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Promising chalcone derivative for glioblastoma therapy

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pharmaceuticals MDPI

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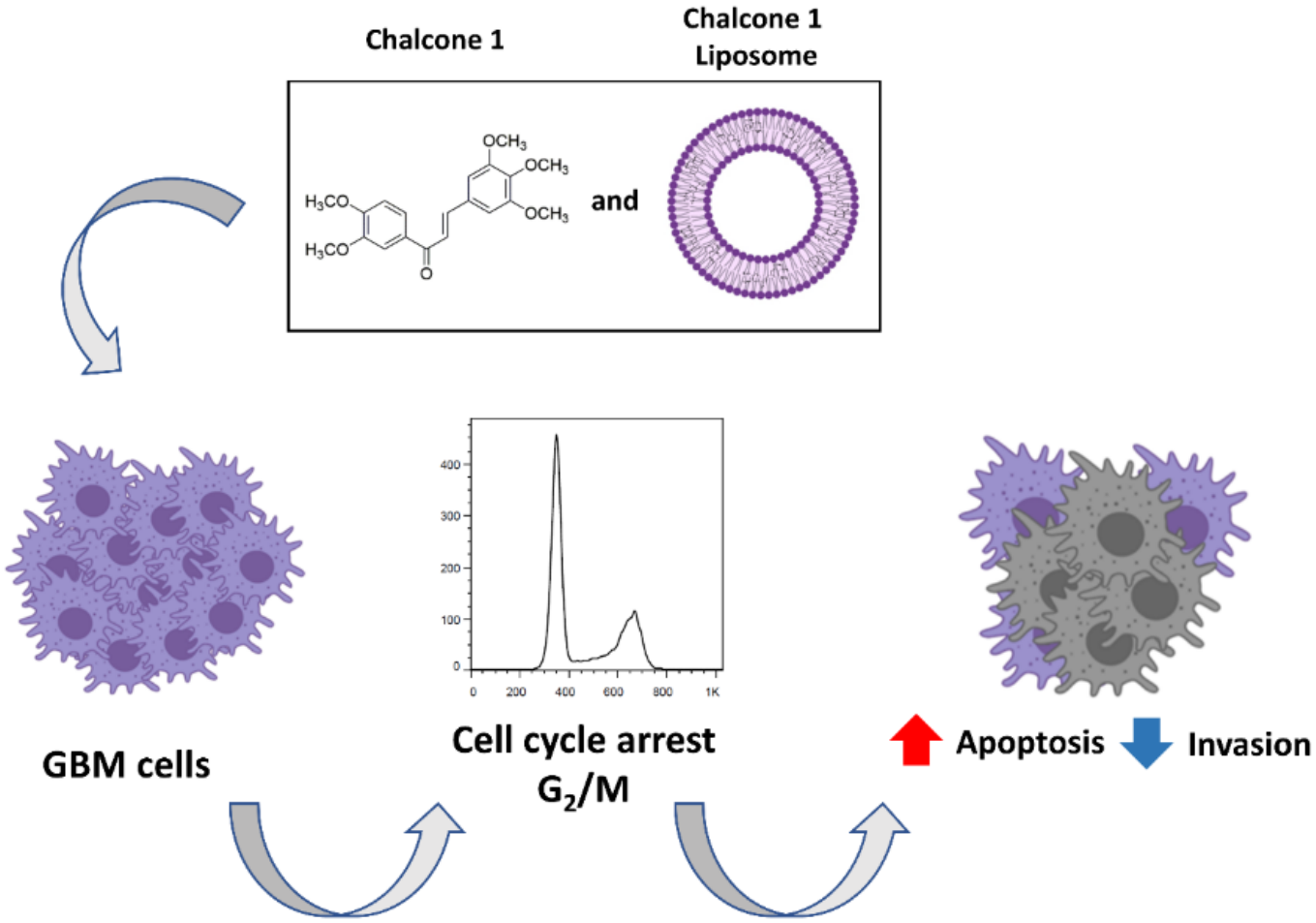
Promising chalcone derivative for glioblastoma therapy



Abstract

Glioblastoma (GBM) is the most frequent and lethal primary brain tumor, rapidly growing and spreading into nearby healthy tissues with devastating effects for patients and those around them. GBM has currently no cure, being the average survival of GBM patients after diagnosis limited to a few months. The drug resistance ability and fast regrowth of GBM are the main problems related to current treatments. The intrinsic high heterogeneity and the microenvironment of these tumors are some of the reasons for the low efficacy of the available treatments. Therefore, new therapy alternatives for this highly aggressive brain cancer are urgently needed. Chalcones are synthetic or naturally occurring compounds that have been widely investigated for cancer targeting. Thus, in this work, chalcone derivatives were tested regarding their inhibitory activity and specificity toward GBM cell lines. The chalcone derivative with the most potent and selective cytotoxic effects on GBM cells was further investigated regarding its ability to reduce critical hallmark features of GBM. This derivative showed to successfully reduce key targets for cancer treatment, namely the invasion and proliferation capacity of tumor cells by inducing cell cycling arrest and cell apoptosis. Moreover, to overcome potential systemic side effects and its poor water solubility, this compound was successfully encapsulated into liposomes. Therapeutic concentrations were incorporated retaining the potent in vitro growth inhibitory effect of the selected chalcone. In conclusion, our results demonstrated that this new formulation can be a promising starting point for the discovery of new and more effective drug treatments for GBM.

Keywords

glioblastoma; chalcone; cell death; drug delivery; liposomes.

