

## ***The antioxidant myth: a medical fairy tale***

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Cranberry capsules. Green tea extract. Effervescent vitamin C. Pomegranate concentrate. Beta carotene. Selenium. Grape seed extract. High-dose vitamin E. Pine bark extract. Bee spit.

You name it, if it's an antioxidant, we'll swallow it by the bucket-load. According to some estimates around half the adults in the US take antioxidant pills daily in the belief they promote good health and stave off disease. We have become antioxidant devotees. But are they doing us any good? Evidence gathered over the past few years shows that at best, antioxidant supplements do little or nothing to benefit our health. At worst, they may even have the opposite effect, promoting the very problems they are supposed to stamp out.

It's little surprise that antioxidants have acquired a reputation as miracle health supplements. As long ago as the 1950s, scientists discovered that many diseases - including heart disease, strokes, cancer, diabetes, cataracts, arthritis and neurodegenerative disorders such as Parkinson's and Alzheimer's - were linked to damage caused by highly destructive chemicals called free radicals.

Free radicals are compounds with unpaired electrons that stabilise themselves by oxidising other molecules - including proteins, carbohydrates, lipids and DNA. In the process they often create more free radicals, sparking off a chain of destruction. Oxidative damage accompanies most, if not all, diseases and has even been proposed as a direct cause of some including lung cancer, atherosclerosis and Alzheimer's.

Free radicals are an unavoidable hazard of being alive. We live in an oxygen-rich atmosphere, and radicals, particularly reactive oxygen species (ROS), are natural by-products of respiration. "One per cent of the oxygen we consume turns into ROS," says biochemist Barry Halliwell from the National University of Singapore. "It doesn't sound like much but humans are big animals and we breathe a lot. Over a year a human body makes 1.7 kilograms of ROS." Exposure to X-rays, ozone, tobacco smoke, air pollutants, microbial infections, industrial chemicals and intensive exercise also trigger free radical production.

In the 1980s, however, a potential weapon against free radical damage appeared on the horizon. Scientists had known for a long time that people

whose diets are rich in fruits and vegetables have a lower incidence of heart disease, diabetes, dementia, stroke and certain types of cancer - the very diseases that are associated with free radical damage. Now there was an explanation. Fruits and vegetables are a rich source of antioxidants that can neutralise free radicals by donating electrons to them.

Green plants are full of antioxidants for good reason. They are especially vulnerable to oxidative stress since they produce pure oxygen during photosynthesis. To protect themselves they manufacture an assortment of potent antioxidants.

And so a hypothesis was born: dietary antioxidants are free-radical sponges that can stave off the diseases of old age. It was a great idea. "Putting two and two together, scientists assumed that these antioxidants were protective, and that taking them as supplements or in fortified foods should decrease oxidative damage and diminish disease," says Halliwell, who pioneered research into free radicals and disease. "It was simple: we said free radicals are bad, antioxidants are good."

The concept helped spawn a colossal supplements industry. According to the US National Institutes of Health (NIH), more than half of US adults take some form of vitamin or mineral supplement at a total cost of \$23 billion a year. The bewildering range of supplements on the shelves makes it hard to say how much of this expenditure goes on antioxidants, but the NIH says it is probably a "large proportion". And their popularity just keeps on growing. SPINS, a market research firm based in San Francisco, estimates that the antioxidant market has grown by 18 per cent in the past year alone.

The best known antioxidants are vitamin E (also known by its chemical name tocopherol), vitamin C, and two broad classes of plant chemicals called polyphenols (including flavonoids) and carotenoids (including beta carotene and lycopene). Most supplements touted as antioxidants contain at least one of these, often as a pure chemical and sometimes as a concentrated plant extract.

Since the early 1990s scientists have been putting these compounds through their paces, using double-blind randomised controlled trials - the gold standard for medical intervention studies. Time and again, however, the supplements failed to pass the test. True, they knock the wind out of free radicals in a test tube. But once inside the human body, they seem strangely powerless. Not only are they bad at preventing oxidative damage, they can even make things worse. Many scientists are now concluding that, at best, they are a waste of time and money. At worst they could be harmful.

The first antioxidant to produce disappointing results was beta carotene. Once a star among supplements, beta carotene pills were recommended to smokers to protect them against lung cancer. This was largely based on the observation, made in the 1970s, that people who ate a lot of carrots - which contain large quantities of beta carotene - had some protection against cancer.

