# Promising Potential of Dietary (Poly)Phenolic Compounds in the Prevention and Treatment of Diabetes Mellitus

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REVIEW ARTICLE

# Promising Potential of Dietary (Poly)Phenolic Compounds in the Prevention and Treatment of Diabetes Mellitus

Tânia R. Dias[a,b], Marco G. Alves[a], Susana Casal[c], Pedro F. Oliveira[b,d], and Branca M. Silva[a,*]

[a]*Centro de Investigação em Ciências da Saúde (CICS-UBI), Universidade da Beira Interior, Rua Marquês d'Ávila e Bolama, 6201-001, Covilhã, Portugal;* [b]*Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS) and Unit for Multidisciplinary Research in Biomedicine (UMIB), University of Porto, Rua de Jorge Viterbo, 4050-313, Porto, Portugal;* [c]*LAQV/REQUIMTE - Laboratory of Bromatology and Hydrology, Faculty of Pharmacy, University of Porto, Rua do Campo Alegre, 4150-755, Porto, Portugal;* [d]*i3S- Instituto de Investigação e Inovação em Saúde, Universidade do Porto, R. Alfredo Allen, 4200-135, Porto, Portugal*

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**Abstract:** ***Background:*** The incidence of diabetes mellitus (DM) is reaching alarming proportions worldwide, particularly because it is increasingly affecting younger people. This reflects the sedentary lifestyle and inappropriate dietary habits, especially due to the advent of processed foods in modern societies. Thus, unsurprisingly, the first medical recommendation to patients with clinically evident DM is the alteration in their eating behaviour, particularly regarding carbohydrates and total energy intake. Despite individual and cultural preferences, human diet makes available a large amount of phytochemicals with therapeutic potential. Phenolic compounds are the most abundant class of phytochemicals in edible plants, fruits and beverages. These compounds have strong antioxidant and anti-inflammatory activities that have been associated with specific features of their chemical structure. Among others, such properties make them promising antidiabetic agents and several mechanisms of action have already been proposed.

***Objective:*** Herein, we discuss the recent findings on the potential of dietary phenolic compounds for the prevention and/or treatment of (pre)diabetes, and associated complications.

***Conclusion:*** A broad range of studies supports the innate potential of phenolic compounds to protect against DM-associated deleterious effects. Their antidiabetic activity has been demonstrated by: i) regulation of carbohydrate metabolism; ii) improvement of glucose uptake; iii) protection of pancreatic β-cells; iv) enhancement of insulin action and v) regulation of crucial signalling pathways to cell homeostasis. Dietary phenolic compounds constitute an easy, safe and cost-effective way to combat the worrying scenario of DM. The interesting particularities of phenolic compounds reinforce the implementation of a (poly)phenolic-rich nutritional regime, not only for (pre)diabetic patients, but also for non-diabetic people.

**Keywords:** Human health, prediabetes, diabetes mellitus, phytochemicals, diet, (Poly)phenols, antioxidants.

## 1. INTRODUCTION

The number of people diagnosed with diabetes mellitus (DM) is epidemically increasing all over the world. The International Diabetes Federation (IDF) has estimated that by the year 2035, the number of DM cases may reach approximately 600 million people, thus affecting more than one in 10 adults worldwide [1]. This metabolic disease, which is mainly characterized by hyperglycaemia [2], is now globally considered one of the most common non-communicable diseases. Due to its high incidence and the vast range of associ-

*Address correspondence to this author at the Health Sciences Research Centre, Faculty of Health Sciences, University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal;
Tel: +351-27-532-9077; Fax: +351-27-532-9099;
E-mail: bmcms@ubi.pt

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ated health complications, DM constitutes a major problem for health care systems [3].

There are two major types of DM: type 1 (T1DM) and type 2 (T2DM). T1DM accounts for 5-10% of the total cases of DM and although it can affect people of all ages, epidemiological studies have shown a higher incidence in children and adolescents [4]. Most of the cases of T1DM have an autoimmune basis, where there is a mistaken attack by the immune system to normal insulin-producing cells (pancreatic β-cells), which culminates in their destruction (type 1a). However, a small minority of cases result from an idiopathic destruction or failure of β-cells (type 1b). Patients with T1DM present an absolute deficiency of insulin, thus they are dependent on the administration of exogenous insulin to survive [5].

On the other hand, in T2DM there is a resistance to insulin action by the insulin-dependent tissues, combined with an insufficient production of insulin to compensate this resistance [6]. This is the most prevalent type of DM worldwide, accounting for 90-95% of all DM cases and it is increasing at a disturbing rate. T2DM can be seen as a "sneaky condition" since its harmful health effects can slowly be built over many years until severe complications become clinically evident [5]. Therefore, patients with T2DM may develop some long-term complications induced by the disease even before it is diagnosed. For that reason, an intermediate state known as prediabetes was established and has been a matter of study in recent years [7-9]. It is considered that patients with blood glucose levels above normal, but not high enough to meet the diagnostic criteria for T2DM are defined as prediabetics [10]. Prediabetes is a warning status to the predisposition of developing T2DM [11]. Though, with the right lifestyle modifications and certain medications, this condition can be reverted or at least controlled. The reversible particularity of prediabetes has made it a popular target of research, in order to find new ways to delay or even avoid the onset of T2DM. Historically, T2DM has always been considered a disease of older people, but nowadays it is increasingly diagnosed in youth. The development of this disorder at relatively young age seems to be a result of the rapid cultural and social changes, as well as the increasing urbanization, which ended up in unhealthy lifestyles [12]. The lack of physical activity and the wrong dietary habits of young people are surprising in such a modern world that offers an easy access to information. This is partly due to the availability of a wide variety of attractive but unhealthy food products such as sugars-rich and/or fats-rich processed foods, and a certain lack of awareness regarding their harmful effects. Many researchers believe that the prevention of DM will pass through a reformulation of educational programs, in order to teach children the lifestyle implications in the predisposition of developing metabolic diseases, such as DM [12-14].

Compelling evidence shows that oxidative stress plays a key role not only in the pathogenesis of prediabetes and DM, but also in the development of late-complications [15]. In living organisms, the levels of free radicals and other reactive species are controlled by inner antioxidant defences. However, these intrinsic antioxidants have a limited ability to counteract free radicals. Most of the times they can minimize, but not completely prevent, oxidative damage to biomolecules, eventually leading to disease [16]. Therefore, exogenous antioxidants with the ability to scavenge free radicals may be of great value in the prevention of the onset and/or progression of human diseases, including DM [17]. Although plants are nutritional sources of macroconstituents as carbohydrates, lipids, proteins and fibers, they are also a rich source of antioxidants and their therapeutic potential has been used since ancient times. Besides observed changes in human eating habits over the years and the different gastronomic cultures, plants continue to represent a large portion of most people's nutrition, but are being increasingly reduced in modern youth eating habits [18]. Interestingly, human diet is very rich in phenolic compounds, which are the most abundant natural antioxidants [19]. There is compelling evidence reporting the benefits of the long-term consumption of phenolics in the prevention of several oxidative stress-induced diseases, such as DM [20, 21]. However, despite the specific biological mechanisms by which phenolic compounds improve human health are largely unknown, it has become clear that their action goes beyond the modulation of oxidative stress. It has been shown that polyphenols can modulate metabolic enzymes, nuclear receptors, gene expression and multiple signalling pathways [22]. This review aims to discuss the most recent findings on the potential of (poly)phenolic compounds in the prevention and/or treatment of (pre)diabetes and associated complications.

## 2. DIETARY SOURCES AND CHEMISTRY OF PHENOLIC COMPOUNDS

Among the several thousands of phenolic compounds that have already been identified in the Plant Kingdom, only a limited number is significantly pre-

sent in human diet. Moreover, phenolic compounds are almost ubiquitous in edible and medicinal plants. Although their diversity makes it difficult to estimate the total content of phenolic compounds in foods, it has been demonstrated that it may be as high as 150 g/kg (in cloves) [23]. Spices, fruits, seeds and vegetables are among the richest dietary sources of phenolic compounds. Additionally, there are some beverages that highly contribute to the daily intake of phenolics: coffee (200-550 mg of phenolics/cup), tea (150-200 mg of phenolics/cup) and wine (200-800 mg of phenolics/glass) [24, 25]. Other (poly)phenol-rich products, include cereals, cocoa products and olive oil [23]. There are so many phenolic-rich foodstuffs that it is really difficult to follow a diet totally free of these phytochemicals. Due to the individual food preferences and country-specific dietary patterns, there is a high variability on the daily content of consumed phenolics. However, it has been reported that people following a diet containing several servings of fruit and vegetables per day, as well as coffee-rich beverages commonly reach a total (poly)phenol intake of 1 g per day [26, 27]. This is a much higher amount relatively to all the other classes of antioxidants, including vitamin C and E [28].

