Combination therapy using Cannabinoids in combating pancreatic cancer

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INTRODUCTION

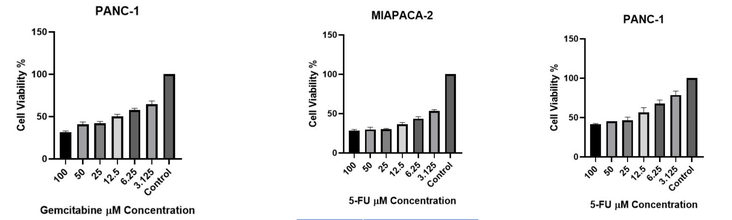
Pancreatic cancer is the fourth cause of morality amongst cancer death which can be due to poor prognosis and drug resistance. As of 2024, the 5-year survival rate increased to 13% compared to the last decade which was less than 5%. The standard treatment for pancreatic cancer is Gemcitabine with combinations 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
- ❖ Western blot was performed in vitro of Mipaca-2 cell line. Miapaca-2 cell line were treated with Cannabidiol, Cannabichromene and the combination of Cannabidiol and Cannabichromene based on their IC50 and IC25 respectively.
- ❖ Migration assay was performed by using inserts with 6 well plates over 48 hours. 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

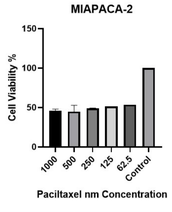
Cell viability studies



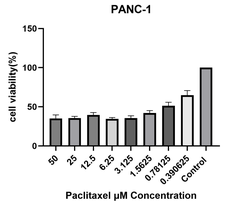
IC50	11.51 µM
SD	1.1

IC50	4.02 µM
SD	0.31

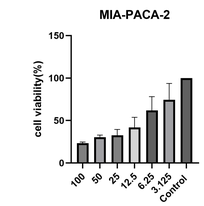
IC50	18.2 µM
SD	1.9



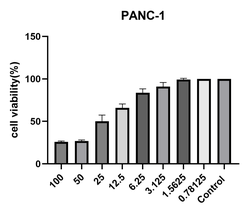
IC50	190 nm
SD	0.01



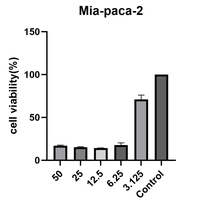
IC50	1.02 µM
SD	0.22



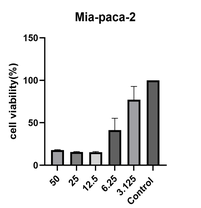
IC50	8.86 µM
SD	0.16



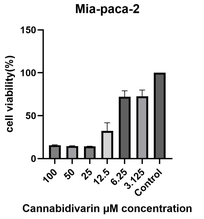
IC50	29.65 µM
SD	3.6



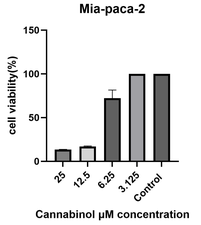
IC50	4.32 µM
SD	0.22



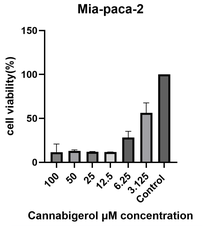
IC50	4.87 µM
SD	0.4



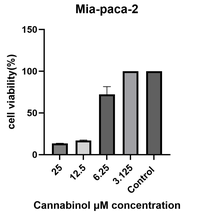
IC50	9.79 µM
SD	1.4



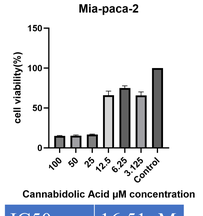
IC50	8.68 µM
SD	0.65



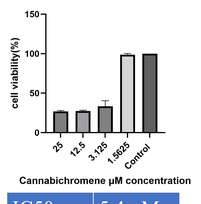
IC50	4.16 µM
SD	0.84



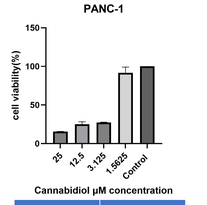
IC50	8.68µM
SD	0.65



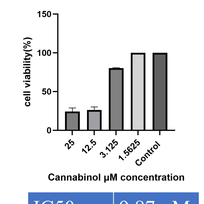
IC50	16.51µM
SD	0.87



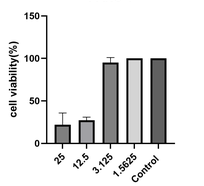
IC50	5.4 µM
SD	0.2



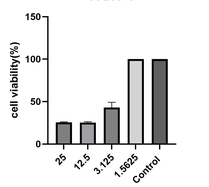
