Aus der Tierklinik für Fortpflanzung
des Fachbereichs Veterinärmedizin
der Freien Universität Berlin

Basic Research in Homeopathy – Development of Plant Bioassays to Investigate Effects of Potentised Preparations

Inaugural-Dissertation
zur Erlangung des Grades eines
Doktors der Veterinärmedizin
an der
Freien Universität Berlin

vorgelegt von
Vera Majewsky
Tierärztin aus Tübingen

Berlin 2017
Journal-Nr.: 3992

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Für meine Mutter, Gisela Majewsky

Es knospt unter den Blättern. Das nennen sie Herbst. (Hilde Domin)

Index

1. Introduction

1.1 Homeopathy – Potentisation, application in practice and controversy

Classical homeopathy is an individual alternative therapy which was developed in the 18th/19th century by Samuel Hahnemann [1] and which is based on some basic assumptions [2]: The remedy proving, the similia principle, and the therapy by diluted and agitated remedies (potencies). One of the basic assumptions of homeopathy is that homeopathic remedies is that every potentised remedy induces specific symptoms if they are given to a healthy person. These symptoms and also the symptoms of the (sometimes toxic) effect of the undiluted original substance are collected to build the specific homeopathic "remedy picture". Walach et al. gives an overview about scientific provings of homeopathic remedies on humans [3]. An example for an actual remedy proving is the randomised, double blind, placebo controlled study of Teut et al., who tested the effect of Galphimia glauca in humans [4]. The prescription of a homeopathic remedy for diseased patients follows the similia rule: the sick human or animal should get the homeopathic remedy whose remedy picture is most similar to the patient`s individual symptoms [2]. Hahnemanns idea behind the similia rule was, that the sick organism reacts against the artifical symptoms caused by the remedy, and by the similarity of artificial symptoms to the sickness/disease of the patient, the body starts to react against the sickness whereby the healthy condition can be regained (induction of self-regulation) [2]. Wiegant and van Wijk investigated the similia principle on cellular level in several research projects [5]. The production of major stress proteins (heat shock proteins (hsps) and glucose-regulated proteins (grps) of H35 hepatoma cells (rat) as response to small doses of different stressors (heavy metals and high temperature) was measured and compared ("remedy picture" on cellular level), searching a stressor which induces a similar stress protein response compared to a high dose of heat shock ("disease picture"). The influence on the survival capacity of the cells by isopathic as well as the homeopathic approach were investigated, different grades of similarity were tested. The authors observed a correlation between similarity and stimulation of the survival capacity of the cells.

Development of veterinary homeopathy started in the same time as human homeopathy [1]. The University of Leipzig preserves a hand-written manucript of an oral presentation of Hahnemann about "Homöopathische Heilkunde der Haustiere", which was written in 1789 [6]. In this manuscript Hahnemann demands systematic remedy provings on animals for correct

homeopathic practice in veterinary medicine. He recommended the formation of homeopathic veterinary schools with the possibility of keeping healthy animals for homeopathic remedy provings. However, homeopathic remedy provings on animals have been performed only fragmentary until today. The missing of a collection of species specific homoeopathic "remedy pictures" of the respective homoeopathic preparations (veterinary homeopathic Materia medica) lead to the often utilized transfer of symptoms of the human homeopathic "remedy pictures" to animal patients. Concerns regarding the transferability of symptoms of human "remedy pictures" to animals are among other reasons mainly based upon the considerable and specific differences between animal species [1].

Beneath classical (individualised) homeopathy, the term homeopathic therapy encompasses also non-individualised homeopathy and combined potentised remedies, often applied with clinical indications such as mastitis, pneumonia, vomiting, diarrhoea, cystitis. Isopathy, the prescription of potentised blood of sick individuals, as well as the prescription of potentised pathogenic agents in the case of an infection, intoxication or allergy by the same agent, is also considered as a variation of homeopathic therapy [7]. Homotoxicological [8] and some anthroposophic remedies also contain combinations of potentised substances [9].
Original substances of potentised medicines can be of animal, plant as well as mineral origin, but also synthetic substances and nosodes (spus, infectious agents or diseased organs) can be used. In Germany the Homöopathisches Arzneibuch HAB [10] provides for each remedy a particular manufacturing process, depending on the characteristics of the original substance. Potencies are diluted in decimal, centesimal steps (D-, and C-Potencies), as well as in millesimal steps (M-potencies) and fifty millesimal-step dilutions (Q- or LM-potencies). Each dilution step is followed by the conveyance of mechanical energy by agitation or rubbing. According to Hahnemann [2], the founder of Homeopathy, this process is believed to release dynamic forces, which should influence the self-healing process of the treated organism. The effect of potentised remedies is believed not to be mainly molecule-dependent, but rather induced by the dynamic forces of the remedies. In potencies higher diluted than Avogadros`s number (> D23 or > C12), it is not likely that any molecule of the original substance is present anymore. Especially the assumption of specific effects by these ultra high diluted remedies is a challenge for science based medicine [11, 12].

Despite worldwide discussions about the evidence of efficacy of homeopathic therapy, classical homeopathy in human medicine is practised all over the world, also in almost every

country of Europe [13]. There are, however, no publications about the prevalence of homeopathic treatments in veterinary medicine. One of the main reasons for the use of homeopathy in livestock is that no withdrawal periods have to be considered for most remedies. In addition, complementary and alternative therapies are prescribed in regulations on organic farming in the US (http://www.ecfr.gov/cgi-bin/text-idx?SID=bb0b76436b2c481d9f8927124b6bf07d&mc=true&node=se7.3.205_1238&rgn=div8), in Europe (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:189:0001:0023:DE:PDF, article 14(1) e) ii)) and in Switzerland (https://www.admin.ch/opc/de/classified-compilation/19970385/201401010000/910.18.pdf, article 16 (3)). The regulations prescribe the use of effective herbal or homeopathic products, minerals and trace elements for the treatment of farm animals in organic agriculture. Only if they are not available, synthetic, allopathic drugs may be used. Aim of these regulations is to reduce the application of antibiotics, hormones and other drugs. However, the claim that effective alternative treatments shall be used is problematic in terms of a scientific view and also regarding animal welfare aspects because the evidence for the efficacy of specific treatments is low to non-existent until now.

1.2 Scientific findings on homeopathy in human medicine

According to the concept of Evidence-based Medicine most reliable findings about efficacy of a therapy can be gained with the help of meta-analyses combining results of several reliable randomised controlled trials (Das deutsche Cochrane Zentrum (2014): Von der Evidenz zur Empfehlung (Klassifikationssysteme). http:/www.cochrane.de/de/evidenz-empfehlung; https://www.veterinaryevidence.org/index.php/ve/article/view/18). Several meta-analyses on humans have been published in the last 20 years in order to resolve the question if clinical effects of homeopathic treatments are placebo or specific effects.

Kleijnen et al. (1991) analysed 105 publications about clinical trials investigating the application of homeopathy in humans, including studies about classical homeopathy, prescription by established indication, combined potentised remedies and isopathy. They found a surprisingly positive evidence in favour for homeopathy in studies with high quality design as well as in low quality studies. However, the low methodological standard and unknown influence of publication bias prevented definitive conclusions about evidence [14].

Regarding the question if clinical efficacy of homeopathy is solely based on placebo effects, Linde et al. (1997) conducted a meta-analysis of placebo-controlled, randomised and/or double blind clinical studies on homeopathy. In total, 89 of 119 identified publications (about classical homeopathy, prescription by established indications, combined homeopathic remedies and isopathy) contained enough data to be included in the meta-analysis. The assessment of methodological quality was done by a self-developed evaluation system and by the Jadad-Score. The meta-analysis of all included 89 studies showed a significant higher effect of homeopathy compared to placebo (average odds ratio 2.45, Confidence interval 2.05-2.93). The sub-group analysis of the 26 high quality studies found a lower, but still significant efficacy of homeopathy compared to placebo (odds ratio 1.66; 95% CI 1.4-3.75). According to the authors a correction of the results concerning possible distortion caused by publication bias did not change the findings. The authors concluded the results are not compatible with the hypothesis that the clinical effects of homeopathy are completely based on placebo. However, they found only insufficient evidence in the analysed studies for efficacy of homeopathy for a single clinical condition and claimed that further rigorous and systematic research is necessary [15].

