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Homeopathy: Curative, Concurrent, and Supportive Cancer Treatment Potential

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Abstract

Background: Homeopathy is used by 12 to 24% of European cancer patients, representing 40.4% of patients at European integrative cancer centers. In 2011, a Swiss literature review on homeopathy led to homeopathic treatment coverage in the Swiss national health insurance program. Homeopathy for curative pediatric cancer treatment is limited to 7.4% in the Netherlands, but, 76.5% of German parents will use homeopathy as part of their children's cancer treatment. The purpose of this paper is to determine what is needed for homeopathy to play a larger role in curative, concurrent, and supportive cancer treatment.

Methods: PubMed searches in September 2016 and January 2017 were performed with search terms "adverse effects, breast cancer, cancer, cervical cancer, endometrial cancer, homeopathy, ovarian cancer, prevention, treatment". Curative, concurrent, and supportive homeopathic cancer treatments material was taken from these searches.

Findings: At least five homeopathic formulations are immunologic adjuvants, activating natural killer cell destruction of cancer and virally infected cells. Ultramolecular Carcinosin, Phytolacca decandra, Conium, Thuja and Klimaktoplan® are appropriate for *in vivo* breast cancer trials. *Lycopodium clavatum* 5C and 15C are ready for *in vivo* cervical cancer trials. Sulphur 30C, may be considered for non-small cell lung adenocarcinoma treatment trials. Conventional cancer treatment associated anxiety, asthenia, depression, dermatitis, folliculitis, hot flushes, insomnia, nausea and vomiting, and stomatitis, respond to numerous homeopathic treatments including hetero-isotherapy.

Conclusion & Significance: *In vitro* studies and retrospective case series indicate that homeopathy could provide curative cancer treatment for an array of cancers: Breast, cervix, gallbladder, liver, lung, oral, pancreas, periampullary, skin, and stomach. Appropriately designed randomized controlled trials (RCT) based on reproducible homeopathic treatments and clinical protocols, with intent-to-treat analysis will have increased validity. If these RCT have positive outcomes homeopathy will secure a position in curative, concurrent, and supportive cancer treatment.

Keywords: Breast cancer; Cancer treatment; Cervical cancer; Chemoradiation adverse effect treatment; Endometrial cancer; Homeopathy; Integrative cancer treatment

Abbreviations and Glossary X: a substance diluted in the ratio 1:10. 6x or 6D-a decimal series dilution; C: a substance diluted in the ratio 1:100. A 200C- a substance that has undergone 200 cycles of dilution and sucussion (agitation); CH: a Hahnemann centesimal dilution. A 1:100 dilution that is then shaken vigorously; M: a substance diluted in the ratio 1:1,000. 50M- a substance that has been diluted and sucussed 50,000 times; CM- a substance that has been diluted and sucussed 100,000 times; MT – Mother Tincture, identified by Φ or Q in India and the United Kingdom; Potentization: Serial dilution and shaking, extracting a formulation's vital nature.

Introduction

Homeopathy is used by 12 to 24% of European oncology patients, representing 40.4% of patients at European integrative oncology centers [1,2]. In 2011, a Swiss review of the literature on homeopathy led to homeopathic treatment coverage in the Swiss national health insurance program [3]. The uptake of, and underlying rationale for homeopathic cancer treatments varies. A child's cancer leads 76.5% of German parents to use homeopathic cancer treatments for their children [4]. Similarly, 72.2% of Dutch parents of pediatric cancer patients choose integrative treatments for their children to promote health and wellbeing [5]. Of the Swiss parents who use integrative treatments for their children's cancer, 49% do so to increase the likelihood of curative treatment [6]. However, only 7.4% of Dutch parents choose integrative treatments to cure their children's cancer, and only 6% of Australian parents used homeopathy for their children who have terminal cancer [5,7].

In Italy 22.8% of cancer patients have previously used homeopathy, but as few as 6.4% may currently use homeopathy [8]. Pearson χ2-test and multivariate logistic regression analyses identified that sense of coherence, an indicator of psychological resilience is associated with current and past use of integrative cancer treatment ($p=0.050$ and $p=0.023$, respectively) [8]. Pre-cancer diagnosis integrative medicine use, and phase of the care process also predicted integrative cancer treatment use ($p<0.001$ and $p=0.012$, respectively) [8]. For each patient homeopathy use also varies with disease course, personal resilience, and prior personal integrative medicine use [8]. Cumulative Wilcoxon test determined that homeopathic cancer treatment initiated on average 18- to 19-months post cancer diagnosis, may significantly extend survival in glioblastoma grade IV, inoperable cholangiocellular cancer, and metastasized sarcoma, overall $p=0.001$ [1].

The foregoing will ascertain the current extent of available homeopathic treatments for curative, concurrent, and supportive cancer care. Homeopathy treatment development in progress and potential directions for homeopathic treatment research will be presented. Adverse effects of homeopathy in particular, and those that apply to medical practice in general will be reviewed.

