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Basic research in homeopathy – the current state of affairs

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Open scientific questions regarding homeopathy

- Homeopathy is a medical method which leads to high customer satisfaction in general practice
  - Patient-rated effectiveness is equal to or higher than conventional medicine in cohort trials investigating real-world effectiveness (Witt et al., Rossignol et al.) at comparable or reduced expenses (Kooreman et al., Studer et al.)
- Basic tenets of Homeopathy
  - Simile principle and potentisation procedure
  - No obvious scientific basis supporting application in medicine
  - No generally accepted theory to explain specific effects of homeopathically potentized substances in high dilution levels
- Are the large effects of homeopathy in daily practice just the effects of a placebo treatment?

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Does the procedure of homeopathic potentisation make any sense?

- Since 1996: Basic Research Dept. at the Institute of Complementary Medicine of the University of Bern
- Aim: investigations with several experimental laboratory models to
  - Assess and characterize effects of homeopathic remedies
  - Develop reliable and reproducible models
  - Investigate pharmaceutical questions (e.g. sterilization methods, stability against external influences such as cell phone radiation)
  - Determine the mode of action of homeopathic preparations
- Evaluation of 17 experimental models

- All publications available on ResearchGate.net

Evaluation of experimental models to study homeopathic preparations

17 models

UV-Spektroscopy
NMR Relaxation Time Measurements
PBMC (Lymphocytes)
Jurkat cells
Basophils
Fibroblasts
Saccharom. cerevisiae / Schizosacchar. pombe (yeasts)
Saccharom. cerevisiae / Arsenic
Lemna gibba (duckweed)
Lemna gibba / Arsenic
Lemna gibba / Ca deficiency
Pisum sativum (dwarf peas)
Lepidium sativum / Biocrystallization
Triticum aestivum / Arsenic
Malus domestica / Dysaphis plantaginea
Malus domestica / Venturia inaequalis
Arabidopsis thaliana / Pseudomonas syringae

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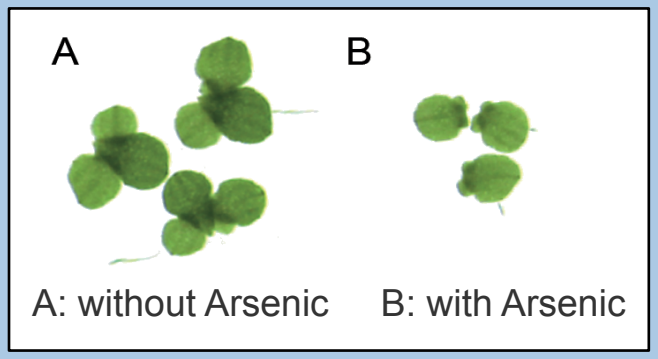
Evaluation of experimental models to study homeopathic preparations

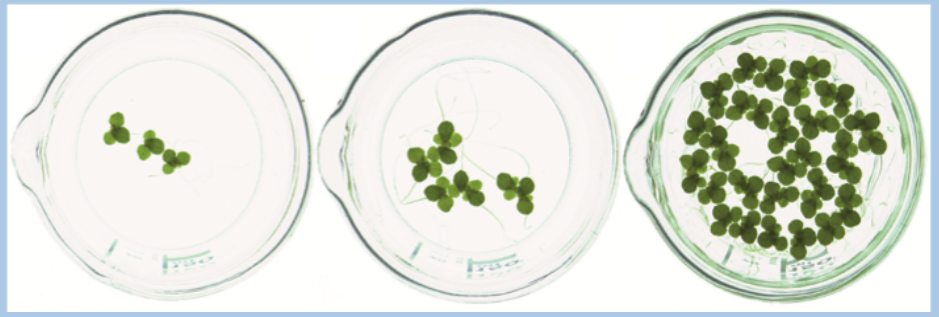
13 out of 17 models **with evidence for specific effects**	
UV-Spektroscopy	**X**
NMR Relaxation Time Measurements	**X**
PBMC (Lymphocytes)	**X**
Jurkat cells	
Basophils	
Fibroblasts	**X**
Saccharom. cerevisiae / Schizosacchar. pombe (yeasts)	**X**
Saccharom. cerevisiae / Arsenic	
Lemna gibba (duckweed)	**X**
Lemna gibba / Arsenic	**X**
Lemna gibba / Ca deficiency	**X**
Pisum sativum (dwarf peas)	**X**
Lepidium sativum / Biocrystallization	**X**
Triticum aestivum / Arsenic	**X**
Malus domestica / Dysaphis plantaginea	**X**
Malus domestica / Venturia inaequalis	
Arabidopsis thaliana / Pseudomonas syringae	**X**

