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Review

Natural products with anti-inflammatory and immunomodulatory activities against autoimmune myocarditis

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ABSTRACT

Myocarditis is an inflammatory disease of the myocardium associated with immune dysfunction which may frequently lead to the development of dilated cardiomyopathy. Experimental autoimmune myocarditis is an animal model which mimics myocarditis in order to allow assessment of the therapeutic effects of different molecules on this disease. We aimed to review the inflammatory and immunological mechanisms involved in the pathogenesis of the myocarditis and finding natural products and phytochemicals with anti-myocarditis activities based on studies of cardiac myosin-induced experimental autoimmune myocarditis in rodents. A number of natural molecules (e.g. apigenin, berberine and quercetin) along with some plant extracts were found to be effective in alleviating experimental autoimmune myocarditis. Upregulation of Th1-type cytokines and elevation of the Th2-type cytokines (IL-4 and IL-10), mitigation of oxidative stress, modulation of mitogen-activated protein kinase signaling pathways and increasing Sarco-endoplasmic reticulum Ca^{2+}-ATPase levels are among the most important anti-myocarditis mechanisms for the retrieved molecules and extracts. Interestingly, there are structural similarities between the anti-EAM compounds, suggesting the presence of similar pharmacophore and enzymatic targets for these molecules. Naturally occurring molecules discussed in the present article are potential anti-myocarditis drugs and future additional animal studies and clinical trials would shed more light on their effectiveness in the treatment of myocarditis and prevention of dilated cardiomyopathy.

Contents

Abbreviations: DCM, dilated cardiomyopathy; EAM, experimental autoimmune myocarditis; CM, cardiac myosin; CHF, heart failure; LV, left ventricular; ECM, extracellular matrix; IL, interleukin; TNF- α, tumor necrosis factor-α; IFN-γ, interferon-γ; STAT, signal transducer and activator of transcription; DM, diabetes mellitus; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; SOD, superoxide dismutase; ICAM-1, intercellular adhesion molecule-1; anti-MyHCα, myosin-specific autoantibodies; Treg cells, T regulatory cells; IR, ischemia reperfusion; ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinases; HW/TL, heart weight/tibial length; SIRT1, silent mating type information regulation 2 homolog 1; RAGE, receptor for advanced glycation endproducts; SERCA2, sarco-endoplasmic reticulum Ca2+-ATPase; OPN, osteopontin; EF, ejection fraction; FS, fractional shortening; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule-1; MPO, myeloperoxidase; DHE, dihydroethidium.

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1. Introduction

Myocarditis is an inflammatory disease of the myocardium associated with immune dysfunction which may frequently lead to the development of dilated cardiomyopathy (DCM) [1]. Myocarditis is diagnosed by endomyocardial biopsy using established immunological, histological and immunohistochemical criteria [2]. The incidence of myocarditis has been difficult to determine because clinical presentations of the disease vary widely. However, autopsy reports have revealed varying estimates ranging from 0.12% to 12%, according to the population studied [3]. Approximately 21% of acute myocarditis patients develop DCM [4]. Lymphocytes and mononuclear cells infiltration, enhanced pro-inflammatory chemokines, cytokines and circulating autoantibodies expression are frequently observed in myocarditis and DCM [5]. Some patients with myocarditis develop a fulminant course followed by death from intractable cardiogenic shock. Unfortunately, no effective treatment strategy for myocarditis has still been introduced [6].

Experimental autoimmune myocarditis (EAM) is a $CD4^+$ T-cell-mediated disorder involving a Th1/Th2 imbalance. It is an animal model of myocarditis induced by immunizing them with cardiac myosin together with complete Freund's adjuvant [7,8]. Cardiac tissue obtained from EAM animals demonstrates enlargement of the heart, dilatation of ventricles, severe myocardial injuries and large areas of myocyte fibrosis similar to those observed in human myocarditis [5,8,9]. This model has been largely used to mimic moycaritis in order to investigate the effects of different molecules on this disease. Medicinal plants and natural products have long been used to manage various diseases. Traditional Medical systems such as Persian Medicine, Chinese Traditional Medicine and Ayurvedic Medicine have used plants to alleviate and cure a wide range of cardiovascular problems [10,11]. Many studies investigated the role of medicinal plants and phytochemicals in alleviating EAM severity. The aim of this article is to review natural products and phytochemicals with antimyocarditis activities based on studies of cardiac myosin (CM)-induced experimental autoimmune myocarditis (EAM) in rodents. The inflammatory and immunological mechanisms involved in the pathogenesis of the myocarditis are also discussed.

