REVIEW

Integrative Nanomedicine: Treating Cancer With Nanoscale Natural Products

综合纳米医学：利用纳米级天然产物治疗癌症

Nanomedicina integral: Tratar el cáncer con productos naturales en nanoescala

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ABSTRACT

Finding safer and more effective treatments for specific cancers remains a significant challenge for integrative clinicians and researchers worldwide. One emerging strategy is the use of nanostructured forms of drugs, vaccines, traditional animal venoms, herbs, and nutraceutical agents in cancer treatment. The recent discovery of nanoparticles in traditional homeopathic medicines adds another point of convergence between modern nanomedicine and alternative interventional strategies. A way in which homeopathic remedies could initiate anticancer effects includes cell-to-cell signaling actions of both exogenous and endogenous (exosome) nanoparticles. The result can be a cascade of modulatory biological events with antiproliferative and pro-apoptotic effects. The Banerji Protocols reflect a multigenerational clinical system developed by homeopathic physicians in India who have treated thousands of patients with cancer. A number of homeopathic remedy sources from the Banerji Protocols (eg, *Calcarea phosphorica; Carcinosin*—tumor-derived breast cancer tissue prepared homeopathically) overlap those already under study in nonhomeopathic nanoparticle and nanovesicle tumor exosome cancer vaccine research. Past research on antineoplastic effects of nano forms of botanical extracts such as *Phytolacca, Gelsemium, Hydrastis, Thuja,* and *Ruta* as well as on homeopathic remedy potencies made from the same types of source materials suggests other important overlaps. The replicated finding of silica, silicon, and nano-silica release from agitation of liquids in glassware adds a proven nonspecific activator and amplifier of immunological effects. Taken together, the nanoparticulate research data and the Banerji Protocols for homeopathic remedies in cancer suggest a way forward for generating advances in cancer treatment with natural product–derived nanomedicines.

摘要

对全世界的综合临床医生和研究人员来说，针对特定癌症找到更安全有效的治疗方法一直是一项严峻的挑战。 一项新兴战略是采用纳米结构形式的药物、疫苗、传统动物毒液、草药和保健食品剂进行癌症治疗。 针对传统顺势疗法药物纳米颗粒（NP）的一项近期发现结果，在现代纳米医学与替代性干预战略之间又新发现了一个共同点。 顺势疗法启动抗癌作用的方式包括外源性和内源性（外泌体）纳米颗粒的细胞间信号活动。 这一结果可能是调节生物活动与抗增殖作用和细胞凋亡作用之间产生的级联反应。 Banerji 实验方案反映了印度顺势疗法医生在治疗了数以千计的癌症患者之后制定的多世代临床系统。 许多源自于 Banerji 实验方案的顺势疗法（如，磷酸钙；癌素—采用顺势疗法从肿瘤中衍生制备的乳腺癌组织）与非顺势疗法纳米颗粒和纳米囊泡肿瘤外泌体癌症疫苗研究中所研究的疗法存在共同之处。 针对纳米形式的植物提取物（如，商陆属、断肠草属、白毛莨属、金钟柏属和芸香属）抗肿瘤作用以及同类原材料的顺势疗法潜能进行的过往研究表明，二者之间还存在其他重要的共同之处。 研究人员从搅动玻璃器皿中液体所释放出的产物中一再发现二氧化硅、硅和纳米硅，为免疫学反应又新找到了一个经证实的非特异性催化剂和放大剂。 综合起来，对癌症的顺势疗法来说，纳米颗粒研究数据和 Banerji 实验方案表明，采用源自于天然产物的纳米医药治疗癌症是推动癌症治疗取得进展的一种方式。

SINOPSIS

Encontrar tratamientos más seguros y más eficaces para cánceres específicos sigue siendo un desafío significativo para los médicos integrales e investigadores en todo el mundo. Una estrategia emergente es el uso de formas nanoestructuradas de fármacos, vacunas, venenos animales tradicionales, hierbas y agentes nutracéuticos en el tratamiento del cáncer. El reciente descubrimiento de las nanopartículas en medicinas homeopáticas tradicionales aporta otro punto de convergencia entre la nanomedicina moderna y las estrategias intervencionistas alternativas. Una manera en la que los remedios homeopáticos podrían iniciar efectos anticancerígenos incluye acciones de señalización entre células de nanopartículas exógenas y endógenas (exosoma). El resultado puede ser una cascada de acontecimientos biológicos moduladores con efectos antiproliferativos y proapoptóticos. Los protocolos de Banerji reflejan un sistema clínico multigeneracional desarrollado por médicos homeopáticos en la India que han tratado a millares de pacientes con cáncer. Un número de fuentes de remedios homeopáticos de los protocolos de Banerji (p. ej., calcárea fosfórica; carcinosina, tejido derivado del tumor de cáncer de mama preparado homeopáticamente) se solapan con aquellos estudiados en la investigación de la vacuna para el cáncer de exosomas tumorales nanovesiculares y nanopartículas no homeopáticas). Anteriores

investigaciones sobre los efectos antineoplásicos de nanoformas de extractos botánicos como la Phytolacca, Gelsemium, Hydrastis, Thuja y Ruta así como sobre la potencia de los remedios homeopáticos derivados de las mismas clases de materiales de origen sugieren otras coincidencias importantes. El descubrimiento replicado de la liberación de silicio, silicona y nanosilicio de la agitación de líquidos en cristal añade un activador inespecífico probado y un amplificador de los efectos inmunológicos. En conjunto, los datos de la investigación de nanopartículas y los protocolos de Banerji de remedios homeopáticos en el cáncer sugieren un camino a seguir para avanzar en el tratamiento del cáncer con nanomedicinas derivadas de productos naturales.

INTRODUCTION

The purpose of this article is to provide an overview of natural product nanomedicine for cancer treatment as a foundation for understanding the more than 200-years-old complementary and alternative medicine (CAM) system of homeopathy. Historically, various homeopaths have reported successful treatment of patients with cancers using natural product–derived medicines.[1-4] Main topics addressed here are (1) the rationale for using nanoscale forms of natural products in cancer treatment; (2) the evidence for homeopathic medicines as nanoparticle-based natural products; (3) data on studies of homeopathy in cancer treatment; and (4) the Banerji Protocols as a promising clinical approach to cancer using homeopathic remedies, with parallels to research on modern manufactured nanoparticles.

Finding safer and more effective treatments for specific cancers remains a significant challenge for integrative clinicians and researchers worldwide. One emerging strategy is the use of nanostructured forms of drugs, vaccines, herbs, and nutraceutical agents in cancer treatment.[5-10] At the nanoscale range, the source material is typically in the ultrafine particle size range of 1 to 100 nanometers (nm) along at least one side, although some consider nanoforms to include particle sizes up to 1000 nanometers (see Table 1 for definitions of common terms in nanoparticle manufacturing).

Poorly soluble drugs or natural source materials pose practical challenges for administration and effective treatment. In such situations, preparing a medicine or natural product in nano form confers multiple advantages over conventional bulk form drugs.[15,16] These

Table 1 Glossary of Nanoparticle Terms[11]

Term	Definition
Nanoparticle	Very small particle made from a specific source material and measuring between 1 and 100 nm in length along at least one side (1 nanometer=10^{-9} m). The very smallest nanoparticles are called quantum dots (size range 1-10 nm long on a side) because of the large percentage of atoms of material close to the surface of the particle and the atom-like quantum mechanical properties that can manifest at that size.
Top-down manufacturing	One of multiple procedures for breaking smaller and smaller particles off an initially larger-scale bulk form material to generate nanoparticles. Examples include mechanical grinding and milling, photolithography, laser beam processing.
Bottom-up manufacturing	One of multiple procedures for building up or assembling a nanostructure or nano-network from small, nanoscale building blocks. Process usually relies on a template. Interactions between the building blocks to assemble the nanostructure can include electrostatic forces, hydrogen bonds, and other weak forces. Examples include organic synthesis by plant or fungal extracts, self assembly on DNA[12] or protein templates,[13] and colloidal aggregation. Silica nanoparticles can form durable biocomposites using living cells as 3-dimensional templates.[14]
Capping agent	A substance added to a nanoparticle manufacturing process that stabilizes the nanoparticles and prevents them from agglomerating together once formed. Examples range from toxic polymer chemicals to natural agents such as ascorbic acid, lactose, or honey.
Agglomeration	Clustering of nanoparticles together into larger structures. This process changes size and surface energies and thus can alter the properties.
Ostwald ripening	A spontaneous thermodynamic process of liquid sols allowed to age. Smaller nanoparticles condense or redeposit onto larger particles. Energetic instability of surface components of the smaller particles contributes to the process.
Brownian motion	Irregular motion of nanoparticles suspended in a liquid solution or gas. Caused by interaction of the particles with the medium or solvent.
Adsorption	The accumulation of solutes, liquids, or gases onto the surface of a nanoparticle. For nanoparticles, adsorption is related in part to the high surface charge and energy.
Self-assembly	The capacity of a system to generate an ordered or organized structure from initially unordered building blocks (see bottom-up manufacturing).
Dopant	An impurity or substance added in very small quantity to a pure semiconductor material to modify its conductive properties. Arsenic, boron, or phosphorus are common dopants for different semiconductor materials, including silicon.

