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Emerging role of resveratrol in the treatment of severe acute pancreatitis

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1. ABSTRACT

Severe acute pancreatitis (SAP) develops in 15-20% of patients with acute pancreatitis. The management of SAP is a challenging task owing to the fact that it can lead to morbid conditions like multiple organ failure and systemic inflammatory response syndrome, if left untreated. Resveratrol, a drug used in Chinese traditional medicine has shown potential to treat many symptoms of SAP due to its multiple physiological actions. It possesses anti-inflammatory and anti-oxidative properties, both of which are essential in SAP. NF-kappaB activation is a major source of pro-inflammatory mediators in SAP. Administration of resveratrol can inhibit NF-kappaB activity as well as reduce the concentrations of TNF-alpha, IL-6 and IL-1. It can also scavenge reactive oxygen species that are capable of extensive tissue damage. Furthermore, resveratrol also exhibits anti-apoptotic properties via regulation of apoptotic mediators such as Bax, Bcl-2, and caspase-3. It also plays a role in calcium regulation and alleviates SAP-induced histopathological distortions in the pancreas. These multi-faceted results support the use of resveratrol in SAP and mandate the need for extensive research on this molecule.

2. INTRODUCTION

Pancreatitis is disease characterized by inflammation of the pancreas. It is caused due to release of pancreatic enzymes from the abdomen that cause inflammation and damage the normal body structures. In about 85% of patients, acute pancreatitis is a mild disease and is usually associated with a rapid recovery within a few days of onset of the illness (1, 2). However, acute pancreatitis sometimes transforms into a potentially fatal form i.e. severe acute pancreatitis (SAP). Its sudden occurrence could lead to severe complications that are potentially lethal despite treatment. The severe clinical course of SAP is characterized by the development of systemic inflammatory response syndrome (SIRS). and multiple organ failure (3, 4). These dysfunctions occur primarily due to intestinal mucosal barrier (IMB). dysfunction causing an imbalance in the intestinal flora ecosystem. The dysfunction aids in the translocation of bacterial endotoxins from the gut to systemic circulation. The translocated bacteria cause activation of macrophages that release inflammatory mediators and cytokines. This adds to the existing pool of cytokines already released due to SAP. High concentrations of cytokines in the systemic

circulation stimulate the septic process that eventually progresses to SIRS (5). Sepsis related organ dysfunction accounts for 20-50% of SAP-induced mortality (6, 7).

Development of SAP could cause structural changes in the pancreatic duct leading to chronic obstructive pancreatitis (8). Adequate treatment is normally predicted on the basis of laboratory data obtained within the first 48 hours of diagnosis (2). These include hematocrit, C-reactive protein, Ranson's criteria, and Acute Physiology and Chronic Health Evaluation (APACHE-II). scores (9, 10). SAP is confirmed when the APACHE-II score on admission is greater than 7, or when more than 3 Ranson criteria are present, or when pancreatic necrosis is greater than 30%, or there is development of an acute pseudocyst, pancreatic abscess, or organ failure (2). A wide variety of cytokines, chemokines, and inflammatory response genes also serve as markers for the development of SAP (11). Unfortunately, this data is not an estimate of the magnitude with which the disease may or may not progress. The unresponsiveness to treatment in different patients could be due to significant alterations in the clinical course of the disease.

Several factors that increase pre-disposition to SAP have been identified. The most common are obesity (BMI $\geq$ 30). and alcohol consumption (12, 13). Alcohol consumption has been associated with reduced intrapancreatic trypsin activation and necrotic acinar cell death instead of apoptosis (13, 14). Genetic predisposition to the development of SAP has contributed to the development of a single nucleotide polymorphism in a monocyte chemotactic protein-1 at position 2518 A/G (15). Around 40-60% of the total number of acute pancreatitis cases are associated with t he presence of gallstones. There is sufficient evidence to suggest that gallstones cause temporary or persistent obstruction of the distal bile duct. This could be one of the causes of pancreatic inflammation although the exact pathogenesis is unknown (16-18).

