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

Iris R. Bell, MD, PhD, *United States*; Barbara Sarter, PhD, APRN, FNP-C, *United States*; Mary Koithan, PhD, RN, *United States*; Prasanta Banerji, FMIH, *India*; Pratip Banerji, MD(Hom), *India*; Shamini Jain, PhD, *United States*; John Ives, PhD, *United States*

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 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、白毛茛属、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*; *carcinosis*, 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

Author Affiliations
Department of Family and Community Medicine, The University of Arizona College of Medicine, Tucson (Dr Bell); College of Nursing, The University of Arizona (Drs Bell and Koithan); Hahn School of Nursing and Health Sciences, University of San Diego, California, and Bastyr University – California (Dr Sarter); PBH Research Foundation, Kolkata, India (Drs Banerji); Samuelli Institute, Alexandria, Virginia (Drs Jain and Ives).

Correspondence
Iris R. Bell, MD, PhD
ibell@email.arizona.edu

Citation
Global Adv Health Med.
2014;3(1):36-53. DOI:
10.7453/gahmj.2013.009

Key Words
Cancer treatment protocols, Banerji Protocols, complementary and alternative medicine, integrative medicine, homeopathy, nanomedicine, nanoparticles, exosomes, nosodes, hormesis, pulsed drug dosing

Disclosure
The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest, and Drs Koithan, Sarter, Banerji, Jain, and Ives disclosed no potential conflicts of interest. Dr Bell disclosed that she is a consultant to Standard Homeopathic/Hylands Inc, a United States–based manufacturer of homeopathic medicines. Dr Bell also disclosed funding to her institution from the National Institutes of Health (NCCAM T32).

investigaciones sobre los efectos anti-neoplásicos 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, silicón 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 Terms¹¹

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 those in 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 modifica-

tions 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 Q₁₀.⁶³ 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 tradition-

al 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 includes⁷²

- 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 succussions (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 trituration⁶⁷ as well as a vehicle for delivering nanoparticles.^{78,79}

The specific alcohol itself (ie, ethanol) and its con-

centration 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 glassware⁸⁷ 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 nanoparticles⁹⁹⁻¹⁰¹ 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 malig-

nant myeloma cells¹⁰⁴ 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}

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 system⁶ can all exert antiproliferative and pro-apoptotic effects on specific cancer cell lines 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

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 $\pm$ 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

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	MG-63 osteosarcoma cells	<i>Calcarea phosphorica</i> 3X ¹⁰⁹ (low potency: bulk and nanoparticles both likely present)	Osteosarcoma (clinical case reports)
Hydroxyapatite nanoparticles ^{118,119-122}	Brain cancer (glioma); decrease toxicity of chemotherapy drugs ¹¹⁸ Leukemia P388 tissue ¹²⁰ Liver tissue Gastric cancer		Brain cancer (glioma)
Tumor cell-derived exosomes ^{6,38-41}	Leukemia Lymphoma Colon melanoma Lung cancer Mesothelioma Skin melanoma Pancreatic cancer cells	<i>Carcinosin</i> 200C ¹¹⁰ (breast cancer tissue nosode remedy)	Breast cancer cells
		<i>Ruta Graveolens</i> 6C ¹⁰⁹ <i>Ruta Graveolens</i> 200C ^{123,124} <i>Thuja</i> 30C and 200C ¹²⁵	Brain cancer (glioma) Ehrlich Ascites Carcinoma and Dalton's Lymphoma Ascites Liver tumor
		<i>Hydrastis</i> 200C ¹²⁴ <i>Hydrastis</i> 1M (1000C) ¹²⁶	Ehrlich Ascites Carcinoma and Dalton's Lymphoma Ascites B16F-10 Melanoma
		<i>Lycopodium</i> 30C ¹²⁷ <i>Lycopodium</i> 200C ¹²⁸ <i>Lycopodium</i> 1M ¹²⁶	Liver cancer Liver cancer B16F-10 Melanoma
<i>Gelsemium sempervirens</i> extract encapsulated with PLGA nanoparticles ^{65,129}	Skin cancer line A375		
<i>Phytolacca decandra</i> extract encapsulated with PLGA nanoparticles ¹³⁰	Lung adenocarcinoma	<i>Phytolacca decandra</i> 200C ¹¹⁰ <i>Conium maculatum</i> 3C ¹¹⁰ <i>Thuja occidentalis</i> 30C ¹¹⁰	MCF-7 and MDA-MB-231 breast cancer cells
		<i>Chelidonium</i> 30C and 200C ¹³¹	Liver tumor
<i>Phytolacca decandra</i> , <i>Gelsemium sempervirens</i> , <i>Hydrastis canadensis</i> , <i>Thuja occidentalis</i> extracts biosynthesize silver nanoparticles ⁹	A375 skin melanoma cells		
		<i>Secale</i> 30C ¹¹⁵	Skin papilloma
<i>Polygala senega</i> extract encapsulated with PLGA nanoparticles ¹³²	A549 lung cancer cells		
		Homeopathic combination medication Canova (originally, <i>Aconitum napellus</i> D11, <i>Arsenicum album</i> D19, <i>Bryonia alba</i> D18, <i>Lachesis mutus</i> D18, <i>Thuja occidentalis</i> 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 protocols¹⁰⁹ 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 nano-form 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	<i>Phytolacca</i> 200C 2x/d; <i>Carcinosin</i> 30C on alternate nights	<i>Phytolacca</i> 200C 2x/d; <i>Carcinosin</i> 30C on alternate nights; <i>Conium maculatum</i> 3C 2x/d	<i>Thuja occidentalis</i> 30C 2x/d; <i>Carcinosin</i> 30C every night	Open ulcer with offensive discharge	<i>Psorinum</i> 1000C on alternate mornings; <i>Antimonium crudum</i> 200C + <i>Arsenicum album</i> 200C 4x/d
Osteosarcoma	<i>Symphytum</i> 200C and <i>Calcarea phosphorica</i> 3X, every 3 h alternately; <i>Carcinosin</i> 30C on alternate nights	<i>Ruta</i> 200C and <i>Calcarea phosphorica</i> 3X, every 3 h alternately	Lung metastasis: Stop <i>Carcinosin</i> and start: <i>Kali carbonicum</i> 200C on alternate days; <i>Thuja</i> 30C 2x/d	Wound infection	<i>Hypericum</i> 200C + <i>Arsenicum album</i> 200C 4x/d
Lung cancer	<i>Kali carbonicum</i> 200C on alternate days; <i>Thuja</i> 30C 2x/d; <i>Ferrum phosphoricum</i> 3X alternating every 3 h with <i>Kali muriaticum</i> 3X	<i>Carbo animalis</i> 200C 2x/d; <i>Bryonia</i> 30C + <i>Aconitum napellus</i> 200C, 2x/d		Cough Chest pain Pleural effusion Hemoptysis	<i>Ipecacuanha</i> 30C 2 pills every 1-3 h <i>Hypericum</i> 200C every 2 h <i>Lycopodium</i> 30C liquid 4x/d <i>Hamamelis</i> 200C + <i>Arnica</i> 200C 4x/d
Pancreatic cancer	<i>Carduus marianus</i> MT and <i>Conium maculatum</i> 3C liquid every 3 h alternately; <i>Chelidonium majus</i> 6X liquid 3x/d	<i>Hydrastis canadensis</i> MT and <i>Chelidonium</i> 6X liquid every 3 h alternately		Pain	<i>Belladonna</i> 3C every 10 min
Liver cancer	<i>Hydrastis canadensis</i> MT and <i>Chelidonium majus</i> 6X liquid every 3 h alternately; <i>Conium maculatum</i> 3C 2x/d	<i>Myrica</i> MT and <i>Hydrastis canadensis</i> MT every 3 h alternately; <i>Carduus marianus</i> MT 2x/d		Pain Nausea	<i>Belladonna</i> 3C every 10 min <i>Tabacum</i> 200C 2x/d or <i>Ipecacuanha</i> 30C 4x/d
Brain cancer	<i>Ruta</i> 6C 2x/d <i>Calcarea phosphorica</i> 3X 2x/d	<i>Thuja occidentalis</i> 1000C 1x/wk, added to first line		Seizures Headache Confusion Vertigo Edema	<i>Cuprum metallicum</i> 6C + <i>Arnica</i> 3C 2x/d <i>Picric Acid</i> 200C+ <i>Belladonna</i> 3C every 10 min <i>Helleborus</i> 30C liquid 2x/d <i>Conium maculatum</i> 3C 2x/d <i>Lycopodium</i> 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.pbhfindia.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 remedies¹⁷¹⁻¹⁷³ 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-Bukhsh¹¹⁵ 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} 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 cancer²⁰² 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 lactose⁷⁸ 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 pro-

