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RESEARCH ARTICLE

The Protective Effects of *Lavender officinalis* Extract Against Impairment of Antioxidant–Detoxification System Induced by Glucose Deprivation Through Nrf2 Expression

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Abstract Despite tremendous progress in the prevention and treatment of cerebral ischemia, stroke remains one of the major causes of mortality and paralysis among the elderly. The design and study of neuroprotective drugs in vitro, such as in the Serum-Glucose Deprivation (SGD) condition, are proved to be efficient to understand how these drugs defend neuronal cells from ischemia-induced damage. Neurological defects and stroke volume are reduced by lavender plant's potent and abundant compounds reduces. In this study, we intend to study the mechanism of a protective effect of the lavender extract on insult caused by glucose deprivation in the PC12 cell line, focusing on the Nrf2 pathway. In order to investigate the protective effects of the extract, the cells were subjected to serum/glucose deprivation for a period of 12 h at non-toxic concentrations and viability was investigated. Expression levels of Nrf2, HO-1, and NQO1 genes were evaluated. Also, the activity of CAT, SOD, and GPx enzymes was measured. The results illustrate an increase in cell viability, expression of HO-1 and NQO1 genes, and enzymatic activity of CAT, SOD, GPx. In conclusion, pretreatment of PC12 cells with hydroalcoholic extract of lavender reinforces antioxidant system and detoxification enzymes under oxidative stress.

Keywords *Lavender* · Serum/glucose deprivation · Antioxidant system

Significance statement: The result of this research introduces lavender officinalis extract as a promising composition to elevate symptoms of ischemic conditions in cells.

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Introduction

Stroke is one of the main causes of death and impacts approximately 795000 individuals worldwide [1]. Ischemic stroke stems from an occlusion in the neck or cerebral arteries, which is due to thrombus, embolus, or stenosis [2]. Thrombolytic treatment options for restoring cerebral blood supply are considered the number one healing approach for cerebral ischemic insult [3, 4]. Tissue plasminogen activator (t-PA) is the only US FDA-approved option for treating ischemic stroke. However, it must be administered within 3 to 4.5 h after the beginning of ischemic stroke [5]. Furthermore, t-PA may cause edema, blood–brain barrier breakdown, or hemorrhage [6]. After thrombolytic treatment, reperfusion often causes intracellular production of reactive oxygen species (ROS), increased intracellular calcium, excitotoxic cell damage, and inflammation, which give rise to irreversible cerebral damage [4]. Therefore, adding neuroprotective agents could protect neurons and prevent reperfusion injury [7].

Physiologically, free radicals or reactive oxygen species such as superoxide, hydrogen peroxide, and hydroxyl radicals are produced through mitochondrial oxidative phosphorylation and normal metabolism. They are highly reactive molecules. Therefore, cells protect themselves against

harms caused by ROS via defensive systems, including the expression of various antioxidative enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, and neutralizing ROS and converting them into water (H2O) and oxygen (O2). The imbalance between ROS production and defense mechanisms against them is known as oxidative stress, resulting in damage to deoxyribonucleic acid (DNA), lipids, and proteins [8–10].

One of the key regulatory pathways that protects cells against oxidative damage is Keap1 (Kelch-like ECH-associated protein 1)/Nrf2 (Nuclear factor erythroid 2-related factor 2) regulatory pathway [11]. Nrf2 is a transcription factor that is transferred to the nucleus during oxidative stress conditions. In the nucleus, it activates the antioxidant response element (ARE) and enhances the expression levels of downstream protective proteins like heme oxygenase-1 (HO-1) and NADPH quinine oxidoreductase-1 (NQO1) [12].

Reoxygenation, whether spontaneously or by thrombolytic reperfusion, delivers oxygen as a substrate for enzymatic oxidation reactions [13]. Brain is prone to oxidative damage caused by ischemia/reperfusion-induced oxygen free radicals due to its high oxygen consumption, high concentration of polyunsaturated fatty acid, and low concentration of antioxidative enzymes [14, 15]. Thus, it is essential to investigate the effects of scavengers of free radicals and antioxidants in ischemia/reperfusion-induced cerebral damage [14].

Green tea has demonstrated a protective impact on ischemia/reperfusion-induced cerebral injury in Mongolian gerbils. Pretreatment with green tea extract alleviated the infarct volume, hydrogen peroxide level, and the number of ischemia/reperfusion-induced apoptotic cells [14].

Another medicinal herb with antioxidative properties is Lavandula officinalis [16]. Lavandula officinalis is a member of the Lamiaceae family. The major components of the *L. officinalis*' aerial parts and flowers include flavonoids, triterpenoids coumarins, linalool, linalyl acetate, and some other monoterpene and sesquiterpenes [17]. Lavender oil remedy reduced the amount of Malondialdehyde (MDA) and reactive oxygen species, enhanced the activity of superoxide dismutase (SOD), catalase, and Glutathione peroxidase, and increased GSH/GSSG ratio [18]. Lavender has been used as a sedative, anti-depressant, anti-inflammatory, and analgesic agent in many countries. Extract of *L. officinalis* diminished the permeability of the blood–brain barrier and improved neurological function in rats [16]. Moreover, Lavender extract positively impacted rats' spatial learning and memory of rats [19].

