Antioxidants in the Treatment of Amyloidosis: a Literature Review

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ABSTRACT

Introduction: The primary objective of this review is to examine the current scientific evidence regarding the role of antioxidants in relation to amyloidosis. Oxidative stress has been studied in amyloidosis, and a narrative review of articles concerning the use of antioxidants in the treatment of these diseases was conducted.

State of the Art: Articles published from 2010 to 2022 are presented, focusing on the use of carvedilol, epigallocatechin gallate (EGCG), resveratrol, and tetracyclines in amyloidosis models and cases.

Discussion/Conclusion: Antioxidant therapy for amyloidosis is in its early stages of development, requiring further clinical studies to assess long-term effectiveness and safety. Antioxidants such as carvedilol and EGCG show significant potential in interfering with amyloid fibrils, but additional research is needed to fully comprehend their impact and viability as long-term treatments.

Key words: amyloidosis, antioxidants, carvedilol, epigallocatechin gallate, tetracyclines, resveratrol.

Antioxidantes en el tratamiento de las amiloidosis: una revisión bibliográfica

RESUMEN

Introducción: el principal objetivo de la presente revisión es conocer la evidencia científica actual sobre el papel de los antioxidantes en relación con las amiloidosis. El estrés oxidativo ha sido estudiado en la amiloidosis y se realizó una revisión narrativa sobre artículos publicados en el uso de antioxidantes en el tratamiento de estas enfermedades.

Estado del arte: se presentan artículos publicados desde el año 2010 hasta el año 2022, en relación con el empleo de carvedilol, epigalocatequina galato (EGCG), resveratrol y tetraciclinas en modelos y casos de amiloidosis.

Discusión/Conclusión: la terapia antioxidante para la amiloidosis está en desarrollo temprano, por lo cual requiere más estudios clínicos para evaluar eficacia y seguridad a largo plazo. Los antioxidantes como el carvedilol y el EGCG muestran gran potencial en interferir con las fibrillas amiloides, pero se necesita más investigación para comprender su impacto completo y viabilidad como tratamiento a largo plazo.

Palabras clave: amiloidosis, antioxidantes, carvedilol, epigalocatequina galato, tetraciclinas, resveratrol.

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INTRODUCTION

Amyloidoses are a group of diseases caused by the misfolding and extracellular deposition of circulating proteins known as amyloid fibrils, which result in organ dysfunction where they deposit[1]. Amyloid deposition can occur in multiple organs (e.g., heart, liver, kidney, skin, eyes, lungs, nervous system), leading to various clinical manifestations. Diagnosis follows a biopsy of the organ suspected of containing amyloid, complemented by laboratory analysis, imaging studies, and other tests if necessary.

Oxidation is a chemical reaction involving the transfer of electrons from a substance to an oxidizing agent. Whenever oxidation occurs, a reduction process happens simultaneously.

Oxygen is a compound that oxidizes other molecules, sometimes generating reactive oxygen species (ROS) consisting of free radicals and other molecules that do not meet that condition. Some ROS play an essential role in cellular signaling[2].

Whenever a radical species attacks other molecules, a chain process begins, involving an initiation stage, a propagation stage, and a final termination stage. In each stage, the species generated may be capable of producing alterations in other molecules. Antioxidants are molecules capable of preventing the excessive oxidation of ROS. They can also play a role in stopping the propagation of the oxidation process, scavenging excited species, or promoting the generation of more enzymatic antioxidants.

Antioxidant systems can be either enzymatic or non-enzymatic. The enzymatic systems consist of a wide variety of enzymes, among which the most important are superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The main representative of the non-enzymatic antioxidant system is glutathione (GSH). These systems enable the elimination of excess ROS, including, among others, superoxide anions (O2•-), hydroxyl radicals (OH•), alkoxyl radicals (RO•), and peroxyl radicals (ROO•). However, our endogenous antioxidant systems require exogenous reducers, such as vitamins C and E, carotenoids, and polyphenols, for proper functioning.

Oxidative stress is the imbalance between reactive oxygen species (ROS) and the organism's antioxidant response capacity. In this regard, there is a continuous demand for exogenous antioxidants to prevent oxidative stress, an imbalance redox state in favor of oxidation. However, high doses of isolated compounds can be toxic due to pro-oxidant effects at elevated concentrations or their potential to react with beneficial concentrations of ROS that are typically present under physiological conditions necessary for optimal cellular function[3].

Regarding the relationship between amyloidosis, oxidative stress, and antioxidants, as early as 1997, research was conducted demonstrating the presence of oxidative stress in biopsies from patients with systemic amyloidosis[4]. Additionally, later studies analyzed the cytotoxic effects of transthyretin (TTR) fibrillogenesis both in vivo and in vitro5, which found neuronal stress in patients with familial amyloid polyneuropathy (FAP); a similar investigation, carried out in transgenic mice, showed early TTR deposition and increased cytotoxic stress at sites related to deposition[6].

