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• *REVIEW* •

Resveratrol: A medical drug for acute pancreatitis

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Abstract

Accumulating evidence demonstrates that resveratrol, a natural polyphenolic compound extracted from plants, inhibit inflammation when administered. It has direct effects on suppression of platelet coagulation and cytokines production in many experimental models. Because microcirculation occlusion and cytokines over-production is involved in many diseases such as acute pancreatitis (AP), the discovery of resveratrol as platelet and cytokines inhibitors has shed light on the treatment of AP, which still has significant mortality and morbidity. It is anticipated that this natural polyphenol could serve as a therapeutic compound in managing AP through different pathways.

Key words: Resveratrol; Drug; Acute pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) is an emergent and severe disease of peptic system and the plasma amylase and lipase values are elevated in most patients[1]. There are different factors leading to AP. However, if dangerous factors are immediately cleared off and do not produce the progressive injury, the pancreatic structure and function can recover to normal. On the contrary, pancreas would encounter injury if the life-threatening factors could not be controlled. For example, severe AP can change the structure of pancreatic duct and finally lead to chronic obstructive pancreatitis. Currently, the diagnosis and management of AP have already become the hot topic of research and has made great progress.

In 1940, Dr. Takaoka extracted resveratrol from plant and found its chemical structure as 3,4',5-trihydroxy-trans-stibene[2]. In recent years, resveratrol has already been found in about 70 plant species. The highest concentration of resveratrol (50-100 μg/g) is found in grape skins. Many biological characters of resveratrol have already been proved, including anti-inflammatory, anti-oxidation, chemopreventive effects, and inhibition of platelet aggregation[3-5]. From the already admitted characters of resveratrol and the factors leading to the occurrence of AP, we can draw a hypothesis that resveratrol has beneficial effects on AP.

Role of cytokines and microcirculatory dysfunction in acute pancreatitis

The transcription and nuclear factor kappa B (NF-kappa B) is an important substance of delivering intracellular signals[6-8]. It can modulate inflammatory procedures and immune reactions. It has already been proved that activation of NF-kappa B and NF-kappa B-medicated cytokine expression can act as one of the major factors for initiating and aggravating AP[9,10]. Furthermore, as an important inflammatory cell of AP, macrophage can release lots of cytokines that have multiple actions, overlap and synergize with each other. Those would make AP prone to develop from local disease to systemic inflammatory reaction syndrome (SIRS) and multiple organ system failure (MOSF)[11-13].

Microcirculatory dysfunction can induce AP as an initial factor and constant microcirculation dysfunction can aggravate pancreatic injury[14,15]. A lot of documents have suggested that the possible mechanism of microcirculatory dysfunction includes increased vascular permeability, reduced blood flow, leukocyte-endothelial cell interaction, ischemia/reperfusion injury, intravascular thrombus formation, and hypercoagulation[16-20]. The intervention in one or more of these processes can prevent at least partly the development of microcirculatory dysfunction in AP[21,22].

The pancreas is an organ highly susceptible to ischemic damage[23-25] and ischemia/reperfusion causes an inflammatory reaction in AP[26]. Several experimental studies have found that ischemia is associated to pancreatic injury. Ischemia/reperfusion injury is increasingly recognized as a common and important mechanism in the pathogenesis of AP and especially in the progression from mild edematous to severe necrotizing form[27].

Effect of resveratrol on the production of cytokines

Surh *et al*[28], showed that resveratrol could suppress the activation of NF-kappa B. Pellegatta *et al*[29], reported that the anti-inflammatory activity of resveratrol could be mediated by its interference with NF-kappa B dependent transcription. In this study, the influence of resveratrol ($\leqslant$1 mmol/L) on the NF-kappa B signaling pathway after TNF-α stimulation of endothelial cells was observed. The result indicated that the long-term treatment of resveratrol could inhibit the nuclear appearance of NF-κB in endothelial cells.

Besides, resveratrol can directly influence the production of macrophage function molecules (inhibiting the production of IL-6 and TNF)[30,31], which are all important inflammation medium in the development of AP[32].

Effect of resveratrol on microcirculation

Many studies have shown that resveratrol can affect the microcirculation of different organs by different mechanisms. They include the effects of resveratrol on NO production, aggregation of platelets, ischemic/reperfusion injury, and tissue factor (TF) expression.

