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Explaining the antioxidant activity of some common non-phenolic components of essential oils

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**Highlights**

- The antioxidant activity of limonene, linalool and citral was investigated.
- The three EO components act as termination-enhancing antioxidants.
- Activity increases with the concentration up to a limit value, then it decreases
- The three EO components become pro-oxidant above a critical concentration.
- Their potential in food protection versus phenolic antioxidants is discussed.

# Explaining the antioxidant activity of some common non-phenolic components of essential oils

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**Running Title:** Antioxidant activity of non-phenolic EO components

## Abstract

Limonene, linalool and citral are common non-phenolic terpenoid components of essential oils, with attributed controversial antioxidant properties. The kinetics of their antioxidant activity was investigated using the inhibited autoxidation of a standard model substrate. Results indicate that antioxidant behavior of limonene, linalool and citral occurs by co-oxidation with the substrate, due to very fast self-termination and cross-termination of the oxidative chain. Rate constants  $k_p$  and  $2k_t$ , ( $M^{-1}s^{-1}$ ) at 30°C were 4.5 and  $3.5 \times 10^6$  for limonene, 2.2 and  $9.0 \times 10^5$  for linalool and 39 and  $1.0 \times 10^8$  for citral. Behavior is bimodal antioxidant/prooxidant depending on the concentration. Calculations at the M05/6-311+g(2df,2p) level indicate that citral reacts selectively at the aldehyde C-H having activation enthalpy and energy respectively lower by 1.3 and 1.8 kcal/mol compared to the most activated allyl position. Their termination-enhancing antioxidant chemistry might be relevant in food preservation and could be exploited under appropriate settings.

**Keywords:** essential oil, autoxidation, antioxidant, peroxy radicals, linalool, limonene, citral

## Chemical compounds investigated in this study

(*R*)-Limonene (PubChem CID: 440917)

Linalool (PubChem CID: 6549)

Citral (PubChem CID: 8843)

Dodecanal (PubChem CID: 8194)

## 55 1. Introduction

56 Among the various strategies aimed at improving food preservation, antioxidants play an important  
57 role because they are able to slow down the oxidation of unsaturated lipids, preventing the  
58 development of rancidity in foods (Caleja, Barros, Antonio, Oliveira, & Ferreira, 2017; Guitard,  
59 Paul, Nardello-Rataj, & Aubry, 2016). In recent years, essential oils have been actively investigated  
60 to replace synthetic antioxidants (Amorati, Foti, & Valgimigli, 2013; Tohidi, Rahimmalek, &  
61 Arzani, 2017). Essential oils are complex mixtures of volatile compounds obtained from aromatic  
62 and medicinal plants mainly by steam distillation (Amorati & Foti, 2012). For instance, thyme and  
63 oregano essential oils have been proposed to contrast oxidative spoilage in various kinds of food  
64 (Otoni, Pontes, Medeiros, & Soares, 2014), in particular meat (Fasseas, Mountzouris, Tarantilis,  
65 Polissiou, & Zervas, 2008) and fish (Kykkidou, Giatrakou, Papavergou, Kontominas, & Savvaidis,  
66 2009). These two essential oils contain significant amount of thymol and carvacrol, two phenolic  
67 components having antioxidant activity similar to that of synthetic phenolic antioxidants, such as  
68 butylated hydroxy toluene (BHT) (Perez-Roses, Risco, Vila, Penalver, & Canigueral, 2016).  
69 Phenols are in fact prototypical chain-breaking antioxidants. They are able to slow down the  
70 peroxidation of unsaturated lipids by formally donating a H-atom from the phenolic hydroxyl group  
71 to a peroxy radicals ( $\text{ROO}\cdot$ ) that is responsible for the propagation of the oxidative radical chain  
72 ( $\text{PhOH} + \text{ROO}\cdot \rightarrow \text{PhO}\cdot + \text{ROOH}$ ) (Amorati, Foti, & Valgimigli, 2013).

73 Unlike peroxy radicals, the resulting phenoxyl radical ( $\text{PhO}\cdot$ ) is normally unable to propagate the  
74 oxidative chain, *i.e.* it is sufficiently unreactive to “wait” in solution until it traps a second peroxy  
75 radical ( $\text{PhO}\cdot + \text{ROO}\cdot \rightarrow \text{non-radical products}$ ), thereby breaking two oxidative chains (Amorati,  
76 Baschieri, Morroni, Gambino, & Valgimigli, 2016).

77 However, in recent years, other essential oils that have no significant content of phenolic  
78 components have been claimed to possess relevant antioxidant activity. Unfortunately, such claims  
79 have rarely been supported by a clear understanding of the mechanisms at the basis of the purported  
80 antioxidant behaviour, and other studies outlining no significant antioxidant activity for the same

81 essential oils have also appeared in the literature, creating a very confusing picture (Amorati, Foti,  
82 & Valgimigli, 2013).

83 For instance, Domingues and co-workers studied the antioxidant activity of coriander essential oil,  
84 which doesn't contain any phenolic component but is rich in linalool, and they reported that  
85 "coriander oil and linalool had relevant radical scavenging properties and an exceptional capacity to  
86 inhibit the lipid peroxidation" (Duarte, Luis, Oleastro, & Domingues, 2016). Maróstica Junior and  
87 co-workers reported that limonene was able to inhibit liver homogenate peroxidation, induced by  
88 ferric chloride and ascorbic acid (Marostica, Silva, Franchi, Nowill, Pastore, & Hyslop, 2009).

89 Bruni and co-workers found that lemongrass (*Cymbopogon citratus*) essential oil, rich in citral, had  
90 a fairly good antioxidant activity toward the autoxidation of linoleic acid, as assessed by the  $\beta$ -  
91 carotene bleaching test (Sacchetti, Maietti, Muzzoli, Scaglianti, Manfredini, Radice, et al., 2005).

92 On the other hand, Ruberto and Baratta, by studying the autoxidation of egg yolk homogenate,  
93 found pro-oxidant effect for linalool, and almost negligible antioxidant effect for limonene and  
94 citral (Ruberto & Baratta, 2000).