Methods

PubMed was searched in September 2016 for publications search terms "homeopathy cancer treatment" from 2012 onwards. PubMed searches in January 2017 were performed with the search terms "adverse effects, homeopathy, breast cancer, cancer, cervical cancer, endometrial cancer, ovarian cancer, prevention, treatment". Curative, concurrent, and supportive homeopathic cancer treatments material was taken from these searches. Thirty-three of 41 articles were included in the initial PubMed search. The cancer type specific PubMed searches yielded 6 duplicate articles. Only two of 20 articles found on the specific adverse effect search were included. Adverse effects of homeopathic cancer treatments were also taken from included articles found on the other searches. Supplemental specific hand searches were performed as needed, yielding 10 articles for a total of 45 included articles. The article selection process is shown in **Figure 1**.

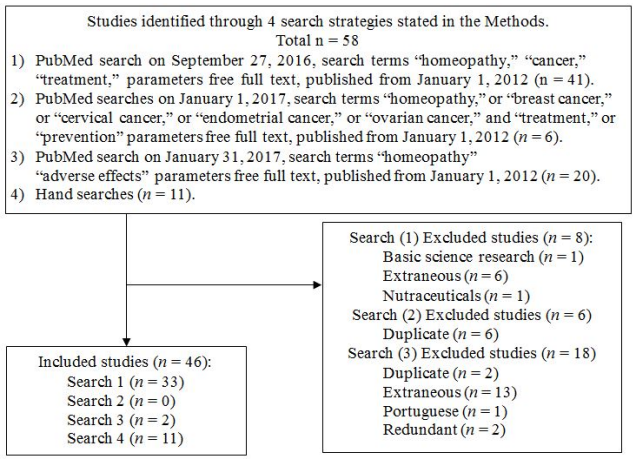

Figure 1: Literature selection flowchart.

Results

Homeopathic cancer treatments

From 1990 to 2005, by prescribing specific homeopathic treatments for specific cancers, the Prasanta Banerji Homeopathic Research Foundation (PBHRF), Kolkata, India, from a base of 17,324 cancer patients, achieved 19% complete regression and 21% stabilization or partial regression rates [3]. Therefore, the American National Cancer Institute (NCI) opened-up to integrative cancer treatment research [3]. Subsequent trials did not reproduce the PBHRF's outcomes [3,9]. The Indian NCI Best Case Series found supportive cases of successful homeopathic treatment of adenoid cystic carcinoma, gastric, gallbladder, lung, and pancreatic adenocarcinomas, and malignant epithelial tumors [10]. The actual treatments used are not provided [10]. A murine trial of the PBHRF medications *Conium maculatum* (hemlock) 200CH, *Thuja occidentalis* (Thuja; Arbor vitae) 200CH, *Phytolacca decandra* (Phyto; poke root) 200CH, *Carcinosinum* (primarily derived from cancerous breast tissue) 200CH, daily at. 1 mL/10 g body weight, found that *Carcinosinum 200CH* resulted in the longest survival and the least adverse effects [11].

The PBHRF combined ultramolecular formulations diluted beyond Avogadro's limit, *Ruta graveolens* (*Ruta*; Rue) 6c and *Calcerea phosphorica* (lime phosphate) 3X protocol have achieved 85.7% complete remission in glioma patients, without adjuvant chemoradiation [3,4]. *Ruta 200C* and *Phosphorus 1M (1000C)* inhibit N′-nitrosodiethylamine (NDEA)-induced hepatocellular carcinoma in rats and 3-methylcholanthrene-induced sarcomas in mice [3]. *Ruta 9c* dosed at 2-mL daily for 8 or more weeks, used to treat locally-advanced solid cancers or metastatic cancers initially produced significantly improved quality of life (QOL) as measured by the EORTC QLQ-C30 questionnaire, that elapsed by the end of the trial in 28 weeks [12].

Ultramolecular *Carcinosin* and *Phyto* display MCF-7 and MDA-MB-231 breast adenocarcinoma cell lines apoptotic and cell cycle delay effects akin to Paclitaxel. Unlike Paclitaxel, Carcinosin and *Phyto* spare normal mammary epithelial cells [3,4]. *Phyto 30CH* trialed against 4T1 breast adenocarcinoma cells in female BALB/c mice showed greater cancer inhibition, reduced metastasis and angiogenesis and tumor weight, than *Phyto 6CH, 12CH, or 200 CH* [13]. Ultramolecular *Conium* and *Thuja* also display apoptotsis and cell cycle delay against MCF-7 and MDA-MB-231 [14]. Traditionally, Conium has been used for breast and cervical cancer treatment [14]. *Thuja* is a homeopathic treatment for polypus tumors and warty lesions [15]. *Thuja* uses bi-phasic reactive oxygen species (ROS) generation to promote cytochrome-c release and caspase-driven mitochondrial apoptosis in MCF-7 cells [15]. A 20 µl/ml dose of 30C *Thuja* achieves time-dependent maximal MCF-7 cell death but spares normal peripheral blood mononuclear cells (PBMC) for 24 hours [15]. *Thuja* also inhibits melanomatous lung metastasis and reduces lung collagen hydroxyproline content in C57BL/6 mice [3].

As with conventional cancer treatment, homeopathic breast cancer treatment can vary based on the cancer subtype. *Calcarea carbonica* may be most used for ductal cancers, then infiltrating cancers, and least used for other breast cancers, including metastatic cancers [16]. *Carcinosin* would be used almost equally for ductal and infiltrating cancers, and about one-third as often for other breast cancers, including metastatic cancer [16]. *Conium* would be the least used, but evenly used across breast cancer types [16]. *Phyto* would be almost exclusively used for non-ductal, non-infiltrating, non-metastatic breast cancers [16]. *Thuja* would be almost evenly used across all breast cancer types other than metastatic breast cancers [16]. Biochemical salt use is evenly distributed across breast cancer subtypes [16]. This treatment distribution achieved a 14% cure rate in a case series of 100 cases, with 41 prevented, 14 palliated, and 31 improved cases [16]. It is unclear what is meant by prevented and improved [16].

