Can Nanoparticles in Homeopathic Remedies Enhance Phototherapy of Cancer? A Hypothetical Model

Ayesha Loonat[1,2] Janice Pellow[2] Heidi Abrahamse[1] Rahul Chandran[1]

[1] Laser Research Centre, Faculty of Health Sciences, University of Johannesburg, Johannesburg, South Africa
[2] Department of Complementary Medicine, Faculty of Health Sciences, University of Johannesburg, Johannesburg, South Africa

Address for correspondence Rahul Chandran, PhD, Laser Research Centre, Faculty of Health Sciences, University of Johannesburg, P.O. Box: 17011, Doornfontein 2028, South Africa (e-mail: rahulc@uj.ac.za).

Homeopathy 2022;111:217–225.

Abstract

The continuous rise in cancer incidence places a massive burden on the health sector to increase efforts in the fight against cancer. As a holistic complementary medicine modality, homeopathy has the potential to assist in the supportive and palliative treatment of cancer patients. Recent empirical studies demonstrate the presence of silica and original source nanoparticles in ultra-high dilutions of several homeopathic medicines. Recent studies have also demonstrated the efficacy of phototherapy in inducing the ablation of cancer cells through laser-activated nanoparticle photosensitizers. A new hypothetical research model is presented herein, in an attempt to investigate and compare the phototherapeutic effects of homeopathic source nanoparticles with photosensitizing nanoparticle agents that have previously been tested.

Keywords
- cancer
- homeopathy
- nanoparticles
- phototherapy
- photosensitizer

Introduction

Cancer is a disease that has afflicted the human race for centuries.[1] Surgery, chemotherapy and radiation remain the cornerstones and have provided the most significant developments in cancer treatments, having substantially improved treatment outcomes and responses. Nevertheless, drawbacks remain, including their high cost and invasiveness, the development of innate and acquired multi-drug resistance, the occurrence of on- and off-target side effects, and the potential for eventual tumor relapse.[2,3] Effective clinical management of cancer therefore remains a global burden and a formidable obstacle in the 21st century.

Homeopathy is a holistic system of medicine with over 200 years of collective clinical experience.[4] It is one of the most widely used complementary medicine modalities globally, and offers potential benefit as an adjunctive treatment option for cancer patients as part of an integrated approach.[5,6] In homeopathy, its key singularity lies in the individualization of the patient: when initiating treatment, the homeopath and the patient are involved in a shared decision-making process to carefully evaluate possible risks and benefits, as well as discuss the patient's concerns and expectations. The opportunity for homeopathic treatment as adjunctive therapy for the supportive care of cancer patients is found in the absence of notable side effects or drug interactions with highly-diluted homeopathic medicines (HMs).[6,7]

The earliest accounts of medical interventions using light can be traced back to the ancient Egyptian and Indian healers, who used sunlight in combination with herbal extracts to treat certain diseases.[8] The recognition of light to combat disease has led to the development of a new branch of medicine known as phototherapy.[9] Today, phototherapy has emerged as a pioneering modality in cancer therapy. Photodynamic therapy (PDT) and photothermal therapy (PTT) are the two types of phototherapies that represent promising tools in the treatment of cancer. PDT is a low-intensity laser irradiation therapy that activates a photosensitizer (PS) to produce cytotoxic reactive oxygen

received
March 31, 2021
accepted after revision
August 2, 2021
published online
November 17, 2021

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0041-1735581.
ISSN 1475-4916.

species (ROS), which in turn induce cell death. PDT therefore can eradicate cancer cells by making use of visible light in specific wavelengths.[10] PTT is an extension of PDT and is defined as a physiochemical therapy that relies on the optical conversion of near-infrared (NIR) irradiation by photosensitizing nanoparticle (NP) agents to generate heat, thereby causing rapid thermal ablation of cancer cells.[11] Compared with other competing therapies, PDT and PTT have several advantages as adjunctive therapies against cancer: they are minimally invasive and have high spatio-temporal precision, thereby producing fewer, less severe, and non-long-term cumulative adverse effects.[9,12]

In the efforts to overcome the limitations of current cancer therapies and with the demand for precision medicine against cancer, nanomedicine has emerged as an integrative approach in biomedical research. It is defined as the medical application of drug-containing NPs for the prevention, treatment and diagnosis of medical conditions.[13,14] Nanomedicine is driven by the knowledge that when substances are engineered into NPs, their biological and physiochemical effects are observably different from their bulk-form counterparts.[15] Their nanoscale size, high surface-to-volume ratio, chemical composition, and presence of targeting ligands have the potential to increase *in-vivo* stability.[15,16] In clinical oncology, nanomedicine aims to improve and enhance the therapeutic index of anti-cancer drugs. This is achieved through the modification of the drug's pharmacokinetics, pharmacodynamics and biodistribution, which in turn improves the precision of drug delivery.[17]

To extend the potential of homeopathy within the medical field, we propose the investigation of selected HMs in a PDT and/or PTT mechanism as a new research model, which could open up avenues for further insight within the respective fields.

Homeopathy in an Oncology Setting

Research on the effects of homeopathy in oncology care and its local effects on cancer cells *in vitro* is currently in its early stages. Whilst strong, evidence-based research regarding the efficacy of homeopathy in oncological care is needed and encouraged, there have been some promising pre-clinical studies related to the homeopathic supportive treatment of cancer. In a randomized controlled trial by Frass et al, adjunctive individualized homeopathic treatment effectively improved the global health status and subjective well-being of cancer patients, when compared with the control group.[18] Similar results were reflected in a prospective observational study by Rostock et al, which showed a clinically relevant and statistically significant improvement in cancer patients' quality of life when treated with homeopathy.[19] In addition to these clinical studies, research evidence has demonstrated the *in-vitro* cytotoxic potential of some HMs, including *Lycopodium clavatum*, *Sarsaparilla*, *Ruta graveolens* and *Phytolacca decandra* in low and ultra-high dilutions, mainly through induction of apoptosis.[20,21] Low doses of ethanolic extracts of *Peumus boldus* homeopathic mother tincture (ø), when combined with the chemotherapeutic agent cisplatin, were shown to significantly reduce cisplatin-induced hepatotoxicity without compromising the anti-cancer effects of the chemotherapeutic agent against hepatocarcinoma cells.[22]

