

## A Brief Review of Potential Neuroprotective Roles of the Culinary Herb *Ocimum basilicum*

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### ABSTRAK

Penyakit neurodegeneratif kebiasaannya menjejaskan golongan yang lebih tua dan ia dicirikan oleh kehilangan neuron secara progresif. Tekanan oksidatif sangat dikaitkan dengan neurodegenerasi. Tumbuhan herba yang disasarkan dalam kajian ini, *Ocimum basilicum*, biasanya digunakan dalam masakan Indochina dan Itali. Kajian farmakologi ke atas *O. basilicum* telah menunjukkan aktiviti antioksidan yang tinggi dengan beberapa kajian yang menunjukkan tindakan neuroprotektif. Kajian kepustakaan ringkas ini menekankan potensi neuroprotektif *O. basilicum* dengan membincangkan tindakan antioksidatif menggunakan ekstrak tumbuhan, minyak pati dan sebatian fitokimia tumbuhan ini pada sistem saraf berdasarkan kajian *in vitro* dan *in vivo*. Maklumat terkumpul mengenai tindakan neuroprotektif *O. basilicum* menunjukkan bahawa perlindungan neuron mungkin disebabkan oleh aktiviti antioksidannya dan sebahagian besarnya disebabkan oleh kehadiran sebatian polifenol seperti asid rosmarinik yang telah dikenal pasti sebagai sebatian utamanya. Walaupun mekanisme tindakan antioksidan *O. basilicum* telah dicadangkan, kajian selanjutnya diperlukan untuk lebih memahami tindakan antioksidan yang membawa kepada peranan neuroprotektif. Berkemungkinan juga tindakan antioksidan *O. basilicum* diperantara kesan sinergisme campuran pelbagai jenis fitokimia aktif semula jadi di dalam tumbuhan. Oleh itu, sasaran khusus bagi perlindungan neuron melalui tindakan antioksidan memerlukan kajian praklinikal dan klinikal yang lebih lanjut untuk mengkaji potensi terapeutik *O. basilicum* terutamanya dalam pencegahan penyakit neurodegeneratif.

**Kata kunci:** antioksidan, neurodegeneratif, neuroprotektif, *Ocimum basilicum*, tekanan oksidatif

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## ABSTRACT

Neurodegenerative diseases commonly affect elderly population and are characterised by progressive neuronal loss. Oxidative stress is highly associated with neurodegeneration. The targeted herbal plant in this review, *Ocimum basilicum* (*O. basilicum*), is typically used in Indochina and Italian cuisine. Pharmacological studies on *O. basilicum* have demonstrated potent antioxidant activities with some reports of neuroprotective actions. This brief review highlights the potential neuroprotective roles of *O. basilicum* by discussing previously documented antioxidative actions of the plant extract, essential oils and its phytochemical compounds on the nervous system based on in vitro and in vivo studies. Accumulating evidence on the neuroprotective action of *O. basilicum* points to a notion that neuroprotection is made possible by way of its antioxidant properties and largely due to the presence of polyphenol compounds such as rosmarinic acid which has been identified as the major constituent. Although the mechanisms of *O. basilicum* antioxidant action have been proposed, further studies are required for better understanding of its antioxidant action leading to neuroprotective roles. It is also possible that the antioxidant actions of *O. basilicum* are mediated through synergism of a mixture of various naturally-occurring bioactive compounds in the plant, as is with many other plant-based food supplements, to produce the putative effects instead of a single bioactive compound from the plant. Therefore, specific targeting of neuroprotection by means of antioxidant actions warrants further preclinical and clinical studies investigating the therapeutic potentials of *O. basilicum* particularly in view of the prevention of neurodegenerative processes.

Keywords: antioxidant, neurodegenerative, neuroprotective *Ocimum basilicum*, oxidative stress

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## INTRODUCTION

The use of medicinal plants and various herbs as supplements to maintain the general wellness of the mental health has received great attention particularly in view of their purported memory enhancing effects and protection against neurodegeneration mediated through antioxidant actions. These plants have been studied to explore their potential therapeutic uses in neurodegenerative diseases

such as Parkinson's and Alzheimer's disease with the latter being a more common type. For example, several *Panax* species and ginsenosides, their major active plant constituents, have been extensively studied for protective roles against neurological disorders which led to their use as a general tonic for improving well-being and to cope with stress (Ong et al. 2015). Similarly, *Ginkgo biloba* supplements are considered as high-claim products based on accumulating clinical

evidence which demonstrated efficacy in the treatment of a wide range of neurological conditions including cognitive impairment and ischemic stroke (Nash & Shah 2015).