Another analysis of available publications by Linde et al. was conducted in 1999, building sub-groups as a function of the Jadad scale and an Internal Validity Scale (IVS). Superiority of homeopathy over placebo was partly declined for studies with higher quality according to the IVS, albeit homeopathy showed significant higher efficacy compared to placebo in all six sub-groups of the Jadad scale. Based on their analysis, Linde et al. concluded that studies with better methodological quality tended to yield less positive results, which weakens their conclusions of the 1997 review [16].

The systematic review of Cucherat et al. (2000) was part of a report for the European Parliament. This review took into account only experiments with potencies higher than C3, as well as preparations fabricated under the description “homeopathical”. The studies had to have one defined main outcome parameter. Studies without blinding were not excluded. Of 118 identified studies only 16 were included in the meta-analysis. Most of the excluded studies did not define a main outcome parameter or had major methodological deficits. Statistical parameter for the meta-analysis was the average significance (p-value). This was chosen because of the very heterogeneous study outcomes concerning diseases, prescription methods and outcome criteria. A combined p-value smaller than 0.05 was defined as rejection of the null hypothesis, meaning the homeopathic treatment effect differed significantly from placebo outcomes. Cucherat et al. found an overall result of $p = 0.000036$ and concluded that

the homeopathic treatment effect differed highly significantly from placebo. In a sub-group analysis, however, which included only the studies with a drop-out of less than 5% (n=5), homeopathic treatment effects did not differ significantly from placebo (p= 0.82). The reduction of the definition of methodological quality to the parameter drop-out led to the concluding assessment of the authors that there was only low evidence for the efficacy of homeopathic treatments compared to placebo, caused by low methodological quality of the studies [17].

Shang et al. performed another meta-analysis in 2005. In the pool of 110 studies, 21 studies with high methodological quality were found, 8 of these high quality studies were included in the final meta-analysis (combined odds ratio 0.88, 95% CI 0.65-0.85). The homeopathy studies were matched to 110 studies of a cochrane library about conventional medicine. 6 high quality studies of the comparison group were included in the final meta-analysis with a combined odds ratio of 0.58 (CI 95% 0.39-0.85). Shang et al. concluded bias in placebo-controlled trials of both homeopathy and conventional medicine, and found no significant evidence for specific effects of homeopathic remedies, but a significant evidence of conventional interventions, which led the authors to the conclusion that clinical effects of homeopathy were placebo effects [18]. The validity of the conclusion of the meta-analysis by Shang et al. was also under debate, because of several methodological deficiencies, such as the non-transparency of the selection of the final eight analysed homeopathic studies. Furthermore a sensitivity analysis was not performed, which could have revealed bias caused by study selection. A further critical point is the high heterogeneity combined with the small number of eight studies in the context of the concluded global statement [19].

A new meta-analysis about individualised homeopathy according to the state of the art of evidence-based medicine was conducted by Mathie et al. 2014 [20, 21]. He differentiated individualised (classical) homeopathy from clinical homeopathy, combined homeopathic remedies and isopathy, similar to the approach chosen by Linde [16]. They evaluated possibility for bias in 7 domains of methodological quality (blinding, randomisation, sponsoring, etc.) corresponding to the Cochrane criteria [22]. From 32 studies 22 were included in the final meta-analysis, and Mathie at al. found a significant positive result for homeopathy (odds ratio 1.53, CI 95% 1.22-1.91). The evaluation of bias, however, led to the classification that only 3 studies were reliable. The small data base of 3 trials with reliable evidence was found to be too small for a decisive answer about the efficacy of individualised homeopathy [21].

1.3 Scientific findings on homeopathy in veterinary medicine

Compared to human homeopathy, there are considerably less clinical studies on veterinary homeopathy.

Looking for evidence of the effect of homeopathy in veterinary medicine, Mathie et al. analysed the publication pool of studies in veterinary homeopathy [23]. Out of 150 publications retrieved, only 38 met the inclusion criteria for the review that were substantive report of a clinical treatment or prophylaxis trial in veterinary homeopathic medicine, randomisation and publication in a peer reviewed journal. 88 publications were rejected because they were not published in a peer-reviewed journal. The 38 included papers represented seven species (cows, pigs, dogs, horses, sheep, chickens and goats). Most of the 21 studies with a therapeutic approach were conducted on cows: 7 studies on mastitis, two studies on diarrhoea, and one study in tick infestation and reproductive disorders, respectively. Three studies on swine investigating homeopathic treatments of braditocia, puerperal disorders, and diarrhoea, respectively, were included. Also three studies on dogs assessing the effect of homeopathic treatments of arthrosis, pseudopregnancy and fear of noise, respectively, were evaluated. One study about deworming of sheep and one investigating the effect of homeopathic treatment of horses with lameness were included [23].

Also in publications on veterinary homeopathy for prophylactic approaches most studies were conducted on cows. Two studies dealt with bovine anoestrus and one study has been published each on the prevention of endometritis, on stress, on immune modulation, on tick infestigation and on infertility, respectively. Four studies on pigs researching the prophylactic effect of homeopathy on infectious diseases, diarrhoea, growth rate and reproductive performance were found, respectively.

Two studies investigated growth-promoting effects of homeopathy in chickens, one study investigated a homeopathic prophylaxis of endometritis in dogs, and in one study horses were treated prophylactically against stress [23].

For further evaluation of internal validity Mathie et al. divided the 38 included papers into two groups, distinguishing placebo-controlled randomised trials from randomised trials controlled by other than placebo (OTP) [24, 25]. Both groups included studies that investigated therapeutic and prophylactic effects by classical homeopathy or non-individualised homeopathic medication (single remedies, combined remedies, isopathy and homotoxicology). Using cochrane methods [26], the reviews aimed to assess risk of bias and to quantify the effect size of homeopathic intervention compared to placebo and to OTP,

respectively. Bias was evaluated by the assessment of seven domains: the method used to generate random sequence; the method of allocation concealment used to implement the random sequence; blinding a) of trial personnel, including animal owner as appropriate; blinding b) of outcome assessors; whether all randomised patients were completely accounted for in the analysis; evidence of selective outcome reporting; evidence of other bias, such as extreme data imbalance at baseline. Vested interest, like research funding or personnel employment or contract, was not taken into account for risk-of-bias assessment, but was reflected in the overall assessment of risk of bias for each RCT. Risk of bias was assessed as "low", "unclear" and "high". Evidence of a study was assessed as reliable, if there was no risk of bias in following domains: randomisation, blinding of trial personnel, blinding of outcome assessors and patients accounted for analysis [24, 25].

The first review [24] of medical conditions studied by randomised placebo-controlled trials included 18 studies. It represented four different species: cattle (10 studies), pigs (5 studies), dogs (two studies) and goats (one study), as well as 11 different medical conditions. There were large differences in sample size, outcome measures and trial endpoint timing. Mathie et al. judged eleven studies to be at high risk for bias. Six studies were assessed to have unclear risk of bias, four of them, however, did not meet the conditions for reliable evidence [24]. Only one study was found to have low risk of bias [27]. Hence, out of 18 studies only three were assessed as trials with reliable evidence [27-29], but the authors excluded a further one of them, because of potential vested interests due to the funding source [29]. This resulted in the end to draw the final conclusions based on two studies: (1) Hektoen et al. conducted a semi-cross-over trial with 39 cattle herds in eastern Norway, funded by the government. Animals with acute bovine mastitis were treated with individualised homeopathy. Mathie et al. extracted the data of this study for the precrossover timepoint and found a non-significant treatment effect (summary effect measure -31, 95% CI -0.97-0.34, p = 0.35) [27]. (2) Camerlink et al. investigated the prophylaxis of diarrhoea in piglets by treating the mother sows with 30K Coli-Nosode. The effect was statistically significant and favoured homeopathy (OR 3.89, 95% CI 1.19-12.68, p = 0.02) [28].

