Marcus Zulian Teixeira

"Homeopathy is not Placebo Effect"

Proof of Scientific Evidence for Homeopathy

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“Homeopathy ***is not*** Placebo Effect”

Proof of Scientific Evidence for Homeopathy

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To Homeopathy,
Science, Philosophy and Healing Art,
which has been enriching Medicine for more than
two centuries.

“Sad time!
It is easier to disintegrate an atom than a prejudice.”

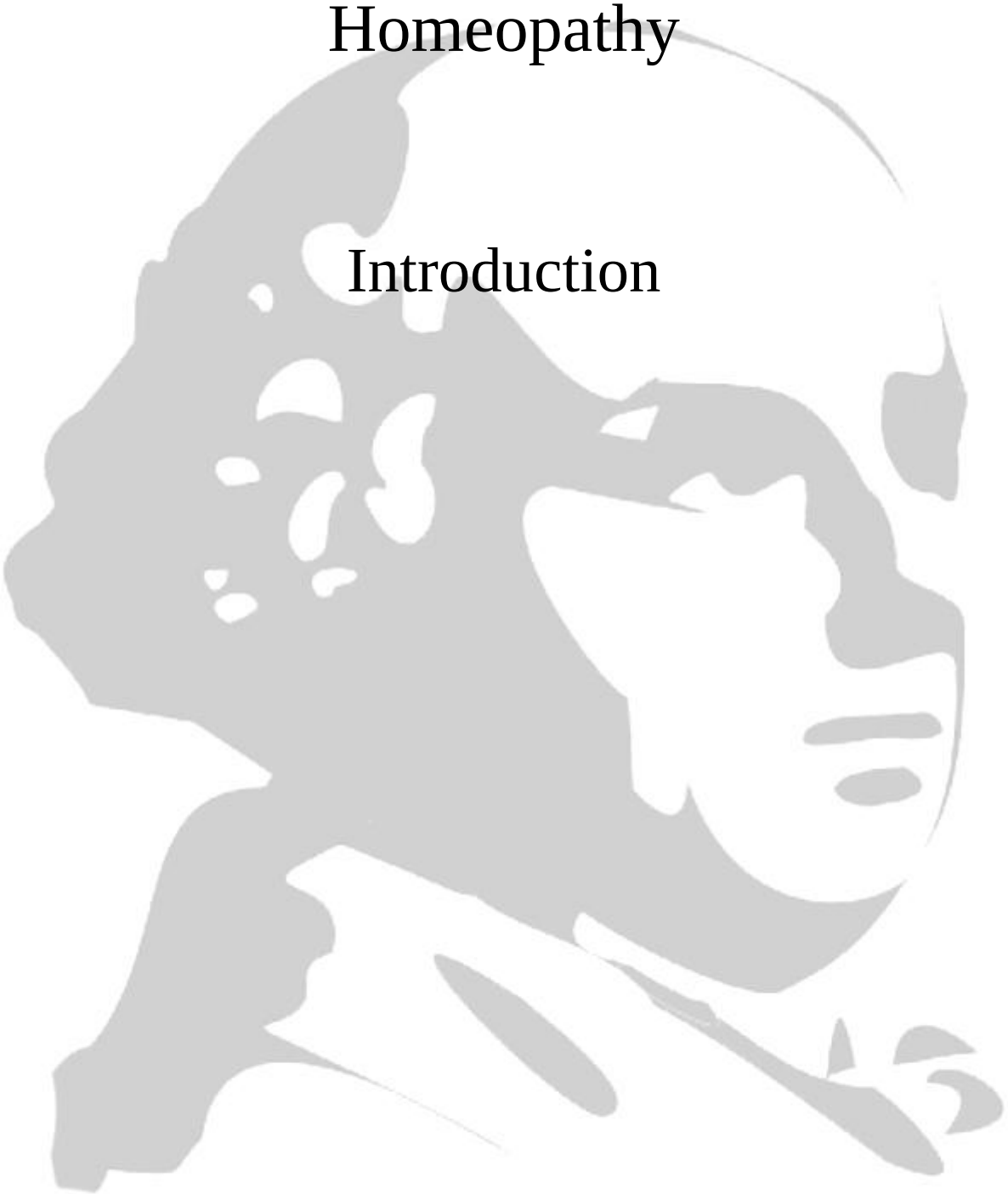
Albert Einstein

Proof of Scientific Evidence for Homeopathy

Summary

Summary

Proof of Scientific Evidence for Homeopathy



Introduction

I. Introduction

Homeopathy has been a medical practice recognized worldwide for more than two centuries, performing care, teaching and research activities in several health institutions and medical schools. It employs a clinical approach based on heterodox and complementary scientific principles (principle of therapeutic similitude, homeopathic pathogenetic experimentation, use of individualized medicines and dynamized or potentiated doses), with the aim of awakening a curative response in the body against its own disorders and/or diseases.

Based on different premises from those used by conventional medical practice, homeopathy is often the target of unfounded and widespread criticism from individuals who systematically deny homeopathic assumptions and any scientific evidence that proves them due to their pseudoskeptical and pseudoscientific stance, which prevents a correct and bias-free analysis.

In order to enlighten doctors, researchers, health professionals and the general public, demystifying culturally rooted dogmatic positions and the pseudoskeptical fallacies that "there is no scientific evidence for homeopathy" and "homeopathy is placebo effect", the Technical Chamber of Homeopathy of the Regional Council of Medicine of the State of São Paulo (TC-Homeopathy, Cremesp) prepared the *"Special Dossier: Scientific Evidence for Homeopathy"* in 2017, made available in three independent editions (online in Portuguese and English; printed in Portuguese) in the *Revista de Homeopatia (São Paulo).* Then, the dossier was published in Spanish in the *La Homeopatía de México* journal in 2023 in an edition commemorating the journal's 90th anniversary.

Encompassing nine narrative reviews on the various lines of homeopathy research and containing hundreds of scientific articles describing experimental and clinical studies, the Dossier highlighted the state of the art of homeopathic science.

Proving and expanding this scientific evidence in 13 chapters, the current work aims to update and clarify knowledge in the area. In addition to elucidating the epistemological premises of the homeopathic model in detail, the work describes the various aspects of basic and clinical research which endorse homeopathic practice and treatment in a continuum of information, data and bibliographic references.

The work discusses various topics related to research in homeopathy, covering everything from “homeopathic clinical epidemiology” to “pseudoskeptic and pseudoscientific strategies used in attacks on homeopathy”, including “pharmacological basis of the principle of similitude”, “experimental studies in biological models”, “randomized controlled clinical trials”, “systematic reviews, meta-analyses and global reports” and “observational studies”, among others.

In view of the fact that it becomes fruitless and tiring to describe and analyze all the studies and experiments from the different research lines, we suggest and systematize in the different chapters for those who want to delve deeper into the areas of interest, bibliographical surveys of existing literature through the different databases.

As we reiterate throughout the work, despite the difficulties and limitations that exist in developing research in homeopathy due to both methodological aspects and the lack of institutional and financial support, the set of experimental and clinical studies described is indisputable proof that “there is scientific evidence for homeopathy” and “homeopathy ***is not*** placebo effect”, contrary to falsely disseminated prejudice. However, new studies must continue to be developed to improve clinical practice and elucidate peculiar aspects of the homeopathic paradigm.

Acting as an integrative and complementary therapy to other specialties, homeopathy can add efficacy, effectiveness, efficiency and safety to medical practice, acting in a curative and preventive manner, reducing symptomatic manifestations and the predisposition to falling ill, with low cost and minimal adverse events, helping doctors to fulfill their “highest and only mission, which is to make sick people healthy, which is called healing” (Samuel Hahnemann, *Organon of Medicine,* § 1).

Proof of Scientific Evidence for Homeopathy

II. Homeopathy

II.1. Introduction

II.2. Scientific evidence of homeopathic principles in databases

II.3. Epistemological premises of homeopathic treatment

II. Homeopathy

II.1. Introduction

Homeopathy is a therapeutic model used worldwide and which, along with other approaches to integrative medicine, has aroused growing interest among users, medical students and doctors[1-3] in recent decades in order to provide safe and effective medical practice, proposing to understand and treat the sick-disease binomial according to a vitalist, globalizing and humanistic anthropological approach[4-6] by valuing the different aspects of the sick individuality.

Homeopathy was founded by the German doctor Samuel Hahnemann in 1796, and constitutes a medical specialization in Brazil, which has been recognized by the Federal Council of Medicine (Conselho Federal de Medicina - CFM) since 1980 (Resolution CFM No. 1000/1980) and with the title of specialist conferred by the Brazilian Medical Association (Associação Médica Brasileira- AMB) since 1990 (Resolution CFM No. 2.068/2013).

Homeopathy develops its activities concomitantly with hegemonic medicine, and disseminates its theoretical, practical and scientific rationale in broad sense postgraduate courses taught by training entities linked to the Brazilian Homeopathic Medical Association (Associação Médica Homeopática Brasileira - AMHB). After the Resolution CFM no. 1634/2002 in 2004, it began to be offered in the medical residency program at the Federal University of the State of Rio de Janeiro (Universidade Federal do Estado do Rio de Janeiro - UNIRIO - Hospital Universitário Gaffrée e Guinle). In addition, three other medical residency programs currently offer homeopathy as an in-service training option (Hospital Regional Público de Betim, Minas Gerais, since 2014; Universidade Federal do Mato Grosso do Sul, since 2015; Instituto Capixaba de Ensino, Pesquisa e Inovação em Saúde, since 2022), with the minimum requirements stipulated by the National Medical Residency Commission (Comissão Nacional de Residência Médica) (Resolution CNRM No. 02/2006).

With the consultation and procedures reimbursed by medical plans and health insurance, it became available in public health services (*sistema único de saúde - SUS*) from 1985 onwards with thousands of specialized doctors practicing in the country. Despite the population's growing demand for therapy, only a small number of Brazilian

municipalities offer homeopathy in their Unified Health System (Sistema Único de Saúde – *SUS*)[7].

Initiatives in global medical education have enabled teaching homeopathic assumptions in medical schools for decades, incorporating teaching, research and assistance activities into the conventional curriculum[1-3]; allowing theoretical information supported by scientific evidence and clinical practices can dissolve prejudice rooted in medical culture[8].

Despite having existed for more than two centuries as a therapeutic option in several countries, homeopathy remains marginalized in the face of modern scientific rationality and the medical profession[9], because it is based on unorthodox concepts that challenge current biomedical thinking. The homeopathic treatment model employs the principle of healing through similitude/similarity, administering infinitesimal doses of unique and individualized medicines that, when previously tried on healthy individuals, caused similar symptoms to those of sick individuals. In order to become a homeopathic medicine, any substance (mineral, vegetable, animal or chemical) must be subjected to these homeopathic pathogenetic experimentation protocols on healthy human beings and have its primary and direct effects described in the Homeopathic Materia Medica.

Aiming to reestablish homeostatic balance, the art of homeopathic healing must be able to identify individual morbid susceptibilities, recognized in the totality of characteristic signs and symptoms manifested by the sick individuality, in order to choose a medicine that awakens a set of similar manifestations in healthy experimenters.

Given that the homeopathic model values psychological and emotional symptoms as high-ranking aspects in the set of human manifestations, whether in homeopathic pathogenetic experimentation or in understanding the etiopathogenesis of organic disorders, this class of subjective and individualizing characteristics is part of the homeopathic healing ideal. Medications that suppress undesirable clinical manifestations without providing proportional psychological and emotional improvements do not satisfy the globalizing conception of the homeopathic healing process.

Therefore, every individualized and well-conducted homeopathic treatment must act in an integrated manner on both psychological and emotional disorders, as well as on general and physical disorders, aiming to provide a state of physical, general, mental, social and spiritual well-being.

In short, the homeopathic model of disease treatment is based on four assumptions or principles: (1) principle of therapeutic similitude or similarity; (2) homeopathic pathogenetic experimentation or trial; (3) individualized medicine (therapeutic individualization); and (4) dynamized or potentized doses (homeopathic ultradilutions). As we will see below, these assumptions are based on several lines of contemporary research[9], contrary to the indistinctly propagated prejudice that "there is no scientific evidence for homeopathy".

II.2. Scientific evidence of homeopathic principles in databases

With the purpose of correlating homeopathic principles with the scientific evidence that underlies them, electronic searches were performed in the MEDLINE database via PubMed and in the LILACS database via Virtual Health Library (VHS) using MeSH and DeCS terms that describe their lines of research, and covering the period until August 2023. The results of the searches are systematized in **Tables 1-4**. Some lines of existing research were cited in the description of each homeopathic assumption, which we will discuss and expand throughout the work.

In relation to the **principle of therapeutic similitude or similarity**, the terms "homeopathy" AND "similia similibus curentur" OR "similitude law" OR "similar law" OR "like cures like" were used and 87 articles were found in the MEDLINE database; while using the terms "homeopathy" AND "rebound effect" retrieved 17 articles. Next, the descriptors "homeopathy" AND "similitude law" OR "similar law" were used in the LILACS database, retrieving 262 articles; then another 27 articles were found using the descriptors "homeopathy" AND "similitude law" OR "similar law" AND "rebound effect" (**Table 1**).

Table 1. Principle of therapeutic similitude or similarity - Systematic search strategy in databases until August 2023 and the results obtained.

Databases	Subject descriptors / Search strategy	Results (articles)
MEDLINE (via PubMed)	"homeopathy" AND "similia similibus curentur" OR "similitude law" OR "similar law" OR "like cures like"	87
	"homeopathy" AND "rebound effect"	17
LILACS (via BVS)	"homeopathy" AND "similitude law" OR "similar law"	262

	"homeopathy" AND "similitude law" OR "similar law" AND "rebound effect"	27

For the assumption of **homeopathic pathogenetic experimentation or trial**, 33 articles were found in MEDLINE using the descriptor "homeopathic pathogenetic trial". In turn, 41 articles were found in LILACS with the descriptors "homeopathy" AND "pathogenetic trial"; another 15 articles were found using the descriptors "homeopathy" AND "pathogenetic experimentation" (**Table 2**).

Table 2. Homeopathic pathogenetic experimentation or trial - Systematic search strategy in databases until August 2023 and the results obtained.

Databases	Subject descriptors / Search strategy	Results (articles)
MEDLINE (via PubMed)	"homeopathic pathogenetic trial"	33
LILACS (via BVS)	"homeopathy" AND "pathogenetic trial"	41
	"homeopathy" AND "pathogenetic experimentation"	15

For the premise of **individualized medicine** (**therapeutic individualization**), 364 articles were found in MEDLINE using the terms "individualized homeopathic treatment" AND "randomized controlled trial"; when the term "meta-analysis" was added to the search, an additional 41 articles were found. Next, 404 articles were found in LILACS, with the terms "homeopathic treatment" AND "randomized controlled trial" (**Table 3**).

Table 3. Individualized medicine (therapeutic individualization) - Systematic search strategy in databases until August 2023 and the results obtained.

Databases	Subject descriptors / Search strategy	Results (articles)
MEDLINE (via PubMed)	"individualized homeopathic treatment" AND "randomized controlled trial"	364
	"individualized homeopathic treatment" AND "randomized controlled trial" AND "meta-analysis"	41
LILACS (via BVS)	"homeopathic treatment" AND "randomized controlled trial"	404

Regarding **dynamized or potentized doses** (**homeopathic ultradilutions**), 129 articles were found in MEDLINE using the terms "homeopathy" AND "basic research" and 37 articles using the terms "homeopathy" AND "memory of water". Similarly, with the descriptors "homeopathy" AND "action mode of homeopathic remedies", 319 articles were found in LILACS; in turn, 189 articles were collected with the descriptors "homeopathy" AND "memory of water" (**Table 4**).

Tabela 4. Dynamized or potentized doses - Systematic search strategy in databases until August 2023 and the results obtained.

Databases	Subject descriptors / Search strategy	Results (articles)
MEDLINE (via PubMed)	"homeopathy" AND "basic research"	129
	"homeopathy" AND "memory of water"	37
LILACS (via BVS)	"homeopathy" AND "action mode of homeopathic remedies"	319
	"homeopathy" AND "water memory"	189

II.3. Epistemological premises of homeopathic treatment

II.3.1. Principle of therapeutic similitude (similarity)

Based on the study of the pharmacological properties of dozens of medicinal substances of his time, in which he observed a secondary reaction (indirect effect) of the organism after the primary action (direct effect) of different classes of drugs, Hahnemann enunciated an aphorism for the general action of medicines on the human constitution.

> "Every force which acts on life, every medicine affects, to a greater or lesser extent, the vital force, causing a certain change in the state of man's health for a greater or lesser period of time. This is called **primary action**. [...] To this action, our vital force strives to oppose its own energy. Such opposite action is part of our conservation force, constituting an automatic activity of the same, called **secondary action** or **reaction**." (*Organon of Medicine,* § 63)[10]

Illustrating this phenomenon or "natural law", Hahnemann describes the primary actions of the medicines of his time, promoting changes in the various physiological systems, and the consequent secondary actions of the organism (vital reaction or maintenance or conservation force), which manifests itself in the sense of neutralizing

the primary disorders promoted by drugs, seeking to return to the homeostatic balance prior to drug intervention.

> "[...] Ingestion of strong coffee is followed by overexcitation (primary action); however, great relaxation and drowsiness (reaction, secondary action) remain for some time if it is not continued to be suppressed through more coffee (palliative, short-lived). After the deep, numbing sleep produced by opium (primary action), the following night will be even more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea follows (secondary action), and after purgatives that irritate the intestines (primary action), obstruction and constipation occur for several days (secondary action). Thus, everywhere, after the primary action of a power (in large doses) capable of profoundly transforming the health state of a healthy organism, it is precisely the opposite that always occurs in the secondary action, through our vital force." (*Organon of Medicine,* § 65)[10]

By administering simple substances to sick individuals which aroused similar symptoms in healthy experimenters, the principle of therapeutic similitude aims to stimulate the organism's reaction against its own disorders or diseases, inducing a curative homeostatic response (*similia similibus curentur*).

Cited since Hippocrates, the principle of similarity (vital or homeostatic reaction) finds its scientific basis in the "rebound effect" of modern drugs (paradoxical reaction of the organism), being described after suspending or changing doses of numerous classes of drugs that act in a palliative way (contrary, opposite or antagonistic) to the symptoms of diseases, aggravating the symptoms initially suppressed by the principle of contrary (*contraria contrariis curentur*). The rebound effect has been confirmed in hundreds of clinical and experimental pharmacology studies[11-24].

Despite the idiosyncratic nature of this rebound phenomenon which manifests itself in a small proportion of individuals, scientific evidence warns of the occurrence of serious and fatal iatrogenic events as a result of this greatly intense paradoxical reaction. Illustrating these serious iatrogenic events, the occurrence of thrombotic events (acute myocardial infarction and stroke) is observed after administration of selective and non-selective anti-inflammatories of cyclooxygenases, secondary to the primary antithrombotic action; irreversible bronchospasms may occur after long-acting bronchodilators; in the case of serotonin reuptake inhibitor antidepressants, exacerbation of depression and suicidal ideation may occur; the emergence of severe forms of

multiple sclerosis and psoriasis has been observed after immunobiologicals used in their treatment; among other classes of drugs [13-24].

When used according to the principle of therapeutic similarity, the magnitude of this rebound effect (vital reaction) can also awaken proportional healing responses. Therefore, since 2003, we have been proposing a systematization for the use of the curative rebound effect of 1,250 modern drugs ("*New Homeopathic Medicines: use of modern drugs according to the principle of similitude*")[25-33], administering to sick individuals, in infinitesimal doses (dynamized or potentized doses), the same drugs that caused similar adverse events,, with the aim of stimulating a homeostatic or paradoxical reaction of the organism against its own disorders.

In a post-doctoral project completed in 2017, we demonstrated the efficacy and safety of this proposal in administering dynamized estrogen (17-beta estradiol) in the homeopathic treatment of chronic pelvic pain in patients with endometriosis refractory to conventional treatments, through a randomized, double-blind and placebo-controlled clinical trial[34-36]. This was possible due to the fact that endometriosis is an estrogen-dependent syndrome and 17-beta estradiol presents a set of signs and symptoms of pathogenetic effects (primary or adverse effects) which are very similar to endometriosis syndrome (anxiety, depression, insomnia, migraine, abdominal pain, dysmenorrhea, dyspareunia and endometrial hyperplasia, among others)[37].

II.3.2. Homeopathic pathogenetic experimentation or trial

In order to acquire knowledge of the healing properties of substances which enable applying the principle of therapeutic similitude, homeopathy uses homeopathic pathogenetic trials or experimentation as a model of clinical pharmacological research (similar to phase 1 pre-clinical pharmacological trials), valuing all classes of symptomatic manifestations (mental, general and physical) aroused by medicines in humans, termed by modern pharmacology as adverse or side effects of drugs.

> "All the pathogenetic effects of each medicine must be known, meaning that all the symptoms and morbid alterations of health which each of them is especially capable of causing in the healthy man must first be observed before one can hope to find and choose, among them, the homeopathic healing means suitable for most natural diseases." (*Organon of Medicine*, § 106)[10]

Following the premises stipulated by Hahnemann (*Organon of Medicine,* § 105-145)[10], around 3,000 substances have been experimented with in these 200 years of homeopathic practice following different pathogenetic experimentation protocols[38], with the aim of knowing and cataloging the "pathogenetic power of medicines, so that when you need to cure, you can choose one among them whose symptomatic manifestations may constitute an artificial disease as similar as possible to the totality of the main symptoms of the natural disease to be cured".

All signs and symptoms aroused in the various pathogenetic trials of these 3,000 homeopathic medicines were compiled for the Homeopathic Materia Medica, following an anatomical-functional systematization.

Homeopathic doctors also use the Homeopathic Symptom Repertory in clinical practice, in which all homeopathic medicines that aroused the same sign/symptom in experiments are grouped under the same "heading", facilitating selection of the homeopathic medicine that encompasses all characteristic signs and symptoms of the individual.

II.3.3. Dynamized or potentized doses (homeopathic ultradilutions)

Contrary to the biochemical and dose-dependent pharmacological model, it is surprising to biomedical reasoning that ultra-diluted (dynamized or potentiated) substances in lower concentrations than Avogadro's constant (6.02×10^{23} mol^{-1}) can trigger a response in biological systems or living beings, which is the main target of criticism of the homeopathic model.

With the initial objective of avoiding intoxications and symptomatic aggravations that the principle of therapeutic similarity could cause in patients, Hahnemann proposed a pharmacotechnical method for preparing homeopathic medicines (method of dynamization or potentiation), in which the substances are diluted and shaked (succussioned) successively with the aim of reducing the primary pathogenetic effect. He observed *a posteriori* that these infinitesimal and imponderable preparations mobilized biological activity in spheres of individuality not reached by weighted doses, with an emphasis on psycho-emotional dynamics (*Organon of Medicine,* § 269)[10].

In a simplified way, the pharmacotechnical method of dynamization or potentiation described in the Brazilian Homeopathic Pharmacopoeia[39] consists of centesimal and successive dilutions of the matrix substance, accompanied by 100 vigorous shaking (succussions) per passage (Hahnemannian centesimal or cH) (**Table 5**).

Table 5. Pharmacotechnical method of preparing homeopathic medicines (dynamization or potentiation) in Hahnemannian centesimal potencies (cH).

Pharmacotechnical method of preparation of homeopathic medicines (cH)
1 part of matrix substance (mineral, vegetable or animal) + 99 parts of water ⇨ 100 succussions ⇨ Dynamization or potency 1cH (10^2 mol^{-1} of matrix substance);
1 part of 1cH + 99 parts of water ⇨ 100 succussions ⇨ potency 2cH (10^4 mol^{-1});
1 part of 2cH + 99 parts of water ⇨ 100 succussions ⇨ potency 3cH (10^6 mol^{-1});
1 part of 3cH + 99 parts of water ⇨ 100 succussions ⇨ potency 4cH (10^8 mol^{-1});
And so on...
Dynamization or potency 12cH ⇨ 10^{24} mol^{-1} of matrix substance (Avogadro's constant: 6,02 x 10^{23} mol^{-1}) ⇨ absence of any gram molecule.

cH: Hahnemannian centesimal potencies.

As previously described, above the 12cH potency these ultradilutions present lower concentrations than Avogadro's constant (6.02 x 10^{23} mol^{-1}), in which there is an absence of any gram molecule of the original substance in the final solution, making them free from of toxicity and/or adverse events[40], as demonstrated by the safety of bisecular homeopathic treatment with toxic substances of high pathogenetic power (*Arsenicum album*, *Atropa belladonna*, *Cuprum metallicum*, *Lachesis muta*, *Phosphorus* and *Rhus toxicodendron,* among many others).

In classic homeopathic treatment, these homeopathic ultradilutions (UDs or HDs in English) are preferably administered in strengths of 12Hc, 30cH, 200cH and 1000cH, in single monthly doses or repeated daily doses, depending on clinical indication (chronic or acute diseases, respectively).

The ability of this medicinal "information" (contained in infinitesimal doses of ultra-diluted substances) to promote changes in physiological systems, in a manner analogous to weighted doses, has been studied in experimental work that employs physicochemical or biological research models.

Some hypotheses based on physical-chemical experimental models seek a scientific explanation for the phenomenon of "information" transmission about the primary effects of substances through homeopathic ultradilutions. Among them, we mention research that studies the electromagnetic modifications of water according to quantum electrodynamics, in which the aqueous solution would not represent an inert cluster of molecules, but rather a dynamic medium, capable of selecting and catalyzing molecular reactions according to the various electromagnetic fields of the solute dissolved inside. Through mathematical and experimental models, they infer that the electromagnetic

field of a solute can generate certain domains of stable coherence in the solvent (with specific structures and vibrations), producing agglomerates or "clusters" of water molecules (with specific sizes, shapes and properties) as an "electromagnetic signature" of the solute in water ("water memory"). Therefore, the water organization would be a dynamic, coherent and reproducible process, associated with long-range and very low intensity electromagnetic interactions, transmitting the "electromagnetic information of the solute" initially diluted and succussioned by the dynamization process[41].

As we will see below in a specific chapter, numerous experimental studies in biological models (*in vitro*, plants and animals), in different areas of scientific knowledge, support the assumption that infinitesimal doses can trigger biological phenomena similar to those obtained with weighted doses of the same substances, supporting the plausibility of using ultradiluted medicines in homeopathic therapy[42,43].

II.3.4. Individualized medicine (therapeutic individualization)

According to Hahnemann, a doctor who calls themself a "legitimate healing artist" must be able to recognize what needs to be cured in each case individually and understand the curative element of medicines, adapting them in quality and quantity to the needs of the patient, according to the principle of therapeutic similitude.

Viewing the illness process as a weakening of the physiological mechanisms of adaptation and compensation, Hahnemann correlated any physiological imbalance to the corresponding symptomatic manifestations presented by the individual, using the set of signs and symptoms (symptomatic totality) as the main reference to diagnose the "vital force illness" (individual predisposition, morbid susceptibility or homeostatic imbalance) and to prescribe the most similar homeopathic medicine to the sick individuality.

> "[...] the totality of its symptoms, *this picture of the disease's inner being that is reflected on the outside, meaning the suffering of the vital force*, must be the main or the only one through which the disease makes known the means of healing that it needs, the only one that can determine the choice of the appropriate means of care - in short, the totality of the symptoms must be the main thing for the healing artist, if not the only thing that they need to know and remove through their art in each case of illness, so that illness can be cured and transformed into health." (*Organon of Medicine*, § 7)[10]

In the set of manifested signs and symptoms, homeopathic semiology selects "the most evident, singular, unusual and characteristic" in each case, disregarding common, general and undefined symptoms due to the inherent absence of individualizing (idiosyncratic) power in them.

> "In this search for a specific homeopathic cure, meaning in this confrontation of the characteristic set of signs of natural disease against the series of symptoms of existing medicines in order to find one whose artificial morbid powers correspond by similarity to the illness to be cured, one must certainly pay special attention and almost exclusively to the *most evident*, *singular*, *unusual and specific* signs and symptoms (characteristic) of the case of illness, because in the series of symptoms produced by the chosen medicine, it is *mainly these which must correspond to very similar symptoms*, so that it is more convenient to cure. The most general and undefined symptoms: lack of appetite, headache, weakness, restless sleep, malaise, etc., deserve little attention due to their vague nature (if they cannot be described more precisely), as something so general can be observed in almost all diseases and medications." (*Organon of Medicine*, § 153)[10]

Associating medicinal individualization with the prescription of "a *single simple* medicinal substance" at a time, Hahnemann is categorically opposed to the concomitant use of more than one homeopathic medicine (mixture of medicines or homeopathic complexes), since homeopathic pathogenetic experimentation, a reference for the correct and safe therapeutic prescription, was carried out with simple and single substances.

> "In no case is treatment *necessary, and therefore it is not permissible* to administer more than a *single*, *simple* medicinal substance at a time to a patient. It is inconceivable that there could be the slightest doubt about what is more in accordance with nature and more rational: prescribing a *single*, *simple* and well-known medicinal substance in a case of illness or mixing several different ones. In the only true, simple and natural art of healing, homeopathy, it is absolutely not permitted to give the patient two different medicinal substances *at once.*" (*Organon of Medicine*, § 273)[10]

Therefore, adequate homeopathic treatment must prioritize **individualization of the single medicine according to the most peculiar and characteristic signs and symptoms of each patient, in their different constitutional aspects (mental, general**

and physical), enabling that each individual may receive distinct single medications for the same disease according to their own susceptibilities or idiosyncrasies (mental, general and physical).

Several randomized controlled clinical trials (RCTs) that disrespected this therapeutic individualization, administering the same medication to different individuals with the same disease (exemplified in the indiscriminate use of *Arnica montana* for inflammatory processes in general)[44], did not show significant results compared to placebo, as they violate the scientific rationality of the homeopathic model. The same occurred with systematic reviews and meta-analyses that grouped RCTs with non-individualized medications[45-47], unlike those that valued individualized therapy[35,48,49].

It is worth mentioning that this process of medicinal individualization requires a period of regular and variable monitoring, in which the responses to the different medicinal hypotheses (single individualized medicines selected through globalizing homeopathic semiology) are evaluated successively, adjusting the medicines, doses and homeopathic potencies to the different susceptibilities of each patient[50].

In addition to these brief citations used to exemplify the scientific basis of each premise of homeopathic treatment, these assumptions or homeopathic principles are based on hundreds of studies in different lines of contemporary research, as we will see later, contrary to the prejudice propagated without distinction by pseudoskeptics and pseudoscientists that “there is no scientific evidence for homeopathy”.

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Proof of Scientific Evidence for Homeopathy

III. Homeopathic clinical epidemiology

III.1. Introduction

III.2. Premises and principles of clinical epidemiology

III.3. Types of epidemiological studies

III.4. Premises and principles of homeopathic clinical epidemiology

III.5. Types of epidemiological studies in homeopathy

III. Homeopathic clinical epidemiology[a,b (1,2)]

III.1. Introduction

When we talk about *science* or *scientific truth*, some determinants must be highlighted:

- Science seeks truth (certainty), meaning that which is in accordance with the reality of facts or phenomena.
- Scientific truth is dynamic and not absolute (transitory in nature), as new information and ways of approaching the same problem are proposed every day.
- The search for truth involves rigorous application of the scientific method, which tests it in an experiment starting from a hypothesis (question), and finally accepts or refutes it.
- Therefore, the scientific method exists to answer questions about various doubts (uncertainties) and seek an approximation of the reality of facts or phenomena.
- When testing a hypothesis through the scientific method, we seek to control all potential sources of systematic and random errors in the study, so that its results and conclusions can be considered valid, reproducible and safe in the end.
- Thus, we can talk about approximation of the truth, since absolute truth is an abstraction.

According to these determinants, *scientific truth* can be defined as the result of empirical observation, controlling for systematic and random errors in the study:

Scientific truth = observed – systematic and random errors

As William Osler (1849-1919), a physician and professor of medicine, devotee of humanistic medicine at the bedside and founder of the Johns Hopkins School of Medicine and Hospital, said: “Who can speak of the uncertainties of medicine as an art? The practice of medicine is art based on science. Medicine is a science of uncertainty

[a] Teixeira MZ. Epidemiologia clínica homeopática: premissas e princípios para a elaboração da pesquisa clínica em homeopatia. Rev Homeopatia (São Paulo). 2022;84(3-4):4-24. https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1402361

[b] Teixeira MZ. Epidemiología Clínica Homeopática: Premisas y Principios para la Elaboración de Investigación Clínica en Homeopatía. Homeopatía Méx. 2023;92(733):23-46. https://homeopatiamex.similia.com.mx/index.php/Revista/article/view/335/301

and an art of probability" (*Aphorisms from his bedside teachings and writings*, Epitomes, 1950).

As in other medical specializations, homeopathy needs to seek the *scientific truth* about its treatment method, answering the doubts that hover over its therapeutic activity through the rigorous application of the scientific method, developing research in the basic and clinical areas of biomedicine. While *basic research* aims to scientifically substantiate homeopathic assumptions, seeking to respond to uncertainties about the biological plausibility of homeopathic medicine, *clinical research* aims to scientifically substantiate homeopathic clinical practice, seeking to respond to uncertainties about the clinical plausibility of homeopathic treatment.

Although there already exists a body of research and scientific evidence that supports clinical practice and homeopathic assumptions[3], new information, approaches and ways of applying the homeopathic proposal for treating diseases must be developed and suggested continuously, with the aim of improving its efficacy and effectiveness against various health disorders.

Epidemiology is a branch of medicine that studies the different factors which intervene in the diffusion and spread of diseases, their frequency, their distribution mode, their evolution and the placement of the necessary means for their prevention, meaning that it studies the peculiarities of diseases or health-related conditions in specific populations. In turn, *clinical epidemiology* deals with clinical practice through the study of variation and determinants of the evolution of diseases, with its knowledge being essential for the correct outline (design and planning) of clinical studies and research.

With the advent of COVID-19 at the beginning of 2020, in response to the request of colleagues to assist in the development of clinical studies which would allow us to suggest homeopathic therapies to combat the epidemic, we presented two live sessions (webinars) on the topic on the Brazilian Homeopathic Medical Association (AMHB) channel on the YouTube social network ("*Lives AMHB #HomepatiaEmAção#*")[4,5], later made available in the Virtual Health Library (VHL)[6,7], in which we cover the following topics:

- "[Homeopathic Clinical Epidemiology in COVID-19: premises for the development of epidemiological studies (Part 1)]"[4,6].
- "[Homeopathic Clinical Epidemiology in COVID-19: premises for developing epidemiological studies in epidemics (Part 2)]"[5,7].

Based on the aforementioned presentations[4-7] and the article published in the *Revista de Homeopatia (São Paulo)* in 2022[1,2], the current review addresses the premises and principles of clinical (homeopathic) epidemiology, highlighting the fundamental aspects for developing clinical research in homeopathy. This material provides a summary of the subject, with the aim of encouraging those interested to further study the reference works[8-11].

III.2. Premises and principles of clinical epidemiology

Background

At the beginning of medical practice, personal experience guided doctors in their decisions. It was observed over time that most of these predictions and personal conclusions were not sustainable, making the traditional "how I do it" unfeasible, still used today by many colleagues to justify their conduct, however heterodox it may be. On the other hand, although several pathophysiological hypotheses have emerged to justify the cause of diseases and their treatment, their validity has often been denied after carrying out controlled clinical trials.

Therefore, there was a need to define more rigorous methods for evaluating scientific evidence to support and equip doctors in their daily activities. Clinical epidemiology arises with this proposal, bringing together the concepts of epidemiology and clinical medicine with the aim of assisting doctors in resolving diagnostic, therapeutic and prognostic doubts (uncertainties) that arise in clinical practice.

A doctor can decide on the validity (certainty) of the results and their applicability in daily clinical practice through methodological knowledge of clinical studies carried out and their critical analysis, with these being some of the objectives of this "basic science for the clinician".

Definition

Clinical epidemiology is a basic science which makes predictions about individual patients by counting clinical events in similar patients and using sound scientific methods in studies of groups of patients to ensure that the predictions are correct.

As stated earlier, clinical epidemiology derives from the two parent disciplines, clinical medicine and epidemiology: it is "clinical", because it seeks to answer clinical questions and guide clinical decisions based on the best available evidence; it is "epidemiology", because many of the methods used to answer these questions were developed by

epidemiologists and because the care of individual patients is viewed in the context of the larger population of which the patient is a member. They started together, then they separated in the last century, but they are starting to interrelate again.

Objective

The objective is to develop and apply clinical observation methods which allow safe predictions and lead to valid conclusions, preventing doctors from being deceived by systematic errors (biases) or random errors (chance), helping them to improve clinical practice.

The objective represents an important approach to obtaining the type of response that clinicians need to make good decisions in the care of their patients, as no doctor will have enough experience to recognize all the subtle and long-term relationships that interact with each other in the characterization of most of diseases.

Therefore, **when preparing clinical studies, in any area of medicine, including homeopathy, the premises and principles of clinical epidemiology must be followed and respected**, so that the results provide safe and valid information, getting closer to the *scientific truth.*

Premises of clinical epidemiology:

- Use of probabilities, as clinical situations involving diagnosis, prognosis and treatment are uncertain and require a numerical estimate that reflects each situation.
- The best estimate for an individual patient is based on previous experience with similar groups of patients.
- Clinical observations can be affected by systematic errors (biases) which can lead to misleading conclusions due to the skills and biases of patients and clinicians.
- Clinical observations are also influenced by chance (random variation).
- Clinicians should guide their practice on observations based on sound scientific principles to avoid being misled, which include controlling bias and estimating the role of chance on outcomes.

Principles of clinical epidemiology

Among the principles and assumptions of clinical epidemiology, we highlight: Population and sample; Probability, risk and statistics; Clinical effect measures (risks); Precision measure (Confidence Interval, CI); Reliability and accuracy of results; Systematic error or bias; Random error or chance; Internal and external validity;

Clinical and statistical significance; Sample size (NNT); and Clinical outcomes, among others.

Population and sample

Population is a group of individuals who live in a certain context or have a common characteristic. When studying a population, we are often unable to obtain data from its entirety, and therefore we resort to samples (subsets) of the population.

The sample can be obtained by convenience or randomly. A random sample is representative of the population and avoids selection bias as it is composed at random and does not depend on the researcher's criteria. A convenience sample is suspected of selection bias as long as its selection criteria are not substantiated.

Probability, risk and statistics

Due to the difficulty in predicting an event or clinical outcome (uncertainty), clinical epidemiology uses probabilities to express its manifestation (measurement of events/outcomes). We deal with probabilities all the time in daily clinical activity. Whether estimating the risk of a patient developing a disease based on risk factors, or analyzing the results of an intervention or diagnostic test based on the patient's clinical data. Probabilistic estimates are made based on prospective studies and are the best inference available to establish prognoses in the clinic.

The event of interest in clinical research can be viewed as a binary response: success or failure. Based on this, we can derive event risk rates and accuracy measures of those rates. Risk is defined as "the probability of an individual developing a change in their health pattern (health-illness) over a certain period of time".

Statistics, "mathematics of uncertainties", is a discipline that collects, classifies and analyzes numerical data systematically. Through inductive procedures, it generalizes the results of a sample to the population under study. There are two types of inductive statistical procedures: estimation of parameters through data description and their precision (mean and standard deviation; event rate and CI) and hypotheses or statistical significance tests (chi-squared and student's t-tests).

The statistical objectives in clinical research are: data description, estimation of parameters, exploration of associations between variables, comparison of groups, and finally, application of regression models. Probability and risk, as well as their practical application, are measures of events or outcomes that assist the statistical interpretation of the results of clinical studies.

As Frank Hyneman Knight (1885-1972), economist and founder of the Chicago School, said, “if you don’t know what will happen, but you are aware of the probabilities, that is risk; if you don’t even know the probabilities, that’s uncertainty”.

Clinical effect measures (risks)

Measuring events is the everyday activity of the clinical researcher. The results of a clinical trial are expressed in number of events and rates, where the denominator represents the number of people at risk (the entire group) and the numerator represents the number of events occurring in the group.

From these numbers, we can derive five important measures of clinical effect: Relative Risk (RR), Absolute Risk Reduction (ARR), Relative Risk Reduction (RRR), Number Needed to Treat (NNT) and Odds Ratio (OR).

