

NEUROPROTECTIVE ACTIVITY OF FULLERENES: A LITERATURE REVIEW¹

ATIVIDADE NEUROPROTETORA DE FULLERENOS: UMA REVISÃO DE LITERATURA

**Patricia Schopf², Pâmela Muraro², Évelin Cogo²,
Tiago Volkmer³, Michele Sagrillo³ and Ivana Zanella⁴**

ABSTRACT

Fullerenes are the most studied carbon nanostructures in biological systems. Several works were carried out highlighting the properties of these structures, where its neuroprotective effect has been gaining prominence. In this context, this study aimed to do a literature review on the neuroprotective capacity of fullerenes and to discuss the main results found. The research was carried out in the Scielo database, where the descriptors used were “neuroprotection and fullerenes”. Based on the results found we can conclude that the neuroprotective effects of fullerenes are promising for the treatment of different dysfunctions in the central nervous system.

Keywords: nanostructure of carbon, nanotechnology, neuroprotection, oxidative stress.

RESUMO

Os fulerenos são as nanoestruturas de carbono mais estudadas em sistemas biológicos. Diversos trabalhos têm sido realizados ressaltando as propriedades dessas estruturas, onde o seu efeito neuroprotetor tem ganhado destaque. Nesse contexto, este estudo teve como objetivo fazer uma revisão de literatura sobre a capacidade neuroprotetora dos fulerenos e discutir os principais resultados encontrados. A pesquisa foi realizada na base de dados Scielo, onde os descritores utilizados foram “neuroprotection and fullerenes”. Baseado nos resultados encontrados podemos concluir que os efeitos neuroprotetores dos fulerenos são promissores para o tratamento de diferentes disfunções no sistema nervoso central.

Palavras-chave: estresse oxidativo, nanoestrutura de carbono, nanotecnologia, neuroproteção.

¹ Study performed at Nanosciences Posgraduate Program.

² Master’s Students of the Nanosciences Posgraduate Program - Franciscan University. E-mail: patyfschopf@gmail.com; pemuraro@gmail.com; evelin_cogo@msn.com

³ Contributors. Professors of the Nanosciences Posgraduate Program - Franciscan University. E-mail: tiagovolkmer@gmail.com; sagrillomr18@gmail.com

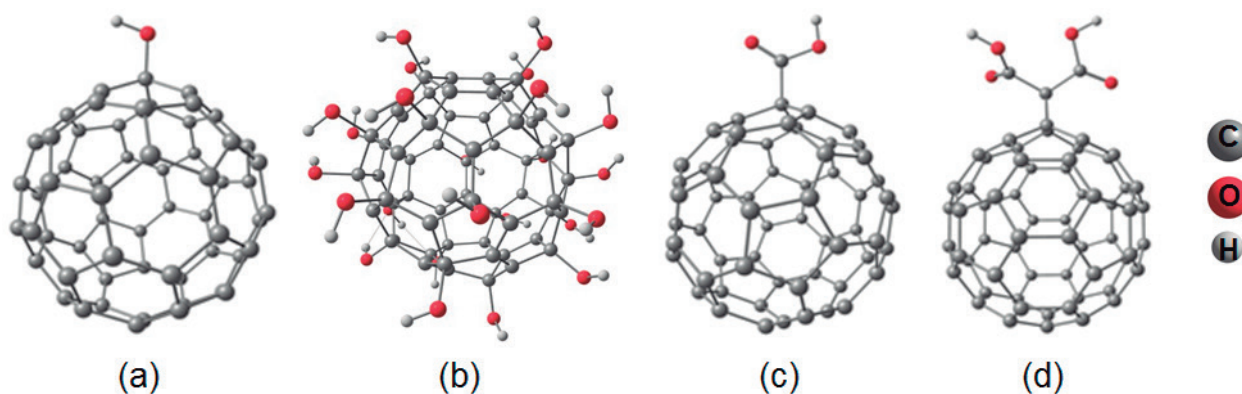
⁴ Advisor. Professors of the Nanosciences Posgraduate Program - Franciscan University. E-mail: ivanazanella@gmail.com

INTRODUCTION

Neurodegenerative diseases are characterized by the progressive loss of neurons that has as consequence several dysfunctions in the central nervous system (KOVACS, 2017). It is not yet understood what leads to neuronal death in these diseases, however oxidative stress caused by genetic and environmental factors may be directly related to this process (CHECKOWAY; LUNDIN; KELADA, 2011). Thus, treatments that protect neuronal cells against oxidative effects are of great interest and importance.

