Al-Nahrain Journal for Engineering Sciences **NJES** 26(3)226-234, 2023
http://doi.org/10.29194/NJES.26030226

Advancements in Laser and Ultrasound Therapeutic Strategies for Cancer Cells: Recent Review

Raghad R. Abdulateef[1], Jamal A. Hassan [2*], Eman G. Khalil[3*]

Authors affiliations:
1) Dept. of Biomedical Eng., College of Engineering, Al-Nahrain University, Baghdad-Iraq.
st.raghad.r.abdulateef@ced.nahrainuniv.edu.iq

2*) Dept. of Biomedical Eng., College of Engineering, Al-Nahrain University, Baghdad-Iraq.
jamal.a.hassan@nahrainuniv.edu.iq

3*) Dept. of Biomedical Eng., College of Engineering, Al-Nahrain University, Baghdad-Iraq.
eman.g.khalil@nahrainuniv.edu.iq

Paper History:

Received: 17th June 2023

Revised: 7th July 2023

Accepted: 16th Aug. 2023

Abstract

Cancer is a disease caused by uncontrollable cell growth and division. Surgery, chemotherapy, radiotherapy, and hormonotherapy are all cancer treatment options. In addition to noninvasive cancer ablative therapy. As an example, ultrasonic therapy, even with low-intensity pulsed ultrasound (LIPUS) or high-intensity focused ultrasound (HIFU), and Laser therapy (photo-biomodulation therapy) in low-level laser therapy (LLLT) with different wavelength ranges from ultraviolet (UV), visible and infrared (IR) that all have demonstrated different results depending on the target of treatment so previous trials therapies are being studied. This paper reviews recent studies on the in vitro treatment effect of ultrasound therapy and laser therapy on normal and cancerous cell lines with specific parameters. The effect of ultrasound results showed a decrease in cell proliferation and an increase in apoptosis in different types of cells, depending especially on sound intensity, known as Special Peak Temporal Average Intensity (I_{SPTA}). While the laser effect is noticed on cell viability, either enhance or inhibit their viability depending upon the dose of exposure and other specific parameters like wavelength, energy density, and power density used in each treatment protocol. The previous studies conclude that each response would have a treatment method with specific parameters, even an increase or decrease in cell viability. Further studies need to be applying these methods in vivo.

Keywords: Low-Intensity Pulsed Ultrasound, High-Intensity Focused Ultrasound, Laser Therapy, Cancer Treatment, In-Vitro Treatment.

استراتيجيات العلاج بالليزر والموجات فوق الصوتية: المراجعات الأخيرة

رغد رسول عبد اللطيف, جمال عبد الجبار حسن, ايمان غضبان خليل

الخلاصة:

مرض السرطان يتسبب عن نمو الخلايا وانقسامها غير المنضبط. الجراحة والعلاج الكيميائي والعلاج الإشعاعي والعلاج الهرموني كلها خيارات لعلاج السرطان. هناك دراسات عن المعالجة باستئصال غير جراحي للسرطان. و على سبيل المثال العلاج بالموجات فوق الصوتية الذي يكون على نوعين: الموجات فوق الصوتية النبضية منخفضة الكثافة (LIPUS) أو الموجات فوق الصوتية المركزة عالية الكثافة (HIFU) ، وايضا العلاج بالليزر (العلاج بالتعديل الحيوي الضوئي) في العلاج بالليزر منخفض المستوى (LLLT) بنطاقات أطوال موجية مختلفة من الأشعة فوق البنفسجية والمرئية والأشعة تحت الحمراء ، كل تلك الدراسات أظهرت نتائج مختلفة باختلاف الهدف المطلوب ولا زالت تلك العلاجات قيد الدراسة. تعرض هذة الورقة البحثية الدراسات السابقة عن تأثير الموجات فوق الصوتية وتأثير الليزر على الخلايا الطبيعية والسرطانية ذات المعلمات المحددة. في النتيجه أظهر تأثير نتائج الموجات فوق الصوتية انخفاضًا في تكاثر الخلايا وزيادة موت الخلايا المبرمج في أنواع مختلفة من الخلايا. بينما لوحظ تأثير الليزر على قابلية الخلية للحياة ، فإنه يتسبب إما في تعزيز أو تثبيط قابليتها للحياة ويعتمد على جرعة التعرض بالإضافة إلى عوامل محددة أخرى مثل الطول الموجي وقدرة الليزر المستخدمة في كل بروتوكول علاج. لخلصت الدراسات السابقة إلى أن كل استجابة ناتجة من طريقة علاج مع معاملات محددة حتى تزيد أو تنقص في حيوية الخلية. مزيد من الدراسات المستقبلية نحتاجها لتطبيق هذه الأساليب في داخل الجسم الحي.

