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Physicochemical Investigations of Homeopathic Preparations: A Systematic Review and Bibliometric Analysis—Part 3

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Abstract

Objectives: In parts I and II of our review of physicochemical research performed on homeopathic preparations, we identified relevant publications and analyzed the data in terms of individual experiments, looking for the most promising techniques that were used in the past. In this third part, we analyze the results of the experiments seeking to extract information about the possible modes of action underpinning homeopathic preparations.

Methods: We summarized the results from the 11 experimental areas previously introduced, extracting the general findings and trends. We also summarized the results in terms of specific research topics: aging, medium used for potentization, sample volume, temperature, material of potentization vessel, and, finally, the use of molecules to probe homeopathic samples.

Results: We identified a number of effects that appear consistently throughout the data: Differences to controls seem to increase with: time, moderate temperature, small samples volume, and in ionic medium, whereas high temperatures seem to abolish differences to controls. Based on the present analysis, there is no consistent evidence to date for the nanoparticle hypothesis to explain specific homeopathic treatment effects. However, the quantum coherence domain hypothesis, the dynamic water cluster hypothesis, and the weak quantum theory are still contenders and need to be further assessed experimentally.

Conclusions: The field requires further targeted experimentation to validate past findings reporting differences between homeopathic dilutions and controls, and to expand these findings by specifically testing the three main working hypotheses that are currently at hand.

Keywords: physics, very high dilutions, serially diluted and agitated solutions, ultrahigh aqueous dilutions

Introduction

In the previous two parts of this review, we found promising experimental evidence supporting the idea that homeopathic dilutions have physicochemical properties different than appropriate controls.[1,2] However, not knowing the mode of action through which homeopathy might work leads to a big stumbling block for research into this medical treatment method.

Several hypotheses have been suggested to explain the preclinical and clinical effects of homeopathic preparations; however, consistent experimental evidence to back those

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hypotheses has been lacking so far (see reviews by Bellavite et al.[3,4] and Guedes et al.[5]). Any explanations of the specific treatment effects induced by homeopathic drugs would have to cover two areas: the pharmaceutical mode of action[3] and the pharmacological mode of action.[4] The latter would have to answer the basic question of pharmacodynamics, that is, how homeopathic remedies work in living organisms, whereas the former would concentrate on the question of the effects at a physicochemical level. In the context of our systematic review of physicochemical investigations,[1,2] we considered it useful to relate the empirical results we identified to some recently discussed hypotheses for the pharmaceutical (physicochemical) mode of action of homeopathic remedies. Not being aware of a recent systematic review of the theories of how homeopathy works on a physicochemical level, we refer to Bellavite et al.,[3] who identified three major conceptual approaches to possibly explain specific remedy effects of homeopathic preparations: the formation of (1) water clusters or clathrates, (2) coherent domains, and (3) nanoparticles from the original substance.[3]

Water clusters—clathrates—were proposed as the mode of action of homeopathic remedies.[6,7] Around molecules of the original substance, shells of water molecules are expected to be formed, mirroring the shape of these molecules. It was speculated that these shells could survive and self-replicate even if the forming molecules were diluted away during the potentization process. These shells were hypothesized to serve as an information carrier of the original molecules, which could be deciphered by receptors on cell surfaces.

The Quantum Coherence Domains (QCD) theory was developed by Preparata and Del Giudice et al.[8,9] This theory predicts the formation of stable water regions or domains in water, which—by carrying some information related to the material potentized—could explain specific remedy properties of homeopathic preparations. A full description of this theory is given elsewhere.[10,11]

More recently, nanoparticles of elements corresponding to the starting material from which the homeopathic sample was made were postulated.[12–16] This launched the idea that the many interesting properties of nanoparticles, which are currently being researched, could serve to explain homeopathic treatment effects.[12–16]

To complete the picture, we mention a fourth approach that invokes non-local effects found in extensions of the quantum theory to macroscales, such as the Weak Quantum Theory (WQT).[17] This theory serves as a formal framework to describe possible quantum-like entanglement effects between the patient, the homeopathic substance, and the practitioner to describe the clinical effects of homeopathy.[18–23]

Other hypotheses have been proposed to explain homeopathic treatment effects on a physicochemical level, such as nano-bubbles,[24] epitaxy,[25] hormesis,[26,27] silica-compounds,[28] isotopic positional correlations,[29] amino acids and peptides,[30] and others. However, the consensus opinion of the authors is that the four main conceptual approaches outlined earlier are currently the most commonly discussed hypotheses within the homeopathic research community. We will, therefore, concentrate on these in our discussion of the results of the evidence coming from the physicochemical experiments analyzed in this review.

Looking from the perspective of physicochemical properties of homeopathic preparations and assuming there is a measurable difference to controls, in part I of our review we searched for published experiments of good quality.[1] Within these, we identified the most promising techniques in part II.[2] In this third part, we seek to draw conclusions from all these experiments in terms of the clues and constraints on possible theories they provide. In light of these findings, we sought to identify avenues for research, which is best able to advance the theory-building efforts by confirming/informing key findings, thus sorting between existing hypotheses and setting constraints on future hypotheses aimed at explaining specific physicochemical properties of homeopathic preparations. It was deemed out of scope for the present article to enter into any discussion of how these physicochemical hypotheses could relate to any pharmacological mode of action.

Methods

The literature search, article selection, and data extraction have already been described in parts I and II of this review.[1,2] In part II, we have identified methods that were often used and further fulfilled important quality criteria (randomization, blinding, statistics, use of succussed controls, use of multiple independent production lots)—which are summarized in the Methodological and Frequency of Investigation (MFI) score (the average of five quality criteria [randomization, blinding, statistics, use of succussed controls, and use of multiple independent production lots] and weighted by the number of studies in that research area).

In this third part of our review, we provide qualitative descriptions of the results of all experiments, concentrating on methods with a high MFI score. The methods with a lower MFI score are briefly discussed, whereas *in extenso* summaries of the evidence coming from all methods is provided in online appendices.

We also extracted information regarding possible influencing factors, such as aging, composition of the potentizing medium, effect of temperature *etc.* on homeopathic preparations. Results of these analyses were grouped into research topics.

Results

Qualitative analysis per experimental areas

In this section, we relate the results from the experiments that looked at differences between homeopathic preparations and controls. *In extenso* analyses per physical method are provided as Supplementary Data S1, and these are summarized later.

Nuclear magnetic resonance (MFI score = 15.8). Thirty experiments (24 publications) were performed by using Nuclear Magnetic Resonance (NMR) techniques.[24,31–53] The majority of experiments ($N = 26$) probed the spin of the hydrogen nucleus, and most studies investigated T1 and/or T2 relaxation times. Twenty-two experiments (73%) reported statistically significant differences between homeopathic samples and controls. Twelve studies were blinded, and 15 were randomized. Demangeat made extensive use of independent series (9 out of 10 experiments), and one other investigation used this rigorous procedure.[32]

Demangeat et al.'s contribution dominates the field, with 10 experiments published (34% of total), 9 of which reported significant differences between homeopathic samples and controls. Demangeat et al.'s results showed a general increase

in T1 for the homeopathic samples,[36,37] an increase in T1 as a function of dilution,[38–40] a decrease in T2 as a function of dilution,[40] and an increase in T1/T2 as a function of dilution.[39,40] These results were interpreted as the sign of lesser structuring (destructuralization) of the homeopathic samples in the earlier publications,[36,37] and as a sign of greater structuring due to nano-sized superstructures within the homeopathic preparations in the more recent publications.[24,40,41]

Three studies explicitly set out to replicate previous results,[31,32,44] and all three were unable to replicate original results. Four publications reported internal replications (two succeeded, two failed to reproduce results).[31,32,38,40]

Summarizing, the more recent investigations with NMR relaxation provide some evidence for nano-sized supramolecular structures within homeopathic remedies.

Spectroscopy (MFI score = 10.2). Thirty-nine experiments (36 publications) using optical spectroscopy were included in this review.[12, 25,48,49,54–85] Eighteen experiments were in the ultraviolet (UV) range, 12 were in the visible range (Vis), and 16 explored the infrared range. Twelve studies reported blinding, 8 reported randomization, and 12 studies reported use of inferential statistics.

Some experiments reported an increase in absorbance versus succussed controls (UV: *Aconitum* globules[68]; UV: *Cuprum Sulfuricum*[71,82]; Vis: *Arg. met.*[12]), and one study reported a decrease in absorbance (UV: *Sulfur*[69]). One study assessed combined results of three independent investigations and observed an increased absorbance of *Cuprum Sulfuricum* compared with succussed controls.[69]

One further study reported general changes in the shape of the spectra compared with unsuccussed controls (UV-Vis: *Natrum Muriaticum* and *Nux vomica*[25]).

A general narrowing of the O-H stretch band ($\sim$3284 nm) was reported for homeopathic preparations.[59,75] Several groups reported a general shift of the O-H band toward lower frequencies.[48,49,59,62,76]

In summary, the majority of studies investigating the average absorbance of preparations compared with succussed controls reported an increase in absorbance (mainly in the UV).