95 Currently, the only well understood example of a non-phenolic essential oil component endowed  
96 with significant antioxidant activity is that of  $\gamma$ -terpinene, a monoterpene component that is able to  
97 slow down the autoxidation of methyl linoleate by a co-oxidation mechanism, where the terpene  
98 causes a faster oxidative chain-termination due to the generation of hydroperoxyl radicals ( $\text{HOO}\cdot$ )  
99 that have very fast self-termination rate constant ( $\text{HOO}\cdot + \text{HOO}\cdot \rightarrow \text{O}_2 + \text{HOOH}$ ) (Foti & Ingold,  
100 2003).

101 Indeed, the possible contribution of other non-phenolic components to the antioxidant activity of  
102 essential oils remains an open question. If confirmed and rationalized their antioxidant activity  
103 might be effectively exploited to supplement that of classical phenolic antioxidants, thus  
104 contributing to extend the shelf-life of easily oxidizable foods. In this work, we investigate in detail  
105 the antioxidant activity of three common non-phenolic essential oil components, limonene, linalool  
106 and citral, to rationalize the contrasting or unexplained results about their activity that can be found

107 in the literature. In order to do so, we studied the kinetics of oxygen uptake in the controlled  
108 inhibited autoxidation of a standard substrate (cumene), since this method is the best established  
109 and the most reliable to afford accurate mechanistic information on direct antioxidant activity  
110 (Amorati, Baschieri & Valgimigli, 2017; Amorati, et al 2016; Amorati, Pedulli, & Valgimigli,  
111 2011; Burton, Doba, Gabe, Hughes, Lee, Prasad, et al., 1985), and we combined the kinetic  
112 measurements with quanto-mechanical calculations, to rationalize the results.

113

## 114 **2. Materials and Methods.**

115 **2.1 Chemicals.** (R)-(+)-Limonene, linalool, citral (mixture of *E/Z* isomers) and dodecanal were  
116 from Sigma-Aldrich (Milan, Italy) and were stored under argon at -18 °C. Cumene  
117 (isopropylbenzene) from Sigma-Aldrich was percolated once on silica and twice on alumina  
118 columns. Azobis-isobutyronitrile (AIBN, Fluka, Milan, Italy) was recrystallized from methanol.  
119 2,6-di-*tert*-Butyl-4-methylphenol (BHT) and 2,2,5,7,8-pentamethyl-6-chromanol (PMHC) were both  
120 purchased from Sigma-Aldrich at the highest available purity and were recrystallized from hexane.

121 **2.2 Autoxidation experiments.** Autoxidation experiments were performed in a two-channel oxygen  
122 uptake apparatus, based on a Validyne DP 15 differential pressure transducer, built in our laboratory  
123 (Amorati, Lynett, Valgimigli, & Pratt, 2012; Amorati, Valgimigli, Diner, Bakhtiari, Saeedi, &  
124 Engman, 2013; Amorati, Zotova, Baschieri, & Valgimigli, 2015). In a typical experiment, an air-  
125 saturated solution of the oxidizable substrate (cumene) containing AIBN was equilibrated with an  
126 identical reference solution containing excess 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMHC,  
127 25 mM). After equilibration, and when a constant O<sub>2</sub> consumption was reached, a concentrated  
128 solution of the essential oil component was injected in the sample flask. The oxygen consumption  
129 in the sample was measured after calibration of the apparatus from the differential pressure recorded  
130 with time between the two channels. Initiation rates,  $R_i$ , were determined for each condition in  
131 preliminary experiments by the inhibitor method using PMHC as a reference antioxidant:  $R_i =$   
132  $2[\text{PMHC}]/\tau$ , where  $\tau$  is the length of the inhibition period (Matera, Gabbanini, Berretti, Amorati, De



133 Nicola, Iori, et al., 2015; Valgimigli, Amorati, Petrucci, Pedulli, Hu, Hanthorn, et al., 2009;  
134 Valgimigli, Bartolomei, Amorati, Haidasz, Hanthorn, Nara, et al., 2013). The concentration range  
135 for the test antioxidants in our experiments was: 28-2800 mM for linalool, 30-1500 mM for  
136 limonene, 0.15-90 mM for Citral and 0.11-56 mM for reference dodocanal.

### 137 **2.3 Calculations.**

138 Geometry optimizations, frequencies, enthalpies and transition states barriers were computed in the  
139 gas phase at M05/6-311+g(2df,2p) (Galano, Munoz-Rugeles, Alvarez-Idaboy, Bao, & Truhlar,  
140 2016; Tishchenko & Truhlar, 2012) theory level, by using Gaussian 09, according to previously  
141 established protocols. Stationary points were confirmed by checking the absence of imaginary  
142 frequencies. Transition states had one imaginary frequency corresponding to the transfer of a H-  
143 atom (see Appendix A). Bond dissociations and reaction enthalpies were calculated also by the high  
144 accuracy composite method CBS-QB3 (Montgomery, Frisch, Ochterski, & Petersson, 1999;  
145 Zielinski, Presseau, Arnorati, Valgimigli, & Pratt, 2014). For the sake of comparison, calculations  
146 were also repeated at the M06-2X/6-311++G(d,p) level of theory (La Rocca et al., 2016; Galano,  
147 2011): the results, summarized in Figure 3S (see Appendix), qualitatively confirm those calculated  
148 at the M05/6-311+g(2df,2p) level.

