Citrus flavanone glucoside hesperidin acts as a novel CaMKII-δ inhibitor to ameliorate cardiac ischemia/reperfusion Injury

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1. Ischemia/reperfusion injury (I/R) contributes to adverse cardio- or cerebro-vascular outcomes.

Effective blood flow is vital to homeostasis. Ischemic diseases, i.e. myocardial infarction and cerebral ischemic stroke, are becoming the leading causes of death in the global. Primarily (Yellon and Hausenloy 2007), distressed or even no blood flow leads to an imbalance between oxygen supply and demand to initiate and exacerbate damage or dysfunction in the area dominated by vessel. To prevent further damage, interventions for prompt restoration of blood flow in injury area are usually taken into account as the first-line solution (Heusch and Gersh 2017). Actually, thrombolysis and percutaneous transluminal coronary angioplasty has been identified as the most effective strategy for rescuing infarcted myocardium and improving the outcome in patients with acute myocardial infarction (Guan et al., 2021).

Although recovery of blood flow is necessary to reverse injury, studies in both animal models and patients with acute infarction clearly suggest that reperfusion of ischemic vessels leads to account for up to 50% of the infarcted zone (Fernandez Rico et al., 2022). This pathogenesis was therefore termed ischemia/reperfusion injury (I/R) which contributes to adverse cardio- or cerebro-vascular outcomes. Accordingly, the underlying molecular mechanism of myocardial I/R injury is key to find strategies for reducing the final infarct area. Indeed, increasing therapeutic strategies are translated to bedside from the bench.

Herein, we will discuss an interesting finding from the Circulation in which Zhang et al identified that citrus flavanone glucoside hesperidin acts as a novel CaMKII-δ
inhibitor to ameliorate cardiac ischemia/reperfusion injury.

2. Identification of myocardic CaMKII-δ9 as the target of hesperidin

Ca2+/calmodulin-dependent kinase II (CaMKII) belongs to serine/threonine protein kinase family. As the most abundant CaMKII-δ splice variant, CaMKII-δ9 mainly locates in the human heart acting as a crucial mediator of DNA damage and death of cardiomyocyte (Zhang et al., 2019). Mechanistically (Yao et al., 2022), CaMKII-δ9 directly interacted with IκBα (NF-κB inhibitor α) to prompt IκBα phosphorylation and activation of I/R-induced cardiac NF-κB signaling. To find the therapeutic target for CaMKII-δ9 in the heart, they used a small-molecule kinase inhibitor library combined with a high-throughput screening system for screening for CaMKII-δ kinase inhibitors. Interestingly and unexpectedly, a flavonoid mainly found in citrus peel, hesperidin was discovered to be a potential CaMKII-δ inhibitor. Furthermore, by using in vitro cultured cardiomyocytes and in vivo rodent models, they identified the protection of hesperadin against I/R injury. As for the mechanism behind it, hesperidin directly binds to CaMKII-δ and specifically blunts its activation by competition with adenosine triphosphate.

In addition, given that hesperidin is an oxindole and was reported to have cellular toxicity to tumor cells as an inhibitor of Aurora B kinase (Hauf et al., 2003, Pollard and Mortimore 2009), the authors also investigated whether hesperidin induces cardiac damage accompanying with inhibition of tumor growth. Consequently, both in vivo and in vitro experiments suggested that CaMKII-δ9 is not required for hesperidin
inhibition of tumor cells (Figure 1).

3. Citrus peel is source of hesperidin

Citrus peel (CP) accounts for around 40–50% of the fresh fruit mass (Singh et al., 2020). It is once thought to be a waste in western but to be a traditional herb in China. However, compared with other edible parts of the fruits, researches demonstrated that CP is a substantial source of naturally occurring phenolic compounds and carotenoids with health enhancing effects (Wang et al., 2014, Wang et al., 2018). Particularly, polymethoxylated flavones (notably nobiletin and tangeretin) and flavanones (generally naringin and hesperidin) are much richer and almost exclusively found in CP. Additionally, the more aged CP is with the more polymethoxylated flavones. Accordingly, bioactivities including anti-oxidative stress and protection against the risk of many chronic diseases is also higher than other edible fruit parts owing to the more abundance of phenolic compounds present in CP (Wang et al., 2018, Li et al., 2014).

According to the phytochemicals analyses of Gold Lotion (GL) formulated by an extract of multiple varieties of citrus peels (Lai et al., 2013, Guang et al., 2020) (Table 1), total flavanones is over 3.5 times the content of polymethoxylated flavones (358.3 ppm w/w versus. 100.5 ppm w/w). Of the verified flavanones, structural analogue naringin (253.6 ppm w/w) is around 2.5 times the content of hesperidin (104.7 ppm w/w). Notably, hesperidin has frequently been used for ischemic cardiovascular conditions such as high blood pressure (Morand et al., 2011, Lu et al., 2022) and atherosclerosis(Salden et al., 2016) through multiple mechanisms including
upregulation of endothelial NO-synthase activity (Rizza et al., 2011) and Ca2+
sensitization of vascular smooth muscle contraction (Lu et al., 2022) and, therefore,
has intrinsic potential to protectively affect EF. Hesperidin, is most commonly. Akin
to hesperidin, naringin and polymethoxylated flavones are also benefit to lower risk of
cardiovascular diseases (Mahmoud et al., 2019, Haidari et al., 2015).

4. Perspectives

Zhang et al (2022) findings suggested that hesperadin is a promising compound
for the joint treatment of cardiovascular diseases and cancer (Zhang et al., 2022).
However, for the translation aim, there are at least two questions that need to be be
investigated in future urgently. Given similarity of structures and abundance in citrus
peel, whether the cardiovascular I/R injury protection and mechanism of hesperitin
are also available in flavanone glucoside naringin and particularly polymethoxylated
flavones which have been considered to be more nutraceutical than hesperidin.
Furthermore, it is expected to explore clinical trial with citrus peel on the ischemic
cardiovascular diseases. Citrus polymethoxylated flavones as well as hesperidin and
naringin may affect blood clotting and platelet activation which are also contribute to
cardiovascular protection. However, there is no observation regarding coagulation in
rodents’ long-term taking hesperidin in this article. Given that
anticoagulant/antiplatelet medications usually monitored in clinic, the safety strategy
of hesperidin supplements in individuals look forward to being established.

Taken together, flavanone glucosides including hesperidin are abundant in citrus
fruits. It will undoubtedly accelerate the translation utilization of orange peel
accompanied by emerging development of nutraceuticals in citrus fruit and peel.

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