

Xenohormesis: health benefits from an eon of plant stress response evolution

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Abstract Xenohormesis is a biological principle that explains how environmentally stressed plants produce bioactive compounds that can confer stress resistance and survival benefits to animals that consume them. Animals can piggyback off products of plants' sophisticated stress response which has evolved as a result of their stationary lifestyle. Factors eliciting the plant stress response can judiciously be employed to maximize yield of health-promoting plant compounds. The xenohormetic plant compounds can, when ingested, improve longevity and fitness by activating the animal's cellular stress response

and can be applied in drug discovery, drug production, and nutritional enhancement of diet.

Keywords Xenohormesis · Hormesis · Mutualism · Heat shock proteins · Ethnopharmacology · Food production

In the last half century, two powerful yet simple concepts have gained increasing prominence in scientific thought. The first is the concept of the adaptive stress response. Research in the science of stress has established that the ability of organisms to respond to physical, chemical, and social stressors is a fundamental process of life (Feder and Hofmann 1999; Selye 1978; Tytell and Hooper 2001; Welch 1993). A particularly key realization in this area is the idea that low levels of stress can improve an organism's health, well-being, adaptability, and fitness through stimulation of the cellular stress response, a phenomenon known as hormesis (Calabrese and Baldwin 2003; Gerber et al. 1999; Rattan 2008). The second concept is the notion of the basic interconnectedness of living organisms on this planet. The field of ecology in particular has established the remarkable degree to which the success or failure of one species depends not only on its inert physical environment but also on the success or failure of the other species sharing that environment (Boucher 1985; Bronstein et al. 2006; Jones et al. 1994; Odling-Smee et al. 2003). The concept of xenohormesis—the process by which one organism benefits from the stress response of another (Howitz et al. 2003; Howitz and Sinclair 2008)—lies at the confluence of these two streams of scientific thought.

The phenomenon of xenohormesis was first named by Howitz and Sinclair (2008; Lamming et al. 2004). As the prefix *xeno* comes from the Greek word meaning stranger or foreigner, xenohormesis describes the phenomenon of a “foreign” organism's stress response producing chemicals

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that yield benefits to another organism. The word most often refers to the ability of stressed plants to confer stress tolerance to animals that consume them.

In this paper, we review and synthesize recent research bearing on the phenomenon of xenohormesis and point to a number of practical implications of the concept for medicine and agronomy. The following sections introduce the stress response of plants, outline the types of xenohormetic relationships that can exist between plants and herbivores, and discuss the variety of xenohormetic substances that can positively impact animal survival and longevity. The paper aims to build on the existing published literature on xenohormesis by aggregating the growing number of examples of stressed plants producing added nutrient value for the animal that consumes them. Additionally, while several mechanisms for xenohormetic action have been proposed (Howitz and Sinclair 2008), we hypothesize a novel pathway by which products of the plant stress response confer stress tolerance and extend longevity in animals. Finally, we discuss the implications of the principle of xenohormesis for maximizing the nutritional and medicinal properties of plants and for addressing the challenges of adaptation and survival in an ever-changing environment.

Plant stress response

While the cellular stress response and stress chaperones are thought to be at least two and a half billion years old (Feder and Hofmann 1999), plants and their stress response have been evolving for almost one billion years. Because the sessile plant cannot physically move away from stressors, environmental extremes of temperature variation, water or nutrient availability, or predation must be endured in place. As a result, the complexity of the plant stress response humbles that of animals (Kotak et al. 2007). Yet, when an animal eats a plant that has activated its stress response, the animal may readily benefit from the plant's travail.

It is not intuitive that stressed plants may offer more beneficial nutrient products than plants grown under seemingly ideal conditions that maximize the crop yield in terms of mass alone. A prime example of such an unexpected outcome is observed in the production of wine, where the best grapes in terms of taste and health benefit often result from relatively dry, sun-exposed, infertile soil (de Andrés-de Prado et al. 2007; Gambuti et al. 2007). Indeed, the synthesis of resveratrol—a polyphenol that activates the mammalian stress response system and extends longevity (Baur and Sinclair 2006; Putics et al. 2008)—is stimulated by UV light, ozone, or pathogen stress (Brehm et al. 1999; Preisig-Müller et al. 1999; Versari et al. 2001; Wang et al. 2008). Resveratrol protects the plant itself by reducing UV damage and eliminating

pathogenic molds (Adrian et al. 1997; Tang et al. 2010). Similarly, drought-stressed strawberries have better taste, antioxidant capacity, and phenol content (Terry et al. 2007), an observation supported by the rich flavor of strawberries found in the wild in contrast to those that are cultivated under more controlled conditions.

