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Extending the Adaptive Network Nanomedicine Model for Homeopathic Medicines: Nanostructures as Salient Cell Danger Signals for Adaptation

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Abstract

This paper examines the growing evidence supporting the adaptive network nanomedicine model for Homeopathic Medicines (HMs) and their actions. Multiple laboratories have identified nanostructures in homeopathically-manufactured medicines at low and high potencies. Replicated studies in mainstream pharmaceutical research and in homeopathy have also demonstrated elevated levels of elemental silicon and/or bioactive silica Nanoparticles (NPs) released from glassware during agitation or multiple homeopathic succussions. The model suggests that (a) very low potency HMs are complex mixtures of bulk, micro- and nanoscale forms of the medicine's natural source material made by prolonged mechanical grinding (trituration) in dry lactose; (b) low and higher potency liquid HMs made in glass containers are nanocomposite materials formed from source NPs, nanosilica-coated source NPs, adjuvant nanosilica and source-doped, coated, seeded or template nanosilica in colloidal solutions that can survive drying. We hypothesize that HMs include hybrid nanostructures of various sources, small sizes, shapes, surface defects, zeta potentials, and surface reactivity. HMs serves as individually-salient, sub toxic virus-like foreign danger signals. Nanosilica would help carry and amplify the fingerprint signal of co-occurring and adsorbed source material on its surfaces at higher liquid potencies. Cell Defense Response (CDR) network constituents that HMs modulate involve gene expression, cytokine release, cell signaling, and cell stress mediators. Once triggered, nonlinear endogenous amplification processes facilitate evolution of the therapeutic response over time.

Keywords: Homeopathy; Nanoparticles; Silica; Adsorption; Surface chemistry; Protein corona; Cell danger response; Danger-Associated Molecular Patterns (DAMP); Biological signaling; Adaptation; Hormesis; Inflammasome; Heat shock proteins; Oxidative stress; Cell stress; Cell signaling; Cytokines; Gene expression

Abbreviations

HSPs: Heat Shock Proteins; AMPs: Antimicrobial Peptides; D-cells: Dendritic Cells; ERVs: Endogenous Retroviruses; LINEs: Long Interspersed Nuclear Elements; meDNA: Methylated DNA; dNTPs: Deoxynucleoside Triphosphates; CNS: Central Nervous System; HMs: Homeopathic Medicines; NPs: Nanoparticles; DAMP: Danger-Associated Molecular Patterns

Introduction

This paper articulates and expands upon a model based on the biological implications of the discovery of source and silica nanostructures in Homeopathic Medicines (HMs). The paper summarizes growing data on the nanotechnology aspects and findings for nanostructures in HMs and discusses ways in which these agents can act at the nanoscale in the body [1,2]. Substantial evidence indicates that nanomaterials possess unique capacities for triggering size-, shape-, and surface property-dependent biological responses, even at very low concentrations [3-7] (Table1). The present model may also have more general implications for exploring novel therapeutic mechanisms such as hormesis [7,8] for the field of nanomedicine and perhaps for evaluating effects of environmentally-relevant, low level nanomaterials in nanotoxicology [9-11].

Homeopathy is a traditional, albeit controversial, system of Complementary and Alternative Medicine (CAM) used worldwide, notably in India, Latin America, the United Kingdom, and Europe. The nature and mechanisms of action of HMs have stirred intense debate throughout the more than 200-year history of homeopathy's existence as a natural product-based system of CAM [12]. Preparation of HMs involves serial steps of dilution of plant, animal, or mineral source materials in dry lactose, ethanol/

water, or water using ratios of 1:10 (X potency series) or 1:100 (C potency series). Each dilution step is followed by extensive mechanical grinding in dry materials or "succussions" in liquid dilutions (i.e., 10 or more agitations/step via manual pounding on a hard but elastic surface or vortexing). For diagnosis and treatment, practitioners of individualized homeopathy obtain detailed clinical and personal/social histories to match a single HM's potential multi-system effects to a given patient's complex symptom and behavioral state or presentation pattern [13].

A number of homeopathic investigators continue to study basic science models involving structured water, but, with only rare exceptions [14], overlook the fact that (a) very low potency insoluble HMs are never diluted in any water at all and that (b) after preparation, even high potency HMs are often dried onto lactose sugar pellets for storage and administration. Nonetheless, data suggest that in liquid solution, the original solutes may induce nanostructure formation of the ethanol-water or water solvent [15-17]. Skeptics continue to insist (incorrectly) that the serial dilution processes of homeopathic manufacturing must theoretically remove any trace of the original source material by the 12C and 24X or higher potencies (i.e., bulk dilution to $(100)^{12}$ or 10^{24} where Avogadro's number of molecules is 6×10^{23}), thus rendering all HMs as presumptive biologically inert placebos [12].

Empirical data, however, only document removal of the bulk forms of the source material during homeopathic manufacturing at higher potencies [18]. Evidence for the persistence of nanoscale forms of the source material by itself and/or the more abundant nanosilica and/or other materials from the agitation of liquid solutions in their containers (typically, but not always glassware) via multiple succussions is growing for both low (e.g., 1X, 2X, 3X, up to 6X, 12X or 6C) and higher (e.g., above 12C or 24X) homeopathic potencies (Tables 2 and 3).

The ability of the HM NPs to survive serial dilutions likely depends upon the multiple succussions (agitation in liquid) that follow every dilution step. Studies demonstrate that succussions induce heterogeneous layering of source NPs in solution for collection in the "dilution" steps, perhaps via air bubble formation of various sizes [18]. No studies have yet examined the impact of different sampling procedures for transferring a measured 1/10 or 1/100 portion of the solution from one preparation step to the next. However, variability in materials and methods is one of multiple potential factors contributing to variability of the final product HMs [19]. Evidence also indicates that agitation of solutions can also embed source NPs into glassware, from which they can leach back into solution over time [20]. To make higher potency HMs, manufacturers usually resort to Korsakovian methods by re-using the same piece of glassware for every serial dilution/succussion step beyond a certain potency, e.g., 15C-25C. Agitation per se also releases silicates and generates potentially bioactive silica NPs throughout the manufacturing process [21,22]. In contrast, the larger bulk form source materials are removed over serial dilutions and succussions [18].

In recent years, the empirical data on HMs support a testable, hypothesis-driven model based on the generation of source and silica and/or other container- and reagent-derived nanoparticles (NPs) in HMs during the manufacturing process [1,2,23,24]. In nanotechnology, grinding or ball milling of materials (comparable to the initial homeopathic manufacturing steps of trituration in dry lactose for very low potencies) as well as sonication and/or water jet treatment (comparable to homeopathic manufacturing steps of repeated succussions in water or water-ethanol diluents at room temperature for higher potencies), generate micro- and nano-sized particles of the original source material [20,25-29] (Table 3). Once generated, NPs in HMs could provide the forms capable of generating the unique electromagnetic, optical, thermal, and quantum mechanical phenomena previously reported in HMs [30-33].

In addition, pharmaceutical research has repeatedly shown that agitation of liquids in glassware generates silica micro- and nanoparticles [22,34]. One study of elements generated during the earliest homeopathic potentiating steps using brown glass bottles also found various substances such as Sodium (Na), Silicon (Si), Magnesium (Mg), Lithium (Li) and other substances as trace contaminants [35]. On interaction with air, the silicon will readily form silica (silicon dioxide). Adding silica NPs to other agents can markedly amplify the biological impact on immune function [36] and anti-cancer cell effects [37-40].

In solution, silica NPs can both (a) adsorb trace amounts of other source materials such as plant, animal, and human proteins, minerals or metal NPs onto their large surface area [41-44] and (b) use other materials, e.g., viruses, plant constituents, or chemical agents, as templates to imprint their structural and chemical information onto surfaces of silica nanostructures [45-48]. Surface-adsorbed materials modify silica NP bio-reactivity [49], potentially carry the source material "fingerprint" [41,50-52], and could amplify the information of the original source [53-56] into higher potencies. Plant extracts can also biosynthesize silica or metal NPs from respective precursors in water [57], leaving trace bioactive specific plant materials on the resultant NP surfaces [58-60]. One study that needs independent replication reported that increasing the numbers of succussions will reduce the particle size of plant source materials into the nanoscale range [61].

