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REVIEW ARTICLE

The Action of Polyphenols in Diabetes Mellitus and Alzheimer's Disease: A Common Agent for Overlapping Pathologies

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Abstract: Diabetes Mellitus (DM) and Alzheimer's disease (AD) are two prevalent diseases in modern societies, which are caused mainly by current lifestyle, aging and genetic alterations. It has already been demonstrated that these two diseases are associated, since individuals suffering from DM are prone to develop AD. Conversely, it is also known that individuals with AD are more susceptible to DM, namely type 2 diabetes (T2DM). Therefore, these two pathologies, although completely different in terms of symptomatology, end up sharing several mechanisms at the molecular level, with the most obvious being the increase of oxidative stress and inflammation.

Polyphenols are natural compounds widely spread in fruits and vegetables whose dietary intake has been considered inversely proportional to the incidence of DM and AD. So, it is believed that this group of phytochemicals may have preventive and therapeutic potential, not only by reducing the risk and delaying the development of these pathologies, but also by improving brain's metabolic profile and cognitive function.

The aim of this review is to understand the extent to which DM and AD are related pathologies, the degree of similarity and the relationship between them, to detail the molecular mechanisms by which polyphenols may exert a protective effect, such as antioxidant and anti-inflammatory effects, and highlight possible advantages of their use as common preventive and therapeutic alternatives.

Keywords: Polyphenols, diabetes mellitus, alzheimer's disease, diabetes mellitus and alzheimer's disease link, antidiabetic therapy, neuroprotection.

1. INTRODUCTION

Lifestyle changes and increased longevity of the population have made more prone the emergence of diseases triggered by imbalanced diets and aging, as is the case of Diabetes Mellitus (DM) and Alzheimer's disease (AD) [1, 2]. DM is one of the most prevalent chronic metabolic diseases in developed countries [3]. Globally, the prevalence of DM has doubled, as the number of adults suffering from DM reached 425 million in 2017 [1], compared to 171 million at the beginning of the 21st century [3]. According to recent projections, this number will continue to rise, and it is expected that by 2045 about 629 million adults will suffer from DM [1]. Alarmingly, there is also a noticeable increasing trend of DM onset among children and adolescents [4]. Meanwhile, AD is the most common neurodegenerative disease worldwide, leading to 60-70% of all cases of dementia [5, 6]. In 2016, nearly 50 million people had AD and it is predicted that by 2050 the number of people affected will be more than 131 million, as the number is expected to double every 20 years [7]. Therefore, DM and AD are a rising trend, affecting more people each year, and present the risk of becoming the major public health problems of the near future, contributing to higher morbidity, disability and mortality [3, 8]. Although the projected increase in DM and AD cases is derived from population growth and aging, the main cause can also be attributed to an increase in risk factors for these diseases [1, 7]. DM and AD are multifactorial diseases that result from a combination of genetic, epigenetic and lifestyle risk factors [9, 10]. As such, common risk factors for these pathologies include advanced age, family history, unbalanced diet, physi-

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cal inactivity, metabolic diseases and smoking [1, 4, 7, 9]. Therefore, a healthy lifestyle is fundamental to reduce risk factors and prevent the development of DM and AD [4, 11].

Interestingly, a study by Liebson *et al.* [12] suggested that DM increased the risk of an individual developing AD. In fact, patients with DM often experience a sharp decline in cognitive function [13, 14]. Despite this, it is not only DM that contributes to AD, as it is known that a large percentage of patients with AD present altered blood glucose levels, which makes them more likely to develop DM [15]. Several studies have evidenced that these diseases are intertwined [13, 14, 16, 17], and therefore, it is important to understand how they are associated and find solutions to combat these two pathologies. However, this is a subject of some controversy [18]. In this context, many studies have been conducted to search for drugs capable of curbing these diseases [19-23] and to search for therapeutic alternatives more affordable and accessible to the population [24-26]. Among DM and AD risk factors, diet is the most easily modifiable [4, 25], which led to an increasing search of nutraceuticals and other natural compounds able not only of protecting against these pathologies, but also able to curb some of its main symptoms [24-27].

In recent years, the number of studies related to phenolic compounds has rapidly increased. This growing interest is related to the recognition of polyphenols as abundant components of our diet showing antioxidant properties. It has been demonstrated that polyphenols play a beneficial role in various diseases such as cancer, cardiovascular diseases, DM, neurodegenerative diseases and many others. However, polyphenols as bioactive substances present in various foods, including a large variety of fruits, nuts, spices, vegetables and herbal infusions, are now the object of study of several researches, not only for their antioxidant properties, but also for the involvement in several other cellular and enzymatic mechanisms where they are believed to have an important role [28]. For that reason, several studies have emerged illustrating that polyphenols are potential multifunctional agents capable of delaying the onset or the progression of these pathologies. [27, 29-31].

This review aims to show the association between DM and AD and to find therapeutic alternatives to prevent and treat both diseases through nutraceuticals consumption, as is the case of polyphenols. Extensively recognized beneficial phenolic compounds and representatives of the most important classes/subclasses, namely catechins, resveratrol and curcumin, as well as others that have been more recently studied, specifically luteolin, quercetin, genistein and gallic acid, are discussed in this review to give a broad perspective of the subject and present new advances in the field. Thus, throughout this article, it will be discussed how polyphenols contribute to antidiabetic and neural protection factors.

2. DIABETES MELLITUS AND ALZHEIMER'S DISEASE: TWO DIFFERENT PATHOLOGIES SHARING CHARACTERISTICS

2.1. Diabetes Mellitus

DM is a metabolic disease that results from a failure in the secretion and/or action of insulin. This hormone is produced in pancreatic β-cells and allows cells to capture glucose to meet energy needs [32]. When insulin is absent or when its function is abnormal, cells are not able to take up glucose, thus it remains in the bloodstream causing hyperglycaemia [33]. In healthy individuals, glycaemia is tightly regulated, and fasting plasma glucose is maintained between 3.9–5.6 mmol/L, while postmeal exceeds this range only up to 3 mmol/L [34]. During the development of DM, the control of blood glucose levels becomes abnormal. In fact, studies have supported the idea that at the prodromal stages of DM, pancreatic β-cells may become dysfunctional, so that insulin resistance occurs before the establishment of DM. In addition, hyperglycaemia decreases the expression of 5' adenosine monophosphate-activated protein kinase (AMPK), and, consequently, the expression of sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase member of the silent information regulator 2 family [35, 36]. In fact, SIRT1 was found to suffer a marked level and activity decrease in the liver and pancreas of rats following induction of DM [35]. AMPK and SIRT1 have a reciprocal activation dynamic in which AMPK activates SIRT1, *via* increasing its substrate NAD [37], while SIRT1 deacetylates and thus activates AMPK [38]. AMPK prevents the production of glucose, cholesterol and triglycerides promoting the oxidation of fatty acids. On the other hand, SIRT1 is responsible for regulating hepatic glucose production, lipid metabolism and stimulate insulin production and its sensitivity, being an important regulator of energy metabolism [36]. Accordingly, transgenic mice that overexpress SIRT1 display improved glucose homeostasis and increased metabolic rates [39]. Moreover, SIRT1, through deacetylation also regulates the activity of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) responsible for suppressing reactive oxygen species (ROS) production and regulator of mitochondrial biogenesis [40]. Thus, AMPK and SIRT1 decrease with DM, leaves no impediment to the production of glucose and ROS [36].

The majority of DM cases are classified as type 1 DM (T1DM) or type 2 DM (T2DM). T1DM is characterized by an autoimmune response of T lymphocytes to insulin-producing β-cells [41]. The loss of pancreatic β-cells is progressive and results in a dramatic decrease or even in the absence of insulin production. As consequence, these individuals are dependent on exogenous administration of insulin to survive. The first symptoms of T1DM generally appear in the early years, and this is why it is known as juvenile-onset DM. Uncontrolled T1DM can lead to ketoacidosis, which can be lethal [32, 33]. Following the trend of DM, the number of T1DM individuals has also been considerably increasing. It is expected that the prevalence of T1DM in individuals younger than 5 years will double until 2020 [42]. Studies indicate that the causes for this self-destruction are genetic, but it is also believed that environmental factors are increasingly contributing to the rise of these numbers [32, 33].

In turn, T2DM accounts for almost 95% of diabetics and is also known as non-insulin dependent DM. It usually tends to appear at advanced ages and in the early stages, a decrease in the sensitivity to insulin is observed [32]. This is called insulin resistance, and to compensate this state, pancreatic β-cells increase the rate of insulin secretion leading to a hyper-

insulinemia. However, with the progression of T2DM, β-pancreatic cells lose the capacity to release adequate amounts of insulin to compensate the resistance to the hormone and individuals develop a more or less severe insulin deficiency. The risk of developing T2DM has a genetic predisposition, but the major risk factors are increased age, obesity and lack of physical exercise [32, 33].

DM is characterized by significant metabolic alterations which are associated with the development of several complications, such as cardiovascular problems, foot ulcers, sexual dysfunction, retinopathy, nephropathy and neurodegenerative diseases [32, 33, 43]. However, depending on the severity degree of DM, polyuria, polydipsia [32], polyphagia [32, 33], weight loss, blurred vision [32], the difficulty of healing [33] and a greater vulnerability to infections [32] also occur. DM is associated with several complications in different organs. For instance, the resulting hyperglycaemia may compromise lung function contributing to the weakness of muscles involved in respiration and decreased gas exchange at the level of the alveoli. Nandhini *et al.* [44] showed that the resistance and efficiency of the ventilatory pump are affected by myopathic and neuropathic changes that in turn affect the respiratory muscles. This is consistent with Davis *et al.* [45] who found that diabetic individuals had a reduced air flow when compared to healthy controls. It is also true that DM is associated with high levels of inflammatory mediators and markers, that in conjunction with microangiopathy, cause changes in lung matrix proteins, compromising lung functions. DM may induce microangiopathic changes in the lung causing an increase in the thickness of the basal lamina that ends-up compromising the gas exchange [46]. It is possible that alterations in the collagen metabolism may impact the capacity of the chest to expand correctly, resulting in significantly lower lung volumes [47].

The efforts to find a cure to DM have greatly increased over the years, with several studies done on this matter, but the standard form of treatment continues to be through dietary and lifestyle modifications and drug therapy with hypoglycaemics, such as sulphonylureas, α-glucosidase inhibitors and thiazolidenediones. When blood glucose levels cannot be controlled in this way there is a need to administer exogenous insulin, which is typically the case of T1DM. However, a healthy diet is fundamental to control DM pathogenesis, as it can help to delay the complications associated with DM or even prevent DM development [48].

