Nutritional PharmEcology: Doses, nutrients, toxins, and medicines

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Synopsis The synthesis of pharmacological techniques and concepts into ecology holds considerable promise for gaining new insights into old questions, uncovering new priorities for research and, ultimately, for consolidating a new sub-discipline within the ecological sciences—PharmEcology. We argue that this potential will best be realized if the boundaries of PharmEcology are drawn broadly to encompass not only toxins and medicines, but also nutrients. The hub of our argument is that PharmEcology shares with the established discipline of nutritional ecology an organismal focus, at the core of which is the notion of evolutionary function. From this functional viewpoint the dividing lines between chemicals traditionally considered as ''toxins,'' ''medicines,'' and ''nutrients'' are often thin, vague, heavily contingent and non-stationary, and thus provide a poor footing for an emerging sub-discipline. We build our argument around three points: nutrients and toxins are not so different, medicines and nutrients are not so different, and even in cases in which nutrients, medicines and toxins can be categorically distinguished, the biological actions of these compounds are heavily interdependent.

Introduction

At a general level, trophic ecology can be abstracted as the process whereby organisms regulate the influx, handling, and efflux of energy and materials relative to their own bodies, while attempting to manipulate, for their own benefit, such exchanges in the bodies of others. This perspective is overtly substrate-neutral, encompassing energy and matter in forms ranging from semen and offspring to toxins, nutrients, and respiratory gases. Historically, this multi-dimensional continuum has been carved into a number of more-or-less discrete specialist subject areas, each focusing on specific aspects of these exchanges, including community and population ecology, evolutionary and life-history theory, nutrition, toxicology, and immunology. The division of labor so-derived has yielded islands of substantial progress, each with its local methodological and conceptual foundations, achievements, and challenges.

Periodically, however, facts, paradigms, or opportunities emerge that expose the deficiencies of the existing boundaries to these subjects. An historical example is the realization by classical ethologists, particularly Niko Tinbergen (Burkhart 1999), that the behavioral phenotypes of animals cannot properly be understood except in relation to the ecological milieu within which they interact. Conversely, community ecologists have become increasingly aware of the need to incorporate into models of ecosystem processes details about the functional characteristics of organisms (e.g. Real 1992; McGill et al. 2006). In some cases the cross-fertilization of ideas that takes place in the hybrid zones between established fields gives rise to centers of activity that ultimately mature into new disciplines. Conspicuous historical examples include population genetics, which grew from the melding of Darwinian theory and Mendelian transmission genetics (Gilbert et al. 1996) and, more recently, ''evo-devo'' (Evolutionary Developmental Biology) (Love 2003) and Darwinian Medicine (Stearns 1999; Trevathan et al. 1999). Such examples remind us that boundaries between subjects are there to guide and structure research, rather than constrain it.

PharmEcology represents a new sortie into the quite expansive *terra incognito* that separates ecology and the applied field of pharmacology: the ''science of drugs, including their composition, uses, and effects.'' At one level this could amount to no more than a low-risk/low-gain transfer of methods and mechanistic detail from pharmacology to the study of plant-animal interactions. Alternatively, the terms of engagement could be more substantial, involving a synthesis of theory that ultimately

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flourishes into a new research discipline. We believe, however, that the latter could not be achieved without drawing the boundaries more broadly, such that they encompass fundamental principles not only from ecology and pharmacology, but also from the established field of nutritional ecology (Raubenheimer et al. 2009).

In this paper we make the argument that the extremely broad definition of trophic ecology with which we opened is the appropriate scale for drawing the boundaries of PharmEcology. Specifically, we caution against adopting from pharmacology and related fields the operationally useful, but theoretically restrictive, taxonomy of ''medicine'' versus ''toxin'' versus ''nutrient'', and advocate that PharmEcology follows nutritional ecology in considering more generally the relationships between consumers, ingested substances, and functional (e.g. health) outcomes. This will avoid the introgression into fundamental biology of such *ad-hoc* constructs as ''neutraceuticals'' and ''functional foods,'' and facilitate the conceptual agility that is required in a fledgling science.

