Antioxidants
not heaven-sent

By Stefan Andrei Anghel

“\textit{It may come as a surprise that the current scientific consensus is that there is no health benefit to taking antioxidant supplements.}”

Walk into any pharmacy or health food store and you are sure to find antioxidant supplements, probably in a wide selection of brands and sizes. For a long time, antioxidants have been viewed as a method to prevent certain diseases and possibly even retard aging. Any randomly chosen person on the street would most likely tell you that antioxidants are “healthy”, or “good for you”, though they would probably not be able to tell you how. It may come as a surprise that the current scientific consensus is that there is no health benefit to taking antioxidant supplements (1). Even more unexpected news came this year when an article announced that antioxidants may actually prevent the health-promoting effects of physical exercise (2). If the model proposed by the authors of the study is correct, then it may turn out that we have been systematically “poisoning” ourselves, increasing our disease risk and shortening our lifespan through antioxidant supplements.

So what exactly are antioxidants? The concept of antioxidants relates to what are collectively termed reactive oxygen species (ROS). Reactive oxygen species (or “free radicals” as they are still sometimes called, although incorrectly from a chemical perspective) are a natural by-product of human metabolism. Because oxygen abounds in each of our cells, it can sometimes pick up electrons from the enzymes that are naturally present to break down nutrients from our food, giving rise to the various types of ROS. These species are called “reactive” because of the ease with which they react with and damage crucial cellular molecules including DNA, proteins and fats (Figure 1). This is where antioxidants come in: they can neutralize ROS. They are able to achieve this by interacting with ROS and becoming oxidized themselves, generating a harmless oxygen compound (like O2 or water) in the process. The oxidized antioxidant can then be recycled (by reduction) or simply disposed of (3). Many chemicals can act as antioxidants, but among the ones most widely consumed by humans are vitamin C (L-ascorbic acid) and vitamin E (alpha-tocopherol) (4).

However, it is important to understand that we are not test tubes. While it is true that ROS will attack DNA and proteins, living cells are able to “fight back” against all sorts of stress through special “repair and neutralize” tools. In the case of ROS, there are multiple protection systems: special enzymes like superoxide dismutase and catalase exist for the sole purpose of ROS neutralization, and a small peptide known as glutathione can efficiently scavenge ROS throughout the cell (5). Despite the existence of these systems, a paradigm has been in place for some years throughout the scientific community that some ROS escape and are able to cause damage to cells, ultimately being responsible for various pathologies and possibly the process of aging (5-6). Lately, however, evidence has surfaced that ROS are not simply unfortunate by-products of our aerobic metabolism. ROS are now regarded as important signaling molecules inside the cell, crucial for the communication between different cell compartments (7-8). Even more
strangely, studies in model organisms have shown that ROS can be mediators of some health-promoting effects (9-10). The most recent of such studies suggests that ROS may be crucial for the proper functioning of the immune system (11). This finding underscores the importance of seeking a better understanding of antioxidants, considering vitamin C is often consumed in large quantities as a remedy for the common cold, despite no evidence of any efficiency (12).

Another study, conducted by Ristow et al., sought to analyze the effects of antioxidants in relation to the health-promoting effects of physical exercise. This study is particularly significant because it was carried out in humans, rather than in model organisms. It is known that physical exercise has many positive effects with respect to general health (13) and is especially efficient at improving glucose metabolism and fighting and preventing type 2 diabetes (14). These latter effects are mediated by an increase in insulin sensitivity: the more sensitive one’s body is to insulin, the less the hormone it takes to lower blood sugar levels and the less susceptible one is to type 2 diabetes.

It is not well understood how physical exercise increases insulin sensitivity, but one hypothesis (which is tested by Ristow et al.) is mitohormesis. Mitohormesis postulates that the burst of ROS induced by the increased metabolism during physical exercise (15), alerts the body to make specific proteins that eventually bring about the final health effects (what these proteins are or how they accomplish the task is still not known). What the authors of the study did was simple: two statistically indistinguishable groups of individuals were asked to exert themselves physically; one group received high doses of antioxidants (vitamins C and E) while the other did not. Their findings fit very well with the mitohormesis model: the group that received no antioxidants had higher-levels of ROS-repair enzymes and higher insulin sensitivity, while the group that received the supplements showed none of these “health-promoting” effects. The antioxidants essentially canceled out all the beneficial effects of exercise. The authors proceeded to put together a model of the process that fits their experimental data (Figure 2).

