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Article

Synergic Antioxidant Effects of the Essential Oil Component γ-Terpinene on High-Temperature Oil Oxidation

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ABSTRACT: The synergic antioxidant activity of γ-terpinene with α-tocopherol, its synthetic analogue 2,2,5,7,8-pentamethyl-6-chromanol (PMHC), BHT, TBHQ, and catechol was studied by measuring the O_2 uptake and the hydroperoxide formation in stripped sunflower oil at 130 °C. Although γ-terpinene was inactive when used alone, it prolonged, in a concentration-dependent manner, the protecting activity of α-tocopherol and of PMHC, while it had no effect on BHT, TBHQ, and catechol. Mechanistic studies performed with alkylnitroxides hydroxy-TEMPO and acetamido-TEMPO, used as molecular probes, suggested that γ-terpinene generates hydroperoxyl ($HOO^{\bullet}$) radicals, that are responsible for the reduction of the tocopheroxyl radical by a H atom transfer. Experiments on commercial sunflower oil showed that γ-terpinene was able to prolong the induction time due to endogenous tocopherols, demonstrating that this terpene is a promising natural antioxidant for food applications at high temperature.

KEYWORDS: *essential oils, tocopherol, autoxidation, peroxidation, synergy, hydroperoxides, nitroxides*

INTRODUCTION

Lipid peroxidation is a major problem for the preservation of edible oils[1] and for the utilization of waste oils for nonfood applications.[2] Bis-allylic positions, and to a lesser extent allylic positions, are prone to react with atmospheric oxygen to form a variety of oxidized compounds including hydroperoxides, epoxides, aldehydes, and acids, which are characterized by bad smell, toxicity, and corrosivity.[3] Besides the obvious deleterious consequences on the organoleptic properties of oils,[4] oxidation processes often lead to the formation of polymeric materials that render handling of waste oils for sustainable production of biofuels a difficult task.[5] From a chemical point of view, lipid peroxidation is a radical-chain reaction sustained by carbon and oxygen-centered radicals, which are responsible for the incorporation of O_2 into organic molecules (Scheme 1A).[6] Antioxidant additives are usually added to reduce the extent of lipid peroxidation in oils. The majority of them are phenols, as these molecules can easily donate a H atom from a phenolic OH group to form a stabilized radical $A^{\bullet}$ that is less capable than $ROO^{\bullet}$ in propagating the oxidative chain (Scheme 1A).[7] One major drawback of phenols is that they act as sacrificial antioxidants, meaning that they are consumed during their activity and thus have limited duration.[7]

In recent years, many research efforts have been directed toward essential oils as a natural alternative to synthetic antioxidants.[8] Essential oils are complex mixtures of volatile compounds obtained mainly by steam-distillation from aromatic and medicinal plants. The antioxidant activity of essential oils rich in phenolic components, such as those extracted from thyme, oregano, and clove, has been explained on the basis of the chemical similarity with phenolic antioxidants.[8] However, other essential oils containing non-phenolic components like limonene, linalool, and citral also behave as antioxidants under specific conditions, because they can interfere with autoxidation radical chain by enhancing the decay of peroxyl radicals.[9] γ-Terpinene, a nonphenolic monoterpene found in several essential oils like citrus, savory, oregano, and others,[10] has been shown to reduce the peroxidation of methyl linoleate and egg yolk phospholipids[11,12] and the peroxidation of low-density lipoproteins.[13]

In our ongoing studies toward improved antioxidant strategies, we observed that γ-terpinene had also the ability to prolong the antioxidant activity of α-tocopherol and of caffeic acid in the autoxidation of lipids in homogeneous solution, whereas it had a weak effect on autoxidation rate when used alone.[10,14] Instead of forming an alkylperoxyl radical like most unsaturated hydrocarbons, γ-terpinene generates an hydroperoxyl radical ($HOO^{\bullet}$)[15] that is able to donate a H-atom to the radical of the antioxidant, reducing it back to the parent phenol (see Scheme 1, reactions B and C).[10] This peculiar property comes from the pro-aromatic character γ-terpinene, as the release of $HOO^{\bullet}$ by a 1,4-intramolecular H-atom transfer allows its aromatization to *para*-cymene, another well-documented component of essential oils (Scheme 1B).[15]

