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CHEMICALS AND HEALTH – THOUGHT FOR FOOD

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□ In our contribution we concisely question and answer some basic notions on food, health, and safety. We show that for some food components such as flavonoids, a whole range of small toxicological effects that have been uncovered the last decade on the whole confer benefits to human health. This development underlines the notion that health is adaptation with respect to the exposures humans experience when consuming food.

INTRODUCTION

The term dose-response could have originated from the early profession of the food taster, since it was the dose of a poison in the food that would harm the emperor, king or pharaoh. The profession of a food taster was a risky occopation. Even the Bible (Genesis 40:21) mentions the reality of its riskiness, both toxicologically as well as religiously and politically. As high priests, they had an important social and religious standing. In that sense it is tempting to compare these important people from the ancient world with the toxicologists of today. However, as the story in Genesis unfolds, the chief cupbearer was restored to his position whereas the chief baker was hanged. This part of the story, of course, is a less attractive aspect of the comparison, although toxciologists do carry a certain responsibility that might bring fame or harm. Indeed, in modern times presidents or candidates are sometimes in danger of being intoxicated by their adversaries, as Viktor Yushchenko, the then presidential candidate in the Ukraine in 2004, has experienced, being intoxicated by dioxin (Sorg *et al.*, 2009).

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Apparently for pharaohs and presidents, food can be rather unsafe and they (should) protect themselves. But how does the consumer ensure that his food is safe?

The consumer, by and large, ostensibly protects himself by choosing those products that are portrayed as natural and thereby safe. Organic farming, despite its pricing, has become popular based exactly on the notion of naturaleness that implies safety. Additionally, consumers tend to buy those products that contain the prefix bio: biosoap, bio vitamin C, bioflavonoid, biochromium. Although chromium is a chemical element, the alliterating term chemo-chromium seems certainly less attractive despite its descriptive accuracy.

The consumer then seems to have a skewed perspective on food safety. But food, obviously, has to be safe; that is without harmful chemicals?

This is an interesting notion that receives too little attention both with regulators and scientists. Food is a complicated mix of many different chemicals with diverging biological activities. Indeed, almost all plants, including crop plants, protect themselves with many a toxin, that are certainly not harmless to humans (Figure 1). Ames famously estimated that of all chemicals we are exposed to, 99.9% are of natural origin. Of all dietary pesticides we consume, 99.99% are of a natural origin. This amounts to daily intake of 1500 mg of natural pesticides and their breakdown products. Human exposure to synthetic pesticide residues amounts to about 0.09 mg per day (Ames and Gold, 2000; Gribble, 2010).

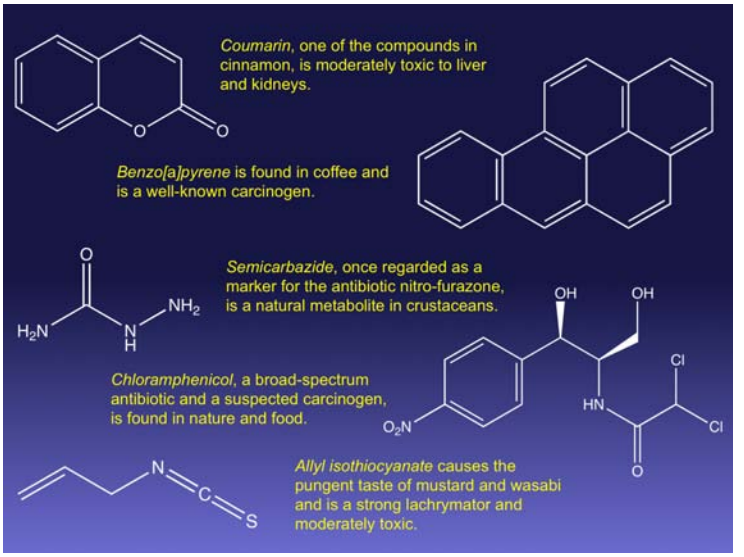

FIGURE 1. Examples of natural toxins found in food.

Pharmacology also uses the toxicity of compounds to the benefit of the patient?

The famous book that describes the physico-chemical basis of therapy is entitled 'Selective toxicity' (Albert, 1951). In this book written by Adrien Albert, pharmacology of drugs is described as a selective form of toxicity. Side effects of drugs can often indeed be regarded as lack of selectivity. This methodology has been quite successful. It reflects the medicinal-chemical approach that is used to design and develop selectively active medicinal molecules. The crux of this approach is best characterised as a single molecule acting toxicologically on a single target. Specificity, concomitantly with the amplitude of this toxicological effect, is central to pharmacology. Put differently, pharmacology is looking for both strong and specific effects. This contrasts with the effects of food (vide infra).

If food contains so many 'toxic' ingredients, couldn't we use food as medicine?

Currently, we increasingly regard food as medicine, and for good reason. Functional foods, for example, support human health and wellbeing, providing health benefit beyond basic nutritional requirements. Food supplements also sold for the benefit of human health are products isolated or purified from food and have been demonstrated to have a physiological benefit or provide protection against chronic disease. Nutraceuticals are food supplements generally sold in medicinal forms and not usually associated with food (Hanekamp *et al.*, 2012).

Pharaohs regarded food to be the bearer of both divinity and vital strength. Current interest in the positive health effects of functional foods, nutraceuticals and herbal medicines seems therefore to be a return to the philosophy of ancient Egypt.

Could we not introduce more specificity in the action of food?

