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Molecular perspective on gemcitabine resistance in PANC-1 and PANC-1GemR pancreatic cancer cells: the potential role of polyphenolic cocktail (PFK5120) in overcoming chemoresistance

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Pancreatic cancer is an aggressive malignancy with a high mortality rate primarily due to late diagnosis and limited treatment options. The efficacy of gemcitabine (GEM) used in standard chemotherapy is decreasing due to the development of resistance. To overcome this problem, natural polyphenols are being investigated as potential adjuvant treatment options. PFK5120, a polyphenol mixture of anticarcinogenic compounds developed by our team and currently in the patent process. This study examined the molecular underpinnings of GEM resistance in pancreatic cancer cells and how PFK5120 may affect it. mRNA expression levels were analyzed using the RT-PCR method. Gene expression analyses in four experimental groups (control, GEM, PFK5120, and GEM + PFK5120) revealed significant molecular alterations associated with drug resistance. PFK5120 alters KRAS and AKT/mTOR signaling pathways, which are crucial to chemotherapy response. These alterations are achieved by modulating different resistance mechanisms in both cell lines. Specifically, PFK5120 suppressed KRAS expression in PANC-1 cells, whereas the combination treatment activated SRC and AKT signaling pathways. Furthermore, the combination therapy suppressed PTEN and NFKB, supporting its potential role in enhancing chemotherapy sensitivity. In PANC-1GemR cells, PFK5120 changed AKT, PIK3CA, and mTOR pathways. This finding, which points to alternative signaling mechanisms in resistant cells, suggests that PFK5120 may affect treatment response. The observation of suppressed NFKB in resistant cells further supports the potential for this alteration to influence inflammatory responses and resistance mechanisms. The results of this study provide a better understanding of the molecular signaling mechanisms underlying gemcitabine resistance, reveal the potential of PFK5120 to enhance chemosensitivity, and suggest that phenolic compound combination therapies may be a novel and effective pancreatic cancer treatment.

P-32-101
Bush medicine in Trinidad and Tobago: a quest for novel plant-based anti-cancer treatments

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"Bush medicine" as it is colloquially termed in Trinidad and Tobago, refers to traditional plant remedies used for the treatment of various ailments. This study was undertaken to identify ethnomedicinal plants used locally by bush medicine practitioners (BMPs) in their healing practices for cancer, and to investigate the phytochemical composition, antioxidant activity (AOA) and cytotoxic activity (CA) of their extracts. Ethical approval was granted, and a structured questionnaire was used to interview thirty (30) consenting BMPs. Five (5) understudied plants were collected at different locations in Trinidad, identified and vouchered at The National Herbarium. The different plant parts were repeatedly macerated in 95% ethanol resulting in eight (8) crude extracts of varying yields, designated as: BB, CH, MaR, MS, JBB, JBF, JBL and JBS. Total phenolic content (TPC) and total tannin content (TTC) were determined using the Folin-Ciocalteu colorimetric method and gallic acid as a standard, while the total flavonoid content (TFC) was quantified via the aluminium chloride colorimetric method with quercetin as a standard. AOA was measured using the DPPH free radical scavenging assay with ascorbic acid as a standard. Screening of the extracts for anticancer effect *in vitro* was conducted on human-derived cell lines, A549 lung cancer, MDA-MB-468 triple negative breast cancer, and PC-3 prostate cancer using the MTT assay. The highest TPC (402.40 ± 0.09 mgGAE/g) and the best AOA (IC_{50} = 0.08 mg/mL) were recorded for the MS extract. CH and JBL extracts showed the highest TTC (249.36 ± 0.01 mgGAE/g) and TFC (80.79 ± 0.05 mgQE/g), respectively. MaR extract displayed preferential CA against MDA-MB-468 (IC_{50} = 6.86 μg/mL) while showing reduced CA for A549 and PC-3 (IC_{50} = 39.45 μg/mL and > 100 μg/mL, respectively). Further studies are underway to explore the potent effect of MaR against breast cancer and to identify the bioactive component(s) responsible for its cytotoxicity. *The authors marked with an asterisk equally contributed to the work.

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Development of a novel small circular DNA decoy inhibitor targeting STAT3 for cancer therapy

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Aberrant activation of Signal Transducer and Activator of Transcription 3 (STAT3) is a hallmark of several cancers, including ovarian and breast cancer. Active STAT3 translocates to the nucleus, where it regulates the expression of several genes involved in cell cycle progression, survival and proliferation, through recognition of specific DNA sequences, called gamma-activated sites (GAS), by the DNA-binding domain (DBD) of STAT3. STAT3's involvement in these key processes makes it a promising therapeutic target. Current STAT3 inhibitors, including chemical compounds and linear DNA-based decoys, face significant challenges, such as limitations in specificity and rapid degradation inside the cell. This study introduces a novel approach using a small circular DNA decoy inhibitor containing three GAS motifs highly specific for the DBD of STAT3. The circular structure enhances the stability of the molecule, potentially improving its half-life inside the cell and the multiple binding sites increase its ability to capture STAT3 more effectively. To construct the circular DNA decoy, single-stranded oligonucleotides with GAS sequences were ligated into a circular form using complementary splint oligonucleotides, followed by annealing to form double-stranded constructs. Circularity was confirmed through enzymatic restriction analysis. A control

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