Biochemistry and Biophysics Reports 27 (2021) 101085

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

Effectiveness of low-power laser therapy in improvement of the peripheral neuropathy induced by xenobiotics in rats

Fathia Abd Elwahid Mannaa [a], Khaled Gamal El-Deen Abdel-Wahhab [a], Eitedal Mahmoud Daoud [b], Aliaa Abdel Rahman El Gendy [b], Maha Mohamed Saber [b], Nevein Naim Fadl [a,*]

[a] Medical Physiology Department, National Research Centre, Dokki, Cairo, 12622, Egypt
[b] Complementary Medicine Department, National Research Centre, Dokki, Cairo, 12622, Egypt

ARTICLE INFO

Keywords:
Low-power laser therapy
Dichloroacetate
Neuropathy
Gabapentin

ABSTRACT

Background: Peripheral neuropathy (PN) is the damage and dysfunction of neurons of the peripheral nervous system. The present study was conducted to estimate the effectiveness of low-power laser therapy (LPLT) in the management of PN in a rats' model.
Methods: PN was induced by giving dichloroacetate (DCA) (250 mg/kg/day) for up to 12 weeks. Four groups of rats were used: control group, PN group, PN group treated with gabapentin and PN group treated with LPLT. The study was conducted for 8 weeks. The management of PN was estimated by behavioral tests which included hot plate and Morris water maze tests. Blood biochemical analysis were carried out.
Results: Using of hot plate test indicated thermal hypoalgesia and using Morris water maze test showed cognitive decline in PN rats. Treatment with LPLT or gabapentin improved both the pain sensations and deteriorated memory that occurred in the PN rats. Biochemical analysis showed that LPLT significantly decreased the elevated beta-endorphin level in PN rats, while gabapentin could not reduce it. Treatment PN rats with LPLT or gabapentin shifted the high levels of TNF-α, IL-1β and IL-10 cytokines back to their normal values. Serum nitric oxide and MDA significantly increased in the PN group together with significant reduction in the rGSH level, these values were significantly improved by LPLT application while this was not the case with gabapentin treatment. Furthermore, treatment with gabapentin or LPLT significantly reduced serum ALAT and ASAT activities which are otherwise increased in the PN group. S100B, PGE2, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, urea and creatinine showed insignificant changes among all groups.
Conclusions: Our results showed that treatment with LPLT is more efficient than gabapentin in ameliorating the peripheral neuropathy induced by xenobiotics.

1. Introduction

Peripheral neuropathy refers to the anatomical damage to the nerves of the peripheral nervous system, and dysfunction of normal nerve physiology [1]. Nerve cells are damaged from diseases and anything that causes impairment in the ability of the body to change nutrients into energy, to circulate oxygen or to process waste products. There are many ways including diabetes that can cause the nerve cells to be vulnerable to damage [2]. All types of peripheral neuropathy display some degree of mitochondrial dysfunction [3,4]. Li et al. [5] and Harris et al. [6] reported that the conservation of plastic innervations needs high consumption of Adenosine triphosphate (ATP) for maintenance of

Abbreviations: PN, Peripheral neuropathy; ATP, Adenosine triphosphate; DCA, Dichloroacetate; LPLT, Low power laser therapy; MDA, malondialdehyde; NO, nitric oxide; rGSH, reduced glutathione; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor- α; IL-1β, interleukin - 1β; IL-10, interleukin −10; S100B, calcium binding protein B; NAD+, Nicotinamide adenine dinucleotide; ATP, adenosine triphosphate; ADP, adenosine diphosphate; PDH, pyruvate dehydrogenase; TCA, cycle tricarboxylic acid cycle or the Krebs cycle; MCTs, monocarboxylate transporters.

* Corresponding author.
E-mail addresses: fa.elwahid@nrc.sci.eg, fathia_98@yahoo.com (F.A.E. Mannaa), kg.el-deen@nrc.sci.eg, kgm194@yahoo.com (K.G.E.-D. Abdel-Wahhab), em.daoud@nrc.sci.eg (E.M. Daoud), aael-gendy@nrc.sci.eg (A.A.R. El Gendy), mm.saber@nrc.sci.eg (M.M. Saber), neveinnf@hotmail.com, nn.fadl@nrc.sci.eg (N.N. Fadl).

https://doi.org/10.1016/j.bbrep.2021.101085
Received 7 June 2021; Received in revised form 16 July 2021; Accepted 19 July 2021

terminals, synapses and growth cone motility. The malnutritional axonal support or environmental affront makes the most distal side of the long axons originating in the small neuronal body vulnerable to damage. Also, impaired autoregulation and vascular supply is likely to cause hypoxic damage in the nerves [7].