In vitro application of mother tincture (MT) and ultramolecular dilution (30C, 200C, 1M, and 10M) of *Sars*aparilla (*Sars*; from wild licorice [*Astragalus glycyphyllos*, *Aralia nudicaulis*, or *Glycyrrhiza lepidota*]) to human renal adenocarcinoma, *Ruta* to human colorectal carcinoma, and *Phyto* to MCF-7 human breast carcinoma cell lines displayed cytotoxicity at all concentrations, $p<0.001$, by one-way analysis of variance (ANOVA) [4]. *Sars MT* was 82.3% cytotoxic, with cytotoxicity continuing after *Sars* removal, *Ruta* MT was 66.5%

cytotoxic, and *Phyto* was 72.6% cytotoxic [4]. These cytotoxicity findings are consistent with the literature [4]. At 48 hours, *Sars*, *Ruta*, and *Phyto* showed a concentration-dependent significant reduction in cell proliferation, $p<0.05$ [4]. *Sars* had a maximum cytotoxicity of 22.1% against MDCK normal kidney epithelial cell line [4]. *Ruta* is associated with down-regulation of B-cell lymphoma 2 (Bcl-2), up-regulation of caspases-3 and -9, Bcl-2-associated X (Bax), p21 and p27 expression leading to intrinsic apoptosis and G2/M cell cycle checkpoint arrest [17]. *Ruta* has shown selective cytotoxicity to Glioblastoma multiforme while sparing normal peripheral blood lymphocytes (PBMC) [3].

In vitro application of *Phyto* MT to A375 melanoma cells indicated ROS elevation, caspase-mediated apoptosis, with minimal PBMC cytotoxicity [18]. *Phyto* MT showed intermediate cytotoxicity to HeLa cervical cancer cells and PC3 prostate cancer cells [18]. Consistent with the above, down-regulation of Bcl-2 and Akt (the gene for protein kinase B), and upregulation of p53 and Bax also occurred [17,18]. *In vitro*, by Student paired t test and one-way ANOVA, *Lycopodium clavatum* (running clubmoss) *5C* and *15C* are dose dependently selectively cytotoxic to HeLa cells ($p<0.001$), and spare PBMC [19]. *L. clavatum* 5C and 15C non-dose dependently induce DNA fragmentation, promote caspase-3 ($p<0.001$) and Bax ($p<0.001$), but reduce apoptotic protease activating factor 1 (Apaf1; $p<0.01$), Bcl-2 ($p<0.001$), and cytochrome-c ($p<0.001$) [19].

In vivo C. carbonica (M8) diluent directly inhibits B16F10 murine melanoma cell adhesion and invasion, and inhibits melanoma growth and metastasis by decreasing perlecan (heparin sulfate proteoglycan 2 [HSPG2]) expression [4,20]. *C. carbonica* 6C produces 30% to 35% cancer cell apoptosis in Ehrlich's ascites carcinoma (EAC), Sarcoma-180 (S-180), MCF-7, MDA-MB-231, and HBL-100 breast cancer bearing Swiss albino mice, providing a survival advantage, $p<0.001$, by Student's t test [21]. *C. carbonica* upregulates Bax, depolarizing mitochondrial membranes and activating caspase cascade, facilitating cytochrome c release, and upregulating p53 [21]. Wild-type p53-expressing MDA-MB-231 cells were least responsive to *C. carbonica* T cell-mediated apoptosis [21]. *C. carbonica* also modulates cancer-induced anti-T-cell proliferation effects and reverses type-2 cytokine bias [21]. With a 27-day treatment regime cancer cells did not develop resistance to *C. carbonica* [21].

Sabal serrulata (Saw Palmetto) displays caspase-independent cytotoxicity in human prostate cancer cells, effective when other homeopathic treatments are ineffective [3]. *Sulphur* is apoptotic to oral cancer, immortalized oral keratinocytes, and neuroblastoma cells [22]. *Sulphur 6C, 30C*, and *200C* showed dose dependent apoptosis against the A549 non-small cell lung adenocarcinoma (NSCLC) cell line, with 20 µl/ml of *Sulphur 30C* being most cytotoxic, $p<0.001$ [22]. *Sulphur* disturbs p65NF-κβ nuclear translocation, association with p300 histone acetylase, and Bcl-2 transcription [22]. *Sulphur* induces p53-p300 cross-talk, increasing p53 transcription and intrinsic mitochondrial death cascade [22].

