

Steroids induced cytotoxicity in hepatic cancer cells

Israa Najm Abdullah Al-Ibadi¹, Abdulkareem Khattar Alhatemi², Majida Malik Meteab Alshammari³

Corresponding author: Israa Najm Abdullah Al-Ibadi

Esraa.najm@qu.edu.iq

¹University of al-qadisiyah /College of veterinary medicine, ² Almanathera general hospital/ department of internal medicine, Alnajaf, Iraq, ³ College of Medicine, Jabir Ibn Hayyan Medical University, Alnajaf, Iraq.

Abstract

Hepatic cancer or Hepatocellular carcinoma is a common tumor of liver, in particular between males and it known as a most fatal cancer between others. The usual therapy is sorafenib. Steroids are known for their cell death effect (apoptosis) in case of leukemia, so they are used as supportive therapy along with other treatments against cancer. The study aims to investigate the cytotoxic effect of steroids upon hepatic cancer cells. HepG2 cells are incubated with 1 μ M of steroid Dexamethasone for three days and cytotoxic effect were evaluated by MTT assay. The results shown a significant inhibitory effect of dexamethasone against hepatoma for certain time and dose.

Background:

cancer of liver cells called hepatoma (J. Li et al., 2019; Liao et al., 2020; J. Liu, Y. Shi, et al., 2019; Qu et al., 2019; Wang et al., 2020), this type of cancer are common especially in aged people (I. M. Chen et al., 2020; Fukuda et al., 2019; Horiuchi et al., 2019; Saez-Carlin et al., 2019; Y. Zhou et al., 2019), this type of cancer are routinely treated by doxorubicin via induction of apoptosis in those malignant cells (Zhang, Luo, & Zhang, 2019), in another study Emodin have been used for its anti-hepatic cancer activity (R. S. Zhou et al., 2019) and the response to treatment and metastatic and invasive ability are found to be correlated with Rev-erbbeta gene in those cells (F. Chen, Zhao, & Xia, 2019). Chicken ovalbumin upstream promoter transcription factor II (COUP-TFII), belong to steroid/thyroid hormone receptor superfamily are considered to intermediate angiogenesis in hepg2 alongside with other tested cancer cell lines (Erdos & Balint, 2019). ASP-3 which is taken from fish that target endothelial growth factor receptor (VEGFR) signaling pathway is an another form of gene targeting therapy (Guo et al., 2019). also herbal derivatives are tested for their suppressive effect against hepg2 cells due to downregulating CYP3A4 gene (Kobayashi, Sugaya, Onose, & Abe, 2019), other drugs are designed to regulate metabolism (J. Liu, Q. Yao, et al., 2019). Steroids are already used in treating leukemia by inducing apoptosis but it frequently

examined for its effect on other tumors(Carretero-Gonzalez, Salamanca Santamaria, Castellano, & de Velasco, 2019; Fukuda et al., 2019; Gupta et al., 2019; Kamieniarz et al., 2019; X. Liu et al., 2019; Mahadeo et al., 2020; Matsubayashi et al., 2019; Pigg, Banks, & Siddall, 2019; Shivaji et al., 2019; Takamatsu et al., 2019). In current study we are investigating the effect of dexamethasone as steroids on viability of hepatic cancer cells.

Methods:

Hep G2 cell line as a model of liver cancer cells which derived from hepatocellular carcinoma are incubated with $1\mu\text{M}$ of steroid Dexamethasone for 27 hrs. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) die for cytotoxicity(Arzi, Hoshyar, Jafarzadeh, Riazi, & Sadeghizadeh, 2020; Rodenak-Kladniew, Castro, Starkel, Galle, & Crespo, 2020) were carried out and the effect was compared with not treated cells to unveil the viability of cells after treatment.