While these mechanistic studies enlightened the possibility of an antioxidant synergy between γ-terpinene and phenolic antioxidants, the effectiveness of this process during high-

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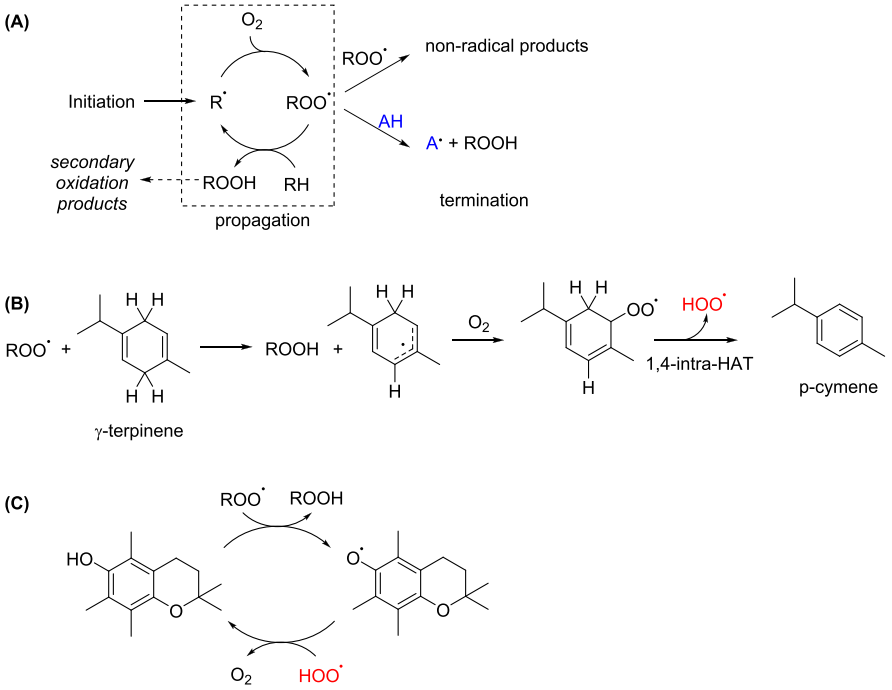
Scheme 1. (A) General Mechanism of Oil Autoxidation and Action of Radical Trapping Antioxidants (RH = Oxidizable Substrate, AH = Antioxidant). (B) Oxidation Mechanism of γ-Terpinene. (C) Mechanism of Regeneration of a α-Tocopherol Analogue by HOO• Radicals



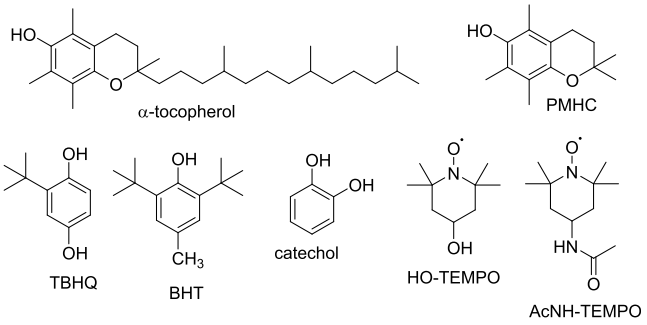
temperature oxidation of bulk unsaturated triacylglycerols has not been demonstrated yet. With respect the model system previously investigated, bulk oils are characterized by a high concentration of H-bond accepting groups (the ester links in triglycerides) that are expected to hamper the H-atom transfer from HOO• to the radical of the antioxidant.[14] Moreover, the high temperature may reduce the stability of γ-terpinene, leading to its disappearance before it can display the coantioxidant activity.

Herein, we report the results of our efforts aimed at evaluating the extent of the antioxidant synergy between γ-terpinene and various phenols during the oxidation of sunflower oil at 130 °C. Sunflower oil was chosen because of its widespread use as a food commodity and because, with its high linoleate levels, it is a challenging oxidizable substrate whose oxidation can be reduced only by very active antioxidants.[16] The investigated antioxidants were represented by α-tocopherol, which is naturally present at different levels in most vegetable oils,[17] and by some synthetic phenols used as food additives (TBHQ and BHT) or as a model for natural polyphenols (catechol).[17] To investigate the synergy mechanism, we used also two dialkylnitroxides stable radicals (HO-TEMPO and AcNH-TEMPO), because it has been demonstrated that these compounds behave as antioxidants when the HOO• radical is present in the system (Scheme 2).[18]

