

Supplementary Table 1. Effect of 0.1% DMSO vehicle control on the viability of MCF-7 breast cancer cells and human foreskin fibroblasts (HFF) at 24 and 72 hours.

Cell Line	Incubation Time	Treatment Condition	Cell Viability (% of untreated control, mean $\pm$ SD)	<i>P</i> -value (vs. untreated control)
MCF-7	24 hours	Untreated control	100.0 $\pm$ 3.2	0.673
		0.1% DMSO	99.2 $\pm$ 2.8	
	72 hours	Untreated control	100.0 $\pm$ 4.1	0.512
		0.1% DMSO	98.5 $\pm$ 3.5	
HFF	24 hours	Untreated control	100.0 $\pm$ 2.9	0.481
		0.1% DMSO	101.3 $\pm$ 2.5	
	72 hours	Untreated control	100.0 $\pm$ 3.4	0.842
		0.1% DMSO	99.6 $\pm$ 3.1	

Data are presented as mean $\pm$ standard deviation (SD) from three independent biological experiments, each performed in technical triplicate. *P*-values were calculated using one-way ANOVA followed by LSD post-hoc test comparing the 0.1% DMSO vehicle control group against the untreated control group. No statistically significant difference was observed at any time point or in any cell line ($p > 0.05$ for all comparisons), confirming that 0.1% DMSO alone does not affect cell viability.

Supplementary Table 2: Detailed Parameters of the MTT Assay Procedure

Parameter	Specification
Cell seeding density	10,000 cells per well
Culture plate type	96-well flat-bottom plate
Incubation time before treatment	24 hours (to achieve confluence)
Drug concentration range	0.1, 1, 10, 100, 1000 µg/mL
Replicates per concentration	6 technical replicates
Treatment incubation periods	24 and 72 hours
MTT solution concentration	2 mg/mL
Volume of MTT added per well	28 µL
MTT incubation time	3 hours
Solubilization agent	DMSO (dimethyl sulfoxide)
Volume of DMSO added per well	100 µL
Solubilization incubation time	15 minutes
Absorbance measurement wavelength	570 nm
Reference wavelength (if used)	630 nm (background subtraction)
Microplate reader model	Synergy HTX (BioTek, USA)

Supplementary Table 3: Comparison of paclitaxel, dapagliflozin, pantoprazole, and their mixture in inhibiting MCF7 cancer cell growth over 24 hours.

Concentration ($\mu\text{g/ml}$)	Cellular proliferation inhibition (mean $\pm$ SD)				LSD
	paclitaxel	dapagliflozin	pantoprazole	mix	
0.1	E 11 $\pm$ 1.5 a	E 0 $\pm$ 0.5 b	D 2 $\pm$ 0.8 b	E 13 $\pm$ 1.2 a	2.8
1	D 18 $\pm$ 2.1 b	D 9 $\pm$ 1.4 c	D 4 $\pm$ 1.0 d	D 28 $\pm$ 2.3 a	3.2
10	C 24 $\pm$ 2.8 b	C 15 $\pm$ 2.1 c	C 16 $\pm$ 2.2 c	C 41 $\pm$ 3.1 a	6.5
100	B 47 $\pm$ 3.9 b	B 37 $\pm$ 3.2 c	B 22 $\pm$ 2.8 d	B 62 $\pm$ 4.2 a	8.1
1000	A 62 $\pm$ 4.5 b	A 49 $\pm$ 3.8 c	A 46 $\pm$ 3.8 c	A 76 $\pm$ 4.8 a	10.9
IC 50	212.5 $\mu\text{g/ml}$	>1000 $\mu\text{g/ml}$	>1000 $\mu\text{g/ml}$	42.8 $\mu\text{g/ml}$	-
LSD value	5.1	2.35	2.85	4.1	-

The data are shown as the mean $\pm$ standard deviation (SD) of cellular proliferation inhibition (%). Within each row, different lowercase letters indicate statistically significant differences ($p < 0.05$) among treatments at the same concentration. Similarly, within each column, different uppercase letters denote significant differences ($p < 0.05$) among treatments at the same concentration, as determined by one-way ANOVA followed by the Least Significant Difference (LSD) post-hoc test. The LSD values represent comparisons between concentrations within each treatment group.

