

**Title:** Antibiotic Effects of Tylosin in the Large Intestine of Swine Fed Sub-Therapeutic Concentrations of Tylan™

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**Technical Abstract:**

Antibiotic effects of Tylosin in the large intestine of swine fed sub-therapeutic concentrations of Tylan™. The objectives of this study were to: 1) measure the concentration of tylosin and bioactive tylosin metabolites in the large intestine of pigs fed a typical corn-soy finishing diet, containing a sub-therapeutic level of tylosin (20 g/907 kg of feed); 2) determine the *in vitro* minimum inhibitory concentration (MIC) for *Micrococcus luteus* and *Brachyspira hyodysenteriae*. Large intestinal digesta of three pigs (107.0 kg ± 2.0) were solvent-extracted and antibacterial compounds were isolated by coupled preparative reverse-phase liquid chromatography (P-RPLC) followed by a plate diffusion assay with *M. luteus* as the indicator microorganism. Four major bioactive fractions were purified to homogeneity by a second P-RPLC step and structures of the compounds were assigned using electrospray-ionization tandem mass spectrometry (MS-MS). The identity, concentration, and yield of bioactive compounds purified from the digesta were: Tylosin A (112.2 ± 8.2 µg/kg, yield = 74%); tylosin D (241.6 ± 19.3 µg/kg, yield = 81%); demycarose-tylosin A (36.0 ± 2.3 µg/kg, yield = 78%); and demycarose-tylosin D (21.0 ± 1.3 µg/kg, yield = 79%). The MIC of purified tylosin A for *M. luteus* was found to be 4.3 ± 1.3 mg/kg, and the MIC for *B. hyodysenteriae* was found to be 1.1 ± 0.4 mg/kg. The MIC of the four bioactive compounds were found to be statistically ( $\alpha = 0.05$ ) identical in MIC assays performed using *M. luteus*. Therefore, the normalized concentration of all bioactive forms of tylosin was used to estimate potential sub-therapeutic effects of tylosin on susceptible bacteria in the gut of swine. The total concentration (0.52 mg/kg) of all bioactive forms of tylosin was found to be in the MIC range of *B. hyodysenteriae* (1.0 ± 0.6 mg/kg). This result suggests that sub-therapeutic levels of tylosin may influence microbial community structure in the gut of swine through direct antibiotic effects. Additionally, results of this study show, for the first time, the identity and concentration of tylosin metabolites in the gut of swine that exhibit antibacterial activity. Key words: Tylosin, growth promotion, antibiotic resistance.