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Revisiting the Polar Paradox Theory: A Critical Overview

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ABSTRACT: The polar paradox is a theory that illustrates the paradoxical behavior of antioxidants in different media and rationalizes the fact that polar antioxidants are more effective in less polar media, such as bulk oils, while nonpolar antioxidants are more effective in relatively more polar media, such as oil-in-water emulsions or liposomes. For 2 decades since it was proposed, the theory has been used to interpret results in antioxidant efficiency studies. However, more recently, new evidence from more comprehensive assessments has emerged that contradicts the polar paradox theory, hence necessitating its re-evaluation. More complex factors in addition to polarity must be taken into account to explain antioxidant efficacy.

KEYWORDS: Polar paradox, antioxidants, bulk lipids, emulsion

1. LIPID OXIDATION AND ANTIOXIDANTS

Lipids are important components of food and biological systems and are susceptible to oxidation that may occur at any stage of food processing and storage, as well as under physiological and/or pathophysiological conditions in living organisms. Lipid oxidation has been a major concern to food scientists and consumers as a major cause of food-quality deterioration and many health complications, including cardiovascular disease and cancer. Lipid autoxidation is a complex process of the free-radical-mediated chain reaction, whose detailed mechanism of action has not yet been fully unravelled. However, it proceeds through three stages of initiation, propagation, and termination and involves initiators or promoters, such as heat, light, oxygen, enzymes, transition metals, metalloproteins, and/or microorganisms. Lipid oxidation pathways and methods of improving its oxidative stability have been discussed elsewhere.[1]

Among the methods employed for preventing lipid oxidation, the addition of antioxidants is the most effective, convenient, and economical strategy for stabilizing food and non-food commodities.[2] Antioxidants can prevent or delay oxidation by scavenging free radicals, quenching singlet oxygen, inactivating peroxides and other reactive oxygen species (ROS), chelating pro-oxidant metal ions, quenching secondary oxidation products, and inhibiting pro-oxidative enzymes, among others.[3] The effectiveness of antioxidants is determined by their chemical structures and may vary depending upon the concentration, temperature, type of oxidation substrate, and physical state of the system media, as well as the presence of antagonists and synergists.[4] Therefore, all relevant factors must be taken into account when selecting or designing antioxidants for a particular application. For example, antioxidants are found to behave differently when used in various media; their activity in bulk oil is different from that in oil-in-water emulsion systems.

With respect to antioxidant effectiveness in different lipid media, the "polar paradox theory" was proposed, which states that polar antioxidants are more effective in less polar media, such as bulk oils, while nonpolar antioxidants are more effective in relatively more polar media, such as oil-in-water emulsions or liposomes.[5] The polar paradox hypothesis has been tested and confirmed by a number of studies using antioxidants of different polarity and rationalized by the interfacial phenomenon. The theory has been generally accepted and used to interpret results in antioxidant studies. However, more recently, new evidence from more comprehensive assessments has emerged that disagrees with the polar paradox, hence necessitating a revisit to this theory.

2. POLAR PARADOX THEORY

Discovery of lipid oxidation and its health implications prompted extensive studies on antioxidants in the late 20th and early 21st century. Among the large body of antioxidant effectiveness data generated from the early studies, there was an obvious emphasis on the use of bulk oils and fats, while antioxidant efficiencies in colloidal displays were often extrapolated from bulk lipid. However, the low surface/volume (LSV) ratios of bulk oils do not necessarily represent the high surface/volume (HSV) ratios of emulsions, micelles, liposomes, biological membranes, and whole tissues, which may affect the oxidation mechanisms and antioxidant behavior. Porter[6] brought up the issue and summarized effectiveness of antioxidants in dry oils and emulsions in relation to their polarity (obtained by ultra-thin layer chromatography tests), after which he proposed the polar paradox hypothesis; i.e., primary antioxidants that are polar or are amphiphiles of high hydrophilic−lipophilic balance (HLB) tend to be more active in bulk oils (LSV), a nonpolar medium, whereas nonpolar or amphiphilic antioxidants with low HLB tend to be more active in polar emulsions (HSV) and polar lipids. Early evidence that supported this hypothesis included studies on trolox, ascorbic, gallic, caffeic, and ferulic acids, among others, which exhibited higher antioxidant efficacies in bulk oil and lower efficacies in emulsions than their correspondent nonpolar alkyl esters.[7−11] In addition, synthetic lipophilic antioxidants, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), were found to be more active in emulsions than in dry lard or vegetable oil; α-, β-, γ-, and δ-tocopherols showed opposite trends in efficacy in liposomes and bulk oil.[12]