2.2. Alzheimer's Disease

The AD is the most frequent neurodegenerative disorder in the elderly. It is characterized by loss of memory and damage to problem-solving ability, spatial skills, language, or socio-affective behaviour. The clinical diagnosis of this disease requires that the individual presents symptoms in at least two of these cognitive domains [49]. However, depending on the stage of the disease, depression, anxiety, apathy and irritability may also be present, while in more severe states individuals show agitation, aggressive behaviour and even hallucinations [50]. AD is a multifactorial disease, caused by both genetic and environmental factors. A small number of cases are caused by autosomal dominant transmission involving genes encoding amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) [51]. AD presents three stages: an initial phase, an intermediate phase and a late stage. In the first phase, the cholinergic neurons located in the hippocampus are affected and cause losses of less significant memories. The intermediate phase may prolong for ten years and is characterized by a decrease in the levels of acetylcholine (ACh) in the neurons responsible for the storage of long-term memories [52]. During this phase, other symptoms, such as personality changes, confusion, anger and lack of orientation begin to appear. ACh is known to play an important role in memory and learning [53]. ACh is synthesized by choline acetyltransferase and hydrolysed by cholinesterase. There are two isoforms of cholinesterase, acetylcholinesterase (AChE) that is very selective for ACh hydrolysis, and butyrylcholinesterase (BChE) that is able to metabolize other molecules [54, 55]. Evidence has indicated that in more advanced stages of AD, AChE levels decrease by about 85%, while BChE levels increase twice and become the main cholinesterase in the brain. As a consequence, the hydrolysis of ACh will become less selective and its concentration in the brain begins to decrease leading to memory loss [54]. However, it is also believed that mitochondria play crucial roles [56, 57]. Mitochondrial function tends to decrease with age [58] and has been described as dysfunctional in brains of rats with AD. Dysfunctional mitochondria present defects in the correct function of electron transport chain, which eventually leads to the production of ROS, which in turn leads to the oxidation of thioredoxin that causes dissociation of signal regulating kinase 1 apoptosis. This interaction results in the activation of c-Jun N-terminal kinases that will increase the expression of β-secretase 1 and PS1, two genes that contribute to the fragmentation of APP, which results in increased production of β-amyloid peptide [59-61]. In the last phase of AD, the cholinergic neurons of the cerebral cortex are affected and stored memories are lost, the patient forgets about his/her past and sometimes even his/her family. This phase is less durable, although it can last for three years, and ends with death [62].

AD is associated with loss of activity in specific brain regions, mainly in the temporal and parietal lobes [63]. The causes are plaques composed of insoluble β-amyloid peptides and neurofibrillary tangles (NFT), composed of hyperphosphorylated tau proteins [5]. These proteins initially have the function of stabilizing the microtubules of the neurons but, when they are hyperphosphorylated, they lose affinity to the tubulins that constitute these microtubules and aggregate to each other, leading to the formation of the NFT [64]. β-amyloid plaques and NFT begin to be present in brain-bound areas of memory and learning where loss of neurons and synapses occurs, and subsequently spread throughout all areas of the brain resulting in the different stages of the disease [5]. The reason for this is unclear, but the main hypotheses have addressed n the modification of β-amyloid peptides. These are comprised of 38 to 43 amino acids and their formation results from the proteolytic process of APP. When APP is normally processed by α-secretase and subsequently by γ-secretase, a compound is formed which is rapidly degraded in the body. However, due to mutations, oxidative stress and aging, APP can be processed by β- and γ-secretase and generate β-amyloid peptides [5]. Because of

this imbalance, the β-amyloid peptides aggregate into soluble oligomers, which merge, giving origin to unsolvable β-amyloid plaques that are to be deposited in the various brain lobes. The β-amyloid plaques in conjunction with NFT can trigger an inflammatory process by activating astrocytes and microglia that lead to increased mobilization of macrophages and lymphocytes, which in turn will release tumour necrosis alpha factor (TNF-α) and interferon gamma. These cytokines increase the levels of β-secretase 1 and APP in astrocytes and microglia contributing to the formation of β-amyloid peptides in these cells causing brain damage [65-68].

It has been noted that SIRT1 is down-regulated in the parietal cortex of AD patients and this loss is correlated with AD progression [69]. Studies show that SIRT1 is capable of promoting α-secretase activity in different models, consequently reducing the production of β-amyloid peptides [70]. Also, SIRT1 deacetylates p53 and forkhead box O (FOXO) proteins, leading to the suppression of their apoptotic activity in neurons and hence promoting neuronal survival [71]. Therefore, SIRT1 loss in AD might promote the accumulation of β-amyloid peptides, consequently originating more β-amyloid plaques, and lead to apoptotic death of neurons. Furthermore, SIRT1 activity reduction has been shown to limit AD brain capacity of generating acetyl-coenzyme A, a precursor of ACh [72], and relates to decreased mitochondrial biogenesis, which contributes to mitochondrial dysfunction [73].

On the other hand, other authors have argued that β-amyloid plaques also alter the permeability of Ca^{2+} channels in glia cells, leading to the formation of Fe^{2+} and Cu^{2+} ions and, consequently, ROS production [74]. Studies have shown that β-amyloid produces hydrogen peroxide and releases substances reactive to thiobarbituric acid. In addition, they induce neurodegeneration through microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, though this mechanism is not entirely understood [75]. The characteristic oxidative stress of AD will affect oligodendrocytes, as they remain with a low concentration of reduced glutathione (GSH) and a high concentration of iron, rendering the cells incapable of eliminating oxygen radicals [74].

Nonetheless, the formation of β-amyloid aggregates can also be triggered by genetic mutations. Mutations in the APP gene may occur in familial forms of AD with early onset (about 40 years of age). The main cause of early-onset familial AD forms is the mutations in the presenilin 1 gene (PSEN1) and presenilin 2 (PSEN2) gene. However, mutations in PSEN1, the gene that encodes for PS1, the core protein of the catalytic subunit of the γ-secretase complex, cause the majority and the most severe forms of the disease. In fact, so far, 219 mutations have been reported in the PSEN1 gene, with the majority being missense mutations and the most common being mutation E280 [76]. Very early onset AD (mean age of 30 years) has also been associated with the pathogenic variants p.Met233Val and p.Tyr256Ser PSEN1 [77]. In turn, late onset is due to the apolipoprotein E (ApoE) gene encoding the ApoE protein, involved in the metabolism of fatty acids. This gene has the APOε2, APOε3 and APOε4 alleles, the latter being a major genetic risk factor for AD [78]. Although it is not yet known the reason why this allele increases the odds of developing AD, it is known that, when present in heterozygosity, the genetic risk is 3-fold increased, whereas in homozygosity, the risk is 10-fold increased [56]. Interestingly, APOε4, contrary to other alleles, has been linked with SIRT1 expression reduction, leading to reduced neuroprotection [79].

Due to the complexity of AD, and although there is still no cure, there are several targets for the therapeutic effects of drugs. The currently available treatments delay ACh degradation, interfere with APP metabolism, and inhibit tau phosphorylation [74].

2.3. The Link between Diabetes Mellitus and Alzheimer's Disease

DM and AD are two diseases that are very prevalent in modern societies contributing to a great decrease in the quality of life. The association between these two diseases is an issue of increasing interest and particular concern for health authorities [80]. Both DM and AD share several common risk factors and developing pathways, which is not surprising once oxidative stress, inflammation and alteration of energy homeostasis appear to be the key mechanisms in both pathologies. Furthermore, one of the main risk factors for the development of DM and AD is aging, which is by itself associated with the increase of the mechanisms mentioned above, as well as with epigenetic changes, the most noteworthy being the decrease in the expression of SIRT1 [81, 82], the histone deacetylase believed to be directly related to regulation of adipogenesis and adipolysis, mitochondrial biogenesis, suppression of β-amyloid production and neuroprotection, therefore the decrease of its expression is prejudicial for both metabolic and neurodegenerative diseases [83-85]. Besides SIRT1 down-regulation with aging, this deacetylase was also found to be down-regulated in DM [35] and AD [69] models, which further supports its involvement in both pathologies.

Leibson *et al.* [12] suggested that DM increased the risk of AD development by 2.27-fold in males and 1.37-fold in females, and that individuals who were being treated with insulin had a 4.3-fold greater risk of developing AD than healthy individuals. In some studies, higher insulin and glucose levels have been detected in AD individuals compared with healthy people [86, 87]. These findings have led to consider that insulin dysfunction, or the resulting hyperglycaemic state, increases the risk for the development of AD (Fig. **1**) [86, 87]. Another line of thought emerged later, arguing that it is the insulin deficiency that causes AD since insulin cannot perform its function in the brain [88, 89] and thus undermines the process of learning and memory retention [90]. The majority of the insulin present in the brain is produced by the β-pancreatic cells and crosses the blood-brain barrier. It acts at the level of the hypothalamus, controls the need for food intake and acts on cognitive functions. Its action begins when it binds to the insulin receptor, therefore activating tyrosine kinase phosphorylation which in turn stimulates other neuronal pathways [91]. Activation of the Sarcoma homology collagen mitogen-activated protein pathway leads to the development of neuronal cell growth and repair processes [92]. Besides this, insulin also induces the production of nitric oxide, essential in learning and memory processes. Thus, problems related to insulin production,