Antioxidant has been widely associated with neuroprotection. The presence of antioxidant melatonin and tryptophan in rice and corn have been demonstrated to protect neurotoxicity in murine hippocampal neuronal cells by the inhibition of reactive oxygen species (ROS) production and modulation of brain-derived neurotrophic factor (BDNF) (Chumpiya et al. 2016). In fact, purple rice extract and its major constituent, cyanidin, were reported to protect against the amyloid beta-induced neuronal cell death by attenuation of ROS and reactive nitrogen species (RNS) associated with modulation of mitochondrial death pathway in SK-N-SH cells (Thummayot et al. 2014). Curcumin, derived from *Curcuma longa*, is a polyphenolic compound and commonly used as food additives in the Indian spice turmeric. Well known for antioxidant and anti-inflammatory properties, curcumin has shown protective effects against hemin-induced neuronal death in primary cultures of cerebellar granule neurons of rats (González-Reyes et al. 2013). Pretreatment with curcumin prior to hemin-induced toxicity increased heme oxygenase-1 (HO-1) expression and glutathione (GSH) levels while attenuated the increase in ROS production (González-Reyes et al. 2013).

*Ocimum basilicum*, generally known as 'sweet basil', is an herbal

plant that belongs to the Lamiaceae family. Naturally, the *Ocimum* genus is widely found in tropical America, Africa, and Asia, and favours warm conditions for growth (Paton et al. 1999). *O. basilicum* is identified as an erect, aromatic, green or purplish branch with hairy stems, and its flowers are white or pale purple (Devika & Shashi 2016). The arrangement of *O. basilicum* leaves exhibit woody green stems that have a sweet taste and pleasant aromatic scent (Sundarraju et al. 2014). It is typically consumed in Asia for its claimed health benefits including for the maintenance of mental health (Bora et al. 2011; Koutroumanidou et al. 2013). The root and flower are used to reduce bowel illnesses and treat cough, respectively, while the leaf is used to treat ringworm infections, menstrual disorders, and reduce fever (Indubala & Ng 2000). The seed is used as a demulcent, stimulant, diuretic and diaphoretic, and for headache treatment (Indubala & Ng 2000).

Modern pharmacological studies suggested that *O. basilicum* showed therapeutic potential, including antioxidant (Berić et al. 2008; Taie et al. 2010; Nguyen et al. 2010; Kaurinovic et al. 2011; Kwee & Niemeyer 2011; Patil et al. 2011; Rameshrad et al. 2015; Chennai et al. 2016; Farouk et al. 2016), anti-inflammatory (Rameshrad et al. 2015; Raina et al. 2016), antihematotoxic (Saha et al. 2012), anticancer (Kathirvel & Ravi 2012), antimicrobial (Ahmad et al. 2016; Srivastava et al. 2014), antifungal (Ahmad et al. 2016), antidiabetic (Chaudhary et al. 2016; Kadan et al. 2016) and neuroprotective

(Koutroumanidou et al. 2013; Bora et al. 2011) actions owing to either its essential oils, crude plant extracts or phytochemical compounds. Table 1 shows the therapeutic effects of *O. basilicum* as previously reported.

The neuroprotective potential of *O. basilicum* by way of its antioxidant properties is discussed. We highlight its major phytochemical components, as well as the plant's extracts, which exhibited antioxidant activities in neuroprotection gathered from in vitro and in vivo studies. To the best of our knowledge, there has been no published clinical literature on this plant product or preparation probably due to limited in vitro and in vivo studies being conducted on this plant. Moreover, several varieties of *O. basilicum* were named by previous researchers, which are sometimes quite confusing due to the lack of standard descriptions for accurate identification. For instance, Carović-Stanko et al. (2011) allocated six clusters of *O. basilicum* from 46 accessions, which were based on morphotypes using the unweighted paired-group method. The 6 morphotypes are true basil, small-leaf basil, lettuce-leaf basil, purple basil (A), purple basil (B) and purple basil (C). Previously, Darrah (1980) classified *O. basilicum* into seven categories: tall slender types (e.g.: Sweet basil); large-leafed, robust types (e.g.: Lettuce leaf/Italian basil); dwarf types (e.g.: Bush basil); compact types (e.g.: var. *thyrsiflora*/Thai basil); *purpurascens*; purple types (e.g.: Dark Opal); and *citriodorum* types (e.g.: lemon-flavoured basil). A study examining 16 accessions of 4 varieties of *O. basilicum*

