

Antioxidants: real medicines?



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A pharmacy degree from Rhodes University led to an ongoing interest in medications of every type, and then led John into medicine, and into a career in clinical pharmacology via the University of Stellenbosch, the University of Kansas (USA), and then UCT and also in the pharmaceutical industry. Nutrition, complementary health, psychopharmacology, bats, dogs, gardening and cars are among his main current interests.

Antioxidants are widely recommended despite the lack of unequivocal clinical trials showing benefits.

It is the function of medicine to assist us to die young — as late as possible.

Greek adage

A casual viewing by any health care practitioner of the items on the shelves of almost every pharmacy or certainly of every health store, will speedily assure the visitor that there is a vast world of herbal, homeopathic, naturopathic, nutritional and other less readily classifiable supplements available to meet the needs of, and to interest and engage — if not confuse and confound — every citizen of our country.

Fortunately, in our task of being informed of allopathic medications, we are assisted by the availability of highly informative official documentation such as the package inserts which are authorised by the Medicines Control Council, and publications such as the *South African Medicines Formulary*.

However, when it comes to the vast array of complementary medications, the ready availability of any, let alone enlightening, information is seriously deficient. The Medicines Regulatory Authorities in many countries are busy devising methods to counter this situation, which may be very helpful in at least contriving to assure the contents and quality of complementary medications.

This preamble sets the scene for an attempt at an evaluation of the antioxidants as constituting real medicines. If any nutritional-type supplements have been subject to widespread orthodox examination, then several well-known antioxidants must qualify. This huge interest derives from the widely held belief

that the antioxidants should have a salutary role to play in the prevention, retardation and even reversal of many of the pathologies that beset the lives of humans and other animals.

OXYGEN FOR LIFE AND DISASTER

Our reliance on oxygen for the maintenance of aerobic life on our Blue Planet is a taken. The total respiratory process is one of making oxygen available to meet the energy needs of every cell in our bodies. We must be cognisant of the fact that oxidation plays a vital role not only in the respiratory chain but also in anti-infective activity, cell division and maturation and apoptosis, immunological processes, vasoactivity, etc. These are essential ‘survival activities’ of living tissue.

It seems that every cell in our bodies is bombarded by thousands of oxidative insults every minute of every day. Damage as a result of excessive or uncontrolled oxidation is widely documented, nowhere more extensively than in the emergence of metabolic and cardiovascular disorders¹ such as atherosclerosis, myocardial infarction, stroke, endothelial dysfunction, peripheral vascular insufficiency, diabetes mellitus, dementias, Parkinson’s disease, and retinal macular degeneration. The serious toxicity of oxygen itself when administered to neonates and especially to premature infants is well known.²

While endogenous metabolic pathways utilise oxidative processes largely for our benefit, various pathological processes such as autoimmune disorders set up oxidative activities against our own tis-

sues. Furthermore, exogenous sources of oxidative stress may shift the balance from benefit to disaster. Smoking burdens every cell with a barrage of oxidants (and other poisons), as does atmospheric pollution from vehicles such as cars and aircraft — jet aircraft in particular; in short, fires (combustion) of every description add to the oxidative load in our environment. A wide variety of medications, radiation such as X-rays, strenuous physical exercise, all forms of inflammation, excess alcohol, trauma of every type etc., add to our oxidative load.

Oxidative stress is obviously countered by myriads of endogenous processes; if this were not so, survival would not be possible. Our bodies are provided with a host of enzyme systems and chemicals that have the ability to ‘neutralise’ oxidative stressors (Fig. 1). But it must be noted that our defensive capacity relies very extensively on our dietary intake of an abundant supply of protective chemicals that are distributed about our organs in amounts appropriate to the demands made upon them.

OXIDATIVE ATTACK

Oxidative attack is held to be responsible for a host of disorders. Table I lists some conditions where oxidative damage is regarded as prominent.

