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OBM Integrative and Complementary Medicine

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Review

The Science of the "Simile"

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Academic Editor: Bruno Galeazzi

Special Issue: Homeopathy

OBM Integrative and Complementary Medicine
2021, volume 6, issue 3
doi:10.21926/obm.icm.2103023

Received: April 20, 2021
Accepted: June 29, 2021
Published: August 11, 2021

Abstract

Homeopathy is often attacked with claims of not being evidence-based or for the implausible nature of its major principles of dilution/potentization and/or the similars ("*similia similibus curentur*"). However, these statements have already been falsified on the experimental ground, besides being incorrect on an epistemological level. Here we provide an updated appraisal of the scientific approach to the principle of Similars and homeopathy, focusing on laboratory models. After a brief historical introduction concerning the early scientific investigations, some recent *in vitro* studies are reviewed, with particular reference to those from our group. The second part is devoted to explaining the homeopathic principle of Similars using conceptual models in the field of complexity science and the theory of dynamic systems.

Keywords

Homeopathy; similia principle; laboratory evidence; conceptual models; hormesis

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1. Introduction

The American Institute of Homeopathy defined homeopathy as "*a unique scientific system of medicine*" predicated on the Law of Similars, *Similia Similibus Curentur*, or "let likes be cured by likes". The Law of Similars (here referred to as the "principle of Similars" or "Similia principle") is the center of this system and any effort to verify or confute this principle represents scientific progress.

However, we must be well aware that homeopathy is not only a science but also an art. Each branch of medicine has in itself aspects that can be approached with scientific criteria and others that are not. This is important for not making the mistake of believing that everything is scientifically explainable according to a reductionist perspective. What is the difference then? Homeopathy is art when applied to a single and unique patient ("individualization"), while it can be seen as a science of therapeutics when the evidence from experimental studies is applied to a group of patients ("generalization") or in laboratory settings.

The eminent French physiologist Claude Bernard (1813-1878) said that: "*L'art c'est moi, la science c'est nous*" (art is "me", science is "us"). Art is subjective, science is objective. Art is more interested in the "quality" of life, science in the quantitative parameters of our physiology and biochemistry. For example, when we say "*people like homeopathy*", we are speaking as "artists"; when we give a percentage of improvement, we speak as "scientists". The question belongs to the art of medicine when the doctor asks "*how are you?*" The question belongs to a scientific issue when he/she is asking "*how long have you been sick?*" Art is qualitative, while science is quantitative.

Homeopathy can be viewed from two sides, and both sides are useful in the practice of this medicine. Here, we survey the principle of Similars to examine its historical background and its scientific consistency. The cornerstone of homeopathy - the whole clinical picture of the individual patient be taken into consideration - is not in dispute. However, basic research allows the Similia principle to be investigated in laboratory animals, cells, tissues, and even at the molecular level. Table 1 reports the glossary of the homeopathic terminologies used in this work.

Table 1 Glossary of the main homeopathic terms used.

Term	Meaning
Principle of similars (or "similia principle" or "the simile")	The fundamental principle of homeopathy according to which a patient can be cured with the same medicine that produces a picture of symptoms similar to the disease itself in the healthy subject.
Dilution/dynamization	The procedure for the preparation of homeopathic medicinal products consisting of serial dilutions in which each dilution step is followed by strong succussion (shaking). The solutions obtained are designated by numbers according to the degree of dilution at each step: for example, the solution obtained after 5 dilutions/dynamizations (1:10) is called 5X, the one obtained after 9 dilutions/dynamizations (1:100) is called 9C. There are other dilution/dynamization scales such as 1: 50,000 (LM).
Potencies	Homeopathic dilutions/dynamizations are also called "potencies" because this term indicates a strong pharmacological activity. It is believed that if the correspondence between the remedy and the

	patient (similarity) is adequate, the higher dilutions/dynamizations have more complete and multidimensional therapeutic action.
Homeopathic pathogenetic trials (HPT-provings)	The procedure by which the effect of medicinal products is tested on a healthy person to describe the fine modifications produced by the treatment. Homeopathic medicine-induced perturbation in a healthy subject is considered as a set of artificially induced symptoms and serves to build the Materia Medica of the remedy.
Arndt-Schulz effect, Hormesis	The phenomenon in which a low dose of medicine has the opposite effect to a high dose. It describes a dose-response curve in the shape of a U or an inverted U.
Wilder's Law of initial value	The phenomenon in which the response to medicine is opposite in a sick (or stressed) subject compared to that in a healthy (or restful) one.
Isotherapy	The therapeutic method based on the treatment of the disease using the agent, which may cause it, and which uses preparations of organic origin such as animal and plant tissues or human secretions.
Vital force, or vital energy, or "dynamis"	The dynamic, self-regulatory capabilities to grow, reproduce, heal, adapt, and survive that all living creatures are endowed with.
Boolean network	A network defined by a set of nodes that can take two values (1 or ON and 0 or OFF) and by functions that determine the relationships between the nodes. At each time step, the function specifies the state of the node given the state to the previous step and that of the linked nodes.
Miasm	According to homeopathy, it is an original predisposition of the person to a particular type of disease, precisely of its constitution. The term comes from the Greek μίασμα, 'contamination'. In modern terms, we suggest to consider the miasms as pathologic dynamic attractors.

2. Experimental Evidence

Homeopathy has been an experimental science since the beginning [1]. However, its presence in the mainstream, peer-reviewed, scientific literature is more recent. That homeopathy is a science and can be engaged in scientific experience is demonstrated by the simple fact that the present century literature on the world's leading scientific publication database has grown about four times over the last 20 years. The authors present a few examples of the scientific approaches to homeopathy.

2.1 Historical Background

Linn John Boyd (1895-1975) was a homeopathic doctor with a scientific vocation; he is little known among homeopaths and even less in the world of mainstream medicine. He wrote a book entirely dedicated to the history of the scientific movement in homeopathy [2]. Boyd was a homeopathic doctor who graduated from the University of Michigan and served as a doctor in the American Navy. For twenty-five years, he served as the professor of internal medicine and professor of pharmacology at the New York Homeopathic Medical College and Flower Hospital. His book "*A Study of the Simile in Medicine*" is an excellent tool for a historical and scientific analysis of the theoretical bases and medical applications of the principle of similarity. It was published in the

United States in 1936 but its contents are still relevant because it deals with the development of the Similia principle - both in ancient medicine and in its applications by homeopathy - in a documented, rational, and critical way. Very few people have managed to do justice to this topic like him.

In his book, Boyd has reported hundreds of experiments that proved the homeopathic research efforts of the so-called scientific movement developed in Germany and the United States during the nineteenth century. From these studies, Boyd concluded that about 50 % of the tested compounds exhibited the phenomenon of inversion of effects on changing the dose (Arndt-Schulz effect). Yet, in this first example, we see "the Simile" as a heuristic principle for a scientist: Boyd aimed to test the principle in laboratory models and to verify its applications, and possibly its mechanisms, in careful experimentation. Hence, the homeopathic principle was a stimulus for scientific research.

The Arndt-Schulz phenomenon [3, 4] was further explored by Walter Siegried Loewe (1884-1963) and others until recent times when it took the name of "hormesis" [5-9]. Hormesis has the restraint that it does not denote all the homeopathic Similia principles [10, 11]. As reported by Boyd, Loewe attempted to formulate a diagram (illustrated in Figure 1), which deals with the question of different doses and their pharmacodynamic effects. He thus presents and discusses the scheme: "*We must ask ourselves the basic question of the transition of a stimulating effect into an inhibiting effect by looking at the total surface of the graphs representing the activity during the time.*"

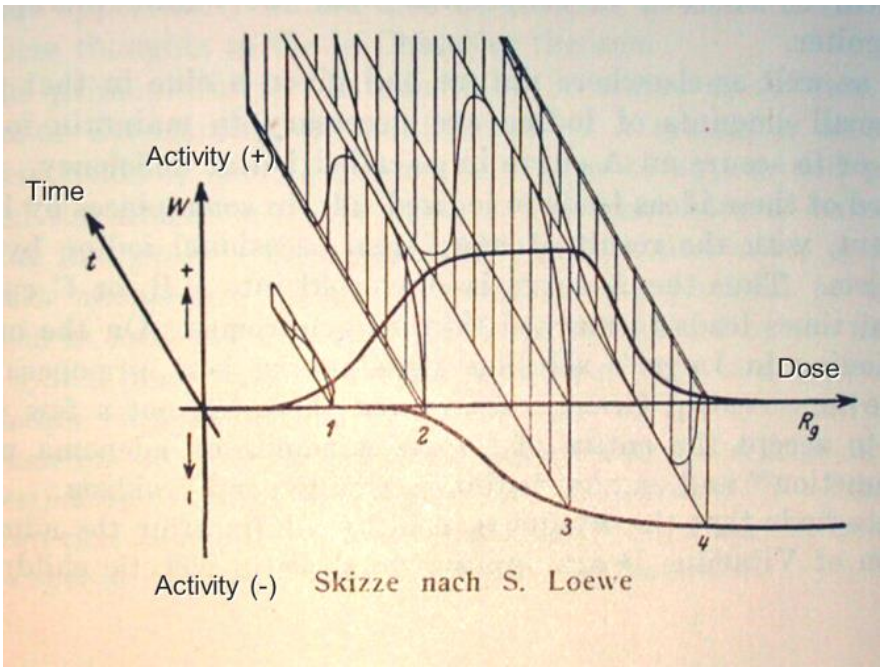

Figure 1 A draft from Boyd's book [2] as discussed in the text.

When the effect is followed gradually in the graph according to increasing doses and time, there is no response kinetics in the area below the activation threshold upon increasing the stimulus strength (on the left): the activity remains zero over time (path 1). By slightly increasing the stimulation (number 2), just above the threshold, there is a small functional response with a positive course, which lasts until the stimulus is exhausted and the activity returns to the basal level. If the other end of the dose-response curve (path 4) is considered, a pure and monophasic inhibition effect is observed with the highest doses. Between these two limits of pure stimulation (2) and pure inhibition (4), there are behaviors described by biphasic or multiphasic kinetics.

A moderate stimulus can probably cause an evident stimulation curve followed by a small and transitory inhibitory effect (path 3). Further, with a greater stimulus (maximum activation level), there is a good stimulation followed by a more evident depression (path 4). With increasing doses, there will then be a progressive accentuation of the depression phase and disappearance of the stimulation phase; this will occur until it reaches the level of the curve described by path 4. These phenomena were described by physiologists in the early decades of the 20th century and interested homeopathic scientists. However, they were almost totally ignored by conventional medicine, linked to the idea that the effect was monophasic and proportional to the dose.

According to the "*Law of initial value*" originally proposed in 1931 by the neuropsychiatrist Joseph Wilder (1895–1976), the concept of inverse effects was further implemented with the observations that the effects of the treatments were dependent on the status of the target system. The concept was already presented by Boyd [2] using experiments with adrenaline effects on cardiovascular activity. He highlighted that the heart response to adrenaline developed in an ortho-sympathetic sense (increase in activity and frequency) when the heart was in normal activity. However, the response to the same trigger consisted of a predominantly depressive phase if the stimulus was applied to a heart that was already in higher ortho-sympathetic activity. Instead of excitatory, the response was of compensatory nature.

Subsequently, this explanation of reverse or paradoxical effects, according to the status of the treated system, was invoked in many fields of medicine [12-18]. However, pharmacologists have begun to consider these «anomalous» phenomena only recently; the «paradoxical pharmacology» is starting to be investigated [19-24].

For example, the following sentences describe this concept as reviewed by Dr. Yun [21]: "*We propose a paradoxical strategy for treating chronic conditions based on harnessing compensatory mechanisms for therapeutic benefit. The therapeutic effect is derived from a compensatory response rather than the drug effect. For conditions that manifest chronic sympathetic bias, such as cardiovascular diseases, judicious administration of adrenergic agonists may induce compensatory downregulation of the baseline sympathovagal ratio. The concept may generalize to many other diseases, especially those involving pathways that exhibit strong homeostatic tendencies such as the neurologic, immune, and endocrine systems*." These ideas are very close to the notion of opposite responses in healthy and sick individuals, as originally proposed by C. F. Samuel Hahnemann (1755 – 1843), the founder of homeopathy.

