

# Naringenin confers cardioprotection against ischemia-reperfusion injury in aged rats

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Recent data of ours demonstrate that naringenin, a flavanone derivative typical of the Citrus genus, possesses cardioprotective effects in rat hearts submitted to ischemia/reperfusion injury [Testai et al., 2013a]. These effects are due, at least in part, to a mitochondria-targeted action, since naringenin activates a mitochondrial calcium-dependent potassium channel (mitoBKCa), localized in the inner mitochondrial membrane, resulting in an influx of potassium ions, a mild depolarization, and then a decrease of calcium uptake into mitochondrial matrix, events responsible for cardioprotection[Testai et al., 2013b].

These results strengthened epidemiological evidence about an inverse correlation between intake of flavonoid-rich foods and mortality for cardiovascular diseases [Tresserra-Rimbau et al., 2014]. A rational strategy against myocardial ischemic disease should be properly focused to contain the damage in elderly patients, who are exposed to an highest risk [Boengler et al., 2009].

For these purposes, this work aimed to evaluate the potential naringenin-induced cardioprotection against ischemia-reperfusion damage in isolated and perfused hearts of aged rats, and to ascertain if mitoBKCa channels still play a relevant pharmacological role.

Aged rats (40-44 weeks) were treated with naringenin (100 mg/Kgi.p.), 2 hours before an overdose of pentobarbital and explant of hearts. Then, the functional recovery and ischemic injury size were evaluated on hearts submitted to 30'ischemia/120'reperfusion cycle (I/R).

Aged hearts showed functional and morphological myocardial damage higher than that observed in matched young ones. As well, a aging-related significant reduction in the mitochondrial function was also observed, in agreement with literature data.

In particular, vehicle-treated aged hearts presented a dramatic I/R-induced damage: indeed the functional recovery (expressed as rate pressure product, RPP, at the 120<sup>th</sup> minute of reperfusion) was 24% of the corresponding pre-ischemic values; accordingly, the morphological analysis showed a large extent (40%) of I/R-injured areas (expressed as % of the whole area of the left ventricle, Ai/A<sub>LV</sub>). In contrast, aged hearts treated with naringenin presented a reduced damage, with RPP of 54% and Ai/A<sub>LV</sub> of 27%. Moreover, naringenin in aged mitochondria exhibited a behaviour of a typical mitoBK activator, suggesting that this channel represents the target of action of the citrus flavanone also in ageing.

Furthermore, works in progress are investigating the mitochondrial expression of two subunits forming the mitoBKCa channel, in order to highlight possible ageing-related differences. As well, the effects of naringenin on cardiomyoblast cell models of ageing will be investigated.

These preliminary results, represent a first interesting step to demonstrate cardioprotective effects of naringenin also in elderly rats, and are endowed with a clear translational and nutraceutical value.

## References

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