Dichloroacetate (DCA), a xenobiotic, have hepatocarcinogenic and hepatotoxicant effects that causes damage to macrophages [8]. It also induces peripheral neuropathy in the form of painful sensations, tingling, and numbness in the extremities in addition to slowing nerve conduction [9]. DCA is a product of water chlorination as well as a metabolite of various drugs and industrial chemicals [10]. Humans have been chronically exposed to DCA through its environmental sources including chlorinated drinking water [11,12] and ground water contaminated with certain industrial solvents and other chlorinated precursors [13].

Gabapentin is the first-line therapy for the treatment of neuropathic pain caused by diabetic neuropathy [14].

Laser is a nonionizing, noninvasive monochromatic electromagnetic high concentrated light beam [15]. Low power laser therapy (LPLT) is used for different musculoskeletal and rheumatologic disease state [16]. Laser therapy accelerates tissue healing and reparation, and restores the functional disability [17]. LPLT is also used in improving tissue ischemia, hypoxia, and inflammation in nerve entrapment neuropathy; it is also used for improving nerve regeneration [18]. In addition, LPLT improves diabetic peripheral neuropathy induced in a rats model [19].

Accordingly, the present study aimed to estimate the potency of LPLT in improving non-diabetic peripheral neuropathy induced by DCA in experimental rats in comparison with gabapentin which used in this study as a reference drug.

2. Materials and methods

2.1. Animals and treatments

Forty male albino rats (150–170 g) were obtained from the animal colony at the National Research Center. The rats were allowed to freely eat and drink water for a week before starting the experiment. There were 5 rats per cage with free access to rodent food and water. All rats were treated in compliance with the institution's standards of care according to the National Research Centre, ethical committee (committee number FWA 00014747). The rats were divided into four groups with 10 rats in each group. The **first group** served as the healthy Control group. The rest of the rats were then given dichloroacetate (DCA) daily for 12 weeks to induce peripheral neuropathy [20]. DCA (250 mg/kg/day) [21] was dissolved in tap water and administered to rats by intragastric gavage, using a stomach tube. Ten of those DCA induced rats served as the **second group**: Peripheral Neuropathy (PN) group. Another ten of the DCA induced rats were then treated daily for 8 weeks with gabapentin (Sigma Co.) at a dose level of 20 mg/kg dissolved in sterilized water [22], and given orally to the animals by a gastric tube. Those rats served as the **third group** (PN rats treated with gabapentin). The last ten DCA induced rats were treated with LPLT (Gallium Arsenide 808 mw Laser) for three sessions/week for 8 weeks. They were treated at three points (planter of foot - poplital fossa - sciatic notch) for 30 s at each point at a dose of 3J/S for each point [23]. Those rats served as the **fourth group** (PN rats treated with LPLT).

At the end of the experimental duration, all 40 rats were subjected to hot-plate and maze tests as behavioral estimation tests.

After one day from the behavioral estimation tests, fasting blood samples were withdrawn from the retro-orbital plexus of rats, under diethyl ether anesthesia, using heparinized and sterile capillary glass tubes into collecting tubes, then blood samples were centrifuged at 3000 rpm for 20 min and blood sera were separated and stored at −80 °C until analysis.

2.2. Behavioral tests

Hotplate test was used to measure pain sensations response to the thermal stimulus following the method described by Mikołajczak et al. [24]. A hot plate apparatus (20 × 20 cm surrounded by Plexiglas box) was used and maintained at 45 °C. Latency to the first hind-paw flick, hind-paw lick or jump was recorded and used as the behavioral end-point. Sessions were cut off after 60 s to avoid skin damage.

Spatial reference memory was evaluated using Morris water maze test according to the method described by Morris et al. [25].

2.3. Biochemical analysis

Prostaglandin E2 (PGE2), interleukin −10 (IL-10), interleukin - 1β (IL-1β) and tumor necrosis factor- α (TNF-α) were determined by enzyme-linked immuno-sorbent assay (ELISA) technique using kits manufactured by ASSAY Pro, USA. Spectrophotometric analysis was used for the determination of serum levels of glucose, nitric oxide, lipid peroxidation, reduced glutathione, creatinine, urea, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels using Kits obtained from Leader Trad Company. The determination of serum ALAT and ASAT activities was carried out spectrophotometry using Kits obtained from Leader Trad Co. Assessment of serum S100B and βeta endorphin was carried out using ELISA kits purchased from ASSAY Pro, USA.

