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Research Paper

Timing-Dependent Effects of Fluoxetine and 808 nm Photobiomodulation in CORT/H_2O_2-Stressed SH-SY5Y Cells

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ABSTRACT

Background: Major depressive disorder is associated with glucocorticoid dysregulation, oxidative stress, inflammation, and mitochondrial disturbance. Cellular systems can examine selected components of these processes but do not reproduce the clinical disorder. To examine the timing-dependent effects of fluoxetine and 808 nm photobiomodulation (PBM), alone and together, in CORT/H_2O_2-stressed SH-SY5Y cells.

Methods: SH-SY5Y cells were exposed concurrently to corticosterone and hydrogen peroxide (100 µM each) for 24 h. Fluoxetine (1 µM) and PBM (808 nm, 50 mW, 0.2 cm^2 beam area, 250 mW/cm^2, 40 s; calculated nominal fluence 10 J/cm^2) were applied before, during, or after stress. Cell viability, malondialdehyde (MDA), reduced glutathione (GSH), and interleukin-6 (IL-6) were assessed. Reported p-values derive from exploratory one-way analyses and do not estimate factorial interactions.

Results: The combined stress condition was associated with lower viability and GSH and higher MDA and IL-6 than the control. In the original exploratory comparisons, co- and post-treatment generally showed more favorable viability and redox outcomes than pretreatment. The combined intervention showed favorable mean responses at several time points, with concurrent treatment showing the broadest redox pattern and post-treatment showing the lowest mean IL-6.

Conclusion: Fluoxetine and PBM were associated with timing-dependent cytoprotective patterns in this cellular stress system. Because factorial interactions were not tested, biochemical endpoints were not documented as cell- or protein-normalized, and the model does not represent major depressive disorder, the findings are hypothesis-generating and do not establish synergy, mechanism, clinical efficacy, or safety.

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Introduction

Major depressive disorder (MDD) constitutes one of the most significant contributors to the global burden of disease, affecting approximately 280 million individuals worldwide and representing a leading cause of disability across all age groups [1]. The World Health Organization has identified MDD as a critical public health priority, with projections indicating a continued rise in prevalence through 2050 [2]. For over five decades, the pharmacological management of MDD has been predicated upon the monoamine hypothesis, which posits that the restoration of monoaminergic neurotransmission, principally serotonergic, noradrenergic, and dopaminergic, constitutes the primary mechanism through which clinical recovery is achieved [3]. However, the limitations of this paradigm have been compellingly demonstrated by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which revealed that fewer than one-third of patients attain remission following an adequate course of first-line selective serotonin reuptake inhibitor (SSRI) therapy [4]. These findings have catalyzed a fundamental reconceptualization of MDD as a complex, multisystemic disorder.

Contemporary evidence indicates that MDD pathophysiology involves the convergent interaction of multiple pathological mechanisms, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, oxidative stress, neuroinflammation, and mitochondrial dysfunction, which operate in a mutually reinforcing and self-perpetuating manner [5]. Chronic HPA axis hyperactivation results in sustained hypercortisolaemia, which precipitates mitochondrial impairment, excessive generation of reactive oxygen species (ROS), and subsequent neuronal damage [5, 6]. Meta-analytical evidence robustly demonstrates that lipid peroxidation products, notably malondialdehyde (MDA), are consistently and significantly elevated in depressed cohorts relative to healthy controls [7]. Furthermore, pro-inflammatory cytokines—particularly interleukin-6 (IL-6) are similarly elevated in patients with MDD, as confirmed by cumulative meta-analyses encompassing thousands of participants [8]. These converging lines of evidence underscore the imperative for therapeutic strategies that simultaneously address multiple pathophysiological domains rather than targeting monoaminergic neurotransmission in isolation.

Fluoxetine, the prototypical selective serotonin reuptake inhibitor (SSRI), may exert actions beyond serotonin-transporter blockade. Studies in other experimental systems report direct binding of antidepressants to tropomyosin receptor kinase B (TrkB), the high-affinity receptor for brain-derived neurotrophic factor (BDNF), with potential consequences for plasticity-related signaling [9]. PBM using near-infrared wavelengths, including 808 nm, has also been investigated as a non-pharmacological intervention. Proposed photobiological mechanisms include photon absorption by cytochrome c oxidase, altered mitochondrial bioenergetics and redox signaling, and downstream Nrf2- and CREB/BDNF-related responses [10,11]. These pathways were not measured in the present study and are introduced only as literature-based hypotheses.

