Reviewer's report

Title: Effect of Gallic acid and Myricetin on ovarian cancer models: a possible alternative antitumoral treatment

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Title: Effect of Gallic acid and Myricetin on ovarian cancer models: a possible alternative antitumoral treatment

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Comments and Suggestions for Authors

The manuscript by Varela-Rodríguez et al. (Manuscript 34172g) evaluates the antineoplastic activity of GA and Myr, first in vitro against human ovarian cancer cell lines (SKOV-3 and OVCAR-3), and then in vivo by peritumoral administration in SKOV-3 cells xenotransplanted in Nu/Nu mice.

The Authors assessed the biological activity of GA and MYR in SKOV-3 and OVCAR-3 cells (ovarian adenocarcinomas) by confocal/transmission electron microscopy, PI-flow cytometry, H2DCF-DA stain, MTT, and Annexin V/PI assay. Molecular targets of the compounds were determined with ACD/I-Labs and SEA. The antineoplastic activity was performed in SKOV-3 cells subcutaneously xenotransplanted into female Nu/Nu mice treated peritumorally with 50 mg/kg of each compound (2 alternate days/week) for 28 days. Controls used were paclitaxel (5 mg/kg) and 20 µL of vehicle. Tumor lesions, organs and sera were evaluated with NMR, USG, histopathological, and paraclinical studies respectively.
The main results were that GA and Myr reduced cell viability by 50 % in SKOV-3 (50 and 166 μg/mL) and OVCAR-3 (43 and 94 μg/mL) cells respectively. Morphological changes in the cell were observed by appreciation in microscopy analyses during the administration of the treatments. These changes suggested the activation of an apoptotic process, that was corroborated via the externalization of phosphatidylserine in the cellular membrane and alterations in the cell permeability. Actually, treatments with GA and Myr for 24 h, induced apoptosis (18.9 / 300 8.1 %) and necrosis (26.6 / 15.1 %) in SKOV-3 cells respectively. In addition, cells treated with GA increased the G2/M phase (8.3 %), while in cells treated with Myr the G0/G1 phase increased (78 %), in comparison with non-treated cells from the vehicle group. Finally, both compounds increased the ROS production in SKOV-3 by 42 and 34 % respectively, compared with the 3.5 % observed in the vehicle group or 76.5 % with 0.3 % H2O2 group.

In vivo studies revealed inhibitory effects on tumor lesions development with GA and MYR up to 50 % with decreased vascularity, necrotic/fibrotic areas, neoplastic stroma retraction and apoptosis. However, toxicological effects were observed with GA treatment, such as leukocyte infiltrate and hepatic parenchyma loss, hypertransaminasemia (ALT: 150.7 ± 25.60 U/L), and hypoazotemia (urea: 33.4 ± 7.4 mg/dL), due to the development of chronic hepatitis.

The Authors suggest that GA and Myr could be used in the chemotherapy of this pathology. However, additional studies are needed to find an adequate therapeutic dose for GA.

General comment

The topic is interesting in its field, and the methodology employed are in general adequate. Actually, some already published papers have studied the anti-tumoral effect of GA. However, the paper presents original data and the results are quite informative, expanding our knowledge in the behavior of phenolic compounds in vivo models. The Authors evaluated the efficacity and toxicity of the peritumorally administration of GA and Myr in an ovarian mice tumor model. They showed that GA and Myr inhibited the development of ovarian tumor lesions present in rodents. They also observed a chronic toxicological effect during the peritumorally administration of GA, then further studies should be performed to define the security of GA.

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In general, the resolution of the figures, 2C, 3B, 3C (immunoflourescence) are not adequate.

- The size of the figures are too small (3B, 3C)
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