Abstract This study investigates the preventive effect of caffeic acid phenethyl ester (CAPE) on pancreatic damage induced by vancomycin (VCM) in rats. Rats were equally divided into three groups: group I (control), group II (only VCM-treated group) and group III (VCM + CAPE-treated groups). VCM was intraperitoneally administered at a dose of 200 mg kg\(^{-1}\) twice daily for 7 days. CAPE was administered orally at 10 \(\mu\text{M mL}^{-1}\) kg\(^{-1}\) dose once daily for 7 days. The first dose of CAPE administration was performed 24 h prior to VCM injection. Blood and pancreas tissue samples were removed and collected after the study. Serum alkaline phosphatase (ALP), amylase, \(\gamma\)-glutamyl transferase (GGT) and lipase activities were determined. Pancreas tissue samples were evaluated with the light microscope. Group II significantly increased serum ALP, amylase, GGT and lipase activities when compared with the control group. Group III significantly decreased serum ALP, amylase, GGT and lipase activities when compared with group II. In histopathological examination, it has been observed that there was a significant pancreatic damage in group II. CAPE exerted prominent structural protection against VCM-induced pancreatic damage and this effect was statistically significant. CAPE caused a marked reduction in the extent of pancreatic damage. We have concluded that it may play an important role in the VCM-induced pancreatic damage and reduce the pancreatic damage both at the biochemical and histopathological aspects.