The aim of this study was to characterize the timing-dependent effects of fluoxetine, 808 nm PBM, and their combined administration in proliferative SH-SY5Y cells exposed concurrently to corticosterone and hydrogen peroxide for 24 h. Viability, MDA, reduced GSH, and IL-6 were assessed. This system was considered an in vitro cellular stress model relevant to selected depression-associated processes, not a direct model of major depressive disorder.

Materials and Methods

Cell Line and Culture Conditions

The SH-SY5Y human neuroblastoma cell line was obtained from the National Cell Bank of Iran (Pasteur Institute, Tehran, Iran) and cultured in RPMI-1640 medium (Gibco, USA) supplemented with 10% (v/v) heat-inactivated fetal bovine serum and 1% (v/v) penicillin–streptomycin (Gibco, USA) at 37°C in a humidified 5% CO_2 atmosphere. Cells were subcultured at approximately 80% confluency using 0.25% trypsin–EDTA and used between passages 15 and 25. No chemical differentiation step was included in the reported protocol; experiments therefore used proliferative/undifferentiated SH-SY5Y cells. Procedures were conducted at the Cell Culture Laboratory, College of Medicine, University of Babylon, Iraq (September 2025–April 2026).

Chemicals and Reagents

Corticosterone (CORT; ≥98% purity; Sigma-Aldrich, Germany) was dissolved in absolute ethanol (100 mM stock; final ethanol ≤0.1% v/v). Hydrogen peroxide (H_2O_2; 30% w/w; Sigma-Aldrich) was freshly diluted in serum-free medium before each experiment. Fluoxetine hydrochloride (≥98%; Sigma-Aldrich) was dissolved in DMSO (10 mM stock; final DMSO ≤0.1% v/v). Vehicle controls containing equivalent solvent concentrations were included in all experiments. MTT,

DTNB, TBA, TCA, and reduced GSH standard were purchased from Sigma-Aldrich.

Establishment of the Dual-Hit Stress Model

Cells were seeded at 1×10^4 cells/well in 96-well plates and allowed to adhere for 24 h. Concentration–response curves were established by exposing cells to CORT (100–500 µM) or H_2O_2 (50–300 µM) for 24 h, with viability assessed by MTT assay. CORT produced a reported viability reduction from 100 µM onward (maximal at 400 µM; mean difference 69.63%, 95% CI 52.71–86.54, $p<0.0001$), and H_2O_2 produced a reported reduction from 100 µM (maximal at 300 µM; mean difference 85.88%, 95% CI 66.05–105.7, $p<0.0001$). For the combined condition, CORT and H_2O_2 were added concurrently to the same wells at 100 µM each and maintained together for 24 h. This condition produced a greater observed mean reduction in viability than either stressor alone and was selected to permit detection of treatment-associated changes; because a CORT × H_2O_2 interaction was not tested, the response is not described as synergistic.

Fluoxetine and Photobiomodulation Dose–Response Screening

Fluoxetine (0.1–50 µM) was screened in CORT/H_2O_2-stressed cells; 1 µM produced the largest reported viability rescue (mean difference 69.42% versus stress, $p<0.0001$), while concentrations ≥10 µM showed diminishing efficacy. Accordingly, 1 µM was selected as the working concentration. PBM was delivered using an 808 nm continuous-wave GaAlAs diode laser (Dragon Laser, China; output power 50 mW; beam area at target 0.2 cm²; irradiance 250 mW/cm²). The probe was positioned perpendicularly above the plate with the lid removed in a darkened environment. Nominal surface fluence was calculated as irradiance × exposure time. Exposure durations of 10–240 s therefore corresponded to 2.5–60 J/cm²; specifically, 40 s corresponded to 10 J/cm² and 240 s to 60 J/cm². A biphasic viability response was observed, with 40 s producing the largest rescue and 240 s producing phototoxicity in the original exploratory comparison ($p=0.0013$). The 40 s exposure (2.0 J radiant energy; nominal surface fluence 10 J/cm²) was selected for subsequent experiments. Safety of fluoxetine and the selected PBM condition was evaluated in unstressed cells [12]. Laser parameters and corrected calculations are summarised in Table 1.

