

Role of Homeopathy in Integrative Cancer Care

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Introduction

Cancer has proven to be a relentless foe in exploiting alternate pathways to resistance to conventional therapies. Cancer patients and survivors often seek alternative approaches while receiving conventional treatments, in the hope of achieving better outcomes in fighting the primary disease, preventing recurrence and improving end of life palliation. Homeopathy is one of such approaches, which was started by physicians in the 19th century based on the theory that any substance that can produce symptoms of disease or illness in a healthy person can cure those symptoms in a sick person using a highly diluted succussed solution (>Avogadro's number or 6.023×10^{23}). In the US, homeopathy is part of the complementary and alternative medicine (CAM) accounting for a \$9 billion market each year [1], with over five million adults and one million children using homeopathy annually [2]. Among the 236 European centers that provide integrative oncology services in the public health system, homeopathy is one of the leading CAM therapies [3]. However, most patients would not discuss their CAM needs or use with their conventional health professionals due to concerns about health professionals' lack of knowledge or interest or fear of negatively impacting their relationship with their health professionals [4]. There is a need for further investigating and possibly integrating feasible and effective alternatives including homeopathic medicines into conventional approaches. Notably, the National Cancer Institute (NCI) Best Case Series Program which invited CAM practitioners treating cancer patients to present data concluded after rigorous evaluations that there was sufficient evidence of a possible efficacy of homeopathic medicine in cancer and that homeopathy warrants further research [5-7].

Despite wide-spread negative views in the scientific community and within the general population at large, many clinical, preclinical and *in vitro* studies indicate the presence of evidence for homeopathy. Homeopathic prophylactic oral formulation for mass immunization using four strains of *Leptospiriosis* administered to 2.3 million people in region of high risk of an epidemic in Cuba in 2007 was found to be effective in significantly decreasing the disease incidence [8,9]. Homeopathic treatment alone using *Ruta* was found to be effective in brain cancer patients with either remission or partial regression [10]. The same study also found that homeopathic *Ruta* can selectively induce cell death in human malignant glioma MGR1, human promyelomonocytic leukemia cell line HL-60, and murine metastatic melanoma K1735 clone X-21, while not adversely affecting proliferation of normal blood lymphocytes [10]. Extended survival time in cancer patients with fatal prognosis such as with glioblastoma, lung, cholangiocellular and pancreatic carcinomas, metastasized sarcoma, and renal cell carcinoma was noted with additive homeopathic treatment in a study with a small sample size [11]. A randomized placebo-controlled trials (RCT) with a sample size of

>1000 patients of hay fever found the use of homeopathic *Galphimia glauca* to be significantly superior over placebo and with success rates similar to conventional antihistamines, but with no side effects [12]. Homeopathy was found to be beneficial in improving quality of life and reducing fatigue and improving Functional Assessment of Chronic Illness Therapy for Cancer scores in cancer patients [13,14]. A significant improvement in the symptoms of the cancer or of the adverse effects of the conventional anticancer therapies such as nausea, insomnia, depression, anxiety, asthenia and hot flushes was seen at a homeopathic clinic funded by the Tuscany Region in Lucca, Italy [15]. Homeopathic *Arsenicum album* was shown to be effective in reducing arsenic poisoning in humans [16,17]. Homeopathy in an integrative approach with conventional medicine has been reported to be used in treating HIV/AIDS in East Africa [18]. A meta-analysis indicated that the clinical effects of homeopathy are not purely due to the placebo effect [19]. Others have also reported specific non-placebo treatment effects [20-23]. Similar positive results were inferred from various RCTs and other studies on homeopathy [24,25]. However, RCTs of individualized homeopathic treatment have to be of a much better quality in order to withstand the critics who equate homeopathy at best with placebo effect [26-28]. Conclusion and interpretation vary depending often on what one is willing to accept as scientific information [29] and further, as a result of bias in the scientific community against homeopathy, it is often easier to publish negative results on homeopathy in the peer-reviewed literature than positive ones [30]. Lack of mechanistic insights has often plagued homeopathy studies, such as the unexplained findings that homeopathic dilutions of anti-IgE antibodies cause human basophil degranulation [31] and homeopathic dilutions of histamine inhibit basophil activation [32].