The fluid from blisters formed in response to scabies infestation is the active ingredient of *Psorinum*. *In vitro*, with WRL-68 normal hepatocyte cells as a control, *Psorinum-6x*, has dose dependent, greater cytotoxicity against A549 NSCLC than HepG2 hepatocellular carcinoma and MCF-7 breast cancer cell lines [23]. *Psorinum-6x* inhibits cell proliferation, arrests cell cycle at sub-G, induces morphological changes (chromatin condensation and nucleosomal fragmentation), DNA damage, and phosphatidyl serine externalization [23]. It is hypothesized that *Psorinum-6x* generates ROS, which depolarizes mitochondrial membranes, driving cytochrome-c into the cytosol [23,24]. Simultaneously, p53 induction activates caspase-3 dependent mitochondria-mediated apoptosis, and reduces Bcl-2 but induces Bax (increasing the Bax:Bcl-2 ratio), thereby increasing apoptosis [23].

The Critical Cancer Management Research Centre & Clinic (CCMRCC) of Kolkata, India formulation of *Psorinum-6x*, is dosed at 0.02 mL/kg body weight/day on an empty stomach for 2 years, as the sole anti-cancer treatment in a hybrid conventional and integrative treatment protocol [9,25]. This regime achieved complete response in metastatic adenocarcinoma of the gallbladder, and partial response in metastatic periampullary and liver adenocarcinoma, all without adverse effects [25]. A retrospective study of 246 gallbladder, liver, lung, oral, pancreatic, and stomach cancer patients also supports *Psorinum* use [25].

In vitro Klimaktoplan®, a menopausal relief formulation with *Cimicifuga racemosais* (black cohosh), *Sepia officinalis* (common cuttlefish), *Strychnos ignatia* (St. Ignatius bean tree), and *Sanguinaria canadensis* (bloodroot) has a concentration-dependent anti-proliferative effect on MCF-7 cells, with 625 and 1,250 µg/mL inhibiting proliferation by 11.1% and 41.7% respectively, $p<0.01$, by Student's t test, without affecting MCF-10A non-malignant mammary cells [26]. Klimaktoplan®'s efficacy is biologically plausible for several reasons. A triterpene glycoside actein constituent of black cohosh has known apoptotic activity against estrogen receptor negative Her2 breast cancer cells [26]. Black cohosh is cytotoxic on estrogen-sensitive and estrogen insensitive breast cancer cells [26]. *Sanguinaria* has demonstrated reactive oxygen species (ROS) dependent apoptotic activity against MDA-MB-231 human breast cancer cells and synergism with tumor necrosis factor apoptosis-inducing ligand (TRAIL)-mediated apoptosis. [26].

In vitro studies found *Murex purpurea*, derived from muricid whelks, using a formulation with minimal 6-bromoisatin, and recommended for endometrial cancer treatment, to be at most minimally effective [27]. 6-bromoisatin is related to indirubin, the active ingredient of *Danggui Luhui Wan*, a traditional Chinese Medicine that treats leukemia, lung, and prostate cancers [27]. *In vitro*, isatins and isatin analogues are anti-proliferative by micro-tubular formation inhibition, chemopreventive, and activate caspases-3 and -7 mediated U937 and Jurkat lymphoma cell line apoptosis [27].

Homeopathy as concurrent cancer treatment: chemosensitization

Concurrent immunotherapy uses immune cells to identify and destroy cancer and virally infected cells, reducing the tumor burden and potential for malignant transformation that conventional cancer treatment must address [28]. NKCs produce immunosurveillant cytokines IL-2, IL-12, IL-18, and IL-21. NKCs quickly and selectively kill cancer and virally infected cells via non major histocompatibility complex class-I (MHC-I) restricted action, before high levels of cell membrane MHC-I molecules are evident [28]. However, conventional chemotherapeutics such as bortezomib, chlorambucil, cladribine, docetaxel, MG-132, paclitaxel, and vinblastine, inhibit NKC-mediated cancer and virally infected cell killing, without preventing NKC activation [28]. Thus, concurrent treatments able to activate NKCs complement conventional chemotherapeutics. Aloe vera, ascorbic acid, and flavonoids increase NKC activity [28]. In a three-month long *in vivo* trial, the homeopathic treatments Ubichinon Compositum®

Glyoxal Compositum®, Katalysatoren® and Traumeel® Coenzyme Compositum®, listed from most to least cytotoxic, demonstrated increased natural killer cell (NKC) cytotoxic activity, $p<0.05$ [28]. Paired-sample t-test of data means and one-way ANOVA analysis of chemotherapy effects on biological markers were used [28].

Homeopathic supportive cancer treatment: chemotherapy adverse effect resolution

Supportive care includes treatment of the adverse effects from usual disease treatments, as well as the treatment of psychological, social, and spiritual problems due to a disease or its usual treatment [29]. Conventional cancer treatments' adverse effects are treated with *Nux vomica* (from *Strychnos nux-vomica L.*), Radium bromatum, *Belladonna*, *Lachesis* (from bushmaster snake venom), and *Sepia*. These homeopathic treatments improve nausea ($p=0.039$), insomnia ($p=008$), depression ($p=0.004$), anxiety ($p=0.007$), asthenia ($p=0.007$), and hot flashes ($p=0.008$) [30]. Female breast cancer patients in a Jadad score 5, triple blind randomized control trial (RCT), studying *Sepia*, *Calcarea carbonica*, Sulfur, *Llachesis*, *Kali arbonicum*, and amyl nitrate containing Hyland's Menopause tablets, *Sanguinaria canadensis*, and *Lachesis*, achieved significantly improved general health [3].