Thus, we decided to assess the effect of *L. officinalis*' extract on PC12 cells in serum/glucose deprivation condition. PC12 cells are isolated from rat adrenal medulla pheochromocytoma.

Material and Methods

Extract Preparation

The *Lavender. officinalis* plant was purchased from a local supplier and then, authenticated in the Medicinal Plants Research Center of Shahrekord University of Medical Sciences. The extract was prepared using maceration method. Pulverized and dried plant aerial parts were mixed with ethanol. After 48 h, the mixture was filtered through filter papers, evaporated by a rotary evaporator (48–50 °C), and dried in a 37 °C heater[17].

Cell Viability Assay with MTT Assay

PC12 cells were obtained from Pasteur Institute (Tehran, Iran). Two types of this line are available: conventional PC12 cells and a well-attached adherent phenotype. The attached form of PC12 cells were used. In order to prevent bias in experiments, treated cells were all in passages 3–5. All cells were maintained in a humidified atmosphere (90%) containing 5% CO_2 at 37 °C. PC12 cells were cultured in high glucose DMEM (4.5 g/L, Dulbecco's minimum essential medium, Gibco, UK) supplemented with 10% FBS (Gibco, UK). Cells were treated in three ways. In the first group, cells were initially treated by *L. officinalis* extract (31.25 µg/ml (based on a pilot study, data not illustrated)) for 6 or 12 h under normal conditions and then subjected to the deprivation conditions without the extract for additional 6 or 12 h (pretreatment-1 group). In the second group, after 6 or 12 h of being treated with the extract (31.25 µg/ml) under normal conditions, cells were treated with extract under deprivation conditions for additional 6 or 12 h (pretreatment-2 group). In the third group, cells experienced the deprivation conditions for 6 h, and then, they were treated with the extract (31.25 µg/ml) under deprivation conditions for 6 h (treatment group). Three control groups were also considered as the following: control 1:5000 cells per well plus DMEM medium with glucose; control 2: 5000 cells were cultured in DMEM media for 24 h, and the media was aspirated, and cells were incubated in glucose-free media for 6 or 12 h; control 3: it is designed like treatment groups expect for adding extract solution.

To test PC12 cells' viability, 5000 PC12 cells were seeded in each well of the 96-well format plate and cultured until they reach a stable situation. Afterward, Cells were pretreated and post-treated under glucose deprivation conditions with a safe concentration of lavender extract (31.25 µg/ml, 12 h).

Gene Expression Evaluation with RT-PCR

The RNA of treated cells in all groups was extracted by TRIzol. Then, their quantity and quality were determined by a Nanodrop. Next, cDNA synthesis was done using the Revert Aid First cDNA Synthesis kit. In order to prevent contamination with genomic DNA, DNAse I enzyme was used before cDNA synthesis. Real-time PCR for Nrf2, HO-1, NQO1, and Beta actin genes was performed using SYBR Green master mix, and the primers were designed by gene runner software. The primers used in RT-PCR analysis were as follows: HO-1 (5′-CCTTCCTGTGTCTTCCTTTGTC-3′ Forward, 5′- CCTCTACCGACCACAGTTCT-3′ Reverse); Nrf2 (5′- GCCTTCCTCTGCTGCCATTAG-3′ Forward, 5′-CGTGCCTTCAGTGTGCTTCT-3′ Reverse); NQO1 (5′-GCAGAGAGGACATCATTCAACTA-3′ Forward, 5′- GTTCATAGCATAGAGGTCAGATTC-3′ Reverse); Beta actin(5′-CCGTGGTGTGGAAGATGTTACT-3′ Forward, 5′- CCGTATGTCCCTGTCGTGTC-3′ Reverse) was chosen as endogenous control (housekeeping genes). For RT-PCR, the reaction mixture (20 µL) contained 1 µL of diluted cDNA,1 µL of each set of oligonucleotide primers, 7 µL nuclease free water, and 10 µL 2X SYBR Green Master Mix (RR041A, Takara Bio). The Real-time PCR conditions included an initial denaturation at 95 °C for 5 min, followed by a 40-cycle amplification consisting of denaturation at 95 °C for 10 s, annealing at 60 °C for 20 s and extension at 72 °C for 30 s. Melting curves were studied to verify qPCR product identity. All reactions were examined in triplicate for each sample. All primer pairs were checked for primer-dimer formation using the three-step protocol described above without the addition of the template. Relative mRNA expression levels were calculated by the $2^{\wedge-\Delta\Delta Ct}$ method.

Enzymatic Activity Measurement

After treating cells according to the above experimental groups, they were washed with PBS and lysed via the specific buffer of the measurement kit (**Padginteb Co, Iran**). Then, the amount of enzymatic activity of SOD, CAT, GPx was measured according to its protocol (Zellbio, German).