Precision measure (Confidence Interval, CI)

The statistical precision of a point estimate is expressed by the confidence interval (CI), usually the 95% confidence interval (95%CI) around the estimate. Its interpretation is as follows: in a bias-free study, there is a 95% probability that the interval includes the true clinical effect of the intervention under investigation.

The 95%CI means that the result will be within this range in 95 of 100 hypothetically performed studies. The five excluded studies represent extreme values (lower and upper limits) that probably occurred by chance (probability of significance or P-value or $p < 0.05$). Therefore, they are excluded from an interval that wants to estimate where certainty is.

The narrower this range, the greater the probability (chance) that this is the true magnitude of the effect. On the other hand, very wide intervals give us less confidence in estimating the clinical effect of the intervention. Statistical precision increases with the statistical power of the study, which in turn depends on the sample size.

Reliability and accuracy of results

Reliability or accuracy is the extent to which measurements of a stable phenomenon are reproducible, meaning they achieve similar results when repeated. A given diagnostic test or therapeutic intervention is reliable or trustworthy when its results are consistently reproduced at different times and places.

Accuracy or precision is the degree to which measurement results correspond to the true state of the phenomena being measured. The accuracy of a measure or practice is measured by the number of true positives and true negatives in relation to all individuals

submitted. Few false positives and false negatives reflect high accuracy. High accuracy reflects small systematic and random errors.

Systematic error or bias

In the common sense, bias, vice or tendency is a distortion of the observer's judgment. It manifests itself as an irrational inclination to attribute a more favorable or unfavorable judgment to something, person or group. **Bias can be a consequence of the observer's involvement with the object of their observation or with prejudices**.

In clinical epidemiology, systematic error or bias is defined as any process, at any stage of inference, which tends to produce results and conclusions that systematically deviate from true values (values that depart from reality). Its effect distorts the estimate of a variable, for example, increasing the mean of a variable or decreasing the prevalence of a characteristic (generating "uncertainty" in the results).

The potential for bias does not mean that it is always present in the study. The issue of bias demands that both the researcher and the evaluator first of all know where and when to look for it, and what to do to avoid it. It is also important to determine the magnitude of the bias and whether it is large enough to modify the study's conclusions and its application in clinical practice. The burden of proof that bias exists or not, whether or not it influenced the results, is always on the investigator.

Therefore, the researcher must be aware of all potential biases, both in the planning phase and in the data collection and analysis phases of the study, in order to guarantee the internal validity of the study. Basically, we have three groups of biases: *selection bias*, *measurement bias* and *confusion bias.*

Selection bias occurs when the study sample is not representative of the population and results from the way individuals were selected for the study. Selection bias can be avoided by inferring chance in patient selection: in a clinical trial, the allocation of patients to each group (active and placebo) must be random, a process we call randomization. This guarantees each individual patient the same chance of being allocated to one group or another. This way, the researcher does not interfere in the process, eliminating selection bias.

Measurement, *evaluation* or *information bias* occurs when the methods of measuring events (outcomes) differ between groups. As causes of measurement bias, we can mention the influence of the examiner (or the person being examined) in data collection; the imprecision in defining the event and choosing its indicators; the low validity of the

collection instrument; etc. There are some strategies to avoid measurement bias, such as: double blinding of study participants (examiner and examinee); correct selection of the event (outcome) and its indicators; choice of valid collection instrument; among others.

Confusion or *confounding bias* occurs when there is no comparability between the groups studied. This happens when variables that produce clinical outcomes are unequally distributed between groups. Two factors are associated ("travel together") and the effect of one of them is confused or distorted by the effect of the other. Several factors can cause confusion bias, when their influence is not valued and minimized in the study design, such as: seasonality, doctor-patient relationship, consultation effect, placebo effect, Hawthorne effect, etc.

Among the confounding biases, **the placebo effect** is the most significant, being responsible for non-specific therapeutic effects to the order of 20-30% on average in various clinical conditions, as demonstrated by meta-analyses of randomized, double-blind and placebo-controlled clinical trials (RCTs)[12,13] (**Table 1**).

Table 1. Placebo Effect - Specific Meta-Analyses of Randomized Controlled Trials.

Diseases	Placebo effect	Randomized controlled trials (RCTs)	References
Ulcerative colitis	26,7%	38 RCTs	Ilnyckyj et al., 1997
Asthma	6,0%	33 RCTs (1243 patients)	Joyce et al., 2000
Major depression	29,7%	75 RCTs	Walsh et al., 2002
Crohn's disease	19,0%	32 RCTs (1047 patients)	Sue t al., 2004
Irritable bowel syndrome	40,0%	45 RCTs (3193 patients)	Patel et al., 2005
Chronic fatigue syndrome	19,6%	29 RCTs (1016 patients)	Cho et al., 2005
Bipolar disorder	31,2%	20 RCTs	Sysko and Walsh., 2007
Migraine	21,0%	32 RCTs	Macedo et al., 2008
Cancer	↓ pain, ↑ appetite, ↑ weight, ↑ activity, ↓ tumor	37 RCTs (1237 patients)	Chvetzoff and Tannock, 2003

The randomized, double-blind and placebo-controlled trial (RCT) is considered the "gold standard" among the various designs of epidemiological studies, in order to avoid (minimize as much as possible) biases and uncertainties in the results.

Random error or chance

Observations on a sample of patients, even if not biased, may be a misrepresentation of the real situation of the population, simply by chance. However, if observations are repeated on many similar samples, the results will show variation around the true value.

Random error arises exclusively from chance and can be estimated by statistical tests. Unlike systematic error, which deviates values in one direction or another, random error varies uniformly around the real value, but without changing it. The divergence between an observation made in the sample and another made in the population solely due to chance is called random or random variation.

Statistics help to estimate and reduce the probability of chance (random variation) being responsible for clinical results by allowing better study design and analysis. However, random variation cannot be completely eliminated, and chance must always be considered when evaluating the results of clinical observations.

Chance affects all steps involved in clinical observations and random variations can occur in the selection (sample) of patients for the study, in the choice of treatment groups and in the measurement of events between groups. Therefore, there is a clear need to quantify the degree to which random variation can be accounted for in the study results. This is done through statistical significance tests (chi-squared and student's t-tests, for example).

The result of these statistical tests is generally reported in terms of probability of significance or P-value (P or p), which indicates the probability that a certain effect could have occurred by chance alone, inferring that there is no relationship between exposure and disease. Therefore, $p < 0.05$ (95%CI) means that there is less than a 5% chance of observing such an extreme result just by chance, concluding that the association between exposure and outcome is statistically significant. Statistical significance is also related to sample size. Statistical tests detect small differences in studies with large samples.

Inverse relationship between accuracy/bias and reliability/chance

The two main sources of error - bias and chance - are not mutually exclusive. Both are present most of the time, and their distinction helps in their management and analysis. In theory, bias can be prevented by adequate study design and conduct (randomization, control group and blinding) or corrected through appropriate data analysis. Unlike identified biases, no statistical treatment can correct unknown biases in the data. In turn, chance cannot be eliminated, but its influence can be minimized by adequate study

design (randomization and sample size) and the remaining error can be estimated by statistics.

Thus, these errors can be minimized if the clinical investigation is planned and conducted appropriately (minimizing systematic errors or biases and increasing accuracy or precision) and subjected to adequate statistical analysis of the data (minimizing random errors or chance and increasing reliability or accuracy).

Internal and external validity

Two fundamental questions arise when we make inferences about a population from observations in a sample: Are the research conclusions correct for the people in the sample? If so, does the sample satisfactorily represent the population of interest? Validity defines the extent to which the results of a study are correct in a given context (method and population).

Internal validity applies to the results of a study carried out under ideal conditions (method and population) and not in other contexts. Internal validity is determined by the planning quality and the study execution, and is threatened by all biases and chance. Internal validity is a necessary but not sufficient condition for clinical observation to be useful. The results of an indisputable study, with high internal validity, can be completely biased if they are generalized to the wrong patients (sampling bias).

External validity concerns the degree of applicability or generalization of the results of a study (internal validity) to other contexts (routine or real-life conditions). Generalizability can rarely be satisfactorily assessed in a single study and multicenter studies can improve this estimate.

Internal validity relates to the effectiveness of a given measure or intervention, while external validity relates to effectiveness.

Clinical and statistical significance

Clinical and statistical significance are not synonymous. It is known that differences in clinical effect between two interventions can be large and not be detected in statistical analysis if the sample is small. On the contrary, differences in effect in large samples, even if very small, can produce significant results. Therefore, the clinical significance that the intervention produces in the patient's prognosis is more important than the statistical significance (P or p), as it is independent of the sample. Thus, clinical significance is assessed by the impact that the study results have on clinical evolution.

Sample size (NNT)

When planning a clinical trial, calculating the sample size or number needed to treat (NNT) is essential, as its internal validity depends on it. To this end, adequate significance and statistical power levels are necessary to detect clinically relevant differences between groups.

Clinical trials with small samples have low statistical power in detecting small to moderate differences (effects) (10 to 20%) between the two interventions. Effects above 50% require samples with thousands of individuals. On the other hand, clinical trials with small samples that show differences between groups above 30% can demonstrate a very significant effect.

The NNT is calculated according to three factors: alpha error, beta error and clinically significant difference (statistical programs).

Clinical outcomes

Clinical outcomes (or end-points) are events which are considered important and objects of the study hypothesis. They are pre-defined in the protocol, collected and verified during the course of the study, or at its end.

The correct choice of clinical outcomes (for each type of study) is of fundamental importance to assess the clinical relevance of the measure or intervention (often, the choice of an inappropriate outcome makes the study unfeasible).

Bias in measuring clinical outcomes must be avoided by blinding those involved, using appropriate measurement methods or instruments and correct and uniform application across groups.

III.3. Types of epidemiological studies

Stages of epidemiological reasoning

A hypothesis regarding a possible association between a certain factor (*exposure*) and the occurrence of an event (*outcome*) may arise from clinical observation, laboratory research or theoretical speculations. Testing this hypothesis must be conducted through epidemiological studies that include comparison groups. To do so, the study must be carried out through systematic data collection and corresponding analysis, with the objective of determining the existence or not of an association between the exposure (*cause*) and the outcome (*effect*) of interest.

Next, it is necessary to evaluate the validity of the possible statistical associations observed, excluding chance (random error), systematic errors (biases) in the data

collection or interpretation and the effect of other variables that may be responsible for the observed association (confounding factors).

Finally, the judgment focuses on the existence of a cause and effect association, taking into account criteria for evaluating the causal association, including: strength of the association, consistency of the obtained results, dose-response effect and biological plausibility, among others.

Types of epidemiological studies

Epidemiological studies can be divided into two large groups: observational studies and experimental studies. Among observational studies, there are descriptive ones (case report or series of cases) and analytical ones (cross-sectional, case-control, cohort and ecological). Among experimental studies, there are randomized and controlled clinical trials (RCT), randomized and controlled clinical trials with groups (clusters), field trials and the community trials (**Table 2**).

Table 2. Types of epidemiological studies.

Types of studies	Alternative name	Study unit
Observational studies		
Descriptive observational studies	Case report or case series	Individual
Analytical observational studies		
Cross-sectional study	Prevalence	Individual
Case-control study	Reference case	Individual
Cohort study	*Longitudinal (Follow-up)*	Individual
Ecological study	Correlation	Population (set)
Experimental studies	**Intervention studies**	
Randomized controlled trial (RCT)	Clinical Trials	Patients
Randomized controlled trial with groups (clusters)		Groups
Field Trial		
Community Essay	Community intervention studies	Healthy individuals in the community

Epidemiological studies are hierarchical according to the level of evidence they present, as a result of the quality of the studies and the reliability of the results, according to different classifications (**Table 3**).

Table 3. Level of evidence of epidemiological studies according to the Oxford Center for Evidence-Based Medicine classification.

Level of evidence	Type and quality of study
1A	Systematic review/ meta-analysis of RCTs

1B	Individual RCT with narrow 95%CI
2A	Systematic review of cohort studies
2B	Well-conducted cohort studies Low-quality RCT
2C	*Outcomes research* Ecological studies
3A	Systematic review of case-control studies
3B	Well-conducted case-control studies
4	Case Series Low-quality cohort and case-control studies
5	Expert opinion

Descriptive observational studies (case reports or case series)

Case reports include a detailed description of one or a few clinical cases, generally a rare clinical event or a new intervention. A case series is a study with a larger number of participants (more than 10) and can be retrospective or prospective.

They are especially useful in the initial exploration of new events (emerging diseases and symptoms, results of new therapies and side effects) and in the initial formulation of new etiological hypotheses, focusing on specific population groups or aspects not investigated in quantitative research that require further information.

Advantages: easy-to-implement first approach; low cost; qualitative, descriptive and exploratory approach; collaborates with the detailed delineation of clinical cases. *Disadvantages*: they have important limitations, which may lead to erroneous conclusions, as they study selected individuals without blinding and a control group (all biases), presenting results and conclusions which only apply to that sample (internal validity) and cannot be generalized.

Analytical observational studies (cross-sectional, case-control and cohort)

All analytical observational studies commonly present the prevalence-incidence bias (Neyman's bias), which is the exclusion of individuals with severe or moderate diseases, resulting in a systematic error in the association or estimated effect of a given exposure or outcome.

This prevalence-incidence bias occurs due to the moment in which cases are included in analytical observational studies: the longer the time between exposure and investigation, the greater the probability of individuals dying or recovering from the disease, and therefore the greater the probability of being excluded from the analysis (deceased or cured cases). This bias is more likely to have a greater impact on long-term illnesses.

Cross-sectional analytical observational study (sectional)

This is a type of study where the exposure-disease relationship in a population is investigated at a particular moment, providing a portrait (section or cut-out) of the situation at that moment. It evaluates the relationship between diseases and other variables of interest existing in a given population (exposure and outcome are measured simultaneously), being used to quantify the prevalence of a disease or risk factor, or the accuracy of a diagnostic test. When investigating epidemic outbreaks, conducting a cross-sectional study measuring various exposures is generally the first step in determining their cause.

General characteristics: random; inference of results; interviews (census or sample, depending on complexity and costs); characterizes certain populations based on the systematic collection of information about events; observations and measurements of the variables of interest (exposure/outcome) are made simultaneously; estimates averages and proportions; does not test cause-effect hypotheses (risk factors), but rather an exposure/outcome association; uses frequency association test or statistical analysis.

Advantages: easy and quick to execute; low cost; objectivity in data collection; does not require follow-up of individuals; ease of obtaining a representative sample; ideal for describing characteristics of events in the population, identifying cases in the community and detecting groups at higher risk. *Disadvantages*: low quality of retrospective data (past exposure can establish present causality); chronological relationship between events can be difficult to establish; prevalence-incidence bias; Current exposure data may not represent past exposure.

Observational analytical case-control study

This constitutes a relatively simple way of investigating the cause of diseases, particularly rare diseases. In this type of study, two similar groups are included from an at-risk population, one with the disease (“case”) and the other without the disease (“control”). Researchers “look into the past” (retrospective study) to measure the exposure frequency to a possible risk factor (effect or outcome) in the two groups. This type of study investigates whether the two groups differ in the proportion of people who have been exposed to the same risk factor, effect or outcome, seeking to confirm a possible causality.

General characteristics: part of the effect towards the cause (from the outcome to the exposure); determines the proportion of people who were exposed to the same risk factor (effect); the sample must be representative of the population that produced the

case; identifies the exposure or risk factor (or protective factor, in the case of vaccines); estimates the relative risk (RR) only when the disease is rare; the "case" (patients) and "control" (non-sick people) groups are investigated to find out whether they were exposed to a certain risk factor and whether this contributed to manifestation of the disease; the selection of "cases" and "controls" must be made regardless of exposure to the study factor.

Advantages: relatively cheap and fast; investigates risk factors; useful in rare diseases; allows consistency of measurements, as exposure and effect are measured at the same time; requires few individuals; useful in studying adverse drug events. *Disadvantages*: vulnerable to bias in the selection of "cases" and "controls"; vulnerable to observation bias (looking for results only where it is most convenient) and prevalence-incidence bias; not suitable for rare exposures or risk factors; cannot obtain estimates of disease incidence.

Observational analytical cohort study (prospective and retrospective)

The term "cohort" is used to describe a group of people who have something in common when they are brought together and who are observed for a period of time to analyze what happens to them. In a cohort study, a group of people is brought together without any of them having suffered the outcome of interest (disease or intervention, for example), but who may suffer it in the future. When the aim is to provide solid information about the risk of the disease, the cohort observations must meet certain criteria in relation to the outcome of interest, observation period and follow-up time.

Outcome of interest: Individuals must be free of the outcome (disease) when they are brought together. Observation period: must be significant according to the natural history of the disease under study. Follow-up time: cohort members need to be observed throughout the study period. An incomplete cohort (significant dropout rate) may not represent the true situation, as individuals may have abandoned the study for some reason related to the outcome under investigation.

In a prospective cohort, individuals are classified upon entry into the study according to characteristics which may be related to the outcome (possible risk factors, for example). In a retrospective or historical cohort, the study is conducted based on the identification of past records of the outcome, following the individuals from that moment to the present. This type of design should not be confused with a case-control study.

Cohort participants are classified as exposed (i.e. having the factor in question) or not exposed for each risk factor. In cohort studies, the disease incidence is compared between two or more groups that differ in terms of exposure to a possible risk factor ("cause-exposure" leading to "outcome-effect").

General characteristics: part of the cause towards the effect (exposure towards the outcome); participants chosen (not at random), forming groups of "exposed" and "not exposed", with common characteristics; observational study of groups "exposed" and "not exposed" to a potential cause of the outcome and who are followed over time; the groups (cohort) are selected so that their members have not presented the outcome of interest, but have the chance to present it; describes the incidence of outcomes over time and analyzes whether there are associations between variables (predictors) and outcomes; prospective or retrospective.

Advantages: exposure is measured before disease onset; rare exposures can be studied by selecting appropriate groups of individuals; more than one effect (outcome) can be studied for the same exposure; the incidence of the outcome can be measured in the "exposed" and "unexposed" groups. *Disadvantages*: long lasting and expensive; changes in the exposure condition and diagnostic criteria may occur during the study period, affecting the classification of individuals into "exposed" and "not exposed", "sick" and "not sick"; loss of individuals during follow-up.

Ecological analytical observational study

Ecological (or correlation) studies are useful for generating hypotheses. The analysis units in an ecological study are groups of people rather than individuals. Ecological studies are used to compare populations in different places at the same time or in a time series to compare the same population at different times (minimizing socioeconomic bias). If the time period in a time series study is very short, such as in a daily time series study, the confounding factor is virtually nil, as the participants serve as their own controls.

Although ecological (or correlation) studies are easy to carry out, they are often difficult to interpret and find explanations for the results, as they are based on data collected for other purposes (routine or secondary data are used to seek correlation of the phenomenon). Furthermore, since the analysis unit is a population, the relationship between exposure and effect at the individual level cannot be established, drawing inappropriate conclusions ("ecological fallacy") when making this correlation. Bias

occurs because the association observed between variables at the group level generally does not represent the association existing at the individual level.

General characteristics: collective; marginal distribution (totals); grouped measures; all variables as a group: aggregate, environmental and global measures; generate etiological hypotheses; test these hypotheses; evaluate the effectiveness of interventions in populations.

Advantages: simple, fast and low cost; works with large populations (international comparisons of disease incidence rates); investigation of disease clusters; availability of large databases. *Disadvantages*: methodological and data analysis problems, such as: limitations in causal inference (population/individual), information of variable quality (data from different sources) and with temporal ambiguity (data collection at different times), confounding factors (occurrence of distinct outcomes), difficulty in statistical analysis because the observation unit is the group, etc.

Experimental or intervention studies

Experimental or intervention studies involve attempts to change the determinants of a disease, such as an exposure or behavior, or to halt the disease progress through treatments or therapeutic interventions. The effects of an intervention are measured by comparing the outcome in the experimental and control groups. Ethical considerations must be observed as they involve interventions in people's health (e.g., the appropriate treatment must be offered to participants, depending on their participation in the experiment; the treatment to be tested must be acceptable in light of current knowledge; the consent of participants is required; etc.).

Experimental studies aim to try to change a variable in one or more groups of people. This may mean eliminating a dietary factor related to an allergic cause or testing a new treatment for a selected group of patients. The main experimental designs are: randomized controlled clinical trial, whose participants are patients; field trial in which participants are healthy people; and community trials, where the participants are members of the community themselves.

Randomized controlled trial (RCT)

A randomized controlled clinical trial (RCT), commonly called a "randomized, double-blind, placebo-controlled trial", is a study which aims to analyze the specific effects of a given intervention. The selected individuals are allocated to the intervention (active

medication) and control (placebo) groups, and the results are evaluated by comparing the outcomes between the groups. The patients are randomly allocated (randomized) to ensure that these groups are equivalent. This ensures comparability between the intervention and control groups from the beginning of the study. Thus, any difference observed between the groups is due to chance and is therefore not affected by selection bias.

The RCT (randomized, double-blind and placebo-controlled trial) is considered the "gold standard" for determining scientific evidence on the effects of a given technology on health. A well-planned and conducted RCT is the type of design which presents the least possibility of biases (selection, measurement and confusion). An RCT must be preceded by a protocol that justifies and describes how the study will be carried out in detail [objectives, patient selection criteria, application of interventions, evaluation methods, execution and monitoring of the study, registration and randomization, ICF, sample size calculation (NNT), statistical analysis, etc.].

General characteristics: part of the cause towards the effect ("exposure" towards the "outcome"); participants chosen at random, forming "study" (active) and "control" (placebo) groups; individuals are randomly assigned to a group treated with the study treatment and a control group that can be treated with a placebo or another known intervention; used to determine the effectiveness of a new treatment (medicine), but also to evaluate adverse events or placebo effects; carried out in the pre-commercialization phase of a new medicine.

Advantages: it is the standard of excellence in studies which aim to evaluate the effectiveness of an intervention in the course of a clinical situation; enables eliminating different biases, as the groups are randomly allocated and the characteristics are distributed in a normal and similar way. *Disadvantages*: high cost, laborious and time-consuming; not always feasible due to ethical aspects; subject to patients being lost to follow-up; they generally evaluate specific disease scenarios; commonly carried out in an academic setting, limiting the generalization of data (external validity or real world).

Field trial

In contrast to clinical trials, field trials involve people who are free of the disease but at risk of developing it. Since participants are disease-free and the purpose is to prevent the occurrence of diseases, even among those of low frequency, field trials involve a large number of people, which makes them expensive and logistically complicated.

Data are collected in the "field", usually among people from the general population and non-institutionalized people.

Field trials can be used to evaluate interventions that aim to reduce exposure, without necessarily measuring the occurrence of health effects. This type of intervention study can be conducted on a small scale and at lower costs, either because it does not involve long-term follow-up, or because it does not require disease measurement as an outcome. One of the largest field trials ever carried out was to test the Salk vaccine to prevent polio, which involved more than a million children.

Community trial

The treatment groups in this type of experiment are communities rather than individuals. This design is particularly appropriate for diseases that have their origins in social conditions and can be easily influenced by interventions aimed at group or individual behavior (i.e. cardiovascular disease). A limitation of this type of design is that only a small number of communities can be included and random allocation of communities is not very practical.

Therefore, other methods are required to ensure that any differences found at the end of the study can be attributed to the intervention and not to differences inherent in the communities. Furthermore, it is difficult to isolate the communities where the intervention is being conducted due to ongoing social changes.

III.4. Premises and principles of homeopathic clinical epidemiology

Objective

Homeopathic clinical epidemiology must associate the premises and principles of the biomedical paradigm (clinical epidemiology), described previously, with the premises and principles of the homeopathic paradigm (homeopathic episteme), adapting classic epidemiological studies to the homeopathic model. In doing so, we will have an increase in the methodological quality of epidemiological studies in homeopathy without disrespecting fundamental aspects of the homeopathic episteme, which is essential for the vital curative reaction (therapeutic response) to be awakened in accordance with the principle of therapeutic similitude.

Premises and principles of the biomedical paradigm (clinical epidemiology)

In an analysis of randomized, double-blind, placebo-controlled homeopathic clinical trials (RCTs) published until the beginning of the 1990s, Kleijnen et al.[14],

epidemiologists from the University of Limburg, observed that basic aspects of clinical epidemiology were neglected in their preparation and publication, such as: significant sample of participants (NNT); correctly executed and described randomization; correctly executed and described double-blind method; correctly described homeopathic symptoms; correctly described medication management; correctly described results; correctly performed and described statistical analysis.

Therefore, in increasing the methodological quality of epidemiological studies in homeopathy, it is essential that the principles of clinical epidemiology (scientific paradigm) are observed when designing research and analyzing results, as previously described: population and sample; probability, risk and statistics; clinical effect measures (risks); precision measure (confidence interval, CI); internal and external validity; reliability and accuracy of results; systematic error or bias; random error or chance; clinical and statistical significance; sample size (NNT); and clinical outcomes, among others.

Premises and principles of the homeopathic paradigm (homeopathic episteme)

On the other hand, when adapting classic epidemiological studies to the homeopathic paradigm (homeopathic clinical epidemiology), including the RCT, it is essential that certain precepts of good homeopathic clinical practice are observed in their design, planning and execution, according to the premises and principles of the homeopathic episteme, such as: individualization of the homeopathic medicine; systematization of criteria for choosing individualized medicine; individualization of doses and potencies of homeopathic medicine; consultation time and study duration that is consistent with the homeopathic model; observation and description of "specific adverse" events throughout treatment; quantitative and qualitative assessment of outcomes, among others[15-20].

Individualization of homeopathic medicine (individualized medicine)

The aim in applying the principle of therapeutic similitude is to awaken a vital and globalizing reaction of the organism, choosing a homeopathic medicine according to the characteristic symptomatic totality of the sick individuality (sick-disease), meaning an individualized homeopathic medicine. Therefore, each sick individual may receive different homeopathic medicines for the same disease. This can be applied in the design of clinical trials with the aim of evaluating the clinical, laboratory and global improvement in pre- and post-treatment, and not the response of all participants to the

same medication (as is done in conventional clinical trials). This individualization of the medicine is a *sine qua non* condition for the vital reaction and therapeutic response to occur, being considered the state of the art of homeopathic treatment.

Systematization of criteria for choosing individualized medication

As previously mentioned, the choice of individualized medication must be based on the characteristic symptomatic totality of the patient-disease binomial, and must encompass the mental, general and physical symptoms of the sick individual. In view of the subjectivity in the analysis and choice of characteristic signs and symptoms, there is a need to discriminate the selection criteria used according to a hierarchization and repertorization pattern of homeopathic signs and symptoms, restricting the variables intrinsic to the medication individualization process and enabling the subsequent reproducibility of the method. In seeking this standardization, it is essential that the researchers involved in the study (prescribing homeopathic doctors) perform the same steps and criteria of the homeopathic approach (anamnesis until prescription) for the group of patients under study.

Individualization of doses and potencies of homeopathic medicine

Just as homeopathic medicine must be individualized, doses and potencies must also be chosen according to the susceptibilities and responses of the patient-disease binomial. Therefore, doses and potencies must be evaluated at each return visit and adjusted according to individual needs, avoiding (for example) unwanted and unnecessary homeopathic aggravations that can confuse assessment of the therapeutic response.

Consultation time and study duration consistent with the homeopathic model

Consultation time is an essential prerogative for conducting an overall homeopathic anamnesis, and the care standard of the researchers involved must be followed according to the semiologic dynamics used in researching the characteristic symptomatic totality. Regarding the study duration, an essential prerogative in the research design, homeopathy requires a longer follow-up time than conventional clinical trials, being divided into periodic consultations so that one can choose the medicine with greater similarity to the sick individuality from among the several hypotheses raised in the repertorization of all the characteristic signs and symptoms. A treatment period of more than six months is suggested to contemplate this individualizing dynamic in the RCT, with monthly reassessments.

Observation and description of specific adverse events throughout treatment

Several specific adverse events may occur after administrating homeopathic medicines, without necessarily indicating an unfavorable outcome. On the contrary, some of these events may indicate a favorable prognosis and reiterate the correct choice of individualized medication. Among the events that must be described, we can mention: homeopathic aggravation (initial worsening of the individual's guiding symptoms, which may indicate correct medication and a favorable prognosis); exonerations (elimination of discharges by the body's natural emunctories, which may indicate a favorable prognosis); return of old symptoms (emergence of old symptoms which disappeared after palliative treatments, which may indicate a favorable prognosis); emergence of new bothersome symptoms, not previously manifested (unfavorable prognosis); among others.

Quantitative and qualitative assessment of outcomes

In view of the fact that homeopathy uses a globalized semiological and therapeutic approach which values the set of aspects manifested by the sick individuality in genesis of the organic-vital imbalance and seeking its rebalancing with individualizing treatment, a multifactorial assessment is necessary so that we can perceive the notion of the response amplitude to the treatment itself. Therefore, together with the objective clinical and laboratory assessment (complementary exams), it is necessary to associate a subjective assessment in which the mental, emotional, social, family, spiritual aspects and existences of the sick individuality can be measured and quantified throughout the treatment. To do this, we can use instruments to assess quality of life, subjective well-being, stress and spirituality/religiosity, among others.

III.5. Types of epidemiological studies in homeopathy

Analogous to classical epidemiological studies, epidemiological studies in homeopathy can be divided into two large groups: observational studies in homeopathy and experimental studies in homeopathy. Among observational studies in homeopathy, there are descriptive studies (case report or case series) and analytical studies (cross-sectional, case-control and cohort). Among the experimental studies in homeopathy, we mainly have randomized, double-blind, placebo-controlled clinical trials (RCTs).

Descriptive observational studies in homeopathy

Hundreds of descriptive observational studies in homeopathy have been conducted following the premises of clinical epidemiology, and are available in scientific literature databases (MEDLINE): case reports[21] and case series[22] (**Table 4**).

There are protocols for preparing and publishing descriptive observational studies in homeopathy (case report or case series)[23], which must be followed when designing them.

Analytical observational studies in homeopathy

Dozens of analytical observational studies in homeopathy have been performed following the premises of clinical epidemiology, and are available in scientific literature databases (MEDLINE): cross-sectional[24], case-control[25] and cohort[26] (**Table 4**).

Analogous to classic descriptive observational studies, there are protocols for preparing and publishing analytical observational studies in homeopathy (cross-sectional, case-control and cohort)[27], which must be followed in their design.

Experimental or intervention studies in homeopathy

Hundreds of randomized, double-blind, placebo-controlled homeopathic clinical trials (RCT) have been carried out following the premises of clinical epidemiology, and are available in scientific literature databases (MEDLINE): randomized controlled trials[28] (**Table 4**).

Analogously to descriptive and analytical observational studies, there are protocols for preparing and publishing randomized, double-blind and placebo-controlled clinical trials in homeopathy[29-32], which must be followed in their design.

Systematic reviews or meta-analyses of randomized clinical trials (RCTs)

As described in **Table 3**, epidemiological studies are hierarchized according to the level of evidence they present as a result of the quality of the studies and the reliability of the results. While randomized controlled trials (RCTs) present level of evidence **1B** (second highest level of evidence), the systematic review or meta-analysis of these RCTs present level of evidence **1A** (highest level of evidence).

Dozens of systematic reviews and meta-analyses of randomized, double-blind and placebo-controlled homeopathic clinical trials (RCTs) have been conducted following

the premises of clinical epidemiology, and are available in scientific literature databases (MEDLINE): systematic review[33] and meta-analysis[34] (**Table 4**).

Similarly to other types of studies, there are protocols for preparing and publishing systematic reviews and meta-analyses in homeopathy[35], which must be followed when designing them.

Table 4. Types of epidemiological studies in homeopathy - Systematic search strategy in the MEDLINE database until August 2023 and the obtained results.

Types of studies in homeopathy	Subject descriptors / Search strategy MEDLINE (via PubMed)	Results (articles)
Descriptive observational studies	Case report "case reports" AND "homeopathy"	301
	Case Series "case series" AND "homeopathy"	51
Analytical observational studies	Cross-sectional study "cross-sectional studies" AND "homeopathy"	155
	Case-control study "case-control studies" AND "homeopathy"	13
	Cohort study "cohort studies" AND "homeopathy"	44
Experimental or interventional studies	Randomized controlled trial (RCT) "randomized controlled trials" AND "homeopathy"	326
Systematic reviews	Systematic review of RCTs "systematic review" AND "randomized controlled trials" AND "homeopathy"	78
Meta-analyses	Meta-analysis of RCTs "meta-analysis" AND "randomized controlled trials" AND "homeopathy"	95

In view of their highest level of evidence (1A), these **systematic reviews of randomized, double-blind and placebo-controlled homeopathic clinical trials (RCTs), with or without meta-analyses**, assume importance in the discussion of scientific evidence for homeopathy, with the majority presenting positive or favorable results in favor of homeopathy compared to placebo or conventional treatments, while a minority presented negative or unfavorable results for homeopathy.

As we will discuss and demonstrate later in specific chapters, **two of these systematic reviews with unfavorable results for homeopathy**[36,37] **were conducted with the implicit intention of discrediting homeopathy in several countries, presenting numerous biases and methodological flaws in their preparation, implementation and analysis,** which were described and debunked in subsequent reanalyses (*post-hoc* analysis) published in several scientific journals and reports ("The homeopathy debate – HRI"[38], "*Será mesmo o fim da homeopatia*"[39], "Vieses nas conclusões da metanálise do The Lancet (2005) sobre a eficácia da homeopatia"[40] and "Vieses do Relatório do Governo Australiano a respeito das evidências científicas do modelo homeopático"[41,42]).

Unfortunately, demonstrating ignorance or denial of this evidence, as well as the premises and principles of clinical epidemiology (described previously) that should guide researchers in the analysis of epidemiological studies of any type, **pseudoskeptics disguised as pseudoscientists**[43-45] **repeat the negative, biased and untrue results of these systematic reviews of low methodological quality in a systematic and indiscriminate manner** (despite having been published in impactful scientific journals, highlighting the conflict of interests in scientific publication[46]) **in mass media (websites, newspapers and non-scientific journals/magazines) and social networks**, constituting widely used strategies by these individuals with the aim of self-promoting through dogmatic and prejudiced denialism against homeopathy and its countless contributions to the treatment of human illnesses, without any justifiable, ethical or worthy reason for consideration.

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Proof of Scientific Evidence for Homeopathy

IV. Overview of homeopathy research - Databases

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IV. Overview of homeopathy research – Databases

IV.1. Introduction

As we described in previous chapters, several lines of scientific research underlie homeopathic principles (basic or experimental research), as well as the effectiveness and safety of homeopathic clinical treatment (clinical research).

In a similar way to other medical specializations, experimental and clinical studies of homeopathy are grouped and described in general and specific databases. While general databases make scientific evidence from all medical specializations available together, specific databases group studies and research into the specialization separately. Therefore, homeopathy databases allow the reader to see the body of scientific evidence that supports the scientific rationality of the homeopathic model.

We will list below some databases, which enable research into experimental and clinical studies in the area in order to highlight the general panorama of research in homeopathy, according to the different lines of existing research. Using a specific database (CAM-QUEST databases), we will describe the variety of homeopathic clinical trials conducted in the different medical specializations and corresponding diseases according to the different types of epidemiological study designs (systematic reviews, meta-analyses, randomized clinical trials and observational studies).

The Homeopathy Research Institute (HRI)[1] is dedicated to evaluating homeopathy using rigorous scientific methods and disseminating the results of its research beyond conventional academic circles. It provides academic and/or financial support to sustain a range of research projects in the UK and abroad. Through the experience and networks of the "HRI Scientific Advisory Committee"[2], it continually reviews the status of homeopathy research at a global level. As it is a rapidly evolving field, both the research questions being asked and the way research studies are conducted may need to be adjusted in light of new information as these findings are evidenced by teams around the world. With a broad research strategy, HRI supports and develops projects in the following areas ("Current projects")[3]: basic or fundamental research ("How do homeopathic medicines work?"), clinical research ("What can homeopathy treat?"), reviews & databases ("Learning more from existing evidence"), data collection ("Learning from day to practice") and researcher meetings ("Informing future research").

The Homeopathy Research Institute (HRI) makes available "Research databases"[4], ("General databases")[5], databases for studies of the various modalities of complementary and alternative medicine or CAM ("CAM-QUEST databases")[6], and specific databases for homeopathic studies ("Homeopathy research databases")[7] on its website. In the specific field of homeopathy, in addition to databases of studies or clinical trials ("CORE-Hom"[8] and "HOMIS"[9]), we found databases for experimental studies in basic research (biological models: *in vitro*, plants and animals) ("Homeopathy Basic Research Experiments database - HomBrex")[10], for homeopathic veterinary studies ("HomVetCR database")[11] and for studies in homeopathic pathogenetic experimentation ("PROVINGS.INFO database")[12].

According to the scientific method, any study or analysis on the efficacy and effectiveness of homeopathy, in both biological models (*in vitro*, plants and animals) and in humans, should use these databases to carry out a bibliographical survey of the existing literature and **analyze the validity of study results according to homeopathic clinical epidemiology parameters (previous chapter), so that a conclusion can be drawn based on scientific evidence about the plausibility of homeopathic treatment.**

IV.2. General databases[5]

General scientific databases group homeopathy research together with that of other medical specializations and other forms of complementary and alternative medicine (CAM).

- "LILACS": The virtual library of health literature from Latin America and the Caribbean currently (2023) contains **more than 6,500 articles on "homeopathy"**.
- "PubMed": Provided by the US National Library of Medicine & National Institutes of Health, this resource currently (2023) provides **more than 6,500 articles on "homeopathy"**.
- "Trip Medical Database": Clinical evidence database for physicians currently (2023) provides **over 2,500 articles on "homeopathy"**.

IV.3. Clinical Outcome Research in Homeopathy (CORE-Hom)[8,13]

- "CORE-Hom"

The "Clinical Outcome Research in Homeopathy (CORE-Hom)"[14] database contains all types of clinical outcome studies, from randomized controlled trials (RCTs) to observational studies.

The CORE-Hom database currently (2023) contains **1,383 homeopathy clinical trials published up to the beginning of 2018**. CORE-Hom is academically rigorous, being the only homeopathy database that provides information on the quality of studies it contains. This valuable resource was the result of a close collaboration between the Homeopathy Research Institute (HRI)[8] and the renowned Karl und Veronica Carstens Foundation[13] in Germany.

According to Clausen et al. ("*CORE-Hom: a powerful and exhaustive database of clinical trials in homeopathy*")[15], the CORE-Hom database was created to respond to the need for a reliable and publicly available information source in the field of clinical research in homeopathy. In May 2014, it performed 1,048 registrations for clinical trials, observational studies and research in the field of homeopathy, including second publications and reanalyses. Of the studies referenced in the database, 352 were published in peer-reviewed journals, 198 of which were randomized controlled trials. The most studied medical conditions were respiratory tract infections (n = 126) and traumatic injuries (n = 110).

IV.4. Homeopathic Intervention Studies (HOMIS)[9]

- "HOMIS"

The objective of the "Homeopathic Intervention Studies (HOMIS)"[9] project was to map the *status quo* of clinical research in homeopathy, identifying all published randomized clinical trials. The project was recently completed and resulted in a published bibliographic study ("*Bibliography of Homeopathic Intervention Studies (HOMIS) in Human Diseases*"[16]) and a searchable online database hosted by the Institute of Complementary and Integrative Medicine at the University of Bern, Switzerland.

According to the Gaertner et al. report[16], 37 online sources, as well as print libraries were searched for "homeopathy" and related terms in eight languages (1980 to March 2021) in preparing the database. Studies were included that compared a homeopathic medicine or intervention with a control in relation to the therapeutic or preventive outcome of a disease (classified according to International Classification of Diseases-

10). Data were independently extracted by two reviewers and analyzed descriptively. **A total of 636 investigations met the inclusion criteria, 541 for therapeutic purposes and 95 for preventive purposes**; in addition, 73% were randomized clinical trials (n = 463), while the remainder were non-randomized studies (n = 173). The main control was placebo (n = 400). The type of homeopathic intervention was classified as multi-constituent or complex (n = 272), classic or individualized (n = 176), routine or clinical (n = 161), and isopathic (n = 19) or diverse (n = 8). The included studies explored the effect of homeopathy on 223 medical indications. The evidence collected was presented in an online database.

