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Advances in Integrative Nanomedicine for Improving Infectious Disease Treatment in Public Health

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Abstract

Introduction—Infectious diseases present public health challenges worldwide. An emerging integrative approach to treating infectious diseases is using nanoparticle (NP) forms of traditional and alternative medicines. Advantages of nanomedicine delivery methods include better disease targeting, especially for intracellular pathogens, ability to cross membranes and enter cells, longer duration drug action, reduced side effects, and cost savings from lower doses.

Methods—We searched Pubmed articles in English with keywords related to nanoparticles and nanomedicine. Nanotechnology terms were also combined with keywords for drug delivery, infectious diseases, herbs, antioxidants, homeopathy, and adaptation.

Results—NPs are very small forms of material substances, measuring 1–100 nanometers along at least one dimension. Compared with bulk forms, NPs' large ratio of surface-area-to-volume confers increased reactivity and adsorptive capacity, with unique electromagnetic, chemical, biological, and quantum properties. Nanotechnology uses natural botanical agents for green manufacturing of less toxic NPs.

Discussion—Nanoparticle herbs and nutriceuticals can treat infections via improved bioavailability and antiinflammatory, antioxidant, and immunomodulatory effects. Recent studies

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Conflict of Interest

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demonstrate that homeopathic medicines may contain source and/or silica nanoparticles because of their traditional manufacturing processes. Homeopathy, as a form of nanomedicine, has a promising history of treating epidemic infectious diseases, including malaria, leptospirosis and HIV/AIDS, in addition to acute upper respiratory infections. Adaptive changes in the host's complex networks underlie effects.

Conclusions—Nanomedicine is integrative, blending modern technology with natural products to reduce toxicity and support immune function. Nanomedicine using traditional agents from alternative systems of medicine can facilitate progress in integrative public health approaches to infectious diseases.

Keywords

Nanomedicine; Drug delivery systems; Medicinal plants; Herbal medicine; Antioxidants; Homeopathy; Nanoparticles; Silica; Infectious disease treatment; Adaptation; Network medicine

Introduction

Infectious diseases continue to present a major public health challenge in both developed and developing countries. Even when modern conventional treatments such as antibiotics or antiretroviral drugs are available for a given type of infection, limitations of their usefulness can arise. Such limitations include emergence of antibiotic resistant bacteria, prohibitive costs and limited accessibility; and poor patient adherence issues. Conventional medical drugs have specific targets, but typically also cause significant side effects. Safety and risk-benefit analyses take on major relevance in mainstream health care decision making.

Whenever possible, integrative practitioners seek to find safer treatments to accomplish their clinical treatment objectives [1]. They often turn to alternative health care approaches for additional options. For example, the literature offers preclinical and clinical evidence in support of the effectiveness of traditional herbs and homeopathic remedies in treating individuals with various acute and chronic infectious and inflammatory conditions. In particular, alternative medical systems such as Ayurveda, Chinese herbalism, homeopathy, and naturopathy can show historical and observational trial evidence of good outcomes, greater safety, patient acceptance, accessibility and cost-savings over conventional drug treatments. Many alternative treatment modalities have multi-target effects [2], strengthening host defenses more than directly destroying infectious agents. Many herbs and homeopathic medicines act as adaptogens, i.e., nontoxic agents that increase the body's global ability to adapt to stress or environmental change without relying on specific local receptor targeting.

However, pragmatic, as well as sociopolitical, issues often confront integrative practitioners seeking to utilize these alternative types of treatments. Various barriers limit widespread inclusion of alternative therapies in public health programs for preventing and treating infections, including only a small number of pharmaceutical clinical trial studies [3, 4], with difficulty in setting reliable standards for purity and activity in the agents under investigation. Although certain herbs and nutriceuticals demonstrate a striking ability to stimulate immune system defenses in vitro or with certain forms of administration in animals, solubility and/or absorption from the gut *in vivo* can be poor. As a result, a practical challenge with some traditional botanical and nutriceutical agents is that the poor solubility and/or absorption prevent clinical effects of the desired magnitude for treating an infectious process as definitively as a conventional pharmacological agent may accomplish (but with even more side effects). Widespread adoption of herbs and other natural products for public health applications then is seen as impractical for a variety of reasons.

In addition, skeptics of homeopathy have historically raised doubts regarding its fundamental scientific plausibility because of the manner of preparing its medicines with a process of serial dilutions and succussions (vigorous shaking). Such critics assert that the resultant medicines could not be biologically producing the effects that have been extensively documented in case studies because of their bulk form dilution, sometimes seemingly past Avogadro's number of molecules. The skeptics may be both partially correct – and incorrect.

New empirical discoveries suggest that even though the *bulk form* source materials might not persist into the more "dilute" remedy potencies, *observable nanoparticle forms* of the source material and silica do persist across all homeopathic potencies, from "lower" to "higher" [5, 6]. The unique properties of nanoparticles would help account for many perplexing findings on homeopathic medicines and reposition homeopathy as a traditional form of adaptive nanomedicine for the organism as a whole network [7–9]. Understanding nanoparticles and their characteristics [10–12] may finally put to rest the skeptics' well-intentioned attacks, which are based on bulk form scientific assumptions, on the preparation methods for homeopathic medicines.