Table 1 provides examples of plants that produce higher concentration of health-promoting substances when enriched by stressful conditions. The table includes hormetic “elicitors” that have been used to increase production of pharmacologically active substances—a practice that could, and perhaps should, be widely applied to future ethno-pharmaceutical production and food agronomy. Indeed, commonly consumed food products like lettuce and fruits can be nutritionally enhanced by cold stress, light stress, water deficit, or nutrient deficit stress (Atkinson et al. 2005; Oh et al. 2009). Heavy metals, salicylic acid, and other compounds can function as hormetic elicitors without compromising crop yield (Kuzel et al. 2009; Zhang et al. 2006). Finally, viral, fungal, and bacterial infection can, in some cases, paradoxically improve the plant's nutritional content via hormesis (Banchio et al. 2010; De Vos et al. 2005; Métraux et al. 1990).

The class of compounds classified as phenols and polyphenols deserve special comment, as they are important categories of secondary metabolites in higher plants that have diverse therapeutic applications. They are divided into flavonoids—which include rutin, quercetin, epigallocatechin gallate (EGCG), isoflavones, and anthocyanidins—and non-flavonoids—including hydroxybenzoic acid and stilbene derivatives such as resveratrol, cinnamic acid, caffeic acid, curcumin, rosmarinic acid, and ferulic acid. Key enzymes for synthesis of phenolic compounds are phenylalanine ammonia-lyase and stilbene synthase, both of which respond to plant stressors as part of the plant defense against infection and environmental challenge (Benoît et al. 2000; Brehm et al. 1999). Phenolic compounds activate the mammalian stress response when ingested, have antioxidant and anti-inflammatory effects, and have therapeutic effects against aging, cancer, type 2 diabetes, neurodegenerative diseases, and renal disease (Bengmark et al. 2009; Kidd 2009; Knutson and Leeuwenburgh 2008; Leonarduzzi et al. 2009). Finally, dietary polyphenol intake in both humans and wild primates (about 14 mg/kg/day) is within the range of having real biological effects (Milton 2003).

Plant–animal xenohormetic relationships

There are multiple potential forms of xenohormetic relationships between plants and animals, including our own species. In some cases, xenohormesis is embedded within an active mutualistic relationship between plant and animal

Table 1 Examples of stressed plants producing higher yields of potentially therapeutic bioactive compounds

