STANDARDIZATION RANT

Stephen Harrod Buhner

Materialism contains a prodigious depth that materialists are a long way from fully grasping.

Ernst Junger

To understand Gaia, we must let go of the mechanistic compartmentalizing conditioning imposed on us since childhood by our society. From an early age nearly all Westerners (and especially young scientists) are exposed to the concept that life has come about due to the operation of blind, meaningless laws of physics and chemistry, and that selfishness underpins the behaviour and evolution of all plants and animals. A child's mind becomes totally ensnared by this style of intellectuality, so that the intuitive, inspirational qualities of the mind are totally ignored. The mind's intuitive ability to see each part of nature as a sub-whole within the greater wholes is destroyed by this sort of education. The result is a totally dry, merely intellectual ecology, not a genuine perception of the dynamic power,

creativity, and integration of nature.

Stephan Harding

We have been trained to think of patterns, with the exception of those of music, as fixed affairs. It is easier and lazier that way but, of course, all nonsense. In truth, the right way to think about the pattern which connects is to think of it as **primarily** *a dance of interacting parts.*

Gregory Bateson

Despite the multiple, synergistic actions of the scores of other constituents in *Salvia miltiorrhiza* reductionists (such as the developers of The Herbal Medicines Compendium) are pushing for standardization of the herb, insisting that it contain a minimum of 0.1 percent tanshinone IIA, 0.2 percent total tanshinones (i.e., the sum of cryptotanshinone, tanshinone I, and tanshinone IIA), and 3.0 percent salvianolic acid B. As has been commonly known for more than 30 years, this approach fails to understand the complex reality of herbal medicines. In some instances this approach (e.g. milk thistle seed, ginkgo) is legitimate, but *only* when it is applied to the final product, especially they are used to treat acute conditions.

In the case of most plants however, including that of *Salvia miltiorrhiza*, the approach is flawed and for the same two reasons. First, there is an inaccurate understanding (which is not correctable) of the true numbers of constituents in the plants. Second, there is absolutely no knowledge nor recognition of the importance of the synergistic interactions between the constituents that *are* known.

While it is true that plants tend to create some constituents that produce marked results when used as isolated chemicals, when these same constituents are examined *in situ* more subtle elements of the reality in which we are embedded begin to emerge. To truly understand medicinal plants, it is fundamental to recognize that none of these constituents were developed by plants in isolation. They were generated in the midst of a spectrum of chemicals and behaviors while the plant was immersed in an ecological scenario to which it was responding. The constituent being viewed in isolation is *in reality* an expression of a complicated chemical communication in which *none* of the other parts are irrelevant to its actions. Even a simple look from a minimally broader perspective reveals errors in the "active constituent" approach. For instance. . .

Berberine, a strong plant antibacterial, is very active against a large number of resistant and non-resistant bacterial organisms. It is considerably more active, however, due to the presence of another constituent in goldenseal (and other

berberine-containing plants), 5'-methoxyhydnocarpin. The constituent 5'-MHC is in fact a multidrug pump inhibitor. It reduces or eliminates the ability of resistant staphylococcus bacteria to eject, from inside its cellular membrane, antibiotic substances that might harm them.

In response to plant bacteria generating resistance to berberine (millennia ago), the plants created a new chemical, 5'-MHC, which has no known function other than to act as an efflux inhibitor, enabling the berberine to remain effective.

> *Plants can't run, they can't hide, they can't call a doctor, or go to the hospital. They have to make their own medicines and they are incredibly good at it, much better than we will ever be. They have had, after all between 170 and 300 millions years of practice. We have had less than a century.*

Goldenseal's creationg of 5'-MHC is one of the reasons the plant is such an effective antibacterial herb in the treatment of resistant infections of the GI tract. However, standardization acolytes never speak of standardizing the plant for this compound, indicating a serious lack of understanding on their parts about the true nature of herbal medicines. And, at the same time, ultimately creating obvious

downstream usage problems similar to those that have accompanied the unrestrained use of pharmaceutical antibiotics in the absence of any real understanding of bacteria.

Compounds such as 5'-MHC are why plants are often more effective than single constituents in treating disease conditions. If goldenseal were standardized for berberine content and if, for some reason, the plant being standardized contained no 5'-MHC, its effectiveness as an antimicrobial would be significantly diminished. Yet 5'-MHC is not considered important enough as a standardization marker since it is not an “active” constituent. Numerous other compounds, rarely recognized by reductionists, are essential for the “active” constituents to actually be effective in practice.