Phenolic compounds are a complex class of naturally-occurring bioactive molecules that result from plants secondary metabolism, more specifically from shikimate and acetate pathways [29]. These phytochemicals are essential to plant pigmentation, growth and reproduction, but they also act as a defence system against ultraviolet radiation, oxidants, and aggression by pathogens [30]. Generally, phenolic compounds with only one phenolic ring are considered simple phenols, while those with more than one phenolic ring are designated as polyphenols. More specifically, considering the number of phenolic rings that they contain and the structural elements that bind these rings to one another, phenolic compounds can be classified into four main classes: phenolic acids (simple phenols), stilbenes, lignans and flavonoids (polyphenols) (Fig. **1**) [31]. In this section, we summarize the main structural properties of each class and the major dietary sources.

### 2.1. Phenolic Acids

Phenolic acids are very abundant among dietary compounds, being particularly common in berries and coffee [32]. They are hydroxyl derivatives of aromatic carboxylic acids that have a single phenolic ring in their structure. The two main types of phenolic acids are classified as hydroxybenzoic acid derivatives (C6-C1) and hydroxycinnamic acid derivatives (C6-C3) [33]. Gallic, protocatechuic and *p*-hydroxybenzoic acids are examples of benzoic acid derivatives (Fig. **1**). Generally, their content in edible plants is lower than that of hydroxycinnamic acid derivatives, which include caffeic, *p*-coumaric, ferulic and sinapic acids. In fact, derivatives of hydroxycinnamic acid are ubiquitous in the Plant Kingdom. Caffeic acid is one of the most common species, being present in many fruits (*e.g.* apples, grapes, plums, tomatoes) and vegetables. Chlorogenic acid, an ester of caffeic acid, is frequently found in coffee (250-750 mg of chlorogenic acid/L) [34] and green tea (340 mg/kg of extract) [35]. Ferulic acid is also abundant in nature and is usually linked with dietary fiber, as it can be mainly found in cereals [36].

### 2.2. Stilbenes

Stilbenes are composed of two phenolic rings linked by a two-carbon methylene bridge and they are characterized by the presence of a 1,2-diphenylethylene nucleus (Fig. **1**) [37]. This class of phenolic compounds appears in very low amounts in our diet, partly due to the fact that the enzyme stilbene synthase, which is involved in stilbene biosynthesis, is not ubiquitously expressed in the Plant Kingdom. However, a well-known polyphenol that belongs to this class is resveratrol (3,4',5-trihydroxy stilbene) and it has already been identified in at least 185 plant species [37]. Resveratrol is mainly found in grapes skin (50-100 mg/kg fresh weight), peanuts, mulberries and red wine (0.3-2 mg/L) [38].

### 2.3. Lignans

Lignans are non-nutrient and non-caloric compounds that present a 2,3-dibenzylbutane structure that is formed by the dimerization of two cinnamic acid residues (Fig. **1**). These polyphenols present a phytoestrogenic action due to their estrogen agonist and antagonist properties [39]. Despite the relatively low content of lignans in food, the most commonly found are lariciresinol, matairesinol, pinoresinol, and secoisolariciresinol [40]. Usually, the lignan content in foods does not exceed 20 mg/kg fresh weight. Nevertheless, there are two lignan-rich dietary sources: flaxseed, which contains 3.4 g/kg fresh weight, mainly secoisolariciresinol [41], and sesame seeds that contain 3.7 g/kg fresh weight [42]. Other minor sources of lignans include cereals, lentils, fruits (pears, prunes) and vegetables (garlic, asparagus, carrots), but their concentration is about 1000 times lower relative to flaxseed [26].

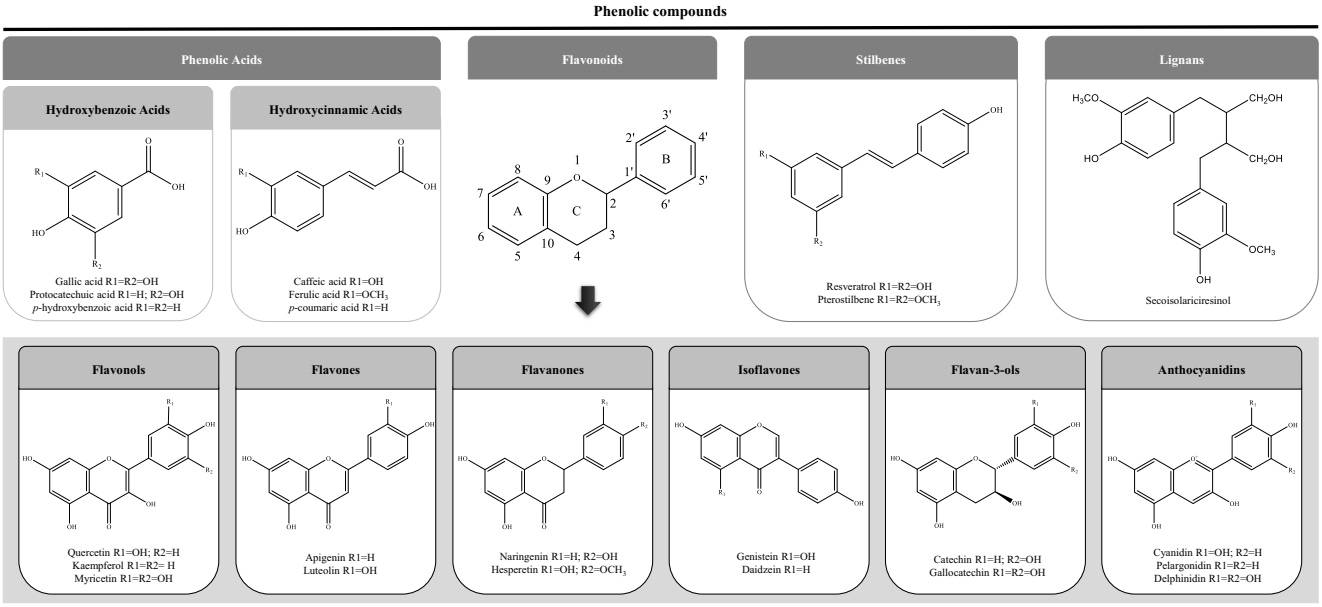


**Fig. (1).** Schematic illustration of the chemical structures of the main classes of phenolic compounds: phenolic acids, flavonoids, stilbenes and lignans. Phenolic acids can be further classified as hydroxybenzoic acid derivatives, such as gallic, protocatechuic and *p*-hydroxybenzoic acids, or hydroxycinnamic acid derivatives, including caffeic, ferulic and *p*-couramic acids. The most abundant phenolic compounds in human diet are flavonoids, which can be subdivided into flavonols (*e.g.* quercetin, kaempferol, myricetin), flavones (*e.g.* apigenin, luteolin), flavanones (*e.g.* naringenin, hesperetin), isoflavones (*e.g.* genistein, daidzein), flavan-3-ols (*e.g.* catechins, gallocatechin) and anthocyanidins (*e.g.* cyanidin, pelargonidin, delphinidin). Stilbenes and lignans are not widely distributed in plants. Among the most well-known stilbenes are resveratrol and pterostilbene, while one of the most abundant lignan is secoisolariciresinol.

## 2.4. Flavonoids

Flavonoids represent the most abundant class of polyphenols in human diet and also the most studied one. Indeed, more than 4000 varieties of flavonoids have been already identified [43]. Flavonoids contain two phenolic rings (A- and B-rings), which are linked by three carbon atoms that form a pyran ring (heterocyclic ring containing oxygen, the C-ring), having a common C6-C3-C6 skeleton structure (Fig. **1**). Depending on the degree of oxidation of the central heterocycle, flavonoids can be divided into six main subclasses: flavonols, flavones, flavanones, isoflavones, flavan-3-ols and anthocyanidins (Fig. **1**) [44]. The individual differences within each group are not only due to the variation in number and arrangement of the hydroxyl groups, but also to their extent of alkylation, methylation and glycosylation. Thus, flavonoids may occur as aglycones, glycosides and methylated derivatives. While glycosides refer to flavonoid molecules coupled to sugar moieties, the aglycone form corresponds to the parent unattached molecule [45]. The most usual substitution occurs with the sugar residue glucose, but there are other possible carbohydrate substitutions such as arabinose, galactose, glucorhamnose, lignin, rhamnose, and xylose [46].