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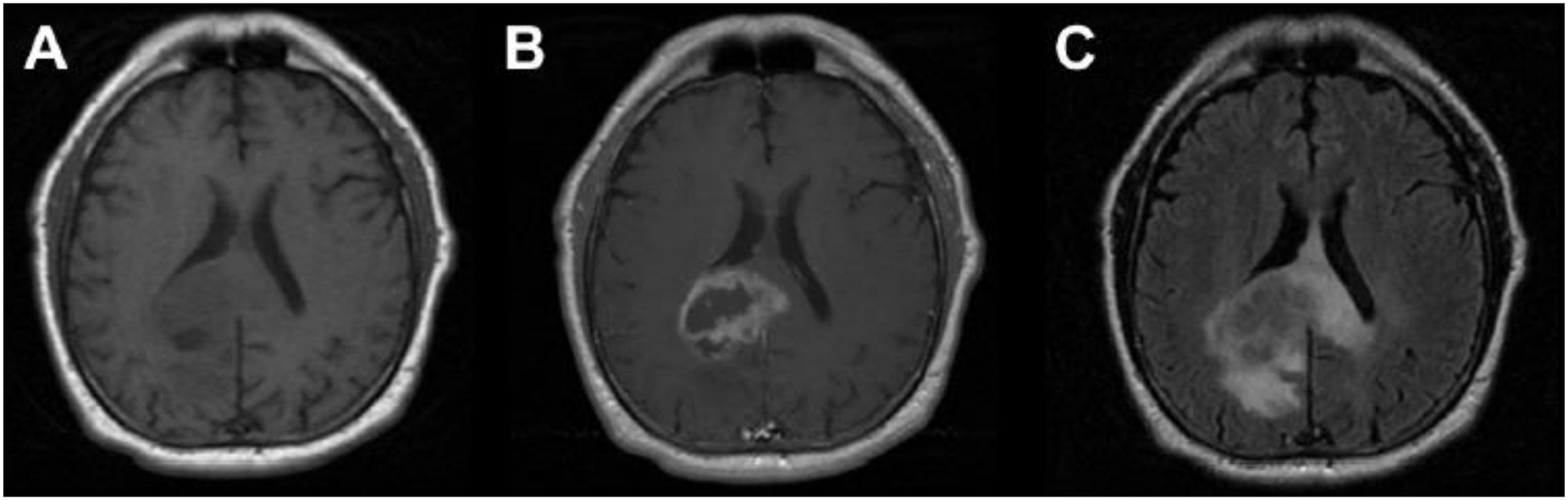
Glioblastoma (GBM)



- **Primary Brain Tumor**
- **Highly heterogeneous**
- **Nuclear atypia**
- **Asymptomatic**