Results:

Steroid treatment suppressed the growth of HepG2 at the above mentioned dose and duration (Fig.1), however other cancer cells have been extensively studied for their response to treatment (Chakraborty et al., 2020; Durkin, Vu, & Lee, 2020; Lee et al., 2020; Roberston et al., 2020; Warsame et al., 2020) and proved dose and duration dependent effect (Coyne & Narayanan, 2019; Daniels-Wells et al., 2019; X. Li et al., 2019; Makdasi et al., 2019; Yamasaki et al., 2019). The real pathway of steroid cytotoxicity in hepatic carcinoma need to be more investigated.

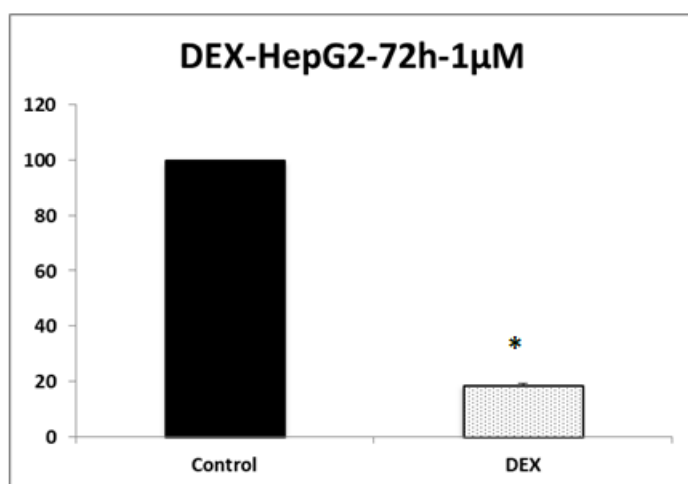


Figure 1 Hepatic cancer cell line treated with dexamethasone $1\mu\text{M}$ for 72hrs , growth inhibition effect are noticed. Experiment repeated 3 times in triplicate , significant different are calculated by T- test

Conclusion:

A standard MTT method was used to determine the cytotoxic/ carcinogenic effect of steroids on liver tumor cells and that revealed it may included in hepatocellular carcinoma therapy

Keywords: steroids, MTT, Hepatic cancer

Steroids inhibition effect against hepatic cancer .

References

- Arzi, L., Hoshyar, R., Jafarzadeh, N., Riazi, G., & Sadeghizadeh, M. (2020). Anti-metastatic properties of a potent herbal combination in cell and mice models of triple negative breast cancer. *Life Sci*, 117245. doi:10.1016/j.lfs.2019.117245
- Carretero-Gonzalez, A., Salamanca Santamaria, J., Castellano, D., & de Velasco, G. (2019). Three case reports: Temporal association between tyrosine-kinase inhibitor-induced hepatitis and immune checkpoint inhibitors in renal cell carcinoma. *Medicine (Baltimore)*, 98(47), e18098. doi:10.1097/MD.00000000000018098
- Chakraborty, R., Bin Riaz, I., Malik, S. U., Marneni, N., Mejia Garcia, A., Anwer, F., . . . Majhail, N. S. (2020). Venous thromboembolism risk with contemporary lenalidomide-based regimens despite thromboprophylaxis in multiple myeloma: A systematic review and meta-analysis. *Cancer*. doi:10.1002/cncr.32682
- Chen, F., Zhao, J. L., & Xia, H. B. (2019). [Rev-erb β Knock-out Affects the Proliferation, Migration and Invasion Ability of Hepatocellular Carcinoma HepG2 Cell Line in vitro]. *Sichuan Da Xue Xue Bao Yi Xue Ban*, 50(4), 520-526.
- Chen, I. M., Johansen, A. Z., Dehlendorff, C., Jensen, B. V., Bojesen, S. E., Pfeiffer, P., . . . Johansen, J. S. (2020). Prognostic Value of Combined Detection of Serum IL6, YKL-40, and C-reactive Protein in Patients with Unresectable Pancreatic Cancer. *Cancer Epidemiol Biomarkers Prev*, 29(1), 176-184. doi:10.1158/1055-9965.EPI-19-0672
- Coyne, C. P., & Narayanan, L. (2019). Mebendazole in simultaneous combination with dexamethasone-(C21-phosphoramidate)-[anti-EGFR] generated utilizing a novel synthesis regimen: dual anti-neoplastic cytotoxicity against pulmonary adenocarcinoma (A549). *J Exp Ther Oncol*, 13(2), 81-118.
- Daniels-Wells, T. R., Candelaria, P. V., Leoh, L. S., Nava, M., Martinez-Maza, O., & Penichet, M. L. (2019). An IgG1 Version of the Anti-transferrin Receptor 1 Antibody ch128.1 Shows Significant Antitumor Activity Against Different Xenograft Models of Multiple

