

Original Article

Nanoparticles Characterization of *Homoeo Agrocare* (agro homeopathic drug) by HRTEM and EDS Analysis

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Abstract

Background Homeopathy as a therapeutic tool is still very nascent in plant science and agriculture. Therapies used for plant growth and diseases are not relevant for plants alone, but they also drastically influence the ecosystem of the organic world too. Pesticides and chemical fertilizers was a boon during the initial phase of the green revolution around the world. Unfortunately, later they became the major reason for the chronic illnesses like cancers and a cause for soil degradation all over. The scenario demands the use of alternative models in agricultural practices in order to prevent diseases and to maintain the health status of the population. This is also very important to get rid of the damages done to the soil. **Aims** The present study aimed at analyzing the material content of the agro-homeopathic drug, 'Homeo agrocare'. **Methodology** High resolution transmission electron microscope (HRTEM) and Energy dispersion spectroscopy (EDS) were used to evaluate the material content of the drug. DLS and HRTEM were used for the analysis of control sample (Pharmaceutical grade alcohol). **Results** (1) Drug solution contains plenty of nanoparticles (NPs). (2) Size of NPs ranges between 4.99nm - 93.09 nm. (3) Twenty elements were identified in fields studied. (4) No particles identified in the control sample by DLS and HRTEM analysis. **Conclusion** Study conclusively proved the presence of NPs of the original drug materials used in the 'Homoeo agrocare' drug solution.

Keywords: Homeopathy, Homeo agrocare, Nanoparticles, Epigenetics, Agro- homeopathy

Introduction

Homeopathic ultra-high dilutions are used universally in the treatment of human, animal and plant diseases. Recent research publications of the author and many others demonstrated the presence of nanoparticles (NPs) in homeopathic ultra-high dilutions [1-15]. As ultra-high dilutions (UHDs) demonstrated the potential in regulating the growth [16-26] and effectiveness in treating a variety of plant diseases [27-32], it is decided to characterize one of the commonly used homeopathic plant remedies in India particularly in the state of Kerala. ('Homoeo agrocare' manufactured by Mini pharma, Kozhikode). Large number of agriculturists have testified the positive qualitative and quantitative impact of this homeopathic drug cocktail upon their crops (fruits, vegetables, rice, arecanut, coconut etc). *Homoeo agrocare* is a combination of 39 homeopathic drug potencies.

Agro-homeopathy is one of the recent approaches in agricultural research yet to be taken to the of mainstream agricultural practice. In recent years, various scientific studies showed that potential homeopathic medicines can alter the physiological activities of plants [16,19,20,21]. It can alter the rate of enzymatic activities, total sugar, protein and chlorophyll contents in plants [17,18,22]. Eradication of biotic and abiotic stresses up to some extent is also made possible by the use of Homeopathy. In the case of biotic stresses; anti-fungal, anti-microbial, anti-insecticidal activities of various homeopathic drugs have been reported. Sometimes other paths of abiotic stress (salt stress, drought stress, cold stress, metal toxicity, mechanical damages etc.) control are costlier or less



efficient. But proper selection of homeopathic drugs can be cost effective and very efficient in terms of abiotic stress tolerance in various crop species [24,27,28,31,32,33].

Ultra-high dilution of homeopathic medicines can be used safely for various purposes in the plant kingdom (seed germination, the betterment of soil health, growth of seedlings, flowering, fruiting, protection against diseases and to overcome environmental stresses). With proper selection of drug and its potency, Agro-homeopathy can be an efficient and very cost-effective alternative that can increase farmers' income by lower input cost of chemical fertilizers and insecticides [33]. Current scenario of universal use of pesticides in agriculture around the world is a major concern as these pesticides perennially damage the ecosystem on earth, generated by nature and sustained for millions of years, which supported the creation and sustenance of every animal and plant species on earth. Recent studies established the harmful effects of pesticides on human health including the development of allergies and varieties of cancers [34-49]. Agro-homeopathy seems to be an ideal choice of replacement for chemical intensive fertilizers and pesticides. Recent studies and research publications well established the fact that homeopathic ultra-high dilutions produce epigenetic modifications in animal models and cell lines [50-67]. Further researches are necessary to understand the potential of these ultra-high dilutions in the treatment of plant diseases and regulate growth without environmental and health impacts.

In human health conditions, homeopathic drugs are prescribed on the basis of 'Similia' principle, therefore the majority of prescriptions are single medicine at a time. But there is a multitude of combination or cocktail homeopathic drugs discovered and marketed around the world, which are also effective in curing many diseases. Identifying a unique constitutional medicine based on individual characteristic signs and symptoms (physical and mental) is a viable option in human beings. But, it is rather difficult to adopt the same approach in plant health conditions. It seems that the discoverer of '*Homoeo agrocare*' adopted a principle of 'selection by plant', the apt element for its own cure rather than individualizing each plant for the selection of suitable drug. '*Homoeo agrocare*' has been a commonly used homeopathic product by farming communities in Kerala for a long time. Farmers who use this cocktail drug in their field are happy with the outcome and the majority of them testify positive outcomes with the '*Homoeo agrocare*' in their agricultural production.