Statistical Analysis

The data were evaluated using SPSS software, and Kruskal–Wallis H test was used to compare variables between the groups. Statistical significance was defined as $P<0.05$.

Results and Discussion

PC12 Cells Viability in Serum/Glucose Deprivation (SGD) in Different Durations

Under the SGD conditions, PC12 cell percentages declined over time. After 3, 6, 12, and 24 h there was 91%, 14%, 9%, and 8% cells, respectively (Fig. 1).

Viability of Cells with Various Doses of L. officinalis Extract After 6 and 12 h

5000 PC12 cells were seeded and cultured in the 96-well plate, and after 24 h, they were treated with different doses of *L. officinalis* extract (0–500 µg/ml) for 6 and 12 h. The control groups without *L. officinalis* extract treatment were evaluated independently for 6 and 12 h (Fig. 2).

The impact of different concentrations of *L. officinalis* extract on the cells after 6 and 12 h was determined with MTT assay and demonstrated in Fig. 3. Different dosages of *L. officinalis* extract (0–500 µg/ml) had no impact ($p>0.05$) (Fig. 2). Finally, we found that 31.25 µg/ml has the best effect on cells to preserve them against cytotoxic effect of ischemia and was chosen as a safe concentration (data not illustrated).

Viability of Pretreated and Treated PC12 Cells in the SGD Conditions for 6 h

The incubation length of 6 and 12 h, as well as the extract concentration of 31.25 g/ml, is chosen based in Figs. 2, 3 and our prior study (data not shown) to test the effect of *L. officinalis* extract under SGD circumstances. As

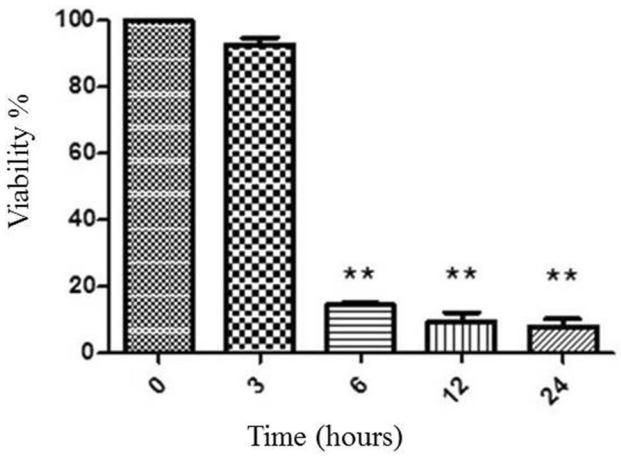

Fig. 1 Comparison of PC12 cells' viability after 3, 6, 12, and 24 h under the SGD conditions. The SGD conditions after 6, 12, and 24 h resulted in the death of about 80% of cells, and the differences with the control group were significant (**$p<0.01$) (mean ± SD, $n=3$

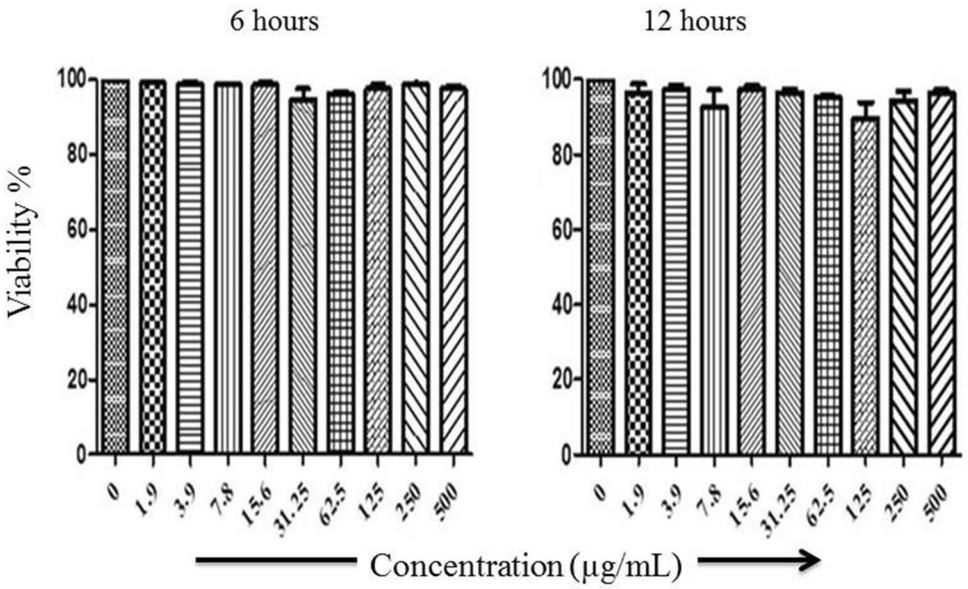

Fig. 2 Effect of various concentrations of *L. officinalis* extract on the PC12 cells' viability after 6 and 12 h (mean ± SD). No significant cytotoxic effects were detected. The tests were done three times for each concentration