advantages include enhanced bioavailability, adsorptive capacity, and intracellular accessibility.[17,18] The smaller nanoparticles can cross cell membranes readily, including thosein the skin and even the blood-brain barrier. Biological targeting with modern nanomedicines is increasingly precise, including ability to foster specific uptake into malignant cells, stop proliferation, and increase apoptosis with less damage to healthy cells.[19-21]

Nanoparticles also can acquire atom-like properties and high surface charge because of their small sizes and large surface area to volume ratios. The altered nanoparticle properties include increased chemical and biological reactivity, electromagnetic, optical, thermal, and quantum effects.[22] In turn, the unique properties of nanomedicines typically reduce required doses by orders of magnitude and improve side effect profiles.[18,23-26] Minor variations in surface properties can enhance nanoparticle uptake, especially into cancer cells, eg, conjugation with the disaccharide sugar lactose.[27,28] Surface adsorption of sugars also may enhance immune system responsivity to antigen delivered in vaccines by nanocarriers such as calcium phosphate.[29]

Nanoparticles under study as diagnostic tools, drug and vaccine delivery vehicles, and biological agents in their own right include

- various metals (eg, silver, gold);
- metal salts (eg, calcium phosphate, magnesium phosphate)[30-32];
- Semiconductors (eg, silicon and its dioxide silica)[33-35];
- lipid- or polysaccharide-based carriers (eg, Poly(lactide-co-glycolic acid) [PLGA] or chitosan)[36,37]; and
- exosomes.[38]

Exosomes are nanosized endogenous vesicles from endosomes released by a variety of cells containing proteins, siRNA, and lipids with capabilities for systemic biological signaling.[6,39-43] Certain exogenous nanoparticles can also trigger exosome release and a cascade of systemic stress-related or pro-apoptotic signaling in the immune and inflammatory pathways as well.[42-46] In the immune system, mature dendritic cells pulsed with exosomes can stimulate antitumor activity.[47] Exosomes derived from malignant tumor cells are also used as experimental cancer treatment vaccines.[6]

NANOSCALE FORMS OF NATURAL PRODUCTS FOR CANCER TREATMENT

One limitation in moving from bench to bedside with nanoparticle diagnostic and therapeutic approaches in mainstream medicine has been concern about the potential toxicity of nanomaterials. Some nanoparticles are especially likely to accumulate in bodily tissues. For instance, unmodified silver or copper nanoparticles can exhibit toxicity risks.[48] Because of their high adsorptive ability and large surface areas, nanoparticles can also retain trace amounts of any toxic solvents, polymer chemicals, botanical agents, or trace metal dopants used in manufacturing.[49] Surface modifications of nanoparticles can create agents with very different chemical and/or biological properties from the "same" nanoparticles with unmodified surfaces.[28,50,51]

An offshoot of this concern has been a shift toward "green manufacturing" methods. For instance, nanotechnologists use natural products such as botanical or herbal agents or other types of living organisms to biosynthesize gold or silver nanoparticles.[9,52,53] Then trace amounts of the more benign plant material remain adsorbed to the outer nanoparticle surfaces, thereby modifying the nanoparticle sizes and biological effects.[9] Manufacturing procedures that attach a benign sugar such as lactose to the surfaces of silver nanoparticles can also markedly enhance nanoparticle uptake into malignant, but not healthy cells.[28] Plant extracts, DNA, and proteins also guide bottom-up manufacturing via self-assembly of silica precursors into crystalline silica nanostructures[54,55] that can resist drying in some preparations.[56]

In addition, researchers make nano-encapsulations of certain natural, less soluble products from herbs or nutraceuticals. Such nanoforms can overcome gastrointestinal uptake and cellular accessibility problems of their respective bulk forms in vivo.[16] Thus, nanoparticle forms of antioxidants with antiinflammatory and antiproliferative properties have markedly enhanced their potential utility for cancer therapy compared with their bulk forms. Examples include nano-forms of curcumin,[37,57-60] quercetin,[5,61,62] and coenzyme Q_{10}.[63] PLGA nano-encapsulated herbal extracts of *Gelsemium sempervirens* also acquire improved anticancer effects.[64,65] Overall, nanoscale forms of natural products add a clinically valuable method for delivering less toxic or nontoxic treatments to people with cancers in which the currently available mainstream approaches are less effective, prone to drug resistance, and/or highly toxic. Given acceptable treatment efficacy, lower toxicity can translate into better patient outcomes.

HOMEOPATHIC REMEDIES AS NANOMEDICINES

Homeopathy is a more than 200-years-old system of alternative medicine developed by the German physician-chemist Samuel Hahnemann, MD. This type of healthcare is used widely around the world. Homeopathy is especially popular in India, the United Kingdom, Germany, France, Belgium, and several Latin American nations. Homeopathic medicines derive from natural mineral, plant, and animal sources, sometimes including diseased tissues (ie, nosodes such as *Carcinosin*, homeopathically prepared breast cancer tumor).[66]

Unlike in conventional healthcare, the classical homeopathic diagnosis (ie, remedy selection) depends on describing the total clinical pattern of biopsychosocial symptoms. Homeopathically relevant symptoms include adaptive behaviors of the individual person as an indivisible complex system. Classical remedy prescriptions then involve matching the patient's complete picture with the previously documented ability of

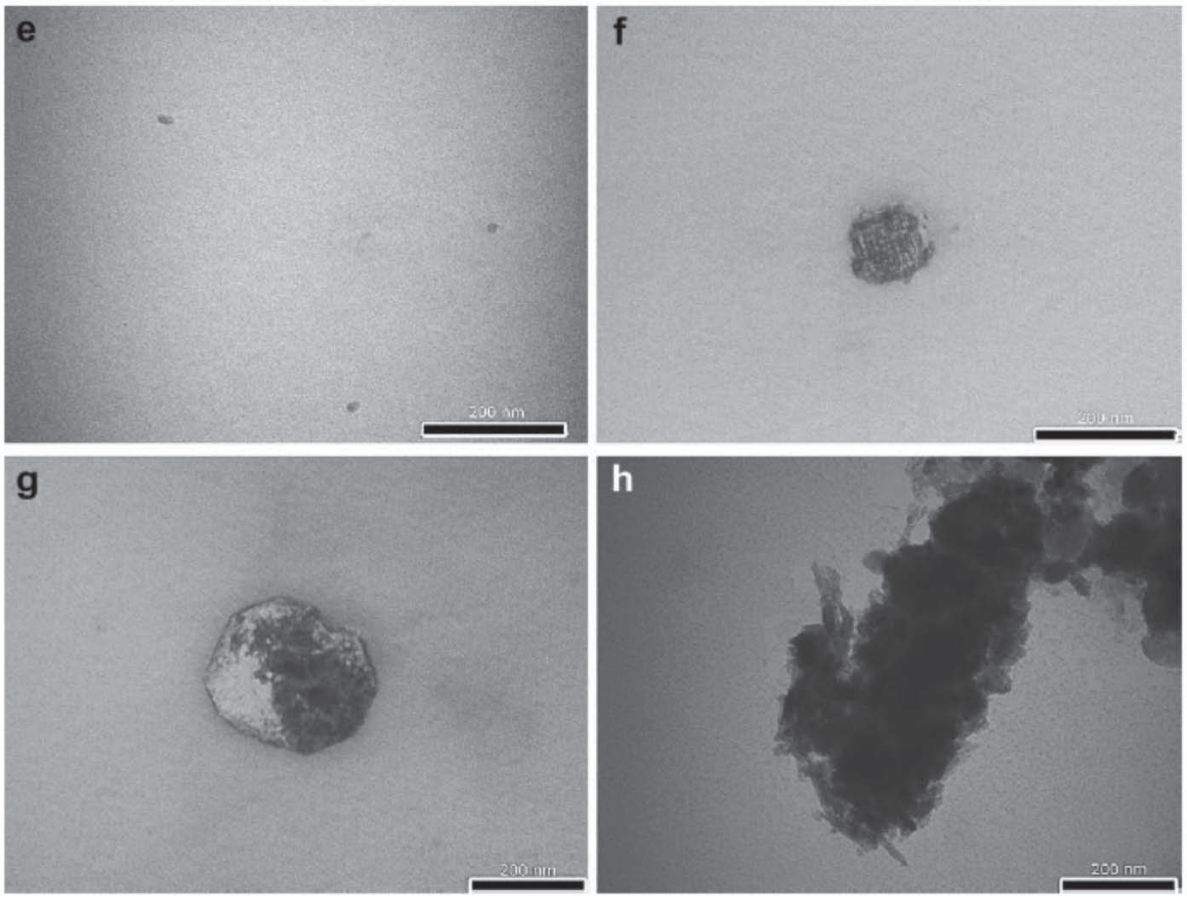

Figure 1 Bright field transmission electron microscope (TEM) images of nanoparticles and aggregates in homeopathically prepared gold (*Aurum metallicum*) at 30C (e) and 200C (f) potencies from Indian manufacturer SBL (originally Sharda Boiron Laboratories, Ltd, Delhi, India) and 30C (g) and 200C (h) potencies from the different Indian manufacturer WSI (Schwabe International GmbH, Germany, per Dr Willmar Schwabe India Pvt Ltd, Noida, Uttar Pradesh, India). Bulk form remedy source material was presumably diluted out of solution beyond the 12C potency. Reprinted with permission from Chikramane et al, 2010.[68]

a specific single remedy to cause the same pattern in healthy persons. Thus, by definition, homeopathic treatment relies on both (1) individual salience and (2) state dependency in the host to elicit beneficial rather than adverse effects. Remedy dosing typically involves pulsed or intermittent administration at lower doses and lower frequency than used in conventional bulk drug treatment.[66]