cesses.²²⁰ Various cancers, for example, may involve maturation arrest of pluripotent 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 exosomes⁶ 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 prescribing⁷¹ 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 Protocols¹ as compared with classic allopathy. 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 metal⁶⁸ and plant⁶⁹ 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 glassware⁸⁵ and (2) plant mother tinctures to biosynthesize nanoparticles from silica⁵⁵ 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 nanoparticles⁸⁵ can augment anticancer effects of traditional natural products such as snake venom¹⁰³⁻¹⁰⁵ and activate heightened immune responsivity to very low quantities of antigens¹⁶⁴ 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 nanoparticles 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-

Acknowledgment

This study was supported in part by National Center for Complementary and Alternative Medicine grant T32 AT01287 (PI: IRB).

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.

REFERENCES

- Banerji P, Banerji P. The Banerji Protocols: a new method of treatment with homeopathic medicine. Kolkata, India: Prasanta Banerji; 2013.
- Banerji P, Campbell DR, Banerji P. Cancer patients treated with the Banerji Protocols utilising homeopathic medicine: a Best Case Series Program of the National Cancer Institute USA. *Oncol Rep.* 2008;20(1):69-74.
- Ramakrishnan AU. A homeopathic approach to cancer. St Louis, MO: Quality Medical Publishing; 2001.
- Master FJ. Homeopathy in cancer. India: Narayana Publishers; 2006.
- Nair HB, Sung B, Yadav VR, Kannappan R, Chaturvedi MM, Aggarwal BB. Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. *Biochem Pharmacol.* 2010;80(12):1833-43.
- Tan A, De La Pena H, Seifalian AM. The application of exosomes as a nanoscale cancer vaccine. *Int J Nanomed.* 2010;5:889-900.
- Bhattacharyya SS, Paul S, De A, et al. Poly (lactide-co-glycolide) acid nanoencapsulation of a synthetic coumarin: cytotoxicity and bio-distribution in mice, in cancer cell line and interaction with calf thymus DNA as target. *Toxicol Appl Pharmacol.* 2011;253(3):270-81.
- Bhattacharyya SS, Paul S, Khuda-Bukhsh AR. Encapsulated plant extract (*Gelsemium sempervirens*) poly (lactide-co-glycolide) nanoparticles enhance cellular uptake and increase bioactivity in vitro. *Exp Biol Med (Maywood)*;235(6):678-88.
- Das S, Das J, Samadder A, Bhattacharyya S, Das D, Khuda-Bukhsh AR. Biosynthesized silver nanoparticles by ethanolic extracts of *Phytolacca decandra*, *Gelsemium sempervirens*, *Hydrastis canadensis* and *Thuja occidentalis* induce differential cytotoxicity through G2/M arrest in A375 cells. *Colloids Surf B Biointerfaces.* 2013 Jan 1;101:325-36.
- Liang XJ. Nanopharmaceutics: the potential application of nanomaterials. Singapore: World Scientific Publishing Co; 2013.
- Ju-Nam Y, Lead JR. Manufactured nanoparticles: an overview of their chemistry, interactions and potential environmental implications. *Sci Total Environ.* 2008;400(1-3):396-414.
- Wang DC, Chen GY, Chen KY, Tsai CH. DNA as a template in self-assembly of Au nano-structure. *IET Nanobiotechnol.* 2011;5(4):132-5.
- Baca HK, Carnes E, Singh S, Ashley C, Lopez D, Brinker CJ. Cell-directed assembly of bio/nano interfaces-a new scheme for cell immobilization. *Acc Chem Res.* 2007;40(9):836-45.
- Kaehr B, Townsend JL, Kalinich RM, et al. Cellular complexity captured in durable silica biocomposites. *Proc Natl Acad Sci U S A.* 2012;109(43):17336-41.
- Merisko-Liversidge E, Liversidge GG. Nanosizing for oral and parenteral drug delivery: a perspective on formulating poorly-water soluble compounds using wet media milling technology. *Adv Drug Deliv Rev.* May 30 2011;63(6):427-440.
- Siddiqui IA, Adhmi VM, Chamcheu JC, Mukhtar H. Impact of nanotechnology in cancer: emphasis on nanochemo-prevention. *Int J Nanomed.* 2012;7:591-605.
- Buzea C, Pacheco II, Robb K. Nanomaterials and nanoparticles: sources and toxicity. *Biointerphases.* 2007;2(4):MR17-71.
- Armstead AL, Li B. Nanomedicine as an emerging approach against intracellular pathogens. *Int J Nanomed.* 2011;6:3281-93.
- Hirsjarvi S, Passirani C, Benoit JP. Passive and active tumour targeting with nano-carriers. *Curr Drug Discov Technol.* 2011;8(3):188-96.
- Hu CM, Zhang L. Nanoparticle-based combination therapy toward overcoming drug resistance in cancer. *Biochem Pharmacol.* 2012;83(8):1104-11.
- Jain KK. Advances in the field of nanomedicine. *BMC Med.* 2010;8:83.
- Roduner E. Size matters: why nanomaterials are different. *Chem Soc Rev.* 2006;35(7):583-92.
- Agadjanian H, Chu D, Hwang JY, et al. Chemotherapy targeting by DNA capture in viral protein particles. *Nanomedicine (Lond).* 2012;7(3):335-52.
- Bershteyn A, Hanson MC, Crespo MP, et al. Robust IgG responses to nanograms of antigen using a biomimetic lipid-coated particle vaccine. *J Control Release.* 2012;157(3):354-65.
- Ahmad Z, Pandey R, Sharma S, Khuller GK. Alginate nanoparticles as antituberculosis drug carriers: formulation development, pharmacokinetics and therapeutic potential. *Indian J Chest Dis Allied Sci.* 2006;48(3):171-6.
- Prakash DJ, Arulkumar S, Sabesan M. Effect of nanohypericum (Hypericum perforatum gold nanoparticles) treatment on restraint stress induced behavioral and biochemical alteration in male albino mice. *Pharmacognosy Res.* 2010;2(6):330-4.
- Jain SK, Gupta Y, Ramalingam L, et al. Lactose-conjugated PLGA nanoparticles for enhanced delivery of rifampicin to the lung for effective treatment of pulmonary tuberculosis. *PDA J Pharm Sci Technol.* May-Jun 2010;64(3):278-87.
