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Review Article

AN UPDATE ON PHARMACOLOGICAL PROPERTIES OF RESVERATROL

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ABSTRACT
Resveratrol, red wine mainly present in grapes acts as a natural phytoalexin and phytoestrogen. It has potent antioxidant activity and then has been implicated in the management of various cardiovascular and inflammatory disorders. Further, it has been also documented to be successful in the reduction of ischemic reperfusion [I/R] injury. It has been found to possess immunosuppressive property and is used as anti-cancer and ameliorates the endothelial functions. Still, no evidence is availible that suggest signaling pathway mechanism associated with resveratrol. Thus, the present review deals with the update of various signaling pathway and therapeutic implications of resveratrol in the management of various disorders.
Keywords: resveratrol, ischemic reperfusion, antioxidant, inflammation.

INTRODUCTION

Resveratrol is a Trans -3, 5, 4'-trihydroxystilbene, mainly present in grapes, peanuts and other food products[1]. Resveratrol has been documented to be involved in the treatment of various cardio-vascular diseases like atherosclerosis, cancers, liver transplants arthiritis and neurodegenerative disorders like Parkinson's, Alzheimer's and Huntington[1-5]. Various evidences indicates that during inflammation and cardiovascular disorders there is increased generation of reactive oxygen species (ROS) via nicotinamide dinucleotide (NADPH) pathway and adenosine mono phosphate (AMP) pathway[6]. Further, various cytokines-like tumor necrosis factor-alpha (TNF-α) and interleukins too are up regulated in inflammatory disorders[7]. It has been reported that Inter cellular adhesion molecules (ICAM), vascular cell adhesion molecules (VCAM), monocyte chemo attractant protein (MCP) and nuclear factor-kappa B (NF-kB) has been reported to be over expressed in inflammation[7, 8]. Resveratrol inhibits ROS mainly by activating AMP activated kinase (AMPK) and also prevented cell senescence[6]. Various evidences indicated that resveratrol attenuates inflammation via inhibition of prostaglandins [PG] production and cyclooxygenase-2 (COX) activity[9]. Further, it inhibits mitogen activated protein kinase (MAPK) activation, lipid per oxidation, platelet aggregations as well as inhibits soluble adhesion molecules like ICAM, VCAM and E-selectin which is mainly responsible for cardio protective effects[8]. Moreover, it has been suggested that resveratrol too play an vital role in process of vasorelaxation and angiogenesis[8,9]. Clinically, Resveratrol is used in the management of cancers, pulmonary hypertension and ischemia injury [10]. Still, no proper evidences are available which suggests the various signaling pathways and therapeutic implications of resveratrol. Hence, the review has been explored to find out the therapeutic implications and signaling pathways associated with various disorders managed by resveratrol.

PATHOPHYSIOLOGY OF PAIN AND INFLAMMATION

Pain is unpleasant sensory and emotional perception commonly associated with tissue damage and in all type disease[11]. Pain is regarded as nociception[40]. Various evidences suggest that in pain various mediators like prostaglandins (PGs), cytokines, interleukins and bradykinin play a pivotal role [11]. During injury it has been reported that there is recruitment of PGs and ROS that are responsible in initiating pain perception[12]. ROS gets activated through inositol 1, 4, 5 triphosphate (IP_3) and that further activates mitogen activated protien kinase (MAPK) and protien kinase A (PKA), which increases neuron excitability and pain [12]. Further, substance P, NF-kB, calcitonin related gene peptide (CGRP), TNF-α and sodium channels (Na+) are also up regulated during pain[13]. Inflammation is mainly assosiated with increase leucocyte migration towards the site of injury along with increased generation of monocyte chemo attractant protien (MCP) [7, 9]. Moreover, ICAM and VCAM are also up regulated during inflammation[9]. Further, it is also documented that there is increase in generation of PG's and COX-2 [9, 12] (fig 1).

RESVERATROL IN CARDIOVASCULAR DISEASES

Resveratrol in ischemic/reperfusion [I/R] injury

Ischemia is mainly caused due to increased production of free radicals like hydroxyl (OH^-) and results in reduced activity of endothelial nitric oxide synthase (eNOS) [14]. During ischemia, neuronal loss brings about membrane depolarization consecutively producing NO and ROS. ROS activated by metabotropic glutamate receptors [mGLUR-5] via inositol triphosphate (IP3) pathway has been reported to activate extracellular receptor kinases (ERK) and protien kinase A (PKA) signaling cascades that increases neuronal excitibility and pain responses [15]. Resveratrol stimulates eNOS activity and also provides its protective and vasorelaxing effects in penumbra area of ischemia as well as down regulates iNOS activity by NF-kB binding inhibition[16].

