Heliyon 9 (2023) e15295

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Effect of 650 nm laser photobiomodulation therapy on the HT-7 (*shenmen*) acupoint in the *Mus musculus* model of Parkinson's disease

Suhariningsih Suhariningsih [a,b,d], Suryani Dyah Astuti [a,b,c,*], Herdiani Nur Kusumawati [c], Amalia Fitriana Mahmud [a], Maya Septriana [d], Lale Rozykulyyeva [c], Yunus Susilo [e], Ardiansyah Syahrom [f]

[a] Department of Physics, Faculty of Sciences and Technology, Airlangga University, Surabaya, 60115, Indonesia
[b] Biophysics and Medical Physics Research Group, Faculty of Sciences and Technology, Airlangga University, Surabaya, 60115, Indonesia
[c] Biomedical Engineering Post Graduate Program, Faculty of Science and Technology, Airlangga University, Surabaya, 60115, Indonesia
[d] Traditional Medicine Study Program, Faculty of Vocational Study, Airlangga University, Surabaya, 60286, Indonesia
[e] Faculty of Engineering, Dr Soetomo University, Surabaya, 60118, Indonesia
[f] Department of Applied Mechanics and Design, Faculty of Mechanical Engineering, Universiti Teknologi Malaysia, 81310 Johor Bahru, Malaysia

ARTICLE INFO

Keywords:
Effective dose
Laser diode
Mus musculus
Parkinson's disease
Photobiomodulation therapy

ABSTRACT

Background: Parkinson's disease is one of the neurodegenerative conditions that impacts 1–2% of the world's population. The only effective therapy for this condition today is to restore the biochemical function of the diseased dopamine neurons by giving them Levodopa or L-3,4-dihydroxyphenylalanine (L-DOPA). The risk of progenitor stem cells, though, is the growth of teratomas or the uncontrolled growth of cells. As a result, an alternative or additional method is needed, such as photobiomodulation therapy using a laser diode. In this research, male mice (*Mus musculus*), which were used as models for Parkinson's disease in an in vivo paraquat study, to determine the optimal dose of photobiomodulation therapy and a laser diode was used as a treatment.

Methods: The three sample groups are Group *P*-L- (control group, induced by 0.9% NaCl), Group P + L- (only caused by paraquat), and Group P + L+. (Treatment group, treated by paraquat and photobiomodulation therapy with a laser diode). Photobiomodulation treatment doses of 0.14 J, 0.29 J, 0.37 J, 0.76 J, 1.14 J, and 1.52 J were used in the P+L+ subgroups (6 groups). The laser diode generated a continuous wave with a wavelength of 658 nm, a beam spot of 2.10 mm, and an output power of 15.42 mW. After treatment, the histopathology results of each sample were inspected under a microscope.

Result: In Parkinson's disease-affected mice, paraquat has been shown to reduce the number of neurons. According to the results of the histopathological examination, photobiomodulation therapy using a laser diode (P + L+) on the HT-7 (*Shenmen*) may raise the quantity of neurons and the proportion of healthy cells in the mouse brain.

Conclusion: The effective radiated energy of the photobiomodulation therapy using laser diode treatment on the muscle musculus cell model of Parkinson's disease is 0.76 J.

* Corresponding author. Airlangga University Faculty of Science and Technology, Universitas Airlangga Fakultas Sains dan Teknologi, Surabaya, East Java, 60115, Indonesia

E-mail address: suryanidyah@fst.unair.ac.id (S.D. Astuti).

https://doi.org/10.1016/j.heliyon.2023.e15295
Received 13 March 2021; Received in revised form 22 March 2023; Accepted 31 March 2023
Available online 7 April 2023

1. Introduction

Parkinson's disease is a neurodegenerative disorder that can cause motor disturbances like stiffness, postural instability, rigidity at rest, and akinesia (bradykinesia). It happens when there is a problem with the nigrostriatal pathway or when dopaminergic neurons in the substantia nigra pars compacta die or are destroyed [1–6]. Along with motor function, this disease also has an impact on brain function, digestive issues, sensory issues, akathisia, olfactory issues, and autonomic issues [7]. Psychiatric symptoms like depression, anxiety, hallucinations, psychosis, delusions, and trouble sleeping have also been found to be caused by anti-Parkinson's treatment [8].

According to study findings, 6.2 million people around the globe had Parkinson's disease in 2015, and 14.2 million are predicted to have it by 2040 [1,9]. The prevalence of Parkinson's disease is between 2 and 3% worldwide. Parkinson's disease is thought to affect 1% of adults over 60, with 1–2 cases per 1000 people being reported at any particular time [10]. This condition, which is more common in individuals between the ages of 40 and 70 and has an average age of 60, only affects about 5% of those under the age of 40 [10,11].

Parkinson's disease can only be treated with levodopa and L-3,4-dihydroxyphenylalanine (L-DOPA), which restores dopamine function [2,4,6,12]. Dopaminergic neurons made from human embryonic stem cells were successfully transplanted into animal models of Parkinson's disease. This was made possible by stem cell therapy [13]. Parkinson's disease treatment has not yet reached a satisfactory level, so we still need new and effective ways to treat it. When progenitor stem cells are used, teratomas or uncontrolled cell growth could happen [6,12]. One of the alternative therapies that has long been used to address neuropsychological problems is the acupuncture approach, which makes use of a number of therapeutic modalities [14–16].