Another interesting field of research involves the modulation of oncogenes through the use of HMs. There are a large number of environmental and lifestyle risk factors associated with the development of cancer. Interactions between environmental exposures and genetic variants of an individual can have a major impact on their epigenome, and may induce the carcinogenic process by disrupting epigenetically maintained patterns of gene expression.[23] Khuda-Bukhsh was one of the first to propose a working hypothesis attempting to explain the mechanism of potentized HMs through the regulation of gene expression.[24] Since then, several studies in support of the theory have been performed. Saha et al revealed how *Condurango* 30c and *Hydrastis canadensis* 30c, through the modulation of gene expression, were able to express a distinctly different pattern of more than 100 HeLa cancer cell genes when compared with controls.[25] In another study, *Condurango* 30c was also shown to trigger crucial epigenetic events of gene modulation, thereby counteracting cancer cell survival.[26] Though further investigations are needed to fully understand their mechanism of action, these studies suggest that HMs may have an important role to play in oncological care.

Photosensitizers in Phototherapy

PSs are compounds that can absorb visible and ultraviolet (UV) light of a definite wavelength and transform it into functional energy.[27] Selecting an appropriate PS is a critical step in the successful execution of phototherapy.[28]

Recent years have shown a steady movement toward the implementation of environmentally sustainable plant extracts and their derivatives for medical applications. Research of plant extracts as PSs for PDT is rapidly developing. Chlorophyll exhibits desirable photosensitive activity, as observed during the process of photosynthesis—the natural method of "harvesting" sunlight.[29] The advantage of using plant extracts as a PS lies in their observed selective action against malignant cells while still maintaining low systemic cytotoxicity against normal cells. They also exhibit favorable optical properties, are readily soluble in aqueous solution, and are relatively cost-effective to manufacture.[30] Curcumin and hypericin, active constituents found in certain medicinal plants, have achieved notable progress in research and have attracted much attention for their anti-cancer properties. Curcumin is an alkaloid found in the turmeric plant (*Curcuma longa*) and belongs to the curcuminoids group.[31] Curcumin holds great potential as a natural PS in PDT (►**Fig. 1**). An *in-vitro* study by Machado et al demonstrated the photosensitizing effects of curcumin-nanoemulsions and PDT on breast adenocarcinoma cell lines.[32] The potential of curcumin as a PS in PDT can also be observed in studies by Sun et al, Baghdan et al, and Jalde et al.[33–35] Hypericin is one of the principal and most biologically active constituents found in *Hypericum perforatum (Hyp-perf)* extracts and has

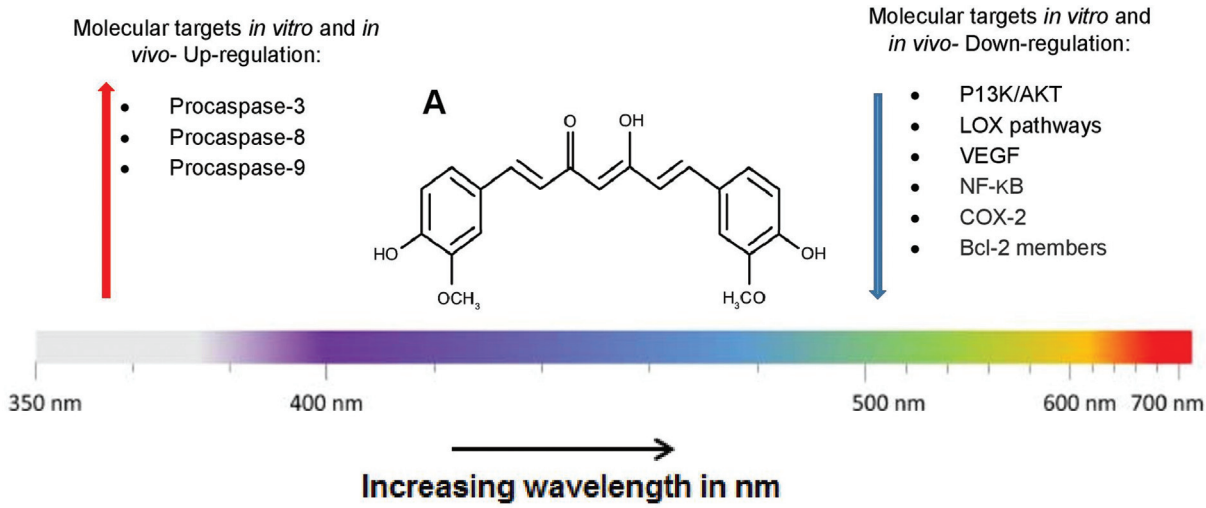

Fig. 1 The photophysical and anti-cancer effects of curcumin. (A) Chemical structure of curcumin. Curcumin can be activated at 440 nm and therefore can absorb blue light. Once photoactivated, it can form efficient cytotoxic reactive oxygen species even at low concentrations. Curcumin can target multiple molecular pathways to induce activation of autophagy and apoptosis and inhibit angiogenesis and tumor growth.

been shown to possess anti-tumor properties (►**Fig. 2**). Due to its strong photosensitivity, hypericin can be used as a natural PS in PDT.[36] The findings in an *in-vitro* and *in-vivo* study by Kim et al suggest that hypericin-mediated PDT induces decreased cell proliferation and cell death via the associated oxidative stress mechanism.[37] The PDT potential of hypericin can be further observed in studies by Kimáková et al and Andrade et al.[38,39] Several studies have also shown how *Lumnitzera racemosa*, *Albizia procera*, *Brassica napus* and *Cornus mas* plant extract induce apoptotic cancer cell death when combined with irradiation.[40–42]

NPs show great promise in amplifying the efficacy of other therapeutics, including PDT and PTT, owing to their unique inherent properties. Since drug delivery is a major challenge in phototherapy, finding PSs that can be incorporated into nanomaterials is undoubtedly desirable. It provides an advantageous opportunity and a means to expand the range of the clinical usefulness and success of PDT/PTT and to enhance specificity.[43]

