Unraveling the therapeutic impact of phytochemicals in cancer through comprehensive transcriptome meta-analysis

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ABSTRACT

Cancer is one of the leading causes of death worldwide. According to WHO, cancer accounted for nearly 20 million deaths in 2022. Naturally occurring phytochemicals are being used in cancer therapy and in mediating the regression of resistant tumors. Meta-analysis of the transcriptome of multiple cancer cell lines treated with phytochemicals revealed the major pathways affected by these compounds. These include angiogenesis, apoptosis, DNA repair, and cell cycle. Although there were indications of cancer prognosis, we identified signs of chemoresistance which may lead to relapse. We also found the impact of anti-oxidant effects of phytochemicals on ROS-affected genes. While some pathways that these phytochemicals act on to bring about cancer regression were common, we found drug-specific and cell-line-specific effects. A comprehensive comparison of phytochemical activity may help identify drugs that can work synergistically with standard-of-care cancer drugs to mitigate drug resistance and toxicity.

KEY QUESTIONS

- How does a phytochemical bring about a block in tumorigenesis ?
- How do different phytochemicals bring about the same phenotype ?
- Do different cell types respond to a phytochemical in the same manner ?
- Can these phytochemicals work synergistically to overcome resistance ?
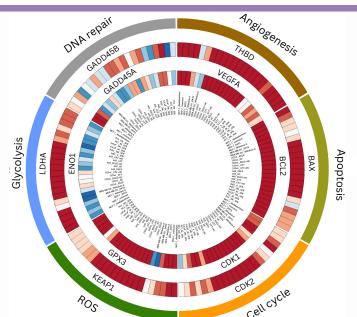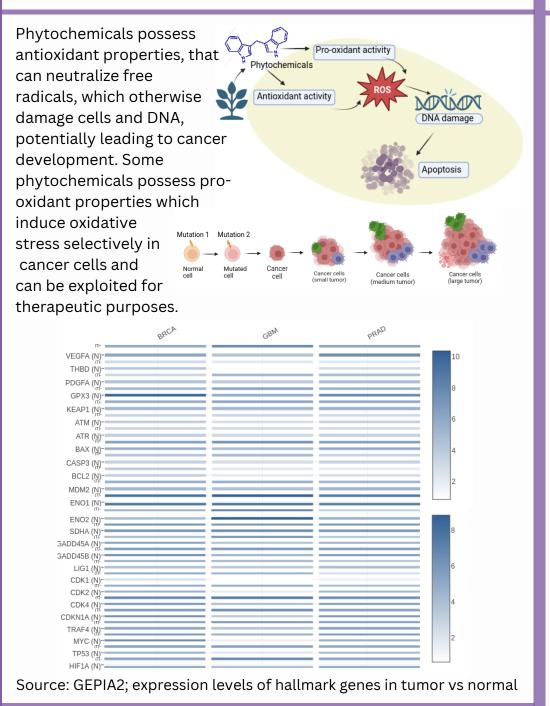
SUMMARY

