Effects of homeopathic high dilutions on *in vitro* models: literature review

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Abstract

Background: the effects of homeopathic high dilutions (HDs) are controversial because they exceed Avogadro's number. Aim: to perform a literature review on the effects of HDs on *in vitro* models. Methods: a systematic search was performed in database PubMed for studies assessing simple HDs on *in vitro* models published from 2007 onward. Results: 28 publications met the inclusion/exclusion criteria; 26 studies demonstrated patent effects of simple HDs on *in vitro* models; most such studies were conducted in countries where homeopathy attained a high level of institutionalization. Conclusions: *in vitro* models patently evidence biological activity of HDs above Avogadro's number and account for effects found in clinical practice. Most studies were conducted in countries where homeopathy is officially recognized, which facilitates access to resources for the development of research.

Keywords

Homeopathy; High dilutions; *In vitro* models; Review

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Introduction

As is known, the action of homeopathic medicines is considered implausible by a part of the scientific community, because they are diluted above Avogadro's number (6 x 10^{-23}). Therefore, the odds of detecting one single molecule in dilutions are practically zero, for which reason homeopathic high dilutions (HDs) cannot have any physical-chemical activity whatsoever [1].

However, countless experimental models sought to explain the effects of HDs in clinical practice and laboratory research. One of such attempts is the so-called "weak quantum theory": based on original research by Atmanspacher et al. [2], several studies suggest that the effects of HDs do not involve local interactions (causal) but a kind of interconnection modeled on the entanglement exhibited by subatomic particles with a common origin [3-7].

According to other authors, the actions of HDs should be understood based on the interaction of starting material and solvent. The information contained in the former is somehow transferred to the latter, which then carries it to the biological target. Indeed, several studies demonstrated measurable physical changes in HDs, including thermoluminescence [8], luminescence delay [9], dielectric dispersion [10,11], fluorescence [12], ultraviolet light transmission [13,14], magnetic properties [15], impedance and other electrical properties [16-18], analogy to spin supercurrents in superfluids [19] and aqueous nanodomain formation [20]. It is worth to call the attention to the studies on proton NMR relaxation started in 1985 [21] and the more than 20 years of research on electromagnetism [7]. A more recent study gathered evidences of the presence of stable water nanostructures in homeopathic HDs through Fourier-transform infrared spectroscopy, visible ultraviolet spectroscopy, fluorescence microscopy and atomic-force microscopy [22].

These studies notwithstanding, the questions on the biological action of HDs remain unanswered. In this regard, a systematic literature review of *in vitro* studies was published in 2007 [23]. *In vitro* studies are free from the complexity and confounding factors inherent to *in vivo* models and clinical trials. In addition, *in vitro* models provide the grounds for the latter and might explain their underlying mechanisms, as well as effects observed in clinical practice. However, the aim of Witt et al.'s review [23] was mainly to assess the methodological quality of studies, rather than their results. The aim of the present study was to perform a descriptive review of publications reporting on *in vitro* effects of simple HDs from 2007 to the present time.

Materials and methods

A search was conducted in February 2017 for articles included in database PubMed published from 2007 onward in any language, using keywords "homeopathy" AND "in vitro". Term "homeopathy" was used because there is no consensus in the literature on how to designate homeopathic HDs (e.g., dynamizations, potencies, serial agitated dilutions, infinitesimal dilutions, etc.). The time frame was established considering that a similar review was published in 2007.

Inclusion criteria: articles describing original research on the effects of simple (not combined) HDs on *in vitro* models. Studies published "ahead of print" in journals included in PubMed were considered.

This search strategy was selected to facilitate direct assessment of the included articles by interested readers, as well as to ensure the methodological quality of the studies (inclusion in database PubMed). For this reason other sources of information were not considered, such as other databases, manual search of references, direct contact with authors, etc.

The analyzed parameters were: 1) country of origin; 2) study aims; 3) tested medicine(s); 4) HD level; 5) experimental model; and 6) effects of HDs compared to controls (positive/negative).