In parallel, fullerene derivatives are being studied due to their different properties and biological applications, where the neuroprotective function of these structures has been highlighted (CHAWLA et al., 2010). Fullerenes are a family of spherical nanostructures derived from carbon, composed of pentagons and hexagons, where their most common form is fullerene with 60 carbon atoms (C_{60}) (KROTO et al., 1985). The fullerenes may appear pure, that is, constituted only by carbon atoms, or functionalized with different molecules (BAKRY et al., 2007; HSIEH et al., 2017). Pure fullerenes are hydrophobic molecules soluble in organic solvents, especially the aromatics (GOODARZI et al., 2017). A number of strategies are used to try to make these structures become water-soluble, among them the chemical modification of these substances with a series of hydrophilic molecules (GOODARZI et al., 2017; SANTOS et al., 2010). The main forms of functionalization of fullerenes occur through covalent bonds with the $-COOH$ and $-OH$ groups (Figure 1). Functionalization makes these structures bioavailable and them suitable for use in biological systems (BAKRY et al., 2007).

Figure 1 - Molecular configuration of functionalized fullerenes with: (a) $-OH$; (b) $(OH)_{24}$; (c) $-COOH$ e (d) $C(COOH)_2$.



Source: authors' construction.

Water-soluble fullerenes have several applications in biological media, however, their use in the central nervous system has gained prominence, since these structures have the ability to cross the blood-brain barrier (HSIEH et al., 2017). In addition, because they are large acceptors of electrons,

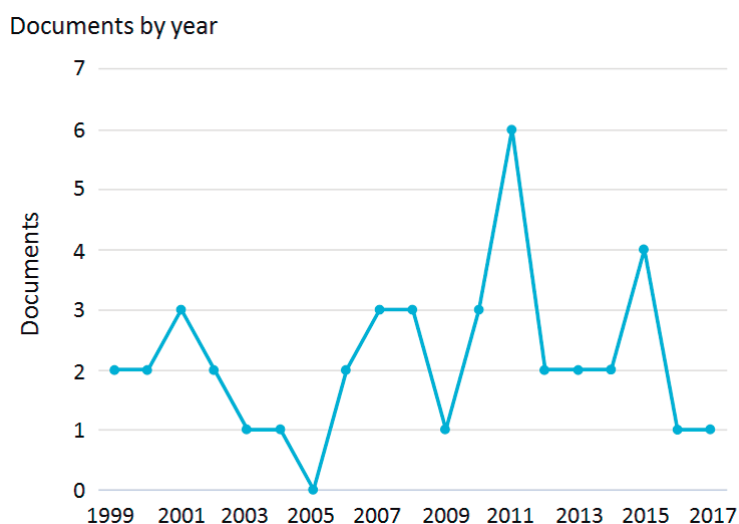
these structures can capture free radicals, protecting against cellular damage in different tissues, including neurons (CHAWLA et al., 2010). The neuroprotective activity of fullerenes is linked to the antioxidant activity of these structures. The capture of reactive oxygen species can prevent the emergence of several pathologies, including chronic diseases such as Alzheimer's and Parkinson's (BAKRY et al., 2007; GOODARZI et al., 2017).

In this context, this work aims to perform a review in the literature of studies that have been carried out exploring the neuroprotective capacity of fullerenes and to discuss the main results found.

MATERIAL AND METHODS

This study consists of a review of the literature that was performed between March and June 2018 in the Scopus database. The research in the database was conducted without delimitation of the year using the following keywords: neuroprotection and fullerenes. Were found 41 documents using these descriptors as shown in the graph of figure 2. Of the 41 documents found, 21 were excluded because they were chapters of books or review articles or because they did not specifically address the ownership of the fullerenes highlighted in this study. The remaining 20 articles were used in the review because they were articles of research whose theme was related to this study.

Figure 2 - Documents found on the Scopus platform using the descriptors “neuroprotection and fullerenes” and their respective years.



Source: Scopus.