Surprisingly, advances in conventional drug targeting and safety [12], herbal product delivery into the body [13, 14] and the nature of homeopathic remedies [5, 6] all converge in the fields of nanotechnology and nanomedicine [15]. The purpose of this paper is to provide a brief introduction and overview of cutting-edge research on nanoparticles (NPs) and nanomedicine, with implications for improving safe and effective integrative treatments for infectious diseases using conventional drugs, botanical agents, nutriceuticals, and homeopathics. The discussion will include emerging research on nanoparticles and homeopathy as an exemplar traditional whole medical system. The data suggest potential physiological adaptive mechanisms in intracellular and systemic networks of the host, more than direct local pharmacological effects. Advances in cutting-edge research on nanotechnology-based drug delivery approaches, of which most integrative providers are not as yet aware, could facilitate major improvements in the capacity to deliver better and safer care for infectious diseases to larger populations.

Methods

The authors searched Pubmed articles in English with keywords related to nanoparticles, nanotechnology, and nanomedicine. The nanomaterial search terms were also combined with keywords for drug delivery, infectious diseases, specific herbs, herbal medicine, antioxidant, and homeopathy. The search revealed 55,697 articles on nanoparticles, 3,143 articles on nanomedicine, 57 articles on nanoparticles and herbs or herbal topics, 1,358 articles on nanoparticles and antioxidants, and 9 articles on nanoparticles, nanobubbles, and homeopathy or homeopathic. The term "low dose nanoparticle" yielded 507 citations. On mechanisms relevant to nanoparticle actions in infectious disease, the search showed 852 articles on hormesis, 201 articles on cross-adaptation, 2,889 articles on heat shock proteins and infection, and 1,020 articles on inflammasome. We focused primarily on papers published within the last 5 years, but also included highly relevant peer-reviewed research articles and reviews from any date identified in the literature search or as key citations in bibliographies of more recent papers. A core set of 79 papers provided the essential information to inform the development of the current paper.

Results

Nanomedicines in Drug and Herb Delivery

Nanoparticles are very small forms of material substances, measuring from 1 to 100 nanometers in diameter along at least one dimension [11]. Nanoparticles can form via physical, chemical, or biological methods, from either a top-down (e.g., milling or otherwise disrupting solid bulk forms of an insoluble substance to generate nanoparticles) [16–18] or bottom-up (e.g., molecular self-assembly of nanoaggregate conformations) approach [19, 20]. Both natural and synthetic NPs occur in the modern world [21, 22].

Nanotechnology is the applied engineering term for manipulating nanomaterials at the atomic and molecular scale [23]. The field encompasses nanomedicine, which strives to utilize nanotechnology to improve health care [15]. Various NPs have applications for diagnosis and treatment [24], but some can cause toxic effects on living systems [10, 22, 25]. Toxic NPs from the environment, for instance, are under study as possible etiological agents in autoimmune diseases, neurodegenerative disorders, and Crohn's disease [10, 21, 22]. Toxic NPs arise from natural and anthropogenic sources of occupational exposures, medicinal applications, and ambient air pollution, including volcanic activities, dusts or petroleum-based fuel combustion products [21, 22, 26]. Several recent reviews discuss the extensive evidence on the toxicity of certain nanoparticles, including adverse cardiopulmonary effects [21, 22, 26].

Generally, smaller NPs are more toxic to cells than larger NPs of the same source material [27, 28]. The state of the recipient living system (e.g., cancerous versus healthy cells) and higher versus lower dose levels [29, 30] also can affect the degree of nanotoxicity. For instance, one study demonstrated greater apoptotic effects of larger versus smaller calcium phosphate nanoparticles in osteosarcoma cells [31]. Several other studies have shown that certain nanoparticles exert selective apoptotic effects on specific breast, lung, liver, or brain glioma cancer cells but not on healthy cells [32–35]. Moreover, other NPs are benign and even activate antiinflammatory, antioxidant and immunostimulatory effects [36–43].

Because of their large surface to volume area, NPs possess unique, sometimes atom-like properties not seen in bulk form versions of the "same" material, e.g., a drug, metal, herb or environmental chemical pollutant [11, 44]. For example, nanoparticles readily cross cell membranes, including the blood-brain barrier [45], and gain access to cells, as well as translocate around the body via blood and lymph [10]. Their access to the inside of cells makes them an attractive tool for delivering treatment with drugs, herbs, and/or antioxidant nutriceuticals to intracellular pathogens [12, 46].

Armstead and Li [12] recently summarized the range of intracellular infectious diseases that nanomedicines may be more effective in treating than conventional bulk form drugs. Such diseases include tuberculosis, HIV (see also [47]), hepatitis C, salmonella [48], typhoid fever, candidiasis, leismaniasis (see also [49]), and malaria (see also [50–52]). For various reasons related to their small size, e.g., better solubility, absorption and uptake, nanoparticle-based medicines can get across cell membranes and reach specific targets more easily than bulk form agents. It is also possible to formulate certain nanoparticle drugs to release their active agent mainly when they are inside the cell, instead of dispersing drug prematurely or indiscriminately, thereby reducing side effect risks while optimizing dose [53].