### *2.4.1. Flavonols*

Flavonols, which have a 3-hydroxy pyran-4-one group on the C-ring and a 2,3-double bound, are widespread in human diet, especially in fruits, vegetables and tea. Quercetin is the most abundant flavonol and is predominantly found in apples (100-300 mg/kg fresh weight) [47], onions (200-600 mg/kg fresh weight) [47] and tea (10-25 mg/L) [48]. Other representative flavonols include myricetin and kaempferol (Fig. **1**). Flavonols are usually present in glycosylated forms, often associated with glucose or rhamnose, with the conjugation occurring at the 3 and 7 positions [49]. The biosynthesis of flavonols depends on the exposure to sunlight [50]. In fact, it has been demonstrated that grape berries can adapt to high light by upregulating the expression of several flavonoid biosynthetic genes present in berry skin, thus leading to an increased content of flavonols [51]. Therefore, different concentrations of flavonols can be found between pieces of fruit from the same tree or between the outer and inner leaves of several vegetables (*e.g.* lettuce and cabbage) [52].

### *2.4.2. Flavones*

Flavones are structurally similar to flavonols, except that they lack a hydroxyl group in the 3-position on the C-ring (Fig. **1**). Although not so common in our diet, flavones have been identified in dietary sources such as pepper (5-10 mg/kg fresh weight), parsley (240-1850 mg/kg fresh weight) and celery (20-140 mg/kg fresh weight) [26]. Flavones often occur in plants in the glycosylated form, being 7-hydroxyl the most common position for sugar substitution [53]. Apigenin, luteolin, wogonin, and baicalein are examples of this class of flavonoids.

### *2.4.3. Flavanones*

Flavanones are characterized by an unsaturated 2,3-bond in the C-ring and the presence of a chiral centre at position 2 (Fig. **1**). In nature, they occur predominantly as the S- or (-)-enantiomer with the C-ring attached to the B-ring at position 2 in the α-configuration [18]. These flavonoids are mainly found in citrus fruits. For instance, orange juice contains about 200-600 mg/L of the flavanone hesperidin [54]. However, it has been reported that a whole citrus fruit may contain a concentration up to 5 times higher than a glass of juice from the same fruit. This is particularly due to some specific parts of the fruit, since the white spongy portion (albedo) and the membranes separating the segments have a very high flavanone content [26]. Generally, flavanones are glycosylated at position 7. Moreover, several flavanone glycosides contribute to the bitter taste of citrus fruits and this bitterness depends on the structure of the sugar moiety. For instance, while the disaccharide neohesperidose imparts a bitter taste, rutinose is flavourless [55].

### *2.4.4. Isoflavones*

In the case of isoflavones, the B-ring is attached to the C-ring in the position 3, rather than in the position 2 as it happens with the other classes of flavonoids [44]. The richest source of isoflavones is soybean, containing 580-3800 mg/kg fresh weight. Consequently, soy milk is also a major source of isoflavones (30-175 mg/L) [56]. Genistein and daidzein are the main isoflavones present in soy products (Fig. **1**). Other dietary sources of isoflavones include several legumes, such as lentils and chickpeas [57]. A significant estrogenic effect (*in vivo*) has been ascribed to these flavonoids [19]. There is evidence reporting that despite the considerable degradation of isoflavones in the gut, their concentrations in the plasma may greatly exceed those of endogenous estrogens. Although they are not steroids, they have hydroxyl groups in positions 7 and 4', which gives them an analogous configuration to that of the hydroxyls in the estradiol molecule. This feature confers isoflavones the ability to bind to estrogen receptors and this particularity led to its classification as phytoestrogens [26].

### *2.4.5. Flavan-3-ols*

Flavan-3-ols are characterized by the absence of the pyran-4-one structure and the 2,3-double bond in the C-ring (Fig. **1**). This class of flavonoids is a very complex one, ranging from the simple monomer form (catechins) to the oligomeric and polymeric form (proanthocyanidins) [44]. In contrast to other classes of flavonoids, flavan-3-ols are not glycosylated in foods. Red wine (80-300 mg/L), beans (350-550 mg/kg fresh weight), and many fruits, such as apricots (100-250 mg/kg fresh weight) and cherries (50-220 mg/kg fresh weight), are among the richest sources of catechins [58, 59]. Moreover, tea is also a major source of catechins. Indeed, its popularity was associated with its stimulating properties and potential health effects, which are mainly ascribed to their catechin content [60]. Different types of tea can be obtained from *Camellia sinensis* (L.) plant according to leaves harvesting and processing: white, green, oolong and black tea [61]. The content of catechins in certain brands of green tea, black tea and fruit infusions (determined by high-performance liquid chromatography - HPLC/DAD) has been reported to be approximately 52-84, 6-48 and 9-14 g/kg of dry leaves, respectively [62]. Based on an average tea consumption of three cups of tea (600 mL), the total intake of tea catechins by UK population has been estimated to be about 400, 90, and 60 mg/day from green tea, black tea, and fruit infusions, respectively [62]. Moreover, other study reported that white tea may contain higher catechins content (up to 33 g/kg of extract, as determined by proton nuclear magnetic resonance - $^{1}$H-NMR) than green tea (18 g/kg of extract) [63]. The most abundant tea catechins are: (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG) and (-)-epigallocatechin gallate (EGCG). More specifically, EGCG is the major catechin present in unfermented teas (white and green tea) [61]. On the other hand, in the process of fermentation during black tea production, catechins are enzymatically oxidized by polyphenol oxidase to more complex polyphenols known as theaflavins (dimers) and thearubigins (polymers) [64]. Theaflavins contribute to the brisk and bright taste of these types of tea, whereas thearubigins provide strength and color. These compounds are also found in semi-fermented teas (oo-

long tea). Oxidized teas usually show a weaker protective effect against free radicals relative to non-fermented teas due to the lower catechin content, but they still demonstrate good antioxidant properties [65].

Proanthocyanidins, also known as condensed tannins, are generally present in foods in association with catechins. The richest sources of proanthocyanidins are fruits (*e.g.* strawberries, blueberries, apples, pears and grapes), but they are also present in chocolate and in some beverages such as coffee, red wine and tea [66]. Proanthocyanidins are responsible for giving flavour and, at the same time, for the astringent character of certain foods and beverages, and for the bitterness of chocolate. This phenomenon results from the formation of complexes with salivary proteins [67]. Besides condensed tannins, there are other classes of tannins, including hydrolysable and complex tannins [68]. Hydrolysable tannins are usually present in low amounts in plants, but they have been described in certain fruits (*e.g.* pomegranate, strawberries, raspberries), clove, barley, rice and oat [69]. These molecules contain a polyol (generally D-glucose) as a central core and the hydroxyl groups are partially or totally esterified with phenolic acids, like gallic acid (gallotannins) or ellagic acid (ellagitannins). This type of tannins is easily hydrolysed by mild acids and bases to yield sugars and phenolic acids [69].

### *2.4.6. Anthocyanidins*

Anthocyanidins are found in red wine, cereals, and certain vegetables (*e.g.* cabbage, beans, onions), but the richest source of these polyphenols are red fruits [70]. Anthocyanidins include a group of water-soluble plant pigments that are responsible for the colour of flowers, fruits and red wine. This property is related to the presence of an oxonium ion on the C-ring (Fig. **1**) and the anthocyanidin content is generally proportional to the colour intensity [71]. Thus, the increase in colour intensity with the fruit ripeness or wine aging is related to the increase in anthocyanidin content. Red wine contains between 200 and 350 mg of anthocyanins/L [72]. When anthocyanidins (aglycone form) are coupled to a sugar moiety, anthocyanins are formed (glycoside form). Generally, glycosylation of anthocyanidins occurs at position 3 with a glucose substitution and this process makes glycosides more resistant to degradation than aglycone forms. Other processes contributing to its resistance include esterification with various organic acids (citric and malic acids) and phenolic acids and the formation of complexes with other flavonoids (copigmentation). The most common anthocyanidin aglycones present in human diet are pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin [73].

