Mini Review

Antioxidant relevance to human health

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Human ecology requires both oxygen and water with the generation from food of an immediate energy source, ATP, by oxidative phosphorylation. A continuing balance between oxidation and antioxidation is necessary for longer less-disabled lives, taking account of oxidative stresses and the critical roles of oxidants in defence against infection, tissue repair and signalling. Antioxidant capacity is derived both exogenously (from food, beverage and sunlight) and endogenously (from enzymatic and non-enzymatic pathways). A number of oxidant food factors service antioxidant metallo-enzymes. The capacity operates extra- or intracellularly. Uric acid is the major antioxidant in primate blood. Uric acid synthesis is increased by dietary fructose from fruit, sugary foods and drinks. This indirect antioxidant effect of fruit is separate from that attributable to its flavonoids. Alcohol also increases serum uric acid. Urate excess and retention is associated with disease. The high prevalence of hyperuricaemia in NE Asia presents a major public health dilemma in regard to putative antioxidant activity of fruit. Each of the antioxidants in these foods is pleiotropic being inter-alia anti-inflammatory, anti-angiogenic or anti-neoplastic. Moreover, food matrices and patterns contribute to the safety of antioxidant consumption. There is no evidence to date that isolated antioxidants as food supplements improve health outcomes or survival; and some that indicate unacceptable risk. Their use as biomarkers of food cannot justify their isolated use. Nevertheless, a spectrum of dietary pluripotential antioxidants for tissues, metabolic and immune systems is advantageous.

Key Words: oxidants, uric acid, toxicity, supplements, pleiotropic functions

WHAT ARE ANTIOXIDANTS?

There is no animal life without oxygen consumption and its conversion to water with the production by leakage from mitochondrial electron transport of free radicles, 7 in the course of oxidative phosphorylation and the production of ATP as the ultimate and immediate source of energy.2,3 Free radicles may also be formed as nitrogen, carbynol, chlorine, sulfur and other reactive species.4,5 During oxidation electrons or hydrogen are transferred from one molecule to another, the latter serving as an antioxidant. Antioxidants, therefore, can stop the formation of free radicals and the chain reactions, which would otherwise result in cell damage or even death. Yet, the process of oxidation plays an important role in the body’s defence against infection or in response to tissue damage; how much is tolerated and in which tissues is a finely tuned piece of physiology.5 Reactive species can also play roles as cellular secondary messengers and regulators or signalling molecules as with nitric oxide6,7 or gaseous sulphur dioxide.7,8 Anti-oxidant capacity is required both extra- and intracellularly (in cytosol, nucleus and mitochondria) for the homeostasis of oxidant status. Physical activity increases the oxidant load, and, if regular, progressively increases the body’s ability to respond to such a load. Pro-oxidant foods are principally those with excessive metals such as manganese, iron, or copper or when vitamin C (ascorbic acid) exceeds that usually obtainable from food by way of supplements.9,10 Because of its involvement with amino acids, proteins and metallo-enzymes, zinc is of greater interest for its pro-antioxidant roles. Likewise, selenium, copper and iron, as part of enzymes like glutathione peroxidase enzymes, superoxide dismutase and catalase, have pro-antioxidant roles. Most plant-derived foods have a range of antioxidant compounds which include vitamin C (at lower exposures), vitamin E (tocopherols and tocotrienols), polyphenols, carotenoids and ubiquinols.11 Some of these molecules are water-soluble and others lipid-soluble; they complement each other and a spectrum of each solubility type is required for antioxidant function to be effective in biological systems. For example, a key function of lipoproteins is anti-oxidant transport of vitamin E types and a family of carotenoids to protect lipoproteins themselves and the tissue to which lipids are delivered. But food not only provides molecules with their

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Manuscript received 7 April 2013.
doi: 10.6133/apjcn.2013.22.2.21
own intrinsic oxidant activity or ability to form part of antioxidant enzymes, it provides substrates or metabolic stimuli for endogenous antioxidants. Chief among these is uric acid whose synthesis is increased by fructose, traditionally from fruit, but now from sugary foods and drinks as well.\textsuperscript{2,12} This indirect antioxidant effect of fruit is separate from that attributable to that of flavonoids. Alcohol also increases serum uric acid concentrations. The foods found to have the highest antioxidant activity include berries with anthocyanins,\textsuperscript{13} nuts and legumes with carotenoids, polyphenols, and tocopherols\textsuperscript{14-16} tomatoes with their lycopene,\textsuperscript{17} sweet potato leaves with a high total polyphenol content (TPP)\textsuperscript{18,19} and vegetable shoots.\textsuperscript{20}

