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Trace Toxins: The Key Component of a Healthful Diet

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Abstract

Although it is well established that a vegetable-rich (Mediterranean) diet is associated with health benefits in later life, the mechanisms and biological origins of this benefit are not well established. This review seeks to identify the components a healthful diet that reduce the individual's suffering from non-communicable disease and extend longevity. We note the difference between the claims made for an essential diet (that prevents deficiency syndromes) and those argued for a diet that also prevents or delays non-communicable diseases and ask: what chemicals in our food induce this added resilience, which is effective against cardiovascular and neurodegenerative diseases, diabetes and even cancer? Working in the framework of acquired resilience (tissue resilience induced by a range of stresses), we arguethat the toxins evolved by plants as part of allelopathy (the competition between plant species) are key in making the 'healthful difference'. We further suggest the recognition of a category of micronutrients additional to the established 'micro' categories of vitamins and trace elements and suggest also that the new category be called 'trace toxins'. Implications of these suggestions are discussed.

Keywords

phytochemicals, plant toxins, stress-induced resilience, acquired resilience, hormesis, healthy diet, mediterranean diet, morbidity, longevity

Introduction

Food

Food is complex in composition but also in its history and in its interaction with our minds, with hunger and appetite and fear of starvation, creating food taboos and fads. It is hard to simplify these psychological complexities, but one way to avoid being distracted by them is to accept that food is what people eat; and that what we eat is determined by what we need, by what is available and by food cultures - what each society is accustomed to gather or produce. Need and plenty are also influential. In times of famine, humans will eat parts of animals that in times of plenty we discard as offal. Facing starvation, we will eat insects, rodents, snakes, horses, dogs and worms, whatever is around. When there is food aplenty, we often give heed to priorities other than satisfying our hunger, adopting diets that we hope will 'cleanse' us or make us glow with health or reduce greenhouse gases or avoid the slaughter of animals.

An approach to describing food less dependent on context is to list the substances we must ingest to maintain our bodies, using more chemical names, like fats and proteins. Using this approach, Table 1 sets out categories of foods that are considered necessary to maintain body tissue, describing the food in chemical terms. The upper part of the Table is entirely

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Table 1. Essential vs Healthful Diets.

A: Components Essential to Avoid Deficiencies		
Macronutrients		
Proteins	10-20 % of calorie intake	These proportions are considered 'balanced'[1]
Fats	~15%	
Carbohydrates	~75%	
Fibre	~30 g/d[1]	
Water	2-3 L/d[2]	
Micronutrients[3]		
Vitamins	In trace Amounts (<0.1g/d)	
Trace Elements	Most < 0.5 g/d; Ca <1.5 g/d in children)	
B: Additional micronutrient that makes a Diet healthful: the trace toxins		
Phytotoxins (resveratrol, curcumin, lycopene, saffron and many more)	All in trace amounts (<500 mg/d). Ideal numbers and doses still to be worked out.	

Table 1: A: The components of an essential diet, sufficient for the body's metabolism, and to avoid deficiency syndromes. B: The additional component proposed here – the trace toxins – which makes the diet healthful, reducing morbidity from non-infectious diseases and increasing longevity. The healthful diet is well known as Mediterranean or MediterrAsian; B identifies the component that makes it healthful.
[1]https://www.ucsfhealth.org/education/increasing-fiber-intake'
[2]https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/water/art-20044256
[3]Recommended intake values from https://nutritionsource.hsph.harvard.edu/vitamins/

unoriginal; it merges a few authorities.[1] It is a list of chemicals that are essential in the human diet, if we are to avoid known deficiencies.

Diets: Essential vs Healthful

Diets are discussed in the scientific literature and beyond in many ways. Our focus is on diets developed for the optimisation of individual health. Among the diets that influenced us are five, each with strong scientific literatures. One is the diet comprising the foods we must eat to avoid known nutritional deficiencies, so a diet of the essentials, an **essential** diet (above). A second emphasises the optimal ratio of protein, carbohydrates and fats consumed, sometimes called the **balanced** diet.[1] A third is the **low glycaemic index diet**, developed because the foods included are, by deliberate choice, those that minimise the post-prandial rise of blood sugar levels, so limiting the damage caused by hyperglycaemia, particularly in relation to diabetes.[2] A fourth is the i**ntermittent fasting diet** (say the 5/2 diet) that reduces morbidity and extends longevity by engaging the resilience-inducing stress of hunger (reviewed,[2,3]). The fifth is the **healthy diet**, with two components: the exclusion of foods optimised ('processed') for tastiness without delivering balance and the inclusion, as the bulk of the diet, of fruits, nuts and vegetables, with some lean meats and fish. Such diets have been called Mediterranean,[4–7] Asian,[8] MediterrAsian[8] or planeterranean.[7]

Of these five, the last has perhaps attracted the widest interest; it has, for example, been inscribed (in 2013, under 'Mediterranean diet') in UNESCO's Representative List of the Intangible Cultural Heritage of Humanity.[3] From these five, we here compare two, the essential diet and the healthy diet, seeking to identify the operative component of the latter that produces the reduction in non-communicable diseases and greater longevity that epidemiologists have catalogued and attributed to it.[4,6–15]

We argue below that the health-giving chemicals of a healthy diet are toxins occurring naturally in the vegetables and fruits and nuts that make up the bulk of the diet. We suggest a slight renaming of the healthy diet as a **healthful** diet (one that actively improves health) and we advocate the recognition of a previously unrecognised category of nutrients, the **trace toxins**.[4] We also discuss pathways by which these toxins improve health - the evolved endogenous pathways of acquired resilience.[2] This suggestion, that the secret to a healthful diet lies in toxins produced by the plants we eat, is counter-intuitive but, followed rigorously, it makes sense of the fads and facts of diet and health. Finally in this essay, we explore the implications of toxin-induced resilience for the understanding of nutrition.