Materials and methods

Samples and preparation

The homeopathic cocktail drug '*Homoeo agrocare*' is a product formulated by Prof. M Abdul Lethif through many years of experimental studies on plant growth and productivity, prevention and cure of plant diseases. The product is manufactured by M/S Mini pharma, a partnership firm registered on 16.11.1999. Prof M Abdul Lethif did his experiments on various plants and combined 39 drugs to create a mixture of homeopathic ultra-high dilutions as a broad spectrum medicine, covering the growth and disease related concerns, as well as the productivity of crops. This cocktail of homeopathic ultra-high dilutions has been formulated from the following 39 drugs: *Aqua marina*, *Acidum aceticum*, *Acidum citricum*, *Acidum lacticum*, *Acidum salicylicum*, *Allium cepa*, *Allium sativa*, *Alumina*, *Ammonium carb*, *Arnica montana*, *Azadiracta indica*, *Baptisia tinctoria*, *Belladonna*, *Berberis vulgaris*, *Boron*, *Bryonia*, *Calcarea carbonicum*, *Calcarea phosphoricum*, *Cina*, *Cuprum metallicum*, *Cuprum oxydatum nigrum*, *Cuprum sulphuricum*, *Dulcamera*, *Ferrum phosphoricum*, *Ferrum sulphuricum*, *Kalium permanganicum*, *Kalium phosphoricum*, *Kalium sulphuricum*, *Natrum muriaticum*, *Natrum phosphoricum*, *Natrum salicylicum*, *Ocimum canum*, *Phosphorus*, *Ricinis communis*, *Ruta graveolens*, *Tanacetum vulgare*, *Teucreum marum verum*, *Zincum metallicum* and



Zincum phosphoricum. The researcher used 37 drugs in 1M potency and *Allium cepa* in 30cH and *Acidum phosphoricum* in 200cH potency for the formulation of the drug mixture. This combination seems to work like a broad spectrum nanomedicine for the plant kingdom. The solutions of all these medicines were mixed in equal quantities to prepare the mother solution. The mother solution is used to medicate the globules. The prescribed number of medicated globules are dissolved in water and used in agriculture fields as well on individual plants.

The combination of the raw materials used for the discovery of this combination was kept under trade secret rules and principles under the control of Mini Pharma, Kozhikode and I am grateful to Prof M Abdul Lethif for revealing the details of the raw materials used in his formulation, after the completion of my characterization experiment of the drug solution in the laboratory.

Homoeo agrocare sample in liquid form (alcohol solution) was procured from M/S Mini Pharma, Kozhikode, India and the selected solution in the manufacturer's sealed bottle was individually sonicated [68] for 20 minutes using bath sonicator. One micro drop of the alcohol solution was extracted from the middle of the bottle with a micropipette. The same was poured on to the TEM grid and left to dry overnight under infrared light (evaporation/dehydration method was used as the sample is prepared in alcohol). The grid was later placed in the TEM chamber, the particles and agglomerates identified, focused, TEM images were taken and particle size measured. The elementary composition of the particles and the weight percentage was measured by means of energy dispersion spectroscopy (EDS). Pharmaceutical grade alcohol was procured from Wilmer Schwabe India, Pvt Ltd, New Delhi and studied as the control. Control sample was also sonicated for 20 minutes using bath sonicator and analysed by DLS (Dynamic Light Scattering) and TEM. TEM analysis of the control sample was performed exactly the same way as that of the drug solution. It was decided to do DLS and HRTEM analysis of the control sample to double check the presence/absence of particles.

Instruments

In the present study, it was decided to use HRTEM and EDS for the analysis of the UHDS of *Homoeo agrocare*. Jeol TEM 2100 with operating voltage 200kV and 200 mesh carbon coated copper grid was used. For EDS, Oxford Instruments INCA equipment was used. Resolution of the HRTEM used was 0.23nm. EDS served to analyse the elementary composition of the identified NPs. EDS detector - 50mm², EDS resolution - 142 ev at 5.9 kev, analysed at 200kv. We performed the analysis on the specified area of the particles. Use of this equipment helped to detect the NPs of smallest size and to analyse their elementary composition. The DLS analysis of the control sample has been done with Horiba scientific nanopartica - nanoparticle analyser SZ-100, path length 100nm.

Study setting

The study was conducted at International and Inter University Center for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, India.

