

EFFECTS OF POLYPHENOLS ON CARDIOVASCULAR AGING

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Summary:

Aging is a variation of the biological process, capable of reducing the individual's adaptation to the environment. In aging, takes place of occurrences initiated by the physiological deterioration with the damage caused to the mitochondrial DNA. Besides the appearance of oxygen-reactive species (ROS), produced by NADPH mitochondrial, activated by the G protein coupled receptor. The ROS can inactivate the enzymes eNOS and MnSOD leading NF-kB. Polyphenols, secondary metabolites of plants, are correlated with improved aging process by different mechanisms. Thus, this review aims to characterize the action of polyphenols on cell senescence, longevity in experimental models, as well as to identify the promoters of lifespan (*in vivo*) contribute to cardiovascular system. In the present research, we describe the molecular targets of phenolic compounds in aging cardiovascular, providing the benefits of them, since the structural heterogeneity of the polyphenols specific arrangements, thus blocking harmful effects on the useful life, thereby altering the structure and function of the vasculature. Quality of life is linked to the balance of aging-related changes, with polyphenol being one of the main cooperators for prevents cardiovascular diseases (CVDs) in aging. In view of this, it is shown that these compounds reduce the mortality rate by guarding senility, configuring aging prevention in prolonging cardiovascular function.

Keywords: Polyphenols, aging, cardiovascular.

1. INTRODUCTION

Aging is a variation of the biological process, capable of reducing the individual's adaptation to the environment, affecting its completeness and corroborating to a higher incidence of cardiovascular diseases (CVDs). It is estimated that by the year 2050, the elderly population (over 65 years) will reach about 1.5 billion, mostly in developing countries [1]. In this age group, CVD will result in 40% of all deaths and rank as the leading cause [2].

In this context, several theories were

raised in order to explain the cellular and molecular mechanisms of aging, giving rise to a unified theory. From this it was defined as a persistent decline of the cellular components, due to the physiological deterioration conceived by non-adaptation during the adult phase, constructing a new evolutionary genetics, what we call senescence. It is characterized by the shortening of telomeres, detected by the cell as damaged DNA. This change causes influence on translation and functionality of vascular and endothelial cellular components [3].

1.1 Changing Young Physiology

The change in young physiology is associated with neurohormonal (eg, reninangiotensin, adrenergic) [4] signaling and autonomous mechanisms of cells, in short, processes that include oxidative stress, protein synthesis and inflammation. Damage to DNA leads to systemic, vascular and cellular changes such as atherosclerosis, hypertension and diabetes (CVDs) [5].

The role of mitochondrial oxidative stress is determinant in the useful life, and mitochondria are essential for the production of ATP via oxidative phosphorylation. Mitochondrial dysfunction occurs due to the appearance of reactive oxygen species (ROS) produced by the NADPH oxidase activation.

However, in addition to increasing NADPH expression, there is also an increase in the expression of eNOS. The eNOS can synthesize nitric oxide (NO), which reacts with superoxide ($O_2^{\bullet-}$), generating nitrite peroxide ($ONOO^-$). Increases $ONOO^-$ inhibits mitochondrial manganese superoxide dismutase (MnSOD) by nitration, resulting in increased $O_2^{\bullet-}$. In addition $O_2^{\bullet-}$ can be reduced to hydrogen peroxide (H_2O_2) by MnSOD [6]. The promoting damage to specific DNA genes, such inactivation of complexes I and IV inhibiting ATP synthesis, repelling the cellular respiration of cardiomyocytes.

The increase of the ROS concentration

can be stimulated by inadaletions catecholamines by angiotensin aldosterone inducing the NADPH oxidase (NOX) activation. Stimulation of the G protein, activates adenylate cyclase which cyclizes ATP in cAMP by increasing PKA, thus inhibiting MnSOD, providing $O_2^{\bullet-}$ and NO^- , corroborating the variation of calcium (Ca^{2+}) function, as well as the Gq protein stimulates PKC in activating NOX producing ROS leading to CVDs associate decreased cardiac function [7].