Results

A total of 61 records were located, which were subjected to title and abstract analysis. As a result, 33 records were excluded, because they did not meet the inclusion criteria. After addition of "ahead of print" published articles, 28 studies were included in the present review. The summary of findings is described in Table 1.

Table 1. Summary of findings in *in vitro* studies conducted with homeopathic high dilutions

Author, year	Country	Aims	Medicines	Dilutions	Experimental model	Effects
Santana et al., 2017 [24]	Brazil	Mechanism of anti-inflammatory action	Antimonium crudum	30cH, 200cH	Macrophage-Leishmania amazonensis co-culture	POSITIVE Reduction followed by increase of macrophage spreading; increased percent parasite internalization; potentiation of parasite-induced reduction of cytokine production
Lima et al., 2016a [25]	Brazil	FSH in HD vs. FSH in ponderable dose	FSH	6cH	Ovine preantral follicle development	POSITIVE Increase of follicle diameter; increased survival rate; greater follicle activation rate on day 1
Lima et al., 2016b [26]	Brazil	FSH in HD vs. FSH in ponderable dose vs. 0.2% alcohol	FSH	6cH	Development, hormone production and gene expression in isolated bovine preantral follicles with or without culture medium addition	POSITIVE On cell proliferation, the effect of 0.2% alcohol was greater vs. FSH 6cH, in turn greater to FSH in ponderable dose; estradiol production increased with all treatments; FSH 6cH induced greater connexin 43 production than FSH in ponderable dose

Wani et al., 2016 [27]	India	Anticancer activity	Terminalia chebula	MT, 6x, 6c, 30c	MDAMB-231 and MCF-7 breast cancer cells, and HEK-293 non-cancer cells; nanoparticles	POSITIVE HDs reduced the viability of cancer cells only; all tested HDs reduced the growth kinetics of cancer cells; nanoparticle structure of HD 6cH differed from MT, with particles of 20 nm of diameter
Mondal et al., 2016 [28]	India	Anticancer activity	Psorinum	6x	A549 human lung epithelial adenocarcino-ma cells	POSITIVE Inhibition of cell proliferation; cell cycle arrest in sub-G; ROS production; mitochondrial membrane depolarization; DNA damage; promotion of apoptosis through caspase-dependent, mitochondria-mediated pathway
Lee et al., 2016 [29]	South Korea	Inflammation modulation	Rhus toxicodendron	4d, 30x, 30c, 200c	Mc3t3-E 1 murine pre-osteoblastic cells	POSITIVE Increased COX-2 mRNA and protein expression; increase of PgE2; reduced NO production
Pasetti et al., 2016 [30]	Brazil	Bacterial resistance	Belladonna, nosode	6c, 30c	MRSA	POSITIVE Inhibition of MRSA growth with reduction of DNAse production; increased susceptibility to oxacillin
Guedes et al., 2016 [31]	Brazil	Amphibian metamorphosis	T3	10cH	Rana (Lithobates) catesbeianus tail explants	POSITIVE T3 10cH influenced T3-induced caspase 3 and 7 mRNA expression, with delay of tadpole metamorphosis
Tupe et al., 2015 [32]	India	Protein glycation	Syzygium jambolanum, Cephalandra indica	MT, 30c, 200c	Human red blood cells	POSITIVE Reduction of glycation markers (fructosamine, protein carbonyls and protein-attached sugar); protection against free thiol and amino groups. Phenols and flavonoids were detected in all samples
Samadder et al., 2015 [33]	India	Anticancer activity	Lycopodium clavatum	5c, 15c	HeLa cervical cancer cells and PBMC	POSITIVE Reduced proliferation and viability of cancer cells, without cytotoxicity on normal PBMC; considerable apoptosis of cancer cells, with DNA fragmentation, increased caspase 3 and Bax protein expression, reduction of Bcl2, Apaf and citochrome c release. Effect similar to cisplatin on cancer cell survival