Results

HRTEM and EDS analysis of Homoeo agrocare



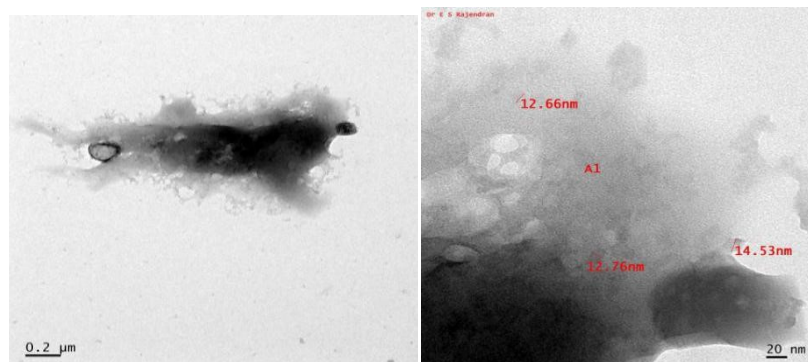
Field I Homeo agrocare**Figure 1****Figure 2 – Magnified image**

Figure 1 and 2 represents the HRTEM images of the particles and agglomerate in Field I. Figure 2 is the magnified image of Figure 1.

Particle size: 12.66nm - 14.53nm

Elements	O	Na	Cl	Si	P	S	Fe	K	Ca	Cu
Wt %	34.56	11.36	2.30	4.29	4.18	2.80	2.39	4.33	4.55	29.32

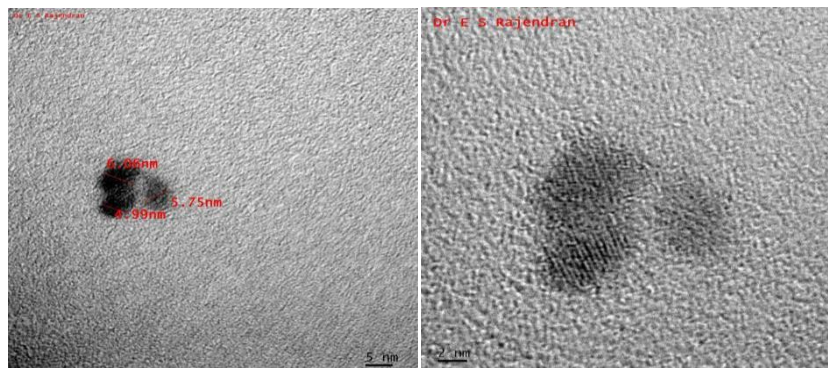
Table 1. Comparative weight percentage of various elements in Field I obtained by EDS**Field II Homeo agrocare****Figure 3****Figure 4 - Magnified image**

Figure 3 and 4 represents the HRTEM images of the particles in Field II. Figure 4 is the magnified image of Figure 3 and Figure 4 is the high resolution lattice fringe phase of Figure 3. Four particles were identified in this field and spectroscopic analysis was done on the same. Particle size: 4.99nm - 6.06nm.

Elements	C	O	Cl	Cr	Fe	Cu	Au	Co	Os
Wt %	87.47	2.5	0.1	0.08	0.13	8.77	0.34	0.13	0.48

Table 2. Comparative weight percentage of various elements in Field II obtained by EDS

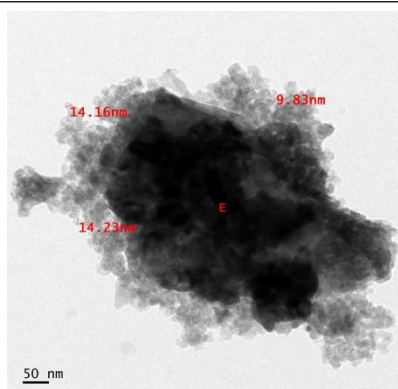
Field III Homeo agrocare

Figure5 - HRTEM images of the particles in Field III. A large agglomerate is seen surrounded by aggregates of particles.

Particle size: 9.83nm - 93.09nm

Elements	C	O	Cl	Si	F	Cr	Mn	Fe	Cu	Ni	Ag	Au	Co
Wt %	13.83	21.31	0.45	10.12	10.06	3.11	1.64	25.07	7.93	0.34	4.08	1.48	0.56

Table 3. Comparative weight percentage of various elements in Field III obtained by EDS