And this is only a tiny glance at a very complex phenomenon. Some compounds in plants, for example, have no known function in the plant other than to reduce the side effects of more pharmacologically active constituents. Plants intentionally generate side-effect-ameliorating compounds for themselves in order to allow them to utilize their potent antimicrobial compounds without suffering the side effects so often experienced by people who use pharmaceuticals. (They are actually a lot smarter than we are.) These compounds are not, and most likely never will be, considered an active constituent. They aren’t sexy enough. They just

help. Nevertheless, without these other compounds, the “active” compounds would not work nearly so well. In some instances they would not work at all.

Such complexities are hardly limited to the berberine plants. For instance, the anticonvulsant actions of the kava lactones in *Piper methysticum* (i.e., yangonin and desmethoxyyangonin) are much stronger when used in combination with other kava constituents that are generally considered irrelevant in any standardization missives. As well, concentrations of yangonin and another lactone, kavain, are much higher in the brain when the *whole plant* extract is used instead of the purified lactones themselves. In other words, some of the other constituents in kava help move the bioactive lactones across the blood/brain barrier and into the brain where they will do the most good. Blood plasma concentrations of kavain is reduced by 50 percent if the purified compound is used rather than an extract of the plant itself.

Plant compounds in *Isatis tinctoria*, a potent antiviral and antiinflammatory herb are also highly synergistic. Tryptanthrin, a strong antiinflammatory in the plant possesses very poor skin penetration capacity however, when the whole plant extract is applied to the skin, penetration of tryptanthrin is significantly enhanced. In other words, applying a salve of pure tryptanthrin to the skin, despite its anti-inflammatory nature, won’t do you much good. But if you make the plant

itself into a salve, the tryptanthrin moves rapidly into the skin and helps reduce skin inflammation. Tryptanthrin is, unfortunately, the compound that is considered important to standardize in the plant. No notice is taken of the other, and rather crucially important, constituents that facilitate skin penetration.

Artemisinin is much more active against malarial parasites if administered with the artemisia flavonoids artemetin and casticin that are normally found in the whole plant extracts. The additional flavones chrysoplenetic-D and chrysospenol also act as potent synergists for the so-called “active” compounds. These latter two compounds are also P-glycoprotein inhibitors thus facilitating the movement of artemisinin and the plants other constituents through the intestinal membrane and into the blood, significantly enhancing the actions of artemisinin in the body. One of the real problems with the use of pure artemisinin is that it does not moves easily across the intestinal membrane. In consequence, lower levels of the drug actually reach the areas that need it. As well, by removing the isolated constituent from the plant and marketing it as a malarial drug (to combat drug-resistant malarial organisms) other constituents in plant that specifically act to inhibit resistance mechanisms in the malarial protozoa are lost. This is why the protozoa worldwide are developing resistance to the drug now that it has been pharmaceuticalized for profit.

Regrettably, the medical reductionists involved in herbal medicine throughout the Western world, and most especially in the United States, have little cognizance of these kinds of complexities. Their view is just too linear. And that linear view does not allow them to understand that plant medicines are in fact so complex that a linear approach will never produce reliable control over medicinal activity in herbal medicines.

A simple look at some of the other constituents in *Salvia miltiorrhiza* shows just how inept the reliance of the Herbal Medicines Compendium on such standardization criteria is when it comes to actually producing plants that are medicinally reliable. As just a couple of examples. . .

While the reductionists want to standardize the plant for salvianolic acid B (SaB), there are in fact, at present count, salvianolic acids A, C, D, E, F, G and K to take into account. These other salvianolic acids have highly synergistic effects with SaB and, in actuality, they form a complex interactive grouping that, together, produce the following medicinal effects: potent antioxidant actions, myocardial ischemic protection, antithrombotic activity, antifibrotic effects, inhibition of diabetes and its complications, and neuroprotection in the brain and CNS. Salvianolic acid A, for example, enhances the action of the herb in the treatment of Alzheimer's disease. It inhibits amyloid beta self-aggregation and

disaggregates pre-formed fibrils, reduces metal-induced aggregation by chelating metal ions, and blocks the formation of ROS in the brain. The combined salvianolic compounds reduce leukocyte-endothelial adherence, inhibit inflammation, reduce metalloproteinase expression from aortic smooth muscle cells, and indirectly modulate immune function. These are some of the root reasons that the plant is so potent for heart disease. The isolated constituents, including SaB, are not as effective when used without the rest of the related compounds. And this still does not look at the effects of caffeic acid and its other derivatives on physiology.