NJES is an **open access Journal** with **ISSN 2521-9154** and **eISSN 2521-9162**

1. Introduction

From the past, right today, cancer ranks as the leading cause of mortality worldwide. It will be accountable for nearly one in every six fatalities[1]. Cancer is a complex and heterogeneous group of diseases characterized by abnormal cell division, uncontrolled growth, and the potential to invade and spread to other body parts[2]. Understanding the characteristics of different types of cancer, their mechanisms of cell division, patterns of spread, and response to treatment is crucial for developing effective therapeutic strategies[3]. There are many types of cancer cells, each with a different cause and treatment. Invasive by different methods, including surgery, chemotherapy, and radiation therapy[4]. In recent years, laser therapy and ultrasound therapeutic techniques in cancer treatment have gained significant attention due to their potential to improve patient outcomes. Studies have shown that laser and ultrasound energy can effectively destroy cancer cells while minimizing damage to surrounding healthy tissue[5, 6]. For instance, laser therapy, also known as phototherapy or photobiomodulation, utilizes specific wavelengths of light to induce biochemical changes within cells[7]. In addition to its direct effects on cancer cells, laser therapy can enhance the efficacy of other treatment modalities when combined with chemotherapy, significantly reducing tumor size [8, 9].

Moreover, ultrasound therapy in the treatment of liver cancer patients. The researchers found that high-intensity focused ultrasound (HIFU) therapy resulted in tumor necrosis and improved overall survival rates[10]. The non-invasive Ultrasound and laser therapy cause cancer's apoptosis (cell death) by using acoustic waves and optic waves to treat tumors; they kill the cancer cells without damaging normal cells[11].

2. Ultrasound Therapy for Cancer Cells

Sonoporation induced by ultrasound-guided microbubble (USMB) collapse has been studied to improve therapeutic drug delivery into cancer cells by overcoming these natural barriers[12]. The strategy of ultrasound therapy is to induce heating due to acoustic waves to treat a disease depending upon depth. There are two types of ultrasonic waves: low intensity typically ranges (30 mW/cm² to 300 mW/cm²) and high intensity with ranges from several hundred W/cm² to a few KW/cm²[13]. High-intensity focused ultrasound (HIFU) ablates tumors non-invasively. HIFUs cause local hyperthermia and destructive cavitation leading to cell lysis, chemotherapeutic uptake, and systemic antitumor immune responses. Focused ultrasound (FUS) kills tumors and healthy tissue. Therefore, when tumors are close to or have invaded important tissue, safely using HIFU frequently necessitates pricey MRI targeting[14]. Cavitation, microstreaming, and radiation force are all components of the high-intensity focused ultrasound process. Acoustic cavitation occurs when gas-filled cavities, known as microbubbles, that form spontaneously or naturally in a vibrated liquid media under the impact of an acoustic wave[15].

While low-intensity pulsed ultrasound (LIPUS) produces a mechanical effect without hyperthermia, which selectively ablates cancer cells using ultrasound waveforms. Cancer cells, DNA content, nuclear-nucleolar volume ratios, cytoskeletal stiffness, and viscoelastic properties support this hypothesis [16]. LIPUS is a more specific, safer method that targets the lesion. It was able to break apart multiple types of cancer cells without damaging healthy cells by scaling down the intensity and carefully tweaking the frequency to match the target cells. So, the difference between HIFUS and LIPUS depends specifically on sound intensity (I_{SPTA}) and frequency range (F) with the type of exposure, either focused continuously or pulsed, as shown in Fig. 1 [17].

Ultrasound treatment depends on different parameters after selecting the type of treatment; these parameters are frequency F, sound intensity (I_{SPTA}), microbubbles concentration (MB), and exposure time (T). The previous studies in Table 1 show the effect of ultrasound on different types of cells.

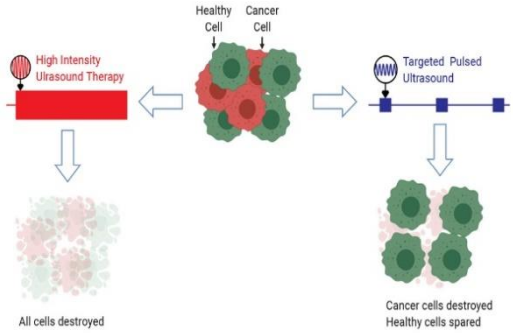

Figure (1): The response of HIFUS and LIPUS on healthy and cancer cells.

Table (1): Summarized previous studies about ultrasound's effect on cells.

Year	*Authors*	*Type of cells*		*Methods*	*Results*
2004	*Michel et al. [18]*	***CO-7***	*Non-human renal cells.*	***1- Electromagnetic shock wave:*** *200µg/ml of DNA plasmid, Energy-density= 0.5mJ/mm²,*	***1-Electromagnetic shock wave*** *linear rate: the rising number of impulses can use an increase of transfection in all cell lines*

