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Effects of curcumin and its derivatives on a glioma cell line

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ABSTRACT

Glioblastomas are highly invasive brain tumors associated with oxidative stress (OS) and chronic inflammation. Curcumin (CUR), the principal bioactive compound of *Curcuma longa*, as well as its natural analogues demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC), exhibit promising therapeutic properties.

The aim of this study was to evaluate the antioxidant effects of CUR, DMC, and BDMC in an *in vitro* model using the LN229 glioma cell line.

LN229 glioblastoma cells and MO3.13 cells as a non-tumor control were cultured in Dulbecco's Modified Eagle Medium (DMEM) under standard conditions. Cells were treated with CUR, DMC, and BDMC for 24 h and 48 h at concentrations selected based on MTT assay results. Antioxidant capacity was assessed using the ferric reducing antioxidant power (FRAP) assay, while lipid peroxidation and protein oxidation were evaluated by measuring malondialdehyde (MDA) and protein carbonyl group levels, respectively, in cell lysates.

Curcumin, demethoxycurcumin, and bisdemethoxycurcumin reduced LN229 cell viability in a time- and dose-dependent manner. Curcumin exhibited the strongest antioxidant activity, significantly decreasing MDA levels and protein carbonyl content ($p < 0.001$). Demethoxycurcumin was the most effective compound in reducing protein oxidation after 48 h, whereas bisdemethoxycurcumin increased MDA levels, suggesting a potential pro-oxidative effect. The FRAP assay confirmed a sustained antioxidant capacity of all compounds, particularly at higher concentrations.

In conclusion, curcumin and its derivatives demonstrated both antioxidant and cytotoxic activities in a time- and dose-dependent manner. Among the tested compounds, curcumin showed the most stable and long-lasting antioxidant and cytotoxic effects, indicating its potential therapeutic value in mitigating oxidative stress–related damage in glioma cells.

INTRODUCTION

Glioblastoma is a term commonly used to describe malignant tumors arising from glial cells, including oligodendrocytes, astrocytes, and ependymal cells. Together with neurons, glial cells constitute the fundamental structural and functional components of nervous tissue. Unlike neurons, glial cells retain the ability to undergo cell division throughout life, which increases the risk of neoplastic transformation [1]. The etiology of glioma development is multifactorial and remains under investigation; proposed risk factors include genetic predisposition, lifestyle, chronic stress, poor dietary habits, and exposure to both ionizing and non-ionizing radiation (e.g., mobile phone use) [2]. Many of these factors can induce a persistent inflammatory state, thereby creating a microenvironment favorable for the development of chronic diseases and cancer [3].

During inflammation, leukocytes and mast cells are recruited to sites of tissue injury, initiating a process known as the respiratory burst. This process leads to the generation of reactive oxygen species (ROS), which is further amplified by inflammatory mediators such as cytokines and chemokines [4]. When transient, ROS production is physiologically beneficial, as ROS participate in pathogen elimination, regulation of cell proliferation, and removal of damaged cells. However, under conditions of chronic inflammation, excessive ROS generation can result in oxidative damage to proteins, lipids, and deoxyribonucleic acid (DNA), thereby destabilizing cellular structures and promoting a microenvironment conducive to tumor cell proliferation [5].

Oxidative stress (OS) is defined as a state in which the balance between ROS production and the capacity of

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antioxidant defense systems to neutralize them is disrupted, leading to cellular and tissue damage [6]. The most biologically relevant ROS in the human body include the superoxide anion radical ($O_2^{\bullet -}$), hydroperoxyl radical ($HO_2^{\bullet}$), hydroxyl radical ($HO^{\bullet}$), and hydrogen peroxide (H_2O_2) [7]. The brain is particularly susceptible to oxidative stress due to its high oxygen consumption and relatively limited antioxidant capacity, which contributes to increased vulnerability to neurodegeneration and tumor development [8].

