REVIEW ARTICLE

A Review of Preclinical Research on the Effects of Photodynamic Therapy and Homeopathic Medicine on Cancer Cells

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ABSTRACT

Context • Cancer occurs as a consequence of the dysregulation of genes during cell division, resulting in an increased proliferation rate and loss of vital checkpoints in cells. Photodynamic therapy (PDT) makes use of photosensitizers, oxygen, and light at visible wavelengths to stimulate formation of reactive oxygen species (ROS) and trigger apoptosis of cancer cells. Homeopathic remedies commonly affect genes, including tumor necrosis factor alpha (TNF-α) and Bcl2, thereby stimulating cancer-cell death.

Objective • The study intended to examine and summarize the latest findings in preclinical, *in vitro*, and *in vivo* studies on the mechanisms of homeopathy and PDT in cancer therapy.

Design • The research team conducted a literature review using extensive databases made available by the University of Johannesburg Library. The databases used, included, Science Direct, Ebsco Host and Pubmed.

Setting • This study took place at the Laser Research Centre, University of Johannesburg.

Results • Studies demonstrated an ability for both homeopathic remedies and photodynamic therapy to induce apoptosis in cancer cells by interfering with mitochondrial pathways leading to a release of cytochrome-*c*, the production of reactive oxygen species and by interfering with cancer cell genes by upregulating p53 and Bax and down-regulating TNF-α.

Conclusions • Both homeopathy and PDT demonstrate antineoplastic effects; however; more research needs to be conducted before any conclusions can be made. (*Altern Ther Health Med.* 2021;27(6):40-50)

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Cancer has become one of the leading causes of death worldwide. Cancer cells are believed to develop due to the dysregulation that can occur during cell proliferation and differentiation, accompanied by a destruction of checkpoint controls and stimulation of cell proliferation.[1] Many mutations can occur, together with the phenomenon chromothripsis, a process that involves an exponential number of genomic rearrangements occurring in a single cellular crisis.[2]

Cancer-related deaths account for 8% of total deaths in South Africa. Cancer incident rates per 100 000 people in Southern Africa are as large as 156.5 in women and 148.7 in men.[3,4] Between 2004 and 2013, the most common cancers occurring in the Eastern Cape Province in South Africa were myeloma or plasma cell neoplasms (13%), chronic myeloid leukemia (17%), and mature lymphoid malignancies (60%).[5]

Another prominent cancer type in the Eastern Cape region is esophageal cancer, believed to be the result of high alcohol consumption and tobacco smoking.[6] Other research has shown a rapid increase in mortality rates for individuals diagnosed with breast cancer (21%), cervical cancer (16%), and prostate cancer (12%). Currently, the global pattern for cancer incidence has shown a decrease in first-world countries and an increase in third-world countries.[7]

Common symptoms of cancer include pain in the pelvis, back, or abdomen in abdominal, prostate, ovarian, and endometrial cancers; a sensation of fullness; difficulty

urinating in bladder, prostate, or endometrial cancer; and sudden and severe weight loss.[8] Conventional cancer treatments include surgery and chemotherapeutic drugs, such as paclitaxel and epirubicin; however, some cancers, such as breast cancer, can become resistant to these drugs.[9,10] Due to the risk of unwanted side effects of conventional cancer treatments, patients have sought other forms of treatment that are less invasive and have fewer side effects, such as homeopathy and photodynamic therapy.

Homeopathy, a form of complementary medicine, has existed since the early 1800s and was discovered by German physician Samuel Hahnemann. Over the years, homeopathic treatment has grown in popularity due to its affordability and low number of side effects. Homeopathy practices are based on the concept of "like cures like." However, new research has shown that homeopathic remedies can act at cellular and genetic levels, resulting in a reduction in tumor incidence, weight, and volume.[11-13] One theory suggests that homeopathic remedies contain nanoparticles, which may influence the genes of cancer cells and elicit cancer-cell apoptosis.[14]

Photodynamic therapy (PDT) makes use of lasers, which emit light at different wavelengths to activate a photosensitizer that produces free oxygen radicals and promotes apoptosis of cancer cells. The use of PDT as a therapy arose with the development of the Ruby and Helium-Neon lasers in the 1960s, and the treatment requires use of different wavelengths. The most effective wavelengths are between 600 and 1070 nm.[15,16] PDT promotes apoptosis of cancer cells by activating cytochrome c-oxidase.[17] Like homeopathy, PDT is an affordable and noninvasive form of treatment and shows promise for the treatment of cancer.[18]

The current review intended to examine and summarize the latest findings in preclinical, *in vitro*, and *in vivo* studies on the mechanisms of homeopathy and PDT in cancer therapy.

METHODS

Procedures

The review took place at the University of Johannesburg and covers the risk factors for and the incidence and treatment of the most common cancers and discusses the emerging topic of homeopathy as a nanomedicine, identifying the ways in which homeopathic remedies can influence genes, the endoplasmic reticulum, and mitochondria to induce cancer cell death. The review also discusses the cell-death mechanisms and compares these mechanisms to those associated with PDT, suggesting the potential of combining these therapies as a possible new treatment modality for cancer.

The research team conducted a novel review using extensive databases, including Pubmed, Ebsco Host and Science Direct. Keywords used included; PDT, cancer, homeopathic nanomedicine, nanomedicine, homeopathy in cancer, PDT in cancer, prostate cancer, lung cancer and photosensitizers. Due to the nature of this novel literature review, the purposes of this review were purely to summarize the latest research findings regarding PDT and homeopathy in cancer therapies. All research pertaining to the latter was included in this review, so long as the research did not date back further than 2010 (unless in exceptional circumstances where information was relevant).

