Ecological Pharmacology: Humans and Plants Coherently Couple Through Phytochemistry

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Abstract

Coherent coupling, the structural congruence of two or more systems due to a history of recurrent interactions, offers a dramatically different view of human's relationships with their environments. Besides challenging the central dogma of biology, this paradigm suggests that humans and plants are mutually engaged in an exchange of information. This interdependence goes beyond plants as merely clothing, shelter, food and medicine, but rather leads to the assertion that we have been shaped by plants and have shaped plants, from phenotype to genotype. In addition, the paradigm of coherent coupling challenges the current pharmacological model which is currently based on using single isolated molecules. The conclusion is reached that due to a history of reiterative phytochemical exchange with plants, heterogenous arrays of plant compounds flowing through a human system may be of vital biological importance to wellness and the healing process.

Isolating the organism from its environment has been a fundamental tenet of studying biological processes. In many laboratories around the world this practice is still followed in hopes of further insight into life processes. However, this may lead to incomplete - or worse - erroneous conclusions. Maturana and Varela[1] propose that due to organisms being inexorably interwoven with their environments, it is impossible to speak of environment and organism as separate entities. They presented this interrelationship as *structural coupling* (and later called coherent coupling) in the landmark book the *Tree of Knowledge*. They define coherent coupling as a history of recurrent interactions leading to the structural congruence between two (or more) systems.[1] In other words, autopoietic (self-organizing) unities, such as organisms and environment, can undergo coupled histories of structural change due to their consistent and constant interactions. Coherent coupling recognizes the congruence between autopoietic systems.[2] This can include the system and its environment or systems affecting systems. In this paradigm, the environment is seen as a medium, which illustrates, the interwoven nature between organism and environment. Development of the autopoietic systems involved thereby arises from transformations that each invokes in the other. This very much challenges the neo-Darwinist evolutionary theory, which in some authors' opinions drastically underestimate the effects and inseparability of the environment and organism.[3-5] Such interdependent relationship is considered unique and diachronic and is a defining principle of an organism and/or the environment.[5]

The construct of coherent coupling professes that organism and environment are mutually enfolded in multiple ways, and what constitutes the world of a given organism is enacted by that organism's history of coupling with its environment.[6] Indeed, on a human level it is well accepted at this juncture that our interwoven nature with our environment provides constant perturbation requiring a systemic reorganization of physiologic function.[7]

While some researchers are realizing the pro-

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Kevin Spelman, Chair of the Clinical Division in the Department of Herbal Medicine at Tai Sophia Institute, has been a practitioner of clinical phytotherapy and Ayurvedic medicine integrating Ayurveda, western herbalism, modern physiology and biophysics for fifteen years of clinical practice. He is currently pursuing a doctorate researching bioactive compounds in medicinal plants at the University of North Carolina and the University of Exeter in the UK. As a biochemist, Mr. Spelman's international work has included the analysis of nutrient levels in women of early childbearing age in West Africa and working with children with neurological disorders in Central America. He has served as faculty at a number of institutions, including the Southwest College of Naturopathic Medicine in Tempe, AZ and the Ayurvedic Institute in Albuquerque, NM. Mr. Spelman also serves on the council of the American Herbalists Guild and is a member of the College of Practitioners of Phytotherapy in the United Kingdom.

