Peanut skins have been regarded as a low economic waste by-product of the peanut industry but they contain high levels of bioactive compounds including catechins and procyanidins, which could benefit human health. This is the first report that investigated the anti-inflammatory effects of peanut skin extracts (PSE) in vitro. Defatted peanut skins were extracted using aqueous solvent mixtures (acetone/water and ethanol/water) and dried to powders. PSE antioxidant activity was determined by Hydrophilic Oxygen Radical Absorbance Capacity (H-ORAC) and Total Phenol assays. PSE extracted with acetone/water had higher ORAC and total phenolic values (3060 µmol Trolox/100 g and 290 mg GAE/g) than PSE extracted with ethanol/water (2620 µmol Trolox/100 g and 250 mg GAE/g, respectively). Raw 264.7 cells were treated with three concentrations of PSE (1, 2.5 and 5% (w/v)) and induced with an inflammatory marker, lipopolysaccharide (LPS) for 16 hours. PGE2 was measured by enzyme linked immunosorbent assay (ELISA). Increasing concentrations of PSE induced with LPS demonstrated a decrease in PGE2 concentration. PSE extracted with acetone or ethanol treatments of 5% showed significantly decreased concentrations of PGE2 activity compared to the negative control (p<0.05). Western blotting analysis showed an inhibition in COX-2 expression as peanut skin extract levels increased suggesting that PSE’s inhibition of PGE2 inhibits COX-2. This study highlights the need to investigate the relationship between antioxidant and anti-inflammatory properties of a waste by-product that has the potential use as anti-inflammatory agent.