Electrical impedance (MFI score = 6.0). In 41 experiments (42 publications), electrical impedance, conductivity, or dielectric dispersion was measured.[60–62,64,66,67,72,86–120] The authors described differences between controls and homeopathic preparations or between potency levels in 33 experiments. Only 5 experiments reported inferential statistics, blinding, and randomization. Elia and his group have a big influence on this field with 17 such experiments, all reporting differences compared with controls.

Most experiments did not use succussed/potentized controls. Elia et al. used a different way to control the experiments: They used analytical methods to determine the amount of sodium in the sample to calculate the theoretical conductivity of a given sample. This theoretical conductivity could then be subtracted from that measured for the homeopathy samples, and this was then referred to as excess conductivity. Many experiments reported excess conductivity for the homeopathic preparations investigated.[88,89,92–99,101,105,107,121,122]

Analytical methods (MFI score = 6.2). This group comprised 22 experiments (18 publications) where analytical methods were used to investigate homeopathic preparations against controls.[12,14–16,33,40,55,60,81,82,103,117,123–128] Three main topics were addressed: decrease of the concentration of potentized substances on dilution, leaching from potentiation vessel wall, and possible differences in concentration between homeopathic preparations and controls.

Analytical methods were used to control the amount of the original substance remaining after a number of dilutions. This was done by detecting the original substance directly using spectroscopic methods[55] or by measuring the amount of starting material using radioactive elements.[55,123,124,126] The findings from this type of research were that the concentrations follow the expected logarithmic law, with variations due to adsorption of material by the vessel walls.

A second use of these techniques was to investigate the leaching of material from the potentization vessel. Several investigations showed that there was considerable leaching from glassware (e.g., Na and Si) and also from polyethylene containers (e.g., Na).[16,117,128]

Several investigations compared homeopathic samples and corresponding controls in terms of their inorganic ion concentrations. Two studies used inferential or descriptive statistics and did not observe any differences between preparations and controls.[33,128] Two further studies without statistical evaluation reported excess concentrations of the inorganic compound potentized.[15,40]

In 2010, Chikramane et al. used Inductively Coupled Plasma—Atomic Emission Spectroscopy to measure trace elements in different commercial homeopathic preparations of metals (*Aurum metallicum*, *Cuprum metallicum*, *Stannum metallicum*, *Zincum metallicum*, *Argentum metallicum*, *Platinum metallicum*). They reported the presence of trace metals in the homeopathic preparations to be greater than in their controls and concluded that the original substance was present even at high dilutions.[15] This work was extended in 2012 with the investigation of specially designed gold-nanoparticles and the notion of ''froth flotation,'' which was shown to be able to carry these particles to dilutions up to 15C under certain conditions.[14] Subsequent investigations by Holandino et al. and Van Wassenhoven et al. were not able to find traces of starting metals beyond 4C in the case of zinc and copper, respectively.[81,125]

There is some evidence for deviations from the expected logarithmic dilution during potentization due to adsorption to and leaching from the potentization vessel walls, and maybe due to froth flotation. There is no solid evidence for a difference in such trace levels of the original material between homeopathic preparations and controls.

Imaging methods (MFI score = 4.6). Thirteen experiments (12 publications) used different microscopic tools such as classical optical microscopy, fluorescence microscopy, electron microscopy, and atomic force microscopy (AFM) to study homeopathic preparations.[12,15,16,54,60,62,64,72,81,125,129–132] In the more recent investigations published (from 2010 onward), nanoparticles and aggregates were identified in most homeopathic preparations as well as controls. Quantitative comparisons between homeopathic dilutions and controls were either not done or not meaningful due to the use of unsuccussed controls or samples from another batch of dilution medium. A few investigations used clean room conditions for production of homeopathic samples;

in all other investigations, unspecific contaminations during production (e.g., leaching from the vessel surface, airborne material from the environment) may be the reason for the particles observed. No clear evidence emerged regarding a possible difference between homeopathic preparations and adequate controls with respect to the number, size, or nature of the nanoparticles observed.

Further, three investigations described measurements of homeopathic preparations by gas discharge photography, a method based on measurements of coronal discharge from samples exposed to high-frequency alternating current at high voltage.[87,133,134] Two of these studies performed a computer-based image analysis with statistical evaluation. In both experiments, significant differences between homeopathic preparations and controls were observed.[133,134]

Various physical (MFI score = 2.6). In this category, we summarized all those experiments that could not be assigned to other categories. Nine experiments (seven publications) were included.[12,53,54,135–138] Five experiments reported differences between homeopathic preparations and controls, but the relevance of the effects observed in three studies is unclear due to the lacking statistical evaluation[137] or the unclear method used.[135] In two experiments, Bell et al. observed a tendency for larger zeta potential of preparations compared with controls, which is interpreted as meaning that the nanoparticles present in the samples (most probably originating from the cork stoppers used during production) tended to be more stable in homeopathic remedies compared with the succussed controls.[12,54] The experiments of the category ''Various Physical'' did not add substantially to the body of evidence.

Luminescence (MFI score = 2.4). Eight photoluminescence studies investigated homeopathic samples.[78,139–145] All investigations reported differences between homeopathic samples and controls. However, various homeopathic substances and measurement protocols were used, and no independent replication trials were found. Further, in most cases, no information was available regarding blinding, randomization, and the number of independent production series.

Three thermoluminescence studies investigated homeopathic samples of LiCl and NaCl specifically prepared in D_2O.[146–148] One publication[148] described an external replication of another investigation.[146] Numerical differences between LiCl 15c and D_2O 15c were observed for the emission peak at 160–200 K in four out of six single experiments,[146–148] with statistical significance for one experiment.[148] One investigation assessed variability by using internal replicates, yielding standard deviations up to 80% of the mean photon counts,[148] pointing to unidentified factors influencing the experimental system. LiCl 15c had a qualitatively similar (but quantitatively less pronounced) effect as LiCl 0.1 mol/L on thermoluminescent emission. LiCl is described as a structure breaking compound suppressing hydrogen bonds.[146]

The experiments using thermoluminescence reported that homeopathic preparations break up water structure. However, some confounding factors remain, and further investigations are required.

Raman spectroscopy (MFI score = 0.8). Raman spectroscopy has been seldom used in homeopathy research. No statistics beyond descriptive were reported in all seven experiments (six publications) assessed.[25,53,74,149–151] Further, most experiments used unsuccussed ethanol as a control, thereby leaving out the possibility of unspecific effects due to the succussion procedure. In the present state of the research, there is only weak evidence for specific properties of homeopathic samples identifiable by Raman spectroscopy.

Calorimetry (MFI score = 0.8). We identified 16 experiments published that examined homeopathic preparations using calorimetry, 13 of which were conducted by Elia et al. using mixing-flow calorimetry.[86,88,93–97,99,104,106,107,122,125,152–154] Except for the study of Holandino et al., all studies showed higher excess heat for potentized substances compared with controls.[125] Overall, considering that this area is dominated by one research group, independent replications are needed before firm conclusions can be drawn.

Chromatography (MFI score = 0.6). Homeopathic preparations were investigated in three experiments published between 1932 and 1959 by using paper chromatography (assessing rising height, without aiming at separation of compounds), however none of these was statistically evaluated.[155–157] In some experiments, the amplitude of the pattern observed for potentized substances was greater than that for the controls (potentized water). Due to the lack of a statistical evaluation, the relevance of the effects reported is difficult to assess.

Electrochemistry (MFI score = 0.2). This set includes nine studies, which measured electrical properties but could not be grouped under electrical impedance.[91,100,102,111,145,158–161] All these experiments tended to report differences between preparations and controls. However, the three relatively old experiments[111,159,160] would need replication. Three investigations by the same Italian group[91,100,102] reported results measuring the electromotive force, which also warrants further investigation.

Qualitative analysis per research topic

In this section, we review the evidence regarding specific research topics: factors that appear to affect the experiments and modalities that come out as significant in the field. *In extenso* analyses by research topic are provided in the Supplementary Data S2, and these are summarized later.

