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Efficacy of Hematoporphyrin mediated photo-sonodynamic therapy on mice breast cancer

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► ***Original article***

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ABSTRACT

***Background*:** A combination of photodynamic and sonodynamic therapy (PSDT) may be a non-invasive method for cancer treatment, which incorporates a combination of low-intensity ultrasound, laser radiation, and a sensitizer agent. The goal of this research was to evaluate the effect of PSDT with Hematoporphyrin-encapsulated Mesoporous silica nanoparticles (HP-MSNs) as a sensitizer in the management of mice breast adenocarcinoma. ***Materials and Methods*:** One hundred and fifty-six female mice (tumor grafted) were separated into 26 groups; including sham, laser (650 nm), 4 groups of laser + HP or MSN-HP (2.5 and 5 mg/kg), 4 groups of laser + ultrasound (1and 3 MHz; 1, 2 W/cm^2), 16 groups of PSDT + HP or HP-MSN. The tumor growth factors were used to assess the procedure findings. ***Results*:** The results indicate that PSDT with an injection of HP or HP-MSN is effective in delaying tumor growth ($P<0.05$). Overall comparison of data showed a non-significant difference between PSDT with HP -MSN groups. The time of T2 and T5 in the groups of PSDT with HP-MSN were increased in comparison with sham and that of PSDT with HP groups ($P<0.05$). The tumor growth inhibition ratio increased in all PSDT groups. This increase was transient and declined over 30 days of treatment. PSDT + HP-MSN had Grade I, while other groups had Grade III malignancy in the histological study. ***Conclusion*:** The research gave profound findings involving the employ of PSDT with HP-MSN as a photo/ sonosensitizer for treating breast adenocarcinoma implanted in mice.

INTRODUCTION

The present idea of PDT (Photodynamic therapy) has started with studies by Lipson and Schwartz (1960) who observed neoplastic lesion fluorescence caused by the injection of Hematoporphyrin preparations [1]. The photosensitizer is one of the crucial components of PDT, apart from light and oxygen [2]. Most photo-sensitizers do not collect in cell nuclei; hence PDT has been recognized as having the lower potential of creating DNA injuries, mutations, and carcinogenesis. But several minutes following light radiation plasma membrane PDT damage can be monitored. These types of damages are swelling, active transport dysfunction, plasma membrane depolarization, and increment of a photosensitizer [1]. The initiation of the PDT process is related to the absorption of a photon by a photosensitizer and subsequent results in intramolecular energy transfer reactions [3]. Since, the absorbed energy is transferred to the adjacent molecules (such as O_2), an increase of singlet oxygen, and rise of radical oxygen species (ROS), which prompt cell death (apoptosis or necrosis) [4]. Tumor destruction from PDT occurred by both programmed (apoptotic) and non-programmed (necrosis) pathways [5].

In a newly developed therapeutic method called sonodynamic therapy (SDT), ultrasound generates ROS for killing cancer cells. On the other hand, SDT as a non-invasive method has deeper penetration ability into the cancer tissue, and effectively increases cytotoxicity that involves the formation, growth, and exploding of gas-filled bubbles in fluids [6,7]. In SDT, ultrasound exposure utilizes with suitable frequency and intensity (1-3 MHz, 0.5-3 W/cm^2). Ultrasound radiation is to be appropriate when an optimal quantity of sensitizer is situated in the tumor area [8]. These waves interact with sonosensitizing agents and as a result, produce free radicals, which cause apoptosis of cancer cells. In fact, this activation is related to the cavitation process [9-11].

Hematoporphyrin (HP) as an SDT sensitizer can maximize the ultrasound effects. The excitation of accumulated sonosensitizers (as Hematoporphyrin) in tumor tissue by ultrasound exposure, resulting in cancer cell killing, due to activated oxygen generated by the sonosensitizer [12]. Furthermore, the drug

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delivery method was developed with the purpose of getting better the results of tumor therapy. The loaded sensitizer would be discharged in reaction to physical stimuli (laser, ultrasound, pH, hyperthermia), and drug concentration may increase in the tumor zones. Mesoporous silica nanoparticles (MSNs) have been considered within the field of treatment. For the discharge of the sensitizer loaded into the Mesoporous Nano-carriers, ultrasound radiation as an external stimulus is extremely considered because in addition to activating sensitivities, allows the spatial and temporal control of drug release at the tumor location, hence increasing therapeutic benefits [13,14]. However, in cancer tissue for the reason that hypoxia, the consequence of PDT and SDT is low, which limits their applications [15]. To overcome the limitation of these two treatment protocols, photo-sonodynamic therapy (PSDT) can help to get a reasonable anti-tumor effect. The ultrasound good tissue penetration and ability of energy focusing into the specific depth of biological tissue overcomes the light -limited penetration [16].