The present paper proposes that the nanoscale versus bulk form of HMs makes a critical difference in understanding how these agents can interact with living systems. By their nature, nanoscale forms differ from bulk (conventional macro scale) forms of any given material with size- and shape-dependent immune, biochemical, electromagnetic, optical, and quantum properties [62-66]. At the nanoscale, particle size, shape, and surface charge as well as ionic constituents, temperature, and pH of the surrounding medium can markedly change the properties and effects of a given type of NP [17,43,62,67-69]. The factors that could particularly foster host adaptive responses encompass virus-like properties of certain NPs [36] and their ability to trigger the cell danger response pathways of the body as exogenous stressors or stimuli [70]. Some larger NPs can exert bacteria-like

effects on living systems as well [71].

Unique features of nanomaterials: virus-like properties and adaptive responses

The nanoscale is the level of biological system organization where viruses (10-150 nm) [62] and virus-like nanomaterials occur [71]. At virus sizes, NPs activate biological activity in part via anti-virus Cell Danger Or Defense Response (CDR) pathways or networks in the body [36,70,71]. In particular, irregular surfaces and rougher virus-like surfaces on NPs, such as the type homeopathic mechanical grinding methods or ball milling would produce [72,73], tend to foster binding of biomolecules and cell uptake better than more perfect surfaces of modern engineered NPs [74,75]. Table 1 lists the virus-like characteristics of the most biologically-active nanomaterials.

In nanotoxicology, despite the same "doses" (e.g., *in vitro* 1 ug/ml, 10 ug/ml), a specific size range (60-120 nm) and zeta potential value (surface charge/stability, e.g., -37 to -41 millivolts) of diesel exhaust nanoparticles are more likely to trigger cytokine activation and protein expression in human immune cells whereas NPs of other sizes and zeta potentials do not trigger bio-reactivity [70]. Finally, different surface coatings of zinc oxide NPs (e.g., triethoxycaprylylsilane or dimethoxydiphenylsilane/triethoxycaprylylsilane cross polymer or uncoated) modify the adaptive responses of human olfactory cells by modulating manifestations of cell stress, inflammatory response (cytokine patterns), and apoptotic cell death [76].

The usual assumptions premised on composition (source material) and dose that are the primary factors for evaluating bulk form conventional pharmaceutical drugs are not sufficient and sometimes not readily applicable at the nanoscale for the "same" source material, including HMs. For instance, simply diluting a stock solution of fullerite carbon-based NPs will produce NPs with morphological properties different from those of the more concentrated stock solution [77]. One size NP of a given source material can exert different effects from another size NP of the same source material, e.g., 80 nm engineered calcium phosphate/hydroxyapatite NPs are more effective at killing osteosarcoma cells than are 20 nm NPs of the "same" source material [78].

In triggering adaptive responses, nanoparticles are known to act on gene expression, cytokine release, and signaling pathways or networks as cell danger signals for the body, in part by activating Danger-Associated Molecular Pattern (DAMP) recognition receptors [79,80].

Endogenous response amplification to NPs is nonlinear and potentially multi-factorial [23], including but not limited to immune/inflammatory/metabolic mediator modulation [81], nervous system cross-sensitization [2], and adaptive changes of hormesis [82]. Nanomaterials are often inherently more potent than their bulk form counterparts [63,83], lowering doses needed for direct effects by orders of magnitude [84], and even lower for adaptive phenomena like vaccine immune responses [53,54,56,85] and hormesis [1,7,8,82].

Source and silica nanoparticles in homeopathically-prepared medicines

Convergent evidence now points to the presence of nanostructures in homeopathically-prepared medicines made from natural, mineral and plant as well as synthetic drug sources (Table 2). In 2010, Chikramane, et al. [19] first reported transmission electron microscope images of source metal NPs, mostly less than 15 nanometers in size, in commercially-made HMs of gold, silver, copper, zinc, platinum, and tin at 6C, 30C, and 200C potencies. They confirmed the presence of the respective source metals using Inductively-Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) up to the parts per billion ranges. Subsequently, these researchers demonstrated that trituration (mechanical grinding) in lactose followed by serial dilutions and succussions (violent agitation of the liquid solution inside glassware), i.e., the unique manufacturing methodology of homeopathy, leads to heterogenous accumulation and transfer of the metal nanoparticles in solution from one "dilution" step to the next, even though bulk forms of the material are removed [18]. Bulk forms of a material are inherently much larger than their nanoscale counterparts, and such differences in their forms can lead to the significant differences in properties as a function of size [64].

Other research groups followed with both electron microscopic and Dynamic Light Scattering (DLS) data showing the formation of nanostructures during homeopathic potentization procedures and/or using homeopathic mother tinctures (herbal extract concentrates) (Table 2). Consistent with a large body of non-homeopathic research in nanotechnology e.g., [27], one study of homeopathically-prepared test materials specifically reported that increasing the number of succussions produced

Table 1: Virus-Mimicking Characteristics of the Most Biologically Active Nanoparticles (NPs).

Finding	Comment
Particle sizes in the range of viruses [36,70]	10-150 nm size range [62]
Virus-like particle surface defects from mechanical grinding (top-down processes [72]) or other manufacturing procedures increase bio-molecular binding and cell uptake [74,75]	Defects include cracks, fissures, roughness, folds, and pores [44,72,86]
Virus-like activation of cell defense response (CDR) mediator pathways/networks [36,81]	CDR changes involve cell metabolism; cell membrane stiffness; antiviral chemical release; autophagy; DNA methylation and histones to alter gene expression, endogenous nucleic-acid-related protection mobilization to produce genetic variants; cell-to-cell signaling mediator release including cytokines and eicosanoids; host behavioral changes [87]

progressively smaller and smaller sizes of nanoparticles of source plant extract materials down to approximately 14 nanometers (nm) [61].

Similarly, analogous to HM manufacturing processes, either prolonged ball milling (grinding) of rice husk ash or longer periods of sonication (agitation of a liquid) of waste eggshells will generate nanoparticles respectively, of silica or of calcium carbonate [26,27]. Sonication of a solution of sodium chloride or potassium iodide will both generate source nanoparticles and embed them into glassware [20]. *Silicea*, *Calcarea Carbonica* ($CaCO_3$), *Natrum Muriaticum* (sea salt, NaCl), and *Kali Iodatum* (KI) are also all widely-used HMs. In nanomedicine research, extracts of source materials such as common plant-derived foods (carrot, ginger, grapefruit) [88,89] or tea [90] generate nanosized vesicles called exosomes that modulate gene expression, cytokine and other biological mediator release in animal or human cells. Exosomes are small sized membrane vesicles that can contain lipids, adhesion and intercellular signaling molecules, proteins and RNAs from their original source cell interior [91].

Meanwhile, other homeopathic investigators repeatedly found that agitation per se releases variable but readily measurable amounts of elemental silicon (which quickly generates silicon dioxide or silica on contact with oxygen) into solution from the inner walls of the glassware in the parts per million ranges (Table 3). The silica appears to be in the form of both larger sized and nanoscale particles with the capacity to interact with proteins and cause inflammatory and/or immune system activation [22,34,92]. Ives et al. [21] originally proposed a silica-based model for HMs. The latter group demonstrated that the homeopathic succussion-released silica stabilized acetylcholine esterase enzyme activity, similar to a finding recently replicated for modern engineered silica nanoparticles coated on their surfaces with polyethyleneimine [43].