Effect of aging. Thirty-five experiments (31 publications) examined the role of the age of samples, 19 of which were conducted by the group of Elia and showed an increase in the excess heat and excess conductivity values of the homeopathic samples over time.[33,62,80,82,88,89,92,94,95,97–99,101,105–110,117,118,124,128,142–144,148,154,162] Other experiments also showed increasing experimental values over time with other research methods; for example, Baumgartner et al. using NMR reported an increased T1 signal in sulfur preparations compared with controls after 1 year[33] or Witt et al. using the REDEM technology (''REsonanzDämpfungs—und EntdämpfungsMessverfahren'') observed higher conductivities in homeopathic preparations compared with succussed controls and an increase in the difference over time (6–30 h).[117,128]

The analysis of the experimental results regarding aging effects indicates that ions leaching from the glassware containers used for production or storage may play an important role in understanding the physicochemical processes in homeopathic preparations. However, the leaching reported by Witt in 2006 happens relatively quickly (6–30 h),[128] whereas some effects reported cover much longer times (several years in some cases), which would indicate that other effects might be responsible for these long timescale observations (Elia hypothesizes homeopathic preparations to be nonequilibrium systems).[101]

Role of potentizing medium. Forty-two experiments (25 publications) used a potentizing medium other than water in the production of homeopathic preparations and corresponding controls.[36,37,39,40,88,91–100,102–104,112,122]

Elia observed more pronounced effects when the medium included solutes such as $NaHCO_3$ and H_4O_4Si in 10^{-5} mol/L, which would be expected in glass containers (due to leaching and contact with the atmosphere).[93] Elia has used such solutions in many publications; however, they present no clear evidence that these solutes do help differentiate homeopathic preparations from controls.[88,91–100,102–104,122]

In 2010, Demangeat observed that using 0.15 mol/L LiCl yielded better differentiation from controls than saline (NaCl 0.15 mol/L), which, in turn, yielded larger differences compared with pure water.[40] In 2014, Elia showed that the presence of even 1% ethanol in the potentizing medium yielded better differentiation than pure water.[107]

The overall findings indicate that the presence of solutes might increase the size of the effect measured, thereby indicating that solutes might be important for the mode of action of homeopathic preparations.

Role of sample volume. Nine experiments (six publications) from the group of Elia report effects related to the volume of the container (from 150 mL down to 0.25 mL).[62,88,96,99,105,107] Excess conductivity and excess heat of mixing are reported to increase with decreasing volume. Decreasing the volume of the container increases the surface-to-volume ratio, thereby most probably increasing leaching effects, which relates back to the potential role of ions in these observations.

Temperature and other external influences. Ten experiments (nine publications) explore the effect of temperature and other possible influence.[39,40,66,69,71,103,114,137,147] Some experiments assessed the effect of heating and UV radiation on homeopathic samples. High temperatures (>70°C) seemed to abolish specific properties of homeopathic preparations in most studies,[40] whereas incubation at moderate temperatures (30°C–50°C) tended to increase differences to controls.[71] UV radiation seemed to have no consistent influence on homeopathic preparations. These observations are compatible with the hypothesis that leaching might affect or interact with homeopathic samples and controls differently (at least at moderate temperatures).

Role of substance of potentizing vessel. Most of the experiments were performed in glass containers (>42% of experiments, 35% was unreported). Experiments not performed in borosilicate glass (90%) tended to report more positive findings. This is compatible with the hypothesis that the presence of ions might play a role in stabilizing the observed phenomena.

Using molecules as probes. Sukul reported changes in the circular dichroism spectra of bovine serum albumin in the presence of homeopathic preparations.[78] Cartwright reported differences in the absorbance of solvatochromic dyes in the UV-Vis range in the presence of a homeopathic preparation.[56–58] The results suggest an interaction between homeopathic preparations and solvatochromic dyes of an electromagnetic nature, proportional to the dipole moment of the dyes. Ambient light was also reported to have an effect on the experiment. These observations are in line with the hypothesis that the hypothetical water structures involved in homeopathy might carry an electric charge or dipole moment.

Isolating structures and characterizing their properties. Elia et al. performed conductivity measurements of simply diluted preparations (i.e., without succussion) and reported a decrease in excess conductivity with increasing dilution of the preparations, supporting the idea that the structures present in the homeopathic samples were being diluted out in this process.[98] Also, lyophilization was used to remove excess water and concentrate the structures. Structures visible under AFM were reported.[62] Elia et al. also performed titration experiments with acid and base solutions, while performing conductometry and calorimetric measurements. Their results suggest that these structures are mainly composed of water, are charged, and have distinct thermodynamic properties.[106]

Discussion

Explorative studies and hypothesis testing

Overall, we found relatively few studies that explicitly stated their working hypothesis (e.g., ''homeopathic potentization has a structuring effect on water, which can be demonstrated by using the XYZ technique''). The reader has to analyze *a posteriori* what the results of such studies actually mean with regard to specific hypotheses. In this sense, most investigations we reviewed could be considered of an exploratory nature, concluding to the presence (or absence) of a difference between homeopathic preparations and controls when investigated by using a particular technique. For the field to progress, we would argue that the field needs more experiments that are specifically designed to test specific hypotheses (see later for some examples).

The research field is still in the process of refining working hypotheses and, as such, is a long way from being able to validate any theory regarding the pharmaceutical mode of action of homeopathy. This state of affairs is often raised as an argument against the validity of the results (clinical and other) reported in the field of homeopathy. It is, however, worth noting that the lack of a theory that is able to explain any given observations in no way diminishes the value of these experimental findings. Historically, in most cases, theories were built, extended, or refined to accommodate novel experimental findings. As an example, quantum mechanics emerged as the result of attempts to understand physical observations, which did not fit within the atomistic

conceptual framework of the time. In this way, observations and experiments have often led the way and shaped the landscape for new theories to emerge. Further, contemporary philosophy of science debates often point out that there are many scientific fields where theory-driven experimental research is somewhat unusual. The philosopher and biologist Hans-Jörg Rheinberger revealed this to be the case for the field of molecular biology.[163] However, theory-driven experimentation, in general, makes sense once the outlines of this landscape are established. We suggest that the field of homeopathy is about to reach a point where theory building makes sense, based on the available experimental evidence, leading to possible theory-driven hypothesis testing in the future.

Distinguishing between homeopathic preparations and succussed controls remains a considerable challenge since the differences measured are in general quite small. If the differences relate to some informational content (see below), the smallness of the effects could be an intrinsic property and very much dependent on the measurement technique and subsequent data analysis. Consider, as a thought example, trying to distinguish the music of two bands by inspecting their respective CDs or to detect the difference between two books by analyzing their pages. If the correct code for translating the patterns (sequences of 0's and 1's on the CD, or the letters on the pages) into understandable language is unknown, it is extremely difficult to properly distinguish the contents. Spectroscopic analysis, for example, could detect the difference between a blank book (or CD) and a full book (or CD); identifying a difference between two books with different contents would be very difficult, however, and also prone to errors, as long as the code is unknown. A further analogy is that of radio wave signals: There again it would be comparably easy to detect the presence or absence of a radio signal but distinguishing between two senders is nearly impossible without a proper receiver that is able to translate the signal into a humanly understandable audio signal. In homeopathic basic research, we are at present lacking such a receiver that is able to translate the signals. The question is whether biological systems might constitute such a receiver, as biological systems appear to be more sensitive to specific homeopathic dilutions.[164]

Main results

The most promising techniques in terms of the quality and quantity of the research generated and the consistency of the results reported were NMR, spectroscopy, and electrical impedance.

Based on the high-quality experiments identified (see tables 6 and 7 in part II of this review[2]), we extracted certain features or properties of homeopathic preparations where the evidence was deemed sufficiently consistent that it makes sense to hypothesize these to be genuine properties of (at least some) homeopathic preparations, open for further experimentation and model building. Relative to succussed controls, these were:

- Increased absorbance in UV spectroscopy (*Cuprum sulfuricum*)
- Increase in T1/T2 NMR relaxation time ratio (*Silicea*, Histamine)
- Increase in thermoluminescence radiation (*Lithium muriaticum*)

Further, based on a qualitative analysis of the publications, we identified the following phenomena relative to unsuccussed controls:

- Presence of nanoparticles
- Excess conductivity
- Excess heat in calorimetric studies
- Interaction with polar dyes, proportionally to polarity of dye

We also extracted a number of effects where the evidence is less strong and requires further investigation to in/validate the findings. These effects were:

- Ionic solutions increase differences with controls
- Moderate temperatures increase differences with controls
- Small sample volumes increase differences with controls
- Aging of the sample increases differences with controls
- High temperatures abolish differences with controls

Experimental evidence led to some working hypotheses regarding tentative specific structures that could be responsible for such properties and effects:

- Structures are charged/polar
- Structures can be strengthened and stabilized by increasing the solvent's ion concentration
- Structures can be concentrated by dehydration/diluted by addition of medium

Theoretical approaches being explored

Later, several conceptual frameworks regarding the pharmaceutical mode of action of homeopathic remedies are explored. As we will demonstrate, some are compatible with the current evidence whereas others seem to be only partially compatible with the available experimental evidence. A full systematic review of all theories of homeopathy (pharmaceutical/physicochemical as well as pharmacological/biological) is beyond the scope of the present review on physicochemical investigations. In the absence of an up-to-date systematic review of homeopathy theories, we will concentrate on the theories we consider most prominent at the moment (see Introduction section), with emphasis on how these are supported/invalidated by the evidence coming out of the experiments we have reviewed. We hereby primarily rely on the results from high-quality experiments (see tables 5–7 in part II of this review[2]).