- Sur I, Cam D, Kahraman M, Baysal A, Culha M. Interaction of multi-functional silver nanoparticles with living cells. *Nanotechnology.* Apr 30 2010;21(17):175104.
- Sahdev P, Podaralla S, Kaushik RS, Perumal O. Calcium phosphate nanoparticles for transcutaneous vaccine delivery. *J Biomed Nanotechnol.* Jan 2013;9(1):132-41.
- Maitra A. Calcium phosphate nanoparticles: second-generation nonviral vectors in gene therapy. *Expert Rev Mol Diagn.* 2005;5(6):893-905.
- Shi Z, Huang X, Liu B, Tao H, Cai Y, Tang R. Biological response of osteosarcoma cells to size-controlled nanostructured hydroxyapatite. *J Biomater Appl.* 2010;25(1):19-37.
- Bhakta G, Shrivastava A, Maitra A. Magnesium phosphate nanoparticles can be efficiently used in vitro and in vivo as non-viral vectors for targeted gene delivery. *J Biomed Nanotechnol.* 2009;5(1):106-14.
- Liu Y, Lou C, Yang H, Shi M, Miyoshi H. Silica nanoparticles as promising drug/gene delivery carriers and fluorescent nano-probes: recent advances. *Curr Cancer Drug Targets.* 2011;11(2):156-63.
- Kleps I, Ignat T, Miu M, et al. Nanostructured silicon particles for medical applications. *J Nanosci Nanotechnol.* 2010;10(4):2694-700.
- Tan YT, Kamiya T, Durrani ZA, Ahmed H. Room temperature nanocrystalline silicon single-electron transistors. *J Appl Phys.* 2003;94(1):633-7.
- Xie H, Smith JW. Fabrication of PLGA nanoparticles with a fluidic nanoprecipitation system. *J Nanobiotechnol.* 2010;8:18.
- Anitha A, Maya S, Deepa N, Chennazhi KP, Nair SV, Jayakumar R. Curcumin-loaded N,O-carboxymethyl chitosan nanoparticles for cancer drug delivery. *J Biomater Sci Polym Ed.* 2011 Jun 28. [Epub ahead of print]
- Sun D, Zhuang X, Zhang S, et al. Exosomes are endogenous nanoparticles that can deliver biological information between cells. *Adv Drug Deliv Rev.* 2013;65(3):342-7.
- Beloribi S, Ristorcelli E, Breuzard G, et al. Exosomal lipids impact notch signaling and induce death of human pancreatic tumoral SOJ-6 cells. *PLoS One.* 2012;7(10):e47480.
- Ristorcelli E, Beraud E, Mathieu S, Lombardo D, Verine A. Essential role of Notch signaling in apoptosis of human pancreatic tumoral cells mediated by exosomal nanoparticles. *Int J Cancer.* 2009;125(5):1016-26.
- Ristorcelli E, Beraud E, Verrando P, et al. Human tumor nanoparticles induce apoptosis of pancreatic cancer cells. *FASEB J.* 2008;22(9):3358-69.
- Zhu M, Li Y, Shi J, Feng W, Nie G, Zhao Y. Exosomes as extrapulmonary signaling conveyors for nanoparticle-induced systemic immune activation. *Small.* 2012;8(3):404-12.
- Zhu M, Tian X, Song X, et al. Nanoparticle-induced exosomes target antigen-presenting cells to initiate Th1-type immune activation. *Small.* 2012;8(18):2841-8.
- Mohamed BM, Verma NK, Prina-Mello A, et al. Activation of stress-related signaling pathway in human cells upon SiO₂ nanoparticles exposure as an early indicator of cytotoxicity. *J Nanobiotechnol.* 2011;9:29.
- Winter M, Beer HD, Hornung V, Kramer U, Schins RP, Forster I. Activation of the inflammasome by amorphous silica and TiO₂ nanoparticles in murine dendritic cells. *Nanotoxicology.* 2011;5(3):326-40.
- Marano F, Hussain S, Rodrigues-Lima F, Baeza-Squiban A, Boland S. Nanoparticles: molecular targets and cell signalling. *Arch Toxicol.* 2011;85(7):733-41.
- Hao S, Bai O, Li F, Yuan J, Laferte S, Xiang J. Mature dendritic cells pulsed with exosomes stimulate efficient cytotoxic T-lymphocyte responses and antitumour immunity. *Immunology.* 2007;120(1):90-102.
- Bowman CR, Bailey FC, Elrod-Erickson M, Neigh AM, Otter RR. Effects of silver nanoparticles on zebrafish (*Danio rerio*) and *Escherichia coli* (ATCC 25922): a comparison of toxicity based on total surface area versus mass concentration of particles in a model eukaryotic and prokaryotic system. *Environ Toxicol Chem.* Aug 2012;31(8):1793-1800.
- Yang J, Sandoval S, Alfaro JG, et al. Red-luminescent europium (III) doped silica nanoshells: synthesis, characterization, and their interaction with HeLa cells. *J Biomed Opt.* 2011;16(6):066012.
- Van Hoecke K, De Schampheleare KA, Ramirez-Garcia S, Van der Meeren P, Smaghe G, Janssen CR. Influence of alumina coating on characteristics and effects of SiO₂ nanoparticles in algal growth inhibition assays at various pH and organic matter contents. *Environ Int.* Aug 2011;37(6):1118-25.
- Christen V, Fent K. Silica nanoparticles and silver-doped silica nanoparticles induce endoplasmic reticulum stress response and alter cytochrome P450A activity. *Chemosphere.* Apr 2012;87(4):423-34.
- Daisy P, Saipriya K. Biochemical analysis of *Cassia fistula* aqueous extract and phytochemically synthesized gold nanoparticles as hypoglycemic treatment for diabetes mellitus. *Int J Nanomed.* 2012;7:1189-202.
- Dipankar C, Murugan S. The green synthesis, characterization and evaluation of the biological activities of silver nanoparticles synthesized from Iresine herbistii leaf aqueous extracts. *Colloids Surf B Biointerfaces.* 2012 Oct 1;98:112-9.
- Belton DJ, Deschaume O, Perry CC. An overview of the fundamentals of the chemistry of silica with relevance to biosilicification and technological advances. *FEBS J.* 2012;279(10):1710-20.
- Perry CC, Keeling-Tucker T. Crystalline silica prepared at room temperature from aqueous solution in the presence of intrasilica bioextracts. *Chem Commun (Camb).* 1998;1998(23):2587-8.
- Baca HK, Carnes EC, Ashley CE, et al. Cell-directed-assembly: directing the formation of nano/bio interfaces and architectures with living cells. *Biochim Biophys Acta.* Mar 2011;1810(3):259-67.
- Bansal SS, Goel M, Aqil F, Vadhanam MV, Gupta RC. Advanced drug delivery sys-