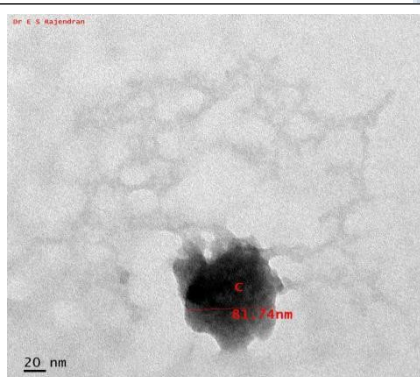
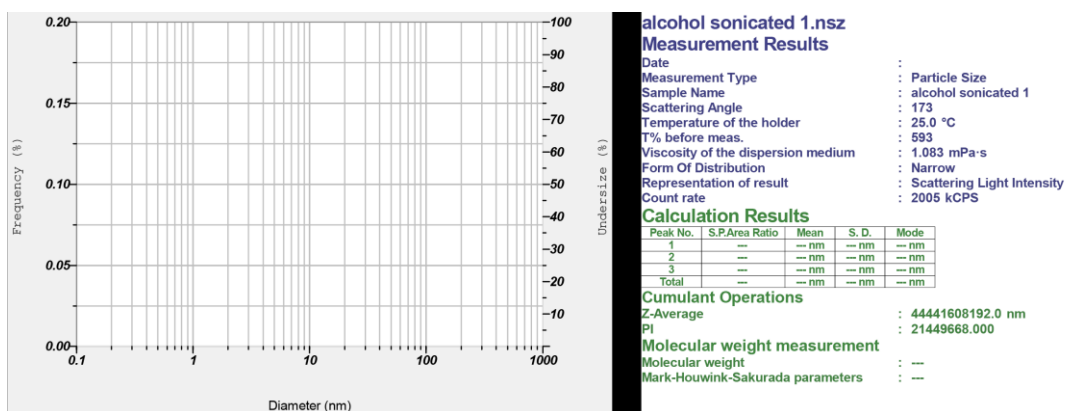
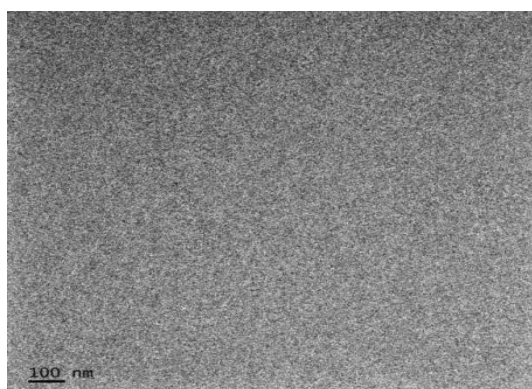
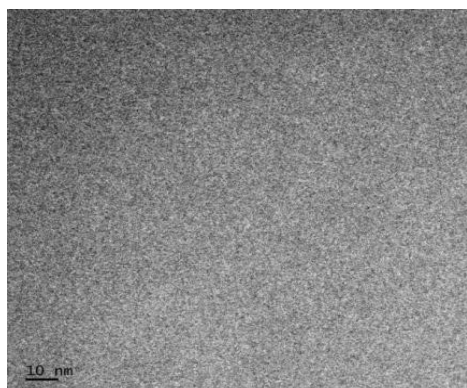
Field IV Homeo agrocare

Figure 6 - HRTEM images of a particle in Field IV.

Particle size: 15.15nm - 81.74nm

Elements	C	O	Na	Cl	Si	P	S	Fe	K	Ca	Cu	Mg	Co
Wt %	74.1	7.47	0.98	0.18	0.34	0.38	0.2	0.19	0.21	3.78	11.5	0.44	0.23

Table 4. Comparative weight percentage of various elements in Field IV obtained by EDS

DLS and HRTEM analysis of control sample (pharmaceutical grade alcohol)**DLS analysis of pharmaceutical grade alcohol****Figure 7.** DLS analysis of pharmaceutical grade alcohol**HRTEM analysis of pharmaceutical grade alcohol****Figure 8.** HRTEM image of control sample (pharmaceutical grade alcohol) in 100nm scale**Figure 9.** HRTEM image of control sample (pharmaceutical grade alcohol) in 10nm scale.

Discussion

The HRTEM and EDS analysis of the homeopathic cocktail agrocare product '*Homoeo agrocare*' shows the presence of nanoscale particles in the drug solution. During the analysis more than 4 TEM fields were studied and the particles analysed. The particle size varied from 4.99nm to 93.09nm. The elementary composition of the particles showed the presence of 20 elements, i.e. C, O, Na, Cl, Si, P, F, S, Cr, Mn, Fe, K, Ca, Cu, Ni, Ag, Au, Mg, Co and Os, which covers the basic elements of majority of drugs used in the formulation. Majority of drugs used in the combination is of plant origin (15 numbers). Remaining drugs are from metallic and mineral sources. Elements like Zn and B are not detected in the studied fields, but there is a high chance of their identification as we analyse more fields. Elements like Ag and Au are seen outside the list of drugs used for the formulation. The identification of these extra elements demands further studies and analysis. The presence of NPs in the combination of '*Homoeo agrocare*' made up of ultra-high dilution of 39 homeopathic drugs can be viewed as a confirmation of the similar results obtained in the earlier studies (1,3,4,5,7,9,12,13,14,15). The presence of NPs in UHDS is not confirming the linearity model of conventional thoughts, hence other scientific possibilities to explain their presence needs to be explored for the future advancement of science. The nanomedicine aspect of homeopathic ultra-high dilutions can open up a new era of inquiry in plant genetics leading to subtle cure for plant diseases. The evidence that homeopathic ultra-high dilution initiates epigenetic modifications like up and down regulations, and switching on and off the genes from bacteria to animal models are pointers to indicate the possibility of the same UHDS to initiate similar modification in plants.

