Combination Therapy Utilizing Cannabinoids and Nab-Paclitaxel in combating pancreatic cancer

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INTRODUCTION

Pancreatic cancer is the fourth cause of morality amongst cancer death which can be due to poor prognosis and drug resistance. As of 2024, the 5-year survival rate increased to 13% compared to the last decade which was less than 5%. The standard treatment for pancreatic cancer is Gemcitabine with combinations of other chemotherapy drugs such as nab-Paclitaxel, 5-FU and Oxaliplatin. Pancreatic cancer cells overly express CB1 and CB2 receptors compare to normal pancreatic cancer cells. These receptors are part of the endocannabinoid system which plays a role in regulating various physiological process including appetite, pain sensation , mood and inflammation. Cannabinoids have been studied extensively in other types of cancer however, the combination of cannabinoids have not been studied in pancreatic cancer.

MATERIALS AND METHODS

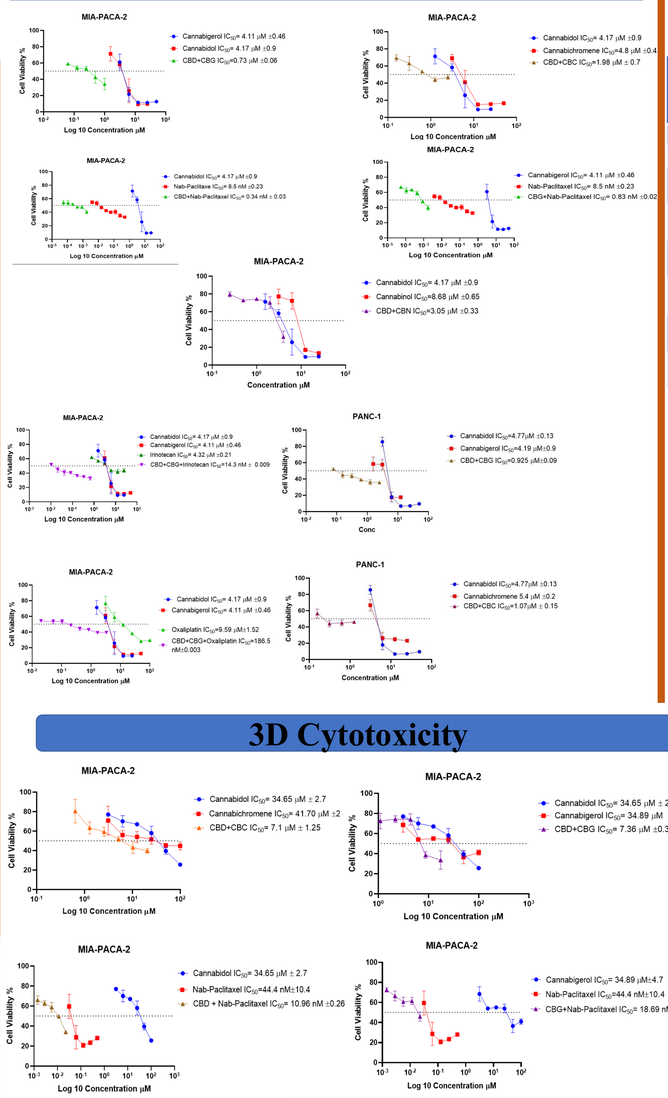
- ❖Several cannabinoids such as Cannabichromene (CBC), Cannabidiol (CBD), Cannabigerol(CBG),Cannabidvarin (CBDV), Cannabinol(CBN) and Cannabidolic acid (CBDa) were screened for their cytotoxicity effect in two pancreatic cancer cell line
- ❖ Combination index were calculated for tested combination using Compusyn software
- ❖ In vivo studies was performed and tumor volume was measured with calipers.
- ❖ Migration assay was performed by transwell invasion plate. Miapaca-2 cell line were treated with Cannabidiol, Cannabichromene and the combination of Cannabidiol and Cannabichromene based on their IC50 and IC25 respectively.

RESULTS AND DISCUSSION

Cell viability studies

Compound	MIAPACA-2 (IC50)	PANC-1(IC50)	PDX (CCT-4IT) (IC50)
Gemcitabine	1.87 µM± 0.13	11.51 µM±1.1	10.66 µM±0.18
5-FU	4.02 µM± 0.31	18.2µM± 1.9	47.39 µM±0.4
Paclitaxel	190 nM ±0.01	1.02 µM± 0.22	21.05µM±0.9
Nab-Paclitaxel	8.59 nM ±0.23	95.79 nM±0.61	-
Irinotecan	4.32µM± 0.21	5.2µM± 0.24	22.49 µM±1
Oxaliplatin	9.59 µM± 1.52	19.29µM± 1.33	83.57 µM±11.49
Cisplatin	8.86µM± 0.16	29.65 µM± 3.6	-
Cannabidiol	4.43µM± 0.9	4.77µM± 0.13	4.05 µM±0.125
Cannabigerol	4.11µM± 0.46	4.19µM± 0.9	4.94 µM±0.17
Cannabichromene	4.87µM± 0.4	5.4µM± 0.2	7.84 µM±0.33
Cannabinol	8.68µM± 0.65	9.87µM± 0.08	5.83 µM±0.2
Cannabidolic acid	16.51µM± 0.87	46.02µM± 0.6	-
Cannabidivarin	9.79µM± 1.4	5.73µM± 0.13	8.37 µM±1.09