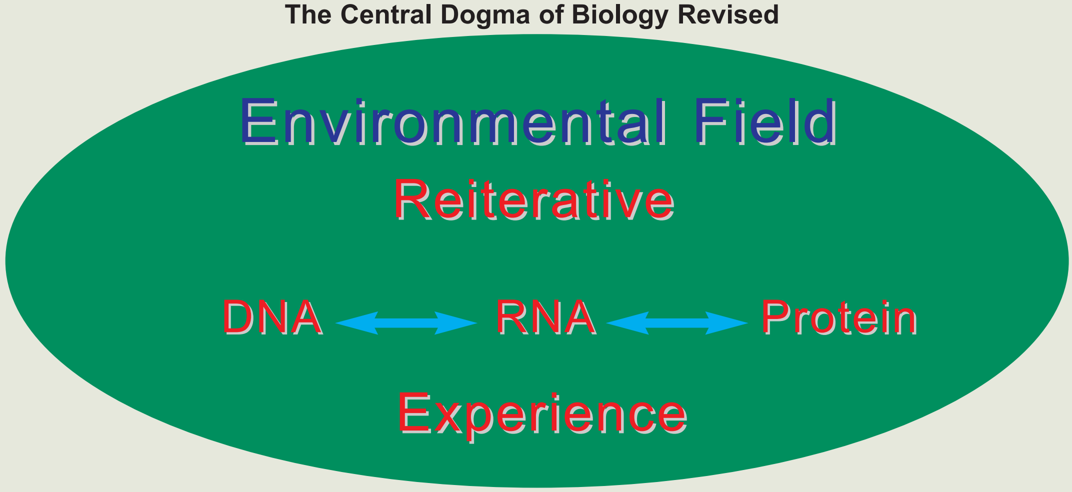
found relationship the environment has with physiological function, especially in regard to health and disease, other researchers have taken it a step further. With meticulous laboratory research, Cairns' group[8] published an extremely controversial paper some years ago stating that mutations can be environmentally directed' not random as Neodarwinists would suggest, but specifically adaptive. Following up on Cairn's work a few years later, Thaler[4] came to the same conclusion, stating that the environment can invoke genotypic change and postulated that both the environment as well as the organism's *perception* of the environment can induce engineering genes to rewrite themselves and thus, rewrite sections of DNA code. Cairns and Thaler were suggesting a complex engagement of organism and environment. What they perhaps did not know was that they had just provided Maturana and Varela with evidence for their coherent coupling construct. This greatly challenged the prevalent Neodarwinists perpective that sees mutations as random events, not specifically adaptive as suggested by Cairns and Thaler. Such a non-Darwinian response, well beyond haphazard natural selection, infers a primary form of intelligence that had developed billions of years ago.[9]

The construct of coherent coupling provides the understanding of an autopoietic systems' ability to be extensively "shaped" by interactions with its environment over time, and vice-versa. Many may see this as fitting of a system to its environment, but this is not what is meant by coherent coupling. Rather, this construct denotes congruence between autopoietic systems and environment due to changes prompted by each other. It is also important not to confuse this construct with coevolution, a subset of evolution that includes population genetics and theoretical ecology. While coevolution accounts for species-species or species-environment interaction, it differs from the coherent coupling paradigm in that the species are still seen separately from their environment and surrounding species. Coevolution still follows the central dogma of biology: Information flows from DNA to RNA, to protein and by extension, to the cell and on to multicellular systems. Crick originally formulated this "dogma" as a negative hypothesis that states that information cannot flow from protein to DNA.[10] What the doctrine of the central dogma of biology implies is that a cell's experience has no effect on DNA sequence.

Maturana and Varela[1] challenge the central dogma when implying, but not stating, that experience can have an effect on DNA. They point out that the confusion is seeing DNA as "uniquely responsible" instead of having an "essential participation". Although the organisms and environment are recognized as autonomous in the coherent coupling model, they are also recognized as inseparably engaged in mutually affecting relationships. The result is that organisms are seen as formed due to historical recurrent interactions with their environment, just as the environment has been formed by its interactions with the organism. This implies that genes were "written" to express such proteins due to the reoccurring experience of the membrane with sodium and/or calcium. On a microcosmic scale, for instance, cellular membranes have coherently coupled with the abundance of sodium and calcium ions. This is seen through the specialization of proteins in the membrane to allow for active transport and the inclusion of metabolic processes that sodium and calcium play. Maturana and Varela[1] challenge the central dogma when implying, but not stating, that experience can have an effect on DNA. They point out that the confusion is seeing DNA as "uniquely responsible" instead of having an "essential participation". On a macrocosmic scale, the paradigm of coherent coupling leads to an easy realization of the Gaia Hypothesis [see *UnifiedEnergetics*™ 1(2):62-6]

The Central Dogma of Biology

The Central Dogma of Biology Revised



where the planetary environment (e.g. temperature, ocean salinity and atmospheric gases) is modified by various species, and in turn, these species genotypically and phenotypically morph to the environment. It has been stated that all "evolution is coevolution";[11] and that all "development is codevelopment";[12] could it be that all evolution and all development is coupling with the environmental coupling?