Elbanan, M. *et al*. 2015, *Neuroimaging Clin N Am*

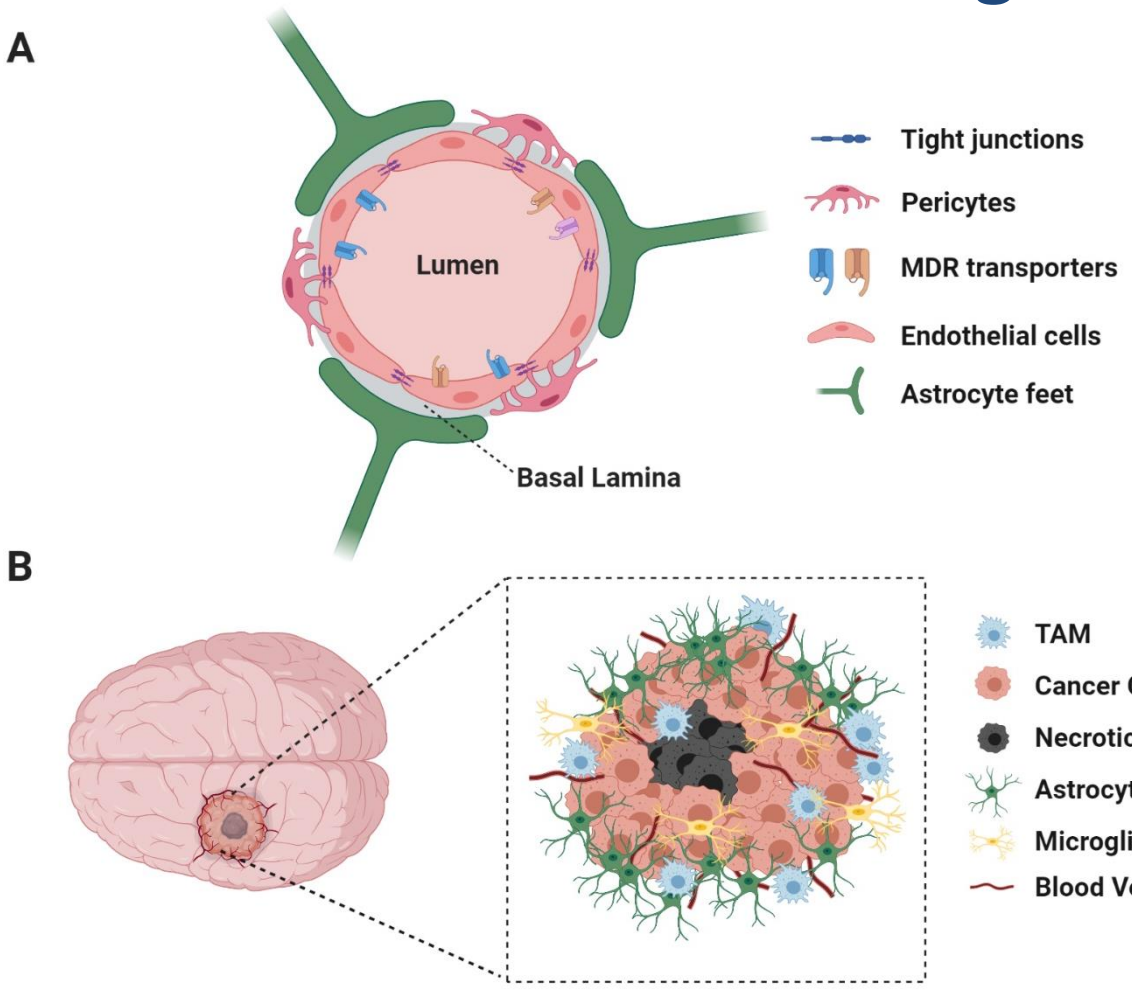
Therapy

- **Surgical resection** is the first line of treatment.
- **Radiotherapy** treatment on a dose schedule.
- **Chemotherapy**, alkylating agent temozolomide (TMZ).

Median survival of 12-15 months after diagnosis

Stupp, R. *et al.* 2005, *The New England Journal of Medicine*

Challenges



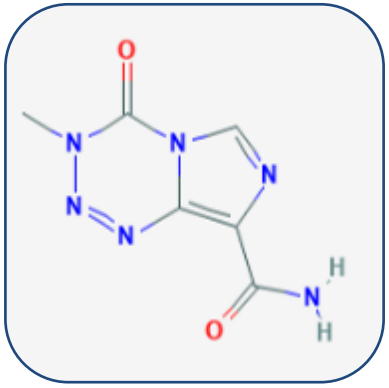
Blood Brain Barrier (BBB)

Tumor Microenvironment

Mendanha, D. *et al.* 2021 *Journal of Controlled Release*

Chemotherapeutic Agents Limitations

TMZ



- Solubility
- Blood circulation time
- Reaching tumor site
- Secondary effects

New Chemotherapeutic agents and Delivery systems are needed

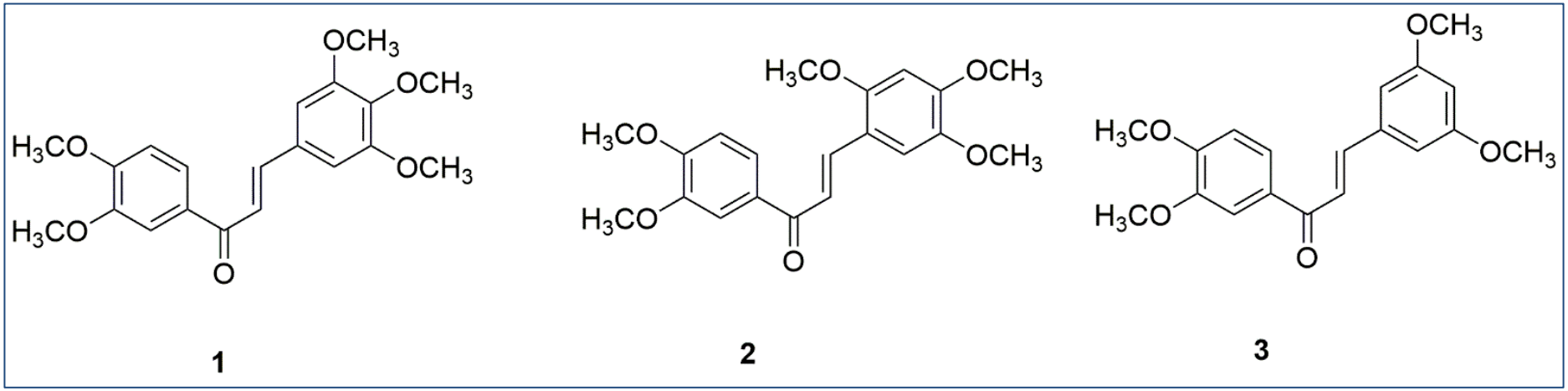
Chalcones

- **Antimicrobial**
- **Anti-inflammatory**
- **Antioxidant**
- **Antitumor**

Simple Chemistry → **Easily obtained by Synthesis** → **Incorporation of functional groups**