The size and morphology of nanoparticles and the nanoclusters that are formed lead to different physico-chemical, biological, electromagnetic [54], magnetic [11, 55, 56], optical [57], thermal [58], and quantum [59] properties from those of the bulk forms of a given substance [10, 11]. Atoms and electrons lie closer to the surfaces of nanoparticles than in

bulk form materials and lead to markedly increased ability to adsorb DNA, proteins, drugs, herbs, lactose, and other nanoparticles onto their surfaces [18, 60–65]. Catalytic capacities and often magnetic properties, are acquired or markedly increased in NPs [11].

Specific cells can be targeted [66–69], effects of a given dose last longer [70], and therapeutic effects are magnified [32]. The dose levels of an agent needed to produce a given response can down shift as much as 1000-fold for the nanoparticle form versus the commercial bulk form, e.g., amount of an antigen needed in a vaccine to stimulate an immune response [71] – see also [72]. One study showed that the nano-form of an anti-tuberculosis drug mixture required only 3 doses, versus 45 doses of the “same” bulk form drugs, to produce a comparable elimination of tubercle bacilli in mice [70].

Table 1 lists exemplar studies of herbalfacilitated nanoparticle medicines drawn from Ayurveda, Chinese medicine, Western herbalism, homeopathic and nutriceutical systems. Preclinical studies indicate that the NP forms of antioxidant and anti-inflammatory herbs can exert heightened ability to stimulate innate immunity, mobilize cytokines, alter generation of reactive oxygen species (free radicals), and exert antibacterial, antiviral, and/or antifungal effects [64, 73–77]. For nutriceuticals with antioxidant, anti-inflammatory, and antimicrobial effects but poor gastrointestinal absorption or bioavailability, e.g., coenzyme Q10 [78–80], quercetin [81], curcumin [39, 82], resveratrol [42], or alpha-lipoic acid [83], nano forms can dramatically improve clinical utility.

For example, the antioxidant quercetin can exert beneficial effects against infections ranging from leishmania [84] and dengue virus type-2 [85] to rhinovirus [86] and influenza virus [87], but bulk forms are poorly absorbed from the gut. Making a lipid nanoparticle form of quercetin improves relative bioavailability 571.4% after oral administration in animals [88]. Another example is silymarin, an herb often used in integrative medicine to support liver function. Attaching silymarin to porous silica nanoparticles generates an orally-administered, sustained release product that maintains higher plasma concentrations of silymarin in animals, compared with bulk form commercial herbal tablets [89]. NP forms make it possible to take advantage of the significantly improved absorption across the gut and entry into target cells for better bioavailability at lower doses.

The ability to amplify these beneficial effects of herbs or nutriceuticals for treatment of infectious diseases by attaching them to nanoparticle carriers [64, 90] and delivering them directly into infected cells throughout the body is a significant advantage. NPs also have other potential public health applications. For instance, compared with crude extract controls, silver nanoparticles synthesized using *Euphorbia hirta* plant leaf extract exert significantly greater larvicidal and pupicidal effects in mosquitoes that transmit malaria [91]. The nanotechnology approach even has potential application to reduce spoilage in antioxidant food packaging films. For instance, the nanoparticle forms of curcumin and ascorbyl dipalmitate exhibit higher antioxidant activities on four different assays than their respective usual bulk forms in water [92].

As a result, nanomedicine researchers have discovered that therapeutic NPs can serve as more effective drug delivery vehicles than conventional bulk form drugs [93, 94]. Empirical studies demonstrate that using NPs for delivery of drugs [95, 96] and/or herbs [14] can (a) better reach their intended targets in the cells of the body; and (b) reduce the total amount of an agent needed to accomplish a therapeutic effect [74]. NP herb or drug forms can not only bypass or dramatically improve upon the poor gastrointestinal absorption and/or solubility problems that limit the usefulness of many different bulk form agents [15, 97], but they can also cross the blood-brain barrier for enhanced delivery into the central nervous system, e.g., for antiretroviral drugs in HIV/AIDS [98]. Inhalation administration routes for certain

nanomedicines and nanoherbs may also be more acceptable and accessible for the general population [99] than injections or pills [100]. In turn, these properties of nanodrugs and nanoherbs can translate into (a) reduced side effect risks; (b) greater effectiveness; and (c) lower costs. These advantages would have a favorable impact on public health.

The Role of Natural Substances in Nanoparticle Manufacturing: Reducing Toxic Risks

Nanoparticles for nanomedicine drug delivery applications include NPs from gold and silver as well as silica [101], calcium and magnesium phosphate [102], carbon [103], chitosan (a linear polysaccharide from the exoskeletons of crustraceans or cell walls of fungi) [82], alginate (a natural polymer) [104], liposomes or lipid nanocapsules [13, 105]. A major limitation in translating advances in medical nanotechnology to the clinical and public health arenas has been uncertainties about the potential cumulative toxicity of the manufacturing processes and/or the drug delivery NPs themselves, especially the metal-based NPs. For example, silver or copper NPs can release toxic ionic forms that can accumulate in cells [106, 107]. Researchers are concerned about the potential toxic accumulation of therapeutic gold or silver NPs inside cells, such as liver and spleen, given their lack of biodegradability [108].