Why are Essential Chemicals Essential?

There are several answers to this question. One is functional, and has been touched on above; without them, we are malnourished (for lack of fats/proteins/carbohydrates) or dehydrated (lack of water), or we suffer deficiency syndromes (lack of micronutrients). One further answer is that essential chemicals are essential because our body cannot synthesise them from other chemicals in our food. Our tissues can synthesise many chemicals, but not those on the essential list. Vitamin D is an exception, but an interesting exception because it demonstrates the rule.

The history of the discovery of vitamin D has been written of elsewhere.[16,17] The conditions caused by a lack of vitamin D (rickets in children, osteomalacia in adults) were recognised well before the vitamin was identified, in the late 19th Century. It was recognised that fish oils as dietary supplements prevented both rickets and the xerophthalmia (night blindness and corneal breakdown) caused by a lack of vitamin A. The chemical identities of these two vitamins (A, the primary diet form being retinol; and D, the primary diet forms being ergocalciferol and cholecalciferol) were then derived from analysis of cod liver oil.

In parallel with the effectiveness of fish oils, it was recognised that rickets was rare in populations living in the tropics. The medical missionary Theobald Palm is credited with that key insight.[16] Once the fish oils and sunlight were identified as effective in preventing it, rickets was largely prevented by public health measures.

The component of sunlight that has the energy to drive a key step in the synthesis of vitamin D (to split the B-ring of 7-dehydroxycholesterol[18]) is UVB (290 -320 nm) and this, in excess, has severe side-effects like skin cancer, making daily tablets arguably the safer option as a public health preventative. Vitamin D is still referred to as a vitamin, perhaps because the ergo- and cholecalciferols remedy a specific deficiency, even though that missionary's insight – that we can synthesise cholecalciferol in the skin, given some sunlight[18] – has been confirmed.

Still another answer – to the question why essential foods are essential - relates to evolution. Plants and animals have co-evolved, over the last 500 million years, with animals relying on plants as food. Because plants provided carbohydrates, fats, protein, fibre and vitamins, animals did not need to evolve pathways to synthesise them, and they became essential in our diet. The trace metals are slightly different; they occur in plant tissues, absorbed from soil, but the metals were formed, biogeologists tell us, from hydrogen, in the intense heat of the earliest stages of our planet's history. Because some metals were present in trace amounts in plants, for which they are metabolically useful as catalysts, they were recruited also into the metabolism of animals.

So, essential nutrients became essential (we suggest) because they were metabolically useful and were available in the plants on which animals relied as food during their evolution. This suggestion does not go beyond standard Darwinian evolutionary theory, but it does raise a question less discussed – was there anything less useful, toxic even, in the plants we evolved to eat? And if there were toxins in plants, as many have argued previously (reviewed[2]), how have those toxins affected the biology of animals? The answer to that question is that animals have turned the toxicity of plants into a significant advantage for their health – toxin-induced resilience.[2] An account of how animals achieved this requires a discussion of plant and animal biology.

The Toxicity of Plants

Why are Plants Toxic to Other Species? Allelopathy and Secondary Metabolites. Plant species compete with each other for soil, water and a place in the sunlight. The weapons deployed by plants in this competition are biological, physical and chemical. Direct biological competition between plant species – outgrowing, out-reproducing competitors– is familiar and much discussed. In a few species, the struggle is physical, as though between animals. The strangler fig, for example, grows from a seed dropped into and lodged in the canopy of a competitor tree, from which air roots grow down, surrounding the host tree's trunk. If the air roots find soil they grow vigorously and wrap the host trunk aggressively, often bringing on the death of the host tree, and leaving the strangler tree in its place.

Since the middle of the last Century, however, it has been understood that the most common weapons in the competition between plant species are toxins, evolved for a silent inter-species combat termed allelopathy.[5] One step in reaching this understanding was the identification in plants of molecules which seemed to have little to do with their growth or reproduction. These 'mystery' chemicals were initially termed 'secondary metabolites'. Why did plants produce them? The answer turned out to include[19] that many (though not all) secondary metabolites function as toxins, deployed in allelopathy. Guerriero and colleagues[19] described them as forming four major classes (terpenoids, phenols, alkaloids and sulphur-containing), their actions including anti-microbial and herbivore-deterrent. Although they have been demonstrated to inhibit neighbouring plants and fungi, the relationship is complex. At high concentrations, for example, the oils of the Western Red cedar tree inhibit predatory fungi, yet at low concentrations seem to stimulate the fungi.[20] When, more recently, Teoh[21] summarised the secondary metabolites in just one class of plants (the orchids) as including 'alkaloids, bibenzyls, phenanthrenes, stilbenoids, phenols, flavonoids, anthocyanins and polysaccharides', they listed their healthful effects in animals that consumed parts of the plant - 'antioxidant, anti-inflammatory, antimicrobial, antihelminthic, anticoagulant, antidiabetic, lipid-lowering' and 'cytotoxic', promoting 'the programmed cell death of cancer cells'. Comparable metabolites appear to be ubiquitous within plants, with over 50,000 described so far in the plant kingdom.[21]

Some of these metabolites have attracted intense scientific analysis and have become familiar. An example is resveratrol, which Bitterman and Chung[22] described as follows:

> Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a well-known polyphenol phytoalexin which is found mainly in the skin of grapes; it has attracted extensive scientific attention due to its potential health benefits related with its cardiovascular (French paradox), chemopreventive, antiobesity, antidiabetic, and neuroprotective properties.