Adaptation of an ecotoxicological assay with *Lemna gibba* (duckweed)

- Homeopathic treatment (*Ars-alb*) of duckweed poisoned with arsenic



Duckweed without Arsenic impairment



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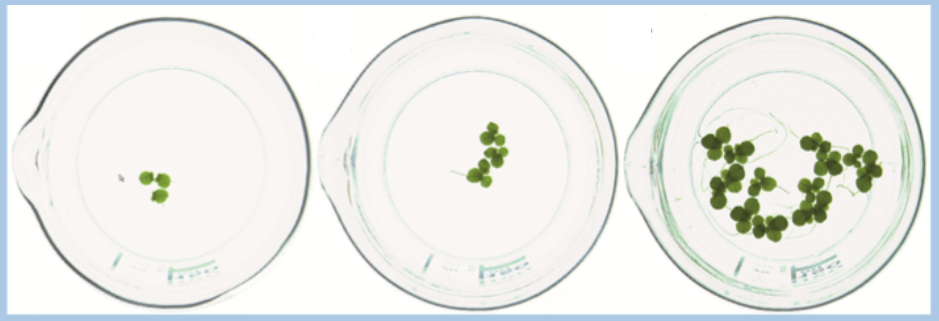
Arsenic-impaired Duckweed



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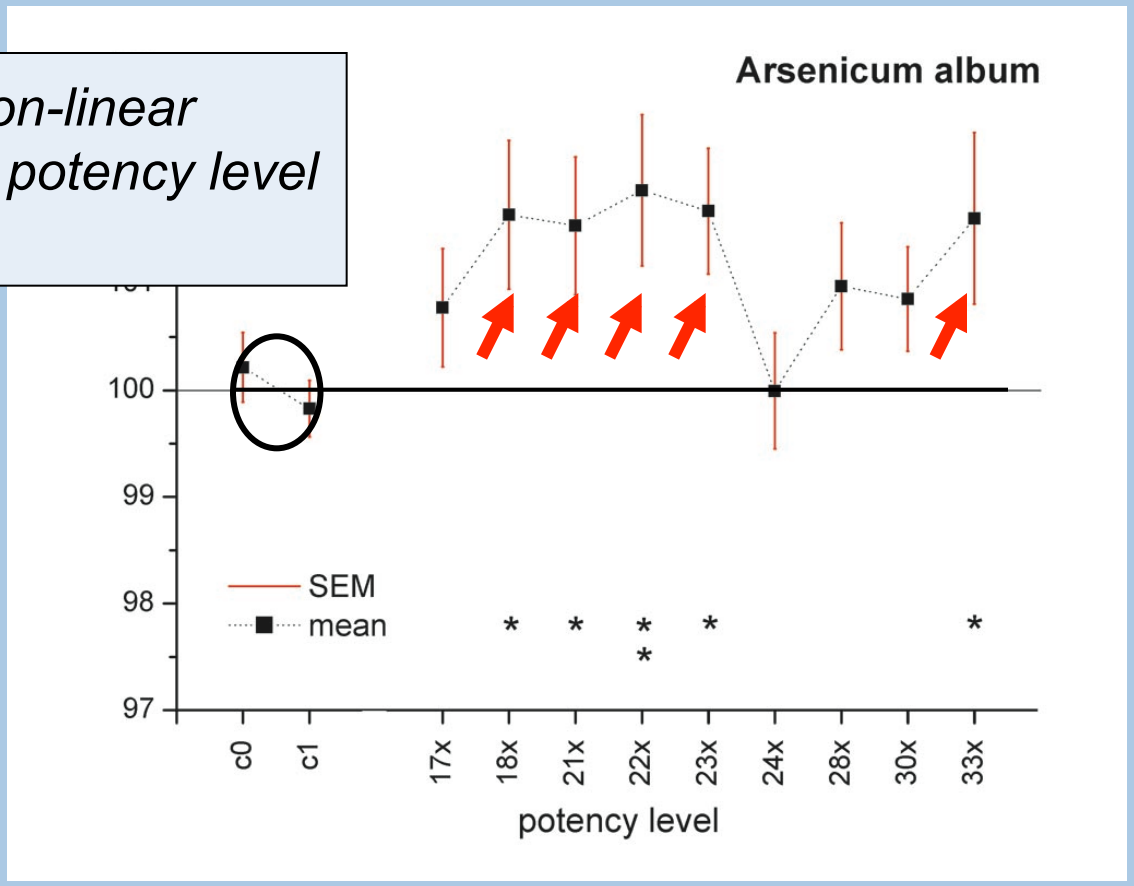
Jäger et al. 2010
ScientificWorldJournal 10:
2112–2129