A recent development in integrative medicine research is the discovery of persistent nanoparticles of source materials (eg, metals, plants) in homeopathic medicines, sometimes referred to as "remedies" (Figure 1).[67-69] Different homeopathic plant remedy tinctures can also biosynthesize silver nanoparticles, with the resultant nanoparticles. The homeopathic plant-modified silver nanoparticles vary slightly in size and demonstrate somewhat different biological effects against a melanoma cancer cell line in vitro as a function of the plant source material.[9] In the latter study, the plant-made variants of silver nanoparticles exhibited anticancer effects involving both cell cycle arrest and apoptosis.

Only recently, some homeopaths and nanoscientists recognized the extensive overlaps between green manufacturing of modern nanoparticles and traditional homeopathic manufacturing methods.[9,68,70] Homeopathic manufacturing standards derive from the empirical techniques originally developed by Hahnemann in the 19th century.[71] The essential process of making homeopathic medicines includes[72]

- natural remedy source materials (plant, mineral, animal, disease tissue sources);
- preparation of ethanolic extracts or tinctures;
- extensive grinding of source materials in lactose; and
- serial dilutions and repeated successions (agitation) in ethanol-water diluent within glass containers.

Homeopathic manufacturing procedures involve preparation of an ethanol-based extract (plants, disease tissue) and/or trituration (grinding or milling) in lactose over a long period of time for insoluble materials. The ground or milled remedy in lactose is then serially diluted, first in dry lactose for the first few steps and then in ethanol-water diluent in glass containers over multiple subsequent steps. The dilution ratios are typically 1/10 (X or D potencies) or 1/100 (C potencies), followed by vigorous agitation of the solution. Manual manufac-

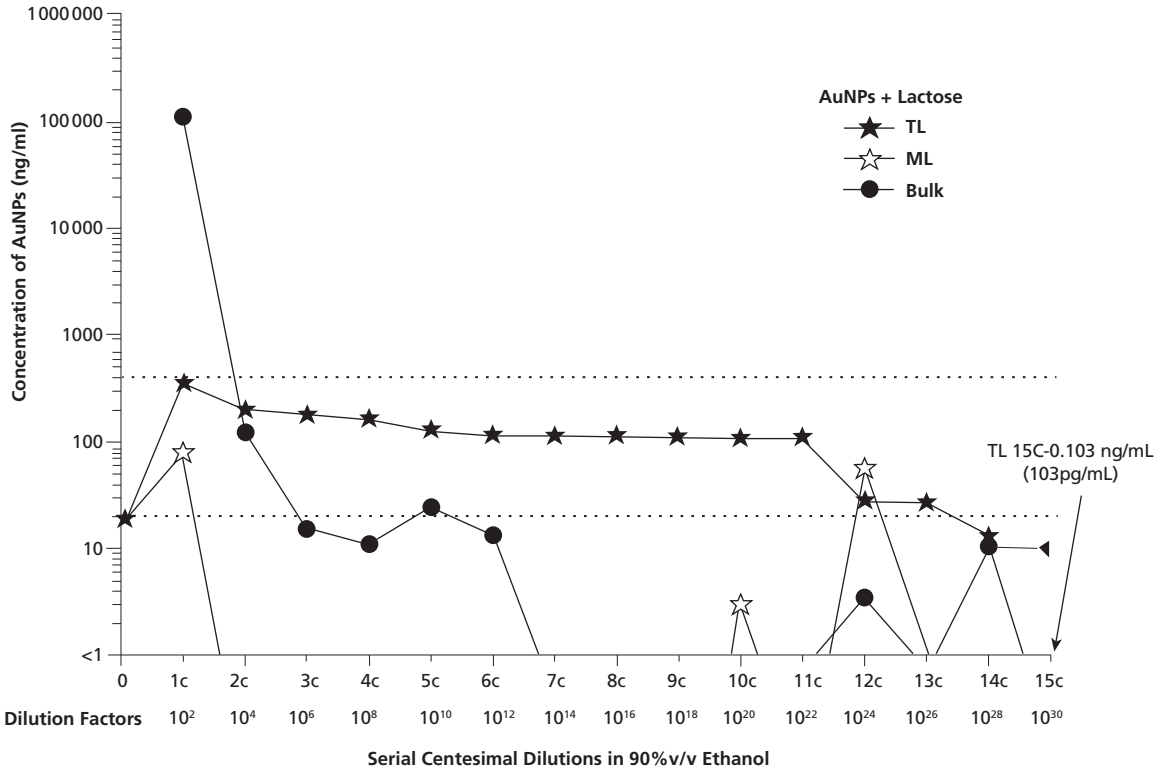

Figure 2 Estimation of gold nanoparticle (AuNPs) concentrations in top layer (TL) and middle layer (ML) after dilution and succussion of commercial AuNPs using classic homeopathic lactose trituration, ethanol-water dilution, and succussion procedures. Beyond the 6C potency, 99% of the AuNPs are transferred to the next dilution. The original authors indicate that these findings result from a bubble-induced froth flotation process of nanoparticles forming a monolayer at the air-liquid interface. Reprinted with permission from Chikramane et al, 2012.[67]

turing methods involve 10-100 vigorous succussions per dilution step (agitation in solution by pounding the glass container against a hard surface).[64]

From the dilution process per se, skeptics have long assumed that homeopathic medicines could not plausibly contain any residual molecules of the source material, at potencies with bulk dilutions past 24X or 12C (ie, diluted past the cut-off for Avogadro's number of molecules). They have generally overlooked the potential role of the other steps in the manufacturing process for generating bioactive agents. Debates over the validity of homeopathy center on this primary dilution argument.[73-77]

However, new data indicate that while the specific manufacturing methods for classically prepared remedies probably remove the bulk source materials early in the process of serial dilutions, they leave a layer of detectable source nanoparticles across all dilutions. The data include remedy potencies diluted past Avogadro's number for bulk materials (Figure 2).[67] Chikramane et al showed heterogenous accumulation of nanoparticles in a top layer as a result of the creation and movement in solution of bubbles and nanobubbles during succussions. The latter group also proposed that the lactose can serve as a capping agent for nanoparticle growth during trituration[67] as well as a vehicle for delivering nanoparticles.[78,79]

The specific alcohol itself (ie, ethanol) and its concentration also can modify the properties of nanoparticles made in liquid solutions.[80-82] Agitating a solution of nanoparticles can also help disperse any spontaneous agglomerations of larger clusters into smaller particles.[83,84] Thus, nanoparticles of the source material are found from the lowest to the highest homeopathic potencies across all dilutions. Dilution appears to remove bulk forms but not nanoscale forms of source material.