RESULTS

Common Cancers

Cancer is a leading cause of death worldwide and a major cause of public-health concern.[19] In 2018, an estimated 18.1 million new cancer cases occurred, with 9.6-million patients succumbing to the disease. The most common cancer worldwide for both genders is lung cancer (LC), accounting for 18.4% of all cases, closely followed by female breast cancer (11.6%) and prostate cancer (7.1%).[20]

Lung cancer. Two subtypes of LC exist: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[21] SCLC, the most commonly occurring subtype, accounts for 85% of all cases worldwide.[22]

LC generally lacks distinct symptoms, therefore leading to diagnosis at later stages of the disease.[23] One factor contributing to its development is the static hyperinflation of lungs in patients with chronic obstructive pulmonary disease (COPD).[24] Other risk factors include interstitial pulmonary fibrosis, smoking, and a history of emphysema.[25]

The Rh (Rhesus) factor is an antigen occurring in the red blood cells of many humans. It is particularly important as a cause of hemolytic disease of the newborn and of incompatibility in blood transfusions. Newer research has found that patients with LC possess high levels of Rh factor, thus suggesting a link between Rh and LC development. However, more research identifying this link is needed.[26]

For patients with NSCLC, common treatments include chemotherapy, radiation, and PD-1 inhibitors, which are immunotherapeutic drugs used in cancer treatment such as nivolumab and pembrolizumab. These drugs block the programmed cell-death protein PD-1, resulting in the destruction of cancer cells by the activation of T-lymphocytes. PD-L1 inhibitors, such as atezolizumab, are also used. These drugs cause cancer-cell apoptosis by inhibiting the programmed death-ligand-1 protein. A new drug regimen has now emerged, which may prove beneficial in the treatment of NSCLC. These drugs include carboplatin, paclitaxel, bevacizumab, and atezolizumab.[27-29] As a final resort, surgery has been shown to be beneficial for Stage 1 LC.[30]

Breast cancer. Female breast cancer has 21 histological subtypes. Each subtype has a different prognosis, course of treatment, and clinical behavior.[31] Due to the large number of breast-cancer subtypes, physicians have categorized breast cancer into 3 therapeutic groups: (1) the human epidermal growth factor receptor 2 (HER2) amplified group, (2) the estrogen-receptor group, and (3) the triple-negative breast-cancer group.[32]

Breast-cancer risk factors include: (1) increased age, (2) a familial history of breast cancer due to inheritance of the BRCA1/2 gene, (3) a high density in breast tissue, (4) a high body mass index, (5) high levels of estrogen and progesterone, (6) chronic cysts, and (7) the presence of a lobular carcinoma in situ from the age of 60.[33,34]

The most common treatments include surgery, chemotherapy, and radiation therapy and use of chemotherapeutic drugs such as adriamycin.[35] The largest complication with the above therapies, however, is the tendency for breast cancer to become resistant to adriamycin, thus increasing the risk of metastasis.[36]

Prostate cancer. Prostate cancer is considered to be growing in severity, with an estimated 499 000 new deaths expected to occur by 2030. Risk factors for prostate cancer are relatively insignificant and include factors such as family history, increased age, and ethnic race.[37] Newer risk factors currently under investigation include insulin-like growth factor 1 (IGF-1) circulating in high concentrations and genetic polymorphisms that increase susceptibility.[38]

Prostate cancer can be diagnosed by use of a digital rectal exam and a blood test, which investigate the levels of the prostate specific antigen (PSA). When performing the digital rectal examination, the physician evaluates the size, shape, and surface of the prostate.[39] Typical treatments include radiation and hormone therapy, androgen blockers, and radical prostatectomy.[40]

Photodynamic Therapy

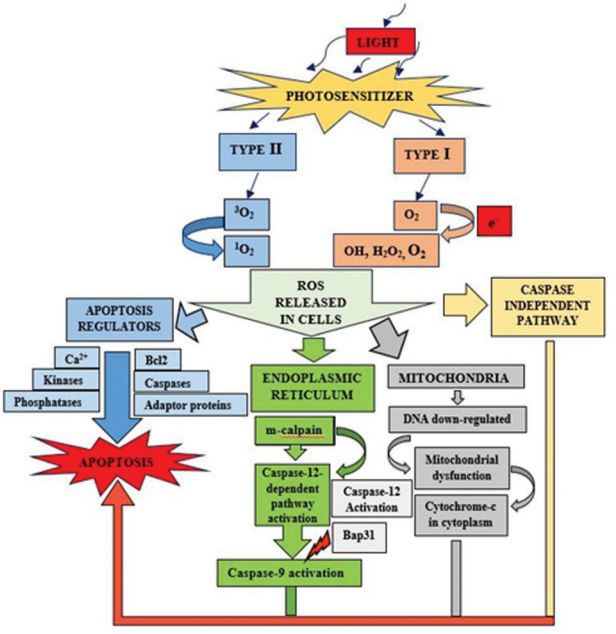
PDT has 3 important components: light, oxygen, and photosensitizers.[41] Photosensitizers function by absorbing light of specific wavelengths and then converting it into an atomic rearrangement and fluorescence, transferring energy across oxygen molecules. This process results in the formation of reactive oxygen species (ROS), which interact with biological structures and lead to the initiation of cell death.[42] Because PDT is localized in its approach, it provides increased accuracy in targeting diseased, as opposed to healthy, tissues. This localization is made possible by the tumour-targeting nature of photosensitizing agents which react with the laser.[43] The distribution of light is determined by the characteristics of the light source as well as the optical properties of the tissue being treated.[44]