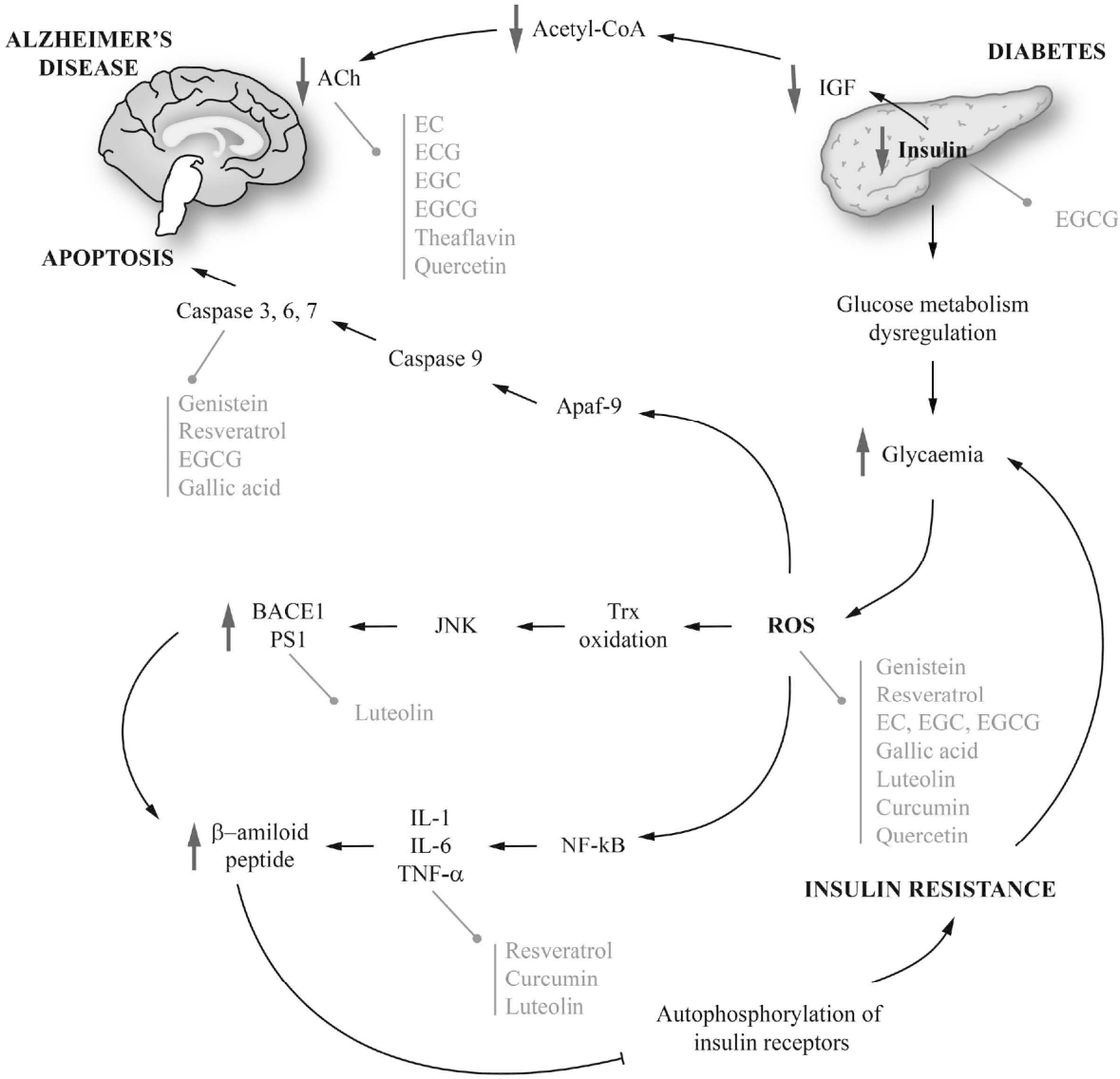

Fig. (1). Schematic representation of overlapping molecular mechanisms involved in the onset and progression of DM and AD that can be modulated by the specific action of phenolic compounds. Decreasing levels of insulin (and/or insulin action), a characteristic of DM, contribute to the decrease in IGF that causes a decrease in acetyl-CoA levels which, consequently, causes a decrease in ACh levels, leading to cognitive decline. In addition, the high levels of ROS (increased due to the dysregulation of glucose metabolism caused by decreased insulin levels and/or insulin action) activate the caspase-dependent pathway that results in cellular apoptosis and, consequently, destroys nerve cells. ROS also oxidize thioredoxin, which increases the expression of the BACE1 and PS1, genes responsible for β-amyloid peptide production. Convergently, the production of this peptide is also enhanced by the release of inflammatory cytokines, such as IL-1, IL-6 and TNF-α, promoted by ROS. Increased β-amyloid peptide production is characteristic of AD and inhibits autophosphorylation of insulin receptors, contributing to increased insulin resistance (characteristic of DM), and therefore, to hyperglycaemia. Phenolic compounds can act in some of the mechanisms previously described, having a positive effect in DM and AD. For instance, EGCG is able to increase insulin secretion, and thus, ameliorate hyperglycaemia. Catechins (namely EC, ECG, EGC and EGCG), theaflavins and quercetin can delay or inhibit the hydrolysis of ACh, preventing the decrease of ACh levels. Several phenolic compounds, such as genistein, resveratrol, EC, EGC, EGCG, gallic acid, luteolin, curcumin and quercetin can act as antioxidants, reducing ROS levels, and therefore reducing the activation of mechanisms of pathogenesis progression. Furthermore, genistein, resveratrol, EGCG and gallic acid are capable of modulating caspase 3, while luteolin can down-regulate PS1 expression, and resveratrol, curcumin and luteolin can decrease inflammatory cytokines release, and so, these compounds can have an inhibiting effect on apoptosis and/or β-amyloid peptide formation besides through ROS modulation. Upwards arrows and downwards arrows (grey) represent increase and decrease, respectively. Arrow-headed lines and bar-headed lines (black) represent activation and inhibition, respectively. The ball-headed lines (grey) represent the effect of the phenolic compounds. Acetyl-CoA - Acetyl-coenzyme A; ACh - Acetylcholine; Apaf-9 - Apoptotic protease activating factor 1; BACE1 - β-secretase 1; EC - Epicatechin; ECG - Epicatechin gallate; EGC - Epigallocatechin; EGCG - Epigallocatechin-3-gallate; IGF - Insulin-like growth factor; IL-1 - Interleukin 1; IL-6 - Interleukin 6; JNK - c-Jun N-terminal kinases; NF-kB - Nuclear factor kappa-light-chain-enhancer of activated B cells; PS1 - Presenilin 1; ROS - Reactive oxygen species; TNF-α - Tumour Necrosis Factor alpha; Trx – Thioredoxin.

action or resistance are at the origin of complications at the level of the central nervous system, including AD [93]. Other evidence that DM and AD are related is the decrease in levels of ACh caused by insulin depletion or resistance. The process of formation of ACh, an important neurotransmitter for control of memory-related brain areas, involves acetyl-coenzyme A and acetyl transferase. When the level of insulin is decreased, the expression of the insulin-like growth factor I (IGF-I), which stimulates the energy metabolism necessary for the formation of acetyl-coenzyme A, also decreases. Furthermore, as previously stated, SIRT1 downregulation, which is verified both in DM and AD, also limits acetyl-coenzyme A formation by decreasing the deacetylation and consequent activation of acetyl-coenzyme A synthetases [72]. Consequently, the formation of acetyl-coenzyme A will be compromised, decreasing the amount available for the formation of ACh. Low insulin levels also decrease the expression of acetyl transferase, required to produce ACh. As with acetyl coenzyme A, the production of acetyl transferase lowers with decreasing insulin since IGF-I also regulates its production, and, as a consequence, ACh production is further decreased (Fig. **1**) [94, 95].

Another common feature of these two diseases is inflammation. The insulin resistance observed in T2DM individuals is associated with elevated levels of interleukin 6 (IL-6) [96]. Likewise, AD is also associated with inflammation [97] being that Htill *et al.* [98] identified IL-6 in β-amyloid plaques of AD patients. Wang *et al.* [99] induced T1DM in mice and found an increase in the generation of β-amyloid plaques (Fig. **1**). In addition, Clodfelder-Miller *et al.* [100] found that after administration of streptozotocin (STZ) the degree of phosphorylation of the tau protein present in neurons, which contributes to the formation of NFT, was higher in the group of diabetic animals when compared to the control group. Moreira *et al.* [56] have shown that brain mitochondria isolated from STZ-induced diabetic rats present a deficit of antioxidant defenses, which increases the susceptibility to ROS attack. It is also thought that insulin resistance may lead to mitochondrial dysfunction and, consequently, to energy homeostasis dysfunction due to reduced adenosine triphosphate (ATP) production, and to increased oxidative stress [80]. As sporadic AD has characteristics of T1DM and T2DM, Monte *et al.* [101] have proposed for it the term type 3 diabetes (T3DM), which consists of reduced insulin production and resistance to insulin action caused by modifications in the interaction between insulin and its cellular receptors. Insulin signaling failures cause disruption of glucose metabolism, which will increase ROS production (Fig. **1**) [51]. This increase leads to changes in the mitochondrial membrane that will increase the permeability of this same membrane. As a result, pro-apoptotic (cytochrome c) proteins that activate apoptotic protease activating factor 1 and pro-caspase 9 will be released. Thus, caspase 9 will be activated along with a cascade of caspase executors (caspases 3, 6, and 7), which will culminate in cellular apoptosis (Fig. **1**) [102]. In addition, increased ROS activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*k*B) transcription factor, promoting the release of pro-inflammatory cytokines, such as TNF-α and interleukin 1 (IL-1), which generates an inflammatory environment, consequently providing the formation of β-amyloids peptides (Fig. **1**) [103]. The NF-*k*B transcription factor signaling pathway is also increased due to the decreased SIRT1 activity, exacerbating neurotoxicity seeing as SIRT1 is normally responsible for interacting with the RelA/p65 subunit of NF-κB and inhibiting its transcription by deacetylating a critical lysine at position 310 [104, 105].

In patients with AD who also suffer from DM, it was observed that the administration of exogenous insulin together with conventional antidiabetic medication (in some cases metformin) had effects on the decrease of β-amyloid plaque deposition and improved the cognitive function of the patients [106-108]. In 1983, Bucht *et al.* [15] analysed 839 individuals with neurodegenerative diseases and, through a glucose tolerance test and blood glucose levels, found that 63 of them had DM. Thus, the hypothesis of these two pathologies being related emerged, although still without knowing in what form. Afterwards, the number of studies increased and, in 2008 Beeri and collaborators administered insulin in adults with AD and observed that the individuals who were submitted to a combined insulin therapy and daily administration of antidiabetic drugs (for example metformin and sodium–glucose cotransporter 2 inhibitors) presented a significant decrease in the formation of β-amyloid plaques in the hippocampus, the entorhinal cortex, and the cerebral cortex, when compared to subjects who were only on insulin or antidiabetic medication [106]. In this way, it is noticed that DM is a risk factor for AD, but the opposite is also true. One evidence is that β-amyloid peptide produced in individuals with AD inhibits the autophosphorylation of insulin receptors, which will prevent the binding of insulin to its receptor and, as a consequence, causes insulin resistance (Fig. **1**). Thus, it is considered that these two pathologies are interconnected through common mechanisms [80, 109].

