Received: 25 July 2021 | Revised: 22 October 2021 | Accepted: 23 October 2021

DOI: 10.1111/1541-4337.12867

COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Comprehensive REVIEWS in Food Science and Food Safety WILEY

Tocopherols as antioxidants in lipid-based systems: The combination of chemical and physicochemical interactions determines their efficiency

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Abstract

Lipid oxidation is a major concern in the food, cosmetic, and pharmaceutical sectors. The degradation of unsaturated lipids affects the nutritional, physicochemical, and organoleptic properties of products and can lead to off-flavors and to the formation of potentially harmful oxidation compounds. To prevent or slow down lipid oxidation, different antioxidant additives are used alone or in combination to achieve the best possible efficiency with the minimum possible quantities. In manufactured products, that is, heterogeneous systems containing lipids as emulsions or bulk phase, the efficiency of an antioxidant is determined not only by its chemical reactivity, but also by its physical properties and its interaction with other compounds present in the products. The antioxidants most widely used on the industrial scale are probably tocopherols, either as natural extracts or pure synthetic molecules. Considerable research has been conducted on their antioxidant activity, but results regarding their efficiency are contradictory. Here, we review the known mechanisms behind the antioxidant activity of tocopherols and discuss the chemical and physical features that determine their efficacy. We first describe their chemical reactivity linked with the main factors that modulate it between efficient antioxidant capacity and potential prooxidant effects. We then describe their chemical interactions with other molecules (phenolic compounds, metals, vitamin C, carotenes, proteins, and phospholipids) that have potential additive, synergistic, or antagonist effects. Finally, we discuss other physical parameters that influence their activity in complex systems including their specific interactions with surfactants in emulsions and their behavior in the presence of association colloids in bulk oils.

Nomenclature: AA, Ascorbic acid; a_w, Water activity; BDE, Bond dissociation energy; CC, Critical concentration; CI, Criegee intermediate; CMC, Critical micelle concentration; DMPC, Dimyristoylphosphatidylcholine; DOPC, Dioleoylphosphatidylcholine; DOPE, Dioleoylphosphatidylethanolamine; IP, Inhibition of formation of hydroperoxide; LH, Lipid; LO•, Lipo alkoxyl radical; LOO•, Lipo peroxyl radical; PC, Phosphatidylcholine; PCA, Principal component analysis; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; PLPC, 1-Palmitoyl-2-lauroyl-sn-glycero-3-phosphocholine; PUFA, Polyunsaturated fatty acid; PV, Peroxide value; RH, Relative humidity; T3, Tocotrienols; TocOH, Tocopherols and tocotrienols; TOH, Tocopherols.

KEYWORDS
antioxidant, bulk oil, emulsion, prooxidant, tocopherols

1 | INTRODUCTION

Preventing lipid oxidation in unsaturated fat-based products is a huge challenge for the agricultural, food, and cosmetics sectors. Lipid deterioration affects the overall quality of products by modifying the nutritional, physicochemical, organoleptic, and sanitary properties of products, causing loss of liposoluble vitamins and unsaturated fatty acids, off-flavors and the formation of harmful chemicals, and so on (Budilarto & Kamal-Eldin, 2015b).

Lipid oxidation is a multifactorial reaction that is influenced by several physicochemical parameters such as the physical structure of the system (i.e., bulk oil/homogeneous system vs. emulsion, liposome/heterogeneous system) such as the partition of molecules within the complex system (location, diffusion in each phase, the presence of others molecules and either activities (antioxidant oxidizable substrates, surfactant, prooxidant) and the physicochemical properties of the global media, pH, ionic strength, and temperature (Decker et al., 2017).

Different techniques can be used to prevent or slow down lipid oxidation. Such techniques act at different levels, for example, during storage and distribution (from raw material to the final product), each step in the transformation process (e.g., the unit operation, intensity, and physicochemical conditions), and formulation with antioxidant additives. Lipid oxidation is caused by oxygen in the presence of initiators (e.g., heat, UV, photosensitizers, transition metal ions, free radicals). It is generally accepted that lipid oxidation takes place via three reaction pathways: (i) nonenzymatic, free radical chain autoxidation, (ii) nonenzymatic and nonradical photooxidation, and (iii) enzymatic oxidation by lipoxygenases. In this review, we focus on autoxidation, which occurs as a free radical mechanism reaction that releases different volatile and nonvolatile molecules (Figure 1). Many studies aim to obtain a deeper knowledge of the complexity of the chemistry of lipid oxidation. For example, Schaich and co-workers (Schaich, 2012, 2020; Schaich et al., 2017) questioned the standard three-stage free radical chain reaction assumed for lipid oxidation (i.e., initiated by H abstraction and propagated by peroxy radicals) and proposed an integrated alternative pathway. According to these authors, many reactions by peroxyl and alkoxyl radicals can compete with H abstraction making lipid oxidation a complex interconnected series of competing reaction pathways and not just a simple free radical chain reaction, as it does not always go through the same pathways and produce the same products (radicals → hydroperoxides → products). The oversimplified free radical chain reaction scheme does not reveal the numerous and complex competing side reactions that occur during lipid oxidation, as a wide range of products are produced simultaneously or at least overlap, rather than a sequence of single reactions or compounds (Schaich et al., 2017).

Similarly, Zeng et al. (2020) proposed an additional pathway where lipid autoxidation is triggered by ●OH addition to the C = C bond of the lipid, followed by addition of O_2 to produce a β-hydroxyl peroxyl radical (Figure 1). C–C bond scission of the β-hydroxyl peroxyl radical produces a Criegee intermediate (CI) and an α-hydroxyl alkyl radical, which is then propagated by chain reactions involving CI.

Considerable work has been carried out to identify the best antioxidants or combinations of antioxidants to delay or prevent lipid oxidation and to ensure optimal efficiency using the minimum possible quantities of the antioxidants concerned. The use of synthetic antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene in food and nonfood products dates back to the 1940s. Today, due to the consumer concerns about synthetic molecules as additives that are suspected of having adverse health effects, interest has been growing in natural molecules or extracts with demonstrable antioxidant properties (Ghorbani Gorji et al., 2019; Moure et al., 2001; Shahidi & Ambigaipalan, 2015).

Many parameters play crucial roles in the behaviors and efficiencies of antioxidants used to combat lipid oxidation. Porter et al. (1989) were among the first authors to show that trying to compare antioxidant behavior either in bulk oils or heterogeneous systems is irrelevant (Porter et al., 1989). They introduced the polar paradox concept, which states that polar antioxidants work best in bulk oils (by placing them at the oil–air interface), whereas nonpolar antioxidants work best in lipid dispersions (by placing them at the oil–water interface) (Figure 2a). To be effective against lipid oxidation, nonpolar antioxidants should be surface active to locate themselves at the lipid–droplet interface, where both lipid hydroperoxides and transition metals can accumulate and come into close proximity (Frankel et al., 1994; Laguerre et al., 2015; Porter et al., 1989; Waraho et al., 2011). However, the polar paradox concept has been the subject of criticism, for example, Zhong and Shahidi (2012) suggested that the polar

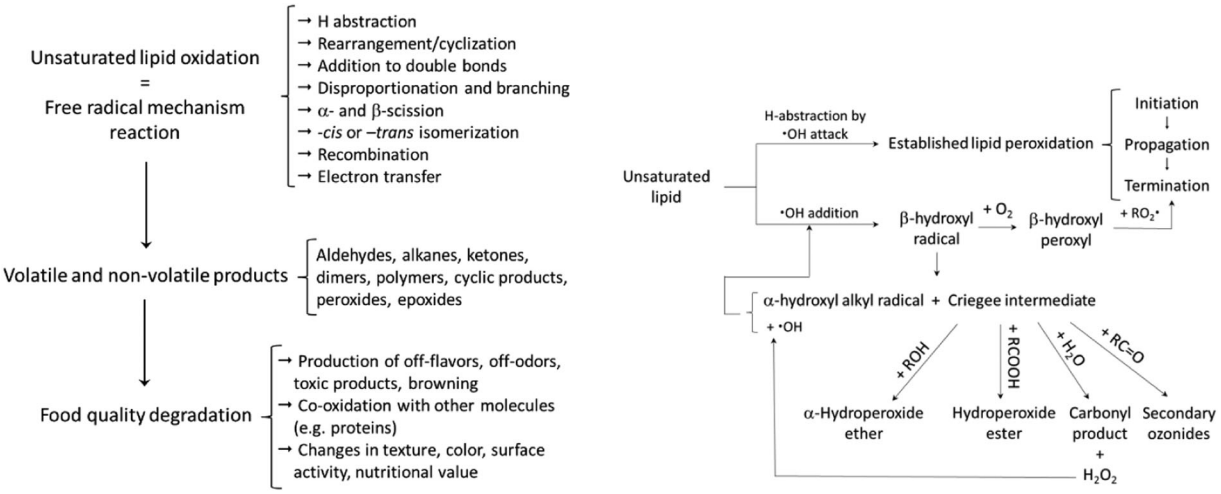

FIGURE 1 Unsaturated lipid autoxidation (adapted from Schaich, 2012) (left) and Criegee intermediate-driven lipid autoxidation (adapted from Zeng et al., 2020) (right). ●OH, hydroxyl, RO_2●, peroxy radical; ROH, alcohol; RCOOH, carboxylic acid; RC = O, aldehyde

paradox is only applicable within specific concentration ranges (Figure 2b) (Zhong & Shahidi, 2012). The validity of the concept depends on both the polarity and the concentration of the antioxidant, meaning that the most efficient antioxidants are the nonpolar ones at concentrations below their critical concentration (CC) and the polar ones at concentrations above this CC (where the polar paradox is valid). The model proposed by Porter et al., with an oil/air interface in the case of bulk oils, has also been contested. Bulk oils are no longer considered to be a homogeneous liquid but rather a water-in-oil nano-emulsion (Figure 2c), because even when refined, bulk oils can contain very small quantities of water and/or surfactant molecules (mono- and diacylglycerols, phospholipids, sterols, etc.) (Chaiyasit et al., 2007; Chen et al., 2013). These molecules organize themselves into reverse micelles named "association colloids," which, depending on their size, morphology, and chemical composition and the potential partitioning of hydrophilic antioxidants and oxidation products within association colloids, have a significant impact on lipid oxidation (Laguerre et al., 2015). As air is less polar than oil, polar antioxidants tend not to migrate to the air–oil interface more than hydrophobic antioxidants (as suggested by the polar paradox). Thus, to be efficient in bulk oil, hydrophilic antioxidants need to be surface active and to get adsorbed in high amount at the interface of the colloid association, where oxidative reactions may be more prevalent.

Moreover, other studies of emulsified systems showed that the polar paradox theory is probably not entirely valid and that more complex phenomena than only their polarity may occur and influence the behavior of antioxidants. For example, when testing homologous series of phenolipids (alkyl esters of phenolic acids), Laguerre et al. (2009) showed that hydrophobicity and antioxidant activity in oil-in-water emulsions increase to a certain extent (corresponding to the critical alkyl chain length) beyond which any lengthening of the alkyl chain led to the collapse of antioxidant activity (Figure 2d) (Laguerre et al., 2009). This phenomenon, which the authors called the "cutoff effect," has also been observed in more complex systems (e.g., liposomes, living cells) (Bayrasy et al., 2013) and reported in a wide range of other studies (Berton-Carabin et al., 2014; Budilarto & Kamal-Eldin, 2015b; Laguerre et al., 2009, 2010).

The results described above underline the major impact of the system itself on lipid oxidation. Autoxidation in heterogeneous lipid dispersions is more complex than autoxidation in bulk oil. In such heterogeneous systems, several factors can influence the oxidation kinetics and behaviors of antioxidants as summarized in Figure 3 (Berton-Carabin et al., 2014; Chaiyasit et al., 2007; Decker et al., 2017; Frankel, 1996; Laguerre et al., 2015, 2017, 2020). These factors include (i) the characteristics of the lipid substrate (class of lipids and degree of unsaturation of the oil), (ii) the presence of other molecules and their water/oil partitioning properties, (iii) the environmental conditions (temperature, oxygen concentration, ultraviolet, potential presence of catalysts (e.g., photosensitizers, metal ions), and (iv) the nature of the emulsion (size, concentration, and physical state of the droplets, the thickness, electrical charge, and composition of the interface layer) (Berton-Carabin et al., 2018).

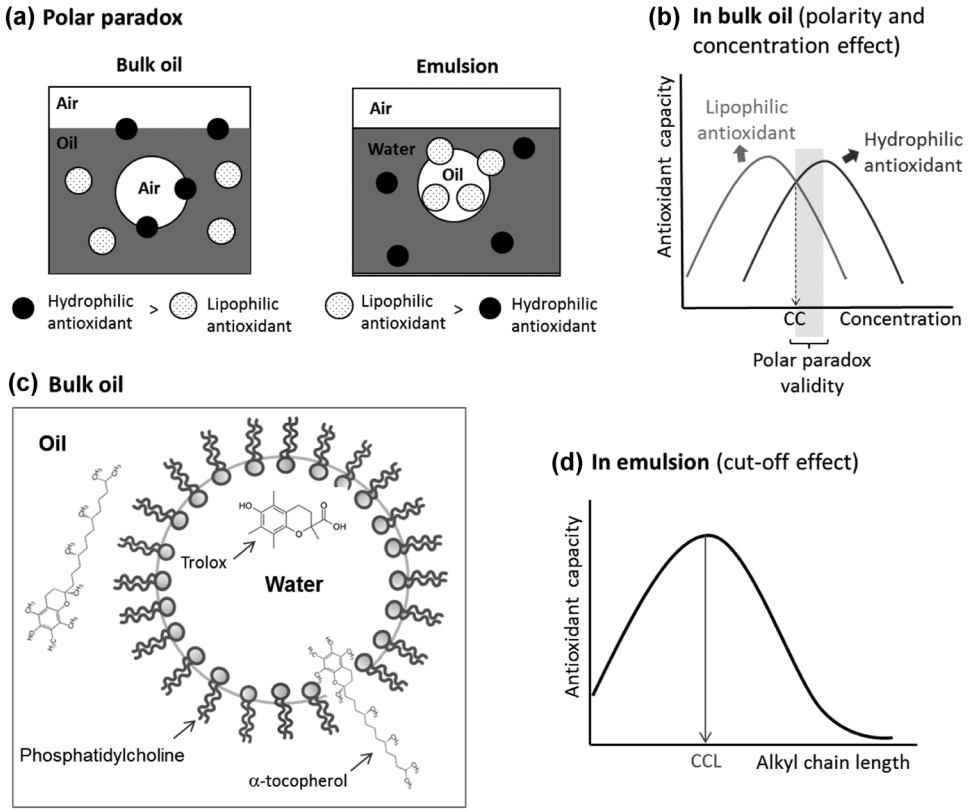

FIGURE 2 Antioxidant activity and interphase distribution of hydrophilic and lipophilic antioxidants according to (a) Porter et al. (1989) and Frankel (1996), (b) Zhong and Shahidi (2012) (CC, critical concentration), and (c) Chen et al. (2013) and of amphiphilic antioxidants (e.g., phenolipids) according to (d) Laguerre et al. (2009, 2010) and Sørensen et al. (2014) (CCL, critical alkyl chain length). All the figures were adapted from the originals

In the context of combating lipid oxidation in food and cosmetic products, and the difficulty caused by the many chemical and physicochemical parameters involved, the most widely used antioxidants on the industrial scale are probably tocopherols (TOH). Indeed, since their discovery in the last century, TOH (and their unsaturated derivatives, tocotrienols [T3]) have attracted strong interest among the scientific community. TOH, particularly α-TOH, are regularly used as food additives, either as extracts or pure synthetic molecules in formulae to protect unsaturated lipids. Although considerable research has been conducted on the antioxidant activity of these molecules to elucidate their mechanisms of action, results regarding their efficiencies are contradictory and some authors have even described them as molecules with potential prooxidant activity (Bakır et al., 2013; Frankel et al., 1959; Martin-Rubio, Sopelana, Ibargoitia, et al., 2018). Here, we review the mechanisms known to be involved in the antioxidant activity of TOH and T3 in lipid oxidation and discuss the chemical and physicochemical factors and interactions that determine their efficacy as antioxidants in multiphase systems.

2 | CHEMICAL BEHAVIOR OF TOCOPHEROLS WITH RESPECT TO LIPID OXIDATION (MECHANISMS AND PRODUCTS)

2.1 | Tocopherols and tocotrienols: Structure and nomenclature

In 1922, Evans and Bishops set light on a new molecule while conducting an interventional nutritional assay on animal model (Evans & Bishop, 1922). They showed that the molecule, which is found in natural foods, was required for reproduction but not for growth. In 1924, similar results were obtained by Sure who named the molecule vitamin E (Sure, 1924). Later, in 1936, Evans et al. gave vitamin E the scientific name of tocopherol (Evans et al., 1936). The name comes from the Greek *tokos* and *phero* meaning "childbirth" and "give birth," respectively, with the ending "-ol" to link it with the presence of the alcohol chemical group. Different forms of tocopherol—β, γ, and δ tocopherols—were identified in 1938 (Emerson, 1938) and 1947 (Stern et al., 1947) and ζ tocopherol in 1955 (Green et al., 1955).

