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Anti-AGE Antioxidants: The Relationship between Free Radicals and Advanced Glycation End-products

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***Abstract*—** *Advanced glycation end-products (AGEs) are molecules both directly and indirectly responsible for many geriatric diseases. Some individuals may accumulate more AGEs than others due to several factors, individuals who accumulate more AGEs tend to manifest diseases such as Alzheimer's, arteriosclerosis and type 2 diabetes earlier in life. Free radicals have direct and indirect influence on the amount of serum and tissue AGEs, which leads to the question of whether the effects of AGEs can be attenuated by using exogenous and endogenous antioxidants. In this paper, we conducted a literature review on the compositions, origins, and associated pathologies of AGEs, in addition to the combat and prevention by antioxidants. Thirty-five scientific papers published between 1994 and 2021 in English and Portuguese were identified via SciELO, PubMed, Elsevier and Scopus. Through this review, we conclude that the direct and indirect relationship between AGEs and free radicals is a fact and no longer a speculation. In addition, there are studies that have been able to show the efficiency of some antioxidants in controlling specific AGEs, now commonly referred to as anti-AGEs antioxidants.*

I. INTRODUCTION

Advanced glycation end-products (AGEs) are molecules that result from chemical reactions taking place both in the body and in the external environment. Most reactions that generate AGEs in the body happen naturally and are considered physiologically normal reactions. However, today, there is much scientific evidence to indicate that AGEs are directly and indirectly responsible for many geriatric diseases, such as Alzheimer's, osteoarthritis and arteriosclerosis [1] [2]. AGEs are linked to geriatric diseases because they tend to accumulate throughout life and tend to prevail, despite having natural mechanisms for their elimination [3].

There are countless types of AGEs, and many are discovered over the course of days. Much of what is understood about the formation of AGEs can be attributed to the scientific findings cataloged by the French scientist Louis Camille Maillard in the beginning of the 20th century. Maillard managed to understand and communicate information about these molecules that until that time were considered to come solely from the external environment. Because of this, his findings are often related to bromatology.

In general, the formation of AGEs consists of blending a carbonyl or aldehyde group of one molecule with an amino group of another molecule. Part of the structure of a

carbohydrate fuses with part of the structure of an amino acid. The results of this fusion – known as glycation – are the Schiff bases which, due to natural chemical interactions, become a new structure called an Amadori product. Amadori products can interact with many other molecules, and of these interactions can result in AGEs [1] [3] [2].

Of all the reactions that an Amadori product can undergo to become an AGE, the one related to free radicals is one of the most cited by the scientific community. Through oxidation, free radicals destabilize the electrons of one or more atoms of Amadori molecules. An example of this is carboxymethylisine, which is an AGE resulting from the interaction between transition metal ions and Amadori products [4].

Many antioxidants have already been shown to be potentially capable of controlling the generation of AGEs, both in vitro and in vivo [5][6]. If AGEs are related to geriatric diseases and some antioxidants can reduce the generation of serum and tissue AGEs, then it is necessary to study these antioxidants to prevent disease.

Free radicals are atoms with an odd number of electrons in their last electron shell [7]. Due to this energetic irregularity, these atoms tend to transmit, split, or steal electrons from other atoms, resulting in changes in the chemical structure of molecules exposed to them [8]. They can be isolated, become part of a molecular region, or compose the entire structure of a molecule [9]. Many types of free radicals are naturally formed in the body, such as the case of hydroxyl radicals (OH•), formed during cell respiration [7].

Antioxidants are substances that can control molecules affected by free radicals by preventing their formation and capturing the free radicals already formed. Regardless of the form, studies show that some antioxidants can decrease free radical exposure to Amadori products, consequently decreasing the formation of AGEs. Such antioxidants are called “anti-AGEs antioxidant”, and can be either naturally generated inside the body or ingested [2].