3. POLYPHENOLS

Phenolic compounds comprise a wide group of natural compounds broadly distributed in a variety of plant-derived foods commonly used in our diet [45], namely in fruits, nuts, cereals, beverages, legumes, spices and many others. They exist in these plant foods as secondary metabolites that protect plants from ultraviolet radiation, oxidative stress and some herbivores, but also to attract insects pollinators [110]. Structurally, they are characterized by the presence of one or more aromatic rings attached to one or more hydroxyl groups [111]. More than 8,000 phenolic compounds have been identified and they are usually organized into subclasses (Fig. **2**) [112] where inclusion criteria in each group may be the source, biological function or chemical structure [113]. A characteristic property of phenolic compounds, particularly of those whose hydroxyl groups occur in the *ortho*- or *para*-position, is their role in redox reactions, where they act as reducing agents and hydrogen donors [110]. Therefore, polyphenols interfere with the oxidation of biomolecules by promptly donating protons to radicals or by reacting with radicals to form compounds that prevent them to react with other molecules [114]. Due to these actions, polyphenols are known as excellent antioxidant molecules. Indeed, there is a positive direct correlation between the an-

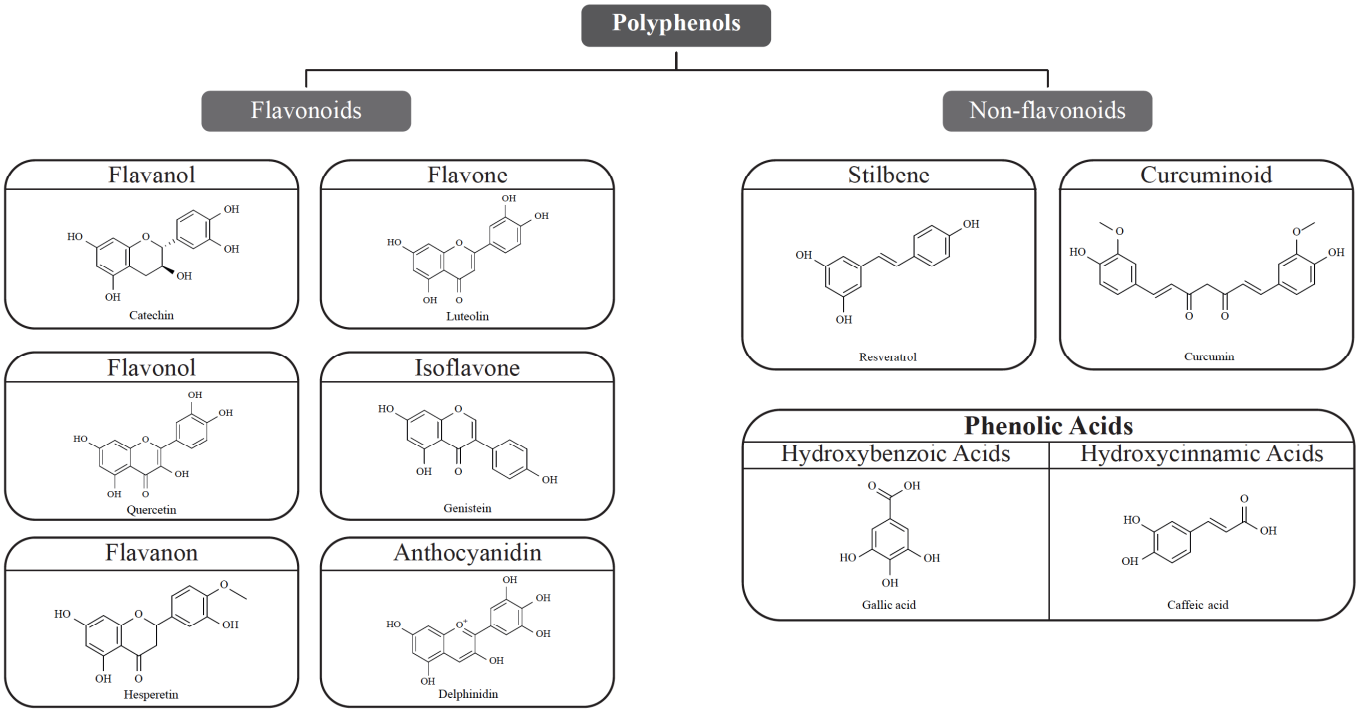

Fig. (2). Schematic illustration of the main chemical structures belonging to the classes and subclasses of phenolic compounds. Division of flavonoids into flavanols (*e.g.* catechin), flavones (*e.g.* luteolin), flavonols (*e.g.* quercetin), isoflavones (*e.g.* genistein), flavanones (*e.g.* hesperetin) and anthocyanidins (*e.g.* delphinidin). Classification of non-flavonoids in stilbenes (*e.g.* resveratrol), curcuminoids (*e.g.* curcumin) and phenolic acids, which can be divided into hydroxybenzoic acids (*e.g.* gallic acid) and hydroxycinnamic acids (*e.g.* caffeic acid).

tioxidant capacity of polyphenols and the number of hydroxyl groups present in the phenolic structure.

3.1. Classes and Subclasses

The organization of phenolic compounds in classes is quite different according to different authors. Some authors have classified them into two great classes: Flavonoids and Non-flavonoids [115]. More frequently, the non-flavonoids have been divided into well-defined classes, resulting in a total of 5 or 6 classes [110, 111, 116]. In this review, three classes of non-Flavonoids - Phenolic acids, Stilbenes, and Curcuminoids - are distinguished regarding their chemical structures, health-promoting properties and biological relevance of their representative members (Fig. **2**).

Flavonoids constitute the largest class of polyphenols, including almost half of all the phenolic compounds identified so far [111]. Most of them are characterized by the presence of two aromatic rings (A and B rings) linked by a pyranic ring (C ring) and, according to the oxidation degree of the pyranic ring, they can be classified into 6 subclasses: flavonols, flavanols, isoflavones, flavanones, flavones and anthocyanins [112]. A representative example of each subclass is presented in Fig. **2**. Naturally occurring flavonoids in foods usually exist as glycosides (bound to one or more sugars) [117].

Structurally, phenolic acids contain one aromatic ring attached to one or more hydroxyl groups and to a carboxylic group. They are divided into two subclasses: derivatives of benzoic acid and derivatives of cinnamic acid (Fig. **2**). In foodstuffs, hydroxycinnamic acids are more common than hydroxybenzoic acids and both subclasses are rarely found in their free form, unless when foods suffer severe processing [118]. A representative example of each subclass is presented in Fig. **2**.

Curcuminoids are characterized by the presence of two aromatic rings symmetrically linked to a β-diketone moiety. Despite their low abundance in foods, their health-promoting properties lead to the creation of this individual class of non-flavonoids [119, 120].

Stilbenes are structurally characterized by the presence of two aromatic rings connected through a double bond. One of the most well-known stilbenes is resveratrol (Fig. **2**). This class is just found in a limited number of plants and therefore is present in very low quantities in the human diet [118, 121].

3.2. Extraction and Analysis

Reliable analysis of phenolic compounds is a process accomplished by several steps. The diversity and complexity of polyphenols, each one with specific physical-chemical and structural properties, is by itself a countless challenge to their extraction, purification, identification and quantification in food products. Furthermore, even the sample type must be taken into count since it determines what pre-treatment is necessary. For example, most samples are solids and, so, undergo a process of pre-treatment consisting of grinding, homogenization, air-drying or freeze-drying, among others. Liquid samples are first filtered or centrifuged [114, 122, 123]. Since most phenolic compounds are natu-

rally found in their source as conjugates, a hydrolysis step is sometimes used to disrupt glycoside or sulphur linkages with the purpose to achieve the highest release of free polyphenols [114, 122, 123]. To avoid degradation of native phenolic compounds, samples are often dried, frozen or lyophilized before extraction to avoid enzymatic degradation. An efficient recovery of phenolic compounds depends on the success of the extraction step. However, it is impossible to set a unique extraction method for polyphenols, since this procedure depends on intrinsic properties of each phytochemical, like the lipophilicity/polarity. Hence, there are different extraction methods for phenolic compounds, but most of them are based on solvent extraction. The solvent can be water, an organic solvent (frequently methanol or ethanol), hydroalcoholic mixtures, or liquefied gas, or combinations of them, under different temperatures and pressures. Solid-liquid and liquid-liquid extractions are the most used procedures, mainly because they are easy to use in common laboratories, efficient, and have wide-ranging applicability [120]. In certain cases where these methods cannot be applied, other options have been used as an alternative, such as Soxhlet extraction, supercritical fluid extraction and microwave assisted extraction [114, 122, 123]. After the extraction, a purification/isolation step is required to purify the desired phenolic compounds from all the contaminants and, eventually, from other polyphenols. For that purification, solid-phase extraction, open column chromatography and preparative high-performance liquid chromatography (HPLC) are the most used [123].

The identification and quantification of phenolic compounds can be performed by a variety of methods, namely by spectrophotometric, chromatographic and electrophoretic methods. Mass spectrometry (MS) can be coupled with these techniques providing incomparable chances in the identification and structure elucidation of polyphenols [114]. Despite the difficulty of selecting the best method to determine phenolic compounds, HPLC/DAD and liquid chromatography–mass spectrometry (LC–MS) have been proposed by several authors as the most suitable techniques for this purpose [124, 125]. In fact, LC–MS has been considered as the most effective method for qualitative and quantitative analysis and even for structural characterization [126].

3.3. Sources on Diet, Metabolism and Bioavailability

The dietary sources of polyphenols, which are mainly fruits and vegetables, and therefore, are part of an healthy diet, contain not only a phenolic compound but a mixture of several phenolic compounds in different chemical forms [127]. According to Commenges *et al.* [128], the dietary consumption of flavonoids (the major class of polyphenols) is around 14,4 mg per day. The determination of dietary polyphenols intake is very difficult because it varies according to the dietary pattern of each person and because there is a lack of information about the number of polyphenols present in each food, mainly in non-processed food [129]. It is important to note that the daily dietary intake of phenolic compounds is not the only concern since the antioxidant potential of each polyphenol in each food is crucial for many bioactivities. Perez-Jimenez *et al*. ranked the 100 richest foods in terms of polyphenols, each with its respective antioxidant content, being clove, peppermint, star anise, cocoa powder, mexican oregan, celery seed, black chokeberry, dark chocolate, black elderberry and chestnut the ten most rich [130]. Noteworthy, the total phenolic content does not directly correspond to the total antioxidant activity, since phenolic compounds are not the only antioxidant compounds present in foods [130]. According to the nutritional recommendations of World Health Organization [131], a healthy diet must include the consumption of at least 400 g (5 portions) of fruits and vegetables a day for an adult. However, it is difficult to define the intake of polyphenols in a healthy diet. In fact, it is extremely difficult to predict their intake based only on the dietary patterns, once their concentrations in foods could vary according to numerous factors, namely genetic, environmental, and technologic factors [28].

3.3.1. Metabolism and Bioavailability

The absorption and metabolism of dietary phenolic compounds is a crucial factor for their bioavailability, which in turn is imperative for the establishment of a significant biological activity. However, absorption and metabolism are affected by the chemical structure of the polyphenol itself and factors related to interpersonal variability, such as enzymatic activities, and systemic factors, for example age, gender and pathologies.

