Resveratrol

Resveratrol (3,4,5-trihydroxystilbene) is a natural product and belongs to one of the important class of polyphenolic compounds, stilbenoids. Resveratrol and other stilbenes are found in grapes, red wine, purple grape juice, peanuts and some berries (Li et al. 2012). Most stilbenes in plants act as antifungal phytoalexins, compounds that are usually synthesized only in response to infection or injury. Resveratrol is first identified in red wine and reported in 1992. Scientists became interested in exploring its potential health benefits. Leading to the hypothesis that resveratrol might help to explain the “French Paradox”- the observation that mortality from coronary heart disease is relatively low in France despite of relatively high levels of dietary saturated fat and cigarette smoking. This led to the idea that regular consumption of red wine might provide additional protection from cardiovascular disease than other forms of alcoholic drink (Li et al. 2012). Resveratrol administration has increased the lifespan of yeast, worms, fruit flies, fish and mice fed with high-calorie diet, but it is not known whether resveratrol will have similar effects in humans (Rascon et al. 2012).

3,4′,5-Trihydroxy-trans-stilbene, 5-[(1E)-2-(4-Hydroxyphenyl)ethenyl]-1,3-benzenediol
Fig: Structure of resveratrol
6.1 Food Sources

Resveratrol is classified by its chemical structure as a polyphenol. These make a huge group of plant compounds that are further broken down into other classifications such as flavonoids and proanthocyanidins. Phytoalexins are antibacterial and anti-fungal chemicals produced by plants as a defense against infection by pathogens, injuries, stresses, UV irradiation, chemicals and climatic conditions (Tosun and Inkaya 2010). Resveratrol is found in grapes, grape products, wine, peanuts, cranberries, strawberry and some other botanical sources. The quantity of resveratrol in these foods ranges from 0.02 mg/L up to 6 mg/L (see Table). Resveratrol belongs to a class of polyphenolic compounds called stilbenes. Resveratrol originates in at least 72 species of plants distributed amongst 31 genera and 12 families. All of the families found to contain resveratrol belong to the spermatophytes division: Vitaceae, Myrtaceae, Dipterocarpaceae, Cyperaceae, Gnetaceae, Leguminosae, Pinaceae, Moraceae, Fagaceae, and Liliaceae. As a dietary source, it is a naturally occurring antioxidant found in grapes, grape products such as wine and some other botanical sources like peanuts, pistachio, strawberries, currants, cranberries and cranberry juice (Tosun and Inkaya 2010).
### Table: Resveratrol concentration in foods

Adapted from Tosun and Inkaya 2010

<table>
<thead>
<tr>
<th>Sources</th>
<th>trans-Resveratrol (mg/L)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wine (Pinot Noir Red)</td>
<td>3.6</td>
<td>Stervbo et al. 2007</td>
</tr>
<tr>
<td>Wine (Merlot, Red)</td>
<td>2.8</td>
<td>Stervbo et al. 2007</td>
</tr>
<tr>
<td>Peanut (Spanish Small White)</td>
<td>1.79</td>
<td>Sanders et al. 2000</td>
</tr>
<tr>
<td>Wine (Cabernet Sauvignon, Red)</td>
<td>1.70</td>
<td>Stervbo et al. 2007</td>
</tr>
<tr>
<td>Dark Chocolate</td>
<td>0.40</td>
<td>Counet et al. 2006</td>
</tr>
<tr>
<td>Peanut butter</td>
<td>0.30</td>
<td>Burns et al. 2002</td>
</tr>
<tr>
<td>Grape (Emir, White)</td>
<td>0.29</td>
<td>Gurbuz et al. 2007</td>
</tr>
<tr>
<td>Cranberry juice</td>
<td>0.24</td>
<td>Wang et al. 2002</td>
</tr>
<tr>
<td>Roasted peanut (Yeojoo)</td>
<td>0.13</td>
<td>Lee et al. 2004</td>
</tr>
<tr>
<td>Strawberry</td>
<td>0.11</td>
<td>Wang et al. 2007</td>
</tr>
</tbody>
</table>