Moreira, J. *et al.* 2021 *Molecules*

Chalcone derivatives



Chemical structure of chalcone derivatives

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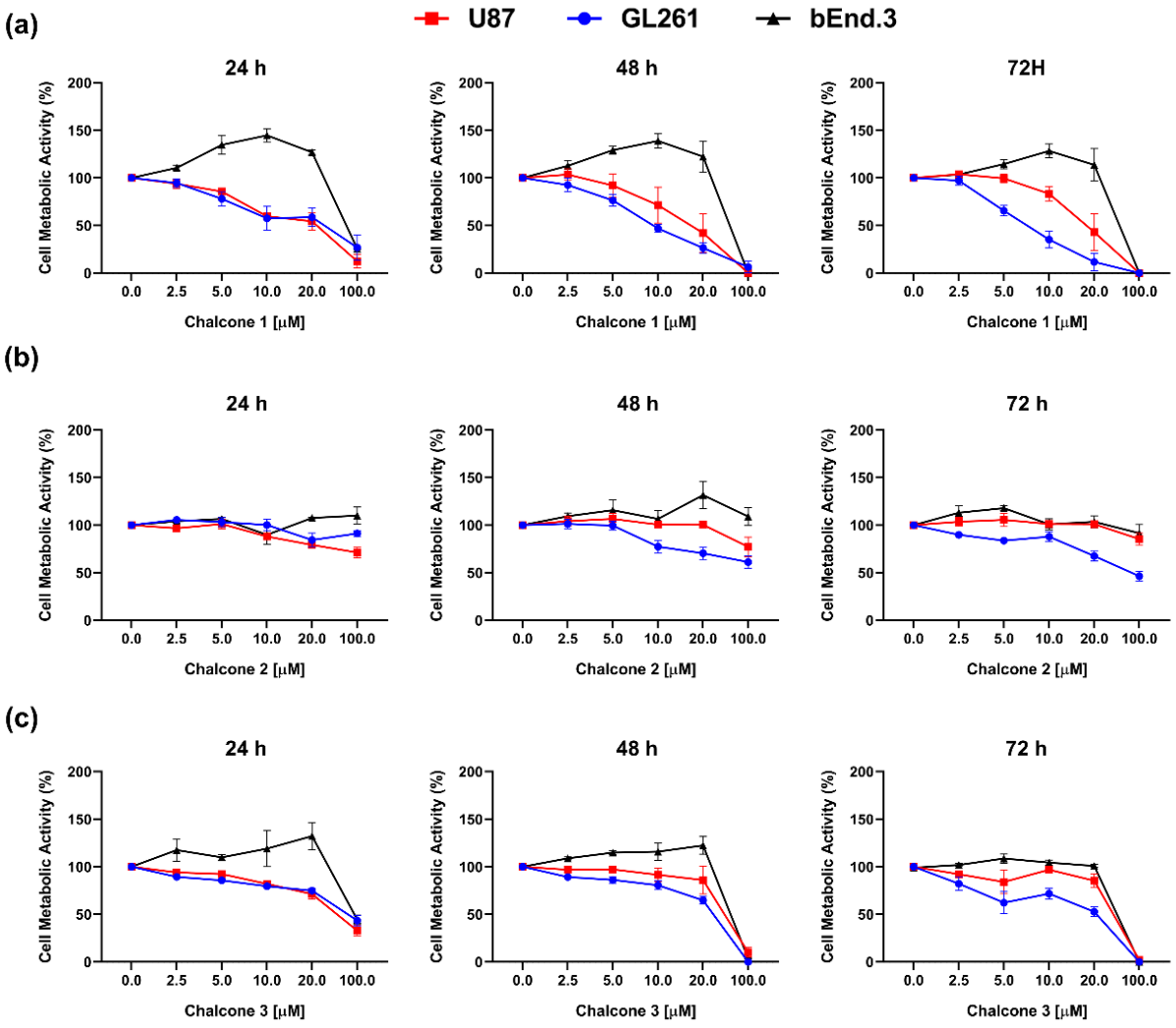
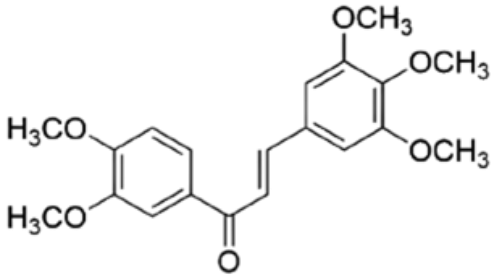
Chalcone derivatives IC_{50} in GBM cells



