

## R E V I E W

# Food supplements based on palmitoylethanolamide plus hydroxytyrosol from olive tree or *Bacopa monnieri* extracts for neurological diseases

Aysba Karim Kiani,<sup>1</sup> Giacinto Abele Donato Miggiano,<sup>2</sup> Barbara Aquilanti,<sup>3</sup> Valeria Velluti,<sup>3</sup> Giuseppina Matera,<sup>3</sup> Lucilla Gagliardi,<sup>3</sup> Matteo Bertelli<sup>4,5</sup>

<sup>1</sup> MAGI EUREGIO, Bolzano, Italy; <sup>2</sup> Human Nutrition Research Center, Sacro Cuore Catholic University, Rome, Italy; <sup>3</sup> UOC Nutrizione Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; <sup>4</sup> MAGI'S LAB, Rovereto (TN), Italy; <sup>5</sup> EBTNA-LAB, Rovereto (TN), Italy

**Abstract.** Neurological disorders like Parkinson disease and Alzheimer disease, spinal cord injury and stroke have some recurrent characteristics such as abnormal protein aggregation, oxidative stress induction, apoptosis, excitotoxicity, perturbation of intracellular Ca<sup>2+</sup> homeostasis and inflammation. To date, there are few effective treatments available and the drugs currently used to manage the symptoms have important side effects. Therefore, research studies are focusing on natural phytochemicals present in diet as bioactive molecules potentially useful against neurodegenerative diseases. In this review, we will discuss the neuroprotective role of palmitoylethanolamide, hydroxytyrosol, and *Bacopa monnieri* extracts against neuroinflammation and neurodegeneration, thereby revealing their remarkable potential as novel therapeutic options for the treatment of neurodegenerative disorders. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** neurodegenerative disorder, palmitoylethanolamide, hydroxytyrosol, *Bacopa monnieri* extracts, dietary phytochemicals, food supplementation

## Introduction

Chronic neurological disorders such as Parkinson disease, Alzheimer disease (AD), and acute neurological disorders, like spinal cord injury and stroke, are linked with high mortality and morbidity, with few effective treatments available.

The worldwide prevalence of AD is around 27 million individuals, Parkinson disease affects 1%-2% of the population above the age of 65, stroke causes 5.7 million (16.6%) deaths per year, and spinal cord injury affects 1.3 million individuals in North America every year. Several pathological characteristics are shared among these neurological diseases like abnormal protein aggregation, oxidative stress induction, apoptosis, excitotoxicity, perturbation of intracellular Ca<sup>2+</sup> homeostasis and inflammation. Recently, several studies

have been focusing on natural dietary phytochemicals as bioactive molecules useful for their protective role in neurodegenerative diseases (1).

## Palmitoylethanolamide

Palmitoylethanolamide (PEA) (C16:0 N-acyl-ethanolamine) is naturally synthesized in various plants, mammal tissues and cells. It belongs to the N-acyl-ethanolamine- (NAE-) based endocannabinoids class (2), and was previously isolated from peanut meal, egg yolk and soy lecithin.

At present, various PEA-containing drugs such as Normast<sup>®</sup>, Nevamast<sup>®</sup>, Gialia<sup>®</sup> are licensed for human use (1,200 mg/day) as food supplement, nutraceutical or diet for medical conditions, depending

on the country (3). From the last decade, some studies proposed that PEA might provide protection from neuroinflammation and neurodegeneration (4).

Because of the poor water solubility, PEA might show limited bioavailability and solubility. Oral administration of 100 mg/kg of PEA in rats has the ability to infiltrate the blood–brain barrier, with a bioavailability for the brain of 0.95%. A study in humans revealed that the administration of PEA results in a 2- to 9-fold increase of plasma concentrations, depending on the dosage (5).

### Mechanism of action

Initially, it was proposed that PEA, being an acylethanolamides, exerts its anti-neuroinflammatory effects through the action of an autacoid local injury antagonist that leads to mast cell down-regulation. Subsequently, preclinical studies have established that PEA is able to activate two different receptors: the orphan receptor GPR55 and PPAR $\alpha$  (6).