- Myeloma: A Brief Communication. *J Immunother.*
doi:10.1097/CJI.0000000000000304
- Durkin, A., Vu, H. Y., & Lee, H. (2020). The VR23 Antitumor Compound Also Shows Strong Anti-Inflammatory Effects in a Human Rheumatoid Arthritis Cell Model and Acute Lung Inflammation in Mice. *J Immunol.* doi:10.4049/jimmunol.1900531
- Erdos, E., & Balint, B. L. (2019). COUP-TFII is a modulator of cell-type-specific genetic programs based on genomic localization maps. *J Biotechnol*, 301, 11-17. doi:10.1016/j.jbiotec.2019.05.305
- Fukuda, W., Hanyu, T., Katayama, M., Mizuki, S., Okada, A., Miyata, M., . . . Inokuma, S. (2019). Risk stratification and clinical course of hepatitis B virus reactivation in rheumatoid arthritis patients with resolved infection: final report of a multicenter prospective observational study at Japanese Red Cross Hospital. *Arthritis Res Ther*, 21(1), 255. doi:10.1186/s13075-019-2053-1
- Guo, Z., Shi, H., Li, C., Luo, Y., Bi, S., Yu, R., . . . Song, L. (2019). Identification and Characterization of a Novel Protein ASP-3 Purified from *Arca subcrenata* and Its Antitumor Mechanism. *Mar Drugs*, 17(9). doi:10.3390/md17090528
- Gupta, K., Hassan, T., Rizwan, S., Hans, B., Jawale, R., & Desilets, D. (2019). Hepatic Sarcoidosis Complicated with Pancreatic Adenocarcinoma. *Case Reports Hepatol*, 2019, 9383019. doi:10.1155/2019/9383019
- Horiuchi, T., Haruki, K., Shiba, H., Sakamoto, T., Saito, N., Shirai, Y., . . . Yanaga, K. (2019). Assessment of Outcome of Hepatic Resection for Extremely Elderly Patients With a Hepatic Malignancy. *Anticancer Res*, 39(11), 6325-6332. doi:10.21873/anticanres.13843
- Kamieniarz, L., Armeni, E., O'Mahony, L. F., Leigh, C., Miah, L., Narayan, A., . . . Toumpanakis, C. (2019). Orbital metastases from neuroendocrine neoplasms: clinical implications and outcomes. *Endocrine*. doi:10.1007/s12020-019-02130-5
- Kobayashi, T., Sugaya, K., Onose, J. I., & Abe, N. (2019). Peppermint (*Mentha piperita* L.) extract effectively inhibits cytochrome P450 3A4 (CYP3A4) mRNA induction in rifampicin-treated HepG2 cells. *Biosci Biotechnol Biochem*, 83(7), 1181-1192. doi:10.1080/09168451.2019.1608802
- Lee, H. S., Kim, K., Kim, S. J., Lee, J. J., Kim, I., Kim, J. S., . . . Korean Multiple Myeloma Working, P. (2020). Pomalidomide, cyclophosphamide, and dexamethasone for elderly patients with relapsed and refractory multiple myeloma: A study of the Korean Multiple Myeloma Working Party (KMMWP-164 study). *Am J Hematol.* doi:10.1002/ajh.25726
- Li, J., Yan, K., Yang, Y., Li, H., Wang, Z., & Xu, X. (2019). [Musashi-1 positively regulates growth and proliferation of hepatoma cells in vitro]. *Nan Fang Yi Ke Da Xue Xue Bao*, 39(12), 1436-1442. doi:10.12122/j.issn.1673-4254.2019.12.07
- Li, X., Liu, Y., Miao, Y., Wang, J., Wang, L., & Wang, E. H. (2019). A rare case of pituitaryoma presenting with severe Cushing disease: A case report and review of literature. *Medicine (Baltimore)*, 98(44), e17772. doi:10.1097/MD.00000000000017772
- Liao, W., Liu, X., Yang, Q., Liu, H., Liang, B., Jiang, J., . . . Ye, L. (2020). Deguelin inhibits HCV replication through suppressing cellular autophagy via down regulation of Beclin1 expression in human hepatoma cells. *Antiviral Res*, 174, 104704. doi:10.1016/j.antiviral.2020.104704
- Liu, J., Shi, Y., Han, J., Zhang, Y., Cao, Z., & Cheng, J. (2019). Quantitative Tracking Tumor Suppression Efficiency of Human Umbilical Cord-Derived Mesenchymal Stem Cells by