II. METHODOLOGY

A scientific review of the literature was conducted. We identified 40 scientific papers written in English and Portuguese between the years 1994 and 2021. Of the 40 papers, only 5 did not meet our search criteria, which was based on compatibility, legitimacy, and clarity of reference sources. The papers were found on the following scientific platforms: SciELO, PubMed, Elsevier and Scopus. The keywords used in the search were: “AGEs”, “antioxidants”, and “free radicals”. In the searches for content in Portuguese, the following keywords were used: “AGEs”, “antioxidantes” and “radicais livres”.

The 35 papers were meticulously reviewed for the following content: advanced glycation end products, free radicals, and antioxidants. This paper presents an introduction to the content and scope of these papers.

III. RESULT

3.1. AGE RECEPTOR-1

AGE Receptor-1, more commonly referred to as “AGER1”, is part of the membranous structure of some human cells. It is often part of an even larger structure called AGE-R complex. AGER1s are considered antioxidants because they serve as receptors for AGE molecules, enabling their endocytosis and subsequent degradation by lysosomes. The destruction of AGEs generates a substance commonly referred to as SIRT1, which promotes less inflammation and oxidative stress, and decreases free radicals, as shown in figure 1 [10]. AGER1s are common in the membrane and endoplasmic reticulum of mesangial cells, cells that occupy the space between the capillaries of a glomerulus. This receptor is present in smaller amounts in patients with kidney diseases, especially kidney diseases as a result of diabetes [10] [11].

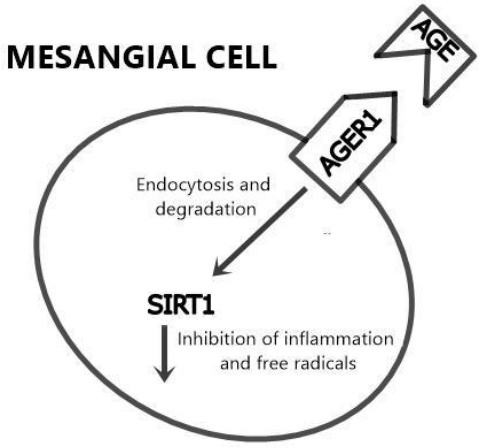

Fig. 1: Formation of SIRT1 by a mesangial cell after recognizing an AGE through its AGER1 receptor.

Some studies have shown that in the face of excessive exposure to AGEs, mesangial cells tend to gradually lose AGER1, which contradicts the belief that their defense would be equivalent to the damage suffered [10].

3.2. SCAVENGER RECEPTOR CLASS B

Scavenger receptors are structures found mainly on the membrane of some leukocytes. They are commonly divided into types A and B, but there have been attempts to

expand the classification to eight classes, A, B, C, D, E, F, G and H. Type B is most related to the control of AGEs. This control is due to the ability of the receptor to interact with oxidized molecules, i.e., the ability to attract molecules that contain atoms with alterations in their number of electrons [12]. It is because of this fact that scavenger type B receptors can be considered anti-AGE antioxidants. AGEs in contact with scavenger receptors are endocytosed and degraded, forming AGEs of low molecular weight as metabolic waste, which are easily excreted by the urinary system. A few studies refer to low molecular weight AGEs resulting from degradation by scavenger cells as "second generation AGEs", and these AGEs can also be highly reactive [13]. However, because its lifespan in the body is extremely short-lived due to excretion through the urine, it does not cause much concern except in patients with kidney problems.

A few studies have sought or are still seeking an alternative for individuals with kidney problems to control circulating AGEs, especially second-generation AGEs, with the efficiency close to that of a healthy person. The lysozyme protein is one of the most mentioned possibilities, its presence in the blood circulation contributes in several ways to the control of AGEs, mainly in the scope of excretion via the kidney [1] [13] [14]. However, there are not enough studies to recommend it in practice as a treatment, not even preventive, especially because many possible mechanisms have not yet been explored, and the performance of these mechanisms are debated.

3.3. ASCORBIC ACID

The antioxidant power of ascorbic acid, better known as vitamin C, has been recognized for many decades. This is why it became the main molecule studied for possible anti-AGE antioxidant actions. Its preventive capability against diseases such as diabetes and arteriosclerosis was already known, even before the understanding of AGEs [15] [16] [17].