In our laboratory, the idea of Similars was at first developed during studies on the functions of neutrophil leukocytes and dose-response experiments with a bacterial product. Different and even opposing effects were obtained according to the doses employed and according to the preliminary treatment to which the cells were subjected. By observing the response curves to a bacterial product called fMLP, it was observed that high doses demonstrated a stimulating effect, while cells pre-treated with low doses of the bacterial endotoxin demonstrated an inverse, inhibitory effect [25-27].

We have also discovered the mechanism of this phenomenon and attributed it to the effect of "gating", that is, the inhibition exercised on the bacterial endotoxin by low doses of a cyclic AMP. The inverse effect (inhibition of cell activity by low doses of a stimulant) is manifested only in cells sensitized with the endotoxin, or in cells from an inflammatory exudate [28, 29]. Moreover, it was observed that the presence of cells in the inflammatory exudate changed their fatty acid composition and their reaction to drugs [30, 31]. This observation was analogous with the

homeopathic concept of difference of sensitivity of sick versus healthy subjects. This peculiar type of cell response at low doses probably performs an important function in the mechanism of chemotaxis, that is, the movement of cells from distant areas to those closer to the inflammatory focus, where they go to meet and kill bacteria.

We then reported several studies with homeopathic compounds under either *in vitro* or *in vivo* conditions on laboratory animals. A microtubule toxin (from *Podophyllum peltatum*) inhibited neutrophils when used at allopathic doses, while it stimulated the neutrophils when used at homeopathic doses (typical hormetic effect) [32]. Moreover, purified podophyllotoxin caused a stimulatory effect (precisely defined as the "priming" effect) on the oxidative metabolism of human neutrophils at doses of 0.1-10 μg/ml, while doses higher than 100 μg/ml of podophyllotoxin inhibited the respiratory burst. Thus, the plant toxin showed a typical biphasic dose-response curve.

2.2 Modern Laboratory Investigations

The scientific medical literature reports many examples of reverse effects, and macrophages lend themselves particularly to this flexibility of responses. The use of the same signals (e.g., special cytokines, or endotoxins) can cause different effects, trigger different responses, sometimes opposite, depending on the state of the cell at the time of treatment. These differences concern the level of the receptors but also the complex network of gene expression, which is very flexible and "learned" from experience.

A related problem is concerning the doses (or "potencies" or "dilution/dynamizations"). The principle of similarity was applied since the beginning both with normal pharmacological doses and with extremely low doses and high dilutions. Hahnemann's master book, in paragraph 278 of the Organon, states that "*How small, in other words, must be the dose of each individual medicine, homeopathically selected for a case of disease, to effect the best cure? (...) Is, as may easily be conceived, not the work of theoretical speculation. (...) Pure experiment, careful observation of the sensitiveness of each patient, and accurate experience can alone determine this in each individual case*". Therefore, in homeopathy, the "dose" is not a dogma, and a genuine experimental approach should be adopted.

However, homeopaths use dilutions beyond the "molecular" limit established by the Avogadro-Loschmidt number (approximately 24 X or 12 C). This is a huge problem related to physics and chemistry [33-35]. Nevertheless, only a minimum part of the issue is dealt with here, limiting ourselves to present a few examples of laboratory evidence on the «doses» or «dilutions».

In recent years, many investigations have used molecular biology tools such as real-time polymerase chain reaction (RT-PCR), DNA-microarrays, and RNA-sequencing that provide useful suggestions on the behavior of human organisms treated with micro amounts of drugs or homeopathic drugs [11]. The results suggest that gene expression is a particularly sensitive response of cells and therefore suitable for revealing the smallest changes induced by high homeopathic dilutions. Table 2 reports an updated list of the laboratory studies wherein the effects of the homeopathic drugs were consistently reported in cell models.

Table 2 Effects of increasing dilutions/dynamizations of several compounds administered under *in vitro* conditions in cellular models as reported in peer-reviewed literature. Table updated from [11].

Potencies	Test compound	Cell type	Effect*
Mother tincture	*Phytolacca decandra* [36, 37]	Melanoma, breast carcinoma	↑ Cytotoxicity
Mother tincture	*Apis mellifera* (whole honeybee) [38]	Human prostate RWPE-1	↑↓ expression of different groups of genes (whole-genome analysis)
Mother tincture	*Ruta graveolens* [39]	Dalton's lymphoma ascites (DLA), Ehrlich ascites carcinoma	↑ Cytotoxicity
Mother tincture	*Carcinosinum* [40]	DLA cells	↑ specific gene expression (p53, pro-apoptotic)
Mother tincture	*Symphytum officinale* [41]	Human mesenchymal cells	↑ Osteogenic differentiation; ↑ Runx2, Osteopontin, and Osteocalcin gene expression
1 M	*Thuja* [42]	DLA cells	↑↓Gene expression (whole-genome analysis)
3X	*Drosera rotundifolia* [43]	16HBE bronchial cells	↑↓Gene expression of epithelial growth, xenobiotic detoxification, and cytokines
4X	*Podophyllum* [32]	Human neutrophils	↑ free radical production, ↓ Adhesion
4X-6X (complex)	*Arnica, Calendula, Hypericum,* and *Symphytum* [44]	3T3 fibroblasts	↑ Cell movement, chemotaxis
6X-12X (complex)	*Calcium fluoratum, Magnesium phophoricum, Acidum silicicum* [45, 46]	Rat osteoblasts	↑ Osteogenesis
2C	Histamine [47, 48]	Human basophils	↓↓ CD203c membrane expression

2C	*Gelsemium sempervirens* [49, 50]	Human neurocytes SH-SY5Y	↓↓ Gene expression (whole genome analysis, RT-PCR array)
2C	*Gelsemium sempervirens* [51]	Cervical cancer HeLa	↑ Cytotoxicity
2C	*Arnica montana* [52-54]	Human PMA-IL-4-differentiated macrophage cell line	↑ Gene expression of four genes with a conserved site of epidermal growth factor(EGF)-like region ($p<0.001$) and three genes of extracellular matrix, including fibronectin
6X	*Phosphorus, Sulfur* [55]	Human neutrophils	↓ free radicals production
8X	*Magnesium phosphoricum, Manganum phosphoricum* [55]	Human neutrophils	↓ free radicals production
3C, 5C, 7C	*Apis mellifera* [38, 56]	Human prostate RWPE-1	↑↓ expression of different groups of genes (whole-genome analysis)
5C	Gelsemium [57]	Rat neurons	↑ Neurosteroids
5C	*Lycopodium clavatum* [58]	Cervical cancer HeLa cells	↑ Apoptosis
6C	*Mercurius solubilis* [59]	Mice peritoneal macrophages	↑ Interferon-γ production, ↓ Free radical production
6C	*Ruta graveolens* [60]	Cell lines from brain cancer, leukemia, and melanoma	↑Cytotoxicity in cancer cells (not in normal lymphocytes)
17X	Gibberellin [61]	Pea seeds	↑ Germination
7X-24X (complex)	*Aconitum, Arsenicum, Asafoetida, Calcarea carbonica, Chelidonium, Cinnamon, Conium, Echinacea, Gelsemium sempervirens, Ipecacuanha, Phosphorus, Rhus toxicodendron, Thuja, Silicea, and Sulfur* [62]	HT29 cells, human macrophages	↓ NF-κβ hyperactivity (reduced expression of reporter gene GFP in transfected HT29 cells), ↓TNF-α release in macrophages
9C	Gelsemine [57]	Rat neurons	↑ Neurosteroids

9C	*Gelsemium sempervirens* [49, 63]	Human neurocytes SH-SY5Y cell line	↓ Gene expression (whole-genome analysis)
10C	Triiodothyronine [64]	Tail cells of *Rana*	↑ Apoptosis in cells treated with 100 nM T3
10C, 12C	*Nux vomica* or *Calendula* [65]	Human gastric epithelial cell line KATO-III	↑ specific gene expression in *H. pylori*-stimulated HB-EGF gene
2C-15C	*Arnica montana* [66]	Human PMA-IL-4-differentiated macrophage cell line	↑↓ Gene expression of several cytokines. Marked non-linearity of the dilution-response
15C	*Arnica montana* [52-54]	Human PMA-IL-4 differentiated macrophage cell line	↑ Expression of genes of extracellular matrix
15C	*Lycopodium clavatum* [58]	Cervical cancer HeLa cell line	↑ Apoptosis
30X	*Rhus toxicodendron* [67]	Primary cultured mouse chondrocytes	↑ specific gene expression (COX-2), ↑ inflammatory response (PGE2 release), ↓ specific gene expression (collagen II; de-differentiation role)
6X, 5C and 15C	Taxol [68]	Breast cancer cell line MCF-7	↓↑ expression of specific genes p53, p21, COX-2, TUBB2A, and TUBB3
16C	Histamine [47, 48, 69]	Human basophils	↓ CD203c membrane expression
14C-18C	Adrenaline [69]	Human basophils	↓ histamine release, ↓ CD 63 and CD203c expression
15C-20C (pooled)	Cadmium [70]	Human lymphocytes	↑ Resistance to cadmium toxicity
45X	Arsenic [71, 72]	Arsenic-intoxicated wheat seeds	↑ Germination, ↓ Gene expression levels
30C	*Arnica montana* [73]	*Escherichia coli*	↑ Resistance to RX toxicity
30C	*Arsenicum album* [74]	*Escherichia coli*	↑ Resistance to arsenic toxicity
30C	*Carcinosinum* [40]	DLA cells	↑ specific gene expression (p53, pro-apoptotic)

30C	*Arsenicum album* [74]	*Saccharomyces cerevisiae*	↑ Resistance to arsenic toxicity, ↓↑ expression of specific genes (apoptotic gene, stress response proteins)
30C	*Carcinosinum* [40]	Mouse primary lung cells	↑ Resistance to benzopyrene toxicity, ↓ free radical production ↓ heat shock protein hsp-90 expression
30C	*Condurango* [77]	H460-non-small cell lung cancer (NSCLC) cells	↓↑ expression of specific genes (apoptotic markers), ↑ Apoptosis, oxidative stress, mitochondrial depolarization
100C	*Sabal serrulata* [78]	PC3 cancer cells	↓ Proliferation
200C	*Ruta graveolens* [39]	DLA cells	↑ Apoptosis
200C	*Mercurius soubilis* [59]	Mice peritoneal macrophages	↓ Free radical production
200C	*Carcinosinum* [40]	DLA cells	↑ specific gene expression (p53, pro-apoptotic)
200C	*Carcinosinum, Hydrastis, Ruta or Thuja* [42]	DLA cells	↑ Apoptosis, ↓↑ Gene expression (whole-genome analysis)
30C and 200C	Sodium butyrate [79]	HEK-293 cell line	↓ TNF-α and IL-10 genes, ↑IL-2 gene

A series of published studies on animal models [80] documented that inverse effects occur when using normal-to-highly diluted doses. The examples include the use of thyroxine on frog pups or aspirin on platelet aggregation and hemostasis systems. They can also be seen in immunological models that demonstrate the mechanism of curing allergy or autoimmunity by allergy-causing substances in people with these diseases. In our laboratory, with the help of pharmacologist Dr. Anita Conforti, the principle of Similars was studied in animal models [81-91].

The first systematic review brought evidence of the *in vitro* biological activity of dynamized solutions on blood cells such as basophils, lymphocytes, granulocytes, and fibroblasts [92]. In a subsequent review [93], 67 experiments were evaluated, and a high potency effect of dilutions/dynamization was recorded in three-fourths of them. Considering the 18 best-quality experimental works, two-thirds of them reported statistically significant positive effects. However, in this review no positive result was stable enough to be reproduced by all researchers.