Thus, whether or not source NPs make their way into a given dose of a homeopathic medicine, it is highly likely that biologically-active nanosilica and even larger silicate aggregates and/or other nanostructures will occur with each succussion step and persist in HMs at higher potencies during classical homeopathic manufacturing. The silicates are known to interact with salts, amino acids, and proteins, e.g., from plant extracts or animal fluids, to form aggregates of 3D gel networks [93]. Depending on pH and amounts of other materials in solution, various sizes of nanosilica can also form [93]. Apart from manufactured forms, biosilica with unique physical properties is well-known to form in the natural environment within single-celled organisms, higher plants [94], and primitive animals such as sponges [93], all of which are commonly-used source materials in homeopathic manufacturing.

Ives, et al. [21] also showed that repeated succussions will first raise, then gradually lower the pH of a homeopathically-prepared solution from alkaline toward a more neutral buffered pH near 7. In turn, this group noted, studies show that this drift of pH values fosters conversion of precursor monomer silicates in a solution into nanoparticle forms of silica [95]. Thus, nanosilica is highly likely to be a key constituent of any homeopathically-prepared potency in liquid solutions made in glass. At the same time, studies have demonstrated that silicates in water can shift between uncondensed monomers to colloidal nanoscale particle forms to larger 3-dimensional silicate structures, depending on conditions in the medium [93]. Both doped nanosilica and the

Table 2: Summary of studies on nanostructures reported in homeopathically-prepared medicines.

Study	Technology	Homeopathically-prepared materials
Chikramane et al. [19]	Transmission electron microscopy, ICP-AES	Gold, silver, copper, zinc, platinum, tin up to 200C
Chikramane et al. [18]	Transmission electron microscopy	Gold NPs up to 15C
Upadhyay and Nayak [96]	Scanning electron microscopy	*Pulsatilla, Belladonna, Colchicum* (plants) up to 15C
Demangeat [15]	Nuclear magnetic resonance	Silica/lactose up to 21C
Das et al. [59]	Transmission electron microscopy, zeta potential	Silver NPs biosynthesized by *Thuja, Hydrastis, Phytolacca, Gelsemium* plant mother tincture extracts
Barve and Chaughule [61]	Dynamic light scattering	*Terminalia arjuna, Holarrhena* plant mother tinctures
Stovbun et al. [97]	Dynamic light scattering	*Phenazepam, Panavir* (synthetic drugs)
Elia et al. [14,98]	Atomic force microscopy, fluorescence microscopy, FT-IR and UV-vis spectroscopy	Water in glassware up to 200C
Konovalov and Ryzhkina [17]	Dynamic light scattering, zeta potential, atomic force microscopy, microelectophoresis, conductivity, ultraviolet and EPR spectroscopy	Nanostructures triggered by highly diluted solutes (alpha tocopherol, ichfan C-10, potassium phenosan) interacting with external physical fields (geomagnetic, low frequency electromagnetic) and solution preparation procedures
Rajendran [99]	Field emission scanning electron microscopy and energy dispersive spectroscopy	Nanoparticles detected at all potencies evaluated, including plant derived *Lycopodium* 6C, 30C, 200C, 1M, 10M, 50M, and CM potencies but not in 90% ethanol (alcohol) controls. NP sizes ranged from 12 nm to 832 nm with varying observations of agglomerates at 6C potency vs. many clusters at extremely high potencies. All verum samples were sonicated prior to evaluation.

smallest sizes of silicon NPs, e.g., silicon quantum dots (e.g., NPs < 10 nm sizes) per se, offer potentially size-tunable semiconductor nanocrystals with (a) nontoxic delivery vehicle properties for organic materials and various drugs on their surfaces and (b) small size-related quantum confinement-related fluorescence [100,101]. Similarly, homeopathically-prepared medicines have exhibited photo luminescent properties distinct from those of control materials in two different laboratories [32,50].

Notably, silica precursors can self-assemble around a virus, plant constituent, chemical toxicant, protein or other templates and/or form a stabilizing shell on the outside of core NPs in solution to form silica shell-source core nanocomposite [45,48,102-105]. Other constituents in the solution such as ethanol or salt concentrations and pH will modify the thickness and/or surface properties of the silica shell [69,103,106-109]. In homeopathy research, Elia et al. [110] have repeatedly demonstrated that raising the pH of homeopathically-prepared solutions to a highly alkaline level will increase the release of heat and specific conductivity significantly more than those of unsuccussed dilute control solutions. Investigators of the latter studies interpreted the heat release as an indication of disrupted order of the materials in solution. Cartwright [51,111] recently reported an essential role for silanol (Si-O-H) groups on the quartz glass surfaces and ions in solution rather than water in carrying the specific information of a given HM. As noted above, plant extracts can also biosynthesize silica NPs, leaving trace amounts of their plant material proteins, nucleic acids and other organic constituents on the surfaces of the resultant silica NPs [57,94].

Is there evidence for biological effects of remedy source-free HMs, but homeopathically–prepared control solutions containing only the silicates from the glassware (i.e. succussed)? In an *in vitro* cell culture wound injury/repair model for experimental wound closure healing, Hostanska et al. [112] recently showed that succussed "controls" were indeed biologically active, though less active than the plant source HM verum compared with unsuccussed solvent controls (Figure 1). Such data are consistent with the presence of bioactivity in the silica previously reported in the succussed "controls."

Homeopaths use silica and each of the four different plant-derived HMs *(Arnica montana* 3X, *Hypericum perforatum* [St. John's Wort] 3X, *Calendula officinalis* [Marigold] 3X, *Symphytum* [Comfrey] 5X) in the verum combination homeopathic product studied by Hostanska et al. [112] for various clinical indications related to injuries and wound healing. Consistent with the homeopathic succussed control findings, a separate nanomedicine study recently demonstrated that silica NPs alone can significantly boost immunogenicity of a protein antigen in a combination formulation even when the silica NPs are not physically attached to the antigen [36]. The silica NP effects occurred only if the NPs were virus-sized (i.e., 50 nm rather than 1000 nm in size).

Independent of homeopathic research, conventional pharmaceutical investigators have replicated the observation that not only glassware, but also plastic, and stainless steel containers and tubing can all release larger and smaller particles into solutions that they contain, especially upon agitation, e.g., end-over-end rotation of a syringe with an air-water and silicone-oil-water interface or unsiliconized syringe with proteins in solution, vortexing or sonication [22,34,92,113,114]. In the case of borosilicate or soda lime glass, such particles include silica micro- and nanoparticles. In turn, any proteins or other substances in the solution form immunogenic complexes with the adjuvant particles. These complexes trigger immune reactions, even after filtering, at concentrations below the limits of detection with available instruments [22].

Waterjet abrasion per se, which is similar to homeopathic manufacturing methods such as succussion and/or fluxion (see Table 4), can break down contaminants in water samples into micro- and nanoscale structures [28,115,116]. Moreover, nano-contaminants in extremely low concentrations in stock reagent supplies can also serve as chemical catalysts for certain reactions [117,118]. Bubbles and nanobubbles can also participate [18].

The data imply that it should be possible to make HMs in plastic [119] or stainless steel containers, but their physical chemistry and biological properties would vary from those made with classical materials and methods in glass. Table 4 illustrates overlaps between homeopathic manufacturing and nanotechnology methods.

Nanosilica is an excellent drug delivery vehicle and serves as an immune stimulating adjuvant in oral vaccines [53,56,120-122]. Nanoscale forms of not only silica, but also conventional drugs, biologics, minerals, herbal extracts, and animal products are known for their small size-related enhanced bioavailability and

Table 3: Concentrations of Elemental Silicon Reported in Homeopathic Medicines and/or Controls Succussed in Glass.