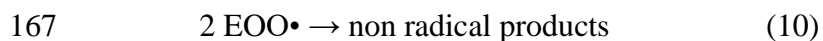
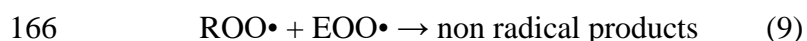
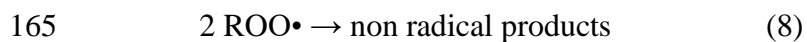
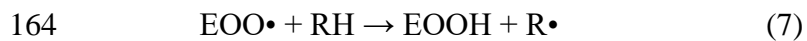
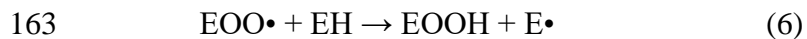
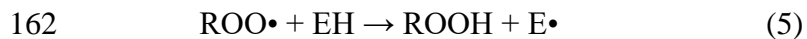
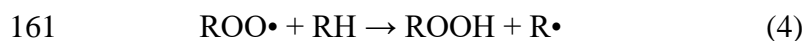
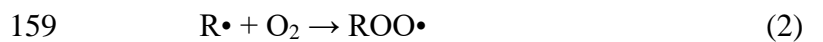
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## 150 **3. Results and discussion**

### 151 **3.1 Inhibited autoxidation studies**

152 The antioxidant activity of linalool, limonene and citral was investigated by studying the O<sub>2</sub>  
153 consumption during the controlled inhibited autoxidation of cumene (isopropylbenzene), which can  
154 be described by eq. 1-10. In the absence of essential oil components (EH) and in the presence of a  
155 source of free radicals (In) and atmospheric O<sub>2</sub>, cumene (RH) is oxidized to cumene hydroperoxide  
156 (ROOH) through a radical-chain mechanism described by equation 1 (initiation), 2 and 4  
157 (propagation), and 8 (termination) (Amorati, et al. 2015; Burton, et al., 1985).

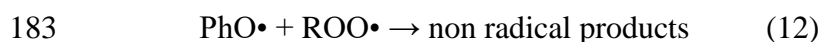
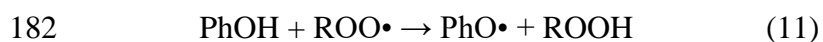




168

169 The source of radicals is represented by the decomposition of azobis-isobutyronitrile (AIBN), a  
 170 liposoluble azo-initiator, at 30 °C, which provides a constant initiation rate, indicated as  $R_i$ . Upon  
 171 addition of increasing amounts of reference phenolic antioxidants (PhOH) like BHT, or PMHC a  
 172 synthetic mimic of natural  $\alpha$ -tocopherol having identical antioxidant performance (Burton, et al.,  
 173 1985) the rate of oxygen consumption is dramatically reduced by the effect of reactions 11 and 12,  
 174 until the antioxidant is consumed, and it is reversely proportional to the concentration of the  
 175 antioxidant - i.e. the antioxidant performance increases linearly with the concentration of the  
 176 antioxidant - as described by Howard-Ingold equation 13 (Burton, et al., 1985) where  $R_i$  is the rate  
 177 of radical initiation (typically  $2-9 \times 10^{-9} \text{ Ms}^{-1}$  in our system) and  $k_p$  is the rate constant of chain  
 178 propagation for cumene ( $k_p = 0.34 \text{ M}^{-1}\text{s}^{-1}$  at 303K; (Amorati, Lynett, Valgimigli, & Pratt, 2012)).  
 179 The term  $k_{inh}$  is usually determined from these kinetic measurements and represents the rate  
 180 constant of reaction of the antioxidant with chain-propagating peroxy radicals ( $ROO\bullet$ ).

181



$$-\frac{d[O_2]_{inh}}{dt} = \frac{k_p [Cumene] R_i}{2k_{inh} [Antiox.]} \quad (13)$$

Unlike phenolic antioxidants, when non-phenolic essential oil components (EH) were added to cumene autoxidizing mixture, no distinct inhibition period was observed and the rate of oxygen consumption was decreased or increased as compared to cumene alone, depending on the concentration of EH, but without a monotonic correlation with the concentration. In other words, EH acted as antioxidant or as pro-oxidant depending on the experimental settings, as illustrated in Figure 1A for citral.

<Figure 1 about here>

When the rate of oxygen consumption (i.e. the rate of autoxidation) was plotted against the concentration of EH added to the system, any of the essential oil components showed a bimodal behavior as illustrated in Figure 1B-D. Below a critical concentration (from 4 % (v/v) for linalool to 0.12 % (v/v) for citral) all components EH reduce the oxidation rate, while at higher concentrations they cause an increase of O<sub>2</sub> uptake.

These experimental results cannot be ascribed to a classical chain-breaking antioxidant action like that observed in the presence of PMHC or BHT, which strongly inhibits cumene autoxidation at concentrations as low as 5-10 μM (Amorati, et al. 2015). On the contrary, a similar behavior was observed by co-oxidizing cumene and certain non-phenolic substrates such as garlic allylsulfides (Amorati & Pedulli, 2008). We reasoned that the explanation of this phenomenon resides in the complex interplay between peroxy radicals generated by the two substrates, ROO• for cumene and EOO• for essential oil components, as described by equations 1-10. Essential oils components generate secondary peroxy radicals that undergo bimolecular self-termination (eq. 10) and cross-termination (eq. 9) much more quickly than tertiary cumylperoxy radicals (eq. 8) (Lucarini, Pedulli, & Valgimigli, 1998). The resulting rate of oxidation for the mixture is lower than for pure cumene because the overall steady-state concentration of peroxy radicals is reduced (Amorati & Pedulli,

2008). The magnitude of the unusual antioxidant effect increases with the reactivity of the components EH with peroxy radicals, i.e. with  $k_5$  and  $k_6$  (eq. 5 and 6), because more peroxy radicals would competitively react with EH rather than with the oxidizable substrate (in this case cumene), and, at the same time, it increases with the rate of termination due to the radicals from EH (sum of eq. 9 and 10) as compared to the self-termination of the substrate (eq. 8). On the other hand, above a critical value of  $k_5$  and  $k_6$  or above a critical concentration of the components EH, autooxidation of EH itself (which acts as co-oxidizable substrate) becomes so significant to carry on the whole autooxidation process, i.e. to increase the rate of O<sub>2</sub> uptake as compared to that measured with neat cumene (that has low rate constant of propagation,  $k_4$ ), which results in the observed pro-oxidant behavior. It should be stressed that such kinetic behavior sharply differentiates this mechanism of inhibition from the classical chain-breaking activity, as the chain breaking activity does not depend on the rate of chain-termination, but only on the rate of reaction of peroxy radicals with the antioxidant. Additionally, there is no upper-limit concentration for chain-breaking antioxidants, as their performance grows monotonically with their concentration.