### 6.2 Metabolism and Bioavailability

Resveratrol when it is administered orally; better absorption takes place in humans. It’s bioavailability is low due to rapid metabolism and elimination. Studies showed the bioavailability of the resveratrol from grape juice contains mostly glucosides of resveratrol, may be even lower than trans-resveratrol. Resveratrol metabolites primarily detected upon oral exposure are trans-resveratrol. Recent studies demonstrate that when six healthy human volunteers took an oral dose of 25 mg of *trans*-resveratrol, only traces of un-metabolized resveratrol were detected in plasma (blood). Plasma concentrations of resveratrol and metabolites peaked around 60 minutes after, at concentrations around 2 micromoles/ liter (Walle et al. 2004). According to the evidences, the oral bioavailability of resveratrol is almost zero due to rapid and extensive metabolism and the consequent formation of various metabolites of resveratrol which are glucuronides and resveratrol sulfates. The potential biologic activity of
resveratrol conjugates should be considered in future investigations (Wenzel and Somoza 2005).

6.3 Biological Activities

6.3.1 Direct Antioxidant Activity

Resveratrol is a natural product; it scavenges the free radicals and oxidants effectively. Resveratrol inhibits low-density lipoprotein (LDL) oxidation. *In vitro* studies, resveratrol had effective antioxidant and radical scavenging activity by the alteration of DPPH, ABTS, DMPD, O$_2^-$ and H$_2$O$_2$ scavenging activities, total antioxidant activity, reducing abilities and Fe$^{2+}$ chelating activities. It can be used in pharmacological and food industry due to its anti-oxidant properties (Gulcin 2009).

6.3.2 Anti inflammatory activity

Resveratrol is used to decrease the levels of pro-inflammatory cytokines *in vivo* and to reduce inflammatory reactions in certain inflammatory diseases (Leiro et al. 2010). Resveratrol has anti-inflammatory activities through modulation of enzymes and pathways that produce mediators of inflammation. Resveratrol does not produce any adverse effects, even consumed at high concentrations. However, resveratrol possesses good potential to be used as an adjunctive or alternative therapy for inflammatory diseases (Udenigwe et al. 2008).

6.3.3 Anti Cancer activity

Resveratrol acts against precancerous or cancer cells by its multiple biochemical and molecular actions. It affects all three discrete stages of carcinogenesis (initiation, promotion and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis,
inflammation, angiogenesis and metastasis. The anticancer property of resveratrol has been supported by its ability to inhibit proliferation of a wide variety of human tumor cells \textit{in vitro} (Bishayee et al. 2009). Anti-cancer effect of resveratrol is associated with induction of apoptosis via mitochondrial pathway alignment (Sun et al. 2008).

\textbf{6.3.4 Anti atherosclerosis activity}

Atherosclerosis, a progressive disease characterized by the accumulation of lipids and fibrous elements in the arteries, is a most important contributor to cardiovascular diseases (Fan et al. 2008). Resveratrol may have protective effects against atherosclerosis. It could receive consideration as a primary preventive agent (Agarwal et al. 2012).

\textbf{6.3.5 Anti Platelet Aggregation activity}

Red wine consists of resveratrol. Low or moderate consumption of red wine has a greater benefit than the consumption of other beverages in the prevention of coronary heart disease and atherosclerosis. This is attributed increasingly to the polyphenol compounds present in red wine. Resveratrol inhibits platelet aggregation both \textit{in vitro} and \textit{in vivo}. This may be one of the mechanisms by which resveratrol prevents atherosclerosis (Wang et al. 2002).

\textbf{6.3.6 Activation of Autophagy in Parkinsonian Cells}

Recently disregulation of the autophagy pathway has been observed in the brains of PD patients and in animal models of PD, indicating the emerging role of autophagy in this disease (Agarwal et al. 2012). In PD models, enhanced clearance of misfolded proteins or injured mitochondria via autophagy has been reported to have neuroprotective role. Resveratrol showed neuroprotective effects by autophagy regulation on PD cells (Wu et al. 2011).
6.3.7 Inhibition of Vascular Cell Adhesion Molecule Expression

Resveratrol shows potent inhibitory effect on inflammation-induced cell-cell adhesion, expression of adhesion molecules and activation of the NF-κB pathway (Deng et al. 2011).