Giovannini *et al*, has shown that preconditioning the hearts with resveratrol, provided cardioprotection as evidenced by improved postischemic ventricular functional recovery (developed pressure and aortic flow) and reduced myocardial infarct size. It was detected that resveratrol could induce the expression of inducible nitric oxide synthase (iNOS) mRNA beginning at 30 min after reperfusion and increasing steadily up to 60 min after reperfusion. The results suggested that resveratrol can precondition the heart in a nitric oxide (NO) dependent manner[33]. Other studies investigated the effect of resveratrol on endothelial function in hypercholesterolemic rabbits. By measuring of plasma endothelia (ET-1) and NO levels, the researchers found that feeding a high cholesterol diet, significantly increased plasma ET-1 and decreased plasma NO concentration. With administration of resveratrol, plasma ET-1 levels statistically decreased, in parallel with a significant elevation in NO level[34]. Wallerath *et al*[35], suggested that resveratrol upregulated NOS mRNA expression in endothelial cells. NOS protein expression and NOS-derived production were also increased after long-term management of resveratrol. However, some trials drew the reverse conclusion, resveratrol regulating down the expression of NO[36,37], so further investigation should be performed.

By measuring platelet aggregation rate by Born's method, Wang *et al*[38], stated that aggregation of platelets *in vitro* by collagen (5 mg/mL), thrombin (0.33 units/mL), and ADP (4 mmol/L) was significantly inhibited by resveratrol in a concentration-dependent manner. Olas *et al*[39], showed the preincubation of washed platelets with resveratrol (25-100 mg/mL, 30 min, 37 ℃), has an inhibitory effect on adhesion of platelet after being activated by LPS alone or LPS with thrombin and the strongest inhibitory effect was caused by resveratrol at the concentration of 100 mg/mL. They drew the conclusion that resveratrol may be an important compound responsible for the reduction of platelet adhesion and could change the reactivity of blood platelets in inflammatory process. The study of Suttnar *et al*[40], also supported that resveratrol has the capacity of inhibiting the aggregation response of washed platelet activated by collagen.

Shigematsu *et al*[41], reported that resveratrol prevents leukocyte recruitment and endothelial barrier disruption in the ischemic/reperfusion injury model in rat constructed by exposing mesenteries to 60 min reperfusion following 20 min ischemia and these effects may be related to the antioxidant properties of resveratrol. These results are consistent with that of other researches on heart, which supported that resveratrol has a beneficial effect on ischemia/reperfusion injury[42-45]. Bradamante *et al*[46], proved that resveratrol can reduce ischemia/reperfusion injury in two time-related cardiac models and long-term moderate resveratrol consumption could play a more significant role in producing cardioprotective effects than short-term one. Moreover, as TF is a cell surface receptor for factor VII (a) and the binding of factor VII (a) to TF initiates, the coagulation cascade. Pendurthi *et al*[47], have shown that resveratrol inhibited the induction of TF expression in endothelial cells and mononuclear cells.

Therapeutic effect of resveratrol on AP

Due to its strong effect of inhibiting activation of NF-kappa B and reducing secondary activation of cytokines, resveratrol is regarded as a promising drug of blocking the initiation and progress of AP. However, the current trial has only proved the inhibiting effect of resveratrol on NF-kappa B from cellular level, its mechanism needs be illustrated with further studies.

Though NO function in AP is still obscure and has disagreements in the public, many scholars think that NO may have a beneficial influence on the capillary organ perfusions, reduce release of amylase and prevent the development of AP[48-50]. As resveratrol may induce the production of NO[4,51], it is possible for resveratrol to improve the capillary organ perfusion in AP.

Pancreatic capillary endothelial barrier dysfunction is an initial and characteristic feature of acute pancreatic injury and pancreatitis, it is related to hypercoagulation[52], increased vascular permeability and leukocyte adhesion. It is partly manifested by increased platelet adhesion and aggregation. Resveratrol can inhibit platelet aggregation both *in vitro* and *in vivo*[53,54] and enhance the integrity of endothelium in atherosclerosis and cardiovascular disease and significantly prevented the cytokine-induced vascular leakage, so it is also possible for resveratrol to prevent the injury of vascular endothelium in AP and reduce the extent of blood coagulation[55,56].

DISCUSSION

Following the deep recognition of the pathogenesis in AP, there have been recently many changes in the management of AP. Pure medical measures and surgical treatment have reverted to comprehensive management and operation should be performed only when there is a secondary infection[57]. However, the current mortality of AP is still very high[58], and new measures are strongly needed.

Many new drugs have appeared as effective methods in managing AP and most of them exert therapeutic effects through different pathways. Being extracted from plants, resveratrol is proved to have various pharmacologic activations (anti-inflammatory, antioxidation, chemopreventive effects and inhibition of platelet aggregation). It has already been regarded as an effective medical drug on the management of arteriosclerosis, cardiac disease and tumor. Though there is still no document to illustrate the function of resveratrol in AP, we can draw the conclusion from upper arguments that resveratrol can have some effects in the management of acute parcreatitis by inhibiting the activation of cytokines

and in improving microcirculation. The primary trial in our laboratory has found that resveratrol could inhibit the production of TNF and IL-6 in pancreatitis, but more researches still need to be performed. Furthermore, its toxicity and pharmacokinetics should be studied further.

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