A Phase III RCT, Jadad/Oxford score ≥ 3/5, of *Cocculine*, a complex homeopathic remedy registered in France for nausea and travel sickness treatment was performed with 431 non-metastatic breast cancer patients before starting six cycles of chemotherapy beginning with three or more cycles of 5-Flurouracil, adriamycin, and cyclophosphamide (FAC 50), 5-Flurouracil, epirubicin, and cyclophosphamide (FEC 100), or Taxotere, adriamycin, and cyclophosphamide (TAC) did not find an effect on nausea, vomiting, global emesis, or quality of life [31]. *Cocculine*, is comprised of *Cocculus indicus 4 CH*, *Nux vomica 4 CH*, *Petroleum 4 CH*, and *Tabacum 4 CH* [31]. Nausea, vomiting, and overall emesis was measured by Functional Living Index for emesis (FLIE) scores [31]. Analysis was by Mann-Whitney U test, Pearson's chi-square test, or Fisher's exact test [31].

Homeopathy is also effective treatment for chemotherapy-induced stomatitis and radiation-induced dermatitis [3,4]. Based on Short Form 36 (SF-36) homeopathic remedies for menopausal symptoms significantly improve breast cancer survivors' QOL, $p=0.02$ for single remedy, and $p=0.03$ for combination remedy [32]. An Austrian, 410-patient RCT compared conventional cancer treatment to conventional cancer treatment with homeopathy that could be changed at each of three visits [33]. At least 20 different homeopathic treatments were used by 10 or more patients in the adjunctive homeopathy group [33]. Significantly improved cognitive, emotional, physical, role, and social functioning, global health status, and subjective wellbeing, as well as, reduced fatigue, pain, dyspnea, insomnia, and appetite loss, $p<05$ in all cases, were achieved by the homeopathy group [33]. Only constipation, diarrhea, and nausea and vomiting were not significantly improved in the homeopathy group [33]. While Bonferroni-Holm adjustment for multiple secondary outcomes was performed, this RCT is limited by lack of intent to treat analysis [33]. Access to other integrative treatments, and the flexible homeopathic treatment selection, preclude facile study replication and transfer protocolized clinical practice.

Hetero-isotherapy uses the substance that caused an adverse reaction in an homeopathic dilution [34]. Recognized in France in 1965, hetero-isotherapy is accepted by the French health insurance system as homeopathic medicine [34]. Hetero-isotherapy solutions gradually changed from 5C to 15C, are taken the day following chemotherapy [34]. *Rhus toxicodendron* associated hetero-isotherapy resolves epithelial growth factor inhibitor caused folliculitis, permitting treatment continuance [34]. Hetero-isotherapy has facilitated completion of 5-year hormone therapy protocols [34]. Cantharis, a nutraceutical treatment for burns, blisters, cystitis, urinary tract infections, and digestive disorders, contains cantharidin, a toxic product of *Lytta vesicatoria* (the Spanish fly or blister beetle) that inhabits honeysuckle and olive trees. *Sorafenib 7c* and *Cantharis 7c* combination hetero-isotherapy resolves *sorafenib* induced hand and foot syndrome within two months [34]. *Sorafenib* is a kinase inhibitor for advanced renal cell carcinoma, advanced hepatocellular carcinoma, and radioactive iodine resistant advanced thyroid carcinoma treatment. If *Sorafenib 7c* and sorafenib are begun simultaneously, Cantharis may be unnecessary [34].

Homeopathy's adverse effects

A systematic review of eight controlled homeopathic cancer treatment trials encompassing 664 participants did not find serious adverse effects [3]. Nonetheless, like conventional treatments, homeopathic treatments cannot be used blindly. *In vitro* application of aristolochic acid containing *Aristolochia clematitis L.* and *Asarum europaeum L.* MT exhibits dose-dependent DNA synthesis inhibition in human hepatoma HepG2 cells, leading to S-phase arrest, despite p53 and p21 induction [35]. Therefore, some nations have banned Aristolochia spp. for carcinogenicity [35]. Nutraceuticals containing Piper methysticum (kava) or Symphytum officinale (comfrey) should also be avoided due to potential hepatoxicity [5]. Kava has been banned in several nations due to potential hepatotoxicity. At 100-fold the recommended therapeutic dose kava has been associated with extrapyramidal adverse effects and reversible, yellow, ichthyosiform kava dermopathy. Comfrey halves healing time, but is associated with pulmonary toxicity and cancer.

In one study, more than 74 integrative medicine preparations contained toxic organic substances as above, excessive heavy metals, or had microbial contaminants [36]. Homeopathic treatments containing allergenic conventional medications without disclosure to the consumer have been voluntarily withdrawn from the United States market [37]. Clearly, numerous homeopathic treatments use known poisonous plant and animal sources [38]. Consistent with this, ultramolecular preparations are necessary for patient's safety [38,39]. Hence it is biologically plausible that ultramolecular, non-succussed preparations are sufficient to produce cellular response, as indicated from *in vitro* studies of Arsenicum album 6CH, 30Ch, and 200CH on the MT4 continuous cell line [40].