Conclusion

This study conclusively proved the presence of NPs of the original drug materials used in the combination of '*Homoeo agrocare*'. Now it is clearly evident that the earlier hypothesis of homeopathic drug action based on the theories of water memory [69-71], formation of clathrates [72], epitaxy [73], silica hypothesis [74] and quantum physical aspects [75,76], etc. in the current model stands nullified with the clear evidence of the material content of the original homeopathic drug elements in nanoscale. But there is a high possibility that these NPs close to atomic scale can initiate quantum mechanical properties in biological systems and modify water structure. It seems that rational use of homeopathic UHDS can improve agricultural production by improving plant health; prevent and cure diseases. Therefore, all the desired results can be achieved without the extensive use of pesticides and chemicals which damage organic life and environment.

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References

- (1) Chikramane PS, Suresh AK, Bellare JR, Kane SG. Extreme homeopathic dilutions retain starting materials: A nanoparticulate perspective. *Homeopathy* 2010; 99: 231-242.
- (2) Upadhyay RP, Nayak C. Homeopathy emerging as nanomedicine. *Int J High Dilution Res* 2011; 10:299-310.
- (3) Rajendran ES. Field Emission Scanning Electron Microscopy (FESEM) and Energy Dispersive Spectroscopy (EDS) studies of centesimal scale potencies of the homeopathic drug *Lycopodium clavatum*. *American Journal of Homeopathic Medicine*, 2015; 108(1): 9 – 18.
- (4) Bell IR, Muralidharan S, Schwartz GE. Nanoparticle characterization of traditional homeopathically - manufactured *Gelsemium sempervirens* medicines and placebo controls. *J Nanomedicine Biotherapeutic Discov* 2015; 5: 136. doi: 10.4172/2155-983X.1000136.
- (5) Bell IR, Muralidharan S. Schwartz GE. Nanoparticle characterization of traditional homeopathically-manufactured Silver (*Argentum metallicum*) medicines and placebo controls. *J Nanomed Nanotechnol* 2015; 6: DOI: 10.4172/2157-7439.1000311
- (6) Konovalov AI, Ryzhkina IS. Highly diluted aqueous solutions: formation of nano – sized molecular assemblies (nanoassociates). *Geochem Int* 2014; 52: 1207–1226.
- (7) Rajendran ES. An evaluation of Avogadro's number in the light of HRTEM and EDS studies of high dilutions of *Ferrum metallicum* 6, 30, 200, 1M, 10M and 50Mc. *Int J High Dilution Res* 2015; 14: 3- 9.
- (8) Nandy P. A review of basic research on homeopathy from a physicist's point of view. *Indian J Res Homeopathy* 2015;9:141-151.
- (9) Rajendran ES. *Nanodynamics – Nanoscience, Homeopathy, Physical sciences, Nanomedicine*. 1st edition. Cochin: Mohna Publications 2015, pp 43 – 246.
- (10) Demangeat J L. Gas nanobubbles and aqueous nanostructures: the crucial role of dynamization. *Homeopathy* 2015; 104: 101-115.
- (11) Elia V, Ausanio G, Gentile F, Germano R, Napoli E, Niccoli M. Experimental evidence of stable water nanostructures in extremely dilute solutions, at standard pressure and temperature. *Homeopathy* 2014; 103: 44-50.
- (12) Rajendran ES. Nano pharmacological aspect of homeopathic drugs - A comparative study of different scales of ultra-high dilutions based on HRTEM Analysis and NP characterization of homeopathic drug *Natrum muriaticum* 6C – CM and LM1 -LM30. *Saudi J. Med. Pharm. Sci* 2017; 3:89-106.
- (13) Rajendran ES. (2017).Homeopathy a material science! Nanoparticle characterization of *Aurum metallicum* 6c, 30c, 200c, 1000c, 10000c, 50000c and 100000c. *Int J Curr Res* 2017; 9: 48923-48927.
- (14) Rajendran ES.(2017).Homeopathy a nanomedicine – identification and characterization of NPs in *Hypericum perforatum* 6C, 30C, 200C, 1M, 10M, 50M and CM.*International Journal of Development Research* 2017;7(4):12425-12431.
- (15) Rajendran ES. Homeopathy seen as personalised Nanomedicine. *Homeopathy* 2019; 108: 66 - 70.

