

## RESVERATROL: MORE THAN A PHYTOCHEMICAL

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*In recent years, alternative and complementary medicine including the plant-based drugs with antioxidant and neuroprotective effects has attracted a growing interest. Resveratrol, a polyphenolic compound which is found in various plant species, has emerged as a promising nutraceutical with therapeutic potentials in neuropsychiatric, cardiometabolic and cancer diseases, also aging. The abundance of research providing promising findings about the multi-spectrum therapeutic applications of resveratrol and its encouraging potential to treat or prevent chronic and age-related disorders has raised a considerable number of clinical trials. Recently, resveratrol is implicated the biology of nerve growth factor (NGF), a critical player in the maintenance of neuronal growth and function. Furthermore, resveratrol affects the endocannabinoid signalling (eCBs) which exerts modulatory effects in the survival signalling pathways, neural plasticity, and a variety of neuroinflammatory and neurodegenerative processes. The therapeutic effects of this ubiquitous signalling system in Alzheimer's disease, epilepsy, multiple sclerosis, mood and movement disorders, spinal cord injury, and stroke have been well-documented. In the present review, the implication of NGF and eCBs in the mechanism of action of resveratrol, that may be of therapeutic significance in neurological and non-neurological disorders, is highlighted. **Biomed Rev 2015; 26: 13-21.***

**Key words:** polyphenol, nerve growth factor, endocannabinoid system, neurological disorders

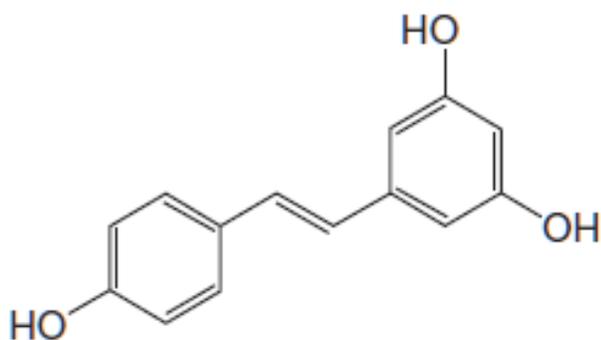
### INTRODUCTION

Over the last few decades, studies on the health benefits of herbs have shown the ability of plants to synthesize a variety of compounds which interact with biological pathways (1). Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene; C<sub>14</sub>H<sub>12</sub>O<sub>3</sub>, Fig. 1), a polyphenolic compound which is found in various

plant species, has shown a wide range of pharmacological activities. This phytochemical (nutraceutical) inhibits the cyclooxygenase-1 and 2 expression and nuclear factor-κB (NF-κB) signalling and reduces the production of proinflammatory cytokines leading to the antiinflammatory and analgesic effects (2). Resveratrol *via* the induction of apoptosis of cancer cells and metabolism of carcinogens as well as

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**Figure 1.** The chemical structure of resveratrol.

inhibition of cancer initiation and progression signalling exerts its anticancer effects (3). Since NF- $\kappa$ B signalling is a well-characterized target of cancers (4), inhibition of this signalling pathway by resveratrol (2) may be implicated in the anticarcinogenic effects of this natural polyphenol. Regarding the cardiometabolic protection, resveratrol inhibits inducible nitric oxide synthase (iNOS) and platelets aggregation, elevates high-density lipoprotein, and reduces low-density lipoprotein, triglycerides, and reactive oxygen species (ROS) accumulation (5). Resveratrol acts against the oxidative stress *via* the up-regulation of antioxidant enzymes synthesis and enhancement of the anti-oxidant capacity, free radical scavenging activity, as well as the inhibition of lipid peroxidation, and regeneration of  $\alpha$ -tocopherol (6). Obesity, because of its complexity and multi-factorial nature, has remained as a challenging medical problem (7). Resveratrol by inhibition of the adipogenesis and down-regulation of lipogenic genes, and enhancement of fat oxidation has shown promising anti-obesity effects (8). In type 2 diabetes mellitus, resveratrol, by activating sirtuin 1, elevates the glucose uptake by muscles and modulates the  $\beta$ -cells insulin secretion (9). Regarding the neuroprotective properties of resveratrol, there are reports indicating its inhibitory effects against the memory deterioration, neuroinflammation, and oxidative stress in the hippocampus. Resveratrol improves the sensorimotor function, modulates the cholinergic neurotransmission, and prevents the oxidative damage of astroglial cells and cognitive decline. This natural compound downregulates the glutamate-induced extracellular signal-regulated kinase activation and interleukin-1 $\beta$  (IL- $\beta$ ) expression in the hippocampus (10-12). Study on the primary cortical neuron cultures has revealed

that resveratrol through the inhibition of intracellular calcium increase and production of ROS exerts the protective effect against N-Methyl-D-aspartate-induced neuronal death (13). Furthermore, this natural polyphenol by antioxidant activities protects the hippocampal neurons against the NO-induced toxicity (14). In Alzheimer's disease, resveratrol has been shown to reduce the intracellular amyloid- $\beta$  peptides, NO production, iNOS expression, prostaglandin E<sub>2</sub> accumulation, and NF- $\kappa$ B translocation (15). Resveratrol exhibits therapeutic potential in other neurodegenerative diseases such as Parkinson's disease (16) and amyotrophic lateral sclerosis (17) that may be due to its antioxidant and anti-inflammatory properties. This polyphenolic compound prevents the spinal cord and brain damage following the ischemia-reperfusion or traumatic injury (18).

