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Lycopene, oxidative cleavage derivatives and antiradical activity

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ABSTRACT

The principal aim of this investigation is to study free radical scavenger capacity of oxidized derivatives of lycopene (LYC) that were reported before as bioactive derivatives/metabolites. The electron transfer mechanism is analyzed in terms of its ionization energies and electron affinities. Lambda maximum (λ_{max}) values are also included. Electron affinity increases and ionization energy decreases as the number of carbon atoms in the backbone and the number of conjugated double bonds augment. The presence of OH improves the electron donor capacity, whereas the presence of the aldehyde group raises the electron acceptor capacity. Di-aldehyde derivatives appear as the best electron acceptors among the molecules investigated. The increased power to accept electrons on the part of the oxidized derivatives may influence anti-cancer properties. Here we report the electronic differences between these molecules. This information will aid in the understanding of different possible mechanisms that may be involved in the prevention of some illnesses like cancer, as reports exist indicating that some of these metabolites can be formed in vivo and are biologically active.

1. Introduction

Lycopene (LYC) is a red carotenoid that can be produced by some plants and microorganisms [1]. It is a natural compound that is omnipresent in the diet of humans all over the world as it is present not only in tomatoes and derivatives but also in watermelon, guava, pink grapefruit and papaya, among others [2,3]. LYC has been shown to exhibit a considerably high antioxidant capacity [4–14] and is associated with a wide spectrum of potentially beneficial health outcomes [15–25]. In this sense, anti-cancer potential is considered to exist [17–25] particularly against prostate cancer [22,23], although causality has not been clearly established due to inherent difficulties. In contrast to the effect of β-carotene among certain risk groups, in the case of LYC there is no observed association between elevated risk of lung cancer and its long-term use as a dietary supplement [24].

LYC has a highly unsaturated structure and can thus be easily oxidized. A typical methodology for obtaining oxidative cleavage derivatives of carotenoids consists in the use of potassium permanganate as an oxidizing agent. For instance this has been used with LYC and β-carotene [26,27] although studies on the interaction of LYC oxidative cleavage derivatives with oxidizing agents are lacking. However, it has recently been shown that the cleavage of β-carotene into a number of these derivatives is accompanied by noticeable changes not only in color but also in antioxidant capacity [28]. More importantly, mammals are known to codify oxygenase enzymes that catalyze the oxidative cleavage of provitamin A carotenoids into retinoids (usually referred to as β,β-carotene 15,15′-monooxygenase 1) and of both provitamin A and non-provitamin A carotenoids (like LYC). The latter enzyme (usually termed as β,β-carotene 9′,10′-dioxygenase) cleaves the carotenoids eccentrically at both the 9,10 and 9′,10′ double bonds, producing oxidized non-volatile apocarotenoids, as well as oxidized volatile cleavage products [29]. Interestingly, the presence of some cleavage oxidative metabolites from LYC has been reported in human plasma [30].

Currently it is thought that these cleavage oxidative metabolites may be biologically active and be involved in some of the actions traditionally attributed to the parent carotenoids [31,32]. Some of the products of LYC that may present bioactive properties include apo-lycopenals, apo-carotenedials, apo-lycopenones, carboxylic acids and epoxides [33–37]. Therefore, a mixture of LYC oxidation products has manifested an enhanced ability to inhibit the growth of leukemia cells [33]. On the other hand, apo-10′-lycopenoic acid appears to promote lung cancer cell growth activity and to suppress lung tumorigenesis [35].

Some efforts have been made to correlate the chemical structure of these compounds with their reactivity [36]. It appears that chemical reactivity is related to the position of the first methyl

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group (with respect to the terminal aldehyde group) and the number of carbon atoms in the backbone chain. The optimal backbone has 12 carbon atoms and the most active derivatives are those with the methyl group located at a distant position. Fig. 1 shows the chemical structure of possible bioactive lycopene cleavage derivatives.

