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Xanthohumol, a novel plant extract, alters neuroendocrine phenotype and inhibits growth of carcinoid cell lines

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Background: Carcinoids produce excessive amounts of active hormones, which cause debilitating symptoms such as intractable diarrhea, flushing, skin breakdown, and abdominal pain. Though these secretions are generally controlled by somatostatin analogs or interferon, some patients are refractory to it. Thus, patients with incurable carcinoid syndrome have a poor quality of life. Therefore, new therapies are required to effectively treat carcinoids. Earlier we have shown that inhibition of AKT pathway resulted in decrease in growth and neuroendocrine (NE) markers in carcinoid cells. The purpose of this study was to determine the effectiveness of xanthohumol, a prenylflavonoid anti-oxidant, on carcinoid tumor cells growth and NE markers that correlate with severity of carcinoid syndrome.

Methods: Human gastrointestinal carcinoid BON and bronchopulmonary carcinoid H727 cells were treated with xanthohumol (0 to 20 μmol/L) or DMSO (solvent). Cellular proliferation was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) growth assay. Proteins were isolated after two days of treatment and were analyzed by Western blot for NE markers and the levels of expression of AKT pathway. Possible role of xanthohumol on this pathway was determined by over expression of active *AKT* with appropriate controls in the presence or absence of Xanthohumol treatment.

Results: Dose-dependent reduction in cell growth as well as markers CgA and achaete scute complex-like 1 (ASCL1), was observed with xanthohumol treatment. Inhibition of AKT pathway was evidenced by a decrease in the level of phosphorylated AKT. Importantly, cells transfected with *AKT* plasmid did not abrogate the effect of xanthohumol.

Conclusions: Treatment with xanthohumol decreases AKT

phosphorylation, but over-expression of active *AKT* did not alter NE phenotype, indicating that AKT pathway regulates carcinoid syndrome markers. Our findings demonstrate for the first time the anti-proliferative and possible anti-carcinoid syndrome effects of xanthohumol in carcinoid cell lines. These results warrant further investigation of xanthohumol to treat and palliate patients with unresectable carcinoid cancer.