Marzotto et al., 2014 [34]	Italy	Gene expression regulation	Gelsemium sempervirens	2c, 3c, 5c, 9c, 30c	SH-SY5Y human neuroblastoma	POSITIVE Changes in the expression of 56 genes on microarray test
Olioso et al., 2014 [35]	Italy	Gene expression regulation	Gelsemium sempervirens	2c	SH-SY5Y human neuroblastoma	POSITIVE Downregulation of most genes in a human neurotransmitter and regulator panel
Siqueira et al., 2013 [36]	Brazil	Effect of influenza virus nosode	Influenza A (A/Aichi/2/68 H3N2)	30x	Biological risk; viral content; effect on MDCK cells and J774G8 murine macrophages	POSITIVE No cytotoxicity; morphological changes in MDCK; changes in MDCK mitochondrial activity; reduced PFK-1 activity in MDCK; increased TNF-α production by macrophages
Huh et al., 2013 [37]	South Korea	Anti-inflammatory activity	Rhus toxicodendron	4x, 30x, 30c, 200c	Primary culture of mice chondrocytes	POSITIVE Increased COX-2 mRNA expression; but for 200c, all HDs inhibited collagen II expression, suggesting chondrocyte dedifferentiation; 30x increased PgE2 release
Lima et al., 2013 [38]	Brazil	Effect of FSH in HD	FSH	6cH, 12cH, 30cH	Survival, activation and growth of ovine preantral follicles	POSITIVE Increased follicle survival and activity; greater follicle and oocyte growth compared to controls; maintenance of follicle viability and ultrastructural integrity after 7-day culture
Mukerjee et al., 2013 [39]	India	Anticancer effect	Thuja occidentalis	30cH	Benzopyrene-induced DNA damage in mice perfused lung cells	POSITIVE Increased cell viability; inhibition of benzopyrene-induced stress through ROS and HSP-90 reduction and glutathione increase
Bishayee et al., 2013 [40]	India	Anticancer action mechanism	Condurango	30cH	Modulation of histone acetylation/dea-cetylation in HeLa human cervical carcinoma cells	POSITIVE Cytotoxic effect; reduced HDAC2 activity; reduced DNA synthesis and cycle cell arrest in G1
Arora et al., 2013 [41]	India	Anticancer action	Sarsaparilla, Ruta graveolens, Phytolacca decandra	30cH, 200cH, 1000cH, 10000 cH	Kidney adenocarcino-ma ACHN (Sars), colorectal carcinoma COLO-205 (Ruta), breast carcinoma MCF-7 (Phyt)	POSITIVE Cytotoxic effect; reduced cell proliferation; apoptosis induction; no effect on non-cancer MDCK cells (Sars)
Preethi et al., 2012 [42]	India	Anticancer action mechanism	Ruta graveolens, Carcinosum, Hydrastis canadensis, Thuja	200c, 1000c	Dalton's lymphoma ascites	POSITIVE Apoptosis induction

			occidentalis			
Ive et al., 2012 [43]	South Africa	Intoxication self-recovery	Arsenicum album	6cH, 30cH, 200cH	MT4 human lymphocytes exposed to arsenic trioxide (As_2O_3)	POSITIVE Increase cell viability; maximum effect 3 days after treatment with Ars 200cH
Oliveira et al., 2012 [44]	Brazil	Immune effects	Mercurius solubilis	6cH, 12cH, 30cH	Mice peritoneal macrophages	POSITIVE Morphological changes typical of the activated state; increased IFNχ and IL-4 secretion; increased NO and ROS production
Das et al., 2012 [45]	India	Gene expression	Arnica montana	30c	Escherichia coli subjected to ultraviolet irradiation	POSITIVE Reduction of DNA damage and oxidative stress; upregulation of gene repair genes
De et al., 2012 [46]	India	Intoxication self-recovery	Arsenicum album	30c	Escherichia coli exposed to sodium arsenine	POSITIVE Reduction of intoxication effects through inhibition of ROS production
Soto et al., 2011 [47]	Brazil	Cell viability	Avena sativa, Pulsatilla nigricans alone and combined	6cH	Sperm motility; cell membrane and acrosome integrity; mitochondrial membrane potential in swine sperm	NEGATIVE
Frenkel et al., 2011 [48]	USA	Anticancer effect	Carcinosinum, Phytolacca decandra, Conium maculatum, Thuja occidentalis	Carc 30c, Con 3c, Phyt 200c, Thuj 30c	MCF-7 (E+ P+) and MDAMB-231 (E- P-) human breast adenocarcinoma	POSITIVE Reduced cell viability; cycle arrest in G1. Carc and Phyt activity equivalent to 0.12 μM paclitaxel
Hofbauer et al. 2010 [49]	Austria	Mechanism of action in gastric ulcer	Nux vomica, Calendula officinalis	10c, 12c	KATO-III human gastric carcinoma cells	POSITIVE Reduced gene expression of H. pylori-induced heparin-binding epidermal growth factor
Patil et al. 2009 [50]	India	Immunomodulating action	Rhus toxicodendron	6cH, 30cH, 200cH, 1000cH	Human PMN function	POSITIVE Increased chemotaxis; increase of oxidative processes; intracellular fungicide action against C. albicans
Stiegling-Vlitalis et al., 2009 [51]	Germany	Physiological effect	Atropine	6x, 32x, 100x	Rat isolated ileum contractility	NEGATIVE

