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The role of non-selective beta-blockers in breast cancer treatment: An in vitro approach

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pharmaceuticals MDPI

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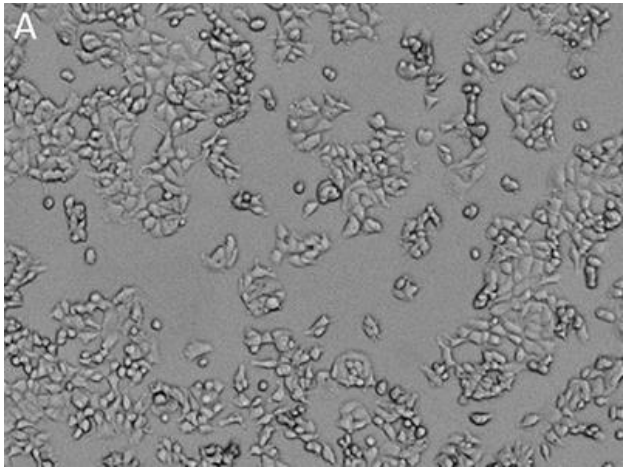
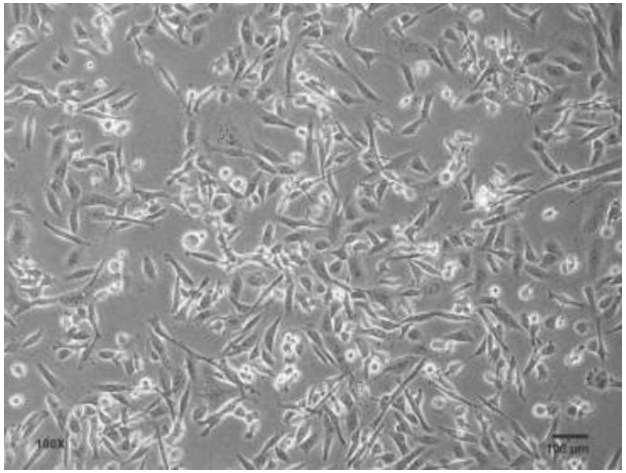
The role of non-selective beta-blockers in breast cancer treatment: An in vitro approach

MCF-7



MDA-MB-231



Drugs tested:

- Propranolol
- Carvedilol
- Methotrexate
- 5-fluorouracil

Cell viability

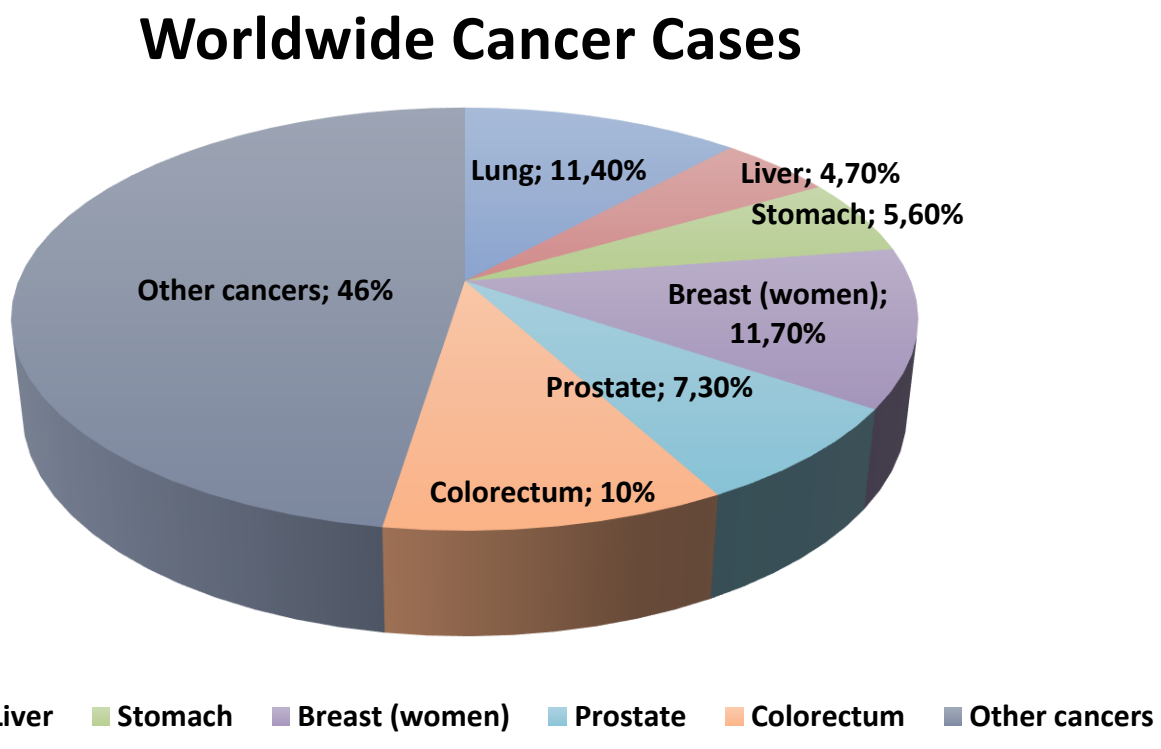
Abstract: Breast cancer is the second most diagnosed type of cancer in the world, although it is more prevalent in women and can affect both women and men. This type of cancer is the fifth leading cause of death. Even though there are multiple treatment protocols, there is a need to develop more effective alternatives. The current study explores the effects on breast cancer cell lines, MCF-7 (metastatic cell line) and MDA-MB-231 (non-metastatic), of pharmaceuticals like β-blockers already prescribed to treat other diseases. Thus, cell lines were exposed, up to 72h, to non-selective β-blockers, propranolol (10-250 µM) and carvedilol (0.1-100 µM), to antimetabolites, methotrexate (0.01-20 µM) and 5-fluorouracil (0.1-50 µM) and cell viability was assessed. The obtained results demonstrated higher sensitivity of MCF-7 to the tested drugs. Based on the estimated medium lethal concentration, carvedilol was the most toxic drug followed by propranolol and cytostatic drugs. Data support the potential application of β-blockers in the treatment of breast cancer.

Keywords: Propranolol; Carvedilol; β-blockers; Breast cancer

Introduction

Cancer cells:

- Oncogenic mutations
- Tumor suppressor mutations
- Abnormal proliferative capacities
- Capacity of spreading through the body-metastasis



Introduction

Breast cancer

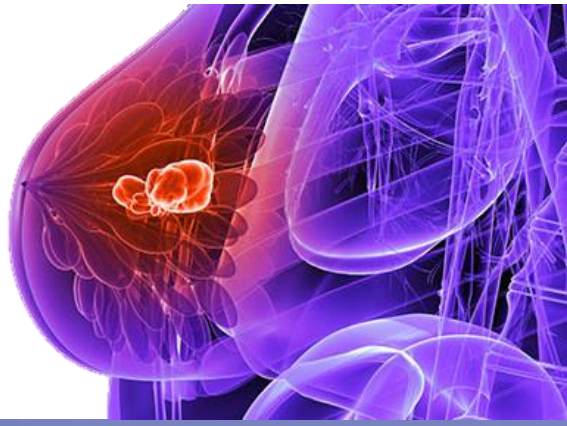
- Affects younger women
- HER2-positive represents 20% of breast cancer cases

5 subtyps:

- ER/PR-positive Luminal A
- ER/PR-positive Luminal B
- ER/PR- negative HER2
- ER/PR- negative basal-like
- ER/PR- negative normal-like

Treatments

- Active surveillance
- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Immunotherapy
- Targeted drug therapy



Introduction

β-blockers

Carvedilol

β-AR antagonist drug

Antagonist activity at α1 adrenergic receptors and β1 e β2.

Propranolol

Non-selective β-blocker

Adrenaline and noradrenaline blocking action on β1 and β2 adrenergic receptors.

