Upregulation of glutathione S-transferase P expression through PI3K/Akt/NF-κB pathway in SH-SY5Y cells is essential for neuroprotective effect of carnosic acid

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Carnosic acid (CA) is a pheolic diterpene in *Rosmarinus officinalis*. Our previous study indicated that CA prevented 6-hydroxydopamine (6-OHDA)-induced apoptosis in SH-SY5Y neuronal cells. Glutathione S-transferase (GST) P (GSTP), a phase II detoxifying enzyme, is the only GST family member expressed in substantia nigra neurons. Here, we investigated whether the protection effect of CA in SH-SY5Y cells treatment with 6-OHDA is related to GSTP expression. Cells were pretreated with CA for 18 h followed by treatment with 100 μM 6-OHDA for 12 h. MTT assay indicated that pretreatment with CA reversed 6-OHDA-inhibited cell viability. The protein expression and enzyme activity of GSTP were increased in the presence of CA. Incubation of cells with CA resulted in significant increases in the phosphorylation of phosphatidylinositol 3-kinase (PI3K)/Akt, the nuclear translocation of NF-κB, but not mitogen-activated protein kinases. Pretreatment with LY294002 (a PI3K/Akt inhibitor) suppressed CA-induced the phosphorylation of IκB kinase (IKK) and IκB, NF-κB nuclear translocation, and NFκB-DNA binding activity as well as GSTP protein. Moreover, the attenuation of 6-OHDA-induced caspase-3 activation and cell death by CA was reversed in the cells treated with GSTP siRNA or LY294002. These results suggest that CA prevents 6-OHDA-induced apoptosis by raising the GSTP expression via the activation of the PI3K/Akt/NF-κB pathway.

**Keywords:** Carnosic acid, 6-hydroxydopamine, glutathione S-transferase P, PI3K/Akt pathway, SH-SY5Y cells