Another review focused exclusively on experimental models with high dilutions (i.e., over the Avogadro limit) that have undergone replication control [94]. A total of 126 studies involving cellular, biochemical, immunological, botanical, biological, and zoological experiments were collated; of which, 98 were replicative studies. They were grouped into 28 experimental models such as those on enzymes, cultured cells, plants, immune cells, isolated organs, amphibians/fish, rats/mice, etc. In total, 24 models with comparable results, 12 models with zero effect, and 6 models with opposite results were replicated. Five models were externally reproduced with comparable results.

2.3 Hormesis

The inversion of effects according to the different doses is called “hormesis”. The phenomenon of hormesis is indisputable. In classic pharmacology and toxicology, hundreds of substances are known to cause inhibition at high concentrations and stimulation at low concentrations (or vice versa) [95-99]. Hormesis is a special example of the Similia principle at the biological and physiopathological levels and is important for the therapeutic use of low doses of toxic substances. However, this phenomenon does not represent the only explanation of the homeopathic principle, which mainly concerns the difference of drug effects between healthy and ill subjects [11, 100].

Oral-specific immunotherapy describes a typical pattern of reversal of effects in the immunological literature [101-103]. Allergen immunotherapy (e.g., for allergy to honeybee venom) has been proven to be a clinically safe and effective strategy to reorient inappropriate immune responses in allergic patients. Administration of allergens via the oral mucosal route using sublingual immunotherapy has gained prominence as effective allergen-specific immunotherapy and can be used as an alternative to subcutaneous injections. To date, sublingual immunotherapy is widely accepted by most allergists.

This phenomenon is due to the presence of regulatory cells (that is, the lymphocytes that suppress abnormal immunological responses). These regulatory cells are activated in the allergic subject by the oral application of extremely low doses of the substance to which the patient is hypersensitive. The same substance that makes a healthy (and susceptible) person allergic may cure a person with an allergy. Thus, this is a clear example of “*Similia similibus curentur*” applied with very low doses and is called “isotherapy”.

The effect of histamine on basophils is another typical example of inverse effects that has a clear explanation. Histamine is an organic nitrogenous compound involved in local immune responses, as

well as in regulating physiological function in the gut and acting as a neurotransmitter for the brain, spinal cord, and uterus. Histamine is involved in the inflammatory response and performs a central role as the mediator of itching. The interesting fact is that the same substance binds to the histamine-H2 receptors of the basophilic cells and mastocytes and inhibits the release of histamine. This is natural feedback to hinder excess inflammation that may be dangerous and painful. Interestingly, various laboratories [104-107], including ours [48, 108], have reported that homeopathic dilutions of histamine, *Apis mellifera*, and *Histaminum* can inhibit the activation of human basophils. In this case, we have evidence that the homeopathically diluted substance works on the same pathway as the natural feedback that is operated by higher doses on the same cell type.

There is strong evidence for the following aspects of the theory:

✓ Under suitable conditions, the dose-response curves are often **nonlinear, biphasic, or multiphasic**: the DOSE-RESPONSE «DOGMA» must be denied.

✓ Several laboratory studies show an **inversion of effects** from HIGH doses (toxic, or maximum achievable effect: e.g., 1 to 10 mmol/L) to LOW doses of drugs (beneficial, e.g., 0.0001 to 0.1 mmol/L) (typical hormesis).

✓ In specific experimental conditions (cells, animals, plants), the effect of homeopathic medicines may be observed in **ULTRA-LOW doses** (e.g., 2C-5C, 0.0000000000001 to 0.00001 mmol/L: high sensitivity of biological systems), and **HIGH DILUTIONS** (beyond Avogadro, e.g., 15C, 30C, no «dose») (in the same direction of effect, there is little evidence of hormesis in high dilutions).

Here, three examples from our laboratory are mentioned.

2.3.1 Histamine and Other Mediators

Histamine [48] inhibited the membrane expression of the activation markers of the basophils at the 2C dilution; this effect was obtained with maximum intensity. The 10C and 11C dilutions did not affect the markers. However, some higher dilutions like 14C and 16C exerted the inhibitory effect, albeit at a lower intensity. The dilutions of the solvent (pure water) never had any effect. The principle of similarity or "inversion of effects" was applicable here because histamine caused acute inflammation when injected or endogenously released in high doses. However, low doses or higher dilutions inhibited the function of the same cells that produced the histamine.

This example is emblematic to show how the inversion of effects is due to the target system response and does not occur with the passage from "low dilutions" (where there are still molecules in weight doses) to "high dilutions or potencies" (where there are only "fingerprints" or "frequencies" of the original molecules in the solvent). A similar effect was reported for the serial dilutions of adrenaline [69] and Gelsemium sempervirens [57, 109]: the "inversion of effect" does not occur due to the mechanism of dilution or dynamization. However, it can be viewed as a pharmacodynamic effect linked to the interaction between the message (drug) and the typical target system and its susceptibility to regulation (activation or inhibition) in a certain experimental condition.

2.3.2 Gelsemium Sempervirens

For the neurocytes treated with *Gelsemium sempervirens* 2C, a reduction was observed in the expression of 49 genes, which was a possible explanation of the anxiolytic-like properties of the plant [49]. Next, a 3C dilution (100 times higher than 2C) inhibited 47 genes while upregulating 2 genes. The 5C dilution downregulated 40 genes, stimulated five genes, and did not affect the

expression of four genes. Noteworthy, the *Gelsemium sempervirens* solution was diluted a million times from the 2C to the 5C dilution, but its pharmacologic activity on gene expression remained. Finally, even with the 30C dilution, there was a "significant imbalance" in favor of inhibiting a greater number of genes. All tests were performed in comparison with a solvent solution, i.e., pure water. With pure water, there was no significant effect: neither stimulation nor inhibition. Thus, the number of genes that randomly increased or decreased or remained zero was similar. This effect cannot be due to chance, and therefore, it was concluded that some specific activity persisted even in higher dilutions beyond the Avogadro constant.

This line of research on *Gelsemium sempervirens* stirred a debate in the literature and resulted in several published papers from our group [50, 63, 87, 89, 91, 110-112]. In animal experiments [87, 110] also, the similarity principle was applicable because *Gelsemium sempervirens* was a toxic substance with a notable tropism on the cells of the nervous system. It caused tremors and irritation, and difficulty in walking (symptoms also of provings). However, high dilutions of this plant cause a state of greater calm and familiarity with open spaces when administered to subjects with anxious symptoms or experimental animals subjected to situations that generate anxiety.

2.3.3 Arnica Montana

Very interesting results were obtained with *Arnica montana* under *in vitro* conditions on human macrophages. The cells differentiated with Interleukin-4 induced a "wound-healing"-like phenotype and were then treated with various homeopathic dilutions of *Arnica montana* (2C, 3C, 5C, 9C, and 15C) for 24 hours. The expression of several genes of cytokines [66] and extracellular matrix [52, 53] was modulated. Another interesting observation was that on subsequent dilution, the activity of most genes whose expression was changed by *Arnica montana* 2C remained modified in the same direction (i.e., upregulated genes remained upregulated and downregulated remained downregulated) even at higher dilutions. However, a few genes showed inversion of effects.

The publication stirred an interesting debate [113, 114]. However, three years after the publication, some people complained against this work, and eventually, the paper was retracted by the same journal PLOS ONE. This could certainly be part of a concerted attack on homeopathy. Later, the tests were repeated with new methods [115], and the main results were confirmed [54].

Arnica montana is a very popular medicine that is used both in homeopathy and phytotherapy (external application only in the latter case) [116]. Here, it was difficult to envisage the application of the Similia principle in laboratory settings. Therefore, the only experience that could provide examples of this "general rule" of pharmacology was the careful clinical study of symptoms in pathogenetic trials, compared with the results of clinical practice.

2.4 Clinical Experience

The homeopathic principles have also been proved in clinical settings. The results obtained from prospective observational research on the homeopathic treatment for patients suffering from headache (migraine and tension-type headache) by our group are described [117]. The research was undertaken by a group of doctors of the Verona Homeopathic Medical School. Fifty-three patients were asked to complete a questionnaire at the beginning of and after 4-6 months of the treatment. Data analysis demonstrated that more than 60 % of the patients experienced an improvement in pain and the limitations caused by pain, as well as in limitations in their social activities and health

in general. Following this experience, further studies were conducted on arthro-rheumatic diseases [118] and diabetic neuropathy [119] with the homeopathic medical association called "*Belladonna*". These studies have been published in scientific literature. Our group has published a few clinical reviews concerning the effect of homeopathy in post-surgical settings [116] and upper respiratory tract diseases [120, 121]. A complete review of this topic is outside the scope of the review.

3. Conceptual Models

Although several models have been proposed to explain the principle of Similars, it can best be understood and appreciated in the framework of complexity science and dynamic systems theory. Several papers have been published on this subject by our group [80, 92, 122-126] and others [127-131] based on the theories of Boolean networks and complex dissipative systems, which demonstrate the relevance of self-organization and adaptation in rationalizing this traditional medical principle.

Our work is aimed at building a model of the vital energy, disease dynamics, and the possible action of homeopathy on them. Technically, this model is not a mathematical one; it is conceptual and a qualitative sketch of the mechanism of a process. The concepts and the language are provided by the dynamic system theory, molecular biology, and general pathology.

The concept of *vital force* (or energy) indicates *a dynamic self-regulatory capability, which all living creatures are undeniably endowed with,* in order to give them a better chance of survival. In general, the living organism can be considered an open dissipative system that operates away from thermodynamic equilibrium and exchanges matter, energy, and information with the environment [132-136].

A useful concept helping in the description of vital energy is to consider its structure as a *"network"*. Networks are complex structures because the state and the changes of each element depend, directly or indirectly, on the state and the changes of the other elements. Therefore, the network behaves as a *coherent* system, whose health state is governed and restored by the well-connectedness of the internal and external processes. Moreover, the iterative changes in the networks depict self-organizing capacity and form dynamic attractors. A simple graphical scheme has been developed by us wherein these features are qualitatively described.

The healthy condition is represented as a scheme of five nodes where each node is linked with two other nodes by stimulating and inhibiting connections (arrows). Independently of the number of nodes and of connections of the net, the two main properties of complex systems are represented here: "*connectedness"* (or connectivity) of individual elements and "*dynamics"*, i.e., the possibility of change during the time (Figure 2). When our vital energy is subjected to some stressor, we exhibit the possibility of adaptation and resistance. However, if the response is inefficient or sub-optimal, the disease can develop.

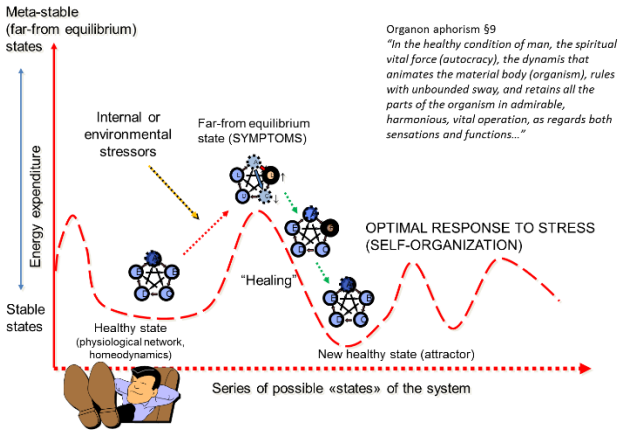

Figure 2 The healing power of the vital force in the "space of energy" («DYNAMIS»).

The basic mechanism of disease is the «suboptimal response to stress», which can have three aspects:

1. Deficit (too little, hypo-)
2. Excess (too much, hyper-)
3. Disorder of connections

These changes in our body generate signs and symptoms, according to Hahnemann: «*Diseases are nothing more than alterations in the state of health which express themselves by morbid signs*» (Organon, §19).

3.1 Networks

One of the most interesting and unexpected properties of complex nonlinear networks is their tendency to occupy a limited number of stable states out of the theoretically huge numbers of states available to them.

These states are called attractors and often have great stability in being the final dynamics of a Boolean network model or because they are situated in a local minimum in the state-space of energy. Networks are considered normal when they are positioned at a more stable level and with lower energy expenditure; thus, they are regarded as ''physiological''. Networks are considered further from equilibrium when they are positioned at higher energy expenditure levels. The "homeopathic" symptoms are emergent properties of a global, individual network [126, 129].