Antimetabolites/ antineoplastics

Methotrexate

Used in cancer treatment and autoimmune diseases

Acts by inhibiting folic acid metabolism.

5-Fluorouracil

Acts by inhibiting the enzyme thymidylate synthase (TS)

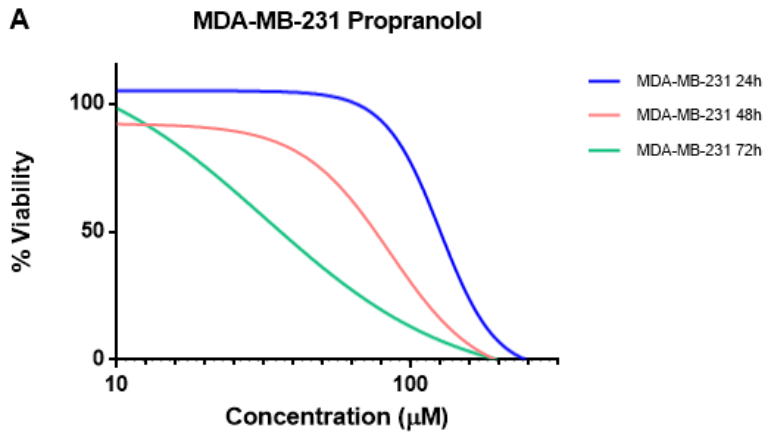
Can be incorporated into DNA and RNA, leading to cytotoxicity and cell death.

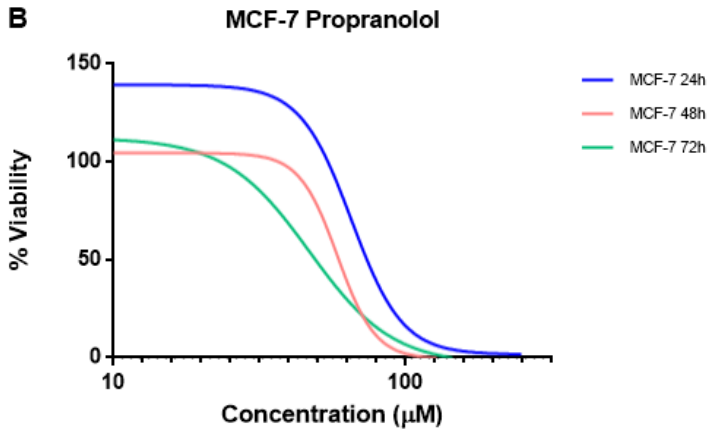
Introduction

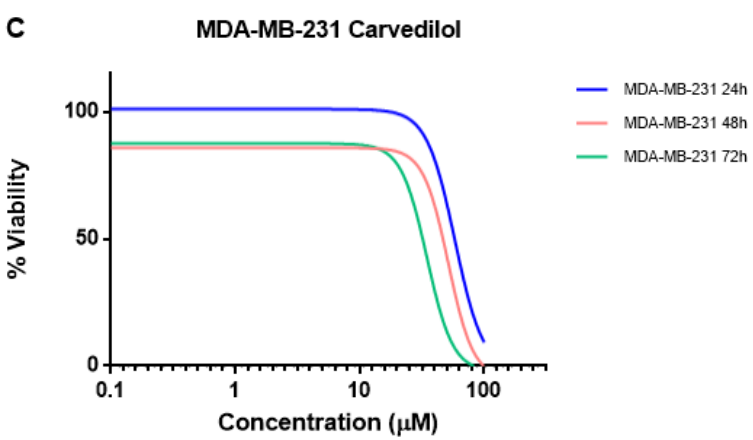
In this study:

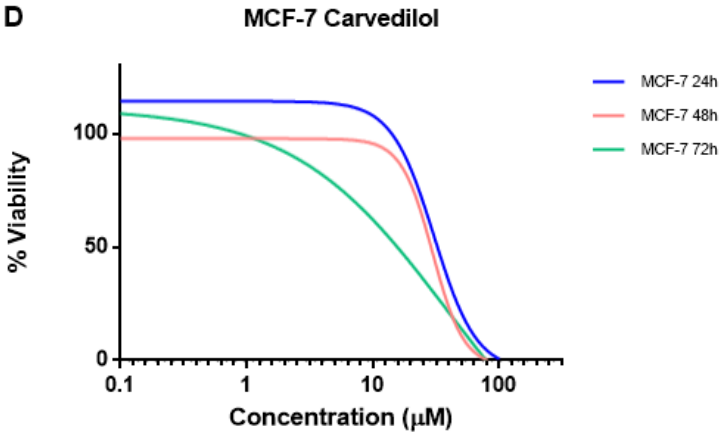
The cytotoxicity of **propranolol** and **carvedilol** (non-selective β-blockers), **methotrexate** and **5-fluorouracil** (antimetabolites/ antineoplastic drugs) was assessed on **MDA-MB-231** (non-metastatic breast cancer cell line) and on **MCF-7** (metastatic breast cancer cell line).