We develop our argument on three fronts: (1) the dividing line between ''nutrient'' and ''toxin'' is broad and hazy, sometimes even imaginary, (2) the important phenomenon of ''self-medication'' in non-human animals can involve compounds that are classified in conventional taxonomies either as nutrients or as natural ''pharmaceuticals,'' and (3) even when a solid case can be made for distinguishing a ''toxin'' from a ''nutrient,'' the biological impacts of the toxin are substantially contingent on the nutritional milieu.

Nutrients are not so different from toxins

When Dobzhansky (1973) famously argued that ''nothing in biology makes sense except in the light of evolution,'' he could as well have added that ''(almost) nothing in evolution makes sense except in the light of function.'' The evolutionary and functional perspectives are powerful heuristics because they provide a framework within which to predict and interpret observations in biological diversity and ecological interactions (Raubenheimer et al. 2009). Not surprisingly, they also direct both informal (e.g. folk knowledge) (Atran 1998) and formal (scientific) ways of categorizing the diversity of compounds that consumers encounter in their interactions with resources. Those compounds that are fitness-enhancing and might elicit appetitive responses (e.g. amino acids, lipids, and sugars) are categorized as ''nutrients,'' while those that are deleterious and trigger aversive and defensive responses (e.g. alkaloids, polyphenolics, and terpenoids) are ''toxins.'' Classifications so-derived are for many purposes operationally valuable, but labeling compounds in this way also presents the danger that the dynamic nature of biology is obscured by a static one-to-one mapping between the chemical structure of compounds and their functional consequences. Our aim for this section is to develop the perspective that ''toxin'' versus ''nutrient'' is a loose dichotomy (see also Berenbaum 1995), and for many purposes a more productive distinction is between the adjectival versions ''toxic'' versus ''nutritious'' or, more generally, ''deleterious'' versus ''beneficial.'' This view is fundamentally different because it takes into account not only the substance, but also the rate at which it is ingested (i.e. the dose). We cite two well-established phenomena to illustrate the point: hormesis and Bertrand's rule. Hormesis and Bertrand's rule are both modern restatements of the ancient wisdom that ''only the dose makes the poison'' (attributed to Paracelsus, 1538) (Stumpf 2006).

Hormesis

Hormesis is a concept developed in toxicology, in which the effects on biological systems (cells, tissues, organs, organisms, and populations) of a substance are reversed with increasing exposure (Calabrese and Baldwin 2003). Hormetic dose-response relationships can take two forms. The most common of these is the inverted U-shape, describing the situation where low doses of a substance are stimulatory and high-doses inhibitory of beneficial biological responses (e.g. growth, fecundity, or longevity) (Fig. 1A). A second form is the ''J-shaped'' curve, where low doses reduce and high doses enhance a deleterious response (e.g. formation of tumors, mortality, and suppression of growth) (Fig. 1B). Hormetic dose-response curves contrast with other dose-response relationships, such as the linear threshold (LT) and linear non-threshold (LNT) models (Fig. 1C and D). Traditionally, LT and, particularly, LNT models have formed the bedrock of dose-response thinking in toxicology (Hayes 2007). Over recent decades, however, it has become apparent that hormetic responses are ubiquitous—they have been observed across a wide range of chemicals, taxa, and biological responses (Calabrese et al. 1999; Calabrese 2005). Indeed, the question has been raised as to whether hormetic responses might be an

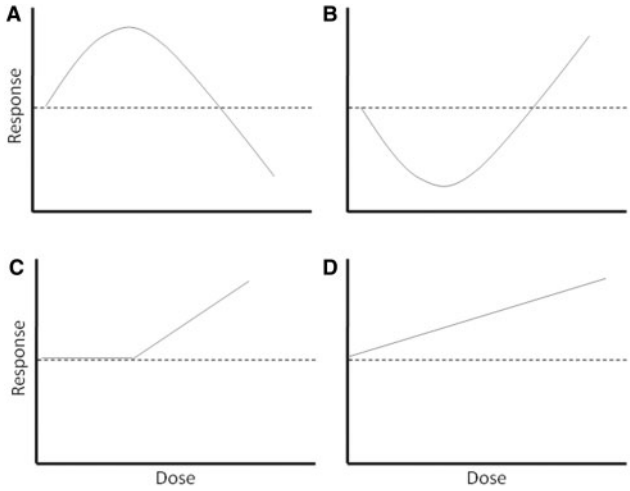

Fig. 1 The hormetic "inverted-U" (**A**) and "j-shaped" (**B**) dose-response curves, contrasted with the non-hormetic linear threshold (**C**) and linear non-threshold (**D**) curves. In each case the dotted horizontal line represents the reference (e.g. control) response.