The French paradox is the observation of low incidences of coronary artery disease in populations, like that of France, with a high-fat diet.[23] The paradox seems real; resveratrol in experimental animals has corresponding good-for-the-heart actions (also reviewed in[2]) but it has been difficult to demonstrate that resveratrol as an intervention in humans has a significant effect. Some summaries (for example https://en.wikipedia.org/wiki/Resveratrol) stress that resveratrol is ineffective in treating cardiovascular disease or cancer, despite the promise seen in animal models. Overall, it seems that resveratrol, and other plant toxins,[2] are impressive in their ability, when taken over long periods of life and at appropriate low doses, to reduce rates of heart disease, neurodegenerative disease (including dementia) and cancer. They are less effective in treating established disease. In a very large epidemiological survey (200 authors, surveying a wide range of dietary supplements for anticancer effects),[24] however, resveratrol was reported to have consistent anti-cancer effects, assessed across a range of cancer 'hallmarks'.

In summary, the common features of the plant toxins include that they are organic molecules, so that plants can produce them from the common biological elements of C, N, O and H and that their toxicity arises from their ability to disrupt the core metabolism or the membrane structure of the 'other' species (competitor plants, parasitic fungi or leaf-eating animals). A few are extremely toxic for animals because they target very fundamental processes, like oxidative phosphorylation (the action of cyanide, with rapid effect) or the synthesis of all proteins, by inhibiting an enzyme (RNA polymerase II, the action of the capstone mushroom toxin amantin,[6] which kills with slower effect). But most are oxidants which, at sufficient dose, damage the proteins of the competitor/predator. The effects of most at high doses are significant but sublethal, typically causing nausea or vomiting in animals when they do not limit their consumption and slowing growth or reproduction in neighbouring plants. For most plant toxins, the low end of the dose-response curve is of particular interest; Calabrese and colleagues[25] for example reviewed the beneficial effects of low doses of resveratrol, terming them hormetic, without exploring high-dose toxic effects. Certainly, high-dose toxicity is less mentioned in reviews of the plant toxins.

The Dose Makes the Toxin; The Dose Makes the Medicine. While it seems common sense to regard notorious plants like deadly nightshade (whose cholinesterases disrupt the autonomic nervous system) and redcap mushrooms (whose complex toxin shuts down protein metabolism) as toxic, and wheat as a trustworthy food, closer acquaintance with the toxicology of food brings the reader to the aphorism: *the dose makes the toxin*. It is attributed to a 16th Century physician Paracelsus[26,27] and has been highly influential in that field. As argued previously,[2,28] toxicologists have long used dose-response relationships to demonstrate dose-dependent tissue responses not evident in the common-sense distinction among pharmakons (medical substances), that this-is-toxic and that-is-edible. One telling example is water. When we are dehydrated, ions (sodium, potassium) in our blood and extracellular fluid become too concentrated; when we are over-hydrated, the same ions become too dilute. Either way (dehydration or hyponatraemia), brain function can fail, we can lose consciousness and total brain failure is not far away. Water is the remedy for dehydration but a toxin when we are hyponatraemic. So, even the most familiar nutrients can be toxic. The role of dose in the assessment of medicines was reviewed a decade ago by Stumpf[29] in his article titled *The dose makes the medicine*, which is a valuable rephrasing of the older *the dose makes the toxin.*

Three Animal Defences Against Plant Toxins: Tolerance, Sequestration, Resilience

Animals have evolved these three defences at least, to the toxins in the plants we eat. The defences are not alternatives; in logic and data, there seems no reason why an individual organism cannot deploy all three. Tolerance and sequestration are described briefly below, to separate them from resilience, which is nearer our main theme.

The Tolerance of Emus

One of the several 'dictionary' meanings of the word tolerance is the capacity of an organism to grow or thrive in an unfavourable environment.[7] As one example, the tolerance of the Australian emu (a large flightless plant eater) for the very toxic phytochemical fluoroacetate is much (100-fold) greater than in many other Australian birds, especially among emus in the south-west corner of Australia's mainland, where plant species that produce fluoroacetate in their foliage are found in high concentration.[30] The molecular bases for the emu's ability to tolerate these plants may include upregulation of enzymes that detoxify the fluoroacetate,[30] an increase in gut flora that detoxify it before it is absorbed[31] and/or the evolution of a toxin-resistant form of the target molecule in the emu. As a footnote to the emu story, the department of the government of the state of Western Australia responsible for its national parks developed a program of baiting in those parks, to reduce the population of carnivores (foxes, cats, dogs) not native to Australia, which were threatening the survival of indigenous marsupials and birds. The rationale of the program was that baits of meat laced with the right dose of fluoroacetate would kill non-indigenous carnivores, but would spare the indigenous fauna, because of their greater tolerance. The success of the program was considerable.[32,8]

More recent considerations of the mechanisms of tolerance have emphasised the successive degradation of ingested bioactive molecules by the acid of the stomach, by digestive enzymes in the small intestine, then by biota in the large intestine and, if any bioactive remnants reach the blood, by detoxifying enzymes in the liver. All that said, breakdown products of phytotoxins do reach measurable levels in the

blood and are important (we argue) in the induction of tissue resilience (below).