Treatment Protocols

Three timing protocols were employed: (i) pre-treatment, in which interventions were administered 24 h before the combined stress exposure; (ii) co-treatment, in which interventions were applied during the 24 h combined stress exposure; and (iii) post-treatment, in which interventions were administered for 24 h after stress removal and medium replacement. Fluoxetine (1 µM), PBM (40 s; nominal 10 J/cm²), and their combined administration were examined in each protocol. For combined-intervention groups, PBM was delivered within 5 min of fluoxetine addition. Each condition comprised at least four technical wells within an experiment, and experiments were independently repeated at least three times. A separately performed experiment/culture batch represents the biological level of replication, whereas wells within that experiment are technical subsamples.

Table 1. 808 nm photobiomodulation parameters and corrected nominal dosimetry.

Parameter	Value
Laser type	GaAlAs diode laser
Wavelength	808 nm
Emission mode	Continuous wave (CW)
Output power	50 mW
Beam area at target	0.2 cm²
Irradiance (power density)	250 mW/cm²
Exposure duration (selected)	40 s
Nominal surface fluence (selected)	10 J/cm² (250 mW/cm² × 40 s)
Radiant energy (selected)	2.0 J (50 mW × 40 s)
Screened exposure range	10–240 s (nominal 2.5–60 J/cm²)
Fluence calculation	Irradiance × exposure time

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Biochemical Assays

Cell viability was quantified by the MTT assayv [13]: Cells were incubated with 0.5 mg/mL MTT for 4 h at 37°C; formazan crystals were dissolved in DMSO, and absorbance was measured at 570 nm (BioTek ELx800, USA). Lipid peroxidation was assessed by the TBARS method: lysates were heated with TBA/TCA reagent at 95°C for 30 min, and MDA-equivalent absorbance was measured at 535 nm ($\varepsilon = 1.56\times10^5\ M^{-1}\ cm^{-1}$). Reduced glutathione was measured by the DTNB method: deproteinised supernatants were reacted with Ellman's reagent in phosphate buffer (pH 8.0), and TNB absorbance was recorded at 412 nm against a standard curve (0–100 µM). IL-6 was quantified by sandwich ELISA (Elabscience; catalogue no. E-EL-H6156) according to the manufacturer's protocol, with absorbance at 450 nm; assay sensitivity was <1.0 pg/mL and the reported coefficient of variation was <10%. The retained methods and analysis summary do not document normalisation of MDA, GSH, or IL-6 to total protein, viable cell number, or another denominator.

Statistical Analysis

Data are presented as mean ± SD from at least three independently repeated experiments, as documented in the retained analysis summary. Analyses were performed using GraphPad Prism (v10.0.2, USA), and normality was assessed using the Shapiro–Wilk test. The reported p-values originated from exploratory one-way ANOVA with Dunnett's test (treatment versus stress control) or Šídák's test (pre-specified pairwise comparisons), with two-tailed $p<0.05$. Technical wells are subsamples and should be averaged within each independent experiment before inferential analysis; however, the retained summary did not permit verification of endpoint-specific aggregation or exact biological n. Because the design includes fluoxetine, PBM, and treatment timing, the original one-way analyses do not estimate factorial main effects or fluoxetine × PBM and treatment × timing interactions. Accordingly, the reported comparisons are interpreted as exploratory, no statistical interaction or synergy is claimed, and no new interaction p values were generated. A confirmatory analysis requires replicate-level data and should use a 2 × 2 CORT × H_2O_2 model for dual-hit validation and a fluoxetine × PBM × timing factorial ANOVA or mixed-effects model with independent experiment included as a blocking/random factor for treatment experiments. Where available, mean differences and 95% confidence intervals are retained.

Results

Validation of the combined cellular stress condition (Fig. 1). CORT and H_2O_2 alone were associated with viabilities of 85.59 ± 4.97% (p=0.0340) and 82.94 ± 4.97% (p=0.0129) of control, respectively, in the original exploratory comparisons. Concurrent CORT/H_2O_2 exposure was associated with a lower mean viability of 59.59 ± 4.97% ($p<0.0001$ versus control). Although the combined condition produced a greater observed reduction than either stressor alone, a CORT × H_2O_2 interaction was not tested and the finding is not interpreted as synergistic

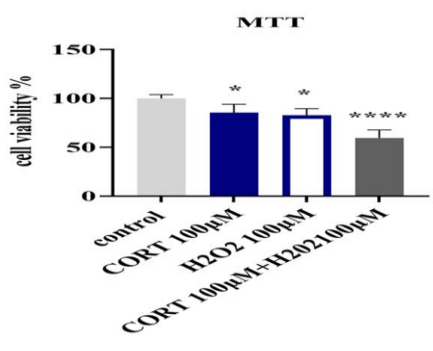

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Figure 1. Effect of CORT (100 µM), H_2O_2 (100 µM), and concurrent CORT/H_2O_2 exposure on SH-SY5Y cell viability measured by MTT. Bars represent mean ± SD from at least three independent experiments, each containing at least four technical wells. Symbols reproduce the original exploratory one-way comparisons; no CORT × H_2O_2 interaction was tested.