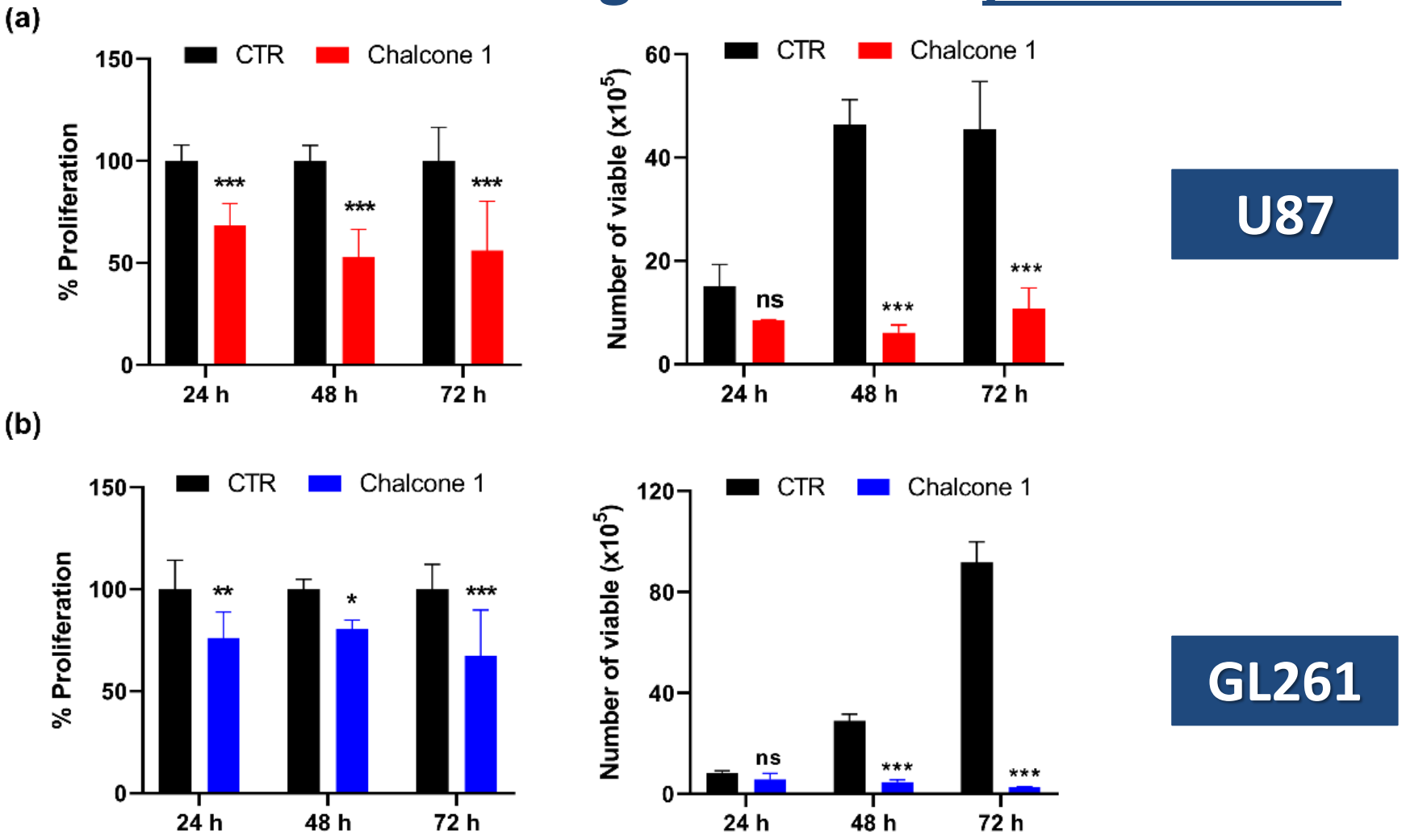


72 h Chalcone 1 IC_{50} [μM]:

- **GL261 - 7.34 μM**
- **U87 – 18.07 μM**
- **bEnd.3 – not applicable**

Mendanha, D. *et al.* 2021 *Molecules*

Chalcone 1 inhibits glioblastoma proliferation



U87

GL261

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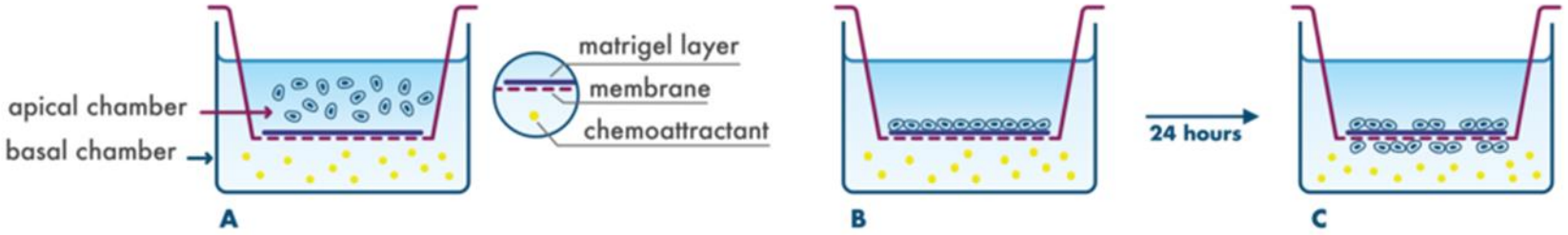
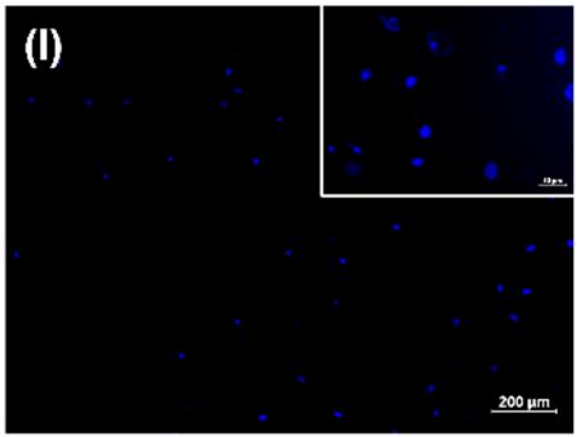
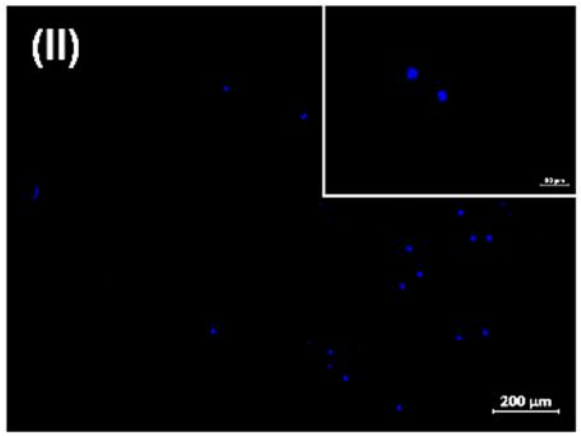
Chalcone 1 inhibits glioblastoma invasion