The third reliable study [29] was excluded because of potentially vested interests due to the funding source. It was funded by Homeopet, an American manufacturer of combined homeopathic remedies for pets, who is supporting research in evidence based medicine of veterinary homeopathic therapy (http://www.homeopet.com/uk/research). Cracknell et al. investigated the effect of a fixed formulation of 5 remedies (6C, 30C) on 35 dogs (versus 40

placebo-treated dogs) with fear of firework noises. After 4 weeks no significant improved fear responses were found (OR 1.28, 95% CI 0.46-3.57, p = 0.63) [29].

In the group of RCTs with low/uncertain risk of bias, extraction of data was possible for six out of seven studies. The results of all studies favoured homeopathy. The high heterogeneity of the studies did not allow disease specific meta-analyses of homeopathic treatment or prophylaxis [24].

In a further publication Mathie et al. conducted a meta-analysis using a random-effects model of the 18 placebo-controlled veterinary homeopathy studies [30]. The hypotheses that effects of homeopathic treatment in animals differ from placebo was tested for following groups and subgroups:

1. Homeopathic treatment or prophylaxis overall (18 studies)
2. Homeopathic treatment overall
    a. Effect of individualised homeopathic treatment (2 studies)
    b. Effect of non-individualised homeopathic treatment (10 studies)
3. Homeopathic prophylaxis overall
    a. Individualised homeopathic prophylaxis (0 studies)
    b. Non-individualised homeopathic prophylaxis (6 studies)

Data could be extracted from 15 of the 18 studies. Nine of the 15 studies were graded having a high risk of bias, six studies had low or unclear risk of bias. The effect size of the main outcome was regarded as the difference between the outcomes of homeopathy and the placebo groups at the pre-determined end-point of the trial, odds ratio with 95% CI for dichotomous measures and standardised mean difference (SMD) with 95% CI for continuous measures. Pooled odds ratio for all 15 trials (hypothesis 1) was 1.69 (95% CI, 1.12 - 2.56), p = 0.01. Odds ratio of hypothesis 1 (treatment or prophylaxis) for the two studies with reliable evidence was 2.62 (95% CI, 1.13 – 6.05), p = 0.02. There was evidence in favour of an efficacy of non individualized prophylaxis (odds ratio 3.89, 95% CI, 1.10 – 12.7), which is based on one study only. No evidence was found regarding hypothesis 2, 2a or 2b (treatment). Additionally, there was no evidence found for hypothesis 1, when analysis was limited to the 9 studies with high risk of bias. This outcome differs from the results of the meta-analysis by Linde et al. about human homeopathy RCTs [16] (1999), who found higher efficacy of homoepopathic treatments compared to placebo in lower quality studies than in high quality studies.

Based on their meta-analysis Mathie et al. concluded that very limited evidence can be identified that the effects of homeopathic treatment or prophylaxis in animals differ from placebo effects [30].

The latest review on veterinary homeopathy by Mathie et al. [25] evaluated the second group of the 38 clinical randomised studies found by previous literature search. The authors investigated the effects of a homeopathic treatment or prophylaxis controlled by other than placebo (OTP) using the same methodology as before. In this approach the effect of homeopathic therapy was compared to a conventional treatment, to no intervention, or homeopathy combined with conventional therapy was compared to conventional intervention alone. Again, the 20 studies were highly heterogeneous, representing 12 different medical conditions in 6 different species. Ten out of 20 studies were assessed to potentially be biased by funding interests. The authors found no study with clearly unbiased funding source.

The assessment of risk of bias was difficult for many of the studies, because of the shortcomings in the quality of reporting. No study was considered to have low risk of bias, 16 studies were graded having high risk of bias in one or more domains. The studies were lacking in blinding, allocation concealment and adequate randomisation. None of the 20 studies has been considered having reliable evidence.

The authors concluded that to date published OTP-controlled trials are incapable of providing useful additional insight into the effectiveness of homeopathic treatment or prophylaxis, due to their poor quality. New and substantially improved OTP-controlled research in individualised and non-individualised veterinary homeopathy is strongly called for [25].

Summarizing, it can be stated that the evidence of veterinary homeopathy bases on only two reliable peer-reviewed placebo-controlled RCT-studies and remains indecisive.

1.4 Basic research in homeopathy

Basic research in homeopathy can use uniform test organisms that enable randomised and blinded trials with big sample sizes under standardised experimental (laboratory) conditions. Such test organisms may be plants (whole plants, plant parts, semen), bacteria, yeasts, cells, but also cell-free systems (e.g. using enzymes). Animal models allow preclinical research for human or veterinary medicine. Biological models of homeopathic basic research aim to investigate the scientific evidence for specific effects by potentised remedies, the similia principle, a possible relationship between potency level and effect, as well as potentisation as

a pharmaceutical technique. Physicochemical research in homeopathy investigates for example the structure of potentised preparations.
A comprehensive collection of scientific publications about basic research in homeopathy can be found in the HomBRex database of the Karl and Veronica Carstens Foundation (Essen, Germany) (www.carstens-stiftung.de/hombrex/). The HomBRex database contained in the year 2013 1383 publications about homeopathic basic research studies [31]. By the end of September 2016 a total of 2211 homeopathic basic research experiments in 1659 original publications were indexed (www.carstens-stiftung.de/hombrex/).

1.4.1 Scientific findings on homeopathy in laboratory animals

In the field of homeopathic basic research using laboratory animals no current meta-analysis has been published. Most frequently used animals were rats and mice. Van Wijk et al. [32] gives an overview about the use of rats in treatment studies on homeopathic basic research. The artificial induced diseases (intoxication, behavioural disturbance, edema/inflammation, itching, cancer, diabetes, arthritis, wound) were treated homologous (isopathic) or heterologous (similia principle), respectively.
In a systematic review Linde et al. [33] (1994) evaluated 105 experimental homeopathic basic research studies on toxicology, including *in vivo* or *in vitro* studies using animals, but also plants, isolated organs, cell or embryo cultures. A quality evaluation system (QE) consisting of 24 to 31 criteria was used to rate the quality of the reported efficacy of homeopathic interventions. A protection index (PI) was calculated from the raw data of each study, defined as the mean outcome from the control group minus the mean outcome of the treatment group divided by the control means times 100. The PI-scores of all interpretable studies with QE over 40% were compared. In addition, a meta-analysis was conducted including only studies, which complied with the following criteria: same toxin used, identical dose and route of administration, identical preparation of potencies and dilution level, identical outcome measures, at least 50% QE, as well as a minimum of 3 qualified experiments.
Out of 105 studies 28 studies with QE scores over 50% showed significant differences compared to the controls. 26 studies (11%) met the criteria for meta-analysis: Twelve independent studies investigated the effect of Arsenicum album 7C in subclinically arsenic-poisoned rats. The protective index of the combined data showed increased arsenic urinary elimination (19.6%, 95 CI 6.9-32.4%) as well as increased faecal elimination (25.5%; 95 CI

8.9-42.1%) compared to control. Blood level of arsenic was reduced by 6.1% (95 CI 3.2-9.2%) compared to control.

Nine studies evaluated the effect of mercury 15C and five studies the effect of mercury 9C injected daily into mice poisoned with a lethal dose of mercury. Survival as outcome parameter was measured after 10 days. Evaluation of the combined data showed a mean reduction of mortality of 40% (95 CI 21.8-58.1%) for the 15C group and 7.2% (95CI -10.1.24.6%) for the 9C group, respectively [33]. An interesting approach in this review is to calculate a meta-analysis not over the heterogeneity of all studies, but for subgroups of studies, which were identical in treatment and complied with defined method quality criteria.

Bellavite et al. published 2009 a review about the use of homeopathic remedies in rodent behavioural and psychopathological models. Eighteen studies were found which investigated the effect of homeopathic potencies on mice and rats in behavioural tests, which are also routinely used in tests of conventional psychotropic drugs. The main focus of this review was to identify appropriate models and tests for preclinical homeopathic research regarding emotional or behavioural problems. Little information is given about detailed methods and statistics, as well as validity of the results [34].

An alternative model is the use of tadpoles from *Rana temporaria*. It was found that Thyroxin 30x induces an inhibiting effect on the metamorphosis of the tadpoles. This effect was internally and externally reproducible, and in a meta-analysis of 26 studies performed across a 20 year period found to be statistically significant [35].