There are several reports concerning the antiradical activity of LYC and it has been reported that one of the mechanisms is the electron transfer reaction between carotenoids and the reactive oxygen species. The electron transfer reaction with the superoxide anion is special, given that in this case the carotenoids accept rather than donate electrons. From this perspective, the antiradical activity of carotenoids against the superoxide ion is related to the capacity to prevent the formation of reactive oxygen species [6,12–14]. It has been reported that very high doses of β-carotene supplementation can increase the risk of lung cancer among smokers and other risk groups [24]. LYC was also included in this investigation, and it has been proved that there is no correlation between cancer risk and the doses of lycopene; however nothing is known about the bioactive derivatives of lycopene.

Even though there are reports about the antiradical activity of lycopene and carotenoids and about the activity of lycopene bioactive derivatives as anticancer substances, little if anything is known about the correlation between the electronic structure and the capacity of lycopene derivatives to prevent oxidative stress. In this report, optimized structures of bioactive derivatives are reported. The oxidized derivatives of LYC used in this investigation are included in Fig. 1, and were reported before [37] as bioactive derivatives/metabolites. Additional derivatives, including mono and di-aldehyde derivatives, are also included to emphasize the trend according to the functional groups. The electron transfer mechanism is analyzed in terms of the ionization energies (IE) and electron affinities (EA). In order to analyze the correlation between the presence of conjugated doubles bonds (cdb) and the emission–absorption spectra, lambda maximum (λ_{max}) values are also included.

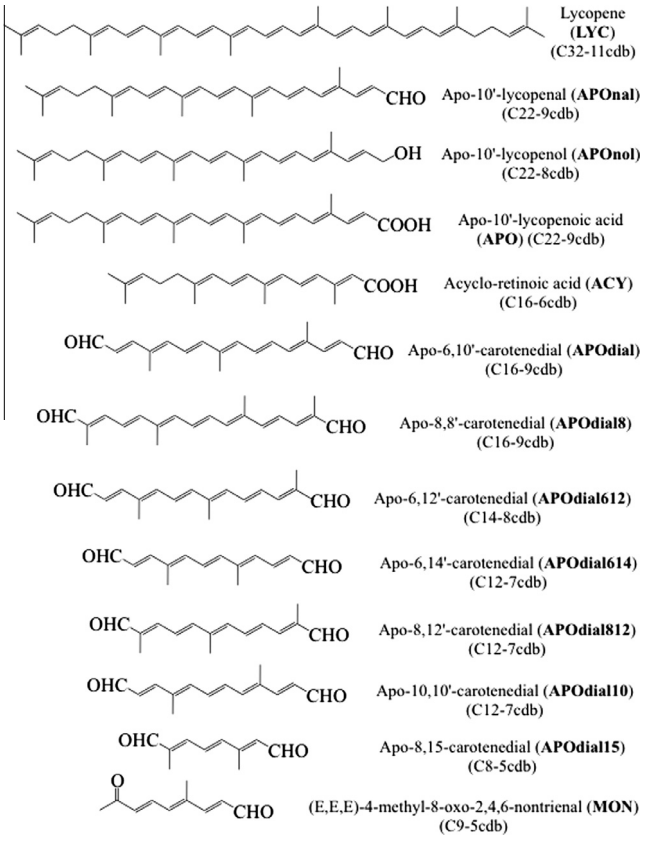


Fig. 1. Molecular structures of lycopene and its bioactive derivatives used in this investigation.

2. Computational details

Gaussian 09 implementation [38] is used to calculate geometry optimization and electronic properties of twelve bioactive derivatives of LYC (Fig. 1). LYC is included for comparison. Initial geometries are fully optimized at B3LYP/6-31G(d) level of theory [39,40]. In order to verify optimized minima, harmonic analyses are performed and local minima are identified (zero imaginary frequencies). The λ_{max} values are obtained by applying time-dependent density functional theory (TDDFT) at CAM-B3LYP/6-311+g(d,p) level of theory [41].