6.3.8 Estrogenic and Anti-estrogenic Activities

Endogenous estrogens are present in humans and other mammals. These are steroidal hormones. The estrogen receptors bind to steroidal hormones within cells. The interactions of estrogen-receptor complex modulate expression of estrogen-responsive genes with unique sequences in DNA. A compound that binds to estrogen receptors and elicits similar responses to endogenous estrogens is considered as an estrogen agonist, while a compound that binds estrogen receptors but prevents or inhibits the response elicited by endogenous estrogens is considered as an estrogen antagonist. The chemical structure of resveratrol is very similar to that of the synthetic estrogen agonist, diethylstilbestrol, suggesting that resveratrol might also function as an estrogen agonist. However, epidemiological evidence indicates that phytoestrogens inhibit cancer formation and growth, reduce cholesterol levels and show benefits in treating osteoporosis. At least some of these activities are mediated through the interaction of phytoestrogens with estrogen receptors alpha and beta (ER alpha and ER beta) (Bowers et al. 2000).

6.3.9 Cardio protective activity

Coronary heart disease (CHD) is a major cause of morbidity and death. Recent studies focussed at an epidemiological phenomenon known as the "French paradox." This observation refers to the coexistence of high risk factors with unanticipated low incidence of CHD and is postulated to be associated with low-
to-moderate consumption of red wine. *In vitro* and animal studies showed that resveratrol exerted multifaceted cardioprotective activities (Wu and Hsieh 2011).

6.3.10 Neuroprotection

Resveratrol activates SIRT1, an NAD-dependent deacetylase. SRT501, a pharmaceutical formulation of resveratrol with enhanced systemic absorption, prevents neuronal loss without suppressing inflammation in mice with relapsing experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). Resveratrol treatment showed neuroprotective effects without immunosuppression, suggesting a potential additive benefit of resveratrol in combination with anti-inflammatory therapies for MS (Fonseca-Kelly et al. 2012).

In cerebral ischemia/reperfusion (I/R), free radicals are known to cause secondary neuronal damage. Resveratrol treatment improves neurological deficits caused by reperfusion injury. Histological examination of CA1 hippocampal region revealed that resveratrol treatment diminished intercellular and pericellular edema and glial cell infiltration (Yousuf et al. 2009).

6.3.11 Longevity

Recent researchers examine the effect of resveratrol on longevity on six species like yeast, nematodes, mice, fruit flies, Mexican fruit flies and turquoise killifish. Longevity is most potent in yeast and nematodes with diminished reliability in most higher-order species. Turquoise killifish were especially sensitive to life-extending effects of resveratrol but showed much variation. Much of the considerable heterogeneity of few species conclusively shows life extension in response to resveratrol. As such, a question arises to the practice of the resveratrol being marketed as a life-extending health supplement for humans (Hector et al. 2012).
References


10. Rascon B, Hubbard BP, Sinclair DA et al. The lifespan extension effects of resveratrol are conserved in the honey bee and may be driven by a mechanism related to caloric restriction. Aging (Albany NY) 2012; 4(7): 499-508


Review of Literature

Resveratrol is a bioflavone, obtained from grape skin. It exerts variety of biochemical and pharmacological effects. Recently considerable interest has been focused on resveratrol because of its anti-oxidant, anti-inflammatory and anti-proliferative activities. Oxidative stress and inflammation are thought to be key pathological events in ischemic reperfusion injury. ROS overproduction leads to inflammatory cascades which further worsen the ischemic condition by damaging lipids, proteins and nucleic acids. There is an increasing evidence supporting the hypothesis that resveratrol can provide protection against neurodegenerative changes associated with cerebral ischemia and reperfusion injury. This chapter reviews the neuroprotective effect of resveratrol that have been studied by several authors in experimental models of cerebral ischemia and reperfusion. Resveratrol has been suggested as a therapeutic agent in cerebral ischemia and reperfusion injury.

Simao et al. 2012 investigated that resveratrol has neuroprotection by its anti-inflammatory effects. In this experiment, adult male rats were subjected to 10 min of four-vessel occlusion and sacrificed at selected post-ischemic time points. They examined inflammatory markers like NF-κB inflammatory cascade, COX-2, iNOS and JNK levels in experimental I/R rats. Finally they found that resveratrol 30 mg/kg pretreatment for 7 days prior to I/R induction, reduces astroglial and microglial activation after I/R. It also decreases I/R-induced NF-κB and JNK activation with decreased COX-2 and iNOS production.