Accordingly, the active mitochondrial oxidative stress NF-kB, binding it to a sequence of 10 base pairs in the promoter region of the gene coding for the k light chain of the antibody molecules of the B cells (kB), thus inducing apoptosis in the endothelial and muscle cells (FIGURE 1) [8-9].

1.2 Polyphenols in Health Promotion and Cardiovascular Disease Prevention

Polyphenols are secondary plant metabolites, which have effects on bitterness, astringency, color, taste, odor and oxidative stability in food [10]. They are classified into flavonoids and not flavonoids, according to the number of phenol rings and structural elements attached to these rings. Their structural characteristics allow them to act as direct eliminators of free radicals, as the catechol group on ring B, the presence of hydroxyl groups in the 3 and 5-positions, and

the 2,3-double bond in conjunction with a 4-Oxofunction of a carbonyl group on ring C [11].

The French paradox has correlated, for decades, that polyphenols are responsible for the decrease in the incidence of cardiovascular diseases and mortality, because these compounds are able to neutralize the oxidative stress load and influence the signaling pathways of aging, provoking more epidemiological studies that demonstrated this same association.

The present study aims to review, bibliographically, the characteristics of polyphenols with action on cell senescence (*in vitro*), longevity in experimental models, as well as the identification of lifespan promoters (*in vivo*) and of the cardiovascular system.

2. METHODS

The work to be developed will follow the precepts of the exploratory study, which will be developed from already elaborated materials, such as scientific articles that will be accessed in the database Scielo, PUBMED, Google Scholar, with the following descriptors: Apoptosis and Aging, Cardiovascular Aging, Cardiovascular Mortality, Lifespan, Oxidative Stress and Polyphenols and Aging.

The data collection will follow an exploratory and selective, in order to obtain answers to the research problem. For the

construction of this review study, 67 articles were counted between the years 2000 and 2017.

3. RESULTS AND DISCUSSIONS

3.1 Polyphenols in Oxidative Stress Reduction

The first theory on aging, proposed by Harman, in 1956, correlates free radicals and aging, since the species of intracellular reactive oxygen is the main determinant in senescence [12]. Reactive oxygen species (ROS), such as superoxide anion ($O_2^{\bullet-}$), H_2O_2 and hydroxyl radical (HO^{\bullet}), consist of species formed by the partial reduction of oxygen. Mechanisms including NADPH, renin angiotensin aldosterone system, eNOS, AMPK and NF- κ B, accompanied by cardiovascular dysfunction, are involved in the production of ROS (FIGURE 1) [13].

Thus, potential therapeutic strategies with actions in lifespan are discussed. ROS form disulfide bonds with cysteine (amino acid present in proteins and enzymes), attacking the nitrogen by altering its function [13], likewise ROS injures the DNA by reacting with the nitrogenous bases, leading to G:C mitochondrial transition mutations to A:T during mtDNA replication, for example [14].

The structural heterogeneity of the polyphenols allows the inhibition of reactive nitrogen species (RNS) and ROS as a result

of specific arrangements [15], thus blocking the damaging effects to mitochondria and

retarding cellular senescence (TABLE 1).