Identifying less toxic and/or biodegradable types of nano-forms, e.g., using lipid-based [43] or calcium phosphate NPs [102], and using lower NP doses [71, 109, 110] are among the current strategies for reducing toxicity in medicinal applications [70, 104]. Silica NPs [24, 26, 111, 112] may offer a potentially safer option in infectious disease treatment [12], as evidence suggests that they can enhance immune reactivity but biodegrade without accumulation [113]. Preliminary data also indicate a similarly lower cytotoxicity for some types of carbon nanotubes [114] and perhaps calcium carbonate [62] or calcium or magnesium phosphate [60, 61]. Chitosan NPs are considered benign [50, 82], and lipid-based NPs are one of the preferred ways to deliver antimalarial agents to infected cells [51].

In addition, chemicals used in the manufacturing process also adsorb, along with the intended drug or herb, onto the surface of the NPs [115]. Consequently, nanotechnology engineers are increasingly seeking more ecofriendly ways to manufacture nanoparticles that avoid or limit reliance on toxic chemical methods [116]. The adsorbed materials can modify the properties, effects, and/or toxicity of the NPs.

For instance, nanotechnology engineers have developed novel biological methods for making NPs. They are turning to aqueous plant extracts and natural phytochemicals rather than synthetic chemicals to generate the gold or silver nanoparticles for nanomedicine applications [117]. In the latter context, investigators have successfully used *Zingiber officinale, Mirubilis jalapa* flower, *Stevia rebaudiana, Cinnamon camphora* leaf, *Cassia fistula* bark [116], *Hibiscus rosa sinensis* [118], tea [119], *Rhizophora mucronata* mangrove leaf [52], *Gnidia glauca* flower [115], *Phytolacca decandra* [120], *Thuja occidental, Hydrastis canadensis, and Gelsemium sempervirens* [117]. Relying on botanical agents to manufacture state-of-the-science NPs makes this aspect of medical nanotechnology truly "integrative."

Homeopathy: 200 Years of Low-Dose Natural Nanomedicines for Infectious Diseases?

Homeopathic Medicines as Nanoparticles—Many therapeutic applications of NPs used as conventional drugs are in preclinical testing phases. Ironically, one of the most controversial systems of alternative medicine, homeopathy, could turn out to be one of the oldest and demonstrably safest [121–124] forms of nanoparticle-based [5, 6] treatment already used worldwide for infectious diseases. That is, one "top-down" way in which modern nanotechnology makes nanoparticles from bulk materials is simply by grinding or

milling insoluble substances for long periods of time [16–18, 125]. This type of milling procedure is a sophisticated mechanized approach [16, 18, 19] to what homeopathic manufacturers have done by hand or simple machines for over 200 years, i.e., trituration of bulk form plant, mineral, or animal source materials in lactose, with mortar and pestle, to make “dry” dilutions of particles [126, 127]. Consequently, the lactose trituration method of manufacturing homeopathic remedies, especially for the lowest potencies of source agents, begins to blur the line between herbal nanomedicines and homeopathic medicines. Nanomedicines include gold or silver [74, 128], silica, calcium or magnesium phosphates as drug or gene delivery vehicles [60, 61, 129], and nanovaccines [71, 130], all of which overlap with the source materials for common low potency homeopathic medicines [131].

To make liquid homeopathic medicine potencies, the milled or ground materials for insoluble sources or ionic salts for soluble sources are serially diluted and succussed in ethanol-water solutions. During liquid dilution manufacturing, the succussions after each dilution step cause intense fluid turbulence from vigorous shaking, agitation, or physical pounding of the glass container against a hard surface [132]. In modern nanotechnology, this type of fluid turbulence produces particle collisions and shearing forces that break off increasingly smaller particles [133].

Both homeopathic [6, 134–136] and non-homeopathic [137] pharmacy research studies indicate that glass can release measurable but variable amounts of silica precursors and silica nanoparticles into solution. Agitation causes glass-derived silica nanoparticles to accelerate aggregration of protein molecules in solution with them [137]. Also, once in aqueous solution at room temperature, silica precursors can form self assembled crystalline silica structures in the presence of plant extracts [138].

Even at liquid dilutions seemingly past Avogadro’s number (e.g., in homeopathic potencies of ≥12C or 24X, beyond Avogadro’s number of 6×10^{23} molecules, where C=bulk dilution factor of 1/100, done 30 times for 30C or 200 times for 200C and then succussed 10 or more times after each “dilution” step), modern electron microscopy and other laboratory analytic methods now show that homeopathic metal-derived medicines still contain source nanoparticles, transferred from dilution to dilution [5]. Using scanning and transmission electron microscopy, a different research group subsequently demonstrated nanostructure forms in three different homeopathic plant medicines at potencies from 1C to 15C [6]. A third research group recently reported the biosynthesis of silver nanoparticles using four different homeopathic plant mother tinctures. The resultant silver nanoparticles had different sizes and biological effects as a function of the specific plant tincture with which they were manufactured [117].

Homeopathic medicines likely contain source particles adsorbed onto lactose particles in lower potencies [18, 63] or silica nanoparticles at higher potencies [73, 134–136, 139]. Variations in dilution and succussion procedures may contribute to the variability in manufacturing results [5, 73, 132]. The nanoparticles would include any metal or mineral-derived source materials [5] or organic plant [64] or animal source materials, as well as lactose [18], silica [6, 134–136, 139] or polypropylene [73] nanocrystals with any plant or animal source proteins and/or nucleic acids adsorbed. Lactose can even adsorb biologically-active animal protein nanoparticles created by electrospraying [63].