(var. *basilicum*, var. *purpurascens*, var. *difforme*, cv. Dark Opal) and 3 other related species (*O. x citriodorum*, *O. tenuiflorum*, *O. minimum*) revealed that a majority of chromosome numbers varied even within the same variety (Paton & Putievsky 1996) possibly due to cross-pollination and according to geographical region, given that the tested accessions originated from different countries. Despite the fact that there are a few review articles discussing *O. basilicum*, this brief review is focused on the neuroprotective potential of *O. basilicum*, particularly via its antioxidant properties.

## MATERIALS AND METHODS

Data sources included 78 references accessed from several major databases, such as ScienceDirect, EBSCOhost, PubMed, Google Scholar and Springer Link. Our data search was performed using the keywords (antioxidant AND "*Ocimum basilicum*"), (neuroprotect\* AND "*Ocimum basilicum*") or ("oxidative stress" AND neurodegenerat\*) while unpublished works as well as congresses communications were excluded. The majority of the pharmacological data were from articles published later than the year 2000. The chemical structures were drawn using the software ChemDraw Ultra 8.0.

## OXIDATIVE STRESS IN NEURODEGENERATION

Oxidation is a redox reaction involving the loss of electrons. It is natural

Table 1: Therapeutic potentials of *O. basilicum*

Therapeutic potentials	Study Details	Plant extract	Essential oils	References
Antioxidant	- Scavenging capacity measurements on DPPH, NO, O <sub>2</sub> <sup>-</sup> , OH radical and H <sub>2</sub> O <sub>2</sub>	/		Kaurinovic et al. 2011
	- Protective effects on lipid peroxidation in liposomes by TBA-assay			
	- DPPH radical scavenging activity	/		Patil et al. 2011; Teofilović et al. 2017
	- Ferric reducing antioxidant power (FRAP) assay	/		McCance et al. 2016
	- DPPH radical scavenging activity		/	Taie et al. 2010
	- DPPH radical scavenging activity - β-Carotene bleaching assay		/	Farouk et al. 2016
Antifungal/ Antimicrobial	Fungal strains:			
	- <i>Aspergillus flavus</i>			
	- <i>Aspergillus niger</i>			
	- <i>Penicillium</i>			
	- <i>Rhizopus solanai</i>	/		Ahmad et al. 2016
	- <i>Alternaria alternate</i>			
	- <i>Candida albicans</i>			
	- <i>Curvularia lunata</i>			
	- <i>Aspergillus fumigates</i>			
Bacteria used:				
- <i>Staphylococcus aureus</i>	/		Khalil 2013	
- <i>Escherichia coli</i>				
Bacteria used:				
- <i>Staphylococcus aureus</i>		/	Araújo Silva et al. 2016	
- <i>Pseudomonas aeruginosa</i>				
Bacteria used:				
- <i>Staphylococcus aureus</i>				
- <i>Bacillus cereus</i>		/	Al Abbasy et al. 2015	
- <i>Escherichia coli</i>				
- <i>Salmonella typhimurium</i>				
Anticancer	Cancer cell line used:			
	- Human cervical cancer cell line (HeLa)			
	- Human laryngeal epithelial carcinoma cells (HEp-2)		/	Kathirvel & Ravi 2012
- NIH 3T3 mouse embryonic fibroblasts				
Anti-inflammatory	Reduced the production of inflammatory mediators and pro-inflammatory cytokines:			
	- Nitric oxide (NO)			
	- Prostaglandin (PGE2)			
	- Inducible nitric oxide synthase (iNOS)	/		Raina et al. 2016
	- Nuclear factor-kappa B (NFκB)			
	- Cyclooxygenase (COX)-2			
	- Leukotriene (LTB4)			
- Matrix metalloproteinase (MMP)-2				

