# At the crossroads from bench to bedside: luteolin is a promising pharmacological agent against myocardial ischemia reperfusion injury

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The study by Bian *et al*. (1) found that luteolin (Lut) inhibited myocardial ischemia/reperfusion injury (IRI) by decreasing miR-208b-3p and increasing Ets1 expression levels in rats. Cokkinos (2) has written an editorial commentary for this study and considered it to be elegant. However, he also raised several interesting questions about the study. As the members of the investigate team, we would like to discuss these issues with counterparts.

The first question is how relevant to the clinical situation are results on IRI alleviation in the experimental setting. In the commentary, Cokkinos (2) cited the position paper of the Working Group of Cellular Biology of the Heart of the European Society of Cardiology (3) which published in *Cardiovasc Res*, 2013. According to the position paper, the experts concluded that there was no effective proven therapy against IRI. It is widely recognized that it is not always possible to translate animal experiments into clinical therapy.

First of all, we reviewed the relative literatures about cardioprotection including the position paper. As now well-known, coronary heart disease (CHD) is the leading cause of death worldwide. The main therapeutic strategy in CHD is reperfusion that could be succeeded either medicine or operation (4,5). However, its major pathophysiological manifestation is myocardial IRI. Despite all of optimal therapies, the morbidity and mortality of CHD remain significant. As such, to find more effective cardioprotective strategies has never been so pressing, novel therapeutic strategies are required to protect the heart from the detrimental effects of IRI, in order to reduce myocardial injury, preserve cardiac function and improve clinical outcomes in patients with CHD (6,7).

Over the last few decades, understanding of the pathophysiology of IRI and concepts of cardioprotection has been revolutionised. Newer strategies such as ischemic preconditioning (IPC), ischemic postconditioning, and remote IPC have been shown to condition the myocardium to IRI and thus reduce the final myocardial infarct size (7). The elucidation of underlying mechanisms in different forms of ischemic conditioning has identified novel targets for cardioprotection amenable to pharmacological manipulation, so called pharmacological conditioning (8).

The study for a pharmacological strategy to protect the heart against IRI preceded the discovery of IPC by many years. Over the past 3 decades, a number of pharmacological cardioprotection strategies were discovered in experimental studies (9). Researches involved conditioning mechanisms have revealed multiple receptors, pathways and end effectors, all of which can be pharmacologically stimulated, such as agents acting on cardiomyocyte receptors (adenosine, bradykinin, opioids, glucagon-like peptide 1, atrial natriuretic peptide, erythropoeitin, insulin), agents acting on intracellular signal transduction pathways (phosphodiesterase-5 inhibitors, glyceryl trinitrate or

nitroglycerin, atorvastatin, delcasertib, nicorandil) and agents acting on the mitochondria (cyclosporine-A) (10-13).

Over the past 30 years, hundreds of experimental pharmacologic conditioning have been reported to protect the ischemic myocardium in experimental animals. However, none has been translated into clinical practice with the exception of early reperfusion (14-16). The reasons for the failure to translate pharmacologic conditioning strategies of cardioprotective effects from the bench to bedside have been extensively discussed in the literatures (3,8-11,14-19). Some experts concluded that the causes of failure can be attributed to inadequacy animal IRI models used in the preclinical cardioprotection studies. Nonetheless, in the position paper which published in 2013 (3), the experts concluded that the failure was not be due to a shortage of potential cardioprotective strategies discovered in the pre-clinical experimental setting (14), but was be due to the inability to successfully translate these promising therapies into interventions that actually improved the outcomes in patients (3,8-11,14-19).

Recently, there were a couple of examples in which the transition from bench to bedside has been successful (20-22). Additionally, several proof-of-concept clinical studies have demonstrated beneficial effects with IPC, ischemic postconditioning and remote ischemic conditioning in a variety of clinical settings (23-26). Pharmacological conditioning can be used as part of a multifaceted approach to improve clinical outcomes in patients with CHD (27,28). In this regard, cardioprotection is not lost in translation. Then, we reviewed again our previous study which verified the positive cardioprotective effects of Lut against IRI both in Langendorff perfused rat hearts and the H9c2 cells (1). According to the literature (14), the results would be more convincing if the animal model is similar to the clinical setting. Therefore, we will improve the animal model in the further studies.