IV.5. Homeopathy Basic Research Experiments database (HomBrex)[10]

- "HomBRex database"

The "Homeopathy Basic Research Experiments (HomBrex)"[10] database indexes studies on biological systems, including human, animal, plant, fungal, and microbial organisms. This database was created by the Carstens Foundation (Carstens Stiftung), and has recently undergone major revisions and improvements. The HomBRex database currently (2023) contains **2,418 basic or fundamental research experiments in homeopathy.**

IV.6. HomVetCR database (HomVetCR)[11]

- "HomVetCR"

The first clinical research database in veterinary homeopathy, "HomVetCR" includes randomized clinical trials, non-randomized clinical trials, observational studies, drug trials, case reports and case series. The HomVetCR database currently (2023) offers **476 trials in veterinary homeopathy.**

IV.7. PROVINGS.INFO database[12]

- "PROVINGS.INFO"

Created by Jörg Wichman, "PROVINGS.INFO"[12] is a specialized database for classification and testing medicines and substances in homeopathy. Some information is available free of charge, while a more extensive collection can be accessed by subscription.

IV.8. CAM-QUEST databases[6,17]

- "CAM-QUEST databases"

With free access, the "CAM-QUEST"[17] is a database taht includes studies and research in nine therapeutic categories – acupuncture, anthroposophy, ayurveda, bioenergetics, homeopathy, manual medicine, mind-body medicine, phytomedicine and TCM. Searches can be conducted by disease, therapeutic approach and study design. With great practicality, the CAM-QUEST provides a quick and easy tool to obtain detailed and accurate information about clinical research in CAM, covering all therapeutic practices and diseases. CAM-QUEST is a regularly updated European research portal.

In the field of "Homeopathy"[18], CAM-QUEST currently (2023) contains **1,893 epidemiological clinical studies of all types** [systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized clinical trials (nRCTs) and observational studies] in the various specializations and corresponding diseases, as we will describe below.

- Pneumology (respiratory diseases): 110 studies [asthma (16), bronchitis (13), influenza (48), cough (16), pneumonia (4) and tuberculosis (13)]; 11 systematic reviews, 6 meta-analyses and 82 RCTs, among others.
- Ophthalmology: 26 studies [conjunctivitis (17), cataracts (5), retinopathy (1) and keratoconjunctivitis (3)]; 17 RCTs, among others.
- Orthopedics: 119 studies [arthritis (50), arthrosis (46), fibromyalgia (11), low back pain (7), osteoporosis (4) and torticollis (1)]; 15 systematic reviews, 10 meta-analyses and 104 RCTs, among others.
- Gynecology: 51 studies [menopause (15), infertility (13), dysmenorrhea (10), endometriosis (8), PMS (3) and leucorrhoea (2)]; 5 systematic reviews, 2 meta-analyses and 76 RCTs, among others.
- Otorhinolaryngology: 120 studies [rhinosinusitis (29), otitis media (27), rhinitis (24), tonsillitis (22), stomatitis (12), pharyngitis (3) and tinnitus (3)]; 6 systematic reviews, 2 meta-analyses and 48 RCTs, among others.
- Urology: 24 studies [prostatic hyperplasia (10), enuresis (6), UTI (4), nephritis (2), prostatitis (1) and urinary incontinence (1)]; 3 systematic reviews, 2 meta-analyses and 13 RCTs, among others.

- Dermatology: 82 studies [atopic dermatitis (29), eczema (15), wart (11), psoriasis (9), acne (7), lichen (4), Herpes zoster (3), Herpes simplex (2), crural ulcer (2)]; 9 systematic reviews, 6 meta-analyses and 50 RCTs, among others.
- Cardiovascular diseases: 53 studies [hypertension (21), stroke (11), hypotension (6), angina pectoris (5), arteriosclerosis (3), cardiac arrhythmia (3), coronary artery disease (3) and CHF (1)]; 2 systematic reviews, 2 meta-analyses and 25 RCTs, among others.
- Immunology: 163 studies [allergies (103), immunostimulation (42), fever (16) and vaccine disorders (2)]; 12 systematic reviews, 10 meta-analyses and 69 RCTs, among others.
- Infections: 84 studies [influenza (48), HIV (24), malaria (5), encephalitis (4), mononucleosis (2) and meningitis (1)]; 14 systematic reviews, 9 meta-analyses and 65 RCTs, among others.
- Oncology: 49 studies [breast (32), pancreas (3), melanoma (3), prostate (2), ovary (2), liver (2), intestine (1), uterus (1), brain (1), head and neck (1) and lung (1)]; 10 systematic reviews, 6 meta-analyses and 28 RCTs, among others.
- Gastroenterology: 70 studies [diarrhea (18), irritable bowel syndrome (15), hepatitis (9), hemorrhoids (5), nausea (5), dyspepsia (4), reflux disease (4), gastritis (4), constipation (3) and ulcerative colitis (3)]; 5 systematic reviews, 5 meta-analyses and 48 RCTs, among others.
- Neurology: 79 studies [migraine (26), headache (19), vertigo (17), neuropathy (6), neuralgia (5), epilepsy (3), trigeminal neuralgia (2), and multiple sclerosis (1)]; 6 systematic reviews, 4 meta-analyses and 36 RCTs, among others.
- Psychiatry: 230 studies [depression (49), ADHD (42), anxiety (41), insomnia (34), chronic fatigue syndrome (23), stress (17), addiction (16), schizophrenia (5), psychosis (2) and eating disorders (1)]; 27 systematic reviews, 18 meta-analyses and 94 RCTs, among others.
- Endocrinology and Metabolism: 46 studies [diabetes mellitus (28), hypothyroidism (5), obesity (5), gout (3), hypercholesterolemia (3) and hyperthyroidism (2)]; 2 systematic reviews, 2 meta-analyses and 23 RCTs, among others.
- Hematic-lymphatic system: 51 studies [hematology (8), edema (8), hematoma (7), anemia (6), thalassemia (6), hemophilia (5), lymphangitis (4), hemorrhage (4),

adenitis (2), and coagulation disorders (1)]; 1 systematic review, 1 meta-analysis and 26 RCTs, among others.

- Among others.

In addition to these classic databases, **other databases and reviews of experiments and studies made available in institutes, organizations and homeopathic societies** can be consulted by those interested in research in homeopathy; in order to see the enormous variety of scientific work carried out in the area, see:

- "HRI - Recommended reading (Peer reviewed journals article)"[19]: Peer-reviewed journals are considered the most reliable source of scientific information. These articles have been selected by HRI staff as being of continued interest to all those interested in homeopathy research.
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[20]: These regularly updated reviews of the "Scientific Framework of Homeopathy" provide notable expert assessments for each domain of homeopathic research. Research domains range from basic research, clinical research, homeopathic pathogenetic assays and clinical verification, to homeopathy applications in epidemic diseases, in dentistry, in veterinary medicine and in agricultural sciences (agrohomeopathy). The Framework also provides valuable insights into homeopathic education, the integration of homeopathy into global health systems, and the knowledge and attitudes of homeopathic consumers.
- Groupe International de Recherche sur l'Infintésimal (GIRI) – "Meetings"[21]: GIRI is a professional scientific society that brings together biologists, pharmacologists, doctors, chemists, physicists and mathematicians from around the world. The distinguishing feature of the group's research activities is the study of "impulses" of ultra-low doses or very high dilutions, including homeopathy. Although the action mechanism of diluted solutions of active ingredients on biological systems is an important concern of GIRI, the group's greatest interest is focused on the possible medicinal and therapeutic relevance of very low doses and high dilutions.

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Proof of Scientific Evidence for Homeopathy

V. Scientific Evidence for Homeopathy (Cremesp Dossier, 2017)

V. Scientific Evidence for Homeopathy (Cremesp Dossier, 2017)

When discussing homeopathy in different situations, we noticed that people often react with expressions of distrust, questioning its scientific proof and the therapeutic validity of the method. The fallacies that "there is no scientific evidence for homeopathy" and "homeopathy is placebo effect" are indistinctly and repeatedly proclaimed in all media, and end up being incorporated into the collective unconscious, serving as pseudoskeptical and pseudoscientific strategies to increase prejudices and radicalize positions contrary to this bicentennial medical practice.

As a result of misinformation or denial of the hundreds of studies that support the homeopathic treatment model in various fields of modern scientific research, these prejudices are periodically fed back with derogatory articles which are contrary to homeopathy published in the mass media (websites, newspapers and non-scientific magazines) and social networks, which rarely disseminate scientific work with positive results that are favorable to homeopathy.

With the aim of clarifying doctors, health professionals, professional associations, researchers, managers, patients and society in general in seeking to demystify these untrue, dogmatic and culturally rooted positions, the Technical Chamber of Homeopathy of the Regional Council of Medicine of the State of São Paulo (TC-Homeopathy, Cremesp)[1], counting on the support of the Institution's directors[2], elaborated the *Special Dossier: "Scientific Evidence for Homeopathy"*[3] in 2017.

This project was supported by the Brazilian Homeopathic Medical Association (Associação Médica Homeopática Brasileira - AMHB) and the São Paulo Medical Homeopathic Association (Associação Paulista de Homeopatia - APH), with the publication of the Dossier in the *Revista de Homeopatia (São Paulo)* in three independent and free-access editions[4]: online in Portuguese[5], online in English[6] and printed in Portuguese[7]. Expanding its dissemination to the Spanish-speaking public, this dossier was published in 2023 in the *La Homeopatía de México* journal in a special edition commemorating the journal's 90th anniversary[8].

In addition to presenting the global panorama of homeopathy as a medical specialization and its inclusion in the curricula of medical schools, the aforementioned Dossier encompasses other narrative reviews on the research lines which underlie homeopathic

scientific assumptions, namely: principle of therapeutic similarity, homeopathic pathogenetic experimentation, use of dynamized doses (ultradilutions) and individualized medicines according to the characteristic symptomatic totality of the patient-disease binomial. Similarly, the efficacy and safety of homeopathic treatment are evidenced in the description of randomized and placebo-controlled clinical trials, as well as in systematic reviews and meta-analyses.

Opening the Dossier, the review "*Homeopathy: a brief description of this medical specialty*"[9-11] addresses the **historical, social and political aspects of the institutionalization of homeopathy in Brazil and its incorporation into healthcare systems**, describing factors that lead the population to seek this form of treatment.

Then the review "*Medical education in non-conventional therapeutics in the world (homeopathy and acupuncture)*"[12-14] highlights the importance dedicated to incorporating teaching homeopathy and acupuncture into the curricula of medical schools in numerous countries in view of the growing interest of the population in their use, and consequently of the medical profession in learning these disciplines, with proposals aimed at students, residents, postgraduates and doctors.

Scientifically supporting **the principle of therapeutic similitude** in the systematic study of the rebound effect of modern drugs, the review "*Scientific basis of the homeopathic healing principle in modern pharmacology*"[15-17] encompasses hundreds of clinical studies (meta-analyses, systematic reviews, randomized placebo-controlled clinical trials, cohort and case-control studies, among others) published in important scientific journals and which attest to the similarity of concepts and manifestations between the rebound phenomenon and the vital reaction or secondary action of the organism awakened by homeopathic treatment. Expanding this evidence source, it describes the use of modern drugs according to the principle of therapeutic similarity, employing the rebound effect (paradoxical reaction of the organism) in a curative way.

Justifying **the plausibility of using dynamized (ultradiluted) doses** in homeopathy, the Dossier brings together three reviews which demonstrate the progress of **basic research in homeopathy in recent decades**, describing hundreds of controlled experiments and dozens of research lines that attest to the effect of ultradilutions on physicochemical and biological models (*in vitro*, plants and animals): "*The soundness of homeopathic fundamental research*"[18-20], "*Effects of homeopathic high dilutions on*

in vitro models: literature review"[21-23] and "*Effects of homeopathic high dilutions on plants: literature review*"[24-26].

Proving that **the positive effects of homeopathic treatment <u>are not</u> exclusively placebo effects**, as is repeated indiscriminately, the review "*Clinical research in homeopathy: systematic reviews and randomized clinical trials*"[27-29] reports the positive results observed in dozens of placebo-controlled homeopathic clinical trials (RCTs) for various clinical conditions, as well as in **systematic reviews and meta-analyses**. These results are exemplified in two randomized, placebo-controlled clinical trials carried out by members of TC-Homeopathy at important Brazilian research institutions: "*Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study*"[30-32] and "*Randomized, double-blind trial on the efficacy of homeopathic treatment in children with recurrent tonsilitis*"[33-35].

Evidencing **the safety of homeopathic medicine**, the review "*Do homeopathic medicines cause drug-dependent adverse effects or aggravations?*"[36-38] demonstrates in randomized, double-blind and placebo-controlled clinical trials (RCTs) that homeopathic medicines produce more adverse effects than placebo, although they are mild and transient.

Completing the dossier, the review "*Do homeopathic medicines induce symptoms in apparently healthy volunteers? The Brazilian contribution to the debate on homeopathic pathogenetic trials*"[39-41] discusses the historical development and state of the art of **homeopathic pathogenetic experimentation**, used to highlight the healing properties of substances (pathogenetic effects in healthy individuals) which enable application of the principle of therapeutic similitude.

Despite the existing difficulties and limitations for developing research in the area, both due to methodological aspects and the lack of institutional and financial support, the hundreds of experimental and clinical studies cited in the aforementioned Dossier, which support homeopathic scientific assumptions and confirm the effectiveness and the safety of the therapy, are indisputable proof that "there is scientific evidence for homeopathy" and "homeopathy ***is not*** placebo effect", contrary to the fallacies spread by denialist, dogmatic and prejudiced individuals[42-44], who claim the right to criticize, defame and belittle everything they do not know and are not interested in knowing. In reality, they are pseudoskeptics disguised as pseudoscientists[42-44].

With the preparation and publication of this Dossier in 2017, under the auspices of the Technical Chamber of Homeopathy (TC-Homeopathy) of Cremesp, we sought to clarify and dispel doubts, as well as raise awareness among fellow doctors and other health professionals about the validity and importance of using homeopathy as an adjuvant and complementary medical practice to other specializations, according to ethical and safe principles. In accordance with this integrative approach, homeopathic practice: enables broadening the understanding of human illness, increases therapeutic resources, contributes to the effectiveness of medicine in treating chronic diseases, minimizes the adverse effects of conventional medicines, and strengthens humanization of the doctor-patient relationship, among other aspects. However, new studies must continue to be developed to improve clinical practice and elucidate unique aspects of the homeopathic paradigm.

In view of the scientific relevance of the material, the Dossier had its importance reiterated in various national (*Jornal da USP*, Federal Council of Medicine of Brazil and Regional Councils of Medicine, among others) and international medical and scientific media (The European Committee for Homeopathy, Liga Medicorum Homoeopathica Internationalis and *The LMHI Letter 2018*, among others), as well as in scientific journals.

In peer-reviewed scientific journals, it was published in *Homeopathy* (2017)[45], in the *Revista Médica de Homeopatía* (2017)[46], as an Editorial in *Revista da Associação Médica Brasileira* (2018)[3], in *Diagnóstico & Tratamento* (2019)[47], in *História, Ciências, Saúde-Manguinhos* (2019)[48], and recently in *Clinics* (2023)[49].

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Proof of Scientific Evidence for Homeopathy

VI. Pharmacological basis of the principle of similitude

VI.1. Introduction

VI.2. The principle of similitude according to the homeopathic model

VI.3. The principle of similitude according to modern pharmacology

VI.4. Epidemiology of the rebound effect of modern drugs

VI.5. New homeopathic medicines: use of modern drugs according to the principle of similitude

VI. Pharmacological basis of the principle of similitude

VI.1. Introduction

As we saw previously, the homeopathic model of disease treatment is based on four pillars, assumptions or principles: (1) principle of therapeutic similitude; (2) homeopathic pathogenetic experimentation or trial; (3) individualized medicine (therapeutic individualization); and (4) dynamized or potentized doses (ultradilutions). Although great importance is attached to dynamized or ultra-diluted doses (produced through serial dilutions and shaking medicinal substances) incorporated into the homeopathic model at a later stage and with the initial objective of minimizing possible symptomatic aggravations resulting from applying therapeutic similarity, the first two premises are the foundations of the homeopathic episteme, leaving the individualized medicine (chosen according to the totality of characteristic signs and symptoms) as the inherent condition for the organism's therapeutic reaction to be awakened.

Using the principle of similitude or similarity as a therapeutic method, homeopathy uses medicines which cause certain signs and symptoms in healthy individuals to treat similar signs and symptoms in sick individuals (*similia similibus curentur*), with the aim of awakening a secondary and curative reaction of the organism against its own disorders.

This secondary reaction (vital, homeostatic or paradoxical) of the organism is based on the "rebound effect" of modern drugs, an adverse event observed after the suspension or discontinuation of numerous classes of drugs which employ the principle of opposites (*contraria contrariis curentur*) as a therapeutic method, exacerbating the signs and symptoms of the underlying disease to levels which are sometimes higher than those previously treated (paradoxical reaction).

Basing the principle of therapeutic similarity on the systematic study of the rebound effect of modern drugs, the review "*Scientific basis of the homeopathic healing principle in modern pharmacology*"[1] previously described in the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017) encompasses hundreds of clinical studies (meta-analyses, systematic reviews, randomized placebo-controlled clinical trials, cohort and case-control studies, among others) published in impactful scientific journals which attest to the similarity of concepts and manifestations between the rebound phenomenon and the vital reaction or secondary action of the organism

awakened by homeopathic treatment. Expanding this source of evidence, it describes the use of modern drugs according to the principle of therapeutic similarity, employing the rebound effect (paradoxical reaction of the organism) in a curative way.

This research line has been systematized in dozens of reviews on the rebound effect of different classes of modern drugs and their possible therapeutic application over the last two decades, having recently been synthesized in some articles published in important scientific journals[2-4]. Next, we will briefly describe it.

VI.2. The principle of similitude according to the homeopathic model

Since Ancient Greece, Hippocrates taught that there were two therapeutic principles: the principle of contrary (*contraria contrariis curentur*) and the principle of similitude (*similia similibus curentur*). Treatment based on the principle of contrary uses substances that act contrary, opposite or palliatively ("anti-") to the symptoms of the disease (e.g., anti-inflammatories, antacids, antidepressants, etc.). This is the main form of treatment employee by conventional medicine. Treatment based on the principle of similarity, employee by homeopathy, uses substances which cause similar symptoms ("homeo") to the symptoms of diseases, with the aim of stimulating the body's reaction against the disorders themselves (e.g., coffee, which causes insomnia, is used homeopathically to treat insomnia; chamomile, which causes colic, is used homeopathically to treat colic; belladonna, which causes fever, is used homeopathically to treat fever, etc.).

When establishing homeopathy in 1796, Samuel Hahnemann based this homeopathic principle on detailed observation of the effect of the drugs of his time on the human organism, stipulating a "universal mechanism of action of medicines":

> "Every force which acts on life, every medicine affects, to a greater or lesser extent, the vital force, causing a certain change in the state of man's health for a greater or lesser period of time. This is called **primary action**. [...] To this action, our vital force strives to oppose its own energy. Such opposite action is part of our conservation force, constituting an automatic activity of the same, called **secondary action** or **reaction**." (*Organon of Medicine,* § 63)[5]

Hahnemann exemplifies this universal mechanism of action of drugs (pharmacodynamics) observed in the different sensations and organic functions in the pharmacological effects of treatments and drugs of his time:

> "[...] The hand that is bathed in hot water initially becomes much hotter than the other that is not bathed (primary action); however, after being removed from the hot water and completely dry again, it becomes cold after some time, and finally much colder than the other (secondary action). After being warmed up by intense physical exercise (primary action), the person is struck by cold and shivering (secondary action). For those who warmed themselves yesterday with plenty of wine (primary action), today any breeze is very cold (opposite action of the organism; secondary). An arm immersed for a long time in very cold water is at first much paler and colder (primary action) than the other; however, out of the water and dry, it then not only becomes hotter than the other, but also red, hot and inflamed (secondary action, reaction of the vital force). Ingestion of strong coffee is followed by overexcitation (primary action); however, great relaxation and drowsiness (reaction; secondary action) remain for some time if they are not continued to be suppressed through more coffee (palliative, short-lived). After the deep, numbing sleep produced by opium (primary action), the following night will be even more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhea follows (secondary action), and after purgatives that irritate the intestines, obstruction and constipation occur for several days (secondary action). Thus, everywhere, after the primary action of a power in large doses that is capable of profoundly transforming the state of health of a healthy organism, it is precisely the opposite that always occurs (if, as has been said, such a fact really exists) in secondary action, through our vital force". (*Organon of Medicine*, § 65)[(5)]

Based on this postulate or "natural law", homeopathy uses this secondary action of the organism as a therapeutic reaction, administering medications to sick individuals which cause similar symptoms to their disorders (principle of similarity), with the aim of stimulating the organism to react against the disease itself.

VI.3. The principle of similitude according to modern pharmacology

In view of scientific rationality and modern pharmacological concepts, the "primary action" described by Hahnemann corresponds to the "therapeutic, adverse and side effects" of conventional drugs. On the other hand, the "secondary action" or "vital reaction" of the homeopathic model corresponds to the "rebound effect" of drugs or the body's "paradoxical reaction", observed after discontinuing numerous classes of drugs

which act in the opposite or contrary way (palliative, antagonistic or enantiopathic) to the signs and symptoms of diseases.

By definition, "rebound effect" means the "production of increased opposing symptoms when the effect of a drug has ended or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it was used to treat may return even stronger when the drug is discontinued or loses effectiveness." Similarly, "paradoxical reaction" means a response from the body that is opposite to the effect of the drug initially predicted[(1)]. In a generalized way, we can understand the rebound effect as an automatic and instinctive manifestation of the body's homeostatic mechanisms in order to reestablish the initial state altered by the primary action of the drug, promoting an opposite effect and contrary to what was expected.

Although little publicized by modern pharmacology as it contradicts conventional treatment (principle of contrary), this rebound effect has been studied and described after suspending or discontinuing numerous classes of modern palliative (antipathic or enantiopathic) drugs. In the last two decades, we have been systematically studying the rebound effect of modern drugs[(6-18)], scientifically confirming Hahnemann's postulate (primary action of the drug followed by secondary and opposite action of the organism) and the homeopathic healing principle.

The following examples illustrate the universality of the rebound phenomenon across the different classes of modern drugs[(6-18)]. Agents used to treat angina pectoris (beta-blockers, calcium channel blockers and nitrates, among others), which promote improvement of angina through their primary action, may trigger exacerbations in the intensity and/or frequency of chest pain after their discontinuation. Drugs used to control high blood pressure [alpha-2 adrenergic agonists, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, monoamine oxidase (MAO) inhibitors, nitrates, sodium nitroprusside and hydralazine, among others] can trigger rebound high blood pressure after the primary biological effect ceases. Antiarrhythmic drugs (adenosine, amiodarone, beta-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine and procainamide, among others) can cause rebound exacerbation of basal ventricular arrhythmias. Medicines with antithrombotic action (argatroban, bezafibrate, heparin, salicylates, warfarin and clopidogrel, among others) can promote thrombotic complications due to the rebound effect. Drugs that have a primary pleiotropic or vasculoprotective effect (statins) can cause rebound endothelial

dysfunction, predisposing the patient to the occurrence of paradoxical vascular accidents.

Similarly, suspending anxiolytic psychiatric medications (barbiturates, benzodiazepines and carbamates, among others), sedative-hypnotics (barbiturates, benzodiazepines, morphine, promethazine and zopiclone, among others), central nervous system stimulants (amphetamines, caffeine, cocaine, mazindol and methylphenidate, among others), antidepressants (tricyclics, MAO inhibitors and selective serotonin reuptake inhibitors (SSRIs), among others) or antipsychotics (clozapine, phenothiazines, haloperidol and pimozide, among others) can trigger rebound worsening of the baseline condition after the primary palliative therapeutic effect ends. Anti-inflammatory drugs (corticosteroids, ibuprofen, indomethacin, paracetamol and salicylates, among others) can trigger a rebound increase in inflammation, as well as rebound thrombotic episodes (ibuprofen, indomethacin, diclofenac, salicylates, rofecoxib and celecoxib, among others) due to their primary antiplatelet action. Analgesic medications (caffeine, calcium channel blockers, clonidine, ergotamine, methysergide, opioids and salicylates, among others) can trigger rebound hyperalgesia.

Diuretics (furosemide, torasemide and triamterene, among others) can cause rebound sodium and potassium retention, with a consequent increase in basal blood volume and blood pressure. Bronchodilators (short and long-acting beta-adrenergics, disodium cromoglycate, epinephrine, ipatropium and nedocromil, among others) can promote rebound bronchoconstriction as a paradoxical reaction of the body to the suspension of primary treatment. Medications with antidyspeptic action (antacids, H_2 receptor antagonists, misoprostol, sucralfate and proton pump inhibitors, among others) can trigger a rebound increase in hydrochloric acid and gastrin production, worsening the baseline condition of gastritis and gastric ulcers. Bone antiresorptive drugs used to treat osteoporosis (bisphosphonates, denosumab and odanacatib, among others) can cause atypical paradoxical fractures due to the rebound increase in osteoclastic activity. The suspension of drugs used to treat multiple sclerosis (glucocorticoids, interferon, glatiramer acetate, natalizumab and fingolimod, among others) can cause a rebound increase in the inflammatory activity of the disease with exacerbation of clinical symptoms and an increase in demyelinating lesions. Immunomodulatory drugs (recombinant monoclonal antibodies and tumor necrosis factor inhibitors, among

others) indicated for the treatment of psoriasis can cause rebound psoriasis after their discontinuation, among other examples[6-18].

Given this evidence from clinical and experimental pharmacology[6-18], the rebound effect presents similar characteristics to the secondary action or vital reaction of the homeopathic model (*Organon of Medicine,* §§ 59, 64 and 69)[5]: (1) causes an organism reaction opposite and with greater intensity than the primary action of the drug; (2) occurs after the primary action of the drug ceases as an automatic manifestation of the organism; (3) independent of the drug, doses, treatment duration or symptom type (disease); (4) presents a magnitude proportional to the primary action of the drug; and (5) manifests itself only in susceptible individuals (idiosyncratic character).

Despite the idiosyncratic nature of the rebound effect which manifests itself in a small percentage of individuals, growing evidence points to the occurrence of serious and fatal adverse events due to this paradoxical reaction of the body after discontinuing different classes of drugs, as we will describe below, reiterating the magnitude of the phenomenon, the need for its knowledge by health professionals, and the benefits of its therapeutic use according to the principle of similarity.

VI.4. Epidemiology of the rebound effect of modern drugs

The rebound effect manifests itself at different intervals (hours to weeks) after the biological effect (half-life) of the drug has been exhausted and its duration is also variable. The time interval between discontinuing drugs and manifestation of the phenomenon is similar for drugs with a short half-life, being on average 10 days for salicylates, 14 days for diclofenac and 9 days for rofecoxib[8,9], 7 days for statins[12], 7-14 days for SSRI antidepressants[8,11] and 7-14 days for proton pump inhibitors (PPIs)[13]. This time is longer in the case of depot drugs (bisphosphonates)[14]. The duration of the rebound effect remains for 30 days with rofecoxib[8,9], 21 days with SSRI antidepressants[8,11] and 30 days with PPIs[13]. The treatment duration is not related to manifestation of the rebound effect.

In comparison to placebo in controlled studies, the average risk of thrombotic strokes was 3.4 times higher after discontinuing salicylates, 1.52 times higher after NSAID withdrawal, and 1.67 times higher after discontinuing rofecoxib[8,9], as well as 1.69 times higher after stopping statins[12]. Similarly, the risk of suicide was 6 times greater

after withdrawal of SSRI antidepressants[11] and the risk of rebound bronchospasm was 4 times greater after discontinuing LABA bronchodilators[8,10].

Illustrating the frequency and magnitude of the rebound phenomenon which can cause serious and fatal adverse events, epidemiological studies show that LABA bronchodilators causes approximately 1 rebound bronchospasm followed by death for every 1,000 patients/year-of-use, corresponding to 4-5 thousand deaths/year in 2004 only in the United States (40-50 thousand worldwide)[8,10]. SSRI antidepressants cause 5 rebound suicidal behaviors for every 1,000 adolescents/year-of-use, corresponding to 16,500 events in 2007 in the United States[8,11]. Salicylates cause approximately 4 episodes of rebound acute myocardial infarction for every 1,000 patients/year-of-use[8,9]. Studies indicate that the incidence of gastric carcinoid tumors has increased in recent decades (400% in men and 900% in women) in association with the increasing consumption of PPIs due to rebound hypergastrinemia[13]. Bisphosphonates cause 1-3 serious atypical paradoxical fractures for every 1,000 patients/year-of-use (0.1-0.3%)[14]. Natalizumab causes rebound worsening of multiple sclerosis in around 10% of patients, with severe demyelination (immune reconstitution inflammatory syndrome) in some cases[15]. Efalizumab causes rebound psoriasis in 15-30% of patients, and may also cause immune reconstitution inflammatory syndrome[18].

VI.5. New homeopathic medicines: use of modern drugs according to the principle of similitude

Expanding this body of evidence, exponents of modern pharmacology have been suggesting a therapeutic strategy called “paradoxical pharmacology” in recent decades, similar to that propagated by the homeopathic model more than two centuries ago, proposing the use of minimum doses of conventional drugs which cause an exacerbation of the disease in the short term to treat this same disease in the long term[19-31].

Similarly, since the beginning of our studies in 1998[6,32-39], we have been proposing to use modern drugs according to the principle of therapeutic similitude, suggesting using drugs which cause similar adverse events to the manifestations of diseases to treat them homeopathically, using the rebound effect (paradoxical reaction) curatively with numerous indications.

Understanding that homeopathic treatment has the use of substances, which cause similar symptoms to those of the disease to be treated as its essential prerogative, it can be applied with any natural or synthetic substance in weighty or infinitesimal doses, as long as the principle of similarity is observed. Therefore, modern drugs could be used according to the principle of therapeutic similarity, as long as they cause similar primary action effects (therapeutic, adverse and side effects) to those in the sick individual. Thus, we would be using the rebound effect of modern drugs in a curative sense.

To make this project feasible, a Homeopathic Materia Medica of Modern Drugs was prepared systematizing all the primary or pathogenetic effects (therapeutic, adverse and side effects) of 1,250 modern drugs described in The United States Pharmacopeia Dispensing Information (USPDI)[40] according to an anatomo-functional distribution (systems or devices), and in accordance with the dynamics used in the chapters of traditional homeopathic medical materials.

In order to facilitate selection of the individualized medicine according to the totality of manifestations similar to the patient-disease binomial (an essential premise for the success of homeopathic treatment), the second stage of the project involved elaborating a Homeopathic Repertory of Modern Drugs, in which the pathogenetic effects and their corresponding medicines were organized in the same anatomical-functional arrangement (systems or devices), following the format of classic homeopathic repertoires.

Entitled "*New Homeopathic Medicines: use of modern drugs according to the principle of similitude*"[32], this project was described and systematized in a digital database composed of three distinct works: 1) "*Scientific basis of the principle of similitude in modern pharmacology*", 2) "*Homeopathic Materia Medica of Modern Drugs*" and 3) "*Homeopathic Repertory of Modern Drugs*".

Allowing this proposal to be known and applied by all interested colleagues, this database was transformed into **a bilingual series of three free access digital books** indexed in the Virtual Health Library (VHL)[2-4].

Series content in Portuguese (VHL):

- "*Fundamentação científica do princípio da similitude na farmacologia moderna*"[41].
- "*Matéria médica homeopática dos fármacos modernos*"[42].

- "*Repertório homeopático dos fármacos modernos*"[43].

Series content in English (VHL):

- *"Scientific basis of the principle of similitude in modern pharmacology"*[44].
- *"Homeopathic materia medica of modern drugs"*[45].
- *"Homeopathic repertory of modern drugs"*[46].

In order to test the clinical and scientific validity of this proposal, we conducted a RCT to evaluate the efficacy and safety of potentized estrogen (dynamized or ultradiluted) in individualized homeopathic treatment of pelvic pain associated with endometriosis (PPAE), in view that estrogen (17 beta-estradiol) can cause "endometrial proliferation or hyperplasia" as an adverse event of its conventional use.

In this post-doctoral project with the Department of Obstetrics and Gynecology of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (HC-FMUSP), we developed a randomized, double-blind, placebo-controlled clinical trial lasting 24 weeks (6 months), including 50 women aged 18-45 years with a diagnosis of deep infiltrative endometriosis (based on magnetic resonance imaging or transvaginal ultrasound after bowel preparation) and score ≥ 5 on a visual analogue scale (Visual Analogue Scale - VAS: 0-10 points) for PPAE[47].

Potentized estrogen (12cH, 18cH and 24cH) or placebo was administered orally twice a day. The primary outcome measure was the difference in the severity of the partial and overall PPAE score (VAS) between weeks 0 and 24, determined by the difference between the mean score of five modalities of chronic pelvic pain (dysmenorrhea, deep dyspareunia, deep pelvic pain acyclic, cyclic intestinal pain and cyclic urinary pain). Secondary outcome measures were mean score differences for quality of life (SF-36 Quality of Life Questionnaire), depression symptoms (Beck Depression Inventory, BDI), and anxiety symptoms (Beck Anxiety Inventory, BAI)[47].

Evidencing the superiority of boosted estrogen over placebo, the study results showed that the overall PPAE score (VAS: 0-50 points) decreased by 12.82 points ($p < 0.001$) in the group treated with potentized estrogen between the baseline (week 0) and week 24 moment. The group that used potentized estrogen also showed a partial score reduction (VAS: 0-10 points) in three PPAE modalities: dysmenorrhea (3.28; $p < 0.001$), acyclic pelvic pain (2.71; $p = 0.009$) and cyclic intestinal pain (3.40; $p < 0.001$). The placebo

group did not show any significant changes in overall or partial PPAE scores. Furthermore, the potentized estrogen group showed significant improvement in three of the eight domains of the SF-36 (bodily pain, vitality and mental health) and in depression symptoms (BDI). The placebo group showed no significant improvement in these secondary outcomes. These results demonstrated the superiority of potentized estrogen over placebo. Few adverse events have been associated with potentized estrogen. Potentized estrogen (12cH, 18cH and 24cH) at a dose of 3 drops twice a day and during 24 weeks of treatment was significantly more effective than placebo in reducing PPAE, improving quality of life and reducing patients' depressive symptoms[48,49].

This RCT was made available in the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017): "*Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study*"[50].

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Proof of Scientific Evidence for Homeopathy

VII. Experimental studies in biological models (*in vitro*, plants and animals)

VII.1. Introduction

VII.2. Experimental studies *in vitro* models

VII.3. Experimental studies in plant models

VII.4. Experimental studies in animal models

VII. Experimental studies in biological models (*in vitro*, plants and animals)

VII.1. Introduction

Given that the homeopathic model of disease treatment is based on unconventional assumptions (principle of therapeutic similitude, homeopathic pathogenetic experimentation and the use of ultra-diluted doses of individualized medicines, chosen according to the totality of signs and symptoms characteristic of the patient-disease binomial), it has found resistance to being accepted by the medical and scientific profession, unaware of its particularities and the evidence which supports them.

Accustomed to the use of massive and increasing doses of medicines which act in a contrary and palliative way to the manifestations of diseases, they consider it "implausible" to apply a treatment that uses ultra-diluted doses of medicines that cause similar disorders to those they wish to cure, despite considering the use of immunotherapy and nanotherapy plausible, which are based on similar foundations to those of the homeopathic episteme.

Among the homeopathic principles, the use of dynamized, potentized or ultradilutions medicines in lower concentrations than Avogadro's constant (absence of molecule-gram of the substance; dilution around $6.02x\ 10^{23}\ mol^{-1}$) arouses the greatest criticism of homeopathic treatment from researchers accustomed to the dose-dependent model of modern pharmacology. Denying the "plausibility" of the effect of homeopathic ultradilutions on living beings, they attribute the evident improvements that follow homeopathic treatment to the doctor-patient relationship (consultation effect) and the placebo effect, among other non-specific aspects.

Clinical and experimental studies (among other research models) are carried out in humans, animals, plants and cell cultures (*in vitro*) in order to demonstrate the effectiveness of homeopathic medicines in treating diseases and the action effectiveness of ultradilutions in biological systems. In this chapter, we will describe the scientific evidence that reiterates the plausibility of the effect of homeopathic ultradilutions (UDs or HDs in English) in biological models (*in vitro*, plants and animals).

Irrefutably, the positive effects of homeopathic HDs in experimental studies with biological models overturn the fallacious hypothesis that "homeopathy is placebo

effect", falsely disseminated by pseudoskeptics and pseudoscientists who systematically deny any evidence in favor of homeopathy.

Reiterating the scientific relevance of the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017) described in chapter V of this work, which encompasses nine narrative reviews on the different lines of research in homeopathy, we highlight the three reviews for the topic in question which describe the numerous experimental studies with HDs in biological models (*in vitro*, plants and animals): 1) "*Effects of homeopathic high dilutions on in vitro models: literature review*"[(1)], 2) "*Effects of homeopathic high dilutions on plants: literature review*"[(2)] and 3) "*The soundness of homeopathic fundamental research*"[(3)].

For the reader who wishes to delve deeper into an evaluation of homeopathy effectiveness in biological models (*in vitro*, plants and animals), noting the hundreds of experiments with homeopathic HDs in this area of scientific investigation, we suggest carrying out a bibliographical survey of the existing literature in the databases cited in chapter IV of this work ("Overview of homeopathy research - Databases"), such as:

- LILACS[(4)]: "homeopathy" AND "experimental research" (113 studies); "homeopathy" AND "basic research" (126 studies); "homeopathy" AND "fundamental research" (31 studies).
- PubMed[(5)]: "homeopathy" AND "experimental research" (205 studies); "homeopathy" AND "basic research" (129 studies); "homeopathy" AND "fundamental research" (43 studies).
- "Homeopathy Basic Research Experiments database (HomBrex)"[(6)]: 2,418 basic research experiments in homeopathy are currently available.
- "HomVetCR database (HomVetCR)"[(7)]: currently offers 476 trials in veterinary homeopathy.
- "HRI - Recommended reading (Peer reviewed journals article)"[(8)].
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[(9)]: in all editions (2016, 2017 and 2020-2021), it describes the experiments of the main homeopathic research lines in biological models (most recent edition (2020-2021)[(10)].
- Groupe International de Recherche sur l'Infintésimal (GIRI) – "Meetings"[(11)].

VII.2. Experimental studies *in vitro* models

The Homeopathy Research Institute (HRI) makes available the highest quality laboratory experimental studies (*in vitro*) with the greatest number of replications on its page "Experimental research"[12], namely: "Basophil degranulation experiment" and "Effect of homeopathic thyroxine on tadpole development".

Basophil degranulation experiment

As the authors of this experimental model explain, "when human polymorphonuclear basophils, a type of white blood cell with immunoglobulin E (IgE) antibodies on their surface, are exposed to anti-IgE antibodies they release histamine from their intracellular granules and alter their coloring properties. This phenomenon can be demonstrated in anti-IgE dilutions ranging from 10^{-2} to 10^{-120}; there are successive degranulation peaks of 40 to 60% of basophils in this range, despite the calculated absence of any anti-IgE molecules at the highest dilutions".

A systematic review of *in vitro* experimental studies[13] found 28 scientific articles published on this research model, among which 23 reported positive results. Among the 11 high-quality publications, 8 reported positive results. The first study using this model reported inhibition of degranulation with ultramolecular dilutions of anti-IgE[14], but these experiments were not reproducible[15,16]. However, subsequent studies using a modified method (using ultradilutions of histamine instead of anti-IgE) showed positive results. These studies have been replicated in several independent laboratories[17,18], as well as in a series of multicenter experiments[19].

Effect of homeopathic thyroxine on tadpole development

The thyroxine hormone stimulates metamorphosis in amphibians. Several teams have tested homeopathic ultradilutions (HDs) of thyroxine in frogs over nearly 20 years by adding it to the bath water in which the tadpoles are kept. Although the exact results vary, 20/22 experiments found the same trend - that 30d thyroxine [diluted beyond Avogadro's limit (6.02×10^{23} mol^{-1}) and using the homeopathic manufacturing process] inhibits tadpole metamorphosis.

An independent meta-analysis of these studies identified 22 experiments - 15 carried out by the original team in Austria and 7 by independent researchers[20]. This effect has already been observed by researchers from Austria, Germany, Switzerland and the Netherlands. This effect was observed in a series of three experiments carried out at the Department of Pathology at FMUSP in Brazil[21-23].