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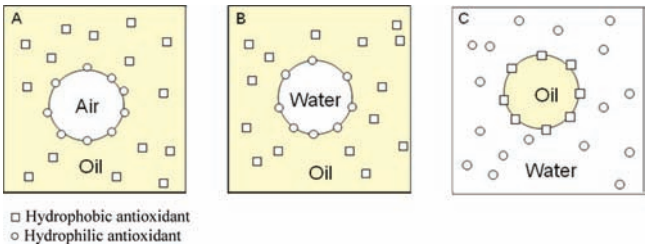

Figure 1. Distribution of antioxidants in (A and B) bulk oil and (C) oil-in-water emulsion according to interfacial phenomena and polar paradox.

A reciprocal relationship was also observed in a homologous series of gallates, among which the less alkylated gallates were more effective in dry oils, while gallates with longer alkyl chains were more effective in emulsions.[13]

The polar paradox hypothesis has significance in the food and medicinal applications of antioxidants, especially in developing new antioxidant strategies, such as producing lipophilic derivatives of naturally occurring antioxidants for use in emulsions, liposomes, and other biological media, because there are very few promising lipophilic or low HLB antioxidants from natural sources. Inspired by the naturally occurring long-chain alkyl esters of caffeic and ferulic acids in shelled oats and sterol and triterpene alcohol esters of caffeic acid in canary seed, a number of "phenolipids" has been synthesized as antioxidant candidates for diverse systems. These phenolipids are ester products of phenols with fatty acids or phenolic acids with fatty alcohols. They display enhanced lipophilicity, and some have shown improved antioxidant activity compared to their parent phenolic compounds in emulsions, whole tissue foods, liposomes, and other HSV media, in agreement with the polar paradox.[14,15]

2.1. Antioxidants in Bulk Lipids. The paradoxical behavior of antioxidants remained an empirical observation until its explanation by the interfacial phenomenon, which turned the polar paradox from an empirical observation into a putative theory. It was found that, in addition to its innate potency, the effectiveness of an antioxidant was also affected by its interfacial properties and partition in the medium.[16]

The physical nature of the lipid medium has a considerable impact on the antioxidant efficacy. Early studies on oxidation in bulk oils were based on the assumption that oxidation occurs in a homogeneous medium. The oil−air interface was considered to be the site where oxidation was initiated and propagated to the inner parts of the oil. The partially fat-soluble polar antioxidants oriented themselves in the oil−air interface, where surface oxidation occurs (Figure 1A) and, therefore, protected the system from oxidative changes.[5,16] However, the distribution of polar antioxidants at the oil−air interface was questioned because air is even less polar than oil. It was later recognized that various micro- or nanoenvironments existing in edible oils affect the chemistry of lipid oxidation and antioxidant action through altering the physical location of lipid substrates and antioxidants.[17] For example, different types of association colloids, including lamellar structure and reverse micelles (in the presence of trace amounts of water from atmospheric moisture), may be formed from self-assembly of amphiphilic compounds naturally occurring as lipid components (e.g., phospholipids) or produced as oxidation products (e.g., hydroperoxides, aldehydes, and ketones). There is now a considerable body of evidence that supports the hypothesis that association colloids are the site of lipid oxidation in bulk oils. Polar antioxidants, instead of being distributed at the oil−air interface, as previously believed, are in fact preferentially located at the interface of the colloids (e.g., oil−water interface) and are hence more effective in inhibiting oxidation than the nonpolar ones that are dissolved in the lipid phase (Figure 1B). This was supported by the fact that, while polar antioxidants were unable to decrease the surface tension, they did decrease the interfacial tension.[17]