To facilitate drug delivery of natural plant metabolites and PSs in phototherapy, they are encapsulated into biodegradable and biocompatible NPs. Furthermore, NPs from iron (Fe) and noble metals such as gold (Au) are frequently employed as versatile photosensitive agents for PDT/PTT applications, as they present with favorable optical and photothermal characteristics. These NPs possess strong NIR absorption due to their high photothermal conversion efficiency. AuNPs have gained superiority over other metal-based NPs due to their enhanced absorption, increased photostability, improved optical-thermal conversion efficiency, and biocompatibility.[12] Several studies

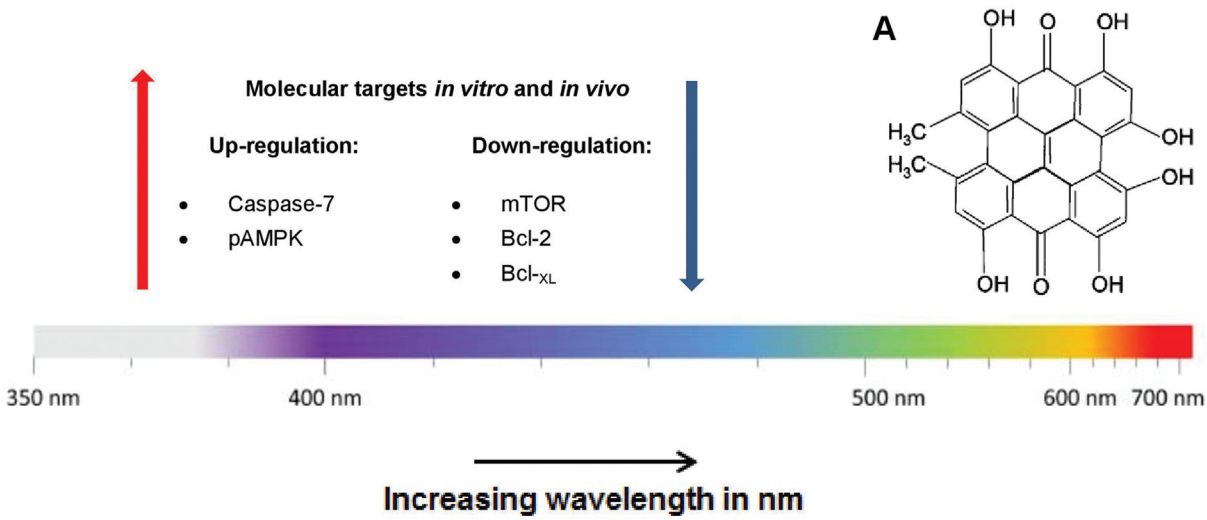

Fig. 2 The photophysical and cytotoxic effects of hypericin. (A) Chemical structure of hypericin. Hypericin belongs to the perylenequinone class of plant-activated photosensitizers. It has a peak absorption band of 660 nm and is therefore activated by orange light. The absorption band falls within the therapeutic window of biological tissue where increased transmission and high singlet oxygen production occur. Hypericin can target multiple molecular pathways to induce apoptosis and inhibit angiogenesis and tumor growth.

have intimated the efficacy of AuNPs in PDT/PTT, where they have been shown to trigger both apoptosis and necrosis in cancer cells.[44,45] AuNPs, when coated with silica (Si), show similar photothermal effects as the uncoated AuNPs but with increased biocompatibility.[45] The molar excitation coefficient of FeNPs is comparable to that of AuNPs but was found to be less expensive and more biocompatible.[46] Liquid metal NPs, when coated with mesoporous Si, demonstrate improved colloidal and thermal stabilization when compared with the uncoated metal NPs, thus establishing mesoporous SiNPs as a promising nanoplatform for improved phototherapy combination strategies.[47]

The Presence of Nanostructures in Homeopathic Medicines

Various controversies regarding the efficacy of homeopathy stem from its high dilutions, specifically those that exceed Avogadro's number.[48] Nanomedicine, however, has provided an alternative hypothesis. Evaluating the presence of NPs has become a highly active aspect of homeopathic research. Nanotechnology researchers have begun to observe the overlap between long-established classical manufacturing methods of HMs and the "top-down" method of NP production employed in modern nanotechnology. During this process, insoluble materials are simply ground or milled for extensive periods. Homeopathic pharmacists have been utilizing this mechanical approach for over 200 years through the process of trituration. The size reduction of the bulk source material is achieved through the combined frictional, shear, impact and compressive forces applied during the mechanical trituration process.[49]

The dilution/potentization process of soluble HMs includes mechanical methods of microfluidization, sonication, vortexing, and manual succussions through vigorous shaking. This in turn causes intense fluid turbulence and particle collisions, and introduces shear forces into the solution that break off increasingly smaller particles of the remedy source. Additionally, this process forms nanobubbles which can cause localized temperature and pressure increases, further breaking down the particle size as well as releasing Si particles from the walls of the glass containers. This process generates homeopathic remedy-source NPs at low potencies and SiNPs at high potencies in colloidal solutions.[4] Homeopathic and non-homeopathic research studies in pharmacy have shown the release of Si precursors and SiNPs from the agitation of the remedy against the glass walls of the containers or vials in which it is prepared. The source material adsorbs onto the SiNPs in the initial 1c potency. The SiNPs then act as a template that carries the structural information of the remedy source material with higher potencies.[50] Temgire et al demonstrated how selected inorganic HMs retain their starting material as silicate-coated NPs. They further proposed a universal hypothesis governing all classes of HMs, which states that the active ingredients of the starting material are retained within the core of micro-mesoporous silica-coated NPs, and that these silica-coated NPs will persist even in high potencies.[51]

"Green synthesis" is a method of procuring metal NPs through cost-effective and environmentally sustainable biological methods with the aid of plant extracts. This process has proved to be far superior and less toxic than other chemical reduction methods.[52] Some research studies have demonstrated how various homeopathic plant-based mother tinctures can biosynthesize silver (Ag) and AgNPs through green synthesis. During this process, the selected herb gets adsorbed onto the surface of NPs with the ability to convey plant-modified biological effects.[53] Das et al demonstrated how the homeopathic mother tinctures *Phytolacca decandra*, *Gelsemium sempervirens, Hydrastis canadensis* and *Thuja occidentalis* can biosynthesize AgNPs from Ag nitrate through rapid green synthesis, which reflects how mother tinctures can utilize nano-precipitation properties to aid in curing disease.[52] Furthermore, several *in-vitro* studies have been performed that demonstrate how nano-encapsulated forms of Ø can produce more potent apoptotic effects than those produced by their un-encapsulated forms. Both *Polygala senega* and *Gelsemium sempervirens* mother tinctures were shown to induce anti-cancer effects on different cell lines, and when in their nano-encapsulated forms they were able to produce enhanced anti-cancer effects due to improved cellular uptake.[54,55]