		MatLu	*Rat prostate carcinoma cells.*	*Frequency= 2Hz.* ***2- FUS:*** *Frequency=1.07MHz, Power=100,200,300W, Time=10s, pulse duration=500ms (10 pulses/sample).*	***2- FUS** non-linear rate:* *Max. transfection achieved at 200W, while at 100 and 300W lower rate. Elevation power will drop the survival rate.*
		RT112	*Human urothelial cancer cell.*		
2012	*J.W. Jenne et al. [19]*	***Prostate, Uterine Fibroids, Bone metastases, and Blood-Brain Barrier (BBB).***		*Frequency= 1MHz* *20-40 pulses* *Power-density=10ms* *Pressure=0.6-0.8 MPa*	*HIFUS cause increased heating on the target while the surrounding tissue isn`t affected by the low intensity.*
2014	*Joji Kusuyama et al. [20]*	***3T3-L1***	*Mouse embryo fibroblast cells.*	*Frequency= 1.5MHz* *Pulse duration= 200µs for 1200 s* I_{SPTA}*=30 mW/cm²*	*LIPUS generated considerable ERK phosphorylation in 3T3-L1, MC3T3-E1, and ST2 cells. However, LIPUS administration did not trigger phosphorylation of p38 and JNK or IB breakdown in any of the tested cell lines.*
		MC3T3-E1	*Osteoblast cells.*		
		Mouse bone marrow.			
2017	*D.Shi MD, et al. [21]*	***MCF-7***	*Breast tumor*	*Microbubbles (MB)=10,20 and 30%,* I_{SPTA}*=0.5,1 and 1.5 W/cm²,* *Time= 30,60 and 90 s,* *Frequency= 100KHz.*	***Cell viability when:*** ***1- Increase MB:*** *MCF-7 and A2780 will increase. Bel7402 and ARO firstly will increase and then decrease.* ***2- Increase*** I_{SPTA}***:*** *Bel7402, A2780, and ARO will increase.* *While MCF-7 increased and then decreased.* ***3- Increase T:*** *MCF-7 and A2780 decreased then increased,* *ARO will increase then decreased, while Bel7402 increased then kept a high level.*
		Bel7402	*Liver tumor.*		
		A2780	*Ovarian tumor.*		
		ARO	*Thyroid tumor.*		
2018	*Nina Qu et al. [22]*	***Human breast cancers:***		*MB=10,20 and 30%,* I_{SPTA}*=0.5,1 and 1.5W/cm²,* *Time= 30,60 and 90 s,* *Frequency= 1MHz,* *Power-density=10ms.*	***Cell viability when:*** ***1- Increase MB:*** *MCF-7, MDA-MB-486, and MCF-7/MDR will increase,* *MDA-MB-231 will have decreased.* ***2-Increase*** I_{SPTA}***:*** *All four cell lines will increase.* ***3-Increase T:*** *MCF-7 doesn`t change,* *MDA-MB-486 and MCF-7/MDR increased,* *MDA-MB-231 decreased.*
		MCF-7			
		MDA-MB-231			
		MDA-MB-486			
		MCF-7/MDR *(multidrug resistance)*			
2020	*David R. et al. [23]*	***4T1***	*Mouse breast cancer.*	*Pulsed US* *Duty cycle =10%,* *Frequency=0.5-0.67MHz,* *Power-density= 20ms,* I_{SPTA}*<5W/cm²,* *Peak negative pressure <1.2 Mpa.*	*LIPUS Inducing cancer cell-specific cytodisruption while leaving healthy blood and immune cells alone. Standing-wave formation and the onset of cavitation were required to disrupt cancer cells.*
		CT26	*Colon fibroblast.*		
		MCF-7, SK-BR-3, MDA-MB231	*Human breast cancers.*		
		CD4, CD8, B, NK	*Human peripheral blood cells.*		
		RBC	*Bovine peripheral blood cells.*		

2022	*L.Landgraf et al. [11]*	***PC-3***	*Human prostate cancer cell.*	*Frequency=1.1MHz, Power-density=20ms,* ***1****-Time=90s, Power 20%,* I_{SPTA}*=2.95W/cm²,* *duty-cycle=10%.* ***2****-Time=90s, Power 40%,* I_{SPTA}*=5.9W/cm².*	*In 3D tumor models, pulsed FUS therapy caused molecular consequences. They observed decreased spheroid development activity and increased DNA double standing break (cell death signal) with spheroid integrity disruption, leading to damage in the specific cancer cells.*
		U87	*Glioblastoma.*		
2023	*Yaozhang Yang et al. [24]*	***A2780***	*Human ovarian cancer cells.*	*Frequency =1 MHz, Time= 60s, Duty cycle=20%,* I_{SPTA}*=0.6, 1, 1.4W/cm².*	*LIUS exposure decreased the viability of A2780 cells and OCSCs in an intensity-dependent manner, with OCSCs being more resistant than A2780 cells.*
		OCSCs	*Human ovarian stem cells.*		