Therapeutic potentials	Study Details	Plant extract	Essential oils	References
Antihyperglycemia	- Reduced paw thickness induced by carrageenan in male Wistar rats - Reduced Myeloperoxidase (MPO) activity	/		Rameshrad et al. 2015
	- Ameliorated altered level of biochemical parameters in streptozotocin-induced diabetic rats (aspartate transaminase, alanine transaminase, alkaline phosphatase, total bilirubin, total protein) - Ameliorated altered levels of serum electrolytes in diabetic rats (Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> ) -Ameliorated altered levels of haematological indices in diabetic rats (red blood cells, white blood cells, haemoglobin, lymphocytes, neutrophils, eosinophils, monocytes, basophils)	/		Chaudhary et al. 2016
Neuroprotection	- Decreased plasma total cholesterol, triglyceride levels and LDL-cholesterol concentrations in triton WR-1339-induced hyperlipidemic mice	/		Harnafi et al. 2008
	- Reduced cerebral infarct size and lipid peroxidation on ischemia and reperfusion-induced cerebral damage and motor dysfunctions in mice - Restored glutathione content in mice brain - Attenuated impairment in short-term memory and motor coordination	/		Bora et al. 2011
	- Reversed the memory deficit induced by scopolamine in mice - Reduced the acetylcholinesterase (AChE) activity and thiobarbituric acid reactive substance (TBARS) levels and increased the reduced glutathione (GSH) levels in hippocampus and cortex.	/		Singh et al. 2016

for biological systems to maintain homeostasis; however, unstable molecules have a tendency to attack other molecules and, subsequently, precipitate a chain reaction. One product of oxidation is reactive oxygen species (ROS), which are generated continuously during cell metabolism

processes. According to Harman (1956), free radicals from cell catabolism contribute to aging and other degenerative diseases. This is why the human body has been equipped with natural antioxidant defences, such as superoxide dismutase (SOD), catalase, and glutathione (GSH), to neutralize

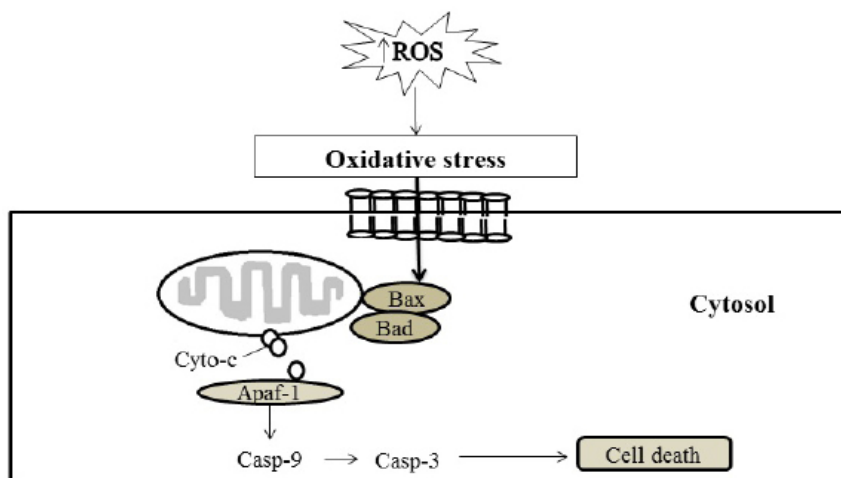


Figure 1: Cell death pathways activated by oxidative stress signal. Reactive oxygen species (ROS) accumulation lead to the oxidative stress event which subsequently activates pro-apoptotic Bcl-2 family members (Bax and Bad) and eventually causes the release of cytochrome *c* (cyto-*c*) via mitochondria transition pores into the cytosol. It then forms a complex with apoptotic protease-activating factor 1 (Apaf-1) and caspase-9 (casp-9). This complex subsequently activates the caspase-3 (casp-3) which indicates the beginning of degradation phase for apoptosis or cell death (Adapted and modified from Mattson 2000).

free radicals. However, if their balance is disturbed, several cascading events are initiated, which may ultimately be harmful to cells. The accumulation of ROS in an impaired antioxidant system leads to oxidative stress. According to Mattson (2000), oxidative stress initiates a cell death event involving pro-apoptotic members of the Bcl-2 family (Figure 1).

The human brain is vulnerable to oxidative stress (Uttara et al. 2009) due to the abundant presence of polyunsaturated fatty acids (PUFA) including linoleic acid and arachidonic acid (Cobb & Cole 2015). Thus, impaired antioxidant defences in the presence of high levels of ROS could lead to worsening of symptoms. Lipid peroxidation products, such as lipid peroxyl radical, which is formed from the reaction of oxidized PUFA and

ROS, initiate a chain reaction for further PUFA oxidation. Hence, an antioxidant system is needed to disrupt the free radical chain-reaction by scavenging peroxyl radicals (Chamulitrat & Mason 1989).