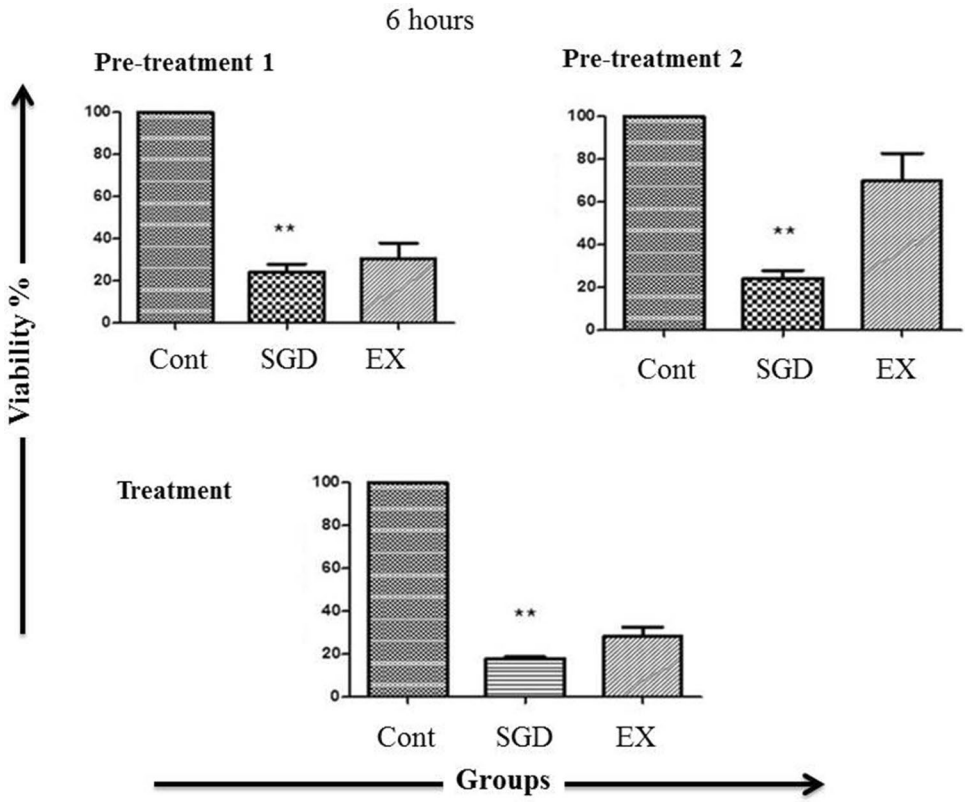

Fig. 3 Comparison of effects of *L. officinalis* extract on PC12 cells under SGD conditions (**$p < 0.01$ vs. control group) (mean ± SD, $n = 3$). (cont: control, SGD: serum glucose deprivation, EX: extract of *L. officinalis)*

demonstrated in Fig. 3, the extract was able to exert protective effects on PC12 cells against the cytotoxicity of deprivation conditions,with the impact being stronger in the pretreatment-2 group, with the impact being stronger in the pretreatment-2 group. Despite the fact that the extract improved the percentage of viable cells under the SGD circumstances, the difference with the SGD group and extract group was insignificant ($p > 0.05$). Furthermore, in the treated group, the extract was able to increase the percentage of live cells in SGD conditions, but the differences with the SGD group were insignificant ($p > 0.05$).

Viability of Pretreated and Treated PC12 Cells in the SGD Conditions for 12 h

As shown in Fig. 4, in two pretreatment groups, the extract could alleviate the SGD conditions' cytotoxic effects on PC12 cells. These effects were more eminent in the pretreatment-2 group, and the differences with the SGD group were remarkable in 31.25 µg/ml dose of the extract ($p < 0.05$).

Evaluation of expression rate of Nrf2, HO-1, NQO1 genes

Expression Rate of Nrf2 Gene in the Experimental Groups

Since *L. officinalis* was the most effective 12 h post-treatment, we chose this timeline for evaluating gene expression. In this experiment, the expression rate of the Nrf2 gene in SGD groups rose distinctively compared to the control group ($p < 0.05$). Pretreatment of PC12 cells by *L. officinalis* extract (31.25 µg/ml) resulted in Nrf2 gene expression substantial increase in pretreated groups (pretreatment-1 and pretreatment-2 groups) which was more significant compared to the groups in deprivation conditions for 12 h ($p < 0.05$) ($p < 0.01$). The extract also boosted Nrf2 gene expression in the treatment group,