Numerous biological processes have been shown to be altered by photon-based light therapy [17,18]. Previous studies have shown that photobiomodulation therapy using red light to treat renal failure [19] and infrared light combined with other types of therapy to treat diabetes is useful [20,21]. This modulation effect is influenced by variables such as light's irradiance, fluence, and wavelength [22,23]. Aside from having no adverse side effects, photobiomodulation therapy also has anti-inflammatory qualities [24,25]. Besides, other studies have shown that this therapy increases angiogenesis and stimulates muscle regeneration [26], liver dysfunction [27], brain [28], and peripheral nerve regeneration [29]. In order to treat both chronic pain and recent pain, photobiomodulation treatment has been widely employed in clinical practice and rehabilitation [30].

Laser acupuncture is a type of photobiomodulation therapy because it has minimal irradiance and no thermal stimulation [31]. Acupuncture is one of the traditional Chinese diagnostic and therapeutic methods that is in high demand with the general population [32,33]. So far, the acupuncture method has proven effective for the treatment of mental disorders [34], liver [27] kidney [19] dysfunction, and hypertension [35]. Some people don't want to try acupuncture because they are afraid of needles. This is especially true now that hepatitis and HIV/AIDS are so common. As a result, acupuncture therapy's tools have been the subject of extensive study. One of the most popular treatment methods is photobiomodulation using laser acupuncture [19,27,36]. This equipment's benefit over an electro stimulator is that it is non-invasive and does not use needle electrodes. Needles can be replaced with low-irradiance visible lasers between 400 and 600 nm and infrared between 600 and 1200 nm when performing acupuncture treatments [22,23]. The fact that laser therapy prevents pain for patients is its finest feature. Acupoint laser stimulation is thought to be the best choice for people who are afraid of needles because it can be done more quickly and poses no infection risk [37]. By aiming laser diode beams at specific acupuncture points, laser diode treatment stimulates energy. Acupuncture's most well-known theory is to balance the body's energy (Qi) [33]. Pain generally does not contribute to the body's energy equilibrium (Qi). It is expected that the energy of the laser beam will balance the body's energy [38]. Because of this, this technique is often used on babies, young children, and older people. There is some therapeutic benefit from acupuncture for anxiousness and cerebellar tremors. A mild tremor that starts early or gets worse quickly is usually easier to treat than a severe tremor that comes on later or gets worse over time. Walton-Hadlock of the USA observed varying degrees of relief in symptoms of tremor and rigidity, as well as decreased dyskinesia, improved balance, and improved circulation, regardless of the stage of the disease, and in several cases enabled a reduction of conventional medications when treating primary Parkinson's disease with tuina and acupuncture (CMA) [3,5,8,10].

Acupuncture uses the HT-7 (*Shenmen*) point to treat cognitive issues [39]. This point is on the palmar wrist crease on the anteromedial side of the wrist, next to the flexor carpi ulnar is muscle (WHO). According to the philosophy of acupuncture, the heart, one of the acupoints of the Heart Channel, is thought to be the "emperor" of the body and in control of everything. It is claimed to direct every other organ. It manages the blood and Qi and controls their flow. Since the heart controls the blood vessels and circulation, Parkinson's patients frequently have a stark, white complexion due to an absence of heart action. Blood is moved through the tissue by the heart, which also communicates with every organ and system of the body, including those responsible for consciousness and emotion. *Shenmen*, also known as HT-7, has an impact on consciousness, memory, thinking, and sleep. As a result, HT-7 (*Shenmen*) can treat and lessen the symptoms of Parkinson's disease, including irritability, mental illness, insomnia, and sadness (ANC) [40]. Many studies have shown that using a laser diode at the HT-7 (*Shenmen*) acupoints to treat photobiomodulation improves the performance of the cholinergic and dopaminergic systems and fixes problems with cognitive, neuronal, and oxidative stress in animal models of Parkinson's disease. Photobiomodulation therapy with a laser diode at 405 nm and 650 nm wavelengths was used in these studies [39].

Even though laser acupuncture has been used in clinical settings for the past 30 years, no one knows for sure how it works [37]. The goal of this study is to see how laser acupuncture affects the HT-7 (*Shenmen*) acupoint in the Parkinson's disease mouse model (*Mus musculus*). Since the therapy works better when there are more dopaminergic neurons, photobiomodulation therapy with a laser diode can be used as an extra treatment for people with Parkinson's to improve their quality of life by balancing their energy [41].

2. Materials and methods

2.1. Ethical approval

Ethical approval was granted by the Universitas Airlangga Faculty of Dental Medicine Health Research Ethical Clearance Commission, with the reference number: 294/HRECC.FODM/V/2019.