Apart from these there are several environmental, metabolic and genetic factors that contribute to the progression of SAP. The prediction of the clinical course of SAP is gaining increasing importance as it underlines the use of adequate treatment options. SAP progresses in two distinct stages that often require specific symptomatic care (19). Due to the rapid progression of the disease surgical intervention is mandatory at some stage of the clinical course. Patients often develop necrotizing SAP that leads to an infection in the damaged pancreatic tissue requiring extensive treatment with antibiotics (20, 21). None of the currently available treatment options can prevent or reduce the intensity with which the disease presents. These factors necessitate the need for alternative approaches for alleviation of SAP. Of the many molecules that are currently being researched for treatment of SAP, resveratrol has shown particular benefits in the mitigation of many pathways involved in SAP. In this review we intend to highlight the use of resveratrol in some of these important pathways, including apoptosis, which are implicated in SAP. Till date, there is no definitive consensus on the mechanism of action of resveratrol. There is a lot of scope for research of this molecule the reasons for which will be evident from this review.

2.1. Data collection and sources

Relevant literature search for this review was carried out using PubMed and Google Scholar. The search terms included "acute pancreatitis," "severe acute pancreatitis," and "resveratrol". Various combinations of these terms were also used to get details on treatment and pathophysiology of the disease as well as the mechanisms of action of resveratrol along with its biological properties. We also conducted searches with MESH terminology (resveratrol and SAP). Since research in this area is relatively new we have tried to incorporate all the relevant current findings that can enable further studies.

3. RESVERATROL (3, 5, 4'-TRIHYDROXY-TRANS-STILBENE).

Resveratrol is a plant phytoalexin commonly employed as a nutritional supplement. For experimental purposes, it is mostly refined from grape peels and the rhizomes of giant knotweeds (22). In grapes, resveratrol is synthesized in response to fungal infections as a result, wines, particularly red wines, has a very high concentration of resveratrol (23, 24). Since resveratrol is a stilbene it is also synthesized in response to UV irradiation or ozone exposure (25, 26). This drug possesses many biological properties including anti-inflammatory, anti-oxidative, anti-coagulant, and chemoprotective properties (23, 25). Resveratrol has been employed in Chinese traditional medicine for use in inflammation, allergy, and hyperlipidemia (27). Over the recent years it has proved its potential in experimental settings for the treatment of various conditions including SAP (28).

3.1. Protective effect of resveratrol against oxidative stress in SAP

Oxidative stress mechanisms are integral in the pathogenesis of many diseases, including SAP. Reactive oxygen species (ROS). are the cause of tissue injury as well as activation of genes that are responsible for the initiation of the inflammatory process. They also act as scavengers of endogenous anti-oxidants that increase the susceptibility of disease- or treatment-related oxidative injury (29). In humans, acute pancreatitis has been associated with glutathione deficiency and the involvement of oxygen free radicals (29, 30). Pancreatic oxygen free radicals were detected in an experimental model of SAP using a chemiluminescence probe and high sensitive photon counting. This technique revealed that free radicals emerge within 2-3 hours of SAP induction (31). They are capable of attacking the aldehyde group of polyunsaturated fatty acids thus initiating lipid peroxidation. Malondialdehyde (MDA). is a product of lipid peroxidation released by this mechanism. It is responsible for loss in membrane stability and release of enzyme precursors from the acinar cells. These precursors activate phospholipase A1 which decomposes lecithinium causing tissue damage (32, 33). An anti-oxidant superoxide dismutase (SOD). is normally released *in vivo* as a response mechanism to prevent further damage to the tissues; however, due to excessive utilization

during SAP, the SOD activity decreases (33). This physiological phenomenon warrants the use of a free radical scavenger in the treatment of SAP.

