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Editorial

CAM, *eCAM*, Bioprospecting: The 21st Century Pyramid

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CAM and a Challenging Pyramid

Pyramids touch us in many ways. According to a popular definition which most of us will understand, a pyramid is a stone structure with a flat (usually) square base and with sloping sides that meet at the top, especially built by the ancient Egyptians as a tomb or by the Aztecs and Mayas as a platform for a temple, raised for edification. Then there are food pyramids that propose to solve the obesity epidemic. How does such a definition fit within the confines of complementary and alternative medicine (CAM), *eCAM* and bioprospecting? What is more, how do we move the ancient and familiar definition to signify the 21st century pyramid and one that is relevant to CAM? At the moment, I do not yet have data on the ancient practices of the Egyptians nor the Aztecs and Mayas as their approaches relate to CAM or to *eCAM*. We do know about historical practices of similar ages in history from Japan and Taiwan, just to cite two recent examples of rigorous presentations (1,2). The relevant CAM pyramid that I will detail could continue to be a hard impenetrable structure unless we are willing to in effect dismantle it, to deconstruct it from bottom up from those points that gird it to unfavorable approaches that are less acceptable in the evidence-based approach to CAM.

A pyramid has recently been published in *Nature Immunology* entitled: 'Complementary and alternative medicine: assessing the evidence for immunological benefits' (3). In this pyramid, there is a hierarchy of evidence. Information regarding the efficacy and safety of any clinical approach, including those of CAM, spans a continuum that ranges at the base all the way to the peak or the pyramid's point, from anecdotes and retrospective studies to small randomized, controlled trials (phase II clinical trials) and large randomized, controlled trials (phase III clinical trials). In my opinion, this paper and its contents, and the pyramid represent a seminal tribute to the role of the immune system in CAM.

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NCCAM and CAM

At the national level CAM is becoming increasingly more prominent in the scientific establishment especially in immunology (3). There seems to be a focus on the innate immune system especially the ubiquitous natural killer (NK) cells (4,5). In terms of a comparative coverage of NK cells and CAM, clearly that by Takeda and Okumura (4) is more recent, thorough and extensive. Two of the tables, for example, cover the known NK receptors and NK activation inducing CAM. Some of the figures are equally informative and elegant. Figure 1, for instance, treats NK cells in tumor surveillance, relationships to cytokines and the critical role they play in the inhibition of angiogensis by tumor development. In Figure 3, there is an all-encompassing coverage of immune system control by the autonomic nervous system where there is depicted the intimate cross-talk between NK cells and their control by the autonomic nervous system.

In 1998, the National Center for Complementary and Alternative Medicine (NCCAM) was established by the US Congress at the National Institutes of Health (Bethesda, MD) to investigate CAM modalities rigorously in order to determine which are beneficial and worthy of further consideration for mainstream practice. Among the many CAM approaches that warrant careful investigation are those that claim to sustain, restore or boost immunity. In this review, Goldrosen and Strauss (3) covered the following topics: use of CAM, regulation of CAM, risks of CAM use, clinical trials of CAM, CAM and immunity, dietary supplements and mind–body approaches. In Table 1, they cover some ongoing, large phase III trials of CAM modalities; in Table 2 some CAM modalities that might mediate their effects through the immune system; and in Table 3 some herbal products that modulate immune responses. Their Box 1 warns of the challenges of conducting clinical trials of CAM.

Figure 1 treats CAM domains and some of the most common examples; a glossary defines nearly 20 such CAM practices. What about the aforementioned CAM pyramid? Depicted in Figure 2 there is a hierarchy of evidence. This CAM pyramid begins at the base with the least desirable of approaches such as anecdotes and case studies which *eCAM* is being careful not to publish unless backed by strong evidence and clear indications of a scientific approach (6). The pinnacle or top of the pyramid is represented by large randomized clinical trials. In ancient mythical terms this height is a tribute to something higher!

Chemists, CAM and Kampo

This is more from the viewpoint of the biologist. Now it seems that chemists are becoming involved in this international CAM movement. Even popular coverage is an everyday occurrence (7,8). Recently Professor Haruki Yamada, a member of the Editorial Board of *eCAM*, informed me of his invitation to lecture at a recent meeting of the American Chemical Society held in San Diego, CA. Of enormous special interest for CAM in general and of course *eCAM* was the American Chemical Society's Newsletter (9). In it there is substantial credit offered to the entire sweep of CAM. Topics included: what is CAM, the top 10 CAMs, how can chemists help? CAM chemical prospecting and drawing a baseline. It is obvious why Professor Yamada was appropriate as an invited participant at this meeting because of his own work that promises an approach to CAM using the evidence-based approach and which has a distinct analytical chemical orientation.