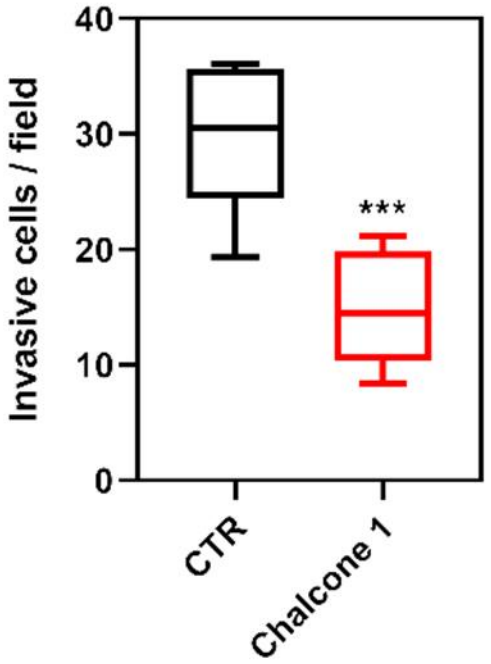




Control



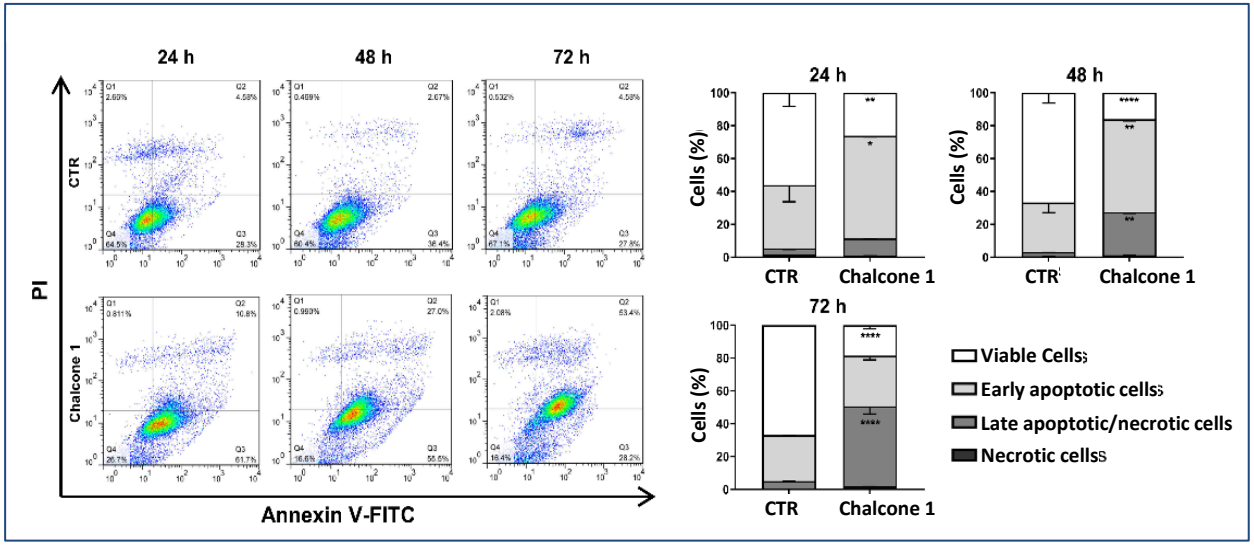
Chalcone 1



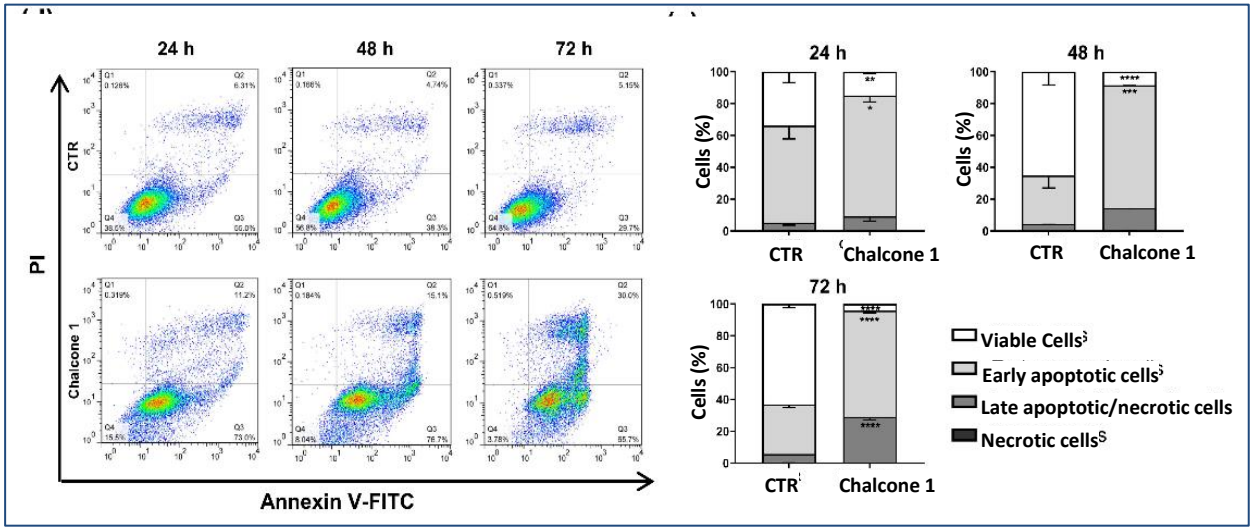
Mendanha, D. *et al.* 2021 *Molecules*

Chalcone 1 induces cell death via apoptosis

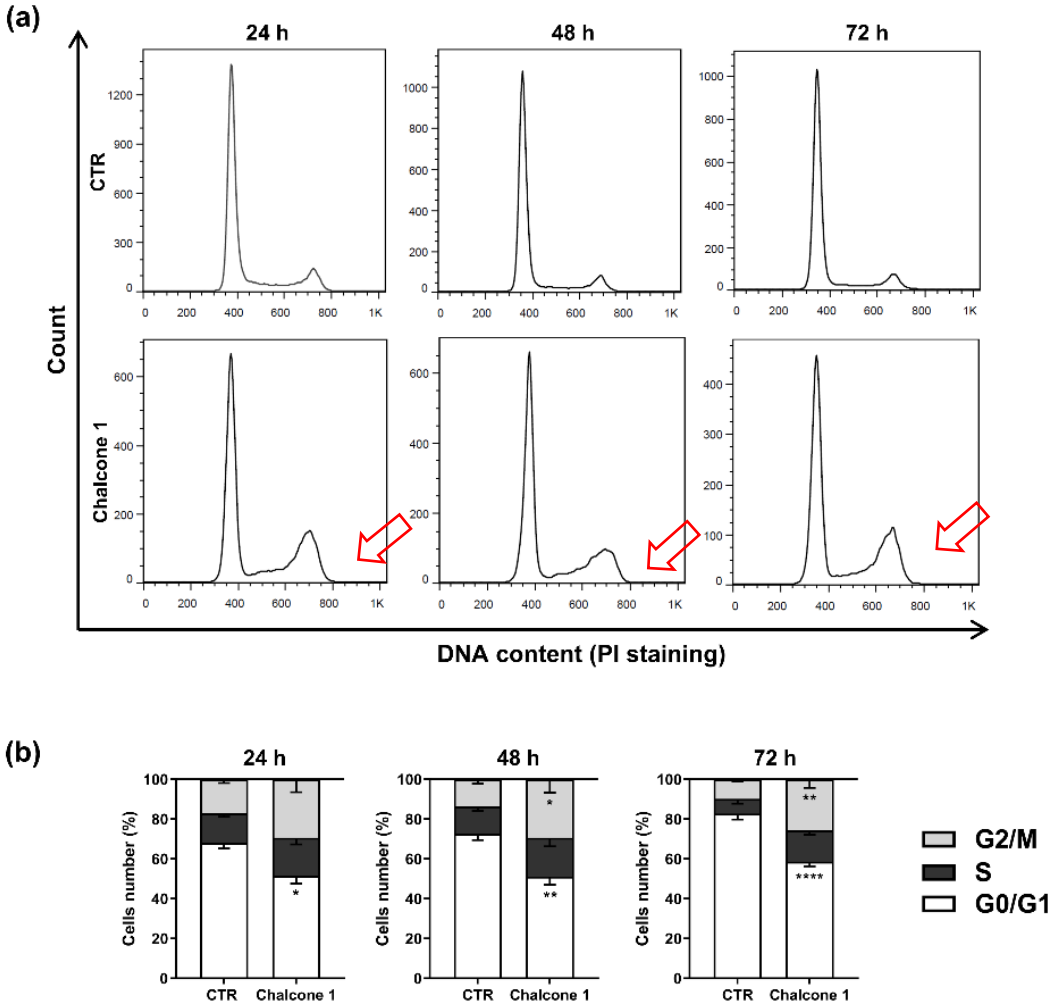