The diabetic state is characterised by a progressive burden of glycation — a process where non-utilisable glucose encumbers (‘glucosylates’) an enormous variety of cellular and subcellular structures and chemicals (the HbA1c level which we use to gauge glycaemic control is a reflection of this glycation process). Glycated structures are particularly prone to oxidation, and thus the term ‘glycooxidation’ has come into use to describe the devastating dual glycation-oxidation

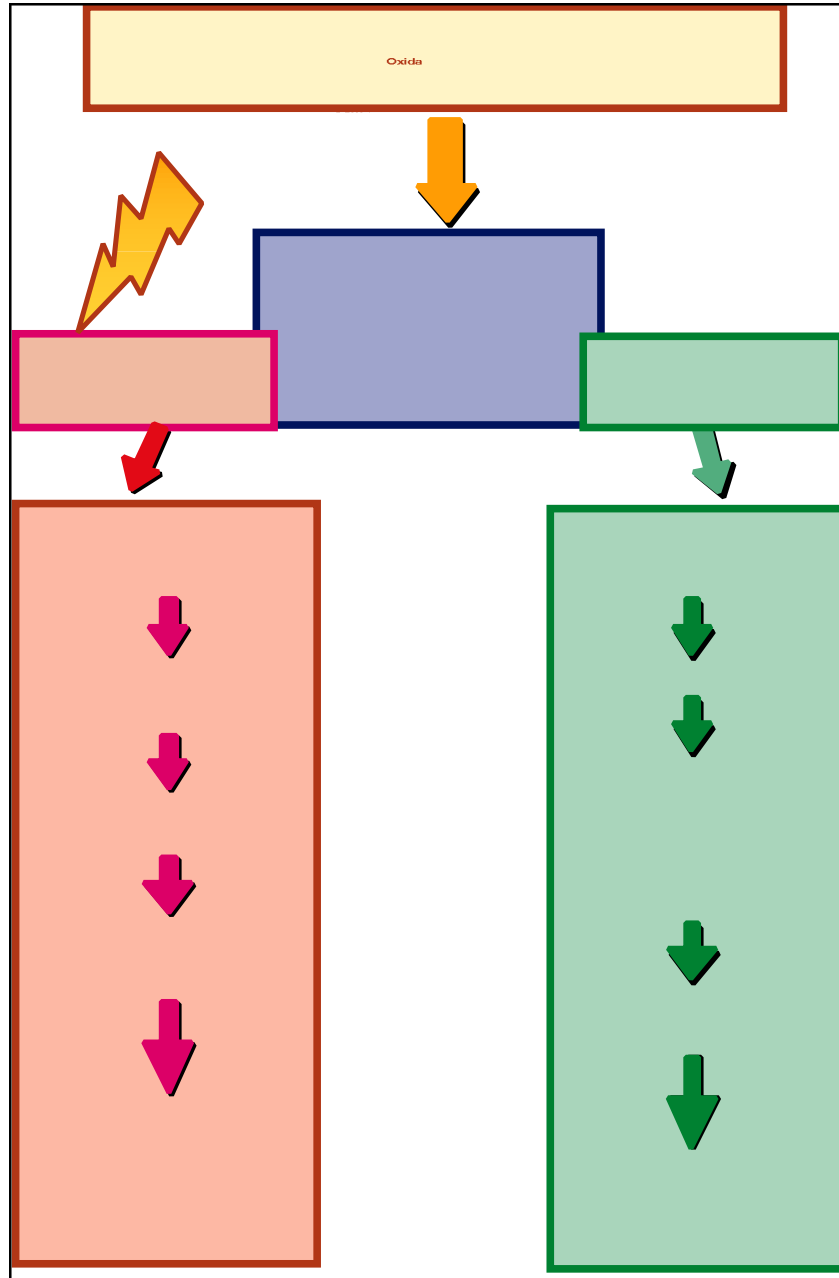


Fig. 1. Repercussions of controlled and uncontrolled ‘combustion.’

Table I. Examples of clinical disorders evoked by oxidative damage

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|---|--|
| <ul style="list-style-type: none"> • Cataracts • Retinal/macular degeneration • Endothelial dysfunction • Atherosclerosis • Hypertension • Cardiac failure • Plaque rupture • Myocardial infarction • Coronary reperfusion injury • Coronary stent restenosis | <ul style="list-style-type: none"> • Raynaud’s disease • Diabetic retinopathy • Diabetic neuropathy • Sunburn • Solar keratoses • Cancers • Amyotrophic lateral sclerosis • Parkinson’s disease • Alzheimer’s disease • Ageing |
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processes that damage the bodies of diabetics in particular. This situation helps to explain the vastly increased risk of diabetics for cardiovascular and other disorders.