Adaptation of an ecotoxicological assay with *Lemna gibba* (duckweed)

- Homeopathic treatment (*Ars-alb*) of duckweed poisoned with arsenic

Discontinuous and non-linear relationship between potency level and effect size



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Evaluation of experimental models to study homeopathic preparations

13 out of 17 models **with evidence for specific effects**	
UV-Spektroscopy	**X**
NMR Relaxation Time Measurements	**X**
PBMC (Lymphocytes)	**X**
Jurkat cells	
Basophils	
Fibroblasts	**X**
Saccharom. cerevisiae / Schizosacchar. pombe (yeasts)	**X**
Saccharom. cerevisiae / Arsenic	
Lemna gibba (duckweed)	**X**
Lemna gibba / Arsenic	**X**
Lemna gibba / Ca deficiency	**X**
Pisum sativum (dwarf peas)	**X**
Lepidium sativum / Biocrystallization	**X**
Triticum aestivum / Arsenic	**X**
Malus domestica / Dysaphis plantaginea	**X**
Malus domestica / Venturia inaequalis	
Arabidopsis thaliana / Pseudomonas syringae	**X**

Scientific standards:

- adequate controls (succussed, potentized)
- randomized & blinded
- several independent experiments (including independent production lots)
- systematic negative control experiments
- adequate statistics

Evaluation of experimental models to study homeopathic preparations

9 out of 13 models with variable effects	
UV-Spektroscopy	X
NMR Relaxation Time Measurements	X
PBMC (Lymphocytes)	X
Jurkat cells	
Basophils	
Fibroblasts	
Saccharom. cerevisiae / Schizosacchar. pombe (yeasts)	X
Saccharom. cerevisiae / Arsenic	
Lemna gibba (duckweed)	X
Lemna gibba / Arsenic	
Lemna gibba / Ca deficiency	X
Pisum sativum (dwarf peas)	X
Lepidium sativum / Biocrystallization	
Triticum aestivum / Arsenic	X
Malus domestica / Dysaphis plantaginea	X
Malus domestica / Venturia inaequalis	
Arabidopsis thaliana / Pseudomonas syringae	

High variability

- within experimental series
- between experimental series
- between different laboratories

Is this a peculiarity of the research field in question?

Are the effects of homeopathic preparations reproducible?

- Are there any independent reproductions (laboratory-internal or -external) of homeopathic basic research experiments?
- Main data source: HomBrex database (with more than 1000 publications): http://www.carstens-stiftung.de/hombrex/
- Yes: Endler et al. Homeopathy (2010) 99, 25–36:
  - 14 models internally reproduced with significant effects
  - 7 models externally reproduced with significant effects
- There seems to be no experimental model (bioassay) that yielded **identical** results when independently reproduced by another research team (with regard to active potency level, effect size and direction)
- In independent reproductions, **results were similar, but not identical**
- What reasons might be responsible for this variability in results?