Thus, according to the most modern concept of the dynamic system theory, the life force (or life energy) is rationalized and represented in a graphical way (Figure 2). Our body is represented as a network of five "nodes" (A, B, C, D, E) interconnected by activation and inhibition links. Each node can be in a resting state (normal), strong activation (marked contour), or inhibition (dotted contour); this simply represents the different possible situations.

The "space or states" or "space of energy" is a useful representation of the possible situations of dynamic systems in the so-called energy landscape. Simulating the trajectories and attractors of the network system in the energy state-space provides a qualitative illustration of the pathological effects occurring due to targeted external perturbations. These changes can lead to permanent, self-sustaining alterations. In the vertical axis, the energy expenditure is reported; higher states are unstable and have the tendency to shift toward more stable states, where the energy expenditure

is lower. In the horizontal axis, the dynamic changes in the network are represented. The area is divided into various sub-spaces representing hills and valleys, where the different possible states or configurations of the system can be located.

This scheme tries to represent in a graphical form the «autocracy» and the «dynamis» that (according to Hahnemann) animate the material body (organism), rule with unbounded sway, and retain all the parts of the organism in admirable, harmonious, vital operation, as regards both sensations and functions. Autocracy can be translated in modern terms as "self-organization". "Dynamis" can be translated as "the dynamic changes in the energy and organization of the system".

An ideal network can be envisaged in a resting state at the bottom of the main attractor; this represents the healthy state in its best, self-organized, dynamic state. In this position, the living system spontaneously dissipates as little energy as possible, maintaining all the active vital functions as ready to mobilize, if the internal or external conditions change. It is not "equilibrium" in a thermodynamic sense wherein the maximum possible entropy and the dissipation of information prevail. This is a "controlled dysequilibrium" wherein fine changes take place under harmonic exchanges of biologic information, which require little adaptation effort. Under these conditions, the "symptoms" that reveal the disturbances of the body and mind are minimal. The healthy person feels the "presence" of one's body to a lesser extent: his/her body does not produce and send alarm signals to the mind.

As also shown in Figure 2, a possible internal or environmental stressor modifies some nodes of the network. The modifications spread in most parts of the network. This shifts the body to a meta-stable state far from equilibrium (higher in the energy landscape). This dynamic state is followed by further changes that are the deterministic consequence of the self-organizing capacity of the dynamic network. The reaction eventually terminates when the damage is repaired, the reaction is turned down, and the equilibrium is restored. This is a spontaneous capacity of vital energy; it is not the disease. In healthy subjects, all the perturbations are followed by a return to normality, except when a disease occurs (this occurrence will be discussed later). However, normality is the homeodynamic, the conservation of life, and the inherent healing capacity.

The healthy living system consumes less energy because it has to perform fewer operations to compensate for disturbances (produced inside or coming from the outside). Energy consumption normally fluctuates during physiological functions and peaks under conditions of increased demand for cell work. This kind of periodic oscillation is completely normal. The disease (both chronic and acute) continues to represent a challenge to the living system that tries to heal or compensate, at least in some parts, in order to survive. This process forces the system or its parts to dissipate more free energy because each change requires biochemical reactions and every biochemical or metabolic reaction requires ATP consumption.

3.2 Symptoms and Provings

At this point, it is important to consider the symptoms as emergent properties of the global and individual networks (Figure 3).

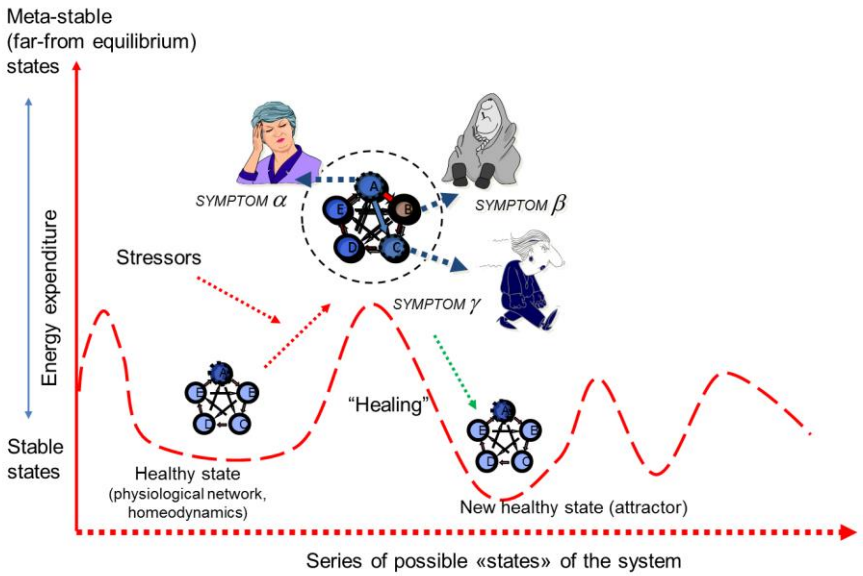

Figure 3 Emergence of signs and symptoms in stressed homeodynamic networks.

In the dynamic evolution of the stressed system, symptoms first appear as "emergent properties" of the physiological networks during the normal stress response. Next, these symptoms express changes in specific networks during natural diseases (strong in acute diseases, subtle in chronic ones). Finally, new symptoms are expected to arise during the challenge of healthy persons with medicines (homeopathic drug proving, or "pathogenetic trials").

The external symptoms represent a unitary phenomenon due to the global interacting modifications of the internal homeodynamic network. Thus, symptoms are not only the expression of "disease" dynamics but also of the "way" in which the whole individual interacts with stressors and disease-related modifications. This is of paramount importance for the classic homeopathic method, which is based on the careful observation and interpretation of symptomatology.

The central pillar of the idea of the "similitude" supports the test of medicines with adequate experiments. Each medicine, given to a healthy person, represents a small or large biological stress (Figure 4). Hence, the affected biological systems (represented here by the network in the energy space) are modified, pushed away from the equilibrium, and generate symptoms. This situation is called "artificial disease" by Hahnemann: We read (§24 of Organon): "*We seek (…) a medicine which among all medicines (whose pathogenetic effects are known from having been tested in healthy individuals) has the power and the tendency to produce an artificial morbid state most similar to that of the case of disease in question*".

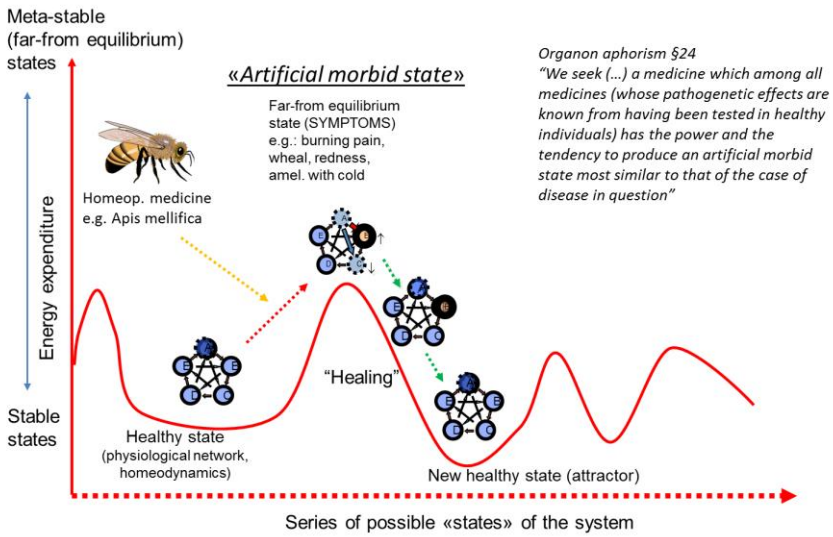

Figure 4 Hahnemann's brilliant idea: the provings of medicines.

However, we should not believe that this "artificial disease" corresponds to our conventional diseases (diabetes, heart attack, Alzheimer's disease, cancer, etc.). The so-called Hahnemannian "artificial morbid state" is a set of modifications of the vital energy pushed away from the equilibrium, which manifests itself with characteristic symptoms. Due to the self-organization of the complex systems, this dynamic state has an inherent capacity to return to the healthy state (attractor) (provided the dose and time of expositions do not destroy the system). In other words, in healthy individuals, a «pathogenic medicine» produces some specific symptoms, but they spontaneously disappear after some time because of the self-organization of the targeted system(s) («spontaneous healing»).

Homeopathic pathogenetic trials (HPT, or provings) are fundamental to homeopathy, but most of the data from the available provings have not been statistically evaluated. Hence, the specificity of the reported symptoms and the differences in these symptoms compared to those reported by people taking a placebo are not clear. The Similia principle was demonstrated to also work in the difficult field of human investigation when "conventional" statistics was applied to the HPT by our group [137] and others [138-140].

In a publication from a double-blind study by Dr. Gustavo Dominici and others, the symptoms induced by proving a medicine were found to decrease spontaneously over time in a few weeks [137]: The "Artificial disease" in a healthy person heals spontaneously thanks to the physiological homeodynamics (vital energy).

3.3 The "Disease"

The next task was to illustrate the concept of disease in the space of energy (figure 5). As stated by Hahnemann, «*Every disease (not entirely surgical) consists only in a special, morbid, dynamic alteration of our vital energy (of the principle of life) manifested in sensation and motion*» (Organon aphorism §29). Sometimes the reactions are not proportionate to the damage. Therefore, some further damages can be observed that are caused not by the first environmental trigger but by a

problem of the reaction itself. This condition is called "acute disease". Its main cause is not a "bad" external or internal factor but a disproportionate reaction that may cause further damage.

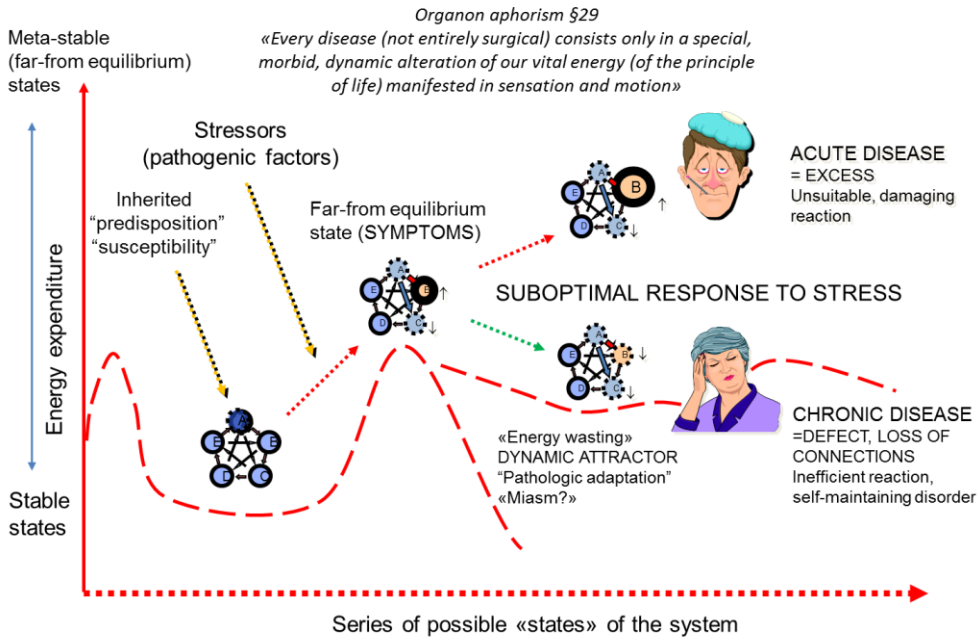

Figure 5 The "disease" as a disorder of the network dynamics in the space of energy.

ACUTE DISEASE here is represented by an EXCESS of reaction (e.g., in the node "B") that indicates an unsuitable, damaging, or disproportionate reaction compared to the needs of an optimal and coordinated reaction. The unwanted "cytokine storm" and "hyper-coagulation" in the advanced stages of COVID-19 are typical examples of disproportionate and counterproductive reactions.