Alternatively, modern homeopathic manufacturing methods sometimes rely on vortexing or sonication rather than manual shaking to accomplish the mixing and succussion, as well using polypropylene tubes rather than the traditional glass vials [73, 135, 136]. The type of succussion and the type of material in the walls of the vial in which the remedy is succussed would measurably affect the properties of the resultant homeopathic medicine [73, 136]. In

addition, nanoparticles undergo spontaneous aggregration into larger particles (which would alter their properties) if left undisturbed for periods of time, a thermodynamic process termed Ostwald ripening [140]. Sonication disperses aggregates of nanostructures that can form after wet-grinding procedures alone [141], thereby likely changing the sizes and properties of the final product [58, 142].

Such findings suggest the possibility that not only the glassware, but also the type, number or duration and force, as well as recency of the succussion procedures could result in biologically meaningful variations in the properties of homeopathic medicines in a specific batch or dose. Differences in ethanol concentration, pH, and/or temperature can also contribute to significant variations in the sizes, shapes and, thus, properties of nanostructures [20, 142]. The well-known reproducibility problems in homeopathic research could relate in part to these multiple variables that can affect nanoparticle formation in complex, nonlinear ways.

Furthermore, the glass-derived silica may be much more than an “artifact” in homeopathic medicines [9]. A body of recent research suggests that nanosilica could play a key role as (a) drug delivery vehicles for homeopathic plant or animal source materials that adsorb onto its surfaces [20, 138, 143, 144]; (b) vehicles for epitaxial transfer and even memory of electromagnetic [145] and/or structural information using the specific remedy source materials as structural template “seeds” and biological guides for bottom-up, self-assembled formation of silica nanostructures [20, 138, 146, 147]; and (c) nonspecific biological amplifiers of specific antigen or remedy source effects on immune cells and pathways [112, 130, 148–150]. For example, adding nanosilica significantly increases the apoptotic and growth arrest effects of a traditional snake venom medicine on human breast cancer cells [32]. In brief, while glass-derived nanosilica would not be necessary to make a homeopathic remedy, the silica, when present, would potentially enhance the bioavailability and biological effects of remedy source-specific nanoparticles in the medicines.

Taken together, the data suggest that, homeopathic medicines may be low doses of mineral, plant, and/or animal source nanoparticles. Nanotechnology studies have shown that trituration [151], drug crystal milling [16, 19, 125, 152], and/or various succussion methods [73] at room temperature can release nanoparticles and nanoaggregates of silica (or polypropylene polymers) and/or source material into colloidal solution [73, 134, 136, 139]. The physician-chemist founder of homeopathy, Samuel Hahnemann, deserves credit for what appears to have been the first description of a practical method for making and safely administering nanomedicines. He interpreted his observations on the ability of trituration and succussion to release unique medicinal properties from bulk form materials within the vitalistic and spiritual conceptual framework of his era [126]. However, Hahnemann’s life (1755–1843) occurred at a time that predated key scientific discoveries and acceptance of the atomic and molecular nature of matter, as well as the unique characteristics of nanoparticles themselves. Rather than rejecting the entire field of homeopathy for its originally vitalistic *interpretations*, it is time for modern scientists to examine seriously the nanomedicine implications of Hahnemann’s *empirical findings* for integrative health care.

That is, such homeopathic preparation steps could represent a crude but effective, top-down technique for mechanically generating nanoparticles [5, 6]. In nanofluids, different amounts of sonication time by itself can increase the size and morphology of nanoparticle and nanocluster aggregates that form from the “same” material [58]. In solution, the enhanced reactivity of NPs can lead to spontaneous changes in shape, NP aggregations and self-assembly [11, 140]. Similarly, homeopathic medicines stored in liquid form at room temperature change their physico-chemical properties over time [153]. Different NPs and aggregates possess different physico-chemical properties from one another because of their

different sizes and shapes [10, 11], even though the original bulk form source was the same substance. [58]. Particle structure, adsorption, aggregation, and self assembled network organization become as important as material source composition in affecting properties at the nano level of scale [147].

Homeopathic Medicines in Infectious Disease Treatment: Cross-Adaptation and Hormesis—Prior research on the basic science of homeopathy [153] converges with evidence from the nanomedicine literature to suggest potential mechanisms of action for low doses of NPs in treating infections. Nanoparticles can exhibit hormetic dose-response patterns [154, 155]. Hormesis is a well-documented nonlinear physiological and cellular phenomenon of adaptation [156–158]. In hormesis, lower doses of a given substance stimulate, whereas higher doses of the same substance inhibit, function in a complex adaptive system [159–164]. The hormetic dose-response range occurs below the no-observed-adverse-effect-level (NOAEL) [165]. Studies suggest that at least some NPs can cause hormesis in low doses [154, 166].

