WATER

Earliest Medicines Evolved from Dangerous Environmental Stressors to Support Life on a Hostile Earth: A Nanoparticle and Water-based Evolutionary Theory

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Abstract

To understand evolution better, biologists should take into account the development of an organism's reaction to stressors (*i.e.*,the secondary action of a stressor) during development, and the subtle role it plays. Hormesis and homeopathic phenomena are just names to classify such secondry properties. These phenomena exploit the secondary action, below that of a pharmacological of toxin dose in a beneficial fashion. An intriguing examination of the biological behavior of the secondary action leads to the proposed theory.

Hormesis seems to be an evolutionary adaptation that provides a buffer against environmental changes. Through the chemical routes, it paved a way for the evolution of molecular mechanisms which gave rise to homeopathic phenomenon. As serial turbulent dilution of environmental stressors is a part of nature, such molecular mechanisms were compelled to develop further, making an organism sensitive to ultramolecular dilution in terms of beneficial secondary action. Nanoparticles along with interfacial water can carry stressor-specific information. Thus the first true medicinal effects which evolved during early life were homeopathic in nature and environmental hormetic stressors were their precursors.

Homeopathy is an adaptive stress-response therapy. While hormesis causes enzymatic and some transcriptional genetic changes, homeopathy operates on a different level of epigenetic modifications. The proposed theory predicts that the hormesity of non-hormetic toxins, at least those with which life evolved, is contained in ultramolecular dilutions. Experimental support is emerging for this theory, and some suggestions have been given for testing and verification. As this theory concerns the evolution of the earliest medicine with an intrinsic role in the evolutionary process, it could influence the whole field of medical science.

Introduction

The German physician Samuel Hahnemann was the first to systematically base therapeutics on the secondary effect or action of a toxin/stressor (Fisher, 2010). He established homeopathy as a therapeutic system in 1796 (Hahnemann, reprint 1970; Bellavite and Signorini, 2002). This system is based on the law of similars ("like

cures like") (Hahnemann, reprint 1970; Bellavite and Signorini, 2002). It posits that when a toxin, or drug, is capable of inducing a series of symptoms in a healthy living system, low doses of the same toxin, or drug, can be a curative for the symptoms (Hahnemann, reprint 1970; Bellavite and Signorini, 2002). Here, the secondary effect of the drug (*i.e.*, the body's reaction), rather than its primary pharmacological action, is exploited (Fisher, 2010). Hormesis, on the other hand, is a biphasic dose-response where, while a high dose of toxin is damaging, a low dose, after an initial dose dependent toxicity response, induces an adaptive beneficial rebound effect on the cell or organism (Stebbing, 1998; Mattson and Calabrese, 2010).

Hormesis was discovered by German pharmacologist Hugo Schultz (1887) in the 1880s. He claimed that the phenomenon of hormesis explained the principle of homeopathy and held this belief throughout his life (Mattson and Calabrese, 2010). On the basis that in homeopathic medicine, dilution of source-drug is increasingly becoming so high that vitually none of the source molecules remain, Mattson and Calabrese (2010) claimed that hormesis and homeopathy are two different phenomena. However, especially after the work of Van Wijk and Wiegant (Van Wijk and Wiegant, 2010; Wiegant and Van Wijk, 2010), Calabrese and Jonas (2010a, 2010b) accepted that homeopathic medicine, only if containing the source-drug in a measurable quantity, may represent hormesis and can be studied biomedically through pre- or post-conditioning hormesis methodology.

Hormesis and homeopathy share two crucial and typical basic similarities: subthreshold doses of toxic substances and an initially induced toxicity by this semi-toxicological dose, followed by a greater compensatory response (Calabrese and Jonas, 2010a). There are, however, many differences between them too (Oberbaum *et al.*, 2010; Oberbaum and Gropp, 2015; Bellavite *et al.*, 2010). Oberbaum and Gropp (2015) and Oberbaum *et al.* (2010) found such differences between hormesis and homeopathy difficult to reconcile, thus refuting the idea that they stem from the same root pathways. Thus the search for common ground remains an intriguing challenge. Confusion about their relationship still prevails, suggesting that a coherent theory on the subject is lacking.

In this paper, the phenomena of hormesis and homeopathy are analysed, and a novel nanoparticle and water-based evolutionary theory is developed which suggests an inherent link between homeopathy and hormesis. Possible experimental verification of this theory is discussed. The work is an extension of the previous contribution (Upadhyay, 2018a).

Homeopathy: Discovery, Controversies and New Scientific Understanding

Discovery

The law of similars has been known since ancient times (Fisher, 2010). Paracelsus stated it as, "What makes a man ill also cures him" (Web ref. 1). While translating a medical treatise, Samuel Hahnemann (1755-1843) was struck by the fact that if *Cinchona*, a drug for malaria, is overdosed, it produces symptoms similar to the disease (Haehl, 2003). This was the turning point in his life which, until then had consisted of practising orthodox medicine (Haehl, 2003). He experimented on himself and other healthy persons with *Cinchona* and then with other drugs. He carefully recorded the symptoms and referred them as a "proving" of the drug/medicine (Hahnemann, reprint 1970; Bellavite and Signorini, 2002). Here, the present author suggests that homeopathy requires a new perspective so that adaptation/evolution

may be better understood. Thus, the proving of a drug turns out to be the collection of adaptive responses of healthy provers to the stressor (drug) in the form of symptoms developed by the provers. Provings are performed with crude drugs as well as medicines prepared from them in high potencies (Kent, reprint 1986). Interestingly, provings of drugs/medicines, through their higher potencies, are required in order to bring out finer characteristics. This shows that secondary action derived from the high potency medicine of a drug can also make a healthy organism sick. The action is more elaborate than primary pharmacological action. Further, it has been stated that if doses of a drug or medicine continue, even after the prover has developed the symptoms (adaptive responses), the symptoms may impinge on the prover for a prolonged period or even for life, making the prover chronically ill (Kent, reprint 1986). Clear instructions to the prover, in drug proving protocols, has been to stop intake of further doses, once proving symptoms develop (Web ref. 2). Thus the present author suggests that homeopathic provings can be taken as simulations of how environmental stressors could impose sickness on biological systems and used to explore curatives for such symptoms.

Hahnemann observed that minute doses of *Cinchona* cured not only some cases of malaria, but other cases where the subject had not suffering neither malaria, nor any fever or chill. He observed that instead of diseases, the importance was that the symptoms (adaptive responses) that developed in patients were similar to those developed in provers (Hahnemann, reprint 1970; Bellavite and Signorini, 2002; Kent, reprint 1986).

In the beginning, Hahnemann prescribed large doses of medicines to patients, as doing so was the orthodox practice (Haehl, 2003). Patients suffered frequently, as these medicines were often toxins; and a high dose was above the toxic threshold. This compelled Hahnemann to dilute his medicines. These treatments can now be distinctly identified as "hormetic" treatments adhering to law of similars. As he saw the value of diluting his medicines, Hahnemann proceeded to dilute them further. He then observed that these diluted medicines were more potent when he administered them to patients at their homes, where he used to go on a horse-cart, bumping over the uneven surface of the road. After trial and error, he reasoned that the jolting received by the remedies during their journeys had somehow increased the potency. Thus Hahnemann hit upon his method of potentization, by delivering violent strokes to the fluid each level of serial dilution. Trituration has been used in Ayurvedic medicine since ancient times, where it is claimed that it enhances the therapeutic power of a drug (Sharma and Prajapati, 2015). However through serial liquid/solid dilutions with succussion/trituration, Hahnemann discovered medicines with particle densities beyond Avogadro's constant.

Hahnemann identified potential drugs for his new therapeutic system. He potentized them individually in as pure form as possible. To standardize his medicine (processed drug), he applied a scale for dilution and it was centesimal (1:99) scale. A 12 times serial dilution with succussions at each dilution level designated as 12C potency of the medicine. The potency corresponded to a source-drug dilution in the ratio of $1{:}10^{24}$. If source-drug concentration in the original (mother) solution was of around 1 mole/L, Avogadro's limit of 1 atom or molecule/L is exceeded at this potency. Thus, according to the scientific understanding of solutions, a dose to a patient, which could be 1/10 of a drop, is unlikely to contain any molecules of the source-drug from which the medicine was prepared.

Hahnemann conducted provings of his medicines on healthy persons to explore

their full therapeutic potential, so that they could be prescribed correctly.

The philosophy he developed for "the healing art" (Hahnemann, reprint 1970) is simply the close observation of nature regarding sickness, as he could make or understand. He proposed the concept of vital force as responsible for maintaining the body's sensations and functions and as the origin for how homeopathic medicines behave (Hahnemann, reprint 1970). The homeopathic "vital force" is similar to that of other medical and philosophical concepts especially the Hippocratic *vis medicatrix naturae* (Teixeira, 2019a). The healing power of nature is an ancient medical principle that includes references to the innate ability of the body to heal itself through an internal response that repairs and rebuilds (Logan and Selhub, 2012). The biomedical concept of homeostasis can be considered as a subset of these properties. Hahnemann proposed further the concept of three miasms which cause chronicity to diseases (Hahnemann, reprint 1970).

Hahnemann explored the homeopathic phenomenon in-depth. He exploited it to develop and establish a viable system of therapeutics called homeopathy.