The plots of O<sub>2</sub>-consumption rate shown in Figure 1 were analyzed by using the co-oxidation reaction scheme (eq. 1-10). By assuming the usual steady-state approximation, the rate of co-oxidation ( $R_{ox}$ ) can be derived as in eq. 14 (Amorati & Pedulli, 2008).

$$R_{ox} = \frac{\{k_4 k_7 [RH]^2 + 2k_5 k_7 [RH][EH] + k_5 k_6 [EH]^2\} R_i^{1/2}}{\{k_8 k_7^2 [EH]^2 + k_9 k_5 k_7 [RH][EH] + k_{10} k_5^2 [EH]^2\}^{1/2}} \quad (14)$$

Here the propagation and the termination rate constants of cumylperoxy radicals,  $k_p = k_4$  and  $2k_t = k_8$ , are known ( $0.32 \text{ M}^{-1} \text{ s}^{-1}$  and  $4.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ , respectively, at 30 °C) (Amorati & Pedulli, 2008). The other rate constants were obtained by fitting the plots of Fig. 1 to eq 14. Results are collected in Table 1.

### 3.2 Mechanism of reaction of limonene, linalool and citral with peroxy radicals

Interestingly, in the case of limonene and linalool, very satisfactory fittings of experimental rate of

234 autoxidation (fig 1 C and D) were obtained when eq. 14 was simplified by assuming that the  
235 kinetics of H-atom abstraction from cumene (RH) or the essential oil components (EH) is  
236 independent from the structure of the peroxy radical (i.e.  $k_4 = k_7$  and  $k_5 = k_6$ ) (Amorati & Pedulli,  
237 2008). This finding was not surprising, since it is well known that the reactivity of alkylperoxy  
238 radicals is similar and largely independent of their structure (Amorati, Lynett, Valgimigli, & Pratt,  
239 2012; Amorati, et al. 2015). The reactions of limonene and linalool can be exemplified as in Figure  
240 2.

241 <Figure 2 about here>

242 Conversely, in the case of citral the same approximation did not afford acceptable matching of  
243 experimental results and unrestricted fittings to eq. 14 (Fig. 1B) indicated that reaction of RH or EH  
244 with peroxy radicals derived from citral (eq. 6 and 7) was much faster than the analogous reactions  
245 with radicals derived from the substrate cumene (eq. 4 and 5). This implies that the peroxy radicals  
246 derived from citral (EOO•) are much more reactive than those derived from the substrate (ROO•),  
247 which suggests that citral autoxidizes by forming acylperoxy radicals, rather than alkylperoxy, i.e.  
248 in citral H-abstraction by peroxy radical occurs at the aldehyde group rather than at the available  
249 allyl positions, similarly to the oxidation of simpler aldehydes (Li, Hong, Chen, Sun, Yang, Yu, et  
250 al., 2016). Ingold and coworkers reported that aliphatic aldehydes are oxidized to peroxydicarboxylic  
251 acids through a radical chain mechanism sustained by acylperoxy radicals (see Figure 3). In the  
252 same work, acylperoxy radicals were found to be about 70 and 60 fold more reactive than  
253 alkylperoxy radicals toward H-atom abstraction from hydrocarbons and from aldehydes,  
254 respectively (Zaikov, Howard, & Ingold, 1969). Such values are identical, respectively, to the ratios  
255  $k_7/k_4$  and  $k_5/k_6$  determined by us with citral (see table 1). Howard and Ingold reported very high  
256 termination constants for acylperoxy radicals (such as  $5.4 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$  at 0°C for heptanal), these  
257 values are in agreement with those reported in Table 1 (Zaikov, et al., 1969).

258 <Figure 3 about here>

259 To verify this explanation and check the role of unsaturated hydrocarbon skeleton in the reactivity  
260 of citral, we comparatively studied the autoxidation of cumene in the presence of dodecanal, an  
261 aliphatic aldehyde. The results are collected in figure 1S (see Appendix) and the corresponding  
262 kinetic constants are reported in Table 1 along with those recorded for citral. It can be noted that  
263 they are indeed very similar to those of citral, indicating that the aldehyde group is the moiety that  
264 characterizes the radical chemistry of citral.

265 Product studies performed by Karlberg et al. on the spontaneous autoxidation of limonene showed  
266 that it yields hydroperoxides in position 6 and epoxides in position 1,2 (Karlberg &  
267 DoomsGoossens, 1997). Such products can be explained as arising from secondary peroxy  
268 radicals, which are formed from H-atom abstraction at the allylic CH<sub>2</sub> groups of the cyclohexene  
269 ring (see Figure 2), in excellent agreement with our kinetic data, affording  $k_5 = k_6 = 4.5 \text{ M}^{-1}\text{s}^{-1}$  at  
270 303 K (for comparison the H atom abstraction from the allylic C-H bonds of methyl oleate and  
271 cyclohexene occurs with a rate constant of 0.89 and 6.0  $\text{M}^{-1}\text{s}^{-1}$ , respectively; (Valgimigli & Pratt,  
272 2012)).

273 Similarly, Skold et al. reported that the spontaneous autoxidation of linalool affords products  
274 (hydroperoxides and epoxides) derived from both tertiary and secondary peroxy radicals formed  
275 upon H-abstraction in allylic positions (Figure 2) (Skold, Borje, Harambasic, & Karlberg, 2004),  
276 again in agreement with our measured average  $k_5 = k_6 = 2.2 \text{ M}^{-1}\text{s}^{-1}$ .

277 Product studies available on citral are instead at odds with the above two compounds. Indeed,  
278 Hagvall et al. showed that the autoxidation products of geranial (one of the two geometric isomers  
279 constituting citral) consists mainly of the corresponding carboxylic acid and peracid (Figure 4, path  
280 A) along with secondary oxidation products that can only be explained as deriving from the  
281 acylperoxy radicals formed after H-atom abstraction from the aldehydic group; conversely, none of  
282 the expected products arising from H-abstraction in allylic position (Figure 4, path B) on the  
283 terpenic hydrocarbon backbone could be observed (Hagvall, Backtorp, Norrby, Karlberg, & Borje,  
284 2011). Such findings are in full agreement with our autoxidation experiments: indeed best-fit kinetic

constants collected in Table 1 indicate that the peroxy radicals formed from citral propagate the oxidation of citral itself 62-fold faster than peroxy radicals derived from cumene with  $k_6$  as large as  $2.4 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$ , almost identical to that recorded for saturated dodecanal.