In Figure 5, the symptoms of acute diseases (with many manifestations of active phenomena like inflammation, fever, and pain) have been schematically depicted. In particular cases, especially when the acute disease hits a system already affected by serious inherited predispositions by other chronic conditions, or the use of toxic substances (alcohol, drugs), the local damage may be serious enough to threaten the life of the subject. Acute illness hurts but, in theory, it can heal spontaneously, at the price of pain and risks to life integrity if very serious.

Inflammatory acute diseases are clear examples of the double-edged sword represented by our defense, reaction, and repair mechanisms. One of the more challenging clinical decisions is to identify an inflammatory process as being the expression of normal homeodynamic reactions or being truly "pathological", i.e., more damaging than beneficial. Moreover, this decision will determine whether the reaction should be pharmacologically regulated or left to heal on its natural course. In most cases, an acute disease may not cause irreversible damages, and eventually, spontaneous (or medically assisted) healing is observed.

On the other hand, the non-optimal response may turn into a CHRONIC disease. This occurs when the system altered by stress changes to find an adaptation with the mechanism of the attractor. The re-organization of the stressed systems takes place in a minimum of energy that does not completely resolve the disorders of homeodynamics; it is difficult to think of healing. Some

imbalances remain, and the energy consumption for adaptation remains high, creating further problems over time. This situation cannot heal spontaneously.

Acute and chronic diseases were distinguished by Hahnemann in paragraph 72 of the Organon. His view is perfectly compatible with this modern model derived from the dynamic system theory with only one exception: at the end of paragraph 72, Hahnemann stated that chronic diseases "*are caused by dynamic infection with a chronic miasm*." The concept of miasm should be revised in more modern terms [141], and this is possible according to the concepts of modern pathology and delineated especially by the theory of dynamic systems.

Here, a perspective of the synthesis of chronic diseases is observed in the modern view:

1. LONGER DURATION – NO SPONTANEOUS HEALING
2. OFTEN PROGRESSIVE
3. BEGIN WITH LITTLE, SUBTLE SYMPTOMS
4. MULTIFACTORIAL

Chronic diseases usually occur due to various interacting causes like inborn susceptibility (e.g., defects of membrane channels, receptors, enzymes, HLA, coagulation, amyloidosis), genetic mutations (RX, tobacco smoke), persisting infectious agents like viruses (e.g., papilloma, HIV, herpes, cytomegalovirus, Epstein-Barr), bacteria (e.g., *Treponema pallidum*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, etc.), prions, environmental factors persisting in the body (e.g., minerals causing silicosis, asbestosis; aluminum nanoparticles of vaccines; diet containing excess amounts of cholesterol, fat, protein glycosylation), psychologic-psychosomatic factors (imbalance of the neuroendocrine response to stress).

Hahnemann correctly discovered the method to exploit the Similia principle through pathogenetic experimentation of medicines. However, his theory of chronic diseases (where he tried to describe the "cause" of diseases in §78-80 of Organon) was incorrect where he maintained that the "cause" of 90 % of diseases was infection (theory of "Psora"). In any case, even without the (outdated) theory of Psora, the Similia principle is scientifically correct as described in the «New principle» (first published in Hufeland's Journal in 1796) and the first 70 aphorisms of the Organon. The original Hahnemann's idea for finding individualized medicines capable of regulating the dynamics of healing remains theoretically correct and experimentally proved.

An important aspect related to this model was the fact that diseases do not affect everyone equally. However, some people are more or less susceptible. This well-accepted fact in contemporary pathology was observed by Hahnemann and described in the Organon: «*The inimical forces, partly psychical, partly physical, to which our terrestrial existence is exposed, which are termed morbific noxious agents, do not possess the power of morbidly deranging the health of man unconditionally; but we are made ill by them only when our organism is sufficiently disposed and susceptible to the attack of the morbific cause that may be present, (…) hence they do not produce disease in everyone nor at all times*.» (Organon aphorism §31).

3.4 Suboptimal Response to Stress

The concept of response to stress was visualized better at the biochemical level using the scheme of Figure 6.

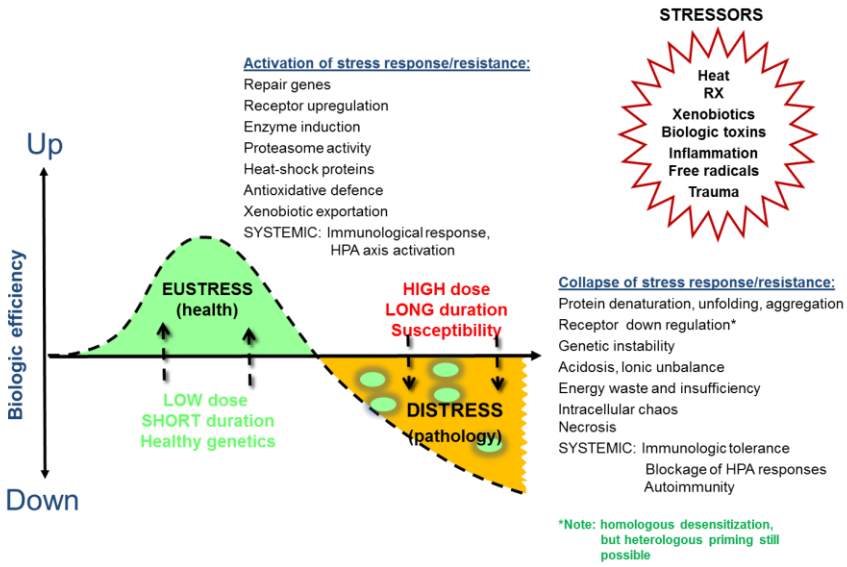

Figure 6 Dynamics of the biologic efficiency and the suboptimal response to stress at a molecular level.

In Figure 6, the concept of "suboptimal stress response" is evaluated from a mechanistic standpoint. All living organisms are capable of responding to stress with a series of defense and adaptation mechanisms to the extent that a little stress is considered useful. Moderate stress ("eustress") causes compensatory responses at the cellular, tissue, and systemic level that increases the biological efficiency. These biological mechanisms include, for example, the repair genes, receptor upregulation, enzyme induction, immunological response, hypothalamus-pituitary-adrenal axis activation, etc.

At the cellular level, sublethal doses of the same stresses provoke a pro-survival response based on several molecular modifications [142]. These changes include Sirtuin-1, Histone deacetylase, AMP-activated protein kinase, the Forkhead family of transcription factors, nuclear factor-2 transcription factor, heat-shock proteins, DNA repair genes, antioxidant enzyme induction, receptor up-regulation, and proteasome activity. Additionally, Bcl-2, an anti-apoptotic protein recognized for its antioxidant and pro-survival functions, plays an important role during oxidative-conditioning hormesis [143]. The suboptimal function of these mechanisms can lead to disease, while their stimulation by a "small" heterologous stress may be one of the molecular mechanisms explaining post-conditioning hormesis at the cellular level [96, 144, 145].

However, if the stress is too strong or too long or the person is particularly susceptible, physiological or biochemical response systems at the cellular level can collapse, and a non-adaptive response follows, which is called "distress". Consequently, protein denaturation, unfolding, aggregation, receptor downregulation, acidosis, ionic unbalance, etc., may occur. In these conditions, the disease cannot heal spontaneously, becomes chronic, and even progressive.

A general model for the action of homeopathic remedies based on stimulation of the organism's biological stress response network has been proposed by Bell and coworkers [146] and by our group [11]. This model is based on the idea that the resilience and recovery from the disease are due to time-dependent sensitization of the host responses that reverse the direction of pathology. Bell and Koithan have shown that [146] some of the physiological components involved in the organism's

response to stress have complex, nonlinear interrelationships. Pathways in the central nervous system, including the amygdala, prefrontal cortex, and hippocampus, are involved in stress responsivity and reward, learning and memory, somatosensory function, emotional function, and motor activity, and regulate and interact with all of the above components. The same authors suggested that this point of view on the disease dynamics may open the way to the use of homeopathic remedies: "*Disease is an emergent outcome when the cumulative stress load overwhelms the adaptive capacity of the system, and the interactions become persistently dysregulated. Targeted, timed disruption of the dysfunctional dynamics of disease affords the system an opportunity to recover normal regulatory relationships and interactions across the biological network. The present model postulates that the correct homeopathic remedy provides such a disruption to initiate adaptive changes*."

3.5 Homeo-Therapy

The role of the "simile" medicine is described in Figure 7: «SIMILE» MEDICINE is THE MEDICINE THAT IN HEALTHY INDIVIDUALS INDUCES SYMPTOMS SIMILAR TO THOSE OF DISEASE. Hahnemann states (Organon aphorism §22): "*Medicines only become remedies and capable of annihilating diseases, because the medicinal substance, by exciting certain effects and symptoms, that is to say, by producing a certain* ***artificial morbid state****, removes and abrogates the symptoms already present, to wit, the natural morbid state we wish to cure*. "

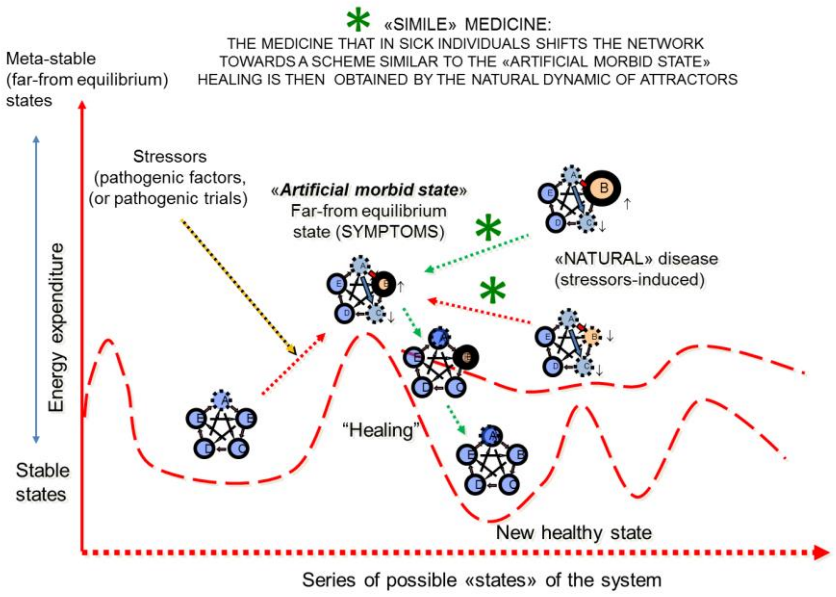

Figure 7 Homeo-therapy, i.e., the «logic» of the Similia principle in the energy landscape.

The "artificial morbid state" is obtained by administering the medicine known through pathogenetic trials on healthy individuals. This is clear and plausible if it is accepted that the power of medicines can be known through accurate testing of the symptoms that medicines are capable of causing in healthy people.

The natural disease and the artificial disease can match in the described network. Matching is done according to the classical theory by a careful comparison of the symptoms that are emergent properties of the network. If the symptoms are similar, it means that the "internal mechanisms" are also similar, that the medicine can touch the same targets that are modified by the disease. This view would seem very paradoxical or even foul for contemporary pharmacology. However, its profound meaning can be appreciated now.

3.6 Why the Artificial Disease is Stronger?

«The curative power of medicines, therefore, depends on their symptoms, similar to the disease but superior to it in strength (§12-26)». In paragraph 30: *«The human body appears to admit of being much more powerfully affected in its health by medicines (partly because we have the regulation of the dose in our own power) than by natural morbid stimuli—for natural diseases are cured and overcome by suitable medicines».*

Now we are in the position to understand what Hahnemann implied when he stated that the artificial disease produced by the medicine was "stronger" than the natural disease.

It certainly did not mean that the disease was more "serious", or that it exhibited "more symptoms"; from this point of view, the artificial disease induced by medicine was much weaker. The «strength» of the artificial disease lied in the fact that it was capable of healing on its own. It was an efficient, well-coordinated disease aimed at healing due to the systems of self-organization (autocracy) evaluated and inherent in the organism. These systems did not function optimally in the case of natural disease, and that is precisely why the natural disease manifested itself.