Furthermore, the succussion process generates readily measurable amounts of silicon, silica (silicon dioxide), and its precursors from the glass walls of the container.[64,69,85,86] Studies on different glassware containing succussed homeopathic remedies, agitated non-homeopathic liquid solutions, and succussed control solutions all demonstrate the variable release of biologically active silica and related chemicals into solution.[69,85,87] Numerous studies show that silicon and silica nanoparticles and crystals can adsorb or attach to source nanoparticles as drug delivery vehicles,[87,88] and/or nonspecifically amplify their biological effects, especially those in the immune system.[45,88,90] Certain forms of porous nanosilicon possess relatively low toxicity and biodegradability in medical applications, including sensitizing the photodynamic killing of cancer cells.[91] Very small silicon nanoparticles (quantum dots), depending on their dopant materials, can also generate unique optical effects and transport electric charges: eg, in solar cells.[92,93]

Notably, as with silver, plant tinctures can also biosynthesize nanocrystals of silica from its precursors.[55] Therefore, in addition to the remedy source nanoparticles, the nanosilica and silica crystals from agitation of liquid solutions within glassware likely provide an additional remedy-modified delivery vehicle and nonspecific amplifier of biological effects related to the specific remedy source.[70,94] The documented variability in release of silicon, silica, and its precursors from different types of glassware[87] could contribute to the well-known variability reported in both basic science and clinical trial studies of homeopathically-prepared medicines.[95,96] From a nanotechnology perspective,[15,82,84,97,98] methodological variations in homeopathic source materials, grinding procedures, dilutions, succussion procedures, pH, temperature, and ethanol concentrations during remedy preparation would also affect the sizes, shapes, amounts, and properties of the final homeopathic medicines. Even aging during storage can significantly change the properties of both nanoparticles[99-101] and homeopathic remedies.[102]

What would the presence of nanosilica add to natural product cancer treatment? Several nonhomeopathic studies of the effects of a traditional Middle Eastern animal venom–derived treatment on cancer cells begin to answer that question. The addition of modern manufactured silica nanoparticles to a snake venom–derived medicine significantly enhanced the apoptotic and growth arrest effects of the treatment on breast cancer cells (Figure 3).[103] The same type of combination treatment (snake venom with silica nanoparticles) also improved anticancer effects against malignant myeloma cells[104] and human prostate cancer cells.[105] Like certain types of nanoparticles,[106-108] some homeopathic remedies with antineoplastic properties exhibit the ability to attack cancer cells while leaving healthy cells intact.[109,110]

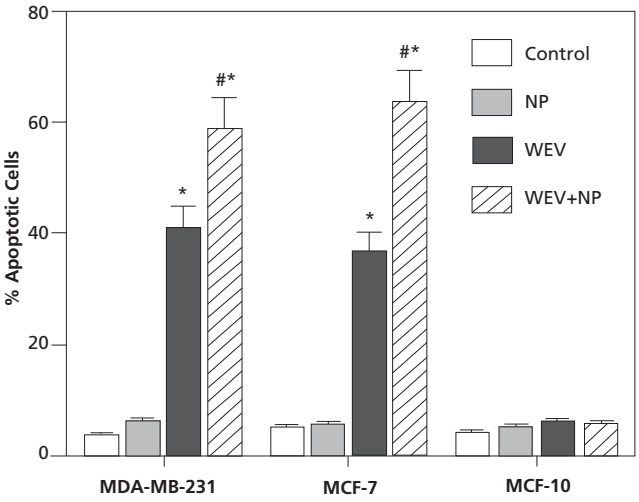

Figure 3 Silica nanoparticles amplify apoptotic effects of biologically active natural agent. Data from five different experiments are expressed as the mean percentage of apoptotic cells ± SEM for the control (open bars), NP-treated (gray bars), WEV-treated (closed black bars), and WEV+NP–treated (hatched bars). *P<.05, WEV-treated vs NP; #P<.05, WEV+NP-treated vs NP; +P<.05, WEV+NP-treated vs WEV-treated cells. WEV=venom of Walterinnesia aegyptia snake; NP=silica nanoparticles. MDA-MB-231 and MCF-7 are human breast cancer cells; MCF-10 are normal breast epithelial cells. Reprinted with permission from publisher S. Karger AG, Basel, from reference.[103]

Most nanomedicine applications of natural products are still in developmental or early clinical trial phases of study.[5,111] However, with the discovery of nanoparticles in homeopathic remedies, both homeopathic manufacturers and modern nanomedicine practice stand to learn from each other. The overall goal would be to improve research and clinical care of people with cancer using less toxic naturally-based interventions.

What nanoscience brings to homeopathy is modern technological methods. Nanomedicine research insights into nanoparticle characterization and how nanoparticles interact with living systems can help homeopathic investigators design better products and improve reproducibility from study to study.[68,112-114] On the other hand, homeopaths possess over two centuries of practical clinical experience and texts on using their naturally-sourced nanoparticles safely to treat patients. Modern nanomedicine could benefit from these real-world homeopathic experiences with nanoparticle-based clinical practice. Multiple studies on cancer cell cultures and animals indicate that both modern nanomedicines and homeopathic remedies have beneficial effects in vitro and in animals toward promoting apoptosis and modulating biological signaling pathways to limit cancer cell growth.[115-117] Accelerating targeted research and identifying optimal treatments for people with cancer could result.

Table 2 lists relevant studies that suggest parallels between some mainstream natural product nanomedicine agents and homeopathic remedy effects. The evidence to date suggests that nanoparticle forms of a number of natural products can treat cancer. For instance, nanoparticles from certain mineral salts such as calcium phosphate,[31,118] the metalloid arsenic,[135] a variety of specific plant extracts (concentrated mother tinctures),[9] animal venom toxin treatments,[103-105,136] and exosomes (endogenous nanoparticles released by bodily cells) from cancerous tissue or dendritic cells of the immune system[6] can all exert antiproliferative and pro-apoptotic effects on specific cancer cell lines in in vitro. Several plant nanoparticle studies used homeopathic mother tinctures to manufacture the nanoparticles.[9] Moreover, studies of specific homeopathic remedies prepared in potencies ranging from 3X to 1000C (1M) made from mineral salts (calcium phosphate), certain plants, and cancerous tissue and used in clinical treatment of people with cancer also reveal similar effects.[1,2,109,110]

As noted above, homeopathy potentially brings to integrative clinical nanomedicine treatment for cancer a well-described practice theory and more than 200 years of clinical experience. For homeopathy, the data indicate high patient satisfaction, very low toxicity, no drug-drug

Table 2 Parallels Between Effects of Modern Nanoparticles and Homeopathically-prepared Medicines on Cancer Cells

Mainstream Nanoparticle Studies	Cancer Cell Types Affected by Nanoparticles	Homeopathically-prepared Medicines	Cancer Cell Types Affected by Homeopathy
Calcium Phosphate Nanoparticles (80 nm size had greater effects than 20 nm size)[31] Hydroxyapatite nanoparticles[118,119-122]	MG-63 osteosarcoma cells Brain cancer (glioma); decrease toxicity of chemotherapy drugs[118] Leukemia P388 tissue[120] Liver tissue Gastric cancer	*Calcarea phosphorica* 3X[109] (low potency: bulk and nanoparticles both likely present)	Osteosarcoma (clinical case reports) Brain cancer (glioma)
Tumor cell-derived exosomes[6,38-41]	Leukemia Lymphoma Colon melanoma Lung cancer Mesothelioma Skin melanoma Pancreatic cancer cells	*Carcinosin* 200C[110] (breast cancer tissue nosode remedy)	Breast cancer cells
		Ruta Graveolens 6C[109] *Ruta Graveolens* 200C[123,124] *Thuja* 30C and 200C[125]	Brain cancer (glioma) Ehrlich Ascites Carcinoma and Dalton's Lymphoma Ascites Liver tumor
		Hydrastis 200C[124] *Hydrastis* 1M (1000C)[126]	Ehrlich Ascites Carcinoma and Dalton's Lymphoma Ascites B16F-10 Melanoma
		Lycopodium 30C[127] *Lycopodium* 200C[128] *Lycopodium* 1M[126]	Liver cancer Liver cancer B16F-10 Melanoma
Gelsemium sempervirens extract encapsulated with PLGA nanoparticles[65,129]	Skin cancer line A375		
Phytolacca decandra extract encapsulated with PLGA nanoparticles[130]	Lung adenocarcinoma	*Phytolacca decandra* 200C[110] *Conium maculatum* 3C[110] *Thuja occidentalis* 30C[110]	MCF-7 and MDA-MB-231 breast cancer cells
		Chelidonium 30C and 200C[131]	Liver tumor
Phytolacca decandra, Gelsemium sempervirens, Hydrastis canadensis, Thuja occidentalis extracts biosynthesize silver nanoparticles[9]	A375 skin melanoma cells		
		Secale 30C[115]	Skin papilloma
Polygala senega extract encapsulated with PLGA nanoparticles[132]	A549 lung cancer cells		
		Homeopathic combination medication Canova (originally, *Aconitum napellus* D11, *Arsenicum album* D19, Bryonia alba D18, *Lachesis mutus* D18, *Thuja occidentalis* D19)[133,134]	Sarcoma 180

PLGA is a copolymer poly(lactic-co-glycolic acid), a widely-used nanoparticle form.
Botanical extracts are homeopathic mother tinctures in ethanolic solutions (concentrated bulk form materials).
Homeopathic potencies are serially diluted and succussed in accord with standard manufacturing methods. "D" potencies are equivalent to "X" decimal potencies (serial dilution factor of 1 part source to 9 parts diluent or solvent or a ratio of 1/10). Each dilution step is followed by 10 or more succussions.

or drug-herb interactions, and low side effect rates.[95,96] Allergic reactions at low potencies may be a minor risk,[137,138] though the rates appear to be extremely low, serious events are rare, and relatedness to the remedies per se uncertain.[96,139,140] In one sense, homeopaths in clinical practice may be many years ahead of conventional physicians in applied understanding of how and when to use nanoparticles of natural products for safe and effective clinical treatment.