2.4. Statistical analysis

One way analysis of variance (ANOVA) was used in data analysis followed by Duncan's multiple range test at level of significance $P \leq 0.05$ [26] using SAS program software; by SAS Institute Inc., Cary, NC, USA, copyright (c) 1998.

3. Results

Peripheral thermal sensitivity was evaluated by the hind paw lick or hind paw flick threshold to indicate heat hyperalgesia. Latency of the hind paw lick was significantly increased in the model of peripheral neuropathy rats (PN) compared with the Control group (Table 1). On the other hand, the latency was significantly reduced in the PN groups treated with LPLT or gabapentin. As demonstrated in (Table 1), the Morris water maze test showed memory improvement in the PN group treated with LPLT more than the PN group treated with gabapentin.

Serum β-endorphin significantly increased in the PN group as compared with the Control group. There was no effect on its level in the PN group treated with gabapentin as compared with the PN group. On the other hand, it was significantly reduced in the PN group treated with LPLT. As mentioned in Fig. 1, S100B showed an insignificant change in all the studied groups.

Prostaglandin E2 (PGE2) showed an insignificant change in all

Table 1
Effect of gabapentin and LPLT on serum glucose, hotplate test and memory test in peripheral neuropathy (PN) modeled rats.

Group	Serum glucose (mg/dl)	hind-paw lick latency (seconds)	Memory test
Control	83 ± 17^{A}	12 ± 1.81^{A}	6/6 healthy memory
PN model	79 ± 18^{A}	17 ± 1.73^{B}	2/6 deteriorated memory
PN + gabapentin	78 ± 14^{A}	10 ± 2.01^{A}	1/6 deteriorated memory
PN model + LPLT	84 ± 16^{A}	13 ± 1.62^{A}	0/6 deteriorated memory

Data represent the average ± SD for 10 rats. Within a column, means superscript with different letters are significantly different at $P \leq 0.05$.

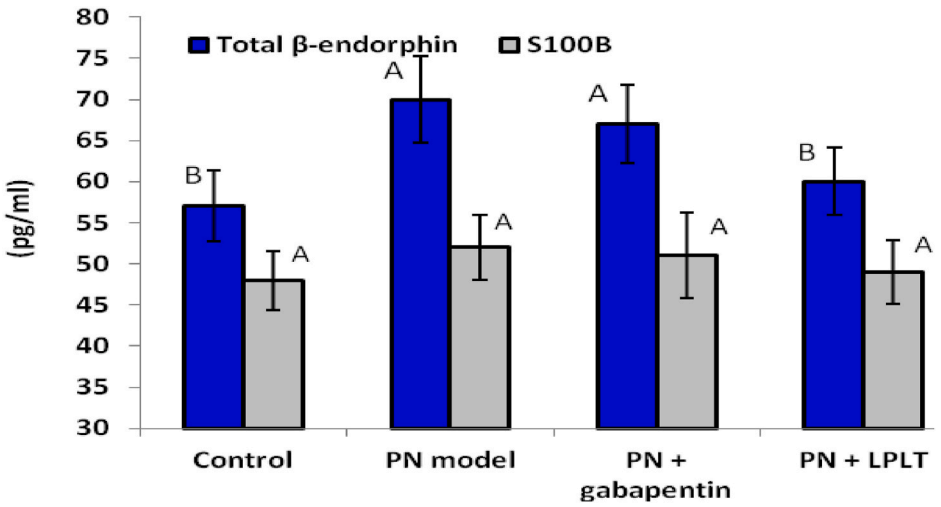

Fig. 1. Effect of gabapentin and LPLT on levels of serum beta-endorphin and S100B in peripheral neuropathy (PN) modeled rats. Data represent the average ± SD for 10 rats. Means superscript with different letters are significantly different at $P \leq 0.05$.

groups. Whereas, the cytokines IL-10, IL-1β and TNF-α revealed significant increases in the PN group. Application of LPLT or Gabapentin administration was significantly reversed the values of these cytokines back to normal (Table 2).

Oxidative stress markers are presented in Table 3. The values of both serum nitric oxide and lipid peroxidation (MDA) in the PN group were significantly increased, whereas the level of glutathione was significantly decreased. Both gabapentin and LPLT significantly ameliorated the values of these markers but LPLT was the most effective.

