In 1776, more than 200 years ago, a German physician Samuel Hahnemann (1755-1843) noticed during experiments on himself that, after taking the malana remedy quinine he experienced symptoms similar to those of patients with malaria. Similar other tests (later termed "provings" in English and Arzneimittelprüfungen in German) were repeated on himself, his family and friends and the basic principle "similia similibus curentur" or "like cures like" was apparently confirmed. The results of his large scale provings led Hahnemann to conclude that if a compound caused symptoms in healthy volunteers, it should then also serve as a remedy for patients who suffer from such symptoms. In course of his experiments Hahnemann noted with great interest that diluting and vigorously shaking his remedies (a process later termed as "potentization") often rendered the remedy more potent in terms of clinical response. Soon this method of treatment with extremely low doses (ultra low doses) became popular. This was a period when very crude methods like application of heat and cold, blood letting, crude surgeries without anesthesia etc. were largely practised and often such treatments brought more pains to the patients than their sufferings due to diseases. Therefore, it was no wonder that homeopathy initially proved to be a revolutionary and successful mode of treatment and received wide acceptance throughout the world unquestionably up to 1880s (Corea 1976). However, homeopathy started facing stiff opposition from rationalists and scientists that led to its rapid and sharp decline yielding room to various other modes of treatment considered to have a more sound scientific footing. The greatest objections to homeopathy and most powerful argument that caused the apparent downfall of homeopathy is perhaps with the potentization and dilution procedure of the homeopathic medicines. In fact, of the three fundamental homeopathic principles postulated, namely, 1] like cures like, 2] individualization of treatment, and 3] increasing efficacy with increasing dilution, the last mentioned one became a target of vehement attack. In fact a great deal of mysticism, to say the least, prevails in connection with the potentization of homeopathic dilutions (Hahnemann 1960, 1976). Existence of even a single molecule of drug substance in the higher homeopathic dilutions exceeding 24 D (i.e potency 12C) has not only

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In homeopathic potentization procedure the mother tincture (e.g. original extract of the plant if the drug is extracted from the plant) is generally diluted with 99 ml of rectified spirit/ethyl alcohol and given 10 succussions or jerks to produce a potency 1C. Similarly 1 ml of the drug solution at potency 1C is again added with 99 ml of 90% ethanol and produce a potency 2C and in this way by successive dilutions and succussions potencies like 30C (10^-6 dilution), 200C (10^-25 dilutions or above are produced).
been challenged but also the proposed concept "higher the homeopathic dilutions stronger
the medicine" is found to be scientifically inconceivable. Notwithstanding repeated provings of
several potentized homeopathic remedies by Hahnemann and his disciples (see Hering 1956;
Hahnemann 1960;70; Nash 1961, Kent 1962) both on healthy and diseased human subjects
the challengers are not convinced and question the validity of such experiments in the light of
modern scientific standards. Often it is argued by non-believers that patients who might be
cured by homeopathic remedies could also probably be cured without any medicine
whatsoever! Further, the challengers quite legitimately ask the believers to suggest and
explain the mechanism of action of the homeopathic medicines which are claimed to act
clinically without having any original drug molecules at such high dilutions.

But there really exists some methodological difficulties in undertaking clinical research
with accepted scientific norms. One such difficulty is quite explicable. There is no fixed
medicine for any particular disease in homeopathy but there are particular medicines for
particular sets of symptoms. The symptoms of the diseases are therefore all important rather
than the disease itself in the selection of the specific drug. A particular medicine among a
group of medicines is to be selected critically based on totality of symptoms. Thus the first
difficulty that is encountered in carrying out clinical trials is the lack of randomized control
trials (RCTs) which are usually carried out double blind and termed as gold standard of
clinical trial methodology (Feinstein 1980). Therefore, as there is not a single specific
treatment for a single disease, the conventional form of clinical trials would demand to
conduct as many clinical trials for as many diseases and as many remedies used in
homeopathy in order to show causal efficacy for all of them (Walach 1998). Thus in order to
find out whether a homeopathic approach is comparable or superior to a standard treatment
in general and for all sorts of patients a randomized comparable study would be called for.
The question to be answered by a double blind randomized control trial with "placebo" (i.e
"vehicle" of the drug) is whether the homeopathic remedies as such are superior to "placebo"
treatment. But in the long last it often becomes difficult to establish the causal efficacy of
homeopathic remedies over and against "placebo". Therefore it was suggested (Kleznen
clinical trials might be helpful in the acceptance of positive clinical effect of a drug over
placebo on human subjects with any given disease (i.e similar set of symptoms).