Antioxidants counteract the harmful effects of ROS by reducing their oxidative potential and converting them into less reactive or inactive forms. The antioxidant defense system operates through two complementary mechanisms: enzymatic and non-enzymatic. Enzymatic antioxidants catalyze reactions that either prevent ROS formation or facilitate their removal [9]. Major endogenous antioxidant enzymes in the brain include catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione S-transferase (GST) [8]. The non-enzymatic antioxidant system consists of radical scavengers that donate electrons to neutralize ROS, including exogenous compounds such as vitamins C, E, and A, coenzyme Q10, and flavonoids, as well as endogenous molecules such as glutathione [9]. An imbalance between ROS generation and antioxidant defense promotes carcinogenesis, and reduced activities of enzymes such as catalase and SOD have been associated with oxidative DNA damage and malignant transformation [7].

Curcumin (CUR) is a biologically active polyphenolic compound derived from *Curcuma longa* (turmeric), a plant belonging to the Zingiberaceae family and widely cultivated in India and other regions of Southeast Asia [5]. The characteristic yellow-orange color of turmeric and many of its health-promoting effects are primarily attributed to curcumin [10]. Although chemically stable, curcumin is highly hydrophobic and exhibits poor aqueous solubility, which markedly limits its absorption and bioavailability [11]. These limitations can be partially overcome by co-administration with dietary fats (e.g., olive oil, avocado, nuts) or with piperine, a bioactive component of black pepper that significantly enhances curcumin bioavailability. Numerous pharmacological properties of curcumin have been documented, including anticancer, anti-inflammatory, neuroprotective, and pro-apoptotic effects in cancer cells [5].

The treatment of central nervous system tumors, such as gliomas, remains challenging primarily because therapeutic agents must cross the blood-brain barrier. Curcumin has been shown to penetrate the blood-brain barrier, making it a promising candidate for brain tumor therapy [5]. Curcumin belongs to the curcuminoid group of bioactive turmeric constituents, accounting for approximately 77% of total curcuminoids, followed by demethoxycurcumin (DMC, ~17%) and bisdemethoxycurcumin (BDMC, ~3%) [10]. Both DMC and BDMC exhibit greater chemical stability than curcumin [12]. Therefore, the aim of this study was to evaluate the antioxidant properties of curcumin, demethoxycurcumin, and bisdemethoxycurcumin in an in vitro model using the LN229 glioma cell line.

MATERIALS AND METHODS

Cell culture

The experiments were performed using the LN229 human glioblastoma cell line (CRL-2611, ATCC). The MO3.13 human oligodendrocytic (glial) cell line (CELLutions Biosystems Inc.) was used as a non-tumor control for cell proliferation and cytotoxicity assessments. Both cell lines were cultured in 75 cm² culture flasks under standard conditions (37°C, 5% CO_2) in Dulbecco's Modified Eagle Medium (DMEM) supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and fetal bovine serum (FBS, 5%).

Cells were passaged every third day using 0.25% trypsin solution, and cell density was maintained at 2-4 × 10^4 cells/mL. For the MTT assay, cells were seeded into 96-well plates and incubated for 24 h and 48 h. Curcumin (CUR), demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) were tested at concentrations ranging from 0.05 to 150 µM. For oxidative stress analyses, cells were seeded into 25 cm² flasks and treated with curcumin and its derivatives at concentrations selected based on MTT assay results (Table 1).

Table 1. Concentrations of curcumin and its derivatives used to stimulate LN229 cell cultures after 24 h and 48 h

In 24 h culture:	In 48 h culture:
50 µM curcumin 46,37 µM curcumin (IC_{50}) 40 µM curcumin	30 µM curcumin 20,11 µM curcumin (IC_{50}) 15 µM curcumin
40 µM demethoxycurcumin 38,26 µM demethoxycurcumin (IC_{50}) 30 µM demethoxycurcumin	30 µM demethoxycurcumin 23,67 µM demethoxycurcumin (IC_{50}) 20 µM demethoxycurcumin
15 µM bisdemethoxycurcumin 13,15 µM bisdemethoxycurcumin (IC_{50}) 10 µM bisdemethoxycurcumin	25 µM bisdemethoxycurcumin 19,83 µM bisdemethoxycurcumin (IC_{50}) 15 µM bisdemethoxycurcumin

Cell lysate preparation

After 24 h and 48 h of incubation, culture media were collected, frozen at -80°C, and stored for further analysis. Adherent cells were washed and lysed with 1 mL of cold lysis buffer consisting of 5 mM potassium phosphate (pH 7.8), 0.9% sodium chloride, and 0.1% glucose. Culture flasks were placed on ice and subjected to sonication to disrupt the cells and release intracellular contents. After 30 min, lysates were transferred to microcentrifuge tubes and centrifuged at 3000 rpm for 15 min. The supernatants were collected and stored at -80°C until further assays.