The presence of micro-NPs in colloidal solution was observed in various potencies of the HM *Hyp-perf*.[56] Chikramane et al demonstrated the presence of AuNPs and its aggregates in the HM *Aurum metallicum* (*Aur-met*) 30c and 200c under transmission electron microscopy. The elemental composition was confirmed by further testing, which showed patterns consistent with the starting material.[48] Kar et al also observed the presence of AuNPs and SiNPs in the HM *Aur-met* 6c, 30c and 200c potencies.[57] Studies by Rajendran and by Bell et al respectively demonstrated evidence for FeNPs in the HM *Ferrum metallicum* (*Ferr-met*) at 6c, 30c and 200c; and for silica-coated AgNPs, SiNPs and AgNPs in traditional homeopathically manufactured *Argentum metallicum* (*Arg-met*) at 6c, 30c and 200c.[58,59] Chikramane et al, in an attempt to assess the biological activity of NP formulations, tested the effects of selected metal-based HMs on human liver cancer (HepG2) cell lines. Results revealed how the remedies were able to induce a proliferation-independent cellular hormetic activation through increased protein synthesis.[60]

The Working Hypothesis

In view of the results obtained from the above studies, it would be of great interest to explore the effects of laser-activated plant, metal and silica-based NPs in selected homeopathically prepared *Hyp-perf, Curcuma longa*, *Aur-met, Arg-met and Ferr-met* at 6c, 30c and 200c potencies and observe how they react in comparison to their previously tested counterparts in PDT and PTT applications.

Since the PDT mechanism, as well as how NPs can independently improve drug delivery, has already been extensively explored in previous research studies, a simple paradigm to test homeopathic source NPs in a PDT

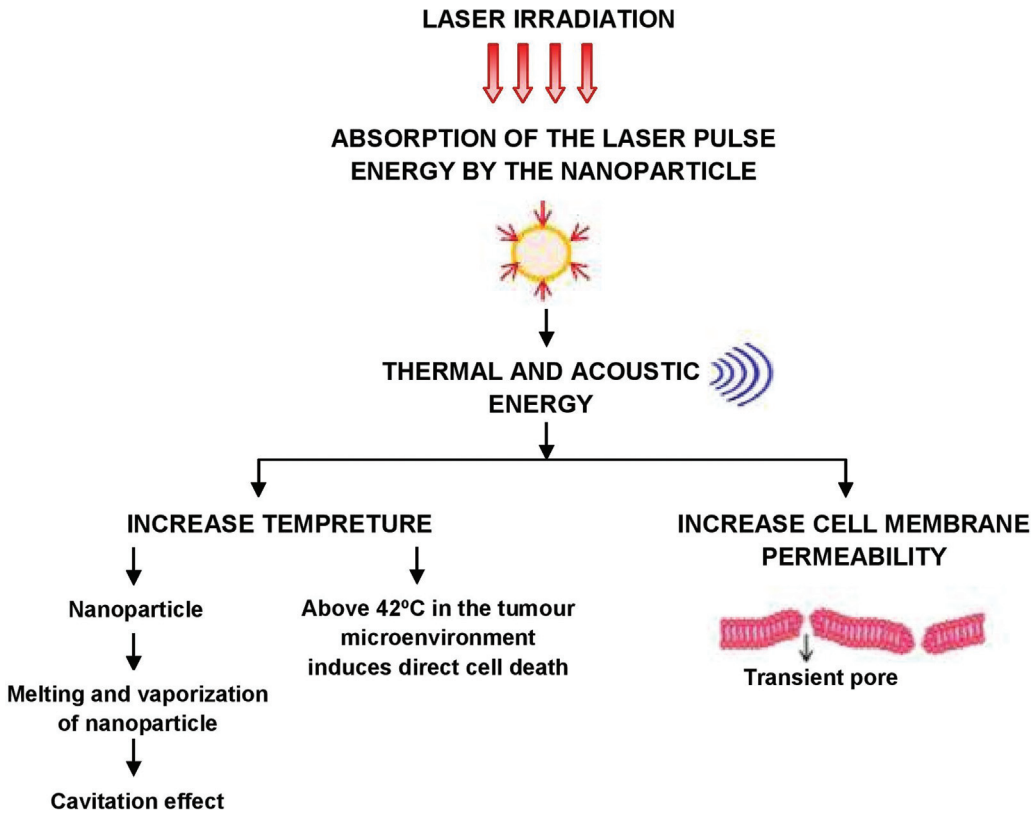

Fig. 3 Melting–heating–vaporization model: The nanoparticle absorbs optical energy from the laser and simultaneously converts it into both thermal and acoustic energy. The cumulative energy produces stresses that can increase the temperature of the nanoparticles as well as the tumor microenvironment, and temporarily the permeability of the cell membrane through the creation of relatively small pores.

mechanism will be discussed. This will be followed by a more in-depth explanatory model describing laser–NP interactions. During the first phase of the PDT reaction, the PS is activated by a specific wavelength of light which converts the PS from its ground state to its active excited triplet state. Once excited, the PS can react with either the surrounding substrates (type 1 reaction) or molecular oxygen (type 2 reaction) to form cytotoxic ROS. The ROS can initiate cell death directly through apoptotic/necrotic pathways or indirectly through the tumor "vasculature shutdown" effect and immune system activation.[61]

It has been shown that the particle heating–melting–vaporization model can be successfully applied to describe the interactions of colloidal NPs with pulsed laser beams (►**Fig. 3**). These NPs when photoactivated can simultaneously produce stressors capable of inducing destruction of cancer cells and increase cell membrane permeability for improved drug delivery for any co-prescribed therapies including chemotherapy.[62]

The laser irradiation can be one of three types – nano-, pico-, and femtosecond – based on the specific pulse width.[63] Femtosecond laser pulses as "microscissors" have emerged as a prodigious tool that can be controlled with great precision.[64] NPs strongly absorb laser pulses from UV to NIR light sources. The interaction between the laser and NP occurs when the electromagnetic waves of the laser pulses interact with the electrons surrounding the NP. Free metal NPs can rapidly assemble a large number of electrons from the laser, thereby causing the electron gas to heat up rapidly. Almost all the energy absorbed by the NP from the laser pulse is spent on the melting–heating–vaporization process.[62]

