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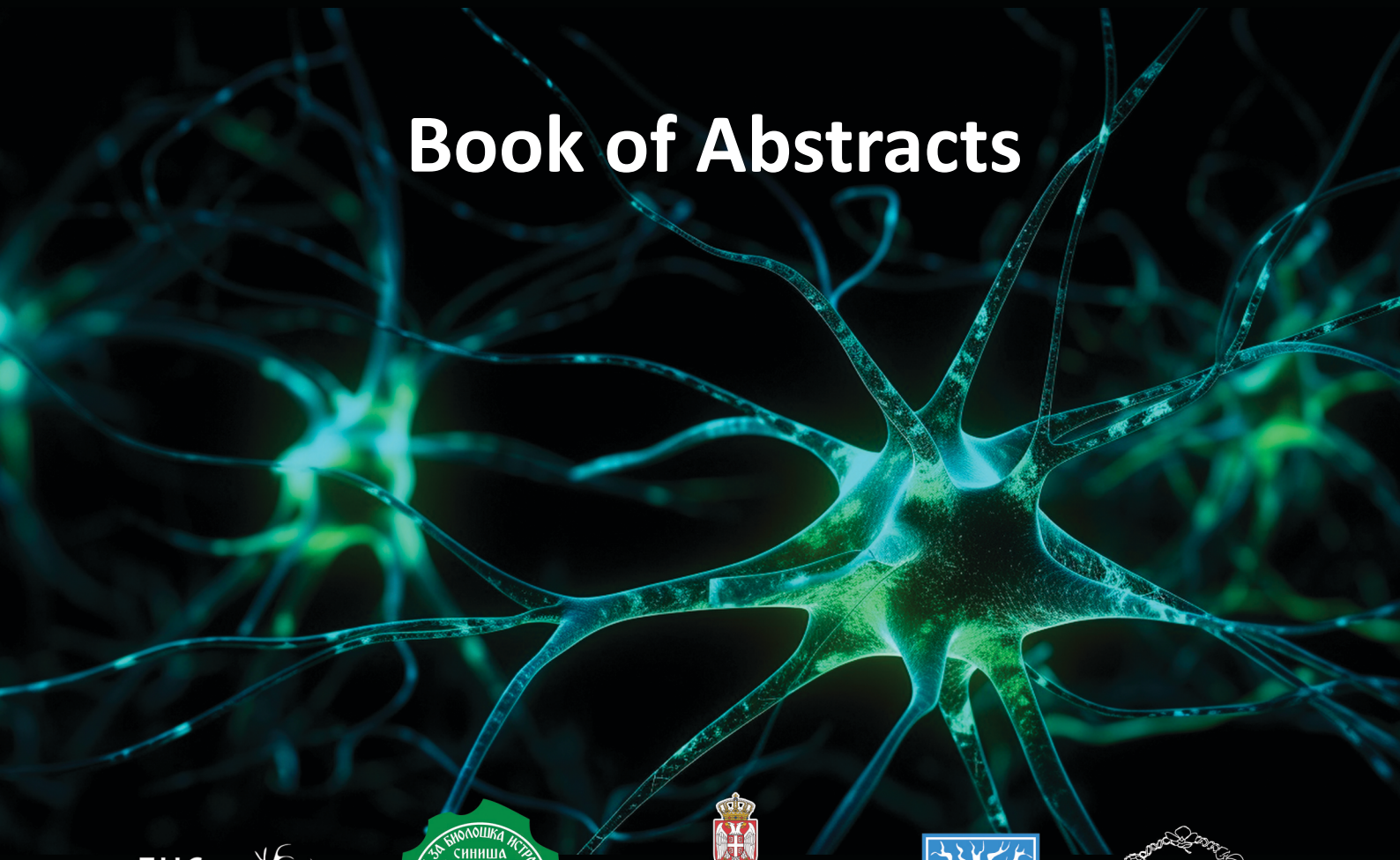

Book of Abstracts

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Evading multidrug resistance in glioblastoma with natural compound sclareol and its novel derivatives

Ema Lupšić [1], Ana Kostić [1], Pavle Stojković [2], Nataša Terzić-Jovanović [3], Miroslav Novaković [3], Paraskev Nedialkov [4], Antoaneta Trendafilova [5], Igor M. Opsenica [2], and Milica Pešić [1]

[1] *Institute for Biological Research "Siniša Stanković" – National Institute of the Republic of Serbia, University of Belgrade, Department of Neurobiology, Belgrade, Serbia*
[2] *University of Belgrade – Faculty of Chemistry, Belgrade, Serbia*
[3] *University of Belgrade - Institute of Chemistry, Technology, and Metallurgy, National Institute of the Republic of Serbia, Belgrade, Serbia*
[4] *Department of Pharmacognosy, Faculty of Pharmacy, Medical University of Sofia, Sofia, Bulgaria*
[5] *Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria*

Background: Glioblastoma is a highly aggressive and resistant brain tumor. P-glycoprotein (P-gp) constitutes the blood-brain barrier and is expressed on the cell membrane of multidrug-resistant (MDR) glioblastoma cells. Our objective was to investigate the anti-glioblastoma effects of sclareol (SCL), a natural diterpene alcohol, and its two derivatives (11c and 12l). **Methods:** Our cellular model included human glioblastoma U87 cell line without P-gp expression, its MDR counterpart U87-TxR with P-gp expression, and normal lung fibroblasts MRC-5. Cytotoxic effects were examined by MTT. P-gp function, cell cycle disturbance, time-dependent cell death induction, the level of reactive oxygen and nitrogen species, and changes in the mitochondrial membrane potential were studied by flow cytometry. **Results:** SCL and its derivatives evaded the MDR in glioblastoma cells, showing lower IC50 values in U87-TxR than in U87, referred to as collateral sensitivity. Both derivatives were more potent than SCL, while 12l was active in the nanomolar range. 11c and 12l displayed greater selectivity towards glioblastoma cells compared to SCL. All compounds significantly disturbed the cell cycle and induced cell death: SCL - late apoptosis and necrosis, 11c - only early apoptosis, and 12l - early and late apoptosis. SCL and its derivatives acted as antioxidants, while 11c and 12l decreased mitochondrial membrane potential. **Conclusion:** SCL derivatives were more potent than SCL. The observed collateral sensitivity in glioblastoma cells can be explained by oxidative stress modulation because although resistant due to P-gp expression, U87-TxR cells are more susceptible to changes in oxidative status than U87 cells.