Some papers have reported impressive results, such as a 50% decrease in serum AGEs in individuals after just 4 weeks with daily administration of vitamin C [18]. According to the pharmaceutical company Merck Sharp and Dohme (MSD), the recommended daily dose of vitamin C is 90mg for men over 19 years old. However, some studies argue that the dosage must be specified for each individual, as each individual's body tends to have particularities that can shape the action of the vitamin, affecting its antioxidant action [19].

The action of vitamin C in combating AGEs consists mainly of two parts; the inhibition of glycation by regulating the cellular transport of glucose [18] [19] [20], and the inhibition of free radicals. The way in which vitamin C inhibits free radicals was discussed once again, this feat was justified by its stimulative relationship with the superoxide dismutase (SOD) enzyme, a circumstance today contrary to the results of important studies [21] [22]. This fact does not discredit the anti-AGEs antioxidant capacity of vitamin C, it only shows that its action involves mechanisms that are not yet fully mastered.

3.4. SELENIUM

Selenium is a chemical element that makes up the structure of molecules in many foods but is usually found only in small amounts, with the exception of Brazil nuts (Bertholletia excelsa) – 100g provides 45 times more selenium than 100g of cooked white rice [23]. It was through the use of Brazil nuts that many studies were carried out on selenium, mainly in relation to anti-oxidation. The results provided evidence for inhibition of AGEs through the reduction of molecules that expose carbonyl groups and result in genetic damage [24].

Molecules (mainly aldehydes) that have carbonyl groups in their chemical structure, are likely to bind to the amino groups of some amino acids. This results in formation of the aforementioned Schiff bases, precursors of Amadori products, and consequently AGEs [1]. Much of Selenium's actions are due to the fact that it composes amino acids called "selenocysteine", amino acids that participate in cellular redox (exchange of electrons between molecules involved in cellular respiration) [24] [25]. In controlled situations, cellular redox correctly manages all electron exchange. Other atypical situations will result in free radicals [25].

3.5. ALPHA-TOCOPHEROL

Tocopherols, better known as vitamin E, are common components of vegetable oils. Their chemical structure can vary between four main forms: α, β, γ and δ-tocopherol. α-tocopherols are most commonly linked to the control of AGEs [26] [27].

Studies consider vitamin E to be the most potent antioxidant against peroxyl free radicals, or those coming from lipoperoxidation, which are the alterations of the lipid components in face of free radicals, mainly reactive oxygens. Lipoperoxidation causes cellular problems mainly related to the cell membrane including identification, entry, and exit of substances [28]. They are given the title of anti-AGE antioxidants by some authors mainly because they decrease the glycated hemoglobin index when administered to volunteers [29] [30], which serves as evidence for a possibility to block the formation of other Amadori products.

3.6. EUK-134 AND MNTBAP

The SOD enzyme, already mentioned in the topic on ascorbic acid, is one of the most potent reactive oxygen inhibitor molecules [3] [7] [19]. It is a difficult molecule to stimulate, as recent studies have demystified the ability of vitamin C to boost serum and tissue SOD levels [21] [22]. Given this situation, many pharmaceutical companies propose developing replicas of SOD enzymes. Of these, two are close to success: the enzyme EUK-134 and MnTBAP [3].

Both synthetic enzymes have been suggested for treatment of kidney dysfunction, type 2 diabetes, and even neurological problems [31] [32] [33] [34]. No negative reviews were found regarding the enzymes, except that the doses used in studies were considerably high, and there were significant variations in administration methodologies. Even so, there are no oral versions in United States or Brazil for use in treatments, only a version for topical use with aesthetic purposes. This use is currently not recognized by the Food and Drug Administration (FDA), nor by National Health Surveillance Agency (ANVISA); however, it is easily found for sale in both countries. Studies involving these synthetic enzymes are also numerous and comprehensive [31] [32] [33] [34] [35]. The reason for not yet having authorization for sale or use in medical practice is not explicit.