The present work is a narrative review that gathers relevant information on the application of antioxidants as a treatment in patients with amyloidosis from 2010 to 2022. The search was conducted on PubMed using "Medical Subject Headings" (MeSH) with articles in both Spanish and English. Initially, we obtained 34 eligible articles, of which we excluded 26 for not falling within the defined study period, leaving a total of 8 articles included.

Estado del arte

Carvedilol

Carvedilol is a non-selective beta-blocker and vasodilator with antioxidant properties[7]. It is a potent antioxidant and a scavenger of oxygen free radicals. Additionally, it has antihypertensive and antianginal properties. It is indicated for cases of heart failure. Its antioxidant capacity has been demonstrated in wild-type transthyretin cardiac amyloidosis (ATTRwt) and secondary amyloidosis (AA).

In 2010, a study was conducted in Portugal using a transgenic mouse model with FAP[8]. The study observed that carvedilol:

- Has no effect on TTR aggregation and stabilization.
- Reduces TTR deposition in the stomach of transgenic animals.
- Significantly decreases in vivo oxidation.
- Reduces endoplasmic reticulum stress and in vivo apoptosis.
- Decreases the toxicity of TTR-induced oligomers in vitro.

In 2011, a rare case report occurred of congestive heart failure as the initial sign of reactive AA amyloidosis associated with rheumatoid arthritis and systemic sclerosis[9]. The patient, a 67-year-old woman, was urgently hospitalized due to chest tightness and exertional dyspnea. She received treatment with anti-tumor necrosis factor therapy, which she tolerated well. Her cardiac function remained stable with a combination of diuretics, an angiotensin II receptor inhibitor, and beta-blockers, including carvedilol.

In 2022, a case report[10] of a 77-year-old patient with ATTRwt amyloidosis and systolic dysfunction mentioned treatment with tafamidis, carvedilol, enalapril, and spironolactone. In this case, we established that neurohormonal blockers could have facilitated cardiac remodeling upon suppression of disease progression by simultaneous administration of tafamidis.

On the other hand, in another article[11], a prospective multicenter study was conducted on patients with transthyretin amyloid cardiomyopathy (ATTR-CM) who received beta-blockers. They had lower mortality compared to untreated controls. Six deaths were recorded in the treatment group, while 15 deaths were recorded among the controls. The cause of death was identified

in 20 of the 21 deceased patients, 17 of whom had a cardiovascular origin (Fig. 1).

Regarding the reported adverse events related to carvedilol, these may be more common in patients with heart failure, so the administered dose should be individualized and closely monitored by a cardiologist. Among the widespread adverse effects are dizziness, headache, fatigue or weakness, hypotension, bradycardia, and weakness upon standing[12].

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is the most abundant catechin in green tea and has potential antioxidant properties. We found two studies conducted in patients with ATTR amyloidosis and light-chain (AL) amyloidosis.

In 2012[13], a study was undertaken using an animal model of FAP. Tissues were analyzed using immunohistochemistry and Western Blot. We observed that EGCG acts as an inhibitor of ATTR aggregation and a disruptor of amyloid fibrils. Given its low toxicity and high tolerability, we concluded that it could have potential benefits for treating ATTR amyloidosis.

In 2016[14], we conducted a phase II trial with oral administration of EGCG capsules in patients with AL amyloidosis. No increases in adverse events were observed, and the therapy was well tolerated. Although a decrease in urinary albumin levels was found in the treated group in patients with evident albuminuria after the start of treatment, its antioxidant activity may not be sufficient to clarify the potential effect of EGCG in patients with AL amyloidosis (see Fig. 1).

A review by González-López 2017 reported that EGCG has been shown in vitro to inhibit amyloid fibril formation and remove already formed deposits. The administration of daily doses of 600 mg demonstrated stabilization of left ventricular mass, evaluated by cardiac magnetic resonance imaging, in patients with ATTR[15,16]. Nuvolone et al. reported that EGCG would act as an inhibitor of amyloidogenesis in AL and ATTR amyloidosis. However, the authors conclude that studies have produced variable results and that improving the quality of the evidence is needed[17].

Tetracyclines

Tetracyclines are bacteriostatic antibiotics that work by inhibiting protein synthesis[18]. Their use had decreased due to the emergence of resistant strains. Their potential antioxidant properties were first reported more than 25 years ago[19]. In that study, it was established that the antioxidant effect of these antibiotics does not stem from their ability to eliminate ROS but rather from their influence on the function of polymorphonuclear leukocytes (PMNL cells), leading to direct anti-inflammatory effects on inflammatory processes.

On the other hand, when searching for its use in amyloidosis, we found a 2013 review[20] discussing the available data on the anti-amyloid activity of tetracyclines in preclinical and clinical studies. These suggest that the drug targets some structural characteristics of amyloid fibrils, such as the quaternary structure of cross-β sheets.

We propose that its beneficial effects result from a peculiar pleiotropic action, which includes its interaction with oligomers and fibril disorganization, as well as its antioxidant, anti-inflammatory, anti-apoptotic, and matrix metalloproteinase inhibitory activities. However, there is controversy regarding this: more recently, an article was published[21] in which–after evaluating a group of transplanted patients treated with doxycycline (a member of the tetracycline group)– it was concluded that there is no clear evidence of its benefit (see Fig. 1).