2.2. Samples

The 24 male BALB/c strain mice (*Mus musculus*) utilized in this research had an age range of 6–7 weeks and a weight range of 20–22 g. They were physically healthy as evidenced by clear eyes, shining leg fur, vigorous movements, and excellent stools. We used a completely random design and the Lemeshow (1997) algorithm to figure out how many times a sample should be repeated. The sample was divided into a Parkinson's group (3 mice) and a healthy group (3 mice) (21 mice). The healthy group was induced intraperitoneally with NaCl (0.9% solvent), while the PD group was induced intraperitoneally with Paraquat. The dosage was given at a rate of 10 mg/kg BW on the first, eighth, and fifteenth days [42,43].

The Parkinson's group was divided into seven subgroups, each consisting of three mice: one control group (P + L-) and six treatment groups (P + L+). Six groups received laser photobiomodulation at various doses and times. As describe in Fig. 1.

2.3. Laser characterization

The illumination source Laser characterization was carried out to determine the peak wavelength using Jasco CT-10 monochromators. The power of the laser was measured using a power meter, model OMM-6810 B–220 V. The temperature of the laser stream, which needed to be below 37 °C, was also measured with a digital thermometer. The laser measurement from Table 1 was shown. Radiant energy is made when the power is multiplied by how long the laser is in contact. The irradiation time is calculated using equation (1) to obtain the fluence [44]:

$$fluence\ (J.cm^{-2}) = intensity\ (W.cm^{-2}) \times irradiation\ time\ (s) \tag{1}$$

2.4. Laser acupuncture experimental set-up

Laser diode photobiomodulation treatment was administered to group P+L+ once daily, beginning on the sixteenth day and continuing for 14 days. Six different radiant energies were present: 0.14, 0.29, 0.37, 0.76, 1.14, and 1.53 J. The flexor carpi ulnaris and the flexor digitorum superficial tendon are positioned between the skin of the HT-7 (*Shenmen*) acupoint [39] on the lateral posterior side of the wrist. The location of HT-7 is shown on Fig. 2.

The mice were terminated after thirty days by being placed in CO_2-gas-filled tubes (euthanasia). Compared to the cervical dislocation procedure, this method is painless. The brain organ is then removed and used to calculate data.

2.5. Preparation and histopathology of brain tissue

The three sample groups (*P*-L-, P + L-, and P + L+) were dissected in order to acquire the brain organ. These tissues were embedded in paraffin for 24 h before being cleaned with 70% ethanol. A sealed container was used to dry the tissues after they had been dehydrated and washed with 0.5% gelatin. Dried tissues were sliced for 4 m of thickness and rinsed at two different water temperatures alternately: 25–26 °C and 38–40 °C. This was done prior to the dehydration process using a hotplate (38–40 °C) kept in the incubator

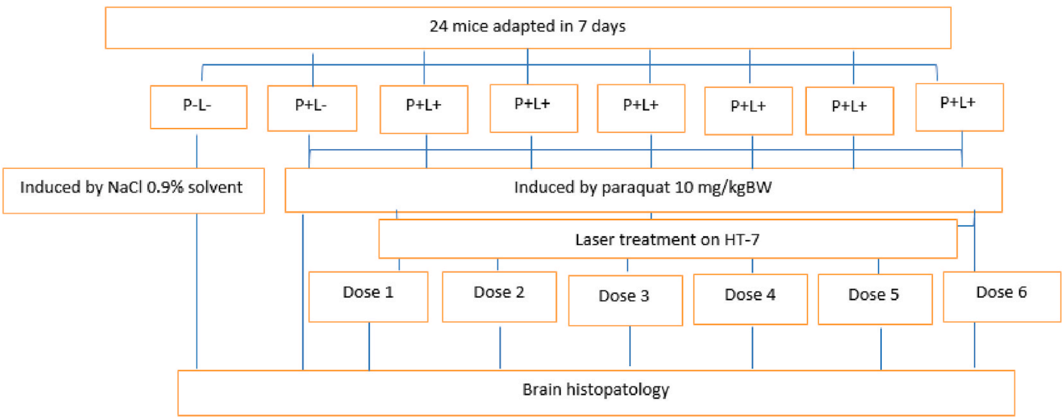

Fig. 1. Set up treatment samples.

Table 1
The characterization of Laser Acupuncture.

Laser parameters	
Parameter	Value
Emitter type	Laser Diode
Center wavelength	657,67 ± 0,07 nm
Operating mode	Continuous-wave (CW)
Polarization	Linear
Beam spot size at the target	≈2.10 ± 0.01 mm^2
Beam divergence	≈12° parallel to the beam ≈26° perpendicular to the beam
Number of points irradiated	1 point HT-7 (*Shenmen*)
Application technique	Skin contact
Aperture diameter	1.64 mm
Power	15,42 ± 0,08 mW
Beam shape	Circular
Variation in laser exposure time	9; 19; 24; 49; 74 ad 99 s
Spectral bandwidth	10 nm
Average radiant power	15,42 ± 0,08 mW
Variation in radiant exposure/fluence	3.13; 13.95; 17.62; 36.00; 54.33; 72.71 J/cm^2
Area irradiated	6 mm^2
Variation in radiant energy	0.14; 0.29; 0.37; 0.76; 1.14; 1.53 J

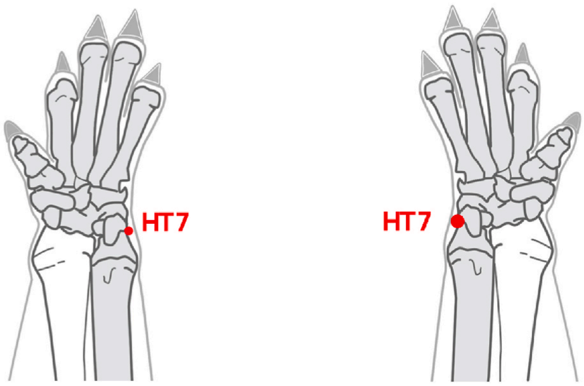

Fig. 2. HT-7 (*Shenmen*) acupoint on mice.

for 24 h at the same temperature.