IV. DISCUSSION

Although many scientific papers do not use the term “AGEs”, it is clear that they indirectly address such molecules. Many nutrition papers tend to link diets rich in antioxidants with a reduction in diseases such as Alzheimer's and arteriosclerosis [20] [21] [22] [26]. This fact, along with the results of research involving anti-AGE antioxidants, makes clear the long-term power of antioxidant-rich diets.

As for the safe doses of the endogenous antioxidants mentioned here, there is no consensus. Some studies used larger amounts, others smaller, than those recommended daily by official bodies, making us question whether the recommended dose can be effective in combating AGEs [6] [18] [20] [24] [30]. In regards to synthetic antioxidants, their absence in the medical field is intriguing, as many of them have more safe studies than some drugs already released for consumption, which leads us to believe that there may be technical or industrial challenges [3] [31] [32] [33] [34].

V. CONCLUSION

We conclude through this review that there is already a scientific consensus that AGEs are responsible for several geriatric diseases. Patients less exposed to AGEs have better success rates in preventing and treating diseases in almost all papers analyzed involving geriatric diseases.

It is also currently a consensus that free radicals trigger higher levels of serum and tissue AGEs, including natural free radicals, such as those coming from cellular respiration. And some antioxidants can indirectly reduce the exposure of individuals to AGEs, as they control important free radicals. Because of this, these antioxidants were named anti-AGE antioxidants by the scientific community.

Finally, we conclude that there are many studies proving the effectiveness of many synthetic antioxidant molecules. However, these molecules seem to have stagnated in their path towards use in medical practice. The reason for this is unclear but could be related to industrial and bureaucratic difficulties.

REFERENCES

[1] Aguiar, M. P. and Caldeira, C.G. (2021) Introdução aos produtos finais de glicação avançada. Revista Científica Multidisciplinar Núcleo do Conhecimento. 06, 85-93. http://dx.doi.org/10.32749/nucleodoconhecimento.com.br/saude/glicacao-avancada

[2] Torres, N. M. P. O., Xavier, J. A., Goulart, M. O. F., Alves, R. B. and Freitas, R. (2018) A Química dos Produtos Finais de Glicação Avançada. Revista Virtual de Química, 10 (2), 375-392. http://dx.doi.org/10.21577/1984-6835.20180029

[3] De’grey, A. (2018) O fim do envelhecimento: os avanços que poderiam reverter o envelhecimento humano durante nossa vida. Strategies for Engineered Negligible Senescence. Publisher: NTZ.

[4] Yim, H.S., Kang, S.O., Hah Y.C., Chock P.B. and Yim M.B. (1995) Free radicals generated during the glycation reaction of amino acids by methylglyoxal. A model study of protein-cross-linked free radicals. Journal of Biological Chemistry, 270 (47), 28228-33. http://dx.doi.org/10.1080/028418501127346846

[5] Rousselot, B. D. (2001) Antioxidant and anti-AGE therapeutics: evaluation and perspectives. J Soc Biol. 195 (4), 391-8. http://dx.doi.org/10.1080/028418501127346846

[6] Starowicz, M. and Zieliński, H. (2019) Inhibition of Advanced Glycation End-Product Formation by High Antioxidant-Leveled Spices Commonly Used in European Cuisine. Antioxidants (Basel), 8 (4):100. http://dx.doi.org/10.3390/antiox8040100.

[7] Ferreira, A. L. A. and Matsubara, L.S. (1997) Radicais livres: conceitos, doenças relacionadas, sistema de defesa e estresse oxidativo. Rev. Assoc. Med. Bras. 43 (1).

https://doi.org/10.1590/S0104-42301997000100014

[8] Lima, E. (2011). Dicionário de termos e nomenclaturas em nanotecnologia e novas ciências. Publisher: Clube de Autores; Edition: 1.

[9] Andrade, F. P. (2011). Material 2: Moléculas, Íons e seus Compostos. Universidade Federal de São João del-Rei. https://ufsj.edu.br/frankimica/quimica_fundamental.php

[10] Costa, M. C. and Baviera, Amanda M. (2019) Avaliação da trigonelina e curcumina, isoladas ou co-administradas em iogurte, em modelo experimental de obesidade e resistência à insulina. Postgraduate Program in Pharmaceutical Sciences (UNESP), doctoral thesis.