- (16) Barbosa IS, Valerio TS, Siqueira CM, Salgueiro AM, Gomes N. Evaluation of the effects of Homeopathic medicines on the seed germination of Brassica oleracea L. var. Italica. *Int J High Dilution Res* 2012; 11 (40): 213 - 214.
- (17) Malarczyk E. The activity of enzymes can be modified by homeopathic dilutions of their effectors. *Int J High Dilution Res* 2012; 11 (40): 185 - 186.
- (18) Mondal S, Sukul NC, Sukul S. Natrum mur 200C promotes seed germination and increases total protein, chlorophyll, rubisco and sugar in early seedlings of cowpea under salt stress. *Int J High Dilution Res* 2012; 11 (40): 128.
- (19) Santos FM, Monfort LE, Castro DM, Pinto JE, Leonardi M, Pistelli L. Characterisation of essential oil and effects on growth of Verbena gratissima plants treated with homeopathic Phosphorus. *Nat prod commun* 2011 Oct; 6(10): 1499 - 504.
- (20) Pfleger A, Hofacker J, Scherer-Prongatz W. The effect of extremely diluted agitated gibberellic acid (10^{-30}) on wheat stock growth - a two researcher pilot study. *Complement Ther Med* 2011 Jun; 19(3): 164 - 169.
- (21) Marques RM, Reis B, Cavazian ACT, Moreira FC, Buchoski M, Silva HA, Lolis M, Bonato CM. Germination and vigour of seed of Sorghum (Sorghum bicolor L. Moench) treated with Arsenicum album. *Int J High Dilution Res* 2012; 10 (36): 239 - 244.
- (22) Bonato CM, Pronca GT, Reis B. Homeopathic drugs Arsenicum album and Sulphur affect the growth and essential oil content of mint (Mentha arvensis L.). *Acta Scientiarum Agronomy*; 2009; 31: 101 - 105.
- (23) Teixeira MZ, Solange MTPG. Effects of homeopathic high dilutions on plants: literature review. *Rev. Homeopatia* 2017; 80(3/4): 104 - 120.
- (24) Fagan RV, Reis B, Schawan-Estrada KRF, Bonato CM. High dilution of Belladonna affect the mycelial growth of Corynespora cassiicola in vitro. *Int J High Dilution Res* 2011; 10(36): 245 - 248.
- (25) Khanna KK, Sudhir Chandra. Effect of homeopathic drug on respiration of germinating fungal spores. *Indian phyto path*, 1992; 45 (3): 348 - 353.
- (26) Lensi MM, Siquiera TT, Silva GH. A pilot study of the influence of Natrum muriaticum 6cH and 30cH in a standardized culture of Phaseolus vulgaris L. *Int J High Dilution Res*, 2016; 9(30): 43 - 50.
- (27) Brizzi M, Elia V, Trebbi G, Nani D, Betti L. The efficacy of ultra molecular aqueous dilutions on a wheat germination model as a function of heat and ageing time. *Evidence based Complementary and alternative medicine*; 2011; 696298 doi: 10.1093/ecam/nep217.
- (28) Betti L, Brizzi M, Nani D, Peruzzi M. Effect of high dilutions of Arsenicum album on wheat seedlings from seed poisoned with the same substance. *British Homeopathic Journal*; 1997; 86:2: 86 - 89.
- (29) Datta SC, Datta R. Homeopathic medicines protect environment, health and development by controlling mulberry disease. *J Homeopath Ayur Med* 2013; 1(1): 1 - 7.
- (30) Datta SC, Datta R. Homeopathic medicine Aakshmoni 200C control mulberry diseases enriching sericulture. *J Curr Chem Pharm SC* 2012; 2(1): 37 - 49.
- (31) Bonfim FPG, Dore RGR, Martins ER, Casali VWD. Germination and vigour of lettuce seeds (Lactuca sativa L) pelleted with homeopathic preparations Alumina and Calcareo carbonica subjected to toxic levels of aluminium. *Int J High Dilution Res* 2010; 9(33): 138 - 146.