HD: high dilution; FSH: follicle-stimulating hormone; PMN: polymorphonuclear cells; C. albicans: *Candida albicans*; ROS: reactive oxygen species; HSP-90: heat shock protein 90; HDAC2: histone deacetylase 2; USA: United States of America; E+/E-: estrogen receptor positive/negative; P+/P-: progesterone receptor positive/negative; COX-2: cyclooxygenase 2; PgE2: prostaglandin E2; PFK-1: 6-phosphofructo-1-kinase; TNF-α: tumor necrosis factor alpha; IFNχ: gamma interferon; IL: interleukin; NO: nitric oxide; MT: mother tincture; PBMN: peripheral blood mononuclear cells; mRNA: messenger RNA; H. pylori: *Helicobacter pylori*; MRSA: Methicillin resistant *Staphylococcus aureus*; T3: triiodothyronine; L. amazonensis: *Leishmania (L.) amazonensis*

Discussion

One single previous review on *in vitro* HDs effects was published by Witt el. in 2007 [23]. In that review, *in vitro* effects were defined as the ones induced by HDs on molecular or cellular systems; the same definition was used in the present review. However these 2 studies differ as to their aims: Witt et al. sought to analyze the quality of studies through a score. In turn, we sought to establish whether HDs induce evident effects on *in vitro* models, as the results have more objective and less complexity compared to *in vivo* models and clinical trials and reproduce effects observed in clinical practice and laboratory research.

The present review included 28 studies that met the inclusion criteria, corresponding to 2.8 studies/year, on average. The previous review by Witt el al. located 67 studies, being 46 published in peer-reviewed journals from 1932 to 2005, corresponding to 0.63 articles/year [23]. Therefore, one might infer that the publication rate considerably increased in the past decade, in parallel to the greater institutionalization of homeopathy in many countries. In addition, 19 studies conducted with HDs above Avogadro's number published from 2010 to 2015 were replications of previous experiments [52-53].

The vast majority of the analyzed studies (n= 20; 71.4%) were performed in just 2 countries, Brazil (n= 9; 32.1%) and India (n= 11; 39.3%); the remainder of the studies was conducted in South Korea (n= 2), Italy (n= 2), South Africa, USA, Austria and Germany (n= 1, respectively). Predominance of Brazilian and Indian studies was previously reported [54]. As reasons, one might mention the high degree of institutionalization of homeopathy in these 2 countries, being homeopathy acknowledged as an official medical specialty, included in the public health system and health insurance. In addition, homeopathy (clinical and pharmaceutics) is taught at universities, which facilitates the access to resources for research.

Both experimental models and parameters exhibited wide heterogeneity. In this regard, the results of the present review agree with the ones reported by Witt et al. [23]. In addition, some of the articles reported on later stages of long-term research projects, some of them started in the 1990s.