U87



GL261



Cell cycle arrest in the G_2/M checkpoint



G_2/M checkpoint

Proliferation

Apoptosis

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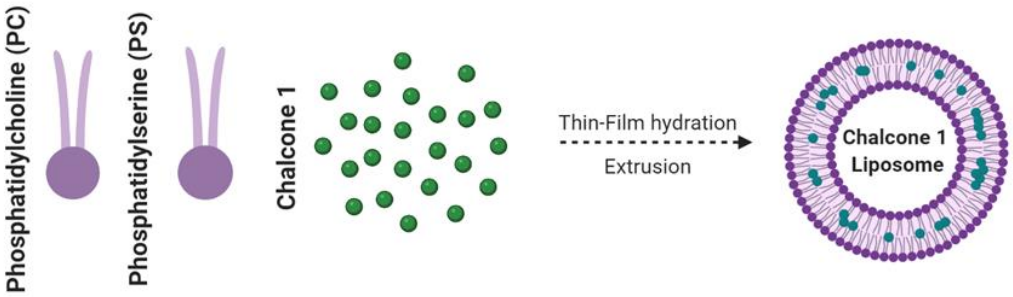
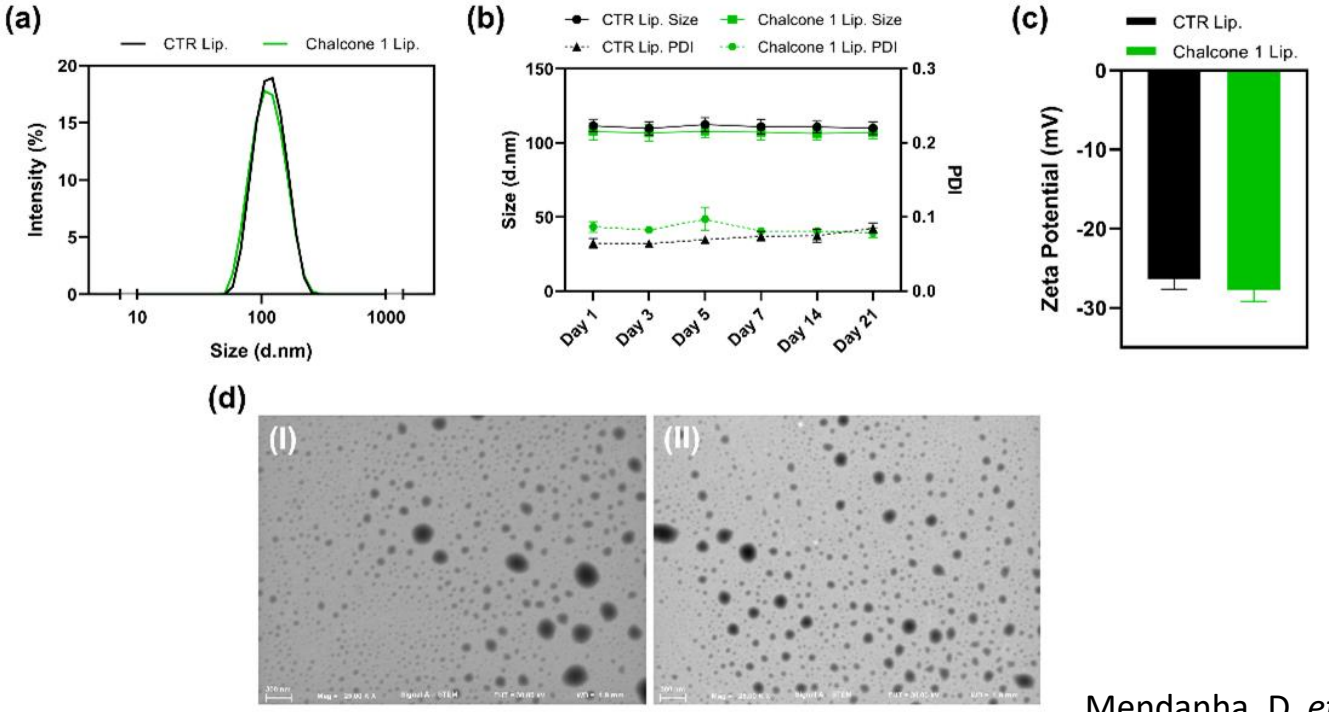
Chalcone 1 loaded liposomes