The theory of photo-sonodynamic therapy (PSDT) is derived from the favored accumulation of sensitizing agents in the cancer tissue, and cell toxicity increment after light/laser or ultrasound radiation. Multiple complex mechanisms are involved in PDT and SDT which refer to reactive oxygen species, mechanical stress, and cavitation process [17]. It is concluded that PSDT was not associated with serious side effects, and may enhance the treatment efficacy of human breast cancer [18]. In agreement, PSDT with Sonoflora (ultrasound 1 MHz/LED 630 nm) had significant therapeutic benefits for some patients with advanced breast cancer [19]. In Miyoshi *et al.* study combination therapy of PDT (Aminolevulinic acid)/SDT (titanium oxide) could help to get a reasonable anti-tumor effect on squamous cell carcinoma [16]. Moreover, the combination of PDT (665 nm) and SDT (3.3 MHz) caused a synergetic effect and improved glioblastoma treatment [20]. In An *et al.* study, PDT (630 nm) and SDT (1 MHz) with Sinoporphyrin sodium inhibited glioma cell proliferation and induced cell apoptosis [21]. Moreover, Hong *et al.* concluded that Ce6-P/ WNEs could be activated in prostate cancer PSDT via light (633 nm) and/or ultrasound (2.1 MHz) to produce ROS [15]. Henceforward, the aim of this research was to examine the effect of PSDT with injected HP-MSNs (as a sensitizer) in the healing of breast adenocarcinoma with the parameters related to tumor growth, animal survival, and pathological examination of the tumor. The novelty of this study was the activation of HP-MSNs with simultaneous emission of dual-frequency ultrasound (1 and 3 MHz) and laser (650 nm) in the management of mice grafted breast adenocarcinoma.

MATERIALS AND METHODS

Drug preparation

The synthesis of MSNs was performed in the sol-gel process by application of an alkoxide precursor (tetraethyl orthosilicate: TEOS, Sigma-Aldrich, Canada), and a surfactant (Cetyltrimethylammonium bromide: CTAB, Sigma-Aldrich, Canada). This method consists of the formation of MSNs under the size range of 60-1000 nm. The particles dried at room temperature and calcined at 550 °C for 3h. HP 50 % (Sigma-Aldrich, Canada) was solved in PBS, pH=7.4 (Sigma-Aldrich, Canada), and kept in the darkroom at 4°C. Subsequently, HP solution was placed adjacent to synthesized nanoparticles. The HP enters into the MSN cavities passively process [22, 23].

Tumor graft

In order to use a syngeneic tumor model, the confirmed murine spontaneous breast adenocarcinoma was extracted from anesthetized primary Balb/C mice (ketamine/xylazine, 30 mg/kg IP, Alfasan Co, Netherlands). The tumor tissue was chopped into fresh pieces with a diameter of 2-3 mm in PBS. A portion of cancer tissue was subcutaneously embedded in the inguinal area of the female receptor animal (Inbred Balb/C, 6-8 weeks). Suture clips were used to close the incision and Cefazolin (200 mg/Kg, Sigma-Aldrich, Canada) was added to mice' water to prevent infection [24].

Ultrasound/Laser radiation

For ultrasound radiation, the mice were anesthetized using intraperitoneal ketamine/ xylazine. Anesthetized mice with grafted tumors were placed move less by a specific holder in the near field of ultrasonic waves (30 cm) in a cubic Plexiglas water tank ($25\times25\times35 cm^3$). Two ultrasonic probes (5 cm diameter) were positioned with perpendicular (90^o) central beam axis to each other. The first source was a 1 MHz (1, 2 W/cm^2) and the second source was a 3 MHz (1, 2 W/cm^2) ultrasonic treatment system (210P and 215A, Novin Medical Engineering, Isfahan, Iran). The experimental mouse was exposed to laser light (150 mW, 650 nm, Tem-laser Technology Co. Ltd, China) simultaneously with dual-frequency ultrasound radiation, and the time of the ultrasound/ laser process was 60 seconds.