Cell viability across treatment protocols (Fig. 2). In the original exploratory comparisons, stressed cells showed lower viability than control (43.40% versus 93.84%; $p<0.0001$). Flx-Co and Flx-Post were associated with higher viability than stress (92.38% and 96.58%; both $p<0.0001$), whereas Flx-Pre-was not (p=0.2812). PBM-Co and PBM-Post were also associated with higher viability (107.3% and 91.04%; both $p<0.0001$), whereas PBM-Pre-was not. The combined-intervention groups showed means of

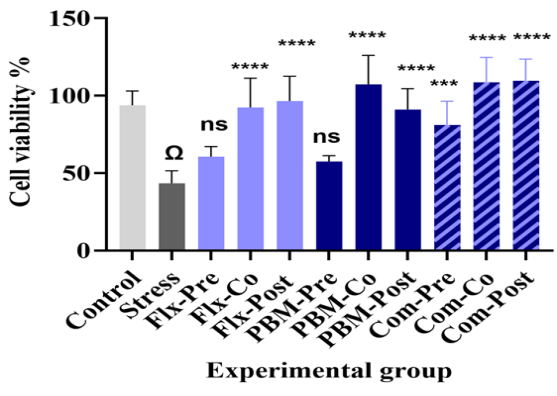

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Figure 2. Cell viability following fluoxetine, PBM, and combined-intervention pre-, co-, and post-treatment protocols in CORT/H_2O_2-stressed SH-SY5Y cells. Bars represent mean ± SD from at least three independent experiments, each containing at least four technical wells. Significance symbols reproduce original exploratory comparisons versus the indicated control; factorial interactions were not tested.

81.18% for Com-Pre (p=0.0006), 108.6% for Com-Co ($p<0.0001$), and 109.7% for Com-Post ($p<0.0001$) relative to the stress comparison. These group-wise results do not establish fluoxetine × PBM or treatment × timing interactions.

MDA concentrations (Fig. 3). In the original exploratory analysis, stress was associated with a higher MDA concentration than control (15.67 versus 8.127 µM; $p<0.0001$). Flx-Co, Flx-Post, all PBM timings, and all combined-intervention timings showed lower MDA than stress (reported p range 0.0485 to <0.0001), with Com-Co showing a mean near the control value.

GSH concentrations (Fig. 4). Stress was associated with a lower GSH concentration than control in the original exploratory analysis (29.30 versus 53.63 µM;

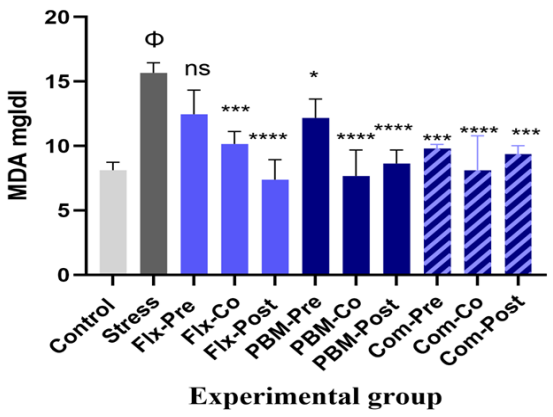

Figure 3. Assay-derived MDA concentrations following treatment protocols. Values are reported as µM in the retained analysis summary; the "mg/dl" wording in the embedded source-figure y-axis is a legacy labelling inconsistency. Bars represent mean ± SD from at least three independent experiments, each containing at least four technical wells. Concentrations were not documented as protein- or cell-normalised, and symbols reproduce original exploratory comparisons.