Hematoxylin Eosin (HE) was used to color the tissues before an Olympus® Microscope CX-21 and Optilab viewer were used to look at them at 400× magnification. The cells in the substantia nigra that have been named seem to have walls, cytoplasm, and nuclei.

2.6. Statistical analysis

Shapiro-Wilk analysis was used in this study to check whether the data were distributed normally. The Shapiro-Wilk Normality Test is one of the most practical and trustworthy normality test methods for small groups. After data transformation showed a value of 0.05, the Kruskal-Wallis and Man-Whitney tests were used to calculate the mean difference between each treatment group. The Kruskal-Walli's test is a non-parametric analysis that uses the interval data's measure. To determine whether there was a difference in the average value of more than two independent sample groups, the data were not normally distributed. With a p-value of 0.005, the Kruskal-Walli's analysis result revealed that at least two treatments were significantly different from one another. Following that, the Mann-Whitney test was used to determine which treatment pairs differed significantly. The Kruskal-Walli's test is followed by the Man Whitney *U* test, which establishes whether there is a substantial difference between categories.

3. Results

Using a power meter OMM-6810 B–220 V, the power of laser acupuncture at a 0 mm distance from the mice's skin is calculated to be (15.42 + 0.08 mW). Stability is essential to making sure that photobiomodulation therapy using a laser diode beam produces the same amount of irradiance on the skin of the mice. The laser diode utilized in this work for photobiomodulation therapy has a beam area of (0.13 ± 0.01) cm2 at 0 mm from the mice's skin, and the smaller the beam area, the higher the fluence. It is necessary to characterize the beam's temperature to make sure it doesn't produce the photothermic effect. The temperature during 99 s of

Table 2
The result of the Kruskal Wallis test.

Group	Radiant energy (J)	N	Neuron Cells	Kruskal – Wallis Test	
				Significance	Conclusion
P− L−	0	3	27.42 ± 0.09	–	–
P + L−	0	3	14.64 ± 0.33	0.002	There was a significant difference
P + LD1	0.14	3	15.58 ± 0.19		There was a significant difference
P + LD2	0.29	3	18.51 ± 0.03		There was a significant difference
P + LD3	0.37	3	18.93 ± 0.07		There was a significant difference
P + LD4	0.76	3	20.52 ± 0.08		There was a significant difference
P + LD5	1.14	3	19.66 ± 0.10		There was a significant difference
P + LD6	1.53	3	17.52 ± 0.20		There was a significant difference.

Table 3
The result of Mann Whitney test.

	Treatments								
Treatments		*P*-L-	P + L-	LD1	LD2	LD3	LD4	LD5	LD6
	P-L-		S	N	N	N	N	N	N
	P + L-			S	S	S	S	S	S
	LD1				N	N	N	N	N
	LD2					N	N	N	N
	LD3						N	N	N
	LD4							N	N
	LD5								N
	LD6								

N: non-significant difference.
S: significant difference.

photobiomodulation treatment using a laser diode beam was (34.52 0.04) ^{o}C. Table 2 displays the statistics and the quantity of neurons in each category. Shapiro Wilk's data normality test revealed p = 0.013, indicating that the data are normally distributed (data $n < 50$).

The Kruskal-Walli's test was also used to look at the differences between the therapies. A non-parametric test called the Kruskal-Walli's test is used to discover whether the average value of more than two independent sample groups differs. The statistics had an interval scale and were not normally distributed. Table 2 displays the Kruskal-Walli's test outcome.

The Kruskal-Walli's test revealed $p = 0.002 < 0.005$, indicating that at least two treatments were statistically different from one another. The Mann-Whitney test was then used to identify the treatment pairs that differed substantially. The results of the Mann-Whitney test are shown in Table 3. The Mann-Whitney test results revealed that a number of treatment groups differed significantly ($p = 0.046$) and not significantly ($p = 0.050$). The use of a laser in any of the treatments produced a statistically significant difference ($p = 0.046$) from the control treatment.

Viewing microscopic slides of the brains of the experimental animals allowed researchers to acquire the findings of their anatomical histology observations. There were three replications of each group and therapy. The results of the histopathology are shown in Fig. 2. This group showed the greatest response to photobiomodulation therapy with laser diode treatment, with 74.82% more live cells counted in the P+L+ group than in the P + L-group, which has Parkinson's disease but is not getting treatment.

