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Review

Polyphenols and AGEs/RAGE axis. Trends and challenges

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ABSTRACT

The formation of advanced glycation end-products (AGEs) is a key pathophysiological event linked not only to the onset and progression of diabetic complications, but also to neurodegeneration, cardiovascular diseases, cancer, and others important human diseases. AGEs contributions to pathophysiology are mainly through the formation of cross-links and by engaging the receptor for advanced glycation end-products (RAGE).

Polyphenols are secondary metabolites found largely in fruits, vegetables, cereals, and beverages, and during many years, important efforts have been made to elucidate their beneficial effects on human health, mainly ascribed to their antioxidant activities.

In the present review, we highlighted the beneficial actions of polyphenols aimed to diminish the harmful consequences of advanced glycation, mainly by the inhibition of ROS formation during glycation, the inhibition of Schiff base, Amadori products, and subsequent dicarbonyls group formation, the activation of the glyoxalase system, as well as by blocking either AGEs-RAGE interaction or cell signaling.

1. Introduction

Advanced glycation end products (AGEs) are a family of compounds that are the products of non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids by the so called Maillard reaction. Although initially described in food browning during thermal processing, its presence in living systems, and particularly their involvement in various pathophysiological context associated to many clinical entities has become AGEs in an intensive field of research. These efforts have been focused on not only to unravel the AGEs formation mechanisms as well as the cellular mechanisms responsible to generate pathological consequences, but also for searching of AGEs inhibitors. There is growing interest in the search of compounds of natural origin that can inhibit glycation. In this context, different natural compounds found in human diet, such as polyphenols, have been found to inhibit protein glycation, mainly from data coming from *in vitro* approaches.

In the present review, literature searching was carried out to identify relevant peer-reviewed research publications devoted to explore the effects of polyphenols on the harmful consequences of advanced glycation, through searching over several online bibliographic electronic databases such as Sciencedirect, PubMed, SciELO, Scopus, Google, Google Scholar, Mendeley, ScienceOpen, SpringerLink and Researchgate. Furthermore, the cross references of the selected manuscript were also taken under consideration through electronic search engines.

2. Ages formation and biological consequences.

The non-enzymatic glycation is a common post-translational modification of some biomolecules and involves the reaction of reducing sugars, such as glucose, fructose, or ribose with the terminal amino groups of proteins, nucleic acids, or phospholipids to form unstable Schiff bases. These compounds evolve into more stable structures called Amadori products, which by a series of rearrangements and/or fragmentation reactions yield the advanced glycation end-products (AGEs) (Ahmed, Thorpe, & Baynes, 1986; Bettiga et al., 2019; Hunt, Bottoms, & Mitchinson, 1993; Hayashi & Namiki, 1980).

Alternatively, reactive dicarbonyl compounds such as methylglyoxal, glyoxal, and 3-deoxyglucosone, are also formed by different pathways, including those derived from the fragmentation of Schiff bases (Namiki pathway), the autoxidation of Amadori products (Hodge-pathway), hexose autoxidation (Wolff pathway). (Thornalley, Yurek-George, & Argirov, 2000; Wolff & Dean, 1987; Thornalley, Langborg, & Minhas, 1999); as well as by-products of the either the glycolytic or polyol pathways (Gugliucci, 2017) and from lipid oxidation (Vistoli et al., 2013). All these dicarbonyl compounds can form isomers with the arginine and lysine residues of proteins, and thus yielding AGEs (see

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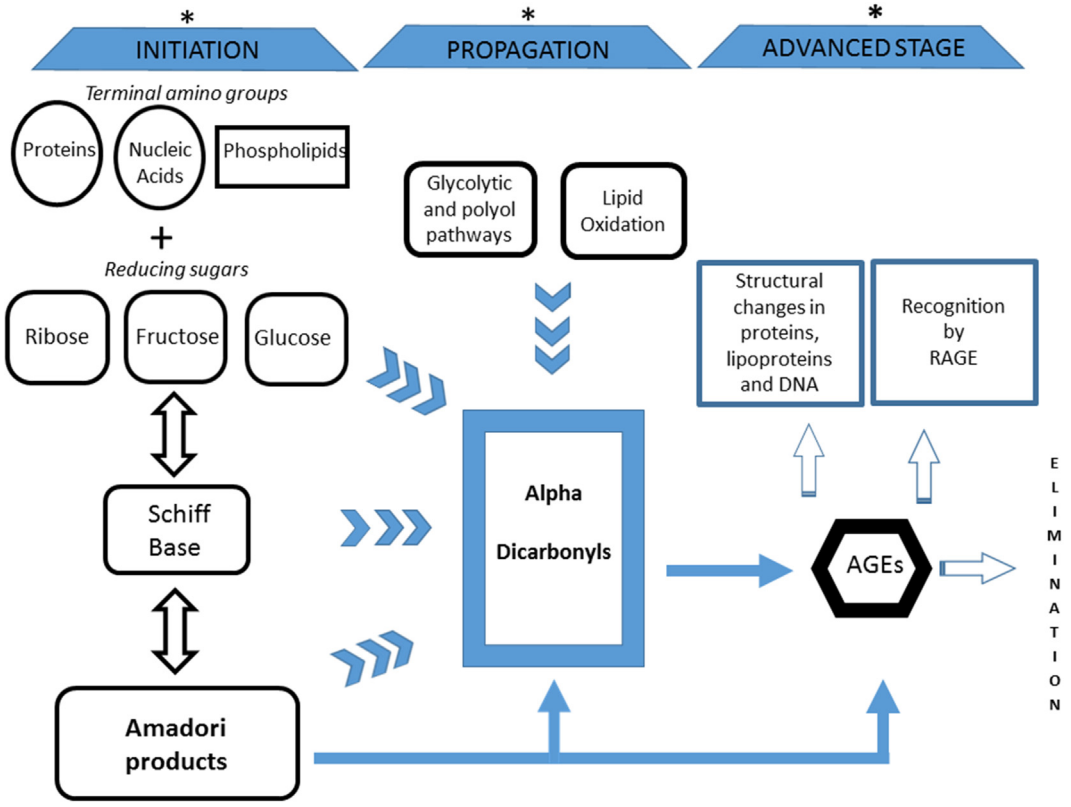