Better efficacy of polar antioxidants in bulk oils has been reported for eriodictyol and caffeic acid, which exhibited better antioxidant activity than the lipophilic BHT.[16] Mateos et al.[18] prepared a series of alkyl ester derivatives (acetate, butyrate, laurate, palmitate, stearate, and oleate) of tyrosol and hydroxytyrosol and found that the lipophilic esters acted as weaker antioxidants in a bulk oil model system compared to the original phenols. In addition, lipophilic hydroxytyrosol ethers (methyl to octadecyl hydroxytyrosol) also showed lower antioxidant activity in bulk oil (measured by the Rancimat method) than hydroxytyrosol itself. In fact, their antioxidant activity followed the order of hydroxytyrosol > hydroxytyrosol ethers > BHT/α-tocopherol, which is in agreement with the polar paradox theory.[19]

2.2. Antioxidants in Emulsions. In addition to the bulk oil state, the unsaturated lipid substrates are present in heterogeneous systems, such as emulsified matrix in foods, cosmetics, and biological environments, including micellar dispersion, emulsion, liposome, and lipoprotein, and are the prime target of oxidation. In fact, it has been recognized that HSV emulsions are the natural conditions, while LSV bulk lipid is more like an artifact that is less common in foods and biological systems. Many food lipids exist as oil-in-water emulsions (e.g., milk, mayonnaise, dressings, dips, sauces, beverages, ice cream, etc.), which are often more susceptible to oxidation than bulk oils because of their higher surface areas that promote interaction of the oil with pro-oxidants in the aqueous phase.

An oil-in-water emulsion generally consists of three essential parts: the lipid droplets, the continuous aqueous phase, and the oil−water interface, where emulsifiers and other surface active compounds are located. The various lipid or nonlipid components (e.g., pro-oxidants and antioxidants) in an emulsion partition themselves among the three different parts according to their solubility characteristics and surface activity, which are in turn determined by their chemical structures and polarity.[17] Antioxidants added to an oil-in-water emulsion exhibit different effectiveness compared to when included in bulk oils because of the existing differences in the physical nature of the two systems.[20] According to the polar paradox, oil-in-water emulsions, in contrast to bulk oils, are better protected from oxidation by nonpolar antioxidants than by polar ones. The higher effectiveness of nonpolar antioxidants in oil-in-water emulsions is primarily attributed to their greater affinity for the oil−water interface. Nonpolar or amphiphilic antioxidants with low HLB are mainly concentrated at the oil−water interface, forming a protective membrane around the lipid droplet, while polar antioxidants are predominantly dissolved in the aqueous phase[16,21] (Figure 1C). Free radicals are scavenged by lipophilic antioxidants at the interface before they can cross the droplet membrane and enter the lipid phase. Localization of antioxidants in the interface of multiphase systems in relation to their polarity was confirmed by the fact that dodecyl chlorogenate decreased interfacial tension (in water/hexadecane) much more than octyl and butyl esters.[22]

Relatively high efficacies of lipophilic antioxidants in heterogeneous lipid systems in comparison to hydrophilic ones have

been reported, supporting the polar paradox theory.[23−26] Cuvelier et al.[25] investigated the activity of 17 phenolic antioxidants on emulsified linoleic acid oxidation induced by iron/ascorbic acid and associated the results with their polarity, the presence of phenolic hydroxyl groups, and metal chelation sites. Their results revealed that the lipophilic antioxidants, α-tocopherol, BHA, and BHT, were among the most efficient antioxidants regardless of the absence of chelation site and single phenolic hydroxyl group in the molecules, suggesting the possible role of antioxidant polarity and partitioning in the medium. The authors concluded that, despite the exceptionally high antioxidant activity of quercetin and isoquercetin, the polar paradox was the strongest factor affecting the efficiency of phenolic antioxidants in the dispersed medium.