MTT cytotoxicity assay

Cell viability and cytotoxicity were assessed using the MTT assay (Cell Proliferation Kit MTT, Sigma-Aldrich). This method is based on the ability of mitochondrial dehydrogenases in metabolically active cells to reduce the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to insoluble formazan crystals with a purple-blue coloration. This reduction occurs only in cells with intact mitochondrial membranes; therefore, the amount of formazan produced reflects cellular metabolic activity.

LN229 and MO3.13 cells were seeded into 96-well plates and incubated with the MTT reagent for 4 h. The resulting formazan crystals were dissolved, and absorbance was measured spectrophotometrically using an ELISA microplate reader to determine cell viability.

Protein quantification in cell lysates

Total protein concentration was determined using the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific). This colorimetric assay is based on the reduction of Cu^{2+} to Cu^{+} by proteins under alkaline conditions (biuret reaction), followed by the formation of a purple-colored complex between bicinchoninic acid (BCA) and Cu^{+} ions. The absorbance of the complex was measured at 562 nm and was directly proportional to protein concentration.

Standards were prepared using bovine serum albumin (BSA). A volume of 25 µL of standards or cell lysates was added to a 96-well plate, followed by 200 µL of working reagent. Plates were incubated at 37°C for 30 min, and absorbance was measured using an ELISA microplate reader (BioTek, EPOCH).

Oxidative stress parameters

FRAP assay

The ferric reducing antioxidant power (FRAP) assay was used to assess total antioxidant capacity by measuring the reduction of Fe^{3+} ions complexed with 2,4,6-tris(2-pyridyl)-1,3,5-triazine (TPTZ) to Fe^{2+}–TPTZ, resulting in an intense blue complex measured at 593 nm. The assay was performed according to the method described by Benzie and Strain [13].

Briefly, 10 µL of standard solutions or cell lysates and 20 µL of distilled water were added to each well of a 96-well plate. The FRAP working reagent was prepared by mixing 20 mL acetate buffer, 2 mL TPTZ solution, and 2 mL $FeCl_3$ solution immediately before use. Subsequently, 200 µL of the working reagent was added to each well, and plates were incubated at 37°C for 30 min. Absorbance was measured immediately after incubation and again after 10 min using an ELISA plate reader (BioTek, EPOCH). Results were expressed as µmol Fe^{2+}/mg protein [13].

Lipid peroxidation **(MDA)**

Lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels, a major end product of polyunsaturated fatty acid oxidation. The assay was performed according to the method described by Ledwożyw *et al.* [14].

Briefly, 80 µL of sample or standard was mixed with 400 µL of trichloroacetic acid (TCA) and incubated for 15 min at room temperature. Subsequently, 240 µL of thiobarbituric acid (TBA) solution was added, and samples were heated for 30 min. After cooling, 640 µL of butanol was added, and samples were vortexed for 3 min and centrifuged at 1500 rpm for 10 min. The butanol phase (200 µL) was transferred to a 96-well plate, and absorbance was measured at 532 nm using an ELISA microplate reader (BioTek, EPOCH). Results were expressed as nmol MDA/mg protein [16].

Protein carbonyl groups

Protein oxidation was evaluated by measuring protein carbonyl group formation using the method described by Mesquita *et al.* [15]. This assay is based on the reaction of protein carbonyl groups with 2,4-dinitrophenylhydrazine (DNPH).

