Background: Despite the advancement of cancer therapy, chemotherapy is still a standard approach in cancer treatment. Doxorubicin (DXR) is a potent chemotherapeutic drug, used for the treatment of both adult and pediatric cancers. However, its clinical use is limited due to acute and chronic cardiotoxicity. DXR-induced cardiotoxicity is attributed mainly to mitophagic dysregulation and oxidative stress. Forskolin (FSK), a natural diterpene derived from the roots of Coleus forskohlii, exerted a cardioprotective effect against several cardiac disorders. This study aimed to reveal the mechanism by which FSK protects against DXR-induced cardiotoxicity in Wistar rats. Methods: Adult male Wistar rats were divided into six groups: Control (vehicle only), FSK (20 mg/ kg orally for 3 weeks), DXR (18 mg/kg intraperitoneally over 2 weeks), FSK + DXR, and chloroquine (CQ)+ FSK+ DXR group (CQ 25 mg/kg, intraperitoneally, for 2 weeks beside FSK and DXR as described). By the end of the third week, serum myocardial injury biomarkers (CK-MB &cTnI) and oxidative stress markers, along with autophagic flux biomarkers (LC3II & P62) in cardiac tissue, were measured by ELISA. Additionally, lncRNA APF expression was analyzed using RT-PCR, while protein levels of p-SIRT1, FOXO1, p-PINK1, and p-Parkin were determined by western blot. Results: FSK significantly attenuated DXR-induced cardiotoxicity, as evidenced by a 3-fold reduction in serum CK-MB activity and a 2-fold decrease in serum cTnI level, compared to the DXR-only group. It also restored redox balance by reducing oxidative stress biomarkers. At the molecular level, FSK reactivated autophagic flux, as indicated by a 2-fold increase in LC3II and a 2-fold reduction in P62 levels. Additionally, FSK upregulated lncRNA APF (by 1.8-fold), p-SIRT1 (by 2.8-fold), p-PINK1 (by 1.8-fold) and p-Parkin (by 1.9-fold) expression and downregulated FOXO1 (by 1.8-fold) expression. CQ, the classical autophagy inhibitor, blunted the cardioprotective effect of FSK. Conclusion: These findings suggested that FSK has a cardioprotective effect against DXR-induced cardiotoxicity by normalizing autophagic flux and enhancing PINK1/Parkin-driven mitophagy upon activation of the SIRT1/FOXO1 pathway.