Controversies

Being inimical to orthodox medicine, homeopathy has been controversial since inception. In the early period, nobody knew that the medicines contained very few, if not none, of the molecules of the drug from which it was prepared: Avogadro's constant was not computed during Hahnemann's lifetime. It is amazing therefore that even then, Hahnemann realized his medicines could not contain its source-drug and so he explained their therapeutic effects as "spirit-like" (Hahnemann, reprint 1970; Upadhyay, 2017). Schultz's support for homeopathy led to his marginalisation as a scientist, but also his discovery of hormesis (Mattson and Calabrese, 2010). The controversy occurred because, unfortunately, medical science has been bitterly divided into two rival camps: orthodox medicine (*i.e.*, allopathy) and homeopathy, making unlikely an unbiased scientific enquiry of any observation related to homeopathy. Further, the notion of "medicine without molecules," unique to homeopathy, has only added fuel to the fire of anti-homeopathy rhetoric. The suggestion that water could keep a memory of past contaminants (Chaplin, 2007) led to the bitter Benveniste – *Nature* controversy, when Benveniste's group (Davenas *et al.*, 1988) could not reproduce the extraordinary experimental claims made by in their *Nature* paper in presence of the visiting Nature team (Maddox *et al.*, 1988; Web ref. 3; Pollack, 2013).

Homeopathy is useful when applied in open practice and produces substantial effects, even in patients with chronic diseases. However, considering only double-blind randomized controlled studies as the criteria of evidence-based medicine (developed for modern/allopathic medicine), it is hard to convince skeptics (Editorial The *Lancet,* 2005) that homeopathy is significantly different from placebo effects (Bellavite *et al.*, 2006). Interestingly these double-blind randomized controlled studies are not suitable for studying hormesis either, as due to individual variability, a hormetic dose which is just below the toxic threshold cannot be generalized (Calabrese *et al.*, 2013; Mattson, 2015). Thus, homeopathy requires evaluative research methodologies that respect the complexity of its diagnostic procedure (Bellavite *et al.*, 2006). Otherwise, as Milgrom (2009) demonstrated, such trials are useless for studying complex therapeutic interventions.

New Scientific Understanding

Many scientists, with non-homeopathic background, have been studying the phenomenon of "magnetization of water" (Otsuka and Ozeki, 2006; Toledo *et al.*, 2008; Coey and Cass, 2000). However

often their work is not taken seriously in science. There are two reasons behind it; first, conventionally magnetization of water seems impossible. Secondly, results so obtained are not very reproducible. It has now been observed that pure water indeed cannot be magnetized but if exposed to oxygen, then this property of water alters and magnetization becomes possible (Otsuka and Ozeki, 2006). Studying extremely pure water through their high precision instruments, Otsuka and Ozeki (2006) also claimed that the phenomenon of water magnetization can be precisely studied in a scientific manner with reproducible results. Previously such results were found not very reproducible because, being a universal solvent, even the "pure water" contains impurities, including the magnetic ones, and the quantity of dissolved oxygen (Toledo *et al.,* 2008). According to some sources, the effect of magnetization of water remains in its "memory" up to 200 hours (Coey and Cass, 2000). Can this memory be extended to a prolonged period? Homeopathy claims this in favor (Kayne, 2006).

Ullman (2006) envisioned homeopathy as belonging to nanopharmacology. Anick and Ives (2007) proposed a hypothesis suggesting that silica or its nanoparticles may play an important role in homeopathy. Later, the nanoscience studies of homeopathic medicines revealed that they contain nanoparticles (Chikramane *et al.*, 2010; Upadhyay and Nayak, 2011; Konovalov and Ryzhkina, 2014; Bell *et al.,* 2015a). On the basis of the study of market-purchased homeopathic medicines as test samples, Chikramane *et al.* (2010) claimed that these nanoparticles contain the source-drug of the medicine irrespective of its dilution degree, and so the medicine is effective. To support their unusual claim, they proposed a hypothesis of froth floatation after succussions containing all the source-drug and its retention as 1% "seed" in subsequent homeopathic dilutions (Chikramane *et al.*, 2010, 2012). Upadhyay (2018a, 2018b) explained that this proposed hypothesis for homeopathic medicine is actually irrelevant to it in a general sense. First, besides metal-based drugs, many drugs are water/alcohol soluble and secondly dilution degrees are unlimited. Upadhyay (2018a, 2018b) explained further that the presence of source-drug in high potency medicine is not possible except as impurity or by contamination. Investigating self-made test samples, Van Wassenhoven *et al.* (2018) could not validate the findings of Chikramane *et al.* (2010). Upadhyay (2017, 2018a, 2018b) explained that to understand homeopathic medicine, one would have to abandon the materialistic view that the physical presence of its source-drug is necessary for therapeutic effects. The process of potentization is actually "dematerializing the matter itself" (Hahnemann, reprint 1970).

Upadhyay and Nayak (2011) examined the self-prepared homeopathic medicines. The presence of silicon-rich nanoparticles were reported in the samples, with the suggestion that the source-drug specific information might be inscribed on them by means of epitaxy. They further suggested that these nanoparticles, along with the interfacial water on their surface, might carry information to the target in the "size" increasing with dilution degree of the medicine. Such a nanoparticle may act as a virus-like systemic stressor, causing a cell to emit danger signals resulting in adaptation (Bell *et al.*, 2015b).

The properties of interfacial water at a hydrophilic surface are different to that of bulk water. Despite numerous studies, the nature of this interfacial water has remained puzzling, and the debate concerning whether it is more solid-like, ice-like, or liquid-like is ongoing (Mante *et al.*, 2014). Homeopathic medicines prepared in an atmosphere of N_2 were found therapeutically ineffective (Fisher, 1991). Water also cannot be "magnetized" in the atmosphere of N_2 or CO_2 (Otsuka and Ozeki, 2006). Fur-

ther, Upadhyay (2017) compared the physicochemical properties of magnetized water with those of exclusion zone (EZ) water and found them similar. Thus it was explained that "magnetization" of water is actually magnetization of EZ water. Further, during UV-vis spectroscopy of homeopathic medicines, Elia *et al.* (2013) observed an absorption peak at around 270 nm, which is characteristic of the presence of EZ water. The phenomenologies of homeopathic dilutions and EZ water are found to be very similar (Elia *et al.*, 2013). For the purpose of carrying out liquid potentization, it is mandatory that at least 1/3 of the bottle remains empty (Kayne, 2006). This empty part contains air (oxygen) and thus the increased pressure during the strokes would facilitate EZ build up.

The presence of oxygen is necessary for EZ build up, as EZ water $H_3O_2^-$ contains more oxygen than bulk water H_2O (Pollack, 2013). It is negatively charged and liquid crystalline in structure. Del Giudice *et al.* (2010) identified it as a macroscopic coherent domain. It forms honeycomb-type flat sheets as happen in ice but without interlinking protons between them (Pollack, 2013). It can be considered a precursor to ice. Conventional chemists are still reluctant to accept it. However evidence is increasing in its favor (Hwang *et al.*, 2018).

Evidence given here suggests that oxygen exposed water under pressure, especially on a hydrophilic surface as interfacial water, forms exclusion zone and that it is an essential part of the observed information retention phenomenon. The nucleator may impart information to this EZ layer, possibly by inscription through removal of oxygen atoms from the hexagonal lattice of the generic EZ without impairing its structural integrity (Pollack, 2013). The large sheets eliminate Brownian instability, but it naturally erodes with time, and therefore it cannot have lasting memory.

Zhang *et al.* (2003) showed that a nanoparticle undergoes structural changes at room temperature as per the nature of the surrounding molecules, and this makes possible its structural state as an environmental sensor. Thus nanoparticle and exclusion zone together as a nanoparticle-exclusion zone shell can retain information for a prolonged period of time as "memory" (Upadhyay, 2017).

Konovalov and Ryzhkina (2014, 2016) studied highly diluted aqueous solutions (10^{-20} to 10^{-6} mole/L). They observed that such dilutions are self-organizing and form nano-scale molecular assemblies mostly of water, and referred to as "nanoassociates." The size of the associates was on the order of 100 to 400 nanometers. Such scales are comparable to that of nanoparticle-EZ shells. They observed further that nanoassociates form only in presence of geomagnetic or weak electromagnetic fields and that these dilutions are bioactive but only in association with these nanoassociates (Konovalov and Ryzhkina, 2014, 2016).

Advances in quantum biology demonstrate that coherence, as a state of order of matter coupled with electromagnetic (EM) fields, is one of the key quantum phenomena of life (Manzalini and Galeazzi, 2019). Theoretical studies have also been carried out to study the nature of homeopathic dilutions through quantum electrodynamics (QED) (Del Giudice *et al.*, 1988; Yinnon and Yinnon, 2011; Yinnon, 2017; Manzalini and Galeazzi, 2019).

Various *in vivo* and *in vitro* models have been proposed to investigate biological and therapeutic effects of homeopathic dilutions. A prolonged and multi-centred study, using an accepted pharmacological model, revealed that high dilutions of histamine, even beyond the Avogadro limit, have a reproducible effect on biological activity in human and mice basophils (Sainte-Laudy and Belon, 2009). The biological activity is reversible in the presence of a histamine H_2 antagonist (ci-

metidine or ranitidine) (Sainte-Laudy and Belon, 2009). Further, the biologically inactive histamine analogues and derivatives such as histidine, 1-Methyl histamine and 3-Methyl histamine, diluted in the same conditions, fail to demonstrate such biological activity (Sainte-Laudy and Belon, 2009). Benveniste's group used a different model for their controversial experiments. It was based on a direct activation of human basophils by anti-IgE dilutions (Davenas *et al.*, 1988). The results have not been reproduced elsewhere and have been widely criticized, mainly on statistical grounds (Sainte-Laudy and Belon, 2009).

For therapeutic effects, Khuda-Bukhsh (1997, 2003, 2014) proposed a hypothesis that homeopathic medicine acts on the genome by modulating disease-promoting gene expression. Many experiments followed and found that potentized homeopathic medicines act at the gene regulatory level according to the following three main types of effects (Teixeira, 2019a; Teixeira, 2019b):

1. Change in the expression pattern of genes

2. Cytotoxicity or apoptosis in cancer cells

3. Therapeutic modification in gene expression

Memory Retention: The Nanoparticle-Exclusion Zone Shell Model

Del Giudice *et al.* (1988) firstly proposed the coherent domains model, based on quantum electrodynamic (QED) superradiance, to explain so-called "memory of water." This model is rooted in quantum field theory, but lacks experimental support (Bellavite *et al.*, 2013). Later Anagnostatos (1994) proposed hydrogen-bonded clusters or clathrates responsible for the perceived memory, and information storage, of homeopathic medicine. Water molecules can form clusters, but the clathrate model is still very speculative for the medicines, which retain a prolonged shelf-life (Bellavite *et al.*, 2013).