After absorption of the laser pulses, there is simultaneous conversion of the optical energy into both thermal and mechanical (acoustic) energy. When the particle absorbs photons, it instantly heats up to temperatures exceeding 1000°C within nanoseconds. The particle's shape, size and aggregation state, as well as the irradiating laser's intensity, wavelength and pulse duration, determine the amount of heat the particle is able to generate.[65] The increase in temperature has pronounced effects on both the particle itself and the surrounding medium/tumor microenvironment (TME). The same was suggested by Pyatenko et al: if there is an adequate transfer of heat between the NP and photon, the particle would rapidly heat up and the energy of the electrons would therefore be transferred to the crystal lattice.[62] When the temperature in TME rises above 42°C, cancer cells can be destroyed immediately.[66]

The photoacoustic effect is defined as a physical phenomenon wherein matter absorbs a short-pulsed laser beam and converts its energy into sound (acoustic wave).[67] The generation of photoacoustic emission by exposure of NPs to laser pulses can be explained through two separate phenomena. The sudden expansion in the NP size due to the increased temperature induces localized pressure changes that eventually emit an acoustic wave.[68] This is termed "the thermoelastic effect" which usually occurs when pulse laser energy

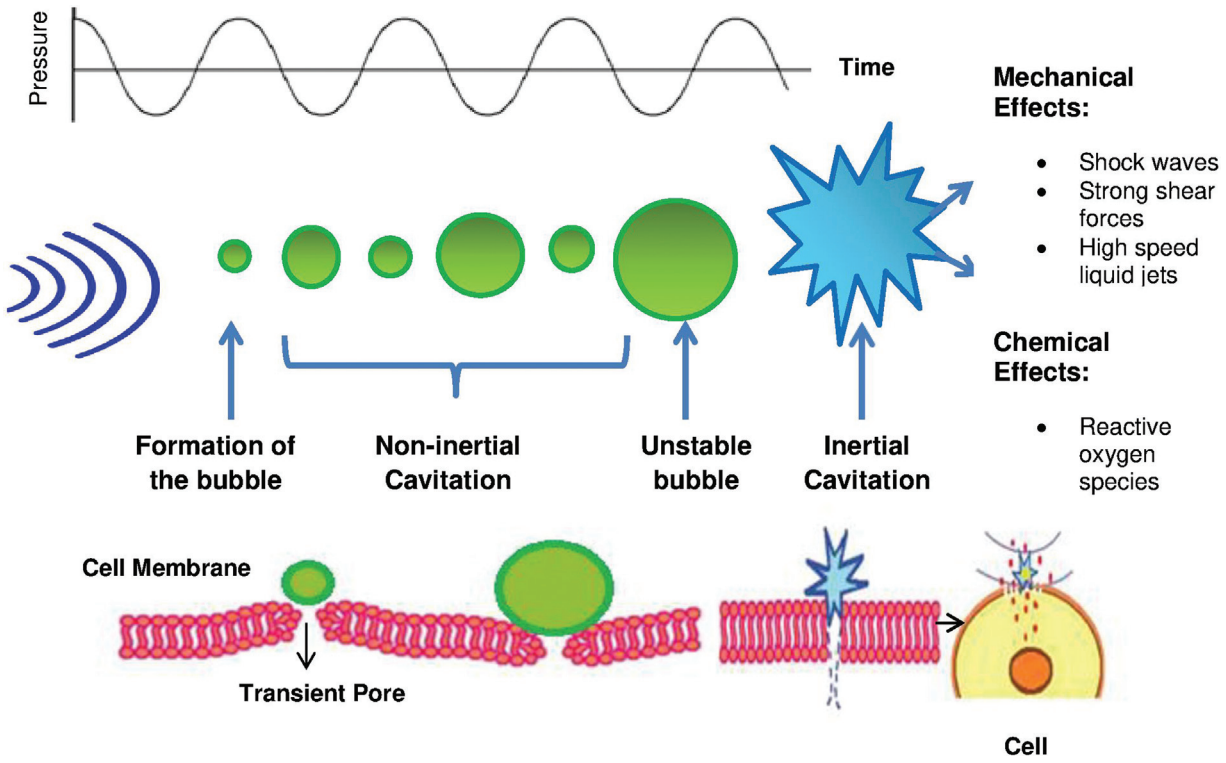

Fig. 4 Cavitation effect: The combined thermal and acoustic energies, if high enough, can induce the vaporization of nanoparticles. This results in the formation of plasma bubbles termed the cavitation effect. During the non-inertial cavitation phase, the bubbles undergo successive oscillations for several acoustic cycles. When pressures elevate, the bubble grows unstable, resulting in its violent collapse, termed the inertial cavitation phase. The collapse of the bubble causes mechanical effects that can propel the drug agent into the tumor site. Further chemical benefits can aid in cancer cell death.

is low. The second phenomenon is termed "the thermal evaporation effect". The energy input in the system can be directly increased by amplifying the laser energy. If both the laser fluence and the number of laser pulses are increased above the threshold value, and enough energy is absorbed, the temperature rise would now be adequate for inducing the vaporization of NPs. The latter phenomenon produces much stronger photoacoustic signals compared with those generated by the thermoelastic expansion effect.[69] The vaporization of NP leads to the formation of bubbles, which is termed "the cavitation effect".