CAM-B3LYP is a relatively new Coulomb-attenuated hybrid exchange–correlation functional that adequately predicts molecular charge-transfer spectra [41]. Likewise, qualitatively good predictions for the spectra of porphyrin, some oligoporphyrins, and chlorophyll were reported; as well as concurring very well with complete-active-space plus second-order Møller–Plesset perturbation theory and symmetry-adapted cluster configuration interaction calculations [42,43]. With this methodology, λ_{max} for LYC in gas phase is 507 nm but if heptane is considered as the solvent, it is equal to 541 nm. The experimental value in hexane is 472 nm. Comparing these two last values, the error is 14%. As we intend to assess tendencies and the differences between the values associated with different functional groups, but are not interested in the exact value of λ_{max}, we consider that we can use these results for the purpose of comparison.

In order to investigate the single electron transfer mechanism, vertical ionization energy (IE) and vertical electron affinity (EA) are obtained from single point calculations of cationic and anionic molecules, using the optimized structure of the neutrals and the B3LYP/6-311+g(d,p) level of theory. A useful tool defined previously is the Full Electron Donor Acceptor Map (FEDAM) [12–14,44,45] In this map (see Fig. 2) IE and EA are plotted and allow us to classify substances as either donors or acceptors of electrons. Electrons will be transferred from molecules located down to the left of the map (good electron donors) to those molecules that are up to the right (good electron acceptors).

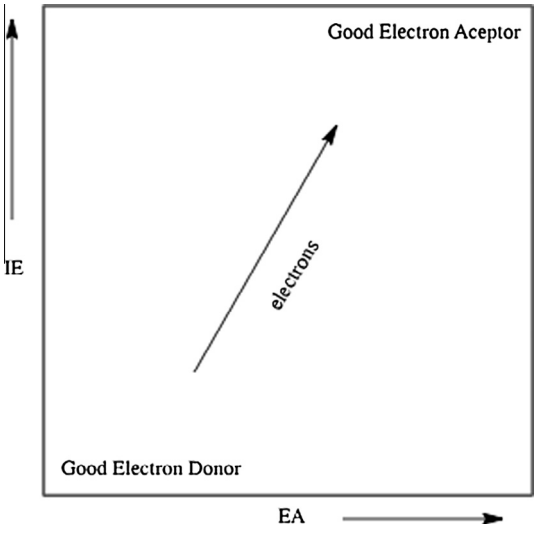


Fig. 2. Full electron donor–acceptor map.

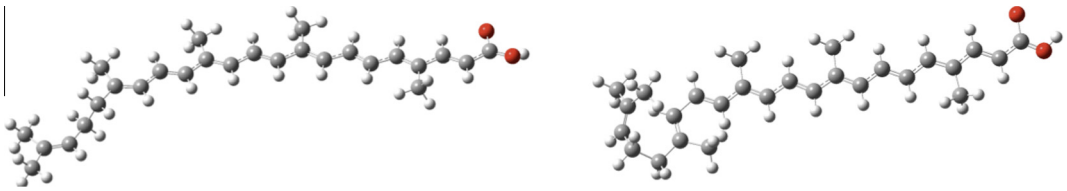
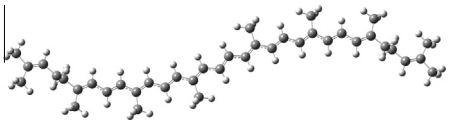
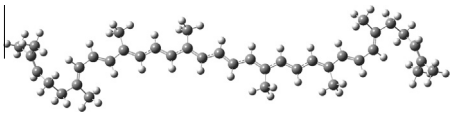
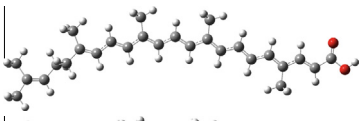
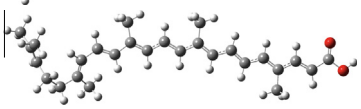
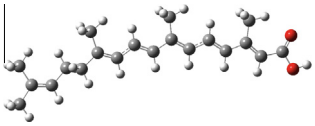
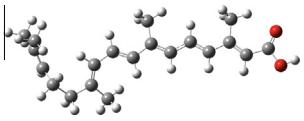


Fig. 3. Two possible initial geometries for APO. One is stretched and the other one is twisted within one side of the molecule.

