doi 10.18699/bgrs2024-13-27

# Antioxidants: good, bad, or ineffective in terms of aging and lifespan? It depends

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**Key words:** aging; lifespan; free radicals; nutrition; experimental gerontology; synthetic and natural antioxidants; age-related diseases

The idea that antioxidants (AO) can be effective geroprotectors became widespread in the second half of the 20th century. It was based on the concept of the leading role of free radicals (FR) – mainly reactive oxygen species (ROS) – in the aging process, formulated by Denham Harman and Nikolay Emanuel. Subsequently, a huge number of experimental works appeared, which substantiated the point of view according to which the introduction into the body of compounds that scavenge FR leads to a slowdown in aging and an increase in lifespan. Actually, for many years, gerontologists used the terms geroprotectors/anti-aging drugs to mainly designate AO of various kinds. In this case, as a rule, we were talking about synthetic AO, the doses of which could be quite easily controlled.

It should be noted that the term “geroprotectors” was coined by scientists from the Institute of Chemical Physics of the USSR Academy of Sciences in the last quarter of the former century specifically in relation to the synthetic AO created in this institution. We studied one of them, epygid (2-ethyl-6-methyl-3-hydroxypyridine hydrochloride), quite intensively in terms of its effect on stationary phase aging of cultured cells of different nature [1, 2]. It turned out that epygid acts differently on different cells. In particular, we were unable to use it to slow down the stationary phase aging of normal embryonic diploid human fibroblasts. As a result, we already then concluded that it is impossible to help “young” cells with high viability and proliferative activity to age more slowly using AO. Unless, of course, you specifically stimulate in them oxidative stress in one way or another, which is used quite often at the present stage of gerontological research [3, 4].

Numerous studies of the geroprotective properties of AO in experiments on laboratory animals, at first glance, have demonstrated their significant effectiveness in slowing down aging and increasing lifespan, both average and maximum. However, firstly, it remained unclear how applicable the data obtained could be for use in humans – including for suppressing the development of age-related diseases such as sporadic Alzheimer's disease [5] – and secondly, many questions arose regarding the correct selection of control objects in such experiments [6]. As a rule, these were animals that either had certain genetic abnormalities or were in unfavorable living conditions, which led to the development of oxidative stress in them. Obviously, AO were quite effective in such cases. The interpretation of the data obtained was also influenced by the still existing differences in the understanding of what aging is [7]. Very often, the classical definition of aging as a set of age-related changes in the body, leading to an increase in the probability of its death, is simply ignored.

We must not forget that FR in the body are often simply necessary for its normal functioning, so it cannot be said that their elimination is always beneficial [8, 9]. In particular, an entire special issue of the journal “Oxidative Medicine and Cellular Longevity” entitled “Harmful and Beneficial Role of ROS 2020” was devoted to this problem [10].

It is also necessary to emphasize that if an overdose of natural AO entering our body with food is practically impossible, then in the case of synthetic AO [11] it becomes quite real and occurs in very many cases, since it is very difficult to determine their concentration in organs and tissues when taking medications with water or food. This, on the one hand, can lead, paradoxically, to the development of oxidative stress (the so-called “antioxidant paradox”) [12], and on the other, suppress the corresponding functions for which FR are necessary [9]. In particular, it was shown that increased mitochondrial ROS production plays an integral role in the acute β-adrenergic-induced inotropic response of cardiomyocytes. This stimulatory effect is mediated via cAMP–PKA-dependent and Ca2+-independent signaling [13]. It is also known that FR (both ROS and reactive nitrogen species) are needed for the normal functioning of the immune system, which provides protection against various infections, as well as for the processes of maturation of cellular structures and for maintaining the functioning of cellular signaling systems [14]. In particular, it is known that phagocytes (neutrophils, macrophages, monocytes) release free radicals to destroy invading pathogenic microbes as part of the body’s defense mechanism against disease [15].

It should be noted that there is even a paradoxical, at first glance, point of view, according to which pro-oxidants in some cases may be more beneficial for the body than AO [16].

Thus, it seems that the popular idea of AO as a panacea against “normal” aging today cannot be considered absolutely proven. Apparently, with the help of AO it is possible to quite successfully combat oxidative stress that occurs in various pathologies, and thereby increase the average lifespan (sometimes even the maximum one). It can be assumed that in some cases this occurs due to a reduction in the “oxidative-stress” manifestations of age-related diseases, which is also not bad, although, apparently, it does not bring us closer to realizing the dream of a “fountain of eternal youth.”

*Conclusion*: So maybe we should still adopt – at least in some cases – the slogan “Freedom for the radicals!”.

*Funding*: This work was supported by ongoing institutional funding. No additional grants to carry out or direct this particular research were obtained.

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