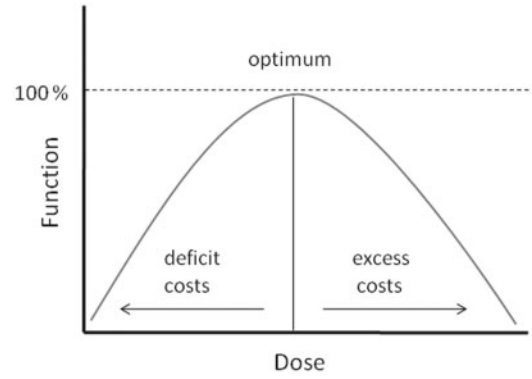

Fig. 2 Bertrand's rule: at low doses of a nutrient increased intake is associated with increasing benefits, but beyond an optimal intake any further increase results in health costs. Modified from Mertz (1981).

evolutionary expectation (Forbes 2000; Parsons 2001). The acceptance of hormesis in mainstream toxicology and biomedical sciences has, however, been surprisingly slow given its long history (see, for example, Calabrese and Baldwin 2000) and strong empirical foundations (Calabrese and Baldwin 2001). The reasons for this are complex, but a failure to consider in experiments the full dose-response curve, and the historical association of hormesis with the scientifically questionable concept of homeopathy (Park 2000), are likely important contributors (Calabrese and Baldwin 1999). Furthermore, hormetic dose-responses have been observed in several sub-disciplines of toxicology and biomedical science, but lack of interactions among these fields has lead to a proliferation of terminology which has obscured the generality of the phenomenon. Recently, this literature has been unified under the concept of hormesis (Calabrese et al. 2007).

Bertrand's rule

We suggest, however, that in its focus on biological stressors the above-mentioned unification has been incomplete; it could have been broader had it encompassed parallel developments in the nutritional sciences. Some workers in the general area of hormesis have noted the commonality between dose-response curves for toxins and nutrients (Luckey and Stone 1960; Hayes 2007), but here we wish to draw attention to largely parallel events that have taken place in the nutritional sciences.

In 1912 French Scientist Gabriel Bertrand established the mathematical foundations of a rule concerning the dose-response curve for mineral nutrients. According to Bertrand's rule (Fig. 2):

> . . . a function for which a nutrient is essential is very low or absent in a theoretical, absolute deficiency, and increases with increasing exposure to the essential nutrient. This increase is followed by a plateau representing the maintenance of optimal function through homeostatic regulation, and a decline of the function toward zero as the regulatory mechanisms are overcome by increasing concentrations that become toxic (Mertz 1981).

The principle of Bertrand's rule is believed to apply to all essential micro-nutrients, with the detailed parameters of the curve depending on the nutrient and on the biological context (Mertz 1981).

Does Bertrand's rule also apply for macronutrients? It has tacitly been assumed that this is not the case, even though there have long existed a number of pointers to the contrary (Raubenheimer et al. 2005). There is, clearly, no question that the first phase of the curve (increasing benefit with amelioration of a deficit) would apply for macronutrients, but the second (plateau) and third (toxic) phases have been less certain. We believe that this uncertainty is attributable to a number of factors. First, the strong emphasis in several sub-fields of nutritional biology on energy being the primary limiting nutritional currency has deflected attention from the possibility that biologically meaningful circumstances might arise whereby the utility of energy-yielding macronutrients would be saturated (plateau stage) or exceeded (toxic phase). Second, it is experimentally challenging to induce animals