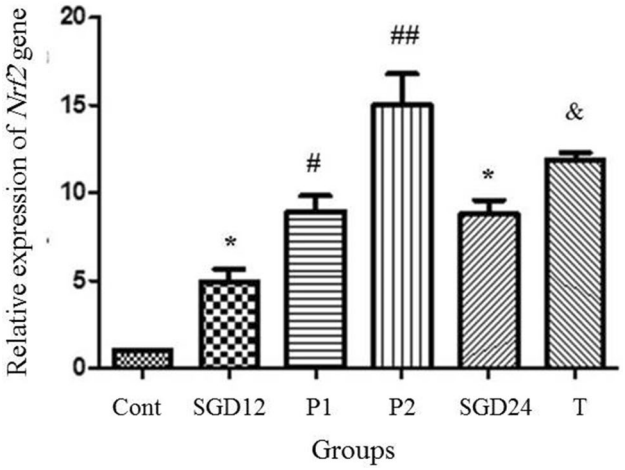

Fig. 5 The expression rate of Nrf2 gene, relative to Beta Actin gene, in PC12 cells under the SGD conditions. mean ± SD, $n = 3$(*$p < 0.05$ vs. group, #$p < 0.05$ vs. SGD group for 12 h, ##$p < 0.01$ vs. SGD group for 12 h, &$p < 0.05$ vs. SGD group for 24 h). Control: healthy cells, SGD12: serum glucose deprivation for 12 h, P1: pretreatment-1 group, P2: pretreatment-2 group, SGD24: serum glucose deprivation for 24 h, T: treatment group

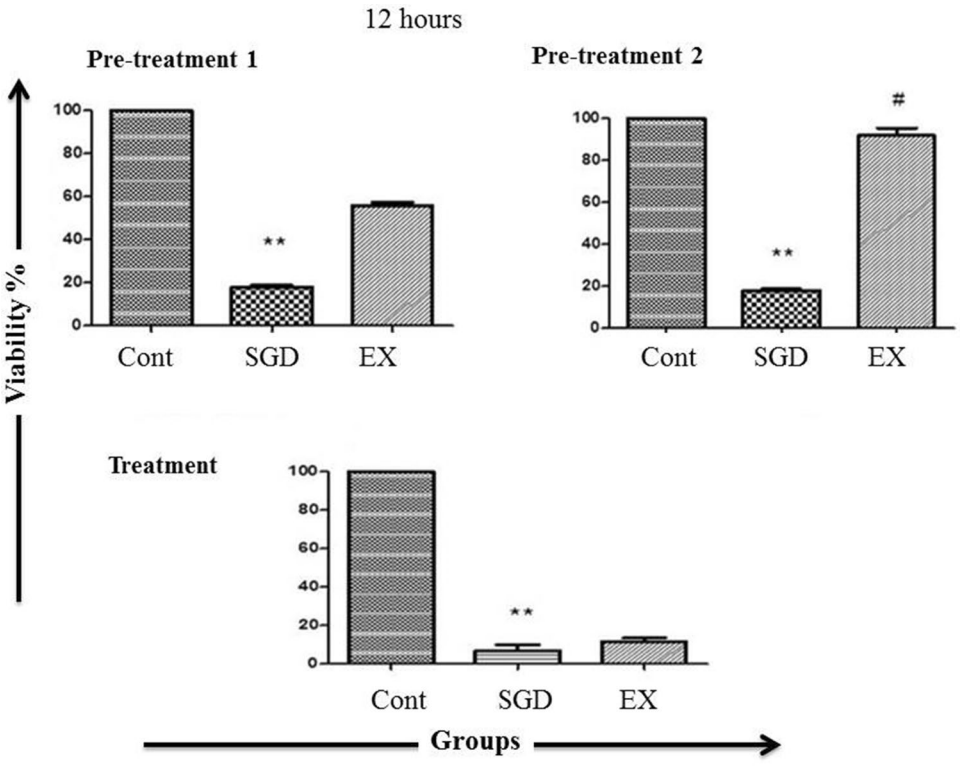

Fig. 4 Comparison of effects of *L. officinalis* extract on PC12 cells under SGD conditions (**$p < 0.01$ vs. control group, #$p < 0.05$ vs. SGD group) (mean ± SD, $n = 3$. cont: control, SGD: serum glucose deprivation, EX: extract of *L. officinalis)*

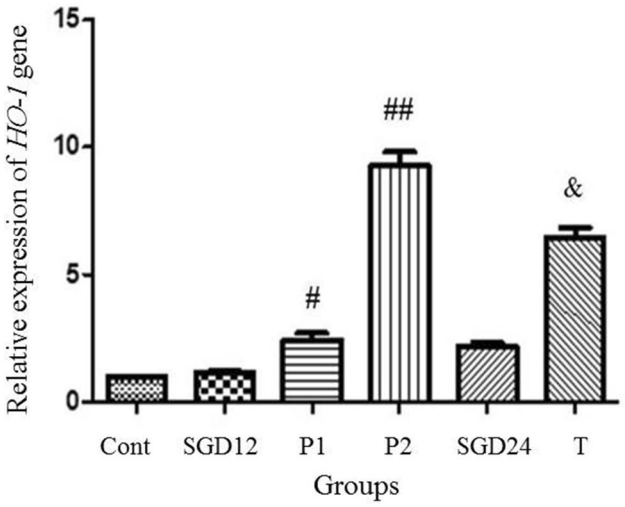

Fig. 6 Expression rate of HO-1 gene, relative to Beta Actin, in PC12 cells under the SGD conditions. mean ± SD, $n = 3$(#$p < 0.05$ vs. SGD group for 12 h, ##$p < 0.01$ vs. SGD group for 12 h, &$p < 0.05$ vs. SGD group for 24 h). Control: healthy cells, SGD12: serum glucose deprivation for 12 h, P1: pretreatment-1 group, P2: pretreatment-2 group, SGD24: serum glucose deprivation for 24 h, T: treatment group