ACTIVE RADICALS

When oxidation occurs, electrical charges in the form of electrons are passed onto susceptible acceptors, which then become what are termed 'active radicals'. If these active radicals are not promptly deactivated, a cascade of electron transfer can follow that has the potential ability to damage the components of every cell, and set in motion inflammatory processes that may become self-propagating.

DNA, RNA, enzymes, mitochondria, cellular and subcellular membranes, lipids and lipoproteins, proteins, and the active elements of rapidly dividing cells are particularly at risk.

Table II. Examples of well-characterised oxidants and active radicals

- Peroxynitrite
- Hydrogen peroxide
- Superoxide anion
- Singlet oxygen
- Peroxyl radical
- Alkoxy radical
- Hydroperoxyl radical
- Nitric oxide radical
- Nitrogen dioxide radical
- Hydroxyl radical
- Ozone
- Homocysteine

Table II lists some of the many active oxidants that have been described and characterised.

Likewise, many of the endogenous quenchers of these oxidants have been discovered and characterised. Endogenous antioxidants may be enzymatic or non-enzymatic.

Table III. Examples of endogenous antioxidants

- Superoxide dismutases – very plentiful in mammals
- Catalases
- Peroxyredoxins
- Metallo-thioneins
- Glutathione and its peroxidase, and its reductase
- Plasma protein thiols which provide sulphhydryl [SH] groups
- Melatonin, oestrogens, DHEA, creatine, taurine, etc.

Table IV. Examples of some antioxidants found in dietary sources

Flavonoids – over 4 000 from edible plant foods have been characterised
Carotenoids – , , , ; lycopene, lutein; more than 600 carotenoids are known
Proanthocyanidins and polyphenols – blue-red/violet pigments in grapes, berries, etc; epicatechins, catechins – tea
Phytosterols – mango, soybeans, butternut, yams
Isoflavones – soy and many pulses, yams
Thiols – garlic, cabbage
Allylic sulfides – garlic, broccoli
Tocotrienols and tocopherols (vit-E) – , , , ; grains, seed oils
Resveratrols – red grapes, red wines
Indoles
Isoprenoids
Glucosinolates
Picinogens
Selenium – critical co-factor for many thio-peroxidases

Some of the many endogenous substances involved in active radical quenching are listed in Table III.

However, as suggested above, our bodies rely on the regular ingestion of a vast array of active-radical quenchers to support their defences against active radical attack.

DIETARY ANTIOXIDANTS

Antioxidant vitamins such as vitamin E, vitamin C, β -carotene, and perhaps lipoic acid, are likely to be well known to most health care practitioners.

Table IV lists some examples of antioxidants found in foodstuffs. It should be noted that plant foods are our greatest source of these potentially protective substances.

While the chief vitamins which have antioxidant capacity are readily recognised, what is much less well known is the fact that vitamin E is a family of 8 vitamins: 4 tocopherols (, , ,) and 4 tocotrienols (, , ,). Yet the almost invariable form used in clinical studies and also found in the vast proportion of supplements, is the racemate (dl form) of α -tocopherol. However, in nature the d-form predominates, but then also it is never found on its own: it is always in association with its natural congeners, γ and δ -tocopherol, and the β , δ and ϵ -tocotrienols. Furthermore, the USA diet — chosen because it is well documented in this regard — contains more α -tocopherol than any other form of vitamin E.³ So why is α -tocopherol the almost invariable choice for clinical stud-

ies and for supplements? No substantial argument is found in favour of this choice. The carotenoid family is some 600 members strong, so we must question why β -carotene is selected for clinical studies as the 'representative' of this large family.