Caffeic acid (and many of its non-salvianolic acid derivatives) produce a number of important biological activities including antioxidant, anti-eschemia reperfusion, antithrombosis, antihypertension, antifibrosis, antivirus and antitumor actions. These actions are highly synergistic with the salvinolic acid compounds *and* the tanshinones (which possess strong antitumor actions among other things). The complex effects of the plant on circulatory disorders and heart disease comes from no isolated compound (SaB) but from the sophisticated interactivity and synergy of *all* the salvinolic acids *and* the caffeic acid and its derivative *and* a great many other compounds not elucidated here.

And, finally, it should be recognized that the diterpenoid tanshinones

tanshionone IIA and cryptotanshinone are poorly bioavailable *unless* they are ingested along with the rest of the compounds in the plant. This includes the entire complex of phenolics and diterpenoids. Transfer across the GI tract membrane is 8 to 10 fold higher *if* the other constituents are present. In other words, they act as P-glycoprotein inhibitors, allowing the "active" substances to bypass the GI tract efflux pumping mechanisms. As Kim, et al, comment, "there are other unknown compounds in the SM extract that have a synergistic effect with tanshinone." **(1)** And these "unknown" compounds enhance the effects of that constituent as well as facilitating its movement across the GI tract membrane.

To be clear, the exact identity, combination, and amounts of those other constituents, and the ones that most efficiently inhibit the P-glycoprotein response, has not been determined – and they probably never will be. The complexity of the synergy of so many compounds makes it impossible to actually identify what is doing what, what is crucial and what, if anything, is not. As Gao, et al, put it, "since there are more than twenty active compounds in Danshen, it is very difficult to predict that one compound will act the same way when it is combined with other compounds." **(2)**

Protocatechuic aldehyde (PAL), another compound in the plant, generally considered to be irrelevant, and very much not a part of the standardization

movement, has important impacts on the pharmacokinetics of the plants other compounds. Chang, et al, comment that "complex, extensive pharmacokinetic interactions were observed among the major water-soluble constituents in the Danshen injection. The content variation of PAL had the most significant effect on the pharmacokinetic behaviors of the other major constituents." **(3)**

Linearity, and the use of an A then B causality approach, begins to fail once you move past three interacting components. It is useless when dealing with whole systems . . . that is, if you want to gain any reliable understanding of what is actually occurring in living organisms. Actually, it is not even all that effective when dealing with simple physics. As Michael Crichton once put it. . .

> *Do you realize the limits of our understanding? Mathematically, we can describe two things interacting, like two planets in space. Three things interacting – three planets in space – well, that becomes a problem. Four or five things interacting, we can't really do it. And inside the cell, there's* one hundred thousand *things interacting.* **(4)**

And to take that a bit further, inside the plant there are many more than one hundred thousand *cells* interacting. To reduce the plant compounds to one or two

or three “active” constituents (and to ignore all the other constituents as irrelevant) is nineteenth century thinking. It is based on inaccurate models of the world. The ramifications for the health of living systems of that thinking surrounds all of us every day of our lives – in the environmental devastation of our planet, in the increasing failure of our medical model. It does not present a pretty picture.

When working with plant medicines we are working with complex, nonlinear, self-organized living systems. Neither they, nor their constituent elements, can be viewed, or understood, in isolation. This is because at the moment of self-organization complexities that can’t be found by the reductive mind come into play. Here is Michael Crichton again . . .

> *It did not take long before the scientists began to notice that complex systems showed certain common behaviors. They started to think of these behaviors as characteristic of all complex systems. They realized that these behaviors could not be explained by analyzing the components of the systems. The time-honored scientific approach of reductionism – taking the watch apart to see how it worked – didn’t get you anywhere with complex systems, because the interesting behavior seemed to arise from the spontaneous interaction of the*

components. **(5)**

In other words, a complex synergy of interactions comes into play and it has nothing to do with "active" constituents. Every part is "active," every part is essential. So . . . your brain may be important but if you lose your heart, pancreas, kidneys, and intestinal tract it will do you no good. All components are crucial, none are extraneous, none are more important.

A reductive reliance on a few compounds and an assertion that those compounds will produce the effects that the plant is noted for (in two thousand years of practice, the length of *Salvia miltiorrhiza* use in China) is misleading in the extreme and will result, in the long run, in plant medicines that do not in fact do what they are being promoted as doing.

A More Accurate Map

To be clear, the constituents that appear to the reductive mind as *the* active constituents should, in fact, be more properly thought of (if you must think this way) as analogous to plants that are thought of as "strong interactors" in ecosystems.