Figure 1: Molecular mechanisms of cellular senescence

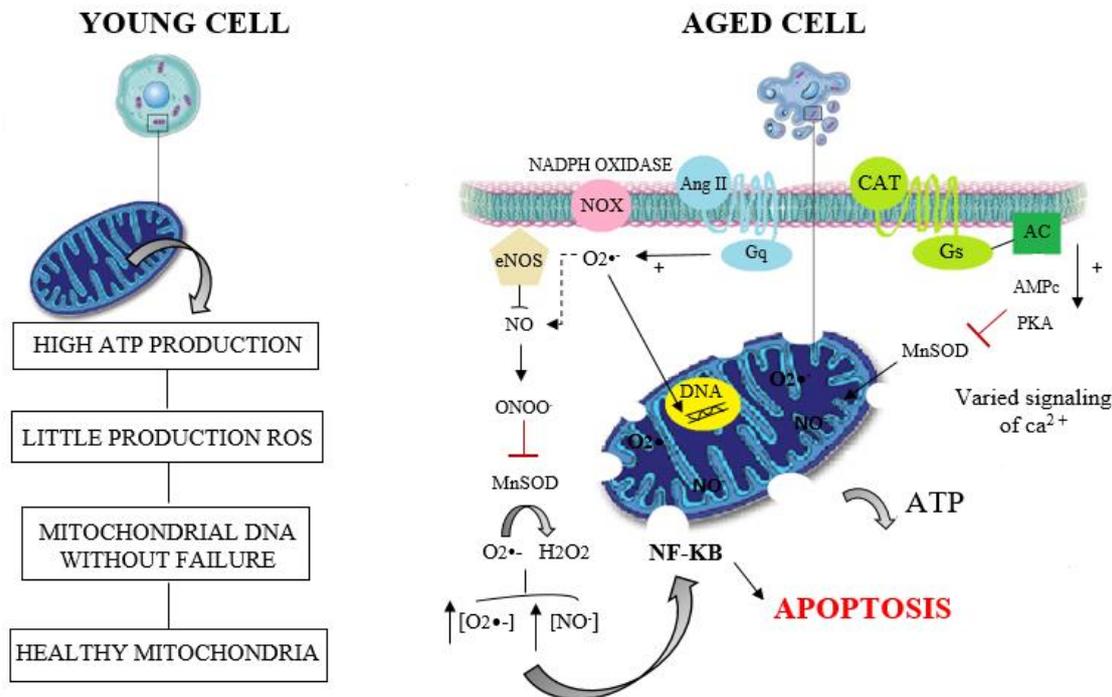


Figure 1 demonstrates the mitochondrial physiology of the young cell and the aged cell. The free radicals produced in aging, cause damage to the DNA, resulting in apoptosis

Resveratrol, a polyphenol present in wines and grapes, has activity in senescence when it indirectly interferes with eNOS by its action on the protein subunits of NADPH, as well as EGCG that mimics NO activity, stimulating cGMP, activating eNOS, which results in vasodilatation, favoring the homeostasis of several biological processes such as cardiac aging.

The NADPH oxidase system is a superoxide anion generator enzyme complex [23] formed by subunits, including p47 and p22 [24]. Quercetin and resveratrol, act on these subunits, respectively, by inhibiting NADPH by translocation.

3.2 Polyphenols in Apoptosis

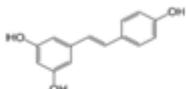
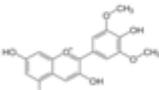
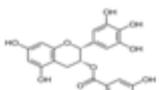
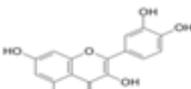
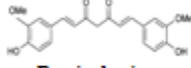
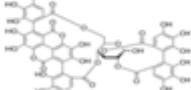
Oxidative stress acts as a second messenger in the activation of the NF- κ B transition factor, consisting of two p65 and p50 subunits [25], which regulates a wide range of processes, such as defense and induced cell death (apoptosis). The hydroxyls, present in the malvidin structure, interact with ROS and RNS, restoring NO activity, preventing the activation of NF- κ B leading to apoptosis. Simultaneously, the curcumin depresses NF- κ B, restricting inflammation.

However, apoptosis is also stimulated by the low activity of eNOS, which is activated primarily by phosphorylation by

the enzyme Akt-kinase (or B protein), which increases the sensitivity of eNOS to basal Ca^{2+} /calmodulin concentrations, thus establishing the function endothelial and muscle cell. The action of this enzyme is reduced in the senescence, the polyphenols,

like the EGCG, act to elevate its function, conferring protection against the apoptosis induced by the oxidative stress. The polyphenols regulates the activity of enzymes and protein that produce the reactive species [26-27].

