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Red Wine May be Used in the Therapy of Myocarditis

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ABSTRACT

Myocarditis is one of the most commonly cardiovascular diseases in clinical practice, but the treatment is always limited at present. Considering the multifactorial etiology of myocarditis, a novel therapeutic agent with multi-bioactivties should be presented. Red wine has been recognized as a favorable natural medicine against a large number of pathologic conditions. Recent results indicate that red wine could effectively decrease inflammatory factors secretion, reduce the migration of neutrophils, antagonize oxidation, and regulate immunity. By these bioactivities of anti-inflammation, anti-oxidation, and immunomodulation, red wine may be an effective therapeutic candidate to manage the symptoms and prevent the recurrence of myocarditis. J. Cell. Biochem. 111: 808–810, 2010.

KEY WORDS: INFLAMMATION; MYOCARDITIS; THERAPEUTICS; RED WINE

Myocarditis is an inflammatory heart muscle disease. Many viruses have been implicated as causes of myocarditis. Myocarditis can lead to sudden death [Feldman and McNamara, 2000], and 5–10% of patients with myocarditis may develop dilated cardiomyopathy (DCM) [Kawai, 1999; Azuma et al., 2004], a major cause of morbidity and mortality among young adults [Drory et al., 1991]. Because the pathogenesis of myocarditis remains unclear, treatment is not directed at the disease itself but instead at managing the symptoms [Uhl, 2008; Cooper, 2009]. There is substantial evidence suggesting that inflammatory response plays a key role in the pathological process. Identifying novel anti-inflammatory may lead to new drugs to treat myocarditis.

Recently, red wine has received considerable attention for its ability reduce the risk of cardiovascular diseases. Moderate daily wine consumption can reduce the incidence of coronary artery diseases (CAD) [Grønbaek et al., 2000; Marfella et al., 2006]. The biological effects of red wine include anti-inflammatory [Estruch et al., 2004; Avellone et al., 2006], anti-oxidation [Canali et al., 2000; Urquiaga et al., 2010], and chemopreventive effects [Magrone et al., 2008a,b; Magrone and Jirillo, 2010]. Though many studies have demonstrated that red wine has powerful protective effect against cardiovascular disease, whether it has effect on myocarditis are still poorly unknown. Accumulating evidence have demonstrated that red wine can downregulate of the inflammatory response through inhibition of synthesis and release of pro-inflammatory mediators, modificate of eicosanoid synthesis, inhibit of activated immune cells, or inhibiting transcription factors such as nuclear factor κB (NF-κB) or the activator protein-1 (AP-1). Hence, we hypothesize that red wine could serve as a therapeutic compound in managing myocarditis.

EFFECT OF RED WINE ON THE PRODUCTION OF CYTOKINES

Although viral infection is the most common initiator of acute myocarditis, the subsequent autoimmune response plays a lead role in myocyte injury [Uhl, 2008]. Mast cells are one of the major effecter cells in the immune response system. Activated mast cells release pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-8, IL-13 and inflammatory mediators including histamine, leukotrienes, serotonin, prostaglandin (PG)E2 as well as PGD2 [Zhu et al., 1999; Royer et al., 2001; Stassen et al., 2001; Kang et al., 2009]. TNF-α is a potent inducer of other inflammatory cytokines, including IL-1, IL-6, IL-8, and granulocyte macrophage-colony stimulating factor (GM-CSF) [Arend and Dayer,

Abbreviations used: AP-1, activator protein-1; CAD, coronary artery diseases; COX, cyclooxygenase; CRP, C-reactive protein; DCM, dilated cardiomyopathy; GM-CSF, granulocyte macrophage-colony stimulating factor; IL, interleukin; JNK, c-Jun N-terminal protein kinase; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemotactic protein-1; MI, myocardial infarction; NF-κB, nuclear factor κB; PI3K, phosphoinositide-3-kinase; PG, prostaglandin; PKC, protein kinase C; TNF-α, tumor necrosis factor α.

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1995; Butler et al., 1995]. There is considerable evidence demonstrating the anti-inflammatory properties of red wine, including inhibition of reactive oxygen species in neutrophils, monocytes and macrophages [Martinez and Moreno, 2000]. The release of various cytokines from macrophages and lymphocytes has been shown to be inhibited by red wine [Feng et al., 2002]. As early as 1990s, several studies have demonstrated that high doses ethanol (>40 mM) significantly decreased TNF-α production by human monocytes in vitro [Verma et al., 1993; Szabo et al., 1996; Arbabi et al., 1999]. Moreover, studies by Canali et al. [2000] reported that treatment with the highest dose of red wine prevented the zinc-deficiency-induced pro-inflammatory cytokines, such as TNF-α and cytokine-induced neutrophil chemoattractant, which likely protects cells against inflammatory processes in mice. A recent study by Marfella et al. [2006] demonstrate that moderate consumption of red wine with meals was associated with significant reductions in oxidative stress and inflammatory reaction and improvement of cardiac function in middle-aged diabetic survivors of a recent myocardial infarction (MI). They found that patients randomized to diet without red wine intake had higher circulating levels of TNF-α, IL-6, IL-18, and C-reactive protein (CRP) and impaired cardiac function as compared with patients randomized to diet with red wine intake. The favourable effect of red wine intake on cardiac function might be because of its ability to decrease circulating TNF-α, IL-6, IL-18, and CRP.