Plant	Stressor	Bioactive product	Benefit
American Mayapple (<i>Podophyllum peltatum</i>)	Light stress (Cushman et al. 2004)	Podophyllom	Cancer, warts, arthritis, psoriasis
<i>Artemisia annua</i>	Light and cold stress (Zeng et al. 2008)	Artemisinin	Anti-malarial (Graham et al. 2010)
Black chokeberry (<i>Aronia melanocarpa</i>)	Catabolites of polyamine biosynthesis, ornithine decarboxylase inhibitor (Hudec et al. 2006)	Phenolic compounds	Phenolic effects: antioxidant, anti-inflammatory, cancer, aging, diabetes, neurodegenerative diseases, renal disease (Bengmark et al. 2009; Kidd 2009; Knutson and Leeuwenburgh 2008; Leonarduzzi et al. 2009)
Black Current (<i>Ribes nigrum</i>)	Ornithine decarboxylase inhibitor, <i>O</i> -phosphoethanolamine, carboxymethyl chitin (Hudec et al. 2009)	Phenolic compounds	Phenolic effects
<i>Cistus clusii</i>	Water deficit stress (Hernandez et al. 2004)	Ascorbic acid, phenolic compounds	Common cold (Heimer et al. 2009), phenolic effects
Cucumber (<i>Cucumis sativus</i>)	Fungal and viral infection (Métraux et al. 1990)	Salicylate	Arthritis, fever, cardiovascular disease (Rainsford 2007)
Curcuma (<i>Curcuma longa</i>)	Nutrient deprivation, heat stress (Li and Zhang 1999; Xia et al. 2005)	Curcumin	Cancer, liver cirrhosis, chronic renal disease, chronic obstructive lung disease, diabetes and Alzheimer's disease, intensive care patients, Crohn's disease (Bengmark et al. 2009)
Dandelion (<i>Taxacum officinale</i>)	Ornithine decarboxylase inhibitor, <i>O</i> -phosphoethanolamine, carboxymethyl chitin (Hudec et al. 2007)	Phenolic compounds	Phenolic effects
Grape (<i>Vitis vinifera</i>)	Heat (Wang et al. 2008), fungal infection (Roldán et al. 2003)	Phenolic compounds	Phenolic effects
Gray poplar (<i>Populus x canescens</i>)	Osmotic stress high salinity (Luo et al. 2009)	Abscisic acid	Diabetes (Guri et al. 2007)
Green algae (<i>Haematococcus pluvialis</i>)	Light and nutrient stress (Vidhyavathi et al. 2008)	Carotenoids (astoxanthin)	Alzheimers disease, skin and eye diseases (Shudo et al. 2009), cardiovascular disease (Fassett and Coombes 2009)
<i>Hypericum brasiliense</i>	Heat and water deficit stress (Nacif de Abreu and Mazzafera 2005)	Phenolic compounds	Phenolic effects
Lavender (<i>Lavandula vera</i>)	Vanadyl sulfate (Georgiev et al. 2006)	Rosmarinic acid	Atopic dermatitis (Lee et al. 2008), antiviral (Swarup et al. 2007), sun screen, cancer (Sánchez-Campillo et al. 2009)
Lettuce (<i>Lactuca sativa</i>)	Heat, cold, light stress (Oh et al. 2009)	Ascorbic acid, alpha-tocopherol, phenolic compounds	Common cold (Heimer et al. 2009), leg cramps (Oh et al. 2009), phenolic effects
Mustard (<i>Arabidopsis</i>)	Bacterial and fungal infection, aphid attack (De Vos et al. 2005)	Jasmonate	Cancer (Cohen and Flescher 2009)
Oregano (<i>Origanum x majoricum</i>)	Bacterial infection (Banchio et al. 2010)	Carvacrol	Antibiotic, antiparasitic, diabetes, analgesic, cancer, anti-inflammatory (Baser 2008)
Prickly pear cactus (<i>Opuntia ficus indica</i>)	Heat stress and pH stress (Chaidee and Pfeiffer 2006)	Betalains	Diabetes, dyslipidemia, gastritis, prostate hypertrophy (Ennouri et al. 2006)
Purple coneflower (<i>Echinacea purpurea</i>)	Acetylsalicylic acid, salicylic acid, methylsalicylate, titanium (IV) ascorbate (Kuzel et al. 2009), ornithine decarboxylase inhibitor, <i>O</i> -phosphoethanolamine, carboxymethyl chitin (Hudec et al. 2007)	Caffeic acid and other phenolic compounds	Cardiovascular disease (Kumaran and Prince 2010), phenolic effects

Table 1 (continued)

Plant	Stressor	Bioactive product	Benefit
Soy beans (<i>Glycine max</i>)	Salicylic acid, methyl salicylate, ethyl acetate (Zhang et al. 2006)	Phenolic compounds	Phenolic effects
St. John's wort <i>Hypericum perforatum</i>	Water deficit stress (Gray et al. 2003)	Hyperforin	Antidepressant (Linde 2009)
Strawberry (<i>Fragaria chiloensis</i>)	Water deficit stress (Terry et al. 2007)	Phenolic compounds	Phenolic effects, improved taste
<i>Taxus yunnanensis</i> cell suspension cultures	Fungal elicitors, yeast elicitors, methyl jasmonate, chitosan, heavy metals, and heat (Zhang and Fevereiro 2007)	Paclitaxel	Cancer
Wheat-rye hybrid (triticale)	Water deficit stress (Hura et al. 2009a, b)	Ferulic acid, phenolic compounds	Neurodegenerative disorders, cardiovascular disease, diabetes, cancer (Barone et al. 2009), phenolic effects
Willow seedlings (<i>Salix sericea</i>)	Beetle herbivory (Fields and Orians 2006)	Salicylate	Improved stress response, longevity, antipyretic, anti-inflammatory (Batulan et al. 2005; Strong et al. 2008)