RESULTS AND DISCUSSIONS

Table 1 shows a summary of the 20 articles selected in the Scopus database to carry out the review.

Table 1 - List of articles used in the study.

Year	Title	Reference
1999	Carboxyfullerene Prevents Iron-Induced Oxidative Stress in Rat Brain	Lin et al. (1999)
2000	Polyhydroxylated C ₆₀ , Fullerenols, as Glutamate Receptor Antagonists and Neuroprotective Agents	Jin et al. (2000)
2001	Neuroprotective Effect of Hexasulfobutylated C ₆₀ on Rats Subjected to Focal Cerebral Ischemia	Huang et al. (2001)
	Systemic administration of a water-soluble hexasulfonated C ₆₀ (FC ₄ S) reduces cerebral ischemia-induced infarct volume in gerbils	Yang et al. (2001)
2002	A New Multi-Charged C ₆₀ Derivative: Synthesis and Biological Properties	Cusan et al. (2002)
2007	Chronic Alcoholization-Induced Damage to Astroglia and Intensification of Lipid Peroxidation in the Rat Brain: Protector Effect of Hydrated Form of Fullerene C ₆₀	Tikhomirov et al. (2007)
	Synthesis of glutathione C ₆₀ derivative and its protective effect on hydrogen peroxide-induced apoptosis in rat pheochromocytoma cells	Hu et al. (2007)
2008	Polyhydroxylated Fullerene Derivative C ₆₀ (OH) ₂₄ Prevents Mitochondrial Dysfunction and Oxidative Damage in an MPP1 ⁺ -Induced Cellular Model of Parkinson's Disease	Cai et al. (2008)
	SOD Activity of carboxyfullerenes predicts their neuroprotective efficacy: a structure-activity study	Ali et al. (2008)
2010	Protective effect of C ₆₀ -methionine derivate on lead-exposed human SH-SY5Y neuroblastoma cells	Chen et al. (2011)
2011	C ₆₀ fullerene-pentoxifylline dyad nanoparticles enhance autophagy to avoid cytotoxic effects caused by the β -amyloid peptide	Lee et al. (2011)
	Modulation of Adenosine Receptors by [60]Fullerene Hydrosoluble Derivative in SK-N-MC Cells	Giust et al. (2011)
2012	Concentration-dependent effects of fulleranol on cultured hippocampal neuron viability	Zha et al. (2012)
2014	Reversal of axonal loss and disability in a mouse model of progressive multiple sclerosis	Basso et al. (2014)
	[60]Fullerene derivative modulates adenosine and metabotropic glutamate receptors gene expression: a possible protective effect against hypoxia	Giust et al. (2014)
2015	Carboxylic Acid Fullerene (C ₆₀) Derivatives Attenuated Neuroinflammatory Responses by Modulating Mitochondrial Dynamics	Ye et al. (2015)
	Fullerenols and glucosamine fullerenes reduce infarct volume and cerebral inflammation after ischemic stroke in normotensive and hypertensive rats	Fluri et al. (2015)
	Neuroprotective Effects of Hydrated Fullerene C ₆₀ : Cortical and Hippocampal EEG Interplay in an Amyloid-Infused Rat Model of Alzheimer's Disease	Vorobyov et al. (2015)
2016	Fullerene C ₆₀ Derivatives Attenuated Microglia-Mediated Prion Peptide Neurotoxicity	Ye at al. (2015)
2017	Fullerenol nanoparticles decrease ischaemia-induced brain injury and oedema through inhibition of oxidative damage and aquaporin-1 expression in ischaemic stroke	Darabi and Mohammadi (2017)

Source: Authors' construction.

The work developed by Yang et al. (2001) aimed to study the neuroprotection of hexasulfonated C₆₀ fullerene in a model of cerebral ischemia *in vivo*. They demonstrated that pretreatment with this nanomaterial significantly reduced the volume of infarction in rodents when compared to the control group. Treatment was done from intraperitoneal injections where doses of 0.5 e 5.0 mg/kg/day were applied in two groups for two weeks. In the rodent group receiving the low dose of 0.5 mg/kg/day, the reduction was 42%. For the group receiving the high dose of 5.0 mg/kg/day, the reduction reached 68%. No adverse effects were observed in the animals during the administration of the hexasulfonated fullerene.