Within such context, the studies conducted by Guedes et al., at School of Medicine, University of São Paulo, and a European multicenter group chaired by Endler, Interuniversity College for Health and Development, Graz, Austria, stand out. Tadpole metamorphosis is a highly complex and well-studied process, highly sensitive to thyroid hormones. Tadpole tail resorption is a focus of much interest among researchers as experimental system for the study of cell death [55]. Along more than 25 years, Endler et al. conducted countless multicenter experiments with many variations of the basic parameters to prove the hypothesis that non-molecular information is conveyed in biological systems [56]. In addition to showing that thyroxin (T4) in HD slows down metamorphosis in *Rana temporaria*, those authors succeeded in establishing a highly reproducible experimental model [53,57]. In turn, the group chaired by Guedes confirmed Endler et al.'s findings in another species, *Rana catesbeiana,* and also showed that triiodothyronine (T3) in HD alters the effect of T3 in pharmacological dose on apoptosis [31, 58-60].

Among the analyzed studies, the ones on the effects and mechanisms of action of HDs in cancer stand out (n= 8; 28.6%), having their point of departure in research started by

Khuda-Bukhsh more than 35 years ago in India [61]. Khuda-Bukhsh was chair of Department of Zoology, Kalyani University, India, and currently is emeritus professor at the same school, having published 118 studies in reputed scientific journals. Still regarding studies on cancer, the one conducted by Frenkel et al. [48] at the prestigious MD Anderson Center, Houston, TX, USA, is deserving of mention. We should further observe that the activity of HDs was equivalent to the one of standard chemotherapy agents, such as cisplatin and paclitaxel [33,48].

The analyzed studies tested a wide variation of HDs in decimal and centesimal scale; in the vast majority of cases HDs exceeded Avogadro's number. The HD most frequently used was 30cH (10^{-60}) (n= 18), followed by 6cH (10^{-12}) and 200c (10^{-400}), corresponding to 9 studies each.

In relation to the recent identification of nanoparticles (NPs) in HDs [62,63] one study investigated the nanoparticle structure of HD and found differences between mother tincture and dilution 6cH; the latter exhibited NPs with 20 nm of diameter [27]. Curiously, one study reported presence of phenol and flavonoid traces even in HD [32].

In Witt et al.'s review, 76% of the studies reported positive outcomes [23]. Differently, in our review only 7.14% of the studies did not detect any effect of the tested HD. One of those studies [47] sought to establish the mechanism of the beneficial action of homeopathic medicines *Avena sativa* and *Pulsatilla nigricans* to improve human and animal fertility [64,65]. The results indicated that such effect might not be attributed to action on the sperm viability.

The other study [51] is the last in a series started in the 1990s on the effects of HD on well-established physiological models, namely, parasympathetic transmitters. In 1997, Cristea et al. [66] reported action of HD of *Belladonna* – homeopathic medicine prepared from *Atropa belladonna* L., the main alkaloid of which is atropine – on rat isolated duodenum contractility. This study was replicated 3 times, including 2 doctoral dissertations defended at Leipzig University, Germany [67-69]. More recently, Nieber et al. [70] tested atropine and *Belladonna* 100d (10^{-100}) on rat isolated ileum; both HD reduced the amplitude of contractions. Similarly, Alecu et al. [71], from Cluj-Napoca University, Romania, tested the possible action of *Belladonna* 7cH (10^{-14}) as antagonist to pilocarpine-induced muscarinic receptor blockade. The results showed that administration of *Belladonna* 7cH after atropine and before pilocarpine reestablished saliva hypersecretion in rats (< 0.0001). Differently, Siegling-Vlatikis et al. [51] did not detect any effect of atropine 6d, 32d or 100d on acetylcholine-induced isolated ileum contractility in rats.

Many different cellular and subcellular actions were evidenced, reiterating results obtained in clinical practice and *in vivo* animal models. The studies by Lima et al., State University of Ceará, Brazil, showed that follicle-stimulating hormone (FSH) 6cH (10^{-12}) increases the viability, survival rate, early activation rate and hormone production in ovine preantral follicles [25,26,38].