- tems of curcumin for cancer chemoprevention. *Cancer Prev Res (Phila)*. 2011;4(8):1158-71.
58. Ghosh D, Choudhury ST, Ghosh S, et al. Nanocapsulated curcumin: oral chemopreventive formulation against diethylnitrosamine induced hepatocellular carcinoma in rat. *Chem Biol Interact*. 2012;195(3):206-14.
 59. Bisht S, Mizuma M, Feldmann G, et al. Systemic administration of polymeric nanoparticle-encapsulated curcumin (NanoCurc) blocks tumor growth and metastases in preclinical models of pancreatic cancer. *Mol Cancer Ther*. 2010;9(8):2255-264.
 60. Chun YS, Bisht S, Chenna V, et al. Intraductal administration of a polymeric nanoparticle formulation of curcumin (NanoCurc) significantly attenuates incidence of mammary tumors in a rodent chemical carcinogenesis model: Implications for breast cancer chemoprevention in at-risk populations. *Carcinogenesis*. 2012;33(11):2242-9.
 61. Leonarduzzi G, Testa G, Sottero B, Gamba P, Poli G. Design and development of nanovehicle-based delivery systems for preventive or therapeutic supplementation with flavonoids. *Curr Med Chem*. 2010;17(1):74-95.
 62. Li H, Zhao X, Ma Y, Zhai G, Li L, Lou H. Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. *J Control Release*. 2009;133(3):238-44.
 63. Beg S, Javed S, Kohli K. Bioavailability enhancement of coenzyme Q10: an extensive review of patents. *Recent Pat Drug Deliv Formul*. 2010;4(3):245-55.
 64. Bhattacharyya SS, Mandal SK, Biswas R, et al. In vitro studies demonstrate anticancer activity of an alkaloid of the plant *Gelsemium sempervirens*. *Exp Biol Med (Maywood)*. 2008;233(12):1591-601.
 65. Bhattacharyya SS, Paul S, Khuda-Bukhs AR. Encapsulated plant extract (*Gelsemium sempervirens*) poly (lactide-co-glycolide) nanoparticles enhance cellular uptake and increase bioactivity in vitro. *Exp Biol Med (Maywood)*. 2010;235(6):678-88.
 66. Fisher P. What is homeopathy? An introduction. *Front Biosci (Elite Ed)*. 2012;4:1669-82.
 67. Chikramane PS, Kalita D, Suresh AK, Kane SG, Bellare JR. Why extreme dilutions reach non-zero asymptotes: a nanoparticulate hypothesis based on froth flotation. *Langmuir*. 2012;28(45):15864-75.
 68. Chikramane PS, Suresh AK, Bellare JR, Kane SG. Extreme homeopathic dilutions retain starting materials: a nanoparticulate perspective. *Homeopathy*. 2010;99(4):231-42.
 69. Upadhyay RP, Nayak C. Homeopathy emerging as nanomedicine. *Int J High Dilution Res*. 2011;10(37):299-310.
 70. Bell IR, Schwartz GE. Adaptive network nanomedicine: an integrated model for homeopathic medicine. *Frontiers in Bioscience (Scholar Ed)*. 2013;5(2):685-708.
 71. Hahnemann S. *Organon of the Medical Art*. 6th ed. Redmond, WA: Birdcage Books; 1843.
 72. Kayne SB. *Homeopathic pharmacy: theory and practice*. 2nd ed. Churchill Livingstone; 2006.
 73. Ludtke R, Rutten AL. The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. *J Clin Epidemiol*. 2008;61(12):1197-204.
 74. Rutten AL, Stolper CE. The 2005 meta-analysis of homeopathy: the importance of post-publication data. *Homeopathy*. Oct 2008;97(4):169-77.
 75. Shang A, Huwiler-Muntener K, Nartey L, et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet*. 2005;366(9487):726-32.
 76. Lancet. The end of homeopathy. *Lancet*. 2005;366:690.
 77. van Haselen R. The end of homeopathy: wishful thinking? *Complement Ther Med*. 2005;13(4):229-230.
 78. Caron V, Willart JF, Lefort R, Derollez P, Daned F, Descamps M. Solid state amorphization kinetic of alpha lactose upon mechanical milling. *Carbohydr Res*. 2011;346(16):2622-8.
 79. Tavares Cardoso MA, Talebi M, Soares PA, Yurteri CU, van Ommen JR. Functionalization of lactose as a biological carrier for bovine serum albumin by electrospraying. *Int J Pharmaceut*. 2011;414(1-2):1-5.
 80. Sand KK, Yang M, Makovicky E, et al. Binding of ethanol on calcite: the role of the OH bond and its relevance to biomineralization. *Langmuir*. 2010;26(19):15239-47.
 81. Yang Y, Yang AL, Yang RQ, Yuan GJ, Shi YL. Investigation of the enhancement fluorescence of ethanol doped SiO₂ nanoparticles. *J Nanosci Nanotechnol*. 2011;11(11):9717-20.
 82. Yoo JW, Yun DS, Kim HJ. Influence of reaction parameters on size and shape of silica nanoparticles. *J Nanosci Nanotechnol*. 2006;6(11):3343-6.
 83. Genina N, Raikonen H, Antikainen O, Heinamaki J, Yliruusi J. Ultrasound-assisted powder-coating technique to improve content uniformity of low-dose solid dosage forms. *AAPS Pharm Sci Tech*. 2010;11(3):1320-7.
 84. Tang C, Zhou T, Yang J, et al. Wet-grinding assisted ultrasonic dispersion of pristine multi-walled carbon nanotubes (MWCNTs) in chitosan solution. *Colloids Surf B Biointerfaces*. 2011;86(1):189-97.
 85. Ives JA, Moffett JR, Arun P, et al. Enzyme stabilization by glass-derived silicates in glass-exposed aqueous solutions. *Homeopathy*. 2010;99(1):15-24.
 86. Demangeat JL. NMR relaxation evidence for solute-induced nanosized structures in ultramolecular aqueous dilutions of silica-lactose. *J Mol Liquids*. 2010;155:71-9.
 87. Liu L, Randolph TW, Carpenter JE. Particles shed from syringe filters and their effects on agitation-induced protein aggregation. *J Pharm Sci*. 2012;101(8):2952-9.