2. MATERIALS AND METHODS

2.1. Materials. All chemicals and solvents were commercially available (Merk, Sigma-Aldrich, Milan, Italy). γ-Terpinene was purified by percolating it twice on basic alumina microcolumns. (±)-α-Tocopherol, 2,2,5,7,8-pentamethyl-6-chromanol (PMHC), *tert*-butyl hydroquinone (TBHQ), 2,6-di-*tert*-butyl-4-methylphenol (BHT), catechol, 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl (HO-TEMPO) and 4-acetamido-2,2,6,6-tetramethylpiperidine 1-oxyl (AcNH-TEMPO), $FeSO_4$ heptahydrate, *tert*-butyl hydroperoxide 70% in H_2O, KSCN, $FeCl_3$, and 2,2 bipyridine were of the highest purity

Scheme 2. Investigated Antioxidants



available and were used as received. Solvents were HPLC-grade and were used without further purification. High-linoleic sunflower oil (SO) was purchased from a local market. Stripped sunflower oil (SSO) was prepared as previously reported by percolation on basic alumina and by treatment with activated carbon.[16] The SO composition was determined by ^{1}H NMR: polyunsaturated chains 59.4 mol %, monounsaturated chains 27.3 mol %, saturated chains 13.3%.[19]

2.2. Measure of O_2 Consumption. Oxygen consumption during the sunflower oil autoxidation was measured by a O_2-sensitive optical probe (Pyroscience GmbH, Aachen, Germany) in a sealed apparatus previously described.[20] Briefly, 2.00 g of oil containing variable amounts of γ-terpinene and/or of the antioxidants are introduced into a 10 or 50 mL round bottomed flask with a magnetic stir bar connected to a miniaturized water-cooled condenser to keep the temperature of the O_2 sensitive probe below 40 °C. The sample is kept under vigorous stirring in a silicone bath at 130 °C. The O_2 probe is calibrated in air before each experiment. The amount of consumed O_2 is calculated from the internal volume of the apparatus.

2.3. Determination of Hydroperoxides. Hydroperoxides were determined by the ferric thiocyanate assay using *tert*-butyl hydroperoxide as a reference. Equal amounts (250 μL) of a solution of $FeSO_4$ heptahydrate (5 mM) in 0.02 M HCl and of KSCN (3%) in MeOH were mixed to the oil or *tert*-butyl hydroperoxide sample

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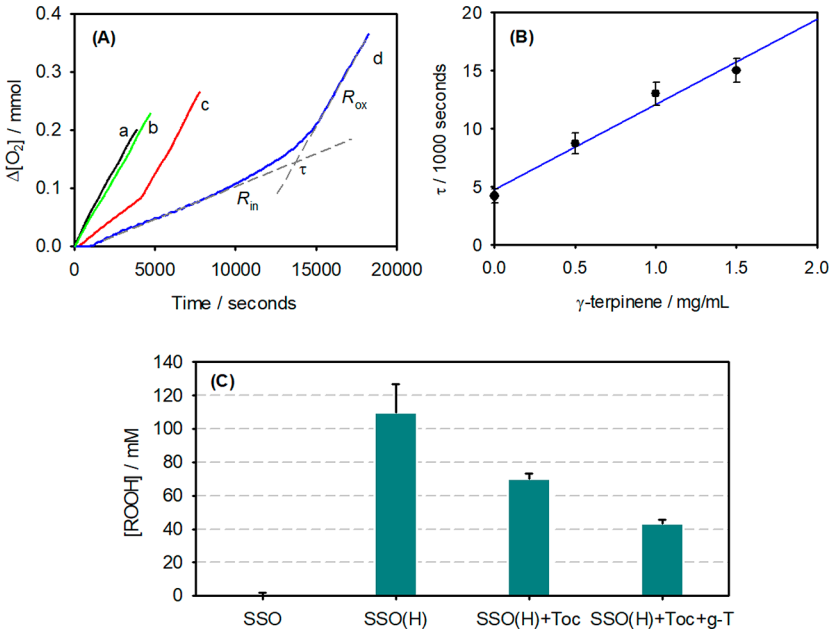