Study	Potencies	Elemental Silicon Concentrations Measured (ppm)
Witt et al. [35] (Germany)	1C	0.1
Ives et al. [21] (USA)	Up to 30C	1-4
Demangeat [15] (France)	6C-21C pooled	15.2-23.2
Upadhyay and Nayak [96] (India)	15C	2.3-2.4

Note: A repeated succussion cycle lowers pH from a 1C to at least a 6C-8C, where the pH plateau at neutral acid-alkaline values in Ives et al. [21] for 7C and 8C potencies. Chikramane et al. [18] noted a plateau at 6C for transfer of metal source nanoparticles from lower to higher potencies. For other salts and ions, different glassware also releases measurable trace amounts of sodium, magnesium, aluminum, calcium, iron, and boron into HM solutions [21,35].

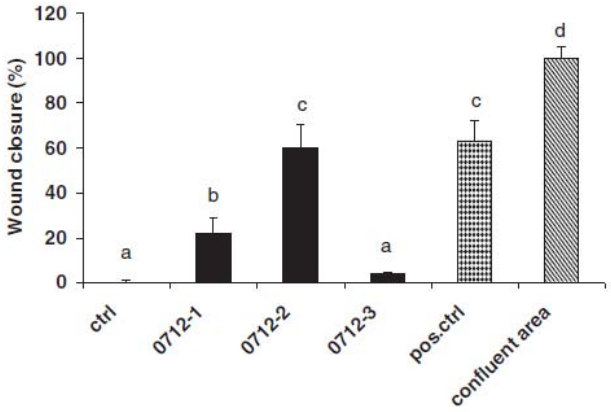

Figure 1: Wound closure effect of homeopathically-prepared substances (0712-1 = succussed solvent; 0712-2 = verum combination low potency HM containing measurable amounts of the source plant materials (4 different plant sources); 0712-3 = unsuccussed solvent). Confluent area = density of cells in wells without experimental wound areas (i.e., uninjured and untreated, representing 100% wound closure). From reference [112], per a Creative Commons Attribution License 4.0.

bioactivity [38,123-126]. Common nanotechnology strategies for tuning the electromagnetic, optical and biochemical properties of NPs include coating the outer surface of a given NP with a nanofilm of another material. In many cases, the coating material for the NPs is silica (creating shell-core NPs). In addition, other strategies for modulating NP properties include adsorbing or doping the surface of given silica or other NP with plant material, serum proteins or trace amounts of another nanomaterial [127-129]. Such procedures modify particle surface chemistry, which is the primary way by which NPs interact with each other and with living systems [44,88].

Nonetheless, skeptics could argue that (a) human beings regularly encounter nanoparticles of various natural and manmade sources in the environment without obvious therapeutic benefit; (b) the amounts of source material nanoparticles reported to date are extremely low and unlikely to exert conventional pharmacological effects. In short, what does finding nanostructures in HMs add to the field of homeopathy? In the present model, the answer relates to the HM providing a salient, individualized low intensity stress or danger signal to the recipient organism as a complex adaptive system [1,2].

Nanoscience research offers a helpful direction for addressing these objections. Recent nanomedicine and nanotoxicology studies indicate that the source and/or silica NPs in a given HM would be most likely to produce significant biological effects if the sizes fall into the range of viruses or smaller [36,70,71] (viruses range in size from 10-150 nm [62]). In addition, bioactive NPs may exhibit relative stability as indicated by certain zeta potential values on their surfaces [70]. Therefore, if NPs play a role in biological actions of HMs, testable hypotheses are that (a) their sizes would need to fall into the nanoscale range for viruses and (b) their surface zeta potentials would need to be sufficiently stable to convey their specific information in a low dose, virus-like manner.

Sizes of NPs of conventional synthetic drugs are often somewhat larger than viruses (> 150 nm), though often smaller than 1000 nm [25,130,131]. Even micro-sized forms of drugs or natural products are known to exhibit greater bioavailability [63,132-134]. However, the nano-drug mechanisms of action are typically more pharmacological (relatively higher dose, direct ligand-receptor effects) than homeopathic (pulsed lower dose, stress adaptive signaling stimulus effects) in nature.

Are there virus-triggered biological mechanisms that nanoparticles are known to mobilize? Do those mechanisms map onto the repeatedly demonstrated ability of HMs to modulate

Table 4: Homeopathic Manufacturing and Parallel Nanotechnology Methods.

Homeopathic Manufacturing Method	Parallel Nanotechnology Methods	Underlying Effects on NP Formation
Trituration of source material in dry lactose (manual grinding or ball milling)-very low potencies	Ball milling	Mechanical grinding of smaller and smaller particles off starting bulk source materials [27,29,135]
Serial dilutions and succussions in water or ethanol-water within glass containers – higher potencies in liquid	Dilution	Dilution physically separates NPs as they form to protect reactive surfaces from inactivation by agglomeration [136], but leads to variability in UV-visible spectroscopic properties between batches [80,137]
	Vortexing, sonication	Mechanical shearing of smaller and smaller particles off the starting bulk source materials [26]
		Embedding formed source nanoparticles into inner walls of glassware via turbulence of liquid [20]
		Release of silica micro- and nanoparticles from inner walls of glassware by agitation [22,34]
Fluxion (rarely used older method for continuous strong flow of water into the same glass container with the starting source material) – alternative manufacturing method for very high potencies in liquid	Water jet abrasion [28]	Mechanical shearing of smaller and smaller particles off the starting bulk source materials [26]
		Embedding formed source nanoparticles into inner walls of glassware via turbulence of liquid [20]
		Release of silica micro- and nanoparticles from inner walls of glassware by agitation [22,34]

gene expression patterns and release biological mediators such as cytokines and other endogenous signaling mediators in the body? To answer these questions, it is important to understand more details of how nanomedicines differ from bulk materials from the same source.

Specific properties of nanomedicines versus bulk form drugs

Multiple specific properties of nanoscale versus bulk form materials can contribute to biological effects of HMs as nanomedicines.

- First, nano-forms are biologically more bioavailable and potent than bulk forms for direct pharmacological actions by orders of magnitude (10-1000x) [63,83,84,123,138].

o Silica and silica NPs from glassware or plant extracts could exert immunomodulating and immune adjuvant effects [53,120,139] as well as demonstrate the capacity for self assembly into stable nanostructures around viruses [45] or plant constituents [48] as templates. In addition, dozens of studies have shown that many different ethanolic plant extracts (e.g., *Equisetum, Quercus, Salvia, Hydrastis, Thuja, Gelsemium, Phytolacca* - source materials also used for making homeopathic plant-derived medicines) can biosynthesize nanoparticles from precursors in solution, including but not limited to silica, gold, silver, and platinum NPs [57,59,60,93,140,141].

- Second, unique to their small size, nanoparticle sizes, shapes, surface areas, surface charges and surface chemistry play a major role in determining the nature of particle interactions with cells and resultant biological activity [133,142-144].

o For some NPs, a factor as simple as coating the surface with lactose leads to improved uptake into cancer cells, but not normal cells [145,146]. Both lactose and silica nano coatings and shells can stabilize the reactive surfaces of NPs [102,145,147,148]. Lactose is a standard material used during dry trituration or grinding/milling of insoluble source materials in homeopathic manufacturing.

- Third, dilution from stock solutions in the laboratory or in the environment has unpredictable effects on NP properties [121].

o NPs are so reactive on their surfaces that they adsorb onto each other and other materials that they encounter. These adsorbed materials can dope and tune the properties of the nanostructure by altering its size and shape, decrease or increase its toxicity, and/or decrease or increase its surface reactivity and biological identity for a living cell [44,133,144]. In many cases, dilution increases available surface area on NPs by avoiding particle agglomeration and leaving smaller but more reactive particles. As a result, some diluted NPs can potentially be even more toxic than a more concentrated solution of the same NPs [77,136,137]. Smaller particles translate into much larger surface area available for adsorbing other materials [149].