Considering the largest class of polyphenols, cleavage of oligomeric flavonoids can occur in the stomach at low pH. All subclasses of flavonoids are metabolized in the jejunum and ileum of the small intestine and the resulting metabolites enter the portal vein reaching the liver where undergo further metabolism. The microflora of the colon degrades the flavonoids into smaller phenolic acids that can also be absorbed into cells and tissues and some of them even cross the blood-brain barrier [132]. Although is clear that polyphenols and their metabolites can cross the blood-brain barrier, reach brain cells and modulate brain bioprocesses, the route by which they cross the barrier (simple diffusion or by carrier-mediated transport) remains unclear. However, studies *in situ*, *in vitro* and *in silico* showed that polyphenol structure and efflux systems influence their brain bioavailability [133, 134]. Nevertheless, most of these metabolites are excreted in urine contributing to a lower bioavailability [132].

Although flavonoids can be absorbed from the gastrointestinal tract, plasma concentrations (bioavailability) are low, usually much inferior to 1 M. Manach *et al.* [135] concluded that the plasma concentrations of total metabolites range from 0 to 4 μM with an intake of 50 mg of aglycone (the non-sugar component that results from hydrolysis of glycosides), like quercetin, genistein or gallic acid. Moreover, the phenolic compounds that are more easily absorbed in humans are isoflavones and gallic acid, followed by catechins, flavanones, and quercetin glucosides, with different kinetics [135]. At concentrations as low as 4 μM, most phenolic compounds are unlikely to have a significant and direct antioxidant effect when ingested in the normal amounts of a healthy diet [111]. Thus, much of the evidence on the beneficial effects of dietary polyphenols is derived from experiments conducted *in vitro* or in animal models using concen-

trations much higher than those generally found in the human diet [136]. However, polyphenols ingestion has been linked with a decrease in the incidence of DM and AD *in vivo* [137, 138], which suggests its actions beyond the usual antioxidant activities [111].

3.4. Bioactivities and Bioeffects

Polyphenols have been implicated as potential preventive and curative agents for a number of diseases, such as AD [110], Huntington's disease [139], Parkinson's disease [140], chronic fatigue syndrome [141], hypercholesterolemia [142], DM [25], stroke [143], several cancers [121], cardiovascular disease [144], autism [145], vitiligo [146], among others [147]. Despite being phenotypically different, these pathologies have oxidative stress and inflammation as common factors. In order to cope with an excess of free radicals produced in oxidative stress, humans have endogenous mechanisms to maintain redox homeostasis but somehow these mechanisms fail or decompensate in pathologic contexts. This is why exogenous sources of antioxidants capable of dealing with the oxidative stress are so important. Among these, dietary polyphenols have been extensively studied for their strong antioxidant capabilities. Among the several possible mechanisms, the radical elimination hypothesis postulates that polyphenols specifically scavenge free radicals by binding to them and blocking their deleterious effect [147]. Although the antioxidant effect is most often reduced only to scavenging and blocking free radical effects, strategies for antioxidant activity go beyond free radicals neutralization (Fig. **1**) and include other activities, such as enzymatic control, iron chelation, regulation of signaling pathways and intervention in the cell cycle [116]. All these bioactivities together allow polyphenols to have more than antioxidant properties but also, anti-inflammatory, probiotic and immune system and epithelium modulator properties [148]. The beneficial effects of polyphenols in many diseases is largely due to their capability of regulating signaling pathways disease-related, such as SIRT1 [149], PGC-1α [38, 150], AMPK [151], mitogen-activated protein kinases (MAPK) which in mammals include the extracellular signal-regulated kinases (ERK), the p38 MAPKs, and the c-Jun NH2-terminal kinases, NF-*k*B, activator protein 1, canonical Wnt and protein kinase C (PKC) [147, 148]. These pathways play a key role in many biological functions, such as cell proliferation, apoptosis, transcription regulation, inflammation, cell signaling, immune responses, learning and memory [147, 148]. Commonly, the role of phenolic compounds in signal pathways regulation is due to redox-sensitive modulation of different signaling cascades [116]. By modulating these signaling pathways, that are indeed engaged in several pathologies and are the targets in many therapeutic strategies, polyphenols appear as promising therapeutic/protective agents in various pathologies [152].

4. POLYPHENOLS AS PROTECTIVE AND THERAPEUTIC AGENTS IN ALZHEIMER'S DISEASE AND DIABETES MELLITUS

4.1. Catechins

Catechins are polyphenols of the flavanol family and are characterized by strong antioxidant power. They are present in green and white teas, cocoa and red wine [24]. The most well-known are catechin, EC, epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG) and they have been studied by several researchers in an attempt to understand their neuroprotective capacity in AD [24]. A previous study showed that green tea consumption was associated with a lower risk of cognitive problems [153]. EGCG (along with EC, ECG and EGC [154]) is one of its main constituents [153] and has been a target of research interests due to its antioxidant capacity, which gives it neuroprotective and antidiabetic effects. EGCG is involved in the control of apoptosis by inhibiting the expression of pro-apoptotic genes, such as Bcl-2-like protein 4 (Bax) and Bcl-2-associated death promoter, inducing anti-apoptotic genes, such as the known B-cell lymphoma 2 (Bcl-2), Bcl-2-like protein 2 and *B-cell lymphoma-extra,* and inhibiting the activity of caspase-3, preventing neuronal cell death (Fig. **1**) [24]. EGCG activates the phosphatidylinositol 3 kinase/ protein kinase b (PI3k-Akt) signaling pathway promoting cell survival and "waking up" cells from the state of senescence. It has the ability to restore the activity of PKC, which will increase the release of a non-amyloidogenic soluble precursor, which will counteract the formation of β-amyloid plaques characteristic of AD. In addition, it protects the brain against inflammation, prevents memory impairment and reduces oxidative stress. Throughout life, iron accumulates progressively in regions, such as the putamen, prefrontal cortex and sensory cortex. With aging this is converted into a substance containing iron with higher reactivity, hemosiderin, promoting oxidative stress. The EGCG exhibits neuroprotective effects due to its ability to chelate the metal ions avoiding the formation of free radicals [153]. In AD, the cholinergic system of the brain is considered very important. Its decline is associated with memory loss, and therefore the drug treatment used to combat this disease inhibits cholinesterases, such as AChE and BChE. Okello *et al.* [155] verified through *in vitro* studies the effect that green and black teas (black tea main constituents are theaflavins, that result from the oxidation and dimerization of catechins [154]) could have on the inhibition of these two cholinesterases. The authors realized that the inhibitory activity of these two teas was dose-dependent, in the range of concentrations which were used (0-0.3 mg/mL). For AChE, the IC_{50} values for green and black teas were 0.03 and 0.06 mg / mL, respectively. In the case of BChE, an IC_{50} value of 0.05 mg / mL was obtained for both teas. In this way, the consumption of these teas seems to delay or inhibit the hydrolysis of ACh, allowing this neurotransmitter to exist in greater concentration in the brain and during a longer period (Fig. **1**).

In DM, EGCG inhibits hepatic production of glucose, controls gluconeogenesis, minimizes β-cell damage and increases insulin sensitivity [156]. Wolfram *et al.* [157] showed that it negatively regulates the expression of phosphoenolpyruvate carboxykinase messenger ribonucleic acid, an enzyme involved in gluconeogenesis. In addition, EGCG increases the levels of glucose transporter genes 1 and 4 (GLUT1, 4) and inhibits the genes involved in fatty acids, triacylglycerols and cholesterol biosynthesis, which results in less DM complications. It increases the transcription factor (erythroid-derived 2) -like 2 that regulates the expression of antioxidant proteins that protect against oxidative stress

[158]. EGCG was also shown to be a positive regulator of SIRT1 expression in H9c2 cardiomyocyte cells. Wu *et al.* [149] found that cultures of diabetic cells with EGCG (10 mM) showed increased SIRT1 expression relative to the group of cells not exposed to EGCG. They suggested that EGCG could enhance the expression of SIRT1 that mediates the effects of oxidative stress by regulating genes that translate into antioxidants. It also increases the activity of endogenous antioxidants, such as superoxide dismutase (SOD), catalase (CAT) [159] and glutathione peroxidase (GSH-Px) that have the function of neutralizing free radicals, guaranteeing the body's homeostasis [160]. In addition, EC, EGC and EGCG inhibit plasma proteins carbonylation (an irreversible modification in oxidized proteins) that results from ROS action characteristic of the hyperglycaemic state (Fig. **1**) [160]. The anti-inflammatory properties are further highlighted since EGCG counteracts the effects of cytokines in the insulin secretion [161]. EGCG increases insulin secretion and reduces blood glucose levels and, thus, ameliorates hyperglycaemia (Fig. **1**) [162]. Taking into account all these properties of the EC, ECG, EGC and EGCG, the study of foods and teas containing them is a matter of interest, since their consumption may be an alternative method to combat chronic diseases, such as DM and AD [24, 153, 161].

In order to reduce hyperglycaemia, glucosidase inhibitors, such as acarbose and miglitol, which act on α-amylase and α-glycosidase (two intestinal enzymes that hydrolyse carbohydrates) are used. However, these inhibitors cause great side effects, namely intestinal disturbances. Thus, Yilmazer-Musa *et al.* [163] studied the potential of green tea, white tea and individual catechins (EC, EGC, ECG, EGCG) to inhibit α-amylase activity (from human saliva) and α-glycosidase (from *Saccharomyces cerevisiae*). These authors noted that green tea had a similar percentage of acarbose-like α-amylase inhibition, while white tea, EC, EGC, ECG and EGCG showed approximately half of that percentage. When comparing the inhibition of α-glucosidase with that conferred by acarbose, both green and white teas had similar percentages, whereas those of ECG and EGCG were slightly higher. However, EC and EGC had lower inhibition power than acarbose and cannot be considered as strong inhibitors of this enzyme.

Among the different types of tea, white tea contains the highest catechins content, especially of EGCG [164-166]. This tea is also composed of other polyphenols, proteins, polysaccharides, minerals, organic acids, lignins and methylxanthines, such as caffeine, theophylline and theobromine [167, 168] and has shown beneficial effects in several tissues of prediabetic animals. Our research group has been devoted to the study the effects of the daily consumption of white tea in various tissues, using an animal model of Wistar rats. Animals were divided into three groups: in two of the groups, prediabetes was chemically induced by using STZ (40 mg / kg), while the third group acted as a control (was injected only with vehicle solution in an equivalent volume). Subsequently, one of the groups with prediabetes consumed white tea during two months, while the other did not, receiving only water [165, 169-171]. As expected, prediabetic rats developed mild blood hyperglycaemia, glucose intolerance and insulin resistance. Interestingly, the daily intake of white tea restored glucose tolerance and insulin sensitivity. Several *in vitro* studies, animal experiments and clinical observations suggest that tea catechins are the main responsible for it [172-174]. Moderate hyperglycaemia led to less lactate accumulation in the brain cortex, due to an increase in its metabolism (increased LDH activity) [165]. Lactate is considered an important metabolic fuel for the cerebral cortex in stressful situations, such as prediabetes, which is in agreement with the decrease noted in the untreated group. Prediabetes also reduced the antioxidant capacity of the brain cortex, increasing the oxidative damage in lipids and proteins but white tea was able to restore the total antioxidant capacity, strongly decreasing lipid peroxidation and protein oxidation. These neuroprotective effects may be attributed to EGCG and other catechins [175-177]. In addition, the expression of CAT, an endogenous antioxidant enzyme considered as one of the most important antioxidant defenses in this tissue, was diminished in prediabetic rats, but white tea reestablished its expression. Thus, all these results allowed us to understand that the daily consumption of white tea, rich in catechins, maybe a cheap and natural alternative to improve the deleterious effects caused by DM and reduce complications in the brain. Moreover, Alves *et al.* [171] studied the benefits of white tea intake in the heart of prediabetic animals. As expected, prediabetes also reduced the heart antioxidant capacity, increasing the oxidative damage in lipids and proteins. Once again, white tea improved the total antioxidant capacity and restored lipid peroxidation levels. These cardioprotective effects may be attributed to tea catechins [178, 179].