Recently, Upadhyay (2017) has developed "The Nanoparticle - EZ Shell Model" to explain the nature of homeopathic medicine which includes magnet-treated-water as source-drugs. This new model is based on research findings about homeopathic medicine, nanoparticle behaviors and water. The model also incorporates observations from the practice of homeopathy. Findings and observations led to the following five hypotheses for the model (Upadhyay, 2017):

1. When adsorbed by a nanoparticle, the source drug changes its structure up to 3C potency. With the adsorbed source drug as nucleator, this structurally modified nanoparticle builds up a modified EZ shell. By such structural modifications, the nanoparticle and its EZ shell acquire source drug-specific information.

2. The 3C potency is the optimal potency for the encoding of source drug specific information. At this potency the presence of source drug is still required, for reinforcement or consolidation of the acquired information. However, its presence is not required at 4C and higher potencies, as modified structures of nanoparticle and its EZ shell become stable.

3. The source drug specific information is in a "crude and condensed" form and evolves gradually with each homeopathic dilution, becoming more "decipherable" to biological systems.

4. In raising higher potencies after 3C potency, during succussions/ trituration, the EZ shells of those nanoparticles present in 1% "seed" strip off and spread as templates for further evolved information, to the nanoparticles present throughout the whole dilution. These nanoparticles then acquire new EZ shells, resulting in further

modified structures. Thus the information evolves, passing from one potency level to next via the modified EZ water.

5. A threshold amount of a source drug or an impurity is required to initiate and then sustain the process of information retention during potentization.

Here it is noteworthy that the EZ erodes with time naturally by combining a hydronium ion (H_3O^+) with EZ structural unit (OH^-), resulting in two water molecules (Pollack, 2013). A steady state is found, however, when energy-driven EZ growth balances natural EZ attrition (Pollack, 2013). Thus the EZ cannot retain information for long as it would fade away with time. For a prolonged memory, it would require the support of hydrophilic nanoparticle as a substrate. Thus magnet-treated water, which forms three different source-drugs in homeopathy, namely magnetic north-pole, south-pole and the whole magnet, can be shelved for a prolonged period but only beyond its 3C potency as happens in the case of other unstable drugs (Upadhyay, 2017).

The Nanoparticle-EZ Shell Model can explain diverse aspects of homeopathic dilutions (Upadhyay, 2017). This model explains the preparation of homeopathic medicine in both solid and liquid forms, dispensing of liquid form medicine in solid form (through medicine-soaked lactose or cane sugar globules) and vice versa, as well as effective administration of medicine also through olfaction or rubbing on the skin etc.

For a model to be accepted, there are two challenges that must be overcome (Upadhyay, 2017): First; homeopathic medicines have a virtually unlimited shelf-life if stored properly. Secondly, they are an extreme dilution, but cannot be extremely pure as water is a universal solvent. Many impurities, some of which used as source-drugs in homeopathy, were detected in trace level even in laboratory made samples of homeopathic medicines (Witt *et al.*, 2006). Then what type of memory does a homeopathic medicine retain and why is this information not vitiated by impurities during the successive dilutions?

The Nanoparticle-EZ Shell Model overcomes both these challenges (Upadhyay, 2017): Water-driven structural changes of hydrophilic nanoparticle is irreversible at room temperature as water, due to its high polarity, cannot be removed from the surface of a nanoparticle (Zhang *et al.*, 2003). Further, water forms thickest EZ at a hydrophilic surface (Chai and Pollack, 2010). This explains the prolonged shelf-life of homeopathic medicine. In addition, the exclusion zone shell of a nanoparticle protects it from impurities and this, under the fifth hypothesis, maintains the integrity of the medicine. It also explains why homeopathy could be established in the 18th century, an era of impure chemistry.

In the Nanoparticle-EZ Shell Model, the nanoparticle-EZ shell is a structural template of the source-drug, including the hidden medicinal properties. This template contains more useful biological information with iteration and dilution (Upadhyay, 2017).

Early Period of Evolution and Development of Hormesis

Life on Earth began in a hostile environment. So adaptation was the heart of evolution (Eldredge, 1995). It is the evolutionary process whereby an organism becomes better able to survive.

In the evolutionary process, the increasing complexity in biological systems is largely to protect the cells and organisms against environmental stressors. Mattson (2010) explains that these cells and organisms have also developed molecular mechanisms to respond adaptively to stress, under the phenomenon known as hormesis.

The occurrence of hormesis can be ex-

plained as an evolutionary adaptation that acts to maintain fitness of a biological system in a changing external environment (Forbes, 2000). Overall, fitness is not likely to be enhanced by hormesis, because all traits of a biological system are unlikely to exhibit simultaneously. Further, toxic agents affect different traits in different ways and to different degrees (Forbes, 2000).

Hormesis is a measure of biological plasticity (Calabrese *et al.*, 2013). It is widely used to describe the relationship between living things (cells, tissues, entire organisms) and the chemical-physical world with which they come into contact. This approach applies to a wide range of significant phenomena – from medicine to ecology (Bellavite *et al.*, 2010). Hormesis is thus, also a general phenomenon. It is fair for the present author to infer that evolutionary processes developed it in a very early period of life's evolution. It would then be able only to utilize the secondary action of stressors, as molecular mechanisms of biological system would not have developed enough to result in homeopathic phenomenon. Consequently environmental stressors would be causing diseases comparatively freely. It would be as if a free-hand "proving" of the stressor on the biological system were occurring. It is known that the higher the harmful exposure to a cell, the lower the dose required for producing a healing response (Van Wijk and Wiegant, 2010; Wiegant and Van Wijk, 2010). So under evolutionary processes, sick biological systems could then develop mechanisms to respond to stressors hormetically below the pharmacological doses as could be found in nature. In terms of survival, it would also be a method for the development of a more effective therapeutic support system.

Evolution of Homeopathic Phenomenon through Hormesis

Hormesis is concerned with the beneficial action of toxins. As such, its therapeutic potential is obvious. It stimulates the activation of stress resistance mechanisms, and so can influence preventive and clinical medicine. But its effect is modest (30 to 60% greater than the control group), and is one of the reasons why it was ignored in the biomedical sciences (Calabrese *et al.*, 2013). As it is short-acting, and non-specific (Calabrese *et al.*, 2013), its therapeutic potential is not very promising. Based on the severity and/or duration of stress, the hormetic pathways fail to protect the cell or organism (Mattson, 2010). Thus diseases ensue with little resistance. Worse, in disease states and aging, the hormetic pathways may be compromised (Mattson, 2010). Scientific investigations of hormesis phenomenon also could not find significant clinical extensions, and Calabrese and Jonas (2010a) even asked if such an extension was possible. The present author suggests that nature had already developed evolutionary processes via one or more hormetic mechanisms and molecular pathways as an offshoot which gradually evolved exclusively useful for potent therapeutic applications. Thereby having given rise to the so–called, "law of similars." There is support for this suggestion from the following sources:

1. The observations of Wiegant and Van Wijk unequivocally support the law of similars at the cellular level, using the post-conditioning hormesis methodology they developed (Wiegant and Van Wijk, 2010; Van Wijk and Wiegant, 2010).

2. Rattan and Deva (2010) realized on the basis of cellular study, that hormesis does have a certain component of "like cures like."

3. Chikramane *et al.* (2017) observed cellular hormetic activation with metal-based high potency homeopathic medicines, and Calabrese (2017) described it as a step towards unification of hormesis and homeopathy.

4. No common root is found for hormesis and homeopathy (Oberbaum and Gropp, 2015; Oberbaum *et al.*, 2010). This observation also favors the suggestion, or at least does not contradict the idea, that homeopathic phenomenon developed through hormesis.

In homeopathy, during a drug proving, the symptoms induced by the drug in healthy provers are codified (Hahnemann, reprint 1970; Bellavite and Signorini, 2002; Kent, reprint 1986; Kayne, 2006). The symptoms are identified here as adaptive responses to a drug-stressor. For the selection of remedy, the patient's symptoms, *i.e.*, adaptive responses to the sickness-causing stressor, are collected and then matched with those adaptive responses collected from provers. Matching, those responses which come from the whole of the patient (general symptoms) is more important, simply because they indicate higher degrees of adaptation than those which come from body parts of a patient (local symptoms) indicating the lower degrees of adaptation. On many occasions, the complaint for which a patient seeks for treatment is not even required to be considered for remedy selection. Here, a comparison with isopathy might help understanding.

Isopathy is a variant of homeopathy (Bellavite and Signorini, 2002). It might appear as a "super-homeopathy," but it provides only a limited therapeutic scope. Here, a remedy is prepared by potentization of the actual cause of illness or its by-product (Bellavite and Signorini, 2002). It is not based on the adaptive responses of a patient. It is not currently taken seriously in homeopathy (Hahnemann, reprint 1970). At a cellular level, heterologous (homeopathic) and homologous (isopathic) studies also show that a heterologous approach gives much better results than a homologous one (Van Wijk and Wiegant, 2010; Wiegant and Van Wijk 2010). Thus homeopathy emerged as an adaptive stress-response therapy. Nanoparticle-EZ shells carrying remedy-specific information may act as systemic stressors, resulting in adaptation.