Resveratrol is an effective scavenger of hydroxyl, superoxide, and metal-induced radicals. It has also been shown to exert a protective effect against lipid peroxidation in the cell membranes and eventually preventing DNA damage caused due to the circulating ROS, during SAP induction (34). It has been observed that SOD levels decrease and MDA levels increase significantly in early SAP, i.e., 3-6 hours following induction (35). Additionally, the levels of serum amylase and pancreatic histological scores increase gradually with progression of SAP. Serum amylase and lipase often serve as markers for initial detection of SAP (1). Resveratrol can prevent the release of oxygen free radicals, byproducts of lipid peroxidation, and enzyme precursors. As a result it helps in the amelioration of pancreatic lesions. Resveratrol treatment causes a significant increase in the release of SOD within the first 6 hours of SAP induction. Serum amylase and pancreatic histopathological scores are also decreased significantly with resveratrol treatment. Another enzyme myeloperoxidase (MPO). is released during SAP and is a measure of neutrophil sequestration. Neutrophil sequestration is yet another source of free radicals that accelerate tissue damage. They also initiate the immediate release of inflammatory cytokines that evoke SIRS. Resveratrol can help prevent damage by reducing neutrophil infiltration in the tissues and by lowering the activity of MPO (32, 33). Reduced neutrophil infiltration can alleviate the effects of SIRS in SAP. Apart from these resveratrol also causes a significant reduction in the ascitic fluid turbidity, pancreatic edema, necrosis, and inflammatory cell infiltration (32).

3.2. Effects of resveratrol on cytokine production during SAP

Lung dysfunction is one of the major causes of SIRS-related death following SAP (36). This occurs primarily due to macrophages that mediate the progression of SAP. Tumor necrosis factor-α (TNF-α). is a vital regulator of pro-inflammatory cytokines and other adhesion molecules (37). Since it is expressed in acinar cells, TNF-α plays an important role in the pathogenesis of SAP by causing activation of immune cells. The action of TNF-α is prominent in the early stages of SAP and slowly diminishes with progression of the disease, thus limiting its effectiveness as a biomarker. However, soluble TNF-α receptor levels can predict the severity of SAP with an accuracy of almost 96% (38). Interleukins-1 and -6 (IL-1 and IL-6). are also responsible for driving the process of SIRS following SAP (39, 40). Reportedly, IL-1 mediates inflammatory pathways in necrosis, a common occurrence with SAP. Furthermore, IL-1 levels have also been used as an indicator to predict the severity of SAP with an accuracy of 82%. Unlike IL-1, IL-6 is not directly responsible for pancreatic damage (38).

IL-6 plays a role in the synthesis of inflammatory proteins and transitioning of an acute response to a chronic condition. IL-6 levels can predict the extent of SAP with an accuracy of 89 to 100% (38). The importance of IL-6 levels is notable within the first 24 hours of an acute pancreatitis attack and is considered superior to the APACHE-II and C-reactive protein scores (41). The release of these cytokines from the macrophages sometimes results in synergistic biological activities that result in the progression of SAP. Anti-cytokine therapy has proved beneficial in the experimental models of SAP. Resveratrol, at a dose higher than 10 mg/kg can inhibit the production of TNF-α and IL-6 in the serum, thus preventing the aggravation of SAP (42). Similarly, a decrease in IL-1 and nitric oxide (NO). has also been observed following resveratrol treatment (43-45). Furthermore, it has also been shown that resveratrol can modulate the production of vascular cell adhesion molecule-1 in TNF-α stimulated endothelial cells (46). The suggested mechanism of action for this occurrence is via the nuclear factor-κB (NF-κB). pathway (43, 47-49). NF-κB plays a critical role in the expression of inflammatory genes by binding to their promoter-enhancer regions. The activity of NF-κB depends on its P50-65 heterodimer to a very large extent. In a state of inactivation NF-κB remains bound to its inhibitor (I-κB).; however, an external stimuli can result in the separation of I-κB. Upon initiation of an inflammatory process, I-κB gets phosphorylated by the enzyme I-κB kinase and dislodges from NF-κB. The free NF-κB subsequently translocates to the nucleus where it can cause activation of the inflammatory genes (50). Resveratrol is capable of blocking the activity of I-κB kinase, thus preventing NF-κB activity and release of inflammatory mediators. ROS contribute to the effects of NF-κB to a great extent (51). They can inhibit I-κB kinase and phosphorylate of the P65 subunit that can reduce the binding ability of NF-κB (Figure 1) (52).