3. Laser Therapy for Cancer Cells

Laser therapy is used to treat several types of cancers. Laser therapy employs light energy to eradicate cancer cells and shrink tumors. As the light energy goes through the cancer cells, it is transformed into heat that kills them. Cancers of the skin, breast, lungs, cervix, and prostate are typically destroyed with laser therapy[25]. Laser-induced thermal therapy (LITT) uses interstitially placed high-power lasers to ablate percutaneously tumors[26]. Laser-induced hyperthermia and LITT heat normal and tumor tissue equally, damaging and killing surrounding healthy tissue[27]. So, there are many types of exposure: continuous wave (CW) or long-pulse laser sources that produce heat-affected zones larger than the tumor, but this harms healthy tissue. Ultra-short pulse lasers with pulse widths from picoseconds to femtoseconds have been used in many emerging biomedical technologies, including laser surgery[28]. Heat-affected zones (HAZs) can form due to long pulse duration. This can weaken the material by causing microcracks, porous structures, and residual stresses. Femtosecond lasers having pulse durations in the order of 10^{-15} s decrease harmful laser-material interaction and, as a result, reduce the likelihood of HAZs. As the pulse duration shortens, the energy and ablation depth rise, while heat diffusion length shortens, and a specifically defined ablation area is ablated without injuring the surrounding tissue, as shown in Fig. 2 [29].

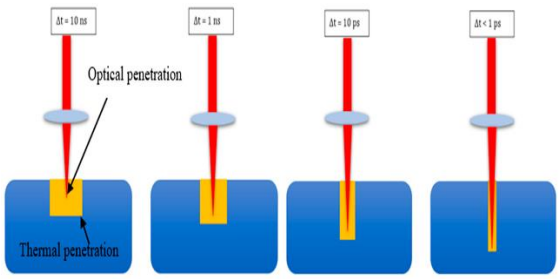

Figure (2): The relation between pulse duration and ablation depth.

A tiny skin incision manually directs the laser beam into the tumor. The cancer cells are subsequently heated and killed by the beam as directed around the tumor. Small tumors inside the breast can occasionally be removed with a laser[30]. Breast cancer can be treated with laser therapy in one of two ways: either as a preoperative procedure to shrink the size and number of cancer cells before surgery or as a postoperative procedure to eradicate any leftover cancer cells after the surgery[31]. It can be used independently and with other cancer therapies, including radiotherapy and chemotherapy. Laser therapy destroys cancer cells and prevents them from growing or spreading. It can also be used to shrink the tumor so that it is easier to remove during surgery[25].

According to some research, laser therapy may also inhibit the development of new blood vessels in tumorous tissue and stop them from growing in healthy tissue[32]. Therefore, laser therapy might stop cancer cells from spreading to other body parts outside the initial tumor site. Additional research is nonetheless required to confirm these possible advantages of laser therapy. Laser treatment depends on different parameters that are adjusted when selecting the type of treatment; these parameters depend on cell line type, wavelength range [UV (>400) nm, visible (400-760) nm, and IR (<760) nm], power density, energy density, and some other differences depend on the conditions of experiment[33]. Table (2) review research dealing with cell laser therapy.

Table (2): Summarized research dealing with laser therapy.

Year	*Author*	*Cells*		*Material*	*Result*
2009	*O.Bozkulak et al. [34]*	***MDA-MB231***	*Human breast cancer cells*	*CW diode laser 809nm* *Power= 60mW* *Intensity= 24J/cm²* *ICG=indocyanine-green.*	*Cell viability immediately decreased due to photo-oxidation from the ICG with a diode laser.*
2010	*Powell et al. [35]*	***MCF-7***	*Human breast adenocarcinoma*	*Three different sources:* *780nm continuous(50mW),* *830nm continuous(30mW),* *904nm pulsed (90mW).* *0.5,1,2,3,4,10,12J/cm² for 780 nm* *0.5,1,2,3,4,10,15J/cm² for 830 and 904nm* *1,2, or 3exposures.*	*Certain laser dosages promote MCF-7 cell growth.* *Multiple exposures had no effect or had dose-response associations that were negative.* *The laser used showed no evidence of malignant transformation cells.* *Bre80hTERT or MDA-MB-435S exposure resulted in minimal alterations in growth rates.*
		MDA-MB-436S	*Human breast ductal carcinoma*		
		SVCT and Bre80hTERT	*Immortalized human mammary epithelial*		
2011	*A. Y. Sajjadi et al. [36]*	***Healthy mice and mice with mammary tumors***		*Focused beam ultra-short pulse diode laser 1552nm,* *Pulse width=1.3ps* *Power= 0.17 to 2.5W* *Energy= 1-5µJ/pulse* *Frequency=2.5–500KHz.*	*Thermal & mechanical damage produce precise ablation of tumors with minimal effect on the surrounding tissue.*
2012	*Schartinger et al. [37]*	***BEAS-2B***	*Human bronchial epithelial cells*	*Diode laser 660nm.* *Power output 350mW.* *Irradiation time 15min;* *Three exposure in subsequent days*	*Human gingival fibroblasts:* *increase Proliferation.* *Non-neoplastic cells (BEAS-2B) and SCC-25 decrease proliferation and induce proapoptotic cells.*
		SCC-25	*Oral squamous cell carcinoma cells*		
		Human gingival fibroblasts			
2013	*B.Crisan, et al. [38]*	***Human fibroblast skin***		*830,980, and2940nm.* *F= 50Hz* *ED= 5.5 J/cm²,* *output Power= 1W,* *Power-density= 0.5W/cm²* *Irradiation time 110s*	*830 and 980 nm:* *Increase mitochondrial activity.* *2940nm:* *Decrease mitochondrial activity,* *Increase apoptosis and necrosis*
2014	*Gomes Herquez et al. [39]*	***SCC25***	*Oral squamous cell carcinoma cells*	*660nm, 30mW* • *0.5J/cm² and irradiance of 0.03W/cm² for 16s* • *1.0J/cm² and irradiance of 0.03W/cm² for 33s.*	*Both densities:* *Increase Proliferation* *Increase Cyclin D1,* *Increase Nuclear b-catenin,* *Decrease E-cadherin,* *Increase MMP-9,* *Increase invasion potential,*
2015	*F.Cialdi et al. [40]*	***Human breast cell lines:*** ***MCF-7*** ***MDA-MB-361***		*808 and 905nm diode laser* ***Firstly:*** *905 nm pulsed, Power-density=100ms,* *Frequency=90KHz.* ***Then:*** *808nm continuous,* *Power =1W,* *Output Power= 500mW,*	*1-Cell viability and proliferation: single treatment doesn't significantly affect proliferation.* *2-Cell cycle doesn't be affected.* *3-Modified the apoptotic threshold*

