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Cellular and metabolomic studies in triple-negative breast cancer cells: assessing genistein's potential as a chemosensitizing agent

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INTRODUCTION & AIM

- Triple-negative breast cancer (TNBC) is a distinct subtype characterized by the absence of estrogen, progesterone, and human epidermal growth factor receptor-2 expression.
- TNBC represents 15–20% of newly diagnosed breast cancer cases and carries a 40% mortality rate within the first 5 years post-diagnosis.
- There is an urgency in enhancing TNBC chemoresistance, one trustworthy option being the use of natural compounds as chemosensitizers.

• **The main objective** of this study was:
  - to improve the sensitivity of TNBC cells to docetaxel by combining it with cytotoxic natural compounds
  - to elucidate their precise molecular mechanisms of action using a cellular and metabolomic approach.

METHODS

I. Cytotoxicity profiles and identification of the inhibitory concentrations causing 20% growth inhibition (IC20)

- **Tested compounds**: docetaxel, genistein (Gen), leontopodic acid (LA) and kaempferol (Kam)
- **TNBC cell lines**: HS578T, MDA-MB-231, MDA-MB-468, cultivated in RPMI medium, supplemented with 10% FBS and 1% pen-strep.
- **Viability assay:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay
- **Exposure time:** 48h

II. Identification of the most potent combination of natural compounds with docetaxel – MTT assay

III. Metabolomics studies

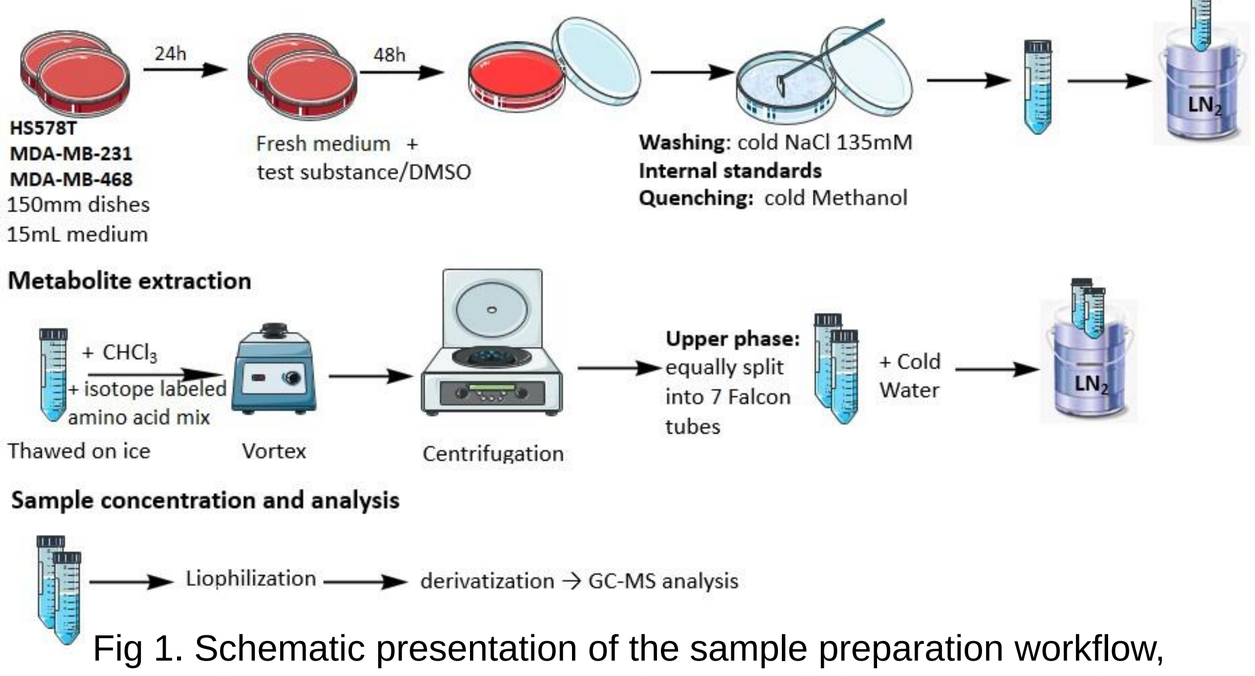
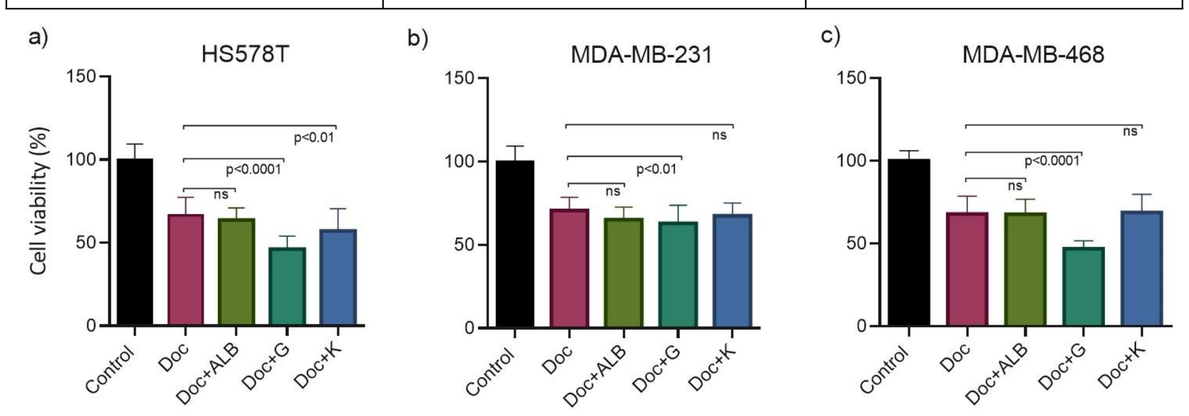