In animal studies, homeopathic *Ruta graveolens* and *Hydrastis canadensis* led to a 95.6% and 95.8% tumor reduction of Ehrlich Ascites Carcinoma and Dalton's Lymphoma Ascites (DLA) and were found to increase the lifespan of the tumor-bearing animals by 49.7%, and 69.4% respectively [33]. The same study reported that homeopathic *Hydrastis* administered orally significantly inhibited the growth of DLA tumors, with 9 out of 15 tumor bearing animals achieving complete tumor remission. There was significant anti-metastatic activity in B16F-10 melanoma-bearing animals treated with homeopathic *Thuja*, *Hydrastis* and *Lycopodium* [33]. Homeopathic *Sabal serrulata* significantly decreased the proliferation of human prostate cancer PC-3 cells and DU-145 cells and significantly decreased prostate tumor xenograft growth in mice [34]. Homeopathic *Ruta*, *Hydrastis*, *Lycopodium*, *Thuja*, *Chelidonium*, *Natrum sulphuricum*, *Cholesterinum* and *Carcinosinum* were found to exhibit immunomodulatory effects while inhibiting chemically induced carcinogenesis [35,36] and hepatotoxicity in rats and mice [37-39]. Homeopathic *Condurango* was found to modulate certain pro- and anti-apoptotic genes related to a caspase-3-mediated apoptotic pathway in benzopyrene-induced lung tumors in rats [40,41].

In vitro, homeopathic Carcinisin, Phytolacca, Conium and Thuja were found to be cytotoxic to breast adenocarcinoma cell lines MCF-7 and MDA-MB-231, causing cell cycle delay/arrest and apoptosis [42]. Homeopathic Thuja was found to significantly ameliorate benzopyrene-induced DNA damage in perfused normal lung cells of mice [43]. Homeopathic Condurango caused G1-phase cell-cycle arrest, a reduction in histone deacetylase 2 activity and DNA synthesis, and was also found to induce epigenetic modifications and alter gene expression profile in cervical cancer HeLa cells [44,45]. Homeopathic Conium maculatum, Sabal serrulata, Thuja occidentalis, Asterias, Phytolacca, and Carcinisin were found to have no measurable effects on expression of cell growth- or apoptosis- related genes in prostate cancer cell lines (DU-145, LNCaP, MAT-LyLu) and breast cancer cell line MDA-MB-231 [46]. However, homeopathic Gelsemium sempervirens was able to change the expression of 56 genes, of which 49 were down-regulated and 7 were overexpressed in human SH-SY5Y neuroblastoma cells; some of the down-regulated genes belong to G-protein coupled receptor signaling pathways, calcium homeostasis, inflammatory response and neuropeptide receptors [47]. Others have reported that although homeopathic treatment significantly slows cancer progression *in vivo* with a reduction in cancer incidence and mortality [48], there is no distinct effects of the same homeopathic medicine on cancer cells *in vitro* and no alterations of gene expression related to apoptosis or cytokines [49] in the tumor tissues mentioned above.

Recent insights into the potential mechanism of action of the scientifically implausible homeopathic ultra-dilutions are based on evidence of presence of nanoparticles of the original substance persisting across all potencies of a homeopathic medicine even those beyond the theoretical Avogadro's limit [50-52]. Presence of the starting raw materials in nanoparticulate form has been unequivocally confirmed in very high dilutions such as $>10^{23}$ dilutions. Chikramane et al showed that once the bulk concentration is below a threshold level of a few ng/ml all of the nanoparticles levitate to the surface and are accommodated as a monolayer at the top where it is preserved and carried to the subsequent step, thereby forming an asymptotic concentration. Thus, they claim that all dilutions are only apparent and not real in terms of the concentrations of the starting raw materials [53]. Specific nanoparticle of the starting substance in homeopathic may treat infections via improved bioavailability and have anti-inflammatory, antioxidant, and immunomodulatory effects [54]. Potentised substance may also change its own pharmacological effects while modulating host response [55]. Homeopathy was under spotlight when Dr. Luc Montagnier, the discoverer of HIV virus, reported on high dilutions (i.e., 10^{10} and 10^{12} dilutions) of bacterial and viral DNA sequence that form specific nanostructures which are responsible for the electro-magnetic signals that can transfer information [56].

In sum, finding safer and effective armamentarium against cancer remains an ongoing challenge. The recent discovery of presence of nanoparticles in homeopathic medicines could provide the rationale and additional impetus for carrying out well designed RCTs and pre-clinical studies in order to settle the question of efficacy of homeopathy in treating cancer and possibly being part of the future integrative medicine in offering safe, and effective way of combating cancer, as well as to understand the mechanism of action of such therapy.

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