1.4.2 Scientific findings in homeopathy using *in vitro* models

A review about basic research in potentised preparations using *in vitro* assays was published in 2007 by Witt et al. [36]. 67 studies using cell free systems (e.g. encymatic models), cell cultures and models with bloodcells were identified. Several replication studies and a multicentre study were conducted with the model of inhibition of human basophil degranulation by potentised histamine [37]. Effective potency levels of a series of potencies differed between internal and external replications [38, 39].

1.4.3 Scientific findings using physical-chemical approaches

In 2003 a review on physico-chemical investigations was published, which included 36 experiments found in 44 publications [40]. Half of the studies were conducted using nuclear

magnetic resonance (NMR). The results were assessed to be reproducible over several studies. Several studies on NMR relaxation found consistent differences between Silicea potencies and agitated control preparations [41], but there was no evidence for stable water clusters [42, 43] that are believed to exist by some homoeopaths [44]. Also studies with UV-spectroscopy found differences between potentised preparations and controls [45]. In addition to NMR relaxation and UV-spectroscopy many different methods have been used in the field of physico-chemical basic research on homeopathic potencies. Only few studies have been published that used electrical impedance, electrochemistry, Raman-spectroscopy, and methods that may lack plausibility [40].

A current systematic review identified by the end of 2015 a total of 155 publications on physico-chemical investigations on potentised preparations [46]. The literature was evaluated by an international expert panel. Publication quality was evaluated using an adapted Manuscript Information Score (MIS), 0 to 2 points are given for lacking, less or more detailed information about experimental procedure, materials, measuring instruments, potentisation method, and controls, respectively. From 155 publications, 109 had a MIS higher or equal to 5. Physico-chemical methods used were NMR (H, C), spectroscopy (UV, VIS, IR, FT-IR, Raman), luminescence, delayed luminescence, thermoluminescence, fluorescence, conductivity, calorimetry, pH, atomic force microscopy, and transmission electron microscopy [46].

1.4.4 Scientific findings in homeopathy using plant models

This dissertation belongs to the field of homeopathic basic research with plants. Compared to animal tests, plant bioassays provide several advantages like easy standardisation of test systems and the avoidance of ethical issues. Due to the lack of information about the current state of basic research in homeopathy with plants, a systematic review project was planned by an international working group. The project was split into three systematic reviews about bioassays with healthy plants, phytopathological models and toxicological plant models [47-49].

The review about basic research in homeopathy with healthy plants (whole plants, plant parts and cells) is the first part of this dissertation [47]. Publications from 1920 to 2009 in English, French, German, Italian, Portuguese and Spanish were included. A Manuscript Information Score (MIS) was developed to evaluate if sufficient information was given in the publications to allow proper interpretation (MIS $\geq$ 5). The developed Study Methods Evaluation Procedure (SMEP) was an instrument to evaluate included studies systematically and extract studies with adequate controls to identify specific effects by homeopathic potencies. Eighty-six

studies were identified in 79 publications, 43 studies included statistics, 29 studies had MIS ≥ 5 and were further evaluated with the help of the SMEP. The methods of 15 studies were appropriate to investigate the specificity of homeopathic potencies [47].

Over all three plant reviews 167 experimental studies in 157 publications were found, 48 of these studies showed high methodological quality. Most frequently used plants were wheat, duckweed and peas, most often used substance for stress induction was arsenic (similar to toxicological animal models). Silver nitrate was the most frequently used substance, followed by arsenic and gibberellic acid. Specific effects were found with potencies below and above the inverse Avogadro number. No linear relationship between potency level and effect found in investigations with serial potencies was observed in any of the studies. Many individual trials with diverse methods and only few replications or reproduction trials were identified [50], which may be an indicator for difficulties with reproducibility.

The diversity of study methods in homeopathic basic research reflects a mainly explorative research approach. In addition, the plurality of methods makes it difficult to compare results and to assess evidence for specifity of potentised preparations. Studies on the internal or external reproducibility are important to validate homeopathic basic research and to conduce to the development of appropriate research models and methods. The lack and the importance of investigations on reproducibility of homeopathic effects led to the decision to conduct, as second part of this dissertation, investigations on the internal reproducibility of results by potentised substances with a *Lemna gibba* L. plant bioassay by Scherr et al. [51, 52].

Overall, valid scientific data for the efficacy of homeopathy is hardly available. This is mainly due to the limited number of publications, the low quality and a high heterogeneity of the reseach methods applied and different aims of the single studies. Regarding the presented reviews and meta-analyses it has also to be taken into account that most projects were performed by very few research groups, which may be a possible source of bias.

2. Research papers

2.1 Review:

Use of homeopathic preparations in experimental studies with healthy plants

Vera Majewsky, Sebastian P. Arlt S, Devika Shah, Claudia Scherr, Tim Jäger, Stephan Baumgartner

Homeopathy, 2009;
Volume 98, Number 4,
Pages: 228-243

DOI: https://doi.org/10.1016/j.homp.2009.09.012

2.2 First experimental investigation:

Reproducibility of effects of homeopathically potentised gibberellic acid on the growth of Lemna gibba L. in a randomised and blinded bioassay

Vera Majewsky, Claudia Scherr, Sebastian P. Arlt, Jonas Kiener, Kristina Frrokaj, Tobias Schindler, Peter Klocke, Stephan Baumgartner

Homeopathy, 2014;
Volume 103, Number 2,
Pages: 113-126

DOI: https://doi.org/10.1016/j.homp.2013.12.004

2.3 Second experimental investigation:

Reproducibility of the effects of homeopathically potentised *Argentum nitricum* on the growth of *Lemna gibba* L. in a randomised and blinded bioassay

Vera Majewsky, Claudia Scherr, Claudia Schneider, Sebastian P. Arlt,

Stephan Baumgartner

Homeopathy, 2017

Volume 106, Number 3,

Pages: 145-154

DOI: https://doi.org/10.1016/j.homp.2017.04.001

3. Discussion

3.1 General aspects

As stated earlier, in all research fields of human and veterinary medicine and also in basic research the scientific evidence of specific effects of homeopathic preparations is weak. Hence, more rigorous research has been called for by many authors in the last decade [23, 53-57]. Sufficient evidence concerning the efficacy of homeopathic interventions has been demanded by several organisations and would be a prerequisite for broader acceptance and legalisation of homeopathy as complementary medical therapy, in humans as well as in animals [57].

Research in veterinary homeopathy may provide information about the evidence of homeopathic diagnosis and therapy in general [54]. Basic research in homeopathy may also help to identify the existence or non-existence of possible mechanisms of action of homeopathic preparations. Adequate scientific methods have to be developed that meet the requirements of valid research and also specific aspects of homeopathy. In that regard these methodologies should adequately address all significant possible sources of bias [58].

Basic research in homeopathy aims to investigate basic questions concerning specific aspects of homeopathy in general. This includes for example investigations on the efficacy of high and ultrahigh diluted potencies or the similia principle. One of the most important aims of homeopathic basic research is to develop appropriate models enabling future research in stability, storability or the pharmaceutical and biological mode of action of homeopathic remedies.

3.2 Review:

Use of homeopathic preparations in experimental studies with healthy plants [47]

The first part of the present thesis is a systematic literature review of homeopathic studies with healthy plants and was published in 2009 [47]. In the same year the Cochrane collaboration started a project to evaluate the first version (2008) of a new tool for assessing risk of bias in randomised trials. Aim of this tool is to support judging the reliability and evidence of RCT that are included into systematic rewiews and meta-analyses [59]. The tool has also been used for the evaluation of human and veterinary RTCs in homeopathy [24, 30, 60]. It was, however, not specifically developed to assess risk of bias in preclinical or basic research studies. Nevertheless, many issues that are covered by the tool are also important for the validity of

laboratory experimental studies. In that regard the present review will be discussed in context of the new Cochrane Collaboration tool.

The tool addresses six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and bias of other origin [59]. It furthermore recommends to focus on internal validity when appraising the quality of a clinical trial, meaning to examine to which extent study methods were chosen to avoid bias. Outcome specific risk of bias and risk of bias in the data as represented in a review rather than as originally reported has to be considered [59].