Clathrates. One of the first hypotheses put forward to explain the effects of homeopathic dilutions referred to water structures called clathrates.[6,7] Clathrates, in general, are inclusion compounds in which a molecule of type A is trapped in a cage formed by a lattice of host molecules type B. In the case of homeopathic remedies, the clathrates were hypothesized to be hydrogen-bonded stable water structures, which form around areas of bigger molecules of the potentized drug. On successive potentization, these clathrates were postulated to self-replicate even if the original drug substance was not present anymore due to the dilution process.

We identified two investigations that specifically assessed this hypothesis and searched for stable water clusters in

homeopathic remedies by NMR spectroscopy (where the detection limit is $\sim 10\,\mu mol/L$).[32] In both investigations, no evidence was found for stable water clusters.[31,32]

Hydrogen-bonded water structures that are stable on a macroscopic timescale (>seconds) are quite improbable based on the current understanding of physics. Around ions or other charged molecules, water clusters (hydration shells) are known to form.[165] These clusters are not static, however, but dynamic, which means that the molecules that belong to these clusters are constantly changing place. Within liquid water, a simplified two-phase-model involving cluster-bound water molecules differing from free (bulk) water molecules characterizes these two phases with respect to their correlation time τ, which can be roughly estimated to $\approx 10^{-11}$ sec in clusters[166] compared with $\approx 10^{-12}$ sec for free water.[167,168]

Wolf et al.[82] formulated a dynamic water cluster hypothesis, which states that the solvent is less structured (more dynamic, with lowered correlation times) after homeopathic potentization. This hypothesis of enhanced molecular motion due to solvent-structure-breaking is compatible with the main results of this review: increased UV absorption,[82] increased T1 NMR relaxation times,[33] and enhanced thermoluminescence radiation.[146–148] Such an increase in molecular mobility could be due to a nonthermal effect, leading to a metastable state of the complex system water.[57] Electromagnetic structures (such as QCD, see the Quantum Coherence Domains section) could be a candidate for such an effect. However, the question of how such dynamic structures could carry relevant information and act as a therapeutically relevant agent remains open at the moment.

Quantum coherence domains. A promising theoretical approach currently being explored is that of QCD, originally proposed by Preparata and Del Giudice et al. on the basis of their work in laser physics, applied to water.[8–10,169] It predicts the presence of water structures of $\sim 100\,nm$ in diameter. This theory is based on a quantum electromagnetic phenomenon and, as such, would, in principle, be compatible with ions interacting with the structures for stability and these structures being charged.[169,170] These predicted structures would be subject to ''thermal erosion'' and would disappear at higher temperatures.[169] These structures could also affect leaching, as they would potentially better accommodate certain ions, effectively taking them out of the surrounding medium and thereby creating differential leaching.[171] There is no in-principle reason that these could not be concentrated or diluted.

The QCD theory also has the advantage that the information would be stored as electromagnetic frequencies, thereby bypassing the need for the original substance to be present and thereby being immune to the dilution problem as long as the information is passed on from dilution to dilution (through the succussion steps).

As the hypothesized QCD water structures would carry electrostatic charges, techniques using such electrical effects might be useful. The observations of an increase in conductivity for homeopathic samples and of excess heat in calorimetric studies[106] could be compatible with that of QCD's. Another example of this might be the coronal or Gas Discharge Method, where the electrical field generated during a rapid discharge through a sample is recorded.[133,172] Another approach might be the use of crystallization assays where such charge effects would be a key role in the forming of distinctive crystallization patterns.[173–175]

More testable predictions from QCD are needed to start a process of validation/invalidation of this theory, which will require considerably more theoretical work.

Nanoparticles. Another hypothesis, which is being actively pursued, is that of nanoparticles of the potentized material being present in even highly diluted homeopathic preparations. Analytical techniques (Inductively Coupled Plasma Mass Spectrometry, Energy Dispersive X-ray Analysis, Transmission Electron Microscopy) have been used in pursuing this hypothesis and have reported the presence of nanoparticles in general and traces of the original material (in the case of metals) even at ultramolecular dilution levels. The nanoparticle hypothesis is to be distinguished from the QCD theory, referred to earlier, where the structures are water based. Here, trace elements of the original material are believed to persist through the dilution/succussion process (potentially through the ''froth flotation'' mechanism[14]) and form the basis for the specific medicinal effects. It is, however, beyond the scope of the present review to enter into a discussion of recent interesting developments in the area of the pharmacological/biological mode of action involving nanoparticles.[13,176]

Though nanoparticles and aggregates were identified in most homeopathic preparations as well as controls, the origin of these nanoparticles is unclear. In some investigations, comparable numbers of nanoparticles were found in homeopathic preparations and controls (such as succussed medium).[81] Thus, the nanoparticles found were not specific to the homeopathic remedy potentized but were contaminants from the production process, for example, from the cork stoppers used during potentization[12,54] or from ambient air, potentization medium, and container walls.[81] In other investigations, nanoparticles were identified in homeopathic remedies of commercial origin,[15] but no controls were measured. Keeping in mind that nanoparticles are ubiquitous, we should expect to find them everywhere unless working in extremely tightly controlled conditions. Also, metals are relatively common in nature and should be expected at trace levels just about everywhere—unless again special care has been taken to control this (use of radiolabeled elements, e.g.). Summarizing, there is no convincing evidence that highly diluted homeopathic preparations contain nanoparticles of the starting material.

Although it is easy to see how such nanoparticles could be concentrated or diluted, it remains unclear why nanoparticles would be sensitive to temperature, to the presence of ions or why they would be influenced by leaching. Further, it is unclear how homeopathic nanoparticles of metals, for instance, would carry any more therapeutically relevant information than the ubiquitous metal nanoparticles present just about everywhere. This argument is even more severe when looking at dilutions of the more ubiquitous (and soluble) organic salts (such as NaCl, KCl *etc.*).

Weak quantum theory. Finally, an interesting theoretical approach has been formulated by using macroscopic quantum entanglements, through the WQT formalism.[17] According to this theory, quantum-like entanglement would take place between the patient, the practitioner, and the homeopathic

remedy. Walach hypothesized that homeopathy might be explained by a double-entangled structure, with one entanglement being between original substance and remedy by means of the potentization process, and a second between disease symptoms of the patient and symptoms of the remedy picture by means of the simile principle.[177] Walach makes two testable predictions regarding these entanglements. The first is that the more time-intensive production processes would produce more potent remedies.[18] The second hypothesis is that the entanglement should get stronger with increasing potency.[177] We did not find physicochemical investigations that addressed either of these predictions.

Based on related considerations, Beauvais hypothesized that centralized blinding eliminates differences between homeopathic samples and controls, whereas local blinding procedures should not influence any such differences.[22,23] We did not find any physicochemical investigation that addressed this prediction.

We conclude that the working hypothesis of macroscopic quantum entanglement as a possible mode of action for homeopathic preparations still needs to be addressed by specifically designed investigations.

Other theoretical approaches. Another hypothesis being envisaged is that the structures might actually be nano-bubbles created during the succussion process.[39,40] We can readily see how such nano-bubbles would be sensitive to temperatures and to ion content, for example. Diluting them would be possible although concentrating them would lead to bubbles joining and eventually coming out of solution. Also, it is unclear how such nano-bubbles could carry any therapeutically relevant information and action.

The idea that silica-compounds[28] are responsible for homeopathic efficacy is in line with the phenomena that moderate temperatures, small sample volumes, and aging of the sample increase differences with controls. However, there is one investigation with homeopathic preparations produced in polyethylene vessels (e.g., without measurable content of Silica) that showed efficacy of such preparations.[40]

The hypothesis that amino acids and peptides[30] are mainly responsible for the mode of action of homeopathic preparations most probably can be ruled out, because many investigations showing differences between homeopathic samples and controls were carried out with pure water and/or highly purified ethanol as potentization medium (without traces of amino acids and peptides).

Conclusions and Outlook

Based on the analysis of the main findings, we conclude that there is empirical evidence for specific physicochemical characteristics of homeopathic preparations (i.e., measurable differences to succussed controls, such as increased UV absorption and increased NMR T1/T2 relaxation time ratios). Further, a number of physical and environmental influences were identified: Differences to controls seem to increase with time, moderate temperature, small sample volume, and in ionic medium, whereas high temperatures seem to abolish differences to controls. No consistent information is available regarding the specificity of homeopathic preparations, that is, when looking for differences between homeopathic preparations made from distinct starting materials or different potency levels. Further, independent replications are rare, and setup stability assessments using systematic negative control experiments are entirely missing.

Based on our analysis, there is no consistent evidence to date for a number of proposed working hypotheses, such as stable clathrates, nanoparticles, nano-bubbles, silica compounds, or peptides as being constitutional for the physicochemical homeopathic mode of action. The QCD hypothesis, the dynamic water cluster hypothesis, and the WQT cannot be excluded at this point and need to be thoroughly assessed experimentally.