Figure 1. Panel A: oxygen consumption during the oxidation of stripped sunflower oil (SSO, 2 g) at 130 °C; without any additive (a), with γ-terpinene (1% w/w) (b); with α-tocopherol (0.1%, w/w) (c); with α-tocopherol (0.1%) and γ-terpinene (1%, w/w) (d). Panel B: duration of the induction period of α-tocopherol 0.1% on increasing γ-terpinene concentration. Panel C: concentration of hydroperoxides in stripped sunflower oil before (SSO) and after heating at 130 °C for 10.000 s without antioxidants (SSO(H)), with α-tocopherol 0.1%, w/w (SSO(H)+Toc), and with α-tocopherol 0.1%, w/w and γ-terpinene 1%, w/w (SSO(H)+Toc+g-T).

Table 1. Descriptors of Sunflower Oil[a] Autoxidation at 130 °C: Slope of O_2 Consumption during the Inhibited Period (R_{in}) or in the Absence of the Antioxidant (R_{ox}),[b] and Duration of the Inhibited Period (τ)[c]

entry		R_{in} (nm/s)	R_{ox} (nm/s)	τ (1000 s)
1	SO	17 ± 3	56 ± 5	6.6 ± 0.2
2	SO + γ-terpinene 1%	9.3 ± 0.3	67 ± 6	11 ± 1
3	SSO		61 ± 5	
4	SSO + γ-terpinene 1%		48 ± 6	
5	SSO + α-tocopherol 0.1%	21 ± 1	54 ± 5	4.2 ± 0.2
6	SSO + α-tocopherol 0.1% + γ-terpinene 1%	13 ± 1	48 ± 5	13.2 ± 0.6
7	SSO + PMHC 0.1%	26 ± 3	50 ± 5	6.1 ± 0.5
8	SSO + PMHC 0.1% + γ-terpinene 1%	11 ± 1	51 ± 5	10.5 ± 0.5
9	SSO + TBHQ 0.1%	14 ± 1	66 ± 6	28 ± 2
10	SSO + TBHQ 0.1% + γ-terpinene 1%	55 ± 5	60 ± 6	31 ± 2
11	SSO + BHT 0.1%	16 ± 2	49 ± 5	7.1 ± 0.5
12	SSO + BHT 0.1% + γ-terpinene 1%	31 ± 2	48 ± 4	6.2 ± 0.4
13	SSO + catechol 0.1%	23 ± 2	66 ± 6	7.5 ± 0.6
14	SSO + catechol 0.1% + γ-terpinene 1%	27 ± 3	45 ± 5	6.2 ± 0.5
15	SSO + HO-TEMPO 0.1%	36 ± 3	60 ± 5	3.7 ± 0.4
16	SSO + HO-TEMPO 0.1% + γ-terpinene 1%	11 ± 1	32 ± 3	15 ± 2
17	SSO + AcNH-TEMPO 0.1%	26 ± 3	45 ± 4	8 ± 1
18	SSO + AcNH-TEMPO 0.1% + γ-terpinene 1%	14 ± 2	21 ± 2	10 ± 1

[a]SO = unpurified sunflower oil, containing intrinsic antioxidants, SSO = stripped sunflower oil. [b]Slope of O_2 consumption without any antioxidant or after the complete consumption of the antioxidant. [c]All concentrations are w/w.

dissolved in methanol (1 mL). After one minute, the absorption at 520 nm was read.[21]

2.4. Determination of Total Tocopherols. In a 10 mL volumetric flask, 100 mg of SO was mixed with 5 mL of toluene. Then, 3.5 mL of 2,2 bipyridine solution (0.07% (w/w) in 95% aqueous ethanol) and 0.5 mL of $FeCl_3$ were added, mixed, and finally, the volume was raised to 10 mL with ethanol (95%). After a 1 min rest, the absorbance was read at 520 nm using a spectrophotometer.[22]

2.5. Statistical Analysis. The results are expressed as the average ± standard deviation (SD) from at least two independent kinetic measurements.