				Duty cycle =50%, *Time= 10min,* *Energy-density= 9J/cm^2,* *irradiance=15mW/cm^2.* *Once per day for three days*	*And modify the percentage of a living cell in early and late apoptotic cells.*
2016	*Aishah B. et al. [41]*	***MDA-MB231***	*Human breast cancer*	***1-****Excimer laser 248nm* *average powers up to 35W* ***2-*** *Nd: YAG laser 1064nm and 532nm* *power up to 500W* *several pulses from 1-6 pulses.*	*1-Cell viability increased after being irradiated with 248nm.* *2-Cell viability slightly decreased after irradiation with 532nm & 1064nm.* *1064nm is more effective in killing the cells than 532nm.* *In both lasers, when the energy increases, the cell viability will decrease.* *Several pulses have no significant effect on the viability of the cells.*
2017	*Kara et al. [42]*	***Saos-2***	*Osteoblast-like osteosarcoma cells*	*Nd-YAG laser 1064nm* *Pulsed mode:* *Power o/p 0.5-1-2-3W,* *Energy 100mJ,* *Frequency:5-10-20-30 Hz,* *Continuous-wave mode:* *Time 30s, and 1 cm distance from the culture media.* *The laser was irradiated 1, 2, and 3 times.*	*Cell proliferation rate was increased in 1 and 2W more than in 3W* *Increase the mitotic activity of cancer tissue cells.* *1.5mW proved to be more successful in cell killing.*
		A549	*Human lung carcinoma cells*		
2018	*G.Bölükbaşı Ateş et al. [43]*	***ATCC***	*Human osteoblast cell line*	*PBM parameters:* *809nm* *10W output power,* *50mW/cm^2 power density* *Energy density= 0.5,1, and 2J/cm^2* *Time=10,20, and 40s*	*ICG treatment alone had an inhibitory effect on cell viability and proliferation.* *PBM, like PDT, destroys cancerous cells and promotes cellular activity.* *In the future, ICG-mediated PBM may offer promising results in bone repair and regenerative medicines.*
2020	*S.Lins Terena et al. [44]*	***HUVEC***	*Human umbilical vein endothelial cells*	*low-level laser* *red (660nm) and infrared (780nm) laser with four different radiance exposures* *40mW,* *1,5,10, and 20J/cm^2,* *1,5,10, and 20s, respectively,* *total energy 0.4,2,4, and 8J,* *beam spot size 0.04cm^2*	***Red laser:*** *enhanced viability and protein concentration.* ***Infrared laser:*** *reduced cell viability and regulating the amount of protein in the cell, with the greatest peak protein content detected on the second day in the group with radiant exposure of 1J/cm2 and 10J/cm2.*
2021	*S.Mirza et al. [45]*	***Rat femoral bone marrow***		*805nm continuous mode,* *O/p power= 0.5,1,1.5, 2W* *Energy = 1,4,7,10J*	*Bone marrow cells will increase at ED=1.27J/cm^2 and o/p power 1.5W.* *The 4th day showed a significant increase compared with the 1st day.*
2022	*N.Suard et al. [46]*	***MCF-7***	*Human breast cancer*	*532 nm,* *Power =1.5,5,100mW,* *Spot size=0.7mm* *Irradiation time:1,5,10, 15min* *Single, double, and triple fractionation with five and*	*100mW laser output good potential in the:* *Single fractionated cell death.* *The fractionated regimen was more effective in*