species, and the substances produced by the stressed plant are specifically targeted to produce benefits for the helper animal species. For example, trees like *Cecropia*, *Acacia*, and *Macaranda* have evolved indirect defense to herbivores by attracting and nourishing other organisms that reduce plant herbivore damage (Heil 2008). Over a century ago, Francis Darwin described a “standing army of ants” that consume *Acacia* food bodies and protect the plant from the ravages of herbivores (Darwin 1877). The damage from herbivore feeding elicits an octadecanoid cascade, which leads to jasmonic acid synthesis and the production of extrafloral nectar and food bodies. These food bodies provide carbohydrates, lipids, amino acids, and micronutrients that attract ants and parasitic wasps that protect against the offending herbivores (Heil 2008; Linsenmair et al. 2001). Plant–animal mutualisms also occur to facilitate the dispersal of seeds and pollination of flowers by animals (Bronstein et al. 2006); consumption of xenohormetic substances in stressed plants may enable animals to more successfully distribute the plant's genes when conditions are difficult.

While mutualism between plants and animals can support a co-evolutionary impetus for xenohormesis, xenohormesis can also occur with no apparent benefit to the plant. In these cases, the animal is able to piggyback on the self-directed adaptive response of the plant. In fact, most of the bioactive compounds listed in Table 1 are simply products of the plant's stress response that protect it from further environmental damage.

Xenohormetic plant compounds can yield benefits to the animal directly, or by activating the animal's own stress defense pathways. The xenohormetic benefit of the *Cecropia*–ant relationship, for example, comes mainly in the form of calories (Heil 2008). Ascorbic acid, flavonoids, and

alpha-tocopherol produced by lettuce and soy act primarily as antioxidants (Leonarduzzi et al. 2009; Oh et al. 2009; Zhang et al. 2006). Other hormetic compounds like podophyllum and paclitaxel have a low dose therapeutic effect, but are quite toxic at higher doses (Biganzoli et al. 2009; Kao et al. 1992). Polyphenols such as resveratrol, curcumin, and carvacrol, on the other hand, are able to stimulate the animal's stress response with minimal systemic toxicity (Allard et al. 2009; Baur and Sinclair 2006; Kato et al. 1998; Scapagnini et al. 2001).

There are several possible explanations for why the animal's stress response should be activated by products of a plant's stress response (Howitz and Sinclair 2008). First, it may occur as a fortunate coincidence, especially in the case of marginally toxic products that produce hormetic benefits via the animal's generalized stress response. Second, it may be due to shared evolutionary history and physiology. Animals and plants, for instance, share a high degree of sequence homology between their stress response signaling pathways, particularly for highly conserved kinases and heat shock proteins (Jiménez et al. 2007). Finally, selection may have favored animal physiology that responds to products of the plant's stress response in order to gauge changing environmental conditions, a hypothesis that has been particularly emphasized in the work of Howitz and colleagues (Howitz et al. 2003; Howitz and Sinclair 2008; Lamming et al. 2004).

Xenohormetic compounds and longevity pathways

Many bioactive plant compounds that are associated with improved animal longevity confer their benefits by activat-

ing or priming cellular survival pathways. The caloric restriction model of inducing robustness and longevity has been used to explain much of hormetic action (Rattan 2008). In fact, the term “caloric restriction mimetics” is often used to describe bioactive compounds with hormetic effects (Ingram et al. 2006; Redman et al. 2008). Recent studies associate caloric deprivation signaling with both activation of the stress response and restoration of energy supply (Canto et al. 2009; Saunders and Verdin 2009).

The key alarm that initiates the response to caloric restriction is lack of available energy in the form of ATP deficit and/or oxidative stress. Figure 1 illustrates a direct pathway that responds to a low energy state and results in a robust stress response and energy recovery. A high AMP/ATP ratio, as occurs with caloric restriction and exercise, activates AMPK (AMP-activated protein kinase), which then, via the NAD⁺/NADH redox state, stimulates sirtuin 1 (SIRT-1) deacetylation of key transcription factors including heat shock factor-1 (HSF-1; Canto et al. 2009). HSF-1 activates most heat shock proteins (Hsps) and is associated with stress survival and longevity extension across diverse species (Saunders and Verdin 2009).