Cavitation is a phenomenon that describes the process of phase transitions between liquid and vapor, or at liquid–solid interfaces, caused by hydrodynamics (►**Fig. 4**). The vapor and cavitation plasma bubbles that form are determined by the density of the laser.[70] The cavitation effect occurs in a two-stage process: the first is termed "non-inertial" or "stable" cavitation, during which the formation of the vapor cavities occur; the second is called "inertial" cavitation, and is when an implosion of the gas bubbles occurs.[71] The gas bubbles undergo successive oscillations for several acoustic cycles. When the pressure elevates, the bubble grows unstable, thereby causing it to collapse violently, which leads to the generation of shock waves, strong shear forces and high-speed liquid jets when in contact with the surrounding inert environment.[72] These forces can then drive the therapeutic agent into the tumor, thereby increasing the delivered dosage and penetration distance to hypoxic and poorly vascularized regions.[73] The collapse of the bubbles further increases the temperature and pressure in the surrounding medium, resulting in a pyrolysis reaction (thermal decomposition of materials at elevated temperatures in an inert atmosphere), leading to the production of ROS and subsequent cancer cell death.[74]

Additionally, when the energies combine, they can in some proportion generate stresses that transiently increase the permeability of cell membranes. Sengupta et al termed this method of intracellular delivery "transient nanoparticle energy transduction" (TNET).[75] According to previous studies, TNET has been shown to deliver molecules into cells with up to 90% efficiency while maintaining approximately 100% cell viability.[76] Small molecules have significantly higher delivery rates than macromolecules. This suggests that TNET creates transient nanopores, thereby advantageously excluding macromolecules either by sieving or by leaving insufficient time for slowly diffusing macromolecules to enter the cell.[75] This results in excellent spatial and temporal precision for the delivery of therapeutic drug agents and thus controlled mediation of cell death.

Hypothesis: In addition to their independent curative abilities in disease, NPs found in selected HMs can act similarly to previously tested NPs in phototherapy to enhance cancer cell death.

Conclusion and Limitations

Combination therapies should aim to overcome the deficiencies of monotherapies in a compensatory and co-operative manner. Homeopathy has shown potential in the palliative and supportive care of oncology patients; however, a lack of high-quality research studies has restricted its implementation in clinical practice. Research regarding the nanoparticulate properties of HMs is being actively pursued. To expand the potential therapeutic use of homeopathy, we suggest a new research model to ascertain the effects of homeopathic sources of plant-based, metal, and SiNPs in PDT/PTT as a previously unexplored possibility. A major challenge lies in the lack of standardization of homeopathic NP formations, due to variations in preparation methods. Further research might aim to optimize NPs from homeopathic formulations as PSs, enhancing their delivery and accumulation in targeted cancer cells and thus improving the effects of PDT.

Highlights

- Photodynamic and photothermal therapy has shown efficacy in inducing cancer cell death by employing versatile photosensitive nanoparticle agents in combination with laser irradiation.
- Empirical studies have demonstrated the presence of nanoparticles in selected plant and metal-based homeopathic medicines.
- A hypothetical model is presented to assess homeopathic source nanoparticles in a photodynamic/photothermal mechanism.

Funding

The authors sincerely thank the South African Research Chairs Initiative of the Department of Science and Technology and the National Research Foundation of South Africa (Grant No 98337), as well as grants received from the University of Johannesburg, the National Research Foundation, and the Council for Scientific and Industrial Research—National Laser Centre's Laser Rental Pool Program.

Conflict of Interest

None declared.

References

1 Faguet GB. A brief history of cancer: age-old milestones underlying our current knowledge database. Int J Cancer 2015; 136:2022–2036
2 Mottaghitalab F, Farokhi M, Fatahi Y, Atyabi F, Dinarvand R. New insights into designing hybrid nanoparticles for lung cancer: diagnosis and treatment. J Control Release 2019;295:250–267
3 Zhang L, Li Y, Chen Q, Xia Y, Zheng W, Jiang X. The construction of drug-resistant cancer cell lines by CRISPR/ Cas9 system for drug screening. Sci Bull 2018;63:1411–1419
4 Bell IR, Koithan M. A model for homeopathic remedy effects: low dose nanoparticles, allostatic cross-adaptation, and time-dependent sensitization in a complex adaptive system. BMC Complement Altern Med 2012;12:191
5 Gaertner K, Lüer SC, Frei-Erb M, von Ammon K. Complementary individual homeopathy in paediatric cancer care: a case series from a University Hospital, Switzerland. Complement Ther Med 2018;41:267–270
6 Bagot J-L. Homeopathy and hetero-isotherapy, an interesting response to the side effects of targeted therapies in oncology. La Revue d'Homéopathie 2017;8:35–41
7 Naudé DF, Stephanie Couchman IM, Maharaj A. Chronic primary insomnia: efficacy of homeopathic simillimum. Homeopathy 2010;99:63–68
8 Hönigsmann H. History of phototherapy in dermatology. Photochem Photobiol Sci 2013;12:16–21
9 Moskvin SV. Low-level laser therapy in Russia: history, science and practice. J Lasers Med Sci 2017;8:56–65
10 Heiskanen V, Hamblin MR. Photobiomodulation: lasers vs. light emitting diodes? Photochem Photobiol Sci 2018;17:1003–1017
11 Chang L, Huang S, Zhao X, et al. Preparation of ROS active and photothermal responsive hydroxyapatite nanoplatforms for anticancer therapy. Mater Sci Eng C 2021;125:112098
12 Lv Z, He S, Wang Y, Zhu X. Noble metal nanomaterials for NIR-triggered photothermal therapy in cancer. Adv Healthc Mater 2021;10:e2001806
13 Choi Y, Hong S. Qualitative and quantitative analysis of patent data in nanomedicine for bridging the gap between research activities and practical applications. World Pat Inf 2020; 60:101943
14 Turan NB, Erkan HS, Engin GO, Bilgili MS. Nanoparticles in the aquatic environment: usage, properties, transformation and toxicity—a review. Process Saf Environ Prot 2019;130:238–249
15 Zhang Z, Dong C, Yu G, et al. Smart and dual-targeted BSA nanomedicine with controllable release by high autolysosome levels. Colloids Surf B Biointerfaces 2019;182:110325
16 Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm J 2018;26:64–70
17 Hare JI, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: an industry perspective. Adv Drug Deliv Rev 2017; 108:25–38
18 Frass M, Friehs H, Thallinger C, et al. Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients—a pragmatic randomized controlled trial. Complement Ther Med 2015;23:309–317
19 Rostock M, Naumann J, Guethlin C, Guenther L, Bartsch HH, Walach H. Classical homeopathy in the treatment of cancer patients—a prospective observational study of two independent cohorts. BMC Cancer 2011;11:19
20 Samadder A, Das S, Das J, Paul A, Boujedaini N, Khuda-Bukhsh AR. The potentized homeopathic drug, Lycopodium clavatum (5C and 15C) has anti-cancer effect on Hela cells in vitro. J Acupunct Meridian Stud 2013;6:180–187
21 Arora S, Aggarwal A, Singla P, Jyoti S, Tandon S. Anti-proliferative effects of homeopathic medicines on human kidney, colon and breast cancer cells. Homeopathy 2013;102:274–282
22 Mondal J, Bishayee K, Panigrahi AK, Khuda-Bukhsh AR. Low doses of ethanolic extract of Boldo (*Peumus boldus*) can ameliorate toxicity generated by cisplatin in normal liver cells of mice in vivo and in WRL-68 cells in vitro, but not in cancer cells in vivo or in vitro. J Integr Med 2014;12:425–438
23 Tiffon C. The impact of nutrition and environmental epigenetics on human health and disease. Int J Mol Sci 2018;19:3425
24 Khuda-Bukhsh A. Potentized homoeopathic drugs act through regulation of gene-expression: a hypothesis to explain their mechanism and pathways of action in vitro. Complement Ther Med 1997;5:43–46
25 Saha S, Roy S. Khuda-Bukhsh. Evidence in support of gene regulatory hypothesis: gene expression profiling manifests homeopathy effect as more than placebo. Int J High Dilution Res 2013; 12:162–167
26 Bishayee K, Sikdar S, Khuda-Bukhsh AR. Evidence of an epigenetic modification in cell-cycle arrest caused by the use of ultra-highly-