## 3. LINKAGE BETWEEN PHENOLIC COMPOUNDS STRUCTURE AND ACTIVITY

Biological properties of phenolic compounds, especially antioxidant activity, bioavailability, and specific interactions with cell receptors and enzymes, are known to be related to their particular chemical structures [44]. According to the arrangement of functional groups in relation to the nuclear structure, phenolics may have radical scavenging, chelating and/or oxidant activity. One of the most notorious properties of phenolic compounds is their anti-oxidative stress activity. Generally, oxidative stress results from an imbalance between the production of free radicals (*e.g.* superoxide anion, hydroxyl and hydrogen peroxide radicals) and the ability of biological antioxidant defence system, such as catalase (CAT, EC 1.11.1.6), superoxide dismutase (SOD, EC 1.15.1.1), glutathione peroxidase (GPx, EC 1.11.1.9) and others to neutralize or remove them [74]. However, the dual role of free radicals in living organisms is of particular concern. Although they are important regulators of certain biological processes (vascular tone and blood pressure) and cellular functions (gene expression, differentiation, mitochondrial function and apoptosis), they are usually unstable and highly reactive [75, 76]. The most common are the ones derived from oxygen, commonly known as reactive oxygen species (ROS). These free radicals are known to induce damage to proteins, membrane lipids and nucleic acids, eventually leading to cell death. The ability of phenolic compounds to delay, inhibit, or prevent oxidative damages gives them the definition of antioxidants. The mechanisms by which phenolics can control oxidative stress include: i) neutralization/reduction of ROS formation, either by modulating the activity of several enzymes or by chelating trace elements involved in ROS generation; ii) scavenging ROS, and iii) restoration of redox homeostasis by enhancing the endogenous defence system [22].

The free radical scavenging capacity of (poly)phenols has been primarily attributed to their aromatic rings and the highly conjugated system with multiple hydroxyl groups, which make them good electron or hydrogen atom donors. The spatial position and number of hydroxyl groups are great determinants of the antioxidant potency of phenolic compounds [44]. In fact, phenolic compounds with catechol groups, which are aromatic rings with two hydroxyl groups in the *ortho*-position, are more potent antioxidants than those

with simple phenol groups (aromatic rings with a single hydroxyl group).

There are several methods to evaluate the antioxidant activity of phenolic compounds, but the most common are the trolox equivalent antioxidant capacity (TEAC), the ferric reducing antioxidant power (FRAP), and the hypochlorite scavenging capacity. Data obtained from these techniques, allowed the sequential organization of phenolic compounds according to the degree of antioxidant activity: simple phenolic acids < hydroxycinnamic acids < flavonols < flavan-3-ols < procyanidin dimers [77]. Concerning phenolic acids, antioxidant activity is known to increase with the distance separating the carbonyl group and the aromatic ring. For that reason, hydroxycinnamic acid derivatives present a more potent antioxidant activity than benzoic acid derivatives [78]. The 7,8-double bound of hydroxycinnamic acids is also an enhancer of their antioxidant potential relative to hydroxybenzoic acids (Fig. **2**). The electron-withdrawing activity of the carboxyl group in phenolic acids has a negative influence on their hydrogen donating abilities, and consequently in their antioxidant potential [79]. However, the substitution of carboxyl group with *O*-alkyl ester groups was reported to increase the antioxidant activity of phenolic acids [80]. The substitution with hydroxyl groups on benzoic ring at the *ortho*-position and/or *para*-position also increases phenolic acids antioxidant activity when compared to other positions and unsubstituted phenolic ring (Fig. **2**) [81]. Moreover, *ortho*-hydroxyl groups were considered to be highly powerful electron donors when compared with *ortho*-methoxy groups [80]. Gallic acid represent the most potent antioxidant among the hydroxybenzoic acids and rosmarinic acid among the hydroxycinnamic acids [77].

The higher antioxidant activity of flavonoids relative to phenolic acids has been related to the increase in the number of hydroxyl aromatic rings (Fig. **3**). The configuration of the B-ring hydroxyl group is the most significant determinant of flavonoids antioxidant activity. Hydroxyl groups of the B-ring stabilize hydroxyl, peroxyl, and peroxynitrite radicals by the donation of hydrogen and an electron to these radicals [44]. In addition, the catechol (3',4'-hydroxyl groups) in the B-ring strongly enhances the antioxidant potential of flavonoids (Fig. **3**). For instance, kaempferol has demonstrated a significantly lower potential to scavenge the radical peroxyl with regard to luteolin, since despite the identical hydroxyl configurations, kaempferol lacks the B-ring catechol [82]. Although the impact of the A-ring hydroxyl configurations on antioxidant activity is still questionable, a 5,7-*m*-dihydroxy arrangement has been reported to increase the TEAC of polyphenols [83]. The role of C-ring itself is also doubtful, given that the chalcones (1,3-diaryl-2-propen-1-ones) class presents antioxidant activity and does not contain a C-ring in its structure [84]. However, the presence of a 3-hydroxyl group in the C-ring has been reported to be involved in the potent scavenging ability of flavan-3-ols and flavonols [79]. These two classes of flavonoids possess a 3',4'-catechol in the B-ring, which has been reported to form intramolecular hydrogen bonds with the free 3-hydroxyl group, thus aligning the B-ring with the heterocycle and A-ring. This torsion angle of the B-ring in relation to the rest of the molecule gives planarity to the structure, which allows conjugation, electron dislocation and a corresponding increase in radicals' stability [82]. A good example is quercetin, which has a 3-hydroxyl group in its structure and a great capacity to inhibit metal and non-metal-induced oxidative damage. Contrastingly, the non-existence of the hydroxyl group at position 3 abrogates coplanarity and conjugation, thereby compromising scavenging ability as it happens in flavones and flavanones [85].

Another factor influencing flavonoids planarity is *O*-methylation of hydroxyl groups [86]. The B-ring is particularly sensitive to the position of the methoxy group. A steric obstruction of the 3'4'-catechol structure by 4'-*O*-methylation significantly compromises the antioxidant capability of the phenolic compound. It has been reported that the 4'-*O*-methylation of quercetin abruptly decreases its potential to inhibit ferrous sulphate-induced lipid peroxidation [86]. Moreover, kaempferol-3',4'-dimethylether presents about half of the scavenging activity of kaempferol against the radical peroxyl [87]. Furthermore, the coupling of carbohydrate moieties to flavonoids also impacts polyphenols antioxidant potential. Aglycones have usually a more potent antioxidant activity than their corresponding glycosides. *O*-glycosylation of the A- or B-ring has been linked with a decrease in radical scavenging activity of polyphenols [88]. Quercetin (aglycone) is a more potent scavenger of the peroxyl radical than its *O*-glycosylated derivatives [86]. However, it has been demonstrated that the steric effects imparted by 4'-glycosylation exert a more suppressive influence than 3- or 7-substitutions, which are the most frequent glycoside forms present in our diet. Moreover, the sugar substitution at position 7 in the A-ring results in a higher antioxidant decrease than 3-glycosylation in the C-ring [44].

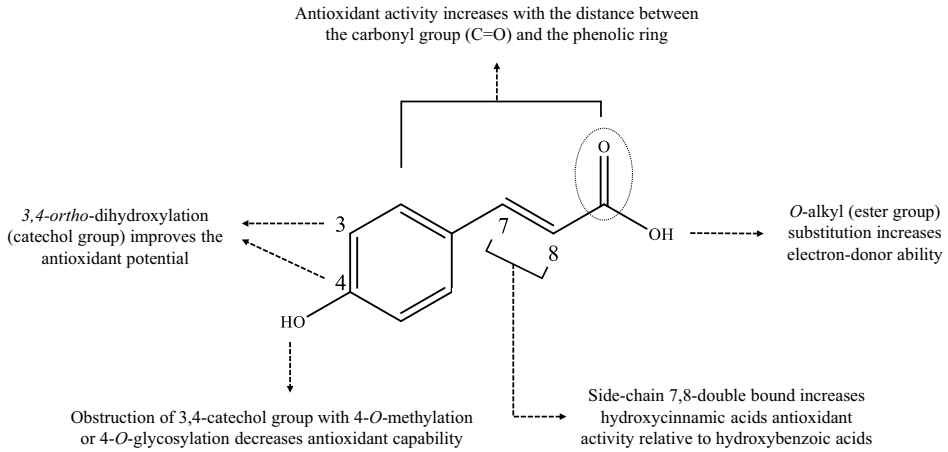


**Fig. (2).** Representation of the key structural features influencing phenolic acids antioxidant activity. Catechol group (3,4-*ortho*-dihydroxylation), side-chain 7,8-double bound and the distance between the carbonyl group (C=O) and the phenolic ring are the main enhancers of phenolic acids antioxidant activity.

