Mitochondria play a crucial role in the cell fate; in particular, reducing the accumulation of calcium in the mitochondrial matrix offers cardioprotection. This affect is achieved by a mild depolarization of the mitochondrial membrane potential, which prevents the assembly and opening of the mitochondrial permeability transition pore. For this reason, mitochondria are an attractive target for pharmacological interventions that prevent ischaemia/reperfusion injury. Isosteviol is a diterpenoid created from the acid hydrolysis of ***Steviarebaudiana*** Bertoni (fam. Asteraceae) glycosides that has shown protective effects against ischaemia/reperfusion injury, which are likely mediated through the activation of mitochondrial adenosine tri-phosphate (ATP)-sensitive potassium (mitoKATP) channels. Some triphenylphosphonium (triPP)-conjugated derivatives of isosteviol have been developed, and to evaluate the possible pharmacological benefits that result from these synthetic modifications, in this study, the mitochondriotropic properties of isosteviol and several triPP-conjugates were investigated in rat cardiac mitochondria and in the rat heart cell line H9c2. This study's main findings highlight the ability of isosteviol to depolarize the mitochondrial membrane potential and reduce calcium uptake by the mitochondria, which are typical functions of mitochondrial potassium channel openings. Moreover, triPP-conjugated derivatives showed a similar behavior to isosteviol but at lower concentrations, indicative of their improved uptake into the mitochondrial matrix. Finally, the cardioprotective property of a selected triPP-conjugated derivative was demonstrated in an in vivo model of acute myocardial infarct.

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