3. RESULTS

3.1. Synergic Effect of α-Tocopherol and γ-Terpinene on the Oxidation of Sunflower Oil. The effect of γ-terpinene 1% (w/w) on the oxidation of purified (stripped) sunflower oil (SSO) in the presence and in the absence of α-tocopherol is reported in Figure 1A. The plots can be analyzed quantitatively by measuring various parameters describing oil oxidation: the inhibited (R_{in}) and noninhibited (R_{ox}) O_2 consumption rates (in nmol/s) and the length of the induction periods (τ, in seconds) (see Figure 1A), as reported in Table 1

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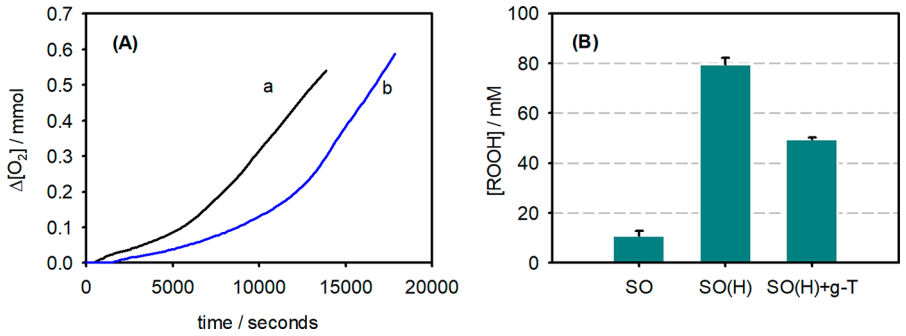

Figure 2. Panel A: oxygen consumption during the oxidation of not-purified sunflower oil (SO, 2 g) at 130 °C; (a) without and (b) with the addition of γ-terpinene (1%, w/w). Panel B: concentration of peroxides in nonpurified sunflower oil before (SO) and after heating at 130 °C for 10.000 s without (SO(H)) and with 1% γ-terpinene (SO(H)+g-T).

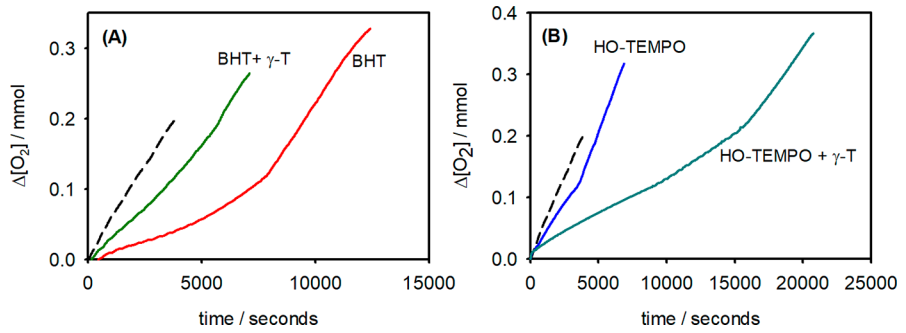

Figure 3. Oxygen consumption during the oxidation of stripped sunflower oil (SSO, 2 g) at 130 °C; without any additive (dashed line) or in the presence of an antioxidant, without or with γ-terpinene (γ-T) 1% w/w. Panel (A): butylated hydroxy toluene (BHT) 0.1%, w/w; panel (B): 4-hydroxy TEMPO (HO-TEMPO) 0.1%, w/w.

(entries 3−6). The O_2 consumption during SSO oxidation is linear because the endogenous antioxidants have been removed. When γ-terpinene is added in the absence of α-tocopherol (line b), there is no change in O_2 consumption rate, while the addition of α-tocopherol causes the onset of an inhibited period (line c). Interestingly, when α-tocopherol and γ-terpinene are present together in the sample, an inhibition period is observed (line d) that is longer than that shown by α-tocopherol alone.

Experiments performed at different γ-terpinene concentrations showed a fairly linear dependence between the induction period length (τ) and the concentration of γ-terpinene (Figure 1B, $R^2 = 0.974$). To confirm these results, we studied the sunflower oil oxidation by measuring the formation of hydroperoxides. The results, reported in Figure 1C, showed that freshly prepared SSO is virtually free of hydroperoxides, while after 10 000 s at 130 °C (i.e., 2.8 h) their level increases considerably. The addition of α-tocopherol reduces the hydroperoxides formation, and the addition of both α-tocopherol and γ-terpinene decreases ROOH concentration even further, in good agreement with O_2 uptake measures.