Photosensitizers. Photosensitizers are considered to be dyes, which have the ability to reflect, absorb, and most important, transfer the energy of the light absorbed to other molecules or to use this energy in various photochemical reactions.[45] Photosensitizers are of 2 types: (1) those that are porphyrin based, such as pthalocyanines, bacteriochlorin, or chlorins, and (2) those that are nonporphyrin based, typically anthracyclines, hypericin, cyanines, and psoralens.[46,47]

The key characteristics of an ideal photosensitizer include: (1) water-solubility; (2) biocompatibility in the absence of light; (3) chemical stability; (4) high oxygen generation; (5) rapid accumulation in target tissues, with rapid clearance from the body; (6) a high molar absorption coefficient between 700 and 900 nm; (7) near-infrared (IR) light absorption; and (8) most important, tumor specificity.[48,49]

ROS generation and PDT-induced cell-death mechanisms. Two main oxidation pathways occur as a result of PDT: Type 1 and Type 2. Type 1 produces radicals and radical ions, which result in ROS formation, whereas Type 2 produces a singlet oxygen as a result of energy being transferred from the photosensitizer to a triplet oxygen (Figure 1).[50] This production of ROS results in the destruction of neoplastic cells by stimulating the process of cell death, and in turn, enhances the cytodamage initiated by PDT.[51,52]

Figure 1. ROS Production in the Presence of Photosensitizers and Following the Events in the Cells. A Type 1 reaction produces reactive species such as hydroxide (OH), hydrogen peroxide (H_2O_2), or singlet oxygen. The Type 2 reaction occurs when the photosensitizer excites a triplet oxygen molecule, leading to a conversion into an excited singlet oxygen molecule. Reactive oxygen species (ROS) interact with cellular organelles, such as the endoplasmic reticulum (ER) or mitochondria, leading to a chain of events that includes activation of caspase pathways and release of cytochrome c into the cytoplasm. These events result in apoptosis of cancer cells.



Apoptosis is the term given to the morphological aspect of cellular death. Apoptosis is typically recognized by condensation of chromatin, fragmentation of the cell's nucleus, and a reduction in the cell's volume. Apoptosis may be considered to be programmed during the check-point process when a cell is determined to be abnormal in chromosomal structure, beginning the apoptotic process. Unprogrammed cell death occurs in the presence of an external stimulus that interferes with the cellular components of an otherwise healthy cell in such a way that it triggers the apoptotic process.[53] The initiation of apoptosis begins with the release of cytochrome c into the cytoplasm, together with the degradation of the cell membrane and nucleus.[54,55]

The specific regulators observed in cellular apoptosis include Bcl-2, caspases, adaptor proteins, phosphatases, calcium ions, and kinases.[52] The caspases are synthesized as zymogens and proenzymes in response to apoptotic signals. These activated caspases result in the morphological and biochemical changes that are characteristic of apoptosis.[56] In

causing cell death, PDT directly targets cellular organelles. such as the endoplasmic reticulum (ER), plasma membranes, golgi-apparatus, lysosomes, and mitochondria.[57]

PDT stimulates oxidative stress among macromolecules, leading to crosslinking, carbonylation, and fragmentation caspase-independent pathways, which are believed to be a major pathway contributing to cell death. When PDT is applied to cells, a significant depletion in calcium-ion (Ca^{2+}) levels occurs in the endoplasmic reticulum, which results in ER dysfunction and eventually cell death.[58]

PDT effects on ER and mitochondria. The most effective photosensitizer that targets the endoplasmic reticulum (ER) is hypericin, which belongs to the naphthodianthrones family and has the ability to stimulate oxidative stress in the ER and result in the onset of autophagy.[59] When ER stress exists, the caspase-12 dependent pathway is triggered,[60] activated by the cleaving of caspase-12 by the Ca^{2+}-dependent protease m-Calpain. This cleaving process leads to the activation of caspase-9, which may interact with the proapoptotic protein Bap31, possibly leading to the apoptosis of cells.[61,62]

Mitochondria play an incredibly important role in the maintenance of cellular stability and activity.[63] Hydrophobic photosensitizers typically target the mitochondria of tumor cells.[64] Mitochondrial DNA experiences a downregulation of the electron transport chain after PDT irradiation, with an increased level of ROS production, which results in further downregulation of the mitochondrial DNA, leading to a cyclical cascade with the end result being mitochondrial dysfunction.[65] Mitochondrially mediated apoptosis is characterized by a release of cytochrome c into the cytosol, which then triggers the apoptosis.[66]

Use of PDT in cancer treatment. PDT has shown promise as a therapeutic modality in the treatment of cancer, allowing the activation of apoptotic pathways in cancer cells *in vitro*.[67] For targeting androgen-insensitive prostate-cancer cells, pheophorbide (PhA) is a light and dose-dependent photosensitizer that has shown a significant ability to induce apoptosis and autophagy by significant production of ROS.[68] This photosensitizer further causes depolarization of the mitochondrial-membrane potentials and arrests the cell cycle at the G_0 and G_1 phase.[69] PhA, together with PDT, has shown remarkable antiproliferative effects on prostate-cancer cells when administered at 670 nm at a 5 J/cm^2 fluency. This administration also prevents colony formation of prostate-cancer cells.[70]

Other photosensitizers that have been investigated for use in prostate-cancer treatment include protoporphyrin IX, tin ethyl etiopurin, motexafin lutetium, meso-tetra hydroxy phenyl chlorin, bacteriopheophorbide, and aluminum phthalocyanine.[71-76] PDT has been shown to reduce tumor size and volume by at least two-thirds via fibrosis leading to atrophy.[77]