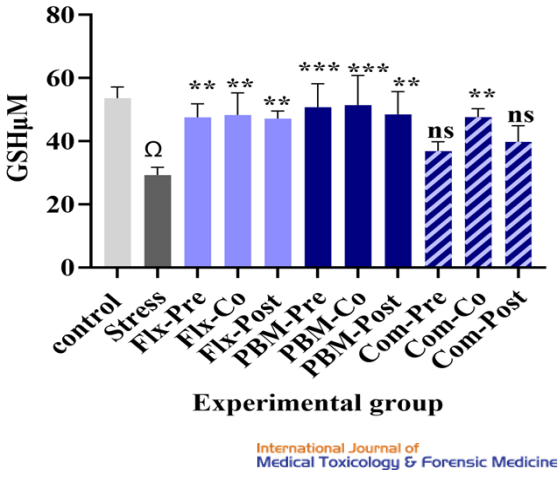

Figure 4. Assay-derived GSH concentrations following treatment protocols. Bars represent mean ± SD from at least three independent experiments, each containing at least four technical wells. Concentrations were not documented as protein- or cell-normalised, and symbols reproduce original exploratory comparisons; factorial interactions were not tested.

p=0.0002). All fluoxetine and PBM timing groups showed higher GSH than stress (reported p range 0.0040 to ≤0.0007). Among the combined-intervention groups, only Com-Co showed a statistically significant exploratory comparison with stress (47.65 µM; p=0.0038).

IL-6 concentrations (Fig. 5). Stress was associated with a higher IL-6 concentration than control in the original exploratory analysis (3.969 versus 2.465 pg/mL;

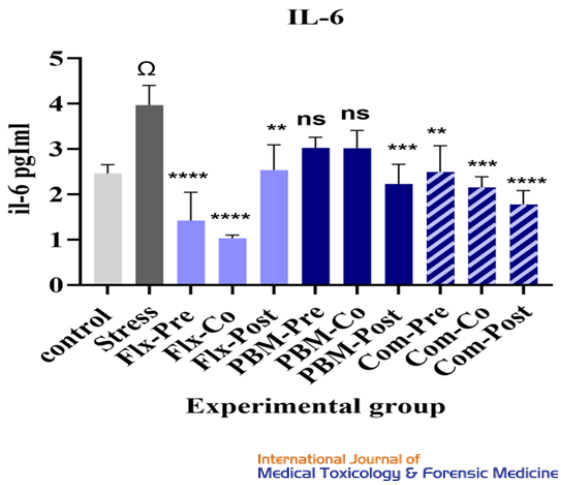

Figure 5. Assay-derived IL-6 concentrations following treatment protocols. Bars represent mean ± SD from at least three independent experiments, each containing at least four technical wells. Concentrations were not documented as protein- or cell-normalised, and symbols reproduce original exploratory comparisons; factorial interactions were not tested.

p=0.0013). All fluoxetine timings and PBM-Post showed lower IL-6 than stress, whereas PBM-Pre and PBM-Co did not. All combined-intervention timings showed lower IL-6 than stress, and Com-Post had the lowest observed mean (1.777 pg/mL; p<0.0001). These group-wise comparisons do not establish an interaction between fluoxetine, PBM, and timing.

Discussion

This study used proliferative/undifferentiated SH-SY5Y human neuroblastoma cells as an acute cellular stress system. SH-SY5Y cells are widely used in neurobiological and toxicological research, but their phenotype depends on differentiation state and they do not reproduce the cellular diversity, circuitry, endocrine regulation, or clinical features of major depressive disorder [14,15]. Concurrent CORT/H_2O_2 exposure produced a greater observed reduction in viability than either stressor alone. This pattern is compatible with the coexistence of glucocorticoid- and oxidant-related stress described in the literature [16–19], but it cannot be designated synergistic because a CORT × H_2O_2 interaction was not estimated.

Fluoxetine at 1 µM was associated with more favorable viability outcomes during co- and post-treatment than during pretreatment in the reported exploratory comparisons, a concentration broadly consistent with prior SH-SY5Y work [20]. Literature from other models suggests that antidepressant binding to TrkB, altered BDNF-related signaling, autophagic clearance, and PI3K/Akt-related survival responses could be relevant to cellular resilience [9, 21, 22]. However, TrkB, BDNF, autophagy, PI3K/Akt activity, apoptosis, and mitochondrial clearance were not

measured here. These mechanisms therefore remain hypotheses and cannot explain the timing pattern demonstrated by the present data.