Huang et al. (2001) studied the effect of hexasulfobutylated fullerene (FC₄S) on focal cerebral ischemia in rats. This article has shown that the FC₄S reduced cerebral infarction size at dosages of 10 and 100 mg/kg, showing a beneficial effect on neuroprotection which may be related to the positive

regulation of nitrogen oxide production. *In vivo* studies have shown that the administration of water-soluble fullerene derivatives did not show acute toxicity in rats, thus the FC₄S is a potential agent for the treatment of focal cerebral ischemia.

In the study of Fluri et al. (2015) the effects of fullerenes conjugated with hydroxyls (OH-F) and glucosamine (GlcN-F) in cerebral infarction and post-ischemic brain inflammation were investigated for the first time in normotensive and hypertensive rats. Treatment with 0.5 mg/kg of OH-F and 5.0 mg/kg of GlcN-F revealed a positive result indicated by the reduction of the volume of the lesion and improves motor deficits. Darabi and Mohammadi (2017) analyzed the protective effect of fullerol in brain lesions in an experimental model of ischemic stroke in rats. The rats received a dose of 100 mg/kg of fullerol via intraperitoneal injection 30 minutes before induction of ischemia. The results indicated that administration of fullerol significantly attenuated the volume of cortex infarction, reducing up to 72% of the volume.

According Ye et al. (2015), the hydroxylated fullerene (C₆₀-OH) and the fullerene modified with the amino group (C₆₀-NH₂) are favorable to the protection of the neuronal cells against the toxicity caused by the microglial activation in prionic diseases. The study was carried out by adding 50 µM of the C₆₀-OH or of the C₆₀-NH₂ for 12 hours in cells in an activated microglia model. They demonstrated that microglial activation was effectively attenuated with both the C₆₀-OH as well as the C₆₀-NH₂. However, the C₆₀-OH performed better when compared to C₆₀-NH₂, inhibiting significantly the excessive production of inflammatory mediators and regulating the production of antioxidant enzymes.

Hu et al. (2007) functionalized C₆₀ fullerene with oxidized glutathione through a covalent modification and studied the therapeutic capacity of this new structure in an *in vitro* apoptosis model. They demonstrated that the 5 µg/mL incorporation of the functionalized fullerene was able to reduce the apoptotic neuronal cell count from 44.7% to 5.40%, without apparent toxicity.

Protection against neuronal death was also studied by Ali et al. (2008), however, using carboxyl-functionalized fullerene. Theoretical and experimental studies were carried out where the carboxyfullerenes mimic a natural superoxide, which acts on the cells controlling the presence of free radicals. Six configurations of the carboxyfullerenes, where these structures contained different numbers of carboxyls and different symmetries. The theoretical study was carried out from computational simulations that demonstrated the reactivity and the affinity of these nanostructures with the superoxide. In the experimental part, the protective action of carboxyfullerenes was verified in a programmed neuronal death model. The results showed that administration of 30 µM of the carboxyfullerene containing six carboxylic groups was able to protect the cells, whereas larger doses of the other configurations studied, such as those containing five, four and three carboxylic groups, were not sufficient for a complete neuroprotective effect.

Another study containing functionalized fullerene was by Lee et al. (2011). In this work, it was incorporated to fullerene polyethylene glycol (PEG-C₆₀) and its pentoxifylline-bearing hybrid (PTX-C₆₀). Neuronal cells were pretreated with 10 µM of each of the functionalized fullerenes and then their effects against β-amyloid-induced toxicity were studied. The results indicated that PEG-C₆₀ and PTX-C₆₀ significantly reduced β-amyloid-induced cytotoxicity, increasing the cellular viability and decreasing the number of reactive oxygen species. PTX-C₆₀ was the most effective with significant protection against cytotoxicity.

The effects of neuroprotection of hydrated fullerenes in an Alzheimer's disease model were also studied (VOROBYOV et al., 2015). In this study, the disease was induced using β-amyloid peptide (Aβ₄₂) in the frontal cortex and hippocampus regions of rats. Fullerene was inserted into the cells at a concentration of 0.5 nm/µL via intracerebral injection before to treatment with the peptide. It was demonstrated through an electroencephalogram (EEG) by measuring the frequency that the nanostructure was able to protect the two regions against the action of the protein, eliminating the effect of Aβ₄₂ on cells.