Moreover, our team study systematically Lut over the years. Lut was chosen as a tool to mimic pharmacologic conditioning because it is a multiple targets agent. The reason can be attributed to a number of factors: (I) Pharmacologic conditioning has different working sites (10-13). In the commentary, Cokkinos (2) has also reviewed that Lut is effective on multi-signalling pathway (NF-κB, PI3K/Akt pathway). In this regard, Lut is better than other conventional agents which work only on single site; (II) Lut can be administered via tail vein injection, which makes it as a feasible agent employed in the clinical settings; (III) Lut is a main member of flavonoid (29). The numerous epidemiological evidence suggest that Lut may play a role in cardioprotection with a diet rich in plant-derived food (30-36).

Lut is a widely distributed flavonoid, a member of a group of naturally occurring polyphenolic compounds found in many fruits, vegetables and medicinal herbs, it is one of the six major subclasses of flavonoids (37). Owing to their antioxidant and antithrombotic properties, the relationship has been explored between flavonoids intake and cardiovascular diseases (37). There is also growing evidence that oral administration of flavonoids could provide protection against myocardial IRI, which would be benefit to people with chronic disorders, such as CHD. In recent years, epidemiological evidence suggests that the higher intake of flavonoids could have a protective effect on CHD (38,39). Generally, Lut is a better pharmacological agent for cardioprotection, it also has numerous evidence of cardioprotection in epidemiology. In the further studies, Lut will be a promising pharmacological agent against myocardial IRI.

The second question is the role of Micro RNA (miR) 208b-3p and its target, Ets-1 protein. In the study of our previous article (1), Lut inhibited myocardial IRI by decreasing miR-208b-3p and increasing Ets1 expression levels. MicroRNAs (miRNAs) are noncoding RNA involved in the post-transcriptional regulation of protein expression, it has been demonstrated that miRNAs may contribute to classical IPC cardioprotection (40). According to the results of recent studies (1,41-43), Lut is an interesting agent, it not only can play a role in multi-signalling pathway, but also can modulate miRNAs in the cardioprotection. The role of Lut in modulating miR-146b-5p and SECA2a/BAG1 against myocardial IRI is processing in our study.

The miR-208b-3p play a significant role by reduce apoptosis against IRI, it has important clinical consequences (1). Moreover, miR-208b-3p has been associated with post infarct myocardial remodeling (44). Therefore, the role of miR-208b-3p should be concerned in myocardial IRI. Meanwhile, increased Ets-1 level reduce apoptosis in cardiomyocytes (1). However, it can induce inflammation and apoptosis in endothelial cells (45). Thus, we agree with the comments of Cokkinos (3), the role of Ets1 on cardiomyocytes needs further study.

The third question is the opposite effect of Lut in different organs. Lut is advanced as being both cardioprotective effects through its inhibition of apoptosis in cardiac cells and anti-neoplastic effects through its promotion of apoptosis and inhibition of angiogenesis.

 

Cokkinos (3) speculates that is the Yin and Yang of Tao philosophy taken too far? This is a very interesting question. Yin and Yang are two complementary forces that taken together describe the nature of real world elements. We describe miRNAs having both characteristics of Yin and Yang because they can contribute to normal function (Yang) but also to autoimmunity, proliferation, and cancer (Yin). Some studies have been working on a number of miRNAs that have these dual characteristics (46). The examples of miRNAs exhibiting dual characteristics are not meant to dampen enthusiasm for the development of such treatment modalities. Rather, they should serve to reinforce the commitment of those who study miRNAs to more thoroughly characterize the mRNA target profile of each miRNA species before launching into drug development (47). Moreover, we speculate that the heterogeneity of miRNAs should not be overlooked. The role of miRNAs in different organs needs further studies.

Despite the numerous challenges described, opportunities are exist for translation of basic findings into clinically effective therapies. It is clear that further intervention to reduce IRI is not only desirable, but also necessary. Pharmacological conditioning strategies are promising interventions for further improving outcomes, particularly for patients suffering from CHD. As well recognized, oriental herbal medication is always be doubted. However, from bench to bedside, it is a challenge and opportunity for Lut in cardioprotection. Lut conditioning is a promising strategy against myocardial IRI, further work is required to optimize the design of experimental animal and clinical studies.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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