Results: beta-blockers







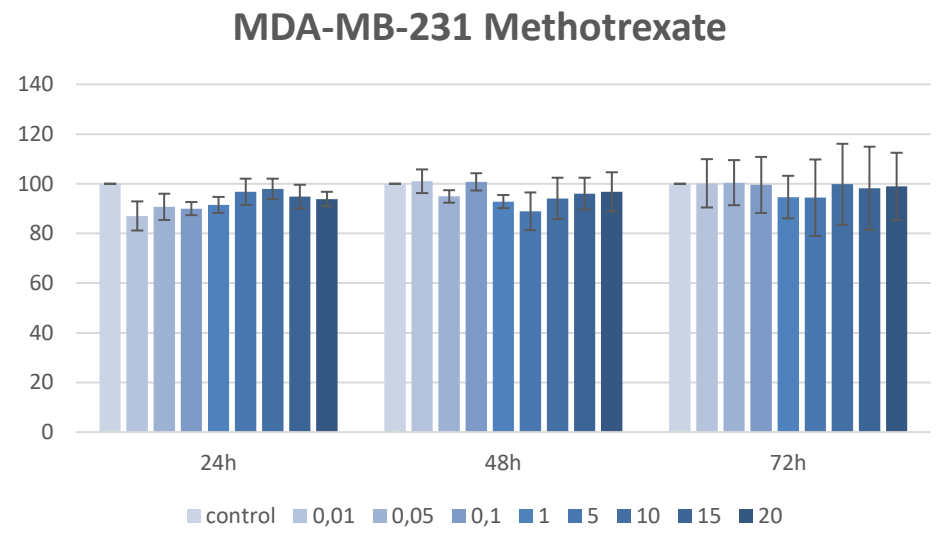


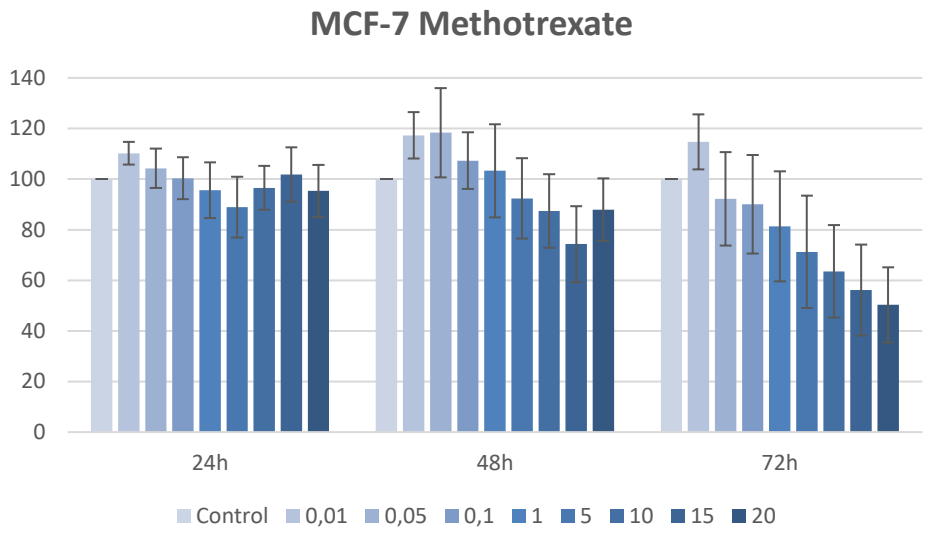
Results and discussion

Propranolol	µM	24 h	48 h	72 h
MDA-MB-231	LD_{50}	125.657	75.661	36.029
	LD_{25}	101.567	49.000	20.162
MCF-7	LD_{50}	73.634	59.005	49.099
	LD_{25}	63.400	50.718	36.617

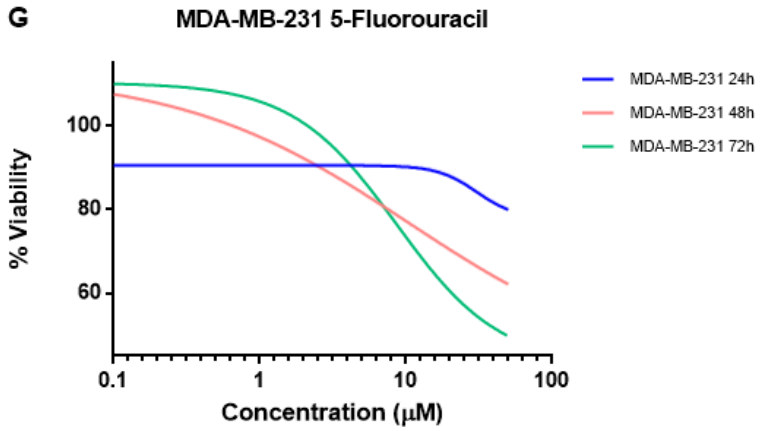
Carvedilol	µM	24 h	48 h	72 h
MDA-MB-231	LD_{50}	57.650	46.494	31.926
	LD_{25}	43.665	32.383	22.373
MCF-7	LD_{50}	32.308	28.717	15.570
	LD_{25}	23.086	20.822	5.694

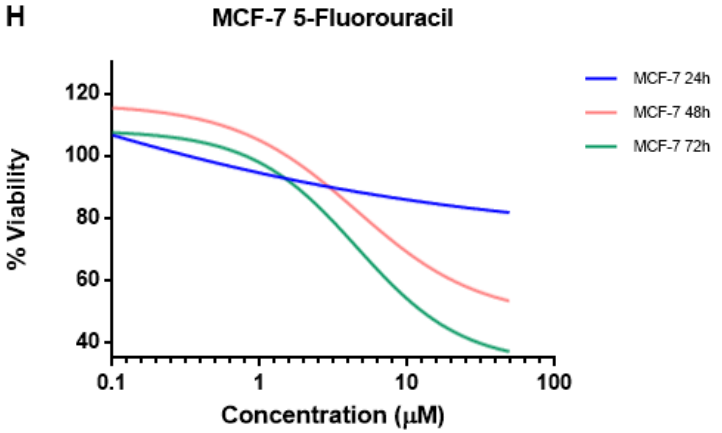
Results and discussion





Results: antimetabolites/ antineoplastics





Results and discussion

5-fluorouracil	µM	24 h	48 h	72 h
MDA-MB-231	LD_{50}	------	351.387	8.674
	LD_{25}	------	12.569	9.21
MCF-7	LD_{50}	------	140.327	12.652
	LD_{25}	------	6.946	3.749

Conclusions and future trends

- β-blockers showed higher toxicity than antimetabolites to the cell lines in study.
- For both cell lines, MDA-MB-231 and MCF-7, the most cytototoxic drug was carvedilol, followed by propranolol and 5-flourouracil.
- Both cell lines demonstrated resistance to the antimetabolite methotrexate.
- As future work, a normal cell line should be added to the work, in order to compare the effects of the tested pharmaceuticals with cancer cell lines.

Acknowledgments

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