PPAR- $\alpha$  is the key molecular target involved in PEA anti-neuroinflammatory effects. PPAR $\alpha$ , after the binding of the ligand, heterodimerizes with the 9-cis-retinoic acid receptor. Then, it interacts with promoter regions of specific genes, thereby triggering complex anti-inflammatory responses (7).

Similarly, PEA is an agonist of GPR55, a cannabinoid receptor that mediates neuroinflammatory responses. The neuroprotective effects induced by GPR55 activation were demonstrated *in vitro* in neural stem cells and *in vivo* in mice, hence suggesting the novel therapeutic potential of GPR55 against the negative hippocampal neurogenesis regulation caused by inflammatory insult in mouse models (8). PEA improves the anti-inflammatory and the anti-nociceptive function by binding to the type 1 transient vanilloid receptor (TRPV1) (9).

In conclusion, PEA through the activation of specific receptors plays a potential protective role against neuroinflammation and neurodegeneration (2).

### Hydroxytyrosol

Parkinson disease, AD, stroke and spinal cord injury share pathological characteristics like oxidative stress induction, inflammation, aggregation of abnormal protein, cytotoxicity, perturbed Ca<sup>2+</sup> homeostasis and apoptosis. There are evidences that support the Mediterranean diet beneficial effects for the prevention of neurodegeneration, probably because of its abundance in phenols (10).

Fruits and leaf extracts of Olive tree (*Olea europaea*) possess anti-hypertensive, anti-inflammatory, antithrombotic, anticancer, antiatherogenic, hypoglycemic and antimicrobial properties. Olive extracts contain various phenolic compounds like hydroxytyrosol, tyrosol, oleuropein oleocanthal and carotenes. Out of these phenolic compounds, only oleocanthal, hydroxytyrosol and tyrosol are able to enter the brain tissue in AD mouse models. Studies on brain slices of hydroxytyrosol-fed mice established that hydroxytyrosol is able to decrease the efflux of lactate dehydrogenase in a dose-dependent manner, and to inhibit the malondialdehyde and fatty acid hydroperoxides generation, thereby showing potential neuroprotective effects of hydroxytyrosol in mouse models of neurodegenerative disorders (11).

The plasma concentration of hydroxytyrosol is dependent on the dietary intake and its endogenous synthesis. The main sources of hydroxytyrosol are olives, extra virgin olive oil and wine. The recommended dietary intake of hydroxytyrosol is estimated to be between 5 to 8.9 mg that could be supplied by 20 mg daily consumption of extra virgin olive oil (12).

The uptake and accumulation of hydroxytyrosol and its metabolites in brain were reported in animal model after feeding them with a dietary supplementation of hydroxytyrosol (5 mg/kg/day) for 21 days. Research studies have established the neuroprotective abilities of hydroxytyrosol metabolites in neuroblastoma and dopaminergic neuronal cells at physiological concentrations. Results of these analyses suggest the neuroprotective activity of hydroxytyrosol by decreasing the oxidative stress at neuronal level (13).

A detailed study on the mechanism of action of hydroxytyrosol indicates that the nuclear factor, erythroid 2 like 2 (NFE2L2) is essential for the neuropro-

tective role of hydroxytyrosol. Hydroxytyrosol, by the activation of Keap1 (Kelch-like erythroid Cap'n'Collar homologue-associated protein 1) and NFE2L2 pathways, activates several cytoprotective enzymes, like glutamate-cysteine ligase, NADH quinone oxidoreductase, thioredoxin reductase and hemoxygenase 1 (14). Furthermore, hydroxytyrosol has a modulatory role in tyrosine kinase, MAPK, PKC and PI3K/Akt pathways, that are involved in cell survival regulation after the oxidative stress exposure (11).

### Anti-inflammatory effect

The anti-inflammatory role of hydroxytyrosol has previously been demonstrated in macrophage cell lines, stimulated by the toll like receptor 4 ligand lipopolysaccharide, it was then established that hydroxytyrosol reduced lipopolysaccharide-induced cytokines secretion, i.e. IL- $\alpha$ , TNF- $\alpha$ , IL- $\beta$ , IL-6 and IL-12, along with chemokines, like CXCL10/IP-10 (C-X-C motif chemokine 10) and MCP-1/CCL2 (monocyte chemoattractant protein 1). A subsequent study demonstrated the modulatory effect of hydroxytyrosol against oxidative stress in lipopolysaccharide-treated RAW264.7 cells through nuclear factor NFE2L2 involvement (15).