In addition to the effects observed in brain and cardiac tissues, the consumption of white tea also causes alterations in the reproductive function. Oliveira *et al.* [145] found that white tea intake improved the oxidative parameters of testicular tissue, resulting in increased antioxidant potential, decreased levels of lipid peroxidation and protein carbonylation. Also in the epididymis, Dias *et al.* [170] reported that levels of phosphofructokinase 1 (an enzyme involved in glycolysis) were decreased in the prediabetic animals. Interestingly, these levels were restored by white tea consumption.

4.2. Luteolin

Luteolin is a flavone present in parsley, celery, orange and spices [121]. Its chemical structure allows it to act as an antioxidant, a free radical scavenger, an anti-inflammatory agent and is thought to be able to inhibit PKC [180]. Its antioxidant activity may be useful for treating diseases related to oxidative stress, such as DM and AD [180]. Wang *et al.* [181] performed a study in male Wistar rats, that were subsequently divided in 6 groups, in which 3 corresponded to controls for diverse experiment conditions and in the other 3 groups, STZ was injected in order to induce AD. In the fourth and fifth groups, besides STZ, luteolin was injected intravenebroventricularly at a dose of 10 and 20 mg / kg respectively. In order to assess memory impairment, the authors performed the Morris water maze test in which, days before, the animals had learned in order to gain memory of how to reach the platform. The results showed that the animals in which luteolin was administered remained longer in the quadrant where the hidden platform was located, regard-

less of the dose of luteolin used. This demonstrates that these animals have lower memory impairment than the non-injected ones and that these can have an improved learning. Therefore, these researchers concluded that this polyphenol improved cognitive function and, consequently, was considered neuroprotective. In this study, the authors suggested that this could be, at least in part, explained by the antioxidant activity of this polyphenol through the inhibition of free radicals production. It has been demonstrated that luteolin eliminates ROS (Fig. **1**) not only by inhibiting the ROS-MAPK-mediated mechanism [182] but also by inhibiting the expression of NADPH oxidase 4, p22phox, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 [183]. Furthermore, luteolin prevents the dispersing of the characteristic plaques of AD through the inactivation of the glycogen synthase kinase-3 alpha isoform which increases the phosphorylation of PS1 protein, forming a compound that will reduce the PS1-APP interaction and hence the generation of β-amyloid plaques (Fig. **1**) [181, 184].

Concerning DM, studies have demonstrated the antidiabetic activity of luteolin. A study by Wang *et al.* [180] showed that administration of luteolin for 8 weeks in diabetic Sprague-Dawley rats decreased blood glucose levels. In addition, it also increased SOD activity and decreased creatinine and blood urea nitrogen in the kidneys. This evidence suggests that luteolin prevents diabetic nephropathy, which may involve a SIRT1-mediated mechanism, seeing as luteolin is capable of increasing SIRT1 expression [185] and this deacetylase has been found to have renal protective effects [36, 186]. hyperglycaemia, insulin resistance, renal lipid accumulation, inflammation and oxidative stress result in kidney cell injury, leading to the development and progression of nephropathy. Therefore, SIRT1 anti-apoptotic, anti-oxidative and anti-inflammatory actions, as well as its regulation of mitochondrial biogenesis, autophagy and metabolism, protects against renal cellular injury [36]. Also Zang *et al.* [187] concluded that this flavone improved blood glucose levels and insulin resistance in KK-A^y (TaJcl) male mice. The ability to decrease insulin resistance arises from the decrease that luteolin causes in TNF-α, a pro-inflammatory cytokine that affects β-cell function and induces resistance (Fig. **1**). Another study by Li *et al.* [188] showed that after administration of luteolin by intraperitoneal injection in adult male Sprague-Dawley rats there was a decrease in blood glucose, an increase in the activity of antioxidants, such as SOD, GSH-Px and CAT, and a decrease in ROS that was more salient with the administration of higher amounts of luteolin (100 and 200 mg / kg). This flavone was also able to increase nuclear factor Nrf2, a defense mechanism against oxidative stress. On the other hand, Kim *et al.* [185] found in Human monocytic cells subject to a condition of hyperlycemia the effects of luteolin in the expression of SIRT1 and FOXO3a. They suggested that hyperglycaemia negatively regulates the SIRT-FOXO3a path resulting in the production of ROS. However, it was found that cells submitted to luteolin treatments had higher levels of SIRT1 and FOXO3a expression and consequently decreased ROS production, suggesting that this polyphenol could be a potential agent for the prevention and treatment of DM. Thus, it is concluded that luteolin has neuroprotective, anti-inflammatory, antidiabetic and antioxidant activity, and is very beneficial to reduce ROS, one of the main problems of DM and AD.

4.3. Quercetin

Quercetin is a flavonol especially found in products such as blueberries, apples, broccoli, beans and tea [121]. It can cross the blood-brain barrier and thus contribute to the protection of brain cells in AD [189]. In addition, the levels of β-amyloid plaques, as well as the reactivity of some glial cells, decreased with quercetin [189]. In one study by Sabogal-Guaqueta *et al*. [189], 25 mg/kg of quercetin were administered through intraperitoneal injections in Homozygous 3xTg-AD and non-transgenic mice with AD for three months, and the deposition levels of these plaques decreased relatively to the untreated group. In agreement with these results the fragmented APP levels also decreased in the treated group, which explains the smaller plaque deposition. Furthermore, it is also known that this polyphenol increases the levels of antioxidant defenses, namely GSH in astrocytes and neurons, thus contributing to the reduction of oxidative stress [189]. With these findings, it is hypothesised that it works as a neuroprotector for individuals with AD [189].

Quercetin is also an AChE inhibitor. In fact, in a study performed by Tota *et al.* [190] in which AD-induced Swiss albino mice were used, the effect of quercetin on the inhibition of AChE activity was observed. In animals with AD the levels of this enzyme are increased which implies a decrease in ACh (Fig. **1**). This decrease is significantly associated with AD complications, so it is important to find natural alternatives to prevent these effects. When using 5 mg of quercetin per kg, these authors found that the activity of AChE decreased significantly. However, lower doses (2.5 mg / kg) had no effect. This demonstrates that although quercetin has effects on the control of AChE activity, this is dependent on the dose ingested, which suggests the need for further studies to define the most appropriate dose to have positive effects on humans.

SIRT1 is also affected by quercetin consumption, as Sarubbo *et al*. [191] found that the daily consumption of this polyphenol (20 mg/kg) by young and elderly Sprague-Dawley rats for 28 days, lead to increased levels of SIRT1 in the elderly rats. SIRT1 plays a key role in regulating memory, seeing as it promotes ACh production, and when SIRT1 levels is impaired cognitive abilities are also affected. In addition, it promotes α-secretase activity [70] and regulates NF-κB signaling, reducing pro-inflammatory responses [191]. Thus, an agent capable of enhancing SIRT1 may improve the quality of life of patients with AD by reducing the levels of β-amyloid plaques and reducing NF-κB levels preventing increased inflammation [191]. However, the mechanism by which SIRT1 levels increases with quercetin consumption is still unclear. It is known that oxidative stress is one of the main factors for the decrease of levels of SIRT1 thus, quercetin due to its antioxidant properties may avoid the consequences of this stress maintaining the levels of SIRT1.

But the benefits of quercetin are not limited to AD alone. There is also evidence that in DM it has anti-inflammatory and antidiabetic capabilities in which quercetin, through the

translocation of GLUT4 and the phosphorylation of AMPK, decreases plasma glucose levels [192]. In the small intestine, it decreases the activity of maltase and glucose transporter 2 (GLUT2) favouring the decrease of the absorption of glucose at the intestinal level, thereby restoring glycaemia [193]. As it is an antioxidant by nature, it removes free radicals (Fig. **1**) [194] through the increase of antioxidant defenses [195], thus reducing lipid peroxidation since there are less free radicals available to damage lipids [196]. However, the low hydrosolubility, low permeability and short half-life are major limitations of this polyphenol. Nevertheless, it still has beneficial effects on the regeneration of β-pancreatic cells. In part, the destruction of these cells is caused by the surrounding inflammatory environment in which there is a release of cytokines that inhibit insulin secretion. ROS also contribute to this DM problem, once they activate NF-kB, which leads to increased p28, resulting in apoptosis. Due to its anti-inflammatory and antioxidant potential, quercetin contributes to the regeneration of these cells [197].

In sum, quercetin has properties that bring many benefits for DM and AD, such as neuroprotection, free radicals scavenging, anti-inflammatory activity and antidiabetic ability.

4.4. Genistein

Genistein is an isoflavone that can be found in products such as soybeans (and their derivatives) [121]. It is known that it is able to cross the blood-brain barrier because it causes the reduction of the toxicity of β-amyloid plaques and the decrease of neurons apoptosis, which is responsible for the great loss of neurons in AD [198]. Therefore, it is presumed that the reduction of this apoptosis contributes to the improvement of the symptoms. Studies in female Sprague-Dawley rats indicate that the intragastric administration of 30 and 60 mg/ kg of genistein reduces the expression of cytochrome c, caspase 3 and Bax leading to a decrease in the number of apoptotic cells and thus contributing as a protective factor for AD (Fig. **1**) [198]. In addition, genistein protects β-pancreatic cells from the high toxicity of cytokines because it induces the inhibition of inducible gene expression of nitric oxide synthase, nitric oxide production and signal transducer suspension (extracellular signal–regulated kinases 1/2 and Janus kinase/signal transducer and activator of transcription). It also protects pancreatic cells expressing the estrogen receptor β through the same receptor along with Bcl-2. It acts as an antioxidant by inducing the expression of enzymes, such as manganese SOD and CAT, and increasing the proportion of reduced GSH / oxidized GSH. Thus, it provides the activity of the antioxidant enzymes leading to the decrease of ROS (Fig. **1**) [199]. It also has an anti-inflammatory effect because it reduces the expression of TNF-α and pro-inflammatory cytokines [200]. Furthermore, the consumption of genistein (1 mg/kg) for 8 weeks by diabetic rats contributed to the increase of SIRT1 levels and decreased expression of NF-κB and IL-1β. Thus, through the expression of SIRT1, treatment with genistein reduced tissue inflammation [201]. Studies have shown that it reduces inflammation caused by DM at the level of the retina, once this polyphenol decreases the tyrosine kinase and stimulates ERK and p38 dependent pathways [202]. However, one of its main problems is the dosage since the concentrations used in *in vitro* studies are always higher than those ingested in foods. To overcome this problem, some studies are already being conducted in order to find other plant-derived compounds that can be used together in order to increase polyphenol efficiency [203].