A large number of allopathic medications are also known to have marked *in vitro* antioxidant properties; these include allopurinol, aspirin, carvedilol (remarkably potent), metformin, paracetamol (in conventional dosage), various steroids such as oestrogens and dehydroepiandrosterone, probucol, some statins, some ACE-inhibitors, some fibrates, N-acetylcysteine, colchicine, verapamil, and more. Whether this antioxidant activity of such medications offers any benefits is unknown.

ANTIOXIDANTS AS THERAPEUTIC AGENTS

Antioxidant supplements are being extensively promoted for their health benefits, but do these supplements do any good? The main thrust of this article is to examine this question.

A very large number of clinical studies have been conducted — at massive expense — to investigate the possible role of various antioxidants in the prevention and containment of chiefly cardiovascular diseases, but also other degenerative disorders and cancers. Essentially this approach derives from epidemiological studies, which have shown that populations with good bodily levels of various antioxidants have less index disease. And the point of departure in such studies is that the antioxidants are regarded as pharmacotherapeutic agents, in the same way as we might consider β -blockers, aspirin or warfarin to be pharmacotherapeutic agents. Thus, the best clinical trials make use of one

or more individual antioxidants and administer them — usually in doses that are decidedly higher than might be found in a good dietary regimen, for periods that vary from months to years, and compare the effects with those of a placebo, in a double-blind controlled manner.

While some benefits have been demonstrated in several of the individual studies, nothing consistent across the studies emerges.

It is recognised that cardiovascular diseases are major morbidity and mortality factors. Efforts at reducing such diseases are universally encouraged, and oxidative mischief is regarded as a universal component in most forms of cardiac and vascular disorders. Thus, in seeking to beneficially modify cardiovascular disease, several antioxidants have been put to the test. Vitamin E (almost invariably as α -tocopherol), vitamin A, β -carotene and vitamin C have received most attention. *In vitro* studies show these vitamins to possess major antioxidant capacity, and large studies have examined the effects of chiefly these antioxidants alone or in various combinations, for their possible ability to modify an array of cardiovascular and other disorders. The outcomes of these studies (and some of them are huge in terms of subject numbers, their time frames and cost) are so disparate that they must urge us to question the advisability of further similar antioxidant studies!

While some benefits have been demonstrated in several of the

individual studies, nothing consistent across the studies emerges.⁴ Indeed, it is a sad situation when studies probing individual antioxidants for possible benefits, actually produce results that show an increase in morbidity and mortality.

So we are left with a real dilemma, but it is certainly pertinent to question if more of the same studies are likely to provide any different or better outcomes.

IS THERE SOME FUNDAMENTAL FLAW IN THE CONCEPTUALISATION OF THESE STUDIES?

By way of attempting to approach this question, let us consider the following:

Over millions of years, evolving humankind has had to cope with lean times and times of plenty, but the consensus is that our forebears survived on diets that were predominantly plant based.⁵⁻⁷ Indeed from an evolutionary and epidemiological point of view, it is only in the immediate past with the 'westernisation' of considerable populations that our diets have included increasing quantities of

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animal products, and in particular large quantities of animal fats from animals that are increasingly fed a non-wild and highly restricted diet.

For example, between 1967 and 1997 in both Asia and the Middle East, per capita availability of calories derived from animal sources more than doubled, and in Malaysia, while total calories available increased by 24% during this same 30-year period, calories available from fat increased by 164%.

However, not only has the intake of animal fats increased over this period, but there is in many westernising countries, an ongoing increase in the availability and intake of saturated fats and of the even more deleterious trans-fatty acids.

Trans-fatty acids raise small dense LDL-cholesterol levels and markedly lower the favourable HDL fractions,⁸ and increase the risk for coronary heart disease.⁹ The acknowledged deleterious effects of such lipids must be taken into account in the overall picture, as must the worldwide increase in obesity and its adverse metabolic repercussions.