Li et al. 2012 tested whether resveratrol play a neuroprotective effect in ischemic rat brain model induced by middle cerebral artery occlusion (MCAO). They have observed that resveratrol treatment alters infarction size, Long-term potentiation
induced by high-frequency stimulation and expression of apoptosis-related proteins, i.e., Bcl-2 and Bax. Finally these results concluded that resveratrol can decrease the harmful effects of cerebral ischemia-reperfusion induced brain injury and has potential neuroprotective effect.

*Simao et al. 2011* suggested that resveratrol has neuroprotective effect by inhibiting underlying oxidative mechanisms. In this study they have estimated infarction (stained with Nissl and fluoro jade C), ROS, nitric oxide (NO), lipid peroxidation and Na⁺/K⁺-ATPase levels after 7 days of I/R injury and concluded that resveratrol may be used as a preventive or therapeutic agent in global cerebral ischemia and reperfusion injury.

*Gresele et al. 2011* suggested that resveratrol contributed to protection from oxidative stress and radical oxygen species production, a facilitating activity on nitric oxide production and activity. The ability to modulate the expression of adhesive molecules by blood cells and the vascular wall seem to be the most important mechanism. This review gave evidence on the activity of resveratrol on vascular function and circulating blood cells in *in vitro* and *in vivo*.

*Li et al. 2011* investigated that resveratrol has protective effect against ischemic injury by alleviating oxidative stress and improving brain energy metabolism. In this study they have examined histological changes and levels of ATP, ADP, AMP, adenosine, inosine, hypoxanthine and xanthine. The levels of malondialdehyde and the activities of xanthine oxidase in brain tissues were analyzed. Their findings showed that resveratrol could exert neuroprotective effect against ischemia injury by improving brain energy metabolism and alleviating oxidative stress via inhibiting xanthine oxidase activity and preventing the
production of hypoxanthine, xanthine and oxygen radicals during ischemia/reperfusion.

**Liu et al. 2011** suggested that resveratrol significantly promotes the recovery of rat dorsal neuronal function after spinal cord injury (SCI) and this effect is related to its characteristics of anti-oxidation, anti-inflammation and anti-apoptosis.

**Sakata et al. 2010** revealed that resveratrol, an enriched bioactive polyphenol in red wine has neuroprotection against heme oxygenase 1 (HO1) induced free-radical or excitotoxicity damage in cultured mouse cortical neuronal cells (a dose- and time-dependent manner).

**Siddiqui et al. 2010** investigated that the neuroprotective potentials of trans-resveratrol against 4-hydroxynonenal (4-HNE) induced damage in PC12 cells. Cells were pretreated with trans-resveratrol (5, 10 and 25 microM) for 24 hr, further exposed to 4-HNE (25 microM) for 2 hr. Reactive oxygen species generation, restoration of intracellular glutathione, and lipid peroxidation levels were significantly reduced in pretreated trans resveratrol cells, as well as in mitochondria-mediated apoptosis markers (Bax, Bcl-2 and Caspase-3) were significantly restored. These findings concluded that trans resveratrol has neuroprotection *in vitro.*

**Zhang et al. 2010** suggested that after brain injury microglia activation occurs. During activation of microglia, various pro-inflammatory factors were released, causing reactive oxygen species production and the activation of signal pathways, which lead to neuroinflammation. In the review they suggested that the microglia is an important target for anti-inflammatory activities of resveratrol in the brain.

**Cheng et al. 2009** suggested that resveratrol inhibited MMP-9 expression by up-regulating PPAR alpha. In this experiment, an oxygen glucose deprivation-
exposed neuron model was used for estimation of MMP-9 and PPAR alpha or gamma expression.

**Wang et al. 2009** suggested that grape polyphenol extract oral administration may have protection against I/R induced rats and emphasized that early intervention may be an effective therapeutic measure for ameliorating brain injury in stroke.

**Kang et al. 2009** reported that resveratrol has exerted a regulatory effect on inflammatory reactions mediated by mast cells. Human mast cell lines (HMC-1) were stimulated with phorbol 12-myristate 13-acetate (PMA) plus A23187 in the presence or absence of resveratrol. ELISA, RT-PCR, real-time RT-PCR, Western blot analysis, fluorescence, and luciferase activity assays were used in this study. Resveratrol significantly inhibited the PMA plus A23187-induction of inflammatory cytokines such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-8.