Now, the patient has lost the ability to coordinate an efficient response to the disease because some sub-systems do not work (they are faulty for suboptimal response to stress) or lack the adequate information to provide a balanced response. This information is provided by homeopathic medicine.

In brief, when the system affected by a natural disease "similar" to the artificial one is treated with a substance capable of inducing a state far from equilibrium as in the healthy subjects, then the system takes up a conformation capable of responding with a series of changes well-oriented to the healing. According to the theory of dynamic attractors, the sick system is "attracted" toward healthy behaviors, or at least closer to the ideal state of health.

The "strength" is given not by the "physical matter" of the medicine but by the energy of the body, i.e., by the evoked normal attractor, which is the normal outcome of the system moving down from a far-from-equilibrium state.

4. Corollaries

This theory has some important corollaries.

4.1 Corollary n. 1. The Totality of Symptoms

The «totality» is not solely related to the present symptoms of the body in the present state of disease, but also to previous symptoms. The DYNAMIC of disease includes various stages with change/s in the networks (different sequential patterns) and then of symptoms during the time. Some symptoms are the expression of normal, useful changes in the network and individual

sensitivity; other symptoms are the expression of suboptimal responses to stress («true disease»). Normally, during the dynamic changes in the networks, the previous («old») symptoms are the expression of healthy responses, i.e., the normal responses of healthy people. Therefore, it is advisable to select the medicine that produces the whole dynamic of symptoms, including the symptoms that were present during the previous stages of the disease.

Note: During the course of life, acute diseases possibly develop "over" chronic diseases, or chronic diseases represent a susceptibility factor for acute episodes. The susceptibility to network alterations is inside an anomalous attractor that is energetically unfavorable. Moreover, from this position, it is easier to go farther from the equilibrium by stressors. For this reason, even when the disease is acute, to facilitate the healing, it is necessary to consider the whole picture of the patient, including "chronic" or constitutional symptoms.

4.2 Corollary n. 2. The Dynamic of Healing

According to our model, the pattern of networks would change (and the symptoms would disappear) from the most recent disease back in time to previous ones (a reversion of the disease process):

- In ACUTE DISEASES, the global intensity of the symptoms decreases during the treatment
- In CHRONIC DISEASES, the global intensity of the symptoms increases in the initial stages of the treatment. Here, the network needs to overcome the energy barrier due to the pathologic attractor.

4.3 Corollary n. 3: HOMEO-THERAPY is compatible with CAUSAL therapy

Causal therapy is the elimination of the cause, that is, the hygiene, the healthy living style, and nutrition, and the use of antimicrobials when really needed and effective. Of course, antibiotics have their own problems that are (or should be) well known by conventional medicine. However, these problems (adverse effects and resistance) do not establish a theoretical incompatibility with the homeopathic approach. The homeopathic approach is much more contrasting with a therapy performed with the sole aim to suppress the symptoms.

5. Synthesis

In conclusion, the theory of the homeopathic "simile" can be formulated with the language and concepts of modern science as in the following seven points.

1. When a healthy organism is perturbed by a physical, chemical, or biological stressor, it produces characteristic signs and symptoms; when caused by a drug, this is regarded as an "artificial disease" that expresses the specific targets of the medicine in the body.
2. The method of drug provings that describes the characteristic patterns of signs and symptoms caused in healthy subjects by several minerals, vegetables, and animal compounds has been scientifically validated.
3. Natural diseases, either acute or chronic, have many different causes but are essentially due to a suboptimal response of the regulating networks (excess, deficit, disorder) to stress.
4. A substance capable of evoking certain symptoms in healthy subjects may evoke a change in the homeodynamic networks (that are already far from equilibrium) when administered to

subjects showing similar symptoms (due to natural diseases). This shifts the perturbed system toward a dynamic attractor that is more proximal to the healthy state.

5. Medicines should be used at the minimum working dose for two reasons: a) to attenuate the pathogenic power if the substance is toxic, b) to interact only with specifically modified and sensitized targets or receptors. This concept has been validated in numerous laboratory experimental models.

6. Serial dilutions followed by succussion ("dynamization") may allow the permanence of pharmacological power in the medicine matter even at higher dilutions (e.g., beyond 20X or 10C). The cellular gene expression is particularly sensitive to this kind of pharmacologic treatment.

7. Even if the traditional theory of "miasms" needs updating, the principle of Similars has been proved in a number of experiments and is justified by the dynamic systems theories. Thus, homeopathy is one of the frontiers of medical science.

Acknowledgments

The experimental work of our group from 2006 to 2016 was supported by Boiron Laboratoires (Lyon) and more recently by Hyland's (Los Angeles, CA). F.A.S. won a research project award from Federazione Italiana Associazioni e Medici Omeopati (FIAMO).

Author Contributions

The author did all the research work of this study.

Competing Interests

Since October 2020 PB has been consultant of Vanda s.r.l., a company that produces homeopathic drugs and food supplements. MM and FAS have not competing interests to declare.

References

1. Bellavite P, Conforti A, Piasere V, Ortolani R. Immunology and homeopathy. 1. Historical background. Evid-Based Complement Altern Med. 2005; 2: 441-452.
2. Boyd LJ. A study of the simile in medicine (Bellavite P. Il simile in medicina. Verona: Cortina; 2001). Philadelphia: Boericke and Tafel; 1936.
3. Schulz-Key H. Uber die theorie der arzneimittelwirkung. Virchow's Archiv. 1877; 108: 423-434.
4. Martius F. Das arndt-schulz grundgesetz. Muench Med Wschr. 1923; 70: 1005-1006.
5. Stebbing AR. Hormesis: The stimulation of growth by low levels of inhibitors. Sci Total Environ. 1982; 22: 213-234.
6. Sagan LA. What is hormesis and why haven't we heard about it before? Health Phys. 1987; 52: 521-525. Available from: https://europepmc.org/article/med/3570794.
7. Calabrese EJ, McCarthy ME, Kenyon E. The occurrence of chemically induced hormesis. Health Phys. 1987; 52: 531-541.
8. Calabrese EJ. Hormesis and homeopathy: Introduction. Hum Exp Toxicol. 2010; 29: 527-529.
9. Dei A, Bernardini S. Hormetic effects of extremely diluted solutions on gene expression. Homeopathy. 2015; 104: 116-122.
10. Oberbaum M, Gropp C. Update on hormesis and its relation to homeopathy. Homeopathy. 2015;

104: 227-233.
11. Bellavite P, Signorini A, Marzotto M, Moratti E, Bonafini C, Olioso D. Cell sensitivity, non-linearity and inverse effects. Homeopathy. 2015; 104: 139-160.
12. Surwillo WW, Arenberg DL. On the law of initial value and the measurement of change. Psychophysiology. 1965; 1: 368-370.
13. Wilder J. Basimetric approach (law of initial value) to biological rhythms. Ann N Y Acad Sci. 1962; 98: 1211-1220.
14. Wilder J. Stimulus and response: The law of initial value. Bristol: Wright; 1967.
15. Rogers RL, Meyer JS, Mortel KF, Mahurin RK, Thornby J. Age-related reductions in cerebral vasomotor reactivity and the law of initial value: A 4-year prospective longitudinal study. J Cereb Blood Flow Metab. 1985; 5: 79-85.
16. Jin P. Toward a reconceptualization of the law of initial value. Psychol Bull. 1992; 111: 176-184.
17. Nishimura N, Ogura C, Ohta I. Effects of the dopamine-related drug bromocriptine on event-related potentials and its relation to the law of initial value. Psychiatry Clin Neurosci. 1995; 49: 79-86.
18. Berntson GG, Uchino BN, Cacioppo JT. Origins of baseline variance and the Law of Initial Values. Psychophysiology. 1994; 31: 204-210.
19. Page C. Paradoxical pharmacology: Turning our pharmacological models upside down. Trends Pharmacol Sci. 2011; 32: 197-200.
20. Fisher P. Does homeopathy have anything to contribute to hormesis? Hum Exp Toxicol. 2010; 29: 555-560.
21. Yun AJ. The intellectual lineage of paradoxical pharmacology strategy. Med Hypotheses. 2005; 65: 815.
22. Xu XJ, Colpaert F, Wiesenfeld-Hallin Z. Opioid hyperalgesia and tolerance versus 5-HT1A receptor-mediated inverse tolerance. Trends Pharmacol Sci. 2003; 24: 634-639.
23. Bode AM, Dong Z. The paradox of arsenic: Molecular mechanisms of cell transformation and chemotherapeutic effects. Crit Rev Oncol Hematol. 2002; 42: 5-24.
24. Bond RA. Is paradoxical pharmacology a strategy worth pursuing? Trends Pharmacol Sci. 2001; 22: 273-276.
25. Bellavite P, Chirumbolo S, Santonastaso C, Biasi D, Lussignoli S, Andrioli G. Dose-dependence of the various functional responses of neutrophils to formylpeptides. Activation, regulation, and inverse effects according to the agonist dose and cell condition. In: Signals and Images. Dordrecht: Springer; 1997.
26. Bellavite P, Andrioli G, Lussignoli S, Signorini A, Ortolani R, Conforti A. A scientific reappraisal of the "principle of similarity". Med Hypotheses. 1997; 49: 203-212.
27. Bellavite P, Lippi G, Signorini A, Andrioli G, Bonazzi L, Ferro I. Nonlinear dose-dependent metabolic and adhesive responses of human neutrophils to chemotactic agents. Bologna: Editrice Compositori; 1993.
28. Biasi D, Bambara LM, Carletto A, Caraffi M, Serra MC, Chirumbolo S, et al. Factor-specific changes in oxidative burst response of human neutrophils in skin-window exudates. Inflammation. 1993; 17: 13-23.
29. Bellavite P, Carletto A, Biasi D, Caramaschi P, Poli F, Suttora F, et al. Studies of skin-window exudate human neutrophils: Complex patterns of adherence to serum-coated surfaces in dependence on FMLP doses. Inflammation. 1994; 18: 575-587.

