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Using polyphenols as a relevant therapy to diabetes and its complications, a review

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ABSTRACT

Diabetes is currently a worldwide health concern. Hyperglycemia, hypertension, obesity, and oxidative stress are the major risk factors that inevitably lead to all the complications from diabetes. These complications severely impact the quality of life of patients, and they can be managed, reduced, or even reverted by several polyphenols, plant extracts and foods rich in these compounds. The goal of this review is to approach diabetes not as a single condition but rather an interconnected combination of risk factors and complications. This work shows that polyphenols have multi target action and effects and they have been systematically proven to be relevant in the reduction of each risk factor and improvement of associated complication.

KEYWORDS

Complications; diabetes; polyphenols; risk factors

Introduction

Diabetes is characterized by high levels of glucose in the blood due to either low production of insulin or ineffective insulin. The elevated glucose levels cause damage to several organs and have a higher impact in the nervous and circulatory systems (World Health Organization 2020).

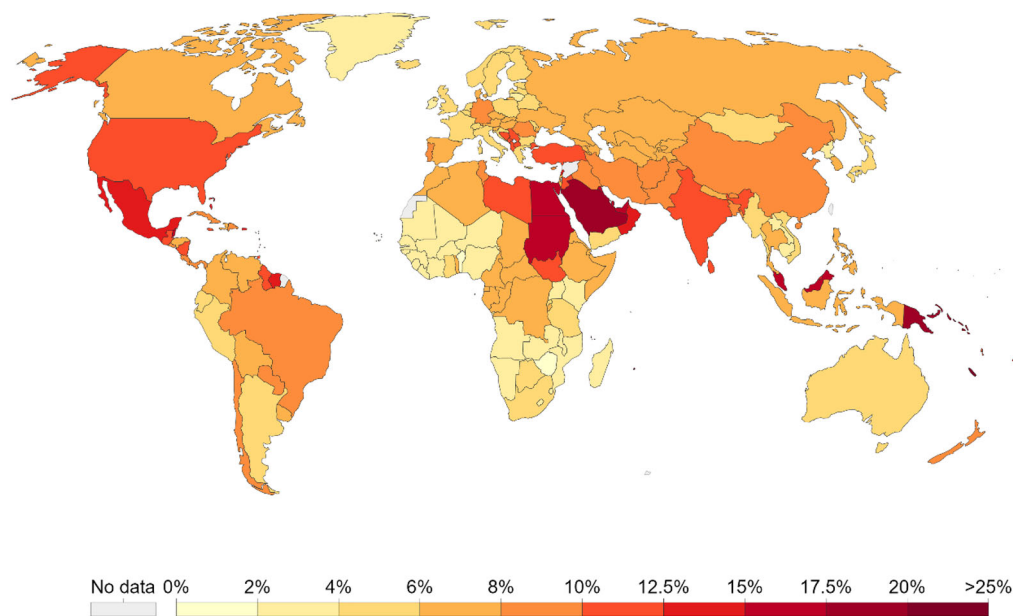
The most common types of diabetes are type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes (Alagesan, Raghupathi, and Sankarnarayanan 2012). T1D is caused by the destruction of the pancreas' beta cells (insulin producing cells). In T2D, the insulin production is generally unhindered it is either defective (mutated) or the individual has developed a resistance to it, making it less effective. Gestational diabetes is a type of diabetes that affects women during pregnancy and increases the risk of developing T2D (Alagesan, Raghupathi, and Sankarnarayanan 2012). Alzheimer's disease (AD) is considered in the work of Monte et al. (2006), Monte and Wands (2008), and Monte (2009) as a type 3 diabetes. Their work also suggests that medication prescribed for diabetes can be used in Alzheimer's patients and reverse some of its effects. The relationship between diabetes and AD is thoroughly reviewed by Silveira et al. (Silveira et al. 2019) who also found that diabetes increased the risk of developing AD.

The International Diabetes Federation's (IDF) atlas for 2019 (International Diabetes Federation 2019a), indicates that 463 million adults have diabetes and 374 million suffer from impaired glucose tolerance (IGT) with nearly 80% of cases being attributed to low and middle income countries (Figure 1). While in 2014 diabetes had an 8.5% prevalence worldwide (World Health Organization 2020), according to the World Health Organization (WHO), in 2019 it reached

9.3% (International Diabetes Federation 2019a). Globally, 50% of diabetes patients are undiagnosed (International Diabetes Federation 2019a), with the amount of undiagnosed patients ranging from nearly 38% in North America to nearly 60% in Africa.

In the EU, diabetes accounted for 2% of all deaths in 2017. In 2019, over 32 million adults had been diagnosed with diabetes, nearly twice