Fig. 1. The formation of Advanced glycation end-products involves the reaction of reducing sugars, such as glucose, fructose, or ribose with the terminal amino groups found in proteins, nucleic acids, or phospholipids to form unstable Schiff bases, which are then converted to more stable structures called Amadori products, which by complex reactions yield advanced glycation end-products (AGEs). In the propagation phase, which is characterized by metal-ion-mediated catalysis and oxygen-induced oxidation reactions, occur the formation of highly reactive dicarbonyls compounds, which in turn also generate a myriad of AGEs. In the advanced stage, these compounds exert their pathophysiological consequences by two main mechanisms; either by inducing structural changes and dysfunction of biomolecules or by interacting with the receptor for advanced glycation end-products (RAGE). Furthermore, AGEs are degraded by enzymatic systems such the Glyoxalases. Polyphenols can interfere or promote reactions in every stage (denoted by asterisks).

Fig. 1).

Glycation is one of the most common types of protein modification. This spontaneous and non-enzymatic reaction affects approximately 0.1–0.2% of the arginine and lysine residues *in vivo* (Thornalley et al., 2003).

In addition to endogenous AGEs formation, dietary intake AGEs could act synergistically to increase the systemic AGEs load. Noteworthy, thermally processed foods and particularly those lipids- and protein-rich foods represent a plentiful source of exogenous AGEs (Vlassara et al., 2002; Uribarri et al., 2005). These dietary AGEs are mainly formed during cooking, by the non-enzymatic browning, also known as the Maillard reaction, which is responsible for the generation of taste, color, and aroma (Hellwig & Henle, 2014).

It is estimated that about 10% of dietary AGEs intake is transported into the circulation, two-thirds of which remained in the body and only one-third of the absorbed AGEs are excreted into the urine within 3 days from ingestion. (Koschinsky et al., 1997; He, Sabol, Mitsuhashi, & Vlassara, 1999).

Although glycation of biomolecules proceeds with a variable rate and extent under physiological conditions, both parameters are markedly affected in several diseases such as diabetes, atherosclerosis, neurodegeneration, chronic kidney disease, cancer, and many other non-infectious diseases, supporting the contributions of these reactions to pathology onset and progression (Uribarri et al., 2015; Chaudhuri et al., 2018; Bettiga et al., 2019).

The formation of advanced glycation end-products has two major mechanisms by which they exerted the disruption of cellular homeostasis. The first one is based on the capacity to induce structural changes on proteins, lipoproteins and DNA (Fournet, Bonté, & Desmoulière, 2018). In this context, glycation of proteins represents the greatest source of variability of modifications in biomolecules with disturbing consequences in homeostasis. Noteworthy, glycation reactions can modify in proteins its site of recognition for enzymes or receptors, and thus resulting in deregulation of recognition, degradation, and turnover of the corresponding proteins (Brownlee, 1995; Taghavi, Habibi-Rezaei, Amani, Saboury, & Moosavi-Movahedi, 2017).

Another event of extreme biological significance is the glycation of extracellular matrix proteins. In this context, glycation reaction can alter either the molecular recognition at specific protein binding sites or the mechanical properties of load-bearing protein such as collagens, mainly due to AGEs crosslinking and thus leading to stiffening of tissues (Reigle et al., 2008; Humphrey, Dufresne, & Schwartz, 2014, Bonnans, Chou, & Werb, 2014; Rojas, Añazco, González, & Araya, 2018).

Enzymes are also targets of the glycation reactions, and thus conformational changes may be induced in the active site, rendering a dysfunctional or even inactive enzyme (Mastorikou, Mackness, Liu, & Mackness, 2008; Morgan, Dean, & Davies, 2002).

Noteworthy, the glycation of enzymes can also have negative consequences in the cellular antioxidant defenses, as reported for the copper-zinc superoxide dismutase, a primary anti-oxidative enzyme that scavenges superoxide anion radicals (Taniguchi, Arai, & Kinoshita, 1989). Glutathione reductase is responsible for maintaining the supply of reduced glutathione as part of its roles in the cellular control of reactive oxygen species. This enzyme is also a target of the glycation reactions, rendering a dysfunctional enzyme and thus reducing intracellular glutathione bioavailability (Banks & Andersen, 2019).

Another set of critical targets of glycation reaction are nucleic acids. Glycation of DNA alters markedly the structure of this macromolecule,

which in turn, leads to depurination, strand breaks and the occurrence of mutational events (Murata-Kamiya, Kamiya, Kaji, & Kasai, 1997; Ahmad et al., 2011).