[11] Lu C., He J. C., Cai, W., Liu, H., Zhu, L. and Vlassara H. (2004) Advanced glycation endproduct (AGE) receptor 1 is a negative regulator of the inflammatory response to AGE in mesangial cells. Proc. Natl. Acad. Sci. U. S. A., 101 (32), 11767-72. http://dx.doi.org/10.1073/pnas.0401588101

[12] PrabhuDas, M.R., Baldwin, C.L., Bollyky, P.L., Bowdish, D.M.E., Drickamer, K., Febbraio, M., Herz, J., Kobzik, L., Krieger, M., Loike, J., McVicker, B., Means, T.K., Moestrup, S.K., Post, S.R., Sawamura, T., Silverstein, S., Speth, R.C., Telfer, J.C., Thiele, G.M., Wang, X.Y., Wright, S.D. and El Khoury, J. (2017) A Consensus Definitive Classification of Scavenger Receptors and Their Roles in Health and Disease. J Immunol. 198 (10), 3775-3789. https://doi.org/10.4049/jimmunol.1700373

[13] Barbosa, J. H. P., Oliveira, S. L. and Seara, L. T. (2008) The role of advanced glycation end-products (AGEs) in the development of vascular diabetic complications. Arq Bras Endocrinol Metab 52 (6). https://doi.org/10.1590/S0004-27302008000600005

[14] Barbosa, J. H. P., Oliveira, S. L. and Seara, L. T. (2008) Dietetics advanced glycation end-products and chronic complications of diabetes. Rev. Nutr. 22 (1). https://doi.org/10.1590/S1415-52732009000100011

[15] Johnston, C. S. and Yen, M. F. (1994) Megadose of vitamin C delays insulin response to a glucose challenge in normoglycemic adults. Am J Clin Nutr, 60 (5), 735-8. https://doi.org/10.1093/ajcn/60.5.735

[16] Kodama, M., Kodama, T., Murakami, M. and Kodama M. (1993) Diabetes mellitus is controlled by vitamin C treatment. In Vivo, 7(6A), 535-42.

[17] Diaz, M.N., Frei, B., Vita, J. A. and Keaney J. F. Jr. (1997) Antioxidants and Atherosclerotic Heart Disease. The New England Journal of Medicine, 337, 408-416. https://doi.org/10.1056/NEJM199708073370607

[18] Vinson, J. and Howard, T. B. (1996) Inhibition of protein glycation and advanced glycation end products by ascorbic acid and other vitamins and nutrients. The Journal of Nutritional Biochemistry 7 (12), 659-663. http://dx.doi.org/10.1016/S0955-2863(96)00128-3

[19] Bianchi, M. L. P. and Antunes, L. M. G. (1999) Free radicals and the main dietary antioxidants. Rev. Nutr. 12 (2). https://doi.org/10.1590/S1415-52731999000200001

[20] Pfeifer, F. S., Brenner, N., Limberger, L. B., Müller, L., Molz, P. and Franke S. I. R. (2016) Influência da vitamina C na glicação da hemoglobina e no dano do DNA no pré-diabetes e diabetes tipo 2: um ensaio clínico cruzado randomizado. Semantic Scholar. Corpus ID: 126160715.

[21] Petry, E. R., Alvarenga, M. L., Cruzat, V. F. and Toledo, J. O. T. (2013) Nutritional supplementation and oxidative stress: implications for physical activity and sport. Rev. Bras. Ciênc. Esporte 35 (4). https://doi.org/10.1590/S0101-32892013000400017

[22] Silva, L. D., Silva, N. C., Santos, R. S., Soares, T. C., Rêgo, M. N., Silva, M. C. L., Fontenelle, L. C., Poltronieri, F. and Marreiro, D. N. (2021) Relationship between vitamin C ingestion and antioxidant enzymes in obese women. Research Society and Development, 10 (3). https://doi.org/10.33448/rsd-v10i3.13489