Meng *et al.* studied the effects of resveratrol on NF-κB activation and subsequent action of inflammatory mediators. It has been observed that activated NF-κB is absent in normal pancreatic cells, but peaks at 3 hours post-SAP induction. The initial activation of NF-κB subsequently releases TNF-α, IL-1, IL-8, and NO in the serum (53). Other studies have also confirmed the NF-κB-induced release of TNF-α and IL-8 (54, 55). Excessive production of NO is responsible for mediating microcirculatory failure in SAP by causing vascular endothelial failure and increasing vascular permeability (56). Since administration of resveratrol can decrease the release of NO, this treatment can prevent extensive vascular damage that contributes to the severity of SAP. Resveratrol is also known to decrease the expression of inducible nitric oxide synthase (iNOS)., which is responsible for the release of NO (Figure 1) (43). However, there are controversial reports on this activity of resveratrol. It has been observed that resveratrol causes cardioprotection by inducing the expression of iNOS and subsequently increasing the NO level (57). A similar observation was also made in endothelial cells of rabbits with hypercholesterolemia. Resveratrol treatment could reverse the cholesterol-induced increase in endothelin-1 and NO levels (58). It has also been reported that NO may reduce the release of amylase and have beneficial effects on the capillary organ perfusion during SAP (59-61). Hence administration of resveratrol could induce NO and improve

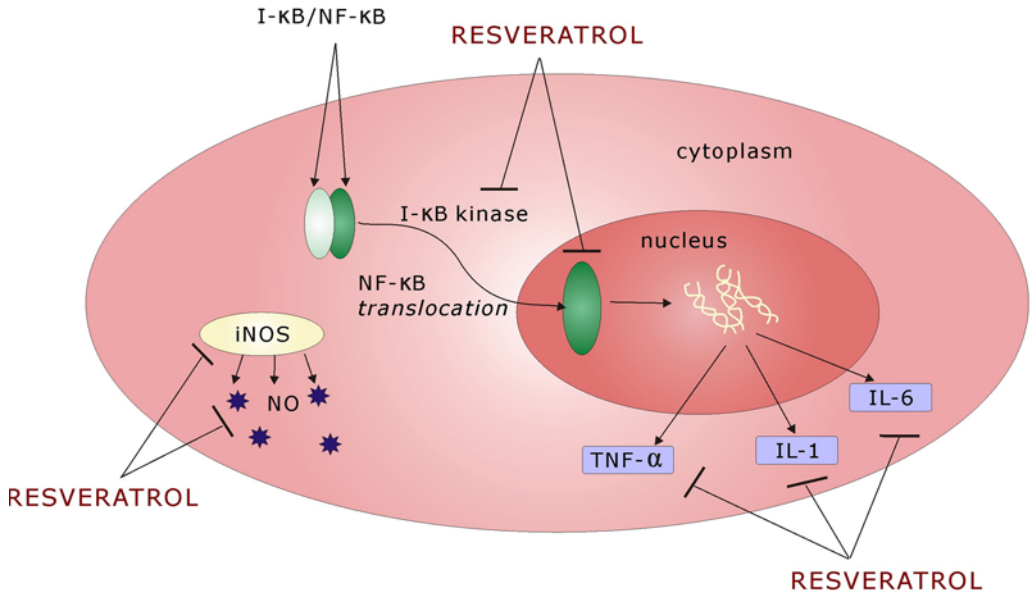

Figure 1. Anti-inflammatory effects of resveratrol. Pro-inflammatory mediators are released during SAP that cause significant tissue injury. Resveratrol can inhibit not only the mediators but also their source i.e. NF-κB. It also inhibits inducible nitric oxide synthase and nitric oxide.

capillary organ perfusion. In light of these opposing findings, it is essential to investigate in detail, the exact mechanisms of action of NO and resveratrol. This information could be vital for treatment of vascular damage during SAP.