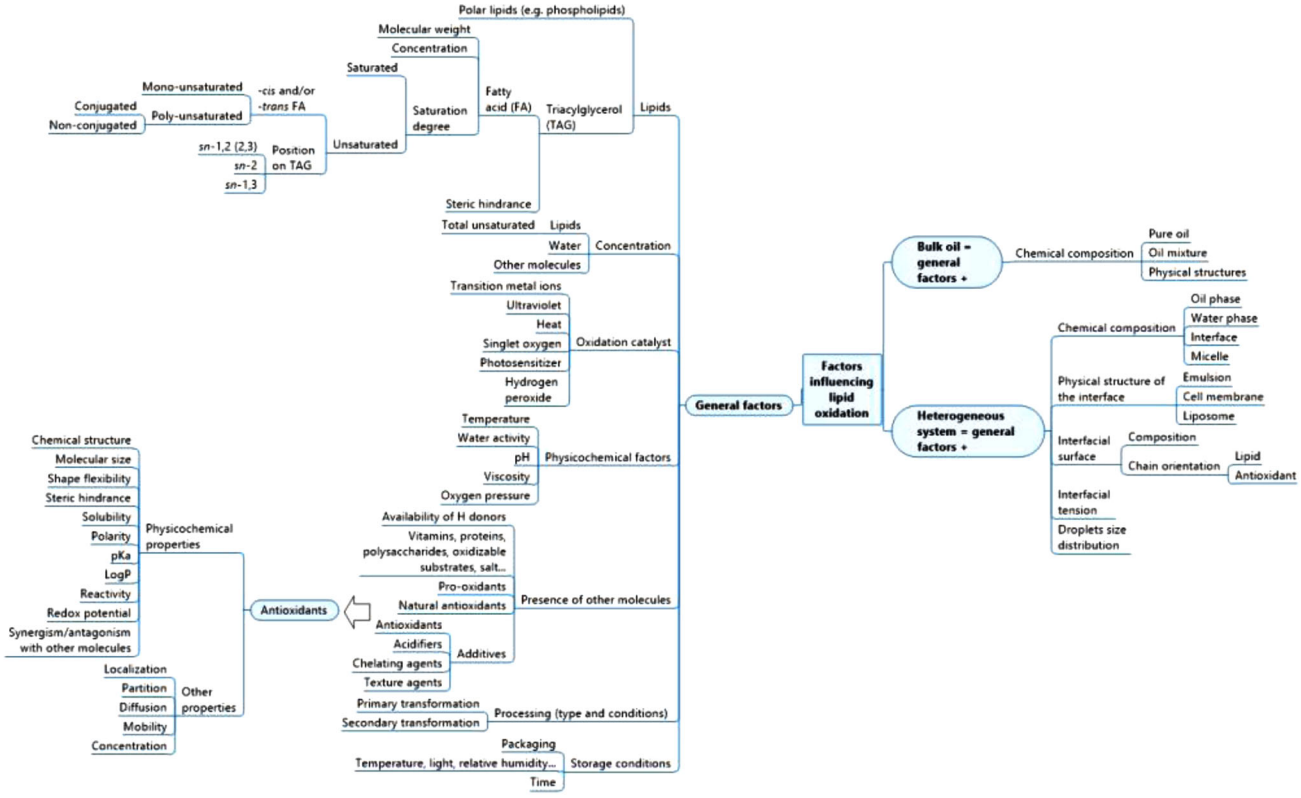

FIGURE 3 Principal factors influencing lipid oxidation in bulk oil and heterogeneous systems

In 1964, ζ tocopherol was renamed "tocotrienol" by the team of Pennock who isolated a new "vitamin E compound" from *Hevea brasiliensis* (Pennock et al., 1964). Since tocopherols and tocotrienols (TocOH) were discovered in the last century, they have continually been subject to the curiosity of the scientific community.

Structurally, TOH and T3 are made of a chromane moiety based on two rings—one phenolic and one heterocyclic—and a phytyl tail (Figure 4). The four tocopherols (α, β, γ, and δ) have saturated tails and vary only in the positions and number of methyl groups on their phenolic ring: α, β/γ, and δ forms have three, two, and one methyl groups on the chromanol ring, respectively. The four tocotrienols (α, β, γ, and δ) only differ from tocopherols by three double bonds in their phytyl tails. TOH and T3 are liposoluble compounds. T3 are found in nature under its esterified forms contrary to TOH that are found as free phenols. The natural forms of TOH have RRR stereochemistry on the three asymmetric carbon atoms of the phytyl chain connected to the chromanol ring. They are synthesized and stored in plant leaves (Mallet et al., 1994; Soll et al., 1980), latex of *Hevea brasiliensis* (Chow & Draper, 1970; Whittle et al., 1966), seeds, and fruits (Górnaś et al., 2015; Horvath et al., 2006). Biosynthesis of TocOH forms is triggered by prenylation of homogentisate. TOH are synthetized from phytyl diphosphate (PDP) as prenyl donor, whereas T are synthesized from geranylgeranyl diphosphate (DellaPenna, 2005; Mène-Saffrané, 2018; Yang et al., 2010). Originally, the name vitamin E was limited to TOH (mostly dl-α-TOH) because of their biological activity, but T3 were later added to this generic term (Sen et al., 2006). However, recently, Azzi (2018) assumed that only α-TOH should be considered as vitamin E, because it was the only one to produce significant results in the prevention and the treatment of diseases associated with vitamin E deficiency.

2.2 | Tocopherol reactivity (antioxidant vs. prooxidant effect)

As mentioned above, lipid (LH) oxidation is a complex chemical reaction (Figures 1 and 3) involving the formation and propagation of lipid radicals, the uptake of oxygen, and the production of miscellaneous breakdown products, including alcohols, ketones, alkanes, aldehydes, epoxides, and ethers (Frankel, 2005; Schaich, 2005). Its mechanisms have been extensively studied, but are still the subject of debate (Schaich, 2020). The multitude of possible reaction pathways and the large number of products that can be generated oblige us to view this reaction in a simplified way based on free radical chemistry, in which lipid peroxyl (LOO•) and alkoxyl (LO•) radicals undergo a number of

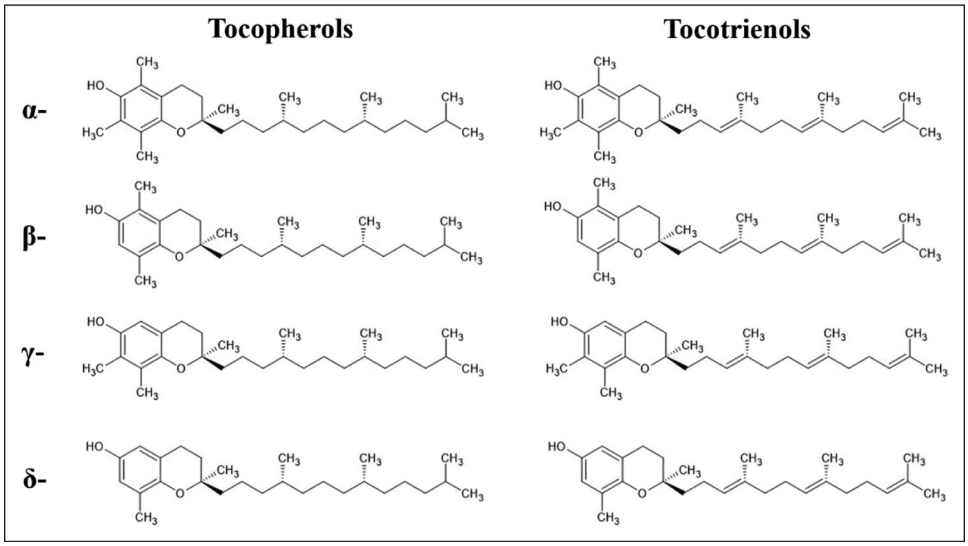

FIGURE 4 The structure of α, β, γ, and δ tocopherols and tocotrienols

alternate reactions in addition to and in competition with hydrogen abstraction. In this context, the antioxidant activity of TocOH is principally due to their ability to donate their phenolic hydrogen. This capacity is closely linked to the bond dissociation energy (BDE) of the phenolic O–H bond. The lower the BDE, the stronger the H-atom donor character, and the reaction with free radicals. In chemical structure, the hydrogen-donating power follows the order $\alpha > \beta = \gamma > \delta$ (+0.273, +0.343, +0.348, and +0.405 volts) (Kamal-Eldin & Appelqvist, 1996). Indeed, electron-releasing moieties in *ortho*- and/or *para* positions facilitate the homolytic fission of the O–H bond, extending the radical lifetime (O•) and increasing reactivity with other radicals (Lucarini et al., 1994). Accordingly, in terms of pure chemical reactivity, α-TocOH (with two *ortho*-methyl substituents) is generally considered as the most effective antioxidant, followed by β- and γ-TocOH (with one *ortho*-methyl substituent) and δ-TocOH (with no *ortho*-methyl substituent). The architecture of the chromane moiety thus appears to be the principal parameter that determines the relative antioxidant efficacy of tocopherols. In contrast, the phytyl tail interferes either very little or even not at all in this chemical reactivity. That is why TOH and T3 have been reported to have largely the same reactivity with free radicals in homogeneous systems (Yoshida et al., 2007). Yet, the results of published studies on in vitro antioxidant activities do not necessarily follow these antioxidant rules and ranking. In particular, the effectiveness of the eight TocOH in lipid dispersion systems or in bulk oil may be unpredictable and rather variable, causing doubts regarding their relative in vitro efficacy (Table 1). Although it is difficult to clearly elucidate the reason for this change in efficacy, we can say that the activity of TocOH as antioxidants is influenced by both its chemical reactivity and its ability to limit other side reactions. Overall, the activity of TocOH as antioxidants not only depends on their absolute chemical reactivities with free radicals, but also on many other side reactions that are governed by chemical and physical interactions with neighboring molecules. In this section, we focus on how the chemical behavior of TocOH with respect to lipid oxidation may be affected.

2.2.1 | Interactions of TocOH in lipid oxidation

TocOH can inhibit lipid oxidation in different ways (Figure 5). For instance, they may chelate transition metal ions, thus forming a complex that will prevent the prooxidant activity catalyzed by metals (A_1) or through physical or chemical quenching reactions with singlet oxygen ($^1O_2$). Physical quenching deactivates the excited state of singlet oxygen ($^1O_2$) into ground state triplet oxygen ($^3O_2$) after energy or charge transfer, for example, the electron transfer mechanism (A_2) (Thomas & Foote, 1978; Yamauchi & Matsushita, 1977). In this case, no consumption of oxygen nor formation of products is observed. The rates of physical quenching of $^1O_2$ by TOH were reported to be in the magnitude of 10^7 to 10^8 M^{-1} s^{-1}, and in the order $\alpha > \beta > \gamma > \delta$ (Kaiser et al., 1990; Neely et al., 1988). Oxidation of a quencher rather than quenching is observed during the chemical quenching of singlet oxygen. Therefore, this chemical quenching leads rather to the formation of degradation or oxidation products of a quencher than to termination products. TocOH may react irreversibly with $^1O_2$ to form a hydroperoxide adduct (TocO–OOH) that decomposes to form secondary products such as hydroperoxy dienone, tocopherol quinone, or tocopherol quinone-epoxide (A_3)

TABLE 1 Antioxidant and pro-oxidant activity of TocOH

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Bulk oil **Olive oil**	Y	αTOH	–	100-500-1000	Best activity at 100 ppm.	Slightly pro-oxidant above 100 ppm.	(Blekas et al., 1995)
Bulk oil **Refined Sunflower oil**	N	αTOH δTOH	αTOH = 670 βTOH = 22 γTOH = 20	100	δTOH shows improved performance in storage experiments	No pro-oxidant activity.	(Carelli et al., 2005)
Bulk oil **Corn oil**	Y	αTOH δTOH αT3 γT3 δT3	–	100-250-700-2000-5000	Best results (PV) at 100–250 ppm for αTOH, αT3. Antioxidant at all concentrations of δTOH, γT3, δT3. Increasing the concentration inhibited the formation of secondary oxidation products.	≥700 ppm: αTOH and αT3 (for PV)	(Dolde & Wang, 2011)
Bulk oil	N	αTOH γTOH δTOH			The naturally occurring αTOH level was correlated with conjugated diene. The potential pro-oxidant activity of αTOH can be attributed to its high chemical reactivity as a free radical scavenger rather than to its abundance in comparison to γTOH or δTOH in the oil.		(Elisia et al., 2013)
Canola oil			αTOH = 50; γTOH = 117; δTOH<1				
Castor oil			αTOH = 8; γTOH = 159; δTOH = 142				
Corn oil			αTOH = 142; γTOH = 492; δTOH = 25				
Cotton oil			αTOH = 233; γTOH = 283; δTOH = 8				
Macadamia			αTOH = 0; γTOH = 0; δTOH = 0				
Olive oil			αTOH = 50; γTOH<1; δTOH<1				
Peanut			αTOH = 110; γTOH = 117; δTOH = 17				
Safflower			αTOH = 108; γTOH = 33				
Soybean oil			αTOH = 42; γTOH = 517; δTOH = 183				
Sunflower oil			αTOH = 158; γTOH = 17; δTOH<1				
fFaxseed. oil			αTOH<1; γTOH = 142; δTOH<1				

(Continues)

TABLE 1 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Bulk oil **Sunflower oil**	Y	αTOH γTOH	-	1-2-4-7-20-40-70-100-200-400-700-1000-1500-2000	γTOH more efficient than αTOH.	No pro-oxidant effect.	(Fuster et al., 1998)
Bulk oil **Refined fish oil**	N	αTOH γ/δTOH δTOH	Not evaluated	2000-20000	At 20000 ppm: δTOH > (γ/δ)TOH > αTOH.	αTOH at 2000–20000 ppm.	(Hamilton et al., 1998)
Bulk oil **Sunflower oil**	Y	αTOH	-	100	αTOH: antioxidant after 7 days.	αTOH: pro-oxidant effect during the first week.	(Hraš et al., 2000)
Bulk oil **Corned oil**	Y	γTOH δTOH	–	γTOH = 5000 δTOH = 100-250-500-750-1000-2000	δTOH: at all concentrations (2000 ppm or below).	γTOH: promoted formation of hydroperoxides but inhibited their decomposition at 5000 ppm.	(Huang et al., 1995)
Bulk oil **Rapeseed oil**	Y	αTOH γTOH δTOH α/γTOH	-	100-2500	δTOH the best (most stable and effective under these low oxygen conditions).	αTOH and γTOH increased lipid oxidation.	(Isnardy et al., 2003)
Bulk oil **Soybean oil**	Y	αTOH γTOH δTOH	–	0-100-500-1000	αTOH = 100 ppm. γTOH < 500 ppm. δTOH < 1000 ppm	αTOH > 100 ppm γTOH > 250 ppm δTOH > 500 ppm	(Jung & Min, 1990)
Bulk oil **Stripped soybean oil** **Grape seed oil** **Palm oil**	Y/N	αTOH γTOH γT3 δT3	– αTOH = 328 γTOH = 17 δTOH = 516 αTOH = 346 αT3 = 260 γT3 = 623 δT3 = 80	5000	Palm oil: δT3 > αT3> αTOH > γT3. Grape seed: γTOH > αTOH > γT3. Stripped soybean oil: δT3 > αT3 > γT3 > αTOH.	No pro-oxidant activity.	(Jung et al., 2018)
Bulk oil **Corn oil**	Y	αTOH	-	10-20-42-84	αTOH: 10–42 ppm. Antioxidant properties of αTOH were greatly influenced by moisture content and by the concentration of αTOH.	αTOH at 84 ppm.	(Kim et al., 2015)
Bulk oil **Lard**	–	αT3 βT3 γT3 δT3	–	0-100-200-300-500-1000	αT3 (100 ppm) improved the oxidative stability. βT3, γT3 and δT3 improved the oxidation stability at all concentrations. Activities of αT3 and βT3 decreased with increasing concentration.	αT3 > 300 ppm up to 6 days.	(Kim, 2014)

(Continues)

TABLE 1 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Bulk oil **Methyl linoleate**		αTOH γTOH	-	0-10-100-500-1000	αTOH = 10 > 100–1000 ppm.	No pro-oxidant activity.	(Kinen et al., 2000)
Bulk oil **Fish oil**	Y	αTOH γTOH δTOH	–	αTOH = 50-2000 γTOH = 100-2000 δTOH = 100-2000	All TOH notably delayed the formation of volatile secondary oxidation products in a concentration-dependent manner.	No pro-oxidant activity.	(Kulås & Ackman, 2001)
Bulk oil **Fish oil**	Y	αTOH γTOH δTOH	-	100-1000	100ppm: αTOH > γTOH > δTOH. 1000 ppm: δTOH > γTOH > αTOH.	No pro-oxidant activity.	(Kulås et al., 2002)
Bulk oil **Rapeseed oil**	Y	αTOH γTOH	–	5-10-50-100-500	αTOH (≤50 ppm) > γTOH. γTOH (>100 ppm) > αTOH.	No pro-oxidant activity.	(Lampi et al., 1999)
Bulk oil **Mixed FAME of cotton seed, linseed, cod liver oil**	Y	αTOH βTOH γTOH δTOH αT3 βT3 γT3	-	10000	In the linoleate system (cottonseed): γTOH and δTOH the most efficient. αTOH, αT3 and βT3 the least effective. In the polyunsaturated systems: γTOH was still good, but δTOH were at the bottom, while αTOH and αT3 were near the top.	No pro-oxidant activity.	(Lea, 1960)
Bulk oil **Refined sunflower oil**	N	γTOH	Not evaluated	200-2000-20000	The higher the concentration of γTOH, the slower the degradation of the oil, except during the initial period	During the first short period of time in accelerated storage conditions, the higher the concentration of γTOH the faster the degradation of linoleic acyl groups and the higher the concentration of hydroperoxides.	(Martínez-Yusta & Guillén, 2019)
Bulk oil **Soybean oil**	N	αTOH γTOH	Not evaluated	αTOH = 2000-20000 γTOH = 200-2000-20000	200 ppm: γTOH no or very minor effect.	αTOH (200 and 2000 ppm) and γTOH (20000 ppm). 20000 ppm: αTOH is more pro-oxidant than γTOH.	(Martin-Rubio, et al., 2018)
Bulk oil **Soybean oil**	N	αTOH	αTOH = 130 βTOH = 22 γTOH = 782 δTOH = 316	20-200-2000-20000-50000	No or very minor antioxidant activity at the lowest concentration.	Increasing αTOH accelerated the production of oxidation products. High concentrations of αTOH promoted the production of hydroperoxides, hydroxy-dienes, keto-dienes, alkadienals.	(Martin-Rubio, Sopelana, Ibargoitia, et al., 2018)

(Continues)

TABLE 1 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Bulk oil **Flaxseed oil**	N	αTOH	αTOH<10; βTOH<10; γTOH = 380 δTOH<10; T3<10	50-100-200-400	Slightly decreased with an increase in concentration.	Pro-oxidant effects at all concentrations and times at 25°C and 40°C, but only at day 30 for 50 ppm and 200 ppm at 60°C.	(Mohanan et al., 2018)
Bulk oil **Flaxseed oil**	N	αTOH	αTOH<10; βTOH<10; γTOH = 380 δTOH<10; T3<10	50-100-200-400	Slightly decreased with an increase in concentration.	Pro-oxidant effects at all concentrations and times at 25°C and 40°C, but only at day 30 for 50 ppm and 200 ppm at 60°C.	(Mohanan et al., 2018)
Bulk oil **Soybean oil**	N	αTOH γTOH δTOH	αTOH = 53; γTOH = 750; δTOH = 268	-	Degradation rates: αTOH > γTOH > δTOH.	No pro-oxidant activity.	(Player et al., 2006)
Bulk oil **Sardine oil**	N	αTOH	Not evaluated	50-100	Storage at +4°C with αTOH (100 ppm) had a beneficial.	No pro-oxidant activity.	(Selmi et al., 2011)
Bulk oil **Methyl linoleate**	-	αTOH	-	1000-10000	No antioxidant activity.	1000-10000 ppm αTOH: increased the amount of hydroperoxides and increased the distribution of the c-t isomers.	(Terao & Matsushita, 1986)
Bulk oil **Coconut oil**	N	αTOH βTOH γTOH δTOH αT3 βT3 γT3 δT3	Total OH-T3 <30	TOH = 100-5000 T3 = 100-1000	TOH: $\alpha < \gamma < \delta$. T3: $\alpha < \beta < \gamma < \delta$.	No pro-oxidant activity.	(Wagner et al., 2001)
Bulk oil **Methyl linoleate**	-	αTOH γTOH αT3 γT3	-	200-500	αT3 and γT3 are slightly more antioxidant than αTOH and γTOH.	No pro-oxidant activity.	(Yamaoka et al., 1985)
Bulk oil **Purified TAG sunflower oil and soybean oil**	N	αTOH γTOH	Undetectable	50-200-1000	Increasing the concentration led to a decrease in antioxidant activity.	No pro-oxidant activity.	(Yanishlieva et al., 2002)