The challenge of reproducibility

Although these laboratory studies demonstrate that homeopathic medicines can exert biological effects, so far no positive results have been stable enough to be reproduced by all researchers in all experiments. However, 75% of experiments with homeopathic HDs *in vitro* show that the substance has an effect and around 75% of replications were positive, as demonstrated by the 2007 systematic review[13].

As scientists gain more experience experimenting with homeopathic HDs, they are gradually understanding which factors are influencing the results, and consequently reproducibility is improving[24]. The basophil and frog experiments described above have proven to be the most repeatable to date, and progress is also being made to find the most reproducible types of experiments in plants, as we will see later. This is the ongoing challenge for basic science researchers in homeopathy.

In the narrative review "*Effects of homeopathic high dilutions on in vitro models: literature review*"[1], published in the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017), the author describes a series of 26 experiments published in the period 2007-2017 (after the 2007 systematic review[13]) which presented positive results (effects) and significant differences in homeopathy compared to control groups, showing the reader different types of homeopathic experiments with HDs carried out in the laboratory (*in vitro* models). We describe these experiments in the table below (**Table 1**), updating the data with more recent studies (2017-2023).

Table 1. Summary of experimental studies with homeopathic HDs *in vitro* models (2007-2023) which showed positive and significant effects of homeopathy.

Author/ Year	Experimental model/ Study aims	Intervention	Effects/ Results
von Ancken et al, 2023[25]	Effect of 15cH Aspirin (vs. succussed water vs. 200 µg/mL aspirin) on the biochemical and morphological activities of macrophages (RAW 264.7)	Aspirin 15cH	POSITIVE Unlike controls, 15cH aspirin reduced the number of TLR-4 expressing cells on the surface ($p = 0.03$) and induced a pseudopod "columnar" morphology of macrophages, indicating changes in cytoskeletal arrangement in the direction of wound healing or tissue repair.
Silva et al., 2022[26]	Effect of *Carcinosinum* (vs. control) on murine mammary adenocarcinoma cells (4T1), including phenotypic changes, viability, HER-2 (human epidermal growth factor receptor type 2) expression, and metastatic potential	*Carcinosinum* (Carc 12cH, 30cH, 200cH)	POSITIVE Unlike the control, 4T1 cells treated with Carc 30cH produced an increase in the number of annexin V-positive cells (apoptosis) and decreased expression of proactivated MMP-9; cells treated with Carc 200cH showed overexpression of HER-2 in the plasma membrane, identified by immunocytochemistry.

Pinto et al., 2021[27]	Effect of *Silicea terra* and *Zincum metallicum* (vs. control) on BCG-infected macrophage (RAW 264.7) activity, according to bacilli internalization, hydrogen peroxide (H_2O_2)/ cytokine production, and lysosomal activity	*Silicea terra* (Sil 6cH, 30cH, 200cH) and *Zincum metallicum* (Zinc 6cH, 30cH, 200cH)	POSITIVE Compared to the control, Sil 200cH induced a significant reduction in H_2O_2 production ($p < 0.001$), as well as higher lysosomal activity ($p \leq 0.001$) and increased IL-10 production ($p \leq 0.05$). The number of internalized bacilli was inversely proportional to the potencies of Zinc, with a statistically significant interaction between dilution and treatment ($p = 0.003$).
Nagai et al., 2019[28]	Effect of *Phosphorus* (vs. control) on macrophage (RAW 264.7) activity infected with *Encephalitozoon cuniculi*, according to fungal internalization, lysosomal activity, cytokine/ chemokine production, and cell ultrastructure	*Phosphorus* (Phos) in various potencies	POSITIVE A progressive time-dependent increase in RANTES (regulation in normal T cell activation, expression, and secretion) and lysosome activity ($p \leq 0.002$) was observed only after treatment with the highest phosphorus potency (Phos 200cH), along with decreased apoptosis rate, intense parasite digestion, and presence of non-internalized spores.
Gonçalves et al., 2017[29]	Effects of *Zincum metallicum* (vs. control) on macrophage (RAW 264.7) activity and melanoma cell lines (B16-F10)	*Zincum metallicum* (Zinc 5c, 6c, 30c)	POSITIVE Zinc 6c changed the phenotype of macrophages with high ROS production to a phenotype with low ROS production. The expression of CD54 macrophages was increased by Zinc 5c. The melanoma cells were not affected by any treatment.
Santana et al., 2017[30]	Co-culture of macrophages and *Leishmania amazonensis* / Anti-inflammatory activity	*Antimonium crudum* (30cH, 200cH)	POSITIVE Reduction followed by increase in macrophage spreading; increase in the percentage of internalization of parasites; potentiation of the reduction of cytokine production induced by the parasite.
Lima et al. 2016[31]	Development of sheep preantral follicles / FSH in HD vs. FSH in weight dose	FSH 6cH	POSITIVE Increased follicular diameter; increased follicular survival rate; higher follicular activation rate on the 1st day of culture.
Lima et al., 2016[32]	Development, hormone production and gene expression of bovine preantral follicles isolated with or without addition of culture medium/FSH in HD vs. weight dose vs. 0.2% alcohol	FSH 6cH	POSITIVE Regarding cell proliferation, 0.2% alcohol had a greater effect than FSH 6cH and the latter greater than FSH at weight dose; estradiol production increased with all treatments; FSH 6cH induced higher production of connectin 43 than FSH by weight.
Wani et al., 2016[33]	Breast cancer cells (MDAMB231 and MCF7) and non-cancerous cancer cells (HEK293); nanoparticle research / Anticancer activity	*Terminalia chebula* (TM, 6d, 6c, 30c)	POSITIVE HDs reduced the viability of only the cancerous strains; all HDs decreased the growth kinetics of cancer cells; the nanoparticulate structure of 6cH differed from that of TM, presenting nanoparticles of 20 nm in diameter.
Mondal et al., 2016[34]	Human lung epithelial adenocarcinoma cells (A549) / Anticancer activity	*Psorinum* 6d	POSITIVE Inhibition of cell proliferation; sub-G stage cell cycle disruption; ROS production; mitochondrial membrane depolarization; DNA damage; Caspase-dependent promotion of mitochondria-mediated apoptosis.

Lee et al., 2016[35]	Murine preosteoblastic cells (mc3t3E 1) / Modulation of inflammation	*Rhus toxicodendron* (4d, 30d, 30c, 200c)	POSITIVE Increased expression of COX-2 mRNA and protein; increased production of PgE2; decreased production of NO.
Pasetti et al., 2016[36]	Methicillin-resistant *Staphylococcus aureus* (MRSA) / Bacterial resistance	*Belladonna* and Nosódio (6c, 30c)	POSITIVE Inhibition of MRSA growth, with reduced production of DNAse; increased vulnerability to oxacillin.
Guedes et al., 2016[23]	*Rana catesbeianus* tail explants / Amphibian metamorphosis	T3 10cH	POSITIVE T3 10cH affects caspase mRNA expression 3 and 7 T3-induced, slowing down the metamorphosis of tadpoles.
Tupe et al., 2015[37]	Human erythrocytes / Protein glycolization	*Syzygium jambolanum* and *Cephalandra indica* (TM, 30c, 200c)	POSITIVE Reduction of glycation markers (fructosamine, protein carbonyls and protein-bound sugar); protection against thiol and free amino groups. Phenols and flavonoids were identified in all samples.
Samadder et al., 2015[38]	HeLa cervical cancer cells and PBMC / Anti-cancer activity	*Lycopodium clavatum* (5c, 15c)	POSITIVE Reduction of proliferation and viability of cancer cells without cytotoxicity over normal PBMCs; considerable apoptosis of cancer cells, with DNA fragmentation, increased expression of caspase 3 and Bax proteins, reduction of Bcl2 and Apaf, and release of cytochrome c. Effect similar to cisplatin on cancer cell survival.
Marzotto et al., 2014[39]	Human neuroblastoma (SHSY5Y) / Regulation of gene expression	*Gelsemium sempervirens* (2c, 3c, 5c, 9c, 30c)	POSITIVE Alteration of the expression of 56 genes in microarray test.
Olioso et al., 2014[40]	Human neuroblastoma (SHSY5Y) / Regulation of gene expression	*Gelsemium sempervirens* 2c	POSITIVE Underexpression of most genes in a panel of human neurotransmitters and regulators.
Siqueira et al., 2013[41]	Biohazard; viral content; Effect on Madin-Darby Canine Kidney (MDCK) cells and Murine Macrophages (J774G8) / Effect of Influenza Virus Nosodium	*Influenza A* (A/Aichi/2/68 H3N2) 30d	POSITIVE No cytotoxicity; morphological changes in MDCK; increased rate of MDCK mitosis; alteration of mitochondrial MDCK activity; decreased PFK-1 activity in MDCK; increased production of TNF-α by macrophages.
Huh et al, 2013[42]	Primary mouse chondrocyte culture / Anti-inflammatory activity	*Rhus toxicoden-dron* (4d, 30d, 30c, 200)c	POSITIVE Increased expression of COX-2 mRNA; except for 200c, the other HDs inhibited the expression of type II collagen, suggesting chondrocyte dedifferentiation; 30x increased PgE2 release.
Lima et al, 2013[43]	Survival, activation and growth of sheep preantral follicles / Effect of FSH HDs	FSH (6cH, 12cH, 30cH)	POSITIVE Increased survival and follicular activity; higher growth of follicles and oocytes compared to controls; maintenance of the viability and ultra-structural integrity of the follicles after 7 days of culture.
Mukerjee et al., 2013[44]	Benzopyrene-induced DNA damage on mouse perfused lung cells / Anticancer activity	*Thuja occidentalis* 30cH	POSITIVE Increased cell viability; inhibition of benzopyrene-induced stress through reduction of ROS and HSP-90, and increase of glutathione.

Bishayee et al., 2013[45]	Modulation of histone acetylation in human cervical cancer cells (HeLa) / Anticancer activity	*Condurango* 30cH	POSITIVE Cytotoxic effect; decreased HDAC2 activity; decreased DNA synthesis and cell cycle disruption in the G1 phase.
Arora et al., 2013[46]	Human renal adenocarcinoma (ACHN) (Sars), Human colorectal carcinoma (COLO205) (Ruta), Human mammary carcinoma(MCF7) (Phyt) / Anticancer activity	*Sarsaparilla, Ruta graveolens* and *Phytolacca decandra* (30c, 200c, 1000c, 10Mc)	POSITIVE Cytotoxic effect; reduction of cell proliferation; induction of apoptosis; no effect (Sars) on non-cancerous MDCK cells.
Preethi et al., 2012[47]	Dalton's lymphoma ascite (DLA) cells / Anticancer activity	*Ruta graveolens, Carcinosinum, Hydrastis canadensis* e *Thuja occidentalis* (200c, 1000c)	POSITIVE Induction of apoptosis.
Ive et al., 2012[48]	Human lymphocytes (MT4) poisoned with Arsenic trioxide / Self-recovery from intoxication	*Arsenicum album* (Ars 6cH, 30cH, 200cH)	POSITIVE Increased cell viability, maximum effect after 3 days of treatment with Ars 200cH.
Oliveira et al., 2012[49]	Mouse peritoneal macrophages / Immune activity	*Mercurius solubilis* (6cH, 12cH, 30cH)	POSITIVE Morphological changes typical of the activated stage; increased secretion of IFN-γ and IL-4; increased production of NO and ROS.
Das et al., 2012[50]	*Escherichia coli* submitted to ultraviolet radiation / Activity on gene expression	*Arnica montana* 30c	POSITIVE Reduction of DNA damage and oxidative stress; over-expression of gene repair genes.
De et al., 2012[51]	*Escherichia coli* submitted to Sodium arsenite poisoning / Self-recovery from poisoning	*Arsenicum álbum* 30c	POSITIVE Reduction of the effects of intoxication by inhibiting the generation of ROS.
Frenkel et al., 2011[52]	Human mammary adenocarcinoma (MCF7) (E+ P+) e MDAMB231 (E P) / Anticancer activity	*Carcinosinum* 30c, *Phytolacca decandra* 200c, *Conium maculatum* 3c and *Thuja occidentalis* 30c	POSITIVE Reduction of cell viability; cell cycle disruption in the G1 phase. Activity of *Carcinosinum* and *Phytolacca decandra* equivalent to that of 0.12 μM paclitaxel.
Hofbauer et al., 2010[53]	Human gastric carcinoma cells (KATOIII) / Activity in gastritis and gastric ulcer	*Nux vomica* and *Calendula officinalis* (10c, 12c)	POSITIVE Reduced gene expression of heparin-bound epidermal growth factor induced by *H. pylori.*
Patil et al., 2009[54]	Human PMN function/Immunomodulatory activity	*Rhus toxicodendron* (6cH, 30cH, 200cH, 1000cH)	POSITIVE Increased chemotaxis; increased oxidative processes; Intracellular fungicidal action against *C. albicans.*

Legends: HD: homeopathic ultradilution; TLR-4: membrane receptor important in activating the innate immune response; FSH: follicle-stimulating hormone; PMN: polymorphonuclear cells; C. albicans: Candida albicans; ROS: reactive oxygen species; HSP-90: heat shock protein 90; HDAC2: histone deacetylator enzyme 2; USA: United States of America; E+/E-: positive/negative for estrogen receptor; P+/P-: positive/negative for progesterone receptor; COX-2: cyclooxygenase 2 enzyme; PgE2: prostaglandin E2; PFK-1: 6-phosphofructo-1-kinase enzyme; TNF-α: tumor necrosis factor-alpha; IFN-γ: interferon gamma; IL: interleukin; NO:

nitric oxide; TM: mother tincture; PBMN: peripheral blood mononuclear cells; mRNA: messenger RNA; H. pylori: Helicobacter pylori; MRSA: Methicillin-resistant Staphylococcus aureus; T3: triiodothyronine; L. amazonensis: Leishmania (L.) amazonensis; MDCK cells: Madin-Darby Canine Kidney cells.

In the fascinating area of "Genomic Homeopathy"[55-59], dozens of *in vitro* experimental studies (in addition to those previously mentioned) demonstrate the action of homeopathic HDs in altering gene expression, in accordance with three types of effects: change in the gene expression pattern, cytotoxicity or apoptosis in cancer cells and therapeutic modification in gene expression. These experiments are available in three tables in one of the articles in the series[56] in order to not inflate the number of references in the chapter, deviating from the objective of the work.

Highlighting the diversity of *in vitro* experimental studies which evaluated the effect of homeopathic HDs in different laboratory research models, we indicate some bibliographical surveys of the literature available in different databases below, as well as in reviews and conference annals:

- LILACS[4]: "homeopathy" AND "experimental research" AND "in vitro" (21 studies); "homeopathy" AND "basic research" AND "in vitro" (103 studies); "homeopathy" AND "fundamental research" AND "in vitro" (9 studies).
- PubMed[5]: "homeopathy" AND "experimental research" AND "in vitro" (31 studies); "homeopathy" AND "basic research" AND "in vitro" (9 studies); "homeopathy" AND "fundamental research" AND "in vitro" (2 studies).
- "Homeopathy Basic Research Experiments database (HomBrex)"[6]: 2,418 basic research experiments in homeopathy are currently available.
- "HRI - Recommended reading (Peer reviewed journals article)"[8].
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[9]: in the first editions (2016 and 2017), the chapters dedicated to "Basic Research" describe experiments with HDs in *in vitro* models*;* then the most recent edition (2020-2021)[10], discusses the evolution of this research line in recent decades ("Basic Science", chapter 10, pp. 167-172).
- Groupe International de Recherche sur l'Infintésimal (GIRI) – "Meetings"[11].

VII.3. Experimental studies in plant models

As mentioned in the *in vitro* experimental studies, the Homeopathy Research Institute (HRI) makes available on its page a synthesis of the results of some reviews on

experimental studies on plants published up to 2012 ("*Use of plants in basic research in homeopathic potentisation*"), which we will expand with other evidence.

In the narrative review "*Effects of homeopathic high dilutions on plants: literature review*"[2], published in the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017), the authors described studies with the best methodological quality which confirmed the positive effect of homeopathic HDs on plants, using the reviews on the topic published until 2015 as sources of references and updating the data with the most recent studies published at the time (2017). Among 167 experimental studies analyzed, 48 met the minimum methodological quality criteria (Manuscript Information Score or MIS ≥ 5) and 29 identified the positive and specific effects of homeopathic ultradilutions on plants, employing appropriate controls.

The main studies which met the inclusion criteria (MIS ≥ 5) were grouped according to the three main research models [healthy plants, diseased plants (phytopathological models) and abiotic stress], with their data synthesized and schematized in the tables below (**Tables 2-4**). As we did in experimental studies in *in vitro* models (VII.2), we have updated this data with more recent experiments (2017-2023).

Table 2. Summary of experimental studies with homeopathic HDs in healthy plants.

Author/ Year	Plant species/ Study aims	Outcomes	Intervention / Control	Intervention application method	Effects/ Results
Abasolo-Pacheco et al., 2020[60]	Turnip (*Brassica napus*) / To evaluate the effect of *Silicea terra*, *Natrum muriaticum* and *Phosphoric acidum* on plant germination, emergence and vegetative development	Variables: % germination/ emergence; stem and radicle length; fresh and dry mass of the aerial parts and radicle; plant height; stem diameter; number of sheets; weight, leaf area and yield	*Silicea terra* (Sil), *Natrum muriaticum* (Nat-m) and *Phosphoric acidum* (Ph-ac) (7cH, 31cH) vs. purified water	Application of the treatments in the Petri dish with seeds (germination), in germination boxes (emergence); and sowing (vegetative development)	Significant differences were observed in all variables and stages of development. The highest germination values corresponded to Sil 7cH and Ph-ac 7cH (100%), surpassing the control group (83.5%). Ph-ac 7cH and Nat-m 31cH stimulated stem growth (3.40 cm) in the germination phase and Nat-m 7cH the root growth (4.07 cm) in the emergence phase. During vegetative development, the plants with the highest yield were those treated with

					Nat-m 7cH. The highest profitability of the crop (71.33%) occurred with Sil 7cH, with a cost/benefit ratio of 1.7%.
Endler et al., 2015[61]	Wheat / To evaluate the effect of dynamized gibberellic acid on seedling growth in autumn vs. winter-spring	Seedling length	Gibberellic acid 30d vs. purified water vs. dynamized water	Application of the treatments in the Petri dish with the seeds	In all experiments conducted in the fall, gibberellic acid 30d reduced** seedling growth. In experiments conducted in winter-spring, the results were inconsistent.
Majewsky et al., 2014[62]	Water duckweed (*Lemna gibba*) / To investigate the effect of dynamized gibberellic acid on seedling growth	Growth rate	Gibberellic acid 14d to 30d vs. water vs. dynamized water	The seedlings were kept in a Becker cup with nutrient solution and one of the treatments	There was an increase** in the growth rate in some dynamizations, but the stage of seedling development seems to affect the response to treatment.
Hribar-Marko et al., 2013[63]	Wheat / To evaluate whether pretreatment with gibberellic acid at minimum dose increases the effect of dynamized gibberellic acid on seedling development	Seedling length	Pre-treatment of seeds with gibberellic acid at minimum dose (10^{-5}, 10^{-4}, 10^{-3}). Gibberellic acid 30d vs. water vs. dynamized water	Application of 2ml of the pretreatment in the Petri dish with the seeds. After 4 hours, application of 3ml of the treatments	In the water-pretreated group, gibberellic acid 30d reduced** seedling growth. In the groups that received the acid in minimum dose, the effect of the dynamized acid in reducing seedling growth was greater the lower the concentration.
Kiefer et al., 2012[64]	Wheat / To evaluate the effect of dynamized gibberellic acid on seed germination	Germinated seeds	Gibberellic acid 30d vs. purified water vs. dynamized water	Application of the treatments in the Petri dish with the seeds	Gibberellic acid 30d reduced** the germination rate in the 2009-2010 experiments; In 2011, there was no difference. Causes for this difference may be the lower viability of the seeds and the season.
Endler et al., 2011[65]	Wheat / To evaluate the effect of dynamized gibberellic acid on seedling growth in different seasons of the year	Seedling length	Gibberellic acid 30d vs. water vs. dynamized water	Application of the treatments in the Petri dish with the seeds	Gibberellic acid 30d reduced** seedling growth. The best effect was obtained in the autumn. Causes for this difference may be lower seed viability, season, and temperature.

Pfleger et al., 2011[66]	Wheat / To evaluate the effect of dynamized gibberellic acid on seedling growth	Seedling length	Gibberellic acid 30d vs. water vs. dynamized water	Application of the treatments in the Petri dish with the seeds	Gibberellic acid 30d reduced** seedling growth.
Santos et al., 2011[67]	*Verbena gratissima* / To study the effect of *Phosphorus* on the growth and concentration of essential oil of the plant	Plant growth parameters and essential oil content	*Phosphorus* 5cH, 6cH, 9cH, 12cH, 15cH, 18cH, 21cH, 24cH, 27cH and 30cH vs. water vs. hydroalcoholic solution	The treatments were applied 3x a week, 100 ml per pot, for 3 months	Some dynamizations, especially the 9cH, increased** the height of the plants and the dry mass of branches and leaves, in addition to the production of essential oil.
Scherr et al., 2009[68]	Water duckweed (*Lemna gibba*) / Analyze the influence of high dilutions on plants	Growth rate	Gibberellic acid, *Argentum nitricum*, kinetin, *Lemma minor* vs. water vs. dynamized water	The plants were selected according to the number of leaves and size and kept in a Becker cup with the treatments	Gibberellic acid 15d, 17d, 18d, 23d and 24d reduced** the growth rate of the plant.
Sukul et al., 2009[69]	Okra / To evaluate the influence of plant growth retardants (CCC, chloroethyltrimethyl-ammonium chloride; MH, maleic hydrazide) on plant development	Growth and physiological variables	CCC 30c, CCC 200c, CCC 30c (with copper nanoparticles) and MH 30 vs. dynamized hydroalcoholic solution	Foliar spray of the treatment diluted 1:500 for two days, twice a day	All treatments increased** plant growth, chlorophyll content, protein and water content in the leaves. CCC 30c with copper nanoparticles was more effective than CCC 30c.
Baumgartner et al., 2008[70]	Dwarf pea / To evaluate the effects of dynamized gibberellic acid on seedling growth	Shoot growth	Gibberellic acid 17d and 18d vs. water vs. dynamized water	The seeds were immersed in the treatments for 24 hours	Gibberellic acid 17d stimulated** seedling growth from seeds harvested in 1997.
Sukul et al., 2008[71]	Pigeon pea / Checking the effect of substances on plant growth	Growth and physiological variables	CCC 30c, CCC 200c, CCC 30c (with copper nanoparticles) and MH 30 vs. dynamized hydroalcoholic solution	Treatment foliar spray diluted 1:500 for eight days	All treatments increased** plant growth, chlorophyll, sugar and protein content.

Scherr et al., 2007[72]	Water duckweed (*Lemna gibba*) / To study the effects of dynamized substances on the growth rate of the plant	Growth rate	*Argentum nitricum*, copper sulfate, gibberellic acid, 3indoleacetic acid, kinetin, lactose, *Lemma minor*, methyl jasmonate, methoxuron, *Phosphorus*, potassium nitrate and *Sulphur* (14d to 30d) vs. water vs. dynamized water	Uniform plants (in relation to the number of leaves and size) were placed in a Becker cup with nutrient solution and then 46.2 ml of the treatments were added	*Argentum nitricum* 24d, 28d and 29d, kinetin 14d, 16d, 20d, 23d, 26d, 27d and 30d, and *Phosphorus* 21d, 25d and 29d affected** the growth rate of the plant during the entire evaluation period.
Baumgartner et al., 2004[73]	Pygmy pea / To evaluate the effect of dynamized plant hormones on seedling growth	Seedling length	Gibberellic acid, kinetin, auxin, apsisic acid (12d to 30d) vs. water vs. dynamized water	The seeds were immersed for 24 hours in the treatment and placed to germinate	Gibberellic acid 13d, 15d, 17d and 23d, and kinetin 19d increased** seedling size.
Chapman 2004[74]	Lettuce / Evaluate the effect of homeopathic medicines on plant growth	Size and weight of plants	Dynamized *Sulphur* and *Silicea terra* vs. dynamized water	The plants received the treatments in the soil	*Sulphur* and *Silicea terra* 1LM affected** plant development.
Andrade et al., 2001[75]	Chambá (*Justicia pectoralis*) / To evaluate the effect of dynamized substances on growth, coumarin production and electromagnetic field	Growth variables, coumarin yield and electromagnetic field	Chambá, *Acanthaceae*, Cumarina, Guaco, *Phosphorus*, *Sulphur*, *Arnica montana* and ácido húmico (3cH) vs. ethanol 3cH 70% vs. ethanol 70%	Weekly sprays (9) of 2.65 ml per plant of a solution with 10 drops/l of water	The treatments Chamba, humic acid, *Arnica montana*, *Phosphorus* and Sulphur 3cH increased** the yield of coumarin.
Brizzi et al., 2000[76]	Wheat / To evaluate the effect of dynamized *Arsenicum album* on seed germination	Number of seeds germinated	*Arsenicum album* (As_2O_3) 23d to 45d vs. water vs. dynamized water	Application of the treatments in the Petri dish with the seeds	*Arsenicum album* 30d, 35d, 40d, 42d and 45d stimulated** seed germination.
Betti et al., 1994[77]	Wheat / Evaluate the effect of *Arsenicum album* on germination	Germination rate	*Arsenicum album* (As_2O_3) 23d, 25d, 30d, 35d, 40d and 45d vs. water vs. water 30d	Application of the treatments in the Petri dish with seeds	*Arsenicum album* 40d and 45d increased** seed germination.

Pongratz and Endler, 1994[78]	Wheat / To study the effect of dynamized silver nitrate on germination and seedling development	Seedling size and germination rate	*Argentum nitricum* 24d vs. water vs. dynamized water	The seeds were immersed in the treatments	*Argentum nitricum* 24d stimulated seedling development.
Endler and Pongratz, 1991[79]	African violet / To evaluate the effect of indolebutyric acid on plant development	Rooting and development of new leaves	Indolebutyric acid 33d vs. dynamized water	Plant immersion	Indolebutyric acid 33d increased rooting.
Pongratz, 1990[80]	Wheat / To evaluate the effect of dynamized silver nitrate on germination and seedling development	Seedling length and germination rate	*Argentum nitricum* 24d vs. dynamized water	Seed soaking	*Argentum nitricum* 24d increased** seedling development.
Noiret and Claude, 1979[81]	Wheat / To evaluate the effect of dynamized copper sulfate on germination and seedling development	Dry and fresh weight	Dynamized CuSO4 (5c, 7c, and 9c) vs. water vs. dynamized water	Seed soaking	There was a reduction** in the variables analyzed.

** Statistically significant difference.

Table 3. Summary of experimental studies with homeopathic HDs in diseased plants (phytopathological models).

Author/ Year	Plant species/ Study aims	Outcomes	Intervention / Control	Intervention application method	Effects/ Results
Ferreira et al., 2021[82]	Lettuce / To investigate whether nosodes of *Meloidogyne enterolobii* can affect the moderate resistance already existing in the lettuce (cultivar 'Elisa')	Nematode reproduction factor and nematode density in roots	Nosodes from *Meloidogyne enterolobii* (6, 18, 30, 42cH) vs. purified water	The treatments were applied to lettuce plants by means of irrigation, with constant daily dosage	Nosodium 6, 18 and 30cH reduced** the nematode reproduction factor and root density. The effect of nosodium was cH-dependent, since nematode reproduction was favored by treatment with 42cH. Nosodium also affected** the lettuce roots, which showed greater or lesser fresh mass and volume depending on the cH applied and the parasitized or not condition.

Lösch et al., 2021[83]	Bell pepper (*Capsicum annuum*) / To evaluate the action of *Sulphur* and *Calcarea carbonica* in the phenological development and control of insects and diseases that naturally affect bell pepper.	Phenological development : shoot height and weekly plant mortality; development of leaves, flowers and fruits / Insect and disease control: number of plants affected, severity of damage and plant recovery	*Sulphur* 30cH and *Calcarea carbonica* 30cH	The applications of the homeopathic preparations occurred every seven days until the time of harvesting the plants, totaling 11 applications for cultivation in the field and 7 applications for plants in the greenhouse, always in the morning	*Sulphur* promoted positive increments in plant development, fruit production and diameter in field cultivation. *Calcarea carbonica* promoted a significant increase in the height of plants grown in greenhouses. Both favored the resilience of plants affected by parasites and diseases, aiding in growth after damage.
Shah-Rossi et al., 2009[84]	*Arábidopsis thaliana* / To verify the effect of different dynamized substances on plants infected by the bacterium *Pseudomonas syringae*	Leaf infection rate	Thirty dynamized substances at 30d vs. water vs. dynamized water	The plants were immersed in the treatments, depositing 1.5 ml in the center of the plant rosette and irrigating the plant with the treatments	Infection reduction** by the Biplantol homeopathic complex.
Datta, 2006[85]	Mulberry / To verify the effect of *Cina maritma* on plants infected with the nematode *Meloidogyne incognita*	Plant growth and infection variables	Cina 200c and Cina MT in treatment before and after inoculation vs. 90% hydroalcoholic solution	The plants were sprayed 4x with an interval of 3 days, with 10 ml of the treatment/plant; Cina MT was diluted 1:40 and Cina 200c 1:20 for spraying	The treatments increased** the length, the fresh weight of branches and roots, the number of leaves per plant and the leaf area; and reduced** the number of galls per plant; application before inoculation was more effective.
Sukul et al., 2006[86]	Okra / Checking the influence of homeopathic medicines on plants infected with the nematode *Meloidogyne incognita*	Number of galls and population of the nematode in the roots	*Cina maritma* 30c, Santonin 30c vs. water vs. hydroalcoholic solution 30c	Spray for 10 days, starting 7 days after inoculation. Each plant received 510 ml of the treatment diluted in water in a ratio of 1:1000	Cina 30c and Santonin 30c reduced** the number of galls and the population of the nematode in the roots; and increased the population in the soil.

Betti et al., 2003[87]	Tobacco / To estimate the effects of Arsenic trioxide (As_2O_3) on plants inoculated with smoke mosaic virus	Hypersensitivity lesions	As_2O_3 5d, 45d, 5cH and 45cH vs. water vs. dynamized water	Ten inoculated discs of the 3rd or 4th leaf were removed from each plant and placed in a Petri dish with 15 ml of treatment	Decimal dynamizations of As_2O_3, especially at 45d, decreased** the number of hypersensitivity lesions.
Sukul et al., 2001[88]	Tomato / To study the effects of dynamized *Cina maritma* on *Meloidogyne incognita*	Number of galls and population of the nematode in the roots	Cina 200c and 1000c vs. 90% hydroalcoholic solution	Foliar spray with 10 ml/plant of the treatments; plants were sprayed for 10 days, 1x/day	Cina 200c reduced** the number of galls/plant; the 2 dynamizations of Cina reduced** the population of the nematode in the roots.
Sukul and Sukul 1999[89]	Caupi / To study the effects of *Cina maritma* 1000c on *Meloidogyne incognita*	Number of galls; nematode population	Cina 1000c vs. 90% hydroalcoholic solution	Foliar spraying	The treatment reduced the number of galls and the population of the nematode in the root and soil.

** Statistically significant difference.

Table 4. Summary of experimental studies with homeopathic HDs in plants subjected to abiotic stress.

Author/ Year	Plant species/ Study aims	Outcomes	Intervention / Control	Intervention application method	Effects/ Results
Boudali et al., 2022[90]	Watercress (*Lepidium sativum*) / To evaluate the effect of dynamized *Zincum metallicum* on induced zinc toxicity in plants	Growth parameters, zinc uptake and biochemical parameters	*Zincum metallicum* (9cH, 15cH) vs. purified water	Cultivation water	Zinc increased** plant growth, photosynthetic pigment content, non-enzymatic antioxidant molecules, and enzymatic activities against zinc-induced oxidative stress.
Jäger et al., 2021[91]	*Lemna gibba* / To investigate the response of water duckweed stressed with Mercury chloride (Merc-c) to dynamized Merc-c	Leaf area growth rate	*Mercurius corrosivus* (Merc-c 24-30d) vs. purified water vs. dynamized water	Water duckweed was moderately stressed with 2.5 mg/L of Mercury chloride (Merc-c) for 48 hours. Subsequently, the plants grew in Merc-c 24-30d or water controls for 7 days	On days 3-7 after the application of the dynamized Merc-c, the growth rates were increased** compared to controls. On days 0–3, growth rates were not influenced by homeopathic preparations.

Brizzi et al., 2011[92]	Wheat / To evaluate the effect of *Arsenicum album* 45d on the germination of seeds previously stressed with As_2O_3	Germination rate	*Arsenicum album* 45d vs. distilled water vs. distilled water 45D	The seeds were stressed with As_2O_3 for 30 minutes and rinsed (60 minutes) in water before the treatments, which were heated for 30 minutes at 20, 40, 70 and 100ºC (for 5 minutes)	*Arsenicum album* 45d stimulated** seed germination; the efficacy of *Arsenicum album* 45d was not altered by heating up to 40ºC, but at 100ºC there was a reduction in efficacy.
Jager et al., 2011[93]	*Lemna gibba* / To evaluate the effect of 11 dynamized substances on plant growth after stress with As_2O_3	Leaf number and area; Leaf coloring	*Arsenicum album*, nosodium (prepared by maceration of plants grown for 48 hours in As_2O_3 medium), gibberellic acid, arsenic solution and other substances in different dynamizations vs. water vs. succussed water	The plants remained for 48 hours in medium with As_2O_3 for intoxication. They were then transferred to another container with the treatments	*Arsenicum album* and dynamized nosode increased** the growth rate of the plants.
Jager et al., 2010[94]	*Lemna gibba* / To evaluate the effect of 3 dynamized substances on plant growth after stress with As_2O_3	Leaf area	*Arsenicum album*, nosodium and gibberellic acid in different dynamizations vs. water vs. dynamized water	The plants remained for 48 hours in medium with As_2O_3 for intoxication. They were then transferred to another container with the treatments	*Arsenicum album* and dynamized node increased** the growth rate of the plants.
Lahnstein et al., 2009[95]	Wheat / To evaluate the effect of dynamized *Arsenicum album* on As_2O_3-stressed seed germination and seedling growth	Shoot growth	*Arsenicum album* 45d vs. distilled water vs. distilled water 45D	The seeds were stressed with As_2O_3 for 30 minutes and then rinsed for 60 minutes in water; then they received 3.3 ml of the treatment	*Arsenicum album* 45d reduced** wheat seedling growth.

Binder et al., 2005[96]	Wheat / Effect of dynamized *Arsenicum album* on seeds stressed with As_2O_3	Seedling growth	*Arsenicum album* 45d vs. distilled water vs. water 45d	The seeds were stressed with 0.1% As_2O_3 for 30 minutes and rinsed in water for 60 minutes; the treatments were placed in the Petri dish with the seeds	*Arsenicum album* 45d reduced** seedling growth when compared to water and water 45d.
Brizzi et al., 2005[97]	To evaluate the effect of dynamized As_2O_3 on the growth of stressed seedlings with sublethal doses of As_2O_3	Seedling length	As_2O_3 5d, 15d, 25d, 35d and 45d vs. distilled water vs. dynamized distilled water vs. diluted and non-succussive As_2O_3	Seeds were stressed with 0.1% As_2O_3 for 30 minutes and rinsed for 60 minutes in water; after, they received 3.2 ml of each treatment	As_2O_3 45d increased** the length of the seedlings.
Brizzi et al., 2000[98]	Wheat / To verify the effect of dynamized *Arsenicum album* on the germination of wheat seeds stressed with As_2O_3	Germination rate	As_2O_3 30d, 40d, 42d, 45d vs. distilled water vs. dynamized distilled water vs. diluted and non-succussive As_2O_3	Seeds were stressed with 0.1% As_2O_3 for 30 minutes and rinsed for 60 minutes in water; the treatments were placed in the Petri dish with the seeds	*Arsenicum album* 40d, 42d e 45d stimulated** the germination of seeds previously stressed or not with As_2O_3; As_2O_3 diluted alone had no effect on germination.
Betti et al., 1997[99]	Wheat / To evaluate the effect of *Arsenicum album* 45d on wheat seeds poisoned with As_2O_3	Shoot and root growth	*Arsenicum album* 45d vs. distilled water	Single application of 3.2 ml of water or *Arsenicum album* 45d in each container	*Arsenicum album* 45d increased** shoot length by 24%.

** Statistically significant difference.

In 2018, a new systematic review[100] updated the experiments that studied the effect of homeopathic HDs on plants. The authors identified 192 publications with 202 experimental studies. In the subgroup of experiments with adequate methodological quality and appropriate control groups to evaluate the specific effects of homeopathic HDs, 95% of studies showed significant differences compared to controls. Then in 2022, another study by the authors[101] provided further scientific evidence that the biological effects of homeopathic HDs "are not due to a placebo effect".

Highlighting the diversity of experimental studies on plants which evaluated the effect of homeopathic HDs in different research models in agronomy, we indicate below some

bibliographical surveys of the literature available in different databases, as well as in reviews and conference annals:

- LILACS[4]: "homeopathy" AND "experimental research" AND "plant" (35 studies); "homeopathy" AND "basic research" AND "plant" (8 studies); "homeopathy" AND "fundamental research" AND "plant" (3 studies).
- PubMed[5]: "homeopathy" AND "experimental research" AND "plant" (54 studies); "homeopathy" AND "basic research" AND "plant" (32 studies); "homeopathy" AND "fundamental research" AND "plant" (4 studies).
- "Homeopathy Basic Research Experiments database (HomBrex)"[6]: 2,418 basic research experiments in homeopathy are currently available.
- "HRI - Recommended reading (Peer reviewed journals article)"[8].
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[9]: in the first editions (2016 and 2017) in the chapters dedicated to "Agrohomeopathy", it describes experiments with HDs in plant models; in the most recent edition (2020-2021)[10], it discusses the evolution of this research line in recent decades ("Homoeopathy for Agriculture", chapter 12, pp. 182-183).
- Groupe International de Recherche sur l'Infintésimal (GIRI) – "Meetings"[11].

VII.4. Experimental studies in animal models

As mentioned in the experimental studies with *in vitro* and vegetable models, the Homeopathy Research Institute (HRI) makes "Veterinary research"[102] available on its page, which is a synthesis of the results of some systematic reviews published in the area of veterinary homeopathy, and which we report below.

Although research on animal models is simpler to carry out, the amount of clinical evidence available for veterinary homeopathy is much smaller than for the use of homeopathy in humans.

Two global systematic reviews by Mathie and Clausen[103,104], published in 2014 and 2015, respectively, summarize some of the evidence from veterinary homeopathy clinical trials at the time. The first review[103] looked at evidence from randomized placebo-controlled trials and the corresponding meta-analysis[105] found weak evidence that homeopathic treatment is different from placebo ($p = 0.01$ for $n = 15$ trials; $p = 0.02$ for $n = 2$ most reliable assays).

The second systematic review[104] evaluated randomized trials comparing homeopathy with something other than placebo (i.e. conventional treatment), but found that the quality of studies in this category was too low to provide useful information about the effectiveness of veterinary homeopathy.

A more recent study published by Doehring and Sundrum in 2016[106] looked at the evidence for homeopathy in the care of food-producing animals, specifically in situations where antibiotics are commonly used. Although the review reached similar conclusions to Mathie and Clausen[103], the methods used were not consistent with a high-quality Cochrane-style systematic review. For example, Doehring and Sundrum evaluated a body of evidence which included uncontrolled, non-randomized observational studies, which were excluded by Mathie and Clausen in their systematic review.

Preventing diarrhea in piglets

According to HRI[102], one of the high-quality placebo-controlled trials identified in the first systematic review[103] was carried out at Wageningen University in the Netherlands[107]. In this triple-blind RCT, 52 pregnant sows were treated with Coli 30K (an isotherapeutic medicine made with the *Escherichia coli* bacteria which causes diarrhea in pigs) or placebo. The sows gave birth to 525 piglets and those in the Coli 30K treated group had six times less diarrhea than the piglets in the placebo group. This result was statistically significant ($p < 0.0001$), meaning it is extremely unlikely to be a false positive result due to chance alone.