According to Table 2 and Fig. 3, the analysis of the histopathological data showed that photobiomodulation therapy raised the number of neuron cells for each radiant energy by 0.14 J in Fig. 3 (c), 0.29 J in Fig. 3 (d), 0.37 J in Fig. 3 (e), 0.76 J in Fig. 3 (f), 1.14 J in Fig. 3 (g), and 1.53 J in Fig. 3 (h). Fig. 3 (a) was the histopathology result on control negative group or *P*-L- and Fig. 3 (b) was control positive group or P + L-. Fig. 4 showed percentage of neuron cell viability. The effective dose of photobiomodulation therapy with laser diode treatment is 0.76 J, which has a 74.8% viability in neuronal cells and a survival rate of 20.52% in other cell types (see Fig. 4).

4. Discussion

To figure out the exact specifications of the laser, it is necessary to use photobiomodulation therapy and laser diode treatment to increase the number of neurons in rodents. The peak wavelength, beam strength, beam area, and beam temperature were all measured to find out what the laser was like. Because red laser diodes can penetrate deeper than other visible light laser diodes, they were used for photobiomodulation treatment [23]. In this work, a red laser diode with a wavelength of (657.67 ± 0.07) nm was employed. Additionally, this laser can transmit 15.42 mW of power when placed 0 mm from the skin of mice. The laser beam temperature is 34.52 °C, and the irradiation time to produce the desired energy dose is 9, 19, 24, 49, 74, and 99 s.

Light interaction with a material is influenced by a variety of phenomena, including refraction, reflection, absorption, and dispersion. Refraction and monitoring are reduced when light is applied perpendicular to the object. The quantity of light irradiance that is absorbed by the target tissue depends on absorption and dispersion. Light dispersion affects the target tissue's light irradiance and irradiation orientation [22]. Visible light (400–600 nm) can't get through because hemoglobin and melanin soak it up [44]. Only a small amount of light above 1400 nm is passed through water due to its high absorption capacity [45].

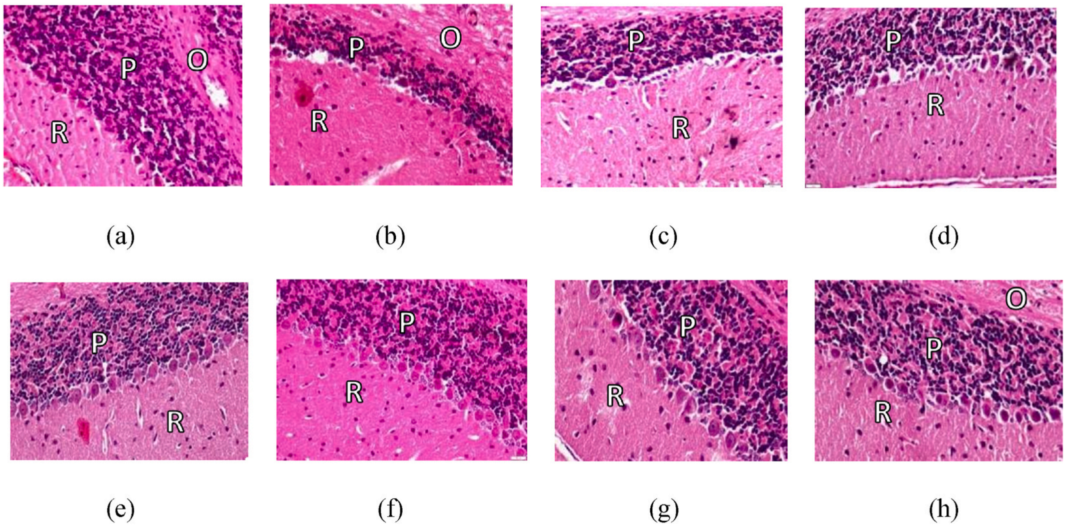

Fig. 3. Histopathology test result: (a) group *P*-L-, (b) P + L-, (c) P + LD1, (d) P + LD2, (e) P + LD3, (f) P + LD4, (g) P + LD5, (h) P + LD6. (Note: PO = stratum oriens, P = stratum pyramidale, R = stratum radiatum). (Magnification 400×, n = 3).

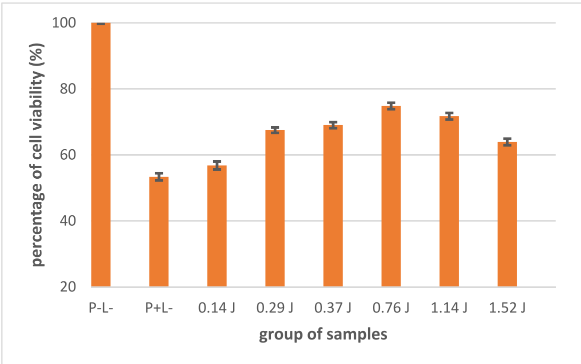

Fig. 4. Percentage of neuron cell viability.

The red and infrared wavelengths, on the other hand, which are frequently employed for laser acupuncture, have less absorption and more transmission. However, collagen has spread some of them out [46]. Human skin transmits light considerably less efficiently at wavelengths below 800 nm, with thicknesses varying from 1 to 3 mm depending on location [45]. According to the Kolarova's study findings, 5–10% of light at 632.8 nm and 6–14% of light at 675 nm were passed through skin that was 1.5–4.1 mm thick [47]. At 632.8 nm, samples of 19-mm skin had a transmittance of 0.3%, which included the subcutaneous fat.