[23] Ferreira, K. (2012) Fontes alimentares de selênio. Universidade Estadual do Norte Fluminense Darcy Ribeiro. https://www.uenf.br/dic/wp-content/uploads/sites/2/2012/08/tabela-selenio-alimentos.pdf

[24] Macan, T. P. and Andrade, V. M. (2017) Efeitos do consumo da castanha-do-Brasil (Bertholletia excelsa H.B.K.) na modulação do estresse oxidativo e instabilidade genômica em indivíduos com diabetes mellitus tipo 2. Universidade do extremo sul catarinense, programa de pós-graduação em ciências da saúde, doctoral thesis.

[25] Reece, J. (2011) Cellular respiration and fermentation. Campbell biology, ed. 10.

[26] Ramalho, V. C. and Jorge, N. (2006) Antioxidants used in oils, fats and fatty foods. Quím. Nova 29 (4). https://doi.org/10.1590/S0100-40422006000400023

[27] Vasques, L. M. and Gelain, D. P. (2011) Regulação de receptores para produtos finais de glicação avançada (RAGE) por vitamina A. Universidade Federal do Rio Grande do Sul, bachelor thesis.

[28] Batista, E. S., Costa, A. G. V. and Sant'ana, H. M. P. (2007) Adding vitamin E to foods: implications for the foods and for human health. Rev. Nutr. 20 (5). https://doi.org/10.1590/S1415-52732007000500008

[29] Fuller, C. J., Chandalia, M., Garg, A., Grundy, S. and Jialal, I. (1996) RRR-alpha-tocopheryl acetate supplementation at pharmacologic doses decreases low-density-lipoprotein oxidative susceptibility but not protein glycation in patients with diabetes mellitus. Am J Clin Nutr. 63 (5), 753-9.

[30] Mehta, R., Shangari, N. and O'Brien, P. J. (2008) Preventing cell death induced by carbonyl stress, oxidative stress or mitochondrial toxins with vitamin B anti-AGE agents. Mol Nutr Food Res. 52 (3), 379-85. http://dx.doi.org/10.1002/mnfr.200600190

[31] Bahramikia, S. and Yazdanparast, R. (2011) EUK-8 and EUK-134 reduce serum glucose and lipids and ameliorate streptozotocin-induced oxidative damage in the pancreas, liver, kidneys, and brain tissues of diabetic rats. Medicinal Chemistry Research 21 (10). http://dx.doi.org/10.1007/s00044-011-9855-2

[32] Chatterjee, P. and Patel, N. S. A. (2004) EUK-134 Reduces Renal Dysfunction and Injury Caused by Oxidative and Nitrosative Stress of the Kidney. American Journal of Nephrology 24 (2), 165-77. http://dx.doi.org/10.1159/000076547

[33] Rong, Y., Doctrow S. R., Tocco, G. and Baudry, M. (1999) EUK-134, a synthetic superoxide dismutase and catalase mimetic, prevents oxidative stress and attenuates kainate-induced neuropathology. Proc Natl Acad Sci U S A. 17;96 (17), 9897-902. http://dx.doi.org/10.1073/pnas.96.17.9897

[34] Zhou, X., Li, M., Xiao, M., Ruan, Q., Chu, Z., Ye, Z., Zhong, L., Zhang, H., Huang, X., Xie, W., Li, L. and Yao, P. (2019) ERβ Accelerates Diabetic Wound Healing by Ameliorating Hyperglycemia-Induced Persistent Oxidative Stress. Front Endocrinol (Lausanne). 10: 499. http://dx.doi.org/10.3389/fendo.2019.00499

[35] Brestoff, J., Brodsky, T., Sosinsky, A., McLoughlin, R., Stansky, E., Fussell, L., Sheppard, A., DiSanto-Rose, M., Kershaw, E. and Reynolds, T. (2015) Manganese [III] Tetrakis [5,10,15,20]-Benzoic Acid Porphyrin Reduces Adiposity and Improves Insulin Action in Mice with Pre-Existing Obesity. PloS one, 10. http://dx.doi.org/10.1371/journal.pone.0137388