**Yousuf et al. 2009** investigated that the resveratrol has neuroprotective effect against cerebral I/R-induced mitochondrial dysfunctions in hippocampus. In this study they used MCAO model of brain ischemia to induce brain infarction. They have examined ATP content and the activity of mitochondrial respiratory complexes, cytochrome c release, DNA fragmentation, mitochondrial glutathione (GSH), glucose 6-phosphate dehydrogenase, serum lactate dehydrogenase, protein carbonyl and intracellular H$_2$O$_2$, brain infarct and histological analysis in I/R and resveratrol treated rats. These findings highlighted the ability of resveratrol in anatomical and functional preservation of ischemic neurovascular units and its relevance in the treatment of ischemic stroke.

**Karaoglan et al. 2008** investigated the efficacy of resveratrol, a stilbene polyphenol and tyrosine kinase inhibitor that occurs naturally in grapes and red
wine, in a murine basilar artery vasospasm model. This study showed that resveratrol induced the relaxation of smooth muscle in the wall of the basilar artery and provided neuroprotection against cerebral ischemia in rat model. These effects may be associated with the anti-oxidant and vasodilatory effects of resveratrol.

Dong et al. 2008 reported that resveratrol has provided an important neuroprotective effect on focal cerebral ischemic injury in the delayed phase. The elevated MMP-2 and VEGF levels might be important in the neuroprotective effect of resveratrol administration by inducing angiogenesis.

Sonmez et al. 2007 aimed to estimate resveratrol effect on behavioral deficits and hippocampal damage in 7-day-old rat pups subjected to continuing injury. In this study they have examined hippocampal damage and behavioral alterations 2 weeks after trauma. Resverarol 100 mg/kg dose treatment after the trauma significantly ameliorated the trauma induced hippocampal neuron loss at ipsilateral and contralateral hippocampal brain regions of rats. Additionally, treatment with resveratrol decreased anxiety and increased cortex/hippocampus dependent memory of animals subjected to blunt head trauma. These findings concluded that resveratrol has a neuroprotective role against trauma induced hippocampal neuron loss associated with cognitive impairment in rats.

Zamin et al. 2006 investigated the neuroprotective effect of resveratrol in an in vitro model of ischemia. They used organotypic hippocampal cultures exposed to oxygen-glucose deprivation (OGD). In OGD-vehicle exposed cultures, about 46% of the hippocampus was labeled with propidium iodide (PI), indicating a robust percentage of cell death. When cultures were treated with resveratrol 10, 25 and 50 microM, the cell death was reduced to 22, 20 and 13% respectively. To
elucidate a possible mechanism by which resveratrol exerts its neuroprotective effect, they have investigated the phosphoinositide3-kinase (PI3-k) pathway using LY294002 (5 microM) and mitogen-activated protein kinase (MAPK) using PD98059 (20 microM). The resveratrol (50 microM) neuroprotection was prevented by LY294002 but was not by PD98059. Immunoblotting revealed that resveratrol 50 microM induced the phosphorylation/activation of Akt and extracellular signal-regulated kinase-1 and -2 (ERK1/2) and the phosphorylation/inactivation of glycogen synthase kinase-3beta (GSK-3beta). These results suggested that PI3-k/Akt pathway is involved in the neuroprotective effect of resveratrol.

**Gao et al. 2006** evaluated the effect of resveratrol on MMP-9 induced by cerebral ischemia-reperfusion in vivo. Male Balb/C mice were treated with resveratrol for 7 days (50 mg/kg, gavage). Thereafter, middle cerebral artery occlusion (MCAO) was performed for 2 h with the help of intraluminal thread. Drug-treated mice showed improvement in necrotic changes in cortex and basal ganglia. Detection of MMP-9 activity and gene expression was performed at various time points after MCAO. The elevated levels of MMP-9 were significantly attenuated in the resveratrol-treated mice as compared to the vehicle treated mice. The study suggests that resveratrol has protective effects against acute ischemic stroke, which could be attributed to its property against MMP-9. Thus, resveratrol may be a potential agent for the treatment of neuronal injury associated with stroke.

**Breuer et al. 2006** investigated that the hydroxystilbene oxyresveratrol (trans-2,3,4,5-tetrahydroxystilbene) was an excellent complementary drug for the treatment of neurodegenerative disorders that causally involved oxidative/nitrosative stress, especially in stroke.
Zhuang et al. 2003 investigated that the resveratrol exerted its neuroprotective abilities by increased heme oxygenase activity, a unique pathway by which this compound can exerted its neuroprotective actions.