Table 1
Optimized structures, relative energy, IE, EA and λ_{max} of two different isomers of LYC, APO and ACY.

Optimized structures	ΔE (kcal/mol)	IE (eV)	EA (eV)	λ_{max} (nm)
Lycopene (LYC)				
	0.0	5.51	1.67	507
	11.95	5.55	1.60	497
Apo-10′-lycopenic acid (APO)				
	0.0	6.14	1.76	461
	5.93	6.18	1.73	456
Acyclo-retinoic acid (ACY)				
	0.0	6.77	1.27	373
	5.90	6.85	1.22	370

3. Results and discussion

LYC derivatives are molecules with conjugated double bonds that are normally stretched but which could be bent. In order to analyze the energy difference between the stretched and the twisted configurations, two possible initial geometries were tested for LYC and two derivatives: Apo-10′-lycopenic acid (APO) and acyclo-retinoic acid (ACY). One of the initial geometries is completely stretched and the other one is twisted within one side of the molecule. For example Fig. 3 reports, the two initial geometries used in the optimization for APO. In Table 1, we report the optimized structures of these three molecules, the energy difference between twisted and stretched structures, IE, EA and λ_{max}.

The stretched structure of LYC is more stable than the bent structure by 11.95 kcal/mol. In this case, only the extended structure is expected in an experiment. For APO and ACY, the stretched structures are more stable than the twisted ones by 5.93 and 5.90 kcal/mol, respectively and we can suppose that they are able to coexist in an experiment. For each isomer, IE and EA are similar and they are not affected by the geometry. As expected, λ_{max} is higher for stretched structures than for bent geometries. The conjugated double bonds produce π bonds where the electrons are delocalized. These π orbitals are not present in the bent portion of the molecules. This increases the excitation energies, reducing the λ_{max}. The comparison between stretched and bent structures is important because these molecules are most likely to be located within the membrane of the cells, and may manifest both configurations. It would thus be interesting to see if the properties assessed in this study are different depending on the geometrical configuration. Apparently, this is not the case, at least theoretically, since IE and EA are similar for both isomers. It is reasonable to hypothesize that these molecules will be stretched rather than being bent, although they may coexist in the membrane. Should this be the case, their properties as free radical scavengers would be virtually the same.

Tables 2 and 3 present the optimized structures, IE, EA and λ_{max} values for LYC and all the derivatives that we are analyzing. The largest λ_{max} value is for LYC followed by APOnal and APO. It is well known that the absorption–emission spectrum is related to the number of conjugated double bonds (cdb). The increment of λ_{max} coincides with the increase in the number of conjugated double bonds. Among the molecules studied, LYC is the one with the largest number of conjugated double bonds and it is the molecule with the largest value for λ_{max}.

Table 2
Optimized structures, IE, EA and λ_{max} of LYC and four oxidized derivatives of LYC.