- Bioluminescence Imaging in Mice Hepatoma Model. *Int J Stem Cells*. doi:10.15283/ijsc19098
- Liu, J., Yao, Q., Xiao, L., Ma, W., Li, F., Lai, B., & Wang, N. (2019). PPARgamma induces NEDD4 gene expression to promote autophagy and insulin action. *FEBS J*. doi:10.1111/febs.15042
- Liu, X., Cui, H., Niu, H., Wang, L., Li, X., Sun, J., . . . Xian, C. J. (2019). Hydrocortisone Suppresses Early Paraneoplastic Inflammation And Angiogenesis To Attenuate Early Hepatocellular Carcinoma Progression In Rats. *Onco Targets Ther*, 12, 9481-9493. doi:10.2147/OTT.S224618
- Mahadeo, K. M., Bajwa, R., Abdel-Azim, H., Lehmann, L. E., Duncan, C., Zantek, N., . . . Marrow, T. (2020). Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syndrome: an international expert position statement. *Lancet Haematol*, 7(1), e61-e72. doi:10.1016/S2352-3026(19)30201-7
- Makdasi, E., Amsili, S., Aronin, A., Prigozhina, T. B., Tzdaka, K., Gozlan, Y. M., . . . Dranitzki Elhalel, M. (2019). Toxicology and Pharmacokinetic Studies in Mice and Non-Human Primates of the Non-Toxic, Efficient, Targeted Hexameric FasL: CTLA4-FasL. *Mol Cancer Ther*. doi:10.1158/1535-7163.MCT-19-0558
- Matsubayashi, H., Ishiwatari, H., Imai, K., Kishida, Y., Ito, S., Hotta, K., . . . Ono, H. (2019). Steroid Therapy and Steroid Response in Autoimmune Pancreatitis. *Int J Mol Sci*, 21(1). doi:10.3390/ijms21010257
- Pigg, N., Banks, J., & Siddall, K. (2019). Metastatic mucinous cystadenocarcinoma of the pancreas presenting as intractable back pain. *BMJ Case Rep*, 12(11). doi:10.1136/bcr-2019-230070
- Qu, J., Wang, W., Feng, Y., Niu, L., Li, M., Yang, J., & Xie, Y. (2019). Cationic Antheraea pernyi Silk Fibroin-Modified Adenovirus-Mediated ING4 and IL-24 Dual Gene Coexpression Vector Suppresses the Growth of Hepatoma Carcinoma Cells. *Int J Nanomedicine*, 14, 9745-9761. doi:10.2147/IJN.S230693
- Roberston, M. J., Raghunathan, S., Potaman, V. N., Zhang, F., Stewart, M. D., McConnell, B. K., & Schwartz, R. J. (2020). CRISPR-Cas9-induced IGF1 gene activation as a tool for enhancing muscle differentiation via multiple isoform expression. *FASEB J*, 34(1), 555-570. doi:10.1096/fj.201901107RR
- Rodenak-Kladniew, B., Castro, A., Starkel, P., Galle, M., & Crespo, R. (2020). 1,8-Cineole promotes G0/G1 cell cycle arrest and oxidative stress-induced senescence in HepG2 cells and sensitizes cells to anti-senescence drugs. *Life Sci*, 117271. doi:10.1016/j.lfs.2020.117271
- Saez-Carlin, P., Garcia-Botella, A., Diez-Valladares, L. I., Ortega Medina, L., Mendez, R., Gonzalez, J. C. M., . . . Torres Garcia, A. J. (2019). Splenic volume as a biomarker of hepatic damage after chemotherapy in patients with resected colorectal liver metastases (CRLM). *Clin Transl Oncol*. doi:10.1007/s12094-019-02245-1
- Shivaji, U. N., Jeffery, L., Gui, X., Smith, S. C. L., Ahmad, O. F., Akbar, A., . . . Iacucci, M. (2019). Immune checkpoint inhibitor-associated gastrointestinal and hepatic adverse events and their management. *Therap Adv Gastroenterol*, 12, 1756284819884196. doi:10.1177/1756284819884196
- Takamatsu, D., Furubayashi, N., Negishi, T., Ieiri, K., Inoue, T., Tsukino, K., & Nakamura, M. (2019). Relapse of aseptic meningitis induced by ipilimumab and nivolumab therapy