Treatment groups and tumor evaluation

The treatment method was started when the tumors reached an average diameter of 7-10 mm. To assess the effect of PSDT with an injection of sensitizer on breast adenocarcinoma, one hundred and fifty-six tumor-bearing female Balb/C mice were separated randomly into 26 groups (n= 6) as well as the sham (solvent injection), laser, 2 groups of laser +

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HP (2.5 and 5 mg/kg), 2 groups of laser + HP-MSN (2.5 and 5 mg/kg), 4 groups of laser + ultrasound (1, 3 MHz at 1 and 2 W/cm^2), 8 groups of PSDT with HP, and 8 groups of PSDT with HP-MSN. Due to the weight of Inbred Balb/C mice (20 ± 2 g), HP or HP-MSNs were injected (10 mg/kg, 0.2 ml, IP) 24h before laser radiation [25]. After PSDT, by a digital caliper, the tumor extension was measured in three different dimensions (a, b, and c) every 3 days. Tumor volume was evaluated by the volume formula (V= 0.5 × a × b × c). The obtained volumes (V) were utilized to assess other mass enlargement parameters as relative volume (Relative volume= $[(V-V_o)/V_o] \times 100$), tumors growth inhibition ratio (IR %= $[1- (V_{x\ day} / V_{cotrol\ day})] \times 100$), and the times involved each cancer mass to reach two (T2) and five times (T5) to the primary tumor volume [25].

Histopathological images of cancer mass sections were obtained 30-days after treatment. Tumor sections were stained with hematoxylin/eosin (Sigma -Aldrich, Canada) to assess tumor grading and malignancy based on Bloom-Richardson (BR) classification (tumor tubule formation, the number of mitosis/10 high power fields, and nuclear grade) [26]. Histopathological analysis was performed blindly.

Statistical analysis

The normal distribution of findings was evaluated with the Tukey test. One-way ANOVA and Kruskal-Wallis tests were used to examine the statistical differences between groups with a 95 % confidence interval (SPSS 16.0, USA). To estimate the survival time of experimental groups Kaplan-Meier survival test was performed.

RESULTS

Results obtained from the relative tumor volume versus days after treatment with laser/ultrasound radiation have been plotted in figure 1A. These results indicate that laser/ultrasound radiation groups had a delayed effective tumor growth. Analysis of data showed a non-significant difference between exposed groups (P>0.05). To validate our findings, we calculated the anti-tumor effects of HP injection prior to laser/ultrasound radiation. Figure 1B, demonstrates the relative tumor volume (%) over time following drug injection. A significant difference was indicated between experimental groups and sham in tumor volume, 15 days post-treatment (P<0.05). Comparison of findings showed non-significant difference between PSDT + HP (2.5 and 5 mg/kg) with laser/ultrasound groups (P>0.05). Figure 1C describes tumor enlargement curves based on the relative volume percent versus during 30 days after radiation. The results confirm that HP-MSN administration prior to laser/ultrasound radiation has an inhibition effect on tumor growth when compared with the sham group (P<0.05). Overall comparison of data showed a significant difference between PSDT + HP-MSN (2.5 and 5 mg/kg) with other experimental groups (P<0.05).

The tumor growth inhibition percent (IR %) was revealed in figure 2A. Inhibition of tumor growth in the laser/ultrasound radiation and photodynamic therapy (PDT) groups was greater than that of the sham group. In all experimental groups, IR was greater than that of the sham group. The tumor growth inhibition ratio increased at 9 days after the execution of treatment and declined over 30 days of post-treatment. Figure 2B, illustrated that the tumor growth inhibition ratio of the groups of PSDT + HP (2.5 and 5 mg/kg) was higher than that of the sham group. The maximum tumor growth inhibition ratio was shown at 12 days after the execution of treatment. The experiment demonstrates that this increase wasn't temporary and persisted over 30 days of treatment. Analysis of data showed a significant difference between PSDT + HP-MSN with other experimental groups (P>0.05). As shown in figure 2C, inhibition of tumor growth in the PSDT + HP-MSN groups was greater than that of the laser and sham groups. The tumor growth inhibition ratio enhanced between 9 - 18 days after the radiation but this effect was transient and declined over 30 days. Thus, PSDT with HP-MSN and ultrasound radiation 3 MHz induced slower tumor growth in comparison with PSDT with HP, photodynamic therapy, and laser/ultrasound radiation.

