Therapeutic options for ild: food or pharma?

During the last part of the previous century many efficacious drugs have been developed for treating a wide variety of diseases. Unfortunately, pharmaceutical treatment for interstitial lung diseases (ild) is stunted. In ild inflammation and oxidative stress are associated and mutually aggravating. This vicious circle can be mitigated with food or food derived compounds. It should be realized that dietary constituents have much milder and frequently less selective effects compared to pharmaceuticals. This can be an advantage in the treatment of multifactorial diseases like sarcoidosis or lung fibrosis. The multifarious action of food also has consequences for the way we should substantiate the effectiveness of nutrients or dietary compounds. Novel strategies are needed to clinically appraise the health benefit of dietary compounds in ild.

BY PROF. DR. AALT BAST

In 1946, the WHO defined health as ‘a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity’. After the Second World War it was realized that health should be for all, taking into account the conjunction of physical, psychological and social factors as determinants. During the last 50 years of the previous century, we were very successful in developing specific pharmaceuticals in an attempt to reach this complete health state. Drugs for many diseases have been designed and a wide array of specifically acting drugs has become available to the physician to treat patients. The medicinal chemist Adrien Albert (1907-1989) described the physicochemical basis of therapy with the term Selective Toxicity. Drugs should act as silver bullets, thus offering simple guaranteed solutions for difficult problems. Molecular selectivity is the buzzword for these compounds. However, with our current understanding of disease, we increasingly recognize that individual factors (genetics, epigenetics) and multifactorial processes determine the disease. We now realize that a risk-free wellbeing is impossible. Health is contingent on the ability to adapt to...
changes. A more appropriate and dynamic definition for health is therefore ‘the ability to adapt’.

Increasing the ability to adapt is not only relevant in the treatment of multifactorial or multisystem disorders like interstitial lung diseases but can even be of value for ‘healthy’ people. Increasing metabolic flexibility can lead to disease prevention thus maintaining health. This new definition of health entails other treatment tactics and different ways of investigating health promoting substances. Treatment should not just aim for a strong selective silver bullet approach but rather for a subtle multitude of physiological effects that is applicable to the individual. Food or food components seem excellently suited in this respect. Physiological effects of food are generally not very selective, the effects are mild and the toxic side effects are generally insignificant.

**Adaptation to oxygen**

One of the most toxic compounds to aerobic life forms is in fact oxygen itself. Probably one of the largest adaptations of life is the adaptation to oxygen by aerobic life forms. Oxygen is extremely hazardous. The health risk of a compound is the hazard of that compound times the exposure to that compound. Early in evolution, i.e. more than 3500 million years ago, anaerobic life begins. Intense solar radiation bombards the surface of the earth. More than 2500 million years ago blue green algae acquired the ability to split water, which released oxygen. More complex cells with nuclei and even multicellular organisms emerged 1300 million years ago. Atmospheric oxygen reached 10 % around 500 million years ago and the formed ozone layer screened out the UV light facilitating the emergence life forms from the sea. Primates appear 65 million years ago and humans around 5 million years ago when the atmospheric oxygen reaches 21%. This hazardous character of oxygen is still clearly discernible. Oxygen easily can take up additional electrons forming various so-called reactive oxygen species (ROS) like superoxide anion free radicals, hydrogen peroxide and very reactive hydroxyl radicals (see figure 1). These ROS may react with all kind of biomolecules and can thus lead to oxidation of membrane bound poly-unsaturated fatty acids, proteins or DNA. This leads to membrane damage, protein receptor or enzyme damage or to oxidation of

---

**Reactive Oxygen Species**

<table>
<thead>
<tr>
<th>Reactive Oxygen Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>$O_2^-$, $H_2O_2$, $\cdot OH$</td>
</tr>
</tbody>
</table>

**Figure 1.** The reactive oxygen species (ROS) superoxide anion free radical, hydrogen peroxide and the hydroxyl radical are formed during various normal physiological reactions by cytochrome P450, which is involved in oxidation of xenobiotics and in the oxidative burst of phagocytic cells, which is involved in killing invading micro-organisms. Too much ROS formation may lead to damage of biomolecules like DNA, proteins or fatty acids. Enzymatic and non-enzymatic protectors prevent this damage to biomolecules.
DNA respectively. The latter may result in carcinogenesis. The paradox of aerobic life is that it also uses this reactivity of oxygen in many physiological reactions. Phagocytic cells produce ROS and thus form a last defense against invading microorganisms. Metabolizing enzymes like the, from an evolutionary point of view, very old metabolizing enzyme cytochrome P450 use ROS to transform xenobiotics into more water soluble metabolites. Many intracellular signal transduction pathways use ROS.