Humans Have Coupled with Phytochemistry

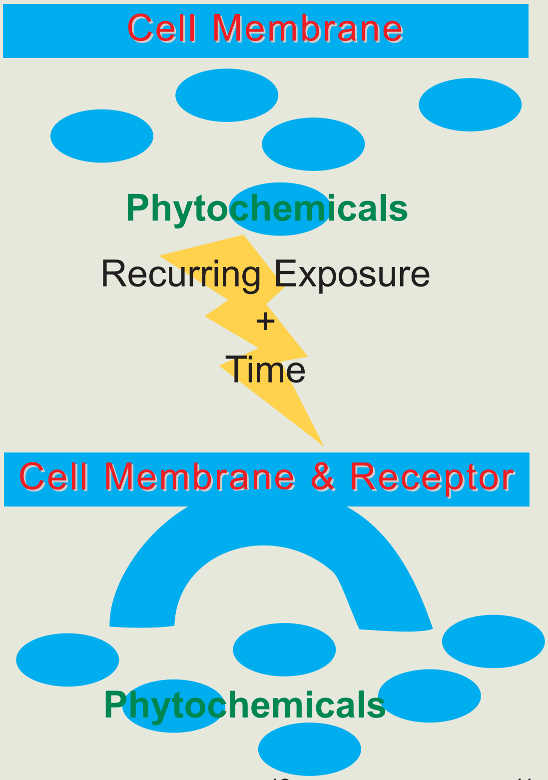
In coherent coupling, due to the constant interwoven nature of organism and environment, there must be some sort of exchange of information to account for species plasticity. Markos[13] defines this exchange that allows species to read their environment, thus integrating into Gaia as "informational flow". The informational flow relevant to the discussion between plants and humans is easily recognized as chemistry - that is, the exchange of molecular messages.

The secondary metabolites of plants are well known to modulate the interrelationships - both positive (i.e. attractant) and negative (i.e. repellent) - between plants and their consumers. The presence of secondary compounds in plants provides information to other species, and it is this authors' belief that due to a reiterative history of interactions, plants and humans are coherently coupled. Humans and plants are mutually enfolded. Plants have always provided shelter, clothing, food and medicine for humans; in turn, we transport, seed, fertilize (human waste) and cultivate plants.

Higher primates have been evolving and have been exposed to plant chemistry for about 88 million years. The higher primates, considered to be omnivores, are nevertheless, primarily herbivores. Over such an evolutionary time scale, all higher primates relied on the predictability of vegetative parts of plants as food sources.[14] This includes *Homo sapiens*, with their 5 – 7 million years of exposure to phytochemistry. Of course, this exposure to various plant parts provided the consumer literally thousands of secondary metabolites. Estimates of the number of plants in the early human diet range from 80 – 220. Clearly if *Homo sapiens* consumed such a regular number and volume of plant foods, they were exposed to a very high number of phytochemicals, a very conservative estimate would be in the range of 8,000 – 22,000, and quite likely an order of magnitude higher. Ames[15] makes an estimate of the number of secondary metabolites in the current human diet taking into account only those secondary metabolites that are also known pesticides. He shows that even with the great reduction in variety in the human diet compared to our hunter-gatherer ancestors, the modern number of secondary metabolites/pesticides in the diet is about 10,000 compounds. Thus, even now we are exposed to a great amount of "information" from plants.

If we have coherently coupled with plants, then by default this means that plants have shaped us through informational molecular exchange, and vice-versa, we have shaped plants. This shaping, if the hypothesis is solid, should range from protein to DNA. It is easy to see that humans have shaped plants by

Coherent Coupling Between Phytochemistry and Eukaryotic Cells



looking at the cultivation of crops; the original species of any of the crop plants have changed drastically due to human intervention. It is not quite as easy to recognize that plants have shaped us, though one obvious, well-known example is the "shaping" of the cytochrome P 450 (CYP 450) genes. This ancient superfamily of enzymes consist of mostly microsomal and mitochondrial proteins and in humans represents about 75 different CYP 450 genes.[16]