Variability in homeopathic basic research assays

- The variability observed in homeopathic basic research can be due to several causes
  - uncontrolled external influences interpreted as treatment effects (false positive results, artifacts)
  - unknown and therefore uncontrolled parameters influencing the effects of dynamized substances
  - inappropriate outcome parameters
  - intrinsic indeterministic features of potentized preparations (as also known in science in chaos theory or quantum physics)

Variability in homeopathic basic research assays

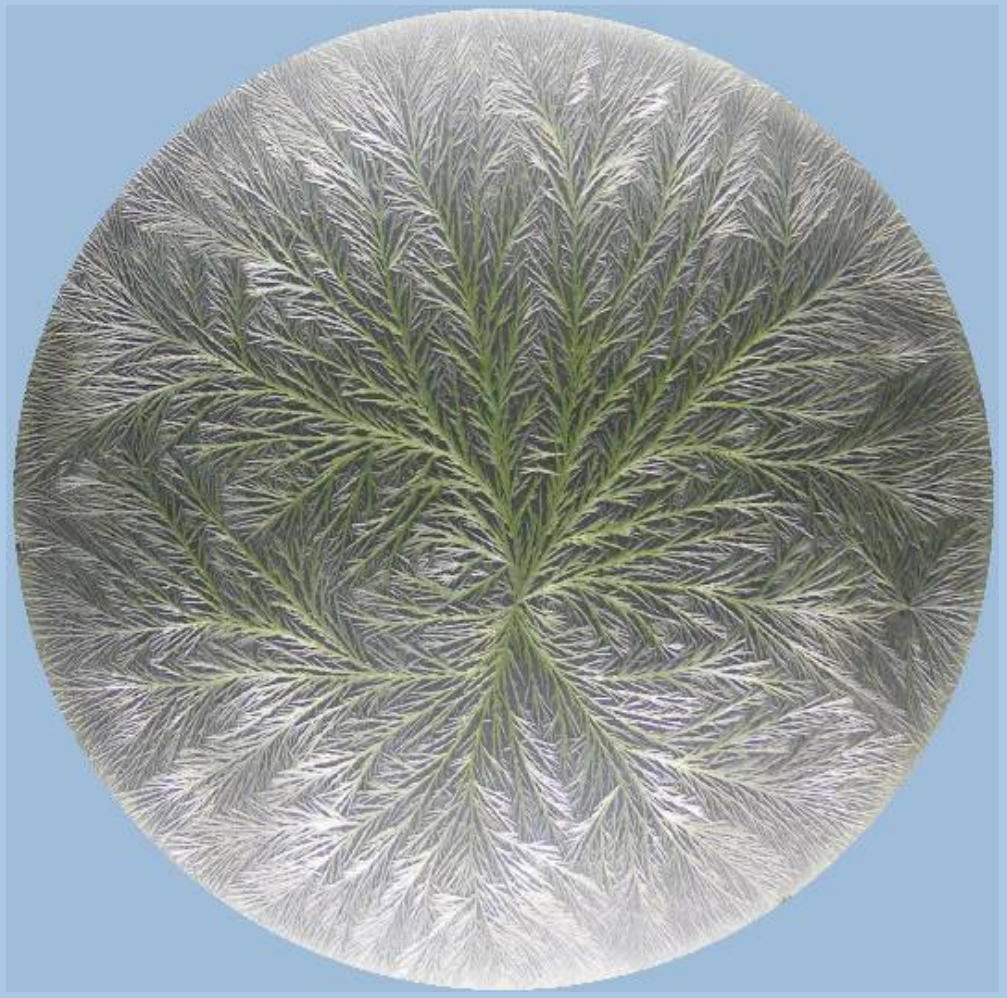
- **Critical system parameters** modulating the effects of potentized substances have been **identified in 4 experimental models** so far: in all cases environmental factors
  - Mice model (isopathic treatment with potentized mercury): annual chronobiological rhythms
    [Cal JC et al. Ann Rev Chronopharmacol 1986; 3: 99–103]
  - Frog metamorphosis system (potencies of thyroxin): biotope altitude (endogenous thyroxin level)
    [Zausner C, Endler PC et al. Perfusion 2002;15:268–276]
  - Dwarf pea system (potencies of gibberellic acid): seed ripeness (endogenous sugar level)
    [Baumgartner S et al: Compl Ther Med 2008;16:183–191]
  - Duckweed system (potencies of gibberellic acid): annual chronobiological rhythms in aerenchym formation (gibbosity)
    [Majewsky et al. Homeopathy 2014;103:113–126]
- Parameters in all cases necessary, but not sufficient for reproducibility