down-regulated   up-regulated

Fig 3. A circos plot explaining the differential expression of genes belonging to different hallmark pathways deregulated in cancer when treated with different phytochemicals
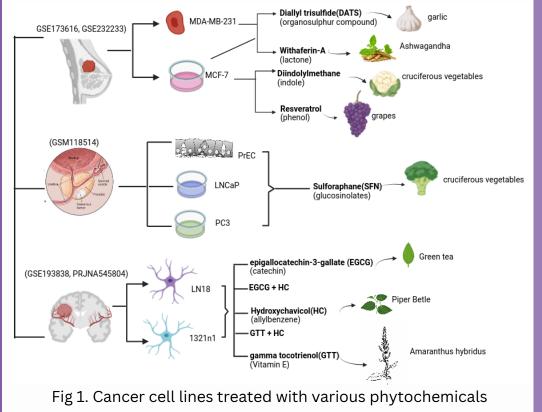
Each sector represents one pathway and every sector has 22 cells, each representing a particular cell line treated with a particular drug.
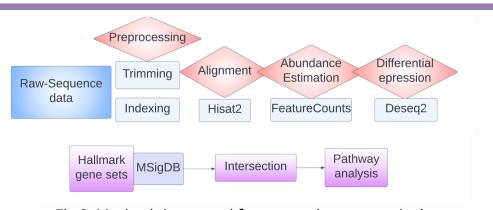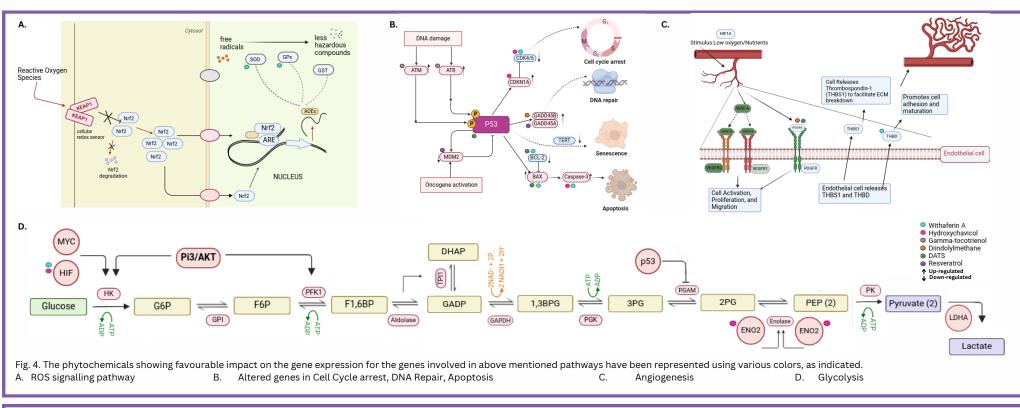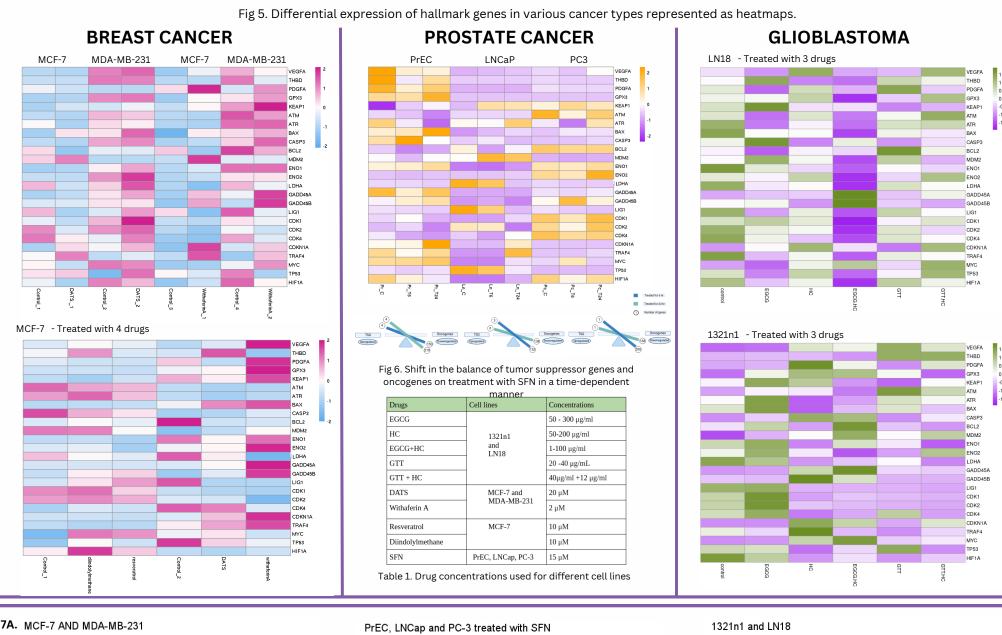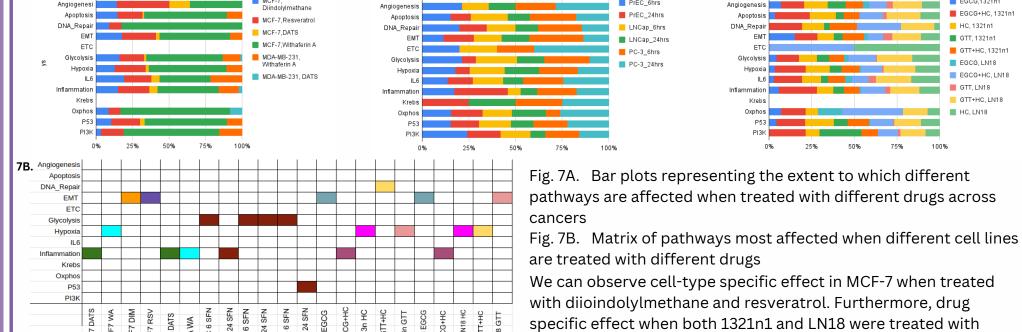
INTRODUCTION