FRUIT AND VEGETABLES

Ample epidemiological studies have shown and continue to show the overall health benefits of a diet rich in fruit and vegetables, and of olive oil^{10,11} and red wine,¹² with a good intake of deep cold-sea fish.¹³⁻¹⁵ Indeed, several such large, long-term population studies have demonstrated benefits not readily achievable with any allopathic medications.¹⁶ The US Nurses Health Study showed an 80% reduction in the incidence of coronary events by 'healthy lifestyle'.¹⁷

A study of a 'Garden of Eden' diet (fruit, vegetables and nuts) given to 10 healthy men and women for 14 days, provided a 30% reduction in

LDL-cholesterol levels and a much-improved LDL/HDL ratio.¹⁸ This suggests that the current 'quick-food supermarket' diet is a disaster.

WHERE DOES THIS LEAVE US?

It seems likely that it is a basic error to regard individual dietary antioxidants as equivalent or even similar to allopathic pharmacotherapeutic agents. We have evolved with an intake of a wide variety of foodstuffs that provide a vast mix of nutrients and antioxidants. Is it not possible, perhaps even probable, that by selecting individual antioxidants for clinical trials (and for everyday supplementation) we create a gross dietary imbalance among these active radical scavengers? Substance for this argument would certainly seem to reside in the fact that individual antioxidants — when present in large quantities — readily become pro-oxidant. Almost every individual antioxidant seems to have the ability to become pro-oxidant when taken out of context — the context being its concentration and its natural congeners as found in whole foodstuffs.

The carotenoid family consists of some 600 members; perhaps by selecting β -carotene as a representative of this family and dosing it in large amounts, the 'best balance' of the carotenoids is grossly disturbed, and then we find either no benefits or much worse — for example an increase in lung cancer.¹⁹ β -carotene in excess readily becomes pro-oxidant.²⁰

Similarly, vitamin E is a family of 8 members, each probably having important roles to play, and dosing with large quantities of any single member may well be disadvantageous; for instance, it has been shown that high intake of α -tocopherol lowers the levels of γ -toco-

pherol.²¹ It is evident that a fine balance exists between the levels of the E vitamins and vitamin C, which is important for the appropriate regeneration of oxidised vitamin E back to its antioxidant form.

Studies examining the role of vitamin E in various conditions have provided us with highly ambiguous information: some studies show minor benefits, many show no benefits at all,²² while some show detrimental effects. The HOPE study compared ramipril with vitamin E supplementation and found no benefits in the vitamin E recipients.²³

When we supplement with large quantities of individual antioxidants, we would seem to be at risk of deleteriously disturbing the optimal antioxidant balance that whole foods would provide.

A paper entitled 'The ambivalence of vitamin E in atherogenesis' is at pains to indicate that vitamin E (as α -tocopherol) can promote peroxidation if co-antioxidants are deficient and it is administered in large doses.²⁴ In a study of patients in Gauteng with familial hypercholesterolaemia, vitamin E supplementation (1 000 mg/day for 2 years) provoked more rapid increase in the intima-media thickness of the carotid arteries than had been found in control subjects.²⁵

Then again in foodstuffs, vitamin C is always present in company with a host of associated antioxidants chiefly as a vast array of

flavonoids. There is some evidence that a daily intake of vitamin C in excess of 200 mg has been associated with an increase of atherosclerotic lesions and regular megadoses raise blood glucose²⁶ and can inactivate vitamin B₁₂.²⁷ Is this because vitamin C in excess becomes pro-oxidant, and/or is it because the balance among all the thousands of antioxidants is detrimentally perturbed? The paper entitled 'Vitamin C: poison, prophylactic or panacea?'²⁸ indicates just how readily excessive vitamin C becomes pro-oxidant, especially in the presence of ionic iron and other metals, with a real propensity to damage DNA.²⁹

Antioxidants as individual agents cannot be recommended in the primary or secondary prevention or treatment of disease

Consider that 30 g of dried almonds contain about 6.5 mg of total vitamin E; we would need to ingest something like 4.3 kg of these almonds to obtain 1 000 mg vitamin E, or 62 cups of wheat germ! From these food sources we would get the total vitamin E family, not just α -tocopherol, along with thousands of other nutrients!

Thus, when we supplement with large quantities of individual antioxidants, we would seem to be at risk of deleteriously disturbing the optimal antioxidant balance that whole foods would provide, probably also inducing pro-oxidative effects, and perturbing the finely balanced metabolic processes of relevant cells.