Table 1: Phenolic compounds with action in cellular senescence

REF.	COMPOUND	CELL	MECHANISM AND EFFECT
[16]	Resveratrol 	Mesenteric artery with endothelium in middle aged rats.	It interacts with eNOS by acting on the subunits of NADPH, preventing the formation of $O_2 \cdot^-$ and the expression of AT1 receptors.
[17]	Malvidin 	Bovine aortic endothelial cell.	It regulates concentrations and NO activity by interacting with ROS and RNS, and inhibit the activation of NF- κ B acting on its ONOO $^-$ intermediate.
[18]	Epigallocatechin-3-gallate (EGCG) 	Aortic of mouse.	It elevates cGMP levels by stimulating the Akt / eNOS pathway, thus leading to vasodilation, reducing cell dysfunction.
[19]	Quercetin 	Aortic of mouse knockout, Apolipoprotein E.	It inhibits the membrane translocation of the p47phox moiety and deactivates the NADPH oxidase complex in MPMs (peritoneal macrophages).
[20-21]	Curcumin 	Vascular cell (muscle).	It inhibits NF- κ B resulting in decreased expression of TNF- α , IL-1 and IL-6.
[22]	Punicalagin 	Cardiomyocytes.	It activates PGC-1 α , as well as expression of complexes I, II, III and IV, favoring the homeostatic production of ATP and active SOD affected by ROS.

Sources: PloS ONE; Chemo-Biological Interactions; Redox Biol; Food and Chemical Toxicology; International Journal of Cardiology; Acta Pharmacol Sin; Scientific Reports.

3.3 Polyphenols in Mitochondrial Biogenesis

The peroxisome proliferator cofactor (PGC-1 α), is a protein complex responsible for increasing the likelihood of a gene being transcribed, interacting with transcription factors but not binding to DNA [28]. Punicalagin acts by activating AMPK,

increasing expression of PGC-1 α , by phosphorylation [29].

Similarly, punicalagin activates superoxide dismutase (SOD), an enzyme that catalyzes $O_2 \cdot^-$ in H_2O_2 , because it undergoes deacetylation by SIRT3, preventing cardiac metabolic disorders [30].

Table 1 shows that polyphenols act in several signaling pathways associated with increased dysfunction of biological processes consisting of changes leading to apoptosis, orchestrated collapse characterized by shrinkage of cells, chromatin condensation and DNA fragmentation, among others [31], disagreeing with longevity.

The longevity is linked to homeostasis which is the balance of aging-related changes [39], as cited in table 2. The experimental models described indicate that the deregulation of the ROS, SOD, GPX, DAF-16, FOXO, p-53 and hsp-16.2 emergent pathways underlies cardiovascular aging.

3.4 Performance of Polyphenols in Emerging Paths

The organism has antioxidant mechanisms, among them, outlined above, the enzyme GPx, which transforms hydrogen peroxide into water [40], and SOD that has its action triggered by oxidative stress, making them the target of components that promote lifespan, as quercetin and anthocyanin. To highlight the anthocyanin that has action in both.

The quercetin, influences senescence increases the translocation of DAF-16 which is a regulator of time and cell resistance to oxidative stress [41], as well as FOXO, similarly activated by the EGCG, also has regulatory activity in the expression of MnSOD [42].

However, EGCG, due to its amplitude of mechanism, acts simultaneously on SIRT1 that mediates the mitochondrial biogenesis and deacetylates the NF-kB transcription cell factor [43-44], inhibiting apoptosis [45].

However, the apoptosis stimulator, p53 [46], is inhibited by curcumin and also by resveratrol, thus increasing DNA stability.

Table 2 encodes that the oxidative stress is vetoed by most of the compounds, among them resveratrol, which in the experimental model *Saccharomyces cerevisiae* elevated lifespan by 70%, making it possible for polyphenols to prolong the shelf life of animals, thus raising interest in studies of their performance in humans (TABLE 3).

The CVD presents a great burden for elderly patients, caregivers and health systems. Structural and functional vessels changes accumulate throughout life, culminating in an increased risk of developing CVDs. The growing elderly population [53] highlights the need to develop new strategies that promote quality of life.

Polyphenols act by nullifying the process of apoptosis and cell resistance by intervening in the pathways that regulate them. The routes are GPx, SOD, DAF-16, FOXO, NF-kB, p53 and their readjustments promote the quality of life.