Phytochemicals possess antioxidant properties, that can neutralize free radicals, which otherwise damage cells and DNA, potentially leading to cancer development. Some phytochemicals possess pro-oxidant properties which induce oxidative stress selectively in cancer cells and can be exploited for therapeutic purposes.

Source: GEPIA2; expression levels of hallmark genes in tumor vs normal

MATERIALS

Fig 1. Cancer cell lines treated with various phytochemicals

METHODOLOGY

Fig 2. Methodology used for transcriptome analysis

RESULTS

Fig. 4. The phytochemicals showing favourable impact on the gene expression for the genes involved in above mentioned pathways have been represented using various colors, as indicated.
A. ROS signalling pathway   B. Altered genes in Cell Cycle arrest, DNA Repair, Apoptosis   C. Angiogenesis   D. Glycolysis

Fig 5. Differential expression of hallmark genes in various cancer types represented as heatmaps.

BREAST CANCER

MCF-7 - Treated with 4 drugs

PROSTATE CANCER

Fig 6. Shift in the balance of tumor suppressor genes and oncogenes on treatment with SFN in a time-dependent manner

Drugs	Cell lines	Concentrations
EGCG	1321n1 and LN18	50 - 300 µg/ml
HC		50-200 µg/ml
EGCG+HC		1-100 µg/ml
GTT		20 -40 µg/ml
GTT + HC		40µg/ml +12 µg/ml
DATS	MCF-7 and MDA-MB-231	20 µM
Withaferin A		2 µM
Resveratrol	MCF-7	10 µM
Diindolylmethane		10 µM
SFN	PrEC, LNCaP, PC-3	15 µM

Table 1. Drug concentrations used for different cell lines

GLIOBLASTOMA

LN18 - Treated with 3 drugs

1321n1 - Treated with 3 drugs

7A. MCF-7 AND MDA-MB-231

PrEC, LNCap and PC-3 treated with SFN

1321n1 and LN18

Fig. 7A. Bar plots representing the extent to which different pathways are affected when treated with different drugs across cancers

Fig. 7B. Matrix of pathways most affected when different cell lines are treated with different drugs

We can observe cell-type specific effect in MCF-7 when treated with diiindolylmethane and resveratrol. Furthermore, drug specific effect when both 1321n1 and LN18 were treated with EGCG and HC can be seen.

ACKNOWLEDGEMENT

REFERENCES

1. Hahm ER, Kim SH, Singh KB, Singh SV. RNA-seq reveals novel cancer-selective and disease subtype-independent mechanistic targets of withaferin A in human breast cancer cells. Mol Carcinog. 2021 Jan;60(1):3-14.
2. Abdul Rahman A, Wan Ngah WZ, Jamal R, Makpol S, Harun R, Mokhtar N. Inhibitory Mechanism of Combined Hydroxychavicol With Epigallocatechin-3-Gallate Against Glioma Cancer Cell Lines: A Transcriptomic Analysis. Front Pharmacol. 2022 Mar 22;13:844199.