PDT in the case of LC may be used either as a treatment on its own or palliatively in combination with chemotherapy to remove bronchial stenosis by opening the bronchial lumen.[78] PDT has shown further success in the treatment of invasive endobronchial tumors, peripheral and pleural tumors. PDT is also often used to treat surgical margins postresection.[79]

NSLC and small cell tumors treated with photofrin photosensitizer, followed by 630 nm at 200 J/cm^2 for 48 h, have shown a remarkable positive response rate (71%).[80] An alternative photosensitizer that has shown success in the treatment of LC is dicarboxymethylamino acetamidophenyl (DTPP), which is a derivative of benzoporhyrin. This photosensitizer, when used at 650 nm, has been shown to inhibit LC cell growth as well as viability by altering cytoskeleton protein changes of these cells.[81]

The effects of PDT and its use in breast-cancer treatment has been researched thoroughly. PDT has been shown to possess a highly toxic effect on MCF-7 breast-cancer cells when applied in combination with phthalocyanines with a red-light irradiation at 15 J/cm^2 fluency.[82] *In vitro* studies have demonstrated that PDT has the ability to induce cell death when applied with photodithazine and light-emitting diodes (LEDs) at a wavelength of 660 nm.[83]

Perhaps the latest finding is the ability of chlorin-based photosensitizers, such as chlorin-bexarotene and its complexes of indium and zinc, to be active against triple-negative breast-cancer cells in nanomolar concentrations. This photosensitizer stimulates cytotoxicity of breast-cancer cells by targeting nuclear and vitamin receptors, which are typically upregulated by these cancer cells.[84] Hematoporphyrin monomethyl ether (HMME), a relatively new porphyrin-related photosensitizer, can be selectively absorbed by tumor cells. Once taken up by the cells, this photosensitizer reduces mitochondrial function and structure, resulting in apoptosis in breast-cancer cells.[85]

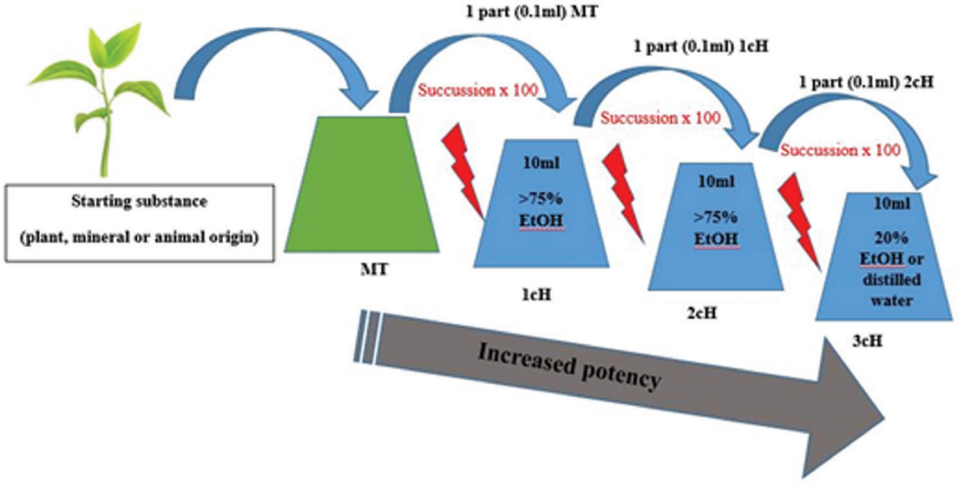
Homoeopathy

Homeopathy is currently one of the most diverse and fastest growing forms of complementary medicine globally. This form of practice uses various protocols and areas of expertise to arrive at a relevant diagnosis and treatment plan, including knowledge of the homeopathic materia medica and repertory, in-depth case-taking and physical examination, anatomical and physiological knowledge, knowledge about various pathologies, and long-term management of a case.[86]

In analyzing a patient's disease, homeopaths investigate the cause of the symptoms in accordance with several models. One is the pathogenic model, which identifies the cause of illness as being an external pathogen. An alternative model, the biological model, acknowledges that a problem with any living system—mental or physical—may have many different causes. The holistic model is broad in its approach, because it acknowledges that illness may have more than one causative stimulus, with the patient expressing this stimulus with a variety of different symptoms.[87]

Homeopathic remedies. Homeopathic remedies are created from many different sources, which include derivatives from the animal, plant, and mineral kingdoms. Their manufacture involves a process referred to as serial dilution, which involves diluting the original starting substance and succussing the solution after each dilution.

Figure 2. Preparation of Homeopathic Medicine. The figure demonstrates the production of a 3cH remedy, prepared at a ratio of 1 part substance to 99 parts vehicle. Because the bottles are 10 ml in volume, 0.1 ml of the mother tincture (MT) would be added to 9.9 ml of >75% Ethanol concentration and succussed 100 times in order to create a 1cH dilution. In order to make a 2cH dilution, 0.1 ml of the 1cH potency will be added to 9.9 ml of >75% ethanol concentration and succussed 100 times. For the final step, 0.1 ml of the 2cH potency will be added to 9.9 ml of a medicinal ethanol concentration of 20% and succussed 100 times in order to create the final 3cH potency required.



Succussion is a process whereby the homeopathic remedy is shaken at a high velocity to successfully disperse the original substance into the vehicle of choice, either ethanol or distilled water (Figure 2).