However, if the non-antioxidant actions of these antioxidants are examined, they are found to be diverse and profound: for example, α -tocopherol has antiplatelet and anticoagulant activity, but γ -tocopherol is much more active in this regard.³⁰ The tocotrienols have significant additional statin-like activity with a notable ability to raise HDL-cholesterol and lower LDL-cholesterol.³¹ The non-antioxidant activities of these antioxidants must also receive attention.³²

WHAT ABOUT WHOLE FOOD EXTRACTS OR CONCENTRATES?

Many so-called phytoceuticals are made available as 'teas', as dry powders, or as concentrated alcoholic or aqueous extracts. It is apparent that such extracts

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contain many of the actives of the original plants. Humankind has used dried herbs of many types down through the millennia, and many herbs have demonstrated health benefits. The 'green pies' of Crete are largely of wild plant origin, and form a valuable component of the diets of those Cretans who follow the traditional diets of former generations, and which confer remarkably low levels of cardiovascular disease.^{33,34} Whole fruits and the juice of plants have been shown to lower body levels of nitrosation products — good evidence of multiple and effective carcinogen reduction.³⁵

Supplementation with n-3 polyunsaturated fatty acids to counter the massive increase in the Western diet of n-6 fatty acid intake, would make a most notable impact on the incidence of many diseases.³⁶⁻³⁹

BASELINE ASPECTS OF ANTIOXIDANT STUDIES

When trials of individual antioxidants are performed, it is most unusual for the investigators to establish the baseline levels of the particular antioxidant in each recipient or to establish their general antioxidant status. Persons who are antioxidant-replete may well respond very differently compared with persons who are deficient; and those who are deficient may well also be deficient in many closely related, and not-so-closely related, dietary essentials. This must contribute to the 'blurring' of effects of these antioxidants, and thus to the highly equivocal overall clinical picture regarding the benefits or demerits of individual antioxidants.

A recent study with placebo control⁴⁰ is pertinent in this regard: it examined the effects of multivitamin-mineral and vitamin E supplementation in persons 60 years of age and older who were known to

be vitamin C and vitamin E replete, and found no benefit from the multivitamin-mineral supplementation, but found a significantly higher incidence and severity of respiratory tract infections in the vitamin E supplemented group. Was the excess vitamin-E being pro-oxidant and deleteriously interfering with the immune response?

CONCLUSION

We require convincing proof of positive effects from supplementation with individual antioxidants, and we must have proof that there is an absence of harm with large daily individual antioxidant intakes before the population at large is enticed — as it currently is — to make use of them.⁴¹

It seems that we need to accept that bodily levels of individual antioxidants are just biomarkers for the adequacy or otherwise of dietary intake. Surely then, it is the *entire diet* that must be optimised and not just a couple of biomarkers?

A healthful lifestyle with no smoking, adequate amounts of physical exercise, and a diet rich in fruits, vegetables, whole grain cereals, dietary fibre and unsaturated fats, and low in salt and saturated and trans-fatty acids, has shown quite spectacular health benefits.

However, this lifestyle is currently quite inadequately recommended, and is grossly overwhelmed by the prevalent acceptance of, and propaganda for, the concept that health can come from a 'pill'. Antioxidants as individual agents cannot be recommended in the primary or secondary prevention or treatment of disease. Only by a good diet as part of a good lifestyle, can this be safely and effectively accomplished.

References available on request

SUGGESTED FURTHER READING

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IN A NUTSHELL

Individual antioxidants are widely advocated for their presumed health benefits.

While the theory seems convincing, major clinical studies show no benefits and some show deleterious repercussions.

The true Mediterranean type diets have been shown to confer remarkable benefits

We give quite insufficient attention given to such overwhelmingly positive information.

Our emphasis should be on actively 'prescribing' a good lifestyle.

A good lifestyle includes a daily intake of a diet rich in fruits and vegetables, and with a balanced intake of omega-3 fatty acids, low in saturated fats and trans-fatty acid, with no smoking and with regular physical exercise.

The benefits of such a lifestyle can't be mimicked by any 'pill or potion'.