HOMEOPATHIC REMEDIES IN CANCER CARE

Although there is a growing research literature on the effects of homeopathic remedies on cancer in cell culture and animal studies, there are very few clinical trials of homeopathy in cancer patients. Most reports in the literature involve case reports.[2,141] A long-articulated concern of mainstream healthcare providers has been the presumption that homeopathy and other forms of complementary and alternative interventions are

ineffective and could dangerously cause patients to delay more effective conventional treatments (ie, conventional chemotherapy, radiation therapy, surgery) of life-threatening serious diseases such as cancer. Partly as a result, homeopathic cancer research in Western countries has largely confined itself to preclinical studies and evaluations of adjunctive treatments of the side effects of conventional cancer treatments.[142]

In that context, one small double-blind placebo-controlled trial showed significant benefits of a complex combination homeopathic remedy Traumeel (Heel, GmbH, Baden-Baden, Germany) for treating chemotherapy-induced stomatitis in children undergoing stem cell transplantation.[143] A positive phase III randomized clinical trial on 254 patients demonstrated that homeopathic *Calendula* was significantly more effective in preventing acute dermatitis during adjuvant radiation therapy than a standard of care topical agent.[144] An observational study of individualized homeopathy for radiation-induced itching in breast cancer patients suggested that homeopaths identified several other specific beneficial remedies for 21 out of 25 individuals.[145]

Other trials of specific remedies for specific conventional cancer treatment side effects were negative or mixed, suggesting either lack of benefit or homeopathic and researcher limitations in choosing and/or managing the correct remedies.[142,146,147] The emergent conclusion from considering both the general and cancer-related homeopathic research literatures is that, as in conventional medicine, proper selection of the correct medicine for a given patient with a given clinical condition makes a difference as to whether or not homeopathic treatments are likely to work. The heterogeneity of patients, diagnoses, and remedy and potency effects make it essential to begin with tapping extensive clinical experience in designing research on homeopathic remedies and cancer that has reasonable face, model, and external validity.[148]

THE BANERJI PROTOCOLS: USING HOMEOPATHIC REMEDIES TO TREAT CANCER

What is the experience of homeopaths in more comprehensive treatment of patients with cancer? India is a country with perhaps the most extensive history in this regard. In contrast with countries such as the United States or United Kingdom, India maintains more than 100 teaching institutions on homeopathy, many associated with universities, including 4- or 5-year homeopathic medical schools. These facilities include hospitals and homeopathic pharmacies, and all government hospitals include homeopathic treatment. Private practitioners often develop large clinics staffed by multiple homeopathic physicians, treating thousands of patients for all types of acute and chronic conditions, including cancers. Several different homeopathic approaches to treating all types of cancers have evolved in this context.[1,3,4]

Only one such approach, the Banerji Protocols, however, has submitted its clinical cases to successful review in the Best Case Series Program of the National Cancer Institute (NCI) in the United States.[2,149] After this review, NCI's Office of Cancer Complementary and Alternative Medicine prioritized additional research on this treatment approach. Nonetheless, historical skepticism about the nature and plausibility of homeopathic remedies as biologically active agents previously limited interest in pursuing research on homeopathy in the United States. The emerging data on the natural nanomedicine nature of homeopathic remedies is beginning to shift the discussion.

The Banerji Protocols are based on the cumulative experience of three generations of homeopaths treating thousands of patients.[1] It is an empiric treatment system developed through careful analysis of observed trends in patient-medicine interaction. These extensive practical experiences ultimately led to standardized disease or symptom-specific protocols for prescribing homeopathic medicines. This standardization of treatment has made it possible to apply rigorous scientific methods to test its efficacy. Collaborators from around the world have recently organized a consortium to coordinate their various efforts to advance the clinical and laboratory research on the Banerji Protocols. Because of their reputation for effective clinical treatment of many cancers that generally have a poor prognosis, we seek to apply the principles of nanoparticle behavior to the particular approach used in these protocols.

Given that an average of 120 to 200 cancer cases a day are treated at the PBH Research Foundation, Kolkata, India, there is a fertile ground for further investigation of this treatment method. A majority of the cancer cases treated at this facility are not treated with any other therapy, although there is no explicit requirement that this be so. In fact, most of the thousands of consultations that are provided to patients from other countries are from patients who have already had or are currently undergoing conventional Western treatment. Concomitant or previous conventional cancer treatment is not considered to be a contraindication to the Banerji Protocols.

However, a recent case review conducted by one of our authors (Sarter, unpublished data) revealed that for all categories of brain neoplasms, the cases that were treated with the Banerji Protocols alone (1) fared substantially better in terms of fewer adverse events than those that were combined with conventional Western treatment and (2) had median survival estimated by the Kaplan Meier method comparable to those reported in the Surveillance, Epidemiology, and End Results database of the NCI (http://seer.cancer.gov/). This provides support for the premise that homeopathic nanomedicines stimulate a robust host-dependent immune response from healthy cells that is typically impaired by chemotherapy and radiation therapy.[150]

Other distinguishing characteristics of the Banerji Protocol are (1) its combination of multiple medicines

into a treatment regimen, (2) repeated daily or weekly dosing over many months, and (3) the actual mixing together of some homeopathic medicines into standardized combination remedies. All of these are in contradiction to traditional classical homeopathy's principles of treatment.[66,151] The protocols for the different types of cancer are mostly customized according to the specific location, organ and tissue type, and the specific medicines, in their specific dilutions and dosage patterns, have been standardized after generations of experience.[1]

Thus, it appears plausible that in addition to a general stimulation of the immune system, there is also a tumor-specific effect in which tumor cells are preferentially killed but normal cells preserved.[105,106] As noted above, nanoparticles are capable of these types of differential effects on diseased vs healthy cells.[31,106,108] One hypothesis for this phenomenon is the greater "leakiness" of blood vessels in tumors. As a result, malignant cells may permit greater uptake of nanomedicines as opposed to healthy cells.[16,152]

Studies conducted to date in which specific tumor cell lines are treated with the Banerji Protocol medicines have supported this hypothesis. One report on the Banerji protocols[109] described 15 patients diagnosed with documented intracranial tumors who were treated exclusively with the homeopathic remedies *Ruta graveolens 6C* and *Calcarea phosphorica 3X* without additional chemotherapy or radiation. Of these 15 patients, six of the seven who had glioma showed complete regression of the tumors. In this study, we also reported that these medicines stimulated induction of survival-signaling pathways in normal lymphocytes and induction of death-signaling pathways in brain cancer cells. Cancer cell death was initiated by telomere erosion and completed through mitotic catastrophe events.[109] Bulk herbal extract forms of *Ruta graveolens* have also demonstrated the ability to exert antitumor effects, but with some caveats on possible risks from prolonged use at high doses.[123,153-156] The ability to use low doses of *Ruta* in nanoparticle form might help reduce such risks.[123,126,157]

More recently, Frenkel et al reported a study of four homeopathic remedies from the Banerji protocols for treating breast cancer.[110] The remedies were tested against two human breast adenocarcinoma cell lines (MCF-7 and MDA-MB-231) and a cell line derived from immortalized normal human mammary epithelial cells. The homeopathic medicines exerted preferential cytotoxic effects against the two breast cancer cell lines, causing cell cycle delay/arrest and apoptosis. These effects were accompanied by altered expression of the cell cycle regulatory proteins, including downregulation of phosphorylated Rb and upregulation of the CDK inhibitor p27. These effects were likely responsible for the cell cycle delay/arrest as well as induction of the apoptotic cascade that manifested in the activation of caspase 7 and cleavage of PARP in the treated cells.[110]

Another distinguishing feature of the Banerji Protocols is the use of both very low and moderately high potency medicines within the same protocol. Very low homeopathically prepared potencies would fall into the mother tincture to 3X range, whereas moderately high potencies would fall into the 30C to 200C range. Dosing in the protocols is generally more frequent than in classical homeopathy, again, because experience has shown this combination pulsed dose approach to be more effective for cancer than the isolated single-dose method typical of classical homeopathy. It should be clarified that when speaking of the potency of a homeopathic medicine, the guiding principle is "less is more," meaning the more serially diluted and succussed the medicine, the higher its potency and apparent duration of action.[158]

Many of the protocols in use for cancer treatment involve the use of medicines that are low potency combined with a high potency. Very low potencies are likely to contain mainly remedy source nanoparticles reduced and stabilized (capped) by lactose. In nanotechnology, capping agents stabilize nanoparticles and keep them from aggregating or agglomerating once formed. Natural products such as sugars, eg, lactose, honey,[159] or ascorbic acid can serve as nanoparticle-reducing and capping agents in water-based solutions (Table 1).[160,161]

In contrast, higher potencies would likely contain both remedy source nanoparticles and various nanosilica/nanosilicon structures from repeated rounds of multiple succussions in ethanolic solutions within glass containers.[69,85,86] As noted elsewhere, evidence shows that nanosilica and other nanoparticle carriers can enhance effects of traditional treatments for cancers such as snake venoms.[103-105,120,162] Silica in nanoform is also generally effective as an adjuvant to boost cellular and immune responses to oral and other vaccines for various conditions.[45,88,90,163,164]

Table 3 lists the Banerji protocols in use for some specific cancers. It is noteworthy that *Calcarea phosphorica* 3X is included in the protocols for two cancers with generally very poor prognoses: brain and bone. These same types of cancers have responded very well to the Banerji Protocols with cases verified by NCI.[1,2,109]

Also noteworthy is the occurrence of complete regressions in a consistent pattern among most of the cancers treated by the Banerji Protocols. Retrospective data collected over a 1-year period on patients treated for lung, brain, and esophageal cancer showed that complete regressions ranged from 22% to 32% (Figure 4). A similar complete regression of approximately 33% of brain neoplasms, including glioblastoma multiforme, over a different 1-year period (2010) was observed after the data in Figure 4 were compiled (Sarter, unpublished data). Although spontaneous regressions are a known phenomenon in oncology, the percentage of complete remissions typically observed at the Prasanta Banerji Homeopathic Research Foundation certainly justifies further investigation of this approach.