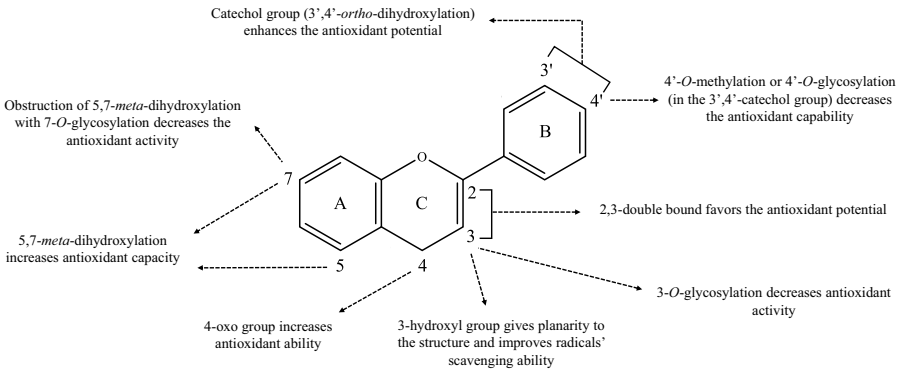


**Fig. (3).** Illustration of the main structure-activity relationships of flavonoids. The strong antioxidant potential of flavonoids is mainly related to the higher number of phenolic rings and hydroxyl groups (OH). The presence of the catechol group (3',4'-*ortho*-dihydroxylation) in the B-ring; 2,3-double bound, 3-hydroxyl group and 4-oxo group in the C-ring; and the 5,7-*meta*-dihydroxylation in the A-ring are key structural features that improve flavonoids antioxidant activity.

A structural arrangement that enhances the antioxidant activity to flavonoids is the presence of a 2,3-double bond in conjugation with a 4-oxo group in the C-ring (Fig. **3**). Several studies demonstrated that flavonoids lacking one of this features or both are less potent antioxidants than those with both elements. For instance, both structures of quercetin and taxifolin have a 4-oxo group in the C-ring, but taxifolin has a saturated bond between carbons 2 and 3. This particularity determines that quercetin is a more potent antioxidant than taxifolin [89]. However, these features are more relevant when the 3-hydroxyl group in the C-ring and the 3'4'-catechol structure in the B-ring are also present, as in the case of flavan-3-ols and flavonols. For example, the TEAC of quercetin has been reported to be 4.7 mM, which is almost twice the TEAC described for (+)-catechin (2.4 mM) [79]. These results illustrate the significance of the 2,3-unsaturated bound and the 4-oxo group.

Finally, despite poorly understood, it is known that the degree of polymerization of flavonoids also influences their antioxidant capabilities. For that reason, procyanidin dimers and trimers are more effective free radical neutralizers than monomeric flavonoids [90].

The structural-activity relationships of stilbenes and lignans are not so well-known as in the case of phenolic acids and flavonoids. Regarding stilbenes, hydroxylation at C4 has been described as a determinant feature to its function [91]. In addition, the increase in the number of hydroxyl groups at the *ortho* position on the phenolic ring of stilbenes was associated with an increase of the free radical scavenging capacity, cytotoxic activity, and anti-inflammatory effects of these compounds [92]. In fact, polyhydroxylated analogs of resveratrol, such as hexahydroxystilbene, evidenced to be more potent inhibitors of the activity of several enzymes [93]. While hydroxyl groups confer more solu-

bility, allowing a better interaction with proteins [94], the methoxylated groups confer resistance to degradation [91]. Although the number hydroxyl and methoxy groups must be under equilibrium, an excessive number of methoxylated groups may impair the interaction with the target protein. The highest radical scavenging capacity of lignans was linked to the presence of catechol (3,4-dihydroxyphenyl) moieties. Moreover, the butanediol structure also revealed an improvement in lignans scavenging activity, whereas a higher degree of oxidation at the benzylic positions decreased this capacity [95].

Despite the strong antioxidant power of phenolic compounds, some features of their chemical structure including the catechol or pyrogallol groups, make them prone to autoxidation reactions. When a phenolic molecule loses an electron or when it acts as a reducing agent, the molecule itself becomes a radical. Even though these radicals can be relatively stable, their oxidized intermediates can become pro-oxidants [44]. For instance, the interaction between polyphenols and transition metal ions can result in pro-oxidant formation, which may lead to adverse effects to human health when present at high concentrations. Interestingly, glycosylation and methylation of hydroxyl groups attenuate the pro-oxidant behaviour of flavonoids [87]. Other factor influencing the antioxidant/oxidant potential of phenolic compounds is pH. Generally, a lower pH increases iron-reducing activity and reduces the ability to chelate and inhibit the catalytic activity of iron. For instance, it has been reported that at pH=7.4, *p*-hydrobenzoic acid presents antioxidant activity, while apigenin-7-glucoside has a pro-oxidative action, whereas at pH=5.8 neither of the phenolics evidenced antioxidant or pro-oxidant activity [96]. It is of extreme importance to understand the structural-activity relationships of phenolic compounds, in order to find the most stable structures with stronger biological activities, while avoiding the most prone to autoxidation.

### 3.1. Absorption, Metabolism and Bioavailability

The absorption and metabolism of dietary phenolic compounds are also influenced by their chemical structure. These processes depend on several factors, such as: the degree of glycosylation, esterification, and polymerization, conjugation with other phenolics, molecular size, and solubility [24]. It is very important to consider the extensive metabolism and chemical alterations that occur once phenolic compounds enter the body, since their health effects depend on the amount consumed and on their bioavailability. This represents one of the biggest problems in the extrapolation of results obtained from *in vitro* experiments to *in vivo* situations, given that the *in vitro* studies allow the utilization of concentrations far greater than what can be expected in the body. Generally, the most abundant phenolic compounds in human diet are not necessarily the most active *in vivo*, either because they have a lower intrinsic activity or because they are poorly absorbed from the intestine, highly metabolized, or rapidly eliminated [26].

While aglycones and some glucosides can be absorbed in the small intestine, phenolic compounds in the glycoside or polymeric form cannot be absorbed in their native form. Typically, the absorption of glycosides involves the cleavage and release of the aglycone moiety. This process occurs by the action of the intestinal enzymes lactase-phlorizin hydrolase (LPH, EC 3.2.1.108; 3.2.1.62), which is localised in the apical membrane of small intestinal epithelial cells, and cytosolic β-glucosidase (CBG, EC 3.2.1.21) [97]. Other phenolics, such as the ones linked to rhamnose, must reach the colonic microflora to be hydrolysed. However, the absorption in the colon is a more protracted and less efficient process. Before being delivered to different tissues or organs by blood circulation to exert their various effects, uptaken polyphenols undergo some degree of phase II metabolism, resulting in phenolic compounds conjugation (methylation, sulfation, and glucuronidation) [26]. The high efficiency of these conjugation mechanisms makes aglycones generally absent in blood or present in low concentrations after consumption of nutritional doses. Once in the portal bloodstream, metabolites rapidly reach the liver, where they can be further metabolized (phase II metabolism). Then, through the bile excretion process, metabolites may be reabsorbed from the gastrointestinal tract, thus returning to the general circulation. This enterohepatic recycling influences the duration of phenolic metabolites within the body, which certainly will have an impact on their biological effect [98].