3.3. Role of resveratrol in SAP-induced apoptosis

Almost 80% of SAP-induced mortality is due to multiple organ failure including liver failure. Due to the extensive release of cytokines in the blood during a SAP attack the liver becomes a primary target. As the functioning of the liver declines, its ability to detoxify also reduces, which is a major cause of morbidity (62). This extensive liver damage can be attributed to the genetic cell death pathway, apoptosis. Apoptosis is known to occur via two established pathways; the death receptor and mitochondrial pathway (63, 64). SAP-induced apoptosis was shown to have mitochondrial origin. This was confirmed by the release of cytochrome-C in early SAP (65). Cytochrome-C and other apoptosis-inducing factors (AIF). induce caspases; these caspases upon entering the cytoplasm cleave the proteins responsible for apoptotic changes (66, 67). The sequential activation of caspases occurs due to the formation of a complex (apoptosome). between cytochrome-C and Apaf-1. This complex recruits pro-caspase 9 that causes activation of caspase-3. Caspase-3 serves as an important molecular marker for cells undergoing apoptosis. The release of mitochondrial cytochrome-C is inhibited by Bcl-2, an anti-apoptotic member of the *Bcl-2* family. Bcl-2 is known to scavenge reactive oxygen species and it also prevents the release of Ca^{+2} from the endoplasmic reticulum (68, 69). Bax, on the other hand is a pro-apoptotic member of the *Bcl-2* family. It has been observed that induction of SAP leads to an increase in Bax and a significant decrease in Bcl-2 expressions. Resveratrol is shown to significantly reduce the levels of Bax and increase the level of Bcl-2 (Figure 2). Elevated levels of caspase-3 observed following SAP induction are also significantly decreased with resveratrol treatment. All of these changes have been observed in the hepatic tissues. Thus, resveratrol could be beneficial in the maintenance of liver function during SAP (65). This is particularly important due to the fact that hepatic injury is a major cause of concern in SAP and often leads to multiple organ failure. Similar effects on the apoptotic mediators Bax and Bcl-2 have also been observed in the intestinal mucosal cells. The ratio of apoptotic cells was also found to be considerably lower with resveratrol treatment following TUNEL analysis (71).

3.4. Miscellaneous benefits of resveratrol in SAP

One of the serious problems associated with SAP is IMB dysfunction. The IMB serves as an important regulator of the endotoxin content within the intestine (5). This physiological function of the barrier depends on the balance between apoptosis and proliferation of the intestinal mucosal cells. Under normal physiological conditions a very small amount of endotoxins is allowed to enter the general circulation, as most of them are eliminated by the Kupffer cells of the liver (68). A dysfunction in the permeability of the IMB could result in an excessive number of endotoxins within the systemic circulation. Since conditions such as SAP lead to excessive cell death (apoptosis)., a shift in the natural balance leads to the destruction of the IMB. The permeability changes of the IMB can be determined by measuring the amount of portal vein endotoxin. In a model of sodium taurocholate-induced pancreatitis it has been shown that portal vein endotoxins significantly increase over a period of time. Treatment with resveratrol can cause a significant reduction in the endotoxin content following SAP induction. This result suggests that resveratrol could be beneficial in protecting the integrity of the IMB during SAP (71).