4.5. Resveratrol

Resveratrol is a non-flavonoid polyphenol of the stilbene class, that can be found in grapes, berries and red wine [121]. It is considered a plant antibiotic that is produced when plants are with a fungal infection or under environmental stress, and it exists in the form of two isomers: trans- and cis-resveratrol. It is known that the former is non-toxic and has a higher potential. Resveratrol can overcome the blood-brain barrier [204] and studies in patients indicate that it induces neuroprotective effects through its anti-inflammation properties [205]. In addition, a study in adult male albino rats showed that resveratrol exhibits anti-inflammatory properties in AD [206]. However, its neuroprotective abilities depend on the doses at which it is consumed. It is able to protect cellular components from the damage caused by oxidative stress since it has a direct action on ROS (Fig. **1**), which is largely due to its antioxidant power, since it promotes the activity of several antioxidant enzymes such as SOD, CAT, GSH-Px and glutathione reductase [207]. Oxidative stress can damage proteins, lipids, nucleic acids, and others. Over time it leads to irreversible neuronal damage. The use of resveratrol, in addition to having a protective role against oxidative stress, also improves the recovery of brain tissue by modulating glial functions, such as glutamate uptake activity, GSH content and S100 calcium-binding protein B secretion [204]. It also has the characteristic of acting on p38 preventing the activation of caspase 3 and, in this way, reducing the apoptosis of neuronal cells (Fig. **1**) [204, 208]. At the level of β-amyloid plaques, it avoids their aggregation as it promotes non-amyloidogenic processing of APP. As explained above, these plaques are formed from the proteolysis of APP through cleavage by the β- and γ-secretase. However, resveratrol promotes proteolysis through α-secretase, therefore preventing the formation of these plaques [204]. Although the mechanisms behind its action as an anti-amyloidogenic are not fully understood, studies show that resveratrol consumption results in AMPK activation, and consequently on SIRT1 activation, which may be a potential pathway by which autophagy and lysosomal clearance of β-amyloid [209], as well as α-secretase activity are promoted [70]. However, a study on AβPP/PS1 mice concluded that resveratrol reduction of β-amyloid deposition was due to increased intracellular proteasomal activity [210]. Resveratrol SIRT1-mediated neuroprotective effect was also previously found in p25 transgenic mouse, a model of AD, where resveratrol administration intravenebroventricularly (5 mg/ml) lead to reduced neurodegeneration in the hippocampus, prevented learning impairment, and decreased acetylation of PGC-1α and p53, known substrates of SIRT1 with a role in neuronal metabolism, detoxification of ROS and apoptosis [211]. In addition, Sarubbo *et al.* [212] also verified the brain anti-aging effects of resveratrol notably through the activation of SIRT1 and the modulation of inflammation by signaling pathways such as NF-κB.

In DM, studies indicate that resveratrol has the capacity to modestly reduce hyperglycaemia and also lead to some improvements in insulin sensitivity in prediabetic patients, namely through the activation of AMPK [213]. This action resembles that of current drugs used to treat DM (for example metformin [214]), which activate AMP-activated protein kinase. This, in turn, will activate the PI3k-Akt pathway, which leads to an increased phosphorylation of glycogen synthase kinase-3, and consequently, its action is inhibited and expression of genes, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase), in the liver decreases, therefore reducing gluconeogenesis [23]. In adult patients, the consumption of 1g / day of resveratrol was sufficient to verify these benefits. Resveratrol beneficial effect on insulin sensitivity was also associated with SIRT1 activation and consequent PGC-1α deacetylation, which affects mitochondrial metabolism [215]. Reduced mitochondrial oxidative capacity can cause insulin resistance through oxidative stress, thus, PGC-1α deacetylation and consequent activation lead to mitochondrial biogenesis, reducing oxidative stress caused by mitochondrial dysfunction [215].

Furthermore, it has been found that this polyphenol can affect the concentration of insulin in the blood [213]. Under normal physiological conditions, the secretion of insulin requires a set of processes that begin with the entry of glucose into the cells through GLUTs. The process then begins with hyperpolarization of the mitochondrial membrane in which ATP is formed increasing the ratio ATP/adenosine diphosphate (ADP). Potassium channels, sensitive to ATP, are closed and the membrane is depolarized. The calcium channels open and check the entrance of this ion to the cells that contribute to the secretion of insulin. Resveratrol acts by decreasing ATP formation which decreases the ATP/ADP ratio and attenuates the secretion of pancreatic insulin. However, the decrease in insulin secretion caused seems to be reversible since it does not cause permanent disturbances in the cells [216]. At the cytokines level, the action of resveratrol is also notorious since it decreases the release of TNF-α, IL-1 and IL-6 (Fig. **1**). In this way, the expression of nitric oxide synthase decreases, contributing to the decrease of nitric oxide production and to the decrease of inflammation [217]. As in AD, in DM it also leads to an improvement in the parameters of oxidative damage, once it increases the activity of the SOD, CAT and GSH-Px. In a study in mice, in which these ingested 22.4 mg / kg of resveratrol, it was also verified the increase of the sensitivity to insulin, thus improving its action [218]. All these data allow the perception of the beneficial properties of resveratrol and that in the future it may be used, in combination with other antidiabetic treatments, in the prevention and treatment of DM [216].

Resveratrol is the polyphenol with the most known SIRT1 association, being identified as an activator of this deacetylase, which has beneficial effects in both AD and DM. However, it should be noted that recent studies show that resveratrol may not be a direct activator of SIRT1 [219], or at least, may not be an allosteric one. Instead, it is suggested that resveratrol effect on SIRT1 may be indirect and through AMPK pathway activation [37] or that resveratrol may be a protein-substrate interaction stabilizer necessary for SIRT1 activation [220]. Nevertheless, SIRT1 appears to be required for resveratrol metabolic functions involving AMPK and PGC-1α [38, 150].

4.6. Curcumin

Curcumin is a non-flavonoid of the curcuminoid family and is found in saffron [221]. This phytochemical is sensitive to UV-vis light, high pH and oxygen [222]. Its half-life in human blood lasts about 8 hours and the half-life increases with decreasing pH [223]. In AD, studies showed that consumption of curcumin leads to a lower incidence of the disease [224, 225]. It has also been discovered that its consumption brings improvements to cognitive function and its power to reduce free radicals levels (Fig. **1**) is superior to that of vitamin E [224]. Garcia-Alloza *et al.* [226] found a reduction in the oxidative damage and the levels of β-amyloid plaques. In fact, some of the existing plaques were eliminated and the formation of new ones was prevented. This decrease in plaque production might be a result of the regulation of phosphorylation of the glycogen synthase kinase-3 beta enzyme, which appears to decrease the activity of PS1 and γ-secretase. Other studies, namely in BALB/c mice have addressed the anti-inflammatory capacity of curcumin, once it inhibits IL-1 signaling [227], and in primary cultured prefrontal cortical neurons found that curcumin prevents the cellular apoptosis, through the inactivation of caspase 3 [228].

In DM, curcumin controls blood glucose levels [229]. In fact, curcumin improves insulin sensitivity and fasting glucose levels since, as resveratrol, it decreases the expression of G-6-Pase and PEPCK, consequently reducing gluconeogenesis. It also decreases the synthesis of fatty acids, cholesterol and triglycerides. Despite the mechanism by which curcumin acts is not fully described, there are at least three possible modes of action. It can act at the intestinal level by inhibiting the absorption of cholesterol; cholesterol can be eliminated from the blood by the low density lipoprotein receptor, whose activity is increased by curcumin; or curcumin can increase the activity of enzymes that degrade cholesterol. It is thought to have a greater influence on intestinal absorption, but there are still no certainties [230]. In addition to these changes, TNF-α and IL-1 levels are reduced in curcumin studies, contributing to anti-inflammatory properties (Fig. **1**) [231]. In a work by Kumar *et al.* [232], in which the development of diabetic cataracts in male Wistar-NIN rats was studied, the authors verified that a diet with 0,01% of this curcuminoid was beneficial because it reversed lipid oxidation, increased the reduced GSH and the general activity of antioxidant enzymes. Also, it is known to be able to improve insulin resistance by acting on TNF-α release [233].

In a study by Jiménez-Flores *et al.* [151] treatment of mice db/db with 0.75% curcumin has been shown to decrease NF-κB expression in hepatic tissue, a key regulator of the inflammatory response. In addition, AMPK expression, which is known to be decreased in diabetic rats, was increased after treatment. AMPK inhibits hepatic glucose production and is associated with SIRT1, playing an important role in the lipid metabolism of hepatocytes. Therefore, its

modulation by curcumin may be a mechanism involved in the beneficial effects caused by this phenolic compound on DM.

In sum, the aforementioned evidence demonstrated the great antioxidant, anti-inflammatory, neuroprotective and anti-hyperglycaemic capacities of curcumin and how it may be an alternative to counteract both AD and DM.

4.7. Gallic Acid

Gallic acid belongs to the non-flavonoid class and to the hydroxybenzoic acids family. It can be found in fruits, such as pomegranate, grapes and some berries, in chocolate, nuts, wine and green tea [121]. This phytochemical has several activities including antioxidant, anti-inflammatory, anti-hyperglycaemic and cardioprotective actions [234]. Hajipour *et al.* [235], when studying the effects of gallic acid in AD, found that it has an antioxidative activity that decreases the brain levels of ROS. Also, González-Sarrías *et al.* [236] carried out an *in vitro* study to understand the effect that this phenolic compound had on ROS levels, redox activity and apoptosis induced by oxidative stress. Those authors found that it significantly decreased hydrogen peroxide-induced cytotoxicity by preventing the production of free radicals that would induce the activation of caspase 9, which in turn leads to the activation of caspase 3, resulting in the activation of the apoptotic pathway (Fig. **1**). Gallic acid restores the redox system, leading to increased reduction capacity and, therefore, restoring the antioxidant defense system.