More interestingly, histones are also targets of non-enzymatic glycation. The role of histones in chromatin packaging is linked to the transcriptional activity of genes (Fischle, Wang, & Allis, 2003) and, therefore play important roles in the epigenetic regulation of gene expression (Jones, 2015).

Noteworthy, different research groups have independently reported glycation of histones may compromise the veracity of chromatin structures and functions (Ansari, Chaudhary, & Dash, 2018; Ashraf et al., 2015; Mir, Uddin, Alam, & Ali, 2017; Gugliucci & Bendayan, 1995).

Furthermore, glycation of biomolecules sometimes may even dampen the whole functioning of biological systems, as reported for the immune system. In this context, glycation can restrict many immunological functions ranging from the impairments of Fc fragment functions in glycated inmmunoglobulins (Dolhofer-Bliesener & Gerbitz, 1990) to a dysfunctional NLRP3 inflammasome-mediated innate immune response (Son et al., 2017).

On the other hand, there are other cellular effects, which are not related to the capacity of glycation reactions to induce structural changes on macromolecules, but rather to the recognition of AGEs by receptors.

3. RAGE/AGEs axis

Several AGEs-binding proteins have been described; most of them are involved in the clearance mechanism of AGEs, mainly through endocytic uptake and degradation (Rojas, Gonzalez, & Añazco, 2018).

However, one of these AGEs-binding proteins, the receptor for advanced glycation products (RAGE), also known as AGER, once engaged; it can generate a robust pro-inflammatory response in many cell types (González, Romero, Rodríguez, Pérez-Castro, & Rojas, 2013; Rojas, Morales, Araya, & Gonzalez, 2017).

Strikingly, ligation of RAGE not only causes an inflammatory gene expression profile but also a positive feed-forward loop, in which inflammatory stimuli activate NF-κB, which induces RAGE expression, followed by a sustained NF-κB activation (Bierhaus et al., 2005).

RAGE engagement induces multiple signaling pathways, including the generation of reactive oxygen species (ROS), mainly due to the activation of NADPH oxidase (NOX) pathway (Wautier et al., 1994; Coughlan et al., 2009; Rojas et al., 2013).

Noteworthy, as the most membrane-proximal event, formin molecule mDia1 binds to the cytoplasmic domain of RAGE, and this interaction is strictly required to activate RAGE-dependent cell signaling responses. Formins such as mDia1 are actin-binding molecules that contribute to signal transduction mechanisms, in part via Rho GTPase signals (Young & Copeland, 2010), and particularly Rac1, which is a key component in NADPH oxidase activation (Hordijk, 2006; Petry, Weitnauer, & Görlach, 2010; Acevedo & González-Billault, 2018).

Far beyond the functional link between RAGE and the activation of NADPH oxidase (NOX) pathway, plasma proteins are extremely susceptible targets for oxidants (Davies, 2016). AOPPs (advanced oxidation protein products) are described as dityrosine-containing cross-linked protein products, which can promote inflammation and thus participate in many pathophysiological disease processes. At present, (AOPPs) are linked to diabetes, chronic renal disease, obesity, immune-mediated inflammatory diseases, neurodegenerative diseases, cancer, metabolic syndrome and atherosclerosis (Cao, Hou, & Nie, 2014; Cristani et al., 2016; Witko-Sarsat et al., 1996; Zhao et al., 2019).

Of note, RAGE is also a receptor of AOPPs and their interaction with RAGE activates NADPH oxidase and thus increasing oxidative stress (Yamamoto & Yamamoto, 2012; Zhou et al., 2012; Wu et al., 2016; Rong et al., 2015).

Oxidative stress and inflammation are indissolubly linked to the pathogenesis of many human diseases. A pivotal player of the inflammatory response is NF-kB, which is a redox-sensitive transcription factor. By activating NF-κB, oxidative stress promotes the expression of pro-inflammatory cytokines and chemokines, and thus promoting the recruitment and activation of leukocytes and resident cells, thereby fueling any inflammatory process (Gloire, Legrand-Poels, & Piette, 2006; Zhang, Wang, et al., 2016; Buelna-Chontal & Zazueta, 2013)

Additionally, it is important to highlight the contribution of ROS to the production of AGEs. In this context, oxidant species derived from both the phagocyte NADPH oxidase or the myeloperoxidase-H2O2-chloride system, promote the formation of AGEs, particularly carboxymethyl lysine (CML), and thus generating an important amplifying loop at inflammation sites (Anderson, Requena, Crowley, Thorpe, & Heinecke, 1999; Anderson & Heinecke, 2003).

Therefore, the searching of molecules able to block either the glycation reaction or RAGE activation and signaling has been regarded as a promising disease-modifying strategy to slow down human aging and disease onset/progression. (Rojas, Morales, Gonzalez, & Araya, 2019; Rowan, Bejarano, & Taylor, 2018; Wautier, Guillausseau , & Wautier, 2017).

In this context, polyphenols are emerging as a very attractive option due not only to their antioxidant and anti-inflammation abilities but also for their potential as antiglycation agents.

4. Polyphenols and RAGE/AGEs axis.

Polyphenols are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens (Beckman, 2000). They are found largely in fruits, vegetables, cereals, and beverages. In food, polyphenols may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability (McDougall, 2017).