- Fourth, key to the effects of higher potency HMs, nanoparticles can exert not only direct pharmacological effects, but also induce indirect, biological adaptive processes via modulation of gene expression and cell-signaling pathways [70, 71,81,76,79].

o Nanoparticles are known to activate the pathogen- and danger-associated molecular pattern (DAMP) receptor recognition and mediator network [81,87,79,150]. The adaptive changes manifest via modulation of gene expression patterns, cytokine and inflammatory mediator release, immune system activation, neuronal effects [151], and biological signaling at the cell-to-cell level [81,76,80]. Cell uptake of silica NPs in the parts per billion (ppb) and parts per million (ppm) ranges occurs [152], and concentrations of various NPs in the ppb to ppm range can exert toxic effects on small organisms in the environment [153,154].

- Fifth, in contrast with ordinary bulk pharmaceutical drugs, NPs are uniquely able to generate aging [155], pH sensitivity [109,156], electromagnetic [157], photoluminescence [158-161], and quantum mechanical effects [162-165].

o These types of phenomena overlap a number of the seemingly unrelated basic science findings previously reported for HMs [30,32,33,50,98]. Even the variations in modern nanotechnology using mechanical manufacturing processes from ball milling and vortexing or sonication to water jet treatment of liquids are empirically shown to generate nanoparticles from larger bulk forms in a top-down manner [20,25,116,166]. Ethanol, the solvent used in a range of concentrations for some HM manufacturing processes, can modify the sizes and surface properties of resultant nanotechnology-generated silica and other NPs [67,166]. Lactose is one of a variety of sugars that act as reducing and/or capping agents to make and stabilize nanoparticles, thereby modifying their biological activity [145,167].

Finally, it is essential to distinguish four interconnected, but separate issues in this area. That is, (i) what are HMs; (ii) what emergent properties of HMs capture and carry the unique information; (iii) how does the specific salient HM/information interact with a specific living system for which it is well-matched or resonant; (iv)how does the body's response evolve over time after the initiating event of interacting with a salient HM? Logically, the nature of the homeopathic information from a given HM, if any, must arise from the nature of manufacturing process and its products.

Nanoparticles are far more than conventional biochemical or pharmaceutical agents in living systems [65,168,169]. A common misunderstanding of the nature of homeopathic NPs is that the dose or concentration must still fall into range for direct pharmacological effects. On the contrary, identifying a nanoscale structure in HMs does not mean that the reported therapeutic effects arise from structural properties of NPs as simple end-organ ligand-receptor effects per se in the conventional pharmaceutical sense. Even in mainstream cancer nanopharmacology, for instance, ultrasound, magnetic fields, and light stimuli can activate certain nano-drugs to release their contents only after they migrate into the target tissue by passive

uptake afforded by their small size [170,171].

NPs can also modulate immune activity. For instance, nanoscale vaccines are much more effective than conventional vaccines at triggering immune system responses against infection or cancer, typically at much lower antigen doses [172-175]. Biosynthesized nanosilver can induce neuronal differentiation by modulating oxidative stress and cell signaling pathways [151]. Notably, to modulate bio-reactivity of the host, biosynthesized NPs can carry trace residual components of the original plant or other biological material that generated the silica or metal NP into the interaction with the body.

Thus, nanomaterials act as stressors for cells and can affect biological systems across the adaptive networks of the body [176-179]. NPs can trigger systemic effects by (a) inducing release of nanoscale vesicles (Exosomes) from cells to initiate immune system reactions [168,169]; (b) activating intracellular inflammasome protein cascade and cytokine release [120]; (c) mobilizing interferon release [71]. Overall, these networks involve modulation of gene expression patterns, cytokine release, cell signaling mediator release, cell and mitochondrial stress responses [77,81]. The effects can cascade into nonlinear amplified responses [23].

Homeopathic medicine nanoparticles as salient systemic stressors

For homeopathic NPs in particular, the salience of the source material's properties to the integrative symptom pattern of the individual organism is a critical factor. A stressor specific for one system is not necessarily a stressor for another system. By analogy, a specific predator odorant as low as in the < 1 part per trillion range is most salient for and detectable by its prey [180]. In classical homeopathic practice, only HMs similar in capability for causing a symptom pattern to the total pre-existing symptom picture in a susceptible individual will elicit a clinical response (similia principle) [181,182]. Even then, the state of the recipient organism at the time of administration determines the direction of change to salient HMs [183]. HMs act most clearly in already previously-stressed cells or organisms rather than those at rest and may have no effect at all in unstressed recipients [184-186]. Finally, some HMs such as *Calcarea Carbonica* (calcium carbonate) in potency initiate immune-modulation, but at the level of the intact host organism as a larger network or system rather than isolated cells *in vitro* [187].

A number of studies from independent laboratories support the hypothesis of homeopathic NPs as salient mild systemic stressors. As Khuda-Bukhsh et al. [188] have previously proposed and demonstrated in experimental skin cancer, HMs can modulate gene expression and signaling proteins in the body without needing to rely on pharmacological tissue-based end organ ligand-receptor effects per se. Others have also demonstrated complex gene expression patterns in response to specific HMs in potency such as *Apis* [189], *Gelsemium* [190], *Arsenicum Album* [191], or a combination of multiple common HMs (commercial product Canova™ [192]).

Wiegant and van Wijk [182] demonstrated hormesis, i.e., low dose reversal in direction of effects using a toxicity model system. The model evoked intracellular heat shock protein (chaperone proteins) stress responses to higher toxic levels of bulk form arsenic or cadmium. The biological stress response reversed towards normal by administering homeopathically-prepared forms of the "same" source materials. They also showed cross-sensitization in which one agent could induce an effect, and the other, chemically unrelated material could modify the observed response [182,185,186]. In biology, cross-sensitization occurs via not only immune, but also non-immune processes [2,193-197]. Separately, other homeopathic investigators have observed that various HMs can modulate cytokine release [187,198-200].

In short, understanding HMs as discrete, pulsed sub toxic doses of natural product nanomedicines [1] helps integrate seemingly diverse empirical observations into a cohesive understanding. That is, NPs in HMs modulate adaptive biological pathways to generate state-dependent bidirectional changes in living systems [183,201].

Low potency homeopathy is likely dominated by a role for the HM source material micro-sized and nanosized particles with greater bioavailability than their respective bulk forms [71]. However, high potency homeopathy is likely dominated by the amplified role of silica NPs modified by trace amounts of the source material NPs and/or, based on prior studies [114], any other materials used during manufacturing [21,51]. The other materials involved in making higher potency HMs can include specific borosilicate or soda lime glassware (or plastic) containers of various sizes and constituents, pipettes for dilution, distilled water, ethanol at various concentrations, and container stoppers (phenol caps, synthetics, rubber, natural cork) [35].

Furthermore, nanoparticles' size and surface-related zeta potential can determine whether or not and to what extent a given NP exerts biological effects [70]. From nanoscale forms, homeopathic information for the organism could arise from a unique cell signaling effect [188], electromagnetic [98] and/or optical signal, and/or quantum mechanical effect (for very small NPs < 10 nm in size) on the interconnected, nonlinear dynamic networks of the body [202]. The specific objective correlates in the properties of NPs in HMs for the biological activity of those HMs remain an important and and as yet relatively unstudied question [61,97].

Despite the claims of skeptics, there is a substantial basic science and preclinical literature demonstrating that HMs at low and high potencies exert biological effects different from placebos on cells, plants, animals, and human subjects [112,188-190,192,198,200,203-215]. Multiple studies have demonstrated the ability of various nanomaterials to trigger the adaptive nonlinear dose-response phenomenon of hormesis at low doses [82]. Hormetic mechanisms also encompass both receptor and/or cell signaling pathways [215].

Table 5 summarizes the variety of overlapping features of nanomaterials and HMs discussed above. Whatever the nature of the homeopathic signal from the HM NPs, Bell et al.

[23] have elsewhere discussed multiple endogenous nonlinear amplification mechanisms by which complex adaptive systems such as human beings or animals can respond to a small, pulsed but salient signal [197], especially from a nanomaterial. Such processes include not only hormesis, but also stochastic resonance and time-dependent sensitization/cross-sensitization [23]. Other papers have outlined the evolving and self-organized nature of the reported changes in the recipient organism after an effective HM treatment using discrete intermittent doses, i.e., pulsed or spaced over time from one another [202,216-218].