Serum ALAT and ASAT activities were significantly increased in the PN group. Treatment with gabapentin or LPLT significantly reversed that and the levels were back to normal. (Fig. 2). The lipid profiles (Table 4) as well as the kidney function markers (Fig. 3) showed insignificant changes among all studied groups.

4. Discussion

In the present study, the use of hot plate test indicated thermal hypoalgesia in DCA-treated rats which represents sensory-motor dysfunction and impairment in pain response. Calcutt et al. [21] reported that DCA induces a primarily axonal disorder leading to peripheral neuropathy. Previously, Calcutt et al. [27], Mizisin et al. [28] and Mizisin et al. [29] mentioned that, DCA inhibits the axonal support by disrupting the metabolic functions of other cells, as it occurs in diabetic neuropathy cells. By glutathione transferase, the DCA is metabolized to glyoxylate in the liver, that enters the general carbon pool [30] and a number of consequences of DCA metabolism [21] that may cause the formation of oxidative stress markers. This was involved in the pathogenesis of a number of neurological diseases including peripheral neuropathy [31]. The mechanisms by which DCA induces peripheral neuropathy were discussed in more detail by Calcutt et al. [21].

Table 2
Effect of gabapentin and LPLT on serum PGE2 and the cytokines levels in peripheral neuropathy (PN) modeled rats.

Group	PGE2 (ng/L)	TNF-α (pg/ml)	IL-1β (pg/ml)	IL-10 (pg/ml)
Control	182 ± 15.2^{A}	32.6 ± 8.1^{A}	747 ± 17.5^{B}	173 ± 12.2^{D}
PN model	203 ± 15.8^{A}	62.2 ± 9.3^{B}	876 ± 16.4^{A}	293 ± 14.1^{A}
PN + gabapentin	195 ± 19.5^{A}	49.7 ± 9.7^{C}	866 ± 33.9^{A}	268 ± 11.6^{B}
PN + LPLT	177 ± 11.3^{A}	42.2 ± 8.3^{C}	771 ± 15.2^{B}	255 ± 2.87^{C}

Data represent the average ± SD for 10 rats. Data represent the average ± SD for 10 rats. Within a column, means superscript with different letters are significantly different at $P \leq 0.05$.

Table 3
Effect of gabapentin and LPLT on oxidative stress markers in peripheral neuropathy (PN) modeled rats.

Group	MDA (μmol/L)	Nitric oxide (μmol/L)	Glutathione (nmol/ml)
Control	1.87 ± 0.15^{B}	183 ± 23.7^{B}	9.8 ± 2.3^{A}
PN model	2.20 ± 0.21^{A}	206 ± 22.6^{A}	8.1 ± 1.8^{B}
PN + gabapentin	2.26 ± 0.22^{A}	198 ± 26.5^{AB}	8.7 ± 2.1^{A}
PN + LPLT	1.72 ± 0.14^{B}	176 ± 14.8^{B}	8.5 ± 1.7^{A}

Data represent the average ± SD for 10 rats. Data represent the average ± SD for 10 rats. Within a column, means superscript with different letters are significantly different at $P \leq 0.05$.

According to our study, hind paw lick latency was significantly decreased in the DCA induced PN group treated with gabapentin or LPLT causing an improvement in pain response. The improvement in pain response in the LPLT treated group was further confirmed by the significant reduction in β-endorphin formation that delayed latency of hind paw lick or escape from the hot plate. As reported previously, β-endorphin modulates pain perception both in the peripheral and the central nervous system [32]. When receiving pain, the pain receptors (through the spinal cord dorsal horn) send signals to the hypothalamus causing the release of substance P, a neuropeptide. In the peripheral nervous system, this signal causes the appointment of T-lymphocytes to the area where pain was perceived, then T-lymphocytes release β-endorphin allowing it to bind to opioid receptors in this localized region, causing direct inhibition of substance P that in turn lowers the number of excitatory pain signals sent to the brain [33,34].

The present study showed that DCA increases the production of β—endorphin but does not affect S100B. The S100B is a glial-specific protein that is mostly elevated in adults as a result of damage in the nervous system [35]. This suggests that DCA mainly affects the function of peripheral nervous system rather than its anatomy.