Based on the adaptive stress response evolutionary theory, there are innumerable elegant hormetic mechanisms, that have evolved with time to meet various challenges (Mattson, 2010). For example, bacteria are developing resistance against antibiotics, which is one of the few examples of evolution that can be studied in real time (Martinez *et al.*, 2009). Then why would not the same hormesis, soon after its own development, have evolved a number of unique mechanisms as an offshoot in the beginning to cope with rising diseases in early biological systems. Thus homeopathic phenomenon could have evolved through hormesis soon after it came into existence and gradually expanded far from it to be so identified.

Besides human beings, homeopathy has been found to also be applicable in animals, (Bonamin *et al.*, 2015), plants (Ucker *et al.*, 2018) and even single-celled organisms (Das *et al.*, 2012). Further, as already mentioned; the law of similars has been verified objectively even in cellular studies *in vitro*. So this law is not resultant only from human observation. Consequently it could develop and contribute in the evolution from an early evolutionary epoch.

In the recent past, many scientists have investigated homeopathic medicines, mostly as ultra-high dilutions potentized beyond Avogadro's limit, with the state-of-the-art tools of molecular biology (Şeker *et al.*, 2018; Olsen, 2017; Bigagli *et al.*, 2016; Chirumbolo and Bjørklund , 2016; Saha *et al.*, 2015; Dei and Bernardini, 2015; Marzotto *et al.*, 2014; Olioso *et al.*, 2014; Das *et al.*, 2012; Preethi *et al.*, 2012; Sunila *et al.*, 2009). Their work confirms the ability of homeopathic medicines to modulate gene expression in cell cultures. For example, Khuda-Bukhsh and colleagues observed

that these medicines differentially triggered epigenetic alterations in microarray gene expression profiles of genes associated with carcinogenesis in HeLa cells when compared against a control *in vitro* (Saha *et al.*, 2015).

All forms of adaptation are encoded in the genome (Sthijns *et al.*, 2016). Hormesis and homeopathy can be easily differentiated from each other on the basis of the duration of adaptation. Sthijns *et al.* (2016) distinguish short-term and long-term adaptation. Short-term adaptation is defined as a direct adaptation carried out in a few seconds or minutes (enzymatic regulation), while long-term adaptation as an adaptation from which the effects can even be noticed after hours, days (transcriptional regulation), months or years, or even generations (epigenetic and genomic effects) (Sthijns *et al.*, 2016). Hormetic adaptation is enzymatic, but also partially transcriptional changes contribute (Sthijns *et al.*, 2016). Thus only relatively short-term adaptive mechanisms can be defined as hormetic (Sthijns *et al.*, 2016). The response to the correctly applied homeopathic medicine, is often prolonged, with largely irreversible and irreproducible or permanent results (Hahnemann, reprint 1970; Bellavite and Signorini, 2002; Kent, reprint 1986; Kayne 2006). Thus the action of homeopathic medicine is deeper than what hormesis can cause, changing parametres of the biological system.

Like hormesis, homeopathic phenomenon, as shown here, is also a form of adaptation to buffer the pre- or post-exposure stressor induced shock. The difference between the two has been made clear and it is that homeopathic phenomenon is exclusively therapeutic and genetically deeper in action than hormesis.

Evolution in light of The Nanoparticle-Exclusion Zone Shell Model

Unexpected solute aggregation often takes place in water during dilution (Samal and Geckeler, 2001; Konovalov and Ryzhkina, 2014). The discovery of this phenomenon may help solve many basic problems related to living systems, such as the origin and evolution of life, which most probably occurred in water in the presence of low concentrations of biologically active compounds (Konovalov and Ryzhkina, 2014). Thus the putative first step in the origin of life was likely the coalescence of dispersed molecules into a more condensed and organized state (Pollack *et al.*, 2009). The sun's radiant energy separates charge in water, and this free charge also demonstrably induces condensation, placing water in a central position in biological life rather than as an incidental participant (Pollack *et al.*, 2009). The charge separation leads to the formation of exclusion zone especially on hydrophilic surfaces (Pollack *et al.*, 2009).

Aqueous interfaces are ubiquitous in nature. They are ultrathin water films that cover most hydrophilic surfaces in water or under high ambient relative humidity (Bjorneholm *et al.,* 2016). The earth is covered by these solid/water interfaces including those on the abundant silica or silicates. Water interfaces play an important role, among others, in geochemistry and environment (Bjorneholm *et al.*, 2016). Their properties are quite different to that of bulk water. As such interfaces generally appear on hydrophilic surfaces, they would naturally also form exclusion zones.

Natural water-borne nanoparticles are ubiquitous; and their small size, ranging from 1 to 100 nanometer, makes them highly mobile and chemically reactive (Hartland *et al.*, 2013). They can bind large amounts of trace metals, which impact the bioavailability of vital and toxic metals in natural waters (Hartland *et al.*, 2013). In fact, the influence of such nanoparticles on the bioavailability of both nutrient and toxic elements has been thought a factor in the evolution and development of higher organ-

isms, potentially buffering environmental systems against change (Tipping, 2001).

Spontaneous repeated dilutions with turbulence of environmental stressors, in the presence of air (oxygen), have always been a part of nature. Natural nanoparticles often contain silica which is ubiquitous on earth. These particles have hydrophilic surfaces with negative electrostatic charge. It makes them ideal for EZ water growth. Thus the condition is similar to that of preparing homeopathic medicine in a glass bottle. "The Nanoparticle - EZ Shell Model" can be applied here. The presence of silica though, is not a necessity for this model to function.

Extremely sick biological systems under post-conditioning (Wiegant and Van Wijk, 2010; Van Wijk and Wiegant, 2010) would have adapted to respond to even lower doses of the available stressors. Such doses of stressor in decreasing quantity could be available from water as repeated turbulent dilutions happen in nature spontaneously. In terms of evolutionary adaptation, biological system had to develop molecular mechanisms and pathways to respond to stressors as low as merely adsorbed on nanoparticles and then even to its apparent specific information stored in nanoparticle-EZ shells present in water.

An organism is full of water and this water is mostly a part of the exclusion zone (Pollack, 2013). As the exclusion zone may retain surface specific information (Pollack, 2013), the present author perceives that in a diseased state, the structure of this exclusion zone would be altered and may contain information about the disease. As the exclusion zone covers the whole organism, it may similarly imply a holistic nature to disease as belonging to the whole organism not a part of it. Thus disease may be addressed by the administration of the similarly altered exclusion zone with the aim of restoring the original exclusion zone state. As per the Nanoparticle-EZ Shell Model, this "medicinal" EZ through nanoparticle-EZ shells contain source-drug specific information which is required here to perform a subtle secondary action. The administration of this "medicinal" EZ may give an initial jolt (hormetic/homeopathic aggravation) and then order would follow in the altered exclusion zone restoring health to the organism. This reasoning agrees with the holistic nature of homeopathy.

The sources of homeopathic drugs are minerals, plants, animals (including secretions of diseased animals/human beings), and even stressors like X-rays, magnetic fields etc (Bellavite and Signorini, 2002; Kayne, 2006). Evidence suggests that life began on the earth through a common origin of minimal "protocell." Minerals played a potential role in protocell's emergence and development (Web ref. 4). They promoted the membrane formation rate and may even acted as catalysts ("prebiotic enzymes") (Web ref. 4). Further as minerals and life co-evolved after the origin of life as a part of the earth's environment, the effect of mineral stressors should be profound on life in comparison to later entries of plant and animal origin stressors. Thus it is fair for the present author to infer that biological systems developed molecular mechanisms and pathways principally to counter the effect of mineral origin stressors. The practice of homeopathy shows that mineral origin drugs (stressors) in general form the deepest and longest acting medicines in comparison to animal or plant origin drugs (stressors), and further raising extremely high homeopathic dilutions (potencies) often suit more to mineral origin medicines for better performance (Bellavite and Signorini, 2002; Kayne, 2006; Kent, reprint 1986).

Minerals are generated during the chemical weathering of rocks (Hartland, 2013). Humic substances are highly abundant organic compounds formed in soils and sediments by the decay of dead plants, microbes and animals (Tipping, 2001). Such an envi-

ronmental stressor as source-drug, influences any water exposed to it. Thus initial potencies of an environmental stressor are formed. A solid potentization (trituration) is also possible in nature with silica-containing materials such as clay, as a diluent. Thus, it may be argued that potentization has always been a part of the evolutionary process, and that the preparation of initial potencies of environmental stressors by nature itself, is a reality. However, if many stressors are present in comparable quantities to counter the medicinal effect of one another, or the water supply contains water collected from many sources, the medical effects may potentially be nullified. Otherwise, the action of such a natural preparation on a suitable biological system can be significant depending on circumstances. Generally the action would be expected to be broad and feeble because the natural preparation forms an initial potency in an enormous dilution. Thus it can have a subtle effect on life. Though in the distant past, when people were living closer to nature, the effect would have been significant. Further, for early life on the "toxic" earth, this effect would have been much more significantly pronounced.

Even today, the water or climate of a place is known to affect life in some way. The rejuvenating properties of the water or climate in certain places has been known since antiquity. Many springs are known for their medicinal properties: *Gettysburg water* is even a medicine included in Homeopathic Materia Medica (Boericke, reprint 2007a). Traveller's indigestion and constipation is also well known in medicine. Many reasons are given for it. One reason perhaps never thought of could be the frequent change of "medicine" in the form of drinking water that traveler consumes. Frequently changing medicinal properties may disturb homeostasis, affecting mainly the abdomen, as being in initial potency.

Hormesis and Ultramolecular Dilution

Hormesis is a part of evolutionary processes, but all the toxic substances are not hormetic, *i.e.,* they are harmful at even low concentratins (Mattson, 2015). The present author argues that at least the natural toxins in which life developed, should be hormetic. In other words, they should have exhibited biphasic dose-response curves. It is suggested here that if they do not stimulate hormetic signaling pathways in a crude material form, they can do so in potentized form. There are several reasons to suggest this:

1. The threshold dose for hormetic effects is arbitrary as there is a break in the dose-axis in dose-response curves, close to its origin (Fisher, 2010).