Danielson[16] points out that CYP 450 genes allow animals to generate a metabolic resistance to plant compounds designed to dissuade grazers and also to allow plants to generate new compounds to deter herbivory. He goes on to point out that these CYP 450 genes in plants and animals have been engaged in a cyclical process, generating novel compounds in plants and generating resistance in animals. Jackson[17] discusses the observation that particular plant compounds, such as alkaloids, glycosides, phenolics, uncommon proteins, unusual free amino acids, steroids, essential oils, terpenes, and resins, are capable of altering the metabolism and potentially changing the biological fitness of humans as well as their domesticated animals, and even the obligate parasites of each species. She points out that detoxication of plant compounds represents an avenue of potentiating individual and group shifts in gastrointestinal function, structure and endocrine metabolism. But this influence on physiology doesn't just stop with transient functional effects.

CYP 450 genes follow an unusual ability to evolve rapidly, following a quick-paced, non-linear time course.[16, 18] A large-scale expansion of the CYP 450 gene family is thought to have provided a cache of proteins from which novel isoforms provided adaptive strategies for metabolizing plant compounds. The resulting diversity in these genes is believed to be due to the reoccurring exchange of molecular information between the secondary metabolites of plants and mammals needing new enzymes to detoxify these defensive compounds.[19] Therefore, the rich exposure of humans to phytochemistry ultimately promoted human biological variability affecting our genes.[17-19] Was it haphazard mutations that lead to such abilities? Or were genotypic changes, as Cairns' and Thaler's work suggest, environmentally directed?

Another example of coherent coupling between plants and humans are the steroid receptors. Specifically, the estrogen receptor is the earliest receptor of the steroid receptor family.[20, 21] The gene structure and ligand-binding properties of the classical estrogen receptor (ER-α) are known to be highly conserved for 300 million years of vertebrate evolution among vertebrates. Thus, the binding of an estrogenic chemical to ER-α in fish, amphibians, reptiles, birds and mammals (including humans) shows relatively little difference.[22-25] Orthodox thought of this protein as occurring only in vertebrates needs revision: The fungal organisms known as microrrhiza living on the roots of plants have a receptor called NodD, which has a high amount of genetic homology with the human estrogen receptor. In addition, plants express proteins that are homologous in sequence and identical in function (the reduction of steroid substrates) to human 5·-reductase enzymes.[26, 27] These proteins are bound by steroids and flavonoids produced by plants.[26, 27] Thus, it is a communication strategy between plants and fungi.[27]

A perspective from an evolutionary context suggest that the communication strategy of plants pertains to us as well. Phytochemical messenger molecules used by symbiotic soil fungi can be sequestered by humans, bind to estrogen receptors and thereby influence gene expression. In discussing that the NodD and the estrogen receptor share no common evolutionary ancestory, Fox[28] attempts to explain this by invoking the construct of convergent evolution – that these different species have responded to similar environmental signals, via natural selection, with the same adaptive traits. However, this leaves this coherence among proteins to mere coincidence. If we view this through the lens of the coherent coupling paradigm, it offers an explanation that carries the favor of cooperativity within an environmental context.

Through this lens, humans and plants would be seen to shape themselves to mutual signals. Wynne-Edwards[29] postulates that plants chosen for domestication may have a higher occurrence of phytoestrogens. This could potentially enhance the ovulatory cyclicity in women, which would might mean more humans to cultivate more crops. Wynne-Edwards goes on to point out that humans have receptors in the nose and cheeks that bind native steroids and plant compounds, which in turn send messages to the brain. Studies have demonstrated that mammals will consume steroids in foods at some times and reject them at other times, depending on physiological and reproductive conditions (e.g. in pregnancy, rats will reject foods with steroids in them). Thus, as coherent coupling implies, there is a plasticity of response between animals and plants.