In 1997, Helmut Sies defined ‘oxidative stress’ as an imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage and explained that oxidants form as normal products of aerobic metabolism and also at greater rates pathophysiological.\textsuperscript{21}

**ENDOGENOUS VERSUS EXOGENOUS**

The body’s antioxidant system is acquired from food intake and generated internally. Internally it comprises enzymatic and non-enzymatic systems. Nevertheless, the enzymatic systems are metallo-enzymes and dependent on diet, a landmark example of which was the discovery of selenium deficiency in China, which has had ecological implications well beyond the immediate problem of cardiomyopathy, even to viral pathogenicity.\textsuperscript{22} The enzymatic systems have a primary intracellular antioxidant role, although connected through this activity to extracellular redox status.

Although partly dependent on diet, uric acid, a product of purine metabolism, is the major antioxidant in primate blood.\textsuperscript{2,12} Other blood antioxidants include the water-soluble vitamin C, glutathione, and lipoic acid and the fat-soluble carotenoids and vitamers of vitamin E which are transported with lipoproteins, along with ubiquinol (the antioxidant form of coenzyme Q10).\textsuperscript{1,2,5} The fat soluble vitamins are also associated with membrane lipoprotein function and its prevention from peroxidation. Even vitamin D, dependent on diet and sun exposure, may have a membrane antioxidant role.\textsuperscript{23} Ubiquinol is part of the mitochondrial electron transport chain and, therefore, multi-functional. Melatonin is a water soluble antioxidant which can cross the blood-brain barrier, but does not undergo redox recycling. The wide spectrum of polyphenolic antioxidants to be obtained from plant-derived foods is likely to complement the rest of the dietary antioxidant nutrients and those internally generated.

Uric acid is of particular interest as a major contributor to redox status, peculiar to primates in whom the enzyme urate oxidase is non-functional unlike other mammals who convert it to allantoin. It is thought that this additional anti-oxidant capacity in humans allowed us to evolve, inter alia, our high energy-consuming brains. A moot point is the stimulus to uric acid production by fructose which, from fruit might be an overall biological advantage with its essential and phyto-nutrient complexity,\textsuperscript{24} but from sweetened beverages might be a metabolic risk.\textsuperscript{25} At the same time, we are prone to urate excess and retention with its associated joint, integument and renal damage, and its association with hypertension and insulin resistance. NE Asians have among the highest prevalences of hyperuricaemia globally.\textsuperscript{26-29} This raises difficult public health and clinical management questions about the overall food-urate acid-health associations in such populations. The findings of Li et al in Shanghai\textsuperscript{30} that dietary and serum antioxidant status is associated with lower prevalence of the metabolic syndrome (although unfortunately uric acid is not reported) may provide an opportunity to allow less risk of diabetes and cardiometabolic disease through dietary antioxidant intake. The findings are supported by antioxidant-plentiful fruit interventions which decrease the expression of diabetes.\textsuperscript{31,32} But, given Halliwell’s argument, dietary diversity might fulfill this objective by mechanisms other than those to do with exogenously-derived antioxidants.\textsuperscript{5}

**FOODS VERSUS FORTIFICATION AND SUPPLEMENTS**

Halliwell estimates that exogenous dietary antioxidants may not have a substantial effect on the net body redox status, because of the extensively distributed and physiologically regulated oxidant-antioxidant pathways.\textsuperscript{3} While there are data bases and many reports of the antioxidant capacity of foods, and the United States Department of Agriculture (USDA) has drawn attention to the differences in ratings dependent on methodology and the lack of evidence of their relevance to human physiology or proven health benefits.\textsuperscript{35}

There is no support from any of several studies that nutrient supplements, including antioxidants, have any beneficial effect on health events or mortality and may increase its risk unless there is frank deficiency.\textsuperscript{38,40}

**ANTIOXIDANT BIOMARKERS**

Measurable risk factors, intermediates of biomarkers have characterised the development of evidence-based medicine with those for cardiovascular disease like blood pressure and lipoproteins, diabetes like body fatness and glycaemic status typical and now traditional. But there has been a proliferation of biomarkers which purport to indicate food intake, its metabolic consequences and genetic predisposition to disease and premature mortality.\textsuperscript{3,31,32,41} They have had mixed utility.\textsuperscript{40} When it comes to antioxidant status and its health implications, the observed changes in intermediates may have additional or alternative explanations.

Those biomarkers that represent damage and are analogues of what may be happening in tissues may have merit. Examples would be the composite of HbA1c and AGEs (advanced glycation end products) for diabetes complications, lipid peroxides in lipoprotein disorders, and damaged DNA,\textsuperscript{42,43} but even here the data are inconsistent. Moreover, the abnormalities may have as much or more to do with endogenous as opposed to exogenous anti-oxidative mechanisms.