Patel *et al.* [234] studied the effect of DM on rats and how gallic acid could contribute to improve their condition. The authors studied the ability of gallic acid to influence the levels of glucose, insulin, triglycerides, and cholesterol in the heart of these rats. In this way, those authors observed that this phytochemical produces an increase of the endogenous antioxidant enzymes SOD, GSH and CAT in the heart and diminishes the peroxidation of lipids. Moreover, it significantly reduces glucose levels and increases insulin levels. In a study by Doan *et al.* [237] intraperitoneal administration of gallic acid (10 mg/kg) has been shown to decrease insulin resistance in C57BL/6 mice. The authors related this decrease with the activation of the AMPK pathway and consequently of SIRT1 suggesting that this phytochemical may be an ally in the treatment of metabolic diseases. In addition, they mention that gallic acid can activate the Akt pathway and decrease gluconeogenic genes, such as PEPCK and glucose 6-phosphatase, contributing to lower glycaemic and insulin resistance levels [237].

Benefits were also found at the level of cardiomyopathy, as it significantly reduces blood pressure, contraction force and increases the cardiac frequency. Gallic acid is also able to reduce free radicals resulting in a decrease in oxidative stress (Fig. **1**) [234]. Also, in the brains of diabetic rats it revealed the ability to reduce free radicals levels and inhibit lipid peroxidation. It decreased oxidative stress and protected β-pancreatic cells, which caused a decrease in blood glucose levels. As in the heart, at the brain level it also increased the activity of enzymes, such as SOD, CAT and GSH, which demonstrates its antioxidant properties [238]. Due to these antioxidant and anti-inflammatory properties, some pharmaceutical companies already use it in food supplements (mainly as an antioxidant agent) [239].

Although there are already several studies in both AD and DM that prove the various properties of this phenolic acid, there is a consensus that it is still necessary to continue investigating the mechanisms underlying these properties and to verify if the concentration present in the foods are sufficient to confer all these benefits [235, 236].

4.8. Therapeutic Potential

In view of the protective effect of polyphenols, these phytochemicals are considered to have a huge preventive and therapeutic potential for DM and AD. DM is a chronic disease and can be controlled with oral hypoglycaemic agents or insulin administration depending on the type of DM, through a healthy diet and regular exercise. However, pharmacological therapy is costly, requires patient training and high-adherence to avoid side effects [31]. Furthermore, increasing morbidity, mortality and the rising prevalence of DM complications reveals that the current pharmacotherapy is not sufficient and supplementary treatments that increase the effectiveness of the therapy are needed for the management of DM [25]. In this context, alterations in lifestyle, especially in dietary habits, can be vital, as they are easy and safe to implement. It has been shown that a healthy diet can help to prevent the development of DM and/or can delay complications associated with the disease [31].

The high consumption of polyphenols-enriched foods has been associated with a lower risk of DM. In a cohort study of elderly people (437 men and 500 women; aged between 65 and 100 years) living in Mediterranean islands (from Cyprus, Mitilini, Samothraki, Kefalonia, Crete, Corfu and Zakynthos islands), long-term tea intake was associated with reduced levels of fasting blood glucose and lower prevalence of DM [137]. Meanwhile, Wedick *et al.* [240], with data from three US cohort studies, observed that a higher consumption of anthocyanins and anthocyanin-enriched foods (*e.g.* blueberries, red apples and strawberries) was associated with a lower risk of T2DM. A meta-analysis analysed data from six prospective cohorts and showed that individuals with the highest intake of flavonoids had a 9% lower risk of DM [241].

Polyphenols are also beneficial to DM patients because of their capacity to improve insulin sensitivity [242, 243], to protect pancreatic β-cells against glucose toxicity, oxidative damage and cell apoptosis, to inhibit α-amylases or α-glucosidases (consequently decreasing starch digestion), to inhibit advanced glycation products formation and to activate signaling pathways that improve glucose uptake in muscle cells and adipocytes [25, 31]. Furthermore, polyphenols can also prevent the long-term development of complications associated with DM, such as cardiovascular disease, neuropathy, nephropathy and retinopathy [25].

On the other hand, the importance of developing new therapies for AD arises from the fact that currently prescribed drugs are only able to reduce symptoms and improve cognitive decline but are not able to prevent or reverse the progression of the disease. It is thought that the lack of effi-

cacy of these drugs is due to the majority being directed towards only one mechanism, in the face of a multifactorial pathology that is characterized by complex relationships between several interconnected biological phenotypes [244]. AD involves various phenomena, such as the formation of amyloid and tau aggregates and cholinesterase disorders, and is exacerbated by oxidative stress, metal deposition, mitochondrial dysfunction, increased immune responses and mechanisms of chronic inflammation [26].

Cohort studies in healthy older people showed that those with the highest polyphenol intakes had a significantly reduced risk of dementia [138] and that polyphenol-enriched diets improved cognition [245]. This is in agreement with Krikorian *et al.* [246], who showed that elderly individuals with mild cognitive decline demonstrated significantly improved verbal learning after drinking grape juice for 12 weeks. Thus, the ability of polyphenols to reduce oxidative stress and inflammation, modulate APP processing, prevent β-amyloid aggregation and favour disruption of preformed NFT, make them ideal for therapeutic use in AD [110].

In this context, polyphenols are a possible alternative form of therapy capable of acting on several mechanisms inherent to the pathologies of DM and AD simultaneously. They also have the advantage of being compounds that are naturally found in the diet, so that their therapeutic implementation can be through a dietary alteration or nutritional supplements, which is more cost-effective, easier to implement, socially acceptable and generally safer [26].

5. LIMITATIONS AND PITFALLS

Despite the proven benefits of polyphenols, there are still limitations to be overcome prior to their implementation as therapeutic agents. The main limitation is the fact that the pharmacological action of polyphenols depends on their bioavailability in the organism. In the case of neurodegenerative diseases, there is also the limiting factor that polyphenols must be able to penetrate the blood-brain barrier, in a biologically active form and in a sufficient dose to exert neuroprotective effects, which might not be possible at the doses available in the diet or in supplements [247]. In addition, not all polyphenols can be absorbed, some are poorly absorbed from the gastrointestinal tract and rapidly eliminated from the body. Metabolic modification of polyphenols may further decrease their effect [247].

In the case of DM, there is even evidence that the pathology itself influences the benefits of polyphenols, causing changes in their pharmacokinetics and bioactivity. Therefore, it is necessary to understand these changes, in order to improve the benefits of these phytochemicals and subsequent clinical outcomes for diabetic patients [31].

Besides, consideration should also be given to possible interactions with other phytochemicals, food components or drugs that may decrease the beneficial effects of polyphenols or lead to toxicity [26]. Also, exaggerated consumption of certain compounds can lead to adverse effects, such as thyroid toxicity, malnutrition, estrogenic activity and infertility [247]. The studies performed on polyphenols influence are usually done during short periods of time, failing to ascertain the long-term effects, and there is no standard for the methods and models used in research. Therefore, both the mechanism and the safety of administration of high doses of polyphenols need to be investigated, in order to verify if they actually act specific to certain pathologies, or whether they only stimulate normal healthy mechanisms [26].

As future perspectives to overcome the current limitations, new strategies, based on nanotechnology and new drug delivery systems, can be used to increase the bioavailability of the polyphenols and promote their penetration into the blood-brain barrier. For example, polyphenols may be encapsulated in phospholipid nanoparticles or incorporated in biodegradable polymers. There is also the possibility of using bioactive analogues to simulate polyphenols action or improve pharmacokinetics and use adjuvants to increase polyphenol uptake by the body. It is also fundamental to study more patients and use bigger samples during longer periods of time, in order to ascertain the effects of long-term treatment with polyphenols [248].

CONCLUSION

It is clear that a complex interplay between environmental, nutritional and genetic factors plays a common role in DM and AD pathogenesis. Therefore, it is worthwhile to try dietary strategies that can counterattack these two pathologies simultaneously. The polyphenols explored in this review can mitigate risk factors, progression and symptoms of DM and AD, as they are able to modulate carbohydrate and lipid metabolism, and they can penetrate the blood-brain barrier, having a neuroprotective effect, contributing to a healthier brain. However, it is not yet possible to fully explain the mechanisms involved in the therapeutic effects of polyphenols in DM and AD, as they are multifunctional agents, able to modulate several processes at the cellular and enzymatic levels and can have epigenetic effects. It is necessary to continue studying polyphenols as potential nutraceuticals and to solve the question of their bioavailability, at concentrations that allow pharmacological action, which is the major limiting challenge to their use as therapeutic agents [110].

LIST OF ABBREVIATIONS

ACh	=	Acetylcholine
AChE	=	Acetylcholinesterase
AD	=	Alzheimer's Disease
ADP	=	Adenosine diphosphate
Akt	=	Protein kinase b
AMPK	=	5' adenosine monophosphate-activated protein kinase
ApoE	=	Apolipoprotein E
APP	=	Amyloid precursor protein
ATP	=	Adenosine triphosphate
Bax	=	Bcl-2-like protein 4
BChE	=	Butyrylcholinesterase
Bcl-2	=	B-cell lymphoma 2

CAT	=	Catalase
DM	=	Diabetes Mellitus
EC	=	Epicatechin
ECG	=	Epicatechin gallate
EGC	=	Epigallocatechin
EGCG	=	Epigallocatechin-3-gallate
ERK	=	Extracellular signal-regulated kinases
FOXO	=	Forkhead box O
G-6-Pase	=	glucose-6-phosphatase
GLUT1	=	Glucose transporter 1
GLUT2	=	Glucose transporter 2
GLUT3	=	Glucose transporter 3
GLUT4	=	Glucose transporter 4
GSH	=	Glutathione
GSH-Px	=	Glutathione peroxidase
IGF-I	=	Insulin-like growth factor I
IL-1	=	Interleukin 1
IL-6	=	Interleukin 6
LC–MS	=	Liquid chromatography-mass spectrometry
LDH	=	Lactate dehydrogenase activity
MAPK	=	Mitogen-activated protein kinases
NAD	=	Nicotinamide adenine dinucleotide
NADPH	=	Nicotinamide adenine dinucleotide phosphate
NF-*k*B	=	Nuclear factor kappa-light-chain-enhancer of activated B cells
NFT	=	Neurofibrillary tangles
PEPCK	=	Phosphoenolpyruvate carboxykinase
PI3K	=	Phosphatidylinositol 3 kinase
PGC-1α	=	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PKC	=	Protein kinase C
PS1	=	Presenilin 1
PSEN1	=	Presenilin 1 gene
ROS	=	Reactive oxygen species
SIRT1	=	Sirtuin 1
SOD	=	Superoxide dismutase
STZ	=	Streptozotocin
T1DM	=	Type 1 diabetes mellitus
T2DM	=	Type 2 diabetes mellitus
TNF-α	=	Tumour Necrosis Factor alpha

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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