The review included in this thesis did focus on the assessment of risk of bias in a similar way, even if some of the systematic judgements suggested by Higgins et al. were not feasible. During literature research and a first reading of articles, aspects of good scientific practice as well as important special topics of homeopathic basic research with plants were reflected, considering theoretical and empirical issues. Instruments were developed which supported a systematic selection of publications as well as structured evaluation of manuscript information and study methods. Main aim was to appraise the current state of homeopathic basic research with healthy plants and to identify studies with appropriate methods to investigate specific effects of homeopathic preparations. Further aims were to extract and collect as much information about studies as possible. This dataset may be used in preparation of future studies that can be based on research findings and open questions of prior work. In addition, this synthesis of knowledge may help to identify promising and appropriate plant models for future basic research.

Due to the fact that high reporting quality of publications is crucial for evaluation of studies and internal validity in a review [61, 62], reporting quality (MIS) and methods quality (SMEP) were assessed separately.

For assessment of reporting quality rating points were given and summed up to an overall MIS score. Based on the score publications were selected which contained appropriate detailed information to be evaluated in a second step (MIS $\geq$ 5). This systematic approach aimed to be as objective as possible, leading to the outcomes: complete information, some information or no information on specific features such as experimental setup, materials, the measuring instruments and procedures, the potentisation procedure and the controls used. Many important study features were only described partly. Most predominant weak reporting was identified in the fields: materials, measuring procedures and potentisation.

For the appraisal of methods used in the studies, the following items of the experimental setup were evaluated using the Study Methods Evaluation procedure (SMEP): randomisation,

blinding, sorts of controls, number of independent experiments and the use of systematic negative control experiments. Thus, this procedure evaluates different aspects of internal validity. In the SMEP no rating points were used as suggested by Higgins et al.[59] An overview about SMEP results, models, treatment and results of the studies is given in table 2 and table 3 of the review.

A systematic presentation of reporting quality was not shown in this review. Including this could have provided information about common possible sources of reporting bias that could have been addressed in future publications on homeopathic research. In addition, the results might have been useful in terms of a tighter distinction between publication quality and study methods quality.

A systematic judgement of the different plant models, the methods used as well as outcome specific risk of bias could have furnished valuable additional information for the planning of future studies.

Assessing the reliability of statistics as well as a new calculation of study outcomes was beyond the aims of the present review, since no quantitative meta-analysis was planned. Until now, only one review on homeopathic basic research has been published which included newly calculated, comparable outcomes and a quantitative meta-analysis [33]. Regarding the shortcomings in internal validity and the heterogeneity of publications on homoeopathic basic research on plants to date, a quantitative meta-analysis in this field was beyond of scope.

A short methodological comparison of a systematic review of medical conditions studied by randomised placebo-controlled trials in veterinary medicine by Mathie et al. 2014 [24] and the presented systematic review [47] will be discussed in the following. A comparison is worthwile because in both research fields the publications are highly heterogeneous in terms of plant or animal species, treated conditions or diseases, and different homeopathic potencies and potency levels. In addition, the review by Mathie et al. included also publications on combined homeopathic and homotoxicological remedies.

Both reviews led to the finding that indexing of publications in online literature databases is fragmentary. Only 15 of 38 eligible publications on veterinary RTCs on homeopathy were found in PubMed [63] and only very few publications on homeopathic basic research in plants were indexed in a standard database [47]. For both research fields the KVC Foundation provides specific databases that contain comprehensive collections of the international available research literature (HomVetCR database:

http://www.carstens-stiftung.de/clinresvet/ and HomBRex database: http://www.carstens-stiftung.de/hombrex/). Reporting as well as study method quality was considered low in both fields. Both reviews were the first systematic reviews of the literature in both of the research fields, respectively.

Expecting higher quality of trial methods and reported information by the peer review process, Mathie et al. included only peer-reviewed publications about RTCs in veterinary homeopathy [63], 75% of the detected literature was excluded from further evaluation, almost half of the not peer-reviewed, excluded literature were theses. In the presented review, peer-review was not evaluated [47]. Selection was based on pre-defined criteria: outcomes measuring by established methods, basic statistics and a Manuscript Information Score ≥ 5 were required. In total 66% of the identified publications were excluded. Both reviews depicted the selection process in a graphic flowchart [24, 47]. Review-methods were determined by the aims and reported in detail in both reviews, respectively. Mathie et al. [24] gives comprehensive information about possible bias in the veterinary studies. The presented review [47] gives a comprehensive overview as well as details of the evaluated heterogeneity of the studies, focusing on studies with appropriate controls to identify specific effects of homeopathic potencies, with the aim to provide a basis for future research (in the sense of a working paper).

Mathie et al. [24] used established Cochrane methods to extract a comparable pool out of the heterogeneity of the initially identified studies. For example, total sample size and associated outcome for studies that comprised more than one homeopathy group was cited calculating the sum of all subjects in the homeopathy groups, and "main outcome measure" was newly defined based on a WHO ranking order, what led also to new single endpoint measures. In general, it can be questioned if levelling and recalculating results from a heterogeneous pool of RCTs is feasible and reliable. It is recommended for future meta-analyses to focus on the use of homeopathy in specific diseases or groups of diseases instead of pooling data from very heterogeneous clinical trials [64]. An example for application of this practice in the field of homeopathic basic research is the critical review and meta-analysis of Linde et al. [33], who calculated outcomes only for subgroups of studies which were identical in treatment and complied with defined method quality criteria.

The low publication and study quality of many of the peer reviewed studies evaluated by Mathie et al. [23, 24, 30, 60] and by the review presented in this thesis [47] should not only initiate

improvements in study planning in homeopathic research, but should also lead to improvements of the peer review processes to raise publication quality of future work.

The PRISMA Statement [62] defines a systematic review as a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that were included in the review. The pre-defined aims of the presented systematic review [47] are short-termed and long-termed. Appropriate methods were systematically used to reduce possible bias. The review shows the importance of research field specific manuscript information features, depicts particularised different plant models for homeopathic basic research as well as necessary methods to enable research on specific effects of homeopathic remedies. Studies investigating specific effects of homeopathic potencies are presented. It discussed specific problems of the research field (manuscript information content, appropriate controls and methods quality, potentisation methods), and research questions found (outcome parameter, possible differing efficacy of different potentisation methods, reproducibility of effects), and gives concrete advice for future research such as implementation of systematic negative controls to prove system stability, simple and easy transferable plant models for investigations in reproducibility and the potentisation process, the usage of standardised potentisation techniques.

3.3 Experimental part:

Reproducibility of effects of homeopathically potentised gibberellic acid on the growth of Lemna gibba L. in a randomised and blinded bioassay [65]

Reproducibillity of the effects of homeopathically potentised Argentum nitricum on the growth of lemna gibba L. in a randomised and blinded bioassay [66]

After several years of exploratory research in homeopathic basic research with plants using different plant models, the reproducibility of the results produced by the test systems was to be examined. This was one major result of the review conducted. The studies by Scherr et al., who developed a bioassay using *Lemna gibba* L. for homeopathic basic research, appeared to be a good test system to assess because of the high quality of the applied methods and the uniform test organism [51, 52, 67]. The second part of the thesis encompasses, therefore, two studies on the reproducibility of effects by homeopathically potentised gibberellic acid and silver nitrate, respectively, on the growth of *Lemna gibba* L. in a blinded and randomised bioassay [65, 66].

Both studies were carried out with high quality methods, appropriate to investigate possible specific effects of potencies. Systematic negative control experiments confirmed the standardisation of laboratory conditions and the stability of the experimental set-up. Comprehensive information about all relevant features of the studies is given in the manucripts. Results were complex, gibbosity, a specific growth state of *Lemna gibba*, appeared to be a crucial parameter influencing reproducibility, variability was found as interesting outcome indicating different remedy effects [65, 66]

Despite good study quality also in these two publications shortcomings can be identified. In both published studies no information was given how concealment of the blinding code was done. This can be judged as unclear risk of bias in the domain "allocation concealment" by external reviewers. Blinding and randomisation was carried out by different external persons, by taping a double letter code on top of the bottle number, so that this was concealed. The person blinding enclosed the code list in a sealed envelope, which was brought to and stored at another institute (S. Baumgartner) in a city 43km apart.