### MAJOR PHYTOCHEMICALS OF *O. basilicum* WITH ANTIOXIDANT POTENTIAL

In recent years, the search for treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's disease is gaining huge attention among researchers. Despite distinct pathogenesis of these diseases, one unifying feature is progressive neuronal death at specific regions in the brain caused by various factors including excessive ROS and poor antioxidant defense mechanisms or a condition

known as oxidative stress (Mattson 2000) and the selected brain neurons in particular are vulnerable to oxidative damage (Chen et al. 2012). The search for new treatment approaches for these diseases have been targeted to prevent their occurrence or delay the progression of neurodegeneration which include exploring the potential of using herbal supplements with antioxidant properties.

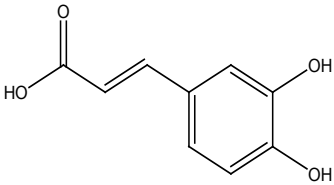
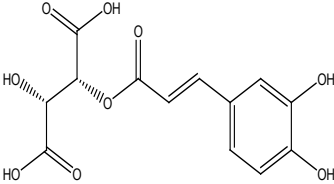
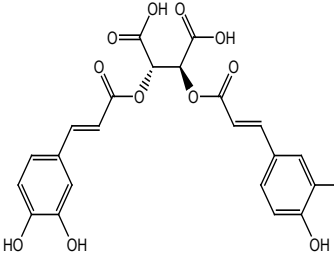
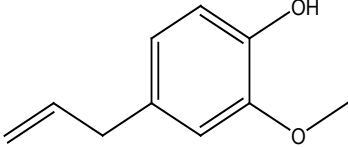
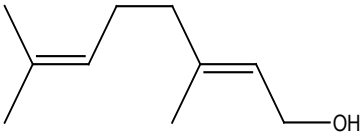
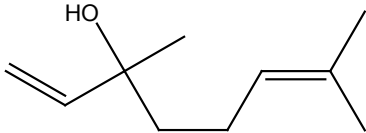
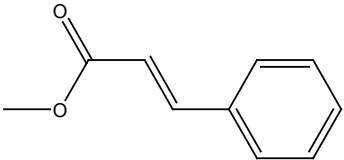
There has been an upsurge of interest in looking for new antioxidants from plants which may be due to the concern of the side effects of synthetic compounds. Extensive studies have been conducted to elucidate naturally-occurring compounds from *O. basilicum*. The chemical structures of major phytochemicals found in *O. basilicum* are presented in Table 2. Of these bioactive compounds, rosmarinic acid, caffeic acid and eugenol from essential oils have been widely reported for their antioxidant properties. However, a majority of these studies were carried out using commercial synthetic compounds obtained from manufacturers and not isolated from the plant. Although major compounds in *O. basilicum* were isolated in other genus or species, a phytochemistry study done by Siddiqui et al. (2007) led to the elucidation of three new compounds isolated from the aerial parts namely basilol, ocimol and basilimoside. However, to the best of our knowledge, no pharmacological effects were reported on these new compounds.

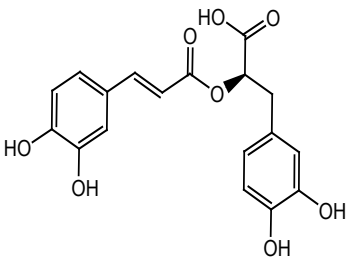
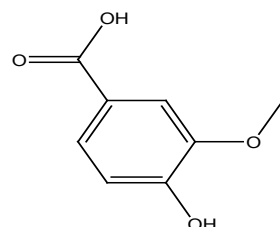
The most abundant polyphenol in *O. basilicum* is rosmarinic acid which is a natural antioxidant that was first