As shown in figure 3, the time need to T2 and T5 in the case of PSDT groups was higher than that in the sham and other experimental groups (p<0.05). Comparison of data showed a non-significant difference between laser and sham groups to reach two times the primary volume (P>0.05). The time of T2 in the case of PDT groups increased in comparison to sham and laser groups (6 *vs* 8 days). Since the maximum time of T2 was shown in PSDT + HP and PSDT + HP-MSN groups (12 and 15 days respectively). Analysis of T5 data showed non-significant differences between sham, laser, laser/ultrasound, and PDT groups (P>0.05). In addition, the required time of five times to the initial volume in PSDT + HP and PSDT + HP-MSN groups were rose (20 and 23 days respectively) compare to the PDT groups (15 days) (P<0.05).

The survival time in the group that received PSDT (HP-MSN) was significantly higher than that of all other groups (P<0.05). Kaplan-Meier analysis of experimental data demonstrated that the 61 days' survival (cumulative survival fraction) was 95 % for the group recovered with PSDT + HP-MSN (5 mg/kg). The survival meantime (with 95 % confidence interval) for the sham, laser, and laser/ultrasound groups was 32, 38, and 38 days respectively; overall comparison test of survival equality for the different levels of groups demonstrated a significant difference

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between experimental groups: Log Rank (Mantel-Cox), P= 0.04.

To verify the PSDT findings, histopathological studies were performed using tumor sections from the different experimental groups. Microscopically assessment of tumor tissue samples indicated that the sham group has some nuclear polymorphism (figure 4A). In the groups that received laser/ ultrasound radiation (figure 4B), the tumor mitotic index was not significantly affected by these physical stimulations. Finally, in the groups that experienced PSDT + HP or HP-MSN (figure 4C), nuclear polymorphism was lower than that of other groups. This finding indicates that polymorphism and dysplasia were affected by combination treatment. The findings based on the Bloom-Richardson classification and tumor grading was presented in table 1. The sham and laser/ultrasound groups had grade III malignancy (poorly-differentiated), while the PSDT+HPMSN group has grade II malignancy (well-differentiated) in the histological study of mice breast adenocarcinoma.