3.2. Effect of γ-Terpinene on the Oxidation of Not-Purified Sunflower Oil. As can be seen from Figure 2A and Table 1 (entries 1 and 2), the O_2 consumption at 130 °C of not purified sunflower oil (SO) shows an inhibited period at the beginning of the reaction of about 2 h, which is due to the antioxidants (mainly represented by α-tocopherol) naturally present in the oil.[23,24] The concentration of the tocopherols in the oil was determined as 490 ± 20 ppm (w/w). When adding γ-terpinene (1%, w/w), the duration of the inhibited period increases to 3.4 h, thus confirming the result obtained with SSO. We also studied SO oxidation by measuring the formation of hydroperoxides. We can see in Figure 2B that SO, before being heated, has a small amount of hydroperoxides (first bar). The second bar shows that, after heating at 130 °C for 10 000 s, a significant quantity of hydroperoxides is formed, which decreases if the reaction is performed with the addition of γ-terpinene (third bar). Overall, the results reported in Figure 2B confirmed the results of the oxygen consumption kinetics.

3.3. Synergy with Phenolic Antioxidants and Mechanistic Studies. The synergic activity of γ-terpinene was also investigated with some commercial phenols. For this purpose, we measured the O_2 consumption profile of SSO oxidation after the addition of 0.1% (w/w) of *tert*-butylhydroquinone (TBHQ), 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMHC, a structural analogue of α-tocopherol missing the phythyl chain), butylated hydroxytoluene (BHT) and catechol (see Scheme 1), in the absence and in the presence of γ-terpinene. To demonstrate the formation of $HOO^{\bullet}$ from γ-terpiene, we used also the two nitroxides HO-TEMPO and AcNH-TEMPO, because TEMPO-derived stable radicals behave as antioxidants when the $HOO^{\bullet}$ radical is present in the system.[18] The measured R_{in} and τ values, reported in Table 1, show that γ-terpinene increases the antioxidant activity only of PMHC, while in the case of the other phenols, it causes a faster oxidation (R_{in} increase) and a shorter duration (τ decrease), as shown for BHT in Figure 3A. However, the nitroxides HO-TEMPO and AcNH-TEMPO that were nearly ineffective when used alone, displayed a large activity improvement after the addition of γ-terpinene (Figure 3B).

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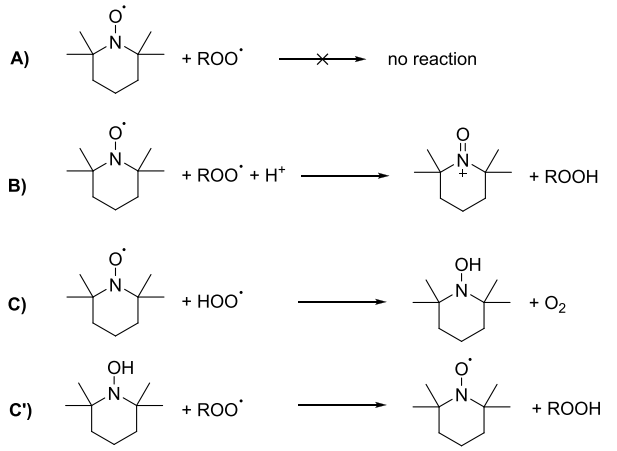
4. DISCUSSION

As can be inferred by comparing entries 3 and 4 in Table 1, γ-terpinene alone possesses no ability to reduce the O_2 consumption rate, as previously observed at 30 °C.[10] This agrees with the fact that γ-terpinene is an easily oxidizable hydrocarbon that participates in the oxidative chain. The HOO• radicals, that are produced during γ-terpinene oxidation, abstract a H atom from allylic and bisallylic positions of fatty acids and of other terpene molecules, thus contributing to the propagation of the autoxidation. The nitroxides HO-TEMPO and AcNH-TEMPO have a negligible effect when used alone (see entries 15 and 17 in Table 1) but become good antioxidants in the presence of γ-terpinene (entries 16 and 18). We and others have previously revealed that TEMPO derivatives are potent but elusive inhibitors of lipid peroxidation. In bulk organic materials, nitroxides are unable to stop lipid peroxidation because they cannot donate a H atom to propagating ROO• radicals (Scheme 3A). However,