By way of clarification, the homeopathic medicine used in this study was made from *E. coli* bacteria, diluted and alternately succussed to produce an HD of 10^{-60} (30K), which means that it should no longer contain any molecules of the original bacteria. The particular technique used, in which the medicine used is made from the same substance that causes the disease being treated, is a subtype of homeopathy called "isopathy", and the medicine produced is an "isotherapy".

As the only existing way to prevent this disease in animals is by using antibiotics, this study must be replicated to confirm its findings as it may provide an effective way to help reduce the overuse of antibiotics in livestock farming while improving the quality of their by-products (meat and milk).

Wound healing disorder and antimicrobial resistance in a horse

According to the HRI[102] and as we described in subchapter III.3 (“Types of epidemiological studies”) of chapter III (“Homeopathic clinical epidemiology”), case reports play a valuable role in documenting the direct experience of individuals, especially when recorded in systematic detail and independently verified. In this recent case report from homeopathic equine veterinarian Dr. Petra Weiermayer (Vienna), a 4-year-old horse with delayed healing associated with antimicrobial-resistant bacteria was successfully treated with homeopathy[108].

The horse did not respond to adequate antibiotic therapy after surgical treatment of a deep lacerated wound on the right front leg. A deep wound swab identified infection with antimicrobial-resistant bacteria. Subsequent treatment with the homeopathic medicine *Silicea terra* resulted in complete resolution of clinical signs of delayed wound healing (putrid inflammation, edema, and seroma) and complete wound closure within five weeks; improvements were maintained for more than a year without recurrence. Importantly, the case was also documented by the responsible independent veterinarian, the horse owner, and other horse owners in the same stable, providing valuable external validation. Considering the global threat of antimicrobial resistance, well-documented cases like this can form the basis of large-scale clinical studies to evaluate the potential impact of homeopathy in administering antibiotics and treating resistant infections, a global threat, as we will see later.

Expanding the analysis of scientific evidence in homeopathic veterinary medicine, in the narrative review “*The soundness of homeopathic fundamental research*”[3], published in the *Special Dossier: “Scientific Evidence for Homeopathy”* (Cremesp Dossier, 2017), the author describes the results of systematic reviews published in 2010[109] and 2015[110].

In the first systematic review (2010)[109] on animal experimentation in homeopathy, the authors showed that the methodology used in research published up to that time was sufficiently adequate to generate reliable data, which mostly showed convergence with information contained in homeopathic materia medica, the main tool used in clinical practice. Furthermore, the experimental models used medicines prepared according to the principles of “isopathy” and “similarity”, and in both cases it was possible to understand the complexity of their systemic actions, especially with regard to modulation of the host-parasite relationship and recovery of the organism’s stability in the face of aggressive stimuli, which was also corroborated by mathematical models[3].

A continuation of the previous study was published in the second systematic review (2015)[110], comprising a review of articles on animal experimentation in homeopathy between 2010-2015. At this stage, 53 articles were identified, covering 12 different animal species, 29 of which were developed with HDs greater (above) than Avogadro's constant (6.02×10^{23} mol^{-1}). As a result, only 2 articles presented negative results, both using commercial homeopathic complexes; one was conducted with fish, and the other with bees. In parallel, studies published after 2010 also presented greater technical refinement compared to the previous period with an association of results also obtained *in vitro*, with three or more replications. A summary of the main findings of these reviews can be seen in **Table 5**[3].

Table 5. Summary of the main findings resulting from two systematic reviews[109,110] on homeopathic studies in animal models published between 2000-2015.

Parameters	**Systematic review published in 2010[109]**
Total experiments	10 on isopathy 23 on similitude
Percentage of randomized samples	100%
Blind protocol	23 yes 10 no
Correlation between blind protocol and positive/negative outcomes	No (p= 0.6456, Fisher's test)
Convergence of experimental results and materia medica	87% for the studies on similitude
Parameters	**Systematic review published in 2015[110]**
Total number of articles	53 articles; 29 with dilutions above, and 10 with dilutions below Avogadro's number
Number of investigated species	12
Positive outcomes	100% for studies above Avogadro's number 80% for studies below Avogadro's number
Percentage of randomized samples	82%
Blind protocol	43%
Internal reproducibility	11%

In the table below (**Table 6**), we describe the summary of some homeopathic clinical studies on animals that demonstrated positive and significant results (effects) of homeopathy compared to the control group (placebo or conventional treatment).

Table 6. Summary of homeopathic clinical studies on animals with positive and significant results (effects) of homeopathy compared to placebo.

Author/ Year	Intervention	Experimental model/ Clinical condition/ Outcomes	Effects/ Results
Narita et al., 2023[111]	*Echinacea angustifolia* 6cH and *Avena sativa* 6cH vs. placebo (hydroalcoholic solution)	To determine the action of homeopathic medicines on hematological and immunological parameters of penguins in the reproductive period	The active group showed a significant increase in the mean corpuscular volume of red blood cells (29.78 ± 52.95 fL), while the control group showed stability/reduction (-3.08 ± 46.36 fL) ($p = 0.049$); a less pronounced increase in the proportion of heterophiles (8.38 ± 12.53%) compared to the control group (18.00 ± 9.37%) ($p = 0.010$); less pronounced reduction in lymphocyte concentration (-4.39 ± 2.21 × 109 cells/L) compared to the control group (-1.56 ± 2.76 × 109 cells/L) ($p = 0.001$); and a less pronounced reduction in the proportion of lymphocytes (-6.75 ± 10.35%) compared to the control group (-17.3 ± 8.73%) ($p = 0.002$). These changes resulted in increased immunity during the reproductive period.
Travagin et al., 2022[112]	*Arnica montana* 30cH vs. 5% hydroalcoholic solution vs. placebo (0.9% NaCl saline solution)	Postoperative analgesia of ovariohysterectomy (OH) in female dogs; The Glasgow Composite Pain Scale was used to analyze the effect of therapy	Analysis of variance (ANOVA) followed by Tukey's test was used to evaluate the test data. Statistical differences were considered significant when $p \leq 0.05$. The *Arnica montana* 30cH group maintained analgesia on average for 17.8 ± 3.6 hours, while the hydroalcoholic solution group did it for 5.1 ± 1.2 hours and the saline group for 4.1 ± 0.9 hours ($p \leq 0.05$).
Joshi et al., 2022[113]	Nosodium of *Leishmania donovani* (Ld) 30c (LdAPN 30c)	To evaluate the anti-leishmania potential of LdAPN 30c, both in an experimental approach in vitro (promastigote forms of *Leishmania donovani*) and in vivo (mice with visceral leishmaniasis, VL mice)	LdAPN 30c exhibited significant anti-leishmania activity against the promastigote forms of Ld and was found to be safe. A study conducted in VL mice revealed that LdAPN 30c resolved the disease by modulating the host immune response towards Th1 type through upregulation of pro-inflammatory cytokines (IFN-γ and IL-17) and inducing nitric oxide (NO) levels in infected macrophages. Hepatic parasite load decreased significantly. Nosodium proved to be safe (no hepatic or renal histological changes were observed in the treated animals).
Pinto et al., 2021[114]	*Mercurius corrosivus* (MC 6, 30, 200cH) vs. different controls	To describe the effects of homeopathic *Mercurius corrosivus* (MC) on the hatching of *Artemia salina* cysts and on mercury bioavailability	Significant delay ($p < 0.0001$) in cyst hatching was observed only after treatment with MC 30cH, compared to controls. This result was associated with an increase in the concentration of total soluble mercury (THg) in water ($p = 0.0018$) and in the chlorine/oxygen ratio ($p < 0.0001$) in the suspended microaggregates, suggesting changes in the bioavailability of mercury. A specific interaction of MC 30cH was found with the solvatochromic dye ET33 ($p = 0.0017$).

Joshi et al., 2020[115]	*Iodium* 30c vs. placebo (alcohol 30c)	To evaluate the anti-leishmania efficacy of *Iodium* 30c in experimental visceral leishmaniasis (VL) (*in vivo* in BALB/c inbred mice)	Animals treated with *Iodium* 30c had a significantly reduced parasite load (to 1503 ± 39 Leishman Donovan Units, LDU) compared to infected controls (4489 ± 256 LDU) ($p < 0.05$): thus, the mean therapeutic efficacy of *Iodium* 30c was 66.5%. In addition, the CD4+ and CD8+ T-cell population increased significantly ($p < 0.05$) after treatment. No toxicity was observed in the liver and kidneys. The efficacy of *Iodium* 30c prophylaxis was 58.3%, while the therapeutic efficacy of amphotericin B was 85.9%.
Balbueno et al., 2020[116]	*Crataegus oxyacantha* MT vs. *Crataegus oxyacantha* 6cH vs. placebo (hydroalcoholic solution)	Treatment of heart failure due to myxomatous mitral valve disease (MMVD) in dogs. Outcomes: echocardiographic parameters, blood tests, and systolic blood pressure (SBP) measurements at 30, 60, 90, and 120 days after initiation of therapy	Dogs that received Crataegus 6cH showed a reduction in SBP 60 days after treatment, while those that received Crataegus MT showed a reduction 90 days after starting therapy. There was significant linear regression when evaluating the effect of treatment with Crataegus 6cH on SBP measurements over the evaluation intervals (linear equation: SBP = 176.57 mm Hg - 0.21x, where x represents days of treatment). There was an increase in both the shortening fraction and the isovolumetric relaxation time for the dogs that received the homeopathic formulation.
Raj et al., 2020[117]	Homeopathic complex (Sulphur 30c, Thuja 30c, Graphites 30c and Psorinum 30c) vs. placebo (distilled water)	Oral papillomatosis in dogs. Outcomes: the dogs were clinically classified according to oral lesions; physical examination, blood count, and serum biochemistry. Biopsy specimens of papillomatous lesions	The homeopathic treatment group showed early recovery with a significant reduction in oral lesions reflected by the clinical score compared to the placebo group.
Ferreira et al., 2018[118]	*Phosphorus* 13cH vs. placebo (hydroalcoholic solution)	To evaluate and correlate the number of myocarditis foci and cytokine production in *Rattus norvegicus* (Wistar lineage), experimentally infected with T. cruzi and treated with *Phosphorus*	Treatment with *Phosphorus* 13cH caused a significant increase in INF-ɣ and TNF-α on the 5th day of infection compared to the control ($p < 0.05$), with recovery on the 24th day. The group treated with *Phosphorus* 13cH had 52.5% fewer foci of myocarditis in the heart than the control group ($p < 0.05$) on the 10th day of infection. The significant increase in cytokines in the treated group on the 5th day of infection is related to a significant decrease in the number of inflammatory foci in the cardiac tissue on the 10th day of infection.
de Paula Coelho et al., 2017[119]	*Cantharis* 6cH vs. placebo (hydroalcoholic solution)	To study the effects of *Cantharis* 6cH on E. coli-induced cystitis, in a randomized blinded placebo-controlled murine experimental model	*Cantharis* 6cH increased IL12p40, IFN-γ and decreased IL10 concentrations in bladder fluid ($p \leq 0.05$); in the bladder mucosa, the proportion between B and T lymphocytes increased (31%) and between B lymphocytes and MIF+ macrophages (57%, $p \leq 0.05$). In the pelvis, instead, the proportion of B/T cells decreased (41%, $p \leq 0.05$) and increased the proportion of M1/M2 macrophages (42%, $p \leq 0.05$). No

			differences were observed in the analysis of the kidney and spleen. Inverted balance of inflammatory cells and cytokines in the mucosa of the bladder and pelvis shows specific local immune modulation induced by *Cantharis* 6cH.
Beceriklisoy et al., 2008[120]	Group I: *Thuja occidentalis* d30; Group II: *Urtica urens* d6; Group III: naloxona (control)	Pseudopregnancy in female dogs. The animals were classified as absent, mild, moderate and severe according to the clinical signs of the mammary glands and behavioral signs during the study	Regarding mammary gland scores, the treatments produced significantly higher success rates in Group I and Group II (100% in both groups) compared to the success rate observed in Group III (37.5%).
Chaudhuri et al., 2007[121]	*Crotalus horridus* 200c vs. diminazine aceturate (conventional treatment)	Babesiosis in dogs; the diagnosis of babesiosis was based on cytological evidence of *Babesia gibsoni* on freshly prepared blood smears	Baseline clinical scores were similar in both groups and showed similar progressive improvement over 14 days. Parasitemia also improved in both groups, but hematological values showed no changes. Crotalus was as effective in the clinical recovery of moderate cases of babesiosis as the standard drug diminazine.

A recent review addresses the evidence on the general use of human and veterinary homeopathy[122], analyzing evidence level 1A studies. Then focusing on studies that investigated the possible use of homeopathy in infections, some level of evidence 1A, 1B, 2C studies and a case report are described in detail. The review concluded that there is evidence of the effectiveness of human and veterinary homeopathy in treating infections and that the problem of antimicrobial resistance represents a global threat; the authors reiterate the favorable recommendations of the World Health Organization (WHO) and the Commission of the European Union (EU) for the use of homeopathy, among other complementary medicine practices, in this and other clinical indications.

With the aim of improving the methodological and scientific quality of homeopathic animal research, recommendations for designing, conducting and reporting randomized controlled trials (RCTs) and observational studies in homeopathic veterinary medicine are available in the literature in some protocols[123,124].

Highlighting other experimental studies on animals which evaluated the effect of homeopathic HDs in various veterinary research models, we indicate some bibliographical surveys of the literature available in different databases below, as well as other reviews and conference annals:

- LILACS[4]: "homeopathy" AND "experimental research" AND "animal" (51 studies); "homeopathy" AND "research" AND "animal" (232 studies); "homeopathy" AND "veterinary" (174 studies).

- PubMed[5]: "homeopathy" AND "experimental research" AND "animal" (88 studies); "homeopathy" AND "research" AND "animal" (328 studies); "homeopathy" AND "veterinary" (311 studies).
- "HomVetCR database (HomVetCR)"[7]: currently offers 476 trials in veterinary homeopathy.
- "HRI - Recommended reading (Peer reviewed journals article)"[8].
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[9]: in the first editions (2016 and 2017) in the chapters dedicated to "Veterinary homeopathy", it describes experiments with HDs in animal models; in the most recent edition (2020-2021)[10], it discusses the evolution of this line of research in recent decades ("Homoeopathy in Veterinary Practice", chapter 11, pp. 173-181).
- Groupe International de Recherche sur l'Infintésimal (GIRI) – "Meetings"[11].

Although we have not addressed the experiments which seek to study the physical-chemical properties of homeopathic HDs with the aim of deepening understanding on the possible mechanism of action of these infinitesimal doses, as we are focusing on the evidence which contradicts the fallacious hypothesis that "homeopathy is placebo effect"; for those interested in this field of homeopathic research (physiochemical models), we suggest reading three recent systematic reviews[125-127] that analyzed and described studies in the area.

In the third review[127] of the aforementioned series to heighten readers' curiosity in this area of research, the authors show that differences between homeopathic HDs and controls were observed in 70% of the approximately 200 experiments studied, in accordance with systematic reviews of procedures of physical-chemical tests. In the subgroup of high-quality experiments, 80% of experiments showed differences between homeopathic HDs and controls, and confirming the high methodological quality of some of these experiments and the response effectiveness of homeopathic HDs, 2-9 replications were carried out in 10 experimental models.

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Proof of Scientific Evidence for Homeopathy

VIII. Randomized controlled clinical trials (RCTs)

VIII.1. Introduction

VIII.2. What scientific evidence is there that homeopathy works?

VIII.3. Randomized, double-blind, placebo-controlled trials

VIII. Randomized controlled clinical trials (RCTs)

VIII.1. Introduction

As we reported in subchapter III.3 (“Types of epidemiological studies”) of chapter III (“Homeopathic clinical epidemiology”) of this work, randomized, double-blind, placebo-controlled clinical trials (RCTs) aim to study the specific effects of a given intervention. The selected individuals are allocated to the intervention (active medication) and control (placebo) groups, and the results are evaluated by comparing the outcomes between the groups. Patients are randomly allocated (randomized) to ensure that these groups are equivalent. This ensures comparability between the intervention and control groups from the beginning of the study. Thus, any difference observed between the groups is due to chance and is therefore not affected by participant selection bias.

The RCT (randomized, double-blind and placebo-controlled trial) is considered the “gold standard” for determining scientific evidence on the effects of a given technology on health. A well-planned and conducted RCT is the type of design that presents the least possibility of biases (selection, measurement and confusion). An RCT must be preceded by a protocol that justifies and describes how the study will be carried out in detail [objectives, patient selection criteria, application of interventions, evaluation methods, study execution and monitoring, registration and randomization, ICF, sample size calculation (NNT), statistical analysis, etc.].

Presenting level 1B of scientific evidence, RCTs with a narrow 95%CI serve as a basis for carrying out future systematic reviews, with or without meta-analyses, as we will see in the next chapters. As we reported in subchapter III.5 (“Types of epidemiological studies in homeopathy”) of chapter III (“Homeopathic clinical epidemiology”), hundreds of randomized and placebo-controlled homeopathic clinical trials have been conducted and are available in various scientific literature databases.

The premises for developing homeopathic RCTs of high methodological and scientific quality according to “conventional” clinical epidemiology are described in several protocols[1-4], which systematize the guidelines and parameters to be followed in the design of this type of epidemiological study.

However, as we emphasize in several chapters of this work, **individualization of the homeopathic medicine (individualized homeopathic medicine), according to the**

characteristic symptomatic totality of the patient-disease binomial, is a *sine qua non* premise in preparing and analyzing homeopathic RCTs of high methodological and scientific quality according to homeopathic clinical epidemiology, as described in subchapter III.4 ("Premises and principles of homeopathic clinical epidemiology") of chapter III ("Homeopathic clinical epidemiology") and demonstrate systematic reviews with recent meta-analyses[5-7].

This premise of high methodological and scientific quality according to homeopathic clinical epidemiology is also evidenced in the clinical effectiveness of individual RCTs that used individualized homeopathic medicines, as we will see below.

Reiterating the scientific relevance of the *Special Dossier "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017), 19 homeopathic RCTs published in the period of 2014-2017 were cited in the review "*Clinical research in homeopathy: systematic reviews and randomized clinical trials*"[8], to exemplify the evidence of this type of study. In this review, the author calculated the annual publication rate of homeopathic RCTs, the percentage of individualized or non-individualized studies, as well as those which showed positive results in favor of homeopathy compared to placebo.

For readers who wish to delve deeper into evaluating the clinical effectiveness of homeopathy according to existing randomized clinical trials, noting the hundreds of RCTs in this area of scientific investigation, we suggest carrying out a bibliographical survey of the existing literature in the databases mentioned in chapter IV of this work ("Overview of research in homeopathy - Databases"), such as:

- LILACS[9]: "homeopathy" AND "clinical trial" (164 studies).
- PubMed[10]: "homeopathy" AND "clinical trials" (902 studies); "homeopathy" AND "randomized controlled trials" (622 studies); "homeopathy" AND "randomized controlled trials" AND "placebo controlled" (336 studies).
- "Trip Medical Database"[11]: "homeopathy" AND "clinical trial" (1,324 studies);
- "Clinical Outcome Research in Homeopathy (CORE-Hom)"[12]: provides 65 clinical trials, published until the beginning of 2018.
- "Homeopathic Intervention Studies (HOMIS)"[13]: provides a total of 636 clinical studies, 541 for therapeutic purposes and 95 for preventive purposes.
- "CAM-QUEST databases"[14]: currently (2023) offers a total of 1,893 homeopathic clinical studies, with 750 "randomized trials".
- "HRI - Recommended reading (Peer reviewed journals article)"[15].

- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[16]: it addresses homeopathic RCTs in all editions (2016, 2017 and 2020-2021) in the chapter "Clinical Research" (most recent edition (2020-2021)[17].

VIII.2. What scientific evidence is there that homeopathy works?

Considering that the scientific evidence for homeopathic medicine is based on the same types of clinical trials used to test conventional medicine treatments, the Homeopathy Research Institute (HRI) makes available "*What scientific evidence is there that homeopathy works?*"[18] on its page; an analysis of the results of homeopathic randomized controlled trials (RCTs) carried out to date, compared with evidence from conventional medicine.

In this survey, a total of 271 randomized clinical trials of homeopathic treatment for 144 clinical conditions were published in peer-reviewed journals by the end of 2022, with sufficient information to analyze the results. **Of the 271 RCTs, 157 were randomized, double-blind and placebo-controlled trials covering 95 different medical conditions.** Analysis of the effects of these homeopathic treatments showed that:

- 43% were positive (67 trials) - finding that homeopathy was effective.
- 3% were negative (5 trials) - finding that homeopathy was ineffective.
- 54% were inconclusive (85 trials).

An analysis of 1,128 systematic reviews of conventional medicine RCTs showed similar results in terms of the proportion of effects (positive, negative or inconclusive)[19]:

- 45% were positive - treatments would likely be beneficial.
- 10% were negative - treatments would likely be harmful.
- 45% were inconclusive - evidence supported neither benefit nor harm.

Although the proportion of positive effects (treatment efficacy) is similar in homeopathy and conventional medicine, in this analysis and in the main outcome (first analysis) of the systematic review with meta-analysis by Shang et al. (110 homeopathic RCTs versus 110 conventional RCTs, paired according to the same clinical outcomes)[20] which we will analyze in the next chapters, it is worth highlighting the great difference in the amount of research carried out between these therapeutic practices. While the first analysis above evaluated only 157 studies out of a total of 271

homeopathic RCTs, the second analysis above evaluated 1,128 out of more than 4,000 Cochrane systematic reviews of conventional medicine published up to 2011, each analyzing multiple RCTs. This highlights the need for more research into homeopathy, particularly large-scale, high-quality replications of the most promising positive studies.

The difference in the amount of research is also not surprising when one considers that only a small fraction of available funding is allocated to "complementary and alternative medicine" (CAM) research. Exemplifying this reality, an analysis in the United Kingdom in 2007 found that only 0.0085% of the total medical research budget was spent on CAM[21]. In the USA, only < 0.4% of the annual medical budget of US$51.1 billion was allocated to be used in CAM in 2023 by the National Center for Complementary and Integrative Health (NCCIH)[22]. These data demystify another fallacy of pseudoskeptics and pseudoscientists who call for the removal of homeopathy from public health systems (for example, The Brazilian Unified Healthcare System - *SUS*), claiming that huge amounts are spent on this treatment to the detriment of conventional medicine.

VIII.3. Randomized, double-blind, placebo-controlled trials (RCTs)

HRI provides the complete list of selected 157 randomized, double-blind, placebo-controlled homeopathic clinical trials ("*Placebo-controlled trials of homeopathic treatment*")[23] which were peer-reviewed and published by 2022 below, distinguishing those with positive, negative or inconclusive effects. Studies from non-peer-reviewed journals and other non-academic sources, prophylaxis studies, crossover designs and single-blind trials were excluded from this list.

We have summarized the results (effects) of some of these studies and other more recent ones in the table below **(Table 1)** to show the reader that dozens of randomized, double-blind, placebo-controlled homeopathic clinical trials (RCTs) presented positive and significant results (effects) compared to placebo in various clinical conditions, demonstrating that "homeopathy is not placebo effect", excluding the studies that will be cited in chapter XII ("Systematic reviews for specific clinical conditions").

Table 1. Summary of randomized, double-blind, placebo-controlled homeopathic clinical trials with positive and significant results (effects).

Author/ Year	Model/ Interventions	Clinical condition/ Outcomes	Effects/ Results

Mandal et al., 2023[24]	Individualized homeopathic medicine vs. placebo	Atopic dermatitis/ Primary outcome: severity of illness using the scale Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD). Secondary outcomes: Atopic Dermatitis Burden Scale for Adults (ADBSA) and Dermatological Life Quality Index (DLQI).	After 6 months of interventions, the differences between groups became statistically significant in the PO-SCORAD (-18.1; 95%CI, -24.0 to -12.2), favoring homeopathy over placebo (F 1.52 = 14.735; $p < 0.001$; bidirectional repeated measures analysis of variance). Between-group differences for secondary outcomes favored homeopathy but were not statistically significant overall (ADBSA: F 1.52 = 0.019; p = 0.891; DLQI: F 1.52 = 0.692; p = 0.409).
Balamurugan et al., 2023[25]	Individualized homeopathic medicine vs. placebo	Psoriasis/ Primary outcome: Psoriasis Area and Severity Index (PASI) and Psoriasis Disability Index (PDI). Secondary outcome: Dermatological Life Quality Index (DLQI).	After 6 months of interventions, improvements were significantly greater in the homeopathy group than in the placebo group in PASI scores (F1, 49 = 10.448, p = 0.002). The scores of the daily activity subscale of the DLQI also produced similar significant results, favoring homeopathy over placebo (F1, 49 = 5.480, p = 0.023). The improvement in total PDI (F1, 49 = 0.063, p = 0.803), total DLQI (F1, 49 = 1.371, p = 0.247) and all other subscales was greater in the homeopathy group than in the placebo group, although it was not statistically significant.
Ghosh et al., 2023[26]	Individualized homeopathic medicine vs. placebo	Hyperuricemia/ Primary outcome: serum uric acid level (SUA). Secondary outcomes: quality of life questionnaire (HUQLQ) and the Measure Yourself Medical Outcome Profile version 2 (MYMOP-2).	The intention-to-treat sample (n = 58) was analyzed. Between-group differences in SUA levels (F 1.56 = 13.833, $p < 0.001$), HUQLQ scores (F 1.56 = 32.982, $p < 0.001$), and MYMOP-2 profile scores (F 1.56 = 23.873, $p < 0.001$) were statistically significant, favoring the homeopathy group over the placebo group, with medium to large effect sizes.
Das et al., 2023[27]	Individualized homeopathic medicine vs. placebo	Irritable bowel syndrome (IBS)/ Primary outcome: IBS Quality of Life questionnaire (IBS-QOL). Secondary outcomes: IBS Severity Scoring System (IBS-SSS) and EQ-5D-5L scores; all measured at baseline and every month, up to 3 months.	Group differences and effect sizes (Cohen's d) were calculated in the intent-to-treat (ITT) sample. The groups were comparable at the start of the study. Recruitment, retention, and attrition rates were 64.5%, 91.7%, and 8.3%, respectively. Group differences in IBS-QOL, IBS-SSS and EQ-5D-5L total scores, favored the active group over placebo overall and at all time points (all $p < 0.001$).
Shahid et al., 2022[28]	Individualized homeopathic medicine vs. placebo	Plantar fasciitis/ Foot Function Index (FFI) questionnaire, as an outcome measure, was administered at baseline and monthly for up to 3 months.	Between-group differences in total FFI score favored active drug over placebo at all time points, with large effect sizes: month 1 (mean difference, -10.0; 95%CI: -15.7 to -4.2; p = 0.001; d = 0.8); month 2 (mean difference, -14.3; 95%CI: -20.4 to -8.2; $p <0.001$; d = 1.1); and month 3 (mean difference, -23.3; 95%CI: -30.5 to -16.2; $p < 0.001$; d = 1.5). Similar significant results were also observed in three FFI subscales

			(% pain, % disability, and % activity limitation).
Ghosh et al., 2021[29]	Individualized homeopathic medicine vs. placebo	Dysmenorrhea/ The outcomes were numerical scales 0-10 (NRS) measuring the intensity of dysmenorrhea pain and Verbal Multidimensional Scoring System (VMSS); measured at baseline and every month, up to 3 months.	The groups were comparable at baseline (all $p > 0.05$). The attrition rate was 10.9% (homeopathy: 7; placebo: 7). Differences between the NRS and VMSS pain groups favored homeopathy over placebo at all time points (all $p < 0.001$, unpaired t-tests, and bidirectional repeated measures analysis of variance) with medium to large effect sizes.
Adi et al., 2020[30]	*Syzygium cumini* 30c vs. placebo	Type 2 diabetes/ Reduction of serum glucose and glycosylated hemoglobin levels at 1, 3 and 6 months of treatment.	At 6 months of treatment, there was a significant reduction in serum glucose and glycosylated hemoglobin levels in the t-test active group ($p = 0.001$). Repeated measures ANOVA also showed a significant difference ($p = 0.0001$).
Frass et al., 2020[31]	Individualized homeopathic medicine vs. placebo vs. no intervention (control)	Additive treatment of patients with non-small cell lung cancer (NSCLC)/ Outcomes: quality of life (QoL) and patient survival.	Quality of life as well as functional and symptom scales showed significant improvements in the homeopathy group when compared to placebo after 9 and 18 weeks of treatment ($p < 0.001$). The median survival time was significantly longer in the homeopathy group (435 days) versus placebo (257 days; $p = 0.010$) as well as versus control (228 days; $p < 0.001$). The survival rate in the homeopathy group differed significantly from placebo ($p = 0.020$) and control ($p < 0.001$).
Yakir et al., 2019[32]	Individualized homeopathic medicine vs. placebo	Premenstrual syndrome (PMS)/ Outcome: differences in changes in average daily premenstrual symptom (PM) scores by the Menstrual Distress Questionnaire (MDQ).	Intention-to-treat analysis (n = 105). With results similar to those of the 2001 study (n = 58), a significantly greater improvement in mean PM scores was observed in the active group (0.443 [standard deviation, SD, 0.32] to 0.287 [SD, 0.20]) compared to placebo (0.426 [SD, 0.34] to 0.340 [SD, 0.39]); $p = 0.043$. Individualized homeopathic medicines showed significantly greater improvement than placebo in PM scores in women with PMS.
Michael et al., 2019[33]	Individualized homeopathic medicine vs. placebo	Insomnia/ Primary outcome: Sleep Diary (6 items; 1: latency to fall asleep, 2: minutes awake in the midnight, 3: minutes awake too early, 4: hours spent in bed, 5: total sleep time in hours, and 6: sleep efficiency). Secondary outcome: Insomnia Severity Index (ISI).	The sample was analyzed by intention-to-treat (n = 60). The trial arms were comparable at the start of the study. In the active group, except for item 3 of the sleep diary ($p = 0.371$), the rest of the results improved significantly (all $p < 0.01$). The differences between the groups were significant for items 4, 5 and 6 ($p < 0.01$) and only significant ($p = 0.014$) for the ISI score with moderate to large effect sizes; but not significant ($p > 0.01$) for the rest of the results.
Qutubud-din et al., 2019[34]	Individualized homeopathic medicine + conventional	Bronchial asthma lasting 3.5 years, on average/ Primary outcome: spirometric	According to intention-to-treat analysis (n = 140), the two arms of the study were comparable at baseline. Between-group differences over 3 and 6 months showed

	treatment vs. placebo + conventional treatment	measurements, percentage of eosinophils in the blood, and serum immunoglobulin E. Secondary outcome: severity of symptoms with different scores.	significant differences in improvement of the homeopathy group compared to the placebo group ($p < 0.01$) with moderate to large effect sizes (Cohen's d) for primary and secondary outcome measures.
Andrade et al., 2019[35]	*Capsicum frutescens* 30cH vs. placebo	Treatment of hot flashes/ Intensity of hot flashes measured by the Measure Yourself Medical Outcome Profile (MYMOP) instrument.	Intensity of hot flashes assessed by MYMOP was higher in placebo group over the 4 weeks of treatment. The OR for treatment response (reduction of at least three MYMOP categories) was 2.78 (95%CI: 0.77 to 10.05; $p < 0.001$).
Oberai et al., 2018[36]	Individualized homeopathic medicine + conventional treatment vs. placebo + conventional treatment	Acute encephalitis syndrome (AES)/ Primary efficacy analysis was based on the Glasgow Outcome Scale (GOS). Morbidity was assessed using the Liverpool Outcome Score for Assessing Children at Follow-up.	Intention-to-treat analysis was performed (n = 612). The primary endpoint, GOS, differed significantly between the active and placebo groups. There was 14.8% death/neurovegetative state in the active group compared to 29.8% in the placebo group. The relative risk was 0.49 (95%CI: 0.36 to 0.68), with an absolute risk reduction of 15.0% (95%CI: 8.6 to 21.6%). The number needed to treat to prevent further death/neurovegetative status was 6.6 (95%CI: 4.6 to 11.6). Proportional probability analysis also revealed a greater effect in the active group: odds ratio 0.40 (95%CI: 0.27 to 0.60)
Adler et al., 2018[37]	*Opium* and *Erythroxylum coca* in LM potencies vs. placebo	Cocaine dependence/ Days of Drug Use, Minnesota Cocaine Craving Scale and 12-Item Short-Form Health Survey scores.	The mean percentage of days of cocaine use in the homeopathy group was 18.1% (standard deviation (SD): 22.3%), compared to 29.8% (SD: 30.6%) in the placebo group ($p < 0.01$).
Sorrentino et al., 2017[38]	*Arnica montana* 1000K vs. placebo	Postoperative hemorrhage and reduction of seroma in mastectomy/ Primary outcome: reduction in blood and serum volumes collected in drainages. Secondary outcome: duration of drainage, self-assessment of pain, and presence of hematomas.	Protocol analysis revealed a lower mean volume of blood and serum collected in drainages with A. montana (-94.40 ml; 95%CI: 22.48-211.28; $p = 0.11$). A regression model including treatment, volume collected at drainage on the day of surgery, and patient weight showed a statistically significant difference in favor of A. montana (-106.28 ml; 95%CI: 9.45-203.11; $p = 0.03$). The volumes collected on the day of surgery and on the following days were significantly lower with A. montana on days 2 ($p = 0.033$) and 3 ($p = 0.0223$).
Teixeira et al., 2017[39,40]	Individualized estrogen 6cH, 18cH, and 24cH vs. placebo	Pelvic pain associated with endometriosis/ Reduction of global and partial endometriosis-associated pelvic pain severity (APD), Beck Depression Inventory, Beck Anxiety Inventory, and quality	Reduction of the overall score in the homeopathy group ($p < 0.001$); reduction in partial scores for dysmenorrhea ($p < 0.001$), non-cyclic pelvic pain ($p < 0.009$), and cyclic bowel pain ($p < 0.001$). The placebo group showed no improvement in any score. The homeopathy group showed significant improvement in 3 domains of the SF-36 (physical pain, vitality and mental health); the placebo group showed no improvement

		of life (SF-36).	at all.
Chaiet et al., 2016[41]	*Arnica montana* vs. placebo	Postoperative rhinoplasty/ Extent and intensity of ecchymosis after rhinoplasty with osteotomy.	The homeopathy group showed a 16.2%, 39.2% and 20.4% reduction in extension on days 2-3, 7 and 9-10 after surgery, tending to significance on day 7 ($p = 0.097$). Lesion intensity increased by 13.1% on day 1, followed by a reduction of 10.9% and 36.3% on days 7 and 9/10, tending to be significant on days 9-10 ($p = 0.074$).
van Haselen et al., 2016[42]	Conventional symptomatic on-demand treatment vs. homeopathic complex (Influcid®) + conventional treatment	Febrile Upper Airway Infections (URTIs)/ Resolution of fever and symptoms of URTIs and Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21) in children.	The homeopathy group needed less symptomatic medication. Symptoms resolved significantly faster ($p = 0.0001$). The proportion of children without fever from the 3rd day onwards was higher. Significant reduction in the total WURSS-21 severity score ($p < 0.0001$).
Siqueira et al., 2016[43]	Isopathic complex vs. InfluBio® (H3N2 30D) vs. placebo	Number of episodes of URTI in 1 year in children aged 1 to 5 years.	There was a significant difference between the groups treated with isopathy and placebo ($p < 0.001$). 30.5% of the children in the placebo group had 3 or more episodes of URI/year, while the InfluBio® group had 1 episode and the isopathic complex group had no episodes.
Frass et al., 2015[44]	Individualized homeopathic medicine vs. placebo	Cancer patients on standard antineoplastic treatment/ General state of health and well-being.	Significant improvement in the homeopathy group in general health status ($p<0.005$) and subjective well-being ($p<0.001$).
Chauhan et al., 2014[45]	Individualized homeopathic medicine vs. placebo	Children with subclinical hypothyroidism and autoimmune thyroiditis/ TSH and antithyroid antibodies (ATPO)	TSH values returned to normal in a higher proportion in the group treated with homeopathy ($p < 0.006$). ATPO values returned to normal in a higher proportion in the homeopathy group ($p < 0.05$). Eight children in the placebo group (10.5%) developed overt hypothyroidism.
Malapane et al., 2014[46]	Homeopathic complex vs. placebo	Acute viral tonsillitis/ Change in signs and symptoms in children (6 to 12 years) on the Wong-Baker FACES Grading scale.	The homeopathy group showed significant improvement in tonsillitis-associated pain, swallowing pain, erythema, and pharyngeal inflammation at the size of the tonsils.
Colau et al., 2012[47]	Homeopathic complex (BRN-01) vs. placebo; Multicenter study	Treatment of menopausal hot flashes/ Primary outcome: hot flashes score (global HFS) compared before, during, and after treatment. Secondary outcomes: quality of life (QoL), symptom severity (HFRDIS), hormone dosage, and adverse events.	Overall HFS over 12 weeks, assessed as the area under the curve (AUC) adjusted for baseline, was significantly lower in the BRN-01 group than in the placebo group (mean ± SD 88.2 ± 6.5 vs. 107.2 ± 6.4; $p = 0.0411$). BRN-01 was well tolerated; the frequency of adverse events (AEs) was similar in the two groups, and no serious AEs were attributed to BRN-01.
Frass et al., 2011[48]	Individualized homeopathic medicine vs. placebo	Adjuvant treatment in severe sepsis (UTI)/ Survival after 30 and 180 days as an outcome measure.	Patients in both groups survived. Baseline characteristics and laboratory parameters did not show significant differences between the groups. At day 30, there was a non-statistically significant survival trend in

			favor of homeopathy (active 81.8%, placebo 67.7%, p=0.19). At day 180, the survival of the active group was statistically significantly higher than placebo (75.8% vs. 50.0%, p=0.043). No adverse effects were observed.
Naudé et al., 2010[49]	Individualized homeopathic medicine vs. placebo	Insomnia/ Sleep Diary (SD) and Sleep Disorder Index (SDI).	The SD data revealed that the homeopathy group showed a significant increase in sleep duration over the course of the study, compared to placebo, which did not. A significant improvement in SDI summary scores and the number of improved individual questions was found in the active group and responses to all 11 questions improved significantly after completion of the study. An initial improvement occurred in the placebo group but was not maintained. The comparison of the results between the groups revealed a statistically significant difference.
Belon et al., 2007[50]	*Arsenicum album* 30cH vs. placebo	To improve the toxicity of arsenic in intoxicated persons/ Outcomes: [arsenic] in urine and blood; biomarkers of toxicity.	The treated group showed positive modulations in the parameters under analysis, suggesting potential for improvement. Most individuals reported improved appetite and overall health.
Robertson et al., 2007[51]	*Arnica montana* 30c vs. placebo	Post-tonsillectomy analgesia/ Primary outcome: change in pain scores (VAS) recorded by the patient on a questionnaire over 14 days postoperatively. Secondary outcomes: analgesic consumption, visits to the general practitioner or hospital, use of antibiotics, day swallowing returned to normal, and day return to work.	111 (58.4%) completed questionnaires were available for analysis. The Arnica group had a significantly greater drop in pain score from day 1 to day 14 (28.3) compared to the placebo group (23.8) ($p < 0.05$). The two groups did not differ significantly in analgesic consumption or any other secondary outcome (number of postoperative visits to the general practitioner, antibiotic use, and readmissions due to secondary hemorrhage). The results suggest that *Arnica montana* 30c administered after tonsillectomy provides a small but statistically significant decrease in pain scores compared to placebo.
Seeley et al., 2006[52]	*Arnica montana* vs. placebo	Postoperative hematomas of facelift surgeries/ Outcomes: postoperative photographs were analyzed using a new computer model for color changes, and subjective evaluations of postoperative ecchymosis were obtained.	No subjective differences were observed between the treatment group and the control group, neither by the patients nor by the professional team. No objective difference in the degree of color change was found. Patients who received *Arnica montana* 30c had a smaller area of ecchymosis on postoperative days 1, 5, 7, and 10. These differences were statistically significant ($p < 0.05$) only on postoperative days 1 ($p < 0.005$) and 7 ($p < 0.001$).
Bernstein et al., 2006[53]	Homeopathic cream of *Mahonia aquifolium* vs. placebo	Psoriasis/ Treatment efficacy and safety were assessed with Psoriasis Area Severity Index (PASI) and Quality of Life Index	The results indicated statistically significant improvements ($p < 0.05$) in PASI and QLI in the Mahonia-treated group, compared to the placebo group. Adverse reactions reported were infrequent, < 1% and minor. The most frequent side effects were rash,

		(QLI) questionnaires at different time points throughout the 12-week study.	burning sensation when applying the cream, and stains on clothing.
Oberbaum et al., 2005[54]	*Arnica montana* (6c, 30c) e *Bellis perennis* (6c, 30c) vs. placebo	Postpartum hemorrhage/ Outcome: hemoglobin (Hb) levels at 48 and 72 hours postpartum.	At 72 hours postpartum, mean Hb levels remained similar after treatment with homeopathic remedies (12.7 versus 12.4) compared to a significant decrease in Hb levels in the placebo group (12.7 versus 11.6; $p < 0.05$), despite the less favorable initial characteristics of the treatment group. The mean difference in Hb levels 72 hours postpartum was -0.29 (95%CI: -1.09 to 0.52) in the treatment group and -1.18 (95%CI: -1.82 to -0.54) in the placebo group ($p < 0.05$).
Frass et al., 2005[55]	*Kali bichromicum* 30c vs. placebo	Decreased fibrous tracheal secretion in intubated patients/ Outcomes: amount of tracheal secretion at day 2 after baseline, time of successful extubation, and length of ICU stay.	The amount of tracheal secretion was significantly reduced in the homeopathy group ($p < 0.0001$). Extubation could be performed significantly earlier in the homeopathy group ($p < 0.0001$). Similarly, the length of ICU stay was significantly shorter in the homeopathy group (4.20 +/- 1.61 days vs. 7.68 +/- 3.60 days, $p < 0.0001$ [mean +/- SD]). These data suggest that *Kali bichromicum* 30c may help decrease the amount of fibrous tracheal secretions in patients with COPD.
Kim et al., 2005[56]	Isotherapic medicine prepared with region-specific allergens vs. placebo	Seasonal allergic rhinitis/ Allergy symptoms using rhinoconjunctivitis quality of life (RQLQ), functional quality of life (MOS SF-36), and work productivity (WPAI) questionnaires.	The RQLQ, MOS SF-36, and WPAI questionnaire scales showed significant positive changes from baseline to 4 weeks in the homeopathy group compared to the placebo group ($p < 0.05$). Subjects reported no adverse effects during the intervention period.
Weather-ley-Jones et al., 2004[57]	Individualized homeopathic medicine vs. placebo	Chronic fatigue syndrome/ Primary outcomes: scores on the Multidimensional Fatigue Inventory (MFI) subscales and proportions of each group that achieved clinically meaningful improvements on each subscale. Secondary outcomes: Fatigue Impact Scale (FIS) and Functional Limitations Profile (CLP).	Patients in the homeopathy group showed significantly greater improvement in the MFI general fatigue subscale (one of the primary outcome measures) and in the physical subscale of the CLP, but not in other subscales. Although the differences between the groups were not statistically significant in four of the five MFI subscales, more people in the homeopathy group showed clinically significant improvement. More people in the active group showed clinical improvement in all primary outcomes (relative risk = 2.75, $p = 0.09$), showing a trend of positive effects.
Bell et al., 2004[58]	Individualized homeopathic medicine (LM potencies) vs. placebo	Fibromyalgia/ Tender point count and pain on examination performed by an external evaluator. Self-rated scales on quality of life, pain, mood, and global health.	Participants in the homeopathy group showed significantly greater improvements in tender point count and pain, quality of life, overall health, and a tendency toward less depression compared to those who received a placebo.