Active ingredient substitution or toxic overconcentration, especially without proof of efficacy and safety, are forms of health fraud in the United States of America [37]. Since October 3, 2010 the United States Food and Drug Administration (FDA) has pursued Hyland's Teething Tablets, purportedly comprised of calcium phosphate, chamomile, crude coffee, and belladonna 12X or 0.0000000000003% alkaloids, which is not the formulation of Dentokind® [37]. Hyland's Teething Tablets had belladonna toxicity and injured babies without proof of efficacy: Agitation, constipation, respiratory and voiding difficulty, lethargy, muscle weakness, seizures, skin flushing, and somnolence occurred following purchase in non-tamper proof containers [37]. Pharmacies have stopped selling Hyland's teething tablets, proving more responsible than the manufacturer [41].

Over the counter sale of homeopathic treatments such as Hyland's teething tablets is an example of lack of supervision of homeopathy. Although only 62% of integrative cancer treatment was under direction of an integrative practitioner, only six adverse effects from homeopathy and phytotherapy were reported by a group of 457 German pediatric cancer patients [42]. The adverse effects ranged from nausea and vomiting, to skin rash and primary aggravation of symptoms, none of which required medical intervention [42]. In one study, homeopathic combination remedies that included mistletoe were associated with increased headaches at 6 and 12 months (p=0.04 and p=0.03, respectively) [32]. Localized injection site reactions occurred in a study of subcutaneous mistletoe therapy [32]. Nonuse of conventional treatment due to homeopathy use can contribute to disease progression, which is considered an adverse effect of homeopathy use, and an indication of unprofessional conduct [38]. Acute lymphatic leukemia is a malignant condition for which this has occurred [38]. There is a blurred distinction between an adverse effect and anticipated homeopathic aggravation from like treating like [38]. Again, professionalism is necessary in the identification and reporting of homeopathic aggravations and genuine adverse effects [43].

Discussion

Clinical trial populations should be age- and gender matched. This is especially true for trials of homeopathic remedies for chemotherapy induced nausea and vomiting prophylaxis. Different drugs induce nausea and vomiting via different mechanisms, and of varying severity [45]. Iatrogenic nausea and vomiting also has age- and gender-based incidence [44,45]. Thus, inconsistent trial outcomes may reflect different trial populations (despite similar diagnosis), different chemotherapeutic regimes, and different outcomes measurements.

Consistent preparation methodology for homeopathic remedies is essential for consistent outcomes. That subsequent trials did not reproduce the PBHRF's outcomes has been attributed to differences in homeopathic treatments' production [3,9]. Logically, preparations with different initial active ingredient constituents and concentrations will achieve different results despite being assigned the same name [27]. Hence, non-reproducibility of the PBHRF's outcomes has been attributed to differences in homeopathic remedies' preparation [3,9].

Standardized formulations with identical amounts of active ingredients should be used in RCT. Formulations containing differing levels of main ingredients, for instance 6-bromoisatin in *M. purpurea*, preclude reproducibility, setting an example to be avoided [27]. It is biologically plausible that an appropriately concentrated 6-bromoisatin containing *M. purpurea* treatment would have anti-cancer activity closer in effectiveness to *Danggui Luhui Wan* [27]. Similarly, nanoparticles and nanobubbles can affect a solution's biochemical and biological activity [39].

It is biologically plausible that homeopathic remedies with caspase-independent cytotoxicity, such as Sulphur, will be effective in situations in which homeopathic treatments that only have caspase-dependent cytotoxicity are ineffective [3]. Just as NKC activating remedies are synergistic with conventional NKC inhibiting chemotherapeutics [28], combinations of treatments with caspase-independent and caspase-dependent cytotoxicity should be synergistic.

Future Research

Fixed integrative medicine protocols are used by 70.2% of European integrative oncology centers [2]. These protocols may pave the way for reproducible clinical trial protocols. Future RCT of homeopathic cancer protocols should use reproducible protocols, allowing execution of corroborating RCT, and transference to clinical practice if appropriate. Use of identical cell lines and animal models in homeopathic, nutraceutical, or phytochemical trials would allow direct comparison across studies and systematic reviews with meta-analyses. Clinical trials should be designed to prevent delayed entry time bias (the delay in first treatment from the point of first diagnosis) and immortal time bias [44]. When only treatment responders are analyzed, selection and positive responder biases can occur, therefore, future RCT should use intent to treat analysis enhancing trial reproducibility and validity [33].

Increased homeopathic treatment potentization procedure standardization is necessary for realistic attempts at reproducibility trials [46]. If consistently prepared remedies are available, corroborating *in vivo* breast cancer trials for the PBHRF standalone ultramolecular glioma treatment protocol, *Ruta graveolens 6c* and *Calcerea phosphorica 3X*. Ultramolecular *Carcinosin*, *Phytolacca decandra*, *Conium*, *Thuja* and Klimaktoplan® are appropriate. Similarly, when the aforementioned preparation and formulation issues have been resolved, numerous homeopathic remedies will be candidates for RCT. *Lycopodium clavatum 5C and 15C* should be considered for *in vivo* cervical cancer trials. *Sulphur 30C*, may be considered for non-small cell lung adenocarcinoma treatment trials. The CCMRCC *Psorinum-6x* formulation could undergo confirmatory trials for gallbladder, lung, oral, pancreatic, stomach, periampullary and liver adenocarcinomas.