Further risk of bias might originate from the fact that blinding of the randomisation codes was revealed for statistical evaluation (but not for any measurement). Study setup was pre-defined. In studies investigating one potency level of a homeopathic remedy compared to one control, statistical analysis can easily be analysed blind. A blinding during the statistical calculations of 19 groups including 2 controls, which should be pooled in the case of no significant difference between the single groups, requires more effort. By the use of a pre-defined statistical procedure (parametrical two way analysis of variance (ANOVA, $\alpha = 5\%$)), risk of bias was reduced [65, 66].

For a possible procedure providing complete blinding in future studies at least two conducting persons and a modification of the experimental setup would be required, including a triple-step-blinding-procedure and giving the SNC experiments a new relevance. First and second blinding step: A person not included in all other work of the study conduction would have to prepare potencies or SNC preparations and encode them for example giving a fixed name for SNC experiments and for potency experiments (1), respectively, and additionally a fixed number code (2) (1, 2, 3, 4, etc. for C_0, C_1, 14x, 15x, etc. or W_1, W_2, W_3, W_4, etc., respectively). The second person, carrying out the experiments as well as statistical analysis, would have to be blinded to the sort of experiment what means, she or he would not be informed if she or he carries out a SNC or a potency experiment, respectively. Blinding of the outcome assessors and the statistical evaluation could be realised by a third and fourth

blinding step, carried out by an external person. Third blinding step (3): coding potencies and controls with the letter code (AA, BB, CC, etc.), as we did in our studies. This blinding is necessary for randomisation of the Lemna-vessels allocation in the growth chamber as well as the measurements by the LemnaTec Scanalyzer. The fourth blinding step could enable blinded statistical calculations (4): For example could the code for control groups be allocated pre-defined, e.g. for succussed and unsuccussed control as well as W_1 and W_2 of SNC experiments always XX and YY (given randomly). For potencies as well as SNC-solutions a flexible code could be given randomly. All four blinding codes have to be concealed by external supervisors. For a blinded statistical evaluation the first code (1) would have to be unrevealed to be able to group potency and SNC experiments, moreover the fourth code for calculating possible succussion effects comparing control groups and calculating the F-test for potencies compared to control. The statistician would not know if she or he evaluates a potency or a SNC experiment. Second (2) and third (3) blinding code must be opened not until after the statistical analysis.

Comparing validity of both studies, reliability of the first publication [65] is higher than reliability of the second study [66], due to different sample sizes in the second study. Additionally, in one series of the second study [66] a significant difference as well as a significant interaction of succussed compared to unsuccussed control group was detected, though until then and never thereafter a succussion effect was found in any of the studies of homeopathic basic research using the *Lemna gibba* L. bioassay. This "irregular" succussion effect was regarded as an artefact of unknown origin. It can, however, not be interpreted as system instability because system stability was proved by the SNC experiments. The ANOVA F-test treatment (*Argentum nitricum* potencies compared to succussed control) was significant in the same study. The Fisher LSD-Test identified 28x as effective potency level. This was the only significant treatment effect of *Argentum nitricum* in this study. Retrospectively it can be discussed, if it is feasible that the significant effect of the succussed control was assessed as artefact while the significant treatment effect by one potency level was not classified as possible artefact. The difference between these two results is, however, that the irregular succussion effect of the water controls c0/c1 was found in only one experiment, while the significant treatment effect was found in a whole series of experiments.

Both studies were funded in parts by an anthroposophic pharmaceutical company (producer of potentised anthroposophic medicines). The sponsors, however, were not involved in planning of the study protocols nor in statistical evaluation, interpretation of the results or drafting the publications [65, 66]. Nevertheless, it is important to give this information for full transparency.

This has been done in all publications. However, both studies might be judged to have high risk of bias concerning vested interests by funding source by external reviewers. Financial ressources in homeopathic research are small, funding of studies in homeopathy is challenging. It is difficult to find financial or material support for research projects in homeopathy beyond groups that are interested in any form in therapies using potentised medicines. The situation appears to be reduced to absurdity, considering the systematic reviews of Mathie et al. [23, 24, 30, 60], who assessed all studies with funding of homeopathic pharmaceutical companies (financial support or only material support in form of homeopathic remedies) as not reliable because of vested interests, but the authors of the reviews were both employed by a homeopathic charity themselves and they are interested in extension of evidence base in homeopathy.

3.4 Outlook

The three publications of the systematic review of the literature of homeopathic basic research using plant-based bioassays [47-49] were based on an international cooperation with the aim to assess the current state of research as well as to further develop quality of homeopathic basic research. The REHBAR guidelines [61] were developed and published with the aim to raise quality of future reporting practice. Further reviews evaluated current state of research in further fields of homeopathic basic research [68-72]. Focusing reproducibility, an overview about replication studies in homeopathic basic research has been published by Endler et al. [73]. Further investigations on internal and external reproducibility of results were conducted using the wheat germination model (simple and easy transferable model) [74, 75]. One of these studies revealed data about system performance controls, proving stability of laboratory conditions [74]. Consequent implementation of high quality standards of methods for the wheat germination model in future studies appears important to raise reliability of the studies using this model.

Distinguishing specific effects of homeopathic remedies from random noise needs particularly high standardisation of the experimental systems. Systematic negative control experiments allow proving system stability and reliability of the results. Apart of the *Lemna gibba* bioassay the use of systematic negative control experiments did not become a common part of homeopathic basic research practice until now.

The *Lemna gibba* L. bioassay was modified by Jäger et al., who developed a test system using impaired duckweed [76]. In their investigations on the effects of potentised *Arsenicum album*, nosode and gibberellic acid on the growth rate of arsenic-impaired Lemna gibba, they found

an increase of growth rate by *Arsenicum album* and nosode potencies [77]. The study included systematic negative control experiments. Further the *Lemna gibba* L. bioassay was modified, investigating the effect of a homeopathic treatment of calcium-deficiency in the cultivation medium of the plants (unpublished data, personal communication B. Lutz). Further investigations in homeopathic basic research with healthy plants of *Lemna gibba* L. were not carried out until now. The experiments with potentised gibberellic acid and *Argentum nitricum* for the treatment of healthy *L. gibba* have not been further repeated. More research would be needed to prove the conclusion that gibbosity enhances the reactivity of *L. gibba* to homeopathic potencies. To what extent the results of the two studies can be transferred to other plant or animal species remains open.

Potential risk of bias has to be considered when planning and evaluating homeopathic basic research studies. In addition, the specific issues of homeopathic basic research have to be addressed to improve future study quality. Enhanced high quality research is highly demanded. A standardised basic research model may in future foster research on many other open research questions. These encompass for example doubted efficacy of high and ultrahigh diluted remedies, the mode of action, the transferability of human remedy pictures to animals, the stability related to external influences, storability, as well as possible influence of different established potentisation techniques on efficacy.

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5. Summary

Basic Research in Homeopathy –
Development of Plant Bioassays to Investigate Effects of Potentised Preparations

Homeopathy is used worldwide in human- as well as in veterinary medicine, though its effectivity is controversially discussed. This dissertation focuses on the interdisciplinary research field of basic research in homeopathy. It investigates the possibility of specific effects of homeopathic preparations in scientific experiments with healthy plants. A comprehensive literatur review was followed by two experimental studies.

Review:

The systematic review about experimental research on effects of homeopathic treatments on healthy plants aimes to give a comprehensive overview about the state of research between 1920 and April 2009, with particular focus on studies investigating specific effects of homeopathic remedies. The literature search included publications in English, German, French, Italian, Spanish and Portoguese, using predefined selection criteria. Studies with healthy whole plants, seeds, plant parts and cells were included. Outcome had to be measured by established procedures and assessed by a statistical evaluation. A Manuscript Information Score (MIS) was developed to include only publications providing enough information for proper interpretation (MIS $\geq$ 5). A Study Methods Evaluation Procedure (SMEP) was used to evaluate the latter studies, and the subgroup of studies with adequate controls to identify specific effects.

A total of 86 studies in 79 publications were identified. Only 43 studies included statistics, 29 of the 43 studies had a MIS $\geq$ 5, and 16 of these 29 studies were investigating specific effects of homeopathic preparations. Specific effects of decimal, centesimal and fifty millesimal potencies were found, also in dilutions far beyond the Avogadro number. In consecutive series of potency levels only some of the tested potencies showed effects. In conclusion, studies showed heterogenous methods and outcome measures and very few studies included investigations concerning reproducibility of outcomes.