Parkinson's disease causes tremors, stiffness, akinesia, bradykinesia, and unstable posture because the substantia nigra pars compacta lose neurons [3]. Parkinson's disease is brought on by paraquat, a chemical that is toxic to nerves and can damage other types of brain neurons, like microglia. The DNA chain breaks in paraquat, which results in cell damage or mortality. Only 53.4% of the total number of live cells were neuron cells in the P + L-group (positive control), which dropped to (14.64 ± 0.33) cells.

Laser acupuncture treatment not only has a photophysical effect, but also a photobiomodulation effect that boosts ATP synthesis in the sensory nerve by triggering the cell respiration chain through cytochrome *c* oxidase (CCO) and concentrating on cellular activity in the mitochondria [38]. When a laser photon collides with the flesh, absorption and dispersion take place. This study uses an exposure distance of 0 cm to avoid dispersion. After photons are received by acupoint HT-7 (*Shenmen*), photobiomodulation will take place and is anticipated to change into electrical energy [39] in the meridian Heart, which is thought to be a source of calm in Traditional Chinese Medicine. According to Fig. 2, this Meridian Heart can produce regeneration to bring the stratum pyramidale's neuron cells into harmonic balance or speed up the regeneration process. An experimental study in rats has demonstrated that laser puncture at HT-7 can reduce neuronal degeneration by improving the function of the cholinergic and dopaminergic systems through the regulation of acetylcholinesterase and monoamine oxidase type B [39]. Acupuncture at HT-7 can affect the central nervous system to produce endogenous opioid peptides to lessen or eliminate pain and function as a sedative. To achieve this, the autonomic nervous system is modulated, and the cortico-hypothalamic-pituitary-adrenal axis is strengthened [48].

Comparing the dose that actually happened in this study showed that the treatment group got more. It was found that 0.76 J of radiant energy, which is about the same as the number of healthy group neuron cells, was the best dose. Results from radiation with

1.14 J and 1.53 J were superior to those from 0.76 J of fluence. Poewe (2017) found that the quantity of energy delivered to the acupoint must be taken into account when using a laser [1]. The results of this research show that since the placement of acupoint HT-7 (*Shenmen*) is superficial, the energy emitted by the laser beam can restore the body's energy at a radiant energy of 0.76 J per acupuncture point.

5. Conclusion

Histopathology showed that the number of neuron cells in group P + L-was lower than in group *P*-L. The best and most successful dose of photobiomodulation therapy with laser diode treatment, according to the number of living cells and the number of neuron cells, was 0.76 J for group P + L+. Photobiomodulation therapy with laser diode treatment on the *Mus musculus* cells model of Parkinson's disease gives off 0.76 J of useful energy.

Author contribution statement

Suryani Dyah Astuti Suhariningsih: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Herdiani Nur Kusumawati: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Amalia Fitriana Mahmud; Maya Septriana; Lale Rozykulyyeva; Yunus Susilo: Performed the experiments; Analyzed and interpreted the data.

Ardiansyah Syahrom: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This research was supported by Universitas Airlangga [837/UN3.14/PT/2020]