3. CHALLENGE TO THE POLAR PARADOX

The polar paradox hypothesis shed light on the effect of the physical nature of lipid medium on antioxidant activity. It has played an undoubtedly positive role in bringing attention to the irrelevance of extrapolating antioxidant effectiveness from bulk oil to emulsions. However, the theory has recently faced challenges as more thorough studies are carried out and inconsistent results are revealed, some of which are not explained or are contradicted by the polar paradox theory. Therefore, it is imperative to re-evaluate the polar paradox theory for a better understanding of antioxidant behavior as affected by their polarity and physical nature of the lipid medium.

Torres de Pinedo et al.[27] studied antioxidant activity of a series of hydroxytyrosol derivatives containing different alkyl chain lengths linking the phenyl ring to the primary alcohol and found that the trend of their antioxidant activity in bulk oil contradicted the polar paradox theory. It has also been demonstrated that lipophilic antioxidant derivatives are not always advantageous in oil-in-water emulsions over their hydrophilic counterparts in terms of antioxidant activity.[22,28,29] A nonlinear relationship existed between polarity and antioxidant efficacy in emulsions for phenolic antioxidants and their alkyl esters, including chlorogenic, rosmarinic, and gallic acids.[28,30,31] Provided that the data supporting or contradicting the polar paradox are both reliable, it may hence be suggested that the polar paradox theory may be a particular case of a much wider global rule. In other words, the linear influence of polarity on antioxidant activity is simply a particular part of a broader nonlinear response. Action of antioxidants is possibly governed by more complex phenomena, and other factors, in addition to polarity, must be taken into account to explain efficiency, examples of which include the mobility and micellization of the antioxidants, as well as the presence and type of emulsifiers in the system.

3.1. Impact of the Molecular Structure on Antioxidant Activity. The polar paradox theory illustrates the activity of antioxidants in relation to their polarity; however, the ways to modulate polarity of antioxidants in many studies pose a challenge to the validity of the assessments. Early studies often attempted to make a universal comparison of efficiencies among antioxidants of varying polarity while ignoring the difference in their innate potency, and the conclusions derived are hence arbitrary. For example, it is inappropriate to attribute the difference in efficiency of ascorbic acid and BHT solely to their polarity. This was improved in later studies by employing a series of homologous compounds in the same category. However, changes of polarity by adding or removing ring substituents in some cases may lead to changes in the O−H bond dissociation enthalpy (BDE) and hence the antioxidant potency of the molecules, which may give a false indication of antioxidant activity in response to polarity.

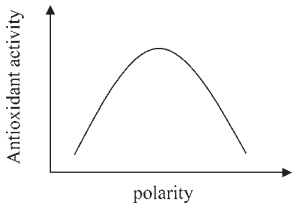

Figure 2. Cutoff effect of antioxidant activity in response to polarity.

Table 1. Optimal Alkyl Chain Length of Lipophilic Phenolic Derivatives as Antioxidants in Emulsions

phenolic antioxidant	derivative with the maximum efficacy	reference
chlorogenic acid	C12 (dodecyl) ester	32
rosmarinic acid	C8 (octyl) ester	30
hydroxytyrosol	C12 (laurate) ester	36
dihydrocaffeic acid	C8 (octyl) ester	37
rutin	C12 (laurate) ester	37