- (32) Jager T, Scherr C, Shah D, Majewsky V, Betti L, Trebbi G, Bonamin L, Simoes-Wust AP, Wolf U, Simon M, Heusser P, Baumgartner S. Use of homeopathic preparations in experimental studies with abiotically stressed plants. *Homeopathy* 2011 Oct; 100(4): 275 - 287.
- (33) Sen S, Chandra I, Khatun MS. Agrohomoepathy: An emerging field of agriculture for higher crop productivity and protection of plants against various stress conditions. *IJRAR* 2018; 5(4): 52 - 56.
- (34) Arzu Ozkara, Dilek Akyil, Muhsin Konak. Pesticides environmental pollution and health. [http: dx.doi.org/10.5772/63094](http://dx.doi.org/10.5772/63094)
- (35) Sheila Hoar Zahu, Mary H Ward. Pesticide and childhood cancer. *Environmental health prospectives* 1998; 106 (3): 893 - 908.
- (36) Kokuva M, Bitsolas N, Hadjigeorgiou M. Pesticide exposure and lympho haomatopoetic cancers: a case - control study in an agricultural region (Larissa, Thessaly, Greece). *BMC public health* 2011; 11(5).
- (37) De Roos AJ, Zahm SH, Cantor KP, Weisenburger D, Holmes F, Burmeister L, Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med.* 2003, 60: e11-10.1136/oem.60.9.e11.
- (38) Bassil KL, Vakil C, Sanborn M, Cole DC, Kaur JS, Kerr KJ. Cancer health effects of pesticides. Systematic review. *Can Fam Physician.* 2007, 53: 1704-1711.
- (39) Orsi L, Delabre L, Monnereau A, Delval P, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, Leporrier M, Hemon D, Troussard X, Cleavel J. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occup Environ Med.* 2009, 66 (Suppl 5): 291-298. 10.1136/oem.2008.040972.
- (40) Van Balen E, Font R, Cavalle' N, Font L, Garcia-Villanueva M, Benavente Y, Brennar P, De Sanjose S. Exposure to non-arsenic pesticides is associated with lymphoma among farmers in Spain. *Occup Environ Med.* 2006, 63: 663-8. 10.1136/oem.2005.024026
- (41) McDuffie HH, Pahwa P, Mc Laughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposure in men: cross-Canada study of pesticide and health. *Cancer Epidemiol Biomarkers Prev.* 2001, 10: 1155-63.
- (42) Kato I, Watanabe-Meserve H, Koerg KL, Baptiste MS, Lillquist PP, Frizzera G, Burke JS, Moseson M, Shore RE. Pesticide product use and risk of non-Hodgkin lymphoma in women. *Environ Health Perspect.* 2004, 112 (Suppl 13): 1275-81. 10.1289/ehp.7070.
- (43) Agopian J, Navarro JM, Gac AC, Lecluse Y, Briand M, Grenot P, Gauduchon P, Ruminy P, Lebailly P, Nadel B, Roulland S. Agricultural pesticide exposure and the molecular connection to lymphomagenesis. *J Exp Med.* 2009, 206 (Suppl 7): 1473-83. 10.1084/jem.20082842.
- (44) Roulland S, Lebailly P, Lecluse Y, Briand M, Pottier D, Gauduchon P. Characterization of the t(14;18) BCL2-IGH translocation in farmers occupationally exposed to pesticides. *Cancer Res.* 2004, 64: 2264-69. 10.1158/0008-5472.CAN-03-3604.
- (45) Chiu BC, Dave BJ, Blair A, Gapstur SM, Zahm SH, Weisenburger DD. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. *Blood.* 2006, 108 (Suppl 4): 1363-9. 10.1182/blood-2005-12-008755.

- (46) Baris D, Silverman DT, Brown LM, Swanson GM, Hayes RB, Schwartz AG, Liff JM, Schoenberg JB, Pottern LM, Greenberg RS, Stewart PA. Occupation, pesticide exposure and risk of multiple myeloma. *Scand J Work Environ Health*. 2004, 30 (Suppl 3): 215-22.
- (47) Lope V, Perez-Gomez B, Aragonés N, Lopez-Abente G, Gustavsson P, Plato N, Zock JP, Pollán M. Occupation, exposure to chemicals, sensitizing agents, and risk of multiple myeloma in Sweden. *Cancer Epidemiol Biomarkers Prev*. 2008, 17 (Suppl 11): 3123-7. 10.1158/1055-9965.EPI-08-0343.
- (48) Van Maele-Fabry G, Duhayon S, Lison D. A systematic review of myeloid leukemias and occupational pesticide exposure. *Cancer Causes Control*. 2007, 18 (Suppl 5): 457-78. 10.1007/s10552-007-0122-2.
- (49) Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. *Cancer Causes Control*. 2007, 18 (Suppl 10): 1209-26. 10.1007/s10552-007-9061-1.
- (50) Khuda-Bukhsh AR. Potentized homeopathic drugs act through regulation of gene expression: a hypothesis to explain their mechanism and pathways of action in vitro. *Complement Ther Med* 1997; 5:43-46.
- (51) Mondal J, Panigrahi AK, Khuda-Bukhsh AR. Anticancer potential of *Conium maculatum* against cancer cells in vitro: Drug-DNA interaction and its ability to induce apoptosis through ROS generation. *Pharmacogn Mag* 2014; 10: 5524-5533.
- (52) Khuda-Bukhsh AR. Current trends in high dilution research with particular reference to gene regulatory hypothesis. *Nucleus* 2014; 57: 3-17.
- (53) Saha AK, Roy S, Khuda-Bukhsh AR. Ultra-highly diluted plant extracts of *Hydrastis canadensis* and *Marsdenia condurango* induce epigenetic modifications and alter gene expression profiles in HeLa cells in vitro. *J Integr Med* 2015; 13: 400-411.
- (54) Mandal SK, Biswas R, Bhattacharyya SS, Paul S, Dutta S, Pathak S, Khuda-Bukhsh AR. Lycopodine from *Lycopodium clavatum* extract inhibits proliferation of HeLa cells through induction of apoptosis via caspase-3 activation. *Eur J pharmacol* 2010; 626:115-122.
- (55) Khuda-Bukhsh AR, Sikdar S. Condurango 30C induces epigenetic modification of lung cancer – specific tumour suppressor genes via demethylation. *Forsch Komplement med* 2015; 22: 172-179.
- (56) Khuda-Bukhsh AR, Bhattacharyya SS, Paul S, Dutta S, Boujedaini N, Belon P. Modulation of signal proteins: A plausible mechanism to explain how a potentized drug *Secale cor* 30C diluted beyond Avogadro's limit combats skin papilloma in mice. *Evid Based Complement Altern Med* 2011; 286320 doi:10.1093/ecam/nep084.
- (57) Das D, De A, Dutta S, Biswas R, Boujedaini N, Khuda-Bukhsh AR. Potentized homeopathic drug *Arsenicum Album* 30C positively modulates protein biomarkers and gene expressions in *Saccharomyces cerevisiae* exposed to arsenite. *Chin J Integr Med* 2011; 9: 752-760.
- (58) Khuda-Bukhsh AR, De A, Das D, Dutta S, Boujedaini N. Analysis of the capability of ultra-highly diluted glucose to increase glucose uptake in arsenite – stressed bacteria *Escherichia coli*. *Chin J Integr Med* 2011; 9:901-912.