(Continues)

TABLE 1 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Bulk oil **Canola** **Sunflower** **Soybean oils**	N	αTOH γTOH δTOH	αTOH = 312 γTOH = 389 δTOH = 95 αTOH = 648 γTOH = 131 δTOH = 713 αTOH = 215 γTOH = 659 δTOH = 264	-	γTOH and δTOH > αTOH.	No pro-oxidant activity.	(Zaunschirm et al., 2018)
Bulk oil **Corn oil**	Y	αTOH	-	9-17-34-70-138	Increasing αTOH concentration led to a decrease in antioxidant activity.	No pro-oxidant activity.	(Zhong & Shahidi, 2012)
Bulk oil **Mackerel oil**	N	αTOH	Considered as negligible	50-100-250-500	50-100 ppm > 250–500 ppm. -40°C > 4°C > 30°C.	No pro-oxidant activity.	(Zuta et al., 2007)
Emulsion o/w **Corn oil**	N	αTOH	Not evaluated	20	αTOH antioxidant (PV) after 15 days.	αTOH increased both PV (<15 days) and hexanal formation.	(Alamed et al., 2009)
Emulsion w/o **Refined sardine oil with lecithin/water**	N	δTOH	Not evaluated	500-1000-2000-3000-4000	δTOH, the effect was intensified with increasing the concentration	No pro-oxidant activity.	(Han et al., 1991)
Emulsion o/w **Fish oil**	N	γTOH	αTOH = 202 γTOH = 28	110-220-440-660-880-1100	γTOH reduced lipid oxidation above 440 ppm. Best antioxidant effect at 660 ppm.	γTOH: 110 ppm and 220 ppm for 6 weeks.	(Horn et al., 2009)
Emulsion o/w **Shark liver oil**	Y	αTOH	–	500	αTOH the best antioxidant tested for both primary and secondary oxidation compounds.	No pro-oxidant activity.	(Jayasinghe et al., 2013)
Emulsion o/w **Cod liver oil and mixture with rapeseed oil**	N	αTOH γTOH	**Cod liver**: αTOH = 330 **Rapeseed oil**: αTOH = 220, γTOH = 330	αTOH+γTOH: 260+360 αTOH: 220 γTOH: 165-330-60	γTOH inhibited oxidation more efficiently than αTOH. γTOH increased efficiency with increasing concentration (165, 330, 660 ppm). αTOH at 110 ppm.	TOH at high concentrations (590 ppm).	(Let et al., 2005)
Emulsion o/w **Refined cod liver oil and rapeseed oil**	N	γTOH	**Cod liver**: αTOH = 200, γTOH = 36 **Rapeseed oil**: αTOH = 220 γTOH = 365	22-88	γTOH: retarding oxidation. EDTA > γTOH > AP.	No pro-oxidant activity.	(Let et al., 2007)

(Continues)

TABLE 1 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Emulsion o/w **Canola oil/caprylic acid**	Y	αTOH	-	200	-	αTOH at 200 ppm (PV, anisidine, and total oxidation)	(Osborn-Barnes & Akoh, 2003b)
Emulsion o/w **Fish oil**	Y	αTOH	–	300	αTOH at 300 ppm.	No pro-oxidant activity.	(Pernin et al., 2019)
Emulsion o/w **Rapeseed oil**	Y	αTOH γTOH δTOH	-	500-1000-2500	δTOH> γTOH > αTOH. The effects were intensified with increasing amounts.	αTOH	(Wagner et al., 2004)
Emulsion w/o **Walnut oil**	Y	αTOH	–	4-40-200-400	Increasing concentration decreased hexanal formation (400 > 200 > 40 > 4), whereas for peroxide, the order of efficiency was 40 > 200 > 400 > 4.	No pro-oxidant activity.	(Yi et al., 2015)
Emulsion o/w **Human milk fat analogue + DHA+soybean oil**	N	αTOH	Not evaluated	50-200	αTOH at 200 ppm 21 day (hexanal)	αTOH at 200 ppm (PV and secondary oxidation products)	(Zou & Akoh, 2015)
Bulk/Emulsion o/w **Refined Menhaden oil**	N	αTOH δTOH	Not evaluated	Bulk: 431 Emulsion: 215	Bulk oil: αTOH > δTOH. Emulsion: δTOH > αTOH.	No pro-oxidant activity.	(Chaiyasit et al., 2005)
Bulk/Emulsion o/w **Linoleic acid, linoleic acid methyl ester, corn oil**	Y	αTOH	-	65-130	65 ppm > 130 ppm, in linoleic acid, for PV and hexanal formation. Antioxidant at both concentrations in methyl linoleate and in stripped corn oil. Emulsion > bulk (methyl linoleate and corn oil).	No pro-oxidant activity with linoleic acid and methyl linoleate systems. Pro-oxidant (hexanal) for αTOH 65 ppm at day 4, 60°C, for stripped corn oil in bulk.	(Huang, Hopia, et al., 1996)
Bulk/Emulsion o/w **Corn oil**	Y	αTOH	–	130 -500	αTOH at 130–500 ppm for both systems.	No pro-oxidant activity.	(Huang, Frankel, et al., 1996)
Bulk/Emulsion o/w **Corn oil**	Y	αTOH γTOH	-	100-250-500-1000	100 ppm: αTOH > γTOH. Higher concentrations: γTOH > αTOH. αTOH in bulk oil (best at 100 ppm), in emulsion (best 250–500 ppm). γTOH in bulk oil (250ppm<max activity<1000 ppm), in emulsion (no difference between 250–1000 ppm).	αTOH in Bulk oil: ≥ 250 ppm. Emulsion: 500 ppm.	(Huang et al., 1994)

(Continues)

TABLE 1 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initial (ppm)	Concentration added (ppm)	Antioxidant activity	Pro-oxidant activity	Ref.
Aqueous micellar system	–	αTOH	–	4000	αTOH at 4000 ppm.	No pro-oxidant activity.	(Aliaga et al., 2016)
Aqueous micellar system	-	αTOH	-	190-380-760-1900-3800-7600-19000-38000-76000	αTOH ≤ 7600 ppm.	αTOH > 7600 ppm. The antioxidant activity of αTOH (PV) may reverse to pro-oxidant activity with increasing concentration.	(Cillard & Cillard, 1980)
Aqueous micellar system	–	αTOH γTOH δTOH	–	76000	γTOH and δTOH.	αTOH.	(Cillard et al., 1980)
Liposomes **PC+cholesterol**	-	αTOH βTOH γTOH δTOH	-	20-40-60	δTOH is less effective than αTOH and γTOH. βTOH unable to prevent oxidation.	αTOH at high concentration (60 ppm).	(Valenzuela et al., 2002)
Liposomes/micelles **Methyl linolenate**	–	αTOH βTOH γTOH δTOH αT3 βT3 γT3 δT3	–	40	TOH and T3 have the same reactivity with radicals and the same antioxidant activity in both systems.	αTOH and αT3 reduced Cu(II) to Cu(I) and exerted pro-oxidant effect in the oxidation of methyl linoleate in SDS micelles.	(Yoshida et al., 2003)

Abbreviations: AP, ascorbyl palmitate; N, nonstripped oil; Y, stripped oil.

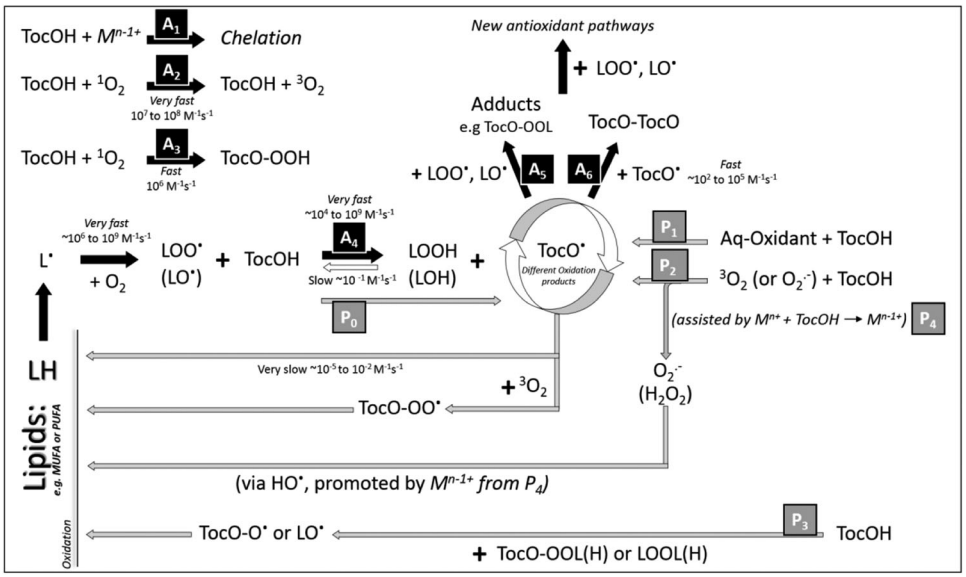

FIGURE 5 Chemical behavior of tocopherols and tocotrienols (TocOH) with respect to the lipid (LH) oxidation pathway (→ antioxidant pathway [A] and ← prooxidant pathway [P])

(Clough et al., 1979; Neely et al., 1988; Yamauchi & Matsushita, 1977). Such reactivity will consume TocOH. Moreover, TocO–OOH hydroperoxides formed in reactions with $^1O_2$ (Clough et al., 1979; Terao & Matsushita, 1980), along with α-tocopherol quinone, α-tocopherol hydroquinone, and tocopherol quinone-epoxide, were shown to promote LH autoxidation (Chapman et al., 2009; Jung & Min, 1992; Kim et al., 2007). The chemical reaction rates of TOH with $^1O_2$ were in the order of magnitude of 10^6 M^{-1} s^{-1} and followed the same order among isomers (Mukai et al., 1991). Subsequently, because the physical quenching kinetic rate is much faster, the quenching process was almost entirely "physical" and TOH deactivated about 120 $^1O_2$ molecules before being destroyed by chemical reaction (Mukai et al., 1991). Obviously, TocOH can also be strongly involved as a free radical scavenger. Most of the time, TocOH quickly transfers a phenolic hydrogen to a lipid radical. Such transfer results in a resonance-stabilized chroman-6-oxyl radical (TocO•) due to the donation of the TocOH phenolic hydrogen to a lipid radical (A_4).

In the induction period of lipid oxidation, TocOH mainly react with peroxy radicals (LOO•), and later with alkoxy radicals (LO•) that have appeared during the propagation period. The intensity of the oxidation parameters, the presence of other molecules nearby, the delocalization of the unpaired electrons that produce radical sites at different positions (*ortho-* and *para-*), and the different possible rearrangements modify the fate of TocO•. For instance, the oxidation of TocOH in presence of water may form many oxidation products by different pathways because electron mobility is enhanced compared to that observed in the lipid phase. In bulk oil, when TocO• are present with other lipid radicals (e.g., LOO• or LO•), the latter are mainly involved in radical–radical coupling (A_5); such coupling results in the formation of different adducts such as TocO–OOL. TocO• tend to react mainly by radical–radical self-coupling (A_6), and dimeric tocopherol products (TocO–TocO) are formed when any other lipid radicals are present. Moreover, α-analog was found to have a low rate constant in the dimerization process (~10^2 M^{-1} s^{-1}) that is presumably due to the steric hindrance of the chromane moiety (two ortho-methyl substituents) to the approach of two TocO• to form the dimer (Lucarini et al., 1994). An important consequence of this slow rate of dimerization is that α-TO• or α-T3O•, which are formed at very low concentrations, will live long enough to trap a second peroxyl radical (A_5). Regardless of the antioxidant pathways, the oxidized tocopherol adducts that are formed may react again with new lipid radicals. This would, in addition, explain the higher activity of γ- or δ-analogs compared to α- and β- in many in vitro systems (Chaiyasit et al., 2005; Fuster et al., 1998; Huang et al., 1995; Wagner et al., 2004), because the former can be dimerized into compounds that may still be effective antioxidants (Kamal-Eldin & Appelqvist, 1996).

Like all antioxidants involved in slow lipid oxidation, TocOH are mainly involved to reduce lipid radicals, and therefore to be oxidized. When this action is limited due to lipids radicals or radical–radical coupling that catches hydrogen(s) or electron(s), this mainly yields an antioxidant response. Yet, antioxidants and/or their oxidized forms may be exposed to other side reactions and react with relatively stable molecules (e.g., molecular oxygen, lipid molecules, and lipid hydroperoxides), which may lead

to a prooxidant response. Generally, a molecule is categorized as prooxidant when its presence triggers an increase in the total radical yield in the system under study. In vitro, this usually happens when the concentrations of primary (hydroperoxide: LOOH) or secondary (aldehydes, ketones, epoxides, etc.) lipid oxidation products increase. In addition, the production of reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radicals often also increases. This usually happens after the rate of lipid peroxidation is stimulated chemically or parallel antioxidant reactions are inhibited. The degree of such reactions is mostly determined by the structure of the antioxidant, its concentration, and the nature of neighboring molecules. There is no doubt that TocOH play a predominant role in the protection of lipids. However, they may also be involved in oxidation routes and, in this case, cause oxidative damage. It is generally accepted that the prooxidant effect of TocOH occurs when TocOH are present at high concentrations associated with the capacity of TocO• to promote or participate in a number of undesirable side reactions (Martin-Rubio, Sopelana, Ibargoitia, et al., 2018). Below are the five reaction mechanisms hypothesized to be behind the prooxidant effects of TocOH:

1. From the reactions of TocO• with lipid hydroperoxides (LOOH) or nonperoxidized LHs: At high concentrations of TocOH, it is unlikely that the reverse reactions (A_4) of TocO• with LOOH have a prooxidant effect because of (i) the higher concentration of unoxidized TocOH compared to TocO•, which shifts the reaction toward A_4, and (ii) the much slower rate of the prooxidant effect compared to A_4, A_5, and A_6 (Becker et al., 2004; Burton & Ingold, 1981; Mukai et al., 1993). However, under certain conditions, TocO• could trigger propagation chains upon H abstraction from LH, leading to an increase in peroxides (LOO•) in the system after competitive and rapid reaction with triplet oxygen (P_0). As the rate is very slow ($\sim 10^{-5}$ to 10^{-2} M^{-1} s^{-1}) (Mukai et al., 1993), the ability of TocO• to give off the radical chain thanks to a reaction with LH in the vicinity has to be combined with its inability to escape and to react with other radicals (e.g., TocO•, LOO•, LO•). Therefore, LH oxidation could also be initiated by TocO• after oxidation reactions of TocOH with attacking aqueous radicals (P_1), residing at, or near, the surface of association colloids in bulk oil, or at the interface of micelles and oil droplets in emulsions. Yet TocOH-mediated peroxidation would not display significant prooxidative behavior in the presence of water-soluble antioxidants such as ascorbic acid (AA), because AA would quickly reduce TocO• to TocOH (Bowry & Stocker, 1993).
2. From the generation of superoxide radical anions ($O_2•^-$) or radical coupling, after reaction of TocOH with triplet molecular oxygen ($^3O_2$): Like most organic compounds, the direct reaction of TocOH with $^3O_2$ is spin-forbidden. Therefore, this way is much less often followed than the way involving hydroperoxides. $^3O_2$ can, however, react with radicals released from TocOH, thereby explaining the prooxidant effect of TocOH. Although very slow, this effect may arise after radical coupling of TocO• with $^3O_2$, leading to TocO–OO• (from P_0, P_1, P_2, P_4). Another prooxidant activity of tocopherols is based on a sum of reactions involving the reduction of $^3O_2$ (P_2). The first step of autoxidation is the one-electron oxidation forming the radical intermediate and the superoxide radical ($O_2•^-$) (or HO_2• under acidic pH, $pK_a = 4.88$). This reaction is endothermic and kinetically unfavorable, with a very slow kinetic rate likely due to the low redox potential of the $O_2/O_2•^-$ couple (−0.33 V at pH 7, 10^5 Pa) (Wood, 1988) and the spin restriction between the reactants. However, in presence of transition metals (such as $M^{n+} = Cu^{2+}$, Fe^{2+}) the one-electron oxidation of TocOH may be substantially enhanced (P_4). Indeed, transition metals, which exist in several spin states, may reduce the spin restriction issue and thus act as catalysts in this process. According to the redox potential involving one-electron transfer (0.89 V, pH 7), the superoxide radical generated ($O_2•^-$) becomes a stronger oxidant. Thus, tocopherols can more easily be involved as electron donors to $O_2•^-$ (**P_2**) leading to the production of hydrogen peroxide (H_2O_2), which is one of the active oxygen species and a precursor of the strongest known oxidizing agent (HO•). The harmful activity of H_2O_2 is not really due to its intrinsic reactivity, but to the subsequent formation of HO• under the action of energetically favored metal reduction.
3. From the decomposition of LOOL(H) or TocO-OOL(H) after reactivity with TocOH (**P_3**): The diffusion of autooxidation reactions by the peroxide is due to the decomposition of LOOH via unimolecular or bimolecular mechanisms. At low to moderate temperatures (<40°C) that favor hydrogen bonding, lipid peroxides can catch hydrogen atom of TocOH, along with the TocO–OOL (or TocO–OOH) adducts, leading to stable lipid alkoxides (LOH) and alkoxy LO• or TocO–O• radicals. In addition to the competing reactions of scission and internal rearrangement that are also fast, these unstable radicals are rapidly prone to abstract a hydrogen atom from LH. Still, these radicals would be neutralized in presence of large amounts of TocOH, and should thus not have a significant prooxidative effect in the early stage of autoxidation. However, the prooxidant effect of TocOH may be enhanced at 40°C by the presence of high levels of hydroperoxides (between 0.45 and

1.43 mol% of peroxide) (Hicks & Gebicki, 1981). Moreover, if the conditions are fulfilled, the decomposition of LOOH from α-TocOH is predicted to be the fastest due to its ability to give its phenolic hydrogen.