2. High potency homeopathic medicines supposedly do not contain any molecules of the source-drug (Upadhyay, 2018a; Upadhyay, 2018b; Van Wassenhoven *et al.*, 2018) but reported to cause hormetic activation (Chikramane *et al.*, 2017).

3. Chemicals like histamine (Sainte-Laudy and Belon, 2009), thyroxine (Endler *et al.*, 2015) and aspirin (Eizayaga *et al.*, 2019) were potentized beyond Avogadro's limit (*i.e.*, > 12C), and biological models responded to these ultrahigh dilutions. The nature of these responses were opposite to those obtained from their pharmacological doses. Thus these responses can be termed as hormetic.

4. Many homeopathic drugs like Silica, Sepia, Lycopodium etc. have no therapeutic value in crude form, but become strongly therapeutic after potentization (Kayne, 2006). Thus a substance, which does not exhibit primary pharmacological action, can exhibit secondary action after potentization.

5. Tautopathy ("tauto" means same) exists (Patel, 1960). It is a variant of homeopathy,

and is used by some who claim it removes or reduces the negative effects of modern medicines, or toxins like insecticides by administering those medicines/toxins in 6C or 30C potency (Patel, 1960). As the source drug/toxin is present materially in 6C potency, such a treatment should be acceptable to conventional biomedical sciences as post-conditioning hormesis.

6. "The Nanoparticle - EZ Shell Model" insures that information specific to any substance can be retained through its potentization (Upadhyay, 2017). As many homeopathic toxic source-drugs are also hormetic agents, this specific "information" can also be bioactive in case of hormesis (Upadhyay, 2018a).

Interestingly, the non-hormetic natural toxin mercury is an important homeopathic medicine in its potentized form, both within and beyond Avogadro's constant (Boericke, reprint 2007b). As both homeopathy and hormesis work below pharmacological doses, potentization can be important for hormesis too. The present author perceives that low or medium potencies may suffice in case of hormesis. Here vivid drug-specific information may not be required, which is the priority of homeopathy because it is based on the law of similars. In some non-hormetic substances, however, it may happen that they become hormetic only at high potency and beyond where their medicinal effects in secondary action are revealed.

Emerging Experimental Support and Possibility of Verification of the Proposed Theory

Experimental support which has already been described makes clear that high dilution effects are a reality and our understanding of them is increasing. It has been a part of nature in which life grew and this fact alone makes it a possible player in evolutionary history. The foremost question is how can it keep the apparent physicochemical information of the source-drug after dilution, and how is this information transferred to living cells *in vitro* and *in vivo*. The Nanoparticle-EZ Shell Model provides a strong base and framework to investigate it further for its intrinsic details. Opportunities are plenty. For example , Rey (2003, 2007) observed that the "signature" of lithium was found detectably in the thermoluminescence spectra of ultramolecular lithium chloride, more marked with dilutions prepared in an oxygen atmosphere and less so in dilutions prepared under reduced pressure, compared to normal atmosphere. This is also true regarding the efficacy of homeopathic medicine prepared under these same conditions (Fisher, 2010). Further these medicines are spoiled in high temperature around/ above 70°C. Recent studies show that they may possess an electric field component (Cartwright, 2019), which the Nanoparticle-EZ Shell Model predicts. Quantum electrodynamics (QED) may be required to be developed for theoretical understanding (Manzalini and Galeazzi, 2019).

Doutremepuich and colleagues have carried out two decade-long reproducible studies on aspirin and its homeopathic dilutions (Eizayaga *et al.*, 2019). They have shown that aspirin, notably 15C, have a pro-thrombotic effect in humans and animals. This is opposed to the effects for which aspirin is known, *i.e.,* anti-thrombotic effect. These studies confirm that aspirin 15C chooses inhibition of cyclooxygenase (COX)-2 pathway to produce the effect, while aspirin is known to function via the inhibition of COX-1 pathway. Further when aspirin 15C was injected shortly after a high dose of aspirin 100 mg/kg b.w., the anti-thrombotic effect could not develop, suggesting that aspirin 15C may have neutralized it. Moreover after one single high material dose of aspirin, Eizayaga *et al.* (2019) observed several days after a pro-thrombotic effect as withdrawal or rebound effect of aspirin.

A model of thyroxine and metamorphosis

of highland amphibians is one more robust example of biological activity of substances diluted beyond the Avogadro limit (Endler *et al.*, 2015). Taking Rana temporaria larvae , Endler *et al.* observed tadpoles develop from the 2-legged to the 4-legged stage. The data collected during the study, repeated over the course of 24 years, shows a reverse effect of extremely diluted and agitated, thyroxine relative to standard thyroxin as a substance. This paradoxical phenomenon was generally consistent in different observations including those from a second centre (Endler *et al.*, 2015). Fisher (2010) claimed that the observed effect is hormetic as in a material dose, thyroxine accelerates metamorphosis, while it has the reverse effect in ultramolecular dilution.

Studies of the modulation of gene expression with traditional homeopathic medicines have shown clearly that their biological activities do not decrease with increasing potency (*i.e.*, dilution with succussions) even beyond the Avogadro limit (Bigagli *et al.*, 2016; Chirumbolo and Bjørklund, 2016; Saha *et al.*, 2015; Dei and Bernardini, 2015; Marzotto *et al.*, 2014; Olioso *et al.*, 2014; Das *et al.*, 2012; Preethi *et al.*, 2012; Sunila *et al.*, 2009). Instead of a conventional homeopathic medicine, Olsen (2017) studied sodium butyrate, a promising therapeutic agent for cancer treatment which targets epigenetic pathways, in dilutions 30C and 200C prepared in homeopathic fashion and found them modulating the transcriptome of HEK 293 cells. Similarly, Seker *et al.* (2018) studied the taxane anti-cancer drugs paclitaxel and docetaxel, used in chemotherapy. Their highly potentized dilutions, without being cytotoxic, showed differential effects on the genes of breast cancer cells with concentration-independent activity (Şeker *et al.*, 2018).

As mentioned earlier, even single-celled organisms can be sensitive to homeopathic dilutions (Das *et al.*, 2012). Thus suitable, simple and short-lived organisms can provide opportunities to study evolution in real time and thus may help in direct testing of the proposed theory or some of its aspects.

There is one important method to biomedically study homeopathic medicines and other potentized toxins for their secondary actions/effects. The method was developed by Van Wijk and Wiegant, and is now identified as a post-conditioning hormesis methodology (Van Wijk and Wiegant, 2010; Wiegant and Van Wijk, 2010). The method can also be used with recent techniques in the field of genomics, including DNA arrays, for more precise results (Wiegant and Van Wijk, 2010). It may shed light on the structure of such medicines/dilutions and their underlying mechanism, as here a cell is made “sick” and then “treated” in simulation.

The typical and paradoxical observations from the practice of homeopathy in themselves are important clues to work upon to explore the underlying working mechanism of secondary effect of drug/toxin which homeopathy exploits (Upadhyay, 2017). Some examples are given below:

1. A true remedy in higher potency (*i.e.*, higher dilution), often acts more strongly, and for a longer period than at lower potency (*i.e,*. lower dilution) (Kent, reprint 1986, Kayne 2006). Some medicines can even act contradictorily at very low versus high potencies. For example, Hepar sulphuris calcareum (Hahnemann’s calcium sulphide) can promote suppuration in lower potencies but abort it in higher potencies (Boericke, reprint 2007c).

2. A tiny amount of homeopathic dilution as remedy constitutes a “dose” to be administered. This dose does not or hardly contains its source-drug. The dose amount is immaterial, if it is sufficient enough to cause a response (Kent, reprint 1986). But it should remain small, as a large dose causes over stimulation, which suffers poor results.

3. Customarily a single dose of the remedy in a suitable potency is administered for a functional duration. The action of the second dose often falls shorter than that of the first dose, and then further dosing in the same potency does not work (Kent, reprint 1986). For further responses from the remedy, its potency has to be changed by a large gap to a different, generally higher one (Kent, reprint 1986). For a higher potency this gap is larger. For example, after exhausting, say, 200C potency of the remedy twice, its potency like 400C, 500C, 580C etc does not cause a reaction but its 1000C (or higher) potency will show a reaction. Or alternatively, a dose of Sulfur, say, in 200C potency can be administered to refresh susceptibility of the patient for the same potency of the remedy to be administered again to work (Kent, reprint 1986). This serves as an exceptional opportunity to explore the underlying molecular mechanism.

4. The repetition of dose of the remedy before the exhaustion of the previous dose is forbidden in homeopathy with the warning that violent aggravation can ensue even spoiling the results (Kent, reprint 1986). However, Desai (1991) and Upadhyay (2003) observed that this warning does not cover very frequent dose repetition of the remedy in high potency in chronic cases. In such cases the remedy acts mildly and without saturating the susceptibility of the patient, while such single dose of the remedy often acts with aggravation. If repetition is very infrequent but occurs prior to the exhaustion of the previous dose, violent aggravation can ensue as per the warning. For chronic cases, Upadhyay (2003, 2017) suggested a law regarding the dosing of homeopathic remedy as: "A single dose palliates, early doses spoil and continuous doses cure."

Both the genome and the old concept of vital force exhibit similar properties and belong to complex and dynamic self-organization systems, as if the cells genome is the biological representation of the "vital force" (Teixeira, 2019a, 2019b). Similarly, homeopathic miasms, *i.e.,* "disposition to chronic diseases," may find their representation in disease-promoting epigenetic modifications (Teixeira, 2019a, 2019b).