## 4. THERAPEUTIC POTENTIAL OF PHENOLIC COMPOUNDS AGAINST DIABETES MELLITUS

Diabetes is a complex health condition that may lead to serious complications and even a whole-body dysregulation. It is widely accepted that oxidative stress plays a preponderant role in the initiation, promotion, and progression of DM [99]. The characteristic hyperglycaemic state observed in diabetic patients is associated with ROS generation, thus subjecting pancreatic β-cells to a pro-oxidant environment [2]. Inter-

estingly, when compared to other tissues, β-cells have a lower abundance of antioxidant defence enzymes, such as SOD, CAT, and GPx [100]. Therefore, the low antioxidant capacity inherent to insulin-producing cells, makes them highly susceptible to dysfunction by the action of ROS. Along with ROS-induced micro and macromolecular damages, several cellular stress-sensitive pathways associated with insulin resistance and decreased insulin secretion may be activated [17]. For instance, ROS molecules such as hydrogen peroxide have been implicated in glucose-stimulated insulin secretion [101]. Evidence from *in vivo* studies demonstrated that oxidative stress associated with hyperglycaemia is involved in the onset of late complication of diabetes, since usually hyperglycaemia is not detected until severe complications become clinically evident [102]. Besides hyperglycaemia, low-grade inflammation and the activation of the innate immune system are also involved in the pathogenesis of T2DM and related-complications such as dyslipidemia and atherosclerosis [103]. Several studies demonstrated a positive correlation between circulating markers of inflammation (C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α)) and insulin resistance/plasma insulin concentration, body mass index (BMI)/waist circumference, and circulating triglyceride and a negative correlation with high-density-lipoprotein (HDL) cholesterol concentration [104, 105].

Hereupon, a regular blood glucose monitoring is essential to prevent the onset/progression of DM, which highlights the importance of studying prediabetes. If detected early, the slight hyperglycaemia evidenced by prediabetics could be controlled with simple measures such as dietary and behavioural alterations. This would drastically reduce healthcare costs. However, since people usually neglect healthcare until they reach a severe and clinically evident state of the disease, prescription of antidiabetic drugs and exogenous insulin becomes necessary [106]. The most common oral antidiabetic drugs for the management of T2DM and hyperglycemia include α-glucosidase inhibitors, biguanides, meglitinides, sulfonylureas and thiazolidindiones [3]. Although these drugs are able to control many aspects of DM, numerous complications can develop, affecting the vascular system, kidneys, retina, lens, peripheral nerves and skin. The treatment of those conditions is extremely costly in terms of longevity and quality of life. Thus, preventive measures can be very useful and the use of natural products has long been considered a good alternative to pharmacological agents. Additionally, the development of most of the current medicines today, was based on natural products properties [3]. For instance, metformin, which is currently the first line treatment for T2DM, is a natural-based antidiabetic drug [107]. Several natural products are very potent antioxidants and it has been shown that the administration of antioxidant supplements can increase the defence capacity of β-cells to oxidative stress [108]. Thus, these cells would be able to abrogate ROS signalling and reduce diabetic complications.

In the past decade, the search for more effective and safe antidiabetic agents has been the focus of many researchers. Dietary phenolic compounds have demonstrated a promising antidiabetic potential [109]. For instance, the consumption of white tea by streptozotocin-induced diabetic male Wistar rats, demonstrated to improve cardiac [110], cerebral cortex [10] and reproductive metabolic [111] and oxidative profiles [112]. An *in vivo* study with non-obese diabetic mice demonstrated a significant reduction in diabetes incidence to 33% and 25%, in mice receiving 1% of dietary grape powder or 250 IU vitamin A/g of food, respectively [113]. Moreover, the combined ingestion of a berry meal (37.5 g of each berry - blackcurrants, bilberries, blueberries, cranberries and strawberries) with 35 g of sucrose by healthy subjects, evidenced the importance of polyphenols in the control of glycaemia after sugar intake [114]. As aforementioned, (poly)phenols are the most abundant antioxidants in human diet, thus, along the day, people can ingest a wide variety of bioactive compounds. Increased intake of dietary phenolic compounds helps to maintain an adequate antioxidant status, balancing the amount of antioxidants and oxidants in living organisms. Not surprisingly, many studies reported the benefits of phenolic compounds against DM [20, 21]. Their use should be supported not only by its anti-hyperglycaemic effect, but also by their safety and lack of secondary effects. According to several studies, the hypoglycaemic potential of phenolic compounds involves: i) the reduction of dietary carbohydrate digestion and intestinal absorption; ii) the modulation of enzymes involved in glucose metabolism; and iii) the improvement of β-cell function and insulin action [115-117]. The identification of the molecular mechanisms responsible for phenolic compounds protection against oxidative and inflammatory-induced damages might lead to the discovery of pharmacological targets for novel therapies to prevent, reverse, or delay the development of DM. In the following section we summarize some of the mechanisms involved in the antidiabetic potential of dietary phenolic compounds.

### 4.1. Underlying Mechanisms of Action

#### *4.1.1. Carbohydrate Metabolism and Glucose Homeostasis*

Glucose homeostasis is maintained by the hormones insulin and glucagon, which tightly control blood glucose concentrations after ingestion of carbohydrate-rich meals [118]. Most starch molecules are digested in the upper gastrointestinal tract, being hydrolysed into α-D-glucopyranose by key enzymes, including salivary/pancreatic α-amylase (EC 3.2.1.1), and intestinal sucrose α-glucosidase (EC 3.2.1.48) and maltase/α-glucosidase (EC 3.2.1.20) [119]. Glucose is imported against its concentration gradient from the intestinal lumen across the apical surface of the epithelial cells by the sodium-dependent glucose cotransporter-1 (SGLT1). Then, glucose is exported down its concentration gradient into the blood by the glucose transporter-2 (GLUT2), which is localized in the basal and lateral membranes of intestinal cells [120]. When glucose reaches the pancreatic islets it is phosphorylated, thus stimulating β-cells to secrete insulin. On the other hand, when blood glucose concentrations decline, α-cells secrete glucagon in order to raise blood glucose levels [121]. The impairment of this regulated carbohydrate metabolism contributes to the development of hyperglycaemia, mainly due to alterations in digestion and absorption of dietary carbohydrates, depletion of glycogen storage and increased gluconeogenesis [122].

One of the most prescribed antidiabetic drugs to control hyperglycaemia in patients with T2DM are α-glucosidase and α-amylase inhibitors. These drugs delay the digestion and absorption of complex carbohydrates by acting as competitive inhibitors of the human α-glucosidase and α-amylase enzymes, thus decreasing the postprandial increase in blood glucose levels [123]. Many phenolic compounds have been reported to inhibit the enzymes α-glucosidase and α-amylase [124]. Phenolic-rich extracts from strawberry and raspberry fruits, which are rich in soluble tannins, have demonstrated to be very effective inhibitors of α-amylase. On the other hand, extracts from blueberry and blackcurrant that contain a higher content in anthocyanins, presented a higher inhibitory potential relative to α-glucosidase rather than to α-amylase [125]. Other tannin-rich extracts from red grapes and red wine also demonstrated to be effective inhibitors of α-amylase [126]. The analysis of the enzymatic inhibitory profile of different types of tea (green, oolong and black teas) showed that black tea is the most potent inhibitor of both enzymes. The half maximal inhibitory concentration ($IC_{50}$) of black tea for α-amylase and α-glucosidase was of 0.42-0.67 and 0.56-0.58 mg of tea leaves/mL, respectively. The inhibitory potential of tea was correlated with its content of theaflavins and catechins [127]. For example, the $IC_{50}$ of EGCG for human α-amylase was reported to be as high as 260 μM [128]. Marine *algae* are popular and abundant food ingredients mainly in Asian countries that also contain a high content of polyphenols [117]. Isolated phlorotannins derived from edible brown alga, such as fucodiphloroethol G, dieckol, 6,6′-bieckol, 7-phloroeckol and phlorofucofuroeckol, have shown a marked inhibitory effect of these enzymes, having $IC_{50}$ values of 19.5, 10.8, 22.2, 49.5, and 19.7 μM to α-glucosidase, respectively, and >500 μM, 124.9 μM, >500 μM, 250.0 μM, and >500 μM to α-amylase, respectively [129].