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

References

[1] W. Poewe, K. Seppi, C. Tanner, G.M. Halliday, P. Brundin, J. Volkmann, A.E. Schrag, A.E. Lang, Parkinson disease, Nat. Rev. Dis. Prim. 3 (2017), 17013.
[2] J.T.S. Fortuna, M. Gralle, D. Beckman, F.S. Neves, L.P. Diniz, P.S. Frost, C.P. Figueiredo, Brain infusion of alpha-synuclein oligomers induces motor and non-motor Parkinson's disease-like symptoms in mice, Behav. Brain Res. 333 (2017) 150–160.
[3] U. Muthane, Managing parkinsonism and Parkinson's disease, RGUHS J.of Med. Sci. 7 (1) (2017) 26–28.
[4] Y. Xie, X. Meng, J. Xiao, J. Zhang J, J. Zhang, Cognitive changes following bilateral deep brain stimulation of subthalamic nucleus in Parkinson's disease: a meta-analysis, BioMed Res. Int. (2016), 3596415.
[5] S.G. Reich, J.M. Savitt, Parkinson's disease, Med. Clin. 103 (2) (2019) 337–350.
[6] M.F. Bastide, W.G. Meissner, B. Picconi, S. Fasano, P.-O. Fernagut, M. Feyder, Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease, Prog. Neurobiol. 132 (2015) 96–168.
[7] R.F. Pfeiffer, Parkinsonism and related disorders non-motor symptoms in Parkinson's disease, Parkinsonism Relat. Disorders 1 (2015) S119–S122.
[8] D. Weintraub, T. Simuni, C. Caspell-Garcia, C. Coffey, S. Lasch, A. Siderowf, Cognitive performance, and neuropsychiatric symptoms in early, untreated Parkinson's disease, Mov. Disord. 30 (7) (2015) 919–927.
[9] E.R. Dorsey, B.R. Bloem, The Parkinson pandemic-A call to action, JAMA Neurol. 75 (1) (2018) 9–10.
[10] O.-B. Tysnes, A. Storstein, Epidemiology of Parkinson's disease, J. Neural. Transm. 124 (8) (2017) 901–905.
[11] J.K. Andersen, S. Chinta, Parkinson's disease and aging, in: F. Sierra, R. Kohanski (Eds.), Advances in Geroscience, Springer International Publishing, Cham, 2016, pp. 229–255.
[12] I. Sebastianutto, M.A. Cenci, mGlu receptors in the treatment of Parkinson's disease and L-DOPA-induced dyskinesia, Curr. Opin. Pharmacol. 38 (2018) 81–89.
[13] J.H. Kim, J.M. Auerbach, J.A. Rodríguez-Gómez, I. Velasco, D. Gavin, N. Lumelsky, R. McKay, Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease, nature 418 (6893) (2002) 50–56..
[14] P. Liang P, Z. Wang, T. Qian, K. Li, Acupuncture stimulation of Taichong (Liv3) and Hegu (LI4) modulates the default mode network activity in Alzheimer's disease, Am J Alzheimers Dis Other Demen 29 (8) (2014) 739–748.
[15] C. Sutalangka, J. Wattanathorn, S. Muchimapura, W. Thukham-Mee, P. Wannanon, T. Tong-un, Laser acupuncture improves memory impairment in an animal model of Alzheimer's disease, J. Acupunct. Meridian Stud. 6 (5) (2013) 247–251.
[16] F. Salehpour, M.R. Hamblin, Photobiomodulation for Parkinson's disease in animal models: a systematic review, Biomolecules 10 (4) (2020) 610.
[17] S.D. Astuti, A. Sulistyo, E.M. Setiawatie, M. Khasanah, H. Purnobasuki, D. Arifianto, Y. Susilo, K.A. Alamsyah, Suhariningsih, A. Syahrom, An in-vivo study of photobiomodulation using 403 nm and 649 nm diode lasers for molar tooth extraction wound healing in Wistar rats, Odontology 110 (2) (2022) 240–253.
[18] J. Enengl, M.R. Hamblin, P. Dungel, Photobiomodulation for Alzheimer's disease: translating basic research to clinical application, J. Alzheim. Dis. 75 (4) (2020) 1073–1082.
[19] S.D. Astuti, B.I. Prasaja, T.A. Prijo, An in vivo photodynamic therapy with diode laser to cell activation of kidney dysfunction, J. Phys. Conf. 853 (2017), 012038.

[20] Suhariningsih, D. Winarni, S.A. Husen, F. Khaleyla, A.P. Putra, S.D. Astuti, The effect of electric field, magnetic field, and infrared ray combination to reduce HOMA-IR index and GLUT 4 in diabetic model of Mus musculus, Laser Med. Sci. 35 (6) (2020) 1315–1321.

[21] SD. Astuti Suhariningsih, S.A. Husen, D. Winarni, D.A. Rahmawati, A. Mukti, A.P. Putra, M. Miftahussurur, The combined effect of magnetic and electric fields using on/off infrared light on the blood sugar level and the diameter of Langerhans islets of diabetic mice, Vet. World 13 (10) (2020) 2286.

[22] F. Salehpour, P. Cassano, N. Rouhi, M.R. Hamblin, L. De Taboada, F. Farajdokht, J. Mahmoudi, Penetration profiles of visible and near-infrared lasers and light-emitting diode light through the head tissues in animal and human species: a review of literature, Photobiomodulation. Photomed. Laser Surg. 37 (10) (2019) 581–595.

[23] J.J. Anders, R.J. Lanzafame, P.R. Arany, Low-level light/laser therapy versus photobiomodulation therapy, Photomed. Laser Surg. 33 (4) (2015) 183–184.

[24] V. Erthal, D. Maria-Ferreira, M.F. de Paula Werner, Anti-inflammatory effect of laser acupuncture in ST36 (Zusanli) acupoint in mouse paw edema, Laser Med. Sci. 31 (2016) 315–322.

[25] L. Lorenzini, A. Giuliani, L. Giardino, L. Calza, Laser acupuncture for acute inflammatory, visceral and neuropathic pain relief: an experimental study in the laboratory rat, Res. Vet. Sci. 88 (1) (2009) 159–165.

[26] J. Nakano, H. Kataoka, I. Sakamoto, T. Origuchi, M. Okita M, T. Yoshimura, Low-level laser irradiation promotes the recovery of atrophied gastrocnemius skeletal muscle in rats, Exp. Physiol. 94 (9) (2009) 1005–1015.

[27] S.D. Astuti, V.S. Victory, A.F. Mahmud, A.P. Putra, D. Winarni, The effects of laser diode treatment on liver dysfunction of *Mus musculus* due to carbofuran exposure: an *in vivo* study, J Adv Vet Anim Res 6 (4) (2019) 499–505.

[28] F. Salehpour, J. Mahmoudi, F. Kamari, S. Sadigh-Eteghad, S.H. Rasta, M.R. Hamblin, Brain photobiomodulation therapy: a narrative review, Mol. Neurobiol. 55 (8) (2018) 6601–6636.