Sequestration: the Extraordinary Things Insects Do with Plant Toxins

Insects share our reliance on vegetation for their diet and must also cope with the toxins in the plants they eat. Many species of insects (caterpillars and bees seem to be the most studied) sequester some of the toxic molecules, still intact and toxic, in their own tissues. Sequestration evolved presumably because it makes the tissues of the caterpillars toxic to their predators, like birds, which then limit their consumption. To achieve this, the insects have evolved several mechanisms, including toxin-resistant forms of the proteins that are targets of the toxins that come with their favourite plant food.[33] So, the toxin initially evolved by the plant for its allelopathic battles with other plant species is re-deployed by the insect, in its protection.[34,35]

In a slightly more complex behaviour, butterflies of a number of species seek out dying plants, specifically to harvest their toxin. The behaviour is known as pharmacophagy:

> Insects are pharmacophageous if they search for certain secondary plant substances directly, take them up, and utilize them for specific purposes other than primary metabolism or (merely) food plant recognition.[36]

Butterflies are at a stage in life where they are not feeding-to-grow on the leaves of plants; their raison-d'etre is reproduction, and they gain the energy for this by sipping sugar-rich nectars. Presumably because nectars are not laced with toxins (because it is to the plants' advantage not to discourage pollinators), some butterflies seek out secondary metabolites/phytotoxins, which they glean from dying plants. In one of the best-studied examples of pharmacophagy,[37] Danainae butterflies harvest 1,2-dehydropyrrolizidine ester alkaloids from dead/drying plants and use the toxins for two purposes - self-defence and as a substrate for the production, by males, of pheromones.

In a variant of pharmacophagy, dubbed kleptopharmacophagy, the much-studied Danainae butterfly has been reported[38] to 'scratch and imbibe' from caterpillars, harvesting phytotoxins from their tissues. So, butterflies 'steal' some of the toxins from caterpillars, to boost their own defenses. Some writers have reported[38] that male butterflies attract mates with an offering of alkaloids, as a 'nuptial gift' of desirable toxins. Pharmacophagy for the purpose of sequestering seems to be rare in vertebrates; it has been described in some species of snakes,[39] but has yet to be reported in mammals. In what way, then, do plant toxins influence plant-eating mammals, like humans?

Toxin-Induced Resilience: in Probably all Animals

Toxin-induced resilience is distinct from tolerance and sequestration in that competitor plants and plant-eaters respond to the stress of plant toxins by upregulating mechanisms that induce resilience in their tissues. Toxin-induced tissue resilience is part of the concept of stress-induced or acquired resilience proposed in,[2] with discussion there of the many phenotypes of resilience.

The distinction between tolerance and resilience has been drawn relatively recently, its acceptance slowed by skepticism, familiarity and a touch of romanticism. Skepticism arose because humans and emus, and every species between and beyond, deal with ingested toxins by partly breaking them down digestively (above). Even if the toxins induce something tissue-positive in the laboratory, then (the skeptic might argue) there is a problem of their low 'bioavailability' in humans: Do plant toxins get to our tissues in amounts sufficient to induce the benefits claimed for them? This question has been addressed, in reports (for resveratrol, for example, in,[40] for lycopene in,[41] for curcumin in,[42] for saffron[43]) that these toxins can each be detected in the blood after ingestion. The levels detected are low, however, and the authors quoted all considered how bioavailability might be increased, for more healthful results in humans. Skepticism arose from a second source because, however strong the evidence from experiments in animals and from epidemiologists about humans, the plant toxins do not work as well as an intervention against established disease (reviewed[2]). In our reading of it, the debate over the healthfulness of dietary phytochemicals has reached a point at which the value of a long-term diet rich in plants is no longer queried; what is still debated is whether the resilience effects arise from the impact of toxins reaching the bloodstream and impacting tissues directly; or whether the induction of resilience is mediated by the gut biota, which can regulate their bioavailablity.[44,45]

This acceptance of the value of plants in the diet has led to discussion whether wild plants can be usefully considered a pharmacy for humans.[46,47] The United Nations Economic Commission for Europe, for example, has established a program of *Forests as Pharmacy*.[9] When that discussion is extended to include cultivated plants (so can plants – wild or cultivated - be usefully considered as a pharmacy for humans?), a less romantic but still powerful idea emerges, that the genomes of modern organisms encode pathways that react to plant toxins by upregulating resilience mechanisms[2]; and that it is this resilience that gives us the survival benefits described by epidemiologists.