According to Yamada (10) 'the efficacy of Kampo medicines cannot be explained by the pharmacological activity of just one active ingredient, and several active ingredients may affect the immune, endocrine, and neural systems of the whole body by several combination effects such as synergistic and or antagonistic effects'. Some of these active ingredients also work through structural modifications to the actual active compounds by endogenous factors such as intestinal bacteria or gastric juice. Because standardization of natural medicine is very important, indicator compounds, hopefully active ingredients should control and fingerprint it using three-dimensional HPLC. Analysis of pharmacological activity related to clinical effects by *in vitro* and *in vivo* biological methods might also be very important to obtain reproducible effects of herbs. In one important figure, a three-dimensional HPLC pattern of one Kampo formula, Juzen-taiho-to (SI-Quan-Da-Bu-Tang in Chinese), is shown (11). Juzen-taiho-to has been used for the treatment of patients recovering from surgery or suffering from diseases by promoting the improvement of their debilitated general condition. Juzen-taiho-to also has been administered to patients with anemia or anorexia. The clinical effects observed suggest that the formula enhances immune responses and improves the functioning of the hematopoietic systems. Since it is possible to prepare HPLC fingerprinting patterns based on the composition of the constituents in each formula, this method is useful for the standardization of not only Kampo medicines but also natural medicines.

Now let us put together the two approaches: biologists (immunological focus of Goldrosen and Strauss) and those of the chemists (Kampo of Yamada) and bioprospecting (Muller and Cooper). As mentioned earlier and as the following reports will confirm, there is a preponderance of focus and emphasis on plants and little or no coverage of natural products from animals. Yet there is ample evidence as we have published recently (5,13–15). Thus bioprospecting is a new frontier for CAM!

Bioprospecting: Invertebrates and Natural Products

From Muller's extensive work, we see a compendium of excellent very supportive work for the real existence of useful products from animals. Examples of compounds that are already in medical use [inhibition of tumor/virus growth (arabinofuranosyl cytosine and arabinofuranosyl adenine)], or are being considered as lead structures [acting as cytostatic and anti-inflammatory secondary metabolites (avarol/avarone), causing induction of apoptosis (sorbicillactone)] or as prototypes for the interference with metabolic pathways common in organisms ranging from sponges to humans [modulation of pathways activated by fungal components (aeroplysinin), inhibition of angiogenesis (2-methylthio-1,4-napthoquinone), immune modulating activity (FK506)] are discussed in this study. In addition, bioactive proteins from sponges are listed [antibacterial activity (pore-forming protein and tachylectin)]. Finally, it is outlined that the skeletal elements—the spicules—serve as blueprints for new biomaterials, especially those based on biosilica, which might be applied in biomedicine. These compounds and biomaterials have been isolated/studied by members of the German Center of Excellence *BIOTEC*marin. The citation of this prime example of what bioprospecting has yielded has been derived from careful analyses of products synthesized and secreted by sponges that are multicellular members of the second animal phylum by classification, the Porifera.

CAM and Earthworm Natural Products

If we turn now to more complex multicellular species where there is an enormous amount of information that is several centuries old, witness the literature pertaining to the earthworm's healing properties (16). Earthworm lytic molecules are antimicrobial and may prove useful as antibacterial agents and prophylatic molecules, an idea that is not far fetched since the discovery of antibiotics was serendipitous. Two molecules, lysenin and eiseniapore, depend to some extent on intracellular lipid trafficking mechanisms. In fact, trafficking dysfunction leads to disease development, such as Tangier disease and Neumann–Pick disease type C, or contributes to the pathogenesis of diseases such as Alzheimer disease and atherosclerosis. Lysenin reacts specifically with fibroblast membranes from patients with Niemann–Pick disease, a rather curious finding, but one that may have some clinical relevance (17). Thus specific binding of lysenin to sphingomyelin on cellular

membranes may prove to be a useful tool to probe the molecular motion and function of sphingomyelin in biological membranes, especially in an effort to explain the mechanism of lysis in earthworms. These results stress the need for concerted analyses of various lytic pathways that may be mediated by the earthworm immunodefense system. Both the products of sponges and those of other animals are of potential importance as great as those being exploited from plants. The goal for the future is successfully to introduce some of these compounds in the treatment of human diseases in order to raise public awareness on the richness and diversity of natural products that could be carefully harvested for the benefit of mankind. This is an example where the scientific approach presents solid evidence that certain molecules are ready for testing.