Table 2: Compounds that promote longevity in experimental models

REF.	COMPOUND	EXPERIMENTAL MODEL	EFFECT
[32]	Anthocyanins	<i>Drosophila melanogaster</i> .	It promoted greater longevity by 18% in flies by activating antioxidant enzymes such as SOD and GPX, reducing oxidative stress.
[33-34]	Flavonol-O-glycosides	Wild-type worms.	It prolongs lifespan by ~ 10% by reducing oxidative damage and suppressing expression of the heat stress response protein hsp-16.2.
[35]	EGCG Epigallocatechin-3-gallate	Wistar rats.	It increases average life by up to 105.0, thus delaying death by 44%. By acting with ROS, they decrease mRNA expressions, transcription NF- κ B and increase the expressions SIRT1 and FOXO3a.
[36]	Quercetin	<i>Caenorhabditis elegans</i> .	It extended the life of <i>C. elegans</i> by 15%. Its action is to eliminate ROS, through its interaction with mitochondrial MnSOD, besides elevating the translocation of the transcription factor FOXO and DAF-16.
[37]	Curcumin	<i>Caenorhabditis elegans</i> .	The longevity stimulated by Curcumin in females of <i>C. Elegans</i> extended by 19% by mitigate aging gene expressions, including p53 and reduce oxidative stress.
[38]	Resveratrol	<i>Saccharomyces Cerevisiae</i> .	The coplanar positioning of the resveratrol rings deacetylates SIRT1 by promoting yeast survival by 70%, since it negatively regulates p53 by increasing DNA stability.

Sources: Food Science Biotechnol; Oxid Med Cell Longev; Current Drug Targets; Aging cell; Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology; Rejuvenation Research; Nature Publishing Group.

3.5 Phenolic Compounds Acting Conversely on Cardiovascular Mortality

Cardiovascular aging is a highly dynamic process. Approaches described in table 3, demonstrate actions in cardiovascular function, altered in age [54]. The insufficiency of antioxidant defense mechanisms is associated with cardiovascular disorders [55]. Resveratrol, therefore, applies extremely important mechanisms by acting on nuclear factor 2 related to erythroid 2 (Nrf2), which is an emerging regulator of cellular resistance to oxidants [56].

However, the oxidizing processes have functional importance for the cells, as in

the oxidative phosphorylation performed in mitochondria. The complete reduction of oxygen leads to the formation of superoxide, a radical that should be decreased by MnSOD, but the function of this enzyme is compromised by age, stimulating, excessively apoptosis [57-58].

Chlorogenic acid acts on the signal transduction of the gene expression of NF- κ B (this being a dose-dependent action), blocking it [59-60], thus repressing apoptosis, making it a strategy for mitochondrial survival, as well as lignan [61]. Similarly, EGCG, which acts on apoptosis by the activation of MnSOD, reestablishes ROS homeostatic levels, making it a potent antioxidant

compound, by the presence of the gallic group in the B ring that reacts with $O_2^{\bullet-}$, leading to

the oxidation of the D ring [62], improving cardiac function and delaying mortality [63].

Table 3: Compounds that promote quality of life in humans

AUTHOR	STUDY OBJECTIVE	RESULT
WU JM./2011	To evaluate the effects of resveratrol on red wine intake.	Resveratrol translocates the Nrf2 transcription factor to the nucleus, regulating antioxidant elements.
SAITO E./2015	To examine mortality, for causes such as heart disease, among other linked green tea consumption and age.	The consumption of ~ 5 cup infusion, per day reduced the risk of death by 0.81-0.94.
MALERBA, S./2013	Systematic review estimated the overall relative risks of mortality, and consumption of chlorogenic acid and other polyphenols.	The antioxidant activity of polyphenols results in a decrease in mortality in middle-aged men and women, with a life extension of 0.98.
TRESSERRA-RIMBAU A./2014	To evaluate the effects between lignan intake and mortality.	Polyphenols reduced the risk of death by 37%, expanding life by 4.8 years.
BUIJSSE, B./2006	To evaluate catechin activity in elderly men and cardiovascular mortality.	Catechin re-establishes NO function, leading to reduction of death by 0.50.
HJARTÅKER, A./2015	To examine the association between the intake of anthocyanins, among others, present in the berries and the risk of mortality.	It reduced from 8 to 10% of mortality of elderly people who had CVD and cancer, reducing also 20% mortality due to stroke.