HSF-1 specifically orchestrates cellular viability by limiting replicative senescence, apoptosis, inflammation, and stress vulnerability (Logan et al. 2009; Meldrum et al. 2003; Pandita et al. 2004; Saunders and Verdin 2009). AMPK activation also limits protein and fat synthesis while stimulating fatty acid oxidation and glycolysis in order to restore the availability of ATP. The net effect on the organism is to meet demands for immediate energy availability and cellular organelle protection. We suggest that an activated stress response plays a fundamental role in conferring fitness and survival benefits to animals consuming stressed plants. In support of this notion, overexpression of HSF-1 extends longevity, while under-

expression reduces it in transgenic animal models (Calderwood et al. 2009; Hsu et al. 2003; Morley and Morimoto 2004). Importantly, plant caloric restriction mimetics can have effects at several steps of the pathway illustrated in Fig. 1. In some cases, it is difficult to identify the predominate level that any particular xenohormetic compound activates; for instance, resveratrol activates both AMPK (Fullerton and Steinberg 2010) and SIRT1 (Westerheide et al. 2009), but it is not yet definitively clear which activation dominates its effect.

To date, the primary bioactive plant compounds known to raise Hsps and to be associated with extension of animal life span are resveratrol (Putics et al. 2008; Westerheide et al. 2009), curcumin (Chen et al. 2001; Kitani et al. 2007; Scapagnini et al. 2001), salicylate (Batulan et al. 2005; Strong et al. 2008), and EGCG (Abbas and Wink 2009; Zhang et al. 2009). Plant compounds that raise Hsps but currently have no proven longevity effects are rosmarinic acid (Rattan et al. 2009), ferulic acid (Calabrese et al. 2008), jasmonic acid (Oh et al. 2005), and carvacrol (Wieten et al. 2010). As a class, these compounds are associated with pleiotropic medicinal benefits that include improved stress tolerance, anti-carcinogenesis, improved glycemic control in diabetes, and reduced cardiovascular disease (see Table 1). The therapeutic promise of these Hsp-augmenting substances and their derivatives are substantial. We should note, however, that because most studies to date have been carried out in cell culture and at super-physiological concentrations, there remain high returns to research focusing on the magnitude of these benefits under more natural conditions.

Another pathway associated with longevity extension that is activated by xenohormetic compounds involves transcription factor nuclear factor-E2-related factor 2 (Nrf2; Godman et al. 2009; Onken and Driscoll 2010). Nrf2 binds antioxidant response elements upstream of cytoprotective stress response proteins such as heme oxygenase and Hsp 22/40/90. The xenohormetic compound curcumin, for example, activates heme oxygenase by regulating Nrf2 (Balogun et al. 2003), while other plant compounds that are not necessarily xenohormetic like sulforaphane (in broccoli) and allicin (in garlic) also activate Nrf2 (Chen et al. 2004; Dinkova-Kostova et al. 2002).

Remarkably, antioxidants like ascorbate, alpha-tocopherol, and some flavonoids have not been associated with improved longevity (Muller et al. 2007). The lack of long-term therapeutic benefit of antioxidants may be partially explained by their suppression of the endogenous stress response. Oxidation products are potent stimulants of HSF-1 activity, and decreasing oxidation in the cell can reduce the HSF-1 stress response (Hooper and Hooper 2004).

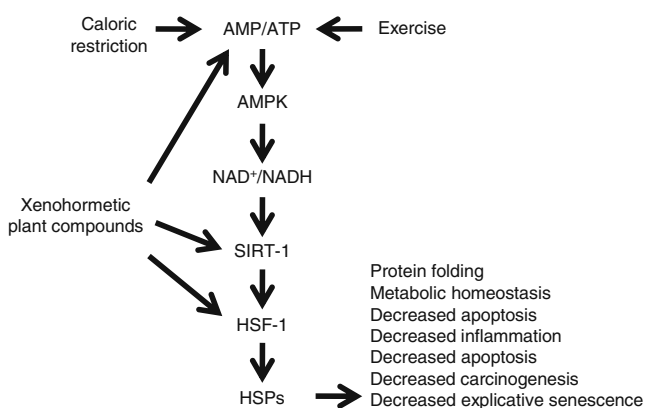


Fig. 1 Longevity pathway demonstrating how caloric restriction, exercise, and stress-derived plant products activate the mammalian stress response

Implications of xenohormesis

How can humans leverage the lessons of xenohormesis? As mentioned above, elicitors can improve production of ethno-pharmaceutical products and the nutrient quality of commonly consumed agricultural products. For instance, the global spread of drug-resistant malaria has created a major demand for the anti-malarial artemisinin, a sesquiterpenoid compound that is synthesized in glandular trichomes of *Artemisia annua* (Graham et al. 2010). The fact that *A. annua*'s glandular trichomes are similar to the food bodies described by Darwin, in that they increase in density and size in response to stress, is probably not a random coincidence; however, unlike the food bodies, they release oils that directly protect the plant from herbivore attack and/or attract pollinators (Schilmiller et al. 2008). Indeed, the hormetic elicitors of cold and light stress increase artemisinin yield in *A. annua* (Zeng et al. 2008) and may be employed to address pharmaceutical production shortages.