4. From the reduction of metal transition (P_4): TocOH and TocO• radicals may also cause the reduction of transition metal ions into low-valent species (e.g., Fe^{3+} to Fe^{2+}) liable to increase the overall yield of radicals through the Fenton reaction (HO•) from H_2O_2 or Fenton-like reactions (LO•) from LOOH or TocO–LOO adducts or to assist the generation of superoxide radical anions ($O_2•^-$). Theoretically, γ- and δ-TOH and T3 should have weaker prooxidant effects than other analogs because of their lower reduction effects on metal transitions, lower reactivity with $O_2•^-$, and the formation of dimerizable compounds that are still active antioxidants, along with the formation of lipid hydroperoxide adducts (e.g., 5-(peroxy)-γ-tocopherone) that will dissociate to become quinone and alkyl alcohol (LOH) (Jung & Min, 1992; Kamal-Eldin & Appelqvist, 1996). Furthermore, the reason for the contradiction between the effectiveness of TocOH and the balance between antioxidant and prooxidant pathways in different experiments cannot only be the presence and the proportion of TocO• radicals. These chemical pathways are most probably significantly affected by dissimilarities in the physical parameters of the system and/or different chemical factors.

2.3 | Major factors affecting tocopherol reactivity

Several intrinsic factors (fatty acid composition and quality of oils, presence of co-antioxidants vs. prooxidants, etc.) and external factors (duration of storage, temperature, etc.) may influence the antioxidant effect of TocOH. We examined 15 studies to evaluate and compare the antioxidant and prooxidant effects of TocOH in bulk oils.

PCA (principal component analysis) provided an overview of all the results obtained by different authors for all TocOH (data not shown). The selected articles listed in Table 1 met the following criteria and had the most common parameters as variables, temperature, and length of storage, concentration of TocOH, and analysis of primary and secondary oxidation products. Restrictions were applied to limit the area of analysis, that is, the maximum added concentration for isoforms was 2000 ppm and the maximum peroxide value (PV) was 100 meq O_2/kg.

The model was based on PV, inhibition of formation of hydroperoxide (IP), the concentration of added isoforms, the length and temperature of storage, and the presence of polyunsaturated fatty acids (PUFA) in oils. As additional variables, we also considered the inhibition of both the *p*-anisidine and hexanal value and the presence of saturated fatty acids, monounsaturated fatty acids, and PUFA in oil. Four components were necessary to describe variations in the model. The first two principal components (PC1 and PC2) explained approximately 63% of the variance in the dataset for the TocOH models in both stripped and unstripped oil.

First, PC1 and PC2 explained 32.87% and 30.37% of variance, respectively. The PCA loadings plot showed that the concentration, the temperature, and PV were correlated and were located in the positive direction of PC1. Conversely, IP was inversely correlated with the others and was located in the negative direction of PC1. IP was also inversely correlated with storage and was located in the positive direction of PC2. The loading plot revealed no isoform clusters. However, this analysis is difficult to interpret, as most authors only treated α-TOH, not all TocOH. Last but not the least, the standard radical chain reaction of lipid oxidation put pressure on the scientific community to examine and evaluate antioxidant efficiency in bulk oils or in emulsions almost only by evaluating LOOH and/or secondary oxidation products (mostly aldehydes). Standard nonspecific methods such as headspace oxygen content, conjugated dienes, or *p*-anisidine value were also used. In addition, a competition between the hydrogen abstraction and many other reactions for LOO• and LO• radicals exists. These radicals, along with LOOH, undergo reactions in parallel and at rates competitive with H atom abstractions that need to be integrated to fully account for the extent of lipid oxidation and hence, to more accurately estimate the efficiency of the antioxidant (Schaich, 2020). A very restrictive analysis of oxidation products could thus introduce a bias in the results because the mechanism pathways and the different classes of oxidation products are not affected by the addition of an antioxidant (e.g., TocOH) in the same way (Huang, Hopia, et al., 1996; Martin-Rubio, Sopelana, & Guillen, 2018; Martin-Rubio, Sopelana, Ibargoitia, et al., 2018). For instance, in addition to its ability to influence the mechanism of autoxidation at high concentrations (Terao & Matsushita, 1986), α-TocOH was found to accelerate the formation of LOOH at higher concentrations in the early stages of oxidation in both bulk and emulsion systems, although on the contrary, it inhibited hexanal formation more strongly (Huang et al., 1994). This ambiguity underlines the importance of using more than one method to determine antioxidant activity. PV, in addition to volatiles such as aldehydes, is still the most convenient approach to roughly estimate oxidative stability, but a systemic approach including monitoring the different types of oxidation compounds would provide more precise data to determine the effect and compare antioxidants with respect to the lipid oxidation mechanisms.

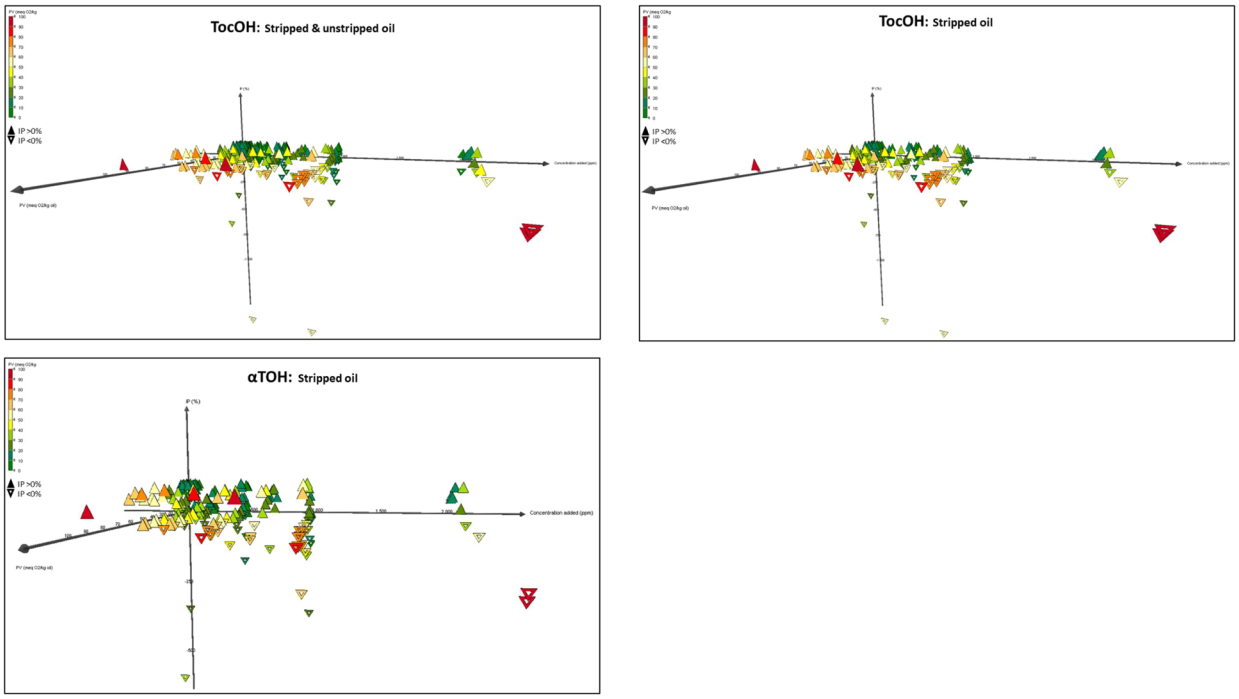

FIGURE 6 Inhibition of hydroperoxide (%) according to the added concentration of TocOH or α-TOH (ppm) and PV (meq O_2/kg oil) in bulk oil. Δ IP > 0%; V IP < 0%. IP = [(hydroperoxide formed in control – hydroperoxide formed in the sample)/hydroperoxide formed in the control] × 100

As mentioned above, the prooxidant effects of TocOH (particularly α isoforms) are known to predominate when high concentrations of TocOH are present in oils. Thus, concentration is a critical parameter. However, the most effective dose of TocOH beyond which their antioxidant activity will switch to prooxidant remains unclear. For example, Jung and Min (1990) reported that the maximum concentration for TocOH to be an antioxidant depends on the nature of the isoform, that is, 100, 500, and 1000 ppm for α, γ, and δ, respectively. Thus, the CC of each TocOH needed for maximum stability depends on the system. To investigate the effect of the concentration in more detail, we produced a three-dimensional representation from data collected with the PCA from 13 representative articles that dealt with antioxidant and prooxidant activity of TocOH in bulk oils (Figure 6). We represent the antioxidant response (normalized in % IP) according to the added concentration of TocOH (normalized in ppm) at different stages of oxidation (normalized with PV). A positive *y*-axis value (% IP) indicated antioxidant activity of TocOH, whereas a negative value indicated prooxidant activity. The first graph shows the response of all isoforms (A), the second, all stripped isoforms, and the last one (C), only the stripped α-TOH.

As shown, most of the experiments analyzed were performed at a concentration ranging from 0 to 1000 ppm, and at all the concentrations tested (up to 2000 ppm), TocOH showed both antioxidant and prooxidant activities. Nevertheless, no clear consensus emerged on a threshold, or on a clear decrease in antioxidant capacity only based on the increasing concentration parameter. A similar interpretation was made of the data collected with stripped oils, for which the representation of TocOH concentrations was more precise, along with concentrations obtained with only α-TOH, which represented 75% of the data. Indeed, the presence of endogenous TocOH in unstripped oils may lead to errors in interpreting the results. For example, adding 200 ppm of α-TOH in bulk and emulsified rapeseed oil that already contained 669 ppm of native tocopherols did not improve the antioxidant effect. In contrast, adding the same quantity (200 ppm) in the same stripped rapeseed oil produced an effective antioxidant effect (Samotyja & Małecka, 2007). Similarly, α-TOH had no prooxidant effect when added at very high concentrations (e.g., 2000 ppm) for the protection of sunflower or rapeseed oils that were previously purified in order to remove native TOH and traces of metals and pigments (Kamal-Eldin & Appelqvist, 1996).

Yet, by analyzing the data with the third dimension (PV), we identified a zone where antioxidant activity of TocOH strongly predominates, whereas beyond this zone, the prooxidant effect prevails (Figure 7). Indeed, up to a value of about 200 ppm, TocOH exhibited almost exclusive antioxidant activity; beyond that, their activity very often switched to prooxidant, except very low levels of oil oxidation (PV < 10).

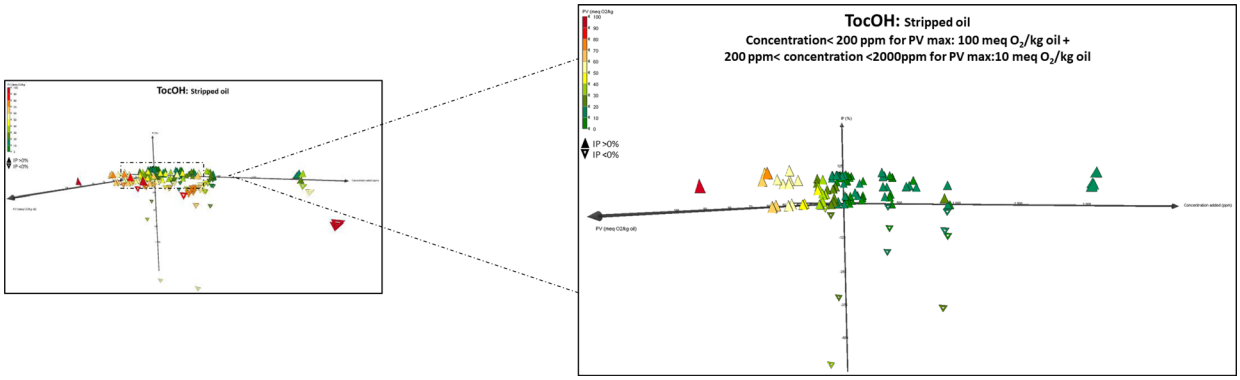

FIGURE 7 Inhibition of hydroperoxide (%) as a function of the added concentration (ppm) of TocOH and PV (meq O_2/kg oil). For a maximum concentration of 200 ppm, PV max = 100 meq O_2/kg and for concentrations between 200 and 2000 ppm, PV max = 10 meq O_2/kg oil. Δ IP > 0%; V IP < 0%. IP = [(hydroperoxide formed in control – hydroperoxide formed in sample)/hydroperoxide formed in control] × 100

Thus, below a concentration of around 200 ppm, the chances of obtaining antioxidant activity regardless of the oxidation state are extremely high. In this region, the antioxidant variation and intensity between experiments and isoforms varies with the internal (pH, water activity [a_w], etc.) and external physicochemical factors (light, temperature, etc.). For example, Kim et al. (2015) showed that for the same concentration (84 ppm), the antioxidant capacity of TOH depended on the water content (Kim et al., 2015). Because water contains prooxidant molecules such as metals, it is involved in the chemistry of lipid oxidation. Indeed, water-soluble prooxidants such as metals are key actors of the oxidation pathways (Barden & Decker, 2016). High a_w increases the mobility of the transition metal, and consequently its probability of being in contact with and reduced by TocOH. On the other hand, water may promote the interaction and possible regeneration of lipophilic TocOH at the interface with water-soluble antioxidants, or protect against hydroperoxide decomposition. The protection process relies on the solvation of the hydroperoxides and on the hydration of metal catalysts (Chen et al., 1992). Temperature was also reported to influence lipid oxidation pathways and TocOH efficiency. $\alpha > \beta > \gamma > \delta$ TocOH was reported to be the order of antioxidant efficiency under low to mild temperatures. At high temperatures (>60°C), however, a reverse order was obtained $\alpha < \beta < \gamma < \delta$ (Lea & Ward, 1959; Rao & Achaya, 1967). Temperature is assumed to affect the reaction kinetics (e.g., radical reactions between the antioxidant and the lipids) because it can reduce the viscosity of the medium, increase the mobility of the molecules (e.g., T°C > T_{fusion}°C of lipids), break hydrogen bonds, and promote the formation of hydrophobic bonds. In addition, the stability and solubilization of molecules (e.g., antioxidants and hydroperoxides) along with the organization and stability of colloidal structures can be modified. In general, increasing the temperature has a negative effect on lipid oxidation by reducing the stability of the antioxidant, and accelerating the decomposition rate of hydroperoxides and reactivity with metal transitions (O'Brien, 1969). However, some authors found that temperature positively affected α-TOH efficiency (Marinova & Yanishlieva, 1992). One possible explanation is that increasing the temperature reduced the solubility of oxygen in oils, resulting in a lower formation rate of the autoxidative peroxide (prooxidant effects of P_0, P_1, P_2, P_4; Figure 5) that is slowly replaced by other antioxidant reactions (e.g., A_4, A_5, A_6, Figure 5). The inversed response (from antioxidant to prooxidant) is assumed to be related to the redox potential of TocOH. The redox potential can theoretically be linked to the capacity of the O–H bond to dissociate (homolytic fission). As previously explained, it is dependent on the structure of TocOH, and it is suspected that δ isomers with higher reduction potential will show inversion of activity at higher concentrations than those with lower reduction potentials (γ, β, α). So, experiments conducted in the same condition and with the equal concentrations of TocOH may show that the concentrations of the TocO• should follow the same order, α- being the earliest prooxidant. To cite one example, Jung and Min (1990) observed that α-TOH (500 ppm in soybean oil) showed a prooxidant capacity, whereas γ-TOH had no noticeable effect, but δ-TOH had an antioxidant effect. Yet, when TocOH are added to bulk oils or lipid dispersions at the best concentrations to obtain the best efficiency of antioxidants, the order of antioxidant ability should be as follows: $\alpha > \beta > \gamma > \delta$. Thus, each TocOH has a CC for maximum stability that is system dependent. Moreover, the switch in TocOH activity also depends on the presence of compounds such as transition metal ions or other oxidizing agents that are needed to assist the prooxidant response. Thus, regarding the TocOH chemical pathways (Figure 5), a systematic increase in TocOH concentration up to thousands of ppm is not required, rather its concentration needs to be optimized. In our opinion,

TocOH (particularly α-TocOH) should be added at the lowest concentration possible so that the probability to form TocO• radical from P_1, P_2, P_3, and P_4 (Figure 5) is reduced.

Interestingly, among the pool of publications we analyzed, we noticed that, beyond 200 ppm the antioxidant activity of TocOH was strongly preserved at low PVs (<10 PV). Therefore, it is difficult to imagine that the involvement of TocO• radicals is the main explanation for this change in the response. Another possible explanation is the capacity of oxidizing agents (e.g., LOOH) to assist the prooxidant activity of TocOH through physical (P_1, P_2, P_4) or physicochemical interactions (P_3). This underlines the need to understand the distribution of antioxidants and their interaction with oxidant species in complex systems such as emulsions. Indeed, in emulsions, different phases coexist, and the physical organization of the environment becomes more important than the reactivity of the various molecular species involved in the lipid oxidation reaction. Porter (1993) with "the polar paradox theory" set the quite counter intuitive hypothesis that nonpolar antioxidants are better antioxidants in system presenting high interfacial surface (e.g., emulsion), whereas polar or hydrophilic antioxidants have better efficacy in bulk oil system presenting low surface-to-volume ratios of lipids (Figure 2). The study of Frankel et al. (1994) supports this paradoxical hypothesis by demonstrating that hydrophilic antioxidants (in their study: Trolox and AA) stabilized better bulk oil system than oil-in-water emulsion. The same study also demonstrated the opposite tendency for lipophilic derivatives (α-TOH and ascorbyl palmitate). This paradox can be mainly explained by the opposite distribution behavior of polar or nonpolar antioxidants in multiphasic systems. Indeed, in such systems, their partition, diffusion into the interphase, and putative vicinity with anti- or prooxidants differ. Castle and Perkins (1986) suggested that the antioxidant capacity of α-TOH in micellar systems is restricted because its inter-micellar diffusion, that is, its capacity to visit each micelle, is slower than the lifetime of peroxy radicals to circulate from one micelle to another. In this continuum of interphase diffusion, micelles could take part in lipid oxidation process, by conveying some important actors of the process such as surface-active molecules, antioxidants, and lipid oxidation products (such as hydroperoxides) (Li et al., 2020). In the same way, it is very likely that TocOH efficiency is modulated by its putative interaction with the micellar phase of the system. Furthermore, this micellar phase may be influenced by the concentration of TocOH, because the number of *ortho* methyl substituents in the phenolic rings (2, 1, and 0 in α-, γ-, and δ-tocopherol, respectively) takes part in the formation of co-micelles with other surfactant molecules. In addition, unlike the chromanol moiety that is similar among TocOH and is responsible for the chemical reactivity, the phytyl tail could result in greater dissimilarity between TOH and T3, as has been observed, for example, with T3, which appeared to be more readily incorporated into liposomal membranes (Yoshida et al., 2007). In addition to its physical structure, the polarity of the medium can also influence the antioxidant/prooxidant reactivity of TocOH via the electrostatic interaction effect. For example, hydrogen bonding with the phenolic group may reduce their antioxidant capacity in protic environments (Iwatsuki et al., 1994), resulting in higher prooxidant effect of α-TOH in aqueous media than in aprotic and nonpolar solvents such as hexane (Cillard & Cillard, 1980; Cillard et al., 1980; Sumarno et al., 1987).