Supplementary Table 4: Comparison of paclitaxel, dapagliflozin, pantoprazole, and their mixture in inhibiting MCF7 cancer cell growth over 72 hours.

Concentration ($\mu\text{g/ml}$)	Cellular proliferation inhibition (mean $\pm$ SD)				LSD
	paclitaxel	dapagliflozin	pantoprazole	mix	
0.1	E 2 $\pm$ 0.8 c	E 4 $\pm$ 1.1 bc	E 5 $\pm$ 1.2 b	E 27 $\pm$ 2.1 a	2.7
1	D 7 $\pm$ 1.2 c	D 17 $\pm$ 2.0 b	D 11 $\pm$ 1.8 c	D 46 $\pm$ 3.1 a	4.5
10	C 16 $\pm$ 2.1 c	C 29 $\pm$ 2.8 b	C 20 $\pm$ 2.5 c	C 56 $\pm$ 3.8 a	5.3
100	B 33 $\pm$ 3.2 c	B 45 $\pm$ 3.6 b	B 37 $\pm$ 3.3 bc	B 72 $\pm$ 4.5 a	8.2
1000	A 39 $\pm$ 3.8 c	A 59 $\pm$ 4.2 b	A 53 $\pm$ 4.1 b	A 86 $\pm$ 5.1 a	9.1
IC 50	>1000 $\mu\text{g/ml}$	357.1 $\mu\text{g/ml}$	812.5 $\mu\text{g/ml}$	4.1 $\mu\text{g/ml}$	-
LSD value	3.9	3.25	3.15	5.2	-

The data are shown as the mean $\pm$ standard deviation (SD) of cellular proliferation inhibition (%). Within each row, different lowercase letters indicate statistically significant differences ($p < 0.05$) among treatments at the same concentration. Similarly, within each column, different uppercase letters denote significant differences ($p < 0.05$) among treatments at the same concentration, as determined by one-way ANOVA followed by the Least Significant Difference (LSD) post-hoc test. The LSD values represent comparisons between concentrations within each treatment group.

Supplementary Table 5: Selective Toxicity Index (SI) of the triple-drug mixture and cisplatin against MCF7 breast cancer cells and normal human foreskin fibroblasts (HFF).

Treatment	Incubation Time	IC ₅₀ (µg/mL)		Selective Toxicity Index (SI)	Interpretation
		(MCF7)	(HFF)		
Triple Mixture	24 hours	42.8	>1000	>23.3	Highly selective
	72 hours	4.1	>1000	>243.9	Highly selective
Paclitaxel	24 hours	212.5	253.3	<0.253	Non-selective
	72 hours	>1000	72.6	0.341	Non-selective

The Selective Toxicity Index (SI) was calculated by dividing the IC₅₀ value in HFF cells by the IC₅₀ value in MCF7 cells. An SI greater than 1 indicates preferential targeting of cancer cells, whereas an SI less than 1 indicates greater toxicity to normal cells. Values marked with ">" suggest that the IC₅₀ exceeds the highest tested concentration of 1000 µg/mL.

Supplementary Table 6: CI and DRI values for the triple mixture of (paclitaxel – dapagliflozin - pantoprazole) after 24 and 72 hours of incubation.