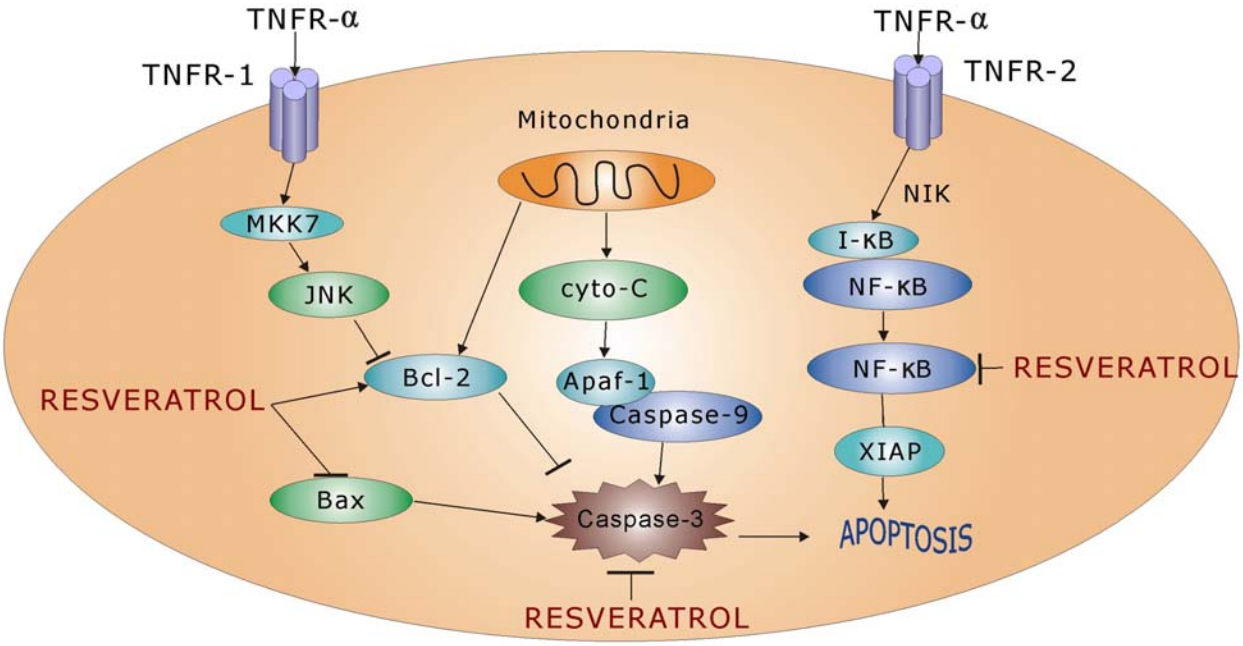

Figure 2. Effects of resveratrol on the apoptosis pathway in SA. The release of cytochrome-C has been observed in SAP, suggested the involvement of mitochondrial apoptotic pathways. Resveratrol can inhibit the pro-inflammatory mediator Bax, caspase-3, and NF-κB and upregulate the anti-apoptotic Bcl-2 protein.

Histopathological changes in the pancreas are very common during a SAP attack. These manifestations include presence of edema, moderate hemorrhage, substantial inflammatory infiltration, villose exfoliation, bleeding, and acinar cell necrosis. These changes were observed within 3 hours of SAP induction. Treatment with resveratrol could visibly alleviate these histopathological changes (71).

SAP triggers disturbances in the normal intracellular calcium concentration. The intracellular calcium overload produced as a result has very important consequences in the pathology of the disease. In an experimental model of SAP, it was observed that the Ca^{+2}/Mg^{+2} ATPase and Ca^{+2} ATPase activity considerably decreased, whereas phospholipase A2 and intracellular Ca^{+2} concentration increased over a period of time. Resveratrol could significantly decrease the intracellular calcium overload thus preventing tissue damage and secondary lung injury occurring due to SAP induction (72).

4. CONCLUSION

Successful management of SAP is a universal issue requiring constant attention. Due to the complicated pathogenesis of SAP, it becomes very hard to provide adequate treatment that can deal with all the symptoms. Resveratrol is known for its multiple actions on the body. The properties of resveratrol are particularly useful in conditions such as SAP. Experimental models of SAP are a fair indicator of pathological progression of SAP. It has been shown that various physiological factors and pathways are affected by resveratrol treatment. One of the most important effects of resveratrol in SAP is NF-κB inhibition. NF-κB directly induces the release of a number of pro-inflammatory mediators such as TNF-α, IL-1, and IL-6. Resveratrol can reduce the concentration of these mediators thus correcting the microcirculatory dysfunction associated with SAP.

Recently, it has also been observed that resveratrol plays a role in reducing the intracellular Ca^{+2} overload. Additionally, resveratrol also plays a suggestive role in preventing SAP-induced apoptosis. Although extensive research is required to confirm the role of resveratrol, preliminary studies have indicated its action in the mitochondrial apoptotic pathway during SAP. Resveratrol can reverse the SAP-induced upregulation of Bax and downregulation of Bcl-2. It can also cause a reduction in the caspase-3 expression, a key regulator of cellular apoptosis. All of these effects were observed in hepatic cells, thus suggesting that resveratrol can retard hepatic injury during a SAP attack. The studies conducted thus far have shown positive results warranting the potential use of resveratrol in SAP. Further studies in this area would provide greater insights to the successful management of SAP that can be extrapolated to human settings.

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