to over-ingest macronutrients in a way that enables the effects of those surpluses on health to be disentangled from the effects of concomitant deficits of other nutrients (Raubenheimer et al. 2005). The reason for this is that the regulatory mechanisms of animals will usually resist large excesses of macronutrients (Raubenheimer and Simpson 1997) (which in itself is suggestive that surpluses, like deficits, are costly). Thus, an increase in the concentrations of macronutrients in foods is usually met by a decrease in overall food consumption (the flip-side of compensatory feeding) (Simpson and Simpson 1990). Consequently, the animal experiences a reduced intake of most food components, and no change or only a moderate increase in macronutrient intake. One way for researchers to avoid this problem is to manipulate the balance of macronutrients in the experimental foods, rather than their overall concentration. Simpson et al. (2004) and Raubenheimer et al. (2005) took this approach to test whether Bertrand's rule is applicable beyond essential micronutrients. We used geometrical analysis (Raubenheimer and Simpson 1993; Simpson and Raubenheimer 1993; Raubenheimer et al. 2009) to obtain an objective measure of the optimal requirements for protein and sugar by *Spodoptera littoralis* caterpillars, and to design foods that constrained the caterpillars to deviate systematically from the optimal intake. In this way we were able to assess the impacts on performance independently for excess sugar, deficiencies of protein, and intake of micronutrients. Our results demonstrated that surplus intake of sugar is deleterious to the growth and survival of *S. littoralis* caterpillars, thus establishing that Bertrand's rule applies also to a specific macronutrient. We suspect that Bertrand's rule is at least as prevalent in nutrition as hormesis is in toxicology (see also Boersma and Elser 2006).

"Toxin" or "toxic"

The striking similarities between the inverted-U shaped hormetic dose-response curve (Fig. 1A) and Bertrand's rule (Fig. 2) suggests that these should not be regarded as distinct phenomena. Both show that the ingestion of a wide range of substances can have positive or negative effects depending on the dose, and from a functional (hence evolutionary) perspective it matters not to the animal whether science has labeled these substances "toxin" or "nutrient." We suggest that in its attempts to understand the relationship between foragers and their chemical environments, PharmEcology should similarly ignore this distinction. A wiser heuristic would distinguish between "beneficial," "neutral," and "toxic" regions of the dose-response curve, regardless of whether the curve pertains to components of the ingesta that have traditionally been the focus of nutrition or toxicology.

This view, we acknowledge, ignores some finer distinctions between "toxins" and "nutrients." Thus, many definitions of "nutrient" broadly stipulate a mechanistic basis for the beneficial effects of nutrients (e.g. "any substance that can be metabolized by an animal to give energy and build tissue"—http://wordnetweb.princeton.edu/), whereas toxins are regarded as substances that disrupt these processes. Even in this perspective, there is a murky middle ground. Ethanol, for example, is widely regarded as a toxic component in the diets of humans and other animals, yet in some human populations it can contribute in the order of 5% of the energy budget and in some individuals considerably more (Prentice 2005). Syrian Golden hamsters can derive up to a third of their energy budget from ethanol, and in choice assays these animals select ethanol over water, even at concentrations as high as 45% (DiBattista and Joachim 1998). Likewise, plant secondary metabolites that are regarded as toxins to some organisms contribute nutritional benefits to others (e.g. Bernays and Woodhead 1982; Slansky 1992). Conversely, there are plant primary metabolites that are nutritious to some herbivores but toxic to others (e.g sterols, see Behmer and Nes 2003).

Some authors have pointed out that the functional view introduces problems of its own. Thus, Calabrese and Baldwin (2002) emphasized that hormesis should not be defined on functional grounds, because of the complexities of attributing biological benefit to an observed response. While we agree with this, we add that the same complexities apply to nutrition and yet functional analysis has been central to that field (Raubenheimer et al. 2009). Relatedly, Forbes (2000) argued that although individual components of fitness (e.g. individual life-history traits) respond hormetically to stressors, evolutionary theory does not predict that fitness as a whole would respond in this way because of the extensive trade-offs that exist among the component traits. This is an interesting perspective, which we feel warrants further research. We note, however, that a similar web of trade-offs exists in the context of nutrition (e.g. Lee et al. 2008; Maklakov et al. 2008), and urge that the requisite investigations are not constrained by the "toxin" versus "nutrient" distinction.