Several studies reported reduction of cancer cell viability, with inhibition of cell proliferation, cell cycle arrest, production of reactive oxygen species (ROS), mitochondrial membrane depolarization, DNA damage, promotion of apoptosis and interference in DNA acetylation/deacetylation [27,28,33,39-42,48].

Similarly, HD were shown to modulate gene and protein expression. In regard to inflammation, studies reported increased expression of cyclooxygenase (COX)-2 mRNA, with increased prostaglandin (Pg) E2 production [29, 37]. In a long series of studies (35, 72-75), the group chaired by Bellavite, University of Verona, Italy, approached the anxiolytic action of homeopathic medicine *Gelsemium sempervirens*. Through sophisticate techniques, such as microarray assay, these authors showed that such action is due to regulation of several genes involved in the mechanism underlying anxiety [35,76].

To be sure, Khuda Bukhsh had suggested 20 years ago that HD act through regulation of gene expression [77]. This hypothesis was tested in dozens of experiments in a wide variety of models. In 2013, it was effectively shown, by means of microarray assay, that the effect of *Condurango* 30cH and *Hydrastis canadensis* 30cH on the gene expression profile of HeLa cells was significantly different compared to placebo in regard to more than 100 genes [78].

As another example of research conducted with *in vitro* biological models, the pioneering work by Passeti et al., Federal University of ABC, São Paulo, Brazil, deserves particular mention. These authors showed that homeopathic (*Belladonna*) and isopathic (diluted and agitated bacteria) HD increase the sensitivity of methicillin-resistant *Staphylococcus aureus* (MRSA) to oxacillin. This group of researchers had previously demonstrated that these same medicines in dilutions 12cH and 30cH were able to significantly inhibit *in vitro* growth of *Streptococcus pyogenes*, while *Arnica montana* promoted bacterial growth [79]. One needs not emphasize the relevance of these findings in the present time, when the presence of multidrug resistant bacteria is felt in everyday clinical practice.

Still concerning infectious diseases, Holandino et al. [80], from Federal University of Rio de Janeiro (UFRJ), have for some time been testing a nosode prepared from the influenza virus. Their studies evidenced a protector effect in clinical practice, which might be accounted for by the action of this medicine in various steps of the anti-infection response, including macrophage activation. Macrophages were also analyzed in a study by Oliveira et al. [81}, in which *Mercurius solubilis* induced morphologic changes typical of the activated state of these cells, increased interferon (IFN)γ and interleukin (IL) 4 secretion and increased nitric oxide (NO) and ROS production.

In turn, Bonamin et al. [82], from Paulista University, São Paulo, Brazil, sought to explain how *Antimonium crudum* develops its previously demonstrated *in vivo* anti-inflammatory and immunomodulating effect (reduced monocyte migration to the infection site; increase of the B cell population in the local lymph nodes). The results showed that *Antimonium crudum* increases macrophage spreading and parasite (*Leishmania amazonensis*) internalization in macrophages, while it has no effect on parasite intracellular digestion, i.e., it has no parasiticide properties. However, production of chemokines (CCCL2) able to attract monocytes is inhibited by treatment. The final result is inhibition of the parasite cycle in the host tissue. This example shows how data gathered in *in vitro* fundamental research, by providing information on the mechanism of action of medicines on the parasite-host relationship, might help clinical practitioners find adequate treatment protocols, particularly when the epidemic genius is used as ground for population-based treatment.

Similarly, relative to leukocytes, Patil et al. [83] found increase of chemotaxis, oxidative processes and intracellular fungicide action against *Candida albicans* with treatment with *Rhus toxicondrendon*, a medicine known for its anti-inflammatory action.

Conclusions

In vitro studies indisputably demonstrate the biological activity of HD above Avogadro's number and account for their effect in clinical practice. Most of the analyzed studies were conducted in countries in which homeopathy is officially recognized, which facilitates the access to resources for research. The information gathered at the cell level helps explain the cell regulation mechanisms triggered by homeopathic treatment. This information might contribute to improve clinical protocols and also understand their limitations.

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