As any new (16) scientific paradigm, mitohormesis has the problem of any emerging model: it lacks substantial evidence, but mostly because little research has been done on the subject, not because the research was not fruitful. However, some supporting evidence has recently surfaced. A mitohormesis-like process seems to be the cause of ischemic preconditioning, a reaction that makes heart cells more tolerant to ischemia-reperfusion (a type of damage to the heart caused by irregular blood flow) (17). Shortly before this article went to print, Loh et al. (18) provided direct causal evidence that a transient increase in ROS increases insulin sensitivity in mice. In addition, one study in the model organism Caenorhabditis elegans (a worm) concluded that mitohormesis may be the underlying mechanism by which caloric restriction extends life-time in this organism (10). Extension of life through caloric restriction is a phenomenon seen in organisms from budding yeast to mammals (19-23), so if the mitohormesis explanation for caloric restriction is indeed true and universal, it may mean that mitohormesis-inducing drugs could someday extend lifespan. Whether mitohormesis turns out to be an accurate model remains to be seen as more research is carried out on the subject.

Studies like Ristow et al. are important because antioxidants are widely consumed as nutritional supplements. Perhaps surprising for some, a recent meta-analysis of a large number of antioxidant studies performed on humans (totaling an incredible 550,000 subjects) established that such supplements have no health-promoting effects (1). Then why do people take antioxidants? Such an analysis is beyond the scope of this article, but the cause is most likely similar to that for the consumption of other supplements such as homeopathic remedies: some questionable science started the trend, and then companies willing to make a profit perpetuated and amplified the legend. The fact that the scientific giant Linus Pauling recommended consumption of vitamin C in doses two orders of magnitude above conventional ones (24) probably did not help the general public focus on the scientific evidence underlying such advice. Also, the so-called free radical theory of aging, which postulates that accumulation of ROS-induced damage brings about aging (5-6) surely contributed to the spread of antioxidant supplements. Regardless of the reason for their popularity, such supplements have become extremely widespread, despite the lack of any data supporting their efficiency.

Now, it is becoming apparent that antioxidants might actually be detrimental to one’s health. It is important to note,
drugs known to increase oxidative stress in model organisms, effectively trying to simulate physical exercise. These studies would need to be designed to induce short bursts of ROS and not a constant increase, and to the best of my knowledge such a design has never been employed. Extreme care is necessary though: tampering with cellular signaling molecules is a very tricky business, and such approaches might turn out to be counterproductive, similar to antioxidant supplements. Also, some ROS-inducing drugs like paraquat are toxic to humans (27) while others, like the antimalarial-drug artesimin (28) clearly are not. Extensive research in model organisms is therefore needed before human trials of such drugs are deployed, but the mitohormesis hypothesis might ultimately provide a pharmaceutical strategy for harnessing some of the health benefits of exercise.

One last thought to take away from such studies relates to nutritional supplements in general. Currently antioxidant supplements can be sold with virtually no restrictions in most countries, even considering the consensus in the scientific community that they don’t actually do anything(1). After all, homeopathic remedies are still around and quite popular in some communities, despite the fact that there is nothing in them but water (29). However, studies such as the one performed by Ristow et al. show that some supplements might actually have deleterious effects on one’s health, although not immediately observable. Just think about how many supplements out there say “extract of […]” on the packaging (in the United States, for example, anything that contains an herb can be sold as a nutritional supplement) (30). Probably most of those don’t have any health effects and only a very small fraction contain any active ingredients in sufficient quantities to show any improvement. But some, as appears to be the case with antioxidant supplements, might have adverse effects that are so complex that they are hard to identify in safety trials. Therefore, next time you are in a pharmacy or health food store reaching for a supplement, it might be a good idea to ask yourself “What scientific evidence shows this will actually help me?”

References
10. T. J. Schultz et al., Cell Metabolism 6, 280 (2007).
18. K. Loh et al., Cell Metabolism 10, 260 (2009).