> *A plant's interior, viewed by itself, reveals an ecosystem in miniature. Its internal structure and relationships are a fractal pattern on a smaller scale of the larger structure and relationships we see in the larger scale of an ecosystem. And that ecosystem is itself only a reflection of the even larger scale of the Gaian system of which it is a part.*

To understand the complexity of plant chemicals acting as medicinals for us, we have to see them as an expressive element of a holistic system. To better understand the inextricable intertangling of plant chemicals within the individual plant body ecosystem, it helps to understand just how ecosystems really *are*.

As researchers Eoin O'Gorman and Mark Emmerson observe, these "natural communities are finely structured, displaying properties that promote stability despite complexity." As this pertains to plant compounds, the entire complex of chemicals have to be seen as part of a finely structured community of chemicals that displays certain properties when viewed as a whole. And those properties are essential to understand when approaching the plant as a healing herb. As O'Gorman and Emmerson continue . . . there is a "nonrandom arrangement of interaction strengths" between the living subunits of the system, that "promotes

community level stability." **(6)** "Nonrandom" here meaning that there is something more than mere chance that is occurring; there is *meaning* in the system's subunits' associations. Further, the concept of interaction strengths is crucial. Medical herbal reductionists tend to see *only* the active compound, that is they focus on what they consider to be the chemical that is most expressive of interaction strength. In typical American fashion they focus on strength in isolation, not the more essential community interrelationships and interactivity.

In a forest ecosystem, as an example, the trees act as what are called "strong interactors," other plants in the system are considered to be "weak" interactors. "Complex ecological networks," as O'Gorman and Emmerson comment, "are characterized by distributions of interaction strengths that are highly skewed, with many weak and a few strong interactors present." **(7)**

O'Gorman and Emmerson conducted experiments where they removed strong interactors from complex ecosystems and found, not surprisingly, that it "produced a dramatic trophic cascade" in the system. That is, the system immediately experienced a phase change, going from a state of high complexity to one much less sophisticated. They comment that . . .

Natural ecosystems are a complex tangle of interactions, with 95% of

> *species typically no more than 3 links apart. This natural complexity persists against the odds because it is governed by fundamental laws and principles that confer stability. One of the most widely accepted of these principles is the pattern of species interactions. There is a tendency to consider biodiversity in terms of taxonomic identities or functional roles, yet every species can be considered as a node in a complex web of interactions. Each node contributes to the overall balance of interactions, whether it is a strong or weak interactor. Given the highly interconnected nature of food webs, any loss of biodiversity could contribute to a ripple effect, changing the pattern of interaction strengths and thus threatening to unbalance the stability conferred by this pattern.* **(8)**

The loss of a strong interactor in such circumstances was found to "have effects disproportionally large, relative to their abundance." But further . . .

> *Fluctuations in population biomass are commonplace, and compensatory actions among species can maintain aggregate biomass. The changes in primary and secondary production shown*

> *here are community-level responses however, suggesting that the insurance effect of community diversity is not sufficient to overwhelm the impacts of [removing] strong interactors. Trophic cascades such as these can alter energy flow, community composition, and habitat provision, and lead to secondary extinctions.* **(9)**

In other words, while the strong interactors remain relatively stable over long time lines (they do change, but very slowly), the weak interactors are in constant flux around them, increasing or decreasing their density, sometimes moving out, others moving in, as the environment in which the system is located changes its nature and needs.

> *This is also true of the chemical composition of medicinal plants. Chemical innovations flow into and out of the plant over time in response to environmental inputs. There is no such thing as a "standard" chemical profile of a plant medicine, something that drives technological medicalists crazy. Every plant's chemical profile is different from season to season and from location to location. And it is supposed to be that way. If, prior to goldenseal's innovation of*

> *5'MHC, the plant had been standardized for a particular chemical profile, once bacteria developed resistance, the plant would have remained standardized for that profile. It would also have become highly ineffective in use. Evolution is ongoing; it has not ended. The diseases we encounter are altering themselves all the time. They possess tremendous genetic flexibility. However, so do the plants. They alter their genome and their chemical relationships right along with the bacteria. The alterations in plant chemical profiles are essential for them to remain functional medicines.*

The numbers and kinds of the weak interactors in an ecosystem changes over time. This keeps the system homeodynamis intact. As the system responds to perturbations, the particular species that are present shift their numbers, their locations and, sometimes, they move on and others take their place. New weak attractors, with different capacities, and chemical production abilities, continually flow through the system over very long time lines in order to keep the system adaptable to altered environmental circumstances. These movements, called *asynchronous fluctuations* in system stability, are actually an element of the system remaining close to the boundary of self-organization. As new plants move

into the system, they then *synchronize* their actions with the rest of the links in the system, much the same way human beings do when two people begin to walk together. Out of this synchronicity come patterns of self-organization that cannot be developed any other way. The same is true of the plant chemicals that exist within a single plant medicine.