Scheme 3. Antioxidant Effect of TEMPO Derivatives under Different Conditions

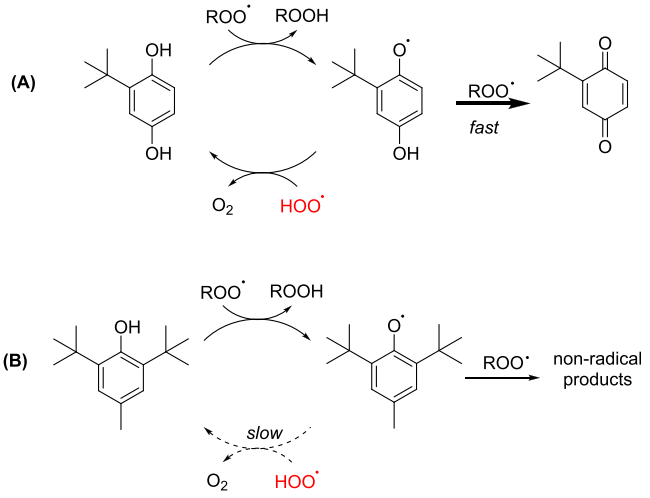


in the presence of acid traces, TEMPO derivatives become antioxidants, because they react with ROO• by a proton-coupled electron transfer mechanism (Scheme 3B).[25,26] The antioxidant activity of nitroxides is also observed in the presence of HOO• radicals, as they form very efficiently an alkoxyamine (R_2NOH) that is capable of reacting with ROO• (Scheme 3C and C′).[18] Therefore, these results represent a proof that HOO• radicals are actually produced in the investigated system.

As evident from Table 1, the synergy is observed only with a limited number of antioxidants, which are α-tocopherol and its synthetic derivative PMHC (entries 6 and 8), while it is absent for TBHQ, BHT, and catechol. These results can be compared to those obtained in a model system consisting of chlorobenzene solutions of oxidizable substrates whose oxidation was initiated by the decomposition of an azoinitiator at 30 °C. Under those conditions, α-tocopherol, PMHC, and the catechol derivative caffeic acid phenethyl ester were capable of act synergistically with γ-terpinene.[10]

A reasonable explanation that can unify all these observations is that the reaction of the radical of the antioxidant with HOO• is not fast enough, at 130 °C, to compete with other reaction pathways, that ultimately lead to the irreversible deactivation of the antioxidant.[27] In the case of TBHQ and catechol, their phenoxyl radicals decay quickly to the respective *para* and *ortho* benzoquinones by H atom transfer to a second ROO•, as shown in Scheme 4A for TBHQ.

Scheme 4. Explanation of the Lack of Synergy between γ-Terpinene and TBHQ or BHT



In the case of BHT, the rate constant of regeneration may be reduced by the steric crowding due to the two *tert*-butyl groups (Scheme 4B). The reason why γ-terpinene causes a decrease of the antioxidant activity of TBHQ and BHT is at the moment unclear and deserves further investigation. A tentative explanation could be an H atom transfer between the radical of the antioxidant and γ-terpinene.[27]

Compared with the other inhibitors, α-tocopherol and PMHC form rather stable and relatively unhindered phenoxyl radicals that do not decay quickly by reacting with ROO• and thus live enough to be regenerated by HOO• as shown in Scheme 1C. Interestingly, α-tocopherol is the main endogenous antioxidant present in sunflower oil,[23,24] thus, γ-terpinene alone is able to extend the induction time of this oil (entries 1 and 2).

In conclusion, we have demonstrated that γ-terpinene increases, in a concentration-dependent manner, the protecting activity of α-tocopherol against sunflower oil autoxidation at 130 °C. Experiments performed on stripped sunflower oil have shown that the synergy mechanism is based on the generation of HOO• radicals, which are formed when γ-terpinene oxidizes with unsaturated lipids. Our results suggest that the natural compound γ-terpinene may be used to boost the antioxidant effect of α-tocopherol, that is naturally present in many foods and edible oils[28,29] and is used as an additive with the code E307. The mixture of γ-terpinene and α-tocopherol may therefore represent a novel antioxidant mixture to be used in food, to replace artificial antioxidants. Moreover, the mixture of γ-terpinene and nitroxides of the TEMPO family may represent a useful strategy for stabilizing oils for nonfood application, such as for biodiesel manufacturing.[2] Future work will address the synergy between γ-terpinene and the other members of the tocopherol family and the activity of nonphenolic essential oil components in heterogeneous systems, such as emulsions, micelles, and liposomes.[30,31]

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Notes

The authors declare no competing financial interest.

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