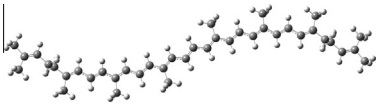
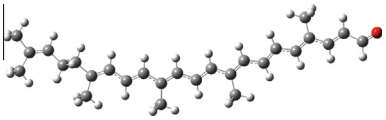
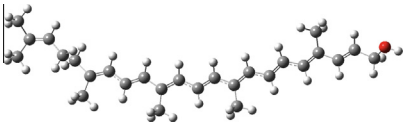
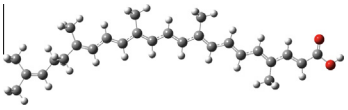
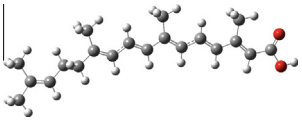
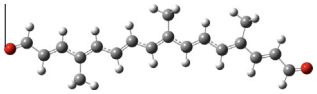
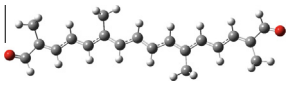
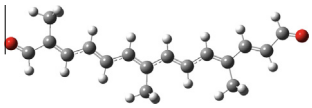
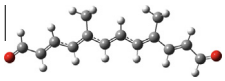
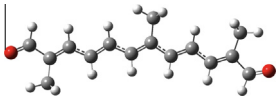
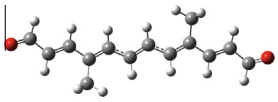
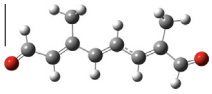
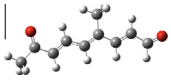
Optimized structures	IE (eV)	EA (eV)	λ_{max} (nm)
Lycopene (LYC) [C32-11cdb] 	5.51	1.67	507
Apo-10′-lycopenal (APOnal) [C22-9cdb] 	6.21	1.87	466
Apo-10′-lycopenol (APOnol) [C22-8cdb] 	5.90	1.35	437
Apo-10′-lycopenoic acid (APO) [C22-9cdb] 	6.14	1.76	461
Acyclo-retinoic acid (ACY) [C16-6cdb] 	6.77	1.27	373

Table 3
Optimized structures, IE, EA and λ_{max} of di-aldehydes derivatives of LYC and MON.

Optimized structures	IE (eV)	EA (eV)	λ_{max} (nm)
Apo-6,10′-carotenedial (APOdial) [C16, 9cdb] 	6.93	2.28	440
Apo-8,8′-carotenedial (APOdial8) [C16, 9cdb] 	6.82	2.26	449
Apo-6,12′-carotenedial (APOdial612) [C14, 8cdb] 	7.15	2.19	416
Apo-6,14′-carotenedial (APOdial614) [C12, 7cdb] 	7.59	2.11	378
Apo-8,12′-carotenedial (APOdial812) [C12, 7cdb] 	7.40	2.10	392
Apo-10,10′-carotenedial (APOdial10) [C12, 7cdb] 	7.56	2.12	383
Apo-8,15-carotenedial (APOdial15) [C8, 5cdb] 	8.48	1.82	317
(E,E,E)-4-methyl-8-oxo-2,4,6-nontrienal (MON) [C9-5cdb] 	8.44	1.71	315

Analyzing the results from Tables 2 and 3, what is noteworthy is the influence of the functional groups on the λ_{max} values. APOnal has 9 cdb (8 in the hydrocarbon backbone plus one in the carboxylic group). Comparing with APO which also has 9 cdb, the λ_{max} is greater for the first than for the second. The difference between these two molecules is the presence of the OH in the carboxylic group, which notably affects the value of λ_{max}. Similar results were reported for other carotenoids. Astaxanthin has two carboxylic acid groups and present larger values of λ_{max} (reddish hue) than β-carotene (orangeish hue) that does not have carboxylic groups. Comparing values from Tables 2 and 3, λ_{max} is in a range of 373 and 466 nm for molecules with 6–9 cdb. For molecules with 5–7 cdb, λ_{max} is lower than 400 nm but higher than 300 nm and therefore they are in the ultraviolet region. The excitation of these molecules is energetically more demanding than the previous examples.

Analyzing IE and EA values of Tables 2 and 3, it is evident that, in general, di-aldehydes (Table 3) present higher IE and EA values than LYC and other derivatives (Table 2). This means that they are not good electron donors but they are the best electron acceptors. Fig. 4 reports the FEDAM of all the molecules under study. In this figure it is clear that di-aldehydes are located up to the right of the FEDAM. APOdial is the best free radical scavenger concerning the electron acceptor mechanism and LYC is the best antioxidant because it is the best electron donor. APOnal and APO have 22 carbon atoms forming the backbone and they present 9 cdb. The differences between them are the functional groups. APOnal is an aldehyde and APO contains a carboxylic acid. The best electron acceptor is the aldehyde (APOnal). The carboxylic acid (APO) is better electron donor but worse electron acceptor than APOnal. Another derivative with 22 carbon atoms in the backbone is APOnol, which is an alcohol. It only has 8 cdb and is a better electron donor and worse electron acceptor than the other two derivatives with 22 carbon atoms in the backbone. Apparently, the presence of

