Table S1. Anticancer effects of cannabinoids with relative references

Cannabinoid	Effects	References

Anandamide (AEA)	Lung cancer: • Inhibition of lung cancer cells spreading Gastrointestinal cancer: • Reduction of cell volume and density; induction of G0/G1 cell cycle arrest and apoptosis (Gastric) • Reduction of tumor growth *in vivo*; downregulation of angiogenic factors VEGF-C, VEGF-R2, and VEGF–R3 *in vivo* (Cholangiocarcinoma) • Tumor suppressive effect via GPR55 depending on JNK activation *in vitro* and *in vivo*(Cholangiocarcinoma) Breast cancer: • Modulation cAMP/protein kinase A and MAPK pathway • Inhibition cell cycle progression G1/S transition Prostate cancer: • Decrease the proliferative action of EGF and cycle cellular arrest in the G1 phase • Increase apoptosis and necrosis	• Winkler et al. [17] • Ortega et al. [42] • DeMorrow et al. [43] • DeMorrow et al. [43] Huang et al. [44] • Kiskovà et al. [74] • Mimeault et al. [86] • Sarfaraz et al. [85]
R(+)-methanandamide (Met-AEA o AM-356)	Gastrointestinal cancers: • G0/G1 cell cycle arrest and necrosis induction (Gastric)	 • Ortega et al. [42]
2-methyl-2′-F-anandamide (Met-F-AEA)	Lung cancer: • In combination with the FAAH inhibitor URB597 caused G0/G1 cell cycle arrest mediated apoptosis • Reduced metastasis inhibiting migratory structures formation as well as MMPs secretion Gastrointestinal cancers: • Increase of AEA availability; decrease of proliferation rate due to CB1 up-regulation through the transcriptional activation of CNR1 promoter(Colorectal) Breast cancer: • Antipoliferative activity • Inhibition of the EMT Thyroid cancer: • Increase apoptosis via activation of p53 signalling and expression of p21	 • Ravi et al. [66] • Ravi ey al. [71] • Proto et al.[45] • Laezza et al.,[79] • Laezza et al., [80] • Grimaldi et al [81] • Cozzolino et al. [105]
arachidonyl-2-chloroethylamide (ACEA)	Lung cancer: • Inhibition of angiogenic and lymphangiogenic factors release Breast cancer: • Decrease the invasive potential of breast cancer stem cells Pancreatic cancer: • Induction of ROS-mediated autophagy via activation of AMPK and inhibition of energetic metabolism	 • Staiano et al. [63] • Elbaz et al. [76] • Dando et al. [100]

	• Inhibition of glycolysis via decreasing of the glycolytic enzymes, GAPDH and PKM2 • Increase of the anticancer potential in combination with gemcitabine	• Donadelli et al.[101]
Δ9-tetrahydrocannabinol (THC o Δ9-THC)	Brain Cancer : • THC reduce tumor grothw in orthotopic and subcutaneous animal models of glioma • Increase in formation of ROS linked with apoptosis • THC and /or CBD induce a cell cycle arrest • THC could reduce pro-angiogenic VEGF levels in two patients with recurrent GBM • THC was able to down regulate TIMP-1 and MMP-2 • clinical trial NCT01812603 of THC:CBD in combination with dose-intense TMZ Lung cancer: • Inhibition of tumor growth *in vivo* and *in vitro* • Reduction of signalling molecules(FAK, ERK1/2 and AKT) involved in survival and ECM remodelling Gastrointestinal cancers: • Induction of apotosis and downregulation of PI3K/Akt pathway (Colorectal) • Inhibition of tumor growth *in vitro* and *in vivo* associated to increased ceramide, ER-stress, PPAR-γ activity and autophagy (Hepatocellular) Pancreatic cancer: • Induction of apoptosis via stimulation of the *de novo* ceramide synthesis and consequent up-regulation of ER stress-related genes *p8*, *atf-4* and *trb3*.	• Rocha et al. [111] • Marcu et al. [113] • Marcu et al., [113] • Blàzquez et al. [117] • Blàzquez et al., [123] • Schultz and Beyer, [128,129], • Munson et al., [65] • Preet et al., [67] • Greenhough et al. [52] • Vara et al. [53] • Carracedo et al. [99]
Cannabidiol (CBD)	Brain cancer: • CBDreduce tumor grothw in orthotopic and xenograft animal models of Glioma • Increase of ROS and upregulation of heat-shock protein (HSP) super family • Induce endothelial cell cytostasis, , inhibited endothelial cell migration and angiogenesis in vivo • Anti-invasive effect in GBM cell lines with inhibition of Id-1 expression • Treatment with CBD inducing autophagy and abrogating the chemoresistance of GSCs at BCNU therapy Lung cancer: • PPARγ-dependent apoptosis; decrease of cellular migration associated to ICAM1 and TIMP1 induction • Decrease of invasiveness associated to PAI1 downregulation Gastrointestinal cancer: • Decrease of cell proliferation, increase of endocannabinoid levels and chemoprotective effect DNA from oxidative insults*in vitro*;reduction of invasion and migration*in vitro*(Colorectal) • Decrease of aberrant crypt foci (ACF) formation, precancerous polyps and tumors in AOM-treated mice counteracting Akt activation induced by AOM (Colorectal)	• Rocha et al. [111] • Scott et al. [114] • Solinas et al. [118] • Soroceanu et al.[121] • Nabissi et al. [126] • Ramer et al. [5] • Ramer et al. [70] • Aviello et al. [49]