<Figure 4 about here>

### 3.3 Computational studies

While our current kinetic studies and previous product studies converge indicating that citral reacts with peroxy radicals at the carbonyl position (Figure 4, path A) rather than at the many available allylic positions (Figure 4, path B), the rationale for such reactivity is not obvious, since C-H bonds at the allylic positions are expected to be weaker than aldehyde C-H groups (Warren, Tronic, & Mayer, 2010), hence their reaction should be more facile. DFT (B3LYP) calculations by Hagvall et al. (2011) indicates that the weakest C-H bond in allylic position in citral is 7.6 kcal/mol weaker than aldehyde C-H bond. The authors suggested that, despite the less favorable thermodynamics, the selective H-abstraction at the aldehyde C-H results from irreversibility of the subsequent reaction of the acyl radical with oxygen to form acylperoxy radicals (Figure 4, path A), as compared to the reversible addition of oxygen to the stabilized allyl radical (path B) formed upon H-abstraction from allylic positions (Hagvall, et al., 2011). Although this suggestion might be correct, kinetic data reported herein indicate it is unlikely to justify the observed lack of reaction at the allylic position in citral, particularly when the reactivity of citral is compared to that of structurally related linalool, where expectedly similarly reversible formation of allylperoxy radicals guarantees efficient oxidative-chain propagation. To rationalize the reactivity of citral we turned to quantum-mechanical calculations. The relative reactivities of the allylic and aldehydic C-H bonds were investigated as shown in Figure 5. To economize on computational resources, the unsaturated hydrocarbon portion of citral was simplified to 2-methyl-2-pentene and the aldehydic portion to 3-methyl-2-butenal, i.e. the molecule was “truncated” into its two subunits. This follows the identical approach previously used by Hagvall, et al., (2011) and is fully justified by the fact that the two portions are electronically isolated: detaching the two subunits will not significantly influence the

311 reactivity of either the aldehyde or the allylic C-H group with peroxy radicals. The enthalpy  
312 difference between the products and the reactants, reported in Figure 5, was computed by high-level  
313 CBS-QB3 and shows that the reaction at the -CH<sub>2</sub>- allylic hydrogens is more exothermic than that at  
314 the aldehydic hydrogen by 5.3 kcal/mol, in qualitative agreement with the results reported by  
315 Hagvall et al (2011), the difference being attributable to the different level of calculation. Our  
316 calculations indicate that bond dissociation enthalpies BDE<sub>C-H</sub> of allylic and aldehyde moieties are  
317 respectively 83.1 and 88.1 kcal/mol at 298K, while the BDE<sub>O-H</sub> of the methylperoxy radical was  
318 computed as 86.2 kcal/mol. Additionally, transition states were computed at the M05/6-  
319 311+g(2df,2p) level of theory, which has been demonstrated to accurately reproduce the barriers of  
320 hydrogen atom transfer reactions (Galano et al., 2016;Tishchenko & Truhlar, 2012).

321 <Figure 5 here>

322

323 Most interestingly, calculations showed that, despite the less favorable thermodynamics, the barrier  
324 for the abstraction of the aldehyde hydrogen is lower by 1.3 kcal/mol as compared to the abstraction  
325 of the hydrogen atom from the most activated allylic position (see Figure 5). For confirmation,  
326 calculations were repeated at the M06-2X/6-311++G(d,p) level (Galano, 2011; La Rocca et al.  
327 2016), and were in qualitative agreement with the above results (see Appendix A for full  
328 comparison among the two methods).

329 When entropy changes are taken into account, the calculated difference in activation energy  
330 between the two reaction pathways is 1.8 kcal/mol. This difference indicates that reaction at  
331 carbonyl position would be faster than reaction at the allylic position by about twenty-fold at 303 K,  
332 fully justifying the experimental observations. Indeed, table 1 indicates that both citral and  
333 dodecanal transfer an H-atom to peroxy radicals at a rate constant (39 and 38 M<sup>-1</sup>s<sup>-1</sup> respectively, at  
334 303 K) about one order of magnitude higher than linalool or limonene (average value 3.4 M<sup>-1</sup>s<sup>-1</sup> at  
335 303 K), where reaction clearly occurs at the allylic position.



336 Natural bond order (NBO) analysis of the two reaction pathways indicated that the bonds being  
337 cleaved and being formed have, as expected, an occupancy of about 1. The occupancies of the  
338 cleaved CH bonds in the TS are nearly equal (0.98 and 0.95 respectively) for the aldehyde and  
339 allylic moieties. The occupancy of the incipient CH<sub>3</sub>OO-H bond is 0.84 in the case of hydrogen  
340 transfer from the aldehyde, and 0.78 in the case of hydrogen transfer from the allylic position (see  
341 Appendix A), supporting the conclusion that reaction at the aldehyde is the preferred reaction path.  
342 By analyzing the molecular orbitals in the TS, we found that the orbitals just below the SOMO have  
343 a delocalization pattern involving both reacting fragments (see Appendix A), this being coherent  
344 with a proton-coupled electron transfer (EPT) mechanism, in analogy with what is found in the case  
345 of the reaction of alkylperoxyl radicals with phenols and other compounds (DiLabio & Johnson,  
346 2007).