In 1992 researchers at the US National Cancer Institute set about testing beta carotene. They recruited more than 18,000 people at high risk of developing lung cancer, either because they smoked or had been exposed to asbestos, and gave around half of them beta carotene supplements. The trial was supposed to run for six years, but the researchers pulled the plug two-thirds of the way through after discovering, to their surprise and horror, that those taking supplements were faring worse than the controls. Their lung cancer rate was 28 per cent higher, and the overall death rate was up 17 per cent. "It was a shock. It not only did no good but had the potential to do harm," Halliwell says.

The researchers couldn't be sure that these increases were not caused by chance, and beta carotene capsules are still widely sold as an antioxidant. Further trials, though, have strengthened the evidence that beta carotene supplements not only fail to protect people against cancer but can also increase the risk of lung cancer in smokers. In May of this year an expert panel convened by the NIH concluded that there was no evidence to recommend beta carotene supplements for the general population, and strong evidence to recommend that smokers avoid it.

It's a similar story with the world's most popular antioxidant. Vitamin E shot to fame in the early 1990s, after two large studies involving more than 127,000 people in total found that those with a diet high in vitamin E were significantly less likely to develop cardiovascular disease. The first study followed 87,245 female nurses for eight years; it found that the top 20 per cent with respect to vitamin E consumption had a 41 per cent lower incidence of cardiovascular disease than the bottom 20 per cent (*New England Journal of Medicine*, vol 328, p 1444). The second study, involving 39,910 male health professionals, found a similar reduction in heart disease risk (*New England Journal of Medicine*, vol 328, p 1450).

The researchers, based at Harvard Medical School and Harvard School of Public Health, even had a plausible mechanism. Evidence was emerging that one of the causes of heart disease was free radical damage to LDLs, tiny packages of lipid and protein that circulate in the bloodstream, delivering fatty acids to cells. It turned out that adding vitamin E to blood samples in the test tube made LDL more resistant to oxidation. Perhaps this was how vitamin E prevented heart disease. "At the biochemical level, the rationale sounded so good - at that time," says Roland Stocker, a biochemist at the University of New South Wales in Sydney, Australia.

Use of vitamin E supplements soared. In 1990, almost nobody took vitamin E; by the end of the decade an estimated 23 million US citizens were knocking back daily doses.

On the back of these positive results, other researchers set up large studies using vitamin E supplements. The results, however, have been almost universally disappointing. Only one experiment - the Cambridge heart antioxidant study (CHAOS) - found a positive effect, a 77 per cent reduced

risk of heart attack. Several others found no protective effect and one even concluded that vitamin E increased the risk of heart failure.

#### **Time for a rethink?**

Other trials designed to test whether vitamin E supplements could prevent cancers, such as the ATBC study in Finland, also came in negative. Vitamin E also did not halt the progression to Alzheimer's disease in people with mild cognitive impairment.

What is more, when scientists went looking for evidence that vitamin E protected LDL against oxidation in the body, not just in the test tube, they found none - except in people with vitamin E deficiency (*Journal of the American Medical Association*, vol 285, p 1178). In fact, despite good evidence that vitamin E is a powerful antioxidant in the test tube, there is now serious doubt that it acts the same way in the body. "Vitamin E is not an antioxidant. In fact it must be protected against oxidation," says Angelo Azzi, a biochemist at Tufts University in Boston, Massachusetts. He points out that vitamin E exists in eight different forms in nature, all of which function as antioxidants in the test tube. Yet the body only uses one form, alpha tocopherol, which is pulled out of the bloodstream by a highly specialised protein in the liver. All the other forms are excreted. Azzi argues that evolution is unlikely to have gone to such great lengths simply to obtain an antioxidant from the diet. "There are millions of antioxidants," he says.

Vitamin E is clearly doing something in the body - it is an essential part of the diet and deficiency leads to neurological problems - but whatever it's doing, it's not an antioxidant.