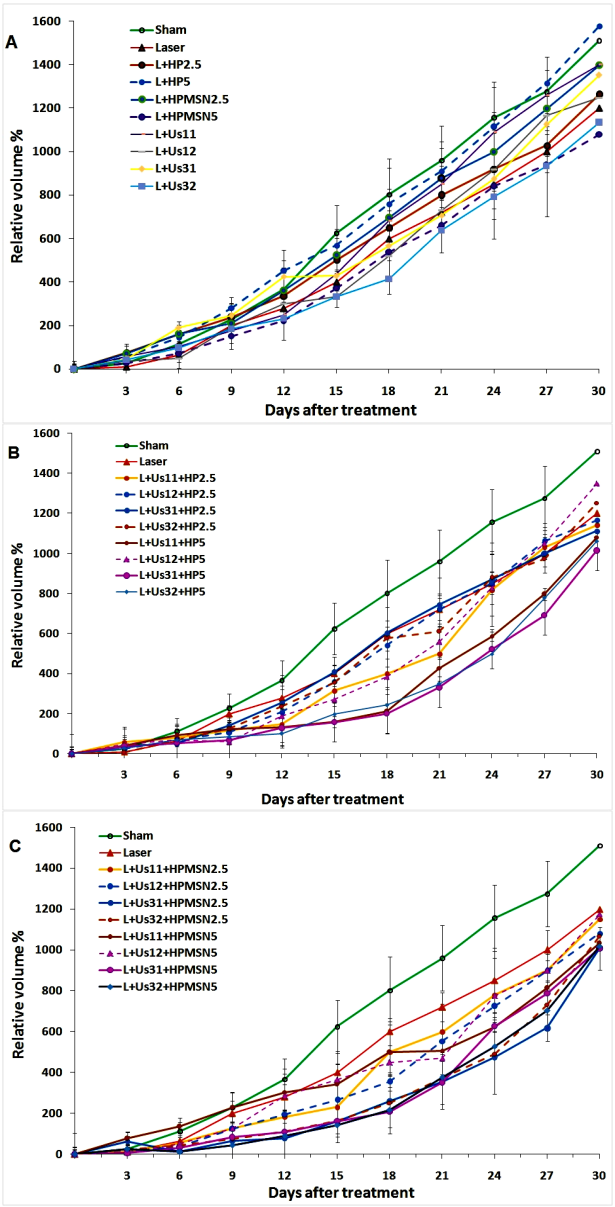


Figure 1. The mean ± SD of the relative volume percent of adenocarcinoma tumors for the following treatment groups: **A)** Photodynamic therapy with HP or HP-MSN; **B)** PSDT + HP; **C)** PSDT + HP-MSN. Overall comparison of data showed a significant difference between PSDT + HP-MSN with other experimental groups (P<0.05). L: laser (650 nm), Us: ultrasound (1, 3 MHz, 1, 2 W/cm2), HP or HP-MSN: (2.5 and 5 mg/kg).

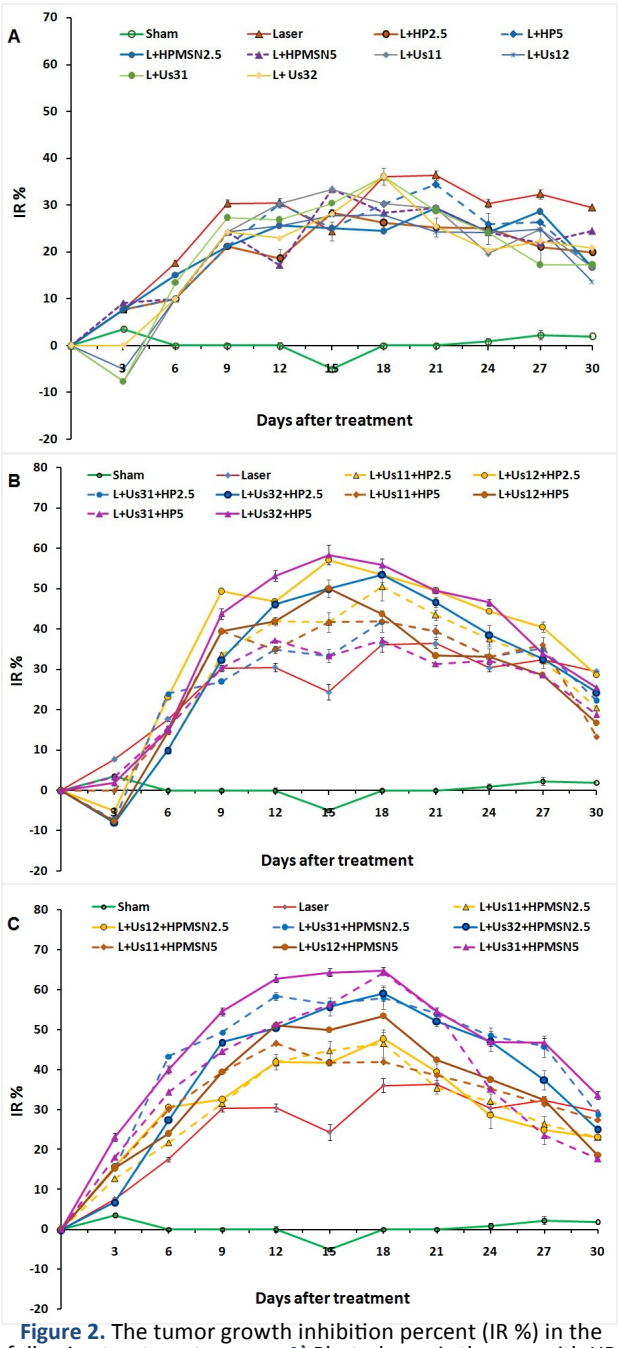


Figure 2. The tumor growth inhibition percent (IR %) in the following treatment groups: **A)** Photodynamic therapy with HP or HP-MSN; **B)** PSDT + HP; **C)** PSDT + HP-MSN. The tumor growth inhibition ratio increased between 9 - 18 days after the initiation of treatment but this effect was transient and declined over 30 days of treatment. L: laser (650 nm), Us: ultrasound (1, 3 MHz, 1, 2 W/cm2), HP or HP-MSN: (2.5 and 5 mg/kg).