From this body of work, it comes out quite clearly that the field requires further targeted experimentation to validate past findings reporting differences between homeopathic dilutions and controls and to expand these findings by testing the different hypotheses that have been proposed. We further noted that there are no recent systematic reviews on pharmaceutical as well as pharmacological concepts to explain specific homeopathic remedy effects; we, therefore, recommend performing such reviews to gain a complete picture of all theoretical approaches on the physicochemical as well as biological level. Emphasis should be placed on possible interactions between pharmaceutical and pharmacological concepts, for example, an informational mode of action might imply that bioassays could be better suited than physicochemical measurements to identify an informational content in homeopathic drugs.

Regarding experimental validation, independent replications are needed to verify the main results of the current analysis, using measurements of the highest quality, including systematic negative control experiments, and by measuring the same samples using different methods. Further, additional systematic investigations are needed to address the question of specificity by comparing homeopathic preparations of different origins and/or different potency levels.

In terms of experimentally assessing specific theoretical models of the physicochemical mode of action, we recommend concentrating on three areas: the QCD hypothesis, the dynamic water cluster hypothesis, and the WQT. The field also needs more efforts in terms of model building, to extract predictions from the different theoretical approaches and to test them systematically to progress toward a more specific working hypothesis for the pharmaceutical mode of action of homeopathic preparations.

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Supplementary Material

Supplementary Data S1
Supplementary Data S2

References

1. Klein SD, Würtenberger S, Wolf U, et al. Physicochemical investigations of homeopathic preparations: A systematic review and bibliometric analysis—Part 1. J Altern Complement Med 2018;24:409–421.

2. Tournier A, Klein SD, Würtenberger S, et al. Physicochemical investigations of homeopathic preparations: A systematic review and bibliometric analysis—Part 2. J Altern Complement Med 2019;25:890–901.
3. Bellavite P, Marzotto M, Olioso D, et al. High-dilution effects revisited. 1. Physicochemical aspects. Homeopathy 2014;103:4–21.
4. Bellavite P, Marzotto M, Olioso D, et al. High-dilution effects revisited. 2. Pharmacodynamic mechanisms. Homeopathy 2014;103:22–43.
5. Guedes JRP, Bonamin LV, Capelozzi VL. Water-related mechanisms proposed for storing and transmitting homeopathic information: Putative links with biological responses. Homeopathy 2018;107:172–180.
6. Anagnostatos GS, Pissis P, Viras K. Possible water cluster formation by dilution and succussions. In: Anagnostatos GS, von Oertzen W, eds. Atomic and Nuclear Clusters. Berlin: Springer, 1995:215–217.
7. Chaplin MF. The memory of water: An overview. Homeopathy 2007;96:143–150.
8. Preparata G. Quantum-field theory of the free-electron laser. Phys Rev A 1988;38:233–237.
9. Del Giudice E, Preparata G, Vitiello G. Water as a free electric dipole laser. Phys Rev Lett 1988;61:1085–1088.
10. Bono I, Del Giudice E, Gamberale L, Henry M. Emergence of the coherent structure of liquid water. Water 2012;4:510–532.
11. Tournier A. Is homeopathy really that implausible. In: Leoni Bonamin SW, ed. Transdisciplinarity and Translationality in High Dilution Research. Newcastle upon Tyne, UK: Cambridge Scholars Publishing, 2019.
12. Bell IR, Muralidharan S, Schwartz GE. Nanoparticle characterization of traditional homeopathically-manufactured silver (*Argentum metallicum*) medicines and placebo controls. Nanomed Nanotechnol 2015;6:311.
13. Bell IR, Schwartz GE. Enhancement of adaptive biological effects by nanotechnology preparation methods in homeopathic medicines. Homeopathy 2015;104:123–138.
14. Chikramane PS, Kalita D, Suresh AK, et al. Why extreme dilutions reach non-zero asymptotes: A nanoparticulate hypothesis based on froth flotation. Langmuir 2012;28: 15864–15875.
15. Chikramane PS, Suresh AK, Bellare JR, Kane SG. Extreme homeopathic dilutions retain starting materials: A nanoparticulate perspective. Homeopathy 2010;99:231–242.
16. Upadhyay RP, Nayak C. Homeopathy emerging as nanomedicine. Int J High Dil Res 2011;10:299–310.
17. Atmanspacher H, Römer H, Walach H. Weak quantum theory: Complementarity and entanglement in physics and beyond. Found Phys 2002;32:379–406.
18. Walach H. Entanglement model of homeopathy as an example of generalized entanglement predicted by weak quantum theory. Forsch Komplementarmed Klass Naturheilkd 2003;10:192–200.
19. Milgrom LR. Patient-practitioner-remedy (PPR) entanglement, part 7: A gyroscopic metaphor for the vital force and its use to illustrate some of the empirical laws of homeopathy. Forsch Komplementarmed Klass Naturheilkd 2004;11:212–223.
20. Milgrom LR. A new geometrical description of entanglement and the curative homeopathic process. J Altern Complement Med 2008;14:329–339.
21. Weingärtner O. What is the therapeutically active ingredient of homeopathic potencies? Homeopathy 2003;92:145–151.
22. Beauvais F. A quantum-like model of homeopathy clinical trials: Importance of in situ randomization and unblinding. Homeopathy 2013;102:106–113.
23. Beauvais F. 'Unconventional' experiments in biology and medicine with optimized design based on quantum-like correlations. Homeopathy 2017;106:55–66.
24. Demangeat JL. Gas nanobubbles and aqueous nanostructures: The crucial role of dynamization. Homeopathy 2015;104:101–115.
25. Rao ML, Roy R, Bell IR, Hoover R. The defining role of structure (including epitaxy) in the plausibility of homeopathy. Homeopathy 2007;96:175–182.
26. Calabrese E. Paradigm lost, paradigm found: The re-emergence of hormesis as a fundamental dose response model in the toxicological sciences. Environ Pollut 2006; 138:379–411.
27. Chikramane P, Suresh AK, Kane S, Bellare J. Metal nanoparticle induced hormetic activation: A novel mechanism of homeopathic medicines. Homeopathy 2017;106:135–144.
28. Anick DJ, Ives JA. The silica hypothesis for homeopathy: Physical chemistry. Homeopathy 2007;96:189–195.
29. Berezin AA. Isotopical positional correlations as a possible model for Benveniste experiments. Med Hypotheses 1990;31:43–45.
30. Strube J, Stolz P, Maier W. Do amino acids and peptides explain the effects of potentized medications? Biol Med 2002;31:17–24.
31. Aabel S, Fossheim S, Rise F. Nuclear magnetic resonance (NMR) studies of homeopathic solutions. Br Homeopath J 2001;90:14–20.
32. Anick DJ. High sensitivity ^{1}H-NMR spectroscopy of homeopathic remedies made in water. BMC Complement Altern Med 2004;4:15.
33. Baumgartner S, Wolf M, Skrabal P, et al. High-field ^{1}H T_1 and T_2 NMR relaxation time measurements of H_2O in homeopathic preparations of quartz, sulfur, and copper sulfate. Naturwissenschaften 2009;96:1079–1089.
34. Botha I, Ross AHA. A nuclear magnetic resonance spectroscopy comparison of 3C trituration derived and 4C trituration derived remedies. Homeopathy 2008;97:196–201.
35. de Alvarenga ES, de Oliveira APM, da Silva RTB, Casali VWD. Effect of Magnesium phosphoricum 12c on Sodium Dodecylsulphate by 13C nuclear magnetic resonance. Int J High Dil Res 2009;8:3–8.
36. Demangeat JL, Demangeat C, Gries P, et al. Modifications of the 4 MHz NMR relaxation times of the protons of the solvent in very high saline dilution of silica/lactose [in French]. J Méd Nucl Biophys 1992;16:135–145.
37. Demangeat JL, Gries P, Poitevin B. Modification of 4 MHz N.M.R. water proton relaxation times in very high diluted aqueous solutions. In: Bastide M, ed. Signals and Images. Dordrecht: Kluwer Academic, 1997:95–110.
38. Demangeat JL, Gries P, Poitevin B, et al. Low-field NMR water proton longitudinal relaxation in ultrahighly diluted aqueous solutions of silica-lactose prepared in glass material for pharmaceutical use. Appl Magn Reson 2004;26: 465–481.
39. Demangeat J-L. NMR water proton relaxation in unheated and heated ultrahigh aqueous dilutions of histamine: Evidence for an air-dependent supramolecular organization of water. J Mol Liq 2009;144:32–39.
40. Demangeat J-L. NMR relaxation evidence for solute-induced nanosized superstructures in ultramolecular aqueous dilutions of silica-lactose. J Mol Liq 2010;155:71–79.