- for metastatic renal cell carcinoma: A case report. *Mol Clin Oncol*, 11(6), 590-594. doi:10.3892/mco.2019.1929
- Wang, Y., Qin, W., Shi, H., Chen, H., Chai, X., Liu, J., . . . Zhang, Q. (2020). A HCBP1 peptide conjugated ruthenium complex for targeted therapy of hepatoma. *Dalton Trans.* doi:10.1039/c9dt03856f
- Warsame, R., LaPlant, B., Kumar, S. K., Laumann, K., Perez Burbano, G., Buadi, F. K., . . . Dispenzieri, A. (2020). Long-term outcomes of IMiD-based trials in patients with immunoglobulin light-chain amyloidosis: a pooled analysis. *Blood Cancer J*, 10(1), 4. doi:10.1038/s41408-019-0266-9
- Yamasaki, S., Kada, A., Nagai, H., Yoshida, I., Choi, I., Miyata, Y., . . . Iwasaki, H. (2019). Rituximab-Mediated Complement-Dependent Cytotoxicity Enhanced by Gemcitabine in Older Patients with Previously Rituximab-Treated Diffuse Large B-Cell Lymphoma: Study Protocol. *Kurume Med J.* doi:10.2739/kurumemedj.MS661001
- Zhang, H., Luo, C., & Zhang, G. (2019). LncRNA MCM3AP-AS1 Regulates Epidermal Growth Factor Receptor and Autophagy to Promote Hepatocellular Carcinoma Metastasis by Interacting with miR-455. *DNA Cell Biol*, 38(8), 857-864. doi:10.1089/dna.2019.4770
- Zhou, R. S., Wang, X. W., Sun, Q. F., Ye, Z. J., Liu, J. W., Zhou, D. H., & Tang, Y. (2019). Anticancer Effects of Emodin on HepG2 Cell: Evidence from Bioinformatic Analysis. *Biomed Res Int*, 2019, 3065818. doi:10.1155/2019/3065818
- Zhou, Y., Peng, H., Xu, H., Li, J., Golovko, M., Cheng, H., . . . Xie, L. (2019). Maternal diet intervention before pregnancy primes offspring lipid metabolism in liver. *Lab Invest.* doi:10.1038/s41374-019-0344-4

IJSER