There is even some evidence that vitamin E supplements can be harmful. Last year, a team led by Edgar Miller of the Johns Hopkins Medical Institutions in Baltimore made headline news when they amalgamated the results of 19 separate trials and concluded that high doses of vitamin E increase overall mortality (*Annals of Internal Medicine*, vol 142, p 37) - though this conclusion remains controversial. "It's flawed," asserts Azzi. "We re-analysed the data and there is no change in mortality." "Most people agree that there is no good evidence that large doses are harmful," adds Stocker.

Vitamin C is another disappointment. "People are still trying to defend it, but you don't get an effect on free radical damage unless you start with people with a vitamin C deficiency," says Halliwell. "I think it is a lost cause." In fact, results from a vast US trial probing the links between diet and health, called the Women's Health Study, suggest that vitamin C supplements may accelerate atherosclerosis in some people with diabetes.

One class of antioxidants that remains relatively unresearched is polyphenols. What little evidence there is comes from epidemiological studies, some of which suggest that polyphenols prevent disease and others of which do not. While polyphenols act as antioxidants in the test tube, it is not clear that they are absorbed into the bloodstream, and if they are, they are swiftly

metabolised. For example, 95 per cent of a flavonoid called resveratrol - the one found in red wine - is destroyed by our digestive system before it enters circulation.

“Just because a food with a certain compound in it is beneficial to health, it does not mean a pill with the same

The conclusion is becoming clear: whatever is behind the health benefits of a diet rich in fruits and vegetables, you cannot reproduce it by taking purified extracts or vitamin supplements. "Just because a food with a certain compound

in it is beneficial, it does not mean a nutraceutical [with the same compound in] is," said Paul Coates, who works in the Office of Dietary Supplements at NIH.

Yet the fact remains that people eating diets abundant in vitamin C, vitamin E, polyphenols and carotenoids are less likely to suffer heart attacks, vascular disease, diabetes and cancer. One explanation is that these people have a generally healthier lifestyle - they exercise more and smoke less, for example. For now, no one knows for sure.

### **Tough vegetables**

There are some ideas. Halliwell still believes that antioxidants are at least partly responsible. He argues that because the polyphenols, carotenoids and vitamins in fruit and vegetables are bound into tough, fibrous material, they hang around in the stomach and colon, where they can neutralise free radicals. The gastrointestinal tract, especially the stomach with its highly acidic environment, is constantly generating reactive oxygen species from food. Supplements may not replicate this effect because they are digested too quickly.

Andrew Shao from the Council for Responsible Nutrition, a supplement industry trade association based in Washington DC, argues along similar lines. He says that pulling a nutrient out of context and testing it in a clinical trial is not appropriate. "Antioxidants should not be expected to perform as drugs," he insists. "That's simply not how nutrients work. They work in concert with each other."

There's yet another, more intriguing explanation. Among the leading sources of dietary antioxidants are tea and coffee, and there is some evidence that green tea in particular is linked with health benefits including reduced risk of cancer and cardiovascular disease. Oddly, though, Halliwell has discovered that tea and coffee are also bursting with reactive oxygen species in the form of hydrogen peroxide.

"Every time you drink a cup of coffee it's a dilute bowl of hydrogen peroxide," says Halliwell. The hydrogen peroxide is there because of the presence of the antioxidants - "antioxidants" is really just another way of saying reducing agent, which can react with oxygen in the water to produce hydrogen

peroxide. Think platinum blond, and you get the picture of what you might be drinking.

But if free radicals are bad for us, how come coffee and tea might be beneficial? One possibility is that they can help nudge our own internal antioxidant systems into action. "There has been a considerable rethink as to what free radicals are doing," says Malcolm Jackson, a biochemist at the University of Liverpool, UK. He believes that in the right quantities radicals can be positively health-enhancing, prompting our cells to fire up their own internal defence machinery: a battery of radical-busting enzymes such as catalase and superoxide dismutase. "Cells are very good at protecting themselves against minor stresses, as long as they are not excessive," says Jackson. "The question is: should we be quenching free radicals at all?"

If it turns out that antioxidants in food work because they generate health-promoting quantities of free radicals, that would be an ironic turnaround. It may also explain why supplements and extracts don't seem to work or may even be dangerous: the doses are too high, and produce too many free radicals.

For now, the advice is simple. "Stick to flavonoid-rich foods, red wine in moderation, tea, fruits and vegetables," says Halliwell. "Don't start taking high-dose supplements or heavily fortified foods, until we know more."

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