3 | CHEMICAL INTERACTION OF TOCOPHEROLS WITH OTHER MOLECULES

The presence of other molecules (e.g., phenolic compounds, vitamin C, carotenes, proteins and peptides, phospholipids, etc.) that interact with TocOH either directly or indirectly may influence their effectiveness with respect to lipid oxidation (Figure 3).

3.1 | Interactions with other antioxidant molecules (from antagonism to additive and synergistic effects)

When several antioxidant molecules are present in an oxidizing lipid media, the total antioxidant capacity may be lower (antagonism), equal (additive), or higher than the sum of their individual effects (the so-called synergistic effect). Antagonism has been shown between α-TOH and phenolic compounds such as rosmarinic acid and caffeic acid (Peyrat-Maillard et al., 2003; Samotyja & Małecka, 2007), as well as with plant extracts rich in polyphenols (Banias et al., 1992; Hraš et al., 2000). Antagonism can be the result of (i) the regeneration of the less effective antioxidant by the more effective antioxidant, (ii) the oxidation of the more effective antioxidant by the radicals of the less effective antioxidant, (iii) competition between the formation of antioxidant radical adducts and regeneration of the antioxidant, and (iv) alteration of the microenvironment of one antioxidant by another antioxidant (Mortensen & Skibsted, 1997a, 1997b; Peyrat-Maillard et al., 2003). However, antagonism mechanisms are not frequently documented, because co-addition of antioxidants usually yields additivity, and even synergism, with respect to lipid oxidation (Table 2). Three main mechanisms could explain the transition from an additive to a synergetic effect with TocOH:

TABLE 2 Interaction and effects of the interaction in bulk or emulsion systems

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Bulk oil **Sunflower oil**	N	αTOH	598		AP	Preserved αTOH.	(Beddows et al., 2001)
Bulk oil **Cod liver oil**	**N**	αTOH	1100	100-500-900	AP, PC, lysine	Synergistic effect: 200ppm αTOH + 100ppm AP, 9000ppm PC, 1000ppm Lysine	(Budilarto & Kamal-Eldin, 2015a)
Bulk oil **Sunflower oil**	**Y**	αTOH γTOH	–	200-600-1000	Mixture of TocOH, metal transition (Fe)	No synergistic or antagonistic interaction was observed when αTOH and γTOH were added together. γTOH is a more efficient antioxidant than αTOH possibly because of the latter's ability to participate in reactions other than those with peroxyl radicals, especially in the presence of trace metal ions.	(Fuster et al., 1998)
Bulk oil **Refined fish oil**	**N**	αTOH γ/δTOH δTOH	Not evaluated	2000-20000	AP, lecithin	Synergistic effect with binary mixtures of lecithin-γ/δ or δTOH. Highest synergism observed with ternary mixture of AP /lecithin/δTOH (20000 ppm)	(Hamilton et al., 1998)
Bulk oil **Sunflower oil**	Y	αTOH	–	100	Rosemary extract	The calculated synergism of rosemary extract and TOH is -0.21%. αTOH reduced the antioxidant effect of rosemary extract, however rosemary extract increased the stability of αTOH.	(Hraš et al., 2000)
Bulk oil **Snflower oil**	Y	αTOH	-	43	4-methylcoumarins and related compounds, AA	Binary mixtures with TOH showed higher lipid oxidative stability than the individual compounds. All ternary mixtures showed synergism:continuous regeneration of αTOH from the antioxidants and AA	(Kancheva et al., 2018)
Bulk oil **Rapeseed oil**	Y	αTOH γTOH	–	5-10-50-100-500	Mixture of TocOH	No pro-oxidant activity of either TOH alone or in a mixture. Addition effect but not synergism. Added separately, γTOH was oxidized before αTOH but in a mixture, γTOH was stable until the αTOH had been consumed.	(Lampi et al., 1999)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Bulk oil **Cod liver oil**	Y	αTOH βTOH δTOH	-	αTOH = 62 βTOH = 342 δTOH = 157	Mixture of TocOH + AP	Mixture of TOH + AP reduced the formation of herring oil odor and flavors. Several groups of volatile oxidation products (i) promotion by TOH, inhibition by TOH+AP (*trans*, *cis* 2,4 heptadienal), (ii) inhibition by TOH and TOH+AP (1-penten-3-ol and 2-propenal), (iii) inhibition by both TOH + AP > TOH (acetic acid), (iv) promotion by both TOH >TOH+AP (2-hexenal)	(Olsen et al., 2005)
Bulk oil **Sunflower oil**	Y	αTOH	–	43-215-430-860-2150-4300	AP	Synergism for αTOH + AP in different ratios (1:1, 1:5 and 1:10) at concentration 430 ppm of αTOH was obtained. Highest synergism at the ratio 1:10 (55.4%) > ratio 1:5 (47.6%) > 1:1 (42.4%). At the lowest concentration (43 ppm) of αTOH only equimolar (1:1) showed synergism (38.1%).	(Slavova-Kazakova A, 2017)
Bulk oil **Purified methyl linoleate**	Y	αTOH	-	1000-10000	AP	Addition of AP containing αTOH inhibited the formation of hydroperoxides almost completely for up to four days. During this period, *cis-trans* hydroperoxides were mostly produced in the same way as when αTOH was used alone.	(Terao & Matsushita, 1986)
Bulk oil **Soybean, sunflower oil**	Y	αTOH βTOH γTOH δTOH	–	Soybean oil: αTOH = 610 βTOH = 10 γTOH = 30 δTOH = 10 Sunflower oil: αTOH = 120 βTOH = 10 γTOH = 610 δTOH = 260	Mixture of TocOH	The typical TOH profile of soybean oil reduced the PV and volatiles in the dark, in comparison to theTOH profile of sunflower oil. Inversely, the TOH profile of sunflower oil inhibited photooxidation	(Warner, 2005)
Bulk oil **Mixed purified fish oil and red or yellow palm olein**	N	αTOH αT3 γT3 δT3	Red palm olein: αTOH = 242 αT3 = 266 γT3 = 367 δT3 = 80 Yellow palm olein: αTOH = 237 αT3 = 265 γT3 = 349 δT3 = 77	-	AP	AP reduced the losses of αTOH and αT3	(Yi et al., 2011)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Butter oil **Butter oil**	Y	αTOH	–	10-25-50	β-carotene, AP	Binary mixture: β-carotene (5 ppm) + αTOH (50 ppm). Highest antioxidant protection with ternary mixture of β-carotene (5 ppm) + αTOH (50 ppm) + AP (50 ppm).	(Karabulut, 2010)
Emulsion w/o **Sunflower oil and palm stearine**	Y	Mix: αTOH γTOH δTOH	-	100-200-250-500-1000	Rosemary extract + lecithin.	200 ppm rosemary + 200 ppm mixed TOH + 1000 ppm lecithin: substitutes for tert-butylhydroquinone to maintain the quality and increase the shelf life of margarine	(Azizkhani & Zandi, 2009)
Emulsion w/o and o/w **Algae**	N	αTOH γTOH δTOH	Not evaluated	–	AA, grape seed extract	Synergy between AA and grape seed extract with αTOH and γTOH	(Chen et al., 2016)
Emulsion **Methyl eleostearate**	Y	αTOH	-	323	AA, G0, (-)EC, EGCG	Synergism with AA. Antagonist interaction with G0, EC and EGCG.	(Durand et al., 2015)
Emulsion o/w **Sunflower oil**	**N**	αTOH βTOH γTOH δTOH	Not evaluated	250 (αTOH = 15.4%, βTOH + γTOH = 59.1%, δTOH = 25.5%)	Green tea extract	Combination of green tea extract (250 ppm) and mixture of TOH (250 ppm) improved (synergistic effect) the antioxidant efficacy compared to individual extracts.	(Ghorbani Gorji et al., 2019)
Emulsion w/o **Sardine oil**	**N**	δTOH	Not evaluated	500-1000-2000-3000-4000	AA	Combination between AA (2000 ppm) and δTOH (4000 ppm): improved (the synergistic effect) the induction period	(Han et al., 1991)
Emulsion o/w **Rapeseed oil (64%) + Fish oil (16%)**	**N**	αTOH γTOH	**Rapeseed oil** αTOH: 231, γTOH: 453 **Fish oil** αTOH: 87, γTOH: 10. + Content in A/L/T mixture	200 (Grindox 1032). 20–40 (Toco70) with distribution of αTOH 16 %, β/γTOH 58 %, and δTOH 26 % w/w	AA, lecithin. Surfactant: Panodan TR (diacetyl tartaric acid ester of mono- and di-acylglycerols of fatty acids)	AA/lecithin/TocOH decreased PV but promoted the formation of fishy and rancid off-flavors in mayonnaise, irrespective of which phase they were added to. The prooxidative effect was partly due to the ability of ascorbic acid to promote iron-catalyzed breakdown of lipid hydroperoxides. Emulsifier (Panodan TR) apparently did not affect the activity of the different TocOH mixtures, but interacted differently with the TocOH mixtures, thereby affecting the physical composition and rheological properties of the mayonnaise.	(Jacobsen et al., 2000)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Emulsion o/w **Rapeseed oil (64%) + Fish oil (16%)**	**N**	αTOH βTOH γTOH δTOH	**Refined rapeseed oil** αTOH: 288, βTOH: 102, γTOH: 496, δTOH: 8 **Fish oil** αTOH: 117	20-40-70-140-280 (Grindox 1032). 20–40 (Toco70) with distribution of αTOH 16 %, β/γTOH 58 %, and δTOH 26% w/w	Mixture of TocOH	The effect of low concentrations of Toco 70 on oxidation was ambiguous, as it depended on the parameter used to evaluate antioxidant efficacy. Low concentrations of Grindox 1032 exerted a weak antioxidative effect. Both high and low levels of Grindox 1032 decreased droplet sizes and increased the values of the rheological parameters. Additional TocOH did not appear to be an efficient antioxidant in fish oil-enriched mayonnaise, perhaps because it cannot prevent the metal-catalyzed decomposition of peroxides	(Jacobsen et al., 2001)
Emulsion o/w **Soybean oil**	Y	αTOH γTOH δTOH	–	600	Peppermint extract	Antioxidant activity (PV): γTOH or δTOH + peppermint > αTOH + peppermint. Anisidine values for all the combinations were better than the control or peppermint alone. Interaction between polyphenol of peppermint and γTOH and δTOH	(Kim & Choe, 2019)
Emulsion o/w **Soybean oil**	Y	αTOH	-	12.9	Rosmarinic acid	Strong synergistic antioxidant activity: rosmarinic acid + αTOH at pH7. Rosmarinic acid regenerates αTOH. A drop in pH from 7 to 3 reduced the synergistic effect. An additive effect was obtained at pH 3.	(Kittipongpittaya, Panya, Phonsatta, et al., 2016)
Emulsion o/w **Refined cod liver oil + rapeseed oil**	**N**	γTOH	**Cod liver** αTOH = 200 γTOH = 36 **Rapeseed oil** αTOH = 220 γTOH = 365	22-88	AP, EDTA	γTOH: retarding oxidation Mixture of γTOH+AP+EDTA: best inhibition of oxidation	(Let et al., 2007)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Emulsion o/w **Milk, refined cod liver oil and (stripped or not) rapeseed oil**	Rapeseed oil: Y Milk and fish oil: N	αTOH γTOH	**Milk** αTOH = 17 **Fish** αTOH = 330 **Rapeseed oil** αTOH = 220 γTOH = 330 **Fish and rapeseed mixture** αTOH = 275 γTOH = 150	Adding TOH AP and oil before emulsification into milk: αTOH: 260, βTOH: 40, γTOH: 360. Adding the different antioxidants to fish oil before emulsification into milk: αTOH: 260, γTOH: 360.	AP	Adding TOH, AP and oil before emulsification into milk: PV: Fish oil+ stripped rapeseed oil+AP increased antioxidant activity during 12 days of storage Adding the different antioxidants to fish oil before emulsification into milk: AP+TOH+EDTA = AP+TOH>>TOH+EDTA>TOH.	(Let et al., 2005)
Emulsion o/w **Canola oil/caprylic acid**	Y	αTOH	–	100-200	Citric acid	Adding αTOH or a combination of the αTOH and citric acid slowed down the formation of hydroperoxides and their subsequent decomposition products in pH 3.0 emulsions in copper catalyzed oxidation. No synergism between the two.	(Osborn-Barnes & Akoh, 2003a)
Emulsion o/w **Canola oil/caprylic acid**	Y	αTOH	-	**100**	β-carotene, genistein, daidzein. Surfactant (sucrose fatty acid ester, WPI)	Combination of αTOH + β-carotene, αTOH + daidzein, and αTOH + genistein exhibited pro-oxidant behavior in primary, secondary, and/or total oxidation in emulsions stored at 50°C for 15 days. No effect of surfactant, except lower oxidation in WPI emulsions.	(Osborn-Barnes & Akoh, 2003b)
Emulsion o/w **Soybean oil**	**Y**	αTOH	–	12.9	R0, R4, R12, R20	αTOH+ R0 or (R4-R12-R20): antioxidant Interaction between R0 and αTOH in surfactant micelles and O/W emulsions. Synergism between the two.	(Panya et al., 2012)
Emulsion o/w **Fish oil**	Y	αTOH	-	**300**	Eugenol, WP	αTOH + WP: increased antioxidant stability eugenol+ αTOH: no significant antioxidant activity.	(Pernin et al., 2019)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Emulsion o/w/ and w/o/w **Olive oil-linseed oil**	**N**	αTOH	Not evaluated	–	Polyphenols in olive oil	αTOH content did not change during the accelerated oxidation of olive oil emulsions, rather a slight increase in the content was observed in the case of O/W emulsions. Hypothesis: synergism αTOH +polyphenols in which olive oil is rich.	(Poyato et al., 2013)
Emulsion o/w **Olive oil and linseed oil (1/1)**	N	TocOH (not precise)	Not evaluated	1000-2000-3000-4000-5000	Catechol	Catechol + TocOH: effective in protecting the PUFA	(Wang et al., 2018)
Emulsion o/w **Corn oil**	Y	αTOH	–	12.9	G0, G3, G8, G12	Synergistic antioxidant activity with αTOH and G3 >G12, G8 and G0. The result of the regeneration of αTOH during O/W emulsions storage with the addition of G0 or G3, G3 could be involved in the regeneration of αTOH from αTOH quinine, while G0 could not.	(Wang et al., 2019)
Emulsion o/w **Human milk fat analogue + DHA+ soybean oil**	N	αTOH	Not evaluated	50-200	β-carotene	A synergistic antioxidant between αTOH and β-carotene	(Zou & Akoh, 2015)
Bulk oil **Sunflower oil** *Emulsion o/w* **Methyl linoleate** *Liposomes*	Y	αTOH	–	Bulk: 0.11-0.22-0.43-0.86 Emulsion: 0.43-0.86-1.68-3.4-6.79	Quercetin	Strong synergism in emulsion: αTOH with quercetin, less in the liposomes and a clear antagonistic effect in bulk oil	(Becker et al., 2007)
Bulk/Emulsion o/w /liposome **Soybean oil**	Y	αTOH	-	Bulk: 107-215-430 Emulsion: 0.34-0.75-1.51-3.01	Açaí seed extracts and grape rachis extracts	In bulk oil: antagonism effect with both combination-absence of regeneration In emulsion: A high ratio of phenolic extracts to αTOH ratio increased the synergistic effects	(Siqueira Melo et al., 2016)
Bulk/Emulsion o/w /liposome **Sunflower oil, methyl linoleate**	Y	αTOH	–	Bulk: 107-215-430 Emulsion: 0.34-0.75-1.51-3.01	Green tea extract, EC, C	Synergistic effects of αTOH and green tea in bulk oil and emulsion. Synergistic effects of αTOH and C and EC in emulsion and liposomes. Antagonistic effects were found in bulk oil for αTOH and C and EC, when their ratio was 1:2, while an additive effect was observed when the antioxidant ratio was 2:1	(Yin et al., 2012)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Bulk/Emulsion o/w **Fish and algae oils**	N/Y (algae 3)	αTOH β+γTOH δTOH	Fish1: αTOH = 536, β+γTOH = 413, δTOH = 160. Fish2: αTOH = 451. Fish2: αTOH = 55, β+γTOH = 24, δTOH = 12. Tuna: αTOH = 171, β+γTOH = 8. Mackerel: αTOH = 11. Salmon: αTOH = 82. Sand eel: αTOH = 76. Algae 1: αTOH = 836. Algae 2: αTOH = 420. Algae 3: αTOH = 1729, β+γTOH = 208.	-	Metal transition (Fe), AP	Antioxidant stability in bulk oil (PV): algae-3 > fish-3 > sand eel > salmon > mackerel > algae-2> tuna > fish-2 > fish-1 > algae-1 >> Stripped algae-3 In emulsion: fish-3 > algae-3 > salmon > sand eel > mackerel > fish-2 > fish-1. Added iron reduced the stability of the fish oil emulsions much more than that of the algal oil emulsion. This difference may be due to a synergistic effect of the mixture of TOH and AP present in the algae 3 oil.	(Frankel et al., 2002)
Bulk/Emulsion o/w **Corn oil**	Y	αTOH	–	100-500	AA, AP	Synergism in both, especially in o/w emulsion αTOH + AA: bulk > o/w emulsion αTOH + AP: emulsion > bulk	(Frankel et al., 1994)
Microemulsion SDS/pentanol/water	-	αTOH	-	150	AA	Synergism between AA and αTOH. Probably αTOH form a 1:1 molecular complex with AA due to the formation of a hydrogen bond	(Drach et al., 2011)
Microemulsion w/o **Refined sardine oil**	N	δTOH	Not evaluated	1000-2000-3000	AA	Synergistic effect	(Yi et al., 1991)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Bulk/Emulsion o/w **Corn oil, methyl linoleate, linoleic acid**	Y	αTOH	-	130	Carnosic acid	Mixtures of carnosic acid and αTOH were less active (PV) than pure carnosic acid. Carnosic acid may protect αTOH from oxidation by a sparing effect. No synergism between carnosic acid and αTOH. Carnosol reduced the oxidative stability of αTOH, and the combination of carnosol and αTOH were actually antagonistic in corn oil.	(Hopia et al., 1996)
Aqueous micellar ***system*** **Linoleic acid** *Emulsion o/w* **Isopropylmyristate**	–	αTOH	–	Micellar solution: 0.43-0.86-1.29-1.72-2.15-2.58. Emulsion: 1.43-2.15-2.58-3.44-3.73-4.3	AA	In both systems: slight synergistic effect at pH 5, and pro-oxidant effect at pH 7. Could be ascribed to a repulsive force between AA (pKa 4.17), and the negative charge of SDS micelles, opposing the regeneration of αTOH.	(Carlotti et al., 1997)
Aqueous Micellar system **Linoleic acid**	-	αTOH	-	0.258-43	Metal transition, quercetin, isorhamnetin	Interaction of αTOH and quercetin or isorhamnetin (best with quercetin). The recycling/regeneration of αTOH is possible by quercetin because the redox potential (at pH 7) of the αTO· radical/αTOH is higher than that of the QR· semiquinone radical/QR. αTOH: pro-oxidant with Cu(II) concentration-dependent.	(Bakır et al., 2013)
Aqueous Micellar system **Linoleic acid**	–	αTOH	–	0.043-0.086-0.129-0.172-0.258-0.344-0.43	Metal transition, AA	Both antioxidant and pro-oxidant activity is linked to the presence and the concentration of CU(II) and AA. αTOH + Cu(II) is antioxidant at 0.043-0.344-0.43, and pro-oxidant at 0.086-0.129-0.172-0.258. αTOH + Cu(II) + AA is antioxidant at 0.043-0.129-0.172, and pro-oxidant at 0.258-0.344-0.43.	(Bakır et al., 2013)