Homeopathic potencies are prepared from the mother tincture (MT), the original extract of the plant, animal, or mineral source that has been macerated in alcohol at a concentration of 63% and diluted in accordance with a scale: (1) a decimal scale, with a 1:10 ratio written as D or X; (2) a centesimal scale, with a 1:100 ratio written as cH, C, or CM when highly diluted, or (3) an LM scale, with a 1:1000 ratio, with the highest diluted potency being referred to as a 50 millesimal potency.[88,89] This dilution process of a crude substance is thought to allow for the formation of nanoparticles, which have been identified as the delivery vehicles of choice, even in extremely diluted remedies of up to 200cH.[90]

Homeopathic remedies make use of many different plant families, each of which may be used for the treatment of various mental and physical conditions.[91] In homeopathy, each plant extract will be used for different symptoms and signs related to various conditions and diseases. Homeopathic remedies made from bitter plants are typically used in the treatment of bowel and liver conditions.Examples of such plant remedies include *Chelidonium majus, Carduus marianus, Veratrum album, Citrullus colocynthis, Lycopodium clavatum, Nux moschata*, and *China officinalis*.[92] The origin, use, and symptoms of these remedies are different and are evaluated in accordance with the homeopathic materia medica by Vermeulen[93] and as depicted in Table 1.

Homeopathy as a nanomedicine. The mechanism of action of homeopathic medicine is not well understood, and much research is currently taking place as a means to identify the mechanisms behind homeopathic remedies. Currently, the latest proposed theory of homeopathy's mechanistic action is based on the theory of nanoparticles. This theory is related to hydrogen protons and their spin and can be described as follows.

Hydrogen protons in a water molecule are the only protons that possess a spin. This spin occurs when a magnetic dipole aligns itself to a magnetic field, referred to as B_o. In accordance with quantum theory, 2 energy levels exist and correspond to the nuclear moment: (1) parallel or low energy and (2) antiparallel. The nuclear spins result in a total magnetization vector M_{z0} that lies parallel to B_o.

When energy equal to these 2 levels is applied, it stimulates a transition from a ground to an excited state. After this excited state has occurred, it's followed by a state of relaxation. Two relaxation times exist, the transverse and the longitudinal. During these relaxation times, a nucleus will transition into a ground state by means of exchanging the excess energy with surrounding molecules.

Using these theories, researchers have observed nanoparticles in homeopathic potencies beyond 12cH.[94] Some remedies studied are *Aurum metallicum*, Natrium muriaticum LM1 to LM30, and Hypericum perforatum 6cH to CM. In a study with Natrium muriaticum and Hypericum perforatum, the researchers concluded that nanoparticles were present in all potencies, even those that were highly diluted.[94]

This concept of nanomedicine could explain how homeopathic remedies are able to have an effect on cells and produce responses in patients who are taking the remedy, even though the remedy has been serially diluted past Avogadro's number ($6.02214076 \times 10^{23}$). It's theorized that this nanostructure of medicinal substances allows homeopathic remedies to work on a cellular level by altering the genetic expression of cells and interacting with cellular receptors, leading to a phenomenon referred to as stochastic resonance, a process that disturbs the membrane potential of cells.[95,96]

Table 1. Commonly Used, Plant-based Homeopathic Remedies. Homeopathic remedies typically have effects across all systems; however, certain remedies have been shown to be specific to a particular organ system. The systems that these remedies affect as well as the common symptoms calling for the use of these remedies have been listed.[93]

Homeopathic Remedy	Common Plant Name	Scientific Name	System Commonly Treated	Symptoms Presented
Chelidonium majus	Greater Celandine	*Chelidonium majus L*	Liver	• Vertigo, with a hepatic disturbance • Sensation of icy coldness in the nape of the neck that radiates to the occiput • Heavy feeling like lead in the occiput • Bitter taste in the mouth • Sensations of a plug in the stomach, with a feeling of constriction in the right hypochondriac region • Sensation of bubbles bursting in abdomen • Feeling of constriction across the umbilical region as if by a string • Numbness in the whole right side of hepatic region with fullness and pressure.
Carduus marianus	Milk Thistle	*Silybum marianum* (L) Gaertn	Liver and portal system, venous system (varicose ulcers and veins)	• Nausea ending in inflated feeling in the abdomen • Sensation of stitches on the left side of the stomach near the splenic region • Empty eructations waking patient at night • Sensations of fullness and tension in hepatic region that is relieved by pressure.
Citrullus colocynthis	Bitter apple	*Citrullus colocynthis* (L)	Head and abdomen	• Heavy feeling in the forehead, with confusion and pressure in the orbits • Sensation of burning pain on left side of head; relief from pain with application of pressure and heat to the forehead • Stitching pains in the right temple • Sensation as if stones are being ground together in the abdominal region • Sensation as if intestines are being squeezed • Excessive nausea and vomiting with drawing pains in the stomach, with bending double providing relief from the pain
China officinalis	Cinchona calisaya/ cinchona officinalis	*Cinchona officianalis* (L)	Bowel, liver, spleen and nervous	• Feeling of stomach being ulcerated, with pain in the pit of stomach and sensations of coldness and emptiness; relief of symptoms when lying on the back • Spasmodic stomach pain with vomit containing undigested food • Pain in hepatic region as if ulcerated • Hematemesis
Lycopodium clavatum	Staghorn clubmoss	*Lycopodium clavatum* (L)	Urinary, abdomen and liver	• Churning and twisting sensations in the abdomen, with sensations of fluttering • Burning in the stomach rising up to the throat when lying down; relief of stomach symptoms by belching • Twisting sensations in the pit of the stomach • Sensation of fermentation in the abdomen • Sensation of a stone or weight in the navel region • Violent gallstone colic • Gripping pains in the left hypochondrium • Flatulent colic • Sensation of stitches in the neck of the bladder and kidney region that are worse in the morning • Aching pain in the right ureter • Urine containing a red sediment like red sand
Nux moschata	Nutmeg	*Myristica fragrans*	Nervous, liver	• Vertigo with sensation of floating, with feeling of head expanding • Cracking sounds in head • Buzzing and ringing sounds in the ears • Difficulty closing the jaw • Sensation of paralyzed and numb tongue • Sensation of something crawling up the esophagus • Feeling of oppression in the stomach, with lots of burning and heat • Violent nausea with abdominal distention • Pressure in liver region as if of something sharp • Spasmodic pains moving from the right to the left hypochondrium
Veratrum album	European white false hellebore	*Veratrum album* (L)	Abdomen	• Sinking and empty sensations in abdomen following a stool • Inability to pass flatus • Pain from abdomen extending to thighs and back • Hyperemia of the liver • Much borborygmi • Feeling of stomach being cold • Extreme vomiting and nausea worse with the least motion • Vomiting of green mucous