Variability in homeopathic basic research assays

- Appropriate outcome parameters for homeopathic basic research systems might be
  - Variability instead of mean measures
    [Nani et al. (2007) Forsch Komplementärmed 14: 301–305]
  - Qualitative outcome parameters such as image features of biocrystallisations or droplet residues
    [Baumgartner et al. (2012) eCAM 125945]
    [Kokornaczyk et al. (2014) Compl Ther Med, in press]
  - Global outcome parameters in complex systems such as the frog metamorphosis velocity in the model of Endler et al. or the mice behaviour in experiments of Bellavite et al.
    [Harrer et al. (2013) Homeopathy 102, 25–30]
    [Bellavite et al. (2012) eCAM 954374]

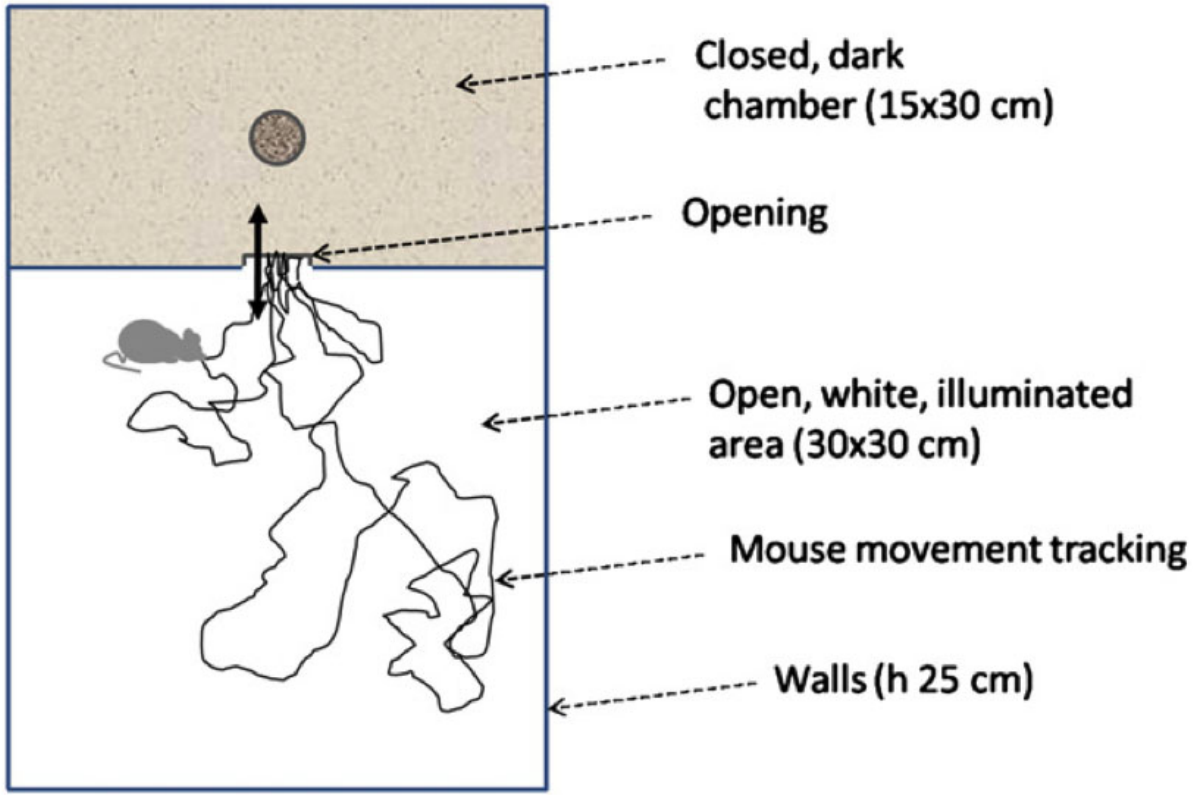
Biocrystallisation of homeopathically treated plants