Of significance, the effects of flavonoids, nonsteroidal secondary metabolites of plants, share key similarities in microrrhiza and mammals. Flavonoids can regulate gene transcription in both groups. Moreover, some of these flavonoids can modulate the endocrine system and regulate mammalian physiology through activity on steroid receptors and prostaglandin synthesizing enzymes.[30] 30 In addition, humans express a protein, the 5α-reductase

enzyme, that are homologous in sequence and identical in function (the reduction of steroid substrates) to a plant protein.[28, 31] Hence, it should be of no surprise that plants have a long history of utilization in treating endocrine ailments; currently, phytochemistry is being explored for the regulation of human fertility. This leads Baker[26] to suggest that flavonoids may have an evolutionary role in steroid hormone activity. More importantly, it is an obvious example of signaling between plants and humans.

That flavonoids are considered conditionally essential nutrients[32] adds to the intrigue. In other words, we have “coupled” with these particular flavonoid “signals” to such a degree that they are critical to our long-term health.[33, 34] One wonders how many other plant compounds enhance human health. As research on plant metabolites continues, it is increasingly obvious that many phytochemicals are at least favorable, if not necessary to human health. Just considering the vitamins and minerals from plant origin makes it obvious that human physiological processes are dependent on the phytochemistry of plants.

The Underpinnings of Pharmacology

One (of many) important hypothesis that derives out of the coherent coupling paradigm is that consumption of plants, a process that has been going on for 300 million years for vertebrates, 88 million years for higher primates, and 5-7 million years for humans, leads to exposure to an array of plant compounds. Never has the consumption of edible food stuffs involved a single, isolated compound. This is of pharmacological significance: Our current model in pharmacology attempts to induce physiological change through the ingestion of one chemical at a time. In an unspoken oversight of the medical sciences, the rationale for the approach of isolation and purification of active constituents from “crude drugs” has never been made explicit.

The general conclusion drawn from a century of research on isolating active constituents from medicinal plants is that medicinal plants typically contain numerous active compounds.[35-39] An interesting point made by Vickers[40] is that multi-constituent plant medicines were not forsaken because of research that demonstrated harmful or ineffective activity, but because they were too complex to study in their multi-constituent form. Nevertheless, pharmacological modeling has used isolation as a fundamental tenet of inducing physiological shifts in humans. Unfortunately, this methodology is deficient in revealing the mode of activity of the bulk of medicinal plants as it neglects the possibility of synergic, additive or antagonist activity of multi-constituent remedies.[41] Moreover, it grossly simplifies human health to only those parameters that fit into a reductionist model.

In a pharmacological paradigm guided by coherent coupling, our physiological processes, to the level of DNA, have undergone a history of recurring biochemical interactions with complex phytochemistry that has lead to the structural congruence of humans and plants. The previously discussed shifts in DNA, the homology of proteins and the ligand-receptor relationhip between humans and plants are examples of “structural congruence”. Humans have integrated with plants so that multiple concurrent biochemical perturbations are ordinary. Reiterative exposure to minute doses of numerous plant metabolites provides constant stimuli for biological adaptation.[17] In turn, this adaptation had profound effects on human health. If system diversity is proportional to system stability, then the stability of health may be seen as a function of chemical diversity due to human-plant coalitions.[17]

Keith and Zimmerman[42] suggest that many genes might need complementary action to modify disease processes. In other words, efficacious therapy might depend on perturbing more than one target. It is quite likely that the ancient human diet, consisting of thousands of plant compounds, influenced many genes simultaneously on a regular basis. Recognition of such multi-factorial biochemical perturbations would eventually advance the understanding of biological molecular networks that modify health status and open up further understanding of pharmacology. The current number of pharmacological targets, ~ 300 – 400, are but a small number of the 10,000 estimated health-modifying genes.[42] Quite likely, the majority of the multitude of plant constituents that humans regularly consumed through their evolutionary process had a positive affect on many of the health-modifying genes due to coherent coupling between humans and plants. It has become increasingly obvious that persons with a phytochemical rich diet have a significantly improved health status over those whom have a diet low in phytochemicals.[43]

A pharmacological model based on human-plant structural congruence not only provides the recognition of plants as sources of medicines, but of a multi-target approach that single-chemical, stand-alone interventions cannot offer. And it returns us to the origins of pharmacology where what humans regularly ingested, somewhere between 80 -220 plants with an estimated 8,000 – 22,000 secondary metabolites, modified multiple physiological processes in a concerted manner. The understanding of the translational response of numerous proteins to multiple perturbations, such as provided through phytochemistry, holds promise for the fields of medicine and biology not because it is new insight, but because it is an ancient process that shaped human physiology. Human physiology, proteins and DNA, have been, at the very least, partially shaped by phytochemistry. Heterogenous arrays of molecules flowing through a human system may be of vital biologically importance to the healing process. Our future medicines perhaps will be multi-component phytochemical mixtures that resemble good, quality food. "Eat your vegetables" may take on a whole new meaning.

