

## Resveratrol in CNS: Dietary Antioxidants to Pharmacological Agents

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The dietary polyphenol resveratrol (3,4',5-trihydroxystilbene), found naturally in food, recently has been receiving attention due to its medical potential. It is widely believed that consumption of red wine, rich in trans- resveratrol (trans-R) and other dietary polyphenols, is the primary cause of the French paradox that evolved considerably since 1992 [1]. It is naturally produced in plants as a response to injury and functions as a phytoalexin that protects against fungal infections. Since then, resveratrol has been extensively studied and has unequivocally demonstrated to have potent antioxidants, anti-inflammatory, anti-proliferative, and anti-angiogenic effects and acts on a number of different targets using various mechanisms that can explain its diverse biological activities in different diseases [2]. Given the widespread role of free radical-mediated damage in neuronal disorders, resveratrol has been extensively used to study the possible neuroprotective effects in preclinical and clinical studies.

Oxidative stress plays a central role in neuronal injury in acute and chronic pathological conditions. We and others have reported that pre and post treatment of trans resveratrol significantly reduced oxidative stress by scavenging the free radicals and improving endogenous defense enzymes and improving the clinical outcome in animal models of stroke, Parkinson's, Alzheimer's, seizures and other CNS injury [3,4]. In addition, resveratrol decreased the level of Matrix metalloproteinases (MMPs), and may reduce CNS permeability to limit the infiltration of leukocytes and other inflammatory mediators into the brain. Furthermore, resveratrol activates the SIRT1, a member of the histone deacetylase class III family of proteins and was found to be decreased in demyelination and neurodegeneration. Recent promising results in a series of clinical trials with mild to moderate dementia have reported decline of cerebrospinal fluid (CSF) beta amyloid and preservation of blood-brain barrier integrity and immune response. The outcome of these trials are the stepping stones to the approval of treatment for dementia [5].

Resveratrol and its major metabolites penetrated the blood-brain barrier and had a measurable concentration in the plasma and CSF as well. Recent preclinical and human studies have demonstrated that even low levels of this compound in the plasma can significantly improve the functional outcomes. Since animals and humans are unable to synthesize polyphenols, they must be ingested from a plant-rich diet to achieve pharmacologic effects. Current pharmacokinetics studies in humans showed that an oral dose of trans-resveratrol, 500 mg, is well tolerated with no adverse effects, while a high dose of 2.5 mg and 5 mg caused mild to moderate gastrointestinal symptoms [6]. Many trials are in progress to determine the appropriate oral dosage given the rapid metabolism of resveratrol, and to develop a more effective drug delivery system of resveratrol that may have a higher bioavailability.

In conclusion, all these studies provide useful considerations for the better planning and design of future clinical research on resveratrol, and determine whether resveratrol is more efficacious in certain patient types. At a pharmaceutical level, companies should explore and focus on developing a resveratrol derivative with better bioavailability.

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