				10min breaks between each.	*killing tumor cells.*
2023	*Safaa Taha et al. [47]*	***T47D***	*Human breast infiltrating ductal carcinoma*	*Femtosecond laser* *Wavelengths:* *1- 380 and 400nm* *2- 420 and 440 nm* *3- 700, 720, 750, and 780nm* *Power=100mW* *Irradiation time=180, 300 or 600 s*	***380 and 400 nm:*** *The growth of cells is markedly inhibited.* ***420 and 440 nm:*** *The viability of the cells was considerably impacted. Also, showed that the ideal exposure time was 10 minutes.* ***700, 720, 750, and 780nm:*** *Various exposure durations had little impact on the cells' viability, which could be insignificant.*

4. Discussions:

The studies and their results, summarized in Table (1), showed the effect of ultrasound on different cell lines, either increasing or decreasing the cell viability, which depends on the parameters used. The ultrasound therapy, either HIPUS, as J.W. Jenne et al. mentioned in 2012, found that the temperature increased in the surrounding normal tissue and the cells in the region of interest[19]. While David R. et al. in 2020 used LIPUS, which led to a selective ablation of cancer cells, leaving healthy cells intact [23]. Also, the response depended on the type of cell line, as D. Shi MD et al. in 2017 and Nina Qu et al. in 2018 studied the effect of each parameter on different types of cell lines. They found that the cell viability changed when increasing the microbubbles concentration, sound intensity, and time of exposure to each type of cell line[21, 22]. Overall the effect of cancer cell viability is directly proportional to I_{SPTA}. Also, a shorter treatment time would be effective in decreasing cell viability.

Moreover, the studies of laser effect on cell lines are shown in Table (2), either by occurrence apoptosis or necrosis of the cell lines. Whereas the study of Safaa Taha et al. in 2023 showed that human breast infiltrating ductal carcinoma, when exposed to different laser wavelengths in different stages [UV, visible, and IR], led to a significant or non-significant effect on the cancer cells, according to the type and the parameters of treatment[47]. While S. Mirza et al. in 2021 tested the laser effect on normal rat femoral bone marrow. Their results showed that laser increases cell viability, which is important in cell regeneration in future work[45]. Overall, the main parameters that lead to ablating cancer cells or stimulating to increase cell viability depend on wavelength and power output, as confirmed by Aishah B. et al. in 2016 when using P=500W with wavelength1064 nm and suggested to be the most effective in decreasing cell viability than 284nm and 532nm[41]. Also, Kara et al. in 2017 noticed that cell proliferation in 1 and 2W more than in 3W [42]. So, the results obtained from previous studies show that the effect of these strategies or treatments depends on different parameters related to the cell type and others related to the treatment method and its setting.

5. Conclusion:

Previous studies manifested that the response of the treated cells with ultrasound or laser offers unique advantages, including targeted delivery, minimal invasiveness, and potential synergistic effects with conventional treatments. Whether these treatments enhance or inhibit cell viability depends on different parameters concerning the therapeutic agent and the type of treated cells. The low-intensity ultrasound treatment may be a promising option for treating cancer cells, even with a short duration of exposure. At the same time, laser treatment has different effects, either increasing or decreasing the cell viability depending on laser parameters, including wavelength, power mode, and energy density. Finally, the effect of ultrasound and laser has the benefit of being an anticancer treatment for other medical purposes, depending on certain parameters.

7. References:

[1] R. L. Siegel, K. D. Miller, N. S. Wagle, and A. Jemal, "Cancer statistics, 2023," *CA: a cancer journal for clinicians,* vol. 73, no. 1, pp. 17-48, 2023.

[2] M. Madaminov and F. Shernazarov, "Breast cancer detection methods, symptoms, causes, treatment," *Science and innovation,* vol. 1, no. D8, pp. 530-535, 2022.

[3] D. A. Lukow and J. M. Sheltzer, "Chromosomal instability and aneuploidy as causes of cancer drug resistance," *Trends in Cancer,* vol. 8, no. 1, pp. 43-53, 2022.

[4] Y. S. Sun *et al.*, "Risk Factors and Preventions of Breast Cancer," (in eng), *Int J Biol Sci,* vol. 13, no. 11, pp. 1387-1397, 2017, doi: 10.7150/ijbs.21635.

[5] E. Ostańska, D. Aebisher, and D. Bartusik-Aebisher, "The potential of photodynamic

therapy in current breast cancer treatment methodologies," *Biomedicine & Pharmacotherapy,* vol. 137, p. 111302, 2021.

[6] P. Tharkar, R. Varanasi, W. S. F. Wong, C. T. Jin, and W. Chrzanowski, "Nano-enhanced drug delivery and therapeutic ultrasound for cancer treatment and beyond," *Frontiers in Bioengineering and Biotechnology,* vol. 7, p. 324, 2019.

[7] C. Dompe *et al.*, "Photobiomodulation—the underlying mechanism and clinical applications," *Journal of clinical medicine,* vol. 9, no. 6, p. 1724, 2020.

[8] D. Mahmood, A. Ahmad, F. Sharif, and S. A. Arslan, "Clinical application of low-level laser therapy (Photo-biomodulation therapy) in the management of breast cancer-related lymphedema: a systematic review," *BMC Cancer,* vol. 22, no. 1, p. 937, 2022.