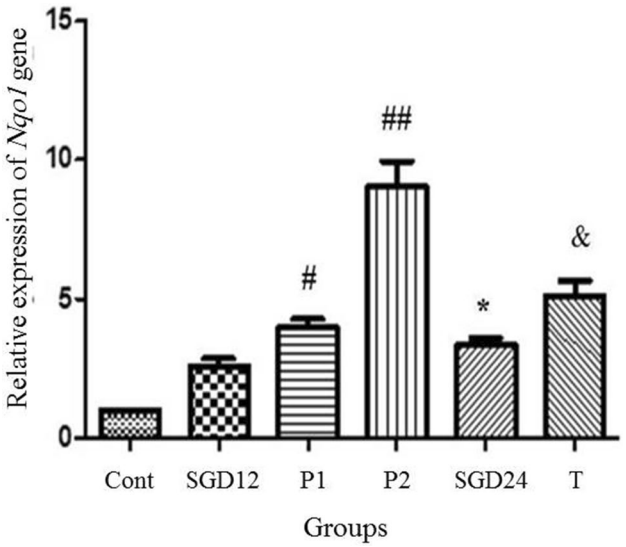

Fig. 7 Expression rate of NQO1 gene, relative to Beta Actin, in PC12 cells under the SGD conditions. mean ± SD, $n = 3$ (*$p < 0.05$ vs. control group, #$p < 0.05$ vs. SGD group for 12 h, ##$p < 0.01$ vs. SGD group for 12 h, &$p < 0.05$ vs. SGD group for 24 h). Control: healthy cells, SGD12: serum glucose deprivation for 12 h, P1: pretreatment-1 group, P2: pretreatment-2 group, SGD24: serum glucose deprivation for 24 h, T: treatment group

considerably higher than SGD group for 24 h ($p < 0.05$) (Fig. 5).

Expression Rate of HO-1 Gene in the Experimental Groups

The findings of this experiment, as shown in Fig. 6, that being exposed to SGD circumstances enhanced the expression rate of the HO-1 gene, though it was not statistically significant ($p > 0.05$). Pretreatment of cells with 31.25 µg/ml concentration of *L. officinalis* extract led to HO-1 gene expression rate's increase in both pretreated groups (pretreatment-1 group and pretreatment-2 group), which was statistically significant ($p < 0.05$) ($p < 0.01$). In the treatment group, the extract was increased the HO-1 gene expression rate, which was statistically significant compared to the SGD group for 24 h ($p < 0.05$).

Expression Rate of NQO1 Gene in the Study Groups

As exhibited in Fig. 7, the results obtained from this experiment suggested that being under the SGD conditions led to an increase in NQO1 gene expression rate, which was noticeable only in 24 h ($p < 0.05$). In both pretreated groups (pretreatment-1 group and pretreatment-2 group), cells' pretreatment with 31.25 µg/ml concentration of *L. officinalis* extract resulted in a raising NQO1 gene expression rate, which was statistically significant ($p < 0.05$) ($p < 0.01$). Moreover, in the treatment group, the extract increased the NQO1 gene expression rate significantly compared to the SGD group for 24 h ($p < 0.05$).

Enzymatic Activity of SOD, CAT, and GPx Enzymes in Experimental Groups

The results of enzymatic activity evaluation of SOD, CAT, and GPx enzymes demonstrated that incubating PC12 cells in SGD conditions caused a decrease in the activity of enzymes compared with the control group, which was statistically significant ($p < 0.05$). Pretreatment of cells with *L. officinalis* extract (31.25 µg/ml) resulted in an elevation of SOD, CAT, and GPx enzymes' activity, and this elevation was notable in the pretreatment-2 group compared to the SGD group for 12 h($p < 0.05$). Also, in the treatment group, the 31.25 µg/ml concentration of *L. officinalis* extract led to an increase in the activity of SOD, CAT, and GPx enzymes which was only considerable for the SOD enzyme in comparison with the SGD group for 24 h ($p < 0.05$) (Fig. 8).