347

### 348 ***3.4 Significance of current results for the antioxidant protection of food***

349 The results reported in Table 1 show that limonene, linalool and citral react with the peroxyl  
350 radicals of cumene with rather low rate constants (4.5, 2.2 and 39 M<sup>-1</sup>s<sup>-1</sup> respectively) as compared  
351 to those of phenolic antioxidants (*e.g.*  $1.1 \times 10^4$  and  $3.2 \times 10^6$  M<sup>-1</sup>s<sup>-1</sup> for BHT and  $\alpha$ -tocopherol,  
352 respectively, at 30°C in chlorobenzene) (Burton, et al., 1985). However, these constants allow those  
353 terpenoids to compete with the oxidizable substrate (bearing relatively unactivated C-H bonds) for  
354 reaction with peroxyl radicals, thereby taking part to oxidative chain-propagation. What makes for  
355 their antioxidant behavior is the higher rate of self-termination and cross-termination of the  
356 terpenoids compared to the oxidizable substrate, thereby increasing the overall chain-termination  
357 and cutting the efficiency of autoxidation. This termination-enhancing antioxidant activity differs  
358 from the chain-breaking behavior of common phenolic antioxidants by three main aspects of  
359 practical relevance: i) their antioxidant performance is less pronounced than that of phenols and  
360 requires higher concentrations; ii) it is not linearly related to their concentration, hence it is much  
361 less predictable; iii) its effectiveness depends on the rate of chain-termination of the oxidizable

362 substrate, being higher for substrates that have more modest chain-termination (whereas for phenols  
363 it depends on substrate's rate of propagation). Despite the above limitations, they could effectively  
364 contribute to the antioxidant behavior of natural essential oils: although they are unlikely to afford  
365 sufficient protection to foodstuff when used alone, they would sum up to the efficacy of the  
366 phenolic components of essential oils and could be effectively exploited in food technology.  
367 Among the investigated compounds, citral has the largest reactivity, which arises from the presence  
368 of the aldehyde group. In this conjunction it is of interest that simple aliphatic aldehydes like  
369 dodecanal had an antioxidant behavior very similar to that of citral (see Appendix A), with might be  
370 relevant for their exploitation in food protection.

371

#### 372 **4. Conclusions**

373 Herein, we have provided a rationale and quantitative kinetic data for the antioxidant behaviour of  
374 limonene, linalool and citral. Such data are likely to reflect also the behaviour of other non-phenolic  
375 terpenoid essential oil components, thereby broadening their relevance. Such compounds act as  
376 termination enhancing antioxidants, bearing similitude to the kinetic behaviour previously assessed  
377 for  $\gamma$ -terpinene (Foti & Ingold, 2003), although, at variance with  $\gamma$ -terpinene, no involvement of the  
378 chemistry of superoxide is found in their antioxidant activity. Although their antioxidant  
379 performance will be expressed only in a rather narrow concentration range and only with some  
380 oxidizable substrates, they can contribute to the antioxidant activity of essential oils and their  
381 chemistry could effectively be exploited in food technology upon testing their performance in the  
382 actual system they are called to protect. In this conjunction it should not be overlooked that raw  
383 essential oils rather than isolated components are most widely appreciated in food products and the  
384 complex interplay among components would deserve deeper understanding, since often synergistic  
385 or antagonistic effects might come into action (Amorati et al., 2013). This fascinating chemistry is  
386 currently been investigated in our group.

387

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392

393 **Appendix A**

394 Results of autoxidation studies for dodecanal, details on theoretical calculations and Cartesian  
395 Coordinates.

396

397 **Declaration of interest**

398 The authors declare no competing financial interest.

399

400 **Abbreviations used**

401 AIBN, azobis-isobutyronitrile; PMHC, 2,2,5,7,8-pentamethyl-6-chromanol; BHT, butylated  
402 hydroxy toluene; EH, oxidizable essential oils components; RH, oxidizable substrate to be  
403 protected; ROO•, peroxy radicals formed by the oxidizable substrate; EOO•, peroxy radicals  
404 formed by the essential oil component; HOO•, hydroperoxy radical.

405

406

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544

**Table 1.** Rate constants ( $\text{M}^{-1}\text{s}^{-1}$ ) at 303K obtained from the fitting of co-oxidation plots of cumene and essential oils components (rate constants' numbering refers to eq. 1-10).

EO component	$k_5^{\text{a}}$	$k_6^{\text{a}}$	$k_7^{\text{a}}$	$k_9^{\text{a}}$	$k_{10}^{\text{a}}$
limonene	4.5 <sup>b</sup>	4.5 <sup>b</sup>	0.32 <sup>c</sup>	$3.4 \times 10^6$	$3.5 \times 10^6$
linalool	2.2 <sup>b</sup>	2.2 <sup>b</sup>	0.32 <sup>c</sup>	$9.3 \times 10^5$	$9.0 \times 10^5$
citral <sup>d</sup>	39	$2.4 \times 10^3$	22.6	$1.2 \times 10^8$	$1.0 \times 10^8$
dodecanal <sup>d</sup>	38	$2.2 \times 10^3$	22.4	$0.5 \times 10^8$	$2.5 \times 10^9$

<sup>a</sup> Errors are estimated to be  $\pm 50\%$  of the reported best fit values.

<sup>b</sup> In fittings,  $k_5$  was set equal to  $k_6$  (see text).

<sup>c</sup> In fittings,  $k_7$  was set equal to  $k_p$  for cumene (see text).

<sup>d</sup> As  $\text{EOO}\cdot$  are acylperoxyl radicals, the cross-propagation constant  $k_7$  is ~70-fold larger than  $k_4$ , and the  $k_6/k_5$  ratio is ~60.