In the science of the human diet, the plant toxins have attracted huge scientific attention. The effects of phytotoxins on mammalian tissues – the upregulation of 'resilience' (reviewed[2,48,49]) - have been described in several ways. First, epidemiological correlations have been established between a vegetable-rich diet and freedom from non-communicable diseases, and also between specific vegetables and the same freedom. Examples of the latter include the role of resveratrol from red grapes in mitigating heart disease (reviewed[2,50]), of saffron in stabilising age-related macular degeneration[51–54] and of lycopene

(tomatoes) in reducing deaths from prostate cancer.[55] Going beyond the health benefits of individual plants, multi-plant reviews[2,24,56] suggest that the benefits are not specific to particular plants. Phytochemicals from many plants also have been reported, for example, to be effective in delaying and mitigating dementia,[57] still a great challenge in the medicine of ageing. And, it seems, with some dangerous exceptions, that any plant may be as effective as another.

Second, it has been noted that all the phytotoxins for which dose-response relationships have been traced exert their effects at low doses (<100 mg/d), and all are toxic to the individual at higher doses (for toxicity data see Table 1 in[2]). This low-dose-good/high-dose-bad relationship fits the concept of hormesis, which can be traced to the Arndt-Schulz 'law' developed in the 19th Century, was named hormesis by Southam and Ehrlich [20] in their report on trees and fungi in the 1940s, and has since been intensively developed by Calabrese and Mattson.[25,28,49,58] An analysis of diet that influenced us is Mattson and Cheng's[48] description of an 'adaptive cell response' to plant toxins,[28] their term 'adaptive' emphasising the evolutionary basis of these pathways. A still more general thesis of stress-induced resilience has been posited in the concept of acquired resilience, which seeks to bring together literatures on several everyday stresses and many phenotypes of resilience.[2]

The feature common to all these formulations is that there is something about plants as food that provides remarkable health benefits for the consumer, a component that, added to an essential diet (Table 1A), makes the diet healthful (Table 1B). The more analytical literatures have identified that 'something' in Mediterranean/planeterranean/MediterrAsian diets as plant toxins and have tackled the mechanisms involved and the nature of resilience.

Mechanisms. The mechanisms of plant toxin-induced resilience have been investigated and reviewed for many phytochemicals or plants considered individually (for example, for resveratrol,[50,59–63] lycopene,[55,64,65] curcumin[49,66–70] and saffron[53,56,71,72]), or in groups of several[2] or of 20 or more,[24,56,57] assessing their effectiveness against a wide range of non-communicable conditions (the proliferation and metastasis of cancer, cognitive loss, depression, anxiety, the protection of DNA[73]), and seeking to identify their mechanisms. The literature is large and the number and variety of mechanisms posited are too great for a ready summary. The review of the actions and mechanisms of saffron (and its major bioactive components crocin, crocetin, safranal) assembled by Butnariu and colleagues[71] is an impressive example of the intensity of work already done on a single plant; their review summarises studies of biological activities (their Table 1), pharmacological properties and mechanisms (their Table 2) and, in smaller number, clinical studies (their Table 3). The authors summarised, for crocetin - considered the active form of crocin (quantitatively the major bioactive molecule in saffron) - as follows:

> Crocetin ….. was demonstrated to inhibit lipid peroxidation, increase the activity of glutathione S-transferase …., GPx, CAT, and SOD, decrease damage marker enzymes such as aryl hydrocarbon hydroxylase ….., LDH, γ-glutamyl transferase… and adenosine deaminase …. In rat liver tissues, (crocetin can) inhibit proliferation of lung cancer cells….., reduce ROS-induced lipid peroxidation of primary hepatocytes of rats…. And reduce the levels of oxidized LDL. Crocetin decreased the expression of TNF-α, interleukin-1β, and induced iNOS in the liver of the haemorrhagic shock model ….. Crocetin also decreased the indomethacin-induced rise in glutathione in nondiabetic and diabetic rats …. and reduced ROS generated by BαP in mice and …. angiotiensin II-induced ROS.

Similarly, Bitterman and colleagues,[22] after reviewing evidence and controversies in the understanding of the actions of resveratrol, concluded (as noted previously[2]):

> Amidst much confusion, it has become clear that resveratrol potentially has several direct targets in the cell. Although the original discovery was as a cyclooxygenase inhibitor, it has subsequently been identified as an activator of Sirt1 ….; an inhibitor of cAMP phosphodiesterases...; an inhibitor of the F1-ATPase...; an inhibitor of the estrogen receptor..., and a modulator of numerous other targets.

These reviews provide an insight into what is known and the intensity of work already reported; but their summaries indicate that a ready account of the mechanisms of plant toxin-induced resilience has still not been achieved. What is not at issue is that the plant toxins affect the molecular chemistry of probably every cell in the body, and that their overall impact at low doses is health-positive, preventing or delaying non-communicable disease.

The Elusiveness of Resilience. The concepts of hormesis[28] and of stress-inducible (acquired) resilience[2] were formulated relatively recently (because the distinction between tolerance and resilience is recent, above), although many of the ideas included in these concepts and much of the evidence, for example that some diets actively make us healthier, are far from new. The broader concepts may have come late because there is no simple image of what diet-induced resilience 'looks like' or of how to measure it. One valid measure is a 'negative'; it is the relative freedom of the resilient individual from non-communicable diseases, so a freedom from signs or symptoms of disease.