The present author has explained that adaptation is central to homeopathy. Like researchers in homeopathy, evolutionary biologists have also started to exploit technological innovations in genomics, to "finally" address long-standing questions about the nature of adaptation (Web ref. 5). Will these questions really be addressed by genomics alone, without taking in account the evolution of homeopathic phenomenon and the role played by it in evolution?

Here, there is relevance of the futuristic observations of Kirschner *et al.* (2000), that soon the robustness of statistical but self-organising molecular, cellular, and organismal functions will ultimately compel us to move beyond genomics to the old "vital forces" to understand their chemistry.

Discussion

Bellavite *et al.* (2010) observed that homeopathy, a therapeutic method, and hormesis, a phenomenon of nature, are quite different from each other, but broad in scope; and thus well- researched methodologies of hormesis can help cast light on the possible mechanisms of action remedies utilize in ultra-low doses. The theory proposed here by the present author suggests that homeopathic phenomenon evolved as an offshoot of hormesis and gradually became an exclusively therapeutic phenomenon, which was later exploited by Hahnemann to establish homeopathy. Thus this theory, which identifies a distinct homeopathic phenomenon and differentiates it from homeopathy, does not contradict the observations of Bellavite *et al.* (2010). Further this theory agrees with the observations of Oberbaum

et al. (2010) and Oberbaum and Gropp (2015) that, despite crucial similarities between hormesis and homeopathy, there are many major differences between them. This theory agrees with Fisher (2010) that homeopathy is the best medical analogue of hormesis. Thus this theory is apparently the culmination of debate started by Calabrese and Jonas (2010a, 2010b) on the relationship between hormesis and homeopathy mitigating the prevailing confusion in their relationship.

Homeopathy is based on the host effects like activation of the immune system rather than direct effects on pathogens (Pannek *et al.*, 2018). Also, by applying the concept of hormesis, the current evidence argues that already approved pharmacological agents could be used therapeutically to increase survival rate of patients with infectious disease via improving disease tolerance (Weis *et al.*, 2017).

A wide range of allopathic drugs, including anxiolytic and anti-epileptic drugs display hormetic features. Some anti-tumor drugs exhibit a sort of reverse hormesis (*i.e.,* the low dose stimulation causes an adverse effect), when tested on human tumor cell lines (Calabrese, 2018). Their *in vitro* study in potentized form, beyond the Avogadro limit, could be intriguing.

If hormetic agents can be potentized effectively, the problem of administering toxic doses instead of hormetic ones may be resolved due to individual variability. Further, it would increase the possibility of replacing some toxic drugs in modern medicine with their cheap non-toxic potentized forms. It may even support and widen the scope of the emerging strategy to find safer and more effective integrative treatments for specific cancers (Gonçalves *et al.*, 2019; Bhattacharya and Zhang, 2015; Bell *et al.*, 2014).

The prolonged study of aspirin carried out by Eizayaga *et al.* (2019) supports the possibility of exploiting secondary effects of suitable modern medicine, derived through its potentized form, for therapeutic applications. Tautopathy can now be taken seriously.

Eizayaga *et al.* (2018) observed that more research will have to be done to find if the withdrawal effect observed several days after a high material dose of aspirin and the effect seen one hour after aspirin 15C are of the same kind. If so, it may be of great significance to public healthcare, as aspirin withdrawal is known to increase the risk of several types of complications (Eizayaga *et al.*, 2019).

Conclusion

Hormesis is an evolutionary adaptation to environmental change. It was insufficient to protect life therapeutically against dangerous environmental stressors. However, developed pathways paved the route to the evolution of such molecular mechanisms where these stressors became medicinal in extreme dilution. The salient features of this evidence-based theory are as follows:

1. If hormesis had enough therapeutic potential to support life on the hostile earth, the homeopathic phenomenon could not have taken place, as the driving Darwinist pressure develop advanced more sophisticated molecular mechanisms would have been absent.

2. Hormesis is a basic and general phenomenon. Soon after its development, homeopathic phenomenon evolved as its offshoot but its further developments were phenomenal with increasing complexity of biological systems, that it gradually moved far from hormesis to be so identified and now have its own independent identity.

3. The homeopathic phenomenon is genetically a deeper therapeutic buffer against environmental stressors and thus a vital

factor in the evolution of life. The whole system of therapeutics called homeopathy is based upon it.

4. First true evolutionary medicines were homeopathic in nature and environmental hormetic stressors were their precursors.

5. Minerals have been the environmental stressors since the origin of life and therefore biological systems could develop molecular mechanisms and pathways more to counter mineral stressors. Thus mineral origin stressors generally form the deepest acting homeopathic medicines in comparison to animal or plant origin stressors.

6. Homeopathy is an adaptive stress-response therapy and so is holistic. It is also holistic because it works through the exclusion zone which includes the whole organism. Its "proving" of drug toxin is the simulation of how environmental stressors sicken organisms in response to imbalance.

7. Exploitation of the beneficial secondary action of drug/toxin is fundamental to therapeutics. As such, the law of similars is a fundamental law of therapeutics, and in its application homeopathy is the fundamental method of cure.

8. Serial turbulent dilutions (*i.e.,* potentization) of environmental stressors are a part of nature and so of evolution. During turbulence, oxygen mixes in water under extra pressure to help in buildup of exclusion zone. Such dilutions so contain nanoparticle-EZ shells which can carry stressor-specific information.

9. The scarcity of suitable stressors as medicines to biological systems led to adaptation first, to sub-pharmacological doses, then to one adsorbed merely via nanoparticles and, ultimately to just relevant information encoded in the nanoparticle-interfacial water. For this development, molecular mechanisms evolved in such a way that at last stressor-specific information becomes therapeutically more important than the stressor itself.

10. Hormesity of non-hormetic natural toxins, with which life grew, is likely to be hidden in their potentized forms.

11. The scope of potentization, which makes homeopathy much more meaningful, may effectively be extended to suitable toxins/chemicals, as used in modern medicine, for their unprecedented therapeutic applications as cheaper, safer and more eco-friendly medicines by exploiting their secondary action.

For future research activity, including the testing of the proposed theory, suggestions are made especially in cellular and molecular biology. The research activity may lead to an understanding of the underlying molecular mechanism involved. As it is realized, homeopathy is inherently linked with hormesis, understanding of one will enhance understanding of the other. If successful, such studies would reveal the scientific intricacies of the ignored but fundamental dimension of pharmacology which leads to exploitation of secondary action of a stressor. This would diffuse the boundary between modern medicine and homeopathy.

Discussion with Reviewers

Reviewer: Please discuss the role that water molecules play in the process.

Author: The role that water molecules plays, along with nanoparticle as its substrate, is apparently to store the information specific to stressor, amplify it, make it bioactive if it is not so, and then to transfer that information to biological system. Biological system's reaction or response to stressor or stressor-specific information is the secondary action of the stressor. But how can a water molecule (H_2O) or even its cluster can hold a memory of its past experience? That is why conventional scientists

do not believe that water can be magnetized or that homeopathic medicine can exist except as placebo. They are even skeptical of the existence of exclusion zone (EZ) water. But with time, increasing evidence is compelling to move beyond convention to explore the nature of this phenomenon.

Pure water (H_2O), as conventional scientists insist, really cannot be magnetized, nor can it have memory. But when exposed to oxygen (air), amazingly this property alters. Oxygen builds up some EZ water. Then it can be magnetized and the properties of such magnetized water can be studied with scientific precision (Otsuka and Ozeki, 2006). It is an EZ ($H_3O_2^-$) layer that gets magnetized, not ordinary or bulk water (H_2O) (Upadhyay, 2017). The effect of exposure to a magnetic field is kept in memory for up to 200 hours (Coey and Cass, 2000), until EZ naturally erodes with time. However, along with nanoparticles as in a nanoparticle-EZ shell, a prolonged memory is possible through a simple process of serial and turbulent dilution called potentization (Upadhyay, 2017). Nanoparticles are sensitive to the environment (Zhang *et al.*, 2003), and layers of EZ water are suitable to hold a memory, possibly by coding through the removal of oxygen atoms from the hexagonal lattice of the generic EZ without impairing its structural integrity (Pollack, 2013).

Evidence suggests that the EZ plays an important role in the evolution of life, especially by facilitating the subtle secondary action of environmental stressors through natural, spontaneous, turbulent dilution. The preparation of homeopathic medicine can be taken as a simulation of such natural dilution process. Homeopathic medicine is an ultra-high dilution of its source-drug/stressor and so it should be extremely vulnerable to impurities, but it is the EZ, which protects it and maintains its integrity. Isn't it amazing? Water can be far more intriguing than what conventional scientists think!

Reviewer: Do different states of water make any difference in the process?

Author: Yes, I have shown that the exclusion zone state of water plays an important role, in a subtle way. Water has four states namely solid, liquid, gas (vapor) and the newly introduced liquid crystalline exclusion zone (Pollack, 2013).

Frozen, gaseous and boiling waters do not have an EZ, nor can they have stressor-specific information. However, homeopathic medicine can be administered through olfaction. An evaporated vesicle has an EZ shell (Pollack, 2013).

Magnetized water losses its properties (or memory) permanently, above 54°C. It is apparently because higher thermal energy at these temperatures become too favourable for EZ buildup to retain the modified EZ structures (Upadhyay, 2017). These structures revert to the generic EZ loosing the stored information. Homeopathic medicine, however, can tolerate heat up to 70°C, because here EZ as shell has a hydrophilic nanoparticle as substrate.

Spontaneous turbulent dilution of environmental stressor happens in nature. The turbulence mixes oxygen, present in air, with water under extra pressure and this is ideal for EZ growth. The whole scene is similar to the preparation of homeopathic medicine where serial dilution of stressor is carried out with violent strokes at each dilution level, mandatorily keeping one third space of bottle empty for air (oxygen).

Biological system is mostly water and most of this water is EZ (Pollack, 2013). Obviously water should play a vital role in the evolution of life. Large part of this role is through its EZ state. The theory proposed here is a humble attempt in this direction.