2D Cytotoxicity



3D Cytotoxicity

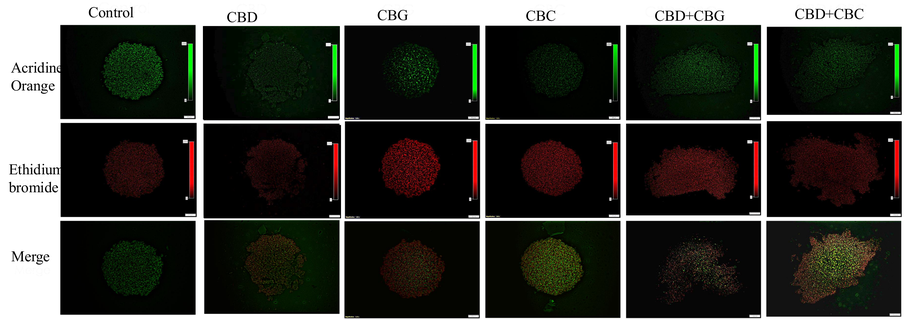
2D Isobiolographic Analysis

Combination	Dose of CBD	Dose Cannabinoid	Dose Standard Care Drug	Combination Index	Synergistic, Additive , Antagonistic
CBD+CBC	2 µM	1.25 µM		0.38	Synergistic
CBD+CBG	2 µM	2 µM		0.36	Synergistic
CBD+Nab-Paclitaxel	1 µM	-	0.05 nM	0.35	Synergism
CBG+Nab-Paclitaxel	1 µM	-	0.875 nM	0.5	Synergism
CBD+CBG+Gemcitabine	670 nm	670 nm	2.6 nM	0.51	Synergistic
CBD+CBG+ Paclitaxel	670 nm	670 nm	0.494 nM	0.62	Synergistic
CBD+CBG+ Irinotecan	670 nm	670 nm	10.39 nM	0.44	Synergistic
CBD+CBG+ Oxaliplatin	670 nm	670 nm	26.04 nM	0.77	Synergistic

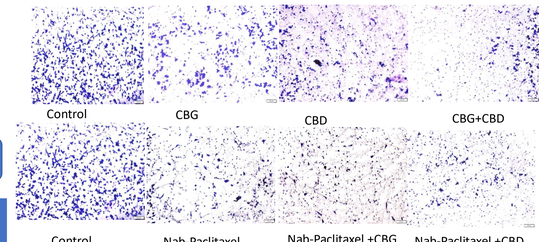
3D Isobiolographic Analysis

Combination	Cannabidiol Dose	Cannabinoid Dose/Standard Care Drug Dose	Combination Index	Synergistic, Additive, Antagonistic
CBD+CBG	17.5 µM	8.75 µM	0.53	Synergism
CBD+CBC	17.5 µM	20.5 µM	0.78	Moderate Synergism
CBD+Nab-Paclitaxel	17.5 µM	22.5 nM	0.5	Synergism

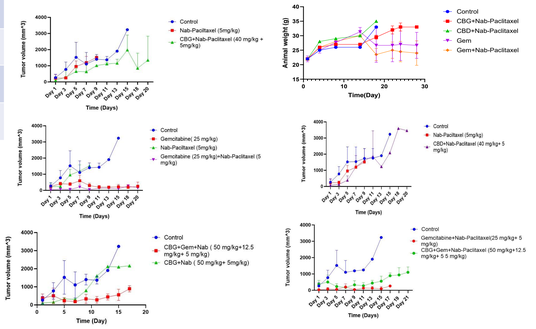
Live/Dead Assay



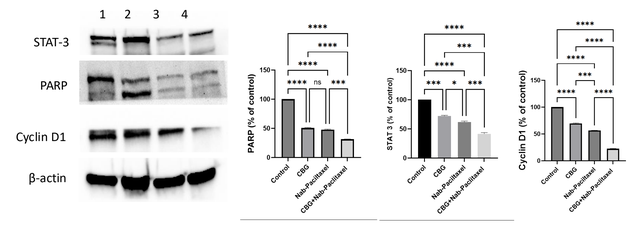
Migration



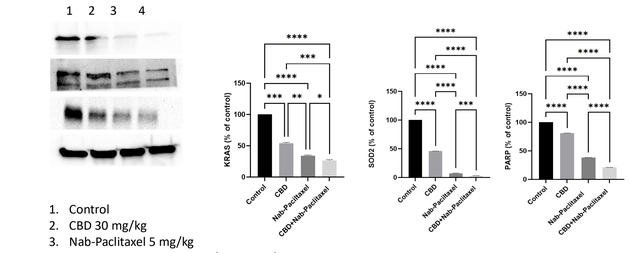
Tumor volume



Western blot



1. Control
2. CBG 30 mg/kg
3. Nab-Paclitaxel 5 mg/kg
4. CBG + Nab-Paclitaxel 40 mg/kg+ 5 mg/kg



1. Control
2. CBD 30 mg/kg
3. Nab-Paclitaxel 5 mg/kg
4. CBD+Nab-Paclitaxel 40 mg/kg + 5 mg/kg

CONCLUSION

CBG + nab-paclitaxel (nab) demonstrated superior anti-tumor efficacy in vivo compared to CBD + nab, despite in vitro studies suggesting otherwise.
Gemcitabine + nab was the most potent combination in vivo but was associated with significant systemic toxicity, as indicated by marked weight loss in mice.
Increasing the dose of CBG further inhibited tumor progression, highlighting its potential as a more effective adjunct to nab-paclitaxel.
CBD + nab combination showed limited efficacy in vivo, as tumor volume continued to increase in treated animals.
These findings underscore the importance of in vivo validation and suggest CBG as a more promising cannabinoid than CBD in combination therapies with nab-paclitaxel.

- Cannabinoids were found to be more cytotoxic as compared to some standard treatment of pancreatic cancer e.g Oxaplatin and Cisplantin
- Further testing of cannabinoids in pancreatic cancer is currently undergoing. (Funded by RCMI Project number-006265

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