Hydroxytyrosol is also able to downregulate the activation of microglial cells. This could be exploited for the treatment of neurodegenerative disorders such as Parkinson disease, which are characterized by neuroinflammation mediated by microglial cells. The reduction of the hydroxytyrosol-induced pro-inflammatory mediators suggests that polyphenol containing diets could reduce neuroinflammation (12).

### Animal models

Hydroxytyrosol shows neuroprotective effects also in animal models. Peng et al. reported the reduction in the neural toxicity and oxidative stress mouse models for the AD, by supplementing the diet with 5 mg of hydroxytyrosol per kg per day for 6 months (16). Another study from Fu and Hu revealed that the administration of 100 mg per kg per day of hydroxyty-

rosol in subarachnoid haemorrhage mice model for 6 weeks causes a significant reduction in oxidative stress and permeability of the blood brain barrier as well as increase in endogenous antioxidant enzymes expression (17). Additionally, *in vitro* experimentation performed on neuronal cell lines by using hydroxytyrosol established a cytoprotective effect in cells of adrenal gland with the decrease of DNA damage caused by H<sub>2</sub>O<sub>2</sub> (13).

### *Bacopa monnieri* extracts

*Bacopa monnieri* (Linn.) belongs to the Scrophulariaceae family. The extract of this plant is traditionally used in Indian medicine/Ayurveda for the treatment of anxiety and improvement of memory and intellect. Besides memory boosting, *Bacopa monnieri* extracts also have other beneficial therapeutic effects in respiratory, cardiac and neuropharmacological disorders such as insomnia, psychosis, depression, and epilepsy. Additionally *Bacopa monnieri* extracts show anti-inflammatory, antipyretic, sedative, analgesic, anti-lipid peroxidative and free radical scavenging activities (18).

A research study by Sharma et al. established that the consumption of 350 mg of *B. monnieri* extracts as a syrup three times a day for almost three months have increased the memory, learning, reaction and perception times in 20 primary school students, without side effects (19). Negi et al. have documented that children suffering from attention deficit hyperactivity disorder had benefits from the consumption of *B. monnieri* (20). They have performed a double-blind, randomized, placebo and controlled clinical trial on 36 children having with attention deficit hyperactivity disorder and found reasonable memory improvement (20).

### Animal studies

Animal studies have established the cognition-enhancing effects like improvement in acquisition and motor learning, consolidation, as well as memory retention in rats treated with extracts from *B. monnieri*. This memory enhancing effects of *B. monnieri* is caused by saponins like bacosides, bacopasaponins or

bacopasides. Similarly, bacopasaponin components are known to facilitate the mental retention during avoidance response among rats and to reverse the memory loss due to neurotoxin, electroshock, phenytoin, scopolamine and immobilization stress (21).

The proposed mechanisms of action involves cholinergic upregulation, antioxidant effects,  $\gamma$ -aminobutyric acidergic modulation, synthesis of protein in brain, serotonergic agonism, as well as regulation of stress hormones in brain (22).

### Phytochemicals of *Bacopa monnieri*

The *Bacopa monnieri* also known as nootropic herb, plays significant role in neuronal repair, neuronal synthesis, synaptic activity restoration, and improvement in brain functions. The basic components of *B. monnieri* includes alkaloid brahmine, herpestine, nicotine, triterpenoid saponins, saponins A, B and C, bacosides A and B, stigmasterol, stigmastanol,  $\beta$ -sitosterol, D-mannitol betulinic acid, pseudojubilogenin glycoside aspartic acid, serine,  $\alpha$ -alanine and glutamic acid (23). All these components of *B. monnieri* influence may have a wide range of effects like tranquillizing, memory enhancing, antidepressant, sedative, cognitive improvement, antioxidant, anticancer, antianxiety, antiepileptic, analgesic, smooth muscle relaxation, antidiabetic, antihypertensive, anti-inflammatory, antipyretic, antilipidemic, antiarthritic, hepatoprotective, antimicrobial and neuroprotective activities (24).