Convergent expert opinion is that hormesis is a nonlinear adaptive, not pharmacological, process that the patient or organism as a complex adaptive system or network generates [154, 167]. The adaptations begin in the cellular defense networks and interact with the other networks of the organism [160, 161, 163, 164, 168–170]. Relevant to their capacity to exert biological effects, as low dose, but highly-catalytic nanoparticles, homeopathic medicines are able to initiate (a) the biphasic dose-response relationship of hormesis [154, 171]; and (b) endogenous time-dependent response amplification and biphasic oscillation processes [7, 8, 172–174]. Integrative medicine researchers have focused on hormesis and complex adaptive systems as potential mechanisms for homeopathic medicine actions at low doses [175]. However, non-homeopathic integrative interventions at relatively low bulk form doses, such as herbs and antioxidant nutriceuticals, also engage hormetic cellular adaptive processes to strengthen host defenses [164, 176]. Nanoforms of nutriceuticals would lower the dose required to evoke the adaptive or hormetic effects within the host.

Given the evidence that homeopathic medicines may be NPs, infectious diseases such as malaria and other epidemics were among the earliest public health problems for which homeopaths reported good outcomes since the inception of this over 200-year old field [126, 127, 177]. Consistent with this claim, animal studies demonstrate an ability of homeopathic *Eupatorium perfoliatum* or *Arsenicum album* to inhibit Plasmodium parasite multiplication [178]. Combinations of other common homeopathic remedies in mice (i.e., *Bryonia alba, Thuja occidentalis, Aconitum napellus, Arsenicum album, and Lachesis*) can inhibit experimental infection with Leishmania amazonensis [179], as can other types of nanoparticles [49, 180–182].

Homeopathic medicines made from botanical sources also exert antiviral effects against multiple human pathogenic respiratory viruses in vitro [183]. Such medicines combine low potencies of *Aconitum napellus, Bryonia alba, Eupatorium, Phosphorus, and Lachesis*. Preliminary clinical trial evidence suggests homeopathic treatment can have beneficial adjunctive benefits in people with HIV/AIDS [184]. Homeopathic diamond given adjunctively to conventional drugs, is one of many remedies anecdotally reported helpful for HIV/AIDS patients in Africa [185] (http://www.homeopathyforhealthinafrica.org/, accessed 06/05/12). Low, but not high, doses of conventional nanodiamond NPs can upregulate phagocytic antibacterial activity of mouse cells *in vitro* [155]. The effects of conventional nanodiamond on antiviral activity are not as yet studied but appear feasible to assess [186, 187].

A large scale public health intervention with prophylactic homeopathically-prepared oral doses of diluted and succussed, inactivated leptospirosis bacteria in 2.3 million people in Cuba demonstrated significant reductions in disease incidence compared with non-intervention regions during a high-risk rainy season [188]. Notably, in conventional nanomedicine research, a one-dose nanoparticle-based vaccination by nasal administration has been shown effective in an animal model of a different bacterial infection, Yesinia pestis (plague) [189]. NP formulations can increase the ability of low doses of a given agent to translocate around the body [190] or stimulate immune responses [71, 72, 155].

As a complete clinical method for administering nanoparticles at nontoxic doses, homeopathy offers significant advantages. In contrast with conventional drugs and many bulk form herbs, drug-drug and drug-herb interactions, are not a problem with homeopathic medicines. Moreover, the likely hormetic adaptive mechanisms of action for homeopathic nanoparticles typically place their dose-response curves into the nontoxic range. Homeopathic treatment also has the advantage of lowering costs via reduced use of symptomatic conventional drugs [121]. Homeopathic medicines themselves are much less expensive, and, for many conditions, require fewer doses than conventional drugs, advantages that can also lower costs and improve patient adherence.

Modern observational, comparative effectiveness, and efficacy studies also indicate a strong track record for homeopathy of faster onset clinical improvements in mild to moderate common acute infections of the upper respiratory tract (e.g., colds, influenza - [191–193]) and ear [194–200]). In vitro, homeopathic remedies made from botanical sources demonstrate antiviral effects and the ability to stimulate patterns of change in pro- and anti-inflammatory cytokine release [183, 201, 202]. Even while dismissing the favorable findings, the otherwise negative (albeit highly flawed - [203–205]) Shang et al's metaanalysis reported a subanalysis of homeopathy efficacy studies restricted to infectious diseases that revealed a strongly significant benefit of homeopathic treatment [206]. In conventional nanomedicine research, nanoparticle-based viral vaccines, gold and other types of NPs are also efficacious against influenza virus [207–209]. Although more clinical research is clearly needed, the evidence exists to support integrating nanoparticle research with homeopathic medicine, in the process of establishing a hormetic or adaptive nanomedicine.

The way in which homeopaths prescribe their medicines differs significantly from conventional pharmacological dosing and relies on small quantities below toxic levels [210]. Homeopathic dosing utilizes not only low doses, but also intermittent pulsed timing of doses, i.e., spaced intermittently in time [211]. Their likely mode of action relates to the ability of low doses of exogenous agents or stress itself to initiate persistent, self-amplified adaptive changes in physiological self-regulation via hormesis and endogenous time-dependent sensitization in the host [7, 8, 174, 212–215]. The low doses of activated nanoparticle forms, by working within the hormetic dose-response range [160–162], would activate broad, endogenous non-pharmacological mechanisms involved in compensatory adaptations to exogenous stressors and stimuli, i.e., the allostatic stress response network [112, 167–169, 216–219]. The stress response network includes heat shock proteins [160–162, 220],cytokines [201, 221, 222], and reactive oxygen species [39]. As a result, pulsed low doses of NPs (i.e., homeopathy) would rely mainly on modulating network-based adaptive, rather than specific local pharmacological, mechanisms of action [7–9].