Cavalcanti et al., 2003[59]	Individualized homeopathic medicine and nosodes (drainers) vs. placebo	Pruritus secondary to hemodialysis/ Pruritus was assessed using a previously published scale. Only patients with baseline values above 25% of the maximum pruritus score were included.	Statistically significant reduction in pruritus score for the active group compared to placebo ($p < 0.05$). According to the patients' evaluation, at the end of the study period, the homeopathic treatment reduced the pruritus score by approximately 49%. Responders were more frequent in the treated group with statistical significance at 30 days (0% vs. 45%, $p = 0.038$).
Yakir et al., 2001[60]	Individualized homeopathic medicine vs. placebo	Premenstrual syndrome (PMS)/ Primary outcome: score of a daily menstrual distress questionnaire (MDQ) before and after treatment. Psychological tests of suggestibility were used to examine the possible effects of suggestion.	Mean MDQ scores decreased from 0.44 to 0.13 ($p < 0.05$) with active treatment and from 0.38 to 0.34 with placebo (NS). (Between groups, $p = 0.057$). Improvement > 30% was seen in 90% of patients receiving active treatment and 37.5% receiving placebo ($p = 0.048$). Homeopathic treatment has been found to be effective in relieving PMS symptoms compared to placebo. The use of symptom clusters in this trial may offer a new approach that will facilitate clinical trials in homeopathy.
Berrebi et al., 2001[61]	*Apis melifica* 6cH + *Bryonia alba* 9cH vs. placebo	Inhibition of lactation and improvement of lactation pain.	Significant improvement in lactation pain (primary endpoint) in parturients in the active vs. placebo group ($p < 0.02$ on D2 and $p < 0.01$ on D4). A similar effect ($p < 0.05$ on D4) was observed for breast tension and spontaneous milk flow. The combination was effective in lactation pain and should be integrated into the therapeutic armamentarium.
Chapman et al., 1999[62]	Individualized homeopathic medicine vs. placebo	Mild traumatic brain injury (MTBI)/ SRH-MTBI Functional Assessment composed of three subtests: Difficulty with Situations Scale (DSS), Symptom Rating Scale (SRS) and Participation in Daily Activities Scale (PDAS).	Analysis of covariance showed that homeopathic treatment was the only significant predictor of improvement in the following subtests: SDH ($p = 0.009$; 95%CI: -0.895 to -0.15), SRS ($p = 0.058$; 95% CI: -0.548 to -0.01) and the Ten Most Common Symptoms of MTBI ($p = 0.027$; 95%CI: -0.766 to -0.048). These results indicate a significant improvement of homeopathic treatment over control and translate into clinically meaningful results.

Reiterating the importance of a careful reading of the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017) for those who seek, without prejudice, confirmation of the clinical efficacy of homeopathy compared to placebo, two randomized, placebo-controlled clinical trials were detailed in the articles "*Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study*"[39,63] and "*Randomized, double-blind trial on the efficacy of homeopathic treatment in children with recurrent tonsilitis*"[64], performed by members of the TC-Homeopathy of Cremesp in renowned Brazilian research institutions.

As we described in subchapter VI.5 ("New homeopathic medicines: use of modern drugs according to the principle of similitude") of chapter VI ("Pharmacological basis of the principle of similitude"), the first study[39,63] was conducted to test the aforementioned proposal through an RCT that evaluated the efficacy and safety of dynamized estrogen (potentized or ultradiluted) in individualized homeopathic treatment of pelvic pain associated with endometriosis (PPAE), given that estrogen (17 beta-estradiol) causes "proliferation or endometrial hyperplasia" as an adverse event in conventional contraceptive use.

In this post-doctoral project with the Department of Obstetrics and Gynecology of the Hospital das Clínicas of the Faculty of Medicine of the Universidade de São Paulo (HC-FMUSP), we developed a randomized, double-blind, placebo-controlled clinical trial lasting 24 weeks (6 months) duration, including 50 women aged 18-45 years with a diagnosis of deep infiltrative endometriosis (based on magnetic resonance imaging or transvaginal ultrasound after bowel preparation) and score ≥ 5 on a visual analogue scale (Visual Analogue Scale - VAS: 0-10 points) for PPAE[65].

Potentized estrogen (12cH, 18cH and 24cH) or placebo was administered orally twice a day. The primary outcome measure was the difference in the severity of the partial and overall PPAE score (VAS) between weeks 0 and 24, determined by the difference between the mean score of five modalities of chronic pelvic pain (dysmenorrhea, deep dyspareunia, acyclic deep pelvic pain, cyclic intestinal pain and cyclic urinary pain). Secondary outcome measures were mean score differences for quality of life (SF-36 Quality of Life Questionnaire), depression symptoms (Beck Depression Inventory, BDI), and anxiety symptoms (Beck Anxiety Inventory, BAI)[65].

Evidencing the superiority of dynamized estrogen over placebo, the study results showed that the overall PPAE score (VAS: 0-50 points) decreased by 12.82 points ($p < 0.001$) in the group treated with dynamized estrogen between the baseline (week 0) and week 24 moment. The group that used potentized estrogen also showed a partial score reduction (VAS: 0-10 points) in three PPAE modalities: dysmenorrhea (3.28; $p < 0.001$), acyclic pelvic pain (2.71; $p = 0.009$) and cyclic intestinal pain (3.40; $p < 0.001$). The placebo group did not show any significant changes in overall or partial PPAE scores. Furthermore, the boosted estrogen group showed significant improvement in three of the eight domains of the SF-36 (bodily pain, vitality and mental health) and in depression symptoms (BDI). The placebo group showed no significant improvement in

these secondary outcomes. These results demonstrated the superiority of potentized estrogen over placebo. Few adverse events have been associated with dynamized estrogen. Therefore, potentized estrogen (12cH, 18cH and 24cH), at a dose of 3 drops twice a day for 24 weeks, was significantly more effective than placebo in reducing PPAE, improving quality of life and reducing depressive symptoms in patients[39,40,63].

The second study[64] described in the Cremesp Dossier (2017) was conducted at the Department of Otorhinolaryngology and Head and Neck Surgery of the Escola Paulista de Medicina da Universidade Federal de São Paulo (EPM-UNIFESP). It evaluated the efficacy and safety of homeopathic treatment in children with recurrent tonsillitis, with surgical indication. It was a prospective, randomized and double-blind study, in which 40 children aged between 3-7 years were included, of which 20 were treated with individualized homeopathic medication and 20 received placebo. The study duration for each patient was 4 months.

The results were evaluated clinically using a standard questionnaire and an otorhinolaryngological examination, on the first and last day of treatment. The occurrence of 5 to 7 episodes of acute tonsillitis per year was used as a criterion for recurrent tonsillitis. The study highlighted the superiority of individualized homeopathic treatment compared to placebo, as the results showed that 14 among the 18 children who completed homeopathic treatment did not present any episode of acute bacterial tonsillitis; 5 patients among the 15 children who received placebo for 4 months did not have tonsillitis, with statistically significant differences ($p = 0.015$). None of the patients had side effects to the prescribed medications. Therefore, homeopathic treatment was effective in children with recurrent tonsillitis when compared to placebo, excluding 14 children (78%) from surgical indication. The homeopathic medicine did not cause adverse events in children[64].

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Proof of Scientific Evidence for Homeopathy

IX. Clinical efficacy of homeopathy: systematic reviews and global reports of randomized controlled trials (RCTs)

IX.1. Introduction

IX.2. Global systematic reviews of RCTs with meta-analyses

IX.3. Systematic review of global RCTS meta-analyses

IX.4. Global systematic review of RCTs without meta-analyses

IX.5. Global descriptive reports

IX. Clinical efficacy of homeopathy: systematic reviews and global reports of randomized controlled trials (RCTs)

IX.1. Introduction

Some systematic reviews of RCTs, with or without meta-analyses, have been performed over the last 30 years to evaluate the clinical efficacy of homeopathy, in addition to the randomized, double-blind, placebo-controlled clinical trials (RCTs) that we described in the previous chapter. Some descriptive reports of RCTs have also been prepared in the last decade, with great diversity in the methodology used to analyze the data set.

Systematic reviews and global reports are those which analyze all RCTs together, regardless of the type of treatment used and the clinical condition being treated (for any clinical indication). On the other hand, systematic reviews and specific reports analyze RCTs of specific types of treatment and/or certain clinical conditions.

As we reported in subchapter III.5 ("Types of epidemiological studies in homeopathy") of chapter III ("Homeopathic clinical epidemiology") of this work, the majority of global systematic reviews of RCTs with meta-analyses (global meta-analyses of RCTs), considered as level 1A of scientific evidence, presented positive or favorable results for homeopathy compared to placebo or conventional treatments, while a minority presented negative or unfavorable results for homeopathy. These conclusions were confirmed and elucidated in a systematic review of global meta-analyses of RCTs published in 2023.

We present an overview and a synthesis of global systematic reviews of RCTs below, with or without meta-analyses, and global descriptive reports of RCTs to inform the reader about these types of epidemiological studies carried out in the area. In subsequent chapters, we will delve deeper into the descriptions and results of these studies, discussing the methodologies used in the analysis of the data sets.

In addition to these global systematic reviews of RCTs, with or without meta-analyses, and the global descriptive reports of RCTS, we will also describe the other types of epidemiological studies in homeopathy in specific chapters, namely: specific systematic reviews (with or without meta-analyses) and analytical observational studies.

For readers who wish to delve deeper into evaluating the clinical effectiveness of homeopathy according to systematic reviews, with or without meta-analyses, we suggest carrying out a bibliographical survey of the existing literature in the databases

mentioned in chapter IV of this work ("Overview of research in homeopathy - Databases"), such as:

- LILACS[1]: "homeopathy" AND "randomized clinical trial" AND "systematic review" (4 studies); "homeopathy" AND "randomized clinical trial" AND "meta-analysis" (4 studies).
- PubMed[2]: "homeopathy" AND "randomized controlled trials" AND "systematic review" (78 studies); "homeopathy" AND "randomized controlled trials" AND "meta-analysis" (95 studies).
- "Trip Medical Database"[3]: "homeopathy" AND "randomized controlled trials" AND "systematic review" (383 studies); "homeopathy" AND "randomized controlled trials" AND "meta-analysis" (293 studies).
- "CAM-QUEST databases"[4]: currently offers a total of 1,893 homeopathic clinical studies, with 113 "systematic reviews" and 69 "meta-analyses".
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[5]: it addresses these types of studies in all editions (2016, 2017 and 2020-2021) in the chapters "Meta-analyses - Systematic Reviews" (most recent edition (2020-2021)[6].

IX.2. Global systematic reviews of RCTs with meta-analyses

The five major global systematic reviews of RCTs with meta-analyses were performed between 1991 and 2005, each conducting a meta-analysis encompassing randomized, double-blind, placebo-controlled homeopathic trials of all types of homeopathic treatment for all clinical conditions.

According to the Homeopathy Research Institute (HRI)[7,8], four of these studies showed positive results[9-12], suggesting that there was some evidence of a homeopathic effect beyond placebo, but that new high-quality research would be necessary to reach definitive conclusions. Only one study presented negative results[13], concluding that homeopathy had no effect beyond placebo (**Table 1**).

Table 1. Global systematic reviews of homeopathic RCTs with meta-analyses.

Global systematic reviews of homeopathic RCTs with meta-analyses (1991-2005)	
Kleijnen et al., 1991[9]	"At the moment the evidence of clinical trials is positive but not sufficient to draw definitive conclusions because most trials are of low methodological quality and because of the unknown role of

	publication bias. This indicates that there is a legitimate case for further evaluation of homoeopathy, but only by means of well performed trials."
Linde et al., 1997[10]	"The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homoeopathy is clearly efficacious for any single clinical condition. Further research on homoeopathy is warranted provided it is rigorous and systematic."
Linde et al., 1999[11]	"We conclude that in the study set investigated, there was clear evidence that studies with better methodological quality tended to yield less positive results. Because summarizing disparate study features into a single score is problematic, meta-regression methods simultaneously investigating the influence of single study features seem the best method for investigating the impact of study quality on outcome."
Cucherat et al., 2000[12]	"There is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results."
Shang et al., 2005[13]	"Biases are present in placebo-controlled trials of both homoeopathy and conventional medicine. When account was taken for these biases in the analysis, there was weak evidence for a specific effect of homoeopathic remedies, but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects."

All five of these global systematic reviews with meta-analyses are out of date, with the first (Kleijnen et al., 1991)[9] created more than 30 years ago, and the last (Shang et al., 2005)[13] more than 15 years ago.

As emphasized by the Homeopathy Research Institute (HRI)[7,8], despite reanalyzes highlighting the numerous biases and methodological flaws of the only study with unfavorable results for homeopathy (*The Lancet,* Shang et al., 2005)[13], this systematic review of homeopathic RCTs with meta-analysis is widely cited in publications with a notorious "anti-homeopathy" bias ("The UK Science & Technology report" and "The Australian NHMRC report"), despite the study only covering data up to 2003, being contradictory to the rest of evidence in this category and questionable as to its scientific reliability.

Similarly, as it is the only global systematic review with meta-analysis that showed negative effects of homeopathy, and although its results were manipulated as

demonstrated by *post hoc* analyses, this study[13] is also the most cited in attacks by pseudoskeptics and pseudoscientists on the homeopathic model.

Mathie et al. published two systematic reviews of RCTs with meta-analyses (2014 and 2017)[14,15] describing more recent and updated studies, addressing one of the main homeopathic epidemiological assumptions for the curative response to occur (vital or homeostatic reaction) and the clinical efficacy of the treatment, meaning the "**individualization of homeopathic medicine**" (individualized homeopathic medicine). Considered an essential aspect in the design of homeopathic clinical trials of high quality homeopathic methodology, as described in subchapter III.4 ("Premises and principles of homeopathic clinical epidemiology") of chapter III ("Homeopathic clinical epidemiology"), its observance is not always followed in the preparation and analysis of homeopathic RCTs by researchers who are unaware of or deny the homeopathic episteme, and their non-observance should be considered an important methodological flaw (bias) in homeopathic clinical epidemiology.

This was clearly proven in the studies cited above: in the systematic review that analyzed RCTs that studied the effectiveness of individualized homeopathic medicines[14,16], the effect of homeopathy showed statistical significance compared to placebo ("homeopathic medicines, when prescribed during individualized treatment, are 1.5- to 2.0-times more likely to have a beneficial effect than placebo"); while in the systematic review that analyzed randomized clinical trials that studied the effect of non-individualized homeopathic medicines compared to placebo[15], this was not observed ("there was no single clinical condition for which meta-analysis included reliable evidence").

IX.3. Systematic review of global RCTs meta-analyses

Reiterating the analyzes and conclusions previously described, a systematic review of global meta-analyses of homeopathic RCTs was published in the *Systematic Reviews* journal[17] at the end of 2023.

This systematic review included six global meta-analyses of previously cited RCTs[10-15], covering individualized homeopathy (I-HOM, n = 2), non-individualized homeopathy (NI-HOM, n = 1) and all types of homeopathy (ALL-HOM = I-HOM + NI-HOM, n = 3). Effect estimates for all RCTs in each meta-analysis showed a significant positive effect of homeopathy compared with placebo (5 of 5 meta-analyses;

no data in only 1). The quality of evidence of the positive effects of homeopathy beyond placebo (high/moderate/low/very low) was high for I-HOM and moderate for ALL-HOM and NI-HOM. There was no support for the alternative hypothesis of no difference in results between homeopathy and placebo[17].

IX.4. Global systematic review of RCTs without meta-analyses

In addition to the global systematic reviews of RCTs with meta-analyses previously presented, in 2015, a global systematic review without meta-analysis was published (The Australian NHMRC report)[18,19], including clinical trials up to 2010 in the study (captured in systematic reviews published up to 03/01/2013) and separating the data by clinical condition. Like the study by Shang et al. (*The Lancet*, 2005)[13], the biased results of this study showed negative effects of homeopathy compared to placebo in several clinical conditions. According to the Homeopathy Research Institute (HRI)[7,8], the NHMRC report attracted international criticism for its unscientific and unprecedented methodology.

As a result, the NHMRC is under investigation, responding to accusations of unethical and unscientific conduct in the preparation, analysis and dissemination of the results of this report, as we will detail in a later chapter.

In addition to these systematic reviews of RCTs with and without meta-analyses, two reports on the scientific evidence for homeopathy were prepared in the United Kingdom and Switzerland in 2010 and 2011, respectively.

IX.5. Global descriptive reports

The UK Science & Technology report[20], written by members of parliament and published in 2010, concluded that homeopathy was ineffective compared to placebo, and is often referred to as the opinion of the UK government. Shrouded in questions about how the "evidence check" was conducted, an "early motion" was created to make the list of these concerns public. Although it was signed by 70 MPs, the Department of Health rejected the report's conclusions.

The 2011 Swiss report[21], compiled on behalf of the Swiss Federal Office for Public Health, presented the results of a seven-year review of the evidence on homeopathy. It concluded that homeopathy, as practiced in Switzerland, is clinically effective,

economical and safe. Since then, homeopathy has become available to the Swiss public as part of their national healthcare scenario.

In this introductory chapter on systematic reviews and global descriptive reports which set out to evaluate the effectiveness of homeopathy compared to placebo through an analysis of randomized controlled clinical trials (RCTs), we provide an overview of what exists in the literature and a synthesis of its results. Next, in subsequent chapters, we will delve deeper into the epidemiological study of these studies, discussing the scientific methodology and possible flaws and biases observed in their preparation, implementation and analysis.

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Proof of Scientific Evidence for Homeopathy

X. Systematic reviews and global reports with positive results of homeopathy compared to placebo

X.1. Introduction

X.2. *British Medical Journal* (1991)

X.3. *The Lancet* (1997)

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X.5. *European Journal of Clinical Pharmacology* (2000)

X.6. *Systematic Reviews* (2014 and 2017)

X.7. Systematic review of global RCTs meta-analyses (*Systematic Reviews*, 2023)

X.8. The Swiss HTA report (2011)

X. Systematic reviews and global reports with positive results of homeopathy compared to placebo

X.1. Introduction

In this chapter, we will discuss the systematic reviews of randomized, double-blind, placebo-controlled trials (RCTs) with meta-analyses and the global reports of RCTs that presented positive and favorable results of homeopathy compared to placebo. In the following chapter, we will address those with negative and unfavorable results for homeopathy, highlighting the methodological flaws and biases in their preparation, implementation and analysis.

Reiterating the scientific relevance of the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017), the systematic reviews with meta-analyses of RCTs that presented favorable results to homeopathy compared to placebo were described in the narrative review "*Clinical research in homeopathy: systematic reviews and randomized clinical trials*"[1], which we will use in the discussion of these studies.

In preparing the aforementioned review[1], the analyzes of the studies produced by the Liga Medicorum Homoeopathica Internationalis (LMHI) ("*The Scientific Framework of Homeopathy"*, 2016)[2] were used as reference.

In addition to the considerations of the material above[1,2], we will also add the analyzes of the Homeopathy Research Institute (HRI) in the discussion of each systematic review or report, significantly based on the section "The Homeopathy Debate"[3].

We will first discuss four global systematic reviews of RCTs with meta-analyses (X.2 to X.6); next, a recently published systematic review of global meta-analyses of RCTs (X.7); and finally on a global descriptive report of RCTs (X.8).

X.2. ***British Medical Journal*** (Kleijnen et al., 1991)[4]

In this first systematic review of randomized, double-blind, placebo-controlled trials (RCTs) with meta-analysis published in the *British Medical Journal* ("Clinical trials of homoeopathy")[4] in 1991, the authors analyzed homeopathic RCTs in any language, reporting the results of various homeopathic treatments in which participants were randomly allocated to intervention (homeopathy) or placebo groups. At the same time, the studies were subjected to analysis of their methodological quality (highlighting the

appreciation of the premise regarding the large sample size; randomization; double-blind method; adequate description of patients' characteristics; accurate description of the intervention; relevant effect measures and well described; and presentation of results in a way that allows readers to verify the analyses).

The systematic search resulted in 107 homeopathic RCTs described in 96 publications, and the methodological quality of the clinical trials was relatively low. For this reason, the authors chose to only analyze studies with the best methodological quality (score 60/100). Regarding the type of studies included, 14 used classical homeopathy (individualized homeopathic medicine), 18 applied one and the same homeopathic treatment to all patients with comparable conventional diagnoses (non-individualized homeopathic medicine), 26 prescribed more than one medicine for each patient (complex of medicines), and 9 consisted of isopathy (homeopathic preparation made with the same agent that causes the disease). If, on the one hand, 42 studies did not offer sufficient data to evaluate the interpretation of the outcomes, on the other hand, the heterogeneity of the studies did not allow for analyzing the studies combined.

Despite these flaws, the authors were able to infer that the positive results indicated a statistically significant difference in the main outcome(s) between the groups (homeopathy and placebo). Therefore, several conclusions were drawn: there was no publication bias in journals in the area, as the chosen vehicle had no relationship with the outcomes; "the evidence is largely positive"; "the number of studies is impressive"; and finally, "**the amount of positive evidence came as a surprise to us. Based on this evidence, we would be ready to accept that homeopathy can be effective, as long as the mechanism of action were demonstrated to be more plausible**".

Conclusions of the authors: "At the moment the evidence of clinical trials is positive but not sufficient to draw definitive conclusions because most trials are of low methodological quality and because of the unknown role of publication bias. This indicates that there is a legitimate case for further evaluation of homoeopathy, but only by means of well performed trials".

X.3. *The Lancet* (Linde et al., 1997)[5]

The systematic review of homeopathic RCTs with meta-analysis carried out by Linde et al. in 1997[5] caused great impact in the academic and scientific world, with a view to definitively concluding that **the positive effects of homeopathy were not exclusively**

placebo effects. This meant that for years, *The Lancet* received communications from researchers outraged by this conclusion, although they did not present plausible counterpoints.

In this study, the authors selected homeopathic RCTs with sufficient information after data extraction for analysis in order to calculate outcome rates in both groups (intervention and placebo). As in the study by Kleijnen et al.[4], the authors included studies with different types of treatment in the review: classical homeopathy (individualized medicine), clinical or nosological homeopathy (medications for a specific diagnosis), complex homeopathy (drug combinations) and isopathy. The quality of the studies was analyzed using the Jadad scale (good quality: > 3 points) and another *ad hoc* scale (good quality: > 5 points).

The systematic search located 186 publications, which were reduced to 89 after applying the inclusion/exclusion criteria. The RCTs were published between 1945 and 1995, had an average of 118 patients and corresponded to 24 clinical categories, with 37% of treatments using low dynamizations (1d to 8d; 1c to 4d), 22% medium dynamizations (9d to 23d; 5c at 11c), and 37% high dilutions (above 23d or 11c). Regarding the quality of the studies, 29% were of high quality (Jadad and *ad hoc* scale), 45% achieved ≥ 3 points on the Jadad scale and 38% ≥ 5 points on the *ad hoc* scale.

The overall Odds Ratio (OR) was 2.45 in favor of homeopathy (95%CI: 2.05–2.93) (remembering that: OR = 1 means that the exposure does not affect the chance of the outcome; OR > 1, that exposure is associated with greater chances of the outcome; and OR < 1, that exposure is associated with lower chances of the outcome). The OR in high-quality RCTs was 1.66 (95%CI: 1.33-2.08). These results are clearly in favor of homeopathy. Furthermore, sensitivity and subgroup analysis did not eliminate their statistical significance. In turn, the OR of studies with positive results reduced by 27% when publication bias was considered, however without loss of statistical significance.

Conclusions of the authors: "The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homoeopathy is clearly efficacious for any single clinical condition. Further research on homoeopathy is warranted provided it is rigorous and systematic".

X.4. *Journal of Clinical Epidemiology* (Linde et al., 1999)[6]

Continuing studies on the clinical efficacy of homeopathy compared to placebo, Linde et al. published a new systematic review with meta-analysis[6] in 1999, exclusively prioritizing homeopathic treatments with individualized medications. In this study, randomized or quasi-randomized clinical trials were included in which individualized homeopathic treatment had been compared with placebo, no treatment or another treatment. The quality of the trials was assessed using a checklist and two scoring systems.

In the review, 32 studies were identified that met the inclusion/exclusion criteria, 28 involving comparison with placebo, 2 with another treatment and 2 with both (placebo and another treatment); the studies had variable quality (two quality scales). Among the 28 randomized, double-blind, placebo-controlled trials, 19 met the criteria and provided sufficient data to be included in the meta-analysis. Studies with sufficient data were analyzed together in a quantitative meta-analysis. Primary studies were consecutively entered into a cumulative meta-analysis according to summary scores derived from the quality assessment scales. All analyzes were performed using meta-regression methods.

Explicitly randomized and double-blind trials, as well as trials with scores above the cut-offs, produced significantly less positive results than those that did not meet this criterion. There was a tendency for effect sizes in cumulative meta-analyses to increase when more studies with lower quality scores were added. However, there was no linear relationship between quality scores and study outcome. As a result, the analysis showed that homeopathy was more effective than placebo (OR 1.62; 95%CI: 1.17–2.23). The authors concluded that "**the results of available randomized trials suggest that individualized homeopathy has a superior effect to placebo**".

Conclusions of the authors: "We conclude that there was clear evidence in the study set investigated that studies with better methodological quality tended to yield less positive results. Because summarizing disparate study features into a single score is problematic, meta-regression methods simultaneously investigating the influence of single study features seem to be the best method for investigating the impact of study quality on outcome."

X.5. *European Journal of Clinical Pharmacology* (Cucherat et al., 2000)[7]

In 2000, Cucherat et al. published a systematic review with meta-analysis of homeopathic RCTs involving any clinical condition[7], published or not until June 1998. The authors located a total of 118 trials, of which 16 (representing 17 comparisons) were included in the meta-analysis, with a total of 2,617 patients.

Evidence was synthesized by combining significance levels (p-values) for the primary outcomes of individual trials. The combined p-value for the 17 comparisons was highly significant (p = 0.000036). However, sensitivity analysis showed that the p-value tended towards a non-significant value (p = 0.08), as trials were excluded gradually based on their quality level. However, the authors concluded that "**there is some evidence that homeopathic treatments are more effective than placebo**".

Conclusions of the authors: "There is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results".

X.6. *Systematic Reviews* (Mathie et al., 2014[8] and 2017[9])

The last two systematic reviews with meta-analyses were carried out by Mathie et al. in 2014[8] and 2017[9], encompassing randomized, double-blind and placebo-controlled clinical trials with individualized and non-individualized homeopathic treatments, respectively, for any clinical condition. The first study analyzed 32 RCTs, corresponding to 24 different clinical conditions, while the second study analyzed 75 RCTs, corresponding to 48 different clinical conditions, with a median of n = 43.5 and n = 62.5 patients per study. Studies of high methodological quality represented a minority in both cases, with a ratio of 1:3 studies.

In the first review[8], 22 RCTs had extractable data for meta-analysis. The combined OR was 1.53 (95%CI: 1.22–1.91; p < 0.01), in favor of homeopathy over placebo. There was no evidence of publication bias. In the subgroup analysis of trials with reliable evidence, the pooled OR was 1.98 (95%CI: 1.16–3.38; p = 0.013). The results therefore indicated that **homeopathic treatments carried out with individualized medicines may have small specific therapeutic effects**.

Conclusions of the authors: "Medicines prescribed in individualised homeopathy may have small, specific treatment effects. Findings are consistent with sub-group data

available in a previous 'global' systematic review. The low or unclear overall quality of the evidence prompts caution in interpreting the findings. New high-quality RCT research is necessary to enable more decisive interpretation".

In the second review[9], 54 RCTs had extractable data for meta-analysis. The overall standardized mean difference (SMD) was -0.33 (95%CI: -0.44 to -0.21; $p < 0.001$), with a reduction to 0.16 (95%CI: -0.31 to -0.02) after adjusting for publication bias. It is worth mentioning that SMD is an effect size measure which is applied in cases where several studies evaluate the same outcome, but in different ways, meaning that it is necessary to standardize the results on a uniform scale before they can be combined. When improvement is associated with lower scores on the outcome measure, SMD < 0 indicates the degree to which the analyzed treatment is more effective than placebo, and conversely, SMD > 0 indicates the degree to which the analyzed treatment is less effective than the placebo.

After adjustment for publication bias, the authors concluded that it was possible to **reject the null hypothesis, meaning that the main outcome of treatment using non-individualized homeopathic medicines cannot be distinguished from placebo**, in the full scope of the clinical conditions investigated. In the subgroup analysis (higher quality clinical trials), the combined SMD decreased to a non-significant value, -0.18 (95%CI: -0.46 to 0.09), indicating that **the effect of non-individualized homeopathic treatment was not was different from placebo, based on reliable evidence**.

Conclusions of the authors: "The quality of the body of evidence is low. A meta-analysis of all extractable data leads to rejection of our null hypothesis, but analysis of a small sub-group of reliable evidence does not support that rejection. Reliable evidence is lacking in condition-specific meta-analyses, precluding relevant conclusions. Better designed and more rigorous RCTs are needed in order to develop an evidence base that can decisively provide reliable effect estimates of non-individualised homeopathic treatment".

As we emphasized in the previous chapters, the results of these two systematic reviews with meta-analyses reiterate **the importance of using individualized medicines in homeopathic treatments, so that the body's healing vital reaction occurs and the positive effects of homeopathy are statistically significant compared to the placebo effects**. We reiterate that this is an essential epistemological premise in the design and preparation of homeopathic clinical trials of high methodological quality, according to

homeopathic clinical epidemiology. **The analysis of randomized clinical trials that disregard this condition, individually or grouped in systematic reviews, will have a high chance of proving ineffective compared to placebo**.

X.7. Systematic review of global RCTs meta-analyses (*Systematic Reviews*, 2023)[10]

With the aim of evaluating the effectiveness of homeopathic treatment, a systematic review of global meta-analyses of homeopathic RCTs was published in the *Systematic Reviews* journal[10] in 2023.

This systematic review included six global meta-analyses of homeopathic RCTs[5-9,11], covering individualized homeopathy (I-HOM, n = 2), non-individualized homeopathy (NI-HOM, n = 1), and all types of homeopathy (ALL-HOM = I-HOM + NI-HOM, n = 3). The meta-analyses comprised between 16 and 110 trials, and the RCTs included were published from 1943 to 2014. The average trial sample size ranged from 45 to 97 patients. The risk of bias (low/unclear/high) was classified as low for three meta-analyses and high for three meta-analyses.

The primary outcome was the effect estimate for all RCTs included in each meta-analysis and after restricting the sample to trials with high methodological quality, according to pre-defined criteria. The risk of bias for each meta-analysis was assessed using the ROBIS (Risk Of Bias In Systematic reviews) tool. The quality of evidence was assessed using the GRADE framework. Statistical analyzes were performed to determine the proportion of meta-analyses showing a significant positive effect of homeopathy versus no significant difference.

Reiterating the conclusions previously described in the individual analysis of the cited meta-analyses, the effect estimates for all RCTs in each meta-analysis showed a significant positive effect of homeopathy compared to placebo (5 of 5 meta-analyses; no data in only 1). Sample-restricted sensitivity analyzes for high-quality trials were available in four meta-analyses; the effect remained significant in three meta-analyses (2 evaluated ALL-HOM, 1 evaluated I-HOM) and was no longer significant in one meta-analysis (which evaluated NI-HOM).

The quality of evidence of the positive effects of homeopathy beyond placebo (high/moderate/low/very low) was high for I-HOM and moderate for ALL-HOM and

NI-HOM. There was no support for the alternative hypothesis of no difference in results between homeopathy and placebo.

According to the authors, global systematic reviews of homeopathic RCTs with meta-analyses[5-9,11] reveal significant positive effects of homeopathy compared to placebo. This is in accordance with laboratory experiments that show partially replicable effects of homeopathically potentiated preparations in physicochemical test systems, *in vitro*, in plants and in animals [as described in chapter VII of this work: "Experimental studies in biological models (*in vitro*, plants and animals)"].

X.8. The Swiss HTA report (2011)[12]

The 2011 Swiss report (The Swiss HTA report)[12], compiled on behalf of the Swiss Federal Office for Public Health, presented the results of a seven-year review of the evidence on homeopathy. It concluded that homeopathy, as practiced in Switzerland, is clinically effective, economical and safe[13]. Since then, homeopathy has become available to the Swiss public as part of their national healthcare scenario.

According to the Homeopathy Research Institute (HRI)[3], this report was commissioned by the Swiss health authorities to inform decision-making on the further inclusion of homeopathy in the list of services covered by statutory health insurance. According to the authors, their report "confirmed homeopathy as a valuable addition to the conventional medical landscape – a status it has long maintained in healthcare practice". To quote the official conclusion of the report: "There is sufficient evidence for the preclinical and clinical effectiveness of homeopathy and for its safety and economy compared with conventional treatment".

Important facts from the Swiss report:

- HTA is a well-recognized research method used to evaluate the effectiveness, safety and cost-effectiveness of treatments in the real world, for example for the UK National Health Service;
- The report was commissioned by the Swiss Federal Office for Public Health (BAG);
- The report summarized the findings of a seven-year review of the evidence on homeopathy, conducted as part of a wider Program of Evaluation of Complementary Medicine (PEK).

What is a Health Technology Assessment (HTA)? HTAs, which provide directly relevant information to decision-makers, are the cornerstone of the UK National Institute for Health Research's (NIHR) strategy to assess the real-world effectiveness, safety and cost-effectiveness of therapeutic interventions for the NHS. Many types of research, such as randomized controlled trials, systematic reviews, and meta-analyses, ask: "Does this treatment work under artificial testing conditions?" On the other hand, HTAs ask much broader questions, such as "Does this treatment work in real-life clinical situations?", "How is it used?", "Is it safe?", and "Is it cost-effective?".

Controversies over the Swiss report:

The strongly positive conclusions of the Swiss HTA report generated controversy in academic circles, including the publication of an accusation of research misconduct[(14)] - a serious accusation against which the authors directly defended themselves in a response article[(15)].

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Proof of Scientific Evidence for Homeopathy

XI. Systematic reviews and global reports with negative results of homeopathy compared to placebo (Methodological flaws)

XI.1. Introduction

XI.2. *The Lancet* (Shang et al., 2005)

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XI.4. The UK Science & Technology report (2010)

XI. Systematic reviews and global reports with negative results of homeopathy compared to placebo

(Methodological flaws)

XI.1. Introduction

In this chapter, we will discuss systematic reviews with meta-analyses and global reports of randomized homeopathic clinical trials that presented negative and unfavorable results of homeopathy compared to placebo, highlighting methodological flaws and biases in their design, implementation and analysis.

Reiterating the scientific relevance of the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017), the reviews and reports that presented unfavorable results to homeopathy compared to placebo were described in the narrative review "*Clinical research in homeopathy: systematic reviews and randomized clinical trials*"[(1)], which we will use in the discussion of these studies. In preparing the aforementioned review[(1)], the analyzes of the studies produced by Liga Medicorum Homoeopathica Internationalis (LMHI) ("*The Scientific Framework of Homeopathy*", 2016)[(2)] were used as a reference.

In addition to the considerations of the material above[(1,2)], we will also add the analyzes of the Homeopathy Research Institute (HRI) in the discussion of each systematic review or report, significantly based on the section "The homeopathy debate"[(3)] and "Clinical trials overview"[(4)].

We will first discuss two global systematic reviews of randomized, double-blind and placebo-controlled clinical trials, with and without meta-analysis (XI.2 and XI.3, respectively), and then a descriptive report of randomized controlled clinical trials (XI.4).

XI.2. *The Lancet* (Shang et al., 2005)[(5)]

As we previously reported, this global systematic review with meta-analysis of RCTs published in 2005 in *The Lancet* ("Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy")[(5)], is widely cited in publications with a notorious "anti-homeopathy" bias as an example of unfavorable results from homeopathy, although several *post hoc* analyzes

(reanalyses) highlighted the biases and methodological flaws of the study, as described in detail by the Homeopathy Research Institute (HRI)[3,4].

For context, **this study set out to analyze 110 homeopathic RCTs** [44% clinical homeopathy, 32% complex homeopathy, 16% classical homeopathy (individualized medicine), 7% isopathy and 1 unclassifiable study] **paired with 110 RCTs of conventional medicine, according to the same diagnostic categories**. The median study size was 65 participants (range 10 to 1573). Regarding the methodological quality of all 220 RCTs, there were more homeopathic than conventional studies with high methodological quality (19% versus 8%, respectively), and studies with worse methodological quality in both groups (fewer participants according to the assumptions of "conventional" clinical epidemiology) showed more beneficial therapeutic effects. However, heterogeneity was lower in homeopathic RCTs, not attributable to chance. The bias was similar in both groups.

In a first analysis with all studies included (110 homeopathic RCTs versus 110 conventional RCTs), the main outcome of the study, both homeopathy and conventional medicine were significantly more effective than placebo. It is worth mentioning that the result of this first and main analysis, including all selected studies, showed the clinical efficacy of homeopathy compared to placebo with a similar magnitude to the 1997 meta-analysis published in *The Lancet* journal[6].