In recent years, it has been shown that resveratrol exerts antidepressant effects *via* the modulation of hypothalamic-pituitary (HPA) axis activity and oxidative-nitrosative stress and inhibition of the production of inflammatory cytokines (19-21). Based on an increasing evidence, neurotrophins, a protein family including the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), NT-4/5, and NT-6 act as the potential mediators of antidepressant responses (22, 23). Neurotrophins mediate their effects by the ligation of two major types of receptors: a high affinity tyrosine kinase (Trk) receptor and a low affinity pan-neurotrophin receptor (p75<sup>NTR</sup>), thus trigger a number of cellular responses including the long-term trophic effects as well as the rapid chemotropic and morphogenetic actions on the developing neurons, synaptic transmission, and neuronal excitability (24-27). Neurotrophins are also implicated in the neuronal plasticity and exhibit neuroprotective effects that might be of therapeutic significance in the neuropsychiatric disorders (28). Indeed, dysfunction of the neurotrophin-related signalling mechanisms is involved in the pathogenesis of a number of psychiatric disorders (23-26). The prototypical neurotrophin, NGF, which regulates the stress and cognitive function (29,30) and mediates the action of a wide variety of psychotropic agents (31-35), along with the eCBs which regulates the neuroprotective processes (36), are implicated in the mechanism of action of resveratrol (37) that will be discussed herein.

## RESEVERATROL AND NGF

Following the discovery of the first neurotrophin, NGF, by the Nobel Laureate Rita Levi-Montalcini (38), further

studies showed that NGF as well as other neurotrophins (e.g. BDNF) affect the neuronal survival and differentiation, exerts a regulatory role in the memory and attention tasks, in neuroendocrine-immune interaction, and neurological disorders (39, 41). Because of its antioxidant, angiogenic and metabotropic (including insulinotropic) properties, NGF is implicated in the molecular mechanisms of cardiometabolic diseases (41, 42, 48 and references therein), accelerates corneal and skin wound healing (43, 44) and plays a fundamental role in tissue engineering (45). Over the last decade, it has been suggested that electroconvulsive treatment or antidepressant drugs may act by increasing neurotrophin contents in the central nervous system (CNS). Based on the ability of NGF to induce the release of hypothalamic vasopressin which plays a crucial role in the formation of social bonding (46), it was suggested that NGF by modulating the neuroendocrine functions is implicated in the molecular mechanisms of emotions. In this respect, the involvement of NGF and BDNF in the pathogenesis of neuropsychiatric disorders (39, 41, 47-49) and in the mechanisms of action of a wide range of psychotropic agents (31-35, 41, 50) were reported. These findings might be of great significance in optimal management of neuropsychiatric disorders. Recently, the involvement of NGF in the mechanism of action of resveratrol has also been reported (37). The elevation of brain NGF levels following chronic treatment with resveratrol indicates that the neurotrophic effect is a slow-developing process. The sustained enhancement of NGF protein contents in the brain regions which regulate the emotional activity may be considered as a mechanism by which resveratrol exerts its therapeutic effects in the neuropsychiatric disorders. Since NGF exerts the stimulatory effect on the cell proliferation (51), therefore, the elevation of frontal cortex NGF following the chronic administration of resveratrol might be of therapeutic significance against the stress-induced reduction in cell proliferation in the frontal cortex (52).

Resveratrol also elevates NGF level in the hippocampus (37). It is noteworthy that NGF plays a pivotal role in learning, hippocampal plasticity, and neurogenesis (29, 30), and induces acetylcholine release in the hippocampus (49) leading to the improved cognitive performance. Therefore, resveratrol by enhancement of the hippocampal NGF may stimulate the hippocampal neurogenesis and improve the cognitive function. Moreover, this nutraceutical increases NGF contents in the olfactory bulb and amygdala (37). The critical role of NGF in the development, regeneration, and maintenance of the

olfactory system of mammals has been well-documented (29, 30, 53). NGF also facilitates the cholinergic neurotransmission between the amygdala and *nucleus basalis* (54) leading to the improvement of cognitive function. Altogether, it appears that elevation of brain NGF, also BDNF, contents constitutes a major part of the biochemical alterations induced by certain psychotropic agents (31-35, 41, 50) including resveratrol (37).