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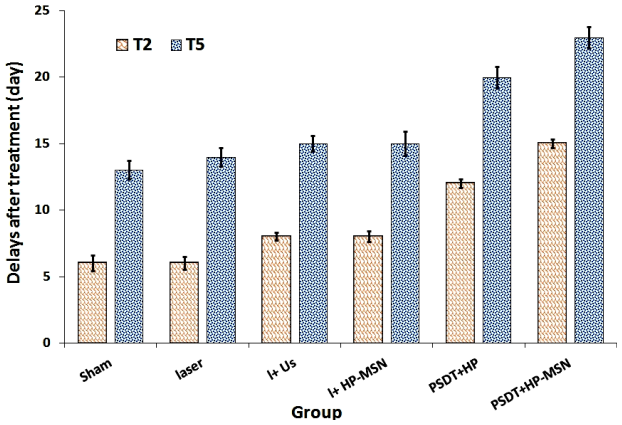


Figure 3. The time required for each tumor volume to reach two (T2) and five times (T5) the initial volume in different experimental groups. The maximum time of T2 was shown in PSDT + HP and PSDT + HP-MSN groups (12 and 15 days respectively). In addition, the required time of five times to the initial volume in PSDT + HP and PSDT + HP-MSN groups were rose to 20 and 23 days respectively. The results represent the mean ± SD as the bar chart.

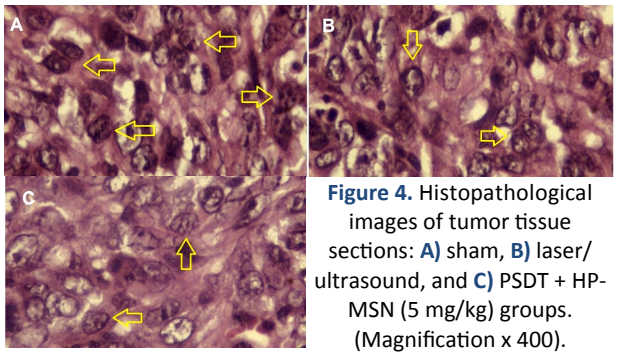


Figure 4. Histopathological images of tumor tissue sections: **A)** sham, **B)** laser/ ultrasound, and **C)** PSDT + HP-MSN (5 mg/kg) groups. (Magnification x 400).

Table 1. Bloom-Richardson (BR) classification of adenocarcinoma tumors in the sham, laser, laser/ultrasound, laser + HP-MSN, and PSDT + HP-MSN experimental groups.

Group	Tumor tubule formation	Number of mitosis	Nuclear grade	Total score	BR grade	Grade
Sham	3	3	3	9	Poorly Differentiated	3
Laser	3	3	3	9	Poorly Differentiated	3
Laser + HP-MSN	3	2	2	7	Moderately Differentiated	2
Laser/ Ultrasound	2	2	2	6	Moderately Differentiated	2
PSDT + HP-MSN	2	1	2	5	Well Differentiated	1

DISCUSSION

The results of experiments were shown that the combination of laser (650 nm) with ultrasound (1 or 3 MHz) radiation and PDT with HP-MSN caused inhibition effect on mice breast adenocarcinoma tumor growth. This effect was transient and declined over 30 days of treatment under the conditions used in this study. In agreement, Banerjee et al. confirmed a potential role for PDT (690 nm) in the management of females' early breast cancer [27] and Aggarwal demonstrated the potential of PDT for treating inflammatory breast cancer cells [28]. Although PDT is very safe in the tissues neighboring to the cancer region, the light penetration depth is limited and often produces less success in tumor treatment [16]. Therefore, the wavelength range 600 - 800 nm with tissue depth penetration of about 8 mm has been determined for clinical PDT, and by reason of high power output and monochromatic quality, lasers became the standard light sources for PDT [3]). PDT applies its effects when light is used to activate a non-toxic photosensitizer. The photochemical process creates reactive oxygen species (ROS). This ROS leads to the destruction of cancer cells through apoptosis or necrosis [29]. Despite the satisfactory results of PDT, the use of this treatment method has been limited due to the light poor penetration and PDT dependence on the existence of oxygen in tumor tissue [30].

Ultrasound to produce bio-effects into the tumor tissue required good penetration and energy focusing into the definite depth [9]. Simultaneous application of ultrasound and a sensitizer comprises mechanical and chemical mechanisms [31]. Porphyrins are molecules that produce active oxygen species after stimulation by visible light and are widely used in PDT. Porphyrin compounds were the first compounds used in the SDT [32]. SDT followed by PDT can help to get a realistic anti-tumor effect because of the ultrasound's deeper penetration into the tumor tissue.