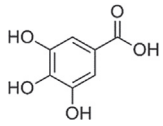
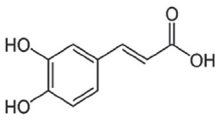
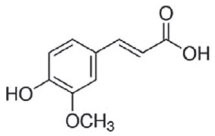
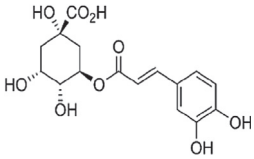
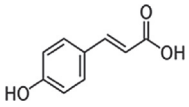
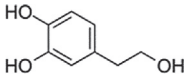
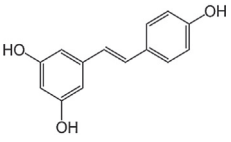
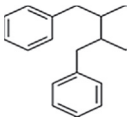
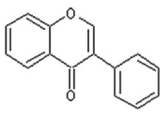
This very heterogeneous family of compounds have attracted the attention of the scientific community throughout the world due to their possible beneficial effects on human health (Vauzour, Rodriguez-Mateos, Corona, Oruna-Concha, & Spencer, 2010; Cory, Passarelli, Szeto, Tamez, & Mattei, 2018; Putnik et al., 2018, Del Rio et al., 2013; Li et al., 2018, Zhang, Tao, Wang, Chen, & Wang, 2015; Fraga, Croft, Kennedy, & Tomás-Barberán, 2019; Xing, Zhang, Qi, Tsao, & Mine, 2019; Khan & Mukhtar, 2018; Ramírez-Garza et al., 2018; Yahfoufi, Alsadi, Jambi, & Matar, 2018; Cianciosi et al., 2018; Serino & Salazar, 2018; Del Turco & Basta, 2017

Polyphenols are generally classified into five different groups, including flavonoids, phenolic acids, phenolic alcohols, stilbenes and lignans. Flavonoids are further divided into flavones, flavanones, flavonols, flavanols, isoflavones, and phenolic acids can be subdivided into hydroxybenzoic and hydroxycinnamic acid derivatives (ĎArchivio et al., 2007; Han, Shen, & Lou, 2007).

Noteworthy, polyphenols are able to diminish the harmful consequences of advanced glycation by different mechanisms, mainly by the inhibition of ROS formation during glycation, the inhibition of Schiff base, Amadori products, and subsequent dicarbonyls group formation, the activation of detoxification, particularly through the glyoxalase system, as well as by blocking of AGEs-RAGE interaction (see Table 1).

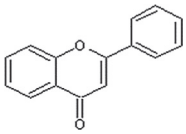
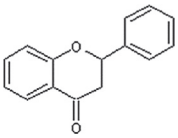
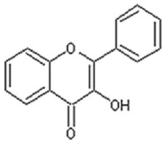
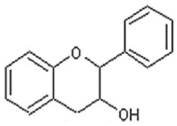
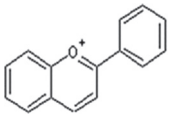
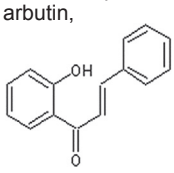
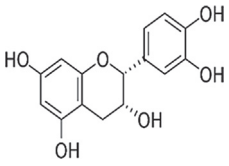
In the present review, literature searching was carried out to identify relevant peer-reviewed research publications devoted to explore the effects of polyphenols on the harmful consequences of advanced glycation, through searching over several online bibliographic electronic databases such as Sciencedirect, PubMed, SciELO, Scopus, Google, Google Scholar, Mendeley, ScienceOpen, SpringerLink and Researchgate. Furthermore, the cross references of the selected manuscript were also taken into consideration through electronic search engines.

Table 1
Antiglycation activities of polyphenols.

Compounds (Examples)	Dietary Sources (Examples)	Mechanisms of action	References
Phenolic acids			
-Gallic acid 	Coffee, pear, apple, basil, oregano	-Radical scavenger -Ion metal chelating activity -Trapping dicarbonyls -Attenuate RAGE expression	(Umadevi et al., 2014; Khangholi et al., 2016; Yeh, Hsia, Lee, & Wu, 2017; Gao, Hu, Hu, & Yang, 2019; Gu, Howell, Dunshea & Suleri, 2019)
-Caffeic acid 	Coffee, tea, wine, pear, apple, basil, oregano, carrots, berries tomatoes, propolis.	-Radical scavenger -Ion metal chelating activity -Trapping dicarbonyls -Attenuate RAGE expression	(Gugliucci et al., 2009; Genaro-Mattos et al., 2015; El-Seedi et al., 2017; Yeh et al., 2017; Ghelani et al., 2018; Gu et al., 2019)
-Ferulic acid 	Whole grains, spinach, parsley, grapes, cereal seeds.	-Radical scavenger -Ion metal chelating activity -Suppression RAGE signaling and expression.	(El-Seedi et al., 2017; Yeh et al., 2017; Zduńska, Dana, Kolodziejczak, & Rotsztejn, 2018; Gu et al., 2019; Chaudhary et al., 2019)
-Chlorogenic acid 	Coffee, tea, mate, many fruits, vegetables	-Radical scavenger -Ion metal chelating activity	(El-Seedi et al., 2017; Yeh et al., 2017; Tajik, Tajik, Mack, & Enck, 2017; Justino et al., 2018; Bains & Gugliucci, 2017; Fernandez-Gomez et al., 2018; Gu et al., 2019)
-Coumaric acid 	Peanuts, beans, tomatoes, carrots, basil, garlic, red wine, vinegar, barley grain	-Radical scavenger -Trapping dicarbonyls	(El-Seedi et al., 2017; Yeh et al., 2017; Gu et al., 2019; Shen et al., 2019; Sabitha et al., 2019)
Phenolic alcohols			
Hydroxytyrosol 	Olive, Olive oils, Olive leaf	-Radical scavenger -Ion metal chelating activity.	(El-Seedi et al., 2017; Navarro, Morales, & Ramos, 2017; Yeh et al., 2017 Gorzynik-Debicka et al., 2018; Serreli & Deiana, 2018; de Las Hazas, Rubio, Macia, & Motilva, 2018; Gu et al., 2019)
Stilbenes			
esveratrol 	Grape skins and seeds, Berries, peanuts, cocoa	-Radical scavenger. -Trapping dicarbonyls -Inhibit RAGE expression -Activation SIRT-1. -Inhibit activation of NF-κB.	(Khazaei et al., 2016; Sarubbo, Esteban, Miralles, & Moranta, 2018; Yeh et al., 2017; Crascì et al., 2018; Salehi et al, 2018; Yılmaz et al., 2018; Wang et al., 2019; Yu, Tao, Zhao, Hu, & Wang, 2018)
Lignans			
Pinoresinol, Sesamin. 	Flax, sunflower, sesame, and pumpkin seeds	-Radical scavenger.	(Pilar et al., 2017; Yeh et al., 2017; Liu et al., 2018; Rodríguez-García, Sánchez-Quesada, Toledo, Delgado-Rodríguez, & Gaforio, 2019; Das & Devi, 2019)
Flavonoids			
Isoflavones: Genistein, daidzein 	Soyabeans and other leguminous	-Radical scavenger -Trapping dicarbonyls.	(Yeh et al., 2017; Zihao & Qingrong, 2017; Crascì et al., 2018; Lutz, Fuentes, Ávila, Alarcón, & Palomo, 2019; Wang et al., 2019, Gu et al., 2019)
	Celery, parsley, red peppers, chamomile, mint, capsicum, citrus fruits, honey, propolis.	-Radical scavenger -Trapping dicarbonyls.	(Panche, Diwan, & Chandra, 2016; Yeh et al., 2017; Hwang et al., 2018; Gu et al., 2019; Karak, 2019)