Inoue et al. 2003 examined whether PPAR alpha agonists and resveratrol would protect the brain against ischemia. Resveratrol (20 mg/kg, 3 days) reduced infarct volume by 36% at 24 h after middle cerebral artery occlusion in wild-type mice. The PPARalpha agonist’s fenofibrate (30 mg/kg, 3 days) and Wy-14643 (30 mg/kg, days) exerted similar brain protection. However, resveratrol and fenofibrate failed to protect the brain in PPAR alpha knockout mice.

Ikeda et al. 2003 suggested that anti-oxidant nutrients such as vitamin E, green tea extract, ginkgo biloba extract, resveratrol and niacin have beneficial effects in cerebral ischemia and recirculation brain injury.

Wang et al. 2002 demonstrated that the resveratrol, a polyphenolic antioxidant, can cross the blood-brain barrier and exert protective effects against cerebral ischemic injury. Transient global cerebral ischemia was induced by occlusion of both common carotid arteries (CCA) for 5 min in mongolian gerbils. Resveratrol was injected i.p. (30 mg/kg body weight), either during or shortly after CCA occlusion, and again at 24 hr after ischemia. They examined blood flow rate before and after CCA occlusion using laser Doppler flowmeter. A time course study was also carried out to assess the bioavailability of resveratrol in serum, liver and brain using high performance liquid chromatography (HPLC). Morphometric measurements indicated extensive delayed neuronal death in the hippocampal CA1 region 4 days after ischemia and that neuron cell death was marked by the increase in reactive astrocytes and microglial cells. Administration of resveratrol, either during or after CCA occlusion, significantly (P<0.05)
decreased DND as well as glial cell activation. Analysis of resveratrol after i.p. injection indicated its presence in serum, liver and brain with peak activity at 1, 4 and 4 hr, respectively.

Sharma et al. 2002 suggested that trans resveratrol involved in preventing the cognitive deficits and reduction of oxidative stress caused by intracerebroventricular (ICV) administration of streptozotocin in rats.

Sinha et al. 2002 suggested that chronic treatment of trans resveratrol was effective in focal ischemia induced by middle cerebral artery (MCA) occlusion in rats. Male Wistar rats were pretreated with trans resveratrol 20 mg/kg i.p. for 21 days and were subjected to focal ischemia by occlusion of MCA using intraluminal thread. After two hours of MCA occlusion reperfusion was allowed by retracting the thread. In this study they were assessed motor performance in animals after 24 hrs and subsequently rats were sacrificed for estimation of markers oxidative stress markers (malondialdehyde and reduced glutathione) and for infarction volume. Significant motor impairment, with elevated levels of MDA and reduced glutathione was observed in the vehicle treated MCA occluded rats. Treatment with trans resveratrol prevented motor impairment, decreased levels of MDA and reduced glutathione and also significantly decreased the volume of infarct as compared to control. These results provided evidence of effectiveness of trans resveratrol in focal ischemia most probably by virtue of its antioxidant property.

Huang et al. 2001 suggested that the resveratrol was a potent neuroprotective agent in focal cerebral ischemia. Its beneficial effects may be related to its anti-platelet aggregation activity, vasodilating effect, antioxidant property or by all
mechanisms together. In this study they performed middle cerebral artery occlusion for 1 hr followed by 24 hr reperfusion in anesthetized Long-Evans rats. 

Wang et al. 2001 investigated that resveratrol might be useful in treating ischemic-induced inflammatory processes in stroke. In this study they have examined cytokine induction and inhibition in rat cortical mixed glial cells exposed to in vitro ischemia-like insults (hypoxia plus glucose deprivation) by anti oxidants. The results showed that interleukin-6 (IL-6) mRNA and protein, but not tumor necrosis factor-alpha (TNF-alpha) or interleukin-1beta (IL-1beta), were induced during hypoxia/hypoglycemia followed by reoxygenation in the mixed glial cells. The accumulation of IL-6 mRNA was induced as early as 15 min after hypoxia/hypoglycemia and its level was further increased after subsequent reoxygenation. Among the antioxidents studied, only resveratrol suppressed IL-6 gene expression and protein secretion in mixed glial cultures under hypoxia/hypoglycemia followed by reoxygenation.
References