2. Myocarditis: pathophysiological aspects

According to the current WHO classification of cardiomyopathies, myocarditis and DCM represent the acute and chronic phases of an inflammatory disease of the myocardium originating from various etiologies including idiopathic, familial/genetic, viral, primarily organ-specific autoimmune or post-infectious immune causes [12,13]. Myocarditis is usually self-limited but approximately half of the acute myocarditis patients with progressive autoimmune myocardial injury demonstrate significant left ventricular (LV) dysfunction and symptoms of heart failure (CHF), arrhythmias, and sudden cardiac death [4,14]. Increasing evidence suggest that inflammation and autoimmunity play crucial roles in the pathogenesis of myocarditis and DCM [12]. It is evident that dysregulation of immune response against cardiac tissue can facilitate programmed death of myocytes and is responsible for the ongoing myocytolytic process [15]. In myocardial inflammation, both cellular and humoral immune responses participate in cardiac remodeling by affecting processes such as extracellular matrix (ECM) degradation, collagen deposition, cardiomyocyte hypertrophy and/or apoptosis leading to vascular injury and cardiomyocyte ischemia. These processes can be mediated by pro-inflammatory cytokines, oxidative stress and mitochondrial dysfunction, alterations of micro- and macrocirculation, metabolic alterations, endothelial dysfunction, NO production, derangement of catecholaminergic stimulation and autonomic dysfunction. Myocardial inflammation can also directly affect cardiomyocyte contractility through disruption of Ca^{2+} homeostasis [4]. However, Most of the mechanisms underlying immune-mediated injury leading to cardiac dysfunction and heart failure remain unknown.

Experimental autoimmune myocarditis (EAM) is a rodent model resembling human giant cell myocarditis, which can lead to DCM[16]. EAM provides insights into the role of the immune responses in the development of DCM and CHF [17]. Histological examination of EAM hearts shows the infiltration of inflammatory cells along with myocardial damage two weeks after cardiac myosin immunization. Thereafter, myocarditis reaches the peak around the third week, and then gradually diminishes during the fourth week. In the later stage, the sixth week, myocarditis progresses to DCM. EAM in rats and mice is a T cell-mediated autoimmune disease [18]. T cells are lymphocytes that play a central role in cell-mediated immunity [19]. Activated T cells ($CD4^+$ and $CD8^+$) secrete chemokines and cytokines which in turn activate other inflammatory cells, such as mast cells, macrophages, and neutrophils [18]. Mast cells are granulocytes normally present in a variety of organ tissues and have been shown to be involved in the pathogenesis of inflammatory diseases including cardiac inflammation and fibrosis. Mast cells produce several cytokines, including interleukin (IL)-1, IL-3, IL-4, IL-5, IL-6, tumor necrosis factor-α (TNF- α), interferon-γ (IFN-γ), and, other central mediators that develop inflammatory reactions [20]. On the other hand, the anti-inflammatory cytokines present a series of immunoregulatory molecules that control the proinflammatory cytokine response [21]. IL-10 is a multifunctional cytokine with the ability of modulating extracellular matrix biosynthesis. The principal function of IL-10 seems to be to limit and terminate inflammatory responses. [18,22]. IL-10 can bind to specific IL-10 receptors located on mast cells to prevent the release of inflammatory mediators [18]. In addition, it has been shown that IL-10-Ig-containing medium, significantly inhibits IL-17 gene expression in IL-1-stimulated spleen cells to restore excessive increase of Th17/Th1 responses in EAM rats [23]. Signal transducer and activator of transcription (STAT) proteins are intracellular transcription factors that are capable of transmitting cytokine signals from the plasma to the nucleus, where they modulate the expression of a variety of target genes through binding to sequence-specific DNA elements [15]. In EAM, modulating the activities of STATs can lead to further suppression of Th17 and Th1 cell differentiation [1].

3. Natural products with the EAC attenuating activities

A number of natural products and medicinal plants have been shown to prevent and alleviate myocarditis using EAM model. Chemical structures of natural products with anti-EAC activities are illustrated in Fig. 1.

Apigenin is a flavon which is widely distributed in vegetables and fruits, especially in celery. Numerous pharmacological studies revealed cardioprotective activities of apigenin [24,25]. Zhang et al. reported that apigenin significantly upregulated serum levels of the Th1-type cytokines (IL-2, IFN-γ, and TNF-α) and elevated the Th2-type cytokines (IL-4 and IL-10) and attenuated the severity of EAM in myocarditis mice. Blood pressure and heart rate were not affected in the treatment groups, indicating that beneficial effects of apigenin on EAM might be independent of blood pressure lowering effects [1].

Moreover, apigenin treatment significantly improved hearts dysfunction, and attenuated cardiac fibrosis induced by type 2 diabetes mellitus (DM) in mice with experimental diabetic cardiomyopathy. The immunohistochemistry showed that DM significantly induced the over-accumulation of 4-hydroxynonenal (a