The PBM screening showed a biphasic viability pattern, consistent in general with dose-dependent responses reported in PBM literature [12, 23]. Corrected dosimetry identifies the selected 40 s exposure as a nominal surface fluence of 10 J/cm², not 3.3 J/cm², and the 240 s exposure as 60 J/cm², not 20 J/cm². These values follow directly from 250 mW/cm² multiplied by exposure time. The nominal calculation does not substitute for direct irradiance mapping at the cell plane or assessment of well-to-well optical variation. Cytochrome c oxidase activity, ATP production, mitochondrial membrane potential, and ROS signaling have been proposed as PBM-responsive processes in other systems [10, 23, 24], but none was measured in this study.

Several combined-intervention groups showed favorable mean responses, particularly Com-Co for viability and GSH and Com-Post for IL-6. These descriptive patterns do not demonstrate that combined treatment was superior to both monotherapies across all endpoints, and they do not establish pharmacological synergy because fluoxetine × PBM and treatment × timing interactions were not tested. Prior studies suggest possible fluoxetine-related effects on TrkB/BDNF and inflammatory signaling and possible PBM-related effects on mitochondrial and NF-κB-associated pathways [9, 10, 25–28]. In the present study, however, no signaling protein, transcription factor, inflammasome component, mitochondrial endpoint, or receptor was measured. The observed IL-6 differences should therefore be interpreted as endpoint changes rather than evidence for NF-κB, NLRP3, or another specific pathway.

The lower GSH and higher MDA observed after combined stress are consistent with disturbed cellular redox balance. GSH is central to neural antioxidant defense, and redox-modulating approaches have been discussed in neuropsychiatric research [29,30]. Antioxidant effects of fluoxetine have also been reported in other experimental systems [31]. Nevertheless, the present MDA, GSH, and IL-6 values were not documented as normalized to total protein, cell number, or viable-cell abundance. Because treatment materially altered MTT viability, part of the apparent biochemical difference could reflect variation in cell abundance rather than a change per cell. The current data therefore support only cautious, assay-level interpretation.

Clinical and preclinical literature provides a rationale for further investigation but does not validate clinical efficacy of the present cellular findings. Fluoxetine has been associated with changes in inflammatory markers in clinical studies [32], and pilot and review literature has examined transcranial PBM for mood disorders [33, 34]. However, exposure of cultured neuroblastoma cells to an 808 nm beam is not equivalent to transcranial delivery, and the present experiment cannot address tissue penetration, pharmacokinetics, neural circuitry, adverse effects, or patient outcomes. Any combined fluoxetine–PBM application therefore requires independent mechanistic, animal, dosimetric, and controlled clinical evaluation, including careful consideration of SSRI tolerability [35].

This study has several important limitations. It used an immortalized, proliferative/undifferentiated SH-SY5Y monoculture exposed acutely to two stressors and therefore represents a cellular stress system rather than major depressive disorder. The endpoint panel was limited to MTT, MDA, GSH, and IL-6; proposed TrkB/BDNF, Nrf2, CREB, PI3K/Akt, NF-κB, inflammasome, apoptosis, and mitochondrial mechanisms were not measured. The retained analysis summary contained exploratory one-way comparisons but not the replicate-level data required for factorial or mixed-effects reanalysis; exact endpoint-specific biological n and technical-well aggregation could not be reconstructed. MDA, GSH, and IL-6 were not documented as normalized to protein or cell number, so group differences may partly reflect cell abundance. PBM fluence was calculated nominally from reported power density and duration rather than verified by irradiance mapping at the cell layer.

Conclusion

In CORT/H_2O_2-stressed SH-SY5Y cells, fluoxetine and 808 nm PBM were associated with timing-dependent changes in viability, MDA, GSH, and IL-6, with co- and post-treatment showing more favorable exploratory patterns than pretreatment for several endpoints. The corrected nominal PBM fluence for the selected 40 s exposure is 10 J/cm². Because factorial interactions were not tested, biochemical endpoints were not documented as normalized, and the model is an acute undifferentiated neuroblastoma-cell system, the findings are hypothesis-generating and do not establish synergy, mechanism, or clinical benefit. Replicate-level confirmatory analysis and mechanistic validation are required.

Ethical Approval

The institutional experimental procedures were approved by the Central Biological Ethics Committee of the College of Medicine, University of Babylon (no. 4-30/7/11/2025). The study used a commercially

sourced immortalised cell line and involved no human participants or animals; informed consent was not applicable.

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Conflicts of Interest

The authors report there are no competing interests to declare.

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