Finally, we predict that if toxins can be nutritious and nutrients toxic then organisms should evolve appetitive and avoidance responses that reflect this duality. There exists considerable evidence that animals balance their intake of foods in ways that avoid ingesting either excesses or deficits of specific nutrients (see above), and in many cases a good deal is known about the mechanisms involved (e.g. Berthoud and Seeley 2000). A recent literature demonstrates that animals also regulate their intake of toxins—leading to the coining of the term ''nutritional toxicology'' (Torregrosa and Dearing 2009). Regulation in this context, however, involves balancing the intake of foods in ways that avoid ingesting a toxic overdose. An interesting question is whether animals also regulate their intake specifically to gain toxins at levels that are beneficial. The phenomenon of ''self-medication'', to which we turn in the following section, suggests that they do.

Nutrients and medicines are not so different

Self-medication, or zoopharmacognosy (Rodriquez and Wrangham 1993), is the phenomenon whereby animals use plant secondary compounds or other non-nutritional substances in preventing or treating disease (Huffman 2003). While this is common practice among traditional human societies (Johns 1990; Huffman 2001), Janzen (1978) drew attention in the scientific literature to the possibility that the same might be the case in non-human animals. Janzen compiled a list of examples of food selection by animals in the wild which could not readily be explained on the basis of requirements for nutrients or avoidance of toxins, and suggested that animals might target these foods for their medicinal properties—e.g. as laxatives, antibiotics, drosop, or antidotes for previously ingested toxins. A significant body of data has since accumulated in support of this suggestion, arising from animals as diverse as chimpanzees, leopards, bears, geese, dogs, and sheep (Villalba and Provenza 2007).

Extensive evidence for self-medication by animals in the wild comes from studies of chimpanzees. These primates are known to target several plant species containing compounds which, at the levels ingested, have medicinal properties, for example, the antibiotic methoxysporalen in *Ficus exasperata* (Rodriguez and Wrangham 1993), the antimalarial liminoids in *Trichilia rubescens* (Krief et al. 2004), and the anti-helmithic sesquiterpene lactones in the pith of *Veronia amygdalena*. Strongly suggestive evidence exists that chimpanzees target at least one of these species, *V. amygdalena*, expressly for its medicinal properties (Huffman 2001, 2003). Despite its year-round availability, this plant is eaten by chimpanzees mainly during the rainy months when infection by nematodes is at its peak, and is apparently targeted especially by animals that show signs of sickness. Some evidence exists that consumption of *V. amygdalena* is associated with recovery of health and a dramatic reduction in parasite load (Huffman 2001).

Given the constraints on experimental work with free-ranging primates, evidence for self-medication in chimpanzees has remained largely correlative and observational (Lozano 1998; Hutchings et al. 2003). However, research on livestock, which has not been constrained in this way, has yielded important experimental evidence for self-medication in non-human mammals, particularly in the context of ameliorating the impacts of ingested toxins. Provenza et al. (2000) showed that sheep fed foods high in tannins selectively eat polyethelyne glycol (PEG), which attenuates the adverse effects of these plant secondary compounds. Furthermore, the time spent foraging at locations where PEG is present increases, relative to results from controls, when tannic acid is added to the food. Sheep also selectively ingest sodium bicarbonate and sodium bentonite and thereby offset the acidic effects of some grains; similarly, they ingest dicalcium phosphate and ameliorate the impacts of ingesting oxalic acid (Villalba et al. 2006). These experiments were able to demonstrate that associative learning forms an important mechanistic basis for self-medication by sheep.