[9] J. Xu, W. Xu, Z. Wang, and Y. Jiang, "Study on combination therapy for lung cancer through pemetrexed-loaded mesoporous polydopamine nanoparticles," *Journal of Biomedical Materials Research Part A,* vol. 111, no. 2, pp. 158-169, 2023.

[10] B. Zhou *et al.*, "HIFU for the treatment of gastric cancer with liver metastases with unsuitable indications for hepatectomy and radiofrequency ablation: a prospective and propensity score-matched study," *BMC Surgery,* vol. 21, no. 1, pp. 1-12, 2021.

[11] L. Landgraf *et al.*, "Focused Ultrasound Treatment of a Spheroid In Vitro Tumour Model," *Cells,* vol. 11, no. 9, p. 1518, 2022.

[12] J. Qin, T.-Y. Wang, and J. K. Willmann, "Sonoporation: Applications for cancer therapy," *Therapeutic Ultrasound,* pp. 263-291, 2016.

[13] J. F. Díaz-Alejo, I. G. Gómez, and J. Earl, "Ultrasounds in cancer therapy: A summary of their use and unexplored potential," *Oncology Reviews,* vol. 16, no. 1, 2022.

[14] R. J. van den Bijgaart, D. C. Eikelenboom, M. Hoogenboom, J. J. Fütterer, M. H. den Brok, and G. J. Adema, "Thermal and mechanical high-intensity focused ultrasound: perspectives on tumor ablation, immune effects, and combination strategies," *Cancer Immunology, Immunotherapy,* vol. 66, pp. 247-258, 2017.

[15] C. P. Phenix, M. Togtema, S. Pichardo, I. Zehbe, and L. Curiel, "High intensity focused ultrasound technology, its scope and applications in therapy and drug delivery," *Journal of Pharmacy & Pharmaceutical Sciences,* vol. 17, no. 1, pp. 136-153, 2014.

[16] P. Xia, Y. Shi, X. Wang, and X. Li, "Advances in the application of low-intensity pulsed ultrasound to mesenchymal stem cells," *Stem Cell Research & Therapy,* vol. 13, no. 1, pp. 1-14, 2022.

[17] D. R. Mittelstein *et al.*, "Selective ablation of cancer cells with low-intensity pulsed ultrasound," *Applied Physics Letters,* vol. 116, no. 1, 2020.

[18] M. S. Michel *et al.*, "Acoustic energy: a new transfection method for cancer of the prostate, cancer of the bladder and benign kidney cells," *Anticancer Research,* vol. 24, no. 4, pp. 2303-2308, 2004.

[19] J. W. Jenne, T. Preusser, and M. Günther, "High-intensity focused ultrasound: principles, therapy guidance, simulations, and applications," *Zeitschrift für Medizinische Physik,* vol. 22, no. 4, pp. 311-322, 2012.

[20] J. Kusuyama, K. Bandow, M. Shamoto, K. Kakimoto, T. Ohnishi, and T. Matsuguchi, "Low-intensity pulsed ultrasound (LIPUS) influences the multilineage differentiation of mesenchymal stem and progenitor cell lines through ROCK-Cot/Tpl2-MEK-ERK signaling pathway," *Journal of Biological Chemistry,* vol. 289, no. 15, pp. 10330-10344, 2014.

[21] D. Shi *et al.*, "Influence of tumor cell lines derived from different tissue on sonoporation efficiency under ultrasound microbubble treatment," *Ultrasonics Sonochemistry,* vol. 38, pp. 598-603, 2017.

[22] N. Qu *et al.*, "Breast cancer cell line phenotype affects sonoporation efficiency under optimal ultrasound microbubble conditions," *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research,* vol. 24, p. 9054, 2018.

[23] D. R. Mittelstein *et al.*, "Selective ablation of cancer cells with low-intensity pulsed ultrasound," *Applied Physics Letters,* vol. 116, no. 1, p. 013701, 2020.

[24] Y. Yang, M. Du, J. Yu, and Z. Chen, "Biomechanical Response of Cancer Stem Cells to Low-intensity Ultrasound," *Journal of Biomechanical Engineering,* vol. 145, no. 9, 2023.

[25] E. Schena, P. Saccomandi, and Y. Fong, "Laser ablation for cancer: past, present and future," *Journal of functional biomaterials,* vol. 8, no. 2, p. 19, 2017.

[26] S. E. Norred and J. A. Johnson, "Magnetic resonance-guided laser-induced thermal therapy for glioblastoma multiforme: a review," *BioMed research international,* vol. 2014, 2014.