isolated from *Rosmarinus officinalis* or rosemary (Petersen & Simmonds 2003). Oxidative molecules are strongly inhibited by rosmarinic acid in in vitro and in vivo studies, as widely reported. It inhibits lipid peroxidation, one of the hallmarks of pathological oxidative stress events, by penetrating lipid membranes using liposomes of 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine without altering cell membrane structure and integrity, which suggests that it is not toxic per se (Fadel et al. 2011). Administered orally, 100 mg/kg of rosmarinic acid reduced ROS levels against ethanol-induced genotoxicity in mice (De Oliveira et al. 2012). The neuroprotective potential of rosmarinic acid were studied in kainate-induced temporal lobe epilepsy in rats. Kainic acid is a known agonist of AMPA/KA receptor wherein its activation leads to neuronal death due to excitotoxicity and excessive production of ROS (Wang et al. 2005). Rats that received 10 mg/kg of daily oral administration of rosmarinic acid for a week showed a reduction in oxidative stress markers, seizure activity and neuronal death compared to the kainate group (Khamse et al. 2015). Fonteles et al. (2015) have also examined the neuroprotective effect of rosmarinic acid administration on a mice model of permanent middle cerebral artery occlusion-induced acute ischemia. Mice treated daily with 20 mg/kg rosmarinic acid for 5 days given intraperitoneally demonstrated reduced infarct size and neurological deficits while markers of neuroprotection such as synaptophysin and BDNF levels were increased



Table 2: Major phytochemicals isolated and identified in *Ocimum basilicum*

Bioactive compounds	Chemical structure	Extraction method	Reference
Caffeic acid		60% ethanol extraction	Srivastava et al., 2014
Caftaric acid		Methanol extraction	Zgorka and Glowniak 2001
Chicoric acid		Acidified methanol (0.1% formic acid v/v) extraction	Lee and Scagel 2009
Eugenol		Acidified methanol (0.1% formic acid v/v) extraction	Lee 2010
Geraniol		60% ethanol extraction	Srivastava et al. 2014
Linalool		Hydrodistillation	Labra et al. 2004
Methyl cinnamate		Hydrodistillation	Al Abbasy et al. 2015
			Kathirvel and Ravi 2012
			Labra et al. 2004
			Al Abbasy et al. 2015
			Hussain et al. 2008
			Kathirvel and Ravi 2012

Bioactive compounds	Chemical structure	Extraction method	Reference
Rosmarinic acid		60% ethanol extraction	Srivastava et al. 2014 Tada et al. 1996 Jayasinghe et al. 2003
		Methanol extraction	Zgorika and Glowinski 2001
		Acidified methanol (0.1% formic acid v/v) extraction	Lee and Scagel 2009 Lee 2010
Vanillic acid		Methanol extraction	Zgorika and Glowinski 2001

(Fonteles et al. 2015). Similarly, an *in vitro* study using an N2A cell model of neurodegeneration, rosmarinic acid was shown to have neuroprotective activities (Ghaffari et al. 2014). The cells were treated with several concentrations of rosmarinic acid prior to H<sub>2</sub>O<sub>2</sub>-induced oxidative stress exhibited a dose-dependent protective effects by reducing ROS production and neuronal loss. The study also found that neuroprotective effects of rosmarinic acid were mediated by the protective gene upregulation; BDNF and tyrosine hydroxylase as well as by the prevention of mitochondria dysfunction (Ghaffari et al. 2014). The half-life of rosmarinic acid in rats was estimated as 8-18 hours in a pharmacokinetic study (Baba et al. 2004). Rosmarinic acid given orally in rats was excreted into the urine in metabolite forms after undergoing

dehydroxylation, methylation and sulfate-conjugation (Nakazawa & Ohsawa 1998; Baba et al. 2004). Yang et al. (2015) formulated rosmarinic acid in a phospholipid complex oil solution which demonstrated enhanced bioavailability and bioefficacy by 2.9 fold compared to the unformulated rosmarinic acid, an observed effect which was also associated with an increase in antioxidative properties. It marks an important finding for an effective delivery medium for rosmarinic acid to improve its bioavailability for further human studies.

Neuroprotective effects of caffeic acid were reported both *in vivo* and *in vitro* by Kim et al. (2013) and Jeong et al. (2011), respectively. In gerbils, 20 mg/kg caffeic acid showed moderate neuroprotection while the hybrid compound of 20 mg/kg caffeic

acid-syringic acid showed strong neuroprotective effects on transient cerebral ischemic damage in the hippocampal CA1 region (Kim et al. 2013). Caffeic acid protected neuronal cells against  $H_2O_2$ -induced cytotoxicity in a dose-dependent manner by exhibiting strong antioxidant activities (Jeong et al. 2011). In a separate study conducted by Anwar et al. (2012), caffeic acid improved learning and memory in an inhibitory avoidance task by decreasing the AChE activity in the cortex and striatum.