Ye et al. (2015) evaluated the neuroprotective effects of carboxyfullerene (C₆₀-COOH). Mitochondrial dysfunction is associated with neuropathies, where the dynamics of mitochondria remains altered in these diseases. Thus, the modulation of mitochondrial dynamics is of utmost importance for the development of new therapeutic strategies for the treatment of neurodegenerative diseases. In this context, the effect of C₆₀-COOH at various concentrations (10-100 µM) or 24 hours on *in vitro* mitochondria dynamics. Treatment with C₆₀-COOH prevented the fragmentation of these organelles, the depolarization of mitochondrial membrane potential and reduced the presence of reactive mitochondrial oxygen species, leading to the reduction of the neuroinflammatory response. In addition, carboxyfullerene was able to maintain cell viability at all concentrations analyzed.

Carboxyfullerene has also been investigated as a neuroprotective agent against oxidative stress by Lin et al. (1999). Oxidative stress was induced by iron in the nigrostriatal dopaminergic system in rats. Subsequently, *in vitro* studies were performed where different concentrations of carboxyfullerene were added (5-500µM). The results showed that carboxyfullerene was able to prevent iron-induced oxidative damage without apparent toxicity at all concentrations analyzed, however, the concentration of 500 µM was able to completely avoid this effect. In addition, the antioxidant capacity of carboxyfullerene was compared with that of vitamin E and melatonin. Carboxyfullerene was about two to five times less potent than vitamin E, but 20 times more potent than melatonin in preventing iron-induced lipid peroxidation.

The relation of adenosine receptors with water-soluble fullerenes was studied by Giust et al. (2011). Adenosine plays an important protective role in neuronal cells, therefore, the presence of adenosine receptors in these cells is critical for such an effect. In this study, the exposure of fullerenes in cells resulted in an increase in these receptors, indicating that fullerene induces protection in neuronal

cells. Were analyzed concentrations of 1, 3, 5 e 10 μM for 2 and 6 hours. None of these concentrations affected cell viability, indicating that carboxyfullerenes were not toxic to cells. However, it was verified the limit of use of carboxyfullerene which would become toxic to cells, where the value found was 1 μM for 6 hours. In another study, Giust et al. (2014) analyzed the effect of water-soluble fullerenes in 25-150 μM in cells SK-N-MC in 24h, 48h e 72h. Exposure to modified fullerenes in these cells did not affect cell viability. In addition, there was an increase in adenosine A_1 and A_{2A} receptors after 24h, which was maintained at 48h and 72h. Here, the fullerene has also been shown to be neuroprotective, can be used as a therapeutic target to prevent degeneration and cell death in neurodegenerative diseases.

The protection of fullerene against neurodegeneration in a model of multiple sclerosis in mice was studied by Basso et al. (2014). In this study, were used carboxyfullerenes which were administered to the mice daily in the concentration of 30 $\mu\text{g}/\text{Kg}$ after 20 days of induction of the disease until the 70th day. The results showed that fullerene was able to reverse axonal damage and demyelination, decreasing the progression of the disease. Furthermore, the functionalized fullerene showed to protect the neurons against oxidative lesions and glutamate lesions when compared to the control group.

Tikhomirov et al. (2007) conducted a study in which rats were submitted to ethyl alcohol for 12 weeks to evaluate lipid peroxidation and the presence of a marker of astrocytes that are toxic to the brain and are caused by excessive alcohol consumption. As predicted, alcohol consumption resulted in an increase in the number of molecular markers of oxidative stress in brain tissues. After this initial study, a group of rats drank the ethyl alcohol along with 30 nM of hydrated fullerene (C₆₀HyFn). It has been demonstrated that C₆₀HyFn has been effective in eliminating the negative effects of ethyl alcohol on the central nervous system.

Chen et al. (2011) functionalized fullerene with methionine (FMD) to inhibit lead toxicity, which is considered to be a neurodegenerative causer in diseases such as Alzheimer's disease. Concentrations of 0.5, 5 e 50 $\mu\text{g ml}^{-1}$ for 1 h of FMD as a pretreatment in neuronal cells exposed to 500 μM lead acetate. The results showed that FMD was able to reduce by up to 13.57% the lead-induced oxidative damage in these cells.

