(OH)$] and corresponding monomer (dehydrozingerone, M_1OH)

Dimer $D_1(OH)_2$ was obtained in 83% yield by Claisen–Schmidt condensation of vanillin dimer (DVa) in the presence of a large excess of LiOH in acetone at room temperature. With a slight modification of the above synthetic procedure, dehydrozingerone, M_1OH, was obtained, starting from vanillin (Va) in acetone, using NaOH as base. All prepared compounds were solid, air-stable and fully characterised. In the synthesis of unsaturated compounds, the M_1OH, and $D_1(OH)_2$ *trans* configuration was exclusively obtained. Fig. 1 presents the scheme of synthesis of dehydrozingerone (M_1OH), the dimer of dehydrozingerone [$D_1(OH)_2$], and also structures of α-tocopherol (TOH, ascorbyl palmitate (AscPH) and curcumin (curcum).

Melting points were determined on a Büchi 530 apparatus (Assago, Italy) and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solutions with a Varian Mercury Plus (Palo Alto, CA) spectrometer at 400 and 100.57 MHz, respectively. Chemical shifts are given in ppm (δ); multiplicates are indicated by s (singlet), d (doublet) or dd (double doublets). Elemental analyses were performed using an elemental analyser (Perkin-Elmer model 240 C, Waltham, MA). Flash chromatography was carried out with silica gel 60, 230–400 mesh (Aldrich, Milano, Italy), eluting with an appropriate solution in the stated v/v proportions. Analytical TLC was performed with either 0.25 mm thick silica gel