41. Demangeat J-L. Nanosized solvent superstructures in ultramolecular aqueous dilutions: Twenty years' research using water proton NMR relaxation. Homeopathy 2013; 102:87–105.
42. Lasne Y, Duplan JC, Mallet JJ. Proof of physical signals of diluted dynamized or ''homeopathic'' solutions [In French]. Bull M.T.S. 2. 1985:o.S.
43. Lasne Y. Properties of ''homeopathic'' solutions, measurement of magnetic relaxation T2 [In French]. Lyon: Université Claude Bernard Lyon 1, U.E.R. Faculté de Pharmacie, 1986.
44. Milgrom LR, King KR, Lee J, Pinkus AS. On the investigation of homeopathic potencies using low resolution NMR T2 relaxation times: An experimental and critical survey of the work of Roland Conte et al. Br Homeopath J 2001;90:5–13.
45. Sacks AD. Nuclear magnetic resonance spectroscopy of homeopathic remedies. J Holist Med 1983;5:172–177.
46. Smith RB, Boericke GW. Changes caused by succussion on N.M.R. patterns and bioassay of bradykinin triacetate (BKTA) succussions and dilutions. J Am Inst Homeopathy 1968;61:197–212.
47. Sukul A, Sarkar P, Sinhababu SP, Sukul NC. Altered solution structure of alcoholic medium of potentized Nux vomica underlies its antialcoholic effect. Br Homeopath J 2000;89:73–77.
48. Sukul NC, De A, Dutta R, et al. Nux vomica 30 prepared with and without succussion shows antialcoholic effect on toads and distinctive molecular association. Br Homeopath J 2001;90:79–85.
49. Sukul NC, Ghosh S, Sinha Babu SP, Sukul A. Strychnos nux-vomica extract and its ultra-high dilution reduce voluntary ethanol intake in rats. J Altern Complement Med 2001;7:187–193.
50. Van Wassenhoven M, Goyens M, Henry M, et al. Nuclear magnetic resonance characterization of traditional homeopathically manufactured copper (*Cuprum metallicum*) and plant (*Gelsemium sempervirens*) medicines and controls. Homeopathy 2017;106:223–239.
51. Weingärtner O. NMR-spectra of sulfur potencies [In German]. Therapeutikon 1989;3:438–442.
52. Weingärtner O. NMR-features that relate to homoeopathic sulphur-potencies. Berlin J Res Homoeoepathy 1990;1:61–68.
53. Weingärtner O. Homeopathic potencies. Wish and reality in the search for therapeutically active components [In German]. Berlin: Springer Verlag, 1992.
54. Bell IR, Muralidharan S, Schwartz GE. Nanoparticle characterization of traditional homeopathically-manufactured *Gelsemium sempervirens* medicines and placebo controls. Nanomed Biother Discov 2015;5:136.
55. Boyd WE. Research on the Low Potencies of Homoeopathy, An Account of Some Physical Properties Indicating Activity. London: Heinemann, 1936.
56. Cartwright SJ. Interaction of homeopathic potencies with the water soluble solvatochromic dye bis-dimethylaminofuchsone. Part 1: pH studies. Homeopathy 2017; 106:37–46.
57. Cartwright SJ. Degree of response to homeopathic potencies correlates with dipole moment size in molecular detectors. Implications for understanding the fundamental nature of serially diluted and successed solutions. Homeopathy 2018;107:19–31.
58. Cartwright SJ. Solvatochromic dyes detect the presence of homeopathic potencies. Homeopathy 2016;105:55–65.
59. Chakraborty I, Datta S, Sukul A, et al. Variation in free and bound water molecules in different homeopathic potencies as revealed by their Fourier Transform Infrared Spectroscopy (FTIR). Int J High Dil Res 2014;13:189–196.
60. Chatterjee A, Paul BK, Kar S, et al. Effect of ultrahigh diluted homeopathic medicines on the electrical properties of PVDF-HFP. Int J High Dil Res 2016;15:10–17.
61. Chibici-Revneanu C. UV spectroscopic and dielectric measurements of water and highly diluted homeopathic drug solutions [In German]. Leipzig: Universität Leipzig, Fakultät f. Biowissenschaften, Pharmazie und Psychologie (Institut für Pharmazie), 2005.
62. Elia V, Ausanio G, Gentile FS, et al. Experimental evidence of stable water nanostructures in extremely dilute solutions, at standard pressure and temperature. Homeopathy 2014;103:44–50.
63. Gautam RS, Tewari KP, Roper NK, Mishra RK. Spectrophotometric analysis of potentisation of *Euphrasia officinalis*. Hahnemann Glean 1977;44:1–5.
64. Gayen A, Mondal D, Bandyopadhyay P, et al. Effect of homeopathic dilutions of cuprum arsenicosum on the electrical properties of poly(vinylidene fluoride-co-hexafluoropropylene). Homeopathy 2018;107:130–136.
65. Gebhardt A. FTIR-spectroscopic investigations of aqueous and ethanolic homeopathic drugs [In German]. Leipzig: Fakultät für Biowissenschaften, Pharmazie und Psychologie, 2002.
66. Heintz E. Physical effects of highly diluted potentised substances [In German]. Die Naturwissenschaften 1941;48:713–725.
67. Heintz E. Remarks to my article: Physical effects of highly diluted potentised substances [In German]. Naturwiss 1942;30:642.
68. Klein SD, Wolf U. Comparison of homeopathic globules prepared from high and ultra-high dilutions of various starting materials by ultraviolet light spectroscopy. Complement Ther Med 2016;24:111–117.
69. Klein SD, Sandig A, Baumgartner S, Wolf U. Differences in median ultraviolet light transmissions of serial homeopathic dilutions of copper sulfate, *Hypericum perforatum*, and sulfur. Evid Based Complement Altern Med 2013;2013:370609.
70. Klein SD, Wolf U. Investigating homeopathic verum and placebo globules with UV spectroscopy. Forsch Komplementarmed 2013;20:295–297.
71. Marschollek B, Nelle M, Wolf M, et al. Effects of exposure to physical factors on homeopathic preparations as determined by ultraviolet light spectroscopy. Thescientificworldjournal 2010;10:49–61.
72. Paul BK, Kar S, Bandyopadhyay P, et al. Significant enhancement of dielectric and conducting properties of electroactive polymer polyvinylidene fluoride films. An innovative use of Ferrum metallicum at different concentrations. Indian J Res Homoeopathy 2016;10:52–58.
73. Piñeros LG, Pombo LM, Delgado C, et al. Effects of additional agitation process on the spectrophotometric profiles of homeopathic high dilutions. Int J High Dil Res 2016;15:10–21.
74. Sarkar T, Konar A, Sukul NC, et al. Vibrational and Raman spectroscopy provide further evidence in support of free OH groups and hydrogen bond strength underlying difference in two more drugs at ultrahigh dilutions. Int J High Dil Res 2016;15:2–10.
75. Sarkar T, Konar A, Sukul NC, et al. Free water molecules and hydrogen bonding form the basis of variation in