Although in pharmacology we indeed look for specificity and amplitude, in food pharmacology, general 'toxicity' is the basis for a multitude of beneficial physiological effects. This is not only related to the many different endogenous food chemicals, but also due to different multifarious effects of one class of compounds or specific representatives of those classes. As an example, the most consumed flavonoid quercetin is abundantly found in onions, apples and red wine. One of the many observed effects of quercetin is its anti-inflammatory effect (Boots *et al.*, 2011). This anti-inflammatory effect comprises various physiological phenomena that are influenced by this specific polyphenol (Boots *et al.*, 2008). Although these individual effects seem to be small, the overall anti-inflammatory effects give rise to the beneficial activity of quercetin (Figure 2).

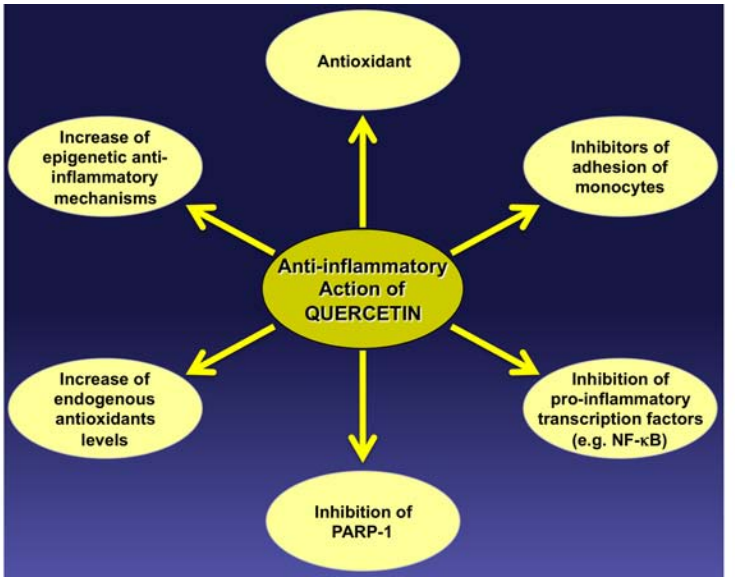

FIGURE 2. Factors involved in the anti-inflammatory action of quercetin.

Could this so-called 'pleiotropic' action of food not be a basis for research?

This is an interesting suggestion, requiring however a proper sense of what human health in fact is. In 1947, the WHO defined health as a 'state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity'. This is a rather static definition of health and difficult to implement on any individual or corporate level. Conversely, a definition that captures the dynamic state of health seems to be closer to how humans behave and live under varying conditions. Health then is defined as the ability to adapt (Weseler and Bast, 2012).

The multitude of effects generated by food expresses this ability to adapt. Nutritional effects are both pleiotropic and relatively small, and fortunately so. The latter is essential, as food consumption is not expected to give huge pharmacological effects as looked for in medicinal pharmacology; rather subtlety is the name of the game in food, ethanol probably being the only exception. Adding the small multiple effects of dietary components –comparable to combi-toxicology- could correspondingly be employed to define a 'beneficial capacity'. Current scientific methodology does not take account thereof: studies defining health aspects of foodstuffs tend to focus on separate, isolated compounds and isolated 'cause-effect'-related identifiable phenomena.

In using mixtures of compounds, however, linearity is a problem. Feedback and adaptation processes will hamper simple linear extrapolation of the effects that occur within a homeostatic range. The *biphasic dose-response curve* seems useful –as it is in toxicology- in elucidating the rela-

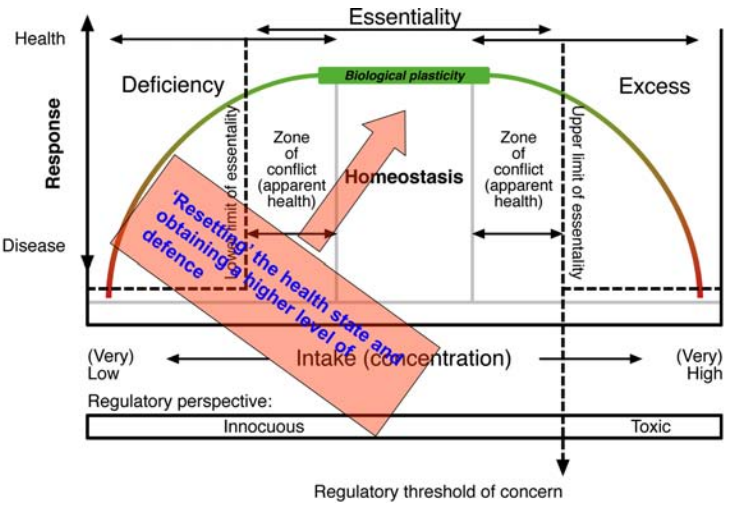

FIGURE 3. Hormesis and food components: 'resetting the health state'.

tion between food and health. The maximum stimulation of studied biological systems, the *performance* of the homeostatic range, typically seems 30-60% greater than the control group, with a width of no more than about a factor of ten (Calabrese *et al.*, 2007).

Recently, we published a paper illustrating the pleiotropic effects of food on health (Weseler *et al.*, 2011). In a randomised control clinical pilotstudy, we established the pleiotropic benefit of monomeric and oligomeric flavanols on vascular health. In this study, various physiological mechanisms implicated in vascular health were distinguished and integrated in a so-called vascular health index.

And in conclusion …

Food consituents can be used to reset the health state, i.e. increase the ability to adapt. These compounds can be used to increase the defence against a stress response. Food derived compounds are far from selective. Therefore, in evaluating the health effect of these food-derived compounds, a multitude of effects rather than a single endpoint should be employed. We summarise these food effects in the now well-known hormetic curve we have drawn here as an inverted U (Figure 3). Finally it should be emphasized that regulatory authorities should take effort to incorporate these emerging insights (Hanekamp and Bast, 2008).

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