Resveratrol treated patients becomes resistant to I/R injury by recovering their post ischemic ventricular functions and reducing the infarct size. Resveratrol has the activity of inhibiting mitochondrial ROS which further leads to cessation of free radical formation during ischemia[16]. Enhancement of NO synthesis by resveratrol is mainly beneficial in ischemia[14]. Resveratrol has peroxyradical scavenging activity which might be helpful in reducing oxidative stress during ischemia and reperfusion[14, 15].

Resveratrol in hypertension

Hypertension is a chronic disease which is generally involved as undesirable symptoms in most of the diseases[15]. It involves various mediators like renin angiotensin aldosterone system (RAAS), endothelin receptor-1 (ET-1), monocyte chemo attractant protein (MCP) and calcitonin related gene peptide (CGRP) [10]. ET-1, produced by vascular endothelium is a potent vasoconstrictor that triggers ROS formation by mitochondrial enzyme dependent process[15, 17]. Further, during

hypertension, there is increase in vasoconstriction, vasomotor tone and sodium ion channel expression[10]. Angiotensin-II, a mediator of renin aldosterone –angiotensin system (RAAS) system is supposed to generates ROS by nicotinamide dihydrogen phosphate oxidase (NADPH) which leads to hypertension[15]. Resveratrol has been implicated in treatment of hypertension by decreasing the generation of ROS and vasoconstriction[14]. Further, increasing the endothelial functions and NO bioavailability and is associated with NAD [P] H oxidize in small arteries[18].

Resveratrol in Atherosclerosis and obesity

Atherosclerosis mainly involves the increase in low density lipids (LDL) and decrease in high density lipids (HDL) [19]. Obesity is the chronic inflammation of adipose tissue and is reported as the major factor responsible for progression of atherosclerosis (fig 2). The various mediators MCP and TNF are involved in progression of atherosclerosis and obesity[7]. It also involves altered insulin sensitivity [20]. MCP hastens the infiltration of macrophages into adipocytes which inturn releases inflammatory cytokines like TNF–α which leads to inflammation and dysfunctioning of adipocytes[7]. MCP also inhibits insulin dependent glucose uptake and expression of adipogenic genes. Resveratrol administration reduces low density lipid [LDL] as well as increases high density lipids (HDL) which is useful in depletion of intima formation i.e. reducing atherosclerosis[14]. Statins are the first line drugs responsible for the reduction of LDL level in blood during atherosclerosis[19]. Resveratrol, a red wine is further useful in the treatment of hyperglycemic shock and insulin sensitivity during obesity[20]. Resveratrol inhibits TNF-α, NF-kB, MCP and cytokine signaling pathway which in turn reduces chronic inflammation of adipocytes leading to decreased atherosclerosis. Thus, it might be used for treatment of obesity.

Resveratrol as anticancer agent

Cancer is mainly assosiated with uncontrolled cell division and differentiation along with increased angiogenesis[8]. Further, it is reported that the process of apoptosis has been decreased during cancer generation by the inhibition of caspase-8-dependent pathway[21]. MAPK activity is also increased along with increased phosphorylation of ERK1/2 and jannus kinase (JNK) which is also another important factor involved in cancers[8, 22]. Activation of serine/threonine protien kinase- AKT (Pk-B) mediated by forkhead protiens (FOXO3a) which mediates cellular apoptosis by the activation of pro-apoptotic genes[23]. Resveratrol reduces the metastasis and causes the cell cycle arrest and also increases apoptosis showing a potent anti-cancer activity[24]. Resveratrol inhibits the Bcl-2 protiens and activates Bax protiens which is documented to be helpful in increasing apoptosis during prevention or treatment or cancers [25].

Resveratrol has been showing its effect as anticancer agent by slowing or halting the stages of cancers[26]. It modulates the gene expression by activating the tumor suppressor gene and toxin destroying genes[27]. It also acts by inhibiting estrogen and androgen uptake which is beneficial in treatment of prostate cancers[28]. Resveratrol also acts by deacetylating mechanism and cause death of cancer cells [29].

