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Review

Molecular understanding of the protective role of natural products on isoproterenol-induced myocardial infarction: A review

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ABSTRACT

Modern medicine has been used to treat myocardial infarction, a subset of cardiovascular diseases, and have been relatively effective but not without adverse effects. Consequently, this issue has stimulated interest in the use of natural products, which may be equally effective and better tolerated. Many studies have investigated the cardioprotective effect of natural products, such as plant-derived phytochemicals, against isoproterenol (ISO)-induced myocardial damage; these have produced promising results on the basis of their antioxidant, anti-atherosclerotic, anti-apoptotic and anti-inflammatory activities. This review briefly introduces the pathophysiology of myocardial infarction (MI) and then addresses the progress of natural product research towards its treatment. We highlight the promising applications and mechanisms of action of plant extracts, phytochemicals and polyherbal formulations towards the treatment of ISO-induced myocardial damage. Most of the products displayed elevated antioxidant levels with decreased oxidative stress and lipid peroxidation, along with restoration of ionic balance and lowered expression of myocardial injury markers, pro-inflammatory cytokines, and apoptotic

Abbreviations: AAT, aspartate aminotransferase; ACC, acetyl CoA carboxylase; ACE, angiotensin converting enzyme; ADMA, asymmetric dimethylarginine; ADP, adenosine diphosphate; AKT, protein kinase B; ALP, alkaline phosphatase; ALT, alanine transaminase; AMPK, 5' adenosine monophosphate (AMP)-activated protein kinase; Ang II, angiotensin II; ARE/GPEI, antioxidant response element/GST P enhancer I; AST, aspartate transaminase; ATP, adenosine triphosphate; Bad, Bcl-2-associated death promoter; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CaMK II, calcium/calmodulin dependent protein kinase II; cas-1, caspase 1; cas-3, caspase 3; cas-7, caspase 7; cas-8, caspase 8; cas-9, caspase 9; CAT, catalase; CD, conjugated dienes; Cer, ceramide; CK, creatine kinase; CK-MB, creatine kinase myocardial band; COX-2, cyclooxygenase-2; CPK, creatine phosphokinase; CPK-MB, creatine phosphokinase-MB; CPT 1, carnitine palmitoyltransferase I; CRP, C-reactive protein; CVDs, cardiovascular diseases; cTnI, cardiac troponin I; cTnT, cardiac troponin T; Cx43, connexin 43; DAP, diastolic arterial pressure; DDAH2, dimethylarginine dimethylaminohydrolase 2; dhSph, dihydrosphingosine; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; ECG, electrocardiogram; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal regulated kinases 1 and 2; ETC, electron transport chain; FFA, free fatty acid; FRAP, ferric-reducing ability of plasma; G6PD, glucose-6-phosphate dehydrogenase; GGT, γ-glutamyl transferase; GOT, glutamic-oxaloacetic transaminase; GPCR, G-protein- coupled receptor; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSK, glycogen synthase kinase; GSSG, glutathione disulphide; GST, glutathione S-transferase; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HO-1, heme oxygenase; HR, heart rate; Hs CRP, high-sensitivity C-reactive protein; Hsp27, heat shock protein 27; HW, heart weight; HW/BW, heart weight to body weight ratio; I, $_{Ca\text{-}LCa\text{-}L}$L-type calcium current; ICDH, isocitrate dehydrogenase; IκB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; IKKB, IκB kinase; IL-10, interleukin 10; IL-1β, interleukin 1β; IL-6, Interleukin 6; iNOS, inducible nitric oxide synthase; ISO, isoproterenol; JNK, c-Jun N-terminal kinase; LCAT, lecithin-cholesterol acyltransferase; LDH, lactate dehydrogenase; LDH-1, lactate dehydrogenase 1; LDH-2, lactate dehydrogenase 2; LDL, low density lipoprotein; LDL-C, low density lipoprotein cholesterol; LHP, lipid hydroperoxide; L-NAME, N-Nitroarginine methyl ester; LOOH, lipoprotein lipid hydroperoxides; 5-LOX, 5-lipoxygenase; LPC, lyso-phosphatidylcholine; LPO, lipid peroxidation; LV ± dP/dt, left ventricular intraventricular pressure rise and decline; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; LVW/BW, left ventricular weight to body weight ratio; LVWI, left ventricular weight index; MAP, mean arterial pressure; MAPK(s), mitogen-activated protein kinase(s); MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MDH, malate dehydrogenase; MI, myocardial infarction; MKPs, MAPK phosphatases; MMP-2, matrix metalloproteinase 2; MMP-9, matrix metalloproteinase 9; MPO, myeloperoxidase; MOH, ministry of health; NCEs, new chemical entities; NEFA, non-esterified fatty acid; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κB-p65, a subunit of NF-kappa-B transcription complex; NO, nitric oxide; NP-SH, nonprotein sulphydydryl; Nrf2, nuclear factor-erythroid 2-related factor 2; PARP, poly ADP ribose polymerase; PC, phosphatidylcholine; PE, phosphatidylethanolamine; p-GSK-3β, phospho- Glycogen synthase kinase-3β; PI, phosphatidylinositol; PI3K, phosphatidylinositol-3-kinase; PKC, protein kinase c; PL, phospholipid; PLA2, phospholipases A2; PMN, polymononuclear; PPAR-γ, peroxisome proliferator-activated receptor γ; RhoA, Ras homolog gene family member A; ROCK, Rho-associated protein kinase; ROCK1, Rho-associated protein kinase 1; ROCK2, Rho-associated protein kinase 2; ROS, reactive oxygen species; SAP, systolic arterial pressure; SDH, succinate dehydrogenase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; SOD, superoxide dismutase; S1PR1, Sphingosine-1-phosphate receptor 1; STAT3, signal transducer and activator of transcription 3; T-AOC, total antioxidant content C; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TCA, tricarboxylic acid; TG, triglyceride; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor-α; TnI, troponin I; TUNEL, terminal deoxy nucleotidyl transderase dUTP nick end labeling; VLDL-C, very-low-density lipoprotein cholesterol; WHO, World Health Organisation; α-KGDH, α-ketoglutarate dehydrogenase; Δψmt, mitochondrial membrane potential.