homeopathic potencies as revealed by vibrational spectroscopy. Int J High Dil Res 2015;14:8–15.
76. Sukul NC, Sinhababu SP, Datta SC, et al. Nematotoxic effect of *Acacia auriculiformis* and *Artemisia nilagerica* against root-knot nematodes. Allelopathy J 2001;8:65–72.
77. Sukul NC, Ghosh S, Sukul A, Sinhababu SP. Variation in Fourier Transform Infrared spectra of some homeopathic potencies and their diluent media. J Altern Complement Med 2005;11:807–812.
78. Sukul NC, Datta S, Sinhababu SP. Conformational changes of bovine serum albumin in 4M urea and ultra high dilutions of different drugs. Sci Cult 2007;73:173–175.
79. Taufiq Khan M. Physical aspects related to the problems in potentised drugs. In: Seitschek R, ed. XXVIII. Internationaler Kongress für homöopathische Medizin. Wien: Österreichische Gesellschaft für Homöopathische Medizin, 1973:473–479.
80. Veith H. Dynamics of agitated fluids [In German]. Biologische Medizin 1976;5:123–125.
81. Van Wassenhoven M, Goyens M, Capieaux E, et al. Nanoparticle characterisation of traditional homeopathically manufactured *Cuprum metallicum* and *Gelsemium sempervirens* medicines and controls. Homeopathy 2018; 107:244–263.
82. Wolf U, Wolf M, Heusser P, et al. Homeopathic preparations of quartz, sulfur and copper sulfate assessed by UV-spectroscopy. Evid Based Complement Alternat Med 2011;2011:Article ID 692798.
83. Wurmser L, Loch P. Experimental research on homeopathic dilutions [In French]. In: LHI, ed. X. Kongress der Liga Homoeopathica Internationalis Budapest 1935. Budapest: o. V., 1935:359–373.
84. Zacharias CR. Implications of contaminants to scientific research in homoeopathy. Br Homeopath J 1995;84:3–5.
85. Zacharias CR. Contaminants in commercial homoeopathic medicines. Br Homeopath J 1995;84:71–74.
86. Anagnostatos GS, Pissis P, Viras K, Soutzidou M. Theory and experiments on high dilutions. In: Ernst E, Hahn EG, eds. Homoeopathy—A Critical Appraisal. Oxford: Butterworth-Heinemann, 1998:153–166.
87. Assumpção R. Electrical impedance and HV plasma images of high dilutions of sodium chloride. Homeopathy 2008;97:129–133.
88. Belon P, Elia V, Elia L, et al. Conductometric and calorimetric studies of the serially diluted and agitated solutions—On the combined anomalous effect of time and volume parameters. J Therm Anal Calorim 2008;93:459–469.
89. Betti L, Elia V, Napoli E, et al. Biological effects and physico-chemical properties of extremely diluted aqueous solutions as a function of aging-time. Front Life Sci 2011; 5:117–126.
90. Brucato A, Stephenson J. Dielectric strength testing of homeopathic dilutions of $HgCl_2$. J Am Inst Homeopathy 1966;59:281–286.
91. Cacace CM, Elia L, Elia V, et al. Conductometric and pH metric titrations of extremely diluted solutions using HCl solutions as titrant A molecular model. J Mol Liq 2009; 146:122–126.
92. Elia V, Baiano S, Duro I, et al. Permanent physico-chemical properties of extremely diluted aqueous solutions of homeopathic medicines. Homeopathy 2004;93:144–150.
93. Elia V, Niccoli M. New physico-chemical properties of extremely diluted aqueous solutions. J Therm Anal Calorim 2004;75:815–836.
94. Elia V, Napoli E, Niccoli M, et al. New physico-chemical properties of extremely diluted aqueous solutions—A calorimetric and conductivity study at 25 degrees C. J Therm Anal Calorim 2004;78:331–342.
95. Elia V, Marchese M, Montanino M, et al. Hydrohysteretic phenomena of ''extremely diluted solutions'' induced by mechanical treatments: A calorimetric and conductometric study at 25 degrees C. J Solution Chem 2005;34:947–960.
96. Elia V, Elia L, Napoli E, Niccoli M. Conductometric and calorimetric studies of serially diluted and agitated solutions: The dependence of intensive parameters on volume. Int J Ecodyn 2006;1:361–372.
97. Elia V, Elia L, Cacace P, et al. 'Extremely diluted solutions' as multi-variable systems—A study of calorimetric and conductometric behaviour as a function of the parameter time. J Therm Anal Calorim 2006;84:317–323.
98. Elia V, Elia L, Montanino M, et al. Conductometric studies of the serially diluted and agitated solutions on an anomalous effect that depends on the dilution process. J Mol Liq 2007;135:158–165.
99. Elia V, Elia L, Marchese M, et al. Interaction of ''''extremely diluted solutions'''' with aqueous solutions of hydrochloric acid and sodium hydroxide—A calorimetric study at 298 K. J Mol Liq 2007;130:15–20.
100. Ciavatta L, Elia V, Napoli E, Niccoli M. New physicochemical properties of extremely diluted solutions. Electromotive force measurements of galvanic cells sensible to the activity of NaCl at 25 degrees C. J Solution Chem 2008;37):1037–1049.
101. Elia V, Elia L, Marchettini N, et al. Physico-chemical properties of aqueous extremely diluted solutions in relation to ageing. J Therm Anal Calorim 2008;93:1003–1011.
102. Elia V, Napoli E, Niccoli M. A molecular model of interaction between extremely diluted solutions and NaOH solutions used as titrant. Conductometric and pHmetric titrations. J Mol Liq 2009;148:45–50.
103. Elia V, Napoli E. Dissipative structures in extremely diluted solutions of homeopathic medicines: A molecular model based on physico-chemical and gravimetric evidences. Int J Des Nat Ecodyn 2010;5:39–48.
104. Elia V, Napoli E, Niccoli M. Thermodynamic parameters for the binding process of the OH- ion with the dissipative structures. Calorimetric and conductometric titrations. J Therm Anal Calorim 2010;102:1111–1118.
105. Elia V, Marrari LA, Napoli E. Aqueous nanostructures in water induced by electromagnetic fields emitted by EDS: A conductometric study of fullerene and carbon nanotube EDS. J Therm Anal Calorim 2012;107:843–851.
106. Elia V, Napoli E, Niccoli M. On the stability of extremely diluted solutions to temperature. J Therm Anal Calorim 2013;113:963–970.
107. Elia V, Marchettini N, Napoli E, Niccoli M. The role of ethanol in extremely diluted solutions. J Therm Anal Calorim 2014;116:477–483.
108. Gay A. Presence of a physical factor in homeopathic dilutions [In French]. Lyon: Editions des Laboratoires P.H.R., 1951.
109. Holandino C, Leal FD, de Olivereira Barcellos B, et al. Chapter 3: Mechanical versus handmade succussions, A physical chemistry comparison. In: Bonamin LV, ed. Signals and Images. Contributions and Contradictions About High Dilution Research. New York: Springer, 2008:37–48.

110. Holandino C, Harduim R, da Veiga VF, et al. Modeling physical-chemical properties of high dilutions, An electrical conductivity study. Int J High Dil Res 2008;7:165–173.
111. Knauer H. Proof of effects of potentised solutions by physicochemical means [In German]. Acta Homoeopath 1969;13:157–164.
112. Knauer H. Contributions to potency research [In German]. Pforzheim, 1970.
113. Mahata CR. Dielectric dispersion studies of some potentised homeopathic medicines reveal structured vehicle. Homeopathy 2013;102:262–267.
114. Ramos de Miranda A. Water and ultra high dilutions, characterization and phenomenology. In: GIRI, ed. 22nd GIRI Meeting, Tuesday, May 20, 2008, Monte Carlo. Monte Carlo: Eigenverlag, 2008:3.
115. Süss WG. Structure and dynamics of high homeopathic potencies—resonance/damping/dedamping measurements (REDEM) [In German]. In: Süss WG, ed. Homöopathische Arzneimittel—wissenschaftliche Grundlagen für die Herstellung, Qualität und Anwendung. Stuttgart: Deutscher Apotheker Verlag, 2004:49–63.
116. Walach H, van Asseldonk T, Bourkas P, et al. Electric measurement of ultra-high dilutions—A blinded controlled experiment. Br Homoeopath J 1998;87:3–12.
117. Witt C. Attempt to measure an immaterial information [In German]. In: Albrecht H, Frühwald M, eds. Jahrbuch Karl und Veronica Carstens-Stiftung. Vol 2. Stuttgart: Hippokrates, 1995:153–165.
118. Witt C, Lüdtke R, Weisshuhn TE, Willich SN. High homeopathic potencies are different from potentized solvent when investigated with the REDEM technology. Forsch Komplementarmed Klass Naturheilkd 2005;12:6–13.
119. Anagnostatos GS, Pisses P, Viras K, Provata M. Theory and experiments on high dilutions. In: Ernst E, Hahn EG, eds. Homoeopathy—A Critical Appraisal. Oxford: Butterworth-Heinemann, 1998:153–166.
120. Witt C. Physical investigation of high homeopathic potencies [In German]. Essen: KVC Verlag, 2000.
121. Resch G, Gutmann V, Schauer H. The shaking effect on the conductivities of liquids. J Ind Chem Soc 1982;59:130–132.
122. Elia V, Napoli E, Niccoli M. On the stability of extremely diluted aqueous solutions at high ionic strength—A calorimetric study at 298 K. J Therm Anal Calorim 2008;92: 643–648.
123. Bonet-Maury P, Deysine A, Vogeli L-M. Investigation of homeopathic dilutions by radioisotopes [In French]. Ann Pharm Franc 1954;12:654–663.
124. Frisse R. Investigation of adsorption and analysis by neutron activation of homeopathic dilutions [In German]. [Thesis] Bonn: Hohe Mathematisch-Naturwissenschaftliche Fakultät, Rheinische Friedrich-Wilhelms-Universität, 1981.
125. Holandino C, Oliveira AP, Homsani F, et al. Structural and thermal analyses of zinc and lactose in homeopathic triturated systems. Homeopathy 2017;106:160–170.
126. Lefebvre N, Aubin M, Ferret-Bouin Y, Vrignaud C. Etude de dilutions homéopathiques hahnémanniennes à l'aide du glucose marqué au carbone 14. Ann Hom Franc 1978;20: 227–235.
127. Pillai MG, Kumar A, Sharma R, Bhasin N. LC-MS based workflows for qualitative and quantitative analysis for homeopathic preparation of hydrastis canadensis. Chromatographia 2014;77:119–131.
128. Witt CM, Lüdtke R, Weisshuhn TER, et al. The role of trace elements in homeopathic preparations and the influence of container material, storage duration, and potentisation. Forsch Komplementarmed Klass Naturheilkd 2006;13:15–21.
129. Kar S, Chakraborty M, Nandy P, et al. Characterization and haemocompatibility of *Aurum metallicum* for its potential therapeutic application. Ind J Res Hom 2017;11: 41–47.
130. Mayrhofer C. Microscopic investigations of homeopathic metal preparations. Illustrated by drawings [In German]. Hygea 1842;16:17–35.
131. Mayrhofer C. Microscopic investigations of homeopathic metal preparations [In German]. Hygea 1842;16:97–106.
132. Temgire MK, Suresh AK, Kane SG, Bellare JR. Establishing the interfacial nano-structure and elemental composition of homeopathic medicines based on inorganic salts: A scientific approach. Homeopathy 2016;105:160–172.
133. Bell IR, Lewis DA, Brooks AJ, et al. Gas discharge visualization evaluation of ultramolecular doses of homeopathic medicines under blinded, controlled conditions. J Altern Complement Med 2003;9:25–38.
134. Jerman I, Berden M, Škarja M. Instrumental measurements of different homeopathic dilutions of potassium iodide in water. Acupunct Electrother Res 1999;24: 29–44.
135. Lenger K. Homeopathic potencies identified by a new magnetic resonance method: Homeopathy—An energetic medicine. Subtle Energies Energy Med 2004;15:225–243.
136. Nain AK, Droliya P, Manchanda RK, et al. Physicochemical studies of homoeopathic formulations (extremely diluted solutions) of acidum salicylicum in ethanol by using volumetric, acoustic, viscometric and refractive index measurements at 298.15, 308.15, 318.15 K. J Mol Liq 2016;215:680–690.
137. Nain AK, Droliya P, Manchanda RK, et al. Physicochemical studies of extremely diluted solutions (homoeopathic formulations) of sulphur in ethanol by using volumetric, acoustic, viscometric and refractive index measurements at different temperatures. J Mol Liq 2015; 211:1082–1094.
138. Silvio M, Arnaldo P. Ultrasonic study of homoeopathic solutions. Br Homoeopath J 1990;79:212–216.
139. Bhattacharyya SS, Mandal SK, Biswas R, et al. In vitro studies demonstrate anticancer activity of an alkaloid of the plant *Gelsemium sempervirens*. Exp Biol Med 2008; 233:1591–1601.
140. Güldenstern W. Measurements of fluorescence of the preparation Aesculus Cortex and of the drug Aesculinum [In German]. Der Merkurstab 2001;54:307–312.
141. Lenger K, Bajpai RP, Drexel M. Delayed luminescence of high homeopathic potencies on sugar globuli. Homeopathy 2008;97:134–140.
142. Lenger K, Bajpai RP, Spielmann M. Identification of unknown homeopathic remedies by delayed luminescence. Cell Biochem Biophys 2014;68:321–334.
143. Lobyshev VI, Tomkevitch MS. Luminescence study of homeopathic remedies. In: Priezzhev AV, Coté GL, eds. Optical Diagnostics and Sensing of Biological Fluids and Glucose and Cholesterol Monitoring, Vol. 4263. Moscow: SPIE, 2001:59–64.
144. Lobyshev VI, Tomkevich MS, Petrushanko IY. Experimental study of potentiated aqueous solutions. Biophysics 2005;50:416–420.
145. Sharma A, Purkait B. Identification of medicinally active ingredient in ultradiluted *Digitalis purpurea*: Fluorescence