Our experiments also show the anti-tumor effect of PSDT + HP, and the comparison of data showed a non-significant difference between PSDT + HP (2.5 and 5 mg/kg) groups. Also, the findings indicated that PSDT with HP-MSN (2.5 and 5 mg/kg) has an inhibition effect on tumor growth. The tumor growth inhibition ratio increased in all experimental groups at 12 days after the initiation of radiation and persisted over 30 days of treatment. Moreover, the required time of T5 to the primary volume in groups of PSDT + HP-MSN (5 mg/kg) was over that of the 2.5 mg/kg group. This means that a combination of laser/ultrasound and HP-MSNs could have a better treatment effect. The structure of Mesoporous channels would allow controllable drug release by mechanical and cavitation effects of ultrasound [33]. The collapse of cavitating bubbles can cause sonomechanical and sonochemical cytotoxic effects and the formation of cytotoxic reactive oxygen species [34]. As Miyoshi *et al.* suggested that ultrasound (1 MHz) can penetrate deeper than laser (635 nm) into the cancer tissue and a combination of PDT/SDT (1 MHz) helps to get a reasonable anti-tumor effect on mice squamous cell carcinoma [16]. Moreover, the findings demonstrated that PSDT enhanced the antitumor efficacy on 4T1 mammary cancer cells compared with SDT (1 MHz) and PDT

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(laser 650 nm) alone [35]. The combination of PDT (665 nm) and SDT (3.3 MHz) have shown an improved glioblastoma cell *in-vitro* and *in-vivo*, which could be referred to as a synergetic effect [20]. In An *et al.* study, PSDT with ^{0}74 nm laser and 5 MHz ultrasound + Sinoporphyrin sodium inhibited glioma cell proliferation and induced cell apoptosis, due to the generation of ROS and affecting protein expression [21]. Moreover, Hong *et al.* proposed that PSDT with light (633 nm) and ultrasound (2.1 MHz) could produce ROS and eradicate prostate cancer cells [20].

The results of our histopathological study (table 1) showed that PSDT (3 MHz) + HP-MSN (5 mg/kg) group had grade I malignancy (well-differentiated) in the histological study of mice breast adenocarcinoma. On the contrary, our previous investigation analysis showed that the results of single-frequency SDT aren't frequency-dependent and not only determined by ultrasound wave power density but also related to HP-MSN injection dose [24]. This change may be related to the photodynamic therapy effect on experimental groups. Hong *et al.*'s study demonstrated that the PDT and SDT could be combined to overcome the limitations of each modality in the hypoxia environment [15]. In theory, the direct tumor cell toxicity effects of these are modalities facilitated by cytotoxic agents generated by photo/sonochemical reactions inside cancer tissue [36]. PSDT has been used in the treatment of many cancers with variable success, but the efficacy of breast adenocarcinoma damage induced by PSDT with HP-MSNs has rarely been reported. Developing advanced materials as PSDT sensitizers can improve the methods of cancer treatment. However, further studies are required to optimize the sensitizer, light/ laser, and ultrasound parameters to find better tumor treatment methods and explain the mechanism of PSDT.

CONCLUSION

It can be deduced that the results of the present research opened new mods for breast cancer management that requires future verification. This study provided profound findings that involve the use of PSDT employing simultaneous exposure to laser (650 nm) and ultrasound (3 MHz) with Hematoporphyrin encapsulated in Mesoporous silica nanoparticles (5 mg/kg) as a photo/sono-sensitizer for treatment of breast adenocarcinoma implanted to mice.

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***Ethics approval*:** All procedures were approved by the Research Ethics Committee of Semnan University of Medical Sciences (IR.SEMUMS.REC.1396.18), which was in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals (NIH Publications No. 8023, revised Edition 1978).

***Conflicts of interest*:** Declared none.

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***Authors' contributions*:** S.Moshfegh: carried out the experiments and data collection. H. Hasanzadeh: cooperated as a scientific adviser to laser/ultrasound radiation. R. Nasr: helped with tumor graft and sample preparation. M. Mirmohammadkhani: carried out the data analysis. M. Jadidi: participated in experiment design and wrote the manuscript.

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