- Biocrystallisation: crystallisation of $CuCl_2$ with added organic extract (ISO standardized food quality test)
- Extract of cress seedlings, germinated in Stannum met. 30x or water 30x
- Series of 15 independent experiments in two laboratories (NL, DK)
- Highly significant effects after computer aided image (texture) analysis
- Baumgartner et al. (2012) eCAM



Animal behavior test with homeopathic remedies

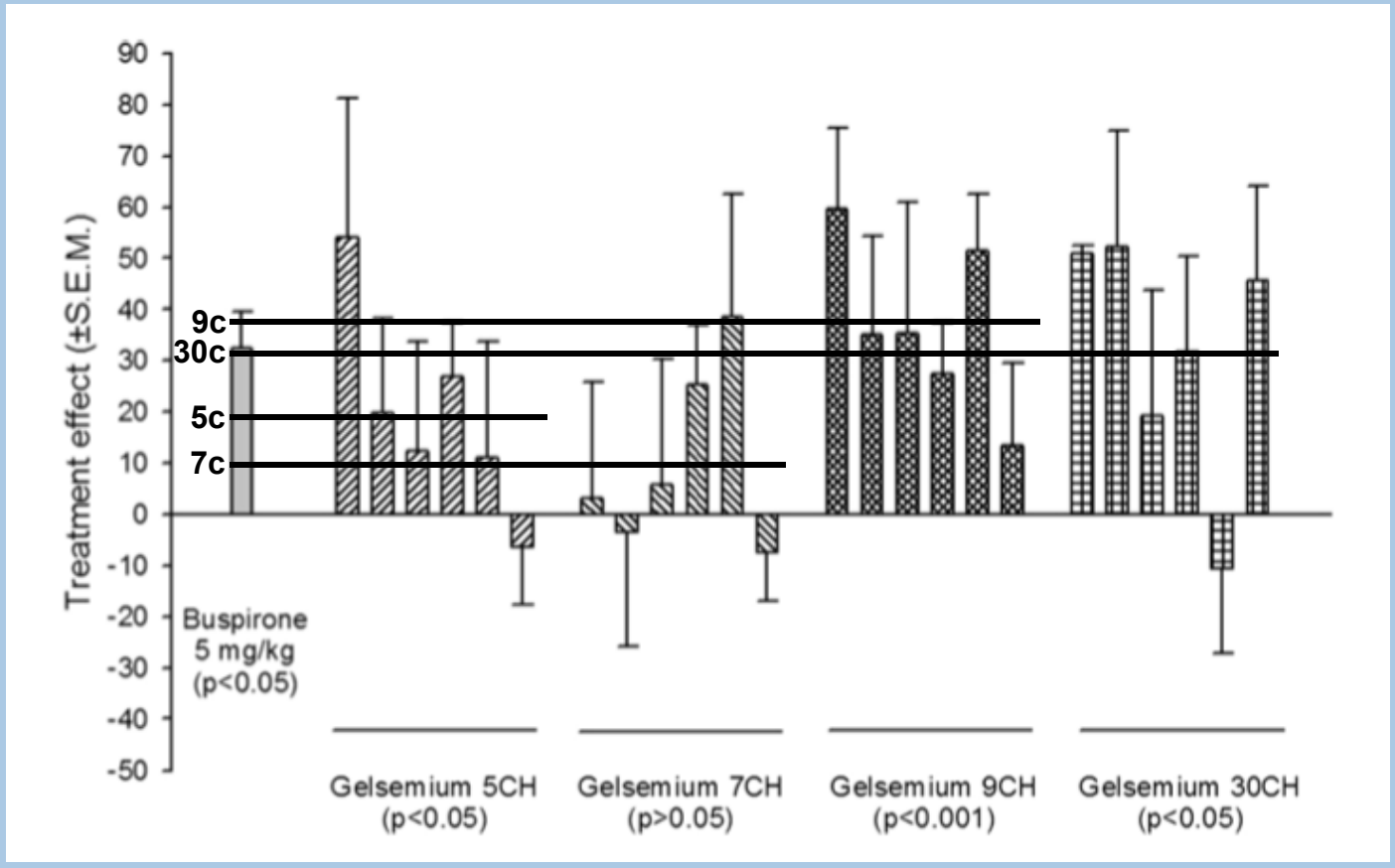
> LD exploration test with mice



Bellavite et al. 2009
Homeopathy 98: 208-227

Animal behavior test with homeopathic remedies

> LD exploration test with mice, treated with Gelsemium



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Effect size of homeopathic treatments as a function of system complexity

Model	Effect size
UV-Spektroscopy	
NMR Relaxation Time Measurements	
PBMC (Lymphocytes)	Cancer cell lines: ≈0%
Jurkat cells	
Basophils	
Fibroblasts	
Saccharom. cerevisiae / Schizosacchar. pombe (yeasts)	Micro-organisms: < 1%
Saccharom. cerevisiae / Arsenic	
Lemna gibba (duckweed)	Plants: up to 10%
Lemna gibba / Arsenic	
Lemna gibba / Ca deficiency	
Pisum sativum (dwarf peas)	
Lepidium sativum / Biocrystallization	
Triticum aestivum / Arsenic	
Malus domestica / Dysaphis plantaginea	Plant-Pathogen-Systems: up to 20%
Malus domestica / Venturia inaequalis	
Arabidopsis thaliana / Pseudomonas syringae	

Effect size of homeopathic treatments as a function of system complexity

- Jonas et al. 2006 Integr Cancer Ther: Male rats were injected with MAT-LyLu (prostate tumor) cells and exposed to several homeopathic remedies
- There was a **23% reduction in tumor incidence** versus controls, and for animals with tumors, there was a **38% reduction in tumor volume** in homeopathically treated animals versus controls