 88. Wang T, Jiang H, Zhao Q, Wang S, Zou M, Cheng G. Enhanced mucosal and systemic immune responses obtained by porous silica nanoparticles used as an oral vaccine adjuvant: effect of silica architecture on immunological properties. *Int J Pharm*. 2012;436(1-2):351-8.
 89. Demento SL, Eisenbarth SC, Foellmer HG, et al. Inflammasome-activating nanoparticles as modular systems for optimizing vaccine efficacy. *Vaccine*. 2009;27(23):3013-21.
 90. Hornung V, Bauernfeind F, Halle A, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol*. 2008;9(8):847-56.
 91. Xiao L, Gu L, Howell SB, Sailor MJ. Porous silicon nanoparticle photosensitizers for singlet oxygen and their phototoxicity against cancer cells. *ACS Nano*. 2011;5(5):3651-9.
 92. Conibeer G, Perez-Wurfl I, Hao X, Di D, Lin D. Si solid-state quantum dot-based materials for tandem solar cells. *Nanoscale Res Lett*. 2012;7:193.
 93. Troia A, Giovannozzi A, Amato G. Preparation of tunable silicon q-dots through ultrasound. *Ultrason Sonochem*. 2009;16(4):448-51.
 94. Anick DJ, Ives JA. The silica hypothesis for homeopathy: physical chemistry. *Homeopathy*. 2007;96(3):189-95.
 95. Witt C, Albrecht H, eds. *New directions in homeopathy research*. Essen, Germany: KVC Verlag; 2009.
 96. Bornhoft G, Matthiessen PF. *Homeopathy in healthcare—effectiveness, appropriateness, safety, costs*. New York: Springer; 2011.
 97. Abbasi AR, Morsali A. Influence of solvents on the morphological properties of AgBr nano-structures prepared using ultrasound irradiation. *Ultrason Sonochem*. 2012;19(3):540-5.
 98. DeCastro CL, Mitchell BS. Nanoparticles from mechanical attrition. In: Baraton MI, editor. *Synthesis, functionalization, and surface treatment of nanoparticles*. Valencia, CA: American Scientific Publisher; 2002:1-15.
 99. Liu Y, Kathan K, Saad W, Prudhomme RK. Ostwald ripening of B-carotene nanoparticles. *Phys Rev Lett*. 2007;98(035102):1-4.
 100. Xin HL, Zheng H. In situ observation of oscillatory growth of bismuth nanoparticles. *Nano Lett*. 2012;12(3):1470-4.
 101. Gualtieri M, Skuland T, Iversen TG, et al. Importance of agglomeration state and exposure conditions for uptake and pro-inflammatory responses to amorphous silica nanoparticles in bronchial epithelial cells. *Nanotoxicology*. 2012;6(7):700-12.
 102. Elia V, Napoli E, Germano R. The 'Memory of Water': an almost deciphered enigma. Dissipative structures in extremely dilute aqueous solutions. *Homeopathy*. 2007;96(3):163-9.
 103. Al-Sadoon MK, Abdel-Maksoud MA, Rabah DM, Badr G. Induction of apoptosis and growth arrest in human breast carcinoma cells by a snake (*Walterinnesia aegyptia*) venom combined with silica nanoparticles: crosstalk between Bcl2 and caspase 3. *Cell Physiol Biochem*. 2012;30(3):653-65.
 104. Sayed D, Al-Sadoon MK, Badr G. Silica nanoparticles sensitize human multiple myeloma cells to snake (*Walterinnesia aegyptia*) venom-induced apoptosis and growth arrest. *Oxid Med Cell Longev*. 2012;2012:386286.
 105. Badr G, Al-Sadoon MK, Rabah DM, Sayed D. Snake (*Walterinnesia aegyptia*) venom-loaded silica nanoparticles induce apoptosis and growth arrest in human prostate cancer cells. *Apoptosis*. 2013;18(3):300-14.
 106. Harhaji I, Isakovic A, Raicevic N, et al. Multiple mechanisms underlying the anticancer action of nanocrystalline fullerene. *Eur J Pharmacol*. 2007;568(1-3):89-98.
 107. Lim KJ, Bisht S, Bar EE, Maitra A, Eberhart CG. A polymeric nanoparticle formulation of curcumin inhibits growth, clonogenicity and stem-like fraction in malignant brain tumors. *Cancer Biol Ther*. 2011 Mar 1;11(5):464-73.
 108. Meng J, Xing J, Wang Y, et al. Epigenetic modulation of human breast cancer by metallofullerene nanoparticles: in vivo treatment and in vitro analysis. *Nanoscale*. 2011;3(11):4713-9.
 109. Pathak S, Multani AS, Banerji P, Banerji P. Ruta 6 selectively induces cell death in brain cancer cells but proliferation in normal peripheral blood lymphocytes: a novel treatment for human brain cancer. *Int J Oncol*. 2003;23(4):975-82.
 110. Frenkel M, Mishra BM, Sen S, et al. Cytotoxic effects of ultra-diluted remedies on breast cancer cells. *Int J Oncol*. 2010;36(2):395-403.
 111. Venditto VJ, Szoka FC, Jr. Cancer nanomedicines: so many papers and so few drugs! *Adv Drug Deliv Rev*. 2013;65(1):80-88.
 112. Bell IR, Koithan M. A model for homeopathic remedy effects: low dose nanoparticles, allostatic cross-adaptation, and time-dependent sensitization in a complex adaptive system. *BMC Complement Altern Med*. 2012;12(1):191.
 113. Bell IR, Koithan M, Brooks AJ. Testing the nanoparticle-allostatic cross-adaptation-sensitization model for homeopathic remedy effects. *Homeopathy*. 2013;102:66-81.
 114. Bell IR, Schwartz GE, Boyer NN, Koithan M, Brooks AJ. Advances in integrative nanomedicine for improving infectious disease treatment in public health. *Eur J Integr Med*. 2013;5(2):126-40.
 115. Khuda-Bukhs AR, Bhattacharyya SS, Paul S, Dutta S, Boujedaini N, Belon P. Modulation of signal proteins: a plausible mechanism to explain how a potentized drug secale cor 30C diluted beyond Avogadro's limit combats skin papilloma in mice. *Evid Based Complement Alternat Med*. Jul 16 2011;2011:286320.
 116. Biswas R, Mandal SK, Dutta S, Bhattacharyya SS, Boujedaini N, Khuda-Bukhs AR. Thujone-rich fraction of *Thuja occidentalis* demonstrates major anti-cancer