## Figure captions

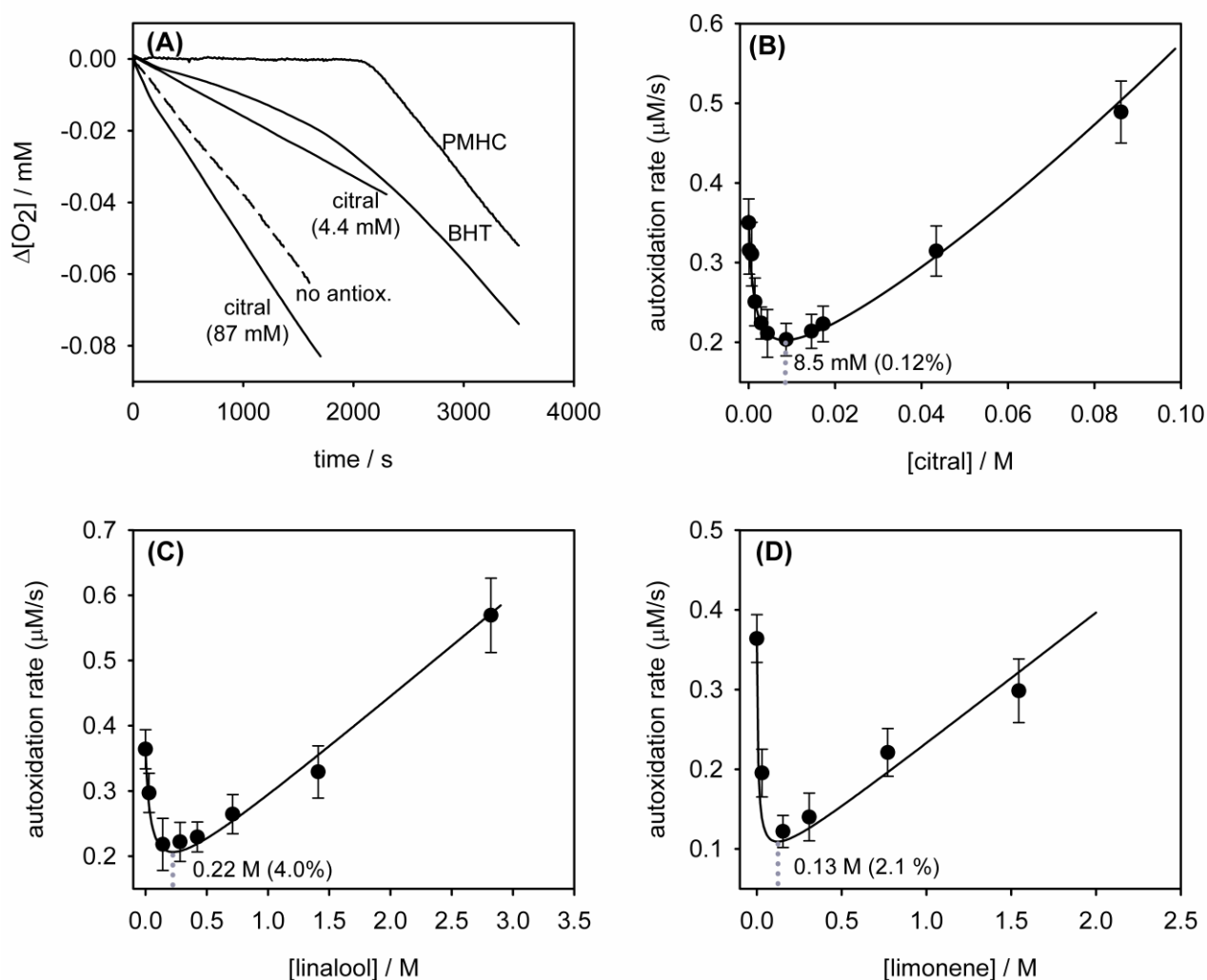
**Figure 1 (A-D).** Plots of O<sub>2</sub> uptake during the autoxidation of cumene (3.5 M) in chlorobenzene initiated by AIBN (0.05 M) at 30 °C in the absence of antioxidants (dotted line) or in the presence of PMHC 5 μM, BHT 5 μM, and citral 4.4 or 87 mM (**A**); measured rate of O<sub>2</sub> uptake as function of the concentration of citral (**B**), or of linalool (**C**), or of limonene (**D**) (±SD, n=3).

**Figure 2.** Peroxyl radicals formed during the autoxidation of limonene and linalool, arising from kinetic measurements in accordance to product studies by Kalberg et al. (1997) and Skold et al. (2004)

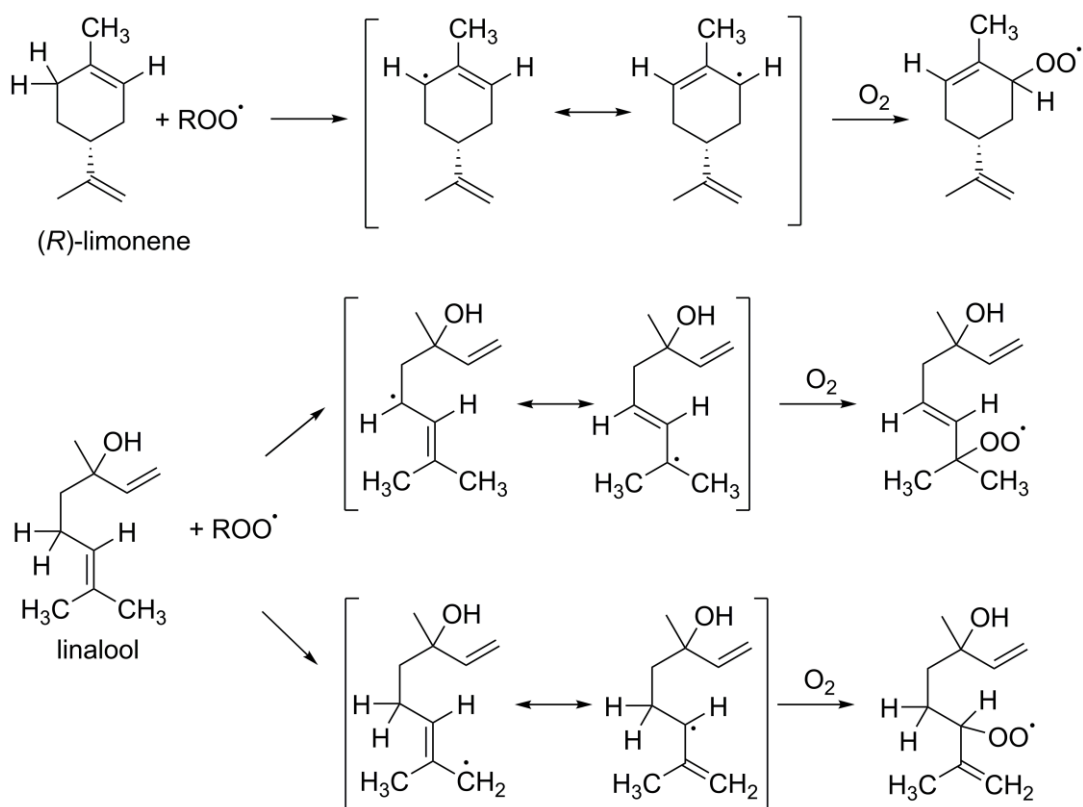
**Figure 3.** Formation of acylperoxyl radicals during the autoxidation of aldehydes.

**Figure 4.** Suggested reaction pathways for the autoxidation of citral with reference to the products studies on geranial (*E* isomer of citral) by Hagvall et al. (2011).