While the original concept of xenohormesis focused on micronutrients (Howitz et al. 2003), the concept can also be extended at the macronutrient level. Vigh and colleagues observed that plants exposed to cold shock increase synthesis of unsaturated fatty acids, increasing membrane fluidity and stabilizing the stressed membrane (Quinn et al. 1989; Vigh et al. 1985). Pertinently, animal consumption of these less saturated fats lowers the animal's threshold for triggering the stress response and is associated with a hearty, less disease-prone state. The hyperfluidization of mammalian cell membranes acts as a signal to initiate the heat shock protein response (Balogh et al. 2005; Nagy et al. 2007). In fact, evidence supporting the positive impact of "healthy" plant and animal oils (e.g., olive oil and omega-3 fatty acids) on our well-being is rapidly expanding (Sofi 2009; Zevenbergen et al. 2009). This xenohormetic process also provides a natural model for the action of the Hsp co-inducing hydroxylamines: like unsaturated plant lipids, these membrane-intercalating compounds are capable of simultaneously reducing the molecular order of specific membrane domains and correcting dysregulated expression of Hsps (Török et al. 2003).

Continued focused research on plants' adaptive stress response will likely lead to the discovery of new health-promoting compounds with significant pharmaceutical promise. Close examination of bioactive products found in plants that survive and thrive in environmentally harsh conditions may reveal potent therapeutic substances. For example, extracts from the prickly pear cactus (*Opuntia ficus indica*) can be effective in reducing the symptoms of excessive alcohol consumption. When ingested, the cactus extract increases Hsp levels and is promoted for use by endurance athletes (Wiesse et al. 2004). The active ingredient may be a betalain, which is associated with

potentially broad medicinal benefits, including treatment of diabetes, dyslipidemia, gastritis, and prostate hypertrophy (Ennouri et al. 2006).

Another insight from an understanding of xenohormesis is that it may partially explain the conundrum currently surrounding many ethno-pharmaceutical studies that too often cannot stand up to standards of scientific reproducibility. From study to study, researchers may not take into consideration variability in the concentration of bioactive compounds elicited by the conditions under which the medicinal plant was grown. For instance, while a number of studies suggest that cinnamon consumption should improve glycemic control in patients with type 2 diabetes mellitus, the result has failed to be confirmed by meta-analysis (Baker et al. 2008). In other words, cinnamon used in one study may not have the same biological effect as cinnamon in another study because it does not have the same concentration of environment-dependent bioactive compounds.

The use of herbs and spices in traditional ethnic cuisines may harness both hormetic and xenohormetic principles. In particular, the use of curcumin, lavender, oregano, mustard (see Table 1), thyme (a source of carvacrol: Baser 2008), and red wine may not only enhance taste but also yield health benefits by priming the consumer's stress response pathways. More generally, while adaptive explanations for the use of spices have focused on their potential effectiveness against pathogens (Billing and Sherman 1998), the theory and data presented here suggest that spices—especially those grown under stressed conditions—may also improve human health via hormetic and xenohormetic pathways (Gerber et al. 1999).

A more global question in this context is whether we are losing important health and nutritional benefits by consuming agricultural products grown in soils and conditions that maximize crop yield but that minimize the stress that would have existed in more natural environments. Has the popularity of controlled mono-cropping in the last few decades affected other species as well? The epidemic of the colony collapse syndrome, for example, has devastated honeybee populations. Is the honeybee no longer ingesting stress-derived and stress-protective bioactive nutrients from a variety of plant species, and therefore becoming more vulnerable itself to life's stresses (Alaux et al. 2010)? Does humanity share a similar risk? As our climate and environment change, it will be more essential than ever for humanity to engage in mutualistic interplay with species at all trophic levels. Perhaps our species can harness the sophisticated stress response of plants to better survive and thrive in a stressful and ever-changing world.

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