(*continued on next page*)

Table 1 (*continued*)

Compounds (Examples)	Dietary Sources (Examples)	Mechanisms of action	References
Flavones: Luteolin, crysin 			
Flavanones: Hesperitin, naringenin 	oranges, lemons and grapes	-Radical scavenger -Trapping dicarbonyls.	(Panche et al., 2016; Yeh et al., 2017; Gu et al., 2019; Karak, 2019)
Flavonols: quercetin, rutin kaempferol, 	onion, leek, broccoli, berries, cocoa, cranberries, kale, celery, lettuce, ripe tomatoes, carrots, tea and red wine	-Radical scavenger -Trapping dicarbonyls -Ion metal chelating activity -Increasing Glo 1 activity	(Panche et al., 2016; Frandsen & Narayanasamy, 2017; Bhuiyan et al., 2017; Nazrul, Bhuiyan, Mitsuhash, Sigetomi, & Ubukata, 2017; Yeh et al., 2017; Crascì et al., 2018; Frandsen & Narayanasamy, 2018; Gu et al., 2019)
Flavanols: catechins, gallocatechins 	grapes, wine, cocoa, beans green tea, pears, apricots, bananas, apples, blueberries, peaches	-Radical scavenger. -Trapping dicarbonyls. -Interfering RAGE signaling. -Suppressing RAGE expression.	Panche et al., 2016; Julius & Hopper, 2017; Yeh et al., 2017; Crascì et al., 2018; Kanlaya & Thongboonkerd, 2019; Gu et al., 2019)
Anthocyanins: Delphinidin, cyanidin, malvidin. 	cranberries, black currants, red grapes, merlot grapes, berries, red wine	-Trapping dicarbonyls.	(Yoon & Shim, 2015; Panche et al., 2016; Yeh et al., 2017; Zihao & Qingrong, 2017; Crascì et al., 2018; Gu et al., 2019)
Chalcons: phloridzin, arbutin, 	Apple, tomatoes, pears, berries, and certain wheat products	-Trapping dicarbonyls.	(Panche et al., 2016; Yeh et al., 2017; Gu et al., 2019; Zhou et al., 2019)
Tannins			
Procyanidins 	cocoa, chocolate, apples, grapes berries, unripened fruits, red wine, tea, pomegranate peel	-Trapping dicarbonyls. - Radical scavenging. -Ion metal chelating activity. -Suppressing RAGE signaling -Inhibiting NF-κB activation	(Jovanovic et al., 2017; Kato et al., 2017; Yeh et al., 2017; Zihao & Qingrong, 2017; Gourlay & Constabel, 2019, Rauf et al., 2019)

4.1. Inhibition of ROS formation during glycation.

It is widely recognized that the early stage of the Maillard reaction is accompanied by the production of a large amount of free radicals (Rizzi, 2003). In addition, the intermediate Schiff bases are also prone to oxidation and then to produce free radicals and reactive carbonyl groups. Therefore, at the early stage of glycation, capturing free radicals and decreasing the production of reactive carbonyl and dicarbonyl groups can inhibit the glycation function (Yeh et al., 2017).