References

1. Maturana HR, Varela FJ. *The tree of knowledge: the biological roots of human understanding*. 1st ed. Boston: New Science Library: Distributed in the United State by Random House; 1987.
2. Maturana H. The Organization of the Living: A Theory of the Living Organization. *International Journal of Man-Machine Studies*. 1975;7(313-32).
3. Cairns RB. Aggression from a developmental perspective: genes, environments and interactions. *Ciba Found Symp.* 1996;194:45-56; discussion 57-60.
4. Thaler DS. The evolution of genetic intelligence. *Science.* Apr 8 1994;264(5156):224-225.
5. Scapini F. Environment and individual: a dialectic relationship. *Riv Biol.* May-Aug 2001;94(2):293-303.
6. Varela FJ, Thompson E, Rosch E. *The embodied mind: cognitive science and human experience*. Cambridge, Mass.: MIT Press; 1991.
7. Schulkin J. Allostasis: a neural behavioral perspective. *Horm Behav*. Jan 2003;43(1):21-27; discussion 28-30.
8. Cairns J, Overbaugh J, Miller S. The origin of mutants. *Nature*. Sep 8 1988;335(6186):142-145.
9. Pechere JC. [How bacteria resist antibiotics: a primary form of collective intelligence?]. *Bull Acad Natl Med*. 2004;188(8):1249-1256.
10. Crick F. Central Dogma Of Molecular Biology. *Nature*. 1970;227(5258):561-&.
11. Kauffman SA. *At home in the universe: the search for laws of self-organization and complexity*. New York: Oxford University Press; 1995.
12. Gilbert SF. The genome in its ecological context: philosophical perspectives on interspecies epigenesis. *Ann N Y Acad Sci*. Dec 2002;981:202-218.
13. Markos A. The ontogeny of Gaia: the role of microorganisms in planetary information network. *J Theor Biol*. Sep 7 1995;176(1):175-180.
14. Johns T. *The origins of human diet and medicine: chemical ecology*. Tucson: University of Arizona Press; 1996.
15. Ames BN, Profet M, Gold LS. Dietary pesticides (99.99% all natural). *Proc Natl Acad Sci*. 1990;87:7777-7781.
16. Danielson PB. The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. *Curr Drug Metab*. Dec 2002;3(6):561-597.
17. Jackson FLC. Secondary Compounds in Plants (Allelochemicals) as Promoters of Human Biological Variability. *Annu Rev Anthropol.* 1991;20:505-546.
18. Nelson DR, Kamataki T, Waxman DJ, et al. The P450 Super family - Update On New Sequences, Gene-Mapping, Accession Numbers, Early Trivial Names Of Enzymes, And Nomenclature. *DNA Cell Biol*. Jan-Feb 1993;12(1):1-51.
19. Gonzalez FJ, Nebert DW. Evolution Of The P450-Gene Superfamily - Animal Plant Warfare, Molecular Drive And Human Genetic-Differences In Drug Oxidation. *Trends Genet.* Jun 1990;6(6):182-186.
20. Wu KH, Tobias ML, Thornton JW, Kelley DB. Estrogen receptors in Xenopus: duplicate genes, splice variants, and tissue-specific expression. *Gen Comp Endocrinol*. Aug 2003;133(1):38-49.
21. Hawkins MB, Thornton JW, Crews D, Skipper JK, Dotte A, Thomas P. Identification of a third distinct estrogen receptor and reclassification of estrogen receptors in teleosts. *PNAS.* Sep 26 2000;97(20):10751-10756.
22. Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environ Health Perspect.* Jun 2003;111(8):994-1006.
23. Katzenellenbogen BS, Katzenellenbogen JA, Mordecai D. Zearalenones: characterization of the estrogenic potencies and receptor interactions of a series of fungal beta-resorcylic acid lactones. *Endocrinology*. July 1, 1979 1979;105(1):33-40.