Conclusion

Clearly, patients can derive benefit from appropriate homeopathy use, yet patients' uptake of homeopathy varies globally. Current global homeopathy use has laid a foundation to be built upon. If the RCTs suggested above, or the equivalent thereof, are accomplished with positive outcomes homeopathy may secure a position in curative cancer treatment. That notwithstanding, access to reputable homeopathic practitioners who practice professionally is necessary to improve the perception of the appropriateness of homeopathy. Properly manufactured homeopathic treatments, which are free from active ingredient substitution, active ingredient overconcentration, contaminants, and prohibited substances are crucial to patient safety and to rebuild the professional reputation of homeopathy. Perhaps then patients' uptake of homeopathy may increase globally and the geographical variances lessen.

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References

1. Gaertner K, Müllner M, Friehs H, Schuster E, Marosi C, et al. (2014) Additive homeopathy in cancer patients: Retrospective survival data from a homeopathic outpatient unit at the Medical University of Vienna. Complement Ther Med 22: 320-332.

2. Rossi E, Vita A, Baccetti S, Di Stefano M, Voller F, et al. (2015) Complementary and alternative medicine for cancer patients: results of the EPAAC survey on integrative oncology centres in Europe. Support Care Cancer 23: 1795-1806.
3. Frenkel M (2015) Is There a Role for Homeopathy in Cancer Care? Questions and Challenges. Curr Oncol Rep 17: 43.
4. Arora S, Aggarwal A, Singla P, Jyoti S, Tandon S (2013) Anti-proliferative effects of homeopathic medicines on human kidney, colon and breast cancer cells. Homeopathy 102: 274-282.
5. Singendonk M, Kaspers GJ, Naafs-Wilstra M, Schouten-van Meeteren A, Loeffen J, et al. (2013) High prevalence of complementary and alternative medicine use in the Dutch pediatric oncology population: A multicenter survey. Eur J Pediatr 172: 31-37.
6. Magi T, Kuehni CE, Torchetti L, Wengenroth L, Luer S, et al. (2015) Use of Complementary and Alternative Medicine in Children with Cancer: A Study at a Swiss University Hospital. PLoS One 10: e0145787.
7. Heath JA, Oh LJ, Clarke NE, Wolfe J (2012) Complementary and alternative medicine use in children with cancer at the end of life. J Palliat Med 15: 1218-1221.
8. Bonacchi A, Fazzi L, Toccafondi A, Cantore M, Mambrini A, et al. (2014) Use and perceived benefits of complementary therapies by cancer patients receiving conventional treatment in Italy. J Pain Symptom Manag 47: 26-34.
9. Pal SK (2013) Homeopathic approach for cancer treatment: my experience. J Altern Complement Med 19: 478-479.
10. Olaku O, Zia F, Santana JM, White JD (2013) The National Cancer Institute best case series program: A summary of cases of cancer patients treated with unconventional therapies in India. Integr Cancer Ther 12: 385-392.
11. Amaral JG, Hurtado EP, Cardoso TN, Petrillo M, Carvalho A, et al. (2014) Pilot Study: evaluation of the efficacy of homeopathic anti-tumor protocols in Ehrlich tumor. IJHDR 13: 143.
12. Freyer G, You B, Villet S, Tartas S, Fournel-Federico C, et al. (2014) Open-label uncontrolled pilot study to evaluate complementary therapy with Ruta graveolens 9c in patients with advanced cancer. Homeopathy 103: 232-238.
13. Nogueira L, de Cavalho JR, Cardoso TN, Dalboni LC, Konno FT, et al. (2016) Phytolacca decandra 30 CH dilution as an anticancer agent in murine mammary adenocarcinoma model. IJHDR 15: 11.
14. Mondal J, Panigrahi AK, Khuda-Bukhsh AR (2014) Anticancer potential of Conium maculatum extract against cancer cells *in vitro*: Drug-DNA interaction and its ability to induce apoptosis through ROS generation. Pharmacogn Mag 10: S524-S533.
15. Saha S, Bhattacharjee P, Mukherjee S, Mazumdar M, Chakraborty S, et al. (2014). Contribution of the ROS-p53 feedback loop in thuja-induced apoptosis of mammary epithelial carcinoma cells. Oncol Rep 31: 1589-1598.
16. Kalra K (2016) Homoeopathy in breast cancer. Natl J Integr Res Med 7: 131-135.
17. Arora S, Tandon S (2014) DNA fragmentation and cell cycle arrest: A hallmark of apoptosis induced by Ruta graveolens in human colon cancer cells. Homeopathy 104: 36-47.
18. Ghosh S, Bishayee K, Paul A, Mukherjee A, Sikdar S, et al. (2013) Homeopathic mother tincture of Phytolacca decandra induces apoptosis in skin melanoma cells by activating caspase-mediated signaling via reactive oxygen species elevation. J Integr Med 11: 116-124.
19. Samadder A, Das S, Das J, Paul A, Boujedaini N, et al. (2013) The potentized homeopathic drug, Lycopodium clavatun (5C and 15C) has anti-cancer effect on HeLa cells *in vitro*. Journal of Acupuncture and Meridian Studies 6: 180-187.
20. Guimarães FSF, Andrade LF, Martins ST, Abud APR, Sene RV, et al. (2010) *In vitro* and *in vivo* anticancer properties of a Calcarea carbonica derivative complex (M8) treatment in a murine melanoma model. BMC Cancer 10:113.