diluted gonolobus condurango extract. J Pharmacopuncture 2013;16:7–13
27 Yoo J-O, Ha K-S. New insights into the mechanisms for photodynamic therapy-induced cancer cell death. Int Rev Cell Mol Biol 2012;295:139–174
28 van Straten D, Mashayekhi V, de Bruijn HS, Oliveira S, Robinson DJ. Oncologic photodynamic therapy: basic principles, current clinical status and future directions. Cancers (Basel) 2017;9:19
29 Gao R, Fu R, Jiao W, et al. Opto-acoustic effect of Au nanoparticles in water under irradiation of pulse laser. Optik (Stuttg) 2020; 202:163512
30 Mansoori B, Mohammadi A, Amin Doustvandi M, et al. Photodynamic therapy for cancer: role of natural products. Photodiagn Photodyn Ther 2019;26:395–404
31 Shahcheraghi SH, Zangui M, Lotfi M, et al. Therapeutic potentials of curcumin in the treatment of glioblastoma multiforme. Curr Pharm Des 2019;25:333–342
32 Machado FC, Adum de Matos RP, Primo FL, Tedesco AC, Rahal P, Calmon MF. Effect of curcumin-nanoemulsion associated with photodynamic therapy in breast adenocarcinoma cell line. Bioorg Med Chem 2019;27:1882–1890
33 Sun M, Zhang Y, He Y, et al. Green synthesis of carrier-free curcumin nanodrugs for light-activated breast cancer photodynamic therapy. Colloids Surf B Biointerfaces 2019;180:313–318
34 Baghdan E, Duse L, Schüer JJ, et al. Development of inhalable curcumin loaded nano-in-microparticles for bronchoscopic photodynamic therapy. Eur J Pharm Sci 2019;132:63–71
35 Jalde SS, Chauhan AK, Lee JH, Chaturvedi PK, Park J-S, Kim Y-W. Synthesis of novel Chlorin e6-curcumin conjugates as photosensitizers for photodynamic therapy against pancreatic carcinoma. Eur J Med Chem 2018;147:66–76
36 Zhang J, Feng C, Xu H, Tan X, Hagedoorn P-L, Ding S. Enhanced hypericin extraction from *Hypericum perforatum L.* by coupling microwave with enzyme-assisted strategy. Ind Crops Prod 2019; 137:231–238
37 Kim H, Kim SW, Seok KH, et al. Hypericin-assisted photodynamic therapy against anaplastic thyroid cancer. Photodiagn Photodyn Ther 2018;24:15–21
38 Kimáková P, Solár P, Fecková B, et al. Photoactivated hypericin increases the expression of SOD-2 and makes MCF-7 cells resistant to photodynamic therapy. Biomed Pharmacother 2017; 85:749–755
39 Andrade GP, Manieri TM, Nunes EA, Viana GM, Cerchiaro G, Ribeiro AO. Comparative in vitro study of photodynamic activity of hypericin and hypericinates in MCF-7 cells. J Photochem Photobiol B 2017;175:89–98
40 Villacorta RB, Roque KFJ, Tapang GA, Jacinto SD. Plant extracts as natural photosensitizers in photodynamic therapy: in vitro activity against human mammary adenocarcinoma MCF-7 cells. Asian Pac J Trop Biomed 2017;7:358–366
41 Choi EB, Lee MW, Park JE, et al. Photodynamic apoptosis and antioxidant activities of Brassica napus extracts in U937 and SK-HEP-1 cells. Appl Biol Chem 2017;60:427–435
42 Laszló IP, Laszló MR, Toma V, et al. The in vivo modulatory effects of Cornus mas extract on photodynamic therapy in experimental tumors. Photodiagn Photodyn Ther 2020;30:101656
43 Yi G, Hong SH, Son J, et al. Recent advances in nanoparticle carriers for photodynamic therapy. Quant Imaging Med Surg 2018;8:433–443
44 Yang W, Liang H, Ma S, Wang D, Huang J. Gold nanoparticle based photothermal therapy: Development and application for effective cancer treatment. Sustain Mater Techno 2019;22:e00109
45 Jabeen F, Najam-ul-Haq M, Javeed R, Huck CW, Bonn GK. Au-nanomaterials as a superior choice for near-infrared photothermal therapy. Molecules 2014;19:20580–20593
46 Khafaji M, Zamani M, Golizadeh M, Bavi O. Inorganic nanomaterials for chemo/photothermal therapy: a promising horizon on effective cancer treatment. Biophys Rev 2019;11:335–352
47 Hu J-J, Liu M-D, Chen Y, et al. Immobilized liquid metal nanoparticles with improved stability and photothermal performance for combinational therapy of tumor. Biomaterials 2019; 207:76–88
48 Chikramane PS, Suresh AK, Bellare JR, Kane SG. Extreme homeopathic dilutions retain starting materials: a nanoparticulate perspective. Homeopathy 2010;99:231–242
49 Kalliantas D, Kassalia ME, Georgiadou A, Karagianni CS. The physical features – size and granularity – of solid materials are strongly affected by trituration in lactose, before turning them into homeopathic solutions. Mater Sci Eng C 2018;93:305–318
50 Bell IR, Schwartz GE, Boyer NN, Koithan M, Brooks AJ. Advances in integrative nanomedicine for improving infectious disease treatment in public health. Eur J Integr Med 2013;5:126–140
51 Temgire MK, Suresh AK, Kane SG, Bellare JR. Establishing the interfacial nano-structure and elemental composition of homeopathic medicines based on inorganic salts: a scientific approach. Homeopathy 2016;105:160–172
52 Das S, Das J, Samadder A, Bhattacharyya SS, Das D, Khuda-Bukhsh AR. Biosynthesized silver nanoparticles by ethanolic extracts of *Phytolacca decandra*, *Gelsemium sempervirens*, *Hydrastis canadensis* and *Thuja occidentalis* induce differential cytotoxicity through G2/M arrest in A375 cells. Colloids Surf B Biointerfaces 2013;101:325–336
53 Bell IR, Sarter B, Koithan M, et al. Integrative nanomedicine: treating cancer with nanoscale natural products. Glob Adv Health Med 2014;3:36–53
54 Paul S, Bhattacharyya SS, Samaddar A, Boujedaini N, Khuda-Bukhsh AR. Anticancer potentials of root extract of Polygala senega against benzo[a]pyrene-induced lung cancer in mice. J Chin Integr Med 2011;9:320–327
55 Bhattacharyya SS, Paul S, Khuda-Bukhsh AR. Encapsulated plant extract (Gelsemium sempervirens) poly (lactide-co-glycolide) nanoparticles enhance cellular uptake and increase bioactivity in vitro. Exp Biol Med (Maywood) 2010;235:678–688
56 Kalliantas D, Kallianta M, Kordatos K, Karagianni CS. Micro-nano particulate compositions of *Hypericum perforatum L* in ultra high diluted succussed solution medicinal products. Heliyon 2021;7: e06604
57 Kar S, Chakraborty M, Nandy P, et al. Characterization and haemocompatibility of *Aurum metallicum* for its potential therapeutic application. Indian J Res Homoeopathy 2017;11:41
58 Rajendran ES. An evaluation of Avogadro's number in the light of HRTEM and EDS studies of high dilutions of *Ferrum metallicum* 6, 30, 200, 1M, 10M and 50Mc. Int J High Dilution Res 2015;14:3–9
59 Bell IR, Muralidharan S, Schwartz GE. Nanoparticle characterization of traditional homeopathically-manufactured silver (*Argentum Metallicum*) medicines and placebo controls. J Nanomed Nanotechnol 2015;6:4
60 Chikramane PS, Suresh AK, Kane SG, Bellare JR. Metal nanoparticle induced hormetic activation: a novel mechanism of homeopathic medicines. Homeopathy 2017;106:135–144
61 Hwang HS, Shin H, Han J, Na K. Combination of photodynamic therapy (PDT) and anti-tumor immunity in cancer therapy. J Pharm Investig 2018;48:143–151
62 Pyatenko A, Wang H, Koshizaki N, Tsuji T. Mechanism of pulse laser interaction with colloidal nanoparticles. Laser Photonics Rev 2013;7:596–604
63 Boulais E, Lachaine R, Hatef A, Meunier M. Plasmonics for pulsed-laser cell nanosurgery: fundamentals and applications. J Photochem Photobiol Chem 2013;17:26–49
64 Banavath HN, Allam SR, Valathati SS, Sharan A, Rajasekaran B. Femtosecond laser pulse assisted photoporation for drug delivery in chronic myelogenous leukemia cells. J Photochem Photobiol B 2018;187:35–40
65 Hashimoto S, Werner D, Uwada T. Studies on the interaction of pulsed lasers with plasmonic gold nanoparticles toward light