Sources: Ann N Y Acad Sci; Ann Epidemiol; Eur J Epidemiol; BMC Med; Arch Intern Med; Eur J Nutri.

Therefore, as shown in figure 2, the polyphenols act in several pathways that cause the aging of the cardiovascular system repressing this process.

Cardiovascular dysfunction, stimulated by ROS, afflicts other molecules such as NO, which has properties in vasodilation, membrane permeability control and action in reducing inflammatory factors, balancing the cell [64]. The lack of NO activity is restored by quercetin, as described in Table 3, maximizing shelf life.

Analogously to chlorogenic acid, anthocyanins act by inhibiting NF-kB

dependent mediators [65], reducing inflammation and the aging process triggered by imbalance of the inflammatory state [12].

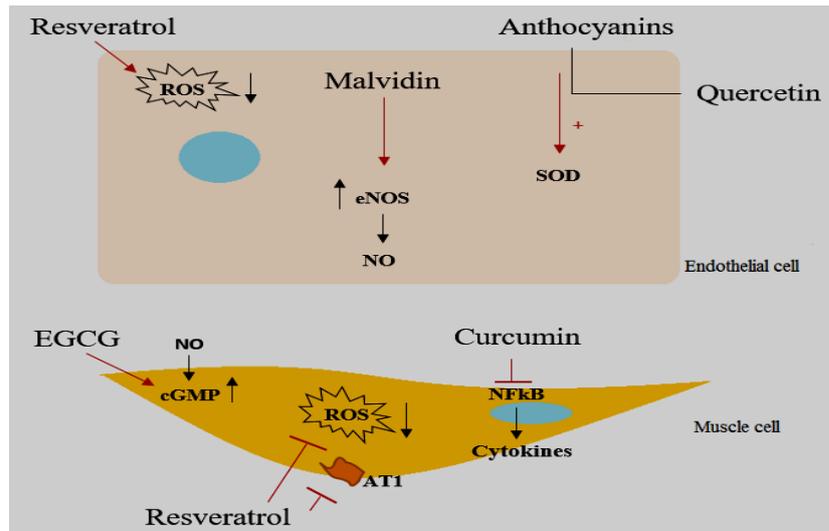
However, the importance of the antioxidant activity of polyphenols demonstrates cardioprotective action, making them adjuvants in the extension of life, since age is one of the main risk factors associated with cardiovascular disease that debilitates the individual, leading to death.

A phenomenon closely related to this is the French paradox that associates resveratrol and the low incidence of mortality [66], as it acts in the emerging

pathways, solving mitochondrial damage and prolonging life, as well as lignan, a present component in the world diet, found in fiber, seeds, grains, vegetables and fruits [67]

prolong life, by consumption, in 4.8 years, preventing the onset of cardiovascular diseases from senility.

Figure 2: Effects of polyphenol on endothelial senescence and muscle cell



Polyphenols have the effect of suppressing ROS, which lead to cellular DNA damage, as well as restoring the activities of ROS and RNS by SOD for example, and the expansion and contraction of the vascular wall, which is performed by eNOS and NO, repressing Thus the oxidative stress that results in apoptosis, limiting aging in the same way by expanding lifespan, by setting up homeostasis.

4. CONCLUSION

Polyphenols can preventing aging, configured lifespan in *in vitro* and *in vivo* studies, including men, women and animals, by its magnitude of structures and mechanisms. They promoted cell homeostasis by slowing the cardiovascular aging process by regulating NF-kB, Akt, SOD, GPx, SIRT1, FOXO, DAF-16, p53, Nrf2. In view of this, it prove yourself that these compounds reduced the mortality rates, which lead to cardiovascular diseases, by acting on the signaling pathways of the process of senescence. In summary, the preponderance of epidemiological and clinical research

indicates, clearly, the veracity of phenolic compounds in protecting the aging cardiac, making it conducive to quality of life.

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