**ANTIOXIDANT TOXICITY**

The most obvious toxicity for antioxidants would be with the ablation of the health protective roles of oxidants which include antimicrobial phagocytosis, detoxification by the cytochrome P-450 complex and apoptotic roles for unwanted cells.\textsuperscript{44}
Some antioxidant nutrients, like vitamin C can assume oxidant roles which may be toxic, like the Fenton reaction when it reduces metal ions as with iron.

Several clinical trials now show that antioxidants, like beta-carotene which is a precursor of vitamin A, can increase the risk of cancer when administered as an isolated supplement. In the APPP (Australian Polyphenol Prevention Project) with interventions of a low fat diet, wheat bran or beta-carotene, while the combination of low fat and wheat bran prevented the recurrence of large adenomatous polyps, beta-carotene increased the risk of any polyp recurrence in women.45,46

DIET, ANTIOXIDANTS AND HEALTH

There has been much interest in antioxidant mechanisms which might explain relationships between dietary quality and health outcomes. For example, mixtures of fruit and vegetables can increase the antioxidant capacity of blood, but at the same time improve folic acid status and decrease homocysteine.47 Thus, the food constituents in question may be several or collectively pleiotropic in their actions and pluripotential insofar as possible outcomes. Nevertheless, it does appear possible for certain compounds with antioxidant properties among others to target particular tissues like areas of the brain to do with cognition and memory as with anthocyanins in berries or in stroke with lycopene. This may be a generalisable phenomenon, but unlikely to be attributable only to antioxidant. Additionally, food plays a major role in determining and setting the body’s intrinsic anti-oxidant capacity; for it to be competent at the right location, at the right time, with the right profile, and to allow oxygen activity to play its part. This requires favourable patterns of eating against a background of physical and mental fitness. In these respects, food diversity captures the broad range of the required nutritional properties, irrespective of mechanism. A meta-analysis of the anti-oxidant rich intake of tea and bladder tumours provides a focus on tea type and what constituents might be involved; but, finally, it is a matter of the tea itself, where and how it is consumed. This outcome directed analysis of the potential health effects of tea, goes beyond studies which look at intermediates or risk factors. Food and beverage intakes, therefore, can provide more of the information needed for redox status and related pathogenetic processes like inflammation, neoplasia, immune responses, energy regulation and ageing.

It is difficult to conceive how isolated supplements, as opposed to food diversity, could tune complex intrinsic oxidant-needs and processes without over-riding homeostatic mechanisms in health. In pathological states, pharmacological approaches to redox status might be used for particular problems subject to the risk-cost-benefit appraisal requirements of therapeutic regulation. For the moment, however, there is no clear-cut evidence that isolated food components confer health advantage by way of their antioxidant characteristics.

AUTHOR DISCLOSURES

The author has no conflicts of interest.

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抗氧化物與人類健康

人類生態需要氧氣及水分，藉由氧化磷酸化作用，用於從食物產生立即能量-ATP。考量氧化壓力及氧化物在對抗感染、組織修補及傳遞訊息的關鍵角色，氧化及抗氧化作用間的不斷平衡，對生命體維持較長久的健全是必要的。抗氧化物能力衍生自外生性(來自食物、飲料及陽光)及內生性(來自酵素及非酵素路徑)。一些具氧化力的食物因子輔助含金屬的抗氧化酵素，在細胞外與細胞內運作。尿酸是靈長類血液中主要的抗氧化物。尿酸合成因來自水果、含糖食物及飲料的膳食果糖而增加。水果的這項間接抗氧化作用與來自於異黃酮的效應是分開的。飲酒也會增加血清尿酸。且尿酸鹽過多及留滯與疾病有關。由於尿酸具可能效益及危險性，使得東北亞地區高盛行率的高尿酸血症在公共衛生上是兩難的。含高抗氧化力的食物，包括莓果、堅果與豆類、番茄及甘薯葉。這些食物中的每種抗氧化物具多效性，諸如抗發炎作用、抗血管增生或是抗腫瘤。再者，食物基質及飲食模式將關係到抗氧化物攝取的安全性。迄今沒有證據顯示，分離抗氧化物當做食品補充劑，可改善健康或是存活狀況；更有一些顯示有無法接受的風險。抗氧化物雖可被視為食物的生物標記，但無法以此推證它們被純化使用的結果。儘管如此，膳食中的各樣多效能抗氧化物，對組織、代謝及免疫系統是有助益的。

關鍵字：抗氧化物、尿酸、毒性、補充劑、多效功用