The plant responds to the environmental scenario in which it lives by producing a complex of compounds that they utilize for a very large number of complex behaviors. Among these is their own, and their ecosystem's healing. The complex of compounds alters its nature from moment to moment to moment in response to environmental inputs. The plants, and this is important, *never* produce the same complex of compounds in every location in which they grow and in any year in which they grow. As bacterial dynamics shift, the plants, *worldwide*, shift their chemical production and constituent spectrum in response.

While the removal of the "strong interactors" in an ecosystem has immediate, detrimental effects on the system, causing its complexity to collapse into a simpler state, the removal of "weak interactors" also has extremely deleterious effects. O'Gorman and Emmerson found that while removal of "weak" interactors did not have as extreme an effect in the short run, those plants play a crucial stabilizing role in the system. In other words, the strong interactors

generate potent effects on the system but the weak interactors modulate those effects toward specific outcomes. More, without the weak interactors, if they are removed, the ecosystem fails. As they note, "Crucially, when strong interactors were present in the community without a sufficient number of weakly interacting species around them" the ecosystem destabilized. **(10)** Weak interactor loss led to "reductions in temporal and spacial stability of ecosystem process rates, community diversity, and resistance." **(11)**

More dynamically (and more accurately), weak and strong interactors can thought of as "links" (as some researchers have it) rather than "actors" in a communicatory network.

> *Though O'Gorman and Emmerson's concept of "nodes" is even better. A node is a point of concentration of matter, where the gravity well becomes strongest, and that "well" immediately generates "gravitational" links to all other nodes in the system. Everything is then connected in a web of stronger and weaker fields – what chaos theory aficionados refer to as strong and weak attractors. They are always to be found in nonlinear systems irrespective of their nature, this includes medicinal plants.*

In all healthy ecosystems, there exists a network of a few strong attractors embedded in a majority field of weak attractors. The strong exert more easily seen effects but they are held in a tightly coupled web of weak attractors that modulate their actions. This same pattern exists within herbal medicines. To understand herbal medicines, for true sophistication to occur, an understanding of this pattern is essential.

The whole interwoven network, with just this combination of attractors, produces a tremendously adaptable ecorange or zone in which each part contributes essential responses that, together, modulate the system's successful adaptation to perturbations. It is not just what species are present that is important, but rather the species' *behaviors*, their interactions with the other species in the network, that is crucial. All together, they make a *community* in which every organism's actions and presence are crucial to continued functionality. To slightly restate . . .

> *The whole interwoven plant network, with just this combination of chemicals, produces a tremendously adaptable medicinal plant in which each part contributes essential responses that, together,*

> *modulate the system's successful adaptation to the treatment of disease conditions. It is not just what chemicals are present, but rather the chemicals' behaviors, their interactions with the other chemicals in the network, that is crucial. All together, they make a community in which every chemical's actions and presence are crucial to continued functionality.*

To give this even a bit more definition, here is a relevant quotation from Iain McGilchrist . . .

> *Water just falls in the way that water has to, and the landscape resists its path in the way it has to. The result of the amorphous water and the form of the landscape is a river. The river is not only passing across the landscape, but entering into it and changing it too, as the landscape has "changed" and yet not changes the water. . . . The river does not exist before the encounter. Only water exists before the encounter, and the river actually comes into being in the process of encountering the landscape.* **(12)**

In essence, they make each other. This same dynamic occurs in the creation of plant medicines inside plants. The world touches the plant, the plant touches back, and the chemicals that are produced are something that emerges out of that touching. The chemical dynamics in such a co-evolved community of chemicals inside a plant are so tightly coupled that they can't legitimately be viewed in isolation from each other. Or as Masanobu Fukuoka once put it

> *The living and holistic biosystem that is nature cannot be broken down or resolved into its parts. Once broken down it dies. Or rather, those who break off a piece of nature lay hold of something that is dead, and, unaware that what they are examining is no longer what they think it to be, claim to understand nature. . . . Because [man] starts out with misconceptions about nature and takes the wrong approach to understanding it, regardless of how rational his thinking, everything winds up all wrong.* **(13)**

To successfully adapt to the changes now present in our world, the old linear models, of necessity, must be abandoned. They are the source of many of the problems we face, including the emergence of stealth and resistant pathogens. The

world, and many of the people within it, are changing. They see the writing on the wall. We in the United States, in the Western nations, must change as well.

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