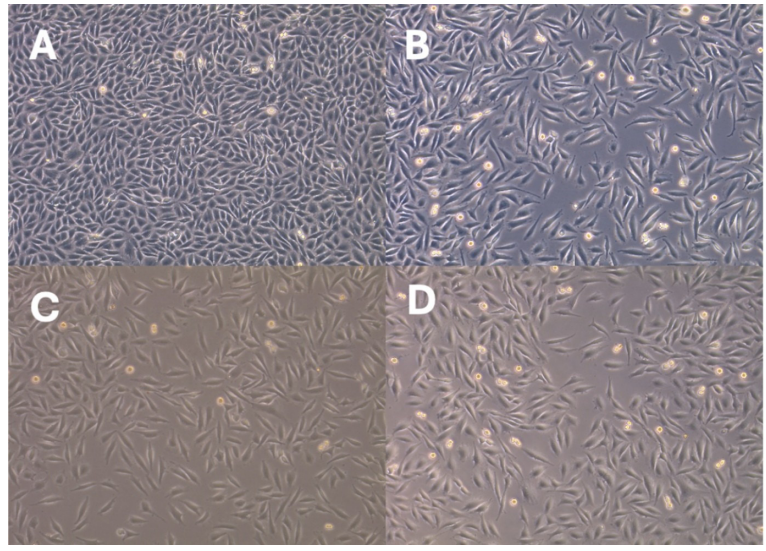
Briefly, 100 µL of DNPH solution (10 mM in 0.5 M H_3PO_4) and 100 µL of sample were added to each well of a 96-well plate and incubated for 10 min. Subsequently, 50 µL of 6 M NaOH was added, and plates were incubated for an additional 10 min in the dark. Absorbance was measured at 450 nm using an ELISA microplate reader (BioTek, EPOCH). Blank controls consisted of DNPH mixed with distilled water. Protein carbonyl content was calculated using the molar extinction coefficient (22.308 $M^{-1} \cdot cm^{-1}$) and expressed as nmol/mg protein [15].

Statistical analysis

Statistical analyses were performed using GraphPad Prism software version 8.0.1. Data were analyzed using one-way analysis of variance (one-way ANOVA) followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$, $p < 0.01$, and $p < 0.001$.

RESULTS AND DISCUSSION

Control cells (Fig. 1A) exhibited typical morphology of normal glial cells, characterized by an elongated shape and evenly distributed nuclei. Cells treated with curcumin (Fig. 1B) showed dispersion and partial rounding, indicating early stages of cell death. Treatment with demethoxycurcumin (Fig. 1C) resulted in a reduced cell number and irregular cell morphology. Bisdemethoxycurcumin (Fig. 1D) also induced morphological alterations consistent with cell death, including changes in cell shape and detachment from the culture surface.



(A) Untreated LN229 control cells;
(B) LN229 cells treated with curcumin at 46.37 µM (IC_{50});
(C) LN229 cells treated with demethoxycurcumin at 38.26 µM (IC_{50});
(D) LN229 cells treated with bisdemethoxycurcumin at 13.15 µM (IC_{50})