In recent years, the important roles of cyclooxygenase (COX)-2 in various tumors and inflammatory diseases have been demonstrated [Kong et al., 2002]. COX-2 is strongly induced in activated monocytes and macrophages, one of the major mediators of inflammatory reactions. Subbaramaiah et al. [1998] indicated that resveratrol, an active ingredient of red wine, suppressed the synthesis of PGE2 by inhibiting COX-2 enzyme activity.

EFFECT OF RED WINE ON THE PRODUCTION OF TRANSCRIPTION FACTORS

Inflammation involves a complex web of cytokine signals, as well as other components of signaling networks that include several kinases, such as mitogen-activated protein kinases (MAPKs), protein kinase C (PKC), phosphoinositide-3-kinase (PI3K), etc [de la Lastra and Villegas, 2005]. MAPKs are activated by translocation to the nucleus, where they phosphorylate a variety of target transcription factors, including NF-κB and AP-1 [Bode and Dong, 2003; Kundu and Surh, 2004]. NF-κB is a transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation, and growth, which is activated by a variety of stimuli, such as carcinogenesis, inflammatory agents, such as TNF-α and H_2O_2, and tumor promoters [Dorai and Aggarwal, 2004]. Extensive research during the last few years has shown that most inflammatory agents mediate their effects through the activation of NF-κB and that most anti-inflammatory agents suppress NF-κB activation [de la Lastra and Villegas, 2005]. Feng et al. [1999] demonstrated that red wine intake inhibited monocyte chemotactic protein-1 (MCP-1) expression in cholesterol-fed rabbits, a protein regulated by NF-κB. Furthermore, study by Blanco-Colio et al. [2000] confirm that red wine intake prevents NF-κB activation in peripheral blood mononuclear cells, a process that activates genes involved in immune and inflammatory responses.

AP-1 is another transcription factor that regulates the expression of several genes that are involved in cell differentiation and proliferation. AP-1 activation can upregulate genes, such as IL-8, among others. Most agents that activate NF-κB also activate AP-1 [Karin et al., 1997; Pervaiz, 2003]. Resveratrol has been shown to inhibit TNF-induced activation of AP-1 [Manna et al., 2000]. The activation of AP-1 is mediated by c-Jun N-terminal protein kinase (JNK) and the upstream kinase MEK (mitogen-activated protein kinase kinase or MAPKK) [Karin and Delhase, 1998]. TNF-induced activities of JNK and MEK were inhibited by resveratrol, thus providing a possible mechanism for AP-1 inhibition [Manna et al., 2000].

THERAPEUTIC EFFECT OF RED WINE ON MYOCARDITIS

Due to its strong effect of inhibiting activation of transcription factors and reducing secondary activation of cytokines, red wine is regarded as a promising drug of blocking the initiation and progress of myocarditis. The most compelling in vivo evidence of the anti-inflammatory role of the red wine is derived from studies of rodents. In the experimental autoimmune myocarditis model in rats, resveratrol significantly ameliorated myocardial injury and preserved cardiac function [Yoshida et al., 2007]. Furthermore, resveratrol can inhibit hyperplasia of myocardial collagen in the mouse model of chronic viral myocarditis, acting as an effective anti-fibrotic agent in the myocardium [Wang et al., 2009]. Therefore, resveratrol may be a therapeutic modality for myocarditis.

CONCLUDING REMARKS

The above evidence suggests that red wine may have a useful therapeutic effect in myocarditis through their anti-inflammatory, anti-oxidative, and immunomodulatory effects. Current data suggest that the direct anti-inflammatory benefits of red wine mainly contribute to its polyphenol, resveratrol. However, other polyphenol of red wine whether have effect on inflammatory response are still uncertain. To investigate the cure effect of red wine, further research could aim at the trial on animal models of myocarditis. Furthermore, its toxicity and pharmacokinetics should be also studied further.

Though there is still no document to illustrate the function of red wine in myocarditis, we can draw the conclusion from upper arguments that red wine can have some effects in the management of myocarditis by inhibiting the activation of cytokines and transcription factors.

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