For Parkinson's disease, Cai et al. (2008) used the polyhydroxylated fullerene derivative (C₆₀(OH)₂₄) as a agent in the prevention and therapy of this disease in an *in vitro* model. Possible effects of free radical scavenging on these cells were studied using 50 μM of the C₆₀(OH)₂₄ for a period of 48 hours. The authors demonstrated that C₆₀(OH)₂₄ has been shown to be an efficient mitochondrial protective antioxidant with elimination activity of direct radicals and indirect antioxidant inducing activity in the Parkinson's disease model.

The biological actions and toxicity of polyhydroxyferulene (fullerol) in different concentrations were studied by Zha et al. (2012) in hippocampal neurons of cultured rats. The results showed that fullerol in low concentrations (1 μM e 5 μM) for 24 hours significantly improved the viability of the hippocampus neuron in approximately 111 and 110% respectively. Concentrations greater than

5 μ M had no effects under cell viability. Exposure to 100 μ M for 48 hours reduced cell viability to approximately 89%. Already the exposure of the cells to 25 μ M and 100 μ M for 72 hours reduced cell viability to 83% and 84%, respectively. These data suggest that fullerol promotes cell death and protects against cell damage, depending on the concentration used.

Cusan et al. (2002) synthesized a novel water-soluble fullerene derivative with three ethylene glycol chains and three ammonium groups to evaluate the ability to capture free radicals in brain cortical cells. Concentrations ranging from 1 to 100 μ M were used. The results indicated that the structure was ineffective for neuroprotection in neuronal lesions caused by free radicals, behaving as a toxic agent, since it induced the reduction of cellular viability. This toxicity can be explained by the surfactant behavior of this derivative. The study of Jin et al. (2000) verified the neuroprotection of hydroxylated fullerenes. The results demonstrated that these fullerenes at a concentration of 50 μ M were able to reduce glutamate-induced neurotoxicity by about 80%. Hydroxylated fullerenes exert neuroprotective functions, blocking glutamate receptors by 50% and decreasing intracellular calcium.

As previously observed, water-soluble fullerenes have shown significant results in the improvement of different diseases that affect the brain. The conjugated fullerene with water-soluble substances and also fullerol were able to significantly attenuate the volume of cerebral ischemia, and consequently lesions in the cortex in rats at different concentrations without toxicity. The best outcome for the treatment of cerebral ischemia was found by Darabi and Mohammadi (2017) who used a dose of 100 mg/kg/day of fullerol and was able to reduce the infarct volume by up to 72%. However, Yang et al. (2001) were able to reduce the infarct volume by 68% using a lower dose (5 mg/kg/day) of a hexasulfonated fullerene.

The effect of fullerenes against brain toxicity caused by Alzheimer's disease has also been studied *in vitro* and *in vivo*. For the *in vitro* study, 10 μ M of PEG-C₆₀ showed better results against β -amyloid-induced toxicity (LEE et al., 2011). In the *in vivo* study, 0.5 nm/ μ L of hydrated fullerenes were able to eliminate the effects of γ -amyloid on brain cells in rats (VOROBYOV et al., 2015).

Furthermore, the use of fullerenes in the treatment of diseases such as Parkinson's disease and sclerosis has been shown to be effective at low concentrations (BASSO et al., 2004; CAI et al., 2008). Basically, water-soluble fullerenes act to decrease the presence of free radicals, preventing oxidative damage in neuronal cells, as seen in several studies. Based on this, we can conclude that these nanostructures have neuroprotective activity.

CONCLUSION

In the literature, it has been found out that functionalized fullerenes form a unique class of compounds with potent antioxidant properties, effective free radical scavengers, which exercise a wide variety of biological activities, including neuroprotective properties. Fullerenes also demonstrated the absence of toxic properties in most studies analyzed and high efficiency, even in small doses. It is

believed that many of the biological functions of fullerenes are due to their antioxidant properties, taking into account the broad spectrum of biological activity of hydrated fullerenes. Fullerenes were highlighted for several authors during this review as a promising nanostructure to be used in the treatment of diseases such as Alzheimer's, Parkinson's, Ischemia and Sclerosis.

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