One of the bioactive compounds isolated from the essential oil of *O. basilicum* is eugenol, which belongs to the phenylpropanoid family and the main constituent in clove oil. Eugenol has been highlighted for its in vitro antioxidative capacity against

1,1-diphenyl-2-picryl-hydrazyl (DPPH) and lipid peroxidation (Gülçin 2011; Nam & Kim 2013). Eugenol has also been isolated from other *Ocimum* species such as *O. gratissimum* Linn., and has shown potent antioxidant activities by scavenging DPPH, hydroxyl and NO radicals in a concentration-dependent manner (Mahapatra & Roy 2014). The neuroprotective effect of eugenol has been evaluated in rats with acrylamide-induced neuropathy. Rats treated with 10 mg/kg eugenol orally thrice a week for five weeks showed signs of reduced oxidative stress markers, intracellular calcium levels and AChE activities in the sciatic nerve and brain cortex (Prasad & Muralidhara 2012). In addition, protection against ischemia-induced neurotoxicity in Mongolian gerbil that received 100 mg/kg and

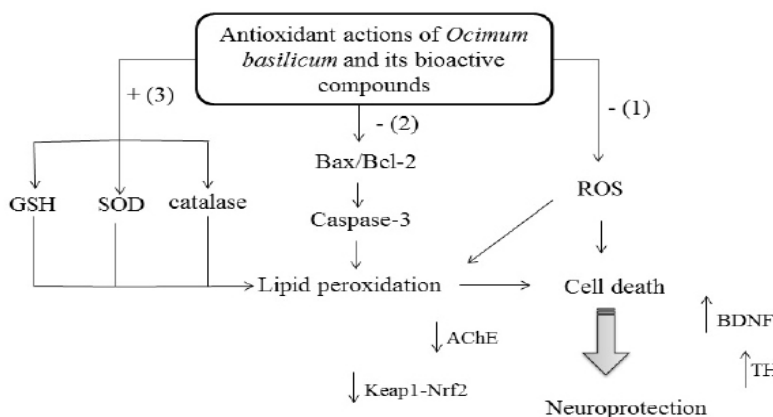


Figure 2: The proposed mechanism of action of *Ocimum basilicum* antioxidant and its bioactive compounds. Three pathways are suggested based on the literature. (1) The inhibition of reactive oxygen species (ROS) by the direct scavenging activities prevents lipid peroxidation as well as cell death. (2) Bioactive compounds of *O. basilicum* reduce the expression of pro-apoptotic signals (Bax/Bcl-2 and caspase-3), which eventually inhibits lipid peroxidation and cell death. (3) *O. basilicum* and its bioactive compounds elevate endogenous antioxidant (glutathione, GSH, superoxide dismutase, SOD and catalase) and subsequently ameliorate lipid peroxidation-induced cell death. Neuroprotective effects of *O. basilicum* and its bioactive compounds also showed restoration of neuronal marker genes (brain-derived neurotrophic factor, BDNF and tyrosine hydroxylase, TH), reduction of acetylcholinesterase (AChE) and inhibition of Keap1-Nrf2 binding.

200 mg/kg of single dose eugenol intraperitoneally was reported by Won et al. (1998). In vitro, eugenol-treated cortical cells showed lower neuronal death and LDH release in NMDA-induced neurotoxicity (Wie et al. 1997). Although the neuroprotective potentials of *O. basilicum* are discussed based on single naturally-occurring compounds which were tested in different models of neurodegeneration, it is possible that their antioxidant actions could also be mediated through synergism if the crude extract of this plant was used instead.

#### **EQ2** PUTATIVE MECHANISMS OF ANTIOXIDANT ACTION OF *O. basilicum* IN NEURODEGENERATIVE DISEASES

Despite the widely reported antioxidant activities of *O. basilicum*, the exact mechanisms for its scavenging activity remain unclear. We suggest possible pathways for its therapeutic antioxidant effects as supported by previous findings on the plant extract and its major phytochemicals as discussed above (Figure 2). Briefly, rosmarinic acid and caffeic acid may directly react with ROS by scavenging free radicals and exhibiting antioxidant activity through prevention of neuronal cell death (Ghaffari et al. 2014; Coelho et al. 2015). Their antioxidative actions were possibly mediated via transfer of an electron from the polyphenol compounds to the free radicals in order to stabilise them (Sueishi et al. 2014). The reduction of Bax/Bcl-2 ratio and caspase-3 expression, pro-apoptotic signals, and lipid peroxidation were