(Continues)

TABLE 2 (Continued)

Type of system	Stripped oil	Type of TocOH	Concentration initiale (ppm)	Concentration added (ppm)	Interaction with	Effect of the interaction	Ref.
Aqueous Micellar system **Linoleic acid**		αTOH		190-380-760-1900-3800-7600-19000-38000-76000-	Surfactant/ hydroperoxides	αTOH + polar protic/aprotic organic solvents: no pro-oxidant effect. αTOH + amphoteric surfactant: antioxidant. Addition of water to DMSO or ACN: pro-oxidant effect of αTOH. The initial concentration of hydroperoxides affected the intensity of the pro-oxidant effect which varied in an inverse ratio to the initial hydroperoxide level.	(Cillard et al., 1980)
Aqueous Micellar system **Methyl linolenate and ethyl palmitate** Liposome **Phosphatidylcholine**	–	αTOH	–	21.5-43-86-129	Metal transition (Cu)	αTOH incorporated into methyl linoleate and ethyl palmitate micelles and also phosphatidylcholine liposomal membranes interacted with copper. αTOH reacts with the free copper(II) ion and results in a more reactive copper(I) ion and may act as a pro-oxidant for lipid peroxidation in the presence of free copper ions.	(Yoshida et al., 1994)
Aqueous Micellar system **Methyl linolenate** Liposome **PLPC and 14:PC**	-	αTOH βTOH γTOH δTOH αT3 βT3 γT3 δT3	-	2.15-215	Metal transition (Cu)	αTOH and αT3, but not the other forms, reduced Cu(II) to Cu(I) together with α-tocopheryl and α-tocotrienyl quinones, respectively and had a pro-oxidant effect in the oxidation.	(Yoshida et al., 2003)
Reverse micelle *DOPC*		αTOH	–	4.31-43.1	Canolol	Antioxidant synergism of canolol and αTOH only in DOPC reverse micelles	(Rokosik et al., 2020)

AA, Ascorbic acid; AP, Ascorbyl palmitate; C, catechin; EC, epicatechin; EGCG, epigallocatechin gallate; G0, gallic acid; G3, propyl gallate; G8, octyl gallate; G12, dodecyl gallate; PC, phosphatidylcholine; R0, Rosmarinic acid; R4, butyl rosmarinate; R12, dodecyl rosmarinate, R20, eicosanoyl rosmarinate; WP, whey protein; WPI, whey protein isolate.

1. TocOH and radical scavengers: Intuitively, having antioxidants working with the same mechanism may not lead to a significant synergistic effect. Introducing another hydrogen donor in addition to TocOH may achieve the same effect as a higher concentration of TocOH. Yet, considering that the relationship between the concentration of TocOH and its antioxidant effect was not predicted to be linear, one can hypothesize that a scavenging antioxidant compound introduced with TocOH at their optimal (low) concentration is responsible for highly efficient protection of lipids. That being said, this would not systematically produce a synergistic effect, but rather an optimal additive antioxidant effect. Considering the complexity of the chemical pathways (Figure 5) and the different factors involved, particularly the physical (micro) structure of the lipid system, this could happen when the radical scavenging ability of the antioxidants differs with the region. Thus, synergistic antioxidant actions may be obtained through the protective effect of one antioxidant by oxidizing itself (Decker, 2002; Pedrielli & Skibsted, 2002). For example, the less effective antioxidant (or its radical produced from oxidation) traps alkyl peroxy radicals, so the best antioxidant does not oxidize, therefore extending the shelf life of products due to prolonged antioxidant activity. This process explains partially the interactions between carotenoids and TocOH (Haila et al., 1996; Zou & Akoh, 2015). Moreover, mixed tocopherol analogs may enable better protection due to synergistic interactions. For instance, Fuster et al. (1998) observed such synergy between both α-TOH and γ-TOH at a maximum concentration of 200 ppm. On the other hand, Lampi et al. (1999) reported an addition effect and no synergism with the same combination of TocOH. The participation of phospholipids possessing a primary amine (e.g., phosphatidylethanolamine [PE] and phosphatidylserine), along with sulfur-containing amino acids (cysteine, cystine, and methionine), in radical-scavenging activity was also reported to have a sparing effect on TocOH and in that way may provide a synergistic effect (Judde et al., 2003; Lambelet et al., 1994).
2. Regeneration of TocOH: The mechanism is effective when TocOH with a substance are together. This substance is able to regenerate TocOH from their oxidation products, mostly the TocO• radical, and hence restore their antioxidant activity. Indeed, TocO• can be reduced through electron transfer from another antioxidant. This mechanism is all the more possible when: (i) the difference in BDE between antioxidants is high, (ii) the synergist has a lower standard reduction potential than TocOH (E0 $\sim$ 0.5 V), and (iii) when the rate constant to react with TocO• is high and resembles that of the reaction constant with alkyl peroxy radicals ($\sim 10^3$ M^{-1} s^{-1}; Figure 5, A_5 or A_6) (Amorati et al., 2002; Decker, 2002; Pedrielli & Skibsted, 2002). Water-soluble antioxidants such as AA, gallic acid, epigallocatechin gallate, epicatechin gallate, epigallocatechin, epicatechin, quercetin, glutathione, and rosmarinic acid and its esters have already been shown to regenerate TocO• in nano-emulsion systems (Niki et al., 1982; Panya et al., 2012; Pedrielli & Skibsted, 2002; Wefers & Sies, 1988; Zhou et al., 2005), whereas PE was found to synergize with α-TOH by regenerating itself from α-tocopherylquinone (Cui et al., 2015; Weng & Gordon, 1993). TocO• was reduced by antioxidants in the water phase. This phenomenon was described by some groups who worked in simple organic media and micellar systems using electron paramagnetic resonance (EPR), pulse radiolysis, or laser flash photolysis (Bisby & Parker, 1991; Packer et al., 1979; Panya et al., 2012; Zhou et al., 2005). TocOH regeneration was also observed in membrane models and postmortem meat (Scarpa et al., 1984; Sharma & Buettner, 1993); the same results were also described in vivo (i.e., TocO• was reduced in biological membranes). However, a lack of understanding persists because no group has succeeded direct observation of TocO• and aqueous phase antioxidant interaction in complex lipid dispersion systems (e.g., oil-in-water [O/W] emulsions). These observations are probably methodological challenges. We can suppose that the process of antioxidant synergy starts with the initial TocOH oxidation and the formation of TocO• (Figure 5, A_4) becoming oriented at the oil and water interface and subsequently being reduced by the water-soluble antioxidant to regenerate TocOH. With the example of AA, its reduction of TocO• is thermodynamically favored by its low reducing potential (E0 $\sim$ 0.28 V and 0.5 V for TocO• vs. TocOH, respectively) (Becker et al., 2004), whereas the efficiency of rosmarinic acid and its esters to reduce α-TO• was shown to be very low because of their higher electron reduction potential (E0 > 1.1 V) (Panya et al., 2012). The interaction between TocOH and carotenoids is another example of synergism. For instance, the prooxidant effect of lutein was inhibited by adding low levels of γ-TOH, and the combination allowed the synergistic effect to inhibit the hydroperoxide formation of triacylglycerols (Haila et al., 1996). The benefit of a combination of a carotenoid and TocOH was attributed by the authors to the capacity of γ-TOH to retard the formation of degradation products of the carotenoid. The regeneration of carotenoid by TocOH is favored because the carotenoid radical cation has a higher potential than TocO• (between >0.5 and 1 V vs. $\sim$0.5 V, respectively) (Jeevarajan & Kispert, 1996; Liu et al., 2000; Niedzwiedzki et al., 2005). Both

the regeneration of carotenoid from its radical cation by TocOH and TocOH regeneration by the carotenoid from the TocO• radical are possible (Edge et al., 1998; Mortensen & Skibsted, 1997a, 1997b; Mortensen et al., 1998).

Some authors proposed that such interactions occur in complex lipid dispersion, but in the absence of direct evidence for interactions between TocO• and water-soluble antioxidants, process of TocOH regeneration does not appeared like essential. Furthermore, the regeneration of the TocO• is not systematically related to better protection of lipids. Indeed, if one molecule of antioxidant regenerates one TocO•, then the molecule of antioxidant is not free to act in oxidation of LH (i.e., reduce oxidizing species). This may be the reason why Durand et al. (2015) observed that, although AA seems to affect the global stability of α-TOH in conventional O/W emulsion, where, possibly, it is able to regenerate α-TOH from TO•, the antioxidant capacity addition could be described like the combination of two separate effects. On the other hand, regeneration of TocO• may be a good way to prevent prooxidant action of TocOH when the latter has been oxidized or when it is located near the surface of reverse aggregates or micelles/interfaces containing attacking aqueous radicals (Figure 5, P_1).

The complexity of the physical (micro)structure of the system is another parameter that may significantly affect this mechanism, either physically or chemically (Figure 3). For instance, the fact that TocOH are located in lipid droplet cores in O/W emulsions could physically isolate TocO• from the water-soluble antioxidants at the interface. Thus, lipid droplet internalization of TocOH may prevent their synergism with the antioxidants present in the aqueous phase. In addition, the composition and architecture of the interface, a region that is only a few nanometers thick composed of oil, water, and surface-active molecules, may affect this chemical regeneration. The net charge of the interface between oil and water depends on the surface-active molecules that compose and stabilize the system, which can be anionic (e.g., SDS), cationic (e.g., DTAB), nonionic (e.g., Tween), or zwitterionic (e.g., phospholipids). The thickness and the structure of molecules present in the interfacial phase (proteins, polysaccharides, etc.) along with the pH, ionic strength, and so forth of the medium may significantly influence the penetration, diffusion, and interaction of molecules, and therefore the regeneration mechanism of TocOH. All these conditions would explain the contradicting results of different experiments. Some studies were unable to demonstrate efficient interaction in O/W emulsions, with no synergistic effect between the TocOH and various antioxidants dispersed in the aqueous phase, whereas other studies, on the contrary, found a strong influence (Kittipongpittaya, Panya, Phonsatta, et al., 2016; Sørensen et al., 2017).

3. Complementary antioxidant action: TocOH may provide significant synergistic effects when combined with antioxidants with metal chelating (detailed in the following paragraph) or a singlet oxygen quenching ability. This phenomenon can be explained by the presence of chelators or oxygen quenchers that reduced the effect of free radical scavengers. Metal chelators mostly interfere during the initial part of oxidation pathway, whereas TocOH are more active during the propagation step. Thus, TocOH showed synergistic effects with phospholipids, amino acids, peptides, and phenolic compounds, which are mainly the result of the metal-chelating activities of the latter, resulting in the production of fewer radicals to be reduced by TocOH. (Bandarra et al., 1999; Bazin et al., 1984; Dziedzic & Hudson, 1984; Hildebrand et al., 1984).

For instance, α-TOH showed a synergistic effect when associated with phospholipids or quercetin, which inhibited metal-catalyzed oxidation through the formation of inactive complexes, whereas α-TOH acts as a free radical scavenger (Hudson & Lewis, 1983; Koidis & Boskou, 2006; Servili & Montedoro, 2002). The antioxidant properties of melanoidins (Maillard reaction products formed between reducing sugars and compounds containing an amino group, e.g., peptides and proteins; This Vo Kientza, 2016) also acted as synergists with TocOH and were partially linked to their metal-chelating properties (Namiki, 1988).

Once again, regardless of the synergistic mechanism involved and their possible interaction with TocOH, the side effects of the complementary antioxidant molecule have to be taken into consideration, as does the nature of antioxidants and prooxidants, their chemical oxidative pathway, their concentration, and the complexity of the physical (micro)structure of the system. All these parameters may lead to different conclusions, even though the studies deal with similar compounds. For instance, synergistic interaction of rosmarinic acid (or caffeic acid) with α-TOH was observed in stripped soybean oil in water emulsion (Panya et al., 2012), whereas other authors observed an antagonistic effect, either in rapeseed oil (in bulk or emulsion) or in an aqueous dispersion system of linoleic acid (Peyrat-Maillard et al., 2003; Samotyja & Małecka, 2007). This consideration is even more important with antioxidant plant extracts that are rich in diverse molecules, in addition to the presence of presumably active antioxidants (e.g., phenolic compounds). For example, Wada and Fang (1992) highlighted a positive synergy between rosemary extracts and α-TOH (500 and 200 ppm, respectively) in a

sardine oil and in frozen–crushed fish meat, whereas other authors found an antagonist effect in rapeseed oil (stripped or raw, bulk or emulsion) (Samotyja & Małecka, 2007).

3.2 | Interaction with prooxidant metal transition

Trace metal catalysts (Fe, Cu, Ni, Co, Mn, etc.) may be present almost everywhere, including in the aqueous or buffer phase, in oils, and in some antioxidant plant extracts. The chemical action of metals on lipid oxidation in multiphasic systems follows several pathways (Schaich, 1992). State metals of higher valence can transfer an electron and result in the direct oxidation of LH; conversely, state metals of lower valence form metal oxygen transition complex and lead to autoxidation (Ingold, 1961; Uri, 1961). Preformed lipid hydroperoxides (LOOH) can get reduced or oxidized by metals. Such reactions trigger the formation of LO• and LOO• radicals, or decompose the hydrogen peroxide into HO•. Therefore, the global kinetics of lipid oxidation process is significantly accelerated because these radicals remove hydrogen faster from any oxidizable substrate than the initial rates of L• formation (Kremer, 1963; Waters, 1971). Besides, metals affect not only the rate of initiation and total extent of lipid oxidation by peroxide decomposition, but also alter the nature and distribution of oxidation products and termination reactions (for instance, rearrangement of LOOH into epoxides can be observed) (Schaich, 2020). Transition metal ions at lower valence states, such as Fe^{2+} and Cu^{+}, can decompose LOOH much faster than those at higher valence states, Fe^{3+} and Cu^{2+} (Schaich, 1992). This is the main explanation for why the antioxidants that reduce metal ions may, under certain circumstances, act as prooxidants (Keceli & Gordon, 2002). Concerning TocOH, it has been shown that α-form reduced cupric iron (Cu^{2+}) leading to an increase in lipid oxidation (Yoshida et al., 2003). In contrast, β-, γ-, and δ- analogs were not able to significantly reduce Cu^{2+}, likely due to their higher oxidation potentials, and consequently had no prooxidant effect (Yoshida et al., 2007). In that context, metal chelators are particularly efficient in limiting lipid oxidation by preventing the various chemical pathways catalyzed by transition metals (e.g., formation of insoluble metal complexes, steric obstruction either between metals and oxidizable food components or between metals and their oxidation products). TocOH do not appear to be strong metal chelators. However, combining TocOH with efficient metal chelators could have synergistic effects (see Section 2.1). Both citric acid and EDTA are the conventional metal chelators used in foods. Yet, metal ions can also get linked up by phospholipids, flavonoids, lignans, polyphenols, AA, proteins, peptides (e.g., carnosine), and free amino acids (e.g., histidine) (Koidis & Boskou, 2006; Rice-Evans et al., 1996; Riisom et al., 1980). The formation of metal/chelator complex has a double effect: (1) it impacts the electron density of the metal and thus modify its redox potential, and (2) it affects the distribution and availability of the metallic ions in the multiphasic system. By this double action, both the balance of reactants in the system and global oxidation reaction are affected. To take a precise example, the formation of EDTA/iron complex will both capture free or weakly complexed iron and will lower the Fe^{3+}/Fe^{2+} redox potential (0.77 vs. 0.12 V). This lowering of potential will induce a faster reduction of lipid hydroperoxides (Mahoney et al., 1986; Schaich, 1992).