In a second analysis, including only studies with the largest number of participants, and considered by conventional clinical epidemiology to be of "better quality" (8 for homeopathy, 6 for conventional medicine), the OR was 0.88 (95%CI: 0. 65-1.19) for the 8 homeopathic RCTs, and 0.58 (95%CI: 0.39-0.85) for the 6 conventional RCTs (OR < 1: defined as beneficial effect). **Based only on this second analysis (disregarding the first and main analysis with all 220 RCTs), the authors concluded that "there was weak evidence for a specific effect of homeopathic remedies, but strong evidence for specific effects of conventional interventions", inferring that "the clinical effects of homeopathy are placebo effects".** This biased conclusion caused the journal to publish its editorial with the title "The end of homoeopathy"[7].

Conclusions of the authors: "Biases are present in placebo-controlled trials of both homoeopathy and conventional medicine. When account was taken for these biases in the analysis, there was weak evidence for a specific effect of homoeopathic remedies,

but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects."

In 2006, we published a reanalysis of the aforementioned systematic review with meta-analysis in the *Diagnóstico & Tratamento* journal ("*Será mesmo o fim da homeopatia?*")[8], and we subsequently expanded the discussion including other reanalyses ("Vieses nas conclusões da metanálise do The Lancet (2005) sobre a eficácia da homeopatia")[9], which we will transcribe below.

XI.2.1. Biases in meta-analysis conclusions on the effectiveness of homeopathy[9]

This meta-analysis published in 2005[5] in the *The Lancet* journal is often cited by detractors of homeopathy as indisputable proof of its lack of clinical efficacy, the result of a superficial and biased analysis that values only the aspects that support their prejudices and they move away from the true scientific spirit of an impartial nature.

By way of political-scientific contextualization and demonstrating the conflict of interests in the preparation of the aforementioned study, it is worth highlighting that it was conducted with the "implicit" intention of opposing a first meta-analysis published in 1997[7] in the same journal, which pointed out "**homeopathy efficacy 2.45 times greater than placebo**" in 89 RCTs described in the literature.

Since the publication of the 2005 meta-analysis (*The Lancet*, Shang et al.)[5], several articles with reanalyses have been published pointing out the biases and methodological flaws of that study[10-16], mainly in relation to *the second and biased analysis* ("when the analysis was limited to large trials of superior quality" according to the number of patients, consisting of only eight homeopathic trials and six conventional or allopathic trials), carried out in a second moment to "contrast" the positive results of homeopathy in *the first and main analysis*, according to the initial objective of the study ("110 homeopathic clinical trials were paired with 110 allopathic clinical trials" and analyzed according to "the same types of diseases and outcomes").

As we highlighted in subchapter III.4 ("Premises and principles of homeopathic clinical epidemiology") of chapter III ("Homeopathic clinical epidemiology"), homeopathic clinical trials of "high methodological quality" must prioritize "individualized medicine" as a fundamental premise for the treatment efficacy (as demonstrated by the systematic reviews by Mathie et al.[17,18], previously described), an aspect which was not valued in the selection of homeopathic RCTs in the current study, as only 16% of the

RCTs selected in the first analysis (and only 2 RCTs from the second analysis) respected "homeopathic individualization" (selection bias for high-quality homeopathic studies, according to homeopathic clinical epidemiology).

Although the reanalyses (*post hoc* analyses)[10-16] clearly and objectively clarify the various methodological flaws of this publication, showing that the study by Shang et al. presents **serious selection bias**, **analysis bias**, and probably ***post hoc* analysis bias**, demonstrating that its conclusions were manipulated and cannot be valued, the true conclusions of the aforementioned systematic review with meta-analysis (*first and main analysis*) can be described as follows:

- Most homeopathic RCTs analyzed show clinically positive and statistically significant results.
- Most conventional RCTs analyzed show clinically positive and statistically significant results.
- Homeopathic RCTs have better methodological quality than their conventional counterparts.
- *Arnica montana* is not effective in treating post-exercise muscle pain for any and all patients.

Regarding *the second analysis* composed of 8 homeopathic RCTs and 6 conventional RCTs "not comparable according to the types of diseases and outcomes", we must conclude that:

- There is evidence that allows us to assume that this subanalysis was carried out *a posteriori* (significant *post-hoc* changes to the research protocol).
- Homeopathic and conventional RCTs were not matched for disease and outcome, as indicated in the original objective.
- The number of patients in the two groups was different.

Therefore, in an impartial epidemiological analysis of the study, these and other aspects indicate the fallacy of the authors' final conclusions, as well as the editorial published in the same edition of the journal ("*The end of homeopathy*")[7], as they were only based on eight homeopathic clinical trials of low methodological quality according to homeopathic clinical epidemiology. On the contrary, based on the first and main analysis of all 220 RCTs as proposed in the methodology of the initial research protocol, this systematic review with meta-analysis indicates that the positive results of homeopathic treatment are "drug-specific effects" and "are not placebo effects".

As a complement to these reanalyses, we suggest reading the topic "The Lancet paper by Shang et al."[19] (Homeopathy Research Institute, "The homeopathy debate")[3].

XI.3. The Australian NHMRC report (2014-2015)[20]

In March 2015, the Australian National Health and Medical Research Council (NHMRC) published a briefing paper on homeopathy ("NHMRC Information Paper: Evidence on the effectiveness of homeopathy for treating health conditions")[20], commonly referred to as "The Australian report".

As a "claimed" study method, a systematic review (without meta-analysis) of the evidence from available systematic reviews (an overview) on the effectiveness of homeopathy in treating a variety of clinical conditions in humans was conducted, in which "homeopathy has proven not be better than placebo for 61 conditions investigated". The report concluded that "**there are no health conditions for which there is reliable evidence that homeopathy is effective**"[21], generating headlines around the world suggesting that the NHMRC had found that homeopathy did not work for any clinical condition[22].

XI.3.1. Biases in report conclusions on the effectiveness of homeopathy

However, four years after the release of the initial results of the "Australian report" (08/26/2019), as described in the Homeopathy Research Institute[3] (The Australian report)[23], the **CEO of the NHMRC, Prof. Anne Kelso**, provided new clarifications on other results which were not initially disclosed[24], concluding that "**contrary to some claims, the review did not conclude that homeopathy was ineffective**".

Conclusions of the CEO of the NHMRC: "Contrary to some claims, the review did not conclude that homeopathy was ineffective. Rather, it stated that "based on the assessment of the evidence of effectiveness of homeopathy, NHMRC concludes that there are no health conditions for which there is reliable evidence that homeopathy is effective"[24].

An extensive investigation by the Australian Homeopathic Association (AHA) into the conduct of the NHMRC, combined with an in-depth scientific analysis of the HRI review, revealed **evidence of serious scientific and procedural misconduct**, including the fact that the published report was the second attempt by the NHMRC – a first report written in 2012 was never released to the public (biased conduct with an evident "anti-

homeopathy" bias, similar to the preparation of the second analysis of the systematic review with meta-analysis published in *The Lancet* journal in 2005[5], as we previously described).

According to Rachel Roberts, Chief Executive of the HRI[23]: "The public has a right to know that there are high-quality studies showing that homeopathy works for some clinical conditions, such as hay fever, sinusitis and diarrhea in children – information which has only been lost due to NHMRC's mishandling of the evidence. If the evidence from conventional medicine were treated this way, there would be protests – and rightly so. The job of the NHMRC was to accurately summarize the body of evidence for homeopathy for the public, a task at which they categorically failed."

First "missing" report has finally been released[25]

After continued campaigning by stakeholders and the general public, the NHMRC finally **released the 2012 draft report**[25] in August 2019, in which the author concluded that there is "encouraging evidence for the effectiveness of homeopathy" in five medical conditions.

Australian report - Main facts[23]:

- **The NHMRC reviewed homeopathy twice,** producing two reports, one in July 2012 and the other released to the public in March 2015.
- **The existence of the first report was not disclosed to the public –** it was only discovered through "Freedom of Information" requests.
- **The NHMRC says it rejected the first report because it was of low quality, despite it being carried out by a reputable scientist** and author of the NHMRC's own guidelines on how to conduct evidence reviews.
- **FOI requests revealed that a member of the NHMRC expert committee overseeing the review process – Professor Fred Mendelsohn – confirmed that the first review is of high quality,** saying: "I am impressed by the rigor, thoroughness and systematic approach given to this assessment [….]. Overall, a lot of excellent work has been done in this review and the results are presented in a systematic, unbiased and convincing manner".
- The NHMRC said the results **of the second report, published in 2015**, were based on a "rigorous assessment of more than 1,800 studies". In fact, **the results were based on just 176 studies**.

- The NHMRC **used a method that has never been used in any other review, before or since. The NHMRC decided that for the trials to be "reliable", they must have at least 150 participants and reach an exceptionally high quality threshold** (as previously mentioned, according to homeopathic clinical epidemiology, selection bias is deemed according to high quality criteria methodological approach for homeopathic studies). This is despite the fact that the NHMRC itself routinely conducts studies with fewer than 150 participants.
- These arbitrary and unprecedented rules meant that **the results of 171 homeopathic trials were completely disregarded as "unreliable"**, **leaving only 5 NHMRC trials considered "reliable"** (selection bias of homeopathic studies, similar to *the second analysis* of the systematic review with a meta-analysis published in *The Lancet* journal in 2005[5]). As they assessed all 5 of these trials as negative, this explains how the NHMRC could conclude that there was no "reliable" evidence.
- Professor Peter Brooks, chair of the NHMRC committee that conducted the 2015 review, **signed the conflict of interest form** stating that he was not "affiliated or associated with any organization whose interests are aligned with or contrary to homeopathy", despite being a member of the "anti-homeopathy" lobby called "Friends of Science in Medicine".
- NHMRC guidelines state that these committees should include experts on the topic being reviewed, **but there were no homeopathy experts** on this committee.

Complaint lodged with the Community Ombudsman[23]

In August 2016, HRI's in-depth scientific analysis was used as part of a complaint to the Commonwealth Ombudsman, lodged by Complementary Medicines Australia, the Australian Homeopathic Association and the Australian Traditional Medicine Society. **An initial assessment concluded that the complaint had sufficient merit to warrant a full investigation into the NHMRC's conduct**. In the months since, this process has involved continued input from both parties, **as the NHMRC responds to accusations of bias, conflict of interest, and scientific misconduct**[26].

According to the HRI ("The Australian report")[23], as the complaint is ongoing, the full analysis (around 60 pages) cannot yet be shared, but the HRI data has provided details demonstrating the following NHMRC methodological and scientific flaws that require retraction in the Australian report:

- Use of an inappropriate scientific method.
- Failure to use standardized and accepted methods.
- Failure to obtain sufficiently accurate data to perform a meaningful review.
- Failure to carry out effective preliminary and public consultation.
- Significant *post-hoc* changes to the research protocol.
- Impact of NHMRC's unusual method on review results.
- More evidence of bias and misreporting.
- Poor reporting – lack of clarity, inconsistencies and errors.
- Evidence that this was a case of deliberate bias, not scientific error.

The real story behind the headlines[23]

Contrary to the NHMRC's findings, there are "well-designed, good-quality studies with sufficient participants for a meaningful result" (to use the NHMRC's description of a reliable study), demonstrating that certain homeopathic treatments are effective for certain conditions, such as fever, sinusitis, upper respiratory tract infections, diarrhea in children and low back pain. The fact that the results of such studies were unjustifiably rejected means that the NHMRC misled the public by misreporting the evidence for the effectiveness of homeopathy.

Other details of this unethical and unscientific misconduct by researchers against homeopathy evidenced in the methodological flaws and biases in the preparation, execution and analysis of the Australian report can be accessed on the aforementioned HRI page ("The Australian report")[23] and in other reanalyses[27,28].

It is worth noting that this biased review, again, was used to justify **the removal of Health Insurance reimbursement for this therapy**. We observed the same "implicit" interest with the preparation of the systematic review with meta-analysis published in *The Lancet* journal in 2005[5] in Switzerland. The same happened in the United Kingdom in 2010, with the Report of the English Parliament, as we will see below.

XI.4. The UK Science & Technology report (2010)[29]

Like the previously cited and currently demystified systematic reviews, this report is also frequently cited by "anti-homeopathy" movements as proof that there is no evidence of the effectiveness of homeopathy compared to placebo; an untrue, false and erroneous assertion.

The report "Evidence Check 2: Homeopathy, Report by the House of Commons Science and Technology Committee"[29], also known as "The UK Science & Technology report" or "Report of the English Parliament" was published in 2010 by a committee of 14 members of the English Parliament (MP commitee, House of Commons). This report concluded that homeopathy works no better than placebo, and that there should be no more funding for research in the area.

XI.4.1. Biases in report conclusions on the effectiveness of homeopathy

We will resort to re-analysis of the report prepared by the Homeopathy Research Institute[3] ("UK Science & Technology report")[30] to discuss the preparation, execution and analysis of "The UK Science & Technology: Evidence Check 2 report (EC2)"[29], highlighting its biases and methodological flaws.

UK Parliament Report – Main facts[30]:

- The report is not a scientific document and therefore should not be considered part of the scientific literature or used as evidence by decision makers.
- It is not just homeopaths who say it is flawed – the report has been widely criticized by people outside the homeopathic field.
- The MP committee excluded all evidence on homeopathy beyond five systematic reviews and based its conclusions on just one of these studies (*The Lancet* paper by Shang et al.)[5].
- The report does not represent the views of the UK government - the Department of Health rejected the report.

Report reliability[30]

As this document continues to be widely cited, its reliability needs to be considered objectively. Although described by some as a "comprehensive review" of the evidence, the "Evidence Check 2 (EC2) report" **is not a scientific document** – it is a report compiled by a committee of 14 members of parliament (MP committee). No systematic scientific method was applied, it was not carried out by academic experts in the field, and the choice of evidence included showed a disturbing bias – both in terms of written submissions and the choice of witnesses allowed to testify orally.

The various flaws in the EC2 report were significant enough to draw widespread criticism from fellow politicians who are familiar with how such evidence checks should be conducted:

- 4 MPs voted on the report: **3 voted to ratify the report** and 1 MP (Ian Stewart) abstained, disagreeing with the report because he was concerned about the "balance of witnesses".
- 70 MPs expressed their concern by signing an Early Day Motion (EDM 908)[31].
- An independent review by Earl Baldwin of Bewdley concluded that the report was "an unreliable source of evidence on homeopathy"[32]. Earl Baldwin's opinion is of particular interest as he served on the House of Lords Science and Technology Sub-Committee which investigated complementary and alternative medicine between 1999-2000, and was therefore familiar with the correct procedures of the Science and Technology Committee and the topic at hand.

These and other problems were described in detail on a website dedicated to the topic: ("*Homeopathy Evidence Check: Evidence check report on homeopathy considered flawed by MPs and dismissed by Government*")[33].

What evidence did the report encompass?[30]

Reliability aside, a second pertinent issue is that EC2 only considered clinical evidence. Even so, **the only clinical evidence considered was the efficacy of homeopathy, not the effectiveness**, i.e. they only looked at trials testing whether homeopathy works under rigidly controlled artificial experimental conditions, not studies testing whether it works in "real patients" under clinical conditions of the real world (external validity).

Only five systematic reviews of randomized clinical trials (RCTs) were considered by the Committee[5,34-37]. From this evidence, the four systematic reviews with meta-analyses that achieved largely positive results in favor of homeopathy[34-37] discussed in the previous chapter were excluded, based entirely on the testimony of Prof. Edzard Ernst[38], main exponent of the "anti-homeopathy" movement in Europe, who stated that (in his opinion), three were outdated and one should really be considered negative. The only study that Ernst did not criticize was *The Lancet* paper by Shang et al.[5], which he described as reaching a "devastatingly negative overall conclusion".

In view of the above, in the analysis of systematic reviews with meta-analysis that showed positive effects of homeopathy compared to placebo (Chapter X) and in the reanalysis of *The Lancet* paper by Shang et al.[5], evidencing the biases and methodological flaws of the study, Edzard Ernst's lying, false and fallacious ("devastatingly negative overall conclusion") confirms his vanguard and notoriety in the worldwide pseudo-skeptical "anti-homeopathy" movement. Following this same

strategy, Brazilian pseudoskeptics, disguised as pseudoscientists, shout in the layman and "non-scientific" media that this study proves that "homeopathy is placebo effect", denying the methodological flaws (biases) clearly evidenced in the detailed re-analyses previously described.

Reliability of the *The Lancet* study[30]

As the conclusion of the EC2 report was effectively only based on the study by Shang et al.[5], once again the quality and reliability of this evidence becomes of paramount importance, as we previously explained.

Reiterating the HRI analysis ("UK Science & Technology report")[30], several concerns were raised about the study by Shang et al.[5], particularly the fact that **their conclusions were only based on 8 trials out of the 110 available** to the authors at the time, and that it fails in a sensitivity analysis[39], meaning **if you change just one of the 8 trials they chose to include in the second analysis**, **the result is the opposite, showing that homeopathy works beyond placebo**. This completely undermines the reliability of the results reported by the article.

Furthermore, none of these 8 RCTs used involve individualized homeopathic treatment – the form of homeopathy considered as "usual care" and which is consistent with the epistemological premises of homeopathic treatment [Chapter III - "Homeopathic clinical epidemiology"), subchapter III.4 ("Premises and principles of homeopathic clinical epidemiology")].

The EC2 report is currently woefully out of date[30]

Although EC2 was published in 2010, the report based its conclusions on systematic reviews published up to 2005. Pseudoskeptic Edzard Ernst also stated in his presentation that his arguments (against homeopathy) were based on evidence published up to 2005[40]. This means that **the evidence discussed in 2010 was at least five years old**.

When re-consulting the current homeopathy scientific evidence databases (Chapter IV, "Overview of homeopathy research – Databases"), it becomes clear that the field of homeopathy research has progressed significantly since the EC2 report, including the publication of the most recent systematic reviews. For example, the review by Mathie et al.[17] published in 2014, found that when homeopathic medicines are prescribed during individualized treatment, they are 1.5 to 2.0 times more likely to have a beneficial effect than placebo.

UK Government Position[30]

The British government's response to the Science & Technology Committee's report was published by the Department of Health in July 2010[41], in which **the government refused to ban homeopathic products based on the recommendations of this report and identified homeopathy as a recognized and widely used system of medicine across the European Union. The government's response emphasized patient choice as one of the main reasons for continuing to fund homeopathy in the NHS**.

As we said previously, this stance taken by the UK Government is in line with other countries (Switzerland and Australia), in which similar biased "anti-homeopathy" reports were produced **with the "implicit intention" of excluding the funding of homeopathy in their respective public health services**[42].

Other reanalyses were published questioning other aspects of the EC2 report, such as the "arguments of implausibility of the effectiveness of homeopathic treatments" used to undermine existing scientific evidence[43,44].

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Proof of Scientific Evidence for Homeopathy

XII. Systematic reviews for specific clinical conditions

XII.1. Introduction

XII.2. Systematic reviews with meta-analyses for specific conditions

XII.3. Systematic reviews without meta-analyses for specific conditions

XII. Systematic reviews for specific clinical conditions

XII.1. Introduction

Some specific systematic reviews of randomized, double-blind, placebo-controlled homeopathic trials (RCTs), with or without meta-analyses, have been conducted over the last few years to evaluate the clinical efficacy of homeopathy. These specific systematic reviews analyzed RCTs of specific treatment types and/or certain clinical conditions.

The following studies are examples of high-quality studies which have shown positive effects of homeopathy compared to placebo and have not been refuted by any other directly comparable study, i.e. testing the same homeopathic treatment for the same clinical condition.

These studies highlight homeopathic treatments that should be explored through further research and could potentially be more widely used.

XII.2. Systematic reviews with meta-analyses for specific conditions

XII.2.1. Allergic rhinitis / Pollinosis / Hay fever

In a first systematic review with meta-analysis, Taylor et al.[1] analyzed a series of four RCTs of homeopathy versus placebo in allergic rhinitis (n = 253)[1-4], observing a mean reduction in symptoms in visual analogue scale scores of 28% (10.9 mm) for homeopathy compared to 3% (1.1 mm) for placebo (95%CI: 4.2–15.4; p = 0.0007). In addition to this subjective analysis, homeopathy caused a significant and clinically relevant improvement in peak nasal inspiratory flow compared to placebo, similar to that found with inhaled steroids.

In a second systematic review with meta-analysis of seven RCTs (n = 752)[5] which analyzed the effect of homeopathic *Galphimia glauca* medicine versus placebo on allergic rhinitis, the improvement rate in ocular symptoms was 1.25 (95%CI: 1.09–1.43) times higher in the homeopathy group than in the placebo group. The success rate of homeopathy was estimated at 79.3% (95%CI: 74.1–85.0%). Estimates of homeopathy success rates were comparable to those of conventional antihistamines, but without side effects.

XII.2.2. Acute childhood diarrhea

In a systematic review with meta-analysis, Jacobs et al.[6] analyzed three RCTs of homeopathy (individualized medicine) versus placebo in childhood diarrhea (n = 242)[7-9], observing that the duration of diarrhea in the homeopathy group was 3.3 days, compared to 4.1 in the placebo group (p = 0.008). The meta-analysis showed a consistent difference in effect size of approximately 0.66 days (p = 0.008). The results of these studies confirmed that individualized homeopathic treatment decreases the duration of acute childhood diarrhea, and that homeopathy should be considered for use as an adjunct to oral rehydration in these cases.

XII.2.3. Irritable bowel syndrome (IBS)

Two systematic reviews with meta-analyses to evaluate the efficacy and safety of homeopathic treatment in irritable bowel syndrome (IBS) were conducted and published by the Cochrane Library in 2013 and 2019, practically by the same authors. In the first systematic review (2013)[10], randomized controlled clinical trials (RCTs), cohort and case-control studies that compared homeopathic treatment with placebo, other control treatments or usual care in adults with IBS were included. A meta-analysis of two RCTs (n = 129) found a statistically significant difference in overall improvement between the homeopathic *Asa foetida* medicine and placebo at a two-week short-term follow-up. Seventy-three percent of patients in the homeopathy group improved compared to 45% of patients receiving placebo (RR 1.61, 95%CI: 1.18 to 2.18). Sixty-eight percent of patients in the homeopathy group improved compared to 52% of patients in the placebo group (1 study, n = 42, RR 1.31, 95%CI: 0.80 to 2.15). None of the included studies reported adverse events.

Then, a meta-analysis of studies evaluating clinical homeopathy (n = 171) was conducted in a second systematic review (2019)[11] including the same types of studies as the first. At the two-week short-term follow-up, overall symptom improvement was experienced by 73% (46/63) of *Asa foetida* participants compared to 45% (30/66) of placebo participants (RR 1.61; 95%CI: 1.18 to 2.18; 2 studies, very low evidence certainty). In the other two-week clinical homeopathy study, 68% (13/19) of those in the *Asa foetida* plus *Nux vomica* arm and 52% (12/23) of those in the placebo arm experienced an overall improvement in symptoms (RR 1.31; 95%CI: 0.80 to 2.15; very low evidence certainty). In the study that compared individualized homeopathic treatment with usual treatment (n = 20), the mean overall improvement score (feeling

unwell) at 12 weeks was 1.44 + 4.55 (n = 9) in the individualized homeopathic treatment arm compared with 1.41 + 1.97 (n = 11) in the usual care arm (MD 0.03; 95%CI: -3.16 to 3.22; very low evidence certainty). In the study comparing individualized homeopathic treatment with usual care, the mean IBS symptom severity score at 6 months was 210.44 + 112.4 (n = 16) in the individualized homeopathic treatment arm compared to 237. 3 + 110.22 (n = 60) in the usual care arm (MD -26.86, 95%CI: -88.59 to 34.87; low evidence certainty). The mean quality of life score (EQ-5D) at 6 months in homeopathy participants was 69.07 (SD 17.35) compared to 63.41 (SD 23.31) in usual care participants (MD 5.66, 95%CI: -4.69 to 16.01; low evidence certainty). In the study comparing individualized homeopathic treatment with supportive listening, the mean IBS symptom severity score at 6 months was 210.44 + 112.4 (n = 16) in the individualized homeopathic treatment arm compared to 262 + 120.72 (n = 18) in the supportive listening arm (MD -51.56, 95%CI: -129.94 to 26.82; very low evidence certainty). The mean quality of life score at six months in the homeopathy participants was 69.07 (SD 17.35) compared to 63.09 (SD 24.38) in the supportive listening participants (MD 5.98, CI 95%: -8.13 to 20.09; very low evidence certainty). None of the included studies reported abdominal pain, changes in stool frequency or consistency, or adverse events.

XII.2.4. Post-operative ileus

In the treatment of postoperative ileus, Barnes et al.[12] carried out meta-analyses of RCTs to determine the effect of homeopathic treatment versus placebo in restoring intestinal peristalsis in patients undergoing abdominal or gynecological surgery. Separate meta-analyses were conducted for any homeopathic treatment versus placebo; homeopathic medicines of potency < 12c versus placebo; homeopathic medicines of potency ≥ 12c versus placebo. A "sensitivity analysis" was performed to test the effect of excluding studies of low methodological quality. The primary outcome was the time to release the first flatulence. Meta-analyses indicated a statistically significant ($p < 0.05$) weighted mean difference (WMD) in favor of homeopathy (compared to placebo) in time until release of the first flatulence. Meta-analyses of the three studies that compared homeopathic remedies with potency ≥ 12c versus placebo showed no significant difference ($p > 0.05$). Meta-analyses of studies comparing homeopathic remedies with potency < 12c with placebo indicated a statistically significant WMD (p

< 0.05) in favor of homeopathy in time until first flatulence. The exclusion of methodologically weak studies did not substantially change any of the results. The authors concluded that there is significant evidence that homeopathic treatment can reduce the duration of paralytic ileus after abdominal or gynecological surgery.

XII.2.5. Attention deficit hyperactivity disorder (ADHD)

In 2022, Gaertner et al.[13] published a systematic review with meta-analysis choosing studies that investigated the effects of individualized homeopathic treatment on ADHD, under any control. Among the six studies analyzed, five were randomized and presented a low to moderate risk of bias; two were controlled versus standard of care and four were placebo-controlled and double-blind. The meta-analysis revealed a significant effect size between studies of Hedges' g = 0.542 (95%CI: 0.311–0.772; z = 4.61; p < 0.001) versus any control, and of g = 0.605 (95%CI: 0.05 –1.16; z = 2.16, p = 0.03) versus placebo (n = 4). Effect estimates are based on studies with an average sample size of 52 participants. The authors concluded that individualized homeopathic treatment showed a clinically relevant and statistically robust effect in treating ADHD.

XII.3. Systematic reviews without meta-analyses for specific conditions

XII.3.1. Acute otitis media (AOM)

In a systematic review that evaluated alternative and complementary medicine (CAM) treatment options in acute otitis media (AOM), Marom et al.[14] analyzed an RCT of homeopathy versus placebo[15], an RCT of homeopathy versus conventional[16], and a prospective observational study[17].

The RCT of homeopathy (individualized medicine) versus placebo[15] consisted of 75 children with AOM who presented otalgia and bulging tympanic membrane lasting ≤ 36hours. Daily scores showed a significant decrease in symptoms at 24 and 64 hours after treatment in favor of homeopathy versus placebo (p < 0.05).

In the RCT that compared conventional and homeopathic treatments[16], 81 children with AOM were randomly distributed into two groups: 41 in conventional treatment (antipyretics and analgesics) and 40 in homeopathic treatment (individualized medicine). As a result, 39 children (97.5%) in the conventional group needed to use antibiotics compared to no children in the homeopathy group. The number of children

showing significant improvement with homeopathic treatment suggests that its early use may have advantages beyond a "watch and wait" approach.

A prospective observational study with 230 children with AOM receiving individualized homeopathic treatment[17] showed that pain control was achieved in approximately 40% of patients after 6 hours and in a further 33% of patients after 12 hours. This resolution rate is 2.4 times faster than in placebo controls. There were no complications observed in the study group, and the approach was 14% cheaper compared to conventional treatment.

XII.3.2. Postoperative inflammation

Brinkhaus et al.[18] developed a systematic review of RCTs to evaluate the effect of homeopathic treatment with *Arnica montana* versus placebo in the postoperative period of knee surgery [swelling and pain after arthroscopy (ART), artificial knee joint implantation (AKJ) and ligament reconstruction crossed (CLR)].The primary outcome parameter was the difference in knee circumference, defined as the ratio of the circumference on day 1 (ART) or day 2 (RCLP and AKJ) after surgery and the baseline circumference. In the analysis of 3 RCTs, a total of 227 patients were enrolled in ART (33% women, mean age 43.2 years), 35 in AKJ (71% women, 67.0 years), and 57 in the CLR study (26% women, 33.4 years). The percentage of changes in knee circumference was similar between the ART (Delta group difference = -0.25%, 95%CI: -0.85 to 0.41, p = 0.204) and AKJ (Delta = -1.68%, 95%CI: -4.24 to 0.77, p = 0.184), and showed that homeopathic arnica has a beneficial effect compared to placebo on RCL (Delta = -1.80%, 95%CI: -3.30 to -0.30, p = 0.019). Patients in all 3 RCTs who received homeopathic arnica showed a trend toward less post-operative swelling compared to patients who received placebo. However, a significant difference in favor of homeopathic arnica was only found in the CLR trial.

A systematic review of the literature demonstrated the potential of homeopathic arnica (*Arnica montana*) and bromelain in improving postoperative outcomes, including edema, bruising and pain control[19]. A total of 29 articles met the inclusion criteria, with 20 and 9 in the arnica and bromelain treatment groups, respectively. There was marked heterogeneity regarding surgical procedure, dosage regimen, measured outcomes, and results. Arnica has been shown to have a mitigating effect on bruising,

most notably after rhinoplasty and face lifting procedures. Bromelain showed a positive effect on reducing trismus, pain and swelling after molar extractions.

XII.3.3. Psychiatric disorders

In a global systematic review of RCTs of homeopathic treatment in psychiatric diseases[20], the effectiveness of homeopathy compared to placebo was found for the group of functional somatic syndromes (fibromyalgia and chronic fatigue syndrome), but not for anxiety or stress. Homeopathy has produced mixed effects in other disorders. No placebo-controlled depression studies were identified. Significant safety data were missing from the reports, but superficial findings suggested good tolerability of homeopathy. A funnel plot across 13 studies did not support publication bias ($\chi(2)(1) = 1.923$, $p = 0.166$).

Three specific systematic reviews of RCTs showed that homeopathic treatment for fibromalgia (FM) has statistically significant efficacy compared to placebo[21-23].

Four RCTs were found in the first systematic review[21] specific to homeopathic treatments, including two feasibility studies. Three studies were placebo-controlled. Invariably, results suggested that homeopathy was better than control interventions in alleviating FM symptoms. Although all RCTs suggested favorable results for homeopathy, reservations were made for definitive conclusions.

In the second systematic review[22], the authors evaluated the evidence for CAM practices in treating FM, employing RCTs which compared the effect of these practices with other treatments or placebo. Three studies with different approaches to homeopathic treatments and moderate methodological quality were identified, showing effective improvement in pain.

A third general systematic review evaluated all systematic reviews of single CAM interventions in the treatment of FM[23], analyzing five systematic reviews and finding evidence of beneficial effects resulting from homeopathy in improving chronic pain.

In a systematic review on the effectiveness of homeopathy in treating insomnia, Cooper and Relton[24] identified four RCTs comparing homeopathic medicines versus placebo. All involved a small number of patients and were of low methodological quality. None demonstrated a statistically significant difference in outcomes between groups, although two showed a trend in favor of homeopathic medicines and three demonstrated significant improvements from baseline in both groups. In the same year as the

publication of this review, Naudé et al.[25] published an RCT with high-quality individualized homeopathic treatment and with a clear report of methodological details, showing significant improvement compared to placebo, and which received praise from Cooper and Relton[26].

XII.3.4. Rheumatological diseases

In 2000, Jonas et al.[27] developed a systematic review with meta-analysis including all RCTs of homeopathic treatment in arthritis and chronic musculoskeletal syndromes (MS). The studies were categorized into two main types of homeopathic treatment: "classical homeopathy" (single individualized medicine selected based on the patient's totality of symptoms) and "non-classical or complex homeopathy" (one or several medicines selected according to specific clinical situations). No subclassification was made according to dilution, as this is not a clinical issue. Six RCTs (n = 392) were included in the analysis, divided into three studies for the treatment of rheumatoid arthritis (RA) (n = 226), one for osteoarthritis (n = 36), one for fibromyalgia (called fibrositis in the report, n = 30) and one for myalgia (n = 60). Five trials showed improvements in quality scores of 60% of the maximum or more in both quality assessments. A trial on the treatment of "myalgia", which studied a commercial mixture of medicines, was classified as being of low quality. The pooled OR for the six studies included in the global meta-analysis was 2.19 with a 95%CI of 1.55 to 3.11 (using the fixed or random effects model). The OR for the five high-quality studies was 2.11 (95%CI: 1.32-3.35; p = 0.002). One study examining the treatment of RA using only complex non-classical homeopathy (n = 1 of 176 patients) had an OR of 2.18 (95%CI: 1.19–4.02; p < 0.01). Two studies on RA using only classical individualized homeopathy (n = 90 patients) had an OR of 2.04 (95%CI: 0.66-6.34; fixed effects model; p = 0.218). The number of controlled clinical trials on the treatment of rheumatic syndromes with homeopathy at the time was few and the results were mixed regarding effectiveness. Overall, it appears that homeopathic remedies work better than a placebo in studies of rheumatic syndromes, but there are too few studies to draw definitive conclusions about the effectiveness of any type of homeopathic treatment in any condition. RA was the most studied condition, with a total of 266 patients across three studies. ORs were around 2.0 in favor of homeopathy, but only non-classical combined remedies showed clear statistical significance.

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Proof of Scientific Evidence for Homeopathy

XIII. Observational studies

XIII.1. Introduction

XIII.2. Analytical observational studies

XIII. Observational studies

XIII.1. Introduction

As we reported in subchapter III.3 (“Types of epidemiological studies”) of chapter III (“Homeopathic clinical epidemiology”), observational studies are divided into descriptive (case report or case series) and analytical (cross-sectional, case-control, cohort and ecological). Due to their ease of execution and low cost, descriptive observational studies are the most abundant in the scientific literature, although they present results and conclusions which only apply to that sample and cannot be generalized to the population (level of evidence 4).

Analytical observational studies have a higher level of evidence (2B-3B) than descriptive studies, but also have limitations, such as prevalence-incidence bias (exclusion of individuals with greater severity), resulting in a systematic error in the association or estimated effect of a particular exposure or outcome.

Cohort studies have the highest level of evidence (2B) among analytical observational studies, presenting the advantages of evaluating thousands of patients in multiple outcomes and in the long term (natural history of diseases in populations, i.e., external validity of the clinical practice). The term “cohort” is used to describe a group of people who have something in common when they are brought together and who are observed over a period of time to analyze what happens to them, whether or not they are receiving treatment.

Upon entry into prospective cohort studies, individuals are classified according to the characteristics that may be related to the outcomes. Retrospective or historical cohort studies are conducted by identifying past records of outcomes, following individuals from that moment to the present.

As we reported in subchapter III.5 (“Types of epidemiological studies in homeopathy), hundreds of observational studies in homeopathy have been carried out and are available in various scientific literature databases.

For readers who wish to delve deeper into the evaluation of the clinical effectiveness of homeopathy according to existing observational studies, we suggest carrying out a bibliographical survey of the existing literature in the databases mentioned in chapter IV of this work (“Overview of research in homeopathy – Databases”), such as:

- LILACS[1]: "homeopathy" AND "observational study" (46 studies); "homeopathy" AND "case report" (127 studies); "homeopathy" AND "case series" (18 studies); "homeopathy" AND "cross-sectional study" (79 studies); "homeopathy" AND "case-control study" (78 studies); "homeopathy" AND "cohort study" (21 studies).
- PubMed[2]: "homeopathy" AND "observational study" (102 studies); "homeopathy" AND "case report" (289 studies); "homeopathy" AND "case series" (63 studies); "homeopathy" AND "cross-sectional study" (206 studies); "homeopathy" AND "case-control study" (101 studies); "homeopathy" AND "cohort study" (328 studies).
- "Trip Medical Database"[3]: "homeopathy" AND "observational study" (797 studies).
- "Clinical Outcome Research in Homeopathy (CORE-Hom)"[4]: provides 48 observational studies ("observational studies"), published until the beginning of 2018.
- "Homeopathic Intervention Studies (HOMIS)"[5]: provides a total of 636 clinical studies, 541 for therapeutic purposes and 95 for preventive purposes.
- "CAM-QUEST databases"[6]: currently (2023) offers a total of 1,893 homeopathic clinical studies, with 914 "observational trials".
- "HRI - Recommended reading (Peer reviewed journals article)"[7].
- Liga Medicorum Homoeopathica Internationalis (LMHI) – "Scientific Framework of Homeopathy"[8]: addresses observational studies in the chapter "Clinical Research" in all editions (2016, 2017 and 2020-2021) (most recent edition (2020-2021)[9].

XIII.2. Analytical observational studies

The Homeopathy Research Institute (HRI) provides the largest observational studies that were conducted in health services and hospitals in different countries on its "Observational studies"[10,11] page.

As we said earlier, what matters most for healthcare providers, patients and doctors is not necessarily how well a treatment performs under the artificially controlled conditions of a randomized controlled trial (RCT) but rather the results observed in daily clinical practice (external validity or situation in the real world).

Therefore, scientific evidence from "uncontrolled" observational studies provides information about changes in thousands of patients who received long-term homeopathic treatment. These studies consistently demonstrate that patients improve clinically after homeopathic treatment (often in chronic conditions that are difficult to treat according to the classical approach), without the inconvenient side effects of modern drugs. Other studies highlight areas of potential economic benefit for public health services, in some cases reducing spending on prescriptions for high-cost conventional medicines.

Exemplifying this evidence, we will describe three robust cohort studies below which present important information about the effectiveness of homeopathic treatment in thousands of patients in the long term and in different clinical conditions, conducted in France[12], Italy[13] and Germany[14]. Next, we will describe a recent study on the clinical effectiveness and cost-effectiveness of homeopathic treatment in various diseases carried out in Germany[15].

EPI_3 Cohort Study (France, 2008-2012)[12]

An epidemiological impact study conducted in France ("*Benchmarking the burden of 100 diseases: results of a nationwide representative survey within general practices*" - EPI3 Cohort Study)[12], also referred to as the "EPI_3 Project", which followed 8,559 patients attending general practitioner offices (family doctors or GPs), was used to evaluate the effectiveness of homeopathic treatment[16]. The authors of this study include Lucien Abenhaim, French Director General of Health, and individuals from respected academic institutions such as the Institute Pasteur of Paris, the University of Bordeaux and McGill University in Montreal.

Main conclusions of the "EPI_3 Project":

- Upper respiratory tract infections (URTI)[17]: Patients treated by GPs trained in homeopathy performed as well clinically as those treated with conventional medicine, but used fewer conventional medicines. This study investigated the use of antibiotics and antipyretics/anti-inflammatories in the treatment of upper respiratory tract infections (URTI). A total of 518 adults and children with URTI were included. Patients who consulted family doctors certified in homeopathy had significantly lower consumption of antibiotics (OR 0.43, 95%CI: 0.27-0.68) and

antipyretics/anti-inflammatories (OR 0.54, 95%CI: 0.38-0.76), with similar evolution in symptoms related.

- Musculoskeletal disorders (MSD)[18]: Patients treated with homeopathy performed as well clinically as those treated with conventional medicine, but they used only half the amount of nonsteroidal anti-inflammatory drugs (NSAIDs) and had fewer NSAID-related side effects. A total of 1,153 eligible patients with MSD were followed for 12 months, comparing groups receiving homeopathy (n = 371) or conventional medicine (CM; n = 272), or a mixed approach involving both approaches (n = 510). Patients did not differ between the groups, except for the MSD chronicity, which was higher in the homeopathy group (62.1%) than in the CM (48.6%) and mixed (50.3%) groups. The twelve-month development of specific functional scores was identical for all groups ($p > 0.05$). After adjustment for propensity scores, NSAID use over 12 months was almost half in the homeopathy group (OR 0.54; 95%CI: 0.38-0.78) compared to the CM group; no statistically significant difference was found in the mixed group (OR 0.81; 95%CI: 0.59-1.15). Patients with MSD seen by homeopathic physicians showed similar clinical progression when less exposed to NSAIDs compared to patients seen in CM practice, with fewer NSAID-related adverse events and no loss of therapeutic opportunity.
- Sleep, anxiety and depressive disorders (SADD)[19]: Patients treated by certified homeopathic physicians were less likely to be prescribed psychotropic medications. The EPI_3 'SADD' study involved 1,572 patients diagnosed with sleep disorders, anxiety and depression who sought treatment from GPs with three different practice preferences: strictly conventional medicine (GP-CM), complementary and mixed conventional medicine (GP-Mx) and certified homeopathic physicians (GP-Ho). Psychotropic medications were more likely to be prescribed by GP-CM (64%) than by GP-Mx (55.4%) and GP-Ho (31.2%). The three patient groups shared similar severity of SADD in terms of comorbidities and quality of life.