observed in the antioxidative actions of rosmarinic acid, which eventually prevent cell death (Chen et al. 2014). In contrast, antioxidant enzyme of SOD was enhanced. Meanwhile, the presence of *O. basilicum* extract (Bora et al. 2011) and rosmarinic acid (Khamse et al. 2015) elevated the endogenous antioxidant GSH and catalase, respectively, which subsequently reduced lipid peroxidation and showed cell protective effects. Neuroprotective effects of rosmarinic acid were also mediated by the expression of BDNF and TH neuronal marker genes, which are important for cell survival because they are involved in neurotransmitter synthesis (Ghaffari et al. 2014). In addition, caffeic acid was reported to inhibit the activation of Keap1-Nrf2 (Pang et al. 2015) and AChE production (Anwar et al. 2012). Although limited, there is conclusive evidence that supports the neuroprotective properties of *O. basilicum* largely due to the presence of natural antioxidant compounds, notably rosmarinic acid and caffeic acid, in this plant as discussed above.

The crude extract of *O. basilicum* were studied by Bora et al. (2011) in an ischemia mouse model. During ischemia or blockade of blood supply particularly to the brain, the elevation of free radicals production associated with the depletion of antioxidant levels eventually leads to oxidative stress. Oral administration of *O. basilicum* extract (100 mg/kg and 200 mg/kg) 60 minutes prior to 15 minutes of global cerebral ischemia, followed by 24 hours reperfusion, demonstrated a reduction in infarct size and lipid

peroxidation while restoring the levels of endogenous antioxidant GSH (Bora et al. 2011). Impairment of short term-memory and motor performance induced by global cerebral ischemia and reperfusion were also prevented by the administration of *O. basilicum*. They suggested that the neuroprotective effects of *O. basilicum* may be contributed by the presence of phenolic, flavonoids and tannin content as well as its antioxidant properties to scavenge free radicals (Bora et al. 2011). In another study, mice which received a longer duration of *O. basilicum* administration (7 days) at higher doses (200 mg/kg and 400 mg/kg) reversed the scopolamine-induced amnesia comparable to the standard anticholinesterase drug; tacrine. These behavioural effects were accompanied with a reduced AChE and TBARS levels and an increase in GSH in the hippocampus and cortex (Singh et al. 2016). Histopathologically, *O. basilicum* extract prevented signs of neurodegeneration which include increased vacuolation and focal gliosis and reduced number of pyramidal cells induced by scopolamine (Singh et al. 2016).

### FUTURE PERSPECTIVES

Polyphenol compounds and essential oils isolated from plants have attracted significant attention among researchers owing to their potent antioxidant activities. The theory of oxidative stress in neurodegeneration is still debatable possibly due to the specificity in the etiology of neurodegenerative diseases. In fact, some clinical trials

have shown no benefits of antioxidant supplementation which even resulted in detrimental effects on cognitive function in Alzheimer's patients (Lloret et al. 2009; Galasko et al. 2012). However, the fact that neuronal cells are highly vulnerable to oxidative stress is evident partly due to a high consumption of oxygen in the brain (Gandhi & Abramov 2012). Therefore, impairment of the antioxidant defence systems may be one of the potential factors leading to neurodegeneration which implicate the importance of antioxidants in preventing or delaying the onset of neurodegeneration. Accumulating data suggest that *O. basilicum* and particularly its polyphenol compounds, demonstrated effective antioxidant effects. The major active compound isolated from *O. basilicum* is rosmarinic acid, which is a polyphenol with potent antioxidant activity (Jayasinghe et al. 2003; Petersen & Simmonds 2003; Fonteles et al. 2015). There is still a growing body of preclinical evidence and none of clinical literature so far to sufficiently support the neuroprotective roles of *O. basilicum* despite the fact that it demonstrated potent antioxidant activities in neuronal cells in vitro and in vivo. Although possible mechanisms of *O. basilicum* antioxidant actions have been proposed, further studies to elucidate its exact mechanisms of action are required for better understanding of its antioxidant actions leading to neuroprotective roles. It is also possible that the antioxidant actions of *O. basilicum* are mediated through synergism of a mixture of various naturally-occurring

bioactive compounds in the plant, requiring an oral administration of the whole plant extract as a food supplement to produce the putative effects instead of products containing a single bioactive compound extracted from the plant. Therefore, specific targeting of neuroprotection by means of antioxidant actions warrants further preclinical and clinical studies investigating the therapeutic potentials of *O. basilicum* particularly in the prevention of neurodegeneration.

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