RESVERATROL IN CENTROL NERVOUS SYSTEM

Resveratrol in Neuroprotection

Mainly neuron related diseases are parkinsonian, alzheimer's, huntington and cerebral ischemia stroke that involves the degeneration of the dopamine neurons[16, 28]. As discussed earlier that ROS formed due to the ↑NADPH activity is too involved in the pathogenesis of neuro-degeneration[16, 18]. It has been further documented in that during CNS disorders there has been increased activity of transcriptional factors. And this increased action of transcriptional factors (NF-kB) further leads to inhibition the synthesis and release of inflammatory mediators by inactivating the immune cells[16]. And during the cerebral ischemia, there is mainly release of excitatory neurons thereby leading to increased production of ROS[30]. Also the microglial cells play an important role in CNS disorders by inhibiting that activation of inflammatory disorders[18]. The oxy form of resveratrol has ability to cross blood brain barrier. It lowers the level of free radicals like hydrogen peroxide (H2O2), nitrous oxide (NO), reactive oxygen species (ROS) and other artificial free radicals like diphenyl picrylhydrazyl (DPPH)[4, 5]. It also kills activated microglia and increases the release of inflammatory mediators and cytokines by the decrease in the generation of ROS[30] (fig 3). By stimulation the eNOS activity, resveratrol might be used for treatment of stroke[9].

RESVERATROL AS MISCELLANEOUS AGENT

Resveratrol as in acute pancreatitis (AP)

Acute pancreatitis (AP) is an emergent and severe disease of peptic system characterized by elevated levels of plasma amylase and lipase[40]. Various factors are responsible for progression of AP[36]. The transcription and nuclear factor kappa B (NF-kappa B) is an important substance that can modulate various inflammatory procedures and immune reactions[35]. It has already been proved that activation of NF-kappa B cytokine expression can act as one of the major factors for initiating and aggravating AP[40]. Generation of ROS are also implicated in AP [34]. ROS attacks polyunsaturated fatty acid's aldehyde group inside the biomembrane, initiating lipid peroxidation and accordingly forming lipid peroxidation products, resulting in the loss of membrane stability and activates phospholipase A1 which decompose lecithinum inside cellular membrane and return to tissue damage[40]. Moreover, neutrophils are the other major cellular source of ROS during acute pancreatitis and can directly release several inflammatory cytokines[37]. Resveratrol treatment might lead to the suppression of NF-κB activation and the subsequent prevention of several inflammatory mediator genes from being actively expressed, thus reducing the sequestration of neutrophils in the pancreas[1, 37].

Ageing mainly involves the cell senescence which alter the normal viability and metabolic activity without affecting cell division process[31]. Resveratrol has been documented to possess anti-aging property by increasing the mitochondrial anti-oxidant level[32]. Further, it causes activation of NF-kB signaling that provides cell protecting[33]. It is also reported that resveratrol activates the longevity gene (P-53 gene) which has functions of extend life and health by promoting intracellular repair and strengthening the blood vessels and thereby protecting brain tissue[34].

Clinically, it has been reported for its use in various kidney diseases and is a potent modulator in sperm production[36, 37]. It has also been reported for its use in various treatments of viral and fungal infections[38, 39].

CONCLUSION

It has been concluded that resveratrol has been documented as a potent drug with a multifaceted functions in CNS and CVS related diseases with lesser number of side effects.

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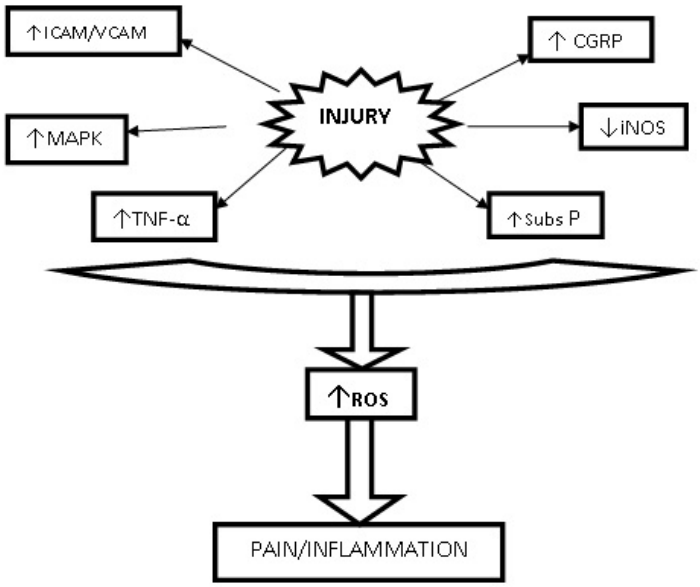

Fig 1: Signaling molecules involved during pain and inflammation. Where, ROS: reactive oxygen species, MAPK: mitogen activated protien kinase, TNF-α: tumor necrosis factor, ICAM: intercellular adhesion molecules, VCAM: vascular cell adhesion molecules, iNOS: nitric oxide synthase, CGRP: c-gene-related protein.