Healthy plant models are regarded to be a promising approach to investigate basic research questions about the specificity of homeopathic preparations by many authors. However, there was a lack of investigations with valid methods, especially studies focusing potentisation techniques, effective potency levels and conditions for reproducibility were lacking.

Experimental work:

Based on the results of the review experimental studies focusing reproducibility of specific homeopathic effects were performed.

The first study investigated if formerly observed effects of homeopathically potentised gibberellic acid in a bioassay with healthy duckweed (*Lemna gibba* L.) were reproducible. Duckweed was grown in potencies (14x–30x) of gibberellic acid (GA_3) and one time succussed and unsuccussed water controls. Outcome parameter area-related growth rate was determined by a computerised image analysis system. Three series including five independent blinded and randomised potency experiments each were carried out. System stability was controlled by three series of five systematic negative control (SNC) experiments. Gibbosity (a specific growth state of *L. gibba*) was investigated as possibly essential factor for reactivity of *L. gibba* towards potentised GA_3 in one series of potency and SNC experiments, respectively. Results were heterogenous: Only in the third series with gibbous *L. gibba* a significant effect ($p=0.009$. F-test) of the homeopathic treatment was observed. Additionally, growth rate increased in contrast to the former study, and effect of most biologically active potency levels differed. Variability in potency experiments was lower than in SNC experiments. The stability of the experimental system was verified by the SNC experiments.

The second study investigated laboratory-internal reproducibility of formerly observed effects of homeopathically potentised Argentum nitricum using the Lemna gibba bioassay. A previous study reported a significant statistical interaction between experiment date and treatment effect of *Argentum nitricum* 14x–30x on the growth rate of duckweed.

According to the first study duckweed was treated with *Argentum nitricum* potencies (14x–30x) as well as succussed and unsuccussed water controls. The outcome parameter area-related growth rate for day 0–7 was measured by a computerised image analysis system in two experimental series, including six and three independent randomised and blinded experiments. Systematic negative control experiments were carried out to investigate system stability. Statistical analysis was performed with full two-way ANOVA and protected Fisher`s LSD test.

The results of the former study could not be reproduced: In the first experimental series a significant treatment effect ($p=0.016$) was observed, while in the second series no effect was found. The stability of the experimental system was verified by systematic negative control experiments. An *a posteriori* subgroup analysis concerning gibbosity revealed the importance of this growth state of *Lemna gibba* for successful reproduction of the statistically significant

interaction in the original study; flat: (p=0.762); slight gibbosity: (p=0.256); medium gibbosity: p=0.031, high gibbosity: p=0.005.
Both studies showed that gibbosity could be one parameter influencing reproducibility of the homeopathic studies with *Lemna gibba* L.. With the original study design (disregarding gibbosity status of *L.gibba*) results of the original studies could not be reproduced. Different physiological states of the test organisms used for bioassays for homeopathic basic research must carefully be considered.

6. Zusammenfassung

Grundlagenforschung Homöopathie – Die Entwicklung von Pflanzen-Bioassays für die Untersuchung homöopathischer Arzneimittel-Effekte

Homöopathie ist eine in Human- und Tiermedizin weltweit angewendete, jedoch betreffend ihrer Wirksamkeit umstrittene Therapie aus dem Bereich der Komplementärmedizin. Diese Dissertation befasst sich mit wissenschaftlichen Untersuchungen im Bereich der Homöopathie-Grundlagenforschung. Es wurde untersucht, inwieweit sich pflanzliche Testsysteme für wissenschaftliche Experimente zu spezifischen Arzneieffekten von homöopathischen Präparaten eignen.
Review:
Ein systematisches Review befasste sich mit Studien über Effekte homöopathischer Präparate auf gesunde Pflanzen aus den Jahren 1920 bis 2009, mit dem Ziel, einen umfassenden Überblick über den Forschungsstand zu geben und solche Studien zu identifizieren, die spezifische homöopathische Arzneimittelwirkungen untersuchten.
Die Literatursuche beinhaltete Publikationen in Englisch, Deutsch, Französisch, Italienisch, Spanisch und Portugiesisch und basierte auf vordefinierten Selektionskriterien. Studien an gesunden Pflanzen, Pflanzensamen, Pflanzenteilen und Pflanzenzellen wurden eingeschlossen. Die Outcome-Parameter mussten mit etablierten Methoden gemessen und statistisch ausgewertet worden sein. Es wurde ein Manuscript Information Score (MIS) entwickelt, mit dessen Hilfe die Studien selektiert wurden, welche ausreichend Informationen im Manuskript beinhalteten, um im weiteren Reviewprozess angemessen beurteilt werden zu können (MIS $\geq$ 5). Eine Study Methods Evaluation Procedure (SMEP) wurde entwickelt, um

die eingeschlossenen Studien genauer zu evaluieren und die Studien mit adäquaten Kontrollen für die Untersuchung spezifischer Effekte zu identifizieren.

Insgesamt wurden 86 Studien in 79 Publikationen identifiziert. Nur 43 Studien beinhalteten statistische Auswertungen, 29 der 43 Studien hatten einen MIS ≥ 5, und bei 16 der 29 Studien war die Methodik hinreichend, um spezifische Arzneimitteleffekte der homöopathischen Präparate zu untersuchen. Es wurden spezifische Effekte von Dezimal-, Centisemal- und 50-Millisemal-Potenzen postuliert, also auch in Verdünnungsstufen weit über der Avogadro`schen Zahl. Wurden Potenzstufenreihen untersucht, so zeigten nur einzelne der Potenzstufen Effekte. Im Gesamten betrachtet stellen sich die publizierten Studien hinsichtlich der Fragestellungen und der Methoden heterogen dar. In nur wenigen Studien wurde die Reproduzierbarkeit der Ergebnisse untersucht. Die gesunde Pflanze könnte nach Ansicht vieler Autoren ein geeignetes Modell sein, um Fragestellungen der Homöopathie-Grundlagenforschung über die Spezifität homöopathischer Präparationen zu untersuchen. Jedoch besteht ein Mangel an Forschungsarbeiten mit qualitativ hochwertigen Methoden. Insbesondere fehlen Studien, welche die verschiedenen Potenzierungstechniken, effektive Potenzstufen einer Reihe und Bedingungen für die Reproduzierbarkeit der Ergebnisse untersuchen.

Experimenteller Teil:

Basierend auf den Ergebnissen des Reviews wurden experimentelle Studien mit dem Schwerpunkt Reproduzierbarkeit spezifischer homöopathischer Effekte durchgeführt

Die erste Studie untersucht die Reproduzierbarkeit vorher beobachteter Effekte mit homöopathisch potenziertem Gibberellin (GA_3, Pflanzenhormon) in einem Bioassay mit *Lemna gibba* L. (Wasserpflanze, Wachstum über vegetative Teilung). Die Pflanzen wurden in den Gibberellin-Potenzen (D14-D30) kultiviert, sowie in zwei Wasserkontrollen mit verschütteltem und unverschütteltem Wasser. Der Outcome-Parameter, die auf die auf die Frond-Oberfläche bezogene Wachstumsrate von Tag 0-7, wurde mit einem digitalen Bildanalyse-System gemessen. Die Daten wurden mit Hilfe der zwei-Wege ANOVA und dem geschützten Fisher`s LSD-Test statistisch ausgewertet. Drei Serien mit je fünf unabhängigen, verblindeten und randomisierten Potenz-Experimenten (PE) wurden durchgeführt. Die Systemstabilität wurde mit Hilfe von drei Serien mit je fünf systematischen Wasserkontrollexperimenten (SNC) untersucht. Je eine Serie der Potenz- und der SNC-Experimente wurde mit gibbösen Lemnas (spezifisches Wachstumsstadium von L. gibba) durchgeführt, um den Einfluss der Gibbosität auf die Reaktionsbereitschaft von L. gibba bezüglich der Behandlung mit potenziertem GA_3 zu untersuchen.