- potentials: evidences from in vitro studies on A375 cells. *Evid Based Complement Alternat Med*. 2011;2011:568148.
117. de Oliveira CC, de Oliveira SM, Goes VM, Probst CM, Krieger MA, Buchi Dde F. Gene expression profiling of macrophages following mice treatment with an immunomodulator medication. *J Cell Biochem*. 2008;104(4):1364-77.
 118. Chu SH, Feng DF, Ma YB, Li ZQ. Hydroxyapatite nanoparticles inhibit the growth of human glioma cells in vitro and in vivo. *Int J Nanomed*. 2012;7:3659-66.
 119. Li G, Huang JM, Aoki H, Li Y, Zhang R, Deng BF. In vivo study on influence of a discrete nano-hydroxyapatite on leukemia P388 tissue in BALB/C mice. *Zhonghua Er Ke Za Zhi*. 2007;45(9):692-6. Chinese.
 120. Li G, Huang J, Li Y, et al. In vitro study on influence of a discrete nano-hydroxyapatite on leukemia P388 cell behavior. *Biomed Mater Eng*. 2007;17(5):321-7.
 121. Hu J, Liu ZS, Tang SL, He YM. Effect of hydroxyapatite nanoparticles on the growth and p53/c-Myc protein expression of implanted hepatic VX2 tumor in rabbits by intravenous injection. *World J Gastroenterol*. 2007;13(20):2798-802.
 122. Chen X, Deng C, Tang S, Zhang M. Mitochondria-dependent apoptosis induced by nanoscale hydroxyapatite in human gastric cancer SGC-7901 cells. *Biol Pharm Bull*. 2007;30(1):128-32.
 123. Kumar KB, Sunila ES, Kuttan G, Preethi KC, Venugopal CN, Kuttan R. Inhibition of chemically induced carcinogenesis by drugs used in homeopathic medicine. *Asian Pac J Cancer Prev*. 2007;8(1):98-102.
 124. Sunila ES, Kuttan G, Preethi KC, Kuttan R. Effect of homeopathic medicines on transplanted tumors in mice. *Asian Pacific J Cancer Prev*. 2007;8:390-4.
 125. Sunila ES, Kuttan R, Preethi KC, Kuttan G. Dynamized preparations in cell culture. *Evid Based Complement Alternat Med*. 2009;6(2):257-63.
 126. Es S, Kuttan G, Kc P, Kuttan R. Effect of homeopathic medicines on transplanted tumors in mice. *Asian Pac J Cancer Prev*. 2007;8(3):390-4.
 127. Pathak S, Kumar Das J, Jyoti Biswas S, Khuda-Bukhsh AR. Protective potentials of a potentized homeopathic drug, *Lycopodium-30*, in ameliorating azo dye induced hepatocarcinogenesis in mice. *Mol Cell Biochem*. 2006;285(1-2):121-31.
 128. Pathak S, Bhattacharjee N, Das JK, et al. Supportive evidence for the anticancerous potential of alternative medicine against hepatocarcinogenesis in mice. *Forsch Komplementmed*. 2007;14(3):148-56.
 129. Khuda-Bukhsh AR, Bhattacharyya SS, Paul S, Boujedaini N. Polymeric nanoparticle encapsulation of a naturally occurring plant scopoletin and its effects on human melanoma cell A375. *Zhong Xi Yi Jie He Xue Bao*. 2010;8(9):853-62.
 130. Das J, Das S, Samadder A, Bhadra K, Khuda-Bukhsh AR. Poly (lactide-co-glycolide) encapsulated extract of *Phytolacca decandra* demonstrates better intervention against induced lung adenocarcinoma in mice and on A549 cells. *Eur J Pharm Sci*. 2012;47(2):313-24.
 131. Biswas SJ, Khuda-Bukhsh AR. Effect of a homeopathic drug, *Chelidonium*, in amelioration of p-DAB induced hepatocarcinogenesis in mice. *BMC Complement Altern Med*. 2002 Apr 10;2:4.
 132. Paul S, Bhattacharyya SS, Boujedaini N, Khuda-Bukhsh AR. Anticancer potentials of root extract of *Polygala senega* and its PLGA nanoparticles-encapsulated form. *Evid Based Complement Alternat Med*. 2011;2011. pii: 517204.
 133. Sato DY, Wal R, de Oliveira CC, et al. Histopathological and immunophenotyping studies on normal and sarcoma 180-bearing mice treated with a complex homeopathic medication. *Homeopathy*. 2005;94(1):26-32.
 134. Leal MF, Antunes LM, Lamarao MF, et al. The protective effect of *Canova* homeopathic medicine in cyclophosphamide-treated non-human primates. *Food Chem Toxicol*. 2012;50(12):4412-20.
 135. Ahn RW BS, Raja MR, Jozefik JK, Spaho L. Nano-encapsulation of arsenic trioxide enhances efficacy against murine lymphoma model while minimizing its impact on ovarian reserve in vitro and in vivo. *PLoS ONE*. 2013;8(3):e58491.
 136. Biswas A, Gomes A, Sengupta J, et al. Nanoparticle-conjugated animal venomotoxins and their possible therapeutic potential. *J Venom Res*. 2012;3:15-21.
 137. Posadzki P, Alotaibi A, Ernst E. Adverse effects of homeopathy: a systematic review of published case reports and case series. *Int J Clin Pract*. 2012;66(12):1178-88.
 138. Walach H, Lewith G, Jonas W. Can you kill your enemy by giving homeopathy? Lack of rigour and lack of logic in the systematic review by Edzard Ernst and colleagues on adverse effects of homeopathy. *Int J Clin Pract*. 2013;67(4):385-6.
 139. Thompson E, Barron S, Spence D. A preliminary audit investigating remedy reactions including adverse events in routine homeopathic practice. *Homeopathy*. 2004;93(4):203-9.
 140. Endrizzi C, Rossi E, Crudeli L, Garibaldi D. Harm in homeopathy: aggravations, adverse drug events or medication errors? *Homeopathy*. 2005;94(4):233-40.
 141. Rajendran ES. Homeopathy as a supportive therapy in cancer. *Homeopathy*. 2004;93(2):99-102.
 142. Kassab S, Cummings M, Berkovitz S, van Haselen R, Fisher P. Homeopathic medicines for adverse effects of cancer treatments. *Cochrane Database Syst Rev*. 2009(2):CD004845.
 143. Oberbaum M, Yaniv I, Ben-Gal Y, et al. A randomized, controlled clinical trial of the homeopathic medication TRAUMEEL S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer*. 2001;92(3):684-90.