Many modern nanoformulations are still in preclinical testing phases. However, two centuries of experience with homeopathic medicines have demonstrated that this type of nanoparticle, administered in low intermittent doses, has an exceptionally positive safety profile for public health applications, even in widespread use across large populations [121].

Homeopathic medicines offer a real-world exemplar of low dose, non-pharmacological nanoparticle treatment within an already established whole system of complementary and alternative medicine (CAM). It is possible that the historic term “homeopathy” will ultimately be replaced with a more pragmatic, scientifically accurate, and neutral term – e.g., adaptive network nanomedicine [9].

There is now an evidence-based, scientifically testable model for homeopathic remedy effects that overlaps with the empirically-documented properties of nanoparticles [7–9]. Homeopathic remedies appear to contain source and silica nanoparticles and are not inert placebos. NP forms of a given bulk form source are highly reactive and catalytic, prone to adsorbing other nanomaterials on their surface. At moderate or high doses, nanoparticles can trigger stronger pharmacological effects; at low doses, NPs mobilize non-pharmacological, biological adaptation, hormesis and endogenous amplification mechanisms [8, 155, 173, 218]. Together with the state of the organism at the time of administration, the intensity or magnitude of the dose helps determine the direction of adaptive change [7, 8, 174, 223]. The enhanced reactivity of NPs could shift the dose-response range for expressing hormesis even lower than with low bulk form doses [154]. This scientifically-grounded perspective puts the substantial body of preclinical and clinical data on homeopathy and other types of nanoparticles from natural sources in a new light.

Discussion

The Stress Response and Cellular Defense Network and Adaptation

Viewing the organism as a complex adaptive network of networks [167–169, 214, 216, 224–227] is a good starting point for developing preventive strategies and more effective integrative treatments for infectious diseases. Periodic mild stressors from multiple different categories, including herbal and nutritional [164, 228], can all induce hormesis and promote better health and survival [167, 229]. In fact, mild stressors both prepare the organism to fend off higher intensity stressors of the same or cross-adapted type in the future and/or to recover from the adverse effects of prior higher intensity stressors, e.g., infections, once established [156, 160–162].

Complex adaptive systems are self-organizing networks [168, 169] whose functions are shaped by changes in the environment [230, 231]. Adaptations begin at the interface with the environment, within the stress response network, which regulates immune, endocrine, nervous system, and metabolic functions [217, 232]. Changes in the stress response network [169, 214] cascade into an amplified and extensive set of adaptations via their interconnections with organs [227] and the host organism as a whole [216, 225, 226, 230]. The direction of adaptive changes is plastic and bipolar. As in drug-related hormesis, lower intensity biological or psychological stressors also induce persistent changes in systemic responsivity in the opposite direction to those of higher intensity stressors [212]. Global and local levels of systemic organization interact and feedback information to modulate each other’s functions and organizational dynamics [225, 233, 234]. Under stress, cellular networks can change their linking pattern structure to improve their chances of survival, but can recover an unstressed linkage pattern when the stress subsides [168, 169].

Local Cellular Defense Mechanisms in Host Adaptation

Effectors in the molecular stress response networks of cells include heat shock proteins, chaperone proteins, lysosomes, DNA repair enzymes, FoxO and other molecular responders to reactive oxygen species (free radicals), sirtuins, and cytokines [167]. Serving as mild environmental stressors for the host organism, natural source, non-drug NPs of plant, mineral, or animal source would modulate and strengthen host adaptive capacities and

resilience [160–162], apart from conventional pharmacological, symptom-suppressing mechanisms. NPs from various natural products, with their enhanced bioavailability, act as hormetins to promote stronger neuroimmune function in the host organism [176, 235–237]. For example, homeopathic NPs can elicit cross-adapted and cross-sensitized hormetic heat shock protein response patterns [160, 161, 220] that would, among other effects, induce innate and adaptive immunity to combat infections and other diseases [238].

One specific example of how either infectious organisms (e.g., bacteria or viruses) or non-viral nanoparticles can initiate such a cascade of adaptive biological events derives from data on the intracellular inflammasomes. Inflammasomes are a multi-protein complex that serves as sensors for microbial DNA patterns and other environmental “danger signals” for the body [148, 239]. A variety of exogenous stimuli, including infectious agents, nanoparticles, and non-infectious crystals of silica, alum, or urate [110, 148, 240, 241], mobilize the immune response by activating the intracellular inflammasomes. Activation of inflammasomes leads to the release of proinflammatory cytokines such as interleukin 1β along with other interconnected regulatory elements of the stress response network [112, 148, 239, 241–243]. Interleukins can then modulate central nervous system function, evoke fevers and inflammation, and change the host’s mood and energy levels [244].