More positive signs of the effectiveness of plant toxins (and of the other everyday stresses included in the concept of acquired resilience - red-infrared light, hunger, hypoxia, exercise, heat) are seen experimentally, when the stress is delivered at a specific time, with an exposure to photobiomodulation, or a period of exercise for example. Then, acute positive responses are seen, including super-performance of muscles,[74–77] super-performance of the

retina,[78] and the acceleration of wound healing.[74,77] Because these stresses act on every cell, at the molecular level, and because their effects seem uniformly tissue-positive, the phenotypes of plant toxins are many. And that can be a problem for the acceptance of these ideas, despite their strong basis in evidence. To re-use a phrase from Niels Finsen[79] (Nobel Laureate in 1903) in a review of the evidence then available of the value of red light – now called photobiomodulation – in accelerating the healing of smallpox lesions: *it all was too wonderful and gave rise to skepticism*.

The Case for a New Category of Essential Foods: the Trace Toxins

Against this background, the idea of plant-toxin-induced tissue resilience brings into the understanding of diets, we suggest, a new category of nutrients, the trace toxins. Of course, the toxins have always been there. The new point is to recognise them as a nutrient group with a particular effect: tissue resilience. The toxins, in all their variety (above) are the plant-produced chemicals that, added to an essential diet (Figure 1A), make a healthful diet (Figure 1B). Their features and effects include that: they are produced by plants and impact humans when we eat plants in our diet; plants have evolved to produce them as part of allelopathy, the competition between plant species for evolutionary survival; they play little or no role in the metabolic or reproductive mechanisms of the plants that produce them but have evolved to kill or suppress competitor plants and fungi and plant-eating insects and herbivorous animals; they have been part of the human diet from our beginnings; the response of our tissues to them has evolved to be hormetic, at low doses upregulating tissue resilience but suffering damage at higher doses; like water, fibre, vitamins and the trace metals, trace toxins do not satisfy hunger, but the tissue resilience they induce at low doses reduces morbidity from non-communicable diseases, and extends longevity.

In summary, the toxins in the plants we rely on for food can damage our tissues if eaten in excess; but at low doses that we have evolved to manage, they add resilience to an otherwise well-fed body. They are the chemicals that make the difference between an essential diet and a healthful diet; and that is, we suggest, a new understanding.

Debts and Implications

Many Debts

The present suggestion – the recognition of trace toxins as a category of nutrients important in the human diet – owes much to preceding work and in particular to the Arndt-Schulz 'law' of the 19th Century[10]; to the idea of hormesis developed in the 20th Century, beginning with the study of interactions between trees and fungi[20] but extending well beyond that[28]; to the insight of Mattson and colleagues that our cells have evolved an 'adaptive response' to plant toxins[28,48]; to the insight of Pallauf and colleagues[8] that bioactive molecules (including plant toxins like polyphenols) may be a mechanism in the healthfulness of the MediterrAsian diet; to the concept of acquired resilience,[2] of which, we would argue, this dietary

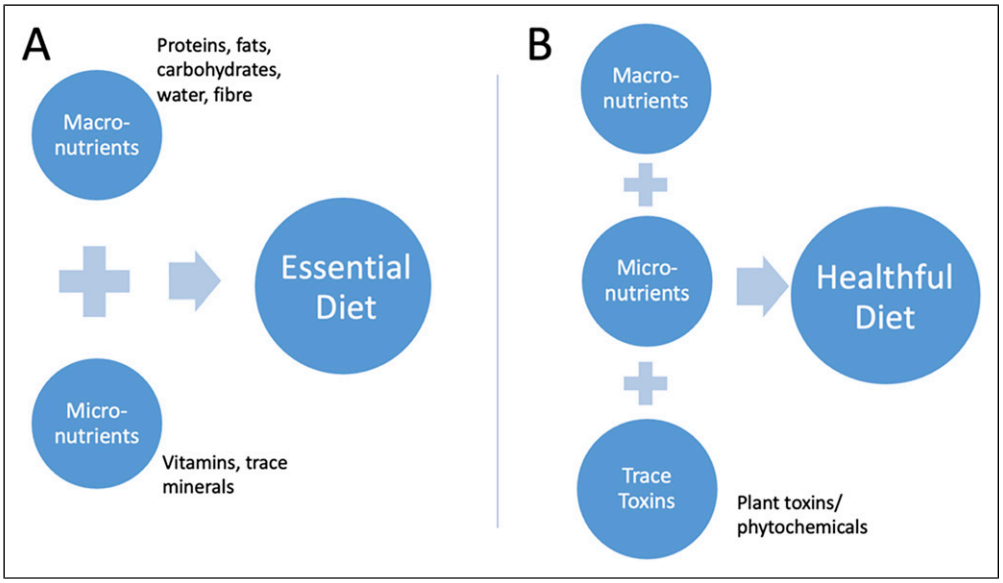

Figure 1. Essential and healthful diets. A: To avoid deficiency syndromes, humans need proteins, fats, carbohydrates (in balanced proportions[1]), water and fibre in largeish amounts (the macro-nutrients), plus vitamins and minerals in small amounts (micro-nutrients). B: Add plant toxins in small amounts (trace toxins) and the diet actively promotes tissue resilience and freedom from non-communicable diseases.

mechanism is part; and to ideas of a healthy diet found in several cultural traditions.