Fig 1. Schematic presentation of the sample preparation workflow, from cell treatment to GC-MS analysis of cellular endometabolites

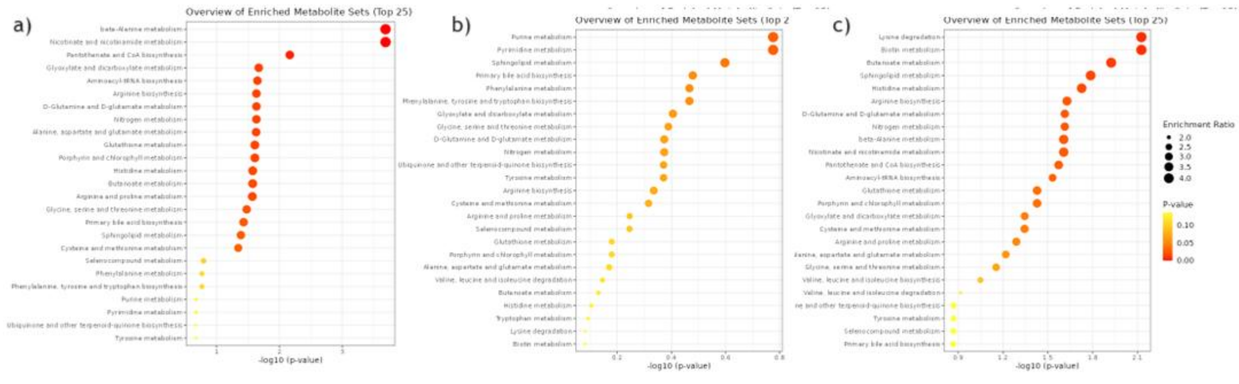
RESULTS & DISCUSSION

I. Table I. The IC20 values obtained for each test substance

Test compound	TNBC cell line	IC_{20}
Leontopodic acid B	HS578T	282.64 µM
	MDA-MB-231	20.52 µM
	MDA-MB-468	140.47 µM
Genistein	HS578T	35.26 µM
	MDA-MB-231	3.80 µM
	MDA-MB-468	96.12 µM
Kampherol	HS578T	40.37 µM
	MDA-MB-231	8.20 µM
	MDA-MB-468	48.51 µM
Docetaxel	HS578T	2.03 nM
	MDA-MB-231	4.55 nM
	MDA-MB-468	0.032nM



II. Fig 2. Impact on cell viability of combinations of docetaxel and a natural compound, observed on a) HS578T cells, b) MDA-MB-231 cells, c) MDA-MB-468 cells



III. Fig 3. Altered metabolic pathways as a result of the combined treatment, docetaxel + genistein, compared to single docetaxel, for:

a) **HS578T cells:** beta-alanine, nicotinamide and nicotinate metabolism
b) **MDA-MB-231 cells:** purine and pyrimidine bases metabolism
c) **MDA-MB-468 cells:** lysine and biotine metabolism

CONCLUSION

- In all cell lines, the combined treatment (docetaxel + genistein) led to changes in amino acid metabolism.
- Employment of natural compounds as chemosensitizers can result in lower docetaxel dosages, limiting the negative effects associated with anticancer drugs and chemoresistance.

ACKNOWLEDGMENTS

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