Evidence also exists that insects self-medicate. Caterpillars of the tiger moths *Grammia incorrupta* (= *geneura*) and *Estigmene acraea* defend themselves against insect parasitoids by sequestering pyrrolizidine alkaloids (PA) from their food plants. These caterpillars have specialist gustatory receptor cells which detect PA even at extremely low levels and stimulate feeding. Bernays and Singer (2005) demonstrated that the PA receptors of parasitized caterpillars fired more rapidly than did receptors of unparasitized controls. Based on previous work demonstrating that increased gustatory responsiveness to PA stimulates feeding, Bernays and Singer concluded that their data revealed a mechanism for increasing the intake of protective chemicals by these caterpillars as a response to parasitization. Singer et al. (2009) extended this work for *G. incorrupta*, and set it in the context of a framework for rigorously detecting cases of therapeutic

self-medication. These authors pointed out that three criteria should be satisfied to verify cases of therapeutic self-medication: (1) the behavior should improve the fitness of animals infected with parasites or pathogens, (2) it should decrease fitness in uninfected animals, and (3) the behavior should be triggered by infection. Singer et al. (2009) presented data suggesting that all three criteria are satisfied for the ingestion of PA by *G. incorrupta*.

Although much remains to be done (Lozano 1998; Hutchings et al. 2003), the work discussed above provides considerable evidence that poisoned or parasitized animals can specifically select foods containing non-nutrient compounds that ameliorate their predicament. Might they similarly select diets with a nutritional profile that neutralizes toxins or reduces parasite load and associated disease? In addressing this question for parasitic infection, Hutching et al. (2003) concluded that the effects of diet during the first phase of the immune response (the acquisition of acquired immunity) is limited, but they cite several experiments that demonstrated a link between diet and subsequent immune response. For example, studies by Cosgrove and Niezen (2000) and Hutchings et al. (2000) have shown that sheep infected with gastrointestinal parasites select a diet relatively high in nitrogen-rich clover. Hutching et al. (2003) pointed out, however, that for these observations to be categorized as self-medication evidence is needed that the shift in diet by infected animals actually does increase resistance to the parasites (criterion 1 of Singer et al. 2009, discussed above).

Lee et al. (2006) produced such evidence for the caterpillar *Spodoptera littoralis* infected with a highly virulent entomopathogen (nucleopolyhedrovirus) (see also Povey et al. 2009). When caterpillars were confined to one of a range of foods varying in their balance of protein and carbohydrate, dietary protein influenced both resistance to pathogen attack and constitutive immunity to a greater extent than did carbohydrate, reflecting the relatively high protein costs of resistance. Moreover, when allowed to self-compose their diet, caterpillars surviving infection increased their relative intake of protein compared with controls and with caterpillars that died of infection. This experiment demonstrates that *S. littoralis* caterpillars are able to combat viral infection by modulating the macronutrient composition of their diet, in the same way that sheep are able to neutralize the effects of toxins, and chimpanzees and caterpillars are able to fight parasitic infection by supplementing their diet with non-nutritional medicines. Furthermore, the experiment was performed within a framework that satisfies the three criteria required by Singer et al. (2009) as definitive evidence for therapeutic self-medication: a diet high in protein increased performance in infected animals, reduced performance in uninfected controls, and was selected only by infected animals.

We conclude from this section that respectable evidence exists that animals can ameliorate the impacts of toxins, parasites and pathogens by flexibly modulating their choice of diet. From a functional viewpoint, whether the targeted medication is nutritional or non-nutritional is a detail which, for many purposes, is irrelevant. A similar conclusion was reached by Villalba and Provenza (2007), who pointed out that in this respect both nutrient and non-nutrient components of food can be represented in geometric (state-space) models of nutrition (Simpson and Raubenheimer 1999; Raubenheimer et al. 2009) as axes with target (optimal) coordinates >0. We agree with this, and in the section that follows provide an example demonstrating another approach to the analysis of nutrient-toxin interactions using state-space methodology.

Toxins and nutrients interact

Above we have argued that for many purposes nutrient and non-nutrient components cannot be categorically distinguished functionally, because both can be nutritious, medicinal, or toxic. On the other hand, there clearly are cases in which nutrients are nutritious and toxins are categorically deleterious—as, for example, in considering at ecologically relevant concentrations many co-evolved defensive compounds (Sotka et al. 2009). The point we wish to make in this section is that even when toxins can be distinguished categorically in this way, it is often the case that their effects can only be understood in the context of the background nutritional milieu.