Figure 1. Morphological changes in LN229 cells after 24 h of treatment

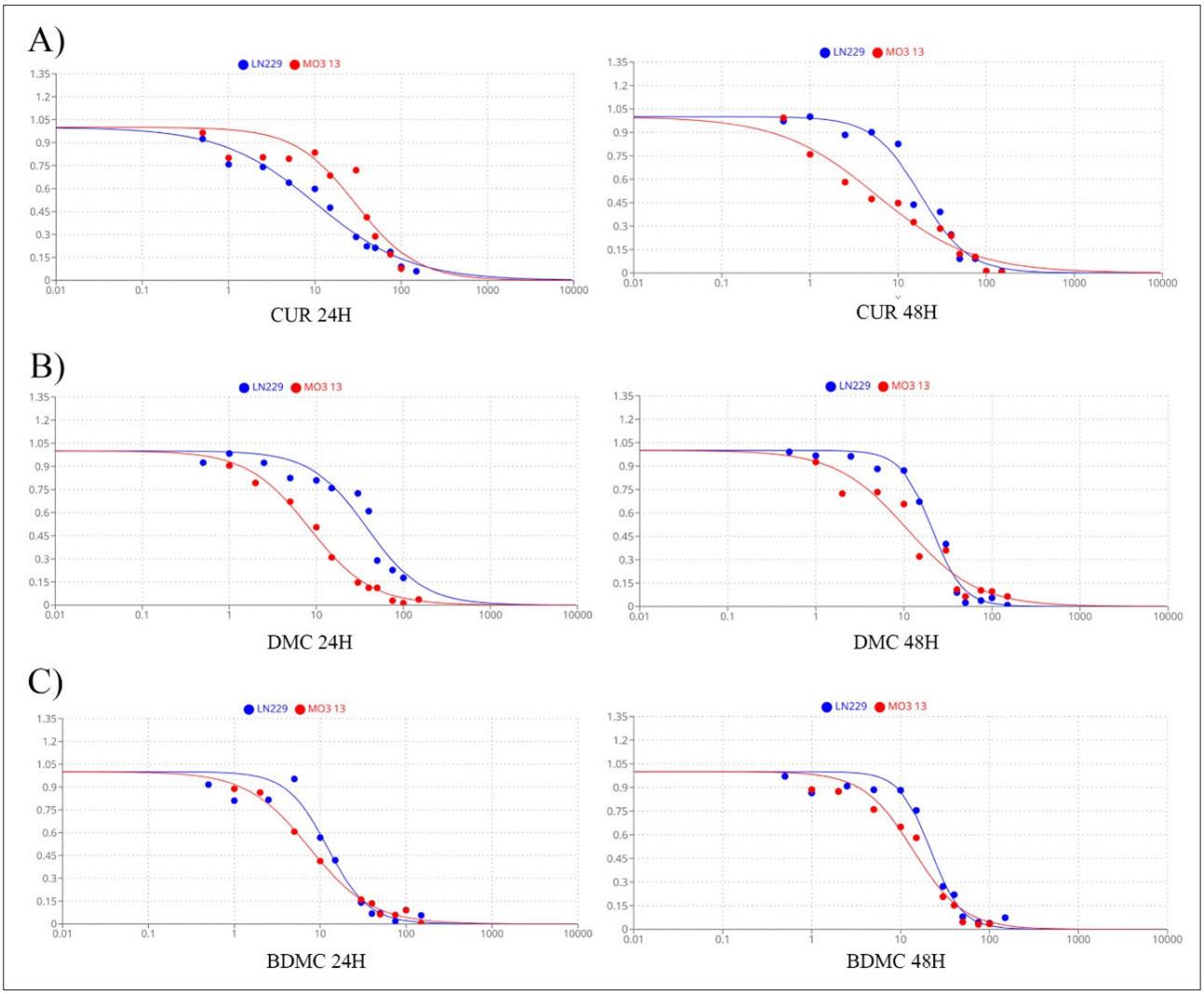
In LN229 cells treated with curcumin for 24 h, the viability curve decreased more rapidly than in the MO3.13 control cell line. After 48 h, this trend was reversed, with the MO3.13 cells showing greater sensitivity to treatment. The IC_{50} value for curcumin in LN229 cells was 46.37 μM after 24 h and decreased to 20.11 μM after 48 h. In contrast, for MO3.13 cells, the IC_{50} value was 62.30 μM at 24 h and markedly decreased to 5.64 μM after 48 h.

For demethoxycurcumin, the viability curve of MO3.13 cells declined more rapidly than that of LN229 cells at both incubation times. In LN229 cells, the IC_{50} value decreased from 38.26 μM after 24 h to 23.67 μM after 48 h. In contrast, the IC_{50} value for MO3.13 cells was 8.29 μM at 24 h and slightly increased to 10.71 μM after prolonged exposure.

In bisdemethoxycurcumin-treated cells, the IC_{50} value for LN229 cells increased from 13.13 μM at 24 h to 19.83 μM after 48 h. A similar trend was observed in MO3.13 cells, where the IC_{50} value increased from 7.48 μM to 13.93 μM after 48 h of treatment (Fig. 2).

