# Preface

Accumulating evidence suggests that diabetes (both type 1 and type 2) is strongly coupled with cardiovascular complications, including cardiac hypertrophy and diastolic dysfunction, which is assumed to be the result of high mitochondrial oxidative stress. Furthermore, diabetes markedly alters the cardiac gene expression patterns of several metabolic, structural, signal transductions, stress response proteins, leading to the development of diabetic cardiomyopathy. These alterations accelerate the susceptibility of the heart muscle to myocardial ischemia-reperfusion (IR) injury, resulting in reduced clinical prognosis after myocardial infarction. Besides, diminished cardiac AMPK activity is known to enhance the vulnerability of hearts to ischemia-reperfusion insult in diabetic rats. Thus, we hypothesised that dysfunction of AMPK and its downstream pathway might contribute a significant role in the pathophysiology of diabetic cardiomyopathy. Since oxidative stress and inflammation responsible for the diabetes-induced deleterious effects, natural products coupled with antioxidant and anti-inflammatory properties, remain potential candidates to overcome diabetic cardiomyopathy. This thesis reports the results of three studies designed to explore the efficacy of pterostilbene (PT), a major bioactive constituent of blueberries, against cardiovascular complications associated with both fructose-fed (type 2) and streptozotocin-induced (type 1) diabetic rat and to identify the mechanism by which PT decreases diabetic cardiomyopathy.

In the first study, by using high-fructose (65%) diet-induced type 2 diabetic rats, we explored whether or not PT improves glucose homeostasis, insulin resistance, metabolic syndrome and oxidative stress. We showed that oral administration of PT is successful in ameliorating glycemic control, insulin sensitivity while diminishing metabolic

disturbances and hepatic oxidative stress in fructose-fed diabetic rats. This study could help to better understand the antidiabetic mechanism of PT, especially in the context of the modulation of insulin resistance and oxidative stress.

In the second study, we scrutinized the mechanism underlying the cardioprotective effects of PT in attenuation of diabetic cardiomyopathy, with particular attention on the AMPK/Nrf2/HO-1 signalling. Using fructose-fed type 2 diabetic rats, we showed that oral administration of PT significantly decreased cardiac hypertrophy, hypertension, oxidative stress, inflammation, NF-κB expression and NLRP3 inflammasome. Further, we demonstrated that PT improved mitochondrial biogenesis as evidenced by increased protein expression of PGC-1α, Complex III and Complex V in fructose-fed diabetic rats. Also, we showed that PT treatment stimulates AMPK, through concomitantly activating Nrf2 and HO-1, which played a critical role in attenuating diabetic cardiomyopathy in fructose-fed diabetic rats. However, these cardioprotective effects of PT were cancelled by AMPK inhibitor, i.e. compound C.

In the third study, we demonstrated that four weeks treatment with PT attenuated myocardial IR injury in rats with streptozotocin-induced diabetes (evidenced by reduced infarct size, LDH, CK-MB, free 8-isoprostane and cardiac apoptosis after myocardial IR), and decreased *in-vitro* HR injury in primarily cultured rat cardiomyocytes incubated with HG (evidenced by preserved cardiomyocytes viability and decreased LDH, oxidative stress and apoptotic index). Further, we showed that AMPK activation is essential for the anti-oxidative, anti-apoptotic action of PT as evidenced by the finding that, compound C blunted the protective effects of PT against myocardial IR injury in diabetes.

Cumulatively, this dissertation provide new data in support of the hypothesis that PT confers cardioprotection against diabetic cardiomyopathy and identify mechanisms underlying its protective role. Importantly, this study showed that PT can act directly on cardiomyocytes and thereby, has the potential to be a cardioprotective agent in diabetic conditions. Finally, the thesis endup with recommendation that PT can be a promising cardioprotective agent for the amelioration of cardiac comorbidities in diabetic condition. The literature cited in this work is listed at the end in the reference section.

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