As noted by Sotka et al. (2009), the modes of interaction of nutrients and toxins are diverse, involving intake, digestion and absorption, as well as post-absorptive effects (Slansky 1992). In relation to intake, an animal's current nutritional state (hence recent feeding history) can exert a powerful influence on its propensity to ingest toxins. Cronin and Hay (1996), for example, showed that sea urchins (*Arabacia punctulata*) avoided foods containing the diterpenoid pachydictoyl A when fed *ad libitum*, but ingested these foods during the first two days of exposure following three days of food deprivation. Thereafter, they once again rejected the treated foods, either as a result of their altered nutritional state or possibly because of aversion learning.

In addition to recent feeding history, the nutrients co-occurring in foods with toxins can also influence the amounts of the toxins ingested. For example, Slansky and Wheeler (1992) showed that a compensatory response to the dilution of the overall nutrient content of diets lead the velvetbean caterpillar (*Anticarsia gemmatalis*) to ingest toxic levels of caffeine, whereas other studies have demonstrated a specific effect of macronutrient balance on the intake of toxins (Raubenheimer 1992; Simpson and Raubenheimer 2001). The water content of food is also known to affect the deterrency of toxins directly, rather than via its effects as a diluent of dietary nutrients (Glendinning and Slanksy 1994).

Many instances are known in which non-nutrient components of plants interact with nutrients to influence the digestion and absorption of foods. The most extensively documented example concerns polyphenolics, which bind to dietary proteins and other macromolecules in the guts of consumers and thereby lower the digestibility and availability of these nutrients (e.g. Tugwell and Branch 1992; Targett and Arnold 2001; Bennick 2002). The nutrient content of foods, and its impact on nutritional state, can similarly influence the post-absorptive handling of toxins. One example concerns the action of xenobiotic-metabolizing cytochrome P450 enzymes, which are sensitive to dietary levels of various nutrients. In general, nutritional deficiencies result in reduced rate of cytochrome P450-mediated xenobiotic metabolism, although in some cases (e.g. thiamine deficiency) the activity of these enzymes might increase (Yang et al. 1992).

This very brief overview of a very large literature is intended to supplement the discussion by Sotka et al. (2009) as an illustration of the ubiquitous and complex nature of interactions between nutrient and non-nutrient components of the diets of consumers. A recent study illustrates how complex and important these interactions can be, and provides a protocol which we believe is well suited to the task of elucidating these complexities. Simpson and Raubenheimer (2001) systematically varied the protein/digestible-carbohydrate macronutrient balance in the diets of locusts (*Locusta migratoria)*, and simultaneously the dietary levels of tannic acid. Results showed that tannic acid had no effect on survival when the foods contained a balanced complement of protein and carbohydrate, but mortality increased on tannic-acid-containing diets with increasing macronutrient imbalance. The same was true both for diets containing a higher than optimal and lower than optimal protein:carbohydrate ratio, but the mechanism of action differed with the direction of dietary imbalance. When foods contained excess carbohydrate relative to protein the primary mode of action for tannic acid was to deter feeding; by contrast, when foods contained excess protein, tannic acid did not affect intake but acted post-ingestively.

Conclusions

We have argued that it may be counter-productive for PharmEcology to lean too heavily on conventional categorizations of chemical compounds into ''toxins,'' ''medicines'' and ''nutrients.'' This is largely because the consequences for animals of ingesting various compounds are massively contingent, depending not just on the chemical structure of the compound but also on, *inter-alia*, the organism (e.g. taxon, developmental stage, nutritional state, and health), the dose, the balance of other compounds in the food and multifarious interactions among these factors. What constitutes a ''toxin,'' ''medicine'' or ''nutrient'' is thus largely case-specific. This contrasts with some other areas of biology, for example human medicine, in which the distinction between ''toxin'' versus ''medicine'' versus ''nutrient'' clearly does have some practical value. In this case, however, the subject of study is a single species (and representative model systems), whereas any number of species fall within the purview of PharmEcology. Even in the sciences of human health, however, the fact that both maxima and minima may be associated with nutritional recommendations, the tight control over prescription medicines, and the strict (often age-specific) recommendations for dosages for many medicines reminds us that, at base, similar considerations apply. The dynamic, functional viewpoint espoused in this paper might thus provide heuristic value not only on the ecological side of PharmEcology, but also in its other parent discipline, pharmacology.

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