30. Carletto A, Biasi D, Bambara LM, Caramaschi P, Bonazzi ML, Lussignoli S, et al. Studies of skin-window exudate human neutrophils: Increased resistance to pentoxifylline of the respiratory burst in primed cells. Inflammation. 1997; 21: 191-203.
31. Carletto A, Bellavite P, Guarini P, Biasi D, Chirumbolo S, Caramaschi P, et al. Changes of fatty acid composition and oxidative metabolism of human neutrophils migrating into an inflammatory exudate. Inflammation. 1996; 20: 123-137.
32. Chirumbolo S, Conforti A, Lussignoli S, Metelmann H, Bellavite P. Effects of Podophyllum peltatum compounds in various preparations dilutions on human neutrophil functions in vitro. Br Homeopath J. 1997; 86: 16-26.
33. Klein SD, Würtenberger S, Wolf U, Baumgartner S, Tournier A. Physicochemical investigations of homeopathic preparations: A systematic review and bibliometric analysis-part 1. J Altern Complement Med. 2018; 24: 409-421.
34. Tournier A, Klein SD, Würtenberger S, Wolf U, Baumgartner S. Physicochemical investigations of homeopathic preparations: A systematic review and bibliometric analysis-part 2. J Altern Complement Med. 2019; 25: 890-901.
35. Tournier A, Würtenberger S, Klein SD, Baumgartner S. Physicochemical investigations of homeopathic preparations: A systematic review and bibliometric analysis-part 3. J Altern Complement Med. 2020; 27: 45-57.
36. Ghosh S, Bishayee K, Paul A, Mukherjee A, Sikdar S, Chakraborty D, et al. Homeopathic mother tincture of Phytolacca decandra induces apoptosis in skin melanoma cells by activating caspase-mediated signaling via reactive oxygen species elevation. J Integr Med. 2013; 11: 116-124.
37. Arora S, Aggarwal A, Singla P, Jyoti S, Tandon S. Anti-proliferative effects of homeopathic medicines on human kidney, colon and breast cancer cells. Homeopathy. 2013; 102: 274-282.
38. Bigagli E, Luceri C, Bernardini S, Dei A, Filippini A, Dolara P. Exploring the effects of homeopathic Apis mellifica preparations on human gene expression profiles. Homeopathy. 2014; 103: 127-132.
39. Preethi KC, Kuttan G, Kuttan R. Anti-tumour activity of ruta graveolens extract. Asian Pac J Cancer Prev. 2006; 7: 439-443.
40. Sunila ES, Kuttan R, Preethi KC, Kuttan G. Dynamized preparations in cell culture. Evid-Based Complement Altern Med. 2009; 6: 257-263.
41. Dey D, Jingar P, Agrawal S, Shrivastava V, Bhattacharya A, Manhas J, et al. Symphytum officinale augments osteogenesis in human bone marrow-derived mesenchymal stem cells in vitro as they differentiate into osteoblasts. J Ethnopharmacol. 2020; 248: 112329.
42. Preethi K, Ellanghiyil S, Kuttan G, Kuttan R. Induction of apoptosis of tumor cells by some potentiated homeopathic drugs: Implications on mechanism of action. Integr Cancer Ther. 2012; 11: 172-182.
43. Arruda-Silva F, Bellavite P, Marzotto M. Low-dose Drosera rotundifolia induces gene expression changes in 16HBE human bronchial epithelial cells. Sci Rep. 2021; 11: 2356.
44. Hostanska K, Rostock M, Melzer J, Baumgartner S, Saller R. A homeopathic remedy from arnica, marigold, St. John inverted question marks wort and comfrey accelerates in vitro wound scratch closure of NIH 3T3 fibroblasts. BMC Complement Altern Med. 2012; 12: 1-9.
45. Manduca P, Marchisio S, Astigiano S, Zanotti S, Galmozzi F, Palermo C, et al. FMS*Calciumfluor specifically increases mRNA levels and induces signaling via MAPK 42,44 and not FAK in differentiating rat osteoblasts. Cell Biol Int. 2005; 29: 629-637.

46. Palermo C, Filanti C, Poggi S, Manduca P. Osteogenesis in vitro in rat tibia-derived osteoblasts is promoted by the homeopathic preparation, FMS*Calciumfluor. Cell Biol Int. 1999; 23: 31-40.
47. Sainte-Laudy J, Belon P. Improvement of flow cytometric analysis of basophil activation inhibition by high histamine dilutions. A novel basophil specific marker: CD 203c. Homeopathy. 2006; 95: 3-8.
48. Chirumbolo S, Brizzi M, Ortolani R, Vella A, Bellavite P. Inhibition of CD203c membrane up-regulation in human basophils by high dilutions of histamine: A controlled replication study. Inflamm Res. 2009; 58: 755-764.
49. Marzotto M, Olioso D, Brizzi M, Tononi P, Cristofoletti M, Bellavite P. Extreme sensitivity of gene expression in human SH-SY5Y neurocytes to ultra-low doses of Gelsemium sempervirens. BMC Complement Altern Med. 2014; 14: 1-20.
50. Olioso D, Marzotto M, Moratti E, Brizzi M, Bellavite P. Effects of Gelsemium sempervirens L. on pathway-focused gene expression profiling in neuronal cells. J Ethnopharmacol. 2014; 153: 535-539.
51. Bhattacharyya SS, Mandal SK, Biswas R, Paul S, Pathak S, Boujedaini N, et al. In vitro studies demonstrate anticancer activity of an alkaloid of the plant Gelsemium sempervirens. Exp Biol Med. 2008; 233: 1591-1601.
52. Marzotto M, Bonafini C, Olioso D, Baruzzi A, Bettinetti L, Di LF, et al. Arnica montana stimulates extracellular matrix gene expression in a macrophage cell line differentiated to wound-healing phenotype. PLoS ONE. 2016; 11: e0166340.
53. Marzotto M, Bonafini C, Olioso D, Bellavite P. Study of the action mechanisms of Arnica montana effects on macrophages. Int J High Dilution Res. 2016; 15: 32-35. Available from: https://www.highdilution.org/index.php/ijhdr/article/view/861.
54. Marzotto M, Arruda-Silva F, Bellavite P. Fibronectin gene up-regulation by arnica montana in human macrophages: Validation by real-time polymerase chain reaction assay. Homeopathy. 2020; 109: 140-145.
55. Chirumbolo S, Signorini A, Bianchi I, Lippi G, Bellavite P. Effects of homeopathic preparations of organic acids and of minerals on the oxidative metabolism of human neutrophils. Br Homeopath J. 1993; 82: 237-244.
56. Bigagli E, Luceri C, Dei A, Bernardini S, Dolara P. Effects of extreme dilutions of Apis mellifica preparations on gene expression profiles of human cells. Dose-Response. 2016; 14: 1559325815626685.
57. Venard C, Boujedaini N, Mensah-Nyagan AG, Patte-Mensah C. Comparative analysis of gelsemine and Gelsemium sempervirens activity on neurosteroid allopregnanolone formation in the spinal cord and limbic system. Evid-Based Complementary Altern Med. 2011; 2011: 1-10.
58. Samadder A, Das S, Das J, Paul A, Boujedaini N, Khuda-Bukhsh AR. The potentized homeopathic drug, Lycopodium clavatum (5C and 15C) has anti-cancer effect on hela cells in vitro. J Acupunct Meridian Stud. 2013; 6: 180-187.
59. de Oliveira SM, de Oliveira CC, Abud AP, Guimaraes FS, Di Bernardi RP, Coletto EL, et al. Mercurius solubilis: Actions on macrophages. Homeopathy. 2011; 100: 228-236.
60. Pathak S, Multani AS, Banerji P, Banerji P. Ruta 6 selectively induces cell death in brain cancer cells but proliferation in normal peripheral blood lymphocytes: A novel treatment for human brain cancer. Int J Oncol. 2003; 23: 975-982.
61. Baumgartner S, Thurneysen A, Heusser P. Growth stimulation of dwarf peas (Pisum sativum L.)

through homeopathic potencies of plant growth substances. Complement Med Res. 2004; 11: 281-292.
62. de Oliveira CC, Abud AP, de Oliveira SM, Guimaraes FS, de Andrade LF, Di Bernardi RP, et al. Developments on drug discovery and on new therapeutics: Highly diluted tinctures act as biological response modifiers. BMC Complement Altern Med. 2011; 11: 1-11.
63. Bellavite P, Bonafini C, Marzotto M. Experimental neuropharmacology of Gelsemium sempervirens: Recent advances and debated issues. J Ayurveda Integr Med. 2018; 9: 69-74.
64. Guedes JR, Carrasco S, Ferreira CM, Bonamin LV, Souza W, Goldenstein-Schainberg C, et al. Ultra high dilution of triiodothyronine modifies cellular apoptosis in Rana catesbeiana tadpole tail in vitro. Homeopathy. 2011; 100: 220-227.
65. Hofbauer R, Pasching E, Moser D, Frass M. Heparin-binding epidermal growth factor expression in KATO-III cells after Helicobacter pylori stimulation under the influence of strychnos Nux vomica and Calendula officinalis. Homeopathy. 2010; 99: 177-182.
66. Olioso D, Marzotto M, Bonafini C, Brizzi M, Bellavite P. Arnica montana effects on gene expression in a human macrophage cell line. Evaluation by quantitative Real-Time PCR. Homeopathy. 2016; 105: 131-147.
67. Huh YH, Kim MJ, Yeo MG. Homeopathic Rhus toxicodendron treatment increased the expression of cyclooxygenase-2 in primary cultured mouse chondrocytes. Homeopathy. 2013; 102: 248-253.
68. Seker S, Guven C, Akcakaya H, Bahtiyar N, Akbas F, Onaran I. Evidence that extreme dilutions of paclitaxel and docetaxel alter gene expression of in vitro breast cancer cells. Homeopathy. 2018; 107: 32-39.
69. Mannaioni PF, Mastroianni R, Mastrangelo D. Adrenaline inhibits the immunological activation of human basophils at pharmacological and ultra-low doses. Med Sci Monit. 2010; 16: BR227-BR232.
70. Walchli C, Baumgartner S, Bastide M. Effect of low doses and high homeopathic potencies in normal and cancerous human lymphocytes: An in vitro isopathic study. J Altern Complement Med. 2006; 12: 421-427.
71. Brizzi M, Lazzarato L, Nani D, Borghini F, Peruzzi M, Betti L. A biostatistical insight into the As2O3 high dilution effects on the rate and variability of wheat seedling growth. Complement Med Res. 2005; 12: 277-283.
72. Marotti I, Betti L, Bregola V, Bosi S, Trebbi G, Borghini G, et al. Transcriptome profiling of wheat seedlings following treatment with ultrahigh diluted arsenic trioxide. Evid-Based Complementary Altern Med. 2014; 2014: 851263.
73. Das S, Saha SK, De A, Das D, Khuda-Bukhsh AR. Potential of the homeopathic remedy, Arnica Montana 30C, to reduce DNA damage in Escherichia coli exposed to ultraviolet irradiation through up-regulation of nucleotide excision repair genes. Chin J Integr Med. 2012; 10: 337-346.
74. De A, Das D, Dutta S, Chakraborty D, Boujedaini N, Khuda-Bukhsh AR. Potentiated homeopathic drug Arsenicum Album 30C inhibits intracellular reactive oxygen species generation and up-regulates expression of arsenic resistance gene in arsenite-exposed bacteria Escherichia coli. Chin J Integr Med. 2012; 10: 210-227.
75. Das D, De A, Dutta S, Biswas R, Boujedaini N, Khuda-Bukhsh AR. Potentized homeopathic drug Arsenicum Album 30C positively modulates protein biomarkers and gene expressions in

Saccharomyces cerevisae exposed to arsenate. Chin J Integr Med. 2011; 9: 752-760.
76. Mukherjee A, Boujedaini N, Khuda-Bukhsh AR. Homeopathic Thuja 30C ameliorates benzo(a)pyrene-induced DNA damage, stress and viability of perfused lung cells of mice in vitro. J Integr Med. 2013; 11: 397-404.
77. Sikdar S, Mukherjee A, Ghosh S, Khuda-Bukhsh AR. Condurango glycoside-rich components stimulate DNA damage-induced cell cycle arrest and ROS-mediated caspase-3 dependent apoptosis through inhibition of cell-proliferation in lung cancer, in vitro and in vivo. Environ Toxicol Pharmacol. 2014; 37: 300-314.
78. MacLaughlin BW, Gutsmuths B, Pretner E, Jonas WB, Ives J, Kulawardane DV, et al. Effects of homeopathic preparations on human prostate cancer growth in cellular and animal models. Integr Cancer Ther. 2006; 5: 362-372.
79. Olsen S. Effects of ultra-high dilutions of sodium butyrate on viability and gene expression in HEK 293 cells. Homeopathy. 2017; 106: 32-36.
80. Bellavite P, Marzotto M, Olioso D, Moratti E, Conforti A. High-dilution effects revisited. 2. Pharmacodynamic mechanisms. Homeopathy. 2014; 103: 22-43.
81. Conforti A, Signorini A, Bellavite P. Effects of high dilutions of histamin and other natural compounds on acute inflammation in rats. Bologna; Compositori: 1993.
82. Conforti A, Lussignoli S, Bertani S, Ortolani R, Verlato G, Bellavite P. Intraperitoneal administration of adjuvant inhibits the development of adjuvant arthritis in rats. Int J Immunopathol Pharmacol. 1995; 8: 113-121.
83. Conforti A, Lussignoli S, Bertani S, Verlato G, Ortolani R, Bellavite P, et al. Specific and long-lasting suppression of rat adjuvant arthritis by low- dose Mycobacterium butyricum. Eur J Pharmacol. 1997; 324: 241-247.
84. Bertani S, Lussignoli S, Andrioli G, Bellavite P, Conforti A. Dual effects of a homeopathic mineral complex on carrageenan-induced oedema in rats. Br Homeopath J. 1999; 88: 101-105.
85. Lussignoli S, Bertani S, Metelmann H, Bellavite P, Conforti A. Effect of Traumeel S®, a homeopathic formulation, on blood-induced inflammation in rats. Complement Ther Med. 1999; 7: 225-230.
86. Marzotto M, Conforti A, Magnani P, Zanolin ME, Bellavite P. Effects of Ignatia amara in mouse behavioural models. Homeopathy. 2012; 101: 57-67.
87. Bellavite P, Magnani P, Zanolin E, Conforti A. Homeopathic doses of gelsemium sempervirens improve the behavior of mice in response to novel environments. Evid-Based Complementary Altern Med. 2011; 2011: 1-10.
88. Bellavite P, Chirumbolo S, Magnani P, Marzotto M, Ortolani R, Vella A, et al. Recherche fondamentale et appliquée dans le domain biologique. Lyon: Jacques André Editeur; 2011.
89. Bellavite P, Magnani P, Marzotto M, Cristofoletti M, Zanolin ME, Conforti A. Mice behavioural models with pooled data analysis of Gelsemium studies and new findings about Ignatia and Aconitum. Int J High Dil Res. 2011; 10: 198-200. Available from: https://www.highdilution.org/index.php/ijhdr/article/view/523.
90. Bellavite P, Magnani P, Conforti A, Marzotto M, Zanolin ME. Effects of high-dilutions in behavioural models: A commentary on critical issues, from reproducibility to plausibility. Int J High Dil Res. 2011; 10: 325-337. Available from: https://www.highdilution.org/index.php/ijhdr/article/view/532.
91. Bellavite P, Conforti A, Marzotto M, Magnani P, Cristofoletti M, Olioso D, et al. Testing