24. Pakdel F, Le Guellec C, Vaillant C, Le Roux MG, Valotaire Y. Identification and estrogen induction of two estrogen receptors (ER) messenger ribonucleic acids in the rainbow trout liver: sequence homology with other ERs. *Mol Endocrinol.* January 1, 1989 1989;3(1):44-51.
25. White R, Jobling S, Hoare SA, Sumpter JP, Parker MG. Environmentally persistent alkylphenolic compounds are estrogenic. *Endocrinology %R 10.1210*/en.135.1.175. July 1, 1994 1994;135(1):175-182.
26. Baker ME. Evolution Of Regulation Of Steroid-Mediated Intercellular Communication In Vertebrates - Insights From Flavonoids, Signals That Mediate Plant Rhizobia Symbiosis. *J Steriod Biochem Mol Biol*. Mar 1992;41(3-8):301-308.
27. Gyorgypal Z, Kondorosi A. Homology Of The Ligand-Binding Regions Of Rhizobium Symbiotic Regulatory Protein Nodd And Vertebrate Nuclear Receptors. *Mol Gen Genetics.* Apr 1991;226(1-2):337-340.
28. Fox JE. Chemical communication threatened by endocrine-disrupting chemicals. *Environ Health Perspect.* May 2004;112(6):648-653.
39. Wynne-Edwards KE. Evolutionary biology of plant defenses against herbivory and their predictive implications for endocrine disruptor susceptibility in vertebrates. *Environ Health Perspect.* May 2001;109(5):443-448.
30. Baker ME. Endocrine Activity Of Plant-Derived Compounds - An Evolutionary Perspective. *Proc Soc Exp Biol Med*. Jan 1995;208(1):131-138.
31. Li JM, Biswas MG, Chao A, Russell DW, Chory J. Conservation of function between mammalian and plant steroid 5 alpha-reductases. *PNAS*. Apr 15 1997;94(8):3554-3559.
32. Challem JJ. Toward a new definition of essential nutrients: is it now time for a third `vitamin' paradigm? *Med Hypotheses*. 1999;52(5):417.
33. Martinez-Valverde I, Periago MJ, Ros G. [Nutritional importance of phenolic compounds in the diet]. *Arch Latinoam Nutr*. Mar 2000;50(1):5-18.
34. Manthey JA, Buslig BS. *Flavonoids in the living system.* New York: Plenum Press; 1998.
35. Williamson EM. Synergy and other interactions in phytomedicines. *Phytomedicine.* Sep 2001;8(5):401-409.
36. Gilbert B, Alves LF. Synergy in plant medicines. *Curr Med Chem.* Jan 2003;10(1):13-20.
37. Singer CJ, Underwood EA. *A short history of medicine*. 2d ed. Oxford: Clarendon Press; 1962.
38. Spelman K. Philosophy in Phytopharmacology: Ockham's Razor vs. Synergy. *J Herbal Pharmacotherapy*.2005;5(2):31-47.
39. Spelman K, Duke JA, Bogenschutz-Godwin MJ. The Synergy Principle in Plants, Pathogens, Insects, Herbivores and Humans. In: Kaufman PB, ed. Natural products from plants. Vol 2e. Boca Raton, Fla.: CRC Press; 2006:475-501.
40. Vickers A. Botanical medicines for the treatment of cancer: rationale, overview of current data, and methodological considerations for phase I and II trials. *Cancer Invest.* 2002;20(7-8):1069-1079.
41. Cech NB. Rigorous science for the study of holistic herbal medicine: Challenges, pitfalls, and the role of mass spectrometry. Paper presented at: 226th ACS National Meeting; September 7-11, 2003; New York, NY.
42. Keith CT, Zimmermann GR. Multi-target lead discovery for networked systems. *Current Drug Discovery*. September 23 2004:19-23.
43. McCarty MF. Proposal for a dietary "phyttochemical index". *Med Hypotheses*. 2004;63(5):813-817.