Other difficulty in conducting research in homeopathy leading to the understanding of
pathways/mechanisms of action of homeopathic drugs, particularly the potencies above
Avogadro's limit (i.e above potency 12), is the physical absence of original drug molecules in
them. Therefore, to track down even the drug molecule prepared from isotopic element (say
potency 30 of isotopic sulfur) within the human body after its oral administration is next to
impossible. This denies a researcher to track down the exact pathways of movements of the
drug substance which in other systems of medicines e.g., allopathy, is quite possible. Further
in science even a hypothesis needs to be based on solid circumstantial evidences and there
is little scope for speculations without scientific footing. Therefore controlled experiments, with
accepted scientific protocols and immaculate experimental designs to arrive at logistic
conclusions can play the key to the crux of the matter. Thus to understand the mechanisms and pathways of action of homeopathy is basically an interdisciplinary problem concerning physics, biology and medicine involving several methodologies of study; physics, for understanding the possible modes of action of succussions of solutions which do not contain even one molecule of the working/drug substance at least theoretically, biology, for an explanation of the extraordinary biological sensitivity, including a mechanism that works according to Hahnemann's basic simile and potency rules, and medicine, to understand besides medical efficacy, the main role in revealing what "placebo" effects are all about and similar phenomena of "mind body" interactions. The decisive point of homeopathy is therefore the argument that homeopathic remedies are not solutions but are succussions of the efficient/drug substance (or imprints instead of mixture in case of "globuli") (Popp 1998).

Thus in the present investigation an attempt was made to make an interdisciplinary approach, albeit restricted more to some interdisciplinary methodologies. The main focus was on to demonstrate unequivocally the efficacy of some potentized homeopathic drugs (diluted beyond Avogadro's limit) in a mammalian model in vivo by accepted scientific protocols from different disciplines, as for example, cytogenetical (conducted by taking endpoints like chromosomal aberrations, micronuclei formation and mitotic index in bone marrow cells, sperm head anomaly), biochemical (quantitative and gel electrophoretic total protein assay, assay of enzymes like lipid peroxidase, glutamate oxaloacetate aminotransferase, glutamate pyruvate aminotransferase, acid and alkaline phosphatases), histological (histology of liver), and electron microscopy (both SEM and TEM of liver) in mice under normal and experimental carcinogenic exposure. However, only cytogenetical parameters were used in mice receiving exposure to ultrasonication. The experiments were so designed as to have an idea of some quantifiable and visible changes as a result of drug administration and also have insight into the possible pathways and mechanism of action by utilizing some knowledge already available in mice model undergoing chronic exposure to hepatocarcinogenic agents or subjected to ultrasonic sound waves. In the present thesis the findings of our sincere effort have been presented in two chapters of which chapter 1 includes the major works on mice undergoing different phases of hepatocarcinogenesis and chapter II deals briefly with the controversial effects of ultrasonication in mice in vivo and their possible amelioration by a potentized homeopathic drug, and critical analysis of the data of both the chapters to arrive at a logical conclusion on possible mechanisms of action of homeopathic drugs. Included in the first chapter are a few preliminary investigations and their first hand results, as for example, histology, scanning electron microscopy and transmission electron microscopy of the liver, gene expression of p53 and Bax protein. The inclusion has been done mainly to understand possibilities of some research aspects in indicating directions of future research that might prove rewarding on successful pursuance. Therefore, understandably this section might look slightly unorganized at the moment.
On the efficacy and mechanisms of action of certain potentized homeopathic drugs: An interdisciplinary experimental approach through induced hepatocarcinogenesis and ultrasonication in mice.

The works embodied in the thesis have been presented in the following two chapters:

Chapter-I

Efficacy of two potentized homeopathic drugs and Vitamin C (L-Ascorbic acid), fed singly and in combination, in amelioration of p-DAB induced hepatocarcinogenesis in mice at cytogenetical, biochemical and ultrastructural levels.

Chapter-II

Cytogenetic effects of ultrasonication in mice and their amelioration by a potentized homeopathic drug Arnica montana-30.