Concerning glucose absorption, several phenolic compounds, such as tea catechins, ferulic and caffeic acids, quercetin, and naringenin, demonstrated to inhibit SGLT1 [130, 131]. Concerning tea catechins, the inhibitory activity was most pronounced by the ones having galloyl residues such as ECG and EGCG [130]. Moreover, certain flavonoids such as myricetin, fisetin, quercetin, and its glucoside precursor isoquercitrin have demonstrated a non-competitive inhibitory action of GLUT2 [132]. Inhibition of SLGT1 and GLUT2 transporters, prevents glucose transport to insulin-responsive cells and avoids the increase in postprandial glucose. Despite these beneficial effects, this inhibitory mechanism has been associated with undesired effects, such as poor intestinal absorption of glucose and galactose and low bioavailability of these compounds in the plasma. For that reason, the specific inhibition of SGLT1 per se was not considered for the development of new antidiabetics [133]. In recent years, the sodium-dependent glucose cotransporter-2 (SGLT2) expressed in the kidney, has also been implicated in the normalization of plasma glucose levels in patients with diabetes [134]. In healthy individuals, most of the plasma glucose that is filtered in the kidney glomerulus is reabsorbed. In fact, less than 1% of the total filtered glucose is excreted in urine. Notably, the process of reabsorption in the kidney is 10% mediated by SGLT1 and 90% by SGLT2 [135], thus illustrating the relevance of SGLT2 to those processes. Regulation of hyperglycaemia by the selective inhibition of SGLT2 involves the prevention of renal glucose reabsorption and promotion of glucose excretion in urine, in a finely regulated mechanism [136]. Actually, SGLT2 is considered a pharmacological target for T2DM treatment and the development of several antidiabetic drugs, such as dapagliflozin, was based on the potential of natural compounds to inhibit SGLT2 [135]. Moreover, the inhibi-

tion of both SGLT1 and SGLT2 have been described as beneficial for glycaemic control in T2DM conditions [137]. A few studies have already reported the potential of phenolic compounds to inhibit both SGLT isoforms, including acerogenin [138] and phlorizin [139].

Some phenolic compounds can regulate key pathways of carbohydrate metabolism and hepatic glucose homeostasis that are usually impaired in DM, including glycolysis, glycogenesis and gluconeogenesis. Thus, phenolic compounds influence peripheral glucose uptake in both insulin sensitive and non-insulin sensitive tissues. It has been shown that phenolic acids stimulate glucose uptake by similar mechanisms as the hypoglycaemic drugs biguanides (*e.g.* metformin) and thiazolodinediones (*e.g.* rosiglitazone) [140]. These antidiabetic drugs act in part through the activation of adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), which is known to be an important player in the regulation of glucose homeostasis [141]. Activation of this pathway has been considered a new treatment for T2DM, but also for obesity and metabolic syndrome. When AMPK is activated, it induces the activation of the phosphatidylinositide 3-kinase (PI3k)/protein kinase B (Akt) pathway, which increases phosphorylation of glycogen synthase kinase-3 (GSK-3), inhibiting its action [142]. Thereby, gene expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase) in the liver decreases, reducing gluconeogenesis [142]. PEPCK and G-6-Pase are vital enzymes for the regulation of hepatic gluconeogenesis. While PEPCK catalyses the conversion of oxaloacetate to phosphoenolpyruvate, G-6-Pase catalyses the final reaction of gluconeogenesis, the formation of glucose from glucose-6-phosphate [143]. The expression of PEPCK and G-6-Pase genes is normally enhanced by glucagon and inhibited by insulin, but in T2DM, their expression becomes insensitive to insulin action. Thus, dysfunctional regulation of these genes has been associated with the pathophysiology of T2DM [144, 145]. Some polyphenols, including *p*-coumaric acid, demonstrated potential to activate AMPK and PI3K [146-148]. Interestingly, the effect of certain polyphenols (resveratrol and apigenin) in the activation of AMPK has been reported to be 50-200 times more potent than metformin [149]. Glucokinase (EC 2.7.1.2) also plays an important role in the regulation of carbohydrate metabolism by acting as a glucose sensor. This enzyme responds to the rise or fall of glucose levels, as happens after a meal or when fasting, respectively. Administration of ferulic acid to T2DM-mice led to increased hepatic glycogen synthesis and glucokinase activity, thus increasing plasma insulin levels and suppressing blood glucose [33]. Supplementation of diabetic rats with hesperidin and naringin also increased hepatic glucokinase activity and glycogen content, and attenuated hepatic gluconeogenesis by decreasing PEPCK and G-6-Pase activities, thus improving glycaemic control [116, 150]. EGCG also showed a downregulation in the expression of PEPCK [151]. Moreover, chlorogenic acid from coffee has been reported to reduce glucose absorption by inhibiting the hydrolysis of glucose-6-phosphate, which could reduce glucose output in the liver. In fact, coffee consumption was associated with a substantially lower risk of developing T2DM [152].

Recently, the mammalian target of rapamycin (mTOR) has been implicated in the pathogenesis of DM. It interacts with the PI3K/Akt pathway and is also responsible for the regulation of carbohydrate metabolism. Structurally, mTOR is composed by two complexes, mTORC1 and mTORC2, which solely differ by their accessory proteins [153]. In general, when PI3K is activated, it recruits Akt to the plasma membrane, where it is activated by mTORC2 and further regulates mTORC1. Thus, mTOR is a major modulator of insulin action. AMPK is also involved in the regulation of this pathway by a dual effect. At the same time, AMPK can stimulate PI3K/Akt pathway and inhibit mTOR signalling [154]. In an insulin-resistance state, PI3K and Akt are not activated, leading to decreased cellular glucose uptake and to increased hepatic gluconeogenesis, which worsens the hyperglycaemic condition. However, mTORC1 is activated because it is not solely dependent on insulin supplies, but also on the high circulating levels of amino acids resulting from the excessive nutrient intake. Activation of mTORC1 inhibits insulin receptor signalling at the cellular membrane, in particular in liver and muscle, contributing to the onset of the diabetic state [155]. Polyphenols have demonstrated ability to interact with mTOR signalling. For instance, resveratrol has been reported to inhibit PI3K/Akt/mTOR pathway by activating AMPK [153]. Furthermore, a family of highly conserved $NAD^+$-dependent deacetylases known as sirtuins, have also been implicated in the regulation of these mechanisms. They act as cellular sensors to detect energy availability and modulate metabolic processes [156]. Resveratrol and quercetin are known to be potent activators of sirtuin 1 (SIRT1), which by itself negatively regulates mTOR signalling [157].

#### *4.1.2. Pancreatic β-Cell Function and Insulin Action*

The hyperglycaemic state of diabetics may result from β-cell dysfunction, insulin resistance of peripheral

tissues (skeletal muscle, adipose tissue and kidney) and defects in insulin signalling pathways. Generally, insulin-mediated signalling lowers blood glucose by: (i) enhancing the uptake of glucose in peripheral tissues through translocation of glucose transporter-4 (GLUT4) to the plasma membrane; (ii) promoting glucose utilization/storage in the liver; and (iii) inhibiting lipolysis and promoting lipogenesis in white adipose tissue [20]. Besides, hyperglycaemia has been associated with increased oxidative stress and inflammation, which involves the activation of the nuclear translocation of nuclear factor-kappa B (NF-κB) and an increased expression of inducible nitric oxide synthase (iNOS), cyclooxygensase-2 (COX-2), and apoptotic enzymes [16, 158]. NF-κB proteins are a family of transcription factors important in inflammation and immunity, which regulate the expression of many genes involved in regulating cell growth, differentiation, development, and apoptosis [159]. One of the genes known to be upregulated by NF-kB proteins is iNOS that is responsible for catalysing the production of nitric oxide (NO) [160]. The increased expression and activity of iNOS leads to excessive NO production, which has been linked to the pathogenesis of many diseases [161]. iNOS expression was also associated with the activation of intracellular signalling proteins, including PI3K and mitogen-activated protein kinases (MAPK), suggesting additional regulatory points for iNOS expression [162-165]. COX-2 is a well-known target of NF-κB that plays a major role in the inflammatory process by catalyzing the production of prostaglandings. Superoxide is a side product of this reaction, and may contribute to oxidative stress and inflammation [166].

It is well known that dietary antioxidants protect pancreatic β-cells from hyperglycaemia-induced oxidative stress. Cinnamon and grape seed polyphenols demonstrated ability to repair diabetic-induced β-cells damages in mice by attenuating hyperglycaemia-induced cytotoxicity [167]. The involved mechanisms comprise the inhibition of NF-kB and iNOS [167, 168]. Several flavonoids such as rutin, quercetin and quercetin pentaacetate have also demonstrated an effective inhibitory activity of iNOS and COX-2 gene expression by blocking NF-kB activation [169]. Moreover, an improvement in natural β-cells antioxidant capacity was also verified by the oral administration of grape seed extract (100 mg/kg/day for 20 consecutive days) to streptozotocin-induced diabetic rats [170]. Grape seed polyphenols were able to reduce lipid and protein oxidation in plasma and hepatic tissue of diabetic rats by increasing the activity of SOD and CAT [170]. In fact, reduced activities of these enzymes are usually found in the liver and pancreas of diabetic patients, resulting in a number of deleterious effects due to the accumulation of free radicals. The specific function of SOD is to protect tissues against ROS by catalysing the conversion of the superoxide radical ($O_2^-$) into hydrogen peroxide ($H_2O_2$) or molecular oxygen ($O_2$) [171]. $H_2O_2$ and other reduced oxygen species have been proposed as activators of the transcription factor NF-κB [172]. CAT is the enzyme responsible for the detoxification of significant amounts of $H_2O_2$ by degrading it into water an oxygen. However, it has been reported that CAT induces the expression of iNOS by increasing gene transcription and mRNA stability [173]. This is consistent with the production of NO, which may react with superoxide leading to the formation of the highly reactive peroxynitrite (ONOO-). Peroxynitrite can modify tyrosine in proteins to create nitrotyrosines, thus potentiating ROS damages to β-cells. This mechanism is believed to be on the basis of β-cell destruction in T1DM [174].