Table 3 Exemplars of Banerji Cancer Protocols With Homeopathic Remedies and Potencies[a]

Type of Cancer	First Line	Second Line	Third Line	Related Symptoms	Symptomatic Treatment
Breast cancer	*Phytolacca* 200C 2x/d; *Carcinosin* 30C on alternate nights	*Phytolacca* 200C 2x/d; *Carcinosin* 30C on alternate nights; *Conium maculatum* 3C 2x/d	*Thuja occidentalis* 30C 2x/d; *Carcinosin* 30C every night	Open ulcer with offensive discharge	*Psorinum* 1000C on alternate mornings; *Antimonium crudum* 200C + *Arsenicum* album 200C 4x/d
Osteosarcoma	*Symphytum* 200C and *Calcarea phosphorica* 3X, every 3 h alternately; *Carcinosin* 30C on alternate nights	*Ruta* 200C and *Calcarea phosphorica* 3X, every 3 h alternately	Lung metastasis: Stop *Carcinosin* and start: *Kali carbonicum* 200C on alternate days; *Thuja* 30C 2x/d	Wound infection	Hypericum 200C + Arsenicum album 200C 4x/d
Lung cancer	*Kali carbonicum* 200C on alternate days; *Thuja* 30C 2x/d; *Ferrrum phosphoricum* 3X alternating every 3 h with *Kali muriaticum* 3X	*Carbo animalis* 200C 2x/d; *Bryonia* 30C + *Aconitum napellus* 200C, 2x/d		Cough Chest pain Pleural effusion Hemoptysis	*Ipecacuanha* 30C 2 pills every 1-3 h *Hypericum* 200C every 2 h *Lycopodium* 30C liquid 4x/d *Hamamaelis* 200C + Arnica 200C 4x/d
Pancreatic cancer	*Carduus marianus* MT and *Conium maculatum* 3C liquid every 3 h alternately; *Chelidonium majus* 6X liquid 3x/d	*Hydrastis canadensis* MT and *Chelidonium* 6X liquid every 3 h alternately		Pain	*Belladonna* 3C every 10 min
Liver cancer	*Hydrastis canadensis* MT and *Chelidonium majus* 6X liquid every 3 h alternately; *Conium maculatum* 3C 2x/d	*Myrica* MT and *Hydrastis canadensis* MT every 3 h alternately; *Carduus marianus* MT 2x/d		Pain Nausea	*Belladonna* 3C every 10 min *Tabacum* 200C 2x/d or *Ipecacuanha* 30C 4x/d
Brain cancer	*Ruta* 6C 2x/d *Calcarea phosphorica* 3X 2x/d	*Thuja occidentalis* 1000C 1x/wk, added to first line		Seizures Headache Confusion Vertigo Edema	*Cuprum metallicum* 6C + Arnica 3C 2x/d *Picric Acid* 200C+ Belladonna 3C every 10 min *Helleborus* 30C liquid 2x/d *Conium maculatum* 3C 2x/d *Lycopodium* 30C liquid 2x/d

[a] Notes on nomenclature and dosages:
MT = mother tincture
X = serial dilutions in 1/10 ratios, with each step followed by 10 or more succussions (agitations)
C = serial dilutions in 1/100 ratios, with each step followed by 10 or more succussions (agitations)
All doses are 2 drops of liquid or 2 size #40 pills unless otherwise specified.
"+" indicates that the two medicines are to be mixed together in equal proportions for administration.

PULSED DOSING, BIOLOGICAL SIGNALING MECHANISMS, AND LOW DOSES

Dosing in homeopathy involves the use of low doses and pulsed intermittent administrations. Interestingly, mainstream oncology has developed pulsed dosing regimens for the more toxic chemotherapy agents to allow recovery of healthy tissue between treatments. Pulsed dosing is also reported in experimental models using exosomes (endogenous vesicular nanoparticles) from cancer tumor, dendritic, or malignant ascitic cells for cancer vaccines.[38,165] The value of intermittent doses in homeopathy[166,167] may be to take advantage of the stimulus properties of the treatment agent and the endogenous adaptive capacity of the recipient biological system to restore healthier homeostatic balance.[70,113,168,169]

A possible objection to the therapeutic value of homeopathic remedy nanoparticles might be that

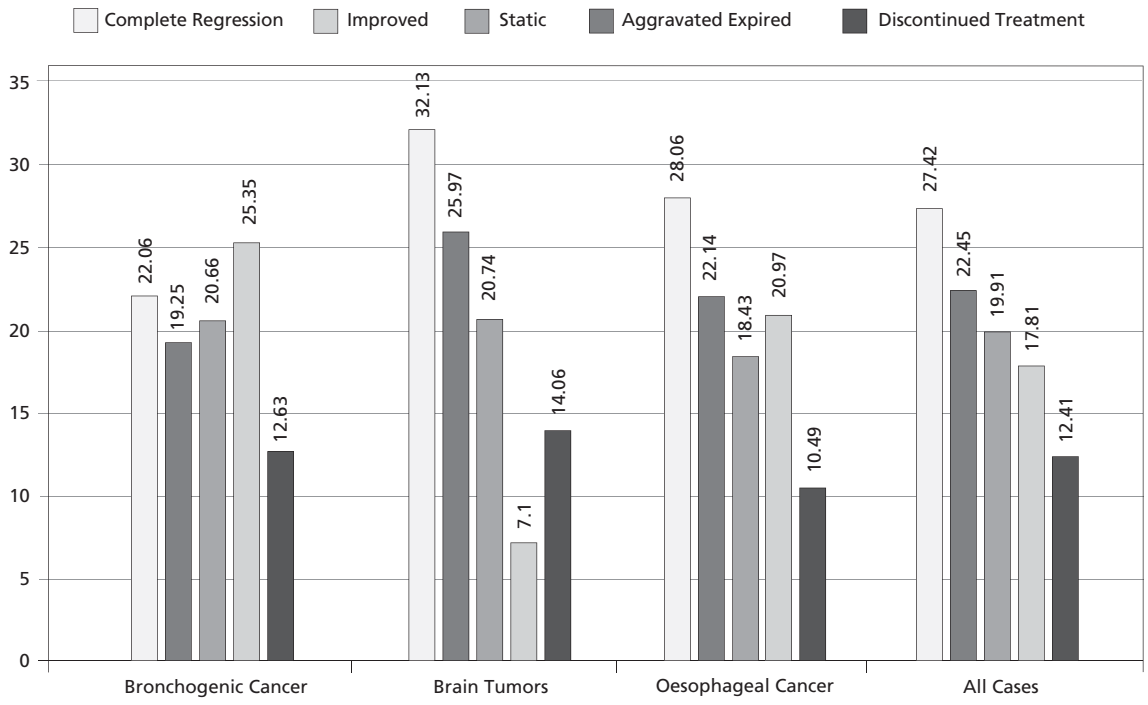

Figure 4 Results of treatment of 1132 cases of lung, brain, and esophageal cancers, August 2006 to August 2007.