#### RESVERATROL AND THE ENDOCANNABINOID SIGNALING

Over the last decade, the eCBs, a group of neuromodulatory lipids and their receptors which regulates the neuronal proliferation and maturation (55), synaptic plasticity (56), emotional reactivity (57), neurotensin neurotransmission (58-59) and neurotrophin signalling (60, 61), has emerged as a topic of great interest in neuroscience and pharmacology. The endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are produced on-demand by the lipid precursors in the neuronal cell membrane and activate two types of G protein-coupled receptors, cannabinoid CB<sub>1</sub> and CB<sub>2</sub>, leading to a wide variety of pathological and physiological processes. The eCBs exerts neuroremodulatory action in various types of diseases (62). In this context, development of anandamide uptake blockers, cannabinoid receptor agonists, and selective inhibitors of endocannabinoid degradation has been the focus of intense research (63, 64). In transsynaptic neuronal changes due to the neurodegenerative processes (65), microglia-induced neurotoxicity, and cytotoxicity induced by the excitatory amino acids (66), the eCBs exerts protective effects (67). In general, the endocannabinoids exert their neuroprotective effects through a variety of mechanisms including the prevention of calcium influx, inhibition of NO and/or glutamate release, and activation of antioxidative mechanisms. Furthermore, activation of the CB<sub>1</sub> receptors leads to the stimulation of phosphoinositide 3-kinase (PI3-K)/AKT signalling pathway and promotion of the cell survival (68). According to the protective effects of the eCBs against the excitotoxic damage and neuronal insult (58, 67), this ubiquitous signalling system might be an emerging target for the therapeutic interventions against the neurological disorders. In Parkinson's disease (PD), the most prevalent neurodegenerative disorder affecting the basal ganglia, dopamine depletion results in a cascade of neurochemical events within the basal ganglia. Endocannabinoids and their synthesizing and degrading enzymes are abundantly found in the basal ganglia (69). Indeed, the striatal eCBs undergoes a profound neurophysiological alteration in order

to restore the homeostasis within the basal ganglia (70). In Huntington's disease, the CB<sub>1</sub> receptor agonists and inhibitors of eCB transport reduce the hyperkinesia associated with the disease (71). Stimulation of the CB<sub>1</sub> or CB<sub>2</sub> receptors results in the anti-inflammatory effects in multiple sclerosis (72). Furthermore, CB<sub>1</sub> agonists promote the oligodendrocyte survival and mRNA expression of myelin protein (73) suggesting that the eCBs not only attenuates the symptoms of the disease, but also improves the function of oligodendrocytes that may be due to its antiinflammatory and neuroprotective effects. In the spinal cord injury, a cascade of cellular and molecular events which occur following the initial damage, is a main target for therapeutic interventions including the application of cannabinoids. In an animal model of the spinal cord injury, a significant increase of the eCB contents has been reported (74) suggesting that activation of the eCBs is a part of the neuroprotective response which is triggered following the injury.

In epilepsy, the imbalance between the inhibitory and excitatory neural circuits leads to the excitotoxicity and neuronal death (75-77). Based on the regulatory effects of the eCBs on the inhibitory and excitatory transmissions and the enhancement of the eCB contents in epilepsy (78), this ubiquitous signalling system may be a promising target for antiepileptic therapies. In ischemic stroke, recombinant tissue plasminogen activator improves the functional outcome in patients, however, it should be administered within a short period of time following the onset of symptoms. The non-psychoactive component of cannabis, cannabidiol, has been shown to inhibit the voltage-sensitive Ca<sup>2+</sup> channels leading to the reduction of excitotoxicity. Administration of cannabidiol 6 h after the cerebral ischemia has led to the neuroprotective effects. Furthermore, cannabidiol has preserved the regional cerebral blood flow and improved the motor coordination even at 3 days after the cerebral ischemia (79) indicating its long-lasting preventive effects on the post-ischemic cerebrovascular events.

In Alzheimer's disease which is associated with neuroinflammation, neurodegeneration, and cognitive impairment (80), the eCBs is of therapeutic significance because of its anti-neuroinflammatory and neuroprotective effects (62, 81). In  $\beta$ -amyloid-induced neurotoxicity, the eCBs may exert protective effects through the inhibition of NO release and activation of mitogen-activated protein kinase pathway (82).