IC50	4.27µM
SD	0.6



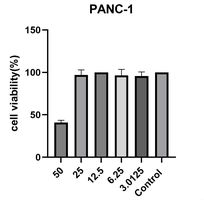
IC50	9.87 µM
SD	0.08



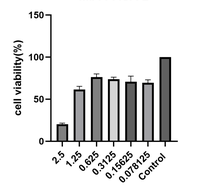
IC50	10.3µM
SD	0.4



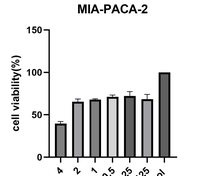
IC50	5.73 µM
SD	0.13



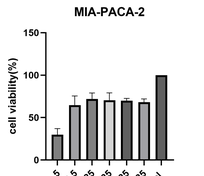
IC50	46.02µM
SD	0.6



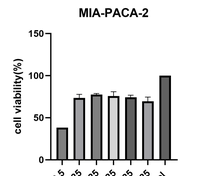
IC50	1.54µM
SD	0.06



IC50	3.05 µM
SD	0.33



IC50	3.6µM
SD	0.37

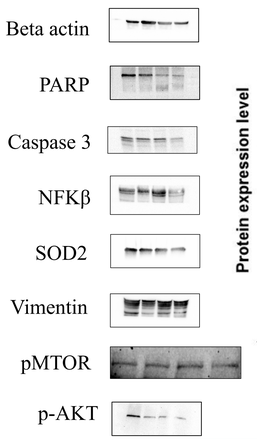


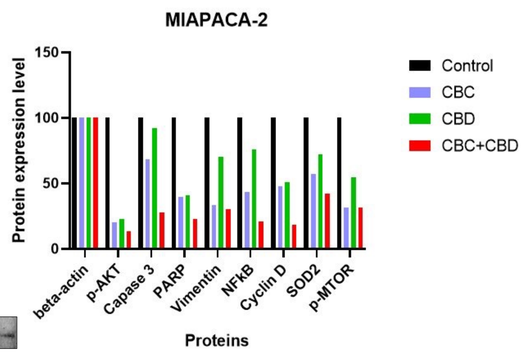
IC50	1.98µM
SD	0.7

Isobolographic analysis Miapaca-2

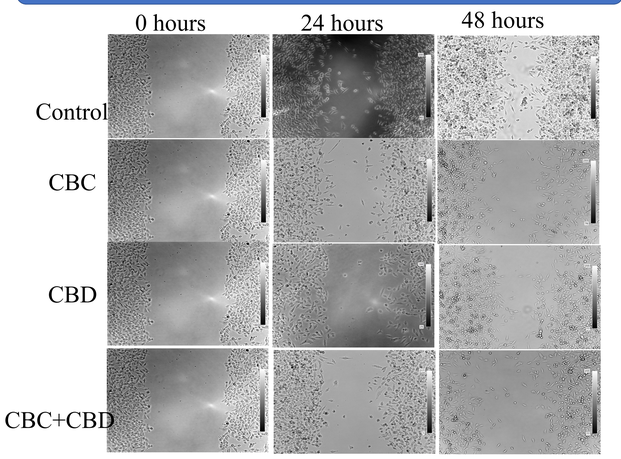
Combination	Dose Cannabinoid	Dose Cannabinoid	Combination Index	Synergistic, Additive , Antagonistic
CBD+CBC	2 µM	1.25 µM	0.38	Synergistic
CBD+CBG	2 µM	2 µM	0.36	Synergistic
CBD+CBN	2 µM	4 µM	0.49	Synergistic
CBD+CBDV	2 µM	5 µM	0.37	Synergistic

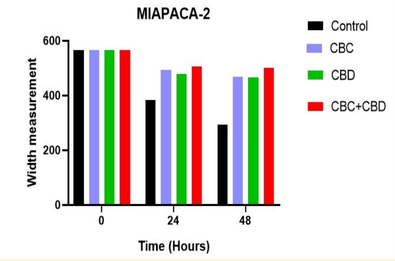
Western blot





Migration





CONCLUSION

Cannabinoids showed significant cytotoxic effect in pancreatic cancer.

- The combination of CBC and CBD demonstrated the most synergy amongst all the combinations.
- Cannabinoids could be an effective adjunct treatment for pancreatic cancer.
- Cannabinoids were found to be more cytotoxic as compared to the standard treatment of pancreatic cancer e.g. taxol, gemcitabine, 5 FU. CBD, CBC could decrease the IC50 of Cisplatin by two-fold, Gemcitabine by eight-fold , and 5-FU by three-fold in Miapaca cell lines.
- Further testing of cannabinoids in pancreatic cancer is currently undergoing.

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REFERENCES

- Arthur, P., Kandol, S., Sun, L. et al. Biophysical, Molecular and Proteomic Profiling of Human Retinal Organoid-Derived Exosomes. Pharm Res (2022). https://doi.org/10.1007/s11095-022-03350-7
- Chirco KR, Chew S, Moore AT, Duncan JL, Lamba DA. Allele-specific gene editing to rescue dominant CRX-associated LCA7 phenotypes in a retinal organoid model. Stem cell reports. 2021;16(11):2690–702.