Source: http://www.pbhrfindia.org/index.php/component/content/archive?year=2011&month=3. Accessed December 3, 2013.

people are constantly exposed to low levels of natural and manmade nanoparticles without curative effects. In fact, at higher levels, certain nanoparticles are toxic and may contribute to various chronic diseases.[17,170] However, there are at least three necessary properties for a given stimulus to initiate endogenous adaptation and even amplification responses: (1) a salient and discrete signal that is recognized as a potential threat to survival of the organism, rising above (and then falling back to) background noise, rather than continuous exposure[70,112,1113,171-175]; (2) a sufficiently low dose of nanoparticles to serve as a danger signal or mild environmental stressor without inducing toxicity: eg a hormetic dose level (see below)[70,168,176,177]; and (3) adequate time for the processes of cellular and organism adaptation and cross-adaptation to take hold, amplify effects, and evolve after cessation of the stimulus.[112,178-183]

The proposed primary targets of homeopathic remedies are mediators of the stress response networks (nervous, endocrine, immune, metabolic) of the body.[70,112] The correct remedies or nanoparticles would serve as mild stressors to initiate hormesis (biological adaptation).[168,184,185] This conceptualization accommodates the use of very low, carefully timed doses.[186] It is also compatible with the work of other investigators showing that homeopathic remedies[171-173] or nanoparticles[168,176] can initiate the adaptive process of hormesis in an organism. A complex cascade of intracellular and intercellular biological mediators would carry out the adaptive changes.[112,187,188]

Khuda-Bukhsh[115] originally proposed modulation of signal proteins as the mechanism by which homeopathic remedies can produce epigenetic changes and effects on regulatory pathways in stopping cancer cell proliferation and inducing apoptosis. Recently we extended this hypothesis to postulate that the pulsed dosing approach of homeopathy is a more general treatment strategy. This approach uses the biological signaling properties of remedies to initiate systemic adaptive changes across the organism as a whole.[70,112-114]

The ability of nanoparticles to release exosomes[42,43] offers an initial focus for future research on homeopathic remedies as biological triggers for salutary responses against cancer. Exosomes have demonstrated cell-to-cell and systemic signaling properties.[39-42] nanoparticles also can enter cells and activate intracellular defense cascades[44,114] involving inflammasomes. Inflammasome protein activation leads to release of cytokines and other self-regulatory elements of the immune system.[45,89,189]

Smaller sized nanosilica (eg, 15 nm diameter) can produce effects on global genomic hypomethylation, which might contribute to subtle modulation of epigenetic expression.[190] Nanosilica also has the capacity for bottom-up self-assembly of three-dimensional nanostructure networks built upon biological templates. These biotemplates include living cells,[13,28] proteins,[191] collagen,[192] and/or DNA[12,14,193-195] itself. Self-assembly processes involving silica in homeopathic remedies might add additional means of amplifying, reproducing, and transmitting structural and perhaps electromagnetic information[196,197] of specific remedies in higher potency.

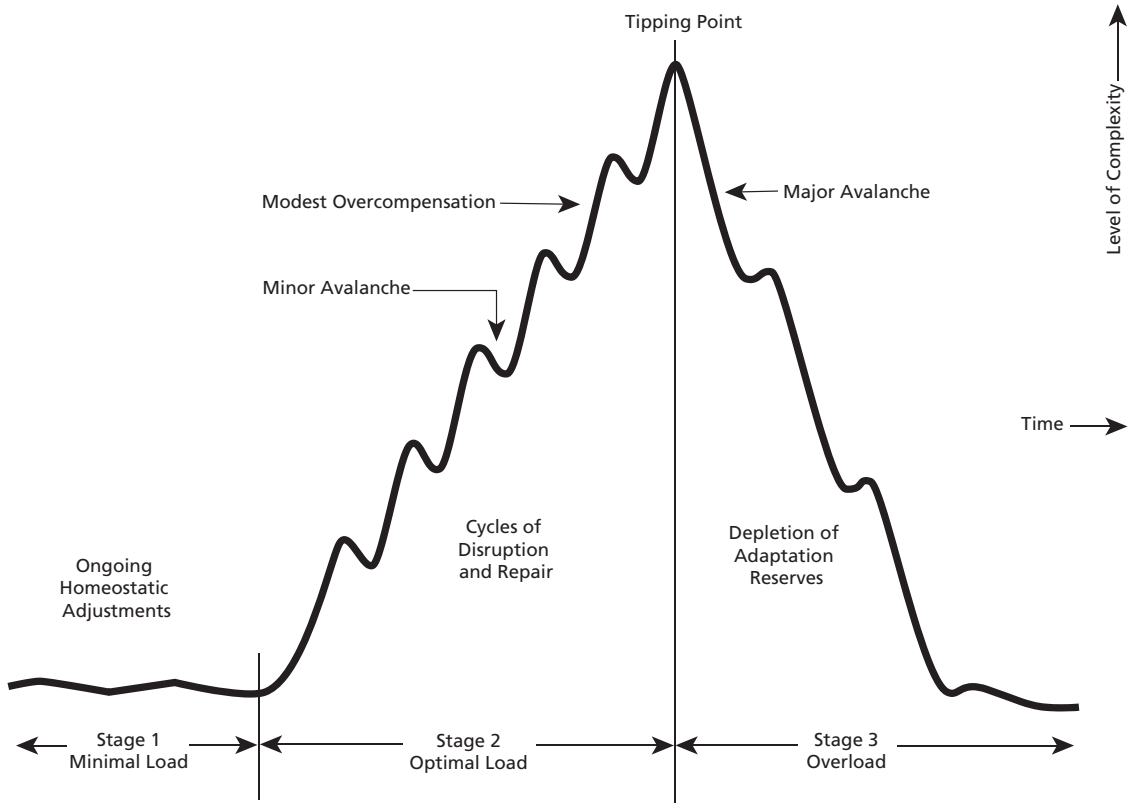

Figure 5 Levels of stress and hormesis, with an optimal stress level that maximally fosters beneficial adaptations. Excessive stress produces overload and development of disease. Homeopathic remedies at low pulsed doses would act therapeutically on the left side of the curve to shape adaptive changes, recovery of complexity, and healing. The dosage and size-related properties of the nanoparticles as a mild cellular and systemic stressor, the adaptability of the cells and organism as complex adaptive systems, and the interaction between the remedy nanoparticles and the system determine the type and direction of effects. The analogy is the nonlinear changes that occur in a sand pile as each grain of sand is added one by one. A single grain of sand arriving at just the critical time can tip the system into an avalanche, thereby triggering vigorous compensatory adaptive responses. Reprinted with permission from Stark et al, 2012.[207]

Hours of agitation via sonication in different solvents can also create extremely small, light-emitting tunable silicon nanoparticles (quantum dots).[93] Some silicon nanomaterials already play emerging roles as not only drug-delivery vehicles,[198] but also semiconductors in microelectronics memory, bioimaging, and nanocatalysis applications.[199] The possible role of homeopathically succussed nanosilicon and nanosilica per se in retaining and transmitting some of the remedy source-specific information at higher homeopathic potencies remains to be explored.[196,197]

Hormesis is the well-documented phenomenon of nonlinear dose-response relationships. In hormesis, a low dose of an agent can stimulate beneficial responses whereas higher doses cause inhibitory or adverse effects.[200] Depending on the nature of the substance, the dose size cutoff point for defining below the toxic level or "no observed adverse effect level" (NOAEL) can vary. In the oncology literature, low dose arsenic has been found to produce anticancer effects, whereas higher, more toxic doses can cause cancer.[201] Recent research demonstrates that a nanoform of arsenic trioxide further improves efficacy against breast cancer[202] and lymphoma while protecting fertility in mice.[119] In homeopathic form, arsenic trioxide is the widely used remedy *Arsenicum album*.[203-205]

Some investigators have proposed that repeated intermittent mild stressors may improve resilience against future more intense stressors and foster longevity via epigenetic adaptations.[177,188,206] Figure 5 highlights the concept of "optimal stress."[207] With sufficient adaptive capacity, an organism can make modest overcompensations to a mild stressor that counteract the immediate effects and strengthen it against future onslaughts. The latter process would involve hormesis. However, more intense, frequent, or prolonged stress would instead overwhelm and kill the system or bring about chronic disease.[170,208,209]

The Banerji protocols also raise new questions. For instance, are there differences in effects and/or mechanisms of low- vs high-potency remedies? Are there differences in the sizes, shapes, and properties of remedy nanoparticles at low vs high potencies? The use of low-potency *Calcarea phosphorica* in combination with other higher-potency remedies may provide a generalized nanoparticulate biological augmentation strategy. *Calcarea phosphorica* 3X is a very low-potency form of calcium phosphate remedy, still well within the range of homeopathic dilutions that would leave both bulk form and nanoform source materials together with

mechanically milled lactose[78] in any given dose. Nanomedicine research has repeatedly shown anticancer properties of nanoparticulates of this mineral salt source substance for a variety of cancers, including glioma, osteosarcoma, leukemia, and gastric and liver malignancies (Table 2).