In the adaptation strategy, aerobic life developed an elaborate enzymatic as well as a non-enzymatic defense against oxygen toxicity. The non-enzymatic antioxidants are supplied via the diet in the form of for example vitamin E and C, carotenoids or polyphenols. Limiting the oxygen toxicity enables normal physiology to exploit the chemical reactivity of oxygen as described here. Clearly, aerobic life can use ROS but pathophysiological aberrations are frequently associated with damage induced by ROS.

Oxidative stress and inflammation

Chronic inflammatory physiological aberrations are frequently associated with ROS induced toxicity. As with oxygen a homeostasis is desirable. Inflammation can assist in maintaining homeostasis. At the same time it may be detrimental if the inflammatory process is too abundant. In that case tissue damage may result. Inflammation can be evoked by oxidative stress. Oxidative stress may lead to activation of the transcription factor NF-xB, following the phosphorylation of the inhibitory factor IxB or via the activation of PARP-1. NF-xB activates the production of pro-inflammatory cytokines and chemokines. This may lead to further attraction and influx of inflammatory cells which further aggravates the situation via the production of ROS. In this way a vicious circle arises (see figure 2). Food and food derived components are excellently suited to mitigate this vicious damaging circle in which oxidative stress and inflammation aggravate each other.

Use of food derived components in ild

Interstitial lung diseases like sarcoidosis and idiopathic pulmonary fibrosis are also strongly associated with the combination oxidative stress/inflammation. The chronic inflammatory process in sarcoidosis is associated with occurrence of oxidative stress. This can be deduced from the increased levels of biomarkers for oxidative stress as exhaled ethane, 8-isoprostanes and oxidized proteins in the bronchoalveolar lavage fluid of sarcoidosis patients. Food or food derived components as for example quercetin, which abundantly occurs in our diet via onions, apples and grapes, reduce markers for oxidative stress and inflammation in sarcoidosis. The polyphenol quercetin is a very potent antioxidant. Moreover the anti-inflammatory action of quercetin has been suggested to occur (at least partly) via the inhibition of NF-xB. Polyphenols in general possess many actions. However, the bioactivities of these plant-derived compounds are mild and not as specific as many pharmaceuticals. One of the few compounds that displayed a clinical effect in IPF is N-acetylcysteine.
is also an antioxidant. It acts directly via its thiol moiety but can also have an indirect effect acting as a precursor of the endogenous antioxidant glutathione.9

**Final reflections**

Not the method but rather the problem should be centerfold. Regulatory agencies currently evaluate nutrients via a classical pharmaceutical approach. It is said that well-defined single endpoints which are used for silver pharmaceutical bullets should preferably also be used for dietary compounds. Health claims are not allowed when these particular, but for food frequently shackled methodologies, are not applied. We suggested that for food derived compounds, new methods should be applied. Scientific evaluation should not solely rely on the classical approach. The scientific evaluation of the effect of food in ild should rather focus on the problem than on the method [see comments on reference 9]. In case of ild it should be realized that it might be less valuable to target a specific molecular pathway than slightly affecting heterogeneous biological aberrancies that, as a whole lead to ild. Food does of course not have a strong specific pharmacological efficacy. This would be undesirable for dietary components. The inherent mild multitude of physiological effects of food might be beneficial in ild. Novel strategies are needed to quantify the health effects of food and food derived components. The mild effects (individually possibly not reaching significance) might be judged via a lung health index approach [see 9]. This resembled the approach suggested by Behr et al.10 testing N-acetylcystein (NAC) in lung fibrosis integrating the effect on vital capacity, CO-transfer factor and delta exercise PaO₂ in a lung function index. Insight in molecular mechanisms might help to understand and optimize and to personalize the treatment with food in ild.

**References**