- **No effects** on cell viability or gene expression were observed when MAT-LyLu cells were exposed ***in vitro*** to the same homeopathic remedies
- Saha et al. 2013 BMC Compl Alt Med: similar results with Swiss albino mice injected with EAC (Ehrlich's ascites carcinoma) cells
- Thus it seems that the biological mode of action of homeopathic remedies is not primarily at a cellular level, but rather on a superordinate organizational level

Basic research into homeopathic potentization: Summary

- Results from high-quality laboratory trials support the notion that highly diluted potentized substances may exert specific effects
- There are active and inactive potency levels (unknown pattern rules) – strongly nonlinear relation between potency level and effect
- Effect size of homeopathic treatments seems to increase with increasing complexity of the bioassay
- Homeopathic basic research models still show a high variability in the results

Basic research into homeopathic potentization: How to move on?

- Further development of promising models
- Determination of the mode of action of highly diluted homeopathic preparations

Basic research into homeopathic potentization: How to move on?

- Further development of promising models
  - using complex models (e.g. entire multicellular organisms and complex/functional outcomes)
    - no cancer cell lines, no microorganisms
    - plants, especially in combination with biocrystallisation or the droplet evaporation method, or plant-pathogen-systems
    - animals: ethically acceptable behavioural experiments (e.g. LD-test with mice)
  - determination of critical parameters influencing system response (reproducibility / multicenter studies)

Basic research into homeopathic potentization: How to move on?