- (59) Marzoto M, Olivos D, Brizzi M, et al. Extreme sensitivity of gene expression in human SH-5Y5Y leukocytes to ultra-low doses of Gelsemium sempervirens. BMC Complement Altern Med 2014; 14: 104-124.
- (60) Sunila ES, Kuttan R, Preethi KC, et al. Dynamized preparations in cell culture. Evid Based Complement Alternat Med 2009; 6:257-263.
- (61) Preethi K, Ellanghiyil S, Kuttan G et al. Induction of apoptosis of tumor cells by some potentiated homeopathic drugs: implications on mechanism of action. Integr Cancer Ther 2012; 11:172-182.
- (62) Mukherjee A, Sikdar S, Bishayee K, et al. Flavonol isolated from ethanolic leaf extracts of Thuja occidentalis arrests the cell cycle at G2-M and induces ROS- independent apoptosis in A549 cells, targeting nuclear DNA. Cell Prolif 2014; 47: 56-71.
- (63) Bishayee K, Chakraborty D, Gosh D, et al. Lycopodine triggers apoptosis by modulation 5-lipoxygenase, and depolarizing mitochondrial membrane potential in androgen sensitive and refractory prostate cancer cells without modulating p53 activity; signaling cascade and drug-DNA interaction. Eur J Pharmacol 2013; 698:110-121.
- (64) Bishayee K, Paul A, Ghosh S et al. Condurango – glycoside-A fraction of Gonolobus condurango induces DNA damage associated senescence and apoptosis via ROS – dependent p53 signaling pathway in HeLa cells. Mol Cell Biochem 2013; 382: 173-183.
- (65) Friso S, Choi SW, Girelli D et al. A common mutation in the 5.10- methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. Proc Natl Acad Sci USA 2002; 99: 5606-5611.
- (66) Baylin SB, Herman JG, Graff JR, et al. Alterations in DNA methylation; a fundamental aspect of neoplasia. Adv Cancer Res 1998; 72:141-196.
- (67) Olsen S. Effects of ultra- high dilutions of sodium butyrate in viability and gene expression in HEK 293 cells. Homeopathy 2017; 106:32-36.
- (68) Fukudome K., Kumamoto Y, Yamaoka K.. Sonication, Fractionation, and Molecular Weight Distribution of Alternating Poly Deoxyribonucleotides: Poly (dG-dC)· Poly (dG-dC) and Poly (dA-dT)· Poly (dA-dT). *Polymer journal* 1995; 27(2): 101-110.
- (70) Davenas E, Beauvais F, Amara J, et al. Human basophil degranulation triggered by very dilute antiserum against IgE. Nature 1988; 333: 816-818.
- (71) Chaplin MF. The memory of water: an overview. Homeopathy 2007; 96:143-150.
- (72) Teixeira J. Can water possibly have memory? A skeptical view. Homeopathy 2007; 96: 158-162.
- (73) Anagnostatos GS. Small water clusters (clathrates) in homeopathic preparation process. In: Endler PC, Schulte J (eds). Ultra High Dilution- Physiology and Physics. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1994, pp 121-128.
- (74) Rao ML, Roy R, Bell IR, Hoover R. The defining role of structure (including epitaxy) in the plausibility of homeopathy. Homeopathy 2007; 96: 175-182.
- (75) Anick DJ, Ives JA. The Silica hypothesis of homeopathy: physical chemistry. Homeopathy 2007; 96:189-195.
- (76) Walach H, Jonas WB, Ives J, Van Wijk R, Weingartner O. Research on homeopathy: state of the art. J Altern Complement Med 2005; 11:813-829.
- (77) Davydov AS. Energy and electron transport in biological systems. In: Ho MW, Popp FA, Warnke U (eds). Bioelectrodynamics and Biocommunication. Singapore. World Scientific Publishing Co Pte Ltd. 1994, Chap 17, pp 411-420.

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