Do antioxidants really help? The endless debate

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This issue of *NutraFoods* includes two papers on antioxidants and their potentially protective role toward free radical-induced damage. This is indeed a very interesting field that is witnessing mixed results in the scientific literature. Let us try to critically summarise the most recent evidence.

Free radicals are extremely reactive and can bind and damage cellular macromolecules such as proteins, sugars, fatty acids and DNA. However, some free radicals and reactive oxygen species do play important roles in our body, in terms of signal transduction. Therefore, eradicating free radical production (which is, by the way, impossible) might not be a good idea. This is further complicated by a careful analysis of the literature on antioxidants and clinical endpoints. The vast majority of epidemiological studies do correlate increased intakes and elevated plasma concentrations of these molecules with lower incidence of degenerative diseases such as cancer, cardiovascular disease and neurodegeneration. All-cause mortality is also negatively correlated with antioxidant intake. On the other hand, controlled clinical trials of antioxidant molecules reached different conclusions. In particular, trials with vitamin E and beta-carotene or their combinations (often blended with vitamin C and selenium) yielded negative results. Indeed, some trials have been in-

terrupted before the planned conclusion because of *higher* incidence of clinical outcomes as compared with placebos. It must be underscored that these trials mostly employed lipophilic antioxidants at high doses and that no patients at high oxidative stress level were selected; this is at odds with what happened, as an example, in trials with statins, which randomised hypercholesterolaemic patients, or in those with anti-hypertensive drugs, which were run on hypertensive subjects. Yet, it is somewhat interesting to note that not only was a positive trend not recorded, but often these trials resulted in effects that were the opposite to what was expected.

How to move forward? One option (which several authors strongly support) is to reject the notion that antioxidants can ameliorate our life by reducing the incidence of degenerative diseases. With this approach we might throw the baby out with the bathwater just because we might have employed wrong approaches and, therefore, obtained disappointing results. What about polyphenols and, in general, natural antioxidants? Indeed, they might prove useful if (1) we consider *in vitro* and epidemiological trials only as starting points for randomised clinical trials; (2) we carefully use the word “natural”, noting that chemistry is indispensable and that natural beta-carotene is indistin-

guishable from natural beta-carotene; and (3) we test mixtures of different antioxidants and select appropriate patients whenever possible.

Last, but not least, we need to take into account that, for polyphenols to work as anti-atherosclerotic antioxidants, free radical-mediated reactions must

take place on the low-density lipid surface, where polyphenols bind and might act as scavengers. In the meantime, we should all continue to look at antioxidants with an open mind and keep a balanced approach to this complex field of research, which urgently needs evidence-based data.