

## Letter to the editor:

### ANTICANCER ACTIVITY OF LUTEOLIN GLYCOSIDES

Ahmed Ghallab

Forensic Medicine and Toxicology Department, Faculty of Veterinary Medicine,  
South Valley University, Qena, Egypt, E-mail: [ghallab@vet.svu.edu.eg](mailto:ghallab@vet.svu.edu.eg)

<http://dx.doi.org/10.17179/excli2020-2747>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>).

#### **Dear Editor,**

Recently, Lee and colleagues published a study on cytostatic effects of luteolin glycosides in MDA-MB-231 breast cancer cells (Lee et al., 2019). Luteolin and its derivate have been shown to inhibit migration of several cell lines (Kim et al., 2012; 2018a, b; Park et al., 2013). In the present study, the authors focused on MDA-MB-231 cells, a HER2-negative, as well as estrogen and progesterone receptor negative cell line, because triple-negative cancer cells represent a challenge in breast cancer therapy (Callmann et al., 2020). The authors demonstrate that luteolin inhibited migration and invasion of MDA-MB-231 cells stimulated with the tumor promoter 12-O-tetradecanoylphorbol-3-acetate already at a non-cytotoxic concentration of 5  $\mu$ M (Lee et al., 2019). At cytotoxic concentrations luteoline caused Fas-mediated apoptosis (Lee et al., 2019).

Improved treatment options of triple negative breast cancer are urgently needed (Wang et al., 2020; Moss et al., 2020). Factors responsible for prognosis and metastasis of breast cancer include the cellular and humoral immune system (Schmidt et al., 2012, 2018; Heimes et al., 2017a, b), cholin metabolism associated genes (Marchan et al., 2017; Lesjak et al., 2014; Stewart et al., 2012), antioxidative factors (Cadenas et al., 2014, 2019; Hellwig et al., 2016), actin associated proteins (Stock et al., 2015; Rommerswinkel et al., 2018), and many more. It will be interesting to learn in future if luteolin glycosides, which show promising effects in breast cancer cell lines *in vitro* will also be efficient in mouse tumor models.

#### **Conflict of interest**

The authors declare no conflict of interest.

#### **REFERENCES**

- Cadenas C, van de Sandt L, Edlund K, Lohr M, Hellwig B, Marchan R, et al. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. *Cell Cycle*. 2014;13:3282-91. doi: 10.4161/15384101.2014.954454.
- Cadenas C, Vosbeck S, Edlund K, Grgas K, Madjar K, Hellwig B, et al. LIPG-promoted lipid storage mediates adaptation to oxidative stress in breast cancer. *Int J Cancer*. 2019;145:901-15. doi: 10.1002/ijc.32138.
- Callmann CE, Cole LE, Kusmierz CD, Huang Z, Horiuchi D, Mirkin CA. Tumor cell lysate-loaded immunostimulatory spherical nucleic acids as therapeutics for triple-negative breast cancer. *Proc Natl Acad Sci U S A*. 2020, online ahead of print. doi: 10.1073/pnas.2005794117.
- Heimes AS, Madjar K, Edlund K, Battista MJ, Almstedt K, Elger T, et al. Subtype-specific prognostic impact of different immune signatures in node-negative breast cancer. *Breast Cancer Res Treat*. 2017a;165:293-300. doi: 10.1007/s10549-017-4327-0.