References

Anagnostatos GS (1994). Small Water Clusters (Clathrates) in the Preparation Process of Homoeopathy. In: Endler P.C., Schulte J. (eds) Ultra High Dilution. Springer, Dordrecht: Kluwer Acad. Publ.1994,121-128.

Anick DJ, Ives JA (2007). The silica hypothesis for homeopathy: physical chemistry. Homeopathy 96:189–195.

Bell IR, Muralidharan S, Schwartz GE (2015a). Nanoparticle characterization of traditional homeopathically-manufactured Gelsemium sempervirens medicines and placebo controls. J Nanomedicine Biotherapeutic Discov. 5:1–13.

Bell IR, Sarter B, Koithan M, Banerji P, Banerji P, Jain S, Ives J (2014). Integrative nanomedicine: treating cancer with nanoscale natural products. Glob Adv Health Med. 3(1):36-53.

Bell IR, Schwartz GE, Frye J, Sarter B, Standish LJ (2015b). Extending the Adaptive Network Nanomedicine Model for Homeopathic Medicines: Nanostructures as Salient Cell Danger Signals for Adaptation. Nanosci Technol 2: 1-22.

Bellavite P, Chirumbolo S, Marzotto M (2010). Hormesis and its relationship with homeopathy. Hum Exp Toxicol 29: 573-579.

Bellavite P, Marzotto M, Olioso D, Moratti E, Conforti A (2013). High-dilution effects revisited.1. Physicochemical aspects. Homeopathy 103(1): 4-21.

Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A (2006). Immunology and Homeopathy. 4. Clinical Studies—Part 2. Evidence-based complementary and alternative medicine: eCAM 3: 397-409.

Bellavite P, Signorini A (2002). The Emerging Science of Homeopathy. North Atlantic Books, Berkeley.

Bhattacharya A, Zhang Y (2015). Role of Homeopathy in Integrative Cancer Care. J Carcinog Mutagene 6:e118.

Bigagli E, Luceri C, Dei A, Bernardini S, Dolara P (2016). Effects of extreme dilutions of Apis mellifica preparations on gene expression profiles of human cells. Dose Response 14: 1-7.

Björneholm O, Hansen MH, Hodgson A, Liu LM, Limmer DT, Michaelides A, Pedevilla P, Rossmeisl J, Shen H, Tocci G, Tyrode E, Walz MM, Werner J, Bluhm H (2016). Water at interfaces. Chemical Reviews 116 (13): 7698-7726.

Boericke W (reprint 2007a). Gettysburg water. Pocket manual of homoeopathic materia medica – With Indian medicine and repertory. Indian books and periodicals publishers, New Delhi.

Boericke W (reprint 2007b). Mercurius solubilis. In: Pocket manual of homoeopathic materia medica – With Indian medicine and repertory. Indian books and periodicals publishers, New Delhi.

Boericke W (reprint 2007c). Hepar Sulphuris Calcareum. In: Pocket manual of homoeopathic materia medica – With Indian medicine and repertory. Indian books and periodicals publishers, New Delhi.

Bonamin LV, Cardoso TN, Carvalho AC, Amaral JG (2015). The use of animal models in homeopathic research- a review of 2010-2014 PubMed indexed papers. Homeopathy 104: 283-291.

Calabrese EJ (2017). Hormesis and homeopathy: a step forward. Homeopathy 106: 131-132.

Calabrese EJ (2018). Hormesis: Path and Progression to Significance. Int J Mol Sci 19(10).

Calabrese EJ, Iavicoli I, Calabrese V (2013). Hormesis: Its impact on medicine and health. Hum Exp Toxicol 32: 120-152.

Calabrese EJ, Jonas W (2010a). Homeopathy, clarifying its relation to hormesis. Hum Exp Toxicol 29: 531-536.

Calabrese EJ, Jonas W (2010b). Evaluating Homeopathic Drugs within a Biomedical Frame work. Hum Exp Toxicol 29: 545-549.

Cartwright SJ (2019). Homeopathic Potencies May Possess an Electric Field (-like) Component: Evidence from the Use of Encapsulated Solvatochromic Dyes. Homeopathy.

Chai B, Pollack GH (2010). Solute-Free Interfacial Zones in Polar Liquids. J Phys Chem B 114(16): 5371–5375.

Chaplin MF (2007). The memory of water: an overview. Homeopathy 96:143–150

Chikramane PS, Suresh AK, Bellare JR, Kane SG (2010). Extreme homeopathic dilutions retain starting materials: a nanoparticulate perspective. Homeopathy 99: 231-242.

Chikramane PS, Kalita D, Suresh AK, Kane SG, Bellare JR (2012). Why extreme dilutions reach non-zero asymptotes: a nanoparticulate hypothesis based on froth flotation. Langmuir 28:15864–15875

Chikramane PS, Suresh AK, Kane SG, Bellare JR (2017). Metal nanoparticle induced hormetic activation: a novel mechanism of homeopathic medicines. Homeopathy 106: 135-144.

Chirumbolo S, Bjørklund G (2016). Arnica Montana Effects on Gene Expression in a Human Macrophage Cell Line: Evaluation by Quantitative Real-Time PCR. Front Immunol 7: 280.

Coey JMD, Cass S (2000). Magnetic water treatment. J Magnetism and Magnetic Materials 209: 71–74.

Das S, Saha SK, De A, Das D, Khuda-Bukhsh AR (2012). Potential of the homeopathic remedy, Arnica Montana 30C, to reduce DNA damage in Escherichia coli exposed to ultraviolet irradiation through upregulation of nucleotide excision repair genes. Zhong Xi Yi Jie He Xue Bao10: 337-346.

Dei A, Bernardini S (2015). Hormetic effects of extremely diluted solutions on gene expression. Homeopathy 104(2):116-22.

Davenas E, Beauvais F, Amara J, Oberbaum M, Robinzon B, Miadonna A, Tedeschi A, Pomeranz B, Fortner P, Belon P, et al (1988). Human basophil degranulation triggered by very dilute antiserum against IgE. Nature 333: 816–818.

Del Giudice E, Preparata G, Vitiello G (1988). Water as a free electric dipole laser. Phys Rev Lett 61: 1085-1088.

Del Giudice E, Spinetti, PR, and Tedeschi A (2010). Water dynamics at the root of metamorphosis in living organisms. Water 2: 566-586.

Desai MB (1991). Manifestations of suppression. In: Mathur, K.N. (Ed). Principles of Prescribing. B Jain Publishers, New Delhi.

Editorial The Lancet (2005). The end of homeopathy. Lancet 366:690.

Eizayaga FX, Belon P, Desplat V, Aguejouf O, Doutremepuich C (2019). Effects of Ultra-Low-Dose Aspirin in Thrombosis and Haemorrhage. Homeopathy. 108(3):158-168.

Eldredge N (1995). Reinventing Darwin: The great debate at the high table of evolutionary theory. John Wiley and sons, New York.

Elia V, Ausanio G, Gentile F, Germano R, Napoli E, Niccoli M (2013). Experimental evidence of stable water nanostructures in extremely dilute solutions, at standard pressure and temperature. Homeopathy.

Endler PC, Pongratz WC, Harrer B, Lingg G, Lothaller H (2015). Amphibians and ultra high diluted thyroxine-further experiments and re-analysis of data. Homeopathy. 104:250-256.

Fisher P (1991). Homeopathy in its home land. Br Homeopath J 80: 238-240.

Fisher P (2010). Does homeopathy have anything to contribute to hormesis? Hum Exp Toxicol 29: 555-560.

Forbes VE (2000). Is hormesis an evolutionary expectation? Functional Ecology 14: 12-24.

Gonçalves JP, Potrich FB, Ferreira Dos Santos ML, Costa Gagosian VS, Rodrigues Rossi G, Jacomasso T, Mendes A, Bonciani Nader H, Brochado Winnischofer SM, Trindade ES, Camargo De Oliveira C (2019). In vitro attenuation of classic metastatic melanoma-related features by highly diluted natural complexes: Molecular and functional analyses. International Journal of Oncology. 3: 721-732.

Haehl R (2003). Samuel Hahnemann His Life and Work. B Jain Publishers, New Delhi.

Hahnemann SFC (reprint 1970). Organon of medicine. 6th edn. B. Jain Publishers New Delhi.

Hartland A, Lead JR, Slaveykova VI, O'Carroll D, Valsami-Jones E (2013). The Environmental Significance of Natural Nanoparticles. Nature Education Knowledge 4(8):7.

Hwang SG, Hong JK, Sharma A, Pollack GH, Bahng G (2018). Exclusion zone and heterogeneous water structure at ambient temperature. PLoS ONE 13(4): e0195057.

Kayne SB (2006). Homeopathic pharmacy: theory and practice. 2 ed, Elsevier Health Sciences.

Kent JT (reprint 1986). Kent's New Remedies: Clinical Cases, Lesser Writings, Aphorisms and Precepts. Pratap Medical Publishers, New Delhi.

Khuda-Bukhsh AR (1997). Potentized homoeopathic drugs act through regulation of gene-expression: a hypothesis to explain their mechanism and pathways of action in vitro. Complement Ther Med. 5:43–46.

Khuda-Bukhsh AR (2003). Towards understanding molecular mechanisms of action of homeopathic drugs: an overview. Mol Cell Biochem 253:339–345.

Khuda-Bukhsh AR (2014). Current trends in high dilution research with particular reference to gene regulatory hypothesis. Nucleus 57:3–17.

Kirschner M, Gerhart J, Mitchison T (2000). Molecular "vitalism." Cell. 7;100(1):79-88.

Konovalov AI, Ryzhkina IS (2014). Highly Diluted Aqueous Solutions: Formation of Nano-Sized Molecular Assemblies (Nanoassociates). Geochemistry International, 52: 1207–1226.