manipulation, heat management, and nanofabrication. J Photochem Photobiol Chem 2012;13:28–54
66 Wang J, Wu X, Shen P, et al. Applications of inorganic nanomaterials in photothermal therapy based on combinational cancer treatment. Int J Nanomedicine 2020;15:1903–1914
67 Xu A-P, Han H-H, Lu J, et al. Charge transfer NIR dyes for improved photoacoustic effect. Dyes Pigm 2016;125:392–398
68 Holguin SY, Thadhani NN, Prausnitz MR. Effect of laser fluence, nanoparticle concentration and total energy input per cell on photoporation of cells. Nanomedicine (Lond) 2018; 14:1667–1677
69 Wu M, Xiong H, Zou H, et al. A laser-activated multifunctional targeted nanoagent for imaging and gene therapy in a mouse xenograft model with retinoblastoma Y79 cells. Acta Biomater 2018;70:211–226
70 Ye L, Zhu X, Liu Y. Numerical study on dual-frequency ultrasonic enhancing cavitation effect based on bubble dynamic evolution. Ultrason Sonochem 2019;59:104744
71 Boffi P, Ferrarese G, Ferrario M, Malavasi S, Mastronardi MV, Mattarei M. Coherent optical fiber interferometric sensor for incipient cavitation index detection. Flow Meas Instrum 2019; 66:37–43
72 Brujan EA. Shock wave emission and cavitation bubble dynamics by femtosecond optical breakdown in polymer solutions. Ultrason Sonochem 2019;58:104694
73 Paris JL, Mannaris C, Cabañas MV, et al. Ultrasound-mediated cavitation-enhanced extravasation of mesoporous silica nanoparticles for controlled-release drug delivery. Chem Eng J 2018; 340:2–8
74 Shanei A, Akbari-Zadeh H, Attaran N, Salamat MR, Baradaran-Ghahfarokhi M. Effect of targeted gold nanoparticles size on acoustic cavitation: an in vitro study on melanoma cells. Ultrasonics 2020;102:106061
75 Sengupta A, Gray MD, Kelly SC, Holguin SY, Thadhani NN, Prausnitz MR. Energy transfer mechanisms during molecular delivery to cells by laser-activated carbon nanoparticles. Biophys J 2017; 112:1258–1269
76 Yang NJ, Hinner MJ. Getting across the cell membrane: an overview for small molecules, peptides, and proteins. Methods Mol Biol 2015;1266:29–53