spectroscopic and cyclic-voltammetric study. J Anal Methods Chem 2012; DOI: 10.1155/2012/109058.
146. Rey L. Thermoluminescence of ultra-high dilutions of lithium chloride and sodium chloride. Phys A 2003;323: 67–74.
147. Rey L. Can low-temperature thermoluminescence cast light on the nature of ultra-high dilutions? Homeopathy 2007;96:170–174.
148. van Wijk R, Bosman S, van Wijk EPA. Thermoluminescence in ultra-high dilution research. J Altern Complement Med 2006;12:437–443.
149. Konar A, Sarkar T, Chakraborty I, et al. Raman spectroscopy reveals variation in free OH groups and hydrogen bond strength in ultrahigh dilutions. Int J High Dil Res 2016;15:2–9.
150. Luu-d-Vinh C. Homeopathic dilutions, control and study using Raman spectroscopy [In French]. Montpellier: Université de Montpellier, Faculté de Pharmacie et Institut Européen des Sciences Pharmaceutiques Industrielles, 1974.
151. Sarkar T, Konar A, Sukul NC, et al. Raman spectroscopy shows difference in drugs at ultrahigh dilution prepared with stepwise mechanical agitation. Int J High Dil Res 2016;15:2–9.
152. Dragan G. Some consideration of coherency in topoenergetic terms, I. high-resolution mixing calorimetry (HRMC) experiments on aqueous solutions. J Therm Anal 1992;38:1497–1508.
153. Elia V, Niccoli M. Thermodynamics of extremely diluted aqueous solutions. Ann N Y Acad Sci 1999;827:241–248.
154. Elia V, Niccoli M. New physico-chemical properties of water induced by mechanical treatments. A calorimetric study at 25°C. J Therm Anal Calorim 2000;61:527–537.
155. Kolisko L. Physiological and physical proof of effectiveness of smallest entities (1923–1959) [In German]. Stuttgart: Arbeitsgemeinschaft anthroposophischer Ärzte, 1959.
156. Maag GW. Investigation of potencies 1x–12x and 1x–33x of silver nitrate [In German]. Dt Z Hom 1932;49:277–285.
157. Maag GW. Investigation of the succession duration of metal potencies [In German]. Dt Z Hom 1933;49:281–286.
158. Bandyopadhyay P, Basu R, Das S, et al. Enhancement of quantum efficiency of a dye-sensitized electrochemical cell by using triturated zinc oxide mixed with two organic dyes, Azure C and Rose bengal. Int J High Dil Res 2017; 16:1–6.
159. Beier K. On physical effects or properties of true high homeopathic potencies [In German]. Leipzig: Universität Leipzig, Med. Fakultät, 1953.
160. Heintz E. A new arrangement to measure physicochemical effects of potencies: the D-probe [In German]. Elemente der Naturwissenschaft 1971;15:33–44.
161. Zembrzuski W, Karbowska B. Determination of Tl(I) ions in homeopathic drugs by differential pulse anodic stripping voltammetry. Indian J Pharm Educ Res 2017;51: 620–625.
162. Elia V, Napoli E, Niccoli M, et al. New physico-chemical properties of extremely dilute solutions. A conductivity study at 25 degrees C in relation to ageing. J Solution Chem 2008;37:85–96.
163. Rheinberger H-J. Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube. Vol 32. Stanford, USA: Stanford University Press, 1997.
164. Ücker A, Baumgartner S, Sokol A, et al. Systematic review of plant-based homeopathic basic research: An update. Homeopathy 2018;107:115–129.
165. Franks F. Water, a Comprehensive Treatise: Aqueous Solutions of Simple Electrolytes. New York, USA: Plenum Press, 1972.
166. Hertz HG. Nuclear magnetic relaxation spectroscopy. In: Franks F, ed. Water, a Comprehensive Treatise: Aqueous Solutions of Simple Electrolytes. New York, USA: Plenum Press, 1972:301–399.
167. Keutsch FN, Saykally RJ. Water clusters: Untangling the mysteries of the liquid, one molecule at a time. Proc Natl Acad Sci U S A 2001;98:10533–10540.
168. Cowan ML, Bruner BD, Huse N, et al. Ultrafast memory loss and energy redistribution in the hydrogen bond network of liquid H_2O. Nature 2005;434:199–202.
169. Del Giudice E. Old and new views on the structure of matter and the special case of living matter. Third International Workshop DICE2006—Quantum Mechanics between Decoherence and Determinism: New Aspects from Particle Physics to Cosmology. J Phys Conf Ser 2007;67: U63–U69.
170. Del Giudice E, Galimberti A, Gamberale L, Preparata G. Electrodynamical coherence in water: A possible origin of the tetrahedral coordination. Mod Phys Lett B 1995;9: 953–961.
171. Yinnon TA, Liu ZQ. Domains formation mediated by electromagnetic fields in very dilute aqueous solutions: 2. Quantum electrodynamic analyses of experimental data on strong electrolyte solutions. Water J 2015;7:48–69.
172. Korotkov KG, Matravers P, Orlov DV, Williams BO. Application of electrophoton capture (EPC) analysis based on gas discharge visualization (GDV) technique in medicine: A systematic review. J Altern Complement Med 2010;16:13–25.
173. Kokornaczyk MO, Scherr C, Bodrova NB, Baumgartner S. Phase-transition-induced pattern formation applied to basic research on homeopathy: A systematic review. Homeopathy 2018;107:181–188.
174. Kokornaczyk MO, Würtenberger S, Baumgartner S. Phenomenological characterization of low-potency homeopathic preparations by means of pattern formation in evaporating droplets. Homeopathy 2019;108:108–120.
175. Kokornaczyk MO, Würtenberger S, Baumgartner S. Impact of succussion on pharmaceutical preparations analyzed by means of patterns from evaporated droplets. Sci Rep 2020;10:570.
176. Bell IR. The complexity of the homeopathic healing response part 2: The role of the homeopathic simillimum as a complex system in initiating recovery from disease. Homeopathy 2020;109:51–64.
177. Walach H. Generalized entanglement: A new theoretical model for understanding the effects of complementary and alternative medicine. J Altern Complement Med 2005;11: 549–559.

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