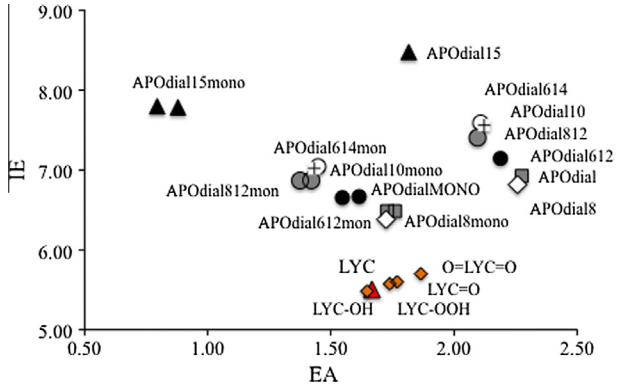
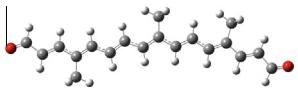
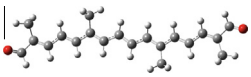
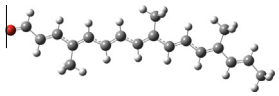
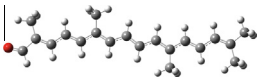
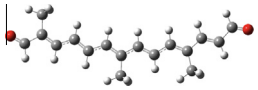
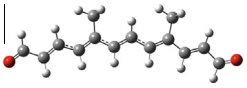
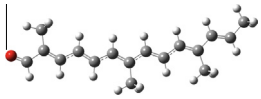
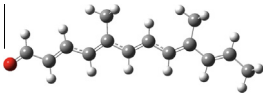
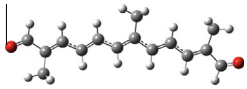
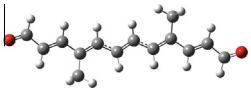
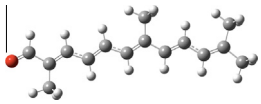
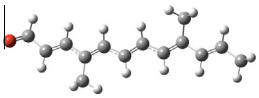


Fig. 4. FEDAM for the molecules under study. Electron affinity (EA) and ionization energy (IE) reported in eV/mol.

OH increases the electron donor capacity, whereas the presence of aldehyde group increases the electron acceptor capacity.

There are two molecules that have a carboxylic acid: ACY and APO. The difference between these two molecules is that ACY has a backbone of 16 carbon atoms and presents 6 cdb, whereas APO has 22 carbon atoms and 9 cdb. ACY is worse electron donor and worse electron acceptor than APO, indicating that the number of carbon atoms and the number of cdb is important. When the back-

Table 4
Mono and di-aldehydes optimized structures, IE and EA (in eV).

Optimized structures	IE	EA	Optimized structures	IE	EA
APOdial 	6.93	2.28	*APOdial8* 	6.82	2.26
APOdialMONO 	6.49	1.76	*APOdial8mono* 	6.38	1.72
APOdial612 	7.15	2.19	*APOdial614* 	7.59	2.11
APOdial612mono 	6.67	1.61	*APOdial614mono* 	7.04	1.45
APOdial812 	7.40	2.10	*APOdial10* 	7.56	2.12
APOdial812mono 	6.87	1.42	*APOdial10mono* 	7.02	1.43

bone is larger with more conjugated double bonds, there are more π orbitals that can accept the electrons (EA is higher) but also the electrons are less attached to the molecule (IE is lower) than in a σ orbital. For this reason, EA increases and EI decreases as the number of carbon atoms of the backbone and the number of conjugated double bonds increase.