The antioxidant activity of the tested compounds was assessed using the FRAP assay. After 24 h of incubation (Fig. 3A), the highest antioxidant capacity was observed in the control group, whereas treatment with curcumin and its derivatives significantly reduced FRAP values ($p < 0.001$), suggesting that the exposure time was insufficient to elicit a protective antioxidant response. This observation was further supported by results obtained after prolonged incubation. After 48 h (Fig. 3B), a significant increase in Fe^{3+}-reducing capacity was observed for all tested compounds. Notably, bisdemethoxycurcumin at the highest concentration (25 μM) markedly exceeded control values ($p < 0.001$), with a statistically significant increase also observed at 15 μM. In contrast, treatment with demethoxycurcumin resulted in a statistically significant decrease in total antioxidant capacity ($p < 0.05$) (Fig. 3).

In LN229 cells cultured for 24 h, a marked reduction in malondialdehyde (MDA) levels was observed compared with the control group. The statistically significant decrease observed for curcumin ($p < 0.001$) indicates its superior antioxidant capacity relative to its derivatives. This reduction persisted after 48 h of incubation, supporting the long-lasting antioxidant activity of curcumin. In contrast, bisdemethoxycurcumin treatment resulted in increased MDA levels, suggesting potential pro-oxidative activity and a short-term antioxidant response ($p < 0.001$) (Fig. 4).



(A) Curcumin (CUR); (B) Demethoxycurcumin (DMC); (C) Bisdemethoxycurcumin (BDMC).
Dose–response curves were generated based on MTT assay results following 24 h and 48 h of treatment. Blue curves represent LN229 glioma cells, and red curves represent MO3.13 control cells

Figure 2. Cell viability curves for LN229 and MO3.13 cell lines treated with curcumin and its analogues for 24 h and 48 h

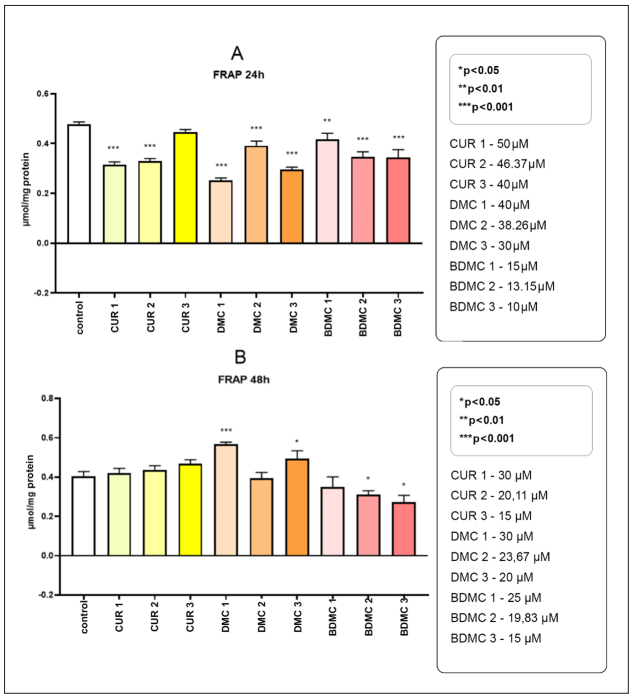


Figure 3. Assessment of antioxidant capacity using the FRAP assay in LN229 cell cultures after 24 h (A) and 48 h (B) of stimulation with curcumin and its derivatives at various concentrations

