Opinion Paper

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Free radical area needs a radical change

Serbest radikal alanında radikal bir değişiklik gerekli

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Abstract: Oxidative stress is a quite popular subject among biochemists. With a key word search of Thomson Reuters Web of Science, a large number of entries were found starting from 1970. By using animal tissues, cell cultures or human subjects, scientists try to establish a relationship between reactive oxygen species and various situations including cancer and aging, and the protective effects of antioxidants in these cases. Some clinical trials of antioxidants are also on their way. There are several oxidative stress markers such as malondialdehyde, thiol status of the cells, superoxide dismutase, catalase and glutathione peroxidase. Although these markers are widely and continuously investigated in various laboratories, they still are not in the repertoire of a routine clinical laboratory as a biomarker of any disease. In this paper, various aspects of "oxidative stress" and antioxidants are investigated and a requirement of a radical change in the area is pointed out.

Keywords: Oxidative stress; Thomson Reuters Web of Science; Reactive oxygen species; Antioxidants.

Özet: Oksidatif stres biyokimya camiasında oldukça popüler bir konudur. "Thomson Reuters Web of Science" da bir anahtar kelime araştırması ile 1970 yılından başlayarak çok büyük rakamlara ulaşılmıştır. Hayvan dokuları, hücre kültürü veya insan deneyleri yardımıyla bilim insanları reaktif oksijen bileşikleri ile kanser ve yaşlanma dahil çok çeşitli durumlar arasında ilişki kurmaya çalışmakta ve bu bozukluklara karşı antioksidanların koruyucu etkilerini araştırmaktadırlar. Bazı klinik denemeler de süregelmektedir. Malondialdehid, hücre tiyol statüsü, süperoksit dismutaz, katalaz ve glutatyon peroksidaz gibi çeşitli oksidatif stress belirteçleri bulunmaktadır. Bu belirteçler çeşitli laboratuvarlar tarafından geniş çapta ve sürekli incelenmesine rağmen, hala hiçbir rutin laboratuvarın repertuarında herhangi bir hastalığın biyobelirteci olarak yer almamaktadırlar. Bu makalede "oksidatif stress"in çeşitli yönleri incelenmekte ve bu sahada radikal bir değişiklik gerektiğine dikkat çekilmektedir.

Anahtar kelimeler: Oksidatif stress; Thomson Reuters Web of Science; Reaktif oksijen bileşikleri; Antioksidanlar.

Introduction

Oxidative stress is a very popular subject among biochemists. With a key word search of Thomson Reuters Web of Science, 234,852 entries were obtained as of 19.07.2016 [1]. The first entry was on oxidative stress relaxation of rubber published in 1955. In 1965 two more entries on oxidative stress of rubber were also published. The first entires in life sciences started in 1970. From 1970 to about 2000, the number of publications increased exponentially. After the year 2000 it continued to increase linearly and is still keeping this trend (Figure 1). The papers coming from Turkey appeared in 1993 for the first time and make up 7815 of the life and health science publications [1]. Seventy-seven articles on the subject have been published in the *Turkish Journal of Biochemistry* since 2007. Key word searches for some other popular subjects such as proteomics, genomics and malaria and DNA repair which were the subjects of the 2015 Nobel Prize yielded much less publications from all the sites. Only the key word "enzyme" surpassed "oxidative stress", although "enzyme and oxidative stress" together, yielded a significant number of publications (Table 1). When the ratios of the publications are investigated, it is seen that the ratio of works on oxidative stress-related subjects are 10 to 20 times higher in Turkey as compared to the other worldwide popular subjects.

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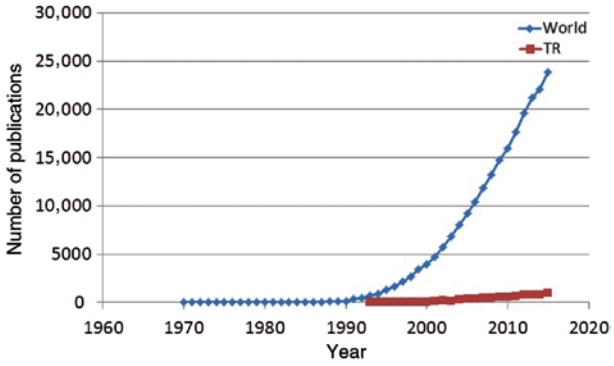


Figure 1: Graph of number of publications included in Web of Science on "oxidative stress" vs. year (blue: whole entries, red: entries from Turkey).

Table 1: Search result of several key words in life science and health science journals between 1970 and 2016, on Thomson Reuters' Web of Science [1], as of 19.07.2016.