A compelling body of evidence suggests that the inhibition of protein glycation by polyphenols is based on their antioxidant properties, since the pioneering works of (Jiang, Woollard, & Wolff, 1990; Sadowska-Bartosz and Bartosz, 2015). In fact, the antiglycation activity strongly correlates with the free radical scavenging activity and polyphenols contents (Ramkissoon, Mahomoodally, Ahmed, & Subratty, 2013; Harris et al., 2014)

Polyphenols are strong antioxidants that can not only neutralize free radicals but also suppress the generation of free radicals, thus reducing the rate of oxidation by inhibiting the formation of or deactivating the active species and precursors of free radicals. More frequently, they act

as direct radical scavengers of the lipid peroxidation chain reactions (chain breakers). Chain-breakers donate an electron to the free radical, neutralizing the radicals and themselves becoming stable (less reactive) radicals, thus stopping the chain reactions (Wolff, Jiang, & Hunt, 1991; Tsao, 2010; Pietta, 2000; Guo, Hsieh, & Hu, 2009)

Many polyphenols, such as catechins, proanthocyanidins, anthocyanin, stilbenoids, and flavonols have been reported to inhibit AGEs formation (Tagliazucchi, Martini & Conte, 2019; Sun, Shen, Zhou & Wang, 2019; Yılmaz et al., 2018; Yeh et al., 2017; Crascì, Lauro, Puglisi, & Panico, 2018; Perron & Brumaghim, 2009; Hou, Wang, Liu, Song, & Liu, 2014; Nagasawa et al., 2003; Liu et al., 2013; Seo, Seo, Han, Ki, & Shin, 2014; Dearlove, Greespam, Hartle, Swanson, & Hargrove, 2008; Ho, Wu, Lin, & Tang, 2010; Lavelli, Corey, Kerr, & Vantaggi, 2011; Harsha, Lavelli, & Scarafoni, 2014; Kazeem, Akanji, Hafizur, & Choundhary, 2012; Sadowska-Bartosz, Galiniak, & Bartosz, 2014, Wu & Yen, 2005).

Additionally, chlorogenic acids, a related polyphenol family of esters, including hydroxycinnamic acids (caffeic acid, ferulic acid, and p-coumaric acid), which represent an abundant group of plant polyphenols presented in the human diet, are also potent inhibitors of protein glycation (Kim et al., 2011; Bains & Gugliucci, 2017; Justino et al., 2018)).

4.2. Chelation of transition metal ions

The role of oxidation reactions in glucose-induced modifications of proteins has been suggested since the late '80s (Wolff & Dean, 1987).

Noteworthy, in hyperglycemic conditions, transition metals in the presence of oxygen catalyze autoxidation of glucose or lipid peroxidation (Hayase et al., 1996). Alterations in iron and copper homeostasis are hallmarks in diabetes, evidenced by deposition of iron and copper in heart, kidney, and other tissues (Backe, Moen, Ellervik, Hansen, & Mandrup-Poulsen, 2016; Qiu, Zhang, Zhu, Wu, & Liang, 2017; Lowe, Taveira-da-Silva, & Hilário-Souzam, 2017; Zheng, Li, Wang, & Cai, 2008; Urui-Adams & Keen, 2005; Fumitaka, Takeshi, Junichi, & Masatomo, 1996).

Of note, polyphenols-enriched extract from Guava leaves inhibited Amadori product formation in a dose-dependent manner through chelating activity mechanism (Wu, Hsieh, Wang, & Chen, 2009). Chlorogenic acids represent an abundant group of plant polyphenols widely present in the human diet also inhibit AGEs formation by metal chelation (Gugliucci, Bastos, Schulze, & Souza, 2009)

Rutin, a citrus flavonoid, also possesses chelating properties and decreases the Fenton reaction as a source of free radical formation (Kostyuk, Potapovich, Kostyuk, & Cherian, 2007). Caffeic acid is reported to bind to iron ions and prevent the oxidative consequences of the Fenton reaction, including lipid peroxidation, DMPO hydroxylation and 2-deoxyribose oxidative degradation (Genaro-Mattos, Maurício, Rettori, Alonso, & Hermes-Lima, 2015). These findings deserves particular attention considering that glycation of heme proteins effectively released free iron from the heme moiety, which in turn can catalyze the Haber-Weiss reaction producing free radicals, particularly hydroxyl (OH) radicals, and thus increasing oxidative stress (Ghelani, Razmovski-Naumovski, Pragada, & Nammi, 2018),

Although many polyphenols are reported as metal ion chelators, it is in this particular biological activity where they exhibit the most significant differences concerning their molecular structure (Amić et al., 2007). In one recent study comparing the chelating capacity of 10 polyphenols, the cathecol moiety, which is present in many other polyphenolic structures, seems to be an essential functional group for metal chelation (Bhuiyan, Mitsuhashi, Sigetomi, & Ubukata, 2017).

4.3. Trapping dicarbonyls

As already mentioned, either the fragmentation of Schiff bases (Namiki pathway), the autoxidation of Amadori products (Hodge-pathway), the hexose autoxidation (Wolff pathway), or by-products from the glycolytic or polyol pathways, can render new reactive dicarbonyl intermediates, such as methylglyoxal (MGO) and glyoxal (GO). These dicarbonyls can then modify proteins to form AGEs of various chemical structures (Singh, Barden, Mori, & Beilin, 2001; Jakus & Rietbrock, 2004; Thornalley et al., 2000).

The increase in reactive dicarbonyl intermediates, also known as “carbonyl stress“, is a consequence of hyperglycemia in diabetes (Brownlee, 2001; Dalle-Donne, Rossi, Giustarini, Milzani, & Colombo, 2003; Rabbani & Thornalley, 2015).