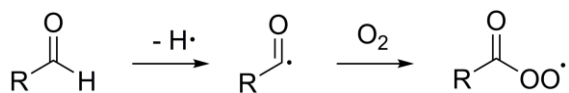
**Figure 5.** Calculated enthalpy of hydrogen atom abstraction from the aldehydic (Path A) or the allylic (Path B) portions of of citral (*E*-isomer) by methylperoxyl radicals at the M05/6-311+g(2df,2p) (<sup>‡</sup>) and CBS-QB3 (<sup>#</sup>) levels of theory. Values for products or TS are relative to the reactants calculated at the same level of theory. Optimized geometries of the transition states calculated at the M05/6-311+g(2df,2p) level are shown.



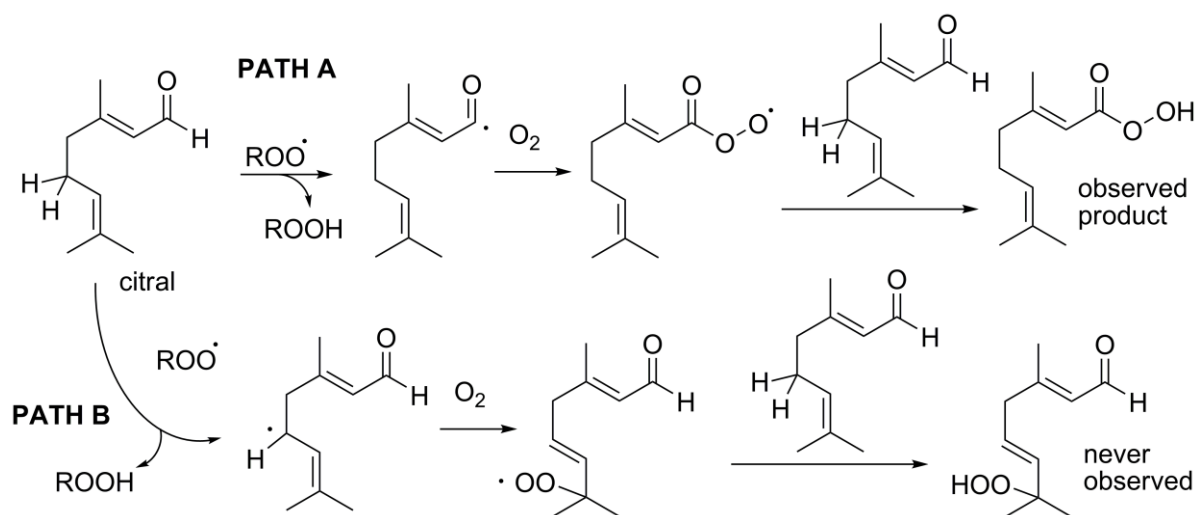
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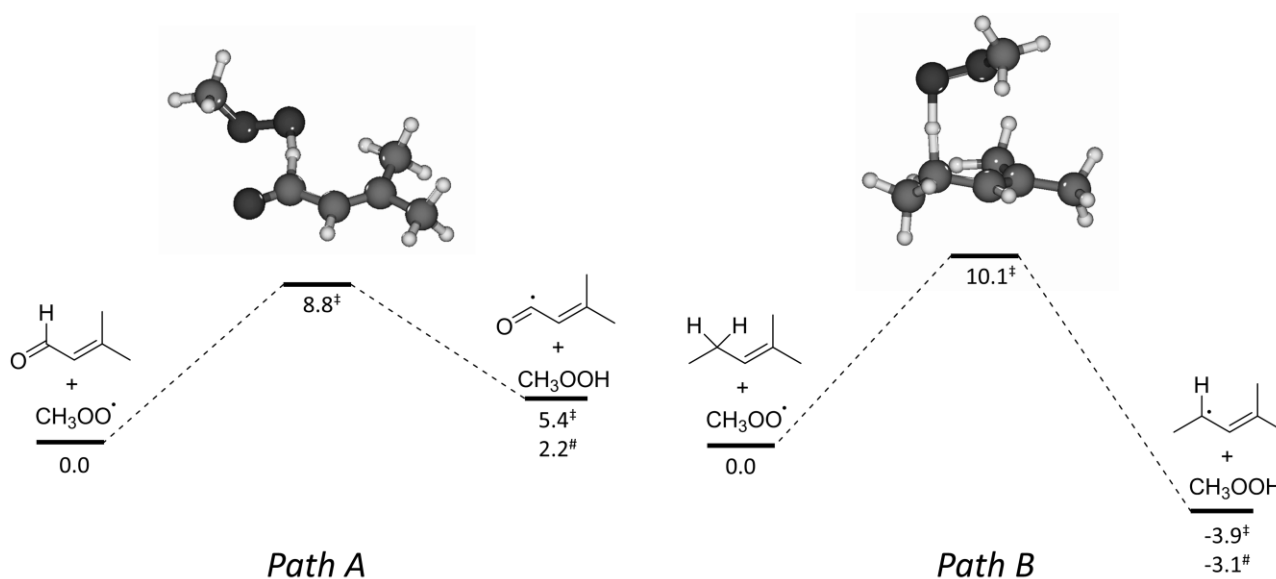
**Figure 2.** Peroxyl radicals formed during the autoxidation of limonene and linalool, arising from kinetic measurements in accordance to product studies by Kalberg et al. (1997) and Skold et al. (2004)



**Figure 3.** Formation of acylperoxyl radicals during the autoxidation of aldehydes.



**Figure 4.** Suggested reaction pathways for the autoxidation of citral with reference to the products studies on geranial (*E* isomer of citral) by Hagvall et al. (2011).



**Figure 5.** Calculated enthalpy of hydrogen atom abstraction from the aldehydic (Path A) or the allylic (Path B) portions of citral (*E*-isomer) by methylperoxy radicals at the M05/6-311+g(2df,2p) (<sup>†</sup>) and CBS-QB3 (<sup>#</sup>) levels of theory. Values for products or TS are relative to the reactants calculated at the same level of theory. Optimized geometries of the transition states calculated at the M05/6-311+g(2df,2p) level are shown.