21. Saha S, Hossain DM, Mukherjee S, Mohanty S, Mazumdar M, et al. (2013) Calcarea carbonica induces apoptosis in cancer cells in p53-dependent manner via an immuno-modulatory circuit. BMC Complem Altern M 13:230.
22. Saha S, Bhattacharjee P, Guha D, Kajal K, Khan P, et al. (2015) Sulphur alters NFÎºB-p300 cross-talk in favour of p53-p300 to induce apoptosis in non-small cell lung carcinoma. Int J Oncol 47: 573-582.
23. Mondal J, Samadder A, Khuda-Bukhsh AR (2016) Psorinum 6 × triggers apoptosis signals in human lung cancer cells. J Integr Med 14: 143-153.
24. Mondal J, Samadder A, Khuda-Bukhsh AR (2015) *In vitro* studies of Psorinum 6x on several human cancer cell lines reveal its anti-cancer potential. IJHDR 14: 13-14.
25. Chatterjee A, Biswas J (2012) A homeopathic approach to treat patients with advanced gallbladder, periampullary, and liver carcinomas: A report of 3 cases. J Altern Complem Med 18: 180-186.
26. Ahn KH, Yi KW, Park HT, Shin JH, Hur JY, et al. (2013) Anti-proliferative effect of Klimaktoplan® on human breast cancer cells. Arch Gynecol Obstet 288: 833-838.
27. Edwards V, Benkendorff K, Young F (2012) Marine compounds selectively induce apoptosis in female reproductive cancer cells but not in primary-derived human reproductive granulosa cells. Marine Drugs 10: 64-83.
28. Toliopoulos IK, Simos Y, Bougiouklis D, Oikonomidis S (2013) Stimulation of natural killer cells by homoeopathic complexes: An *in vitro* and *in vivo* pilot study in advanced cancer patients. Cell Biochem Funct 31: 713-718.
29. United States Department of Health and Human Services (2016) NCI Dictionary of Cancer Terms.
30. Rossi E, Picchi M, Panozzo M, Di Stefano M, Baccetti S (2015) Integration of homeopathy and complementary medicine in the public health system in Italy: national regulation and regional experiences. Journal of Medicine and the Person 13: 45.
31. Pérol D, Provençal J, Hardy-Bessard AC, Coeffic D, Jacquin JP, et al. (2012) Can treatment with Cocculine improve the control of chemotherapy-induced emesis in early breast cancer patients? A randomized, multi-centered, double-blind, placebo-controlled Phase III trial. BMC Cancer, 12: 603.
32. Shneerson C, Taskila T, Gale N, Greenfield S, Chen YF (2013) The effect of complementary and alternative medicine on the quality of life of cancer survivors: a systematic review and meta-analyses. Complement Ther Med 21: 417-429.
33. Frass M, Friehs H, Thallinger C, Sohal NK, Marosi C, et al. (2015) Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients —A pragmatic randomized controlled trial. Complement Ther Med 23: 309-317.
34. Bagot JL (2016) Using hetero-isotherapics in cancer supportive care: the fruit of fifteen years of experience. Homeopathy 105: 119-125.
35. Nitzsche D, Melzig MF, Arlt VM (2013) Evaluation of the cytotoxicity and genotoxicity of aristolochic acid I - a component of Aristolochiaceae plant extracts used in homeopathy. Environ Toxicol Pharmacol 35: 325-334.
36. Ben-Ayre E, Ali-Shtayeh MS, Nejmi M, Schiff E, Hassan E, et al. (2012) Integrative oncology research in the Middle East: Weaving traditional and complementary medicine in supportive care. Support Care Cancer 20: 557-564.
37. Van Dusen V, Pray WS (2014) Recent actions of the US Food and Drug Administration against illegal homeopathic products. Focus on Alternative and Complementary Therapies 19: 177-83.
38. Posadzki P, Alotaibi A, Ernst E (2012) Adverse effects of homeopathy: a systematic review of published case reports and case series. Int J Clin Pract 66: 1178-1188.
39. Chirumbolo S (2014) Adverse effects and homeopathy: may remedies yet contain noxious or toxic molecules? Brit J Clin Pharmaco 78:184-185.
40. Ive EC, Couchman IM, Reddy L (2012) Therapeutic effect of Arsenicum album on leukocytes. Int J Mol Sci 13: 3979-3987.
41. Voelker R (2016) Safe Relief for Teething Symptoms. JAMA. 316: 1957.

42. Gottschling S, Meyer S, Längler A, Scharifi G, Ebinger F, et al. (2014) Differences in use of complementary and alternative medicine between children and adolescents with cancer in Germany: A population based survey. Pediatr Blood Cancer 61: 488-492.
43. Stub T, Salamonsen A, Alraek T (2012) Is it possible to distinguish homeopathic aggravation from adverse effects? A qualitative study. Forsch Komplementmed 19:13–19.
44. Aust N (2016) Prolonged lifetime by adjunct homeopathy in cancer patients-A case of immortal time bias. Complement Ther Med 24: 80.
45. Aung TY, Soo S (2011) Drug induced nausea and vomiting: An overview. IOSR Journal of Pharmacy and Biological Sciences, 11: 5-9.
46. Majewsky V, Scherr C, Arlt P, Kiener J, Frrokaj K, et al. (2014) Reproducibility of effects of homeopathically potentised gibberellic acid on the growth of Lemna gibba L. in a randomised and blinded bioassay. Homeopathy 103: 113-126.