homeopathy in mouse emotional response models: Pooled data analysis of two series of studies. Evid-Based Complementary Altern Med. 2012; 2012: 954374.
92. Bellavite P, Conforti A, Pontarollo F, Ortolani R. Immunology and homeopathy. 2. Cells of the immune system and inflammation. Evid-Based Complementary Altern Med. 2006; 3: 13-24.
93. Witt CM, Bluth M, Albrecht H, Weisshuhn TE, Baumgartner S, Willich SN. The in vitro evidence for an effect of high homeopathic potencies--a systematic review of the literature. Complement Ther Med. 2007; 15: 128-138.
94. Endler PC, Bellavite P, Bonamin L, Jager T, Mazon S. Replications of fundamental research models in ultra high dilutions 1994 and 2015 - update on a bibliometric study. Homeopathy. 2015; 104: 234-245.
95. Bellavite P, Chirumbolo S, Marzotto M. Hormesis and its relationship with homeopathy. Hum Exp Toxicol. 2010; 29: 573-579.
96. Van Wijk R, Wiegant FA. Postconditioning hormesis and the similia principle. Front Biosci. 2011; 3: 1128-1138.
97. Upadhyay RP. The materialist view of homeopathy: An alternative hypothesis and the connection with hormesis. Homeopathy. 2018: 107: 46-49.
98. Bell IR, Schwartz GE. Enhancement of adaptive biological effects by nanotechnology preparation methods in homeopathic medicines. Homeopathy. 2015; 104: 123-138.
99. Calabrese EJ. Hormesis within a mechanistic context. Homeopathy. 2015; 104: 90-96.
100. Oberbaum M, Frass M, Gropp C. Unequal brothers: Are homeopathy and hormesis linked? Homeopathy. 2015; 104: 97-100.
101. Canonica GW, Compalati E, Fumagalli F, Passalacqua G. Sublingual and oral immunotherapy. Immunol Allergy Clin North Am. 2004; 24: 685-704.
102. Allam JP, Novak N. Immunological mechanisms of sublingual immunotherapy. Curr Opin Allergy Clin Immunol. 2014; 14: 564-569.
103. Moingeon P, Mascarell L. Differences and similarities between sublingual immunotherapy of allergy and oral tolerance. Semin Immunol. 2017; 30: 52-60.
104. Poitevin B, Davenas E, Benveniste J. In vitro immunological degranulation of human basophils is modulated by lung histamine and Apis mellifica. Br J Clin Pharmacol. 1988; 25: 439-444.
105. Sainte-Laudy J, Belon P. Inhibition of human basophil activation by high dilutions of histamine. Agent Actions. 1993; 38: C245-C247.
106. Sainte-Laudy J, Belon P. Inhibition of basophil activation by histamine: A sensitive and reproducible model for the study of the biological activity of high dilutions. Homeopathy. 2009; 98: 186-197.
107. Poitevin B. Survey of immuno-allergological ultra high dilution research. Homeopathy. 2015; 104: 269-276.
108. Bonamin LV, Bellavite P. Immunological models in high dilution research following M Bastide. Homeopathy. 2015; 104: 263-268.
109. Venard C, Boujedaini N, Belon P, Mensah-Nyagan AG, Patte-Mensah C. Regulation of neurosteroid allopregnanolone biosynthesis in the rat spinal cord by glycine and the alkaloidal analogs strychnine and gelsemine. Neuroscience. 2008; 153: 154-161.
110. Magnani P, Conforti A, Zanolin E, Marzotto M, Bellavite P. Dose-effect study of Gelsemium sempervirens in high dilutions on anxiety-related responses in mice. Psychopharmacology. 2010; 210: 533-545.

111. Bellavite P, Marzotto M, Olioso D, Cristofoletti M, Brizzi M, Tononi P, et al. Cellular and transcriptional responses of SH-SY5Y human neurocytes following in vitro exposure to Gelsemium sempervirens. Int J High Dilution Res. 2012; 11: 144-146. Available from: https://www.highdilution.org/index.php/ijhdr/article/view/603.
112. Bellavite P, Magnani P, Conforti A, Marzotto M, Zanolin M. Response to a comment by Luigi Cervo and Valter Torri on: "Dose-effect study of Gelsemium sempervirens in high dilutions on anxiety-related responses in mice" (Magnani P. et al. Psychopharmacology, 2010). Psychopharmacology. 2012; 220: 441-442.
113. Bellavite P, Marzotto M, Bonafini C. Arnica montana experimental studies: Confounders and biases? J Integr Med. 2018; 16: 72-76.
114. Bellavite P, Marzotto M, Bonafini C. Critical comments and methodological variations in Arnica montana's research studies. J Ayurveda Integr Med. 2018; 9: 238-239.
115. Bellavite P, Marzotto M. Comments on the retraction by PLoS ONE of a laboratory study on arnica montana. Homeopathy. 2019; 108: 291-293.
116. Iannitti T, Morales-Medina JC, Bellavite P, Rottigni V, Palmieri B. Effectiveness and safety of arnica montana in post-surgical setting, pain and inflammation. Am J Ther. 2016; 23: e184-e197.
117. Muscari-Tomaioli G, Allegri F, Miali E, Pomposelli R, Tubia P, Targhetta A, et al. Observational study of quality of life in patients with headache, receiving homeopathic treatment. Br Homeopath J. 2001; 90: 189-197.
118. Pomposelli R, Codecà G, Bergonzi R, Andreoni C, Salvi G, Costini G, et al. Terapia omeopatica in pazienti con patologia artroreumatica. Medicina Naturale. 2003; 13: 44-50.
119. Pomposelli R, Piasere V, Andreoni C, Costini G, Tonini E, Spalluzzi A, et al. Observational study of homeopathic and conventional therapies in patients with diabetic polyneuropathy. Homeopathy. 2009; 98: 17-25.
120. Bellavite P, Marzotto M, Chirumbolo S, Conforti A. Advances in homeopathy and immunology: A review of clinical research. Front Biosci. 2011; 3: 1363-1389.
121. Bellavite P, Marzotto M, Andreoli B. Homeopathic treatments of upper respiratory and otorhinolaryngologic infections: A review of randomized and observational studies. J Altern Complement Integr Med. 2019; 5: 068.
122. Bellavite P, Signorini A. Physiopathological models of the similia principle. Proceedings of the 51st L.M.H.I. International Congress; 1996 October 2-6; Capri.
123. Bellavite P, Lussignoli S, Semizzi M, Ortolani R, Signorini A. The similia principle: From cellular models to regulation of homeostasis. Br Homeopath J. 1997; 86: 73-85.
124. Bellavite P. Complexity science and homeopathy. A synthetic overview. Homeopathy. 2003; 92: 203-212.
125. Bellavite P, Ortolani R, Pontarollo F, Pitari G, Conforti A. Immunology and Homeopathy. 5. The Rationale of the 'Simile'. Evid-Based Complementary Altern Med. 2007; 4: 149-163.
126. Bellavite P, Olioso D, Marzotto M, Moratti E, Conforti A. A dynamic network model of the similia principle. Complement Ther Med. 2013; 21: 750-761.
127. Schwartz GE, Russek LG, Bell IR, Riley D. Plausibility of homeopathy and conventional chemical therapy: The systemic memory resonance hypothesis. Med Hypotheses. 2000; 54: 634-637.
128. Bell IR, Baldwin CM, Schwartz GE. Translating a nonlinear systems theory model for homeopathy into empirical tests. Altern Ther Health Med. 2002; 8; 58-66. Available from: https://pubmed.ncbi.nlm.nih.gov/12017501.

129. Bell IR, Schwartz GE. Adaptive network nanomedicine: An integrated model for homeopathic medicine. Front Biosci. 2013; 5: 685-708.
130. 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.
131. Bell IR. The complexity of the homeopathic healing response part 1: The role of the body as a complex adaptive system in simillimum-initiated recovery from disease. Homeopathy. 2020; 109: 42-50.
132. Nicolis G. Introduction to nonlinear science. Cambridge: Cambridge University Press; 1995.
133. Capra F. The web of life: A new synthesis of mind and matter. New York: Doubleday-Anchor Book; 1996.
134. Griffiths F. Complexity science and its relevance for primary health care research. Ann Fam Med. 2007; 5: 377-378.
135. Grossi E, Buscema M. Introduction to artificial neural networks. Eur J Gastroenterol Hepatol. 2007; 19: 1046-1054.
136. Holden LM. Complex adaptive systems: Concept analysis. J Adv Nurs. 2005; 52: 651-657.
137. Dominici G, Bellavite P, di SC, Gulia P, Pitari G. Double-blind, placebo-controlled homeopathic pathogenetic trials: Symptom collection and analysis. Homeopathy. 2006; 95: 123-130.
138. Walach H, Teut M. Scientific proving of ultra high dilutions on humans. Homeopathy. 2015; 104: 322-327.
139. Walach H, Mollinger H, Sherr J, Schneider R. Homeopathic pathogenetic trials produce more specific than non-specific symptoms: Results from two double-blind placebo controlled trials. J Psychopharmacol. 2008; 22: 543-552.
140. Shah R. Effect of orally administered potentized capsaicin and dihydrocapsaicin in humans: A homeopathic pathogenetic trial. Complement Med Res. 2014; 21: 172-177.
141. Bellavite P, Pettigrew A. Miasms and modern pathology. Homeopathy. 2004; 93: 65-66.
142. Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, et al. Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. Toxicol Appl Pharmacol. 2007; 222: 122-128.
143. Luna-Lopez A, Gonzalez-Puertos VY, Romero-Ontiveros J, Ventura-Gallegos JL, Zentella A, Gomez-Quiroz LE, et al. A noncanonical NF-kappaB pathway through the p50 subunit regulates Bcl-2 overexpression during an oxidative-conditioning hormesis response. Free Radic Biol Med. 2013; 63: 41-50.
144. Wiegant FA, Prins HA, Van WR. Postconditioning hormesis put in perspective: An overview of experimental and clinical studies. Dose Response. 2011; 9: 209-224.
145. Van Wijk R, Wiegant FA. Postconditioning hormesis and the homeopathic similia principle: Molecular aspects. Hum Exp Toxicol. 2010; 29: 561-565.
146. Bell IR, Koithan M. A model for homeopathic remedy effects: Low dose nanoparticles, allostatic cross-adaptation, and time-dependent sensitization in a complex adaptive system. BMC Complementary Altern Med. 2012; 12: 1-21.

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