24-hour incubation period						
(concentration µg/ml) The ratio of paclitaxel, dapagliflozin, and pantoprazole in the mixture is (1:1:1)		CI score	Combination outcome	DRI value		
mixture	Individual concentrations of mixture drugs			PTX	dpf	ptz
0.1	0.0333	0.00705	Very Strong Synergism	271.018*	1041.41*	416.871*
1	0.333	0.00922	Very Strong Synergism	334.159*	253.771*	436.745*
10	3.333	0.03497	Very Strong Synergism	153.480*	43.5713*	181.720*
100	33.333	0.11735	Strong Synergism	144.393*	9.64656*	147.837*
1000	333.333	0.58446	Synergism	82.3942*	1.78876*	75.3524*
72-hour incubation period						
0.1	0.0333	0.00854	Very Strong Synergism	201.248*	402.638*	923.612*
1	0.333	0.00611	Very Strong Synergism	376.811*	389.057*	1123.84*
10	3.333	0.01778	Very Strong Synergism	154.338*	115.905*	374.088*
100	33.333	0.02148	Very Strong Synergism	182.433*	78.4408*	307.477*
1000	333.333	0.01692	Very Strong Synergism	388.362*	83.7137*	417.416*

Compusyn software was used to calculate the Combination Index (CI) and Dose Reduction Index (DRI) values. A CI above 1 signifies antagonism, a CI of exactly 1 indicates an additive effect, and a CI below 1 suggests synergy. A DRI greater than 1 reflects decreased toxicity. An asterisk (*) marks a beneficial reduction in the effective cytotoxic concentration.(52). **PTX:** paclitaxel, **dpf:** dapagliflozin, **ptz:** pantoprazole.

Supplementary Table 7: ELISA Biomarker Quantification in MCF-7 Cells

Treatment Group	HIF-1 α (pg/mg protein)	p-mTOR (pg/mg protein)	Cathepsin D (ng/mg protein)	LC3B-II (ng/mg protein)	Cleaved Caspase-3 (pg/mg protein)
Untreated Control	A 450.2 $\pm$ 25.3	A 320.5 $\pm$ 18.7	A 180.3 $\pm$ 12.4	A 85.6 $\pm$ 7.2	C 15.3 $\pm$ 2.1
Paclitaxel monotherapy (212.5 μ g/mL)	C 620.8 $\pm$ 30.1	B 510.2 $\pm$ 28.9	B 250.6 $\pm$ 18.9	B 120.3 $\pm$ 9.8	B 45.6 $\pm$ 4.3
Dapagliflozin monotherapy (0.33 μ g/mL)	AB 430.5 $\pm$ 22.4	A 305.8 $\pm$ 20.1	A 175.8 $\pm$ 10.2	A 90.1 $\pm$ 6.5	C 18.9 $\pm$ 2.5
Pantoprazole monotherapy (0.33 μ g/mL)	B 410.3 $\pm$ 24.6	A 295.6 $\pm$ 17.3	A 168.9 $\pm$ 11.8	A 88.7 $\pm$ 7.8	C 20.1 $\pm$ 2.8
Triple Combination (1 μ g/mL total)	D 280.6 $\pm$ 18.9	C 185.4 $\pm$ 15.2	C 95.3 $\pm$ 8.7	C 210.5 $\pm$ 12.6	A 110.8 $\pm$ 9.4
LSD	32.1	25.8	18.3	12.7	8.6

Results are exhibited as (average $\pm$ standard deviation) from three separate biological experiments. Within each column, diverse capital letters (A, B, C, D) revealed statistically significant differences ($p < 0.05$) among treatment groups, based on one-way ANOVA followed by the Least Significant Difference (LSD) test. The LSD: least significant difference.

Supplementary Table 8: ELISA Biomarker Quantification in HFF Cells

Treatment Group	NF-κB p65 (pg/mg protein)	HO-1 (ng/mg protein)	Bcl-2 (pg/mg protein)	Bax (pg/mg protein)	Bax/Bcl-2 Ratio
Untreated Control	A 120.5 ± 10.2	A 15.3 ± 1.8	A 450.3 ± 25.6	A 85.6 ± 7.2	A 0.19 ± 0.03
Paclitaxel monotherapy (212.5 µg/mL)	A 480.6 ± 32.1	B 65.8 ± 5.9	B 220.1 ± 18.9	B 320.5 ± 22.4	B 1.46 ± 0.12
Dapagliflozin monotherapy (0.33 µg/mL)	A 115.8 ± 9.8	A 16.1 ± 2.1	A 440.8 ± 24.3	A 90.1 ± 8.2	A 0.20 ± 0.04
Pantoprazole monotherapy (0.33 µg/mL)	A 110.4 ± 8.9	A 17.2 ± 2.0	A 460.2 ± 26.7	A 88.7 ± 7.9	A 0.19 ± 0.03
Triple mixture (1 µg/mL total)	A 130.2 ± 11.3	A 18.9 ± 2.3	A 430.5 ± 23.8	A 95.3 ± 8.6	A 0.22 ± 0.04
LSD	36.8	6.4	42.5	24.9	0.16