- Further development of promising models:
- According to Endler et al. 2010 there are five independently replicated models with comparable results:
  - Growth of wheat seedlings after treatment with potencies of silver nitrate,
  - Human basophil degranulation after treatment with potencies of histamine,
  - Amphibian metamorphosis after treatment with potencies of thyroxin or thyroidinum,
  - Experimental hepatitis of the rat due to poisoning with carbon tetrachloride after treatment with phosphorus,
  - Contraction of rat intestine in vitro after treatment with potencies of Atropa belladonna or atropine sulfate.

Basic research into homeopathic potentization: How to move on?

- Further development of promising models
  - using complex models (e.g. entire organisms and complex/ functional outcomes)
    - plants, especially in combination with biocrystallisation or the droplet evaporation method, or plant-pathogen-systems
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  - determination of critical parameters influencing system response (reproducibility / multicenter studies)

- Determination of the mode of action of highly diluted homeopathic preparations

Physicochemical Drug Structure

- Several theories hypothesize the formation of stable water clusters mirroring the molecular structure of the solvate (e.g. Anagnostatos 1991, 1994)
- However, reorientation time of water molecules belonging to water clusters is ≈10^{-11} sec. (compared to ≈10^{-12} sec. in free water) – thus each molecule in a water cluster changes its position 100000000000 times per second…
- Water clusters are not static, but dynamic – which makes it difficult to store information
- Until now, **no evidence has been found for stable water clusters in homeopathic potencies** (Aabel 2001; Anick 2004)

Physicochemical Drug Structure

- On the contrary, several experimental investigations with standard physical methods suggest an **increase** of water molecule dynamics in homeopathic preparations
  - NMR relaxation: Demangeat 1992, 1997, 2010, 2013 Baumgartner 2009
  - UV spectroscopy: Wolf 2011; Marschollek 2010
  - Thermodynamics: Elia 2000
- Hypothesis of a non-thermal energy field in homeopathic potencies, serving as carrier of the homeopathic information?
- This hypothesis may remind of the wording used by Hahnemann: homeopathic remedies as „dynamizations“ of a crude substance

What did Hahnemann think?

- The homeopathic system of medicine develops... the inner, spirit-like medical powers of the crude substances by a peculiar procedure...
- [The procedure of potentization] develops latent hidden dynamic powers of the crude substances... into spirit-like medical power, which in itself is not perceivable with our senses, but for which the globule becomes the carrier... and manifests the healing power of this invisible force...

— S. Hahnemann, Organon, 6th edition, §269–270

Is there a local force-like mode of action of highly diluted homeopathic potencies?

- Hahnemann compared the effects of homeopathic potencies to the effects of gravitation and magnetic forces (§ 11)
  - for the effects of forces of classical physics, no material contact between cause and effect is necessary
  - the homeopathic „forces“ primarily act on the living body only, however
- If the mode of action of homeopathic preparations is of a force-like (immaterial) nature, action at a distance might be possible

Is there a local force-like mode of action of highly diluted homeopathic potencies?

- Such a „force or energy field“ may lead to cross-contamination and consequently to false-negative results – and may be responsible for some of the reproducibility problems in dynamization research (and maybe even in clinical trials!)
- Is there a possibility to avoid any such cross-contamination? By shielding? By what materials?
- The answer to these questions can be obtained by „classical“ experiments and will furnish relevant information
  - to identify the mode of action of dynamized preparations and
  - to reduce cross-contamination in preclinical and clinical trials

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Summary

- **Key challenge N° 1** in homeopathic basic research is to **develop suitable laboratory models** (to investigate not only the potentisation procedure, but also the simile principle)
- **Key challenge N° 2** in homeopathic basic research is to **identify the mode of action** of highly potentized remedies:
  - local material- or force-like, or non-local entanglement-like?
  - reproducibly deterministic, chaotic, inherently indeterministic?
- Though theses challenges are considerable, substantial progress has been made in the last years, implying promising prospects for the future