Given the properties of nanomaterials, it is possible that the salient information conveyed from the HM to the individual organism sets the healing response in motion in multiple ways. Based on the evidence, the communication of the information could derive from the HM NP-generated biochemical, immunomodulatory, electromagnetic, magnetic, or optical/photon-based signals and/or from quantum mechanical phenomena [219].

Table 5: Overlapping Characteristics of Classical Homeopathic Medicines (HMs) and Modern Manufactured Nanoparticles (NPs) (see text for details).

Findings
HMs and NPs in sub toxic doses both show ability to modulate biological activity through changes in gene expression, signaling protein release, cytokine release, and/or oxidative stress patterns
Variability in physical chemistry, ultraviolet visible spectroscopy and bioactivity findings is common in both HMs and NPs as an inherent function of properties of the form rather than composition of the agent
HMs and modern NPs both exhibit susceptibility to aging in solution with resultant changes in properties; pH, temperature, salt and ethanol concentration-dependent effects occur

The biology of the cell danger response network and adaptation: biological plasticity

In the Nanoparticle-Cross-Adaptation-Sensitization (NPCAS) model for homeopathy as adaptive network nanomedicine [1,2,23,220], the correct HM or simillimum uses low concentrations of Nanoparticles (NPs) as a biologically meaningful or salient danger signal, alarm, or threat to trigger health-promoting beneficial changes in the organism as a complex adaptive system [221,222]. Consistent with an adaptation or biological plasticity model, the physician-chemist founder of homeopathy, Samuel Hahnemann MD, originally postulated that the correct HM elicits the body's "counter-action" to the direct effects of the salient HM [223]. Recovery from disease emerges from the body's adaptive reaction to the mild stressor of the correct HM.

The indirect biological pathways of adaptation and cross-adaptation in the body, rather than direct local end organ ligand-receptor pharmacological mechanisms would better account for the clinical phenomenology of homeopathic treatment (Figure 2). In specific, independent laboratories have found that different HMs play an immuno-modulatory role in specific biological models [187,224-226].

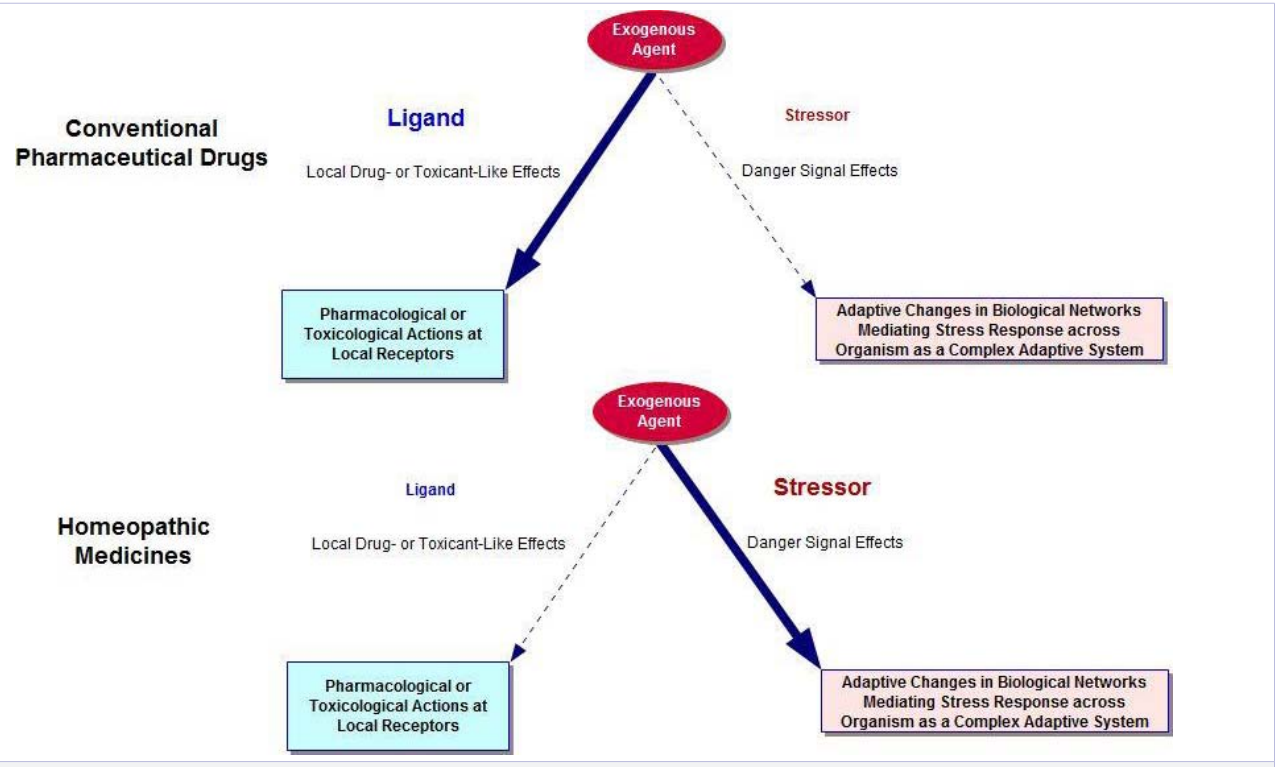

Figure 2: Conventional Pharmaceutical Medicine Focuses on Direct Local Ligand-Receptor Properties of the Agent (High Bulk Doses) whereas Homeopathic Adaptive Network Nanomedicine Focuses on the Individualized Stressor Properties of the Agent for the Organism as a Whole (Low Nanoscale Doses) to Initiate Adaptation.

To maintain a focus on theory-driven testable hypotheses that arise from the present model, the remainder of the discussion will address potential biological mediation of the observed changes in living systems. One convergent conclusion from several different laboratories [187,192,211,227] is that HMs act by modulation of immune, inflammatory, and biological signaling, including changing gene expression patterns. In other words, rather than acting on local end organ tissue receptors per se, the NPs in HMs may act mainly via modulation of adaptive biological pathways in the body involved in the stress response (see Table 6). These interconnected pathways include immune, inflammatory, hormonal, metabolic, and nervous system mediation [228].

The diffuse network nature of the Cell Danger Response (CDR) system of the body provides a rational foundation for understanding the individual clinical response to an HM. Nanomaterials are one form of emerging exogenous danger signal for types of the endogenous Pattern Recognition Receptors (PRRs). PRRs initiate a dynamic and diffuse cascade of subsequent biological signaling events across the body [81]. Other types of PRRs include those that recognize Pathogen-Associated Molecular Patterns (PAMPs, e.g., viruses and bacteria), damage-associated molecular patterns (DAMPs or "alarmins," e.g., heat shock proteins - HSPs) and related nanoparticle-associated molecular patterns [81,87,79,179,229]. Nanoparticles tend to trigger responses related to viruses, whereas larger micro-sized particles affect responses related to bacteria [71].

The cell danger response is implicated in a wide range of acute and chronic diseases [87], including many conditions that homeopaths sometimes report treating successfully, e.g., viral and bacterial infections [210,227,230] and sepsis [231], tissue injury [183,232], various allergies [233-238], autoimmune diseases [239], fibromyalgia [240], traumatic brain injury [241], attention deficit disorder [242], autism [243], and cancer [244,245]. The body has evolved mechanisms involving endogenous DAMPs as biological signals that detect and signify nano- and micro-scale and molecular threats to its survival [79,81]. The threats can be microbial pathogens, tissue damage, certain endogenous mediators, nanomaterials, or endogenous homeostatic disturbances (e.g., inflammation, hypoxia, acidity, metabolic stress) [81] (Figure 3).