3.3 | Physical interactions to drive chemical pathways (e.g., lipid hydroperoxides and phospholipids)

The chemical reactivity between molecules lies in their capacity to interact, so they have to be in each other's vicinity. In multiphasic systems, in which some surface-active molecules can get aggregated and define specific phases or substructures, the relative distribution of molecules acting in the oxidation process is difficult. For instance, lipid hydroperoxides (LOOH) or phospholipids trigger the formation of microstructures (e.g., reversed micelles in bulk oils) that change the partition and interactions between molecules. Altogether, these modulations of distribution alter the global oxidation process of the system (Huang, Hopia, et al., 1996). Antioxidants such as TocOH may alter the distribution of oxidation products. Indeed, TocOH can influence the relative abundance of the oxidative products, for example, in the qualitative and quantitative variation in the proportion of LOOH isomers, and their subsequent secondary decomposition products (Coxon et al., 1984; Frankel & Gardner, 1989; Peers & Coxon, 1983; Peers et al., 1981; Terao & Matsushita, 1986; Yamagata et al., 1983). These results suggest that (i) TocOH interact with LOOH, perhaps through hydrogen bonding assisted by van der Waals interactions, and (ii) lipid oxidation products are affected by the capacity of antioxidants (e.g., TocOH) to interact, or self-assemble, with primary oxidation products. Similarly, phospholipids are known to influence the antioxidant behavior of TocOH through a physically assisted mechanism that affects their distribution and consequently their antioxidant effect (Koga & Terao, 1995). Phospholipids, in addition to the water level found in commercial refined oil, can self-assemble in bulk oils to form microstructures such as reverse micelles that can incorporate antioxidant compounds (e.g., TocOH) (Chen et al., 2010), and consequently influence the microenvironment

where lipid oxidation chemistry occurs. For instance, association colloids formed by dioleoylphosphatidylcholine (DOPC) in stripped soybean oil had a prooxidant effect, and DOPC reverse micelles improved the antioxidant activity of low concentrations (10 μM) of α-TOH or Trolox, whereas the opposite effect was found at a higher concentration (100 μM) (Chen et al., 2011), likely due to competition between antioxidant (free radical scavenging) and prooxidant (reduction of transition metals) activities. Interestingly, the dioleoylphosphatidylethanolamine (DOPE) reverse micelle did not catch α-TOH in contrast to the DOPC reverse micelles. Thus, the physical location of α-TOH did not change in DOPE reverse micelles. However, the regeneration of α-TOH quinone by DOPE primary amine head group likely via an ionic mechanism increased the antioxidant capacity (Cui et al., 2015). Trolox that is polar than α-TOH was also more antioxidant in the presence of both DOPC and DOPE reverse micelles because it got segregated into the aqueous-phase microenvironment of reverse aggregates, closer to the oil–water interface than α-TOH (Cui et al., 2015) (Figure 2c). In conclusion, TocOH interactions with surface-active molecules may alter their physical location, which in turn would alter the overall impact on lipid oxidation.

4 | THE PHYSICAL DISTRIBUTION OF TOCOPHEROLS IN SYSTEMS MODULATES THEIR ANTIOXIDANT EFFECT

Understanding the location (distance from the interface, lateral distribution), orientation, and mobility of TocOH in heterogeneous systems and bilayers of phospholipids representative of biological membrane is a key aspect of their antioxidant role. TocOH may in turn impact membrane fluidity and the molecular mobility of reactive components in the vicinity of membranes. Recent experimentation, modeling, and theoretical studies have elucidated the molecular mechanisms underlying cooperation between membrane components and several phenolic compounds including TocOH, vitamin C, and polyphenols. These antioxidants form a noncovalent association with the lipid bilayer close to the membrane/internal part of the assembly interface. Such a supramolecular association and location is hypothesized to favor antioxidants regeneration (Fabre et al., 2015). More generally, the distribution of TocOH in heterogeneous systems can be seen as a dynamic picture influenced by the present amphiphiles, their state of association, phase, and charge, and the presence of other synergetic antioxidants.

4.1 | Specificity of interactions with phospholipids

Among the pioneer works, Hildebrand et al. (1984) demonstrated that combining phospholipids (PL) and TocOH enhanced their antioxidant effect on stabilizing refined bulk oils. The work of these authors was based on the empirical observation that crude oil containing phospholipids at concentrations of 0%–1% was more stable than refined oil. They tested a factorial combination of three levels of soybean TocOH (blend of three isomers and α, δ, and γ at respective levels of 5.4%, 44.9%, and 49.8%; tocopherol at levels of 0, 1.2, and 4–5 mg/g oil) and two levels of PL (0 and 5 mg/g oil phosphatidylcholine [PC] and PE, and 0 and 2.5 mg/g oil phosphatidic acid (PA) and phosphatidylinositol [PI]). The efficacy of such combinations was determined by measuring the induction period in days before refined soybean oil incubated at 110°C reached a PV value of 100 meq/kg. The most effective stabilization was reached by adding either all PL at highest levels, plus TocOH at intermediate to high levels (1.2–4 mg/g oil), or the highest levels of PC and PE (5 mg/g oil), and a similar amount of TocOH. Alone, neither TocOH nor PL were as effective. Among the PL, the same authors concluded that PE and PI were the most effective in increasing oil stability, although proof of real higher efficacy of PI in this experiment can be questioned. Concerning the mechanism behind PL protection and synergy with TocOH, the authors excluded simple prooxidant metal chelation by PL (citric acid added as a control to test this hypothesis) and rather proposed the hypothesis that PL could increase TocOH capacity of free radical termination. Indeed, they hypothesized that some reactive PL groups (amine for PE and PC, reducing sugar for PI) could facilitate H or electron transfer to TocOH and their regeneration.

Following this thread, Judde et al. (2003) tested the addition of standard lecithins at 1% w/w concentration in various oils with given FA and TocOH composition. Overall, the addition had a protective effect against oxidation. However, protection depended not only on the phospholipid profile of the tested lecithin (lecithins containing high amounts of PC and PE were more efficient), but also on the FA profile in the tested oil. Lastly, the type of TocOH present in the oil also influenced antioxidant capacity (strong synergetic effect was evidenced for mixtures of γ- and δ-tocopherols with lecithin but no effect was evidenced for α-tocopherol). In terms of the FA profile of the oil, the authors established that the addition of lecithin (1% w/w) was effective in stabilizing linoleic oils that contain a natural blend of γ/δ-tocopherols, but not PUFA oils that naturally contain mainly α-tocopherols. To further test this hypothesis and to untangle the effects of

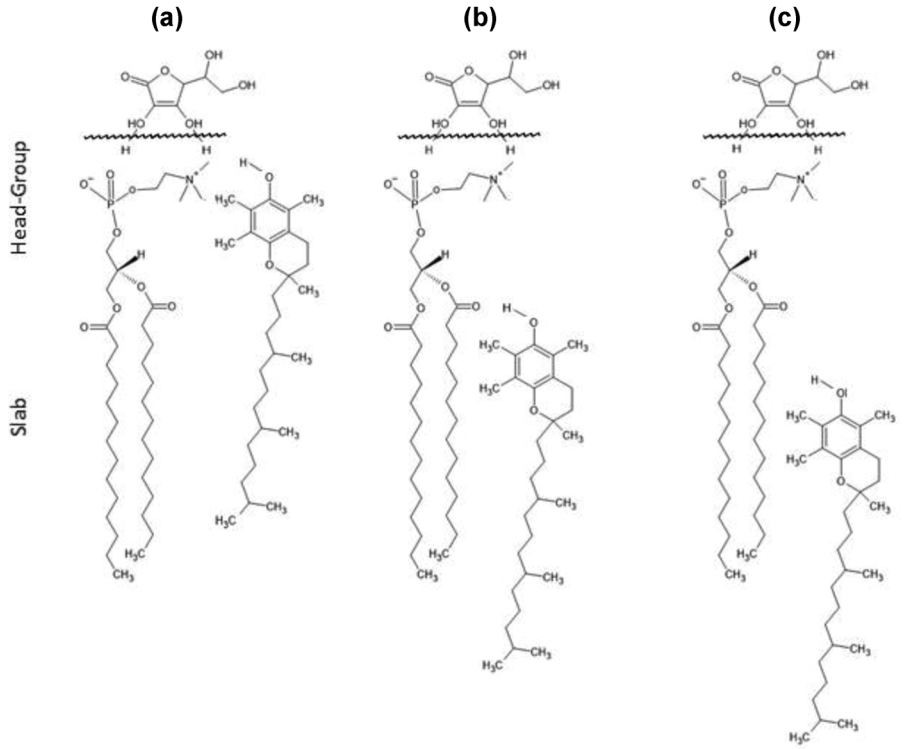

FIGURE 8 Schematic models of the location of tocopherol in the lipid bilayer. Adapted from Afri et al. (2004)

TocOH isoforms and the FA profile, they assessed the stability of methyl esters blended with various TocOH and in the presence of 1% w/w lecithin. The addition of α- or δ-tocopherol resulted in slower oxidation kinetics for all methyl esters. Particularly for linoleate and linolenate, these results confirmed the greater antioxidant efficiency of the γ-/δ-tocopherol mixture compared to α-tocopherol alone. Concerning PUFA methyl esters, the addition of lecithin improved the efficiency of the tocopherols, particularly γ-/δ-tocopherols. The model with methyl esters thus confirmed the previous observations concerning linoleic or linolenic oils rich in γ- or δ-tocopherols such as rapeseed, soy, and walnut.

In the 1990s, the physical interaction between TocOH and phospholipids was introduced for a better understanding of their chemical synergy (Salgado et al., 1993). Combining nuclear magnetic resonance (NMR) (31P), Fourier-transform infrared spetroscopy (FTIR). and light microscopy, these authors demonstrated that α-TocOH tends to stabilize bilayers of PC instead of micelle.

Since then, several experimental and modeling studies have proven that the location and association of TocOH within membrane glycerophospholipids enhances their efficiency. For example, the vertical location of TocOH in phospholipid membrane was investigated in depth. The three hypotheses summarized in Figure 8 were initially proposed (Fukuzawa et al., 1993). Experimental evaluation of TocOH analogs in the liposomal bilayer of dimyristoylphosphatidylcholine (DMPC) was conducted using the 13C NMR chemical-shift/polarity correlation technique to shed light on the physical framework favoring "lipid-active antioxidant" recycling by hydrophilic AA (Afri et al., 2004). Using a quite high load of TocOH (TocOH/DMPC ratio of 1:5, i.e., 17 mol%), these authors established that the tocopherol chromanol hydroxyl C6 group lies very close to water interface between location A and B (Figure 8) where it can abstract H from AA (Figure 8c).

The vertical distribution of α-tocopherol, that is, with the chromanol ring located in the upper part of the hydrophobic bilayer and the tail chain parallel to the PC acyl chains, was proven more recently in saturated PC (DMPC, DPPC) by coupling physical characterization (small- and wide-angle X-ray diffraction, fluorescence quenching, and 1H nuclear Overhauser enhancement spectroscopy [NOESY] magic-angle spinning [MAS]–NMR spectroscopy (Ausili et al., 2018).

There is now quite a consensus that α-TOH location close to lipid–water interface is universal and has been checked experimentally in various model bilayers (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine, 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-L-serine, and sphingomyelin bilayers) by Marquardt et al. (2015). However, one exception was reported by same authors (Marquardt et al., 2014) in artificial DMPC bilayers.

Molecular dynamic simulations can predict the location of TocOH in membrane. A simulation in a lipid bilayer

comprising DOPC molecules indicated that TocOH are generally inserted below the membrane/water interface but reach the bilayer center (Fabre, 2015). More precisely, simulation but also experimental data (Marquardt et al., 2013) evidenced that the extremity of C5-methyl group of TocOH is located 1.5–1.7 nm from the center of the bilayer. α-TOH insertion in the bilayer is hypothesized to favor the location of the OH group close to the lipid polar head group, that is, close to the interface where it promotes lipid oxidation. Fabre et al. (2015) stated that the OH group of TocOH, which is responsible for free radical scavenging by hydrogen atom transfer, was mainly located close to the lipid polar head groups, that is, at the lipid/water interface, suggesting inhibition of both the initiation and propagation steps of lipid oxidation. In addition to the vertical location, the lateral distribution of TocOH within a liposomal bilayer can be questioned, as this distribution is also dependent on the composition and heterogeneity of the bilayer. It was hypothesized that α-TOH have more affinity for PUFA and thus get segregated in the fluid zone of heterogeneous membrane (Atkinson et al., 2010) and reduce fluid–gel membrane transitions (Paz Sánchez-Migallón et al., 1996). In addition, and as can be inferred from chemical mobility, α-tocopherol is oxidized faster in liquid phase than in gel phase (Fukuzawa, 2008).

Another important point to address is the vertical and lateral mobility of TocOH within the bilayer, which is not yet settled and is highly influenced by the chemical composition of the bilayer. It was suggested very early that α-tocopherol lateral diffusion coefficient was 100 times higher than that of PC (egg yolk) (4.8×10^{-6} cm ^{2} s^{-1} at 25°C vs. 0.9–1.8×10^{-8} cm ^{2} s^{-1} at 20°C, respectively) favoring its action as a mobile antioxidant barrier (Fukuzawa et al., 1992).

Boonnoy et al. (2017) investigated the dynamic distribution of α-tocopherol in oxidized bilayers using molecular dynamic simulations. The authors showed that the addition of α-tocopherol in bilayers of 1-palmitoyl-2-linoleoyl-sn-3-phosphocholine and the two aldehydes deriving from it (1-palmitoyl-2-(9-oxo-nonanoyl)-sn-3-phosphocholine and 1-palmitoyl-2-(12-oxo-cis-9-dodecenoyl)-sn-3-phosphocholine) at a ratio of 1:1 tended to reduce or even inhibit pore formation within the bilayer at high α-TOH concentrations. Such pores result from the tendency of oxidized lipids to aggregate, a phenomenon that subtends the formation of a water pore across the bilayer. A mechanism of protection has been proposed, suggesting that α-tocopherol traps the polar group of the oxidized lipids at the membrane interface.

Still using molecular dynamic simulations (Boonnoy et al., 2018) confirmed that α-tocopherol remained buried in the lipid bilayer containing oxidized lipids and with the hydroxyl group in contact with the interface. Model bilayers were based on 1-palmitoyl-2-lauroyl-sn-glycero-3-phosphocholine (PLPC). Oxidation was modeled using 1:1 binary mixtures of PLPC and one of its four main oxidative derivative products (either hydroperoxides [1-palmitoyl-2-(9-hydroperoxytrans-10, cis-12-octadecadienoyl)-sn-glycero-3-phosphocholine, 9-tc and 1-palmitoyl-2-(13-hydroperoxy-trans-11,cis-9-octadecadienoyl)-sn-glycero-3-phosphocholine, 13-tc] or aldehydes [1-palmitoyl-2-(9-oxo-nonanoyl)-sn-glycero-3-phosphocholine, 9-al and 1-stearoyl-2-(12-oxo-cis-9-dodecenoyl)-snglycero-3-phosphocholine]). Inter-bilayer flip-flop was observed and enhanced (higher frequency) in the aldehyde lipid bilayer. These authors demonstrated that flip-flop rates hinge on the type of oxidized species present in the bilayer. α-TOH were initially studied at concentrations ranging from 0% to 11.1% but higher concentrations—5.9% and 11.1%—led to much slower passive penetration into the bilayer (over several microseconds, whereas 100- to 1000-fold faster penetration occurred at lower concentrations). Such high initial concentrations could even lead to pore formation in the bilayer.

Accordingly, the strong physical interactions of phospholipids with TocOH will eventually modify the antioxidant effect of the latter. For example, Koga and Terao (1995) evaluated the effect of phospholipids on the radical-scavenging activity of TocOH using methyl esters as oxidizable substrate. These authors observed that phospholipids boosted the action of TocOH when oxidation was triggered by a water-soluble radical initiator but that TocOH had no significant effect when a lipid-soluble radical initiator was used. According to the authors, these results imply that phospholipids enhance the accessibility of TocOH toward the chain-initiating radicals in an aqueous microenvironment. To explain such an effect, they hypothesized that TocOH is positioned in the aggregation form of phospholipids (reverse micelles) with the phenolic head group located near the polar region where aqueous peroxyl radicals are generated (Rokosik et al., 2020).

4.2 | Specificity of interactions with surfactants in emulsions and resulting antioxidant activity

Small amphiphilic molecules, also known as surfactants, can also modify antioxidant activity especially in biphasic systems (O/W or W/O emulsions) by modulating the physical location of the antioxidant. For example, concerning TocOH, Lopez-Martinez and Rocha-Uribe (2018) evaluated the efficiency of α-TOH for the protection of an oil-in-water model emulsion stabilized either by Tween 65 or Tween 80 emulsifier and compared the antioxidant efficacy to its

partitioning in the emulsion. They showed that α-TOH was not efficient as an antioxidant when Tween 80 was used and was only slightly prooxidant when Tween 65 was used. The same authors calculated that more than 98% of α-TOH present were located in the oily phase, therefore limiting its capacity to act as an antioxidant at the interface. Moreover, they considered that the diffusion of α-TOH from one lipid droplet to another by their micellization with surfactants molecule was improbable due to the low affinity of TocOH for the aqueous phase. These results partially contradict the results obtained by Kiralan et al. (2014) who observed TocOH micellization with surfactants. These authors investigated the effect of increasing concentrations (0.1%, 0.5%, and 1%) of a nonionic surfactant (polyoxyethylene sorbitol ester) on the partitioning behavior and antioxidant activity of various TocOH isoforms (α, γ, and δ; 10–100 μM) in an O/W stripped soybean oil/phosphate buffer (pH 7.0) system. Whatever the concentration, the addition of surfactant increased the concentration of TocOH in the aqueous phase due to the formation of mixed micelles but without modifying the order of increasing solubility of the tocopherol isoform, that is, δ- > γ- > α-TOH. The addition of surfactants enhanced the antioxidant activity of the two isoforms δ (tested at 10 μM) and α (tested at 35 μM) but the effect on the δ isoform was stronger. The concentration effect of surfactant was correlated with the increase in the concentration of tocopherol in the subphase. These authors hypothesized that surfactant micelles help dissolving TocOH out of the lipid droplet. In addition, they hypothesized that the combination of surfactants and TocOH micelles plays the double role of "vehicles" and also of "reservoir" to restore oxidized TocOH at the interface (Figure 9).

The discrepancies between the results obtained by Kiralan et al. (2014) and Lopez-Martinez and Rocha-Uribe (2018) could be due not only to the different nature of the emulsifiers used in the two studies but also to the difference in the type of the emulsion tested, as one study worked with a 10% oil/water emulsion, whereas the other used much more oil (around 80%). Such parameters could favor (or not) the transport of TocOH through the micellization effect. In that context, one can cite the study by Losada-Barreiro et al. (2013), who evaluated the effects of the hydrophile–lipophile balance (HLB) and of the concentration of emulsifier on the distribution of α-TOH (among other studied antioxidants) in emulsions. They used an emulsion composed of stripped corn oil stabilized by a mixture of various nonionic surfactants including Tween 20, 40, and 80 and Span 20 to fix the global HLB value, and evaluated the partitioning of the antioxidant molecule between the oil, aqueous, or interfacial regions. They showed that increasing the concentration of the emulsifier (surfactant volume fractions of 0.04) led to the presence of more than 50% of α-TOH at the interface and that this incorporation was favored in the case of lower HLB of surfactants. Although not actually studied in the work by Losada-Barreiro et al., cited here, their results emphasize the fact that the efficiency of TocOH as antioxidants in emulsion can be influenced by their interaction with surfactants, and that these interactions depend on the type of surfactant. Similarly, Panya et al. (2012) observed that Tween 20 micelles could modify TocOH partitioning in emulsions and drag them to the aqueous phase where their synergistic effect with water-soluble antioxidant (in that case, rosmarinic acid) was optimized, resulting in enhanced antioxidant protection.