Homeopathy in the Public Health System of Tuscany (Italy, 1988-2008)[13]

Since 1996, complementary medicine (CM), including homeopathy, has been continuously integrated into the public healthcare system in the Tuscany Region of

Italy. This includes three main homeopathic clinics in the city of Lucca: the general medicine homeopathic clinic (created in 1998), the homeopathic clinic for women (created in 2003) and the CM and Diet clinic in Oncology (created in 2010). After 20 years of this clinical experience in the "real world", observational longitudinal data collection on 5,877 patients and 20 studies published in specialized journals ("*Integration of homeopathy and complementary medicine in the Tuscan Public Health System and the experience of the homeopathic clinic of the Lucca Hospital*")[13], the results were evident: homeopathy and CM are recognized as valuable tools to satisfy the needs of the Tuscan population, who in turn received an efficient and long-lasting homeopathic service at affordable costs.

The impact of improvements in patients' clinical conditions was assessed before and after homeopathic treatment using the Outcome in Relation to Daily Living (ORIDL) assessment tool. Improvements in ORIDL were observed in 88.8% of patients overall in general homeopathic practice, and significant improvements were observed in 68.1%; in the women's clinic, improvements were observed in 74.1% and significant improvements in 61.2%. Complementary and integrative homeopathic treatment of the adverse effects of antineoplastic therapies in the oncology clinic was effective in 89.1% of oncology patients followed, mainly for hot flashes, nausea, depression, asthenia and anxiety[13].

8-Year Multicenter Longitudinal Cohort Study (Germany, 2006-2014)[14]

This study which followed more than 3,500 adults and children who received routine homeopathic care by general practitioners, reached the following conclusions: "patients who seek homeopathic treatment are likely to improve considerably". At baseline, 97% of participants were diagnosed with some chronic complaint, with 95% declaring prior conventional treatment for their condition. The severity of the disease decreased significantly ($p < 0.001$) between the beginning of the study, after 2 years and after 8 years of homeopathic treatment. Remarkably, the numbers after 8 years were almost identical to those at the 2-year follow-up, indicating sustained long-term health benefits ("*How healthy are chronically ill patients after eight years of homeopathic treatment?--Results from a long term observational study*")[14].

This 8-year multicenter longitudinal cohort study focused on patients in routine care treated by general practitioners with additional qualifications in homeopathy. The study

included 3,709 patients, 73% of whom contributed data for the 8-year follow-up, i.e., 2,722 adults (72.8% women, baseline age 41.0 ± 12.3) and 819 children (48.4% women, age 6.5 ± 4.0). The most frequent diagnoses were allergic rhinitis and headache in adults, and atopic dermatitis and multiple recurrent infections in children[14].

The main outcome measures using conventional medical research instruments included quality of life (QoL) assessments and numerical severity scales. One in two patients experienced 50% reductions in symptom severity after 8 years, with corresponding changes in quality of life measures. Of adults, almost 50% of respondents (67.4% of the total study population) had "clinically relevant successful treatment" (severity of complaints reduced by 2 points or more on a 10-point scale); the number in children was 80%. Younger age, female sex and more severe disease at the beginning of the study were predictive factors for better therapeutic success[14].

Clinical effectiveness and cost-effectiveness of homeopathic treatment (Germany, 2020)[15]

Several German health insurance companies are offering integrated care contracts for homeopathy (ICCHs), which cover reimbursement for homeopathic treatment. The effectiveness and cost-effectiveness of these contracts are highly debated. Thus, a comparative, prospective, observational study was conducted to evaluate the effectiveness and cost-effectiveness of homeopathic treatment after additional enrollment in an ICCH, in which ICCH participants (HOM group) were compared with matched persons (in diagnosis, sex and age) of insured people who received only conventional care (CON group) ("*Effectiveness and cost-effectiveness of treatment with additional enrollment to a homeopathic integrated care contract in Germany*")[15].

Insured people with migraine or headache, allergic rhinitis, asthma, atopic dermatitis and depression were included in this prospective cohort study. The primary clinical effectiveness outcomes were adjusted baseline scores from diagnostic-specific questionnaires (e.g., RQLQ, AQLQ, DLQI, BDI-II) after 6 months. The primary cost-effectiveness outcomes were baseline adjusted total costs from the insurer's perspective relative to quality-adjusted life years (QALYs) achieved. Costs were derived from health claims data and QALYs were calculated based on SF-12 data.

Data from 2,524 participants (1,543 HOM groups) were analyzed in the studied sample. The primary effectiveness results after six months of treatment were statistically

significant in favor of the HOM group for migraine or headache (Δ = difference between groups, days with headache: -0.9, p = 0.042), asthma (Δ -AQLQ(S): + 0.4, p = 0.014), atopic dermatitis (Δ-DLQI: -5.6, p ≤ 0.001) and depression (Δ-BDI-II: -5.6, p ≤ 0.001). BDI-II differences reached the minimum clinically important difference. Adjusted mean total costs over 12 months were higher in the HOM group from the insurer's perspective for all diagnoses, with migraine or headache, atopic dermatitis and depression suggesting cost-effectiveness in terms of additional costs per QALY gain.
After additional enrollment in ICCH, treatment of participants with depression showed minimally relevant clinical improvements. From the insurer's point of view, treatment with ICCH registration resulted in higher costs for all diagnoses, but appeared to be cost-effective for migraine or headache, atopic dermatitis and depression, according to internationally used threshold values. Based on the study design and other limitations, the authors concluded that the results should be considered with caution and no conclusions about the effectiveness of specific treatment components can be made without further research.

Next, we will systematize the analytical observational studies which evaluated the effectiveness of homeopathic treatment cited by the HRI ("Observational studies")[10,11] and other more recent ones in the table below (**Table 1**).

Table 1. Analytical observational studies that evaluated homeopathic treatment.

Author/ Year	Type of study/ Health service/ Population served/ Effectiveness/ Clinical conditions treated
Thompson et al., 2016[20]	Confirming the results of the 2005 study[25], this recent audit of just under 200 patients conducted at Bristol Homeopathic Hospital demonstrated that patients with long-term illnesses who receive homeopathic care experience statistically significant improvements in presenting symptoms and well-being. A total of 198 patients were evaluated at 1 to 5 visits using a patient-reported outcome measure (MYMOP2). The most common conditions observed were neoplasms, psychological and genitourinary complaints, while the most commonly reported symptoms were pain, mental symptoms and tiredness/fatigue. The intention-to-treat analysis showed that a mean change in MYMOP2 score of 1.24 was achieved from the first to the last visit, with improvements being statistically significant for both those who completed and those who did not complete treatment (p < 0.001).
Roll et al., 2013[21]	In this long-term, multicenter, evaluator-blinded, prospective cohort study, 135 children (48 homeopathy, 87 conventional) with mild to moderate atopic eczema were enrolled by their respective physicians. Depending on the physician's specialization, the primary treatment was standard conventional treatment or individualized homeopathy as provided in routine medical care. The main outcome was SCORAD (SCORing Atopic Dermatitis) at 36 months by a blinded evaluator. Other outcomes included quality of life, consumption of conventional medicines, safety, and disease-related costs 6, 12, and 36 months after baseline. A multilevel ANCOVA was used, with a physician as a random effect and the following fixed effects: age, sex, baseline value, severity score, social class, and parental expectancy. The adjusted mean SCORAD showed no significant differences between the

	groups at 36 months (13.7 95% CI [7.9-19.5] vs. 14.9 [10.4-19.4], p = 0.741). SCORAD response rates at 36 months were similar in both groups (33% response: homeopathy 63.9% vs. conventional 64.5%, p = 0.94; 50% response: 52.0% vs. 52.3%, p = 0.974). Total costs were higher in the homeopathic group versus the conventional group (months 31-36 €200.54 [€132.33-268.76] vs. €68.86 [9.13-128.58], p = 0.005). The number of reported adverse events was also similar in the two groups.
Witt et al., 2009[22]	A prospective, multicenter, observational, comparative, non-randomized study examined the efficacy, safety, and costs of homeopathic versus conventional treatment in usual care. A total of 135 children (homeopathy n = 48 vs. conventional n = 87) with mild to moderate atopic eczema were included. The primary endpoint was SCORAD (Scoring Atopic Dermatitis) at 6 months. Other outcomes at 6 and 12 months also included parents' and children's quality of life, use of conventional medicine, safety of treatment, and disease-related costs. The adjusted SCORAD showed no significant differences between the groups at both 6 months (homeopathy 22.49 ± 3.02 [mean ± SE] vs. conventional 18.20 ± 2.31, p = 0.290) and 12 months (17.41 ± 3.01 vs. 17.29 ± 2.31, p = 0.974). Adjusted costs were higher in the homeopathic group than in the conventional group: in the first 6 months €935.02 vs. €514.44, p = 0.026, and during 12 months €1,524.23 vs. €721.21, p = 0.001. Quality of life was not significantly different between the two groups.
Thompson et al., 2008[23]	In this pilot study, data from 1,602 patient follow-up visits across all five NHS homeopathic hospitals were collected together over a one-month period. At their second homeopathic visit, 34% of follow-up patients overall reported an improvement that affected their daily life. For patients at the sixth visit, the corresponding improvement rate was 59%. Eczema, chronic fatigue syndrome, menopausal disorder, osteoarthritis and depression were the five most commonly reported clinical conditions. Patients referred to NHS homeopathic hospitals typically have chronic conditions for which available conventional treatments have not been sufficiently effective. In total, the study identified 235 distinct medical complaints treated in hospitals over the course of a month. Many patients had multiple diseases.
Keil et al., 2008[24]	A prospective multicenter cohort study evaluated, over a period of 12 months, whether homeopathic treatment could influence the signs/symptoms of eczema and quality of life (QoL) compared to conventional treatment. Children with eczema aged 1 to 16 years were recruited from primary care offices. Patients (or parents) assessed eczema symptoms by numerical scales, as well as disease-specific Atopie Lebensqualitaets-Fragebogen (ALF) and overall quality of life (KINDL, KITA). A total of 118 children were included: 54 in the homeopathy group (mean age ± SD was 5.1 ± 3.3 years; 56% boys) and 64 in conventional medicine (6.2 ± 3.8 years; 61% boys). Eczema symptoms improved in both treatment options, with no significant difference between the groups: 3.5-2.5 versus 3.4-2.1; p = 0.447 (adjusted). Disease-related quality of life improved similarly in both groups.
Spence et al., 2005[25]	An observational study at Bristol Homeopathic Hospital included more than 6,500 consecutive patients with more than 23,000 visits over a six-year period; 70% of the patients followed reported improvement in health, 50% with significant improvement. The greatest improvements were reported in childhood eczema or asthma, irritable bowel syndrome, menopausal disorders, and migraine.
Witt et al., 2005[26]	A study commissioned by a German health insurance company to determine whether it should continue to cover homeopathic treatment evaluated the value of homeopathy in the treatment of chronic conditions, often seen in general clinical practice: 493 patients (315 adults, 178 children) treated by general practitioners received conventional medicine or homeopathy. The study found that patients in the homeopathy group reported significant clinical improvement compared to the conventional medicine group (p = 0.002), with no significant difference in cost. In the subgroup of children, the evaluations also showed a significant clinical improvement of homeopathy compared to conventional medicine (p < 0.001). Conditions treated included headache, low back pain, depression, insomnia, and sinusitis in adults, and atopic dermatitis, allergic rhinitis, and asthma in children. After the publication of this study, the insurance company (Innungskrankenkasse Hamburg) decided to continue to cover homeopathic treatment.
Sharples et al., 2003[27]	A survey of 500 patients at the Royal London Homeopathic Hospital showed that many patients were able to reduce or discontinue conventional medication after homeopathic treatment. The extent of improvement varied between diagnoses, e.g., 72% of patients with skin complaints reported being able to discontinue or reduce conventional medication; for cancer patients there was no reduction. The study also showed that many patients turn to

	homeopathy out of concerns about the safety of conventional treatment.
Richardson 2001[28]	Research on the results of homeopathic treatment carried out at the Regional Department of Homeopathic Medicine in Liverpool (UK), during 12 months (06/1999 to 05/2000), using self-assessment by the Glasgow Homeopathic Hospital Outcome Score (GHHOS). Overall, 76.6% of patients reported an improvement in their condition since the start of treatment, while 60.3% scored +2, +3, or +4 on GHHOS. 52% of patients reduced conventional medication. The main conditions treated were osteoarthritis, eczema, chronic fatigue syndrome, asthma, anxiety, headaches, inflammatory arthritis, and irritable bowel syndrome.
Clover, 2000[29]	Research on the results of homeopathic treatment carried out at Tunbridge Wells Homeopathic Hospital (UK) during the year 1997. The aim of this study was to evaluate: (a) the range of diagnoses presented by patients and (b) patients' own impressions of the benefits. 1,372 questionnaires were completed by patients after consultations to record their impressions of the effects of homeopathic treatment. Patients were asked to score their responses on a scale of +3 to -3. The three main diagnostic groups were dermatology, musculoskeletal diseases, and malignancies, especially carcinoma of the breast. Overall, 74% of patients recorded positive benefits, with 55% recording scores of +3 or +2.

Although it does not apply to the main purpose of this work, the discussion about public spending on homeopathy is a topic frequently raised by pseudoskeptics and pseudoscientists who dogmatically and systematically deny the beneficial effects of homeopathy as an adjuvant therapy in numerous clinical conditions, as we have been describing throughout the work. These pseudo-researchers argue that public money should not be spent on homeopathy because "there is no evidence that it works" or "taxpayer money should not be spent on placebos".

As we described some observational studies which have investigated the costs of homeopathic treatment compared to conventional treatments, as well as the cost-effectiveness (cost-benefit) of homeopathy, we will outline some comments on this aspect. Although we have already addressed this issue in an article published in the *Jornal da USP* in 2019 *("[Expenditures on homeopathy in the SUS are derisory when compared to other medical specialties]"*)[30], we will describe some of these positions below together with the position of the Homeopathy Research Institute (HRI) on the topic ("NHS homeopathy in the spotlight")[31,32].

As we described in the the "*Jornal da USP* (28/11/2019)"[30], "*[Spending on integrative practices in the SUS corresponds to 0.008% of outpatient and hospital expenses]*":

- "Just as the aforementioned dossier fulfills the role of demystifying the fallacy that "there is no scientific evidence for homeopathy", a study by researcher Islândia Maria Carvalho de Souza[33], specialist in health systems management, with a Master's degree and Doctorate from the Escola Nacional of Fiocruz Public Health, "demonstrated that *expenses with all PICS in the SUS related to*

outpatient and hospital expenses correspond to 0.008% of the total of these expenses (i.e., only R$ 2.6 million of an amount of R$ 33 billion), demystifying the fallacy that "billions of reais are spent on homeopathy in the *SUS*", a justification defended by groups of dogmatic skeptics for this medical specialization to be removed from the *SUS*, depriving thousands of patients of receiving relief for their physical and mental problems: "*Spending on integrative practices in the SUS corresponds to 0.008% of outpatient and hospital expenses*"[33]. Similarly, contradicting a similar movement in Germany which requested the end of reimbursement for homeopathic medicines with the allegation that "huge amounts of taxpayers' money were spent on this benefit", the German Minister of Health, Jens Spahn, stated in 09/17/2019 that "your ministry does not intend to force the country's health insurers to stop subsidizing homeopathic services". Without going into the merits of scientific evidence, he justified his position on the paltry expenses of this type of treatment: "While the country's health plan operators subsidize the purchase of € 40 billion in conventional medications per year, reimbursement for homeopathic treatments barely reaches € 20 million", he stated, meaning that *just 0.0005% of spending on conventional medicines*: "*German minister opposes the end of subsidies for homeopath"*[34]. With this evidence, the prejudiced, dogmatic and fallacious premises against maintaining and expanding the provision of homeopathy in the *SUS* lose validity"[30].

With a similar percentage of expenses, according to research by Homeopathy Research Institute (HRI) ("NHS homeopathy in the spotlight")[31,32], "only around £ 4 million (0.004%) of the total National Health Service (NHS, UK) annual budget of £ 100 billion is spent on homeopathy":

- "Some people take the position that public money should not be spent on homeopathy because "there is no evidence that it works" or "taxpayer money should not be spent on placebos". This is not an argument limited to the UK, but is repeated across the world - especially in Europe - where homeopathy funding or discounts are available from national healthcare budgets. However, very few people have access to the data needed to effectively evaluate this argument. Although NHS funding of homeopathy has ceased in the UK, the following points highlight more general issues with the argument against public funding of

homeopathy. How much does homeopathy cost? In 2016, just £ 92,412 was spent on 40,000 homeopathy prescriptions, out of a total spend of £ 9.2 billion[35]. Of the total NHS budget of £ 100 billion per year, around £ 4 million (0.004%) is spent annually on Homeopathy[36,37] if we include everything from managing hospital departments to paying doctors. When considering the cost-benefit ratio, it must be remembered that if homeopathic patients were not treated with this service, they would have to be treated by other departments with more expensive conventional medicines. Homeopathy should be considered in the same way as all other NHS treatments"[31,32].

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Proof of Scientific Evidence for Homeopathy

XIV. Pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy

XIV.1. Introduction

XIV.2. Pseudoskepticism and pseudoscience/ Pseudoskeptics and pseudoscientists

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XIV.1. Introduction

Homeopathy has been a medical practice recognized worldwide for over 200 years, providing care, teaching and research activities in various professional associations and medical schools. It employs a clinical approach based on specific and complementary scientific principles with the aim of awakening a curative response in the body against its own disorders and/or diseases.

In view of being based on different assumptions from those used by conventional medical practice, it is often the target of unfounded and widespread criticism by individuals who systematically deny homeopathic principles and any scientific evidence that proves them, as they are wrapped in a dogmatic denialism that prevents a correct and prejudice-free analysis. They are pseudoskeptics disguised as pseudoscientists.

To clarify doctors, researchers, health professionals and the general population, demystifying culturally ingrained dogmatic positions and the pseudoskeptical fallacies that "there is no scientific evidence for homeopathy" and "homeopathy is placebo effect", the Technical Chamber of Homeopathy of the Regional Council of Medicine of the State of São Paulo (TC-Homeopathy, Cremesp) prepared and published the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017)[d] in 2017, freely available in the *Revista de Homeopatia (São Paulo)*, the scientific journal of the São Paulo Homeopathic Medical Association (APH).

Encompassing nine narrative reviews in different lines of homeopathic research (historical-social, medical education, pharmacological, basic, clinical, patient safety and pathogenetic) and two randomized and placebo-controlled clinical trials developed by members of TC-Homeopathy, containing hundreds of scientific articles published in

[a] Teixeira MZ. Falácias pseudocéticas e pseudocientíficas do "Contradossiê das Evidências sobre a Homeopatia" [Pseudoskeptical and pseudoscientific fallacies of the "Counterdossier of Evidence on Homeopathy"]. São Paulo: Marcus Zulian Teixeira, 2020; 49 p. https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1145551

[b] Teixeira MZ. Estratégias pseudocéticas e pseudocientíficas usadas em ataques à homeopatia [Pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy]. São Paulo: Marcus Zulian Teixeira, 2021; 74 p. https://www.amazon.com/dp/b09lr9m7xg

[c] Teixeira MZ. Pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy. Rev Assoc Med Bras. 2021;67(6):777-780. https://doi.org/10.1590/1806-9282.20210367

[d] Teixeira MZ. Special Dossier: "Scientific Evidence for Homeopathy". Rev Assoc Med Bras. 2018;64(2):93-94. https://doi.org/10.1590/1806-9282.64.02.93

numerous indexed and peer-reviewed scientific journals, this dossier highlights the state of the art of research in homeopathy for the medical and scientific profession, as well as for the general public.

Disturbed by the excellence of this vast body of evidence, a group of pseudoskeptics and pseudoscientists who are part of the *Instituto Questão de Ciência* (IQC) published a derisory and fallacious manuscript in November 2020 entitled "Contradossiê das Evidências sobre a Homeopatia" ["Counterdossier of Evidence on Homeopathy"], with the aim to evaluate the articles published in the *Special Dossier: "Scientific Evidence for Homeopathy"* according to "the best scientific rigor" and "inform the population about what science says about the supposed effectiveness of homeopathy".

Unfortunately, none of this occurred in the aforementioned manuscript. Contrary to the announced "better scientific rigor" in the analysis of articles, what is observed throughout the text is a set of criticisms based on known "pseudoskeptical strategies" to discredit and disqualify certain scientific work, such as: tendency to deny, instead of doubting; use of personal attacks; attempt to disqualify proponents of new ideas by pejoratively labeling them pseudoscientists, promoters or practitioners of pathological science; carrying out judgments without a complete and conclusive investigation; presentation of insufficient or unconvincing evidence (absence of evidence); presentation of counter-evidence that is not substantiated or based only on plausibility, instead of being based on evidence; tendency to disqualify any and all evidence; suggestion that unconvincing evidence is sufficient to assume that a theory is false; vitriolic, slanderous or derogatory tone in comments; non-specific and superficial comments; dissemination in the mass media (non-scientific); among others.

In two free access digital books *"Falácias pseudocéticas e pseudocientíficas do "Contradossiê das Evidências sobre a Homeopatia" ["Pseudoskeptical and pseudoscientific fallacies of the "Counterdossier of Evidence on Homeopathy"]*[(1)] and *"Estratégias pseudocéticas e pseudocientíficas usadas em ataques à homeopatia" ["Pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy"]*[(2)] and in an article published in an important scientific journal ("*Pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy*")[(3)], we highlight these pseudoskeptical and pseudoscientific strategies in the general chapters of the aforementioned manuscripts and in the apocryphal criticisms of these "experienced and renowned researchers in their areas of concentration" to the articles we authored,

stripping them of the false and hypocritical image of being "defenders of science", as they call themselves in the aforementioned counterdossier.

In order not to deviate from the objective of this work, we will focus on highlighting the "pseudoskeptical and pseudoscientific strategies used in attacks on homeopathy" (and in other areas of scientific knowledge and unconventional medicine), leaving it up to the readers to evaluate the criticisms against the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017) by reading the aforementioned works[1-3].

XIV.2. Pseudoskepticism and pseudoscience/ Pseudoskeptics and pseudoscientists

On October 19, 2020, a manifesto against legislation that supports non-conventional health therapies was published in Europe, drawn up by 2,750 signatories from 44 countries. Written by pseudoskeptic societies or organizations without academic and scientific expressiveness, which have pseudoskeptics and pseudoscientists in their corporate body who claim the right to criticize health practices that they do not accept due to personal and autocratic opinion, systematically despising and denying any scientific evidence to support them.

I say "pseudoskeptic" societies or organizations because the doctrinal current of true "skepticism", founded in ancient Greece by the philosopher Pyrrho (4th century BC), argues that "it is not possible to affirm the absolute truth of anything, and it is necessary to be in constant questioning"[4]. The term "pseudoskepticism" emerged in the second half of the 19th century, indicating the explicit tendency towards "negationism", rather than the ethical and objective questioning proposed by Greek skepticism.

> "The term skepticism ended up designating a negative attitude of thought in common language. The skeptic is often not only seen as a hesitant or timid spirit who does not speak out about anything, but as one who takes refuge in criticism about anything that is advanced, or about anything that he can say. Likewise, it is still believed that skepticism is the school of refusal and categorical denial. In reality, and due to its own etymology (skepsis in Greek meaning 'examination'), skepticism would veto any decided position, starting even with that which would consist of affirming, long before Pyrrhus and like Metrodorus of Abdera, that we only know one thing: that we know nothing. Skeptics call themselves zetetics, meaning researchers; of ephetics, who practice the suspension of judgment; of aporetics, philosophers of the obstacle,

> of perplexity and of results not found. [...] To understand skepticism, it is therefore necessary to answer these two questions successively: what did ancient skepticism consist of? Why has skepticism, in the history of philosophy, been ignored and betrayed its intention and value?"[4]

In 1987, Marcelo Truzzi (1935-2003)[5], Danish sociologist and professor of sociology based in the USA (Eastern Michigan University), prepared a very enlightening analysis of the term "pseudoskepticism" or "pathological skepticism", saying that it is used to denote forms of skepticism which deviate from objectivity by denying everything that is dogmatically ignorant, instead of doubting, investigating and accepting the evidence that appears with an agnostic and neutral position, with an open mind and free from prejudice[6].

> "Since 'skepticism' correctly refers to doubt rather than denial - not belief rather than belief - critics who take the negative rather than the agnostic position but still call themselves 'skeptics' are in fact 'pseudoskeptics' and have, I believe, gained a false advantage by usurping that label."[6]
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> "Critics who make negative claims but who mistakenly call themselves 'skeptics' often act as if they have absolutely no burden of proof on them, even though such a position would only be appropriate for the agnostic or true skeptic. One result of this is that many critics seem to feel that it is only necessary to present a case for their counter-claim based on 'plausibility' rather than empirical evidence. [...] Showing that evidence is not convincing is not enough to completely rule it out. If a critic asserts that the result was due to failure X, that critic then has the burden of proof to demonstrate that failure X could and probably did produce such a result under those circumstances."[6]

In his impartial analysis, Marcello Truzzi argues that pseudoskeptics present the following conduct[6]:

#1: Tendency to deny rather than doubt.

#2: Use of personal attacks.

#3: Attempt to disqualify proponents of new ideas by pejoratively labeling them "pseudoscientists", "promoters" or "practitioners of pathological science".

#4: Holding judgments without a complete and conclusive investigation.

#5: Presentation of insufficient or unconvincing evidence.

#6: Presentation of unsubstantiated counter-evidence or based only on "plausibility", instead of being based on evidence.

#7: Tendency to disqualify "any and all" evidence.

#8: Suggestion that "unconvincing" evidence is enough to assume a theory is false.

Marcoen J. F. Cabbolet[7], affiliated researcher at the Department of Philosophy, Center for Logic and Philosophy of Science, Free University of Brussels (Belgium), scholar of elementary or particle physics ("*Elementary Process Theory*")[8], in his essay "*Tell-Tale Signs of Pseudoskepticism (Bogus Skepticism)*"[9], states that "pseudoskepticism, which typically portrays one's work as contemptible with scientifically unsound polemics, is a modern threat to the traditional pattern of discussion in science and popular science".

Thus, "where the skeptic only states that they do not believe someone else's statements, the pseudoskeptic comes up with statements and these are always (very) negative. But pseudoskepticism is not just making negative claims: the key words are 'dishonesty' and 'foul play'. And it's not meant to uncover the truth, but just to discredit someone's research". According to Cabbolet, "pseudoskepticism has the same connotation as pseudoscience: both imply a drastic departure from the framework of a scientific discourse".[9]

In another article[10], Cabbolet addresses this "pseudoscience", describing the "scientific misconduct" in a clear and objective way with several classic examples which leads to "falsely negative conclusions about someone else's work". He clarifies that "three known issues are identified as specific forms of such scientific misconduct: biased assessment of quality, defamation, and condoning scientific misconduct". The article reiterates that pseudoskepticism is at the central focus of this scientific misconduct, which aims to "progress negative conclusions about someone else's work that are false". Suggesting that this stance may be "a calculated strategy", rather than a passionate attitude, it provides recommendations to prevent and deal with these three forms of scientific misconduct through educational and punitive measures.[10]

XIV.3. Tell-tale signs of pseudoskepticism (bogus or pathological skepticism)

In the first essay cited[9], Cabbolet describes and explains in detail the **tell-tale signs of pseudoskepticism (bogus skepticism), initially described by Marcelo Truzzi**

(pathological skepticism)[6], through which the conduct and strategy of the pseudoskeptic can be notably recognized (**Table 1**).

Table 1. Tell-tale signs of pseudoskepticism (bogus or pathological skepticism)[9]

Seven tell-tale signs of pseudoskepticism	
#1: ad hominem attacks	Typically, a pseudoskeptic is so eager to portray the author of the targeted work as an amateur that he resorts to ad hominem attacks: this is a rhetorical technique that is absolutely inadmissible in a scientific discourse, and therefore this is the number one tell-tale sign that a piece is nothing but a pseudoskeptical attack. It is thus a real giveaway when the author of the targeted work is called 'incompetent', an 'amateur', a 'charlatan', a 'crackpot', 'ignorant', 'only out to brag about it in a pub', etc. So, the occurrence of any of these words alone is already an indication that the entire piece is of doubtful merit.
#2: vitriolic tone	Typically, a pseudoskeptical attack portrays the targeted work as despicable: usually this is done by riddling the text with belittling phrases and strong pejoratives. Consequently, the piece has a vitriolic or even libelous tone that is immediately evident even from a quick superficial reading: that tone is the tell-tale sign of pseudoskepticism. The archetypical belittling phrase is 'every first-year student could have come up with the same thing'. Illustrative examples of strong pejoratives are 'nonsense', 'perverse', 'a disgrace', 'worth-less', 'meaningless', 'inferior', 'devoid of content', 'complete rubbish', and the like, which are then typically said about the targeted work as a whole.
#3: non-specific comments	In science, when commenting on someone else's work, one very specifically addresses the details of the work in question. A pseudoskeptic, however, typically doesn't go through the hard work of really understanding the targeted work. This feature manifests itself in superficiality of the comments. It is therefore a tell-tale sign of pseudoskepticism when a piece concerns nothing but negative allegations at the metalevel, that is, negative allegations about the targeted work as a whole, without going into the details of the targeted work.
#4: absence of proof	Another typical feature of pseudoskeptics is that they have no shame: one of the most shameless ways to attack someone else's work is to put forward outright fabrications, which, if true, would imply gross incompetence of the author of the targeted work. But fabrications cannot be proven by their very nature. Consequently, absence of proof of the (usually grave) allegations in a piece is a sure tell-tale sign of pseudoskepticism at its worst, and a strong indication that the piece may contain fabricated allegations. An illustrative example is an absence of proof of the one statement that is probably the most abused phrase of all in modern science: 'this work is of insufficient scientific quality'. In a pseudoskeptical attack, this is typically said of the targeted work without specifying which criteria of scientific quality are not met, and why or how they are not met - there are peer review reports that consist of just this one phrase.
#5: false metaphors	In science, comments on someone else's work remain confined to that work: one doesn't indulge oneself in metaphors. In a pseudoskeptical attack, however, often the targeted work is compared to a theory that is known to be false or that is obviously ridiculous, as if it is the same thing. Illustrative examples are phrases like 'this is the same as saying that the earth is at', or 'this is the same as saying that the phenomenon is caused by angels': these are tell-tale signs of a pseudoskeptical attack. There are more sophisticated cases, but the point is that this use of metaphors is a rhetorical technique that is absolutely inadmissible in a scientific discourse. The error is the same in all these cases: contrary to what is stated by the pseudoskeptic, it is not at all the same thing.

#6: contradiction with history and basic principles of science	When attacking a new theory that has not yet been experimentally tested, a pseudoskeptical piece often blatantly contradicts well-known facts from the history of science, as well as basic scientific principles. The three archetypical examples that turn up time and time again are (i) stating that scientific discoveries are nowadays only made by large international collaborations, to insinuate that the work of a single author cannot be a scientific discovery; (ii) stating that scientific theories are always developed from experimental facts, to insinuate that anything else cannot ever be a scientific theory; and (iii) using an accepted model (other than Einstein's Special Relativity) beyond its established area of application as a criterion of truth, to insinuate that a work that contradicts that model cannot be a scientific theory. The arguments (i) and (ii) completely ignore that virtually all of modern science is built on the work of individuals, who more often than not theoretically predicted phenomena before these were experimentally observed (Einstein: time dilation and curvature of space; Dirac: antimatter), and who often did their groundbreaking work in relative isolation (Einstein, Bohr). The argument (iii) ignores the fact that historical breakthroughs in science often went squarely against the accepted model of the time, and contradicts a basic principle of science, put into words by Feynman as follows: 'experiment is the sole judge of scientific truth'.
#7: straight to the mass media	It is a bad sign when a scientific claim is taken straight to the mass media (e.g. the cold nuclear fusion case), but it is an equally bad sign when an attack on someone else's work is taken straight to the mass media. When writing a scientific critical comment on a work, the right method is to first contact its author and discuss the criticism with him/her. When submitting the critical comment for publication in a scientific journal, one is often required to present evidence of such a prior contact with the author of the targeted work. But not so the pseudoskeptic. Typically, he doesn't contact the author of the targeted work, nor does he attempt to publish his 'findings' in a peer reviewed journal: he takes his allegations straight to the mass media. So an editor of a newspaper or university weekly who sees that an attack on someone's work is submitted for publication, can - especially when the piece contains grave accusations - simply ask for evidence of contact with the author of the targeted work: any failure to provide such evidence is then a tell-tale sign that the piece is nothing but a pseudoskeptical attack, and an indication that it may contain fabrications.

Highlighting the arrogant, haughty, unethical and anti-scientific stance of these pseudo-skeptics covered by subterfuge, Cabbolet adds[(9)]:

> "Furthermore, but this is not an immediate sign, pseudoskeptics never publish a retraction. Generally in science, if researcher A publishes a claim and researcher B refutes the evidence, then A publishes a retraction of the claim. But this does not happen with the pseudoskeptic. Even when faced with conclusive evidence that their claims are false, they will refuse to publish a retraction or publicly acknowledge that the claims were fabricated: the typical pseudoskeptic will cling to their fabrications as if no words had been spoken - as in the biblical proverbs, as a dog returns to its own vomit, or as a washed sow returns to the pool of mud (2 Pet 2:22). This only appears after some discussion, but indicates that the original claim was a pseudoskeptical attack."[(9)]

Cabbolet expands his analysis to the scientific environment, indicating that pseudoskepticism is also very common in reports of peer reviews of scientific publications, in all knowledge areas, when the pseudoscientific opinion of a reviewer denies publication of an article that disagrees with their dogmatic view, even if it meets all the requirements of the scientific method. This can sometimes be observed when we forward scientific articles on homeopathy to non-homeopathic journals[9].

> "Pseudoskepticism rarely appears in peer review reports in the public domain, because these reports are confidential, but it is not something that rarely occurs, nor is it limited to any specific branch of science: its occurrence in physics, mathematics, and philosophy is so widespread that probably every researcher working in these areas has encountered it at least once in their career. Evidence that it occurred on a large scale in the 1950s can be found in the literature, for example (Schweber, 1989). Furthermore, pseudoskepticism is not limited to confidential peer review reports: it also occurs in opinion pieces in university newspapers and weeklies, as well as in articles in popular science magazines; in particular, when coming from professional scientists with a university affiliation, or even a Nobel laureate, it can severely discredit someone's work because readers generally trust authorities and will therefore believe the claims to be true."[9]

Paradoxically, following the ploy or pseudoskeptical conduct of #7 (directly to the mass media)[9], the fallacies and allegations of pseudoskeptics against homeopathy are repeatedly transmitted through opinion articles and interviews in newspapers and various popular media (refraining from following the usual scientific path of submitting their claims to a peer-reviewed scientific journal), with this strategy being possible as long as the organization or group of pseudoskeptics has a good press office and spends huge amounts on this strategy.

In accordance with these behaviors, pseudoskeptics opposed to homeopathy act according to double standards: they "demand" that homeopathic researchers publish their studies in "non-homeopathic" scientific journals (whereas, in any medical specialization, studies relating to the same are published in specialized journals), but they discard this premise in the massive dissemination of their pseudoscientific fallacies[1-3]. As we said, they propagate their biased and prejudiced allegations, widely and unrestrictedly, in popular newspapers, social media and various television channels ("pseudoscientific" communication), stripping themselves of the false and hypocritical

image of being "defenders of science", as they generally call themselves: "Our duty, as scientists and scientific communication professionals, is to inform the population about what science says about the supposed effectiveness of homeopathy. Our job here was simply to apply the best scientific rigor to the articles presented as evidence, and report the results" ("[Counterdossier of Evidence on Homeopathy]", pp. 8 and 9).

As we evidenced in detail in the works initially cited[1,2] in the analysis of the criticisms of the articles we authored published in the *Special Dossier: "Scientific Evidence for Homeopathy"* (Cremesp Dossier, 2017), the "application of this best scientific rigor" by so-called "scientists and scientific communication professionals" was suffering and deplorable, denoting a lack of compliance with basic premises of the scientific method, with a simple careful reading of the article to be criticized among them (?!). Immature and puerile conduct without justification when carried out by individuals who call themselves "experienced and renowned researchers in their areas of concentration".

Exemplifying the humble, skeptical and unprejudiced conduct of the true researcher observed in the posture of important personalities who offered humanity with their discoveries and inventions, let us remember the phrase of the self-taught genius Leonardo da Vinci, one of the most emblematic figures of the Cultural Renaissance, and who stood out as a scientist, mathematician, astronomer, engineer, painter, sculptor, architect, draftsman, anatomist, botanist, poet and musician, among other talents, as well as having a deep understanding of philosophy and human nature:

> "A little knowledge makes people feel proud. Lots of knowledge make you feel humble. This is how the grainless ears disdainfully raise their heads to the sky, while the floods lower them to the earth, their mother." (Leonardo da Vinci)

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Proof of Scientific Evidence for Homeopathy

XV. Conclusion

XV. Conclusion

Homeopathy proposes to understand and treat the sick-disease binomial according to a vitalist, globalizing and humanist anthropological approach, valuing the different aspects of the sick individuality; it specifically contributes to maintaining health and organic homeostasis, and acts as an therapeutic alternative for different health disorders and types of diseases.

However, in order to achieve this objective, homeopathic therapy must be well conducted and follow the epistemological premises of the homeopathic model, among which include application of therapeutic similarity between the set of signs and symptoms of the sick individuality (characteristic symptomatic totality of the sick-disease binomial) and the set of pathogenetic signs and symptoms awakened by the medicine in the healthy individual, meaning individualization of the homeopathic medicine.

Several RCTs and their systematic reviews with meta-analyses which disrespected this therapeutic individualization, administering the same medicine to different individuals with the same disease did not show significant results compared to placebo, as they violated the scientific rationality of the homeopathic model (homeopathic episteme).

In order for these minimum requirements of good homeopathic clinical practice to be met, the conduct of the homeopathic physician must follow a broad and specific protocol, as the prescription quality is directly related to case management (individualizing and globalizing homeopathic semiology), the selection of signs and symptoms (valuation and repertorization of signs and symptoms) and the differential diagnosis between the different medicinal hypotheses through the study of Homeopathic Materia Medica.

In view of human complexity, this process of individualizing homeopathic medicine requires a period of regular and variable accompaniment, in which the responses to the different medicinal hypotheses are evaluated successively, adjusting the medicines, doses and homeopathic potencies to the different susceptibilities (psychological, emotional, general and physical) of each patient.

Despite these difficulties inherent to every type of holistic therapeutic approach which seeks to understand and treat human beings in a global, integral and non-reductionist way, homeopathy can act as an adjuvant and complementary to the various existing

conventional treatments, adding efficacy, effectiveness, efficiency and security to medical practice, both curatively and preventively, reducing symptomatic manifestations and the predisposition to becoming ill, with low cost and minimal adverse events.

Although these prerogatives intrinsic to individualizing homeopathic treatment limit clinical practice with greater speed, scope and breadth, as well as development of a greater number of studies in the area, the set of existing experimental and clinical studies described in this work which support the assumptions of homeopathic medicines and confirm the effectiveness and safety of the therapy, it is indisputable proof that "there is scientific evidence for homeopathy" and "homeopathy is not placebo effect", contradicting the prejudice falsely disseminated by pseudoskeptics and pseudoscientists.

However, the development of scientific research in homeopathy must be continued, so that new studies contribute to improve and facilitate homeopathic clinical practice, elucidating unique and peculiar aspects of the homeopathic paradigm which can enable its therapeutic application in a faster, broader, and more effective way.