 144. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. Phase III randomized trial of *Calendula officinalis* compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. *J Clin Oncol*. 2004;22(8):1447-53.
 145. Schlappack O. Homeopathic treatment of radiation-induced itching in breast cancer patients. A prospective observational study. *Homeopathy*. 2004;93(4):210-215.
 146. Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial. *J Altern Complement Med*. 2005;11(1):21-27.
 147. Frei H, Everts R, von Ammon K, et al. Randomised controlled trials of homeopathy in hyperactive children: treatment procedure leads to an unconventional study design experience with open-label homeopathic treatment preceding the Swiss ADHD placebo controlled, randomised, double-blind, cross-over trial. *Homeopathy*. 2007;96(1):35-41.
 148. Mathie RT, Roniger H, Van Wassenhoven M, et al. Method for appraising model validity of randomised controlled trials of homeopathic treatment: multi-rater concordance study. *BMC Med Res Methodol*. Apr 17 2012;12(1):49.
 149. Olaku O, Zia F, Santana JM, White JD. The National Cancer Institute Best Case Series Program: a summary of cases of cancer patients treated with unconventional therapies in India. *Integr Cancer Ther*. 2013;12(5):385-92.
 150. Smit E, Oberholzer HM, Pretorius E. A review of immunomodulators with reference to *Canova*. *Homeopathy*. 2009;98(3):169-76.
 151. Owen D. Principles and practice of homeopathy: the therapeutic and healing process. London: Churchill Livingstone; 2007.
 152. Danhier F, Feron O, Preat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anticancer drug delivery. *J Control Release*. 2010;148(2):135-46.
 153. Fadlalla K, Watson A, Yehualaesht T, Turner T, Samuel T. *Ruta graveolens* extract induces DNA damage pathways and blocks Akt activation to inhibit cancer cell proliferation and survival. *Anticancer Res*. 2011;31(1):233-41.
 154. Preethi KC, Kuttan G, Kuttan R. Anti-tumor activity of *Ruta graveolens* extract. *Asian Pac J Cancer Prev*. 2006;7(3):439-43.
 155. Preethi KC, Nair CK, Kuttan R. Clastogenic potential of *Ruta graveolens* extract and a homeopathic preparation in mouse bone marrow cells. *Asian Pac J Cancer Prev*. 2008;9(4):763-9.
 156. Varamini P, Soltani M, Ghaderi A. Cell cycle analysis and cytotoxic potential of *Ruta graveolens* against human tumor cell lines. *Neoplasma*. 2009;56(6):490-3.
 157. Preethi K, Ellanghiyil S, Kuttan G, Kuttan R. Induction of apoptosis of tumor cells by some potentiated homeopathic drugs: implications on mechanism of action. *Integr Cancer Ther*. 2012;11(2):172-82.
 158. Sukul NC, Bala, SK, Bhattacharyya, B. Prolonged cataleptogenic effects of potentized homeopathic drugs. *Psychopharmacology*. 1986;89:338-9.
 159. Philip D. Honey mediated green synthesis of gold nanoparticles. *Spectrochim Acta A Mol Biomol Spectrosc*. Aug 15 2009;73(4):650-3.
 160. Gutierrez-Wing C, Velazquez-Salazar JJ, Jose-Yacamán M. Procedures for the synthesis and capping of metal nanoparticles. *Methods Mol Biol*. 2012;906:3-19.
 161. Sur I, Altunbek M, Kahraman M, Culha M. The influence of the surface chemistry of silver nanoparticles on cell death. *Nanotechnology*. Sep 21 2012;23(37):375102.
 162. Badr G, Al-Sadoon MK, El-Toni AM, Daghestani M. *Walterinnesia aegyptia* venom combined with silica nanoparticles enhances the functioning of normal lymphocytes through PI3K/AKT, NFκappaB and ERK signaling. *Lipids Health Dis*. 2012;11:27.
 163. Simovic S, Ghouchi-Eskandar N, Sinn AM, Losic D, Prestidge CA. Silica materials in drug delivery applications. *Curr Drug Discov Technol*. 2011;8(3):269-76.
 164. Mahony D, Cavallaro AS, Stahr F, Mahony TJ, Qiao SZ, Mitter N. Mesoporous silica nanoparticles act as a self-adjuvant for ovalbumin model antigen in mice. *Small*. 2013 Sep 23;9(18):3138-46.
 165. Elamanchili P, Lutsiak CM, Hamdy S, Diwan M, Samuel J. "Pathogen-mimicking" nanoparticles for vaccine delivery to dendritic cells. *J Immunother*. 2007;30(4):378-95.
 166. Datta S, Biswas SJ, Khuda-Bukhsh AR. Comparative efficacy of two microdoses of a potentized homeopathic drug, *Cadmium Sulphoricum*, in reducing genotoxic effects produced by cadmium chloride in mice: a time course study. *Evid Based Complement Alternat Med*. 2004;1(3):291-300.
 167. Bhattacharjee N, Khuda-Bukhsh AR. Two homeopathic remedies used intermittently provide additional protective effects against hepatotoxicity induced by carcinogens in mice. *J Acupunct Meridian Stud*. 2012;5(4):166-75.
 168. Iavicoli I, Calabrese EJ, Nascarella MA. Exposure to nanoparticles and hormones. *Dose Response*. 2010;8(4):501-17.
 169. Sugarman J, Tsai S, Santamaria P, Khadra A. Quantifying the importance of pMHC valency, total pMHC dose and frequency on nanoparticle therapeutic efficacy. *Immunol Cell Biol*. 2013;91:350-9.
 170. Winnik FM, Maysinger D. Quantum dot cytotoxicity and ways to reduce it. *Acc Chem Res*. 2013 Mar 19;46(3):672-80.
 171. Van Wijk R, Wiegant FA. Postconditioning hormones and the homeopathic Similia principle: molecular aspects. *Hum Exp Toxicol*. 2010;29(7):561-5.
 172. Van Wijk R, Wiegant FA. Postconditioning hormones and the similia principle. *Front Biosci (Elite Ed)*. 2011;3:128-38.
 173. Wiegant FA, Prins HA, Van Wijk R. Postconditioning hormones put in perspective: an overview of experimental and clinical studies. *Dose Response*. 2011;9(2):209-24.

174. McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. *PLoS Comput Biol*. 2009;5(5):e1000348.
175. Torres JL, Ruiz MAG. Stochastic resonance and the homeopathic effect. *British Homeopathic J*. 1996;85(3):134-40.
176. Nascarella MA, Calabrese EJ. A method to evaluate hormesis in nanoparticle dose-responses. *Dose Response*. 2012;10(3):344-54.
177. Vaiserman AM. Hormesis, adaptive epigenetic reorganization, and implications for human health and longevity. *Dose Response*. 2010;8(1):16-21.
178. Leri F, Zhou Y, Carmichael B, Cummins E, Kreek MJ. Treatment-like steady-state methadone in rats interferes with incubation of cocaine sensitization and associated alterations in gene expression. *Eur Neuropsychopharmacol*. 2012;22(2):143-52.
179. Milisav I, Poljak B, Suput D. Adaptive response, evidence of cross-resistance and its potential clinical use. *Int J Mol Sci*. 2012;13(9):10771-806.
180. Kagias K, Nehammer C, Pocock R. Neuronal responses to physiological stress. *Front Genet*. 2012;3:222.
181. Frank MG, Thompson BM, Watkins LR, Maier SF. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. *Brain Behav Immun*. 2012;26(2):337-45.
182. Antelman SM, Caggiula AR. Oscillation follows drug sensitization: implications. *Crit Rev Neurobiol*. 1996;10(1):101-17.
183. Caggiula AR, Antelman SM, Kucinski BJ, et al. Oscillatory-sensitization model of repeated drug exposure: cocaine's effects on shock-induced hypoalgesia. *Prog Neuropsychopharmacol Biol Psychiatry*. 1998 Apr;22(3):511-21.
184. Snow ET, Sykora P, Durham TR, Klein CB. Arsenic, mode of action at biologically plausible low doses: what are the implications for low dose cancer risk? *Toxicol Appl Pharmacol*. 2005;207(2 Suppl):557-64.
185. Calabrese E, Iavicoli I, Calabrese V. Hormesis: Its impact on medicine and health. *Hum Exp Toxicol*. 2013;32(2):120-52.
186. Pinamonti G, Marro J, Torres JJ. Stochastic resonance crossovers in complex networks. *PLoS One*. 2012;7(12):e31170.
187. Demirovic D, Rattan SI. Curcumin induces stress response and hormetically modulates wound healing ability of human skin fibroblasts undergoing ageing in vitro. *Biogerontology*. 2011;12(5):437-444.
188. Demirovic D, Rattan SI. Establishing cellular stress response profiles as biomarkers of homeodynamics, health and hormesis. *Exp Gerontol*. 2013;48(1):94-8.
189. Sandberg WJ, Lag M, Holme JA, et al. Comparison of non-crystalline silica nanoparticles in IL-1 β release from macrophages. *Part Fibre Toxicol*. 2012;9(1):32.
190. Gong C, Tao G, Yang L, Liu J, Liu Q, Zhuang Z. SiO₂ nanoparticles induce global genomic hypomethylation in HaCaT cells. *Biochem Biophys Res Commun*. 2010;397(3):397-400.
191. Khrapin CY, Pristinski D, Dunphy DR, Brinker CJ, Kaehr B. Protein-directed assembly of arbitrary three-dimensional nanoporous silica architectures. *ACS Nano*. 2011;5(2):1401-9.
192. Aime C, Mosser G, Pemboung G, Bouteiller L, Coradin T. Controlling the nanobio interface to build collagen-silica self-assembled networks. *Nanoscale*. 2012 Nov 21;4(22):7127-34.
193. Tan SJ, Campolongo MJ, Luo D, Cheng W. Building plasmonic nanostructures with DNA. *Nat Nanotechnol*. 2011;6(5):268-76.
194. Wang L, Xu L, Kuang H, Xu C, Kotov NA. Dynamic nanoparticle assemblies. *Acc Chem Res*. 2012 Nov 20;45(11):1916-26.
195. Wu J, Silvent J, Coradin T, Aime C. Biochemical investigation of the formation of three-dimensional networks from DNA-grafted large silica particles. *Langmuir*. 2012;28(4):2156-65.
196. Montagnier L, Aissa J, Ferris S, Montagnier J-L, Lavallec C. Electromagnetic signals are produced by aqueous nanostructures derived from bacterial DNA sequences. *Interdiscip Sci Comput Life Sci*. 2009;1:81-90.
197. Relais S, Leheny RL, Reven L, Sutton M. Memory effect in composites of liquid crystal and silica aerosol. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2011;84(6):061705.
198. Salonen J, Kaukonen AM, Hirvonen J, Lehto VP. Mesoporous silicon in drug delivery applications. *J Pharm Sci*. 2008;97(2):632-53.
199. Kang Z, Liu Y, Lee ST. Small-sized silicon nanoparticles: new nanolights and nanocatalysts. *Nanoscale*. 2011;3(3):777-91.
200. Calabrese EJ, Mattson MP. Hormesis provides a generalized quantitative estimate of biological plasticity. *J Cell Commun Signal*. 2011;5(1):25-38.
201. Li X, Ding X, Adrian TE. Arsenic trioxide induces apoptosis in pancreatic cancer cells via changes in cell cycle, caspase activation, and GADD expression. *Pancreas*. 2003;27(2):174-9.
202. Ahn RW, Chen F, Chen H, et al. A novel nanoparticulate formulation of arsenic trioxide with enhanced therapeutic efficacy in a murine model of breast cancer. *Clin Cancer Res*. 2010;16(14):3607-17.
203. Boericke W. Pocket manual of homeopathic Materia Medica. Santa Rosa, CA: Boericke and Tafel, Inc; 1927.
204. Das D, De A, Dutta S, Biswas R, Boujedaini N, Khuda-Bukhsh AR. Potentized homeopathic drug *Arsenicum Album* 30C positively modulates protein biomarkers and gene expressions in *Saccharomyces cerevisiae* exposed to arsenate. *Zhong Xi Yi Jie He Xue Bao*. Jul 2011;9(7):752-60.
205. Seligmann IC, Lima PD, Cardoso PC, et al. The anticancer homeopathic composite "Canova Method" is not genotoxic for human lymphocytes in vitro. *Genet Mol Res*. 2003;2(2):223-8.
206. Vaiserman AM. Hormesis and epigenetics: is there a link? *Ageing Res Rev*. 2011;10(4):413-21.
207. Stark M. The sandpile model: optimal stress and hormesis. *Dose Response*. 2012;10(1):66-74.
208. Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. *Trends Cogn Sci*. 2011;15(12):576-84.
209. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35(1):2-16.
210. Bellavite P, Conforti A, Marzotto M, et al. Testing homeopathy in mouse emotional response models: pooled data analysis of two series of studies. *Evid Based Complement Alternat Med*. 2012;2012:954374.
211. Malarczyk E, Pazdzioch-Czochra M, Graz M, Kochmanska-Rdest J, Jarosz-Wilkolazka A. Nonlinear changes in the activity of the oxygen-dependent demethylase system in *Rhodococcus erythropolis* cells in the presence of low and very low doses of formaldehyde. *Nonlinear Biomed Phys*. 2011;5(1):9.
212. Stovbun SV, Kiselev AV, Zanin AM, et al. Effects of physicochemical forms of phenazepam and Panavir on their action at ultra-low doses. *Bull Exp Biol Med*. 2012;153(4):455-8.
213. Napierska D, Thomassen LC, Rabolli V, et al. Size-dependent cytotoxicity of monodisperse silica nanoparticles in human endothelial cells. *Small*. 2009;5(7):846-53.
214. Cao G, Wang Y. Nanostructures and nanomaterials: synthesis, properties, and applications, 2nd ed. Singapore: World Scientific Publishing Co; 2011.
215. Koithan M, Bell IR, Niemeyer K, Pincus D. A complex systems science perspective for whole systems of CAM research. *Forsch Komplementmed*. 2012;19(Suppl 1):7-14.
216. Antaris AL, Robinson JT, Yaghi OK, et al. Ultra-low doses of chirality sorted (6,5) carbon nanotubes for simultaneous tumor imaging and photothermal therapy. *ACS Nano*. 2013;7(4):3644-52.
217. Foo J, Michor F. Evolution of resistance to targeted anticancer therapies during continuous and pulsed administration strategies. *PLoS Comput Biol*. Nov 2009;5(11):e1000557.
218. Gary-Bobo M, Vaillant O, Maynadier M, et al. Targeting multiplicity: the key factor for anticancer nanoparticles. *Curr Med Chem*. 2013;20(15):1946-55.
219. Sun J, Luo C, Wang Y, He Z. The holistic 3M modality of drug delivery nanosystems for cancer therapy. *Nanoscale*. 2013;5(3):845-59.
220. Smith SB, Dampier W, Tozeren A, Brown JR, Magid-Slav M. Identification of common biological pathways and drug targets across multiple respiratory viruses based on human host gene expression analysis. *PLoS One*. 2012;7(3):e33174.
221. Ribas A, Tumei PC. Cancer therapy: tumours switch to resist. *Nature*. 2012;490(7420):347-8.
222. Sell S. Cellular origin of cancer: dedifferentiation or stem cell maturation arrest? *Environ Health Perspect*. 1993;101 Suppl 5:15-26.
223. Vijayakar P. Genetic Materia Medica. Tri-miasmatic Materia Medica. Mumbai, India: Preeti Vijayakar; 2011.
224. Bell NC, Minelli C, Tompkins J, Stevens MM, Shard AG. Emerging techniques for submicrometer particle sizing applied to stober silica. *Langmuir*. 2012;28(29):10860-72.
225. Gerce-Taylor C, Atay S, Tullis RH, Kesimer M, Taylor DD. Nanoparticle analysis of circulating cell-derived vesicles in ovarian cancer patients. *Anal Biochem*. 2012;428(1):44-53.
226. Pyrgiotakis G, Bhowmick TK, Finton K, et al. Cell (A549)-particle (Jasada Bhasma) interactions using Raman spectroscopy. *Biopolymers*. 2008;89(6):555-64.
227. Rao M, Roy R, Bell IR. Characterization of the structure of ultra dilute sols with remarkable biological properties. *Mater Lett*. 2008;62:1487-90.
228. Dragovic RA, Gardiner C, Brooks AS, et al. Sizing and phenotyping of cellular vesicles using nanoparticle tracking analysis. *Nanomedicine*. 2011;7(6):780-8.
229. Soo CY, Song Y, Zheng Y, et al. Nanoparticle tracking analysis monitors microvesicle and exosome secretion from immune cells. *Immunology*. 2012;136(2):192-7.
230. Zhang Y, Yang M, Portney NG, et al. Zeta potential: a surface electrical characteristic to probe the interaction of nanoparticles with normal and cancer human breast epithelial cells. *Biomed Microdevices*. Apr 2008;10(2):321-328.
231. Banerji P, Campbell DR. Cancer patients treated with the Banerji Protocols utilising homeopathic medicine: a Best Case Series Program of the National Cancer Institute USA. *Oncol Rep*. Jul 2008;20(1):69-74.
232. Magnani P, Conforti A, Zanolin E, Marzotto M, Bellavite P. Dose-effect study of *Gelsemium sempervirens* in high dilutions on anxiety-related responses in mice. *Psychopharmacology (Berl)*. Jul 2010;210(4):533-545.
233. Philip D. Green synthesis of gold and silver nanoparticles using *Hibiscus rosa sinensis*. *Physica E Low Dimens Sys Nanostruct*. 2010;42:1417-24.