Quercetin inhibits growth of pancreatic cancer in vitro and in vivo

Background and Aim: Polyphenols are common constituents of many fruits and vegetables, and have recently gained interest as potential therapeutic agents for various human malignancies. The most abundant of these polyphenols are flavonoids – quercetin being the most ubiquitous. The aim of this study was to assess the growth-inhibitory and anti-angiogenic properties of quercetin on pancreatic cancer (PaCa) cells *in vitro* and *in vivo*.
Methods and Results: Using cell count and BrdU assay, we measured a dose-dependent inhibition of cell proliferation by quercetin (0-75μM) for MIA PaCa-2 (MP) and BxPC-3 (Bx) cells ($p<0.001$ at 30μM). Quercetin (10 μM) increased apoptosis by 22% and 8% in MP and Bx, respectively ($p<0.05$). Further, quercetin (10 μM) inhibited mRNA and protein expression of the pro-angiogenic chemokine CXCL8 ($p<0.05$) in both cell lines as measured by ELISA and real-time PCR. Conditioned media from PaCa cells treated with 50 μM quercetin reduced endothelial cell tube formation by ~50% compared to control ($p<0.05$). A feeding study was conducted utilizing an orthotopic xenograft model of PaCa in nude mice. Luciferase-expressing MP ($3x10^6$) cells were injected subcutaneously into the flank of donor mice. After four weeks, 1 mm^3 donor tumor sections were transplanted into the pancreatic tail of recipient mice. These animals were randomly allocated to control diet or 1% quercetin diet groups utilizing the AIN93G-based diet (n=12 per group). In addition, 6 mice from each group were injected weekly with gemcitabine (120 mg/kg mouse, i.p.). Animals were imaged weekly after tumor implantation until sacrifice at 6 weeks. Light emission was reduced in animals receiving quercetin, gemcitabine, and both treatments by 12%, 8%, and 16%, respectively at day 24. Furthermore, CXCL8 serum levels were significantly reduced in the quercetin/gemcitabine group ($p<0.001$). Using HPLC analysis, quercetin and its metabolite, isorhamnetin, were detected in tumor tissues (2.6 ± 2.7 and 2.1 ± 0.9 nmol/gram, respectively). **Conclusion:** Quercetin significantly inhibits the growth of PaCa *in vitro* and in an orthotopic murine model. PaCa growth was inhibited utilizing a bioavailable quercetin preparation in the diet. Quercetin may, in part, be acting through a reduction of angiogenesis. From this data we surmise that quercetin may be useful as an adjunct to current treatment for pancreatic cancer.

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