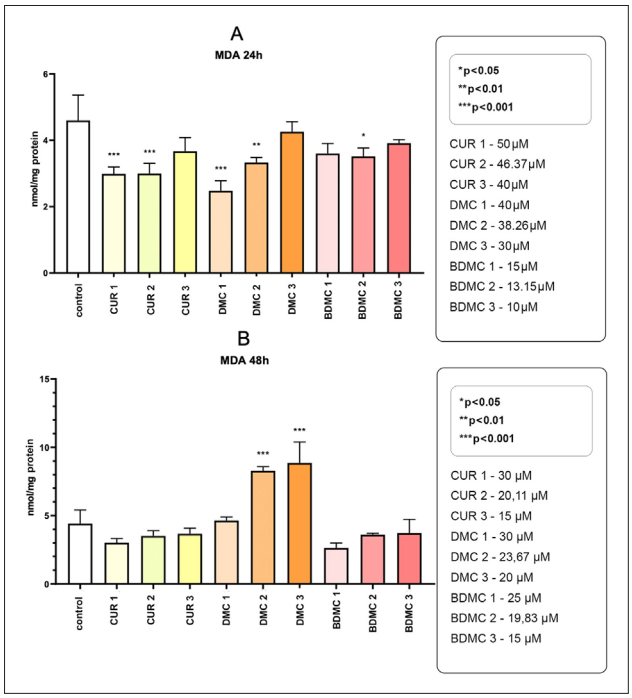


Figure 4. Evaluation of malondialdehyde (MDA) release from LN229 cells after 24 h (A) and 48 h (B) of treatment with curcumin and its derivatives at various concentrations

Protein carbonyl group levels, serving as markers of oxidative protein damage, were significantly reduced after 24 h of treatment with curcumin, demethoxycurcumin, and bisdemethoxycurcumin compared with the control group ($p < 0.001$), confirming their protective effects against oxidative stress. After 48 h, protein carbonyl levels remained decreased, with the lowest values observed for demethoxycurcumin ($p < 0.001$), indicating a sustained antioxidant effect of the tested compounds (Fig. 5).

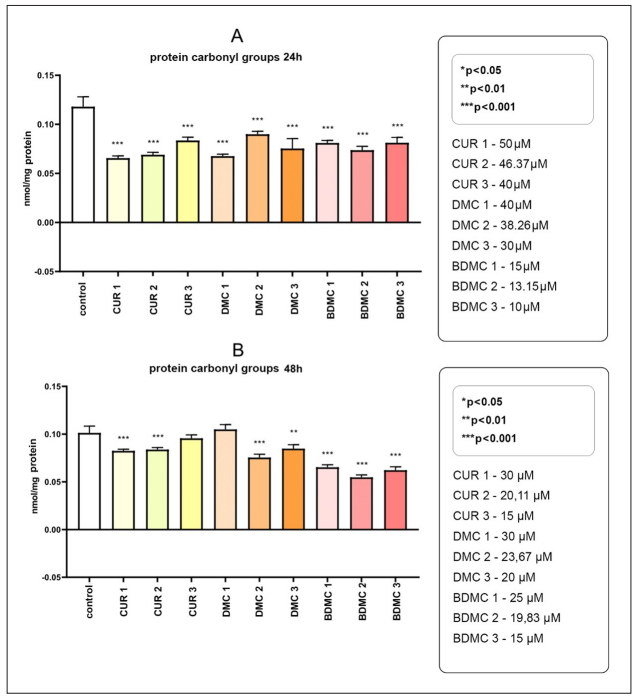


Figure 5. Evaluation of protein carbonyl group levels in LN229 cells after 24 h (A) and 48 h (B) of treatment with curcumin and its derivatives at various concentrations

Previous studies have demonstrated that curcumin can either increase or decrease reactive oxygen species (ROS) levels depending on cellular context and experimental conditions [5]. Curcumin enhances the efficacy of chemotherapy and radiotherapy while protecting healthy tissues and reducing the malignancy of glioma stem cells [16]. Its anticancer activity has been linked to inhibition of the MAPK/ERK signaling pathway, which plays a key role in glioma cell motility, invasiveness, and resistance to chemotherapy. Curcumin has been shown to induce cell cycle arrest, promote apoptosis, and inhibit migration, proliferation, and the G1 to S phase transition in malignant glioma cells in a dose-dependent manner [17]. However, the poor bioavailability of curcumin, resulting from rapid metabolism and systemic elimination, remains a major limitation and a focus of ongoing research [18]. Consequently, curcumin analogues have attracted increasing attention [19].

Studies conducted on LN229 and GBM8401 glioblastoma cells have shown that curcumin and its analogues induce apoptosis, cell cycle arrest, and ROS generation [20]. Sandur *et al.* demonstrated that commercially available mixtures of curcumin and its derivatives exhibit greater biological activity than pure curcumin alone, particularly in the inhibition of nuclear factor kappa B (NF-κB) activation [21]. Although curcumin is the most abundant curcuminoid, each component of the mixture contributes to the overall biological activity, enhancing therapeutic potential through synergistic effects [22].