### Neuroprotective role of *Bacopa monnieri* against oxidative stress

Although the precise mechanism of *B. monnieri* action is not fully understood, evidences suggest that *B. monnieri* neuroprotective action might be attributed to the combined effect of cholinergic modulation as well as antioxidant effects, in fact *Bacopa monnieri* extracts are able to enhance the enzymatic antioxidant activities of superoxide dismutase and catalase (25).

In a research study, Anbarasi et al. showed that the bacoside A has a neuroprotective role against the oxidative stress in rats brain exposed to the smoke of

cigarettes by the assessment of anti-oxidants concentration (26). In particular, the researchers found that after a daily administration of 10 mg/kg of aqueous bacoside A in those rats, brain levels of vitamin C, vitamin A, vitamin E and glutathione increased significantly after *B. monnieri* administration. Furthermore, the administration of Bacoside A elevated the levels of superoxide dismutase and glutathione, and re-established the levels of selenium and zinc (27).

### *Bacopa monnieri* and epilepsy

Epilepsy is a complex neurological disorder caused by the hyper excitability with asymmetrical electrical activity bursts in various regions of the central nervous system.

*B. monnieri* is mostly used as a traditional medicine for the treatment of neurological diseases like epilepsy, in fact *B. monnieri* extracts, such as bacosides and saponins, are known to enhance the transmission of nerve impulse (28).

Rats with pentylene tetrazole-epilepsy induced show a decrease in acetyl cholinesterase and ATPases activity levels in different brain regions. Those levels increased after treatment with *Bacopa monnieri* extracts. This could be the reason of the antiepileptogenic and neuroprotective effects of *B. monnieri* extracts (25).

The gamma amino butyric acid (GABA) is the main inhibitory neurotransmitter of cerebral cortex and disturbances of its activity might result in seizures. For instance, the reduced activity of GABA receptors and glutamate decarboxylase in cerebral cortex has a significant role in the initiation of seizures as well as in mood disorders associated with epilepsy. The treatment with bacoside A reveals its therapeutic potential by reversing the pathological changes in the GABA receptors expression (29).

### *Bacopa monnieri* extract and Alzheimer disease

*B. monnieri* exhibits therapeutic potential for neurodegenerative diseases such as Alzheimer disease (AD) (30). In particular, research studies revealed that *B. monnieri* facilitates the mechanisms of free radical

scavenging and protects the cells of hippocampus, striatum and prefrontal cortex against DNA damage and cytotoxicity typical of AD. In addition, it reduces the activity of lipoxigenase enzyme that in turn decreases lipid peroxidation and increase glutathione peroxidase activity. As aforementioned, *B. monnieri* administration has a protective effect on cholinergic neurons, furthermore, it also decreases the deposition of hippocampal  $\beta$ -amyloids and stress-induced hippocampal damage. Additionally, in humans, *B. monnieri* extracts improve the total memory score with maximum progress in logical memory. Most importantly, *B. monnieri* administration has not revealed any serious side effect (31).

For therapeutic use, *B. monnieri* can be administered as a purified butter-based oral supplement (Brahmi Ghritam) or in powdered form (Churna) or as tablets.

*B. monnieri* showed very promising results for utilization as a novel therapeutic agent in AD, however further studies verification are needed to evaluate its efficiency and rule out any side effects (32).

## Conclusion

Neurological disorders like Parkinson disease, Alzheimer disease and epilepsy are associated with neuroinflammation and neurodegeneration. Since there are few effective treatment without side effects available, recent studies have focused on the use of phytochemicals naturally present in diet as bioactive molecules for the fight against neurodegeneration. PEA, hydroxytyrosol, and *Bacopa monnieri* have already showed their neuroprotective effect in animal models and could be further investigated to explore their promising results against neurodegeneration in humans.

**Conflict of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:  
Stefano Paolacci  
Via delle Maioliche, 57/D, Rovereto (TN), Italy  
E-mail: stefano.paolacci@assomagi.org