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 successed 50,000 times; CM- a substance that has been diluted and successed 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.](image)

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]. A murine trial of the PBHRF medications Conium maculatum (hemlock) 200CH, Thuja occidentalis (Thuja; Arbor vitae) 200CH, Phytolaca 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 Calcarea 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 apoptosis 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 polypos tumors and wart 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 melanomatos 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 carboonica 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 Sarsaparilla (Sars; 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%

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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 PMBC 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 up-regulation 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 non-dose dependently induce DNA cleavage, and Phyto showed a concentration-dependent apoptosis (p<0.001), and cytochrome-c (p<0.001) [19].

In vivo C. carbonica (M8) diluent directly induces B16F10 murine melanoma cell adhesion and invasion, and induces melanoma growth and metastasis by decreasing perlecain (heparin sulfate proteoglycan 2 [HSPG2]) expression [4,20]. C. carbonica 6C produces 30% to 35% mitochondrial death cascade [22]. p300 cross-talk, increasing p53 transcription and intrinsic Bcl-2 transcription [22]. Sulphur induces p53-kinase B), and upregulation of p53 and Bax also occurred [17,18]. In a 27-day treatment regime cancer cells depolarizing 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 periauricular 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 racemosa (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 Dansgai 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]. NKCsa produce immunosurveillance 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 NKCsc 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 (NK) 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 vomiaca (from Strychnos nux-vomiaca L.), Radium bromatum, Belladonna, Lachesis (from bushmaster snake venom), and Sepia. These homeopathic treatments improve nausea (p=0.039), insomnia (p=0.008), 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, Lachesis, Kali arbo nicum, and amylnitrate 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-Fluorouracil, adriamycin, and cyclophosphamide (FAC 50), 5-Fluorouracil, 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 vomiaca 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<0.05 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]. Cantharisis, a nutraceutical treatment for burns, blisters, cystitis, urinary tract infections, and digestive disorders, contains cantharadolin, a toxic product of Lytta vesicatoria (the Spanish fly or blister beetle) that inhibits honey suckle 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, Cantharisis 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 Sympyllum officinale (comfrey) should also be avoided due to potential hepatotoxicity [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-successed 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 *Calceara 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, perianpillary 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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