Die Resultate waren uneinheitlich: Nur in der dritten Serie (mit gibbösen Lemnas) wurde ein signifikanter globaler Effekt (p=0.009, F-Test) der homöopathischen Behandlung beobachtet. Zudem gab es im Unterschied zur Originalstudie einen Anstieg der Wachstumsrate und die Effekte der meisten der „aktiven" Potenzstufen unterschieden sich. Die Variabilität war in den Potenz-Experimenten niedriger als in den SNC-Experimenten.

Die zweite Studie untersucht die Labor-interne Reproduzierbarkeit früher beobachteter Effekte von homöopathisch potenziertem *Argentum nitricum* mit dem Lemna gibba-Bioassay.

In der Originalstudie wurde von einer statistisch signifikanten Wechselwirkung zwischen Experimentdatum und dem Behandlungseffekt von *Argentum nitricum* D14–D30 auf die Wachstumsrate von Lemna gibba berichtet.

Entsprechend der GA_3-Studie wurden die Lemnas mit Argentum nitricum Potenzen (D14–D30) sowie mit der verschüttelten und der unverschüttelten Wasserkontrolle behandelt. Die Wachstumsrate von Tag 0 – 7 wurde mit dem digitalen Bildanalysesystem gemessen. Zwei Serien wurden mit sechs und mit drei unabhängigen verblindeten und randomisierten Experimenten durchgeführt. Die statistische Auswertung fand mit Hilfe der zwei-Wege ANOVA und dem geschützten Fisher`s LSD-Test statt.

Die Resultate der Originalstudie konnten nicht reproduziert werden: In der ersten Serie konnte ein signifikanter Effekt der homöopathischen Behandlung ermittelt werden (p= 0.016, F-Test), während in der zweiten Serie kein Effekt beobachtet wurde. Die Systemstabilität wurde durch SNC-Experimente kontrolliert. In einer a posteriori Untergruppenanalyse wurde der Einfluss der Gibbosität auf die Resultate untersucht und es zeigte sich die Wichtigkeit dieser Wachstumsphase für eine erfolgreiche Reproduzierung der statistisch signifikanten Wechselwirkung der Vorgängerstudie: nicht gibbös: p= 0.762; leichte Gibbosität: p= 0.256; mittlere Gibbosität: p= 0.031; hohe Gibbosität: p= 0.005.

Beide Studien zeigten, dass die gibböse Wachstumsphase ein die Reproduzierbarkeit beeinflussender Parameter in Homöopathie-Studien mit *Lemna gibba* L. sein kann. Mit dem ursprünglichen Studiendesign, welches den gibbösen Status der Pflanzen nicht beachtete, konnten die Resultate der Originalstudien nicht reproduziert werden. In zukünftigen Studien der Homöopathie-Grundlagenforschung sollten die physiologischen Stadien der Testorganismen sorgfältig bedacht werden.

7. Publications

Majewsky V, Arlt S, Shah D, Scherr C, Jäger T, Baumgartner S.:
Use of homeopathic preparations in experimental studies with healthy plants. Homeopathy. 2009; 98(4): 228-243.

Majewsky V, Scherr C, Arlt S, et al.:
Reproducibility of effects of homeopathically potentised gibberellic acid on the growth of Lemna gibba L. in a randomised and blinded bioassay. Homeopathy. 2014; 103(2): 113-126.

Majewsky V, Scherr C, Schneider C, Arlt S, Baumgartner S.:
Reproducibility of the effects of homeopathically potentised Argentum nitricum on the growth of Lemna gibba L. in a randomised and blinded bioassay. accepted by Homeopathy. 2017.

Participated:

Betti L, Trebbi G, Majewsky V, et al.: “Use of homeopathic preparations in phytopathological models an field trials: a critical review”, Homeopathy (2009), 98 (4), 244-266

Betti L, Trebbi G, Nani D, Majewsky V, et al.: “Models with Plants, Microorganisms and Viruses for Basic Research in Homeopathy” in “Signals and Images – Contributions and Contradictions about High Dilution Research”, Springer Verlag 2008

Jäger T, Scherr C, Shah D, Majewsky V, et al.: “Use of homeopathic preparations in experimental studies with abiotically stressed plants” Homeopathy (2011) 100, 275-287

Jäger T, Scherr C, Shah D, Majewsky V, et al.: „Use of plant-based bioassays in homeopathic basic research“, Homeopathy (2015) 104 (4), 277-282

Lectures at Conferences

[1] Baumgartner S, Shah D, Majewsky V, Thurneysen A, Heusser P: Growth Stimulation of dwarf peas (Pisum sativum L.) through homeopathic potencies of plant growth substances. Improving the Success of Homeopathy 5, London, UK, Jan. 26–27, 2006

[2] Baumgartner S, Majewsky V: Wie reproduzierbar ist die Wirkung von homöopathisch potenziertem Gibberellin bei Zwergerbsen? (How Reproducible are the Effects of Homeopathically Potentised Gibberellic Acid on Dwarf Peas?). Annual Meeting of the Potency Research Group, Arlesheim, Switzerland, June 16, 2006

[3] Baumgartner S, Heusser P, Jäger T, Lutz B, Majewsky V, Scherr C, Shah-Rossi D, Wälchli C, Wolf U: Grundlagenforschung zu potenzierten Substanzen: von Lili Kolisko bis heute (Basic research in potentized substances: from Lili Kolisko until today). 3. Wissenschaftskongress Anthroposophische Medizin, Berlin, March 8–9, 2012. Abstract published in Der Merkurstab 65 (2012), p. 155–156

[4] Baumgartner S, Heusser P, Jäger T, Lutz B, Majewsky V, Scherr C, Shah-Rossi D, Wälchli C, Wolf U: Grundlagenforschung zu potenzierten Substanzen: Herausforderungen für die Zukunft (Basic research in potentized substances: challenges for the future). 3. Wissenschaftskongress Anthroposophische Medizin, Berlin, March 8–9, 2012

[5] Baumgartner S, Betti L, Heusser P, Jäger T, Scherr C, Majewsky V, Wolf U: Use of plant bioassays in homeopathic basic research – a systematic review. XXVI GIRI Symposium, Florence, Italy, September 20–22, 2012. Abstract published in the International Journal on High Dilution Research 11 (2012), p. 140–141

Posters at Conferences

[1] Majewsky V, Heuwieser W, Klocke P, Baumgartner S: Growth Stimulation of Dwarf Peas (*Pisum sativum* L.) through Homeopathic Potencies of Gibberellic acid. International Congress on Complementary Medicine Research, Munich, Germany, May 11–13, 2007

[2] Baumgartner S, Betti L, Heusser P, Jäger T, Majewsky M, Scherr C, Wolf U: Use of plant-based bioassays in homeopathic basic research – a systematic review. International Research Congress on Integrative Medicine and Health, Portland, USA, May 15–18, 2012. Abstract published in BMC Complementary and Alternative Medicine 2012, 12 (Suppl. 1): P34

[3] Majewsky V, Scherr C, Arlt SP, Klocke P, Baumgartner S: Reproducibility of effects of the homeopathic dilutions 14x – 30x of gibberellic acid on growth of *Lemna gibba* L. XXVI GIRI Symposium, Florence, Italy, September 20–22, 2012. Abstract published in the International Journal on High Dilution Research 11 (2012), p. 196–197

[4] Majewsky V, Scherr C, Arlt SP, Kiener J, Frrokaj K, Schindler T, Klocke P, Baumgartner S: Reproducibility of effects of homeopathically potentised gibberellic acid on the growth of *Lemna gibba* L. in a randomised and blinded bioassay. Tag der Forschung, University of Witten-Herdecke, Germany, December 6, 2013

[5] Majewsky V, Scherr C, Schneider C, Arlt SP, Baumgartner S: Reproducibility of the effects of homeopathically potentised *Argentum nitricum* on the growth of *Lemna gibba* L. in a randomised and blinded bioassay. 3rd HRI International Homeopathy Research Conference, St. Julians, Malta, June 8–11, 2017

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9. Deklaration of Independence

Hiermit bestätige ich, dass ich die vorliegende Dissertation selbständig angefertigt habe. Ich versichere, dass ich nur die angegebenen Quellen und Hilfen verwendet habe.

Wädenswil, den 21.3.2017

Vera Majewsky

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