At cellular and subcellular levels, laser radiation causes its improvement in peripheral nervous system through electronic excitation of the photoceptor molecules [36]. This in turn causes redox-regulation by Nicotinamide adenine dinucleotide (NAD+) and NADH [37] variation in the formation of single oxygen and superoxide, and a change in the biochemical activity [38]. In the mitochondrial membrane, the electron transport increases the metabolism and proliferation of cells including generation of adenosine triphosphate (ATP) from adenosine

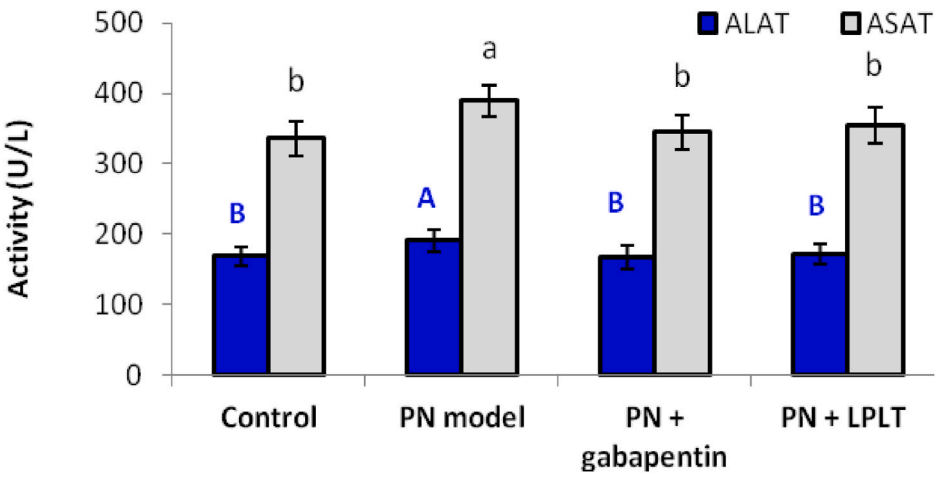

Fig. 2. Effect of gabapentin and LPLT on activities of serum ALAT and ASAT of peripheral neuropathy (PN) modeled rats. Data represent the average ± SD for 10 rats. Means superscript with different letters are significantly different at $P \leq 0.05$.

Table 4
Effect of gabapentin and LPLT on the levels of some lipid profile markers in serum of peripheral neuropathy (PN) modeled rats.

Group	Cholesterol (mg/dl)	Triglycerides (mg/dl)	LDL- Cholesterol (mg/dl)	HDL- Cholesterol (mg/dl)
Control	75.6 ± 10.9^{A}	47.1 ± 5.1^{A}	42.2 ± 7.6^{A}	31.3 ± 12.3^{A}
PN model	71.8 ± 11.1^{A}	44.3 ± 5.8^{A}	45.1 ± 6.6^{A}	27.2 ± 11.7^{A}
PN + gabapentin	78.5 ± 13.1^{A}	48.6 ± 6.7^{A}	44.7 ± 7.1^{A}	32.5 ± 13.4^{A}
PN + LPLT	69.4 ± 10.6^{A}	45.3 ± 4.1^{A}	43.5 ± 5.8^{A}	31.5 ± 12.1^{A}

Data represent the average ± SD for 10 rats. Data represent the average ± SD for 10 rats. Within a column, means superscript with different letters are significantly different at $P \leq 0.05$.

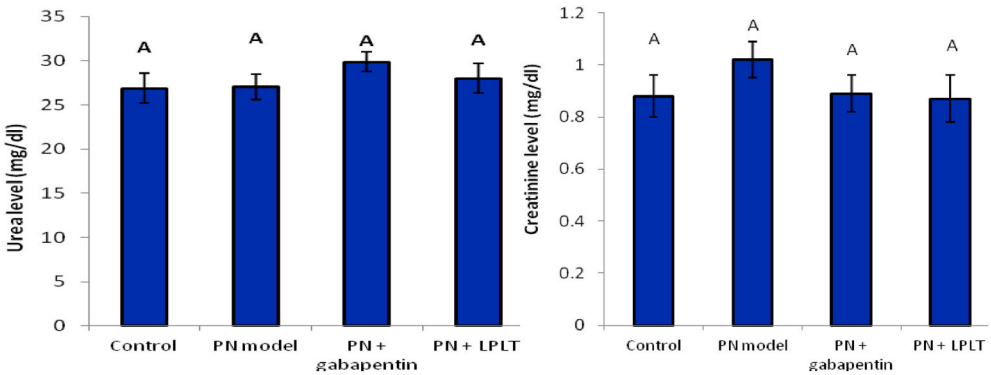

Fig. 3. Effect of gabapentin or LPLT on levels of serum urea and creatinine in peripheral neuropathy (PN) modeled rats. Data represent the average ± SD for 10 rats. Means superscript with different letters are significantly different at $P \leq 0.05$.

diphosphate (ADP) causing an increase in DNA and protein syntheses [16]. This accelerates the recovery of the injured nerve cells and enhances its function.