Other authors have also described the influence of the nature of the emulsifier on the partitioning of TocOH in emulsion and TocOH activity. For example, using a stripped fish oil emulsion with either whey proteins or Tween 80 as emulsifiers, Pernin et al. (2019) studied the efficiency of α-TOH and found that α-TOH were efficient in the presence of whey proteins, but not in the presence of Tween 80. As an explanation, they suggested that the more compact organization of Tween 80 at the interface compared to that of whey proteins would limit the accessibility of α-TOH to the interface in the presence of Tween 80 and thus hinder the potential activity of α-TOH. Similarly, Yi et al. (2018) evaluated the behavior of α-TOH in corn oil-in-water emulsions containing anionic (SDS), neutral (Tween 20), and cationic (CTAB) charged emulsifiers and studied different types of lipid oxidation using riboflavin photosensitization, photooxidation, or autoxidation. Their results showed that, whatever the type of induced oxidation, α-TOH were efficient antioxidants in the presence of a cationic emulsifier. With a neutral emulsifier, the same molecule acted as an antioxidant with riboflavin photosensitization, whereas it showed a prooxidant effect at photooxidation. Concerning anionic emulsifier, α-TOH activity differed with the concentration and types of oxidative stress. Finally, one can also cite Schwarz et al. (2000), who compared the behavior of α-TOH in homogenous or emulsified systems (oil-in-water or water-in-oil emulsions) and evaluated their interaction with emulsifiers. In their study, these authors used different types of emulsion: o/w emulsion containing ceteareth-15 and glyceryl stearate (HLB value = 12.1), o/w emulsion containing polyglyceryl glucose methyl distearate (HLB value = 11.5), w/o emulsion containing polysiloxane polyalcohol polyether copolymer (HLB value = 5.1), and w/o emulsion contained polyglyceryl-3 oleate (HLB value = 5.1). In contrast to the other antioxidants tested (gallic acid and its propyl ester, Trolox, carnosic acid and its methyl ester), α-TOH inhibited hydroperoxide formation in polysiloxane polyalcohol polyether copolymer W/O emulsion and polyglyceryl glucose methyl distearate O/W emulsion to the same

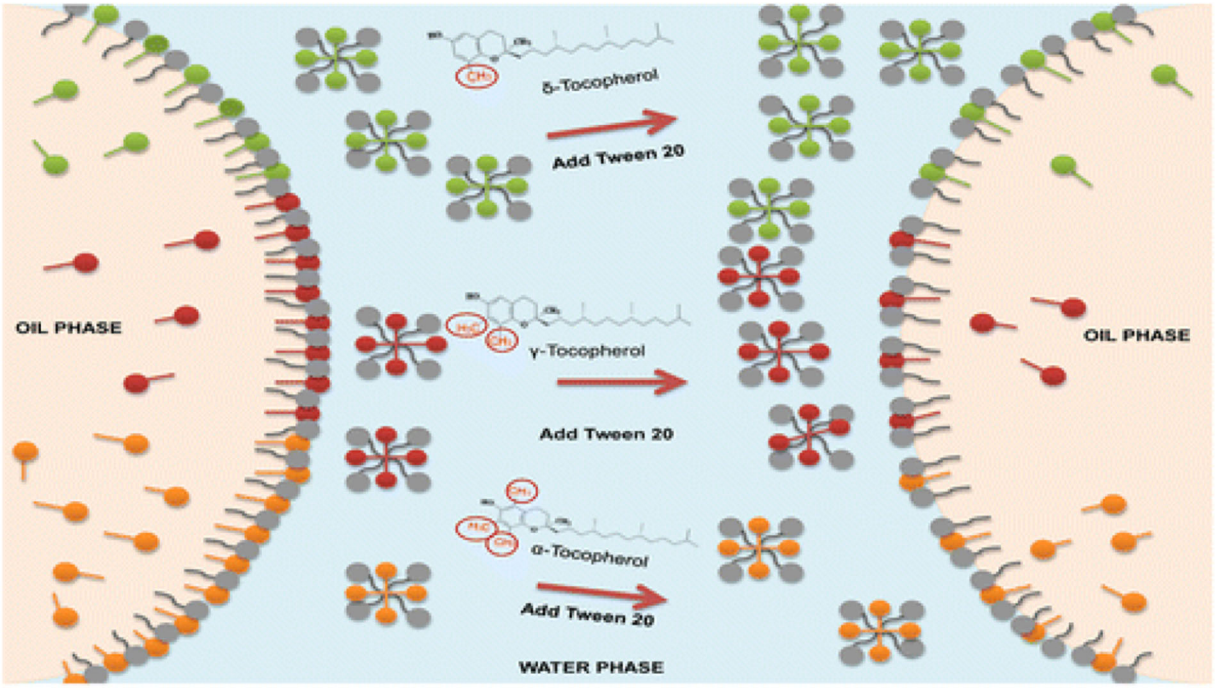

FIGURE 9 Reprinted with permission from Kiralan et al. (2014).Copyright 2014 American Chemical Society

extent as in bulk oil. However, the inhibition of oxidation by α-TOH was much less pronounced in ceteareth-15 and glyceryl stearate O/W emulsion and in polyglyceryl-3 oleate W/O emulsion. In the homogenous system, the authors used a bulk oil containing emulsifiers with the same emulsifier/oil ratio as in the previous emulsions. They observed that mixtures of ceteareth-15/glyceryl stearate and polyglyceryl glucose methyl/distearate emulsifiers increased α-TOH activity, whereas polyglyceryl-3 oleate strongly reduced α-TOH activity. To explain their results, the authors postulated that the emulsifiers they tested were capable of solubilizing a portion of α-TOH and of bringing it to the interfacial area to express optimized activity and that this capacity of the emulsifier was of course influenced by its type. However, to the best of our knowledge, there is a lack of rational studies that evaluate the molecular interactions between TocOH and emulsifiers, and how the type of TocOH and the nature of the emulsifiers can affect such interactions and participate in the relocation of TocOH in the interfacial area of emulsions or bulk oils (associate colloids). However, one can cite the work by Pastoriza-Gallego et al. (2009) who used a "combined linear sweep voltammetry (LSV)/pseudophase kinetic model" to determine the transfer entropies of α-TOH between the oil and interface in an emulsion. With this model, these authors were able to estimate the most appropriate concentration of surfactant to obtain an optimized α-TOH concentration at the interface. The same research group (Sanchez-Paz et al, 2008) used the same pseudophase kinetic model to estimate the constants that describe α-TOH partitioning between the oil/interfacial and water/interfacial regions of tributyrin/Brij 30/water emulsions. Here again, they were able to determine the concentration of surfactant that produced the best distribution of the antioxidant in the interfacial region.

The example above illustrates the potential advantage of using physicochemical interactions to regulate TocOH partitioning in heterogenous systems, and hence optimize their resulting antioxidant efficiency. In that sense, Schröeder et al. (2020) conceived an innovative approach to optimize the antioxidant effects of TocOH in emulsions by formulating them in Pickering particles that would act as both emulsion stabilizers and as reservoirs of antioxidants that would locate in the interfacial area. These authors observed that the systems based on Pickering particles formulation allow TocOH to reside for a substantial period at the interface during the initiation step of lipid oxidation. The extended location of the antioxidant at the site of oxidation would favor its effect and limit oxidation diffusion from one lipid droplet to another.

4.3 | Interactions of TocOH with association colloids in bulk oils and resulting antioxidant activity

In the case of bulk oil systems, as mentioned previously, the presence and nature of association colloids strongly influence the activity and efficiency of TocOH. These reverse micelles are stabilized by minor surface-active

components (fatty acids, partial glycerides, phospholipids, sterols) that are not completely removed during the oil refining processes and can form reverse micelles in the presence of small quantities of water (around 300 ppm) (Chaiyasit et al., 2007; Xenakis et al., 2010). Amphiphilic substances such as lipid hydroperoxides and prooxidant metals concentrate colloids within these associations and favor the production of free radicals from LOOH. Koga and Terao (1995) were pioneers to set the hypothesis that "oil–water interface resulting from residual traces of water in the system" was the main site of oxidation in bulk oil systems (Koga & Terao, 1995). Indeed, they showed that the antioxidant capacity of α-TOH in a bulk oil containing 1% (v/v) of water was increased by phospholipids. With a water-soluble azo compound (AAPH) releasing free radicals in the water phase, increasing the concentrations of phospholipids decreased the concentration of α-TOH. They hypothesized that α-TOH are located in the association colloids in bulk oils and that phospholipids increase the exposure of α-TOH to the water phase. The same kind of observation was made by Chen et al. (2011) who used a stripped soybean oil to determine the activity of α-TOH and its polar counterpart (Trolox) in the presence or absence of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) micelles (Chen et al., 2011). At low concentrations (10 μM), these authors showed that the activities of both α-TOH and Trolox were enhanced, whereas at higher concentrations (100 μM), they decreased. They highlighted that the concentration of Trolox increased in the reverse micelles, so it could explain why it was more efficient than α-TOH.

In the context of the presence of association colloids in bulk oils, some authors tried to evaluate the effect of relative humidity (RH) on the antioxidant properties of TocOH. For instance, Kim et al. (2015) evaluated the effect of RH with different concentrations of α-TOH in stripped corn oil. The same concentration of α-TOH showed different levels of oxidative stability under different RH conditions. Generally, lower RH was associated with higher oxidative stability. In addition, a high concentration of a-tocopherol (84 ppm) had more prooxidative properties than a low concentration (10 ppm). These results suggest that both the concentration and moisture content play an important role in the antioxidant properties of TocOH in bulk oils. The authors concluded that at low RH, different forces drive oxidation compared to high RH, and attributed their result to the number of association colloids present in the system. Unfortunately, colloids depending on the RH values were not quantified in their study. In a comparable work, the same research group studied the stability of α-TOH in stripped corn oils with or without added γ-TOH quantified under different levels of RH (0%–93%) (Jung et al., 2016). These authors have shown that the moisture acts on the stability of both α- and γ-TOH but also on the oxidative stability of the oil. Moisture, the presence of γ-TOH, and the concentration of α-TOH affect significantly the stability of α-TOH. α-TOH at a concentration of up to 100 ppm was the least stable at 75% RH; the best stability of α-TOH was obtained at 93% RH and with concentration of 200 ppm, whereas the worst stability of α-TOH was obtained under 0% RH with the presence of γ-TOH. Although, here again, the presence of association colloids was not correlated with RH, the authors suggested that γ-TOH, with only few lipophilic properties in the chromane ring moiety, may be the best candidate for the inside positioning into association colloids. Therefore, γ-TOH may not be properly located on the interface of oils and water. This fact would imply that more γ-TOH can be retained than α-TOH. Accordingly, γ-TOH in lower moisture content environment may more likely get in the vicinity of prooxidative factors, thereby reducing their oxidative stability. However, contradictory results were obtained by Kittipongpittaya, Panya, and Decker (2016). They used stripped corn oils that were supplemented with either 400 or 1000 ppm of water and evaluated the oil's resistance to oxidation. The lag time of lipid oxidation did not depend significantly on water content. In presence of water, the lag time of hydroperoxides decreased and hexanal concentration increased in bulk oil containing oleic acid, stigmasterol, and Trolox. On the other hand, the antioxidant capacity of α-TOH did not change significantly with 1000 ppm of water. The authors hypothesized that, because this antioxidant was not measured as surface active, it may present in the oil media and water could not act on the oxidative stability. Moreover, the same team (Kittipongpittaya et al., 2014) showed that minor oil surface-active components such as DOPC, DOPE, stigmasterol, oleic acid, and DAG were able to get adsorbed at the oil–water interface and therefore induced a reduction of interfacial tension. In addition, DOPC and DOPE could aggregate at the critical micelle concentration (CMC) of 40 and 200 μmol/kg oil, respectively (Kittipongpittaya et al., 2014). Association colloids appeared with CMC as low as 20 μmol/kg oil due to a blend with other minor molecules. However, the authors observed that these physical structures did not affect the antioxidative efficiency of TocOH at 10 and 50 μmol/kg oil. More recently, several studies reported that the performance of TocOH in bulk oils was correlated with their interactions with association colloids. Kim et al. (2019) studied the effect of added lecithin (300–3000 ppm) on the oxidative stability of nonstripped or stripped corn oil. The effectiveness of TocOH as antioxidant in nonstripped oil was highest when lecithin was present near or above and above CMC (1288 ppm). In this situation, lecithins with moisture formed association colloids in

the bulk oil and these colloids were able to incorporate lipophilic TocOH in their structure, thus making them efficient antioxidants and resulting in high oxidative stability. In parallel, more residual TocOH were observed when the concentration of lecithin was higher than CMC. Rokosik et al. (2020) investigated the interaction of canolol (4-vinylsyringol) and α-TOH in rapeseed oil in the presence of association colloids (reverse micelles) made of DOPC (Rokosik et al., 2020). Using fluorescence measurements, the authors were able to show that canolol was incorporated into the structure of DOPC reverse micelles, whereas no interactions between α-TOH and association colloids were demonstrated. Still, the presence of association colloids was shown to affect the antioxidant efficiency of both compounds. In the absence of DPOC micelles, an antioxidant action of α-TOH was observed at 10 and 100 μmol amounts when hexanal concentrations were measured. Interestingly, the authors reported that at high concentrations of α-TOH (100 μmol) a prooxidant effect was rapidly observed. They attributed this phenomenon to the possible association of amphiphilic lipid oxidation products (hydroperoxides, aldehydes) with α-TOH to form reverse micelles that would decrease the antioxidant efficiency. This hypothesis was corroborated by the fact that reverse micelles formed with α-TOH were observed by the fluorescence measurements of the N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt (NBD-PE) probe and this formation is influenced by the concentration of α-TOH. In the presence of DOPOC micelles, when primary oxidation compounds were measured, α-TOH at 10 μmol showed a significant prooxidant effect. The same observation was made at higher amounts (100 μmol) but the effect was less pronounced. Here again, a change in the composition of DOPC reverse micelles was confirmed with NBD-PE probes resulting in a modification of the efficiency of the antioxidant. These results are in accordance with the results obtained by Cui et al (2015) who also reported that reverse micelles with a combination of DOPC and α-TOH may have prooxidant capacity (Cui et al., 2015).

5 | CONCLUSION

For many years now, antioxidants have been used to combat lipid oxidation in food, cosmetics, and pharmaceutical products. Among these additives, tocopherols, either as natural extracts or in synthetic pure form (mainly as α-TOH), are probably the most widely used. Although their efficiency in protecting unsaturated lipids from oxidative degradation is recognized, their mechanism of action has still not been completely characterized and depends on many factors especially in complex systems such as real products. In such products, the efficiency of a given antioxidant is driven not only by its chemical reactivity but also by its physical behavior (i.e., its distribution within the product) and its interactions with other substances present in the product. The abundant literature on tocopherols as antioxidants is sometimes contradictory but nevertheless underlines the fact that it is strongly system dependent. In terms of chemical reactivity, the antioxidant activity of tocopherols is principally due to their ability to donate their phenolic hydrogen and can theoretically be predicted based on the structure of the four tocopherol isomers (α, β, γ, and δ-TocOH). However, the results of many published studies show that prediction is impossible and that in practice, the effectiveness of each tocopherol isomer in lipid dispersion systems or in bulk oil is unpredictable as it depends on many side reactions involving neighboring molecules. The fate of TocO• radicals will depend on various parameters leading to different chemical pathways, and consequently, to different degrees of efficiency of tocopherols as antioxidants depending on the product in which they are used. In certain cases, especially when used at high concentrations, tocopherols may also be involved in oxidation routes and contribute to lipid degradation by complex chemical pathways. Nevertheless, the most effective dose of tocopherols beyond which their antioxidant activity will switch to prooxidant is still not clear. However, the PCA we performed on several research articles focused on this topic tends to show that up to a value of about 200 ppm, TocOH exhibited only antioxidant activity, whereas beyond that value, TocOH activity very often switched to prooxidant, except for very low level of oil oxidation. The effects of the interaction of tocopherols with other antioxidant molecules are also crucial to guarantee an effective antioxidant system. However, here again, the results reported in the literature vary between synergistic or antagonist effects and the chemical interactions involved are complex. When all the antioxidant molecules are in contact within the final product, such interactions are difficult to predict. Finally, the complexity of the physical (micro)structure of the system may also significantly affect the efficiency of tocopherols as antioxidants. In particular, the physical distribution of tocopherols between the different phases of the systems will influence their activity. Although considerable data exist regarding the interactions between tocopherols and phospholipids (mainly in biological membranes), in emulsions, some recent literatures underline the importance of the micellization phenomena of surfactants and tocopherols that affect the partitioning of the tocopherols and increase or alter their antioxidant effect. Here again, some results are contradictory meaning more research is required to elucidate the specific

mechanisms. Yet, these results suggest that the conception of new antioxidant systems involving interactions between tocopherols and surfactants could be promising in emulsified systems. Similarly, a better understanding of how tocopherols interact with association colloids present in bulk oils should also help to optimize activity against lipid oxidation.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

Nathalie Barouh: Conceptualization; data curation; formal analysis; investigation; methodology; writing—original draft; writing—review and editing. Claire Bourlieu-Lacanal: Conceptualization; formal analysis; methodology; writing—review and editing. Erwann Durand: Conceptualization; visualization; Writing—review & editing and Pierre Villeneuve: Conceptualization; methodology; visualization; Writing—review & editing. Maria-Cruz Figueroa-Espinoza: Visualization; Writing—review & editing conceptualized the idea of the study. Nathalie Barouh, Claire Bourlieu-Lacanal, and Pierre Villeneuve performed methodology. Nathalie Barouh performed investigation, curated the data, and prepared the original draft. Nathalie Barouh and Claire Bourlieu-Lacanal performed formal analysis. Nathalie Barouh, Erwann Durand, and Maria Figueroa-Espinoza performed visualization. All authors wrote, reviewed, and edited the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Barouh, N., Bourlieu-Lacanal, C., Figueroa-Espinoza, M. C., Durand, E., & Villeneuve, P. (2022). Tocopherols as antioxidants in lipid-based systems: The combination of chemical and physicochemical interactions determines their efficiency. *Compr Rev Food Sci Food Saf. 21,*642–688. https://doi.org/10.1111/1541-4337.12867