Key words	Number of entries from all addresses	Number of entries from Turkey	Ratio of the entries (Turkey/all, $\times 10^{-2}$)
"Oxidative stress"	234,849	7815	3.328
"Lipid peroxidation"	84,922	5432	6.396
Proteomics	47,450	165	0.348
Genomics	48,346	164	0.339
"DNA Repair"	41,967	273	0.650
Malaria	68,543	188	0.274
Enzyme	923,828	12,570	1.361
Enzyme + "Oxidative Stress"	48,596	2315	4.764

Oxidative stress in summary

The summary of the subject and its correlates are as follows: aerobic organisms need oxygen to metabolize nutrients to produce energy. During metabolism several reactive oxygen species are formed: superoxide radicals, hydrogen peroxide, hydroxyl radical and hydroxyl ions are reactive oxygen species (ROS). These reactive oxygen species give rise to "oxidative stress" and may damage cells. Several defense systems are developed by the organisms to prevent oxidative stress: antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) [2]. Several antioxidant vitamins also prevent cellular damage caused by the ROS. Lipid peroxidation is a term which goes hand in hand with oxidative stress. Lipid peroxidation is the degradation of lipids as a result of oxidative damage. Polyunsaturated lipids are susceptible to an oxidative attack by ROS. The result is a chain reaction with the production of end products such as malondialdehyde (MDA) [3].

Experiments on oxidative stress

By use of animal tissues, cell cultures or human subjects, scientists try to establish relationships between oxidants and various diseases. The hypothesis is that: oxidative stress comes out due to an unbalance between oxidizing agents and antioxidants. This stress can be due to several environmental factors. Oxidative damage to DNA, proteins and other macromolecules may lead to a wide range of human diseases. The list of diseases related to oxidative stress includes: cancer, diabetes, heart failure, myocardial infarction, atherosclerosis, brain diseases, autism, aging, and many others [4]. In fact, there is a group of scientists who blame almost everything on oxidative stress created by ROS. There are many journals devoted to the subject, such as, *Oxidative Medicine and Cellular Longevity*, *Free Radical Biology and Medicine*, *Journal of Cellular Neuroscience and Oxidative Stress*, *Antioxidants*, *Antioxidants & Redox Signaling*, *Free Radicals and Antioxidants*, *Antioxidants and Redox Signaling Journal*, *Oxidants and Antioxidants in Medical Science*, etc. Several international congresses are also frequently organized. The publications devoted to the subject increases and so the number of citations to the papers also are on increase.

Oxidative stress markers are: antioxidant enzymes, SOD, catalase, GPx, lipid peroxidation product MDA, glutathione and the thiol status of the cell [5]. Although they are widely and continuously investigated in various laboratories, and despite the large number of publications over the last 40–45 years, none of these markers could be introduced to routine clinical biochemistry laboratories. The number of publications and the number of citations continue to increase.

Antioxidants as drugs

The other aspect of the antioxidants is that there is a big market for them as drugs. A new report from the Grand View Research, Inc. states that: "The natural antioxidants market is expected to grow rapidly, and will be worth $4.14 billion by 2022" [6]. If oxidants play a role in many diseases and if antioxidant enzymes require some cofactors for their activity, it is normal that many drugs have an antioxidant action; and insufficient intake of these may lead to low antioxidant activity. Examples are vitamin E, vitamin C, selenium, retinol, zinc, riboflavin and molybdenum. So, there are many publications on making use of these minerals, vitamins and many plant extracts claiming to prevent oxidative stress. The publications and the

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Table 2: Search result of "oxidative stress" and several other key words on Thomson Reuters' Web of Science, as of 23.06.2016.

Key words	Number of entries from all addresses	Number of entries from Turkey	Ratio of the entries (Turkey/all, $\times 10^{-2}$)
Selenium	4115	345	8.384
Zinc	6415	283	4.412
Iron	11,829	236	1.995
Manganese	4577	92	2.010
Resveratrol	2246	132	5.877
Garlic	551	22	3.993
Curcumin	1727	79	4.574
Many other plant extracts	many	many	not determined

market support each other reciprocally. The search results of some antioxidants and "oxidative stress" on Thomson Reuters' Web of Science is shown in Table 2.

Several clinical trials of antioxidants are also on their way. Goodman et al. investigated the large (at least 7000 participants) trials which test the effect of antioxidant supplements in preventing cancer and concludes that despite testing various antioxidants, "none of the completed trials produced convincing evidence to justify the use of traditional antioxidant-related vitamins or minerals for cancer prevention" [7].

Negative results

In fact there are also some negative results. The transcription factor NRF2 is a basic leucine zipper protein and activation of the NF-E2-related factor-2 (NRF2)-antioxidant response element signaling pathway is a defense mechanism against oxidative stress [8]. Several drugs targeting the NFE2L2 pathway are being studied for treatment of several diseases related to the oxidative stress. Experiments with murine cell cultures showed that Nrf2 transcription induced by several oncogenes promoted ROS detoxification and tumorigenesis [9]. In other studies, antioxidants accelerated tumor metastasis in lung cancer [10] and melanoma [11]. These findings suggest that antioxidants, which reduce ROS, may be causing harm instead of preventing disease. Free radicals, which are thought to promote cancer, may actually slow tumor growth. This subject entered the top 10 list of *Nature* on "false beliefs and wishful thinking" in second rank as "antioxidants are good and oxidants are bad" in 2015 [12]. The author compares the theory "free radicals cause ageing, so one needs to have antioxidants" to the gravity and relativity theories that have reached the public, and also attracts the attention to the growing market of drug industry.

In summary, the field has wasted enormous time and resources both as manpower and as grants for the last 45 years. At the recently organized international congresses, negative results of antioxidants are being discussed [13] which signifies a requirement for a radical change in the area.

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