In this context, the trapping capacity of dicarbonyls compounds has been reported for some polyphenols. That is the case for (−)-epigallocatechin-3-gallate (EGCG), the major bioactive green tea polyphenol, which can efficiently trap reactive dicarbonyl compounds (MGO or GO) (Sang et al., 2007). Additionally, both phloretin and its glucoside, phloridzin, the major bioactive apple polyphenols can efficiently trap reactive MGO or GO (Shao et al., 2008; Zhou, Gong, & Wang, 2019).

The same activities have been also reported for resveratrol, quercetin, (+)-catechin, (−)-epicatechin, chlorogenic acid and [6]-gingerol (Sampath, Zhu, Sang, & Ahmedna, 2016; Bhuiyan et al., 2017; Kahngholi et al., 2016; Kim, Zhuo, Wang, Lee, & Lim, 2018; Yılmaz et al., 2018). Genistein, a naturally occurring isoflavone derived from soy products, also shows significant trapping effects of MGO (Lv, Shao, Chen, Ho, & Sang, 2011).

Furthermore, procyanidins widely present in various species of berries (blueberries, blackberries, strawberries, raspberries, cranberries) as well as in flowers of the ancient Magnolia genus, prevented AGEs formation by trapping α-dicarbonyl compounds (Wang, Yagiz, Buran, Nunes, & Gu, 2011; Kato et al., 2017).

Of note, it has been suggested that dicarbonyls trapping functions is supported by the presence of many hydroxyl groups found on the basic structure of the phenolic acid (Yeh et al., 2017; Khangholi, Majid, Berwary, Ahmad, & Aziz, 2016; Cai et al., 2011)

4.4. Activation of detoxification: The glyoxalase system

The glyoxalase pathway facilitates the neutralization of highly reactive dicarbonyls, being the methylglyoxal (MG) the principal target, which is converted to d-lactate (Allaman, Belanger, & Magistretti, 2015). Therefore, increasing the expression of Glo1 seems to an effective strategy to counter dicarbonyl stress (Xue et al., 2012).

Flavonoids have shown effectiveness in the modulation of the glyoxalase pathway and MG detoxification. The flavonoids morin and quercetin increased Glo 1 activity and glutathione (GSH) concentration while reducing the concentration of MG (Frandsen & Narayanasamy, 2017; Frandsen & Narayanasamy, 2018).

Noteworthy, in a clinical trial conducted in obese subjects, pharmaceutical doses of trans-resveratrol (tRES) and hesperetin (HESP) coformulation produced a 22% increase in Glo1 activity of peripheral blood mononuclear cells (Xue et al., 2016).

These results have open a new perspective to the use of polyphenols as small-molecule inducers of Glo1, by exploiting the ARE/Nrf2-dependent GLO1 gene. transcription (Rabbani & Thornalley, 2019).

However, the action of polyphenols on glyoxalase pathways seems to be controversial, because curcumin, baicalein, luteolin, and isolupalbigenin have been reported to inhibit *in vitro* the glyoxalase system (Santel et al., 2011; Takasawa et al., 2008; Zhang, Zhai, et al., 2016).

Noteworthy, structure-activity relationship analysis suggests that the hydroxy groups at the B ring in the basic structure of flavonoids seem to contribute to glyoxalase inhibitory activity (Takasawa et al., 2008).

4.5. Interfering RAGE expression and signaling.

(−)-Epigallocatechin gallate exhibits protective effects against

AGEs-induced injury not only through its antioxidative properties but also by interfering with AGEs-RAGE interaction mediated pathways (Lee & Lee, 2007; Burckhardt et al., 2008; Kanlaya & Thongboonkerd, 2019).

A polyphenols-enriched preparation from *Hibiscus sabdariffa*, mainly composed by protocatechuic acid, catechin, epigallocatechin, caffeic acid, and epigallocatechin gallate was able to suppress RAGE expression in both *in vitro* and *in vivo* models (Huang et al., 2009; Peng et al., 2011).

Additionally, gallic acid a hydroxybenzoic acid occurring mostly in certain red fruits, black radish, and onion can attenuate RAGE expression (Umadevi, Gopi, & Elangovan, 2014).

The case of resveratrol is particularly interesting because it can inhibit not only RAGE expression (Khazaei et al., 2016; Moridi et al., 2015) by a mechanism involving the activation of peroxisome proliferator-activated receptor (PPAR)-gamma (Zhang et al., 2010), but also by interfering RAGE signaling cascade (Buttari et al., 2013).

The inhibition of RAGE expression by elevating PPAR-gamma activity seems to be quite interesting, considering another member of the polyphenols family; curcumin can suppress RAGE expression by the same mechanism (Lin, Tang, Kang, Feng, & Chen, 2012).

Of note, interesting efforts have been recently made in the field of molecular docking, to model the interaction between a small molecule and a protein at the atomic level. Recently, it has been reported that curcumin can bind to RAGE with a strong binding affinity (Sriramoju & Goetz, 2019), and thus blocking the interaction with ligands.

Finally, it is worth to be mentioned the effects of polyphenols to SIRT1, a member of the sirtuin family. SIRT1 can inhibit the NF-κB signaling pathway by deacetylating lysine 310 of RelA/p65 subunit of NF-kB (Rahman & Islam, 2011).

Activation of NF-kB is linked to transcription of RAGE gene itself. In this context, it is important to highlight that many polyphenols, including quercetin, silibinin, daidzein, curcumin phloridzin, resveratrol and even the S17834, a synthetic polyphenol, can activate NAD-dependent deacetylase sirtuin-1 (SIRT1) (Ayissi, Ebrahimi, & Schluesenner, 2014; Sarubbo, Esteban, Miralles, & Moranta, 2018), and as consequence, inhibit the transcription of RAGE.