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parameters. Likewise, lipid profiles were positively altered and histopathological improvements could be seen from, for example, the better membrane integrity, decreased necrosis, edema, infarct size, and leukocyte infiltration. This review highlights promising results towards the amelioration of ISO-induced myocardial damage, which suggest the direction for future research on natural products that could be used to treat MI.

Contents

1. Introduction

Cardiovascular diseases (CVDs) are the major cause of mortality around the world. These diseases comprise a range of disorders within the heart and blood vessels, including coronary heart diseases, cerebrovascular diseases, peripheral arterial and rheumatic heart diseases, pulmonary embolism, deep vein thrombosis. In 2004, WHO estimated 17.1 million deaths were due to CVDs, which accounts for at least 29% of global deaths. It has been predicted that 23.6 million people will be diagnosed with CVDs annually by 2030 [1]. CVDs are also the leading cause of death in Malaysia and this is shown from the increasing trend of hospitalization and death records through the decade [1]. Based on the records from Ministry of Health (MOH), 6.91% of total admissions to government hospitals in 2009 and 24.5% of deaths in government hospitals in 2010 were CVD-related [2].

Risk factors for CVDs can be classified into modifiable and non-modifiable risk factors. The modifiable risk factors concern the lifestyle and behavior of the individual, including smoking, obesity, stress, unhealthy diet, sedentary lifestyle, and diseases such as hypertension, dyslipidemias, diabetes mellitus, and hypercholesterolemia [1–3]. The Fourth National Health and Morbidity survey in 2011 suggested that hypertension was the prime risk factor (32.7% prevalence rate), followed by diabetes mellitus (24.8%), and obesity (15.1%) [1]. On the other hand, non-modifiable risk factors include age, gender, family history, as well as ethnicity [1,2].

Currently, there have been improvements in cardiovascular health with the introduction of individual and population-focused strategies, as well as a developed healthcare system [3]. The establishment of a primary healthcare system or coronary care unit has reduced the mortality of patients in hospitals by half [4]. Cardiovascular research and translation have progressed with discovering treatments acting through different targets including chemokines, microRNAs, high-density lipoproteins (HDL), and the regeneration process [5]. In Malaysia, health campaigns and screenings are implemented by the Malaysian Ministry of Health to not only increase public awareness on healthy lifestyles but also to treat modifiable risk factors with anti-hypertensives, lipid-modifying drugs and diabetic medicines [1].

Myocardial infarction (MI) can be defined as necrosis of the heart muscle emerging from continuous acute myocardial ischemia [6]. MI falls into different types; these are spontaneous MI (MI type 1), MI secondary to an ischemic imbalance (MI type 2), cardiac death due to MI (MI type 3), and MI associated with revascularization procedures (MI type 4 and 5). Abnormalities in the ECG are detected during infarctions [6]. MI leads to tissue damage involving both necrosis and apoptosis, with distinctive morphological changes and alterations in basic cardiovascular function [7]. Furthermore, MI causes ventricular remodeling as an adaptive response, because ventricular function is highly regulated by mechanical and neurohormonal means [8]. Ventricular remodeling begins with the expansion of the infarct area, followed by ventricular rupture and formation of an aneurysm, as a result of localized inflammatory response and migration of macrophages, monocytes and neutrophils to the infarcted region. In the late phases of remodeling, the ventricle dilates with distortion of its shape, stimulates both the sympathetic nervous system and the renin-angiotensin-aldosterone system, releases natriuretic peptides, and associates with mural hypertrophy [8].

Previous reviews have addressed the roles of natural products particularly phytochemicals, against isoproterenol-induced myocardial damage [9,10]. However, the present review not only includes the results of previous studies investigating the effects of phytochemicals, but also covers the effects of plant extracts, plant derivatives/analogues, polyherbal, and herbo-mineral formulations on MI. The studies were selected based on the method of inducing myocardial damage solely *via* isoproterenol (ISO) administration.

2. Isoproterenol-induced myocardial damage

The induction of myocardial damage was previously performed through surgical procedures such as aorta banding, infusion of β-adrenegic agonists via implanted osmotic mini-pumps, and coronary artery ligation; these procedures produce a high incidence of morbidity and mortality, not only from the procedures themselves, but also from infections and complications such as pneumothorax [11,12]. The administration of isoproterenol (ISO) in animals provided a rapid, simple and non-invasive method, producing myocardial damage similar to that seen in acute MI in humans [11,12]. The low mortality, high reproducibility and validity compared with other animal models make it more suitable for the evaluation of cardioprotective agents [12,13]. ISO or 4-[1-hydroxy-2-(propan-2-ylamino) ethyl] benzene-1, 2-diol, is a