Many Implications

One implication of the present suggestion is that – to be healthy – we may not need to minimise consumption our favourite (non-Mediterranean) foods, like meat or white bread, but that we should make sure we get our daily dose of plant toxins. There may be other reasons to eat less meat - to control our weight or to manage diabetes, or because meat production is so polluting of the atmosphere or to spare the animals. But meats that humans eat, and the more processed breads, are still nutritious, meeting essential needs of protein and carbohydrates; if only they were a bit toxic.

Further, eating vegetables may not be necessary to achieve resilience. Resveratrol and lycopene and curcumin and saffron and green tea extract and gingko can, in many societies, be purchased in capsules, in our local health food store. The evidence seems strong that consumption of plant toxins separate from the plants that make them brings the benefits of a vegetable diet. Conversely, it seems that we can identify what is wrong with the 'Western' diet, low in vegetables, rich with meats, sugars and dairy products.[4] As noted previousy,[2] the problem is not that the Western diet is somehow toxic, so causing non-communicable diseases, but that it is not toxic enough.

A further implication is that 'processed' foods are bad for us not because they are somehow toxic but because they too are not toxic enough, because their processing has removed parts of the foods that contain resilience-inducing toxins. An example is the milling of wheat. Millers have learnt to separate the bran and the germ of the wheat kernel from the endosperm (Figure 4 in[80]) and then to use the endosperm to produce white flour, which can sensibly be regarded as more processed than whole-kernel flour. White flour contains carbohydrates and protein, so it is nutritious, but whole-kernel flour also contains toxins which the plant had evolved to concentrate in the bran that encases the endosperm, to discourage predation on its seeds. So, white flour is nutritious but whole-kernel flour is better for us because it contains poisons that upregulate resilience pathways. And that is a new way of understanding the nutritional values of different breads.

Finally among the implications, the present analysis suggests the practical value of understanding food in evolutionary terms, of understanding that our bodies have evolved to react to the various elements of food that vertebrates have always relied on. Toxin-induced resilience is a long-unrecognised part of good health. When recognised, the idea gives us, and the professionals we go to for advice, a remarkably effective way of delaying/preventing the non-communicable ailments we all are at risk of, especially later in life.

What are the Research Challenges?. Perhaps the major research challenge presented by this idea of trace toxins is the need for dose-response data, partly to know how much plant material needs to be eaten, but also to test the idea, discussed above, that the impact of vegetable toxins on our tissues is hormetic, inducing a resilience response at low doses, and able to poison the consumer at high doses. Epidemiologists have established associations between dietary toxins at low doses and reduced morbidity and delayed mortality (Section 1, 2), but multi-step dose-response relationships are uncommon in the literature. One example, but in a rodent model,[81] traced the onset of neuroprotection by dietary saffron, over 10 daily low doses. The problem in gaining human dose-response data is that the outcome measure (lower morbidity, mortality) requires decades of exposure. Such data, when they becomes available, may (or may not) contain surprises about the association between dietary plants and human health.

A second challenge in understanding the toxin-induced resilience response is presented by the huge number of plant toxins known to have evolved (Section 1.4.1). How the resilience response evolved to cope with that variety is a question still in need of an answer.

Questions Raised

One test of a scientific concept is whether, once formulated, it allows the asking of interesting, testable questions. Here are several that arise from the idea of trace toxins.

What Should we eat for Minimal Morbidity, Maximal Longevity?. At this point in the debate over diet, it seems clear that vegetable-rich diets reduce morbidity and mortality from a range of non-communicable disease. Reviews of a range of plant toxins (for example[57]) suggest that many such toxins, and therefore many plants, induce the same resilience phenotype and, where it has been tested, by the same pathways. Evidence of the particular value of one vegetable-rich diet as against another (Mediterranean vs Asian, for example) does not seem to be available. Claims of the value of single vegetables are readily found, but harder to find is rigorous evidence that one vegetable is more effective than another, or that some combination of a few vegetables is particularly effective. It seems possible that all phytotoxins found in the plants we rely on as food, or a few or any, can induce the same tissue resilience.

What are the Right Doses for Resilience? And What if we Get the dose Wrong?. We reviewed previously what is known of the doses of plant toxins appropriate to induced tissue resilience.[2] The resilience response seems inducible by doses of (for humans) less than 100 mg/d of the plant toxin.[2] Conversely, doses of >5 g/d of, for example, saffron have been reported to cause gastrointestinal bleeding and vomiting[11]; such reports have yet to appear in the scientific literature, presumably because toxicity at high doses is not interesting. For comparison, the recommended daily intake of vitamin D is 15 μg/d and the upper safe level, above which toxicity results, is

100 µg/d[12]; for vitamin A the corresponding levels are 700 µg/d and 3000 µg/d[13].

If our daily intake of phytotoxins is too low to induce resilience, our body remains vulnerable to the diseases that epidemiologists have identified as more common in people on a low-vegetable ("Western") diet (heart disease, the neurodegenerations, diabetes). The relationship between dose and effect is thus not linear, but hormetic.[28] Hormesis sometimes seems elusive as a concept, because of its tenet that the same pharmakon can be a toxin or a tonic, depending on dose. In practical terms, however, dose instructions for the trace toxins are easily complied with - they should be taken daily, as in the successful Mediterranean/MediterrAsian diets, at the appropriate low doses.