In the present study, we evaluated the cytotoxic and antioxidant effects of curcumin, demethoxycurcumin, and bisdemethoxycurcumin in the LN229 human glioblastoma cell line. The analysis of oxidative stress-related parameters, including FRAP, MDA, and protein carbonyl content, revealed time- and dose-dependent effects. Curcumin exhibited the most stable and long-lasting antioxidant activity,

while DMC and BDMC also reduced oxidative stress markers. However, prolonged exposure to BDMC increased MDA levels, suggesting possible pro-oxidative effects under specific conditions.

These findings are consistent with previous reports demonstrating the anticancer and antioxidant properties of curcuminoids. Lou *et al.* showed that curcumin and its analogues suppress glioma cell viability by promoting apoptosis, ROS production, and cell cycle arrest, with curcumin exhibiting the highest cytotoxic potential [19]. Burrata *et al.* reported that curcumin protects PC12 cells against protein oxidation, supporting our observation of reduced protein carbonyl content following curcumin treatment [23]. Furthermore, a meta-analysis by Jakubczyk *et al.* demonstrated that curcumin supplementation increases total antioxidant capacity and tends to reduce MDA levels [24].

Overall, our results indicate that curcumin exerts the strongest and most sustained antioxidant and cytotoxic effects among the tested curcuminoids. These properties highlight the therapeutic potential of curcumin and its derivatives in glioblastoma treatment, while also emphasizing the importance of exposure time and compound-specific effects on oxidative stress pathways.

CONCLUSIONS

Analysis of the MTT assay results and the marked decrease in IC_{50} values over time demonstrated that both LN229 and MO3.13 cell lines exhibited increased sensitivity to curcumin after 48 hours of exposure compared to 24 hours. Prolonged exposure enhanced curcumin's ability to reduce cell viability, which may be a relevant factor when considering its potential application in therapeutic strategies.

The observed effects of demethoxycurcumin and bisdemethoxycurcumin indicate that exposure duration plays a critical role in determining their biological activity, with varying responses between different cell lines. This time-dependent behavior should be taken into account when evaluating curcumin derivatives as potential therapeutic agents.

Results of the FRAP assay confirmed the iron-reducing capacity of bisdemethoxycurcumin, supporting its antioxidant properties. Overall, the antioxidant effectiveness of curcumin and its derivatives was more pronounced after 48 hours, demonstrating a clear time-dependent activity.

Analysis of lipid peroxidation revealed that the effects of curcumin and its analogues on MDA levels depend on both concentration and exposure time. Among the tested compounds, curcumin exhibited the greatest stability and the most sustained antioxidant activity. Furthermore, the assessment of protein carbonyl groups showed that curcumin and its derivatives exerted significant protective effects against oxidative protein damage. The persistence of these effects at both 24 and 48 hours indicates long-term efficacy in reducing protein oxidation.

Taken together, these findings suggest that curcumin and its derivatives possess considerable potential for therapeutic applications aimed at mitigating the harmful effects of oxidative stress.

ABBREVIATIONS

CUR – curcumin
DMC – demethoxycurcumin
BDMC – bisdemethoxycurcumin
OS – oxidative stress
LN229 – human glioblastoma cell line
MO3.13 – human oligodendrocyte cell line
DMEM – Dulbecco's Modified Eagle Medium
MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
FRAP – ferric reducing antioxidant power
MDA – malondialdehyde
ROS – reactive oxygen species
CAT – catalase
SOD – superoxide dismutase
GR – glutathione reductase
GPx – glutathione peroxidase
GST – glutathione S-transferase
FBS – fetal bovine serum
BCA – bicinchoninic acid
BSA – bovine serum albumin
TBA – thiobarbituric acid
TCA – trichloroacetic acid
DNPH – 2,4-dinitrophenylhydrazine
ANOVA – analysis of variance
IC_{50} – half maximal inhibitory concentration
MAPK/ERK – extracellular signal-regulated kinase pathway
NF-κB – nuclear factor kappa B
PC12 – rat pheochromocytoma cell line
GBM8401 – human glioblastoma cell line

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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