This study was carried out to evaluate the neuroprotective activity of polysaccharide extracts isolated from *Perilla frutescens* (PEPF) in H_2O_2-treated HT22 hippocampus cells. The PEPF treatment was found to increase the anti-oxidant activities of HT22 hippocampus cells. PEPF treatment resulted in a significant protection of HT22 hippocampus cells against H_2O_2-induced neurotoxicity, this protection ultimately occurred through an inhibition of ROS-mediated intracellular Ca^{2+} levels leading to MAPKs and NF-κB, as well as the accumulation of PI3K/AKT and Nrf2-mediated HO-1/NQO1 pathways. Furthermore, PEPF not only decreased the expression of Bax, cytochrome *c*, and cleaved caspases-3, -8, and -9, but also increased the expression of PARP and Bcl-2 in the H_2O_2-treated HT22 hippocampus cells, which overall contributed to the neuroprotective action. PEPF retains its mitochondrial membrane potential and reduces the elevated levels of sub-G1 phase and apoptotic morphological features induced by H_2O_2. It also reduces the malondialdehyde levels and enhances the intracellular SOD activity.