[27] S. Missios, K. Bekelis, and G. H. Barnett, "Renaissance of laser interstitial thermal ablation," *Neurosurgical Focus,* vol. 38, no. 3, p. E13, 2015.
[28] M. A. Ansari, M. Erfanzadeh, and E. Mohajerani, "Mechanisms of laser-tissue interaction: II. Tissue thermal properties," *Journal of lasers in medical sciences,* vol. 4, no. 3, p. 99, 2013.
[29] A. B. Kaligar *et al.*, "Femtosecond laser-based additive manufacturing: Current status and perspectives," *Quantum Beam Science,* vol. 6, no. 1, p. 5, 2022.
[30] Y. Z. Peng, L. J. Yang, H. H. Lo, B. Y. K. Law, and V. K. W. Wong, "Tumor Therapeutic Modes," *New Nanomaterials and Techniques for Tumor-targeted Systems,* pp. 135-229, 2020.
[31] S. M. Banerjee *et al.*, "Photodynamic therapy in primary breast cancer," *Journal of clinical medicine,* vol. 9, no. 2, p. 483, 2020.
[32] G. Ottaviani *et al.*, "Laser therapy inhibits tumor growth in mice by promoting immune surveillance and vessel normalization," *EBioMedicine,* vol. 11, pp. 165-172, 2016.
[33] S. Bordin-Aykroyd, R. Dias, and E. Lynch, "Laser-tissue interaction," *EC Dental Science,* vol. 18, no. 9, pp. 2303-2308, 2019.
[34] O. Bozkulak, R. F. Yamauchi, O. Tabakoglu, and M. Gulsoy, "Photo-toxic effects of 809-nm diode laser and indocyanine green on MDA-MB231 breast cancer cells," *Photodiagnosis and photodynamic therapy,* vol. 6, no. 2, pp. 117-121, 2009.
[35] K. Powell, P. Low, P. A. McDonnell, E.-L. Laakso, and S. J. Ralph, "The effect of laser irradiation on proliferation of human breast carcinoma, melanoma, and immortalized mammary epithelial cells," *Photomedicine and laser surgery,* vol. 28, no. 1, pp. 115-123, 2010.
[36] A. Y. Sajjadi, K. Mitra, and M. Grace, "Ablation of subsurface tumors using an ultra-short pulse laser," *Optics and Lasers in Engineering,* vol. 49, no. 3, pp. 451-456, 2011.
[37] V. H. Schartinger, O. Galvan, H. Riechelmann, and J. Dudás, "Differential responses of fibroblasts, non-neoplastic epithelial cells, and oral carcinoma cells to low-level laser therapy," *Supportive care in cancer,* vol. 20, pp. 523-529, 2012.
[38] B. Crisan, O. Soritau, M. Baciut, R. Campion, L. Crisan, and G. Baciut, "Influence of three laser wavelengths on human fibroblasts cell culture," *Lasers in medical science,* vol. 28, pp. 457-463, 2013.
[39] Á. C. Gomes Henriques *et al.*, "Low-level laser therapy promotes proliferation and invasion of oral squamous cell carcinoma cells," *Lasers in medical science,* vol. 29, pp. 1385-1395, 2014.
[40] F. Cialdai *et al.*, "In vitro study on the safety of near-infrared laser therapy in its potential application as postmastectomy lymphedema treatment," *Journal of Photochemistry and Photobiology B: Biology,* vol. 151, pp. 285-296, 2015.
[41] A. Badruzzaman, N. Bidin, and S. P. M. Bohari, "The effect of laser irradiation on the viability of human breast cancer cell, MDA-MB-231," *Jurnal Teknologi,* vol. 78, no. 3, 2016.
[42] C. Kara, H. Selamet, C. Gökmenoğlu, and N. Kara, "Low-level laser therapy induces increased viability and proliferation in isolated cancer cells," *Cell proliferation,* vol. 51, no. 2, p. e12417, 2018.
[43] G. B. Ateş, A. Ak, B. Garipcan, and M. Gülsoy, "Indocyanine green-mediated photobiomodulation on human osteoblast cells," *Lasers in Medical Science,* vol. 33, pp. 1591-1599, 2018.
[44] S. M. L. Terena, R. A. Mesquita-Ferrari, A. M. de Siqueira Araújo, K. P. S. Fernandes, and M. H. Fernandes, "Photobiomodulation alters the viability of HUVECs cells," *Lasers in Medical Science,* vol. 36, pp. 83-90, 2021.
[45] S. Mirza *et al.*, "The effect of 805 nm near-infrared photobiomodulation on proliferation and differentiation of bone marrow stem cells in murine rats," *European Review for Medical and Pharmacological Sciences,* vol. 25, no. 20, pp. 6319-6325, 2021.
[46] N. Suardi, P. M. Khaniabadi, A. Taggo, S. F. M. Zulbaharin, D. K. M. Azman, and S. J. Gemanam, "Fractionated low-level laser irradiation on breast cancer (MCF 7 cells) treatment," *Lasers in Medical Science,* vol. 37, no. 2, pp. 1265-1271, 2022/03/01 2022, doi 10.1007/s10103-021-03384-0.
[47] S. Taha, W. R. Mohamed, M. A. Elhemely, A. O. El-Gendy, and T. Mohamed, "Tunable femtosecond laser suppresses the proliferation of breast cancer in vitro," *Journal of Photochemistry and Photobiology B: Biology,* vol. 240, p. 112665, 2023.