Criticism has occurred, however, with regard to the origin of the nanoparticles found in homeopathic remedies. One particular study demonstrating this finding was conducted in 2010 by John Ives et al. The study found that solutes from glass containers were transferred into the solvent when exposed to the high-energy succussions in homeopathic remedy preparations. The silicates found to be present in these solutes included sodium, silicon, and boron at micromolar concentrations.[97]

Effects of homeopathic remedies on gene expression. When the body succumbs to illness, the genetic expression of the individual changes as a result of the up- and down-regulation of genes in response to illness. Recent studies have shwon an ability for homeopathic remedies to interfere with various genes of an individual.[98] remedies can be found in Table 2.

One study investigating the effects of 2 homeopathic remedies—Condurango 30cH and Hydrastis canadensis 30cH—observed that these remedies had the ability to upregulate and downregulate genes. After treatment with Condurango 30cH and H. canadensis 30cH, it was observed that a difference of >1.5 fold existed between the 2 remedies concerning the 36 carcinogenic genes that they could influence. This indicated that not only do these homeopathic

Table 2. Summary of the Genes Affected by Homeopathic Remedies

Homeopathic Remedy	Genes Influenced	Reference
Sodium butyrate 30cH and 200cH	30cH: Upregulated: IL2 Downregulated: TNF-**α** 200cH: Downregulated: IL10	Saha et al, 2013[99]
Gelsemium semperivens 2cH, 5cH and 9cH	Upregulated 7 and downregulated 49 genetic transcripts in neurocytes	Olsen, 2017[100] Marzotto et al, 2014[101]
Arnica Montana 5cH- 15cH	Upregulated: CXCL1; CXCl2; Bone morphogenetic protein; IL 8 Downregulated: MMP1	Venard et al, 2011[102]
Apis mellifica 3cH, 5cH and 7cH	Upregulated: IL1-β, IL-1α Downregulated: TNF-α; Nfk-β; IL-5; IL-6; Wnt; IL18; CX3CL	Olioso et al, 2016[104]
Phytolacca decandra Ethanolic extract	Upregulated: p53; caspase-3; Bax Downregulated: Bcl-2; Akt	Ghosh et al, 2013[120]
Psorinum 6cH	Upregulated: Bax; p53 Downregulated: Bcl-2	Arora et al, 2013[114]
Ruta graveolens mother tincture and 30cH	Normalizes β-actin	Mondal et al, 2016 [115] Arora and Tandon, 2015[116]

remedies have the ability to alter genetic expression but also that each remedy may alter different genes.[99]

An ultrahigh dilution of sodium butyrate in a 30cH and 200cH potency was found to change the expression of interleukin-2 (IL-2), IL-10 and TNF-α genes in HEK 293 cells. This preparation was found to alter these genes by raising levels of IL-2 and decreasing levels of TNF-α in the presence of the 30cH preparation and by lowering levels of IL-10 in the 200cH preparation.[100]

Gelsemium semperivens has been found to downregulate 49 and upregulate 7 out of 45033 transcripts in neurocytes, in a 2cH potency. The downregulation of these transcripts was found to reduce cellular excitability because the affected genes belong to the surface receptors involved in G protein-coupled receptor (GPCR) signaling as well as calcium homeostasis. The cascade of events caused by these genetic-expression changes has been shown to result in a downregulation in olfactory transduction and inflammatory response.[101] *G. semperivens* has also been found to stimulate allopregnanolone biosynthesis by altering genetic expression at a potency of 5cH, as well as at 9cH, although the stimulation of this potency was significantly lower than that of the 5cH.[102]

Homeopathically prepared *Arnica montana*, traditionally used in wound healing, has been shown to have a significant ability to increase the genetic expression of CXC chemokine ligand 1 (CXCL1), upregulating CXC chemokine ligand 2 (CXCl2), bone morphogenetic protein, and IL-8. This upregulation enables positive neutrophil recruitment, together with angiogenesis. *A. montana* has also been found to downregulate matrix metallopeptidase 1 (MMP1) coding for metalloproteinase.[103]

Apis mellifica, a remedy used most commonly for its anti-inflammatory effects, may be able to modulate many genes when applied in potencies of 3cH, 5cH, and 7cH. These preparations have shown the ability to downregulate TNF-α, nuclear factor kappa beta (Nfk-β), IL-5, IL-6, Wnt, IL-18, and CX3CL and to upregulate IL-1β and IL-1α.[104]

Homeopathy's effect on cellular mechanisms. Currently little information is available about homeopathic remedies and their mechanisms *in vitro* because the field is relatively new. However, some research has shown promise in understanding how homeopathic remedies affect cells on a cellular level.

A homeopathic preparation known as Engystol-N is used as an immunomodulator. Past research has shown that this preparation can stimulate generation of neutrophil and cytokine superoxide anion by T Lymphocytes.[105] Because of this activity, Engystol-N can stimulate lymphokine secretion, which thus confirms the immunomodulatory effect of the preparation.

