Naringenin

- CRMP2 phosphorylation regulates polarization and spinal infiltration of CD4+ T lymphocytes, inhibits spinal glial activation, and arthritic pain
- Naringenin Protected Against Blood Brain Barrier Breakdown after Ischemic Stroke through GSK-3beta/ beta-Catenin Pathway
- Therapeutic potential of plant-derived natural compounds in Alzheimer's disease: Targeting microglia-mediated neuroinflammation
- Naringenin ameliorates amyloid-beta pathology and neuroinflammation in Alzheimer's disease
- Targeting CD8⁺ T cells with natural products for tumor therapy: Revealing insights into the mechanisms
- Naringenin Alleviates Radiation-Induced Intestinal Injury by Inhibiting TRPV6 in Mice
- Let-7g Upregulation Attenuated the KRAS-PI3K-Rac1-Akt Axis-Mediated Bioenergetic Functions
- Citrus Naringenin Increases Neuron Survival in Optic Nerve Crush Injury Model by Inhibiting JNK-JUN Pathway

Naringenin is a natural dihydro flavonoid abundant in grapefruit.

Protection against blood-brain barrier (BBB) dysfunction is key to reducing cerebral ischemia injury as its breakdown causes edema formation and extravasation of blood components and immune cells. The maintenance of BBB integrity requires the GSK-3β/β-catenin pathway activity. Naringenin (NAR), an effective monomer from Chinese herbal medicine, had a potent protective effect on brain inflammation and oxidative injury. However, whether NAR could protect the integrity of BBB during cerebral ischemia injury and the involvement of the GSK-3β/β-catenin pathway in the beneficial effect of NAR was unknown. Therefore, the mouse middle cerebral artery occlusion/reperfusion (IR) model was employed to answer these questions. NAR was intraperitoneally administrated once daily for 6 days immediately after IR with a dose of 10 mg/kg. BBB damage was evaluated with Evans blue. Protein levels of GSK-3β and β-catenin in vascular endothelial cells at penumbra were assessed with western blotting and immunofluorescence. The experimental data suggested that NAR improved neurological deficits, and decreased the percentage of infarct volumes and neuronal apoptosis at 7d after IR. NAR improved BBB damage as evidenced by a lower permeability of Evans blue dye and upregulation of tight junction proteins such as zonula occludens-1(ZO-1), Occludin, and Claudin-5. Importantly, GSK-3β/β-catenin pathway activity was related to the improvement of BBB integrity rendered by NAR. Our findings demonstrated that NAR might become a potential therapeutic drug for IR [1].

Naringenin exhibits potential protective effects on myocardial mitochondria under stress conditions. However, the detailed downstream signaling pathway involved remains uncovered.

Previous studies suggested the cognition protective effect of naringenin in various cognitive deficit models, such as type 2 diabetic rat models and chemicals (e.g., lipopolysaccharide, scopolamine) treated rodents. However, the effects of naringenin on aging animals and the potential mechanisms are still unclear. In this study, we investigated the influence of naringenin administration on learning deficits in aging mice. High-fat diet-fed SAMP8 mice were employed as an age-related model of Alzheimer's disease. Dietary administration of 0.2% naringenin for 12 weeks significantly improved

the spatial learning and memory performance of the high-fat diet-fed SAMP8 mice in both the Barnes and Morris Water Maze tests. Further mechanism research indicated that naringenin reduced Aβ production, tau-hyperphosphorylation, oxidative stress, and neuroinflammation in the brain. This research provides additional evidence for the treatment effect of naringenin on Alzheimer's disease. PRACTICAL APPLICATIONS: Naringenin, also known as 4',5,7-thrihydroxyflflavanone, is a natural dihydro flavonoid abundant in grapefruit and other citrus fruits. The current study first demonstrated the improvement effect of naringenin on cognition deficits in HFD-fed SAMP8 mice, an aging mouse model. Potential mechanisms were also systematically explained by exploring the amyloid-β (Aβ) accumulation, tau hyperphosphorylation, oxidative stress, and neuroinflammation in the brain of mice. This study provides further evidence for the utilization of naringenin as an effective treatment agent for Alzheimer's disease [2)].

Mitochondrial disease contributed greatly to myocardial Reperfusion injury-induced cardiomyocyte apoptosis. This study was designed to elucidate naringenin's mitochondrial protective actions during MI/R, focusing on AMPK-SIRT3 signaling. Sprague-Dawley rats were administered naringenin (50 mg kg-1 d-1) and subjected to MI/R surgery in the presence or absence of compound C (0.25 mg kg-1, Com.C, an AMPK inhibitor) co-treatment. An in vitro study was performed on H9c2 cardiomyoblasts subjected to simulated ischemia-reperfusion treatment. Before the treatment, the cells were administered with naringenin (80 μmol L-1) with or without SIRT3 siRNA/AMPK1α siRNA transfection. Naringenin improved post-reperfusion left ventricular systolic pressure and the instantaneous first derivative of left ventricular pressure, and reduced the infarction size and myocardial apoptosis index by suppressing mitochondrial oxidative stress damage (as evidenced by decreased mitochondrial cytochrome c release and oxidative markers) and enhancing mitochondrial biogenesis [as evidenced by increased NRF1, TFAM and oxidative phosphorylation subunit complexes (II, III and IV)]. These protective actions were abolished by Com.C (in vivo) or SIRT3 siRNA (in vitro) administration. Further investigation revealed that Com.C (in vivo) or AMPK1α siRNA (in vitro) markedly suppressed PGC-1α and SIRT3 levels while SIRT3 siRNA (in vitro) inhibited SIRT3 expression without significantly changing AMPK phosphorylation and PGC-1α levels. Taken together, we found that naringenin directly inhibits mitochondrial oxidative stress damage and preserves mitochondrial biogenesis, thus attenuating MI/R injury. Importantly, AMPK-SIRT3 signaling played a key role in this process [3)].

The effects of naringenin on ER stress as well as oxidative stress under MI/R condition and the detailed mechanisms remain poorly defined. This study investigated the protective effect of naringenin on MI/R-injured heart with a focus on cyclic guanosine monophosphate- (cGMP-) dependent protein kinase (PKG) signaling. Sprague-Dawley rats were treated with naringenin (50 mg/kg/d) and subjected to MI/R surgery with or without KT5823 (2 mg/kg, a selective inhibitor of PKG) cotreatment. The cellular experiment was conducted on H9c2 cardiomyoblasts subjected to simulated ischemia-reperfusion treatment. Before the treatment, the cells were incubated with naringenin (80 μmol/L). PKGIα siRNA was employed to inhibit PKG signaling. Our in vivo and in vitro data showed that naringenin effectively improved heart function while it attenuated myocardial apoptosis and infarction. Furthermore, pretreatment with naringenin suppressed MI/R-induced oxidative stress as well as ER stress as evidenced by decreased superoxide generation, myocardial MDA level, gp91 phox expression, and phosphorylation of PERK, IRE1α, and EIF2α as well as reduced ATF6 and CHOP. Importantly, naringenin significantly activated myocardial cGMP-PKGIα signaling while inhibition of PKG signaling with KT5823 (in vivo) or siRNA (in vitro) not only abolished these actions but also blunted naringenin's inhibitory effects against oxidative stress and ER stress. In summary, our study demonstrates that naringenin treatment protects against MI/R injury by reducing oxidative stress and

ER stress via cGMP-PKGIα signaling. Its cardioprotective effect deserves further clinical study [4].

1)
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