Immune and/or non-immune (metabolic, inflammatory, nervous system, hormonal) adaptive pathways participate in biological stress responses. One immunological example is IgE-based allergic adjuvant reactions to nanoparticles such as carbon nanotubes [246]. Apart from immune hyper reactivity, however, the threat does not have to be so intense as to kill the cell or individual organism [247]. Rather, even low dose, sub toxic levels of NPs can still elicit cell oxidative stress responses [80,248] and thus activate a cascade of endogenous "alarmin" signaling events throughout the body [71,249] (see also Figure 4).

Nanomaterials are among the types of exogenous stimuli that act as danger signals for dendritic cells in the immune system to respond with release of endogenous biological danger signals [81]. Furthermore, silica NPs can activate the intracellular inflammasome protein cascade, another component of the diffuse danger sensing and signaling biochemical network of the body [250]. Inflammasome activation induces cytokine release, e.g., interleukin 1b [251]. Other endogenous alarmins lead to purinergic signaling [252]. These extracellular signals are mediated by purine nucleotides such as ATP (adenosine triphosphate) and are also associated with intracellular inflammasome activation followed by extracellular cytokine release [253].

Endogenous mediators such as ATP can play one metabolic role when inside an intact cell, but an alarmin role when released outside a damaged cell [253]. Heat shock proteins, other mediators within the cell danger response network, are among the endogenous molecular alarmin signaling structures in response to cell damage or other types of biological threat. A series of previous studies by van Wijk and Wiegant [182,185,186,254] have repeatedly demonstrated that homeopathically-prepared materials can modulate heat shock protein activation patterns.

The important point in the current model for homeopathic medicines is that the danger signal triggers a complex nonlinear, self-regulatory cascade of endogenous mediator and modulator activation events [188,255]. These events constitute an adaptive response that tries to strengthen the organism against the danger [247]. It is the cross-adaptive or cross-sensitized [256] nature of the HM as an individual danger signal to the pre-existing pattern of maladaptation and dysfunction in the individual

Response	Stressors	Effectors	Molecular markers
Heat shock response (HSR)	Heat, heavy metals, antibiotics, protein denaturation	Heat shock proteins, proteasome and other proteases	Translocation of HSF-1 into the nucleus; induction of HSP72 (HSPA1A)
Unfolded protein response (UPR)	Unfolded and misfolded proteins in ER	Chaperones and co-chaperones	Activation of transcription factor 6 (ATF-6); CHOP (GADD153)
Autophagic response	Food limitation, hypoxia, damaged organelles	Autophagosomes, Lysosomes	Altered LC3-I and LC3-II ratio; increased number of lysosomes; degradation of damaged mitochondria
DNA damage response (DDR)	Radiation, oxidants, free radicals	DNA repair enzymes	Translocation of ATRIP to the nucleus; increased levels of checkpoint proteins p53, p16, p21, mortalin
Antioxidant response	Free radicals, reactive oxygen species, pro-oxidants	Nrf-2, heme oxygenase, FOXO	HO-1; FOXO protein levels
Sirtuin response	Energy depletion	Sirtuins	Sirtuin-1 protein level; NAD/NADH ratio
Inflammatory response	Pathogens, allergens, damaged macromolecules	Cytokines, nitric oxide synthase, COX-2	Increased level of NF-κB protein and inflammatory interleukins

Table 6: Main Molecular Level Stress Response Pathways (Part of the Cell Danger Response System) and their Respective Inducers and Effectors in Human Cells [257]. Reprinted with permission.

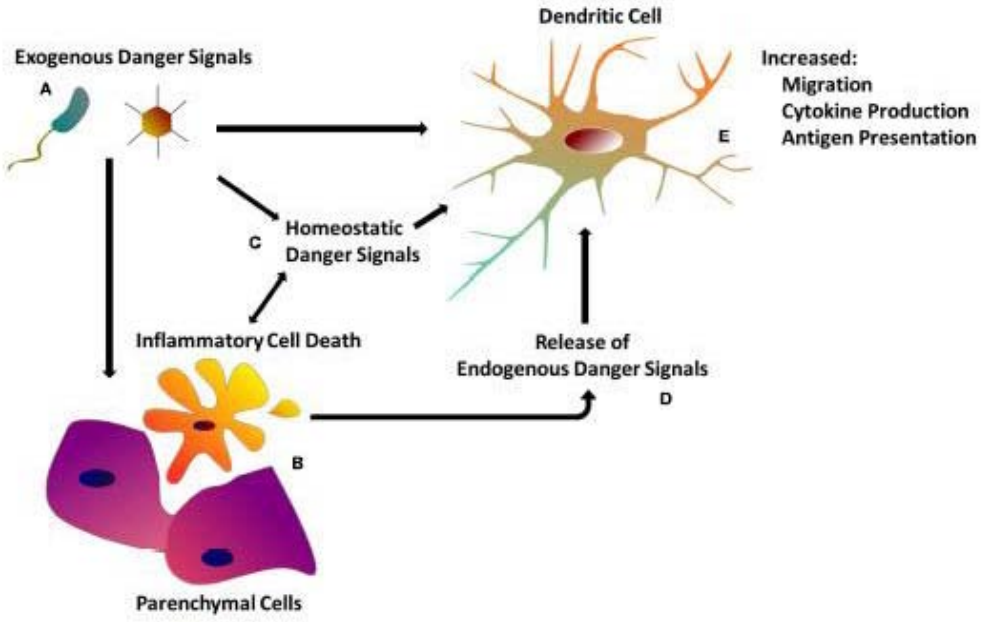

Figure 3: The dendritic cell response to danger. (Reprinted under Creative Commons Attribution License CC-BY 4.0 from reference [81].

(A) Exogenous danger signals include pathogen-associated molecular patterns, as well as exogenous particulate matter. Exogenous danger signals activate DCs (dendritic cells) directly via pattern recognition receptors, or indirectly though tissue damage (B) and homeostatic perturbations (C). (B) Inflammatory cell death as a result of tissue injury or programmed necrosis causes the release of endogenous danger signals (D) which also activate DCs. (C) Homeostatic perturbations such as those found in inflamed tissue (e.g., decreased pH, hypoxia) may also act as endogenous danger signals, influencing DC immune functions. (E) DCs integrate both exogenous and endogenous danger signals in order to orchestrate the appropriate immune response.

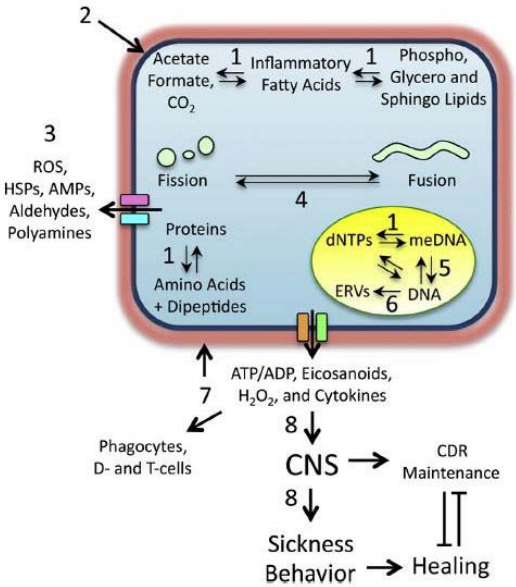

Figure 4: Functions of the acute Cell Danger Response (CDR) [87]: From cell stressor to systemic effects. Reprinted with Creative Commons 3.0 License.