CAM and an Informative Triangle: A New Pyramid

Since for many scientists, entering the world of CAM has challenged long-established ways of looking at the world, I propose that for a moment we look at the pyramid in yet another way and watch as it transforms itself into a triangle. In its new form, the hierarchy disappears and we can see the balance of three separate elements and the relationships between these parts. The triangle delineates the balance that is at the core of many holistic medicines. One example of this is Olalde's triangle of health, introduced in our last issue of *eCAM*. He describes the triangle as a 'governing dynamic, that survival potential of any living system depended on enhancing the three constituents that structure its common denominator. These essential factors are energy, intelligence and organization—three sided but with no layering from bottom up. His hypothesis under this scope proposes that the survival potential (health) of every human being could be improved by a synergetic increase of any or all of these three factors because they were interdependent (18). To paraphrase Olalde, the basis for the hypothesis was the premise that the triangle's integrity constituted a reflection of the entropic status of the organism. This could then be enhanced by providing survival energy and information to the cells, furnishing negative entropy from herbs, to create an endogenous healing tendency within the body—called syntropy. This new view of an ancient structure points to an essential quality of scientific research, especially in the varied world of CAM: the ability to see the objects of our study as if we are seeing them for the first time. By so doing, we are able to re-think theories and hypotheses that have been long accepted, and have the courage to embark on a new search that will eventually lead to new and exciting healing modalities with a firm evidence base.

References

1. Suzuki N, Ohno S, Kamei T, Yoshiki Y, Kikuchi, Y, Okubo K et al. Complementary and alternative medicine in Japan. In Cooper EL, Yamaguchi N (eds). Complementary and Alternative Approaches to Biomedicine. Kluwer Academic/Plenum Publishers, 2004, 9–26.
2. Chen CF, Shum YC, Yang SP. The modernization of Traditional Chinese Medicine in Taiwan—past, present and future. In Cooper EL, Yamaguchi N (eds). Complementary and Alternative Approaches to Biomedicine. Kluwer Academic/Plenum Publishers, 2004, 35–42.
3. Goldrosen MH, Strauss SE. Complementary and alternative medicine: assessing the evidence for immunological benefits. *Nat Rev Immunol* 2004;4:912–21.
4. Takeda K, Okumura K. CAM and NK cells. *eCAM* 2004;1:17–27.
5. Cooper EL. Commentary on CAM and NK cells by Kazuyoshi Takeda and Ko Okumura. *eCAM* 2004;1:29–34.
6. Cooper EL. Complementary and alternative medicine, when rigorous, can be science. *eCAM* 2004;1:1–5.
7. Roberti P. Agopuntura e omeopatia per una medicine integrata: le medicine naturali dedicate alle donne. *Med Nat* 2005a;2:24.
8. Roberti P. Una nuova rivista sulla recerca EBM nelle mnc. *Med Nat* 2005b;2:24.
9. Gorder PF. Complementary and alternative medicine. *Chemistry* Winter 2005;25–29.
10. Yamada H. New scientific approach for natural medicine: examples of Kampo medicine. In Cooper EL, Yamaguchi N (eds). Complementary and Alternative Approaches to Biomedicine. Kluwer Academic/Plenum Publishers, 2004, 27–34.
11. Kiyohara H, Matsumoto T, Yamada H. Combination effects of herbs in a multi-herbal formula: expression of Juzen-taiho-to's immuno-modulatory activity on the intestinal immune system. *eCAM* 2004;1:83–91.
12. Müller WEG, Schröder HC, Wiens M, Perovic-Ottstadt S, Batel R, Müller IM. Traditional and modern biomedical prospecting: part II—the benefits: approaches for a sustainable exploitation of biodiversity (secondary metabolites and biomaterials from sponges). *eCAM* 2004; 1:133–44.
13. Cooper EL. Bioprospecting: a CAM frontier. *eCAM* 2005;2:1–3.
14. Cooper EL. Drug discovery, CAM and natural products. *eCAM* 2004c;1: 215–7.
15. Wallace RW. Drugs from the sea: harvesting the results of aeons of chemical evolution. *Mol Med Today*, 1997;3:291–9.
16. Cooper EL, Ru B, Weng N. Earthworms: sources of antimicrobial and anticancer molecules. In Cooper EL, Yamaguchi N (eds). Complementary and Alternative Approaches to Biomedicine. Kluwer Academic/Plenum Publishers, 2004, 359–390.
17. Yamaji A, Sekizawa Y, Emoto K, Sakuraba H, Inoue K, Kobayashi H et al. Lysenin, a novel sphingomyelin-specific binding protein. *J Biol Chem* 273:300–6.
18. Olalde Rangel JA, The systemic theory of living systems and relevance to CAM. *eCAM* 2005;2:13–8.