Does Toxin-Induced-Resilience Fade with Age?. There is evidence that several forms of stress-induced resilience fade with age, for example hypoxia-induced resilience of the retina.[82] There is also evidence that exercise in late age can restore the resilience response at least partially (reviewed in[2]). These aspects of resilience are highly relevant to the optimisation of health in late life but require further study. The concept of toxin-induced resilience helps formulate these testable questions.

Why does Toxin-Induced Resilience not Unleash Cancers?. Our guess, early in our work with phytotoxins/trace toxins, was that they might well give resilience to cancers, accelerating their growth and metastasis. For reasons still emerging, when dietary trace toxins are tested in animal models or studied clinically or epidemiologically in humans, there seems to be little evidence that cancers are made resilient. For many plant toxins, testing indicates that their effects are anti-cancer, reducing proliferation, inhibiting metastasis, protecting the genome from damage and inhibiting immune checkpoints.[61,83–85]

Are any Foods Free of Toxins?. There appear to be few toxins in the meats that humans consume or in refined sugars and flours, considered staples in the Western diet.[5] These low-toxin foods are nutritious, supplying proteins, fats and carbohydrates, but they lack the plant toxins that induce tissue resilience. By contrast, probably all vegetables, fruits and nuts contain significant levels of plant toxins; hence the success of vegetarian/Mediterranean/planeterranean/MediterrAsian diets in reducing morbidity from non-communicable diseases.

Is there a Trace-Toxin-Deficiency Syndrome?. We know a considerable amount about deficiencies of the macronutrients (malnutrition in its many forms), of vitamins (scurvy, rickets, xerophthalmagia) and of the trace metals (many diffuse symptoms, See Table 1 in[86]). What is the phenotype when people lack plant toxins in their diet? The toxin-deficient phenotype comprises the ills that epidemiologists[4–6] list against a 'Western' diet: higher and earlier incidence of non-communicable diseases (cardiovascular, neurodegenerative, diabetes, some cancers) and correspondingly decreased longevity. To place these ideas of stress-induced resilience in a still wider context, we note the 'parable' of the trees that 'knew no wind'. We wrote in[2]:

> There is an analogy in the resilience of trees. In the Biosphere 2 venture, trees grown inside the sphere did not experience wind. They grew well but tended to collapse before reaching maturity. Without wind, it turned out, trees do not form "stress wood" at points in their branched structure where wind normally induces the local formation of either "compression" wood or "tensile" wood. …(T)rees use the stress of wind to induce the production of tougher wood, at locations that bear the stress. Without wind, still-young trees collapse under their own weight ……. The analogy seems strong with still-young humans maturing without daily exposure to everyday stresses – (like) the plant toxins - and "collapsing" with early morbidity and mortality.

So, in trees, limb collapse could be understood as part of a 'wind-stress deficiency syndrome'. More generally, it seems that many, perhaps all organisms have evolved a resilience response to stress, whether the organisms are plant or animal, whether the stress comes from plant toxins or wind or hunger or exercise. When humans develop ways of reducing that stress, for example by milling the toxins out of flour, there is a risk of toxin deficiency; more positively, when we understand that, there is a simple path back to resilience, via the vegetable market or the forest or the health food store. In taking that path, we would be following the pharmacophageous insects, seeking plants for a dose of their toxins. Differing from the insects, we would not be seeking the toxins to sequester into our flesh, to discourage those predators that are big and fierce enough to eat us, but to upregulate our resilience pathways, to be freer of non-communicable disease, and enjoy greater longevity.

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Notes

1. https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/dietary-reference-intakes/consumer-

guide-dris-dietary-reference-intakes.html; https://www.britannica.com/science/human-nutrition/Essential-nutrients; https://www.nccih.nih.gov/health/vitamins-and-minerals
2. See: https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/low-glycemic-index-diet/art-20048478
3. https://ich.unesco.org/en/RL/mediterranean-diet-00884
4. The idea of healthfulness goes back at least to the early 19th Century. For example, the term 'constitutional', in the sense of a 'constitutional' walk - good for one's bodily constitution - is traced by one dictionary (Merriam-Webster) to 1829. Historians of diet note much older advocacy of certain diets for certain ailments, so diets as treatments. But, arguably, the idea of 'healthfulness' includes the idea or hope that certain foods can make us extra-healthy.
5. The term, constructed from two Greek words, implies 'mutual suffering'; it was coined in German (*Allelpathie*) by the Austrian scholar Hans Molisch (see https://en.wikipedia.org/wiki/Allelopathy). More recently, and despite the origins of the term, its use has expanded to include all forms of chemical-mediated interactions between plants, whether toxic or not. It is used here in its original meaning – of plants poisoning each other.
6. https://en.wikipedia.org/wiki/Amanita_phalloides
7. Merriam Webster Dictionary, online.
8. See also https://en.wikipedia.org/wiki/Sodium_fluoroacetate
9. https://unece.org/forests-as-pharmacy#:~:text=Our%20Forests%20as%20Pharmacy%20campaign,cancer%2C%20cardiovascular%20and%20respiratory%20diseases.
10. https://en.wikipedia.org/wiki/Arndt%E2%80%93Schulz_rule
11. https://www.rxlist.com/supplements/saffron.htm
12. https://ods.od.nih.gov/factsheets/VitaminD-Consumer/
13. https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/

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