As in the case of the cell-death mechanisms of PDT, homeopathic remedies have also shown the ability to target the mitochondria of cells. One study found that A. montana 30cH can inhibit lipid peroxidation in mitochondrial cell membranes, and in turn, prevent membrane permeabilization induced by ferrous ion (Fe2+) and Ca^{2+}.[106] When cells were under oxidative stress, the *A. montana* 30cH was found to further decrease oxygen consumption of mitochondria.

Another study was conducted on the effects of Ubichinon compositum and Coenzyme compositum on mitochondrial activity in bovine sperm, and the results showed that both remedies can drastically enhance mitochondrial activity while maintaining the structure of chromatin and integrity of acrosomes.[107] With the above effects in mind, future research evaluating the synergistic effects of *A. montana* 30cH, Ubichinon compositum, and Coenzyme compositum with PDT on mitochondria of cancer cells may prove to be of value.

Homeopathic remedies prepared as concentrations may have dilution factors of anywhere up to 10-60 (30cH) and even 10-400 (200cH). One study investigated the effects of metal-derived homeopathic remedies—*Argentum metallicum, Stannum metallicum, Zincum metallicum, Aurum metallicum,* and *Plumbum metallicum* potentized—on the hormesis of HepG2 cells and showed that 3 of these remedies—*Aurum metallicum, Stannum metallicum*, and *Zincum metallicum* prepared at potencies of 30cH and 200cH—could significantly induce the activation of hormesis. These homeopathic remedies were thus prepared at concentrations with dilution factors of 10-60 and 10-400. The remedies were found to induce protein synthesis, which was independent of cellular proliferation.[108]

A theory as to how the nanoparticles of homeopathic remedies can affect cells includes the hypothesis that the body

Table 3. Homeopathic Remedies in the Treatment of Various Cancers. The table shows remedies that studies have shown are either successful or unsuccessful in stimulating apoptosis in cancer cells.

Cancer	Cell Line Used	Homeopathic Remedies Studied	Results of Study	Study Ref and Year
Prostate	• LNCaP • DUI45 • MAT-LyLu	• *C. maculatum* 1000cH • *S. serrulata* 200cH • *T. occidentalis* 1000cH • Carcinosinum 1000cH	All remedies: • Reduced mean tumor volume by 38% reduction • Reduced PCNA-positive cells by 6% • Increased apoptotic positive nuclei	*In vivo* Renu et al, 2019[111]
	• DU145 • PC-3	• *T. occidentalis* • *C. maculatum* • *S. serrulata* 100cH	*S. Serrulata* 100cH: • Reduced proliferation rate 33% *T. occidentalis* and *C. maculatum*: • Showed no changes	*In vitro* Jonas et al, 2006[112]
Breast	MCF-7	• *P. decandra* MT	• Induced apoptosis of cells • Induced 72.6% cytotoxicity	*In vitro* Arora et al, 2013[114]
		• *T. occidentalis* • *C. maculatum* • Carcinosin • *S. serrulata* in varying potencies from 12cH to 1000cK	• Was unable to reduce cellular proliferation *in vitro* or tumor volume *in vivo*	*In vitro* and *In vivo* MacLaughlin et al, 2006[113]
Lung	A549	Psorinum 6cH	• Caused ROS formation • Caused MMP depolarization • Released Cytochrome c	*In vitro* Mondal et al, 2016[115]
Colon	COLO-205	• *Ruta graveolens* MT and 30cH	• Induced apoptosis • Caused chromatin condensation • Caused phosphatidylserine externalization	*In vitro* Arora and Tandon, 2015[116] Fadlalla et al, 2011[117]
Melanoma	B16F10	• Phosphorous 30cH • Arsenicum sulphuratum flavum 30cH	Melanogenesis	*In vitro* Samidha et al, 2017[118]
	A375	Phytolacca	• Upregulated p53, caspase-3, and Bax • Downregulated bcl-2 and Akt	*In vitro* Ghosh et al, 2013[120]
Pulmonary Metastatic Melanoma and Subcutaneous Melanoma	Mouse models	Commercially available M1 that includes: • *Aconitum napellus* • *Arsenicum album* • *Asa foetida* • *C. carbonica* • *C. majus* • *Cinnamonum* • *Conium maculatum* • *Echinacea purpurea* • *Gelsemium semperivens* • Ipecacuanha • Phosphorous • *Rhus toxixodendron* • Silicea • Sulphur • *T. occidentalis* • *Phytolacca decandra*	• Decreased angiogenesis • Increased β-catenin • Decreased AT1R and CD11/ Gr-1	*In vivo* de Andrade et al, 2016[119]

registers the nanoparticles as a threat or environmental stress. This initiates an adaptive response whereby endogenous changes occur. These changes include cross-adaptation and cross-sensitization. This reaction is termed the allostatic stress response, which further includes inflammatory and noninflammatory mediators and the autonomic and central nervous systems.[109,110] Much more research needs to be conducted, however, before this theory can be regarded as true.

Use of homeopathy in cancer treatment. A range of illnesses have been reported to have been successfully treated with homeopathic remedies, leading to the increase in popularity of this form of medicine.[111] Much research has been conducted on the antineoplastic effects of homeopathic remedies and their effects on cancer cells *in vitro* and *in vivo*. A summary of the information can be found in Table 3.