Oral administration of phenolic-rich chestnut extract (300 mg/kg twice a day for 12 consecutive days) in STZ-induced diabetic rats had favourable effects on serum glucose and viability of β-cell through attenuation of oxidative stress, enhancing the natural antioxidant system, and inhibition of lipid peroxidation [175]. Isoflavones, particularly genistein, also act as agonists of AMPK signalling, thus amplifying glucose-induced insulin secretion by β-cells [176, 177]. Furthermore, genistein demonstrated to induce protein expression of cyclin D1, which is a major cell-cycle regulator of β-cell growth and subsequently improve β-cell proliferation and survival [178]. Results from *in vitro* studies showed that some polyphenolic compounds such as quercetin, resveratrol and EGCG improve insulin-dependent glucose uptake in muscle cells and adipocytes by translocation of GLUT4 to plasma membrane and also through induction of the AMPK pathway [39, 40]. It has also been reported that the stilbene resveratrol improves glucose tolerance, attenuates β-cell loss and reduces β-cell oxidative stress *via* the same mechanisms, thus delaying T2DM progress [179, 180].

Although glucose is the major regulator of insulin secretion, incretin gut factors have been estimated to be responsible for as much as 50% of the insulin secretion observed after an oral glucose load. The regulation of the secretion of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike polypeptide-1 (GLP-1) are also involved in the control of postprandial glucose by phenolic com-

pounds [181]. GLP-1 plays a dominant role in modulating $\beta$-cell function (insulin production and $\beta$-cell proliferation/protection), reducing glucagon secretion, attenuating gastric emptying, and decreasing appetite/weight gain [182]. However, it has a short half-life, since it is cleaved in a short-time to dipeptidyl peptidase-4 (DPP-4) [183]. GLP-1 analogues (*e.g.* exenatide and liraglutide) and DPP-4 inhibitors (*e.g.* sitagliptin, vildagliptin, saxagliptin, and linagliptin) are actually considered classes of antidiabetic drugs. It has been demonstrated that the chronic administration of resveratrol (60 mg/kg/day, for five weeks) to high-fat diet-induced diabetic mice, led to an increase in GLP-1 secretion and consequently in insulin secretion. The concomitant treatment with a DPP-4 inhibitor (sitagliptin; 5 mg/day) exacerbated the mechanism, controlling glycaemia [184]. Procyanidins from cacao liquor also induced an increase in GLP-1 and insulin secretion levels in the plasma of mice, 60 min after administration [185]. Thus, the improvement of hyperglycaemia through an incretin-like effect is also important in diabetics.

The high intake of dietary sugars (more than 10% of daily calories as sugar) is associated with poor glycaemic control, leading to a decrease in insulin sensitivity [186]. When peripheral tissues became resistant to insulin, T2DM progresses, and the risk factor for developing hypertension, obesity and cardiovascular diseases is exacerbated. The daily consumption of high-cocoa polyphenol-rich chocolate by T2DM individuals demonstrated an improvement in the atherosclerotic cholesterol profile by increasing HDL cholesterol and improving the cholesterol:HDL ratio without affecting weight, inflammatory markers, insulin resistance or glycaemic control [187]. Furthermore, the ingestion of 1-6 g of cinnamon per day by T2DM patients reduced fasting blood glucose (18-29%), total cholesterol (12-26%) and LDL-cholesterol (7-27%) [188].

## FUTURE PERSPECTIVES

Phenolic compounds present promising properties that are beneficial not only for DM, but also for other human diseases. Their therapeutic potentialities are reinforced by the fact that they are easily consumed through daily diet. Moreover, food and beverages usually contain a mixture of phenolic compounds in their composition. Thus, the ingestion of phenolic-rich dietary sources increases the effectiveness of these compounds due to a potential synergism between them. However, dietary phenolics can be seen as a double-edged sword: they can be strong antioxidants against oxidative stress and inflammation, but they can also display pro-oxidant activity when consumed in high doses, such as in the case of some food supplements. The most stable structures, adequate and safe doses of phenolic compounds should be further investigated.

In this review, we have discussed how phenolic compounds present interesting properties for the prevention/treatment of DM, such as the modulation of carbohydrate metabolism, glucose homeostasis, insulin secretion and insulin resistance. Although not fully understood, we have highlighted several of the involved mechanisms of action and possible targets of study. We believe that the control of this epidemic disease would pass through the regulation of key transporters and enzymes of carbohydrate metabolism such as GLUTs and SGLTs, as well as the modulation of several pathways, including recent targets such as mTOR and sirtuins. Among the dietary poly(phenolic) compounds we have to highlight the potential of antioxidants, which effectively attenuate oxidative stress, promote endogenous antioxidant defence system, and modulate oxidant/antioxidant balance. We suggest that phenolic compounds as a part of individual's dietary habits, are a good intervention to counter the alarming proportions of DM, and its associated complications.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| Akt | = | Protein kinase B |
| AMPK | = | Adenosine 5'-monophosphate-activated protein kinase |
| BMI | = | Body mass index |
| CAT | = | Catalase |
| CBG | = | Cytosolic beta-glucosidase |
| CG | = | Catechin gallate |
| COX-2 | = | Cyclooxygensase-2 |
| CRP | = | C-reactive protein |
| DM | = | Diabetes mellitus |
| DPP-4 | = | Dipeptidyl peptidase-4 |
| EC | = | (-)-Epicatechin |
| ECG | = | (-)-Epicatechin gallate |
| EGC | = | (-)-Epigallocatechin |
| EGCG | = | (-)-Epigallocatechin gallate |
| FRAP | = | Ferric reducing antioxidant power |
| G-6-Pase | = | Glucose-6-phosphatase |

| | | |
|---|---|---|
| GIP | = | Glucose-dependent insulinotropic polypeptide |
| GLP-1 | = | Glucagonlike polypeptide-1 |
| GLUT2 | = | Glucose transporter-2 |
| GLUT4 | = | Glucose transporter-4 |
| GPx | = | Gluthatione peroxidase |
| HDL | = | High-density-lipoprotein |
| HPLC | = | High performance liquid chromatography |
| $IC_{50}$ | = | Half maximal inhibitory concentration |
| IDF | = | International Diabetes Federation |
| IL-6 | = | Interleukin-6 |
| iNOS | = | Inducible nitric oxide synthase |
| LDL | = | Low-density lipoprotein |
| LPH | = | Lactase-phlorizin hydrolase |
| MAPK | = | Mitogen-activated protein kinases |
| mTOR | = | Mammalian target of rapamycin |
| mTORC1 | = | Mammalian target of rapamycin complex 1 |
| mTORC2 | = | Mammalian target of rapamycin complex 2 |
| NF-κB | = | Nuclear factor-kappa B |
| NMR | = | Nuclear magnetic resonance |
| NO | = | Nitric oxide |
| PEPCK | = | Phosphoenolpyruvate carboxykinase |
| PI3K | = | Phosphoinositide 3-kinases |
| ROS | = | Reactive oxygen species |
| SGLT1 | = | Sodium-dependent glucose cotransporter-1 |
| SGLT2 | = | Sodium-dependent glucose cotransporter-2 |
| SIRT1 | = | Sirtuin 1 |
| SOD | = | Superoxide dismutase |
| T1DM | = | Type 1 diabetes mellitus |
| T2DM | = | Type 2 diabetes mellitus |
| TEAC | = | Trolox equivalent antioxidant capacity |
| TNF-α | = | Tumor necrosis factor α |

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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