DCA causes cognitive decline. This effect may be attributed to the reduction in lactic acid level which is used as a main energy substrate for brain [39]. DCA is currently used for treatment of lactic acidosis and regulates pyruvate dehydrogenase (PDH). DCA enhances PDH and entry of pyruvate into the TCA cycle, thus directly reducing lactate efflux into the extracellular space [40–42]. Lactate which is the end-product of glycolysis, can be turned back to pyruvate by a reversible reaction that is catalyzed by LDH. This reaction submits a significant energy source for the brain, as its glycogen stores are relatively limited and, in the absence of exogenous glucose and within a few minutes, the lactic acid is rapidly consumed by neurons. Additionally, in the brain the gluconeogenic activity is negligible, therefore, neurons largely depend on lactate as a main energy substrate. Also, astrocytes are important in metabolizing glucose and production of lactate that is delivered to the nearby neurons [43] where it is used as an oxidative fuel [39]. The delivery of lactate from astrocytes to neurons is controlled by monocarboxylate transporters (MCTs). The MCT dysfunctions are related to many pathologies of the central nervous system that include cognitive defects, epilepsy and metabolic disorders [39].

According to the present study, in the DCA induced rats, cytokines TNF-α, IL-10 and IL-1β were significantly increased while prostaglandin E2 (PGE2) showed an insignificant increase. These increases may be due to the formation of oxidative stress markers formed during DCA metabolism which increases the production of pro-inflammatory cytokines [44] such as IL-1β and TNF-α [45]. The cytokines were found to be increased in nerve dysfunction [46]. The cytokine IL-10 may also represent a compensatory or neuroprotective mechanism in case of nerve damage [47].

Our study showed that treatment with gabapentin or LPLT

significantly reduced the levels of these cytokines back to normal values. This indicates that LPLT has the ability to minimize inflammations. These results are in analogue with that obtained by Yamaura et al. [48] who reported that, LPLT treatment reduces proinflammatory cytokines such as IL-1β and TNF-α, in patients with rheumatoid arthritis. Moreover, prostaglandin concentrations were also reduced with LPLT therapy in patients with bilateral Achilles tendinitis [49,50].

The current study showed that serum nitric oxide and lipid peroxidation markedly increased in the DCA-induced group along with significant decrease in reduced glutathione. These results are consistent with the those of Hassoun et al. [51]. The measured liver function markers (ALAT and ASAT) also increased by DCA intake. These markers were significantly ameliorated when DCA-induced rats were treated with either gabapentin or LPLT. Previously, it was found that DCA induces oxidative stress in the hepatic tissue of mice after subacute and sub chronic exposure [52]. Other research reported that exposure to DCA at and above clinical concentrations causes oxidative stress biomarkers, decreases viability in hepatocytes, and leads to hepatocarcinogenesis [51–53]. Previous studies by Mizutani et al. [49] and Yamaura et al. [48] demonstrated that the function of LPLT therapy in reducing the oxidative stress and ameliorating liver function may be due to its anti-inflammatory activity.

On the other hand, the measured lipid profile markers showed insignificant changes among the different studied groups. However, these observations are not parallel with the results of Stacpoole et al. [54] and Ribes et al. [55] who found a significant decrease in plasma cholesterol and triglycerides levels by DCA intake. The dispute in the reports about cholesterol and triglycerides may be attributed to differences in species, duration of treatment or dose of DCA. Our results also showed that DCA did not affect urea and creatinine.

5. Conclusions

Our results provide further evidence that LPLT is more efficient than gabapentin at the used doses in the management of peripheral neuropathy induced by xenobiotics. LPLT could be used as monotherapy or in addition to pharmaceutical drugs like gabapentin. However, further studies with higher gabapentin doses are needed to give a complete and real comparison between gabapentin and LPLT, taking into account the side effects of these doses.

Funding

The authors declare that this study is part of a research project No. 010010318 under title: Efficacy of low-level laser therapy (LLLT) in the management of diabetic and non diabetic neuropathy funded by National Research Centre, Giza, Egypt from year 2013–2016.

Declaration of competing interest

All authors declare that they have no competing interests.

Acknowledgements

Authors would like to thank the authorities of National Research Centre, Giza, Egypt, for providing the facilities and supporting by the fund (Project Code: 010010318) to carry out this work.

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