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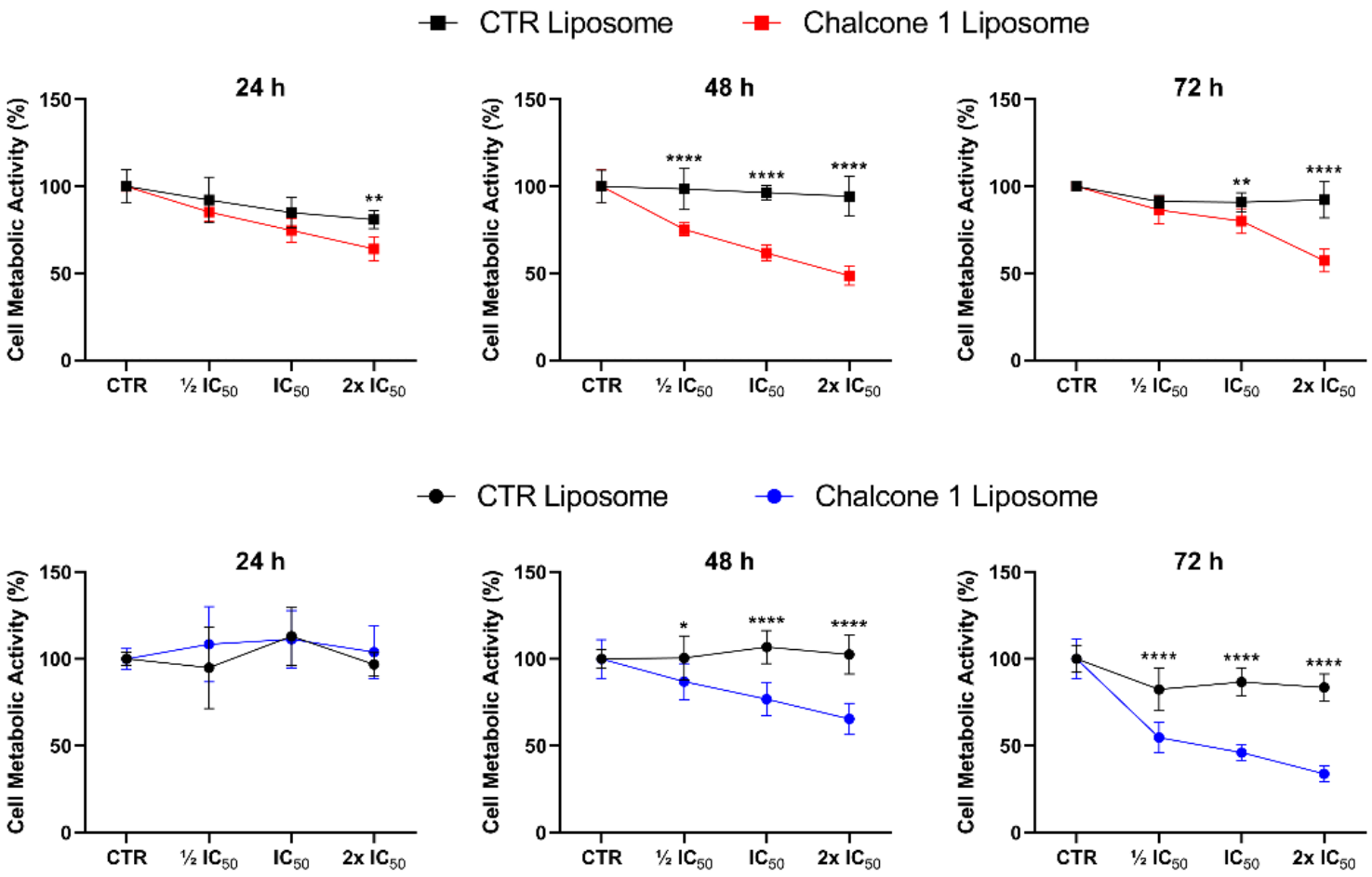
Biological assessment of chalcone 1 loaded liposome



Mendanha, D. *et al.* 2021 *Molecules*

Conclusions

- Chalcone derivative 1 presents **antiproliferative** and **anti-invasion** activities towards GBM.
- Apoptosis induced in GBM cells by chalcone 1 derivative is triggered by **cell cycle arrest** in G_2/M checkpoint.
- **Liposomes** loaded with chalcone 1 were successfully developed.
- Liposomes loaded with chalcone derivatives can provide **new treatment alternatives** to GBM.

Future Perspectives

- Assessment of **signaling pathways** on GBM cells after treatment.
- Analysis of **apoptotic pathways** (intrinsic vs extrinsic pathways).
- Development of **biofunctionalized liposomes –** BBB crossing and GBM targeting - to deliver chalcone 1.
- ***In vivo*** assays – Orthotopic intracranial GBM model.

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