In this study, PC12 cells were subjected to a serum/glucose deprivation model to imitate neuronal ischemia events and the protective mechanism of *L. officinalis* hydroalcoholic extract. In this study, the viability of PC12 cells exposed to SGD was measured by MTT. The results of the MTT assay indicated that serum/glucose deprivation diminished the viability of cultured PC12 cells, which was attenuated by *L. officinalis* hydroalcoholic extract pretreatment. In both pretreatment groups, the extract led to the alleviation

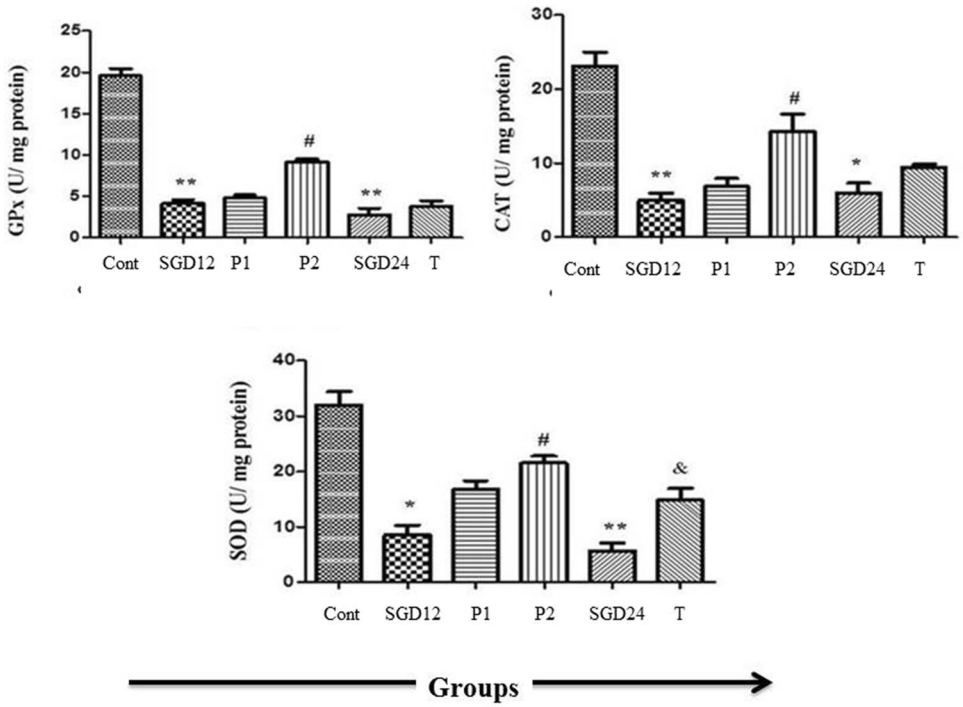

Fig. 8 SOD, CAT, and GPx enzymatic activity in PC12 cells under the SGD conditions. mean ± SD, $n = 3$(*$p < 0.05$ vs. control group, **$p < 0.01$ vs. control group, #$p < 0.05$ vs. SGD group for 12 h, &$p < 0.05$ vs. SGD group for 24 h). Control: healthy cells, SGD12: serum glucose deprivation for 12 h, P1: pretreatment-1 group, P2: pretreatment-2 group, SGD24: serum glucose deprivation for 24 h, T: treatment group

of cytotoxic effects of the SGD conditions on PC12 cells, and these effects were more pronounced when the extract was present for 12 h in the deprivation conditions (pretreatment-2 group). Additionally, the most effective concentration of the extract was 31.25 µg/ml.

Due to the importance of glucose metabolism, Liu et al. evaluated the effect of glucose deprivation on PC12 cells. Their findings revealed that glucose deprivation resulted in cell death via apoptosis and necrosis. Additionally, the role of ROS accumulation in cytotoxicity of glucose deprivation was demonstrated [20]. In fact, there is evidence indicating the significant role of oxidative stress in the ischemia/reoxygenation process [21]. Cells are equipped with endogenous antioxidant systems to defend against the oxidative stress created in many diseases. One of these pathways is the antioxidant/electrophile response element (ARE/EpRE)-regulated phase II detoxifying enzymes and antioxidants [22].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a significant regulator of antioxidant genes.

In normal circumstances, Nrf2 is maintained in the cytoplasm by binding to Kelch-like ECH-associated protein 1 (Keap1) and constantly experiences ubiquitination and degradation. Nevertheless, during oxidative stress, this bound is destroyed, and Nrf2 translocated into the nucleus where it binds to the promoter of antioxidant response element (ARE) gene and increases the expression of antioxidant enzymes like NADPH quinone oxidoreductase-1 (NQO1), glutathione S-transferase A1 (Gsta1) [23, 24]. Nrf2 has been recognized as a significant role player in neuroprotection against pro-oxidant events. Evidence shows that Nrf2 deficiency causes exacerbation of neuronal degeneration. Furthermore, reports demonstrate that the Nrf2 activator counteracted several manifestations of diabetic neuropathy [4].

Heme oxygenase-1 (HO-1) is an index of cellular oxidative stress and the rate-limiting enzyme of heme degradation to biliverdin, iron, and CO. It is one of the ARE-regulated phase II detoxifying enzymes and antioxidants regulated by Nrf2. HO-1 has remarkable antioxidant and neuroprotective properties [22, 25].