The acute CDR includes 8 functional changes in cell structure, physiology, metabolism, and gene expression. These are: 1) shift cellular metabolism from polymer to monomer synthesis to prevent the hijacking and assembly of cellular resources by intracellular pathogens, 2) stiffen the cell membranes to limit superinfection and pathogen egress, 3) release antiviral and antimicrobial chemicals into the pericellular environment, 4) increase autophagy, mitochondrial fission, and mitophagy to facilitate removal of intracellular pathogens and biogenesis centers,5) change DNA methylation and histone modification to alter gene expression, 6) mobilize endogenous retroviruses and LINEs to produce genetic variations, 7) warn neighboring cells and distant effectors cells of the danger with extracellular nucleotides, H_2O_2, eicosanoids, metabolites, and cytokines, and 8) alter the behavior of the host to prevent the spread of infection to kin, and sleep patterns to facilitate healing.

that leads to the actual reversal in direction of the response back towards the health [1,2,23,220]. Such a nonlinear process would be a type of individualized cross-sensitization (between the original large magnitude biological stressors causing disease and the small HM NP discrete pulsed signal), post conditioning hormesis [182,185,258], or oscillation from cross-sensitization [186,195,196,259-261]. Healing emerges in the recipient complex adaptive system as the restoration of homeostatic normal functioning and resilience to future stressors [202, 247,262] (Figure 4).

In turn, endogenous biological danger signals such as cytokines then carry and potentiate the message concerning existence of a salient threat danger to the rest of the body's defense systems, including the brain. Researchers now consider the pro-inflammatory cytokine interleukin 1a, for example, as an alarmin or marker of oxidative stress for various chronic conditions associated with inflammation [263]. The self-regulatory results of defense system pathway activation include complex modulation of inflammatory and anti-inflammatory events [228,264,265].

Notably, ingredients of several different single and combination homeopathic medicines increase and/or decrease certain pro-inflammatory and anti-inflammatory cytokines under specific conditions [192,198-200,266]. Determining the potential role of homeopathic medicine NPs as modulators of cytokine release, heat shock protein activation patterns and other components of the danger signal pathways is one of several appropriate experimental directions to pursue.

Immune/inflammatory and brain/neural pathways also communicate with one another bidirectional concerning exogenous threats [228,267]. Bell et al. have repeatedly demonstrated that sniffing individually-salient HMs versus double-blind placebos significantly changes quantitative Electroencephalographic (qEEG) responses acutely and induces sensitization over time [205,206]. Thus, data indicate that sensory signaling and central nervous system sensitization can play a role in HM effects.

Taken together, the evidence indicates that when an HM dose at a given higher potency contains source material NPs in very small sizes [268] and adjuvant (amplifying) silica NPs from the glassware, it will be biologically more potent than (a) an HM dose at a low potency, i.e., higher concentration of larger sized, less reactive particles and residual bulk material; or (b) the same dose of source NPs lacking nanosilica as adsorbent, stabilizer and amplifier. Biologically, small NPs have extremely high bioavailability and unimpeded capacity to cross cell membranes [62,63].

Once in contact with physiological fluids, serum proteins will adsorb onto the HM nanoparticles surfaces and create a unique biological signature for the composite nanomaterial in the body per se (protein corona) [49,79,130,142,144]. Shape and surface chemistry variations of nanoparticles such as silica NPs modulate the nature of the unique protein corona that adsorbs to the NPs [142,269,270]. According to Walkey and Chan [144], it is necessary to characterize not only the NPs, but also the unique pattern of adsorbed proteins, i.e., the protein corona "adsorbome" that immediately attaches to the NPs on introduction to biological fluids, especially serum proteins [133,144]. This enables researchers to know the "biological identity" of the protein-nanocomposite structures that will develop on interaction with the body [269,271,272]. They propose that it is the biological identity, not the manufactured synthetic nanoparticle identity, which leads to the physiological response.

Considering homeopathy as a form of adaptive network nanomedicine [1] rather than conventional pharmacology leads to predictions consistent with clinical observations. For example, activating the CDR excessively with disease-fostering high intensity stressors overwhelms homeostatic/allostatic dynamics [228,264,265,273] and fosters the emergence of disease and sickness behavior (including fatigue) (Figure 4). Conversely, successful homeopathic treatment with individually chosen low dose, i.e., sub toxic levels of, NPs should reverse this process. HMs would achieve their effects by modulating the adaptive dynamics of the same pre-sensitized metabolic, immune, and neural CDR pathways back toward resilience and health (including the emergent effect of greater global sense of energy and well-being) [1,2,23,188]. Modulating the plasticity of the nervous system pathways per se may reflect quantum mechanical dynamics [274,275].

Conclusion

Clinically and experimentally, homeopaths report that HMs act best in an organism that is already sick or stressed [183,184,276]. In fact, to trigger a reversal in direction, the biological activity of salient HMs probably leverages the pattern of pre-existing large magnitude adaptations that the organism has already generated to the original severe stressor(s) (i.e., oscillation after pre-sensitization or post conditioning hormesis) [2,182]. Much research remains ahead on the adaptive cell danger response (CDR) and its postulated relationship to homeopathic treatment as a mild discrete but salient systemic cross-stressor to the original insult(s). Nevertheless, it is likely that a program of theory-driven research based on the adaptive network nanomedicine model for homeopathy will advance the field more rapidly than uncoordinated basic science studies [277].

Figure 4 shows the putative components of the acute cell danger response and pathways to sickness or to healing. Like NPs, (a) homeopathic medicines can modulate reactive oxygen species [278-281], heat shock proteins [185,254,282], and cytokine release [187,192,198,199,266] and trigger biological signaling cascades in cancer cells [187,188]; and (b) nanoparticles constitute an emerging type of danger signal for cells [81]. Consequently, further systematic examination of the effects of low dose HMs and their constituent NPs on the cell danger response pathway network is likely to be productive [257,282].

Understanding low and high potency homeopathic medicines as various types of nanomedicine opens the door to studying potential mechanisms of action [283]. Very low potencies would exert direct pharmacological and/or hypersensitivity effects

related to enhanced bioavailability, drug delivery capacity and duration of action of natural source nanomaterials [284]. Higher potencies in water would bring about their effects as virus-like systemic stressors (i.e., indirectly), based mainly on source-modified silica nanomaterial properties. As salient nano-enhanced signals at higher potencies, the concentrations of the pulsed doses of a well-chosen HM can be very low and still trigger individual bio-reactivity in a state-dependent, nonlinear manner (cf., [203]).

In addition to small amounts of source material NPs, the more prevalent silica NPs would include source-doped nanosilica or silica-shell/source-core NPs, together acting as nanosilica-amplified immune adjuvant [36,53,55,56,121], sub toxic metabolic stressors [80,285], nanocatalysts [117,286], and/or nanomaterial-induced exogenous danger signals triggering a cell danger response [253]. The clinically reported extended duration of evolving responses to a given HM dose [214] in multiple bodily systems across the organism [287] would reflect the interconnected self-organizing state of the organism and capacity for nonlinear amplification and change [202].

The nature of the specific signal from the homeopathic nanomaterial may emerge from the biochemical [284], electromagnetic [33,98,288], magnetic [289], photon [32,50], and/or quantum mechanical [30,290,291] properties of nanomaterials at different potencies and in various contexts [30,292]. Available evidence suggests that the nature of homeopathic medicines and their mechanisms of action on living systems are complex and multivariate. While any given study may have its limitations and flaws, the convergence of evidence surrounding the major observations on which this model is based is extensive.

Now the biological effects of homeopathic medicines are accessible for objective quantitative study with the sophisticated and highly sensitive tools and technologies of nanobiology. Examining whether or not the specific physical properties of the nanomaterials in HMs, e.g., certain sizes, shapes, surface areas, surface charges (zeta potentials), and/or adsorbents/ dopants, correlate with their effects *in vitro* and *in vivo* on subsystems involved in biological adaptation (cf. [49,65,70,76]) is the next major empirical question for the present hypothesis-driven research model.

Conflict of Interest

Dr. Bell is a consultant to Standard Homeopathic/ Hyland's Inc, a US-based manufacturer of homeopathic remedies. This company did not finance the preparation of this paper or any of the research cited in the article.

Authors' Contribution

The authors discussed the overall conceptual approach presented in this paper. Iris Bell wrote the initial draft, and the co-authors edited the text, adding key points of clarification.

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Declarations

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