[29] R.I. Barbosa, A.M. Marcolino, R.R. de Jesus Guirro, N. Mazzer, C.H. Barbieri, M. de Cassia Registro Fonseca, Comparative effects of wavelengths of low-power laser in regeneration of sciatic nerve in rats following crushing lesion, Laser Med. Sci. 25 (3) (2010) 423–430.

[30] L. Baratto, L. Calza, R. Capra, M. Gallamini, L. Giardino, A. Giuliani, L. Lorenzini, S. Traverso, Ultra-low-level laser therapy, Laser Med. Sci. 26 (1) (2010) 103–112.

[31] C.W. Hsieh, J.H. Wu, C.H. Hsieh, Q.F. Wang, J.H. Chen, Different brain network activations induced by modulation and nonmodulation laser acupuncture, Evid. Base Compl. Alternative Med. (2011), 951258.

[32] Suhariningsih, R.N. Aisyah, N. Fitriyah, S.D. Astuti, T.A. Prijo, A. Imandiri, Electrical potential profile investigation of kidney acupuncture point using acupotentiograph, AIP Conf. Proc. AIP Publish. LLC 2314 (1) (2020), 060008.

[33] T. Rahmawati, N. Fitriyah, S.D. Astuti, M. Septriana, Bioenergy alteration in white rats (Rattus norvegicus) due to the acupuncture needle stimulation, J. Phys. Conf. 1505 (1) (2020), 012066. IOP Publishing.

[34] I. Quah-Smith, S. Sachdev, W. Wen, X. Chen, M.A. William Ma, The brain effects of laser acupuncture in healthy individuals: an FMRI investigation, PLoS One 5 (9) (2010), e12619.

[35] J. Zhang, N. Marquina, G. Oxinos, A. Sau, Derek Ng, Effect of laser acupoint treatment on blood pressure and body weight—a pilot study, J. Chiropr. Med. 7 (4) (2008) 134–139.

[36] S.V. Moskvin, Low-level laser therapy in Russia: history, science and practice, J. Laser Med. Sci. 8 (2) (2017) 56–65.

[37] P. Whittaker, Laser acupuncture: past, present, and future, Laser Med. Sci. 19 (2) (2004) 69–80.

[38] U. Petermann, Laser acupuncture and local laser therapy in veterinary medicine with overview of applied laser types and clinical uses, Am. J. Tradit. Chin. Vet. Med. 12 (1) (2017) 89–101.

[39] J. Wattanathorn, C. Sutalangka, Laser acupuncture at HT7 acupoint improves cognitive deficit, neuronal loss, oxidative stress, and functions of cholinergic and dopaminergic systems in animal model of Parkinson's disease, in: Evidence-Based Complementary and Alternative Medicine vol. 2014, ECAM, 2014, 937601.

[40] V. Hopwood, C. Donnellan, Acupuncture in Neurological Conditions, Elsevier Health Sciences, 2010, pp. 6–7.

[41] Y.-C. Yun, D. Jang, S.-B. Yoon, D. Kim, D.-H. Choi, O.-S. Kwon, Laser acupuncture exerts neuroprotective effects via regulation of creb, bdnf, bcl-2, and bax gene expressions in the Hippocampus, Evid. Base Compl. Alternative Med. (2017), 7181637.

[42] K. Li, X. Cheng, J. Jiang, J. Wang, J. Xie, X. Hu, The toxic influence of paraquat on hippocampal neurogenesis in adult mice, Food Chem. Toxicol. 106 (Pt A) (2017) 356–366.

[43] F. Richter, L. Gabby, K.A. McDowell, C.K. Mulligan, K. De La Rosa, P.C. Sioshansi, Effects of decreased dopamine transporter levels on nigrostriatal neurons and paraquat/maneb toxicity in mice, Neurobiol. Aging 51 (2017) 54–66.

[44] S.D. Astuti, D. Arifianto, N.D. Drantantiyas, A.M. Nasution, Efficacy of CNC-diode laser combine with chlorophylls to eliminate staphylococcus aureus biofilm, in: 2016 International Seminar on Sensors, Instrumentation, Measurement and Metrology, *ISSIMM)* IEEE, 2016, pp. 57–61.

[45] S. Wan, J.A. Parrish, R.R. Anderson, M. Madden, Transmittance of nonionizing radiation in human tissues, Photochem. Photobiol. 34 (6) (1981) 679–681.

[46] R.R. Anderson, Optics of the skin, in: H.W. Lim, N.A. Soter (Eds.), Clinical Photomedicine, Marcel Dekker, New York, 1993, pp. 19–35.

[47] H. Kolarova, D. Ditrichova, J. Wagner, Penetration of laser light into the skin in vitro, Laser Surg. Med. 24 (3) (1999) 231–235.

[48] D.H. Kim, N.J. Kim, R.J. Zhao, D.H. Kim, C.H. Yang, H.Y. Kim, Effects of acupuncture on the anxiety-like behavior induced by withdrawal from chronic morphine use, Neurosci. Lett. 664 (2018) 38–42.