However, the Banerji protocols also use much higher potencies of plant and cancer nosode remedies (ie, more highly diluted and succussed, with only source nanoparticles and presumably no residual source bulk form material remaining). Higher remedy potencies also typically contain glass-derived silica and/or silicon in bulk and nano forms.[85,86] Are there optimal potencies for eliciting the best anticancer effects with the lowest risks? Basic science studies on homeopathic remedies in non-cancer models suggest that this may be the case.[210,211] Consecutive potencies appear not to exhibit linear dose-response relationships but rather oscillatory or sinusoidal bidirectional types of nonlinear curves.[211,212]

Knowing the composition of a material will not always reliably predict the nature or direction of its effects in nanoparticulate form.[213] A large body of research on the properties of top-down manufactured nanoparticles suggests that their properties are highly sensitive to slight variations in size, shape, defects, and surface charge.[9,22,31,82,97,214] Such structural variables may be contributing in complex ways to remedy effects and variability from study to study or patient to patient.[112] The complex adaptive network nature of living systems, including human beings and animals, adds the likelihood of state-dependent nonlinear dynamical processes in the nature of the interactive response to any salient exogenous biological signal.[70,215] Even conventional nanomaterials can still convey therapeutic effects at very low doses when tested.[216]

Furthermore, the Banerji Protocols use multiple remedies at the same time, an approach that diverges from classical homeopathic practice.[1] However, the evidence from mainstream oncology research suggests the potential therapeutic value of combining multiple therapies to overcome epigenetic-based resistance to any single intervention or cancer type.[217-219] Studying the incremental or synergistic effects of various single vs combinations of remedies on specific cancer cell lines would therefore be a crucial component of future research programs in this area. Earlier research on the combination remedy *Canova* supports this possibility. *Canova* originally contained a fixed combination of four or five different homeopathic remedies to target various cancers and infections. The current *Canova* formula for immune support in the United States includes 17 remedies, including homeopathic arsenic trioxide (*Arsenicum Album* 17X), a snake venom (*Lachesis mutus* 18X), silica (*Silicea* 18X), and the plant *Thuja occidentalis* 16X; see also Table 2).

Human beings have a limited repertoire of ways in which their bodies can react to stressors or disease processes.[220] Various cancers, for example, may involve maturation arrest of pluripotential stem cells and/or dedifferentiation of mature cells.[221,222] Thus, need for the full person–focused individualization of remedy selection in classical homeopathy may become clinically less essential in the setting of neoplastic cells. The Banerji Protocols and other homeopathic cancer treatment programs, therefore, may represent a valid approach for using homeopathic remedies to address the usual clinical presentation of a given cancer. In this type of disease, many patients will show limited, circumscribed variants of possible mechanisms and symptom manifestations. At the same time, various classical homeopaths in India and other countries also claim extraordinary case reports of positive outcomes in individualized homeopathic treatment of some of their own cancer patients.[203,223]

NEXT STEPS

Existing research expertise on the biological effects of homeopathic remedies on cancer cells can inform the design of new nanomedicine studies on ways to use less toxic natural products in cancer treatment.[5] Available data point to the need for studies on the possible role of exosomes in the initial interface of homeopathic remedies as nanoparticles conveying salient biological signals to bodily cells. Comparison of effects from (1) traditionally made homeopathic remedies such as the mineral salt *Calcarea Phosphorica*,[109] plant remedy *Gelsemium sempervirens*,[64] and the nosode breast cancer tumor remedy *Carcinosin*[110] with (2) modern nanoparticles such as calcium phosphate nanoparticles,[31] nano-encapsulated *Gelsemium* extract,[65] and breast cancer tumor–derived exosomes[6] would be useful. Techniques such as nanoparticle tracking analysis,[224,225] scanning electron microscopy, and ultraviolet visual and Raman spectroscopy[226,227] combined with fluorescent-labeled antibodies provide contemporary research tools to evaluate and characterize exosomes released during cell interactions with remedies and nanoparticulates.[225,228,229]

Finally, although the Banerji Protocols from India involve more diagnosis-related remedy selection than classical homeopathy, they still employ a flexible, albeit limited, set of remedies, partially individualized in their approach to specific types of cancers and associated symptoms. From a public health perspective, the Banerji approach strikes a pragmatic balance between the ideals of complete individualization of remedy selection in classical homeopathic constitutional prescribing[71] and the need for broader accessibility of homeopathic treatment to large, often indigent, populations worldwide.

The systemization of the Banerji approach also might permit dissemination to busy integrative clinicians who may lack the years of detailed homeopathic education needed for accurate constitutional remedy selection and case management in classical homeopathic practice.[147] A larger number of integrative

healthcare providers can learn the essential decision trees of the Banerji Protocols[1] as compared with classic alhomeopathy. Nonetheless, systematic comparative effectiveness studies of the Banerji Protocols vs (1) fully individualized classical homeopathic treatment and (2) conventional drugs and radiation treatment would better reveal the optimal clinical strategies.

Key next steps for preclinical and clinical research could involve the following.

- Replicating and extending electron microscopy studies on homeopathic remedies in independent laboratories to focus on Banerji Protocol remedies and specific homeopathic remedies previously demonstrated to exhibit antineoplastic effects in vitro or in vivo.
- Systematically applying widely used nanoparticle characterization methods to evaluate effects of varying pH, temperature, ethanol concentration, dilution procedures, succussion methods, glassware, and age of solution on the size, shape, stability, and biological effects of nanoparticles in specific homeopathic remedies made from plants, minerals, animal venoms, and malignant tumor cells. Methods would include
  - measuring particle zeta potentials, dynamic light scattering (DLS), and conducting nanoparticle tracking analysis (NTA) of remedies[192,224,230] and
  - characterizing and comparing homeopathic medicine potencies found most effective in the Banerji protocols[1,216] with other potencies of the "same" medicine, given evidence in previous research that all potencies of a given agent are not comparably active[231,232] and that nanocluster size can lead to nonlinear dose-response findings.[22]
- Identifying biochemical or physiological biomarkers used in conventional cancer research to use for testing dose-response relationships of specific homeopathic remedies.
  - A wide range of doses from possible beneficial hormetic range to toxic should be evaluated.
  - Exosome release, inflammasome proteins and cytokine activation patterns are possible biomarker candidates in addition to known mediators involved in blocking cancer cell proliferation and facilitating apoptosis of malignant cells.
- Using cell culture and animal models to determine the comparative advantages and disadvantages of homeopathically prepared vs modern manufactured nanoparticle forms and doses of specific natural products found most promising from outcomes study data.
- Pursuing clinical outcomes studies, comparative effectiveness trials, and randomized controlled trials based on the most promising Banerji Protocols for specific cancers. Candidate conditions include brain tumors (gliomas, glioblastomas multiforme) and osteosarcomas.

CONCLUSIONS

The overlaps between the manufacturing, nature, and properties of nanoparticles and those of homeopathic remedies merit additional examination.[70,112-114] Given the recent empirical findings of source nanoparticles at low and high potencies of metal[68] and plant[69] homeopathic remedies and even some homeopathically prepared conventional drugs,[212] the similarities in effects of nanoparticles and homeopathic remedies on cancer cell lines add rationale for further investigation. The fact that many homeopathic remedies begin as source materials milled/ground in lactose for hours makes initial generation of top-down nanoparticles obligatory.[98] The documented ability of (1) succussions to release silica and nanosilica from the inside walls of glassware[85] and (2) plant mother tinctures to biosynthesize nanoparticles from silica[55] or metal precursors[9,233] in solution offer additional routes for making other types of nanoparticles in liquid remedies. Succussions, like sonication,[84] could also disperse larger nanoparticles into smaller particles.

Once formed, nanoparticles accumulate heterogeneously in colloidal solution and are transferred from container to container after succussions during homeopathic manufacturing procedures.[67] These data empirically address the main historical objection of skeptics to the persistence of specific source material in higher homeopathic dilutions. Based on nanotechnology,[214] it is also possible that either (1) the remedy nanoparticles attach to, coat, dope, and/or modify the silica and silicon nanoparticles at the "higher" liquid potencies or (2) some silica nanoparticles form shells around the remedy source nanoparticle cores as templates. With or without attachment of remedy source materials to silica and/or silicon nanoparticles, nonhomeopathy studies show that silica nanoparticles[85] can augment anticancer effects of traditional natural products such as snake venom[103-105] and activate heightened immune responsivity to very low quantities of antigens[164] and vaccines overall.[88,89]

Overall, the Banerji cancer protocols raise integrative healthcare possibilities for blending the traditional clinical wisdom of experienced homeopathic practitioners from India on how to select and dose nanoparticulates for cancer treatment with the advanced contemporary methods of manufacturing nanoparticles using more replicable modern nanotechnology. Together, these concepts and tools suggest the possibility of accelerating evidence-based advances in natural product nanomedicine for treatment of people with cancer.

AUTHORS' CONTRIBUTIONS

This article began with discussions among the authors about the Banerji protocols and their interest in pursuing systematic and rigorous research to follow up the National Cancer Institute Best Case Series findings. IRB initially drafted the article; BS, PB, and PB drafted the section on the Banerji Protocols. MK edited the article for clarity and context of integrative cancer care in com-

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plex adaptive systems. SJ and JI edited the information on biological effects of nanoparticles and homeopathic remedies. All authors edited, revised, and approved the final article.

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