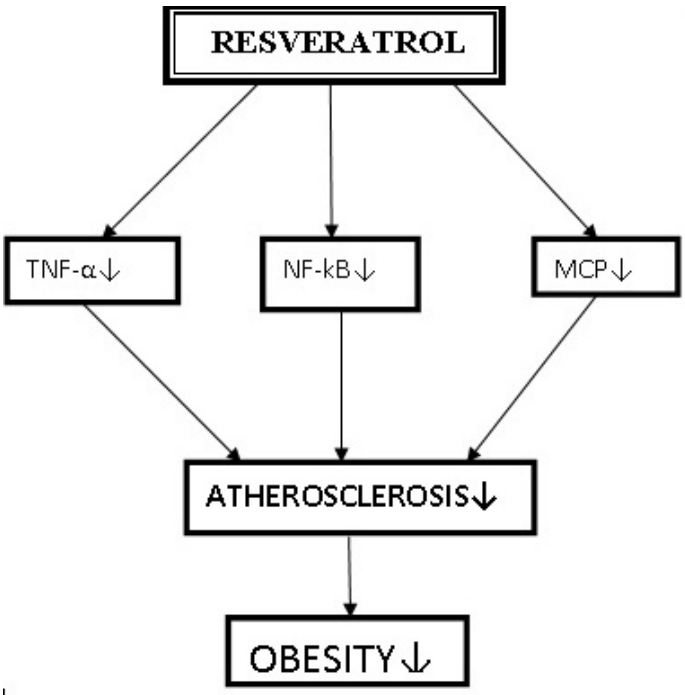

Fig 2: Signaling mechanism of resveratrol in obesity.

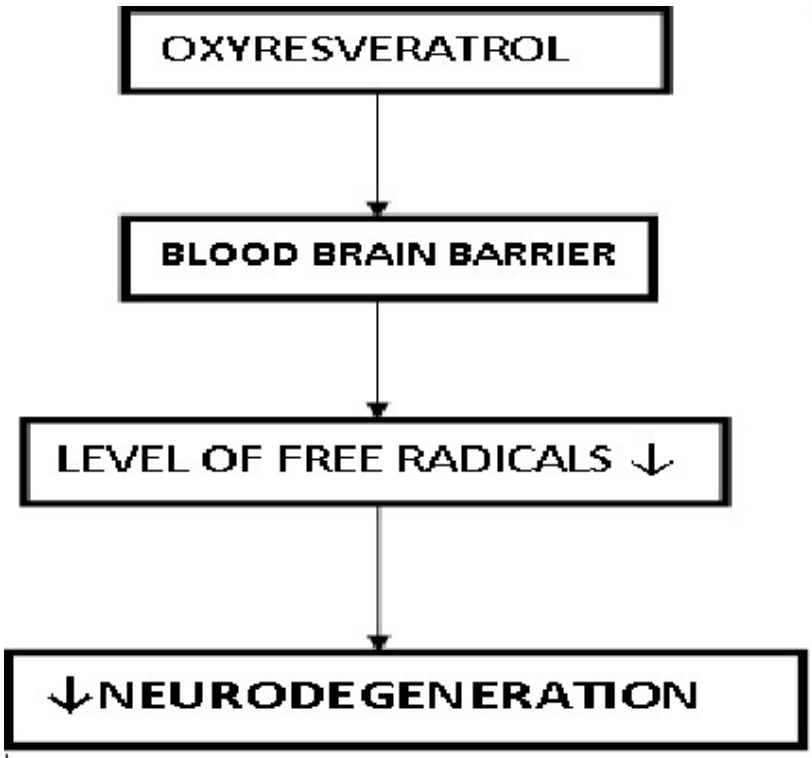

Fig 3: Schematic representation of action of resveratrol on brain