In the setting of established pathogen infection, low dose hormetic nanoparticles salient to the organism’s pre-existing adaptational state would signal that a new, low intensity danger or reactive stressor [219], i.e., nontoxic doses of the herbal, nutriceutical, or homeopathic nanoparticles, have entered the body [148, 239, 241, 245]. Then the low dose nanoparticles and nanocrystallites would trigger the beneficial adaptive mechanisms [163, 164, 176], by serving as a low dose “danger” or “alerting” signal to bodily cells in the host to make changes that would lead, for instance, to enhanced immune activation and/or free radical attacks against intracellular infectious agents.

In additional to bidirectionality, the adaptational networks of the body appear to have substantial capacity for cross-adapted and/or cross-sensitized responses [8, 9]. As a result, a stressor from one category can initiate adaptations that modify the reactions to a subsequent stressor from an entirely different category [174, 246, 247]. Thus, adapting to anoxia may improve subsequent ability to tolerate extreme cold temperatures [247]. For instance, repeated intermittent exposures to psychological stress or sucrose ingestion or formaldehyde inhalation may heighten the magnitude or even change the direction of subsequent reactions to amphetamine or cocaine [213, 248–251]. Thus, administering nanoparticle hormetins in low dose has the potential for mobilizing endogenously amplified changes that can improve rather than impair the ability to overcome an infection or other types of stress.

Summary and Conclusions

Nanoparticle research has produced substantial progress toward improving natural product and drug delivery methods for treatment of infectious diseases. Nanomedicine is already integrative, blending state-of-the-science manufacturing technology with herbal and botanical sources to reduce toxicity. NPs offer the promise of more efficient and targeted treatments in a range of infectious diseases, especially intracellular pathogens with important public health implications, such as tuberculosis, HIV/AIDS, leishmania, and malaria [12]. Nanoparticle forms facilitate use of oral and nasal modes of administration [252, 253]. Isopathic public health interventions to reduce epidemics with diluted and succussed but attenuated oral low dose infectious agents, modeled after the leptospirosis project in Cuba [188], appear feasible and merit additional evaluation.

At the practical level, modern nanoparticle formulations can lower drug, vaccine, herb, and nutriceutical doses and release their active agent only once inside target cells, thereby lowering drug-drug interactions and side effects [70, 104, 207, 254–256]. The potential benefits are improved outcomes and safety as well as lowered treatment costs as a result of reduced dose levels and oral or inhalation administration. Integrative treatments that support the patient's adaptive networks will lead to functional self reorganization of the patient as a biological network [225]. The result can be host expression of a more robust cellular defense system against infections and other stressors [163, 164, 231]. The advantage for public health is to reduce the risks of fostering drug-resistant organisms.

That is, not only the patient, but also the infectious organisms are complex adaptive systems. Conventional drug treatments for infections mainly ignore the host and, by directly attacking the infectious agent, stimulate dynamical adaptations in the bacteria, viruses, or fungi as complex adaptive systems. As a result, the adapting infectious agent self-reorganizes and evolves to overcome the adverse effects of the drugs for its own survival [168, 169], i.e., develop drug resistance. Thus, wider adoption of integrative strategies discussed in this paper to reduce inappropriate use of conventional antibiotic, antiviral, or antifungal drugs could substantially contribute to improvements in public health.

The development of biodegradable and nontoxic NPs from natural sources constitute an essential advance for translation from bench to integrative clinical application. Traditional herbs from Ayurveda or Chinese medicine [14, 40], as well as antioxidant nutriceuticals [42, 257, 258] that can strengthen immune function and improve resistance to infection are better absorbed and more active in nanoparticle than in ordinary bulk form. Homeopathic remedy (hormetic) nanoparticles offer an over 200 year, real world precedent for the pragmatic utility, safety, and cost-effectiveness of low dose adaptive network nanomedicine [7, 9] for large segments of the population, including in epidemics. The primary integrative therapeutic goal is to stimulate improved adaptive resilience in the host organism as a complex network.

Further research should focus on defining best practices for manufacturing, distributing, and administering nanoparticle-based integrative treatments using natural products for infectious diseases. Given limitations of conventional antibiotic drugs from the emergence of treatment-resistant organisms, developing safe and effective nanomedicines from natural products that bolster host resistance and self healing mechanisms from infections should be a priority for new funding initiatives. Nanomedicine using traditional agents from alternative systems of health care represents an important and timely opportunity for progress in promoting integrative public health in both developed and developing nations.

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Table 1

Exemplar Studies of Herbal-Facilitated Nanoparticle Product Production

Herb or Botanical	Nanoparticle Type	References
Hypericum	Gold	[74]
Gelsemium sempervirens	Poly(lactide-co-glycolide)	[64]
Gelsemium sempervirens	Silica (glass), Polypropylene	[73]
Rosmarinus officinalis	Magnetite (iron oxide/oleic acid)	[75]
Magnolia bark	Magnolia bark extract	[76]
Gingko biloba	monomethyl poly(ethylene glycol)–poly (lactide-co-glycolide)–monomethyl-poly(ethylene-glycol), MeO–PEG–PLGA–PEG–OMe polymers	[77]
Cassia fistula	Gold	[116]
Thuja occidentalis *Phytolacca decandra* *Hydrastis Canadensis* *Gelsemium sempervirens*	Silver	[117]
Equisetum telmateia	Silica	[138]