In amyotrophic lateral sclerosis, one of most the debilitating

neurodegenerative disorder which is characterised by the degeneration of motor neurons, the eCBs has shown anti-inflammatory and neuroprotective effects by the prevention of excitotoxic damage and preservation of glutamate homeostasis (83). Following the identification of the endocannabinoid binding sites in *substantia gelatinosa*, analgesic effects of the eCBs in both acute and chronic pain were identified (84, 85). The interaction between the opioid signalling and eCBs is also well-documented (86). Based on these multi-target bioactivities of the eCBs, its potential implication in the mechanism through which resveratrol regulates brain NGF contents has been investigated. It has been found that resveratrol affects brain NGF levels under the regulatory drive of CB<sub>1</sub> receptors (37). Furthermore, the brain eCB contents are increased following the chronic treatment with resveratrol (37). It appears that the eCBs activation is required, at least in part, for the neuroprotective actions of resveratrol against the various types of neurological disorders.

Regarding the mood disorders, compounds which affect the eCBs function have been shown to regulate the monoamine-mediated neurotransmission and activity of HPA axis (87). In the limbic brain regions where the neuronal activity is altered in depression (88), endocannabinoids are found at moderate to high levels (87). Indeed, the regulatory role of the eCB enhancers on mood (57), has opened a new line of research in antidepressant drug discovery and development of novel antidepressants. Cannabinoids may be beneficial against the anxiety-related disorders as the CB<sub>1</sub> receptor antagonist, SR141716A, has been shown to induce anxiety-like responses (89). Chronic exposure to a wide range of psychotropic agents has resulted in a significant enhancement of eCB contents in the brain regions which regulate the synaptic plasticity and emotional behaviour (32-35, 37). In fact, the brain regional distribution of endocannabinoids following the administration of psychotropic agents represents the important role of the eCBs in the development of effective coping strategies to the emotional responses. As recently reported, four-week once-daily injections of resveratrol results in a sustained elevation of anandamide and 2-AG contents in the brain regions implicated in the modulation of emotional behaviour and synaptic plasticity (37). This finding indicate the existence of an intrinsic eCB tone which is involved in the mechanism of action of resveratrol.

Following chronic administration of resveratrol, NGF and endocannabinoids have been increased in the same brain regions suggesting that the regulatory effect of resveratrol

on brain NGF contents depends on the coordinated release of endocannabinoids. It appears that a balance between NGF and eCB signalling mediates the pharmacological effects of this natural polyphenolic compound. In addition to its intrinsic radical scavenging activity, resveratrol reduces the production of tumour necrosis factor- $\alpha$ , IL-1 $\beta$ , NF- $\kappa$ B, NO, and the expression of iNOS gene. This natural polyphenol upregulates the activities of protein kinase C and heme oxygenase leading to the neuroprotective effects. In fact, multiple intracellular signalling pathways and molecular targets are involved in the mechanism of action of resveratrol (90). Involvement of the extracellular signal-regulated kinase cascade, noradrenaline and serotonin system, and HPA axis in the antidepressant-like effects of resveratrol has been previously demonstrated (91,92). Based on the recent findings, the brain NGF and eCBs are also implicated in the mechanism of action of resveratrol. In this context, resveratrol by affecting NGF and eCBs might be of therapeutic significance in a wide variety of diseases which are associated with abnormal NGF or eCBs. Resveratrol enhances the brain NGF contents under the regulatory drive of CB<sub>1</sub> receptors indicating the importance of the endogenous cannabinoid activity in the neurotrophic action of this nutraceutical.

In recent years, smart delivery of drugs, neurotrophins, and nutrients has been the focus of intense research. In nanotechnology-based approaches, nanoencapsulation of nutraceuticals, application of nanosensors and computational modelling have been the emerging topics (93-97). In this respect, designing the nanoformulations of resveratrol has led to the increased cellular uptake and improved bioavailability (98, 99). This may result in a better efficacy, reduced dose and potential side effects of this nutraceutical which has shown multi-spectrum therapeutic applications.

## CONCLUSION

For over a decade, natural products with antioxidant, anti-inflammatory, metabotropic and neuroprotective effects have been the focus of intense research. Resveratrol, a naturally occurring polyphenolic compound, has shown multi-spectrum therapeutic applications. Besides its therapeutic potential in ischemia, cancer, diabetes, and cardiometabolic disorders, resveratrol has proved to be a promising therapeutic agent against the neurodegenerative disorders. In recent years, identification of the biological functions of the eCBs has resulted in a better understanding of the pathological processes which occur in the CNS.

Compounds which regulate the activity of the eCBs, have shown beneficial effects against various disorders in which the currently available drugs have shown limited efficacy. The eCBs as the modulator of the neurodegenerative and neuroinflammatory processes is indeed a promising target for the pharmacotherapy of chronic CNS disorders. Resveratrol by affecting the eCBs and NGF with well-documented regulatory actions in the neuroprotective processes and emotional activity might be a valuable therapeutic agent against a wide variety of disorders associated with abnormal eCB or NGF signalling.

Conflict of interest: the authors declare no conflict of interest.

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