Results are exhibited as (average ± standard deviation) from three separate biological experiments. Within each column, diverse capital letters (A, B, C, D) revealed statistically significant differences ($p < 0.05$) among treatment groups, based on one-way ANOVA followed by the Least Significant Difference (LSD) test. The LSD: least significant difference

Supplementary Table 9: Comparative Molecular Docking Results: Binding Affinities.

Target	Test Compound	Binding Affinity (ΔG , kcal/mol)	Reference Inhibitor	Binding Affinity (ΔG , kcal/mol)	Affinity Ratio (Test/Ref)	Synergistic Impact Score
PDK1	Dapagliflozin	-8.4	Dichloroacetate	-4.2	2.00	8.7
Cathepsin D	Pantoprazole	-8.3	Odanacatib	-8.8	0.94	8.5
SGLT2	Dapagliflozin	-8.3	—	—	—	8.4
MMP9	Pantoprazole	-9.0	Marimastat	-7.3	1.23	8.9
TRPV1	Dapagliflozin	-8.4	SB-705498	-8.0	1.05	8.2
COX-2	Pantoprazole	-8.8	Celecoxib	-8.1	1.09	8.7

The Synergistic Impact Score (SIS) was derived via a weighted, multi-criterion assessment on a 1–10 continuum, accounting for binding affinity, interaction complexity, and target relevance within the framework of the postulated triple-agent mechanism. **IMPORTANT CAVEAT:** The SIS is an unverified, newly introduced index designed exclusively for hypothesis generation and the exploratory ordering of computational docking forecasts. This metric lacks empirical substantiation and must not be construed as a quantitative indicator of genuine biological cooperativity. Elevated SIS values indicate a predicted greater likelihood of contributing to the overall synergistic effect as postulated in this exploratory model; nevertheless, such projections require empirical verification. The presence of a dash (—) indicates the lack of a reference inhibitor for comparative purposes in the given target context.

Supplementary Table 10: In Silico Prediction of Potential Pharmacokinetic Drug-Drug Interactions within the Triple Combination – Hypothesis-Generating Observations

Precipitant Drug	Object Drug	Interacting System	Predicted Effect	Likelihood	Hypothetical Clinical Outcome
Pantoprazole	Paclitaxel	CYP3A4 Inhibition	Elevate Systemic exposure (AUC) of Paclitaxel	Weak / Possible	Theoretically enhanced antitumor efficacy, but also potentially increased paclitaxel-associated toxicities
Pantoprazole	Paclitaxel	P-gp Inhibition	elevate Intracellular accumulation of Paclitaxel	Weak / Possible	Hypothetically may overcome efflux-based resistance, consistent with observed DRI
Pantoprazole	Dapagliflozin	P-gp Inhibition	Elevate Bioavailability & tissue levels of Dapagliflozin	Possible	May theoretically support metabolic reprogramming effects; minimal impact on glycemic control expected
Dapagliflozin	Paclitaxel	--	No significant interaction predicted	Unlikely	—

AUC, Area Under the Curve; **P-gp**, P-glycoprotein; **DRI**, Dose Reduction Index. This table presents hypothesis-generating in silico predictions derived from literature mining and the Liverpool Drug Interaction Group database. These predictions have not been experimentally validated in this study. The concentrations used in our in vitro experiments (0.33–333 µg/mL for pantoprazole) substantially exceed typical human plasma levels (~5–10 µg/mL). Therefore, these findings should be interpreted cautiously and considered speculative until confirmed in physiologically relevant models.