In the studies where a homologous series of antioxidants is investigated, the size of the antioxidant molecule seems to interfere with the activity−polarity relationship. Nonlinear behavior has been reported for lipophilic alkyl esters of phenolic antioxidants in emulsified medium; i.e., antioxidant activity increases as the alkyl chain lengthens until a threshold is reached, after which further chain length extension leads to a drastic decrease in activity.[30−32] This nonlinear phenomenon, referred to as the cutoff effect (Figure 2), has largely been observed in cultured cell studies and for a diverse range of biological activities, such as antimicrobial, anesthetic, and cytotoxic properties, which increase with hydrophobicity up to a certain level and then begin to diminish.[33−35] Several studies have revealed that short−medium-chain lipophilic esters are able to improve the efficacy of phenolic antioxidants in emulsion better than long-chain esters (Table 1). For instance, among the homologous series of chlorogenic acid esters (methyl, butyl, octyl, dodecyl, hexadecyl, octadecyl, and eicosyl), the highest antioxidant activity was observed for dodecyl chlorogenate.[32] Octyl rosmarinate was found to be more effective than rosmarinic acid and its eicosyl ester.[30] Hydroxytyrosyl laurate exhibited similar or even decreased antioxidant efficacies when compared to its acetate, butyrate, and octanoate counterparts in an oil-in-water emulsion.[36] The cutoff effect was also observed for lipophilized dihydrocaffeic acid and rutin esters. Octyl dihydrocaffeate was a stronger antioxidant than oleyl dihydrocaffeate, and rutin laurate was a stronger antioxidant than rutin palmitate.[37]

The nonlinear behavior or cutoff effect of antioxidants in emulsified media may be explained by their partitioning, location, and mobility in the multiphase system, which are influenced by both polarity and their molecular size. As already mentioned, the partitioning properties of antioxidants in heterogeneous systems are crucial for their activities. It was found from partition analysis that the concentration of chlorogenates in the aqueous phase decreased with increased alkyl chain length, with the dodecyl ester presenting the lowest concentration, which correlated well with their antioxidant efficacies.[32] Further extension in chain length (above 12 carbon atoms) resulted in an unexpected

increase in partitioning in the aqueous phase. The authors suggested that this could be due to the micellization process of the long-chain chlrogenates, facilitating their existence as micelles or other aggregates in the water phase. The esters with long alkyl chains are generally amphiphilic and may aggregate readily in the medium rather than orienting themselves at the interfacial layer.

There are, however, situations that the overall partitioning of antioxidants is not responsible for differences in activity. For example, the chlorogenates showed no improvement in antioxidant activity when the alkyl chain length increased from 0 to 8 carbon atoms, while a constant concentration decrease in the water phase was observed.[32] In the case of rosmarinates, the dodecyl ester showed the lowest partitioning in water, while the highest antioxidant efficacy was reported for the octyl ester.[30] It is suggested that, in addition to the partitioning, the exact location of antioxidants in the discontinuous phase (interfacial layer or oil droplet) is important for the activity of the antioxidants involved. As the chain length increases, the lipophilicity increases and the partitioning into the discontinuous phase increases up to a maximum level, after which the antioxidants may be driven from the interface of the emulsion to the core of the oil droplet.[30] The highly hydrophobic antioxidants located in the oil droplets provide less protection against oxidation than those located at the interface, which may explain, to some extent, the cutoff effect. Moreover, the orientation and the depth of location of antioxidants in the interfacial layer as well as the interaction with the membrane may also affect their effectiveness. For example, the lipophilic eicosapentaenoate ester of epigallocatechin gallate (EGCG) prepared in our laboratory had a higher rate of incorporation into liposome but displayed a lower antioxidant activity than the EGCG itself.[14] Some polyphenols are located on the membrane surface, while others may permeate deeper into the hydrophobic region of the lipid bilayers, as observed for different catechins.[38,39] It has been suggested that antioxidants located on the membrane surface or those (interface antioxidants) located in the polar region of the bilayer near the hydrophobic−hydrophilic border are effective in protecting the membranes against oxidation.[40] On the other hand, some antioxidants may even perturb the membrane, leading to compromised protection or even a pro-oxidant effect.[39,41]

The molecular size of antioxidants may also influence their effectiveness by decreasing their mobility in the multiphase system, resulting in the cutoff effect. Antioxidants with bulky structures, such as phenolic derivatives containing long alkyl chains, have lower mobility, because of steric hindrance, than those with a smaller size and, thus, decreased diffusibility toward the reactive centers, i.e., oxidizable substrates and free radicals.[42] Moreover, the increase in the alkyl chain may also introduce a hydrophobic interaction between the antioxidant molecule and the environment (e.g., the emulsifiers or membrane), leading to decreased mobility and diffusion of the antioxidant to the oxidation site.[28,43]

3.2. Other Challenges to the Polar Paradox Theory. In addition to the cutoff effect as a result of molecular size, applicability of the polar paradox has also been questioned in other situations. For example, the quantity and type (cationic, anionic, and non-ionic) of emulsifier in a heterogeneous system can drastically change the effectiveness of antioxidants, altering the polarity−effectiveness relationship proposed by the polar paradox theory.[28,44] The effect of the emulsifier on antioxidant activity is mostly through modification of antioxidant distribution in the emulsified medium. The emulsifier saturates the interfacial membrane, thus leaving less interfacial area available for antioxidants. In other words, emulsifiers compete with antioxidants for localization at the interface, where oxidation is prevalent. Moreover, emulsifiers in high quantities (above the critical micelle concentration) form micelles, which may trap antioxidants in these self-assembled structures and carry them to the water phase. Therefore, mass transfer of antioxidants in emulsions between micelles and the oil−water interface must be taken into consideration. The non-ionic emulsifiers are more likely to facilitate antioxidant exchange between micelles and the interface; i.e., antioxidants can diffuse freely between the phases and pseudo-phases, while ionic emulsifier micelles may not allow for a sufficient approximation of micelles and the interface because of electrostatic repulsion.[45,46] It has been hypothesized that the antioxidants solubilized by the micellar pseudo-phase are not so active,[46] thus compromising the overall antioxidant activity in the emulsion system.

The concentration of an antioxidant seems to affect the polarity−effectiveness relationship. Preliminary results in our laboratory suggest that the polar paradox is only applicable over certain concentration ranges. When the antioxidant activity of EGCG is compared to its lipophilic ester derivative (stearate) in bulk oil, it was found that, at lower concentrations, the ester was more active, while EGCG was more active at higher concentrations.[14] It is hypothesized that, at low concentrations, the effect of solubility in oil dominates over the effect of interfacial phenomenon on antioxidant efficiency; thus, nonpolar antioxidants with better fat solubility have greater efficacies than their polar counterparts, whereas the reverse is true at higher concentrations. Our preliminary results have also revealed a similar trend for trolox/α-tocopherol, ascorbic acid/ascorbyl palmitate, and gallic acid/propyl gallate. It is thus possible that the polar paradox theory only applies when the antioxidant reaches a critical concentration, so that interfacial phenomenon dominates over the solubility issue. However, more research is needed for confirmation of this hypothesis.

In addition to the factors mentioned above, the mechanism of action of an antioxidant in inhibiting oxidation may influence its activity in multiphase media, thus interfering with its polarity−activity relationship. Some antioxidants prevent or retard initiation of oxidation by quenching the initiators, while others minimize the oxidative damage by breaking the propagation chain. For initiator quenchers, the polar antioxidants can inhibit the initiation of oxidation at the interface (where most initiators are located) more effectively than nonpolar ones in the lipid phase, whereas the reverse is true for chain-breaking antioxidants. This is due to the fact that nonpolar chain-breaking antioxidants are more efficient in inhibiting the propagation reaction in the lipid phase, where the nonpolar oxygen molecules are preferentially dissolved. It is also worth noting that some phenolic antioxidants may act as pro-oxidants at higher concentrations,[47−49] giving rise to false indication of antioxidant activity in response to polarity. Pro-oxidant activity of phenolic compounds may arise from metal reduction or the formation of phenoxyl radicals that can initiate radical chain reactions at high concentrations.

In summary, the polar paradox theory successfully explained the different behaviors of antioxidants in various media over the last 2 decades. However, the activity−polarity relationship proposed by the polar paradox theory needs to be reconsidered as more contradictory results are being reported. It is suggested that the polar paradox theory may be a particular case of a much wider global picture. Hence, more comprehensive studies are

required to better understand the behavior of antioxidants in different media.

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