The present study revealed that PC12 cells exposed to the SGD conditions could lead to antioxidative pathway activation due to oxidative stress induction in cells. As RT-PCR results showed, the SGD conditions resulted in an increase in the expression of Nrf2, NQO1, and HO-1 genes, which indicates the activation of the antioxidative pathway of cells to defend against induced oxidative stress. Treatment of the cells with the *L. officinalis* extract was helpful in the cell's defense against oxidative stress and led to an increase in the expression of antioxidative pathway genes such as Nrf2, NQO1, and HO-1. Moreover, the present study results demonstrated that SGD conditions could result in a decrease in detoxifying enzymes such as CAT, SOD, and GPx, which can cause cellular damage and oxidative stress intolerance.

The presence of the *L. officinalis* extract increased in the activity of detoxification enzymes and helped the cells to maintain homeostasis. Pretreatment of cells with *L. officinalis* extract before and during the exposure to SGD conditions had more significant effects on increasing the power of the antioxidative system of cells to defend against oxidative stress conditions.

In the study of Mousavi et al., the protective effects of *Nigella sativa L.* and thymoquinone (TQ) on PC12 cells under SGD conditions were investigated. It was shown that SGD conditions for 6 and 18 h significantly reduced the viability of cells compared with the control group, which is in accordance with our study. They also reported that two hours pretreatment of cells with *N. sativa* extract and TQ led to the protection of cells against SGD-induced cytotoxicity and a decrease in SGD-induced ROS production. They suggested that the antioxidant properties of *N. sativa* extract and TQ could mediate their protective effects under SGD conditions [26].

The study of Forouzanfar et al. revealed that pretreatment of PC12 cells for 2 h with pomegranate (*Punica granatum* L.) extracts led to the protection of cells against the SGD conditions. This protective effect was attributed to its antioxidant properties [27].

The results of the study of Gue et al. elucidated that exposure of PC12 cells to oxygen and glucose deprivation 12 h/reperfusion 24 h (OGD/R) caused an increase in apoptosis, ROS generation, and expression of P53. However, they declined the expression of antioxidant enzymes and Nrf2 protein and its downstream genes, cell viability, and membrane potential of mitochondria. Pretreatment of PC12 cells with apigenin for 6 h attenuated OGD/R-induced effects via antioxidant and antiapoptotic properties through modulating Nrf2 and P53 expression levels [28].

Huang et al. found that panaxatriol saponins (PTS), the main component of *Panax notoginseng*, protected PC12 cells against the OGD/R cytotoxicity. It increased the expression of HO-1 in PC12 cells through Nrf2 pathway activation, which in turn was activated by PI3K/Akt, as the upstream pathway [29].

Several studies also have focused on the neuroprotective effects of *L. officinalis.* For instance, in the study of Pan Xu et al., lavender oil (LO) improved the cognitive function of scopolamine-induced mice. It also protected PC12 cells against the cytotoxicity of H_2O_2. PC12 cells exposure to H_2O_2 decreased the cell viability and increased LDH release compared to the control group. LO declined ROS accumulation, extracellular NO, mitochondrial membrane potential drop, and LDH release compared to H_2O_2 treated group [30].

In the experiment of Hancianu et al., antioxidant and antiapoptotic properties of lavender essential oils in scopolamine-treated rats were exhibited. Lavender essential oils increased the activity of antioxidant enzymes (SOD, GPx, and CAT) and diminished malondialdehyde (MDA) level, an indicator of lipid peroxidation, in temporal lobe homogenates of rats. Antioxidant and antiapoptotic properties of lavender essential oils were suggested as the primary strategy of their neuroprotection against scopolamine-induced oxidative stress in rats' brain.

Wang et al. evaluated the effect of LO on ischemia/reperfusion brain injury in mice. In their experiment, LO reduced the neurologic deficit, size of infarction, the level of ROS and MDA, and increased the activity of SOD, CAT, GSH-Px. They suggested that neuroprotective impacts of LO on ischemia/reperfusion cerebral injury might be related to its antioxidant activity [18]. This is in line with the result of the present study.

Conclusion

Overall, these results suggested that the protective effect of *L. officinalis* extract on PC12 cells under SGD conditions could be attributed to the augmentation of the antioxidant system and detoxifying enzymes.

This experiment manifested that pretreatment of PC12 cells in SGD conditions with *L. officinalis* extract healed the negative effect of the SGD condition. Investigating the antioxidant–detoxification pathway showed that Lavender extract increased the expression of the antioxidant pathway's kye genes such as Nrf2, NQO1, and HO-1 and also increased the enzymatic activity of CAT, SOD, and GPx enzymes which play key roles in the antioxidant–detoxification pathway. More detailed research on the composition of Lavender Officinalis extract and the cellular mechanisms engaged with the healing effect of Lavender extract could facilitate the use of herbal medicine to control and treat ischemia-caused insults.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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