	• Induction of apoptosis due to ROS production by mitochondria, ER stress induction and NoxA activation (Colorectal) • Anti-angiogenetic and anti-metastatic effects associated to VEGF downregulation*in vivo;* reduction IL-6 and IL-8 serum levels (Colorectal) <u>Breast cancer</u> • Inhibition of cell viability • Induction of apoptosis/autophagy and ROS generation • Cell cycle arrest at the G1/S transition (via CB1-R) and at the G2/M phase (via CB2-R) • Invasiveness reduction via ID-1 • Inhibition cell migration and angiogenesis • Modulation tumor microenvironment and cytokine production • Increase overexpression of the TRPV2 in TNBC cells <u>Prostate cancer:</u> • Inhibits spheroid formation in cancer stem cells from LNCaP • Downregulate VEGF, PSA and proinflammatory cytokines IL-6/IL.8 • In *vivo* reduce tumor size in LNCaP xenografted mice	• Jeong et al. [50] • Honarmand et al. [51] • Shivastava et al. [75] • Kiskovà et al. [74] • Elbaz et al. [76] • Elbaz et al. [78] • Sharma et al. [91] • De Patrocellis et al. [92]
Cannabinol (CBN)	<u>Lung cancer</u>: • Inhibition of tumor growth *in vivo* and *in vitro*	• Munson et al. [65]
JWH-015	<u>Lung cancer</u>: • EMT inhibition and TAMs recruitment inhibition at the tumor site *in vivo* • Inhibition of EGF-induced proliferation, migration and invasion in NSCLC cell lines and tumor growth and dissemination *in vivo* <u>Gastrointestinal cancers</u>: • Inhibition of tumor growth in vitro and in vivo associated to increased ceramide, ER-stress, PPAR-γ activity and autophagy (Hepatocellular)	• Ravi et al. [71] • Preet et al.[64] • Vara et al. [53]
JWH-133	<u>Brain Cancer:</u> • Inibithion of angiogenesis of malignant gliomas after local administration of nonpsychotic cannabinoid JWH-133 to mice <u>Lung cancer</u>: • Decrease of cellular migration after ICAM1 and TIMP1 induction • Inhibition of angiogenic and lymphangiogenic factors release <u>Thyroid cancer</u>: • Regression of thyroid tumours generated in nude mice by inoculation of the TC cells ARO/CB2	• Blàzquez et al. [116] • Ramer et al. [5] • Staiano et al. [63] • Shi et al., [106]
Win55,212-2	<u>Lung cancer</u>:	

	• Inhibition of EGF-induced proliferation, migration and invasion in NSCLC cell lines and tumor growth and dissemination *in vivo* Gastrointestinal cancer: • Inhibition of proliferation and pro-apoptotic effect*in vitro*(Gastric) • Inhibition of Akt activation and release inhibition of pro-migratory factors (MMP2, VEGF-A) *in vitro* and *in vivo* (Gastric) Prostate cancer: • Inhibition cells survival, growth and proliferation by inhibition of PI3K/Akt/mTOR axis	• Preet et al. [64] • Xian et al. [59] • Xian et al. [60] • Morell et al. [89]
AM251	Pancreatic cancer: • Induction of cytotoxic effects via a receptor-independent mechanism in Mia PaCa2 cell line	• Fogli et al. [103]
pyrrolo-1,5-benzoxazepine-15	Gastrointestinal cancer: • Inhibition of proliferation and pro-apoptotic effect in CRC cell lines; synergistic interaction with 5-FU(Colorectal)	• Fiore et al. [46]
Rimonabant (SR141716)	Brain Cancer: • Cell proliferation arrest, induction caspase-dependent apoptosis and upregulation of the expression of NKG2D ligands Gastrointestinal cancer: • Induction of G2/M arrest and mitotic catastrophe *in vitro;* inhibition of ACF number *in vivo* (Colorectal) • Wnt/β-catenin canonical pathway inhibition *in vitro* and *in vivo* associated to β-catenin degradation and TCF/LEF transcriptional inhibition (Colorectal) • Improvement of 5-FU efficacy in CRC *in vitro* models; • Decrease of CD133+/CD44+population and spheroid formation • Synergistic effect with Oxaliplatin in CRC models	• Ciaglia et al. [119] • Santoro et al. [55] • Proto et al. [56] • Fiore et al. [57] • Gazzerro et al. [58]
URB597	Lung cancer: • Inhibition of lung cancer cells spreading • Enforced the effect Met-F-AEA in inhibiting EGFR phosphorylation and its downstream signal transduction pathways Gastrointestinal cancer: • Reduction of CRC cell lines proliferation	• Winkler et al., 2016 [17] • Ravi et al., 2014 [66] • Proto et al., 2012 [45]

GW405833 (GW)	Pancreatic cancer: • Induction of ROS-mediated autophagy via activation of AMPK and inhibition of energetic metabolism • Inhibition of glycolysis via decreasing of the glycolytic enzymes, GAPDH and PKM2 • Increase of the anticancer potential in combination with gemcitabine	• Dando et al., 2013 [100] • Donadelli et al., 2011 [101]
2-Arachidonoylglycerol 2-AG	Prostate cancer: • Inactivation of protein kinase A and inhibition of the invasive ability of the cells Pancreatic cancer: • Inhibition of cancer cell proliferation both *in vitro* and orthotopic animal models • Immunomodulatory effects in tumour microenvironment	• Nithipatikom et al., 2004 [87] • Qiu et al., 2019 [102]