The article by García Pavía on the diagnosis and treatment of cardiac amyloidosis and the 2021 Guideline for the specific pharmacological treatment of transthyretin amyloid cardiomyopathy both refer to doxycycline as a molecule under investigation that may accelerate the clearance and elimination of cardiac deposits. Although the combination of doxycycline with ursodeoxycholic acid was analyzed in phase II studies, with variable results and primarily gastrointestinal and skin-related adverse events, the quality of the evidence was very low to recommend it for the treatment of amyloidosis [22,23].

Similarly, a review by González-López et al. (2017) reports that the preliminary results of phase II studies of doxycycline in combination with tauroursodeoxycholic acid showed a protective effect with less worsening of cardiac function. However, all studies reported a high dropout rate, mainly due to side effects, particularly photosensitivity and gastrointestinal disturbances[16].

Resveratrol

Resveratrol is a natural polyphenol found in numerous plants and fruits such as peanuts, blackberries, blueberries, and, especially, in grapes and red wine[20,24].

In 2011[25] we studied 23 resveratrol analogs as inhibitors of induced cytotoxicity in a tissue culture model of cardiac amyloidosis. We found that resveratrol and its analogs kinetically stabilize the native tetramer, preventing the formation of cytotoxic species. It has also been shown that resveratrol can accelerate the formation of soluble nontoxic aggregates and its tested analogs can assemble monomeric TTR subunits to form the native nontoxic tetramer (see Fig. 1).

DISCUSSION

This narrative review describes the use and characteristics of drugs evaluated for their antioxidant capacity in amyloidosis. It is important to note that this capacity is still in early development[26]. The various studies that have assessed these compounds are mostly phase I, II, observational studies, or case series, which makes it difficult to generalize the results and evaluate the quality of the evidence.

Additional clinical studies are needed to determine the long-term efficacy and safety of these treatments in patients. For instance, randomized clinical trials with larger sample sizes are necessary to validate the effectiveness of antioxidant therapies in managing

Figure 1. Summary of the characteristics of the drugs used and their antioxidant capacity

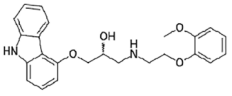
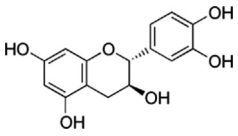
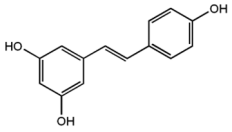
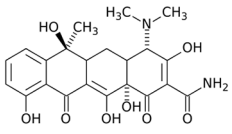
	Dose	Frequency	Period	Structure	Antioxidant grade	Sample characteristic	Study
Carvedilol	2 mg/kg	Daily	3 months		Little antioxidant action from its structure	ransgenic mice carrying human mutation TTR Val30Met	Macedo et al.[8] Imamura et al.[10]
	2.5 mg	not specified	6 months			Patient 77 years	Wada et al.[9]
	2.5 mg	not specified	6 months			Patient 67 years	Barge-Caballero et al.[11]
	12.5 mg	not specified	varies ccording to cohort entry			Group of patients	
EGCG	100 mg/kg	Daily	6 months		4 OH that could act as proton donors	Transgenic mice carrying human mutation TTR Val30Met	Ferreira et al.[13]
	126 mg	not specified	6 months			Group of patients	Meshitsuka et al. [14]
Resveratro					3 OH that could act as proton donors	AC16 cells (in vitro)	Bourgault et al.[25] Stoilova et al.[20]
Tetracycline	The doses generally used are 250 to 1000 mg per day for 5 days, 100 to 200 mg per day for 6 days, and 50 to 100 mg per day for 7 days. This applies to both short-term and long-term treatments. (Systematic Review)				2 OH and 1 keto group that could play a role in the antioxidant action	*	

Figure 1. Summary of the characteristics of the drugs used and their antioxidant capacity

amyloidosis. Long-term follow-up studies are also essential to evaluate the sustained impact and safety profile of these treatments. Furthermore, investigating the potential synergistic effects of combining antioxidants with existing treatments for amyloidosis could improve outcomes and provide insights into novel treatment strategies.

Research on antioxidant therapy in amyloidosis has yielded promising results, especially in the cases of carvedilol and EGCG. These antioxidants show potential in interfering with the formation and toxicity of amyloid fibrils, which could translate into an efficient therapeutic approach for this complex disease. However, more research and clinical studies are needed to understand their impact on the progression of amyloidosis and their viability as long-term treatments. The complexity of amyloidosis and its relationship with oxidative stress suggests the need for multidisciplinary approaches that address both amyloid formation and the mitigation of oxidative stress.

CONCLUSION

Antioxidant therapy in amyloidosis, especially with carvedilol and EGCG, shows therapeutic potential, but further research is needed, including clinical trials with larger sample sizes, to validate its long-term efficacy and safety and to explore possible combinations with existing treatments. The complexity of the disease underscores the need for multidisciplinary approaches.

Conflicts of Interest: The authors declare no conflicts of interest.

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