5. Concluding remarks and future challenges

At present, a compelling body of evidence demonstrates the beneficial effects of polyphenols on human health. Most of the published work supporting that conclusion suggest that the putative beneficial effects of polyphenols are frequently ascribed to their antioxidant activity (Tresserra-Rimbau, Lamuela-Raventos, & Moreno, 2018). However, recent data suggest that polyphenols can exert their beneficial effects by a compendium of mechanisms, other than their antioxidant activities, such the activation of transcription factors involved in antioxidant responsive capacity, metal chelating, and their capacity to bind to several proteins and thus impacting cellular homeostasis. In this context, the capacity of polyphenols to modulate the RAGE/AGEs axis deserves particular attention considering that the searching of molecules able to block either the glycation reaction or RAGE activation and signaling has been regarded as a promising disease-modifying strategy to slow down human aging and disease onset/progression. Most data concerning the activity of polyphenols on modulating RAGE/AGEs axis activation have been mainly derived from both *in vitro* and *in vivo* models. At this point, it is necessary to go a step further and more research is needed, particularly on subjects affected by pathologies where the RAGE/AGEs axis is markedly activated.

Finally, to face up this new challenge, researchers must keep in mind some aspects to assess any beneficial effects of polyphenols, including the anti-glycation activity (Mena & Del Rio, 2018).

Extrapolation of results of *in vitro* studies on the *in vivo* situation should viewed with caution, because of many crucial elements have not been considered in a plethora of data obtained from *in vitro* assays.

Among these factors are, mechanisms of glycation, selected dosages, experimental designs reflecting a physiological approach, as well as bioavailability problems. Although glucose is the bodýs most prevalent reducing sugars, it is important to highlight that aldehyde isoform of glucose is only the 0, 2% of whole pool, therefore glucose is one of the least active sugars in relation to glycation (Krautwald & Münch, 2010). In fact, there is a consensus for their reactivity in the glycation reaction, being the sequence ribose > fructose > glucose (Aragno & Mastrocola, 2017). However, glucose is still the main sugar used in the vast majority of *in vitro* assays.

Quite interesting are the data showing that the inhibition of glycation by polyphenols only resulted when the protein target (BSA) was pre-incubated with phenolic acids, under glycoxidative conditions at low glucose concentrations (glucose 5 or 10 mM plus H2O2 10 nM), and thus suggesting that oxidative stress plays an important role in glycation in normoglycaemia (Vlassopoulos, Lean, & Combet, 2014). In this context, it is important to highlight that although AGEs formation is markedly accelerated in diabetes because of the increased availability of glucose; the reaction occurs at a constant but slow rate in the normal body, starting in early embryonic development, and accumulate with time, being relevant in the pathophysiology of ageing.

Another important factor to be considered is the relative concentrations of both the reactants and inhibitors. In a classical glycation reaction protocol, glucose is used up to 500 mM, compared with the 7 mM or higher on two separate tests for diabetes diagnosis and the 5,5mM reported as the global mean fasting blood level (Danaei et al., 2011).

Similar situations are observed for the concentrations of polyphenols tested *in vitro*, when important differences are observed between the tested concentrations and the blood levels reported after a long-term feeding intervention (Vassopoulos, Lean & Combet 2014)

Marked differences in bioavailability have been reported for different members of the family; mainly defined by the facts that most polyphenols are present in food as glycosides, some of them are even hydrolyzed in the intestine, and gut microbiota is a key factor in determining the metabolic fate of polyphenols (Manach, Scalbert, Morand, Remesy, & Jimenez, 2004; Duda-Chodak, Tarko, Satora, & Sroka, 2015; Williamson & Clifford, 2017; Bento-Silva et al., 2019; Kawabata, Yoshioka, & Terao, 2019).

Furthermore, polyphenols can, selectively modulate the intestinal microbiome, therefore, stratification in clinical trials according to metabotypes is necessary to fully assess the biological activity of polyphenols (Espín, González-Sarrías, & Tomás-Barberán, 2017; Milenkovic et al., 2017; Yuan et al., 2018; Pavlidou, Giaginis, Fasoulas, & Petridis, 2018; Rowland et al., 2018; Shortt et al., 2018). Therefore, and considering the growing body of revealing evidences, the effects of the microbiota should be considered when discussing the health effects of polyphenols. In addition, caution is needed in interpreting results derived from animal models, because of the marked differences in microbiota between rodent and humans.

In summary, evidence-based well-designed placebo-controlled, double-blind preclinical/clinical trials on large samples, considering different ethnicities, varying age groups, genders, socioeconomic status, well-accepted testing biomarkers, as well as the of significant and astringent intervention methods, are required to validate the health effects of polyphenols. In this context, and although different trials have provided evidences that polyphenols can prevent protein glycation *in vivo* (Palma-Duran, Vlassopoulos, Lean, Govan, & Combet, 2017; Del Turco & Basta, 2016), some discrepancies still remains, probably due to very short intervention periods as well as not using any biomarker indicating that an increase of serum/urine polyphenol levels has been achieved during the intervention.

Nevertheless, and being conscious of the limitations already mentioned, these results have open up a new challenge for healthy food formulation based on polyphenolic-enriched foods in order to prevent the deleterious effects of AGEs on human health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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