Konovalov AI, Ryzhkina IS (2016). Nanoassociates as a possible basic element of scientific foundation of homeopathy. 1st Eurasian Congress on homeopathic medicine and 25th Congress of Asian Homeopathic Medical League, Moscow 14-15 October 2016.

Logan AC, Selhub EM (2012). Vis Medicatrix naturae: does nature "minister to the mind?"

BioPsychoSocial Med. 6:11.

Maddox J, Randi J, Stewart WW (1988). "High-dilution" experiments a delusion. Nature 334(6180): 287-91.

Mante P, Chen C, Wen Y, Chen H, Yang S, Huang Y, Ju Chen I, Chen Y, Gusev V, Chen M, Kuo J, Sheu J, Sun C (2014). Probing Hydrophilic Interface of Solid/Liquid-Water by Nanoultrasonics. Scientific reports. 4. 6249.

Manzalini A, Galeazzi B (2019). Explaining Homeopathy with Quantum Electrodynamics. Homeopathy. 108(3):169-176.

Martinez JL, Fajardo A, Garmendia L, Hernandez A, Linares JF, Martínez-Solano L, Sánchez MB (2009). A global view of antibiotic resistance. FEMS Microbiol Rev. 33(1):44-65.

Marzotto M, Olioso D, Brizzi M, Tononi P, Cristofoletti M, Bellavite P (2014). Extreme sensitivity of gene expression in human SHSY5Y neurocytes to ultra-low doses of Gelsemium sempervirens. BMC Complement Altern Med 19(14):104.

Mattson MP (2010). The fundamental role of hormesis in evolution. In: Mattson MP, Calabrese EJ, eds. Hormesis: A Revolution in Biology, Toxicology and Medicine. New York: Springer 57-68.

Mattson MP (2015). What doesn't kill you. Sci Am. 313:40–45.

Mattson MP, Calabrese EJ (2010). Hormesis: What It Is and Why It Matters. In: Mattson. MP, Calabrese EJ, eds. Hormesis: A Revolution in Biology, Toxicology and Medicine. New York: Springer 1-13.

Milgrom LR (2009). Gold standards, golden calves, and random reproducibility: Why homeopaths at last have something to smile about. J Altern Complement Med 15:205–207.

Oberbaum M, Gropp C (2015). Update on hormesis and its relation to Homeopathy. Homeopathy 104: 227-233.

Oberbaum M, Singer SR, Samuels N (2010). Hormesis and homeopathy: Bridge over troubled waters. Hum Exp Toxicol 29: 567-571.

Olioso D, Marzotto M, Moratti E, Brizzi M, Bellavite P (2014). Effects of Gelsemium sempervirens L. on pathway-focused gene expression profiling in neuronal cells. J Ethnopharmacol 153: 535-539.

Olsen S (2017). Effects of ultra-high dilutions of sodium butyrate on viability and gene expression in HEK 293 cells. Homeopathy 106: 32-36.

Otsuka I, Ozeki S (2006). Does magnetic treatment of water change its properties? J Phy Chem B Lett 110: 1509-1512.

Pannek J, Kurmann C, Imbach E, Amsler F, Pannek-Rademacher S (2018). In Vitro Effects of Homeopathic Drugs on Cultured Escherichia coli. Homeopathy. 107(2):150-154.

Patel RP (1960). What is tautopathy? Indian Books & Periodicals Publishers, New Delhi.

Pollack GH (2013). The Fourth Phase of Water: Beyond Solid, Liquid, and Vapor. Ebner and Sons Publishers, Seattle.

Pollack GH, Figueroa X, Zhao Q (2009). Molecules, Water, and Radiant Energy: New Clues for the Origin of Life. Int. J. Mol. Sci. 2009, 10, 1419-1429.

Preethi K, Ellanghiyil S, Kuttan G, Kuttan R (2012). Induction of apoptosis of tumor cells by some potentiated homeopathic drugs: implications on mechanism of action. Integr Cancer Ther 11: 172-182.

Rattan S, Deva T (2010). Testing the hormetic nature of homeopathic interventions through stress response pathways. Hum exp toxicol 29: 551-554.

Rey L (2003). Thermo luminescence of ultra-high dilutions of lithium chloride and sodium chloride. Physica (A) 323:67–74.

Rey L (2007). Can low temperature thermo luminescence cast light on the nature of ultra-high dilutions?. Homeopathy 96:170–174.

Saha SK, Roy S, Khuda-Bukhsh AR (2015). Ultra-highly diluted plant extracts of Hydrastis canadensis and Marsdenia condurango induce epigenetic modifications and alter gene expression profiles in HeLa cells in vitro. J Integr Med 13(6):400-11.

Sainte-Laudy J, Belon P (2009). Inhibition of basophil activation by histamine: A sensitive and reproducible model for study of biological activity of high dilutions, Homeopathy. 98:186–197.

Samal S, Geckeler KE (2001). Unexpected solute aggregation in water on dilution. Chem Commun 2224–2225.

Schulz H (1887). Zur Lehre von der Arzneiwirdung. Virchows Arch Pathol Anat Physiol Klin Med 108: 423-445.

Şeker S, Güven C, Akçakaya H, Bahtiyar N, Akbaş F, Onaran İ (2018). Evidence that Extreme Dilutions of Paclitaxel and Docetaxel Alter Gene Expression of In Vitro Breast Cancer Cells. Homeopathy 107: 32-39.

Sharma R, Prajapati PK (2015). Liquid media's in Bhavana Samskara: A pharmaceutico-therapeutic prospect. J Phytopharmacology. 4(1): 49-57.

Stebbing ARD (1998): A theory for growth hormesis.

Mutat Res 403: 24–258.

Sthijns MMJPE, Weseler AR, Bast A, Haenen GRMM (2016). Time in Redox Adaptation Processes: From Evolution to Hormesis. Int J Mol Sci 17(10).

Sunila ES, Kuttan R, Preethi KC, Kuttan G (2009). Dynamized preparations in cell culture. Evid Based Complement Alternat Med 6: 257-263.

Teixeira MZ (2019a). Correlation between Vitalism and Genetics According to the Paradigm of Complexity. Homeopathy.

Teixeira MZ (2019b). Isopathic use of auto-sarcode of DNA as anti-miasmatic homeopathic medicine and modulator of gene expression? Homeopathy.

Tipping E (2001). Cation binding by humic substances. University Press, Cambridge.

Toledo EJL, Ramalho TC, Magriotis ZM (2008). Influence of magnetic field on physical–chemical properties of the liquid water: insights from experimental and theoretical models. J Mol Struct 888: 409–415.

Ucker A, Baumgartner S, Jager T (2018). Systematic review of plant-based homeopathic basic research: An update. Homeopathy 107: 115-129.

Ullman D (2006). Let's have a serious discussion of nanopharmacology and homeopathy. FASEB J. 20:2661.

Upadhyay RP (2003). Need of frequent repetition of the remedy in high potency in chronic cases with causal hypothesis. Townsend Lett 235: 80-84.

Upadhyay RP (2017). The possible mechanism of memory through nanoparticles and exclusion zones. Water 7: 158-176.

Upadhyay RP (2018a). The Materialist View of Homeopathy: An Alternative Hypothesis and the Connection with Hormesis. Homeopathy 107: 46-49.

Upadhyay RP (2018b). Nanoscience Study of homeopathic Medicine. Homeopathy 108(01): 071-072.

Upadhyay RP, Nayak C (2011). Homeopathy emerging as nanomedicine. Int J High Dilution Res 10: 299–310.

Van Wassenhoven M, Goyens M, Capieaux E, Devos P, Dorfman P (2018). Nanoparticle characterization of traditional homeopathically manufactured Cuprum metallicum and Gelsemium sempervirens medicines and controls. Homeopathy 107: 244-263.

Van Wijk R, Wiegant F (2010). Post-Conditioning Hormesis and the Homeopathic Similia Principle: Molecular Aspects, Hum Exp Toxicol 16: 45-50.

Weis S, Rubio I, Ludwig K, Weigel C, Jentho E (2017). Hormesis and Defense of Infectious Disease. Int J Mol Sci. 15;18(6).

Wiegant F, Van Wijk R (2010). The Similia principle: results obtained in a cellular model system. Homeopathy 99: 3-14.

Witt, CM, Ludtke R, Weisshuhn TE, Quint P, Willich SN (2006). The role of trace elements in homeopathic preparations and the influence of container material, storage duration, and potentization. Forsch Komplementarmed.

Yinnon TA (2017). Very Dilute Aqueous Solutions — Structural and Electromagnetic Phenomena. Water 9: 28-66.

Yinnon TA, Yinnon CA (2011). Electric dipole aggregates in very dilute polar liquids: Theory and experimental evidence. Int J Mod Phys B 25: 3707-3743.

Zhang H, Gilbert B, Huang F, Banfield JF (2003). Water-driven structure transformation in nanoparticles at room temperature. Nature 424: 1025-1029.

Web References

1. Paracelsus. Biography & Facts. https://www.britannica.com/biography/Paracelsus [accessed on 14 January 2019].

2. CCRH, New Delhi. Homoeopathic Drug Proving: Randomised double-blind placebo-controlled trial. http://www.ijrh.org/article.asp?issn=0974-7168;year=2015;volume=9;issue=1;spage=3;epage=11;aulast=Central [May 26, 2019].

3. Memory of Water. http://www1.lsbu.ac.uk/water/memory_of_water.html#r346 [accessed on 12 July 2019]

4. The Potential Roles of Minerals in the Origins of Life – NASA. https://www.grc.nasa.gov [accessed on 1 August 2019]

5. Genomics of Adaptation and Speciation. https://www.frontiersin.org/research-topics/6731/genomics-of-adaptation-and-speciation [accessed on 1 August 2019]