- Heimes AS, Madjar K, Edlund K, Battista MJ, Almstedt K, Gebhard S, et al. Prognostic significance of interferon regulating factor 4 (IRF4) in node-negative breast cancer. *J Cancer Res Clin Oncol*. 2017b; 143:1123-31. doi: 10.1007/s00432-017-2377-7.
- Hellwig B, Madjar K, Edlund K, Marchan R, Cadenas C, Heimes AS, et al. Epsin family member 3 and ribosome-related genes are associated with late metastasis in estrogen receptor-positive breast cancer and long-term survival in non-small cell lung cancer using a genome-wide identification and validation strategy. *PLoS One*. 2016;11:e0167585. doi: 10.1371/journal.pone.0167585.
- Kim MJ, Woo JS, Kwon CH, Kim JH, Kim YK, Kim KH. Luteolin induces apoptotic cell death through AIF nuclear translocation mediated by activation of ERK and p38 in human breast cancer cell lines. *Cell Biol Int*. 2012;36:339–344. doi: 10.1042/CBI20110394.
- Kim SJ, Pham TH, Bak Y, Ryu HW, Oh SR, Yoon DY. 7-Methoxy-luteolin-8-C-beta-6-deoxy-xylo-pyranos-3-uloside exactly (mLU8C-PU) isolated from *Arthraxon hispidus* inhibits migratory and invasive responses mediated via downregulation of MMP-9 and IL-8 expression in MCF-7 breast cancer cells. *Environ Toxicol*. 2018a;33:1143–52. doi: 10.1002/tox.22620.
- Kim SJ, Pham TH, Bak Y, Ryu HW, Oh SR, Yoon DY. Orientin inhibits invasion by suppressing MMP-9 and IL-8 expression via the PKC $\alpha$ /ERK/AP-1/STAT3-mediated signaling pathways in TPA-treated MCF-7 breast cancer cells. *Phytomedicine*. 2018b;50:35–42. doi: 10.1016/j.phymed.2018.09.172.
- Lee J, Park SH, Lee J, Chun H, Choi MK, Yoon JH, et al. Differential effects of luteolin and its glycosides on invasion and apoptosis in MDA-MB-231 triple-negative breast cancer cells. *EXCLI J*. 2019;18:750-63. doi: 10.17179/excli2019-1459.
- Lesjak MS, Marchan R, Stewart JD, Rempel E, Rahnenführer J, Hengstler JG. EDI3 links choline metabolism to integrin expression, cell adhesion and spreading. *Cell Adh Migr*. 2014;8:499-508. doi: 10.4161/cam.29284.
- Marchan R, Büttner B, Lambert J, Edlund K, Glaeser I, Blaszkewicz M, et al. Glycerol-3-phosphate Ayl-transferase 1 promotes tumor cell migration and poor survival in ovarian carcinoma. *Cancer Res*. 2017;77: 4589-601. doi: 10.1158/0008-5472.CAN-16-2065.
- Moss JL, Tatalovich Z, Zhu L, Morgan C, Cronin KA. Triple-negative breast cancer incidence in the United States: ecological correlations with area-level socio-demographics, healthcare, and health behaviors. *Breast Cancer*. 2020; online ahead of print. doi: 10.1007/s12282-020-01132-w.
- Park SH, Kim JH, Lee DH, Kang JW, Song HH, Oh S-R, et al. Luteolin 8-C-beta-fucopyranoside inhibits invasion and suppresses TPA-induced MMP-9 and IL-8 via ERK/AP-1 and ERK/NF-kappaB signaling in MCF-7 breast cancer cells. *Biochimie*. 2013;95:2082–90. doi: 10.1016/j.biochi.2013.07.021.
- Rommerswinkel N, Keil S, Adawy A, Hengstler JG, Niggemann B, Zänker KS, et al.  $\beta$ -Heregulin impairs EGF induced PLC- $\gamma$ 1 signalling in human breast cancer cells. *Cell Signal*. 2018;52:23-34. doi: 10.1016/j.cellsig.2018.08.016.
- Schmidt M, Hellwig B, Hammad S, Othman A, Lohr M, Chen Z, et al. A comprehensive analysis of human gene expression profiles identifies stromal immunoglobulin  $\kappa$  C as a compatible prognostic marker in human solid tumors. *Clin Cancer Res*. 2012;18:2695-703. doi: 10.1158/1078-0432.CCR-11-2210.
- Schmidt M, Weyer-Elberich V, Hengstler JG, Heimes AS, Almstedt K, Gerhold-Ay A, et al. Prognostic impact of CD4-positive T cell subsets in early breast cancer: a study based on the FinHer trial patient population. *Breast Cancer Res*. 2018;20:15. doi: 10.1186/s13058-018-0942-x.
- Stewart JD, Marchan R, Lesjak MS, Lambert J, Hergenroeder R, Ellis JK, et al. Choline-releasing glycerophosphodiesterase EDI3 drives tumor cell migration and metastasis. *Proc Natl Acad Sci U S A*. 2012;109:8155-60. doi: 10.1073/pnas.1117654109.
- Stock AM, Klee F, Edlund K, Grinberg M, Hammad S, Marchan R, et al. Gelsolin is associated with longer metastasis-free survival and reduced cell migration in estrogen receptor-positive breast cancer. *Anticancer Res*. 2015;35:5277-85.
- Wang SC, Sun HL, Hsu YH, Liu SH, Lii CK, Tsai CH, et al.  $\alpha$ -Linolenic acid inhibits the migration of human triple-negative breast cancer cells by attenuating twist1 expression and suppressing twist1-mediated epithelial-mesenchymal transition. *Biochem Pharmacol*. 2020; 180:114152. doi: 10.1016/j.bcp.2020.114152.