Jonas and colleagues investigated the effects of 4 homeopathic remedies—Conium maculatum 1000cH, Sabal serrulata 200cH, Thuja occidentalis 1000cH, and Carcinosin 1000cH—on prostate-cancer cell lines LNCaP, DU145, and MAT-LyLu.[112] The study included in-vivo experiments on 4-to-5-week-old Copenhagen rats that had been inoculated with 10 000 MAT-LyLu cells in 100 µL of phosphate-buffered saline (PBS) and given 100 µL of the above-mentioned homeopathic remedies or a placebo (control group). Results of this study showed a decreased tumor burden in animals treated with homeopathic remedies compared to the control group, with a 38% reduction in mean tumor volume for the intervention groups. Homeopathically treated animals had a reduction in proliferating cell nuclear antigen (PCNA)-positive cells and an increase in apoptotic positive nuclei as compared to the control group.

Another study investigated the effects of the same homeopathic remedies on prostate-cancer cell lines DU- 145 and PC-3. The *in vitro* results for proliferation found that the PC-3 cells showed a reduced proliferation rate of 33% after 24 and 72 h of treatment with *S. serrulata* 100cH, and the DU-145

proliferation significantly decreased by 23% after 24 h. This study, however, found no effects with *T. occidentalis* or *C. maculatum* on cell proliferation of prostate-cancer cell lines. The study further investigated the use of these same remedies in various potencies on breast-cancer cells as well as in breast tumors in rats and found that none of these remedies had an ability to reduce tumor size or volume.[113] The potential therapeutic relationship of the above remedies with the PDT wavelength of 670 nm at 5 J/cm^2 fluency, which has shown success in the treatment of prostate-cancer cell lines, may yield a further area for investigation.[69]

The effects of the homeopathic remedy *Phytolacca decandra* MT on MCF-7 breast-cancer cells *in vitro* was studied after 48 h of treatment. A significant cytotoxicity of 72.6% was observed in the cells treated with this remedy; it was further observed that cytotoxicity decreased with further dilutions. Homeopathically prepared *P. decandra* has been found to induce all key features of apoptosis in cancer cells, such as cellular membrane blebbing, DNA fragmentation, and chromatin condensation.[114]

Very little research into the use of homeopathy in LC has been conducted. However, one particular *in vitro* study conducted in 2016 made use of a homeopathic remedy called Psorinum 6cH. This study observed that proliferation of A549 LC cells after 24 h treatment was inhibited and the cell cycle arrested at the sub-G_1 phase. Psorinum 6cH further demonstrated the ability to induce formation of ROS, DNA damage, and phosphatidyl serine externalization. The treatment also resulted in the release of cytochrome c, reduced Bcl-2, and increased Bax and p53 expression and activation of caspase-3, which initiated the mitochondrially mediated, caspase-3-dependent apoptotic pathway in A549 LC cells.[115] Whether or not this remedy would be as effective, if not more effective, if combined with PDT at a wavelength of 630 nm at 200 J/cm^2 for 48 h, which was successful in the treatment of LC cells, may require further investigation.[79]

Ruta graveolens mother tincture 30cH has demonstrated significant results with the initiation of apoptosis in the colon-cancer cells COLO-205 *in vitro*. These 2 potencies produced significant cytotoxicity. A remarkable feature of this remedy was that it was found to be selective toward cancer cells and didn't interfere with healthy normal cells. *R. graveolens* has been shown to reduce colonies of cells and further interacted with genes, particularly β-actin, and normalized them. Chromatin condensation and externalization of phosphatidylserine was also demonstrated.[116,117]

A study conducted by Samidha et al. found that 2 homeopathic remedies, Phosphorous 30cH and Arsenicum sulphuratum flavum 30cH, had the ability to stimulate melanogenesis in the B16F10 melanoma cell line.[118] A separate study investigated the efficacy of a commercially available homeopathic remedy, M1, which consists of several remedies.

The study observed that mice treated with this remedy had a reduction in primary tumor formation as well as in metastatic melanoma, a reduction of angiogenesis and proliferation with increased β-catenin, and a lowered expression of AT1R and CD11/Gr-1.[119] *Phytolacca decandra* has also shown promissae in the treatment of melanoma. This remedy was shown to produce a decreased proliferation of A375 cells with ROS generation and damage of DNA. Genes were also affected by this remedy, whereby *P. decandra* stimulated the upregulation of p53, caspase-3, and Bax and the downregulation of Bcl-2 and Akt.[120]

DISCUSSION

Cancer has exponentially increased in occurrence around the world and in South Africa. Prostate cancer, breast cancer, and LC are the most prevalent regardless of the country or region. These cancers are also responsible for the majority of deaths worldwide. The most commonly followed treatments for these cancers include surgery, chemotherapy, and radiotherapy. However, due to the side effects of these conventional treatments, research into complementary and alternative cancer treatment has been increasing.

PDT and homeopathy have been shown to have antineoplastic effects in both *in vitro* and *in vivo* animal studies. Both PDT and homeopathic treatments have demonstrated the ability to reduce cancer-cell viability and proliferation by interacting with mitochondrial function, ROS generation, and cellular membranes. These therapies have also shown the ability to induce cytochrome-c release, thus placing stress on cancer cells and causing apoptosis.

Homeopathic remedies may also affect cellular mechanisms by altering genetic expression of cancer cells, making them more vulnerable to oxidative stress. This mechanism of action requires confirmation, with repetition of the current research. Further research into the nanoparticle structure as well as the mechanism of action of homeopathic remedies needs to be conducted, especially with the observation that the nanoparticles present in the remedies may originate from the glass containers in which they are produced.

With both homeopathic medicine and PDT possessing potentially similar cellular mechanisms, further research into the benefits of a combination of PDT and homeopathy to combat cancer cells, by enhancing the effect of each treatment modality, may be warranted.

CONCLUSIONS

Both homeopathy and PDT demonstrate antineoplastic effects; however; more research needs to be conducted before any conclusions can be made.

AUTHORS' DISCLOSURE STATEMENT

The authors have no conflicts of interest related to the study.

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