Apocynin, also known as acetovanillone, is a natural organic compound structurally related to vanillin. It has been isolated from a variety of plant sources and is being studied for its variety of pharmacological properties.

Yingze et al. used the NOX2 inhibitor apocynin to study the role of NOX2 in brain injury and functional recovery in a middle cerebral artery occlusion (MCAO) stroke mouse model. Infarct size, neurological deficits, and behavior were evaluated on days 3, 7, 10, and 14 after reperfusion. In addition, dynamic NOX2-induced ROS levels were measured by dihydroethidium (DHE) staining. Autophagy, inflammasomes, and angiogenesis were measured by immunofluorescence staining and western blotting. RNA sequencing was performed, and bioinformatics technology was used to analyze differentially expressed genes (DEGs), as well as the enrichment of biological functions and signaling pathways in ischemia penumbra at 7 days after reperfusion. Then, Akt pathway-related proteins were further evaluated by western blotting.

The results showed that apocynin injection attenuated infarct size and mortality 3 days after stroke but promoted mortality and blocked functional recovery from 5 to 14 days after stroke. DHE staining showed that ROS levels were increased at 3 days after reperfusion and then gradually declined in WT mice, and these levels were significantly reduced by the NOX2 inhibitor apocynin. RNA-Seq analysis indicated that apocynin activated the immune response under hypoxic conditions. The immunofluorescence and western blot results demonstrated that apocynin inhibited the NLRP3 inflammasome and promoted angiogenesis at 3 days but promoted the NLRP3 inflammasome and inhibited angiogenesis at 7 and 14 days after stroke, which was mediated by regulating autophagy activation. Furthermore, RNA-Seq and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated that apocynin injection resulted in PI3K-Akt signaling pathway enrichment after 7 days of MCAO. We then used an animal model to show that apocynin decreased the protein levels of phosphorylated PI3K and Akt and NF-κB p65, confirming that the PI3K-Akt-NF-κB pathway is involved in apocynin-mediated activation of inflammation and inhibition of angiogenesis.

NOX2-induced ROS production is a double-edged sword that exacerbates brain injury in the acute phase but promotes functional recovery. This effect appears to be achieved by inhibiting NLRP3 inflammasome activation and promoting angiogenesis via autophagy activation [1)].

1)
Yingze Y, Zhihong J, Tong J, Yina L, Zhi Z, Xu Z, Xiaoxing X, Lijuan G. NOX2-mediated reactive oxygen species are double-edged swords in focal cerebral ischemia in mice. J Neuroinflammation. 2022 Jul 14;19(1):184. doi: 10.1186/s12974-022-02551-6. PMID: 35836200.