It is clear that the presence of an aldehyde group augments the electron acceptor capacity but diminishes electron donor ability. The presence of more aldehyde groups increments EA and IE. APOnal is an aldehyde derivative, that is worse electron acceptor (EA smaller) but better electron donor (IE smaller) than di-aldehydes. As expected, the number of cdb is directly related with EA and λ_{max}. However, LYC has the highest number of cdb and does not present the highest EA value. Apparently, the functional groups have greatest influence on the electron donor acceptor properties. In order to corroborate this hypothesis, in Table 4 and Fig. 4 we report results for mono and di-aldehydes of compounds with the same chain lengths. As can be seen, all di-aldehydes present higher IE and EA values than mono-aldehydes, validating the hypothesis, i.e. more aldehyde groups augment the electron acceptor capacity and diminished the electron donor ability. To emphasize the influence of different functional groups, Fig. 4 and Table 5 also reports results for four LYC derivatives. The functional groups are mono (LYC═O), di-aldehydes (O═LYC═O), OH (LYC—OH) and OOH (LYC—OOH). The best electron acceptor is de di-aldehyde derivative and it is also the worse electron donor. LYC—OOH is worse electron donor and better electron acceptor than LYC—OH. This emphasizes the influence of these functional groups on the IE and EA values.

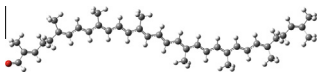
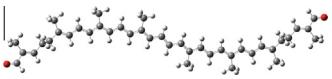
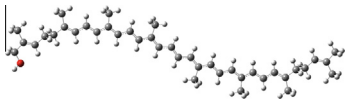
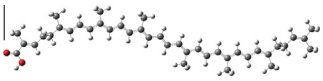
Comparing the di-aldehydes derivatives, it is possible to find a direct correlation between the number of carbon atoms of the backbone and the conjugated double bonds, with the electron donor acceptor capacity. As the number of carbon atoms of the backbone and the conjugated double bonds increase, EA also enlarges but IE decreases. APOdial and APOdial8 present 16 carbon atoms and 9 cdb. They are the best electron acceptors (EA larger) and the best electron donors (IE smaller) among the di-aldehydes derivatives. APOdial612 has 14 carbon atoms and 8 cdb in the backbone, whereas ADOdial614, ADOdial812 and ADOdial10 present 12 carbon atoms and 7 cdb. EA is larger and IE is smaller for APOdial612 than for the other three derivatives. The shortest di-aldehyde is APOdial5 with only 8 carbon atoms in the backbone and 5 cdb. It is the worst electron acceptor and the worse electron donor. MON is not a di-aldehyde derivative. It has 9 carbon atoms forming the backbone and 5 cdb. Its properties are similar to the properties of APOdial15. In summary, when comparing molecules with the same functional groups it is possible to say that larger chains have more room to accept electrons but the presence of conjugated double bonds result electrons being freer to go.

The size of the carbon chain and the number of conjugated double bonds is not the only characteristic that affects the electron donor or acceptor capability. LYC has the largest backbone (32 carbon atoms) with the largest number of conjugated double bonds (11) and it is the best electron donor but it is not the best electron acceptor.

As explained, the presence of functional groups with oxygen modifies the electron donor acceptor capacity. Oxygen is more electronegative than carbon and for this reason electrons are more attached to molecules that contain oxygen. The presence of oxygen increases EA and IE. It has been reported that a mixture of LYC oxidation products, like those reported here, enhances the ability to inhibit the growth of leukemia cells [33] and therefore it is reasonable to surmise that the increased ability to accept electrons could to some extent influence anti-cancer properties.

It has been suggested that carotenoids might cause a pro-oxidant effect that could be harmful. A pro-oxidant causes oxidation i.e. oxidized other compounds. When a substance is oxidized, it loses electrons. In this context, carotenoids need to accept electrons to be pro-oxidant, and higher values of EA indicate that the substance is a better pro-oxidant. However, pro-oxidant effects are not always harmful. As an example, it was previously reported

Table 5
Optimized structures, IE and EA (in eV) of four derivatives of LYC.

Optimized structures	IE	EA	Optimized structures	IE	EA
LYC=O 	5.60	1.77	*O=LYC=O* 	5.70	1.87
LYC—OH 	5.48	1.65	*LYC—OOH* 	5.58	1.74

that another mechanism to prevent oxidative stress is to accept electrons, i.e. the pro-oxidant effect [13]. More investigation is necessary to decide whether pro-oxidant effects are beneficial or dangerous, although it is reasonable to suppose that this may depend on many factors [10,11].

The results of this investigation indicate that, at least for the molecules that we are analyzing, to be a pro-oxidant might be beneficial because it may relate to anti-cancer activity. These are the facts: (a) no reports indicate dangerous effects caused by any of the molecules investigated here; (b) largest di-aldehydes (12 or more C atoms in the backbone) present higher EA values than LYC, and therefore they are better pro-oxidants, better electron acceptors than LYC; and (c) there is evidence that the some oxidized derivatives of LYC are able to impose anti-cancer activity through different mechanisms [33,36].

The theoretical results reported in this study indicate that the main difference between LYC and derivatives is the pro-oxidant capacity. This could be interested for gaining further insight into their anti-cancer activity. It is clear that the cancer and anti-cancer capability are very complicated and the electron transfer reaction is a very simple model that is certainly not the only underlying mechanism. However, these results provide us with an idea about the electronic differences between these molecules. Being a pro-oxidant is in no sense negligible, as these molecules may be able to oxidize DNA molecules and participate in carcinogenic or anti-carcinogenic events.

Experimental data have revealed that aldehyde and in particular di-aldehyde derivatives are active compounds with greater activity than the corresponding acids. The activity is apparently related to the position of the methyl group as well as the number of carbon atoms in the backbone chain. The best active components present the methyl groups at a distant position and 12 carbon atoms forming the backbone. Specifically apo-6,14′-carotenedial (APOdial614) is one of the best active groups. In this compound, two methyl groups are at a distant position relative to the terminal aldehydes' position. There is another di-aldehyde derivative (APOdial10) that has also a backbone with 12 carbon atoms and the methyl groups at a distant position, but it is different to APOdial614 because it has two methyl groups at the same position with respect to the two terminal aldehydes. The calculated properties for both molecules are similar (IE, EA and λ_{max}) and similar reactivity is expected. Apparently, the position of the methyl groups is less important than the size of the carbon chain. With the results reported here we can hypothesized that di-aldehyde derivatives are active compounds with greater activity than the corresponding acids because the electron affinity is larger for the former than it is for the latter.

4. Conclusions

Our theoretical data indicate that LYC and oxidized derivatives most stable geometries are stretched rather than bent structures but that they may coexist in the membrane, as the energy difference between these two conformations is not very large. Should this be the case, their properties as free radical scavengers are expected to be similar.

As expected, the increment of λ_{max} coincides with the increase in the number of conjugated double bonds, but there is also an influence of the functional groups. The presence of the carboxylic acid group affects the value of λ_{max}, as reported previously for other carotenoids.

EA increases and IE decreases as the number of carbon atoms of the backbone and the number of conjugated double bonds increases. The presence of OH increases the electron donor capacity, whereas the presence of aldehyde group increases the electron acceptor capacity. When the backbone is larger with more conjugated double bonds, there are more π orbitals that are able to accept the electrons (EA is higher) but also the electrons are less attached to the molecule (IE is lower) than in a σ orbital. In summary, when comparing molecules with the same functional groups it is possible to say that larger chains have more room to accept electrons but the presence of conjugated double bonds makes it easier for electrons to break free.

The increased ability to accept electrons of the oxidized derivatives may partially influence anti-cancer properties. It is clear that the cancer and anti-cancer capability are very complicated and the electron transfer reaction is a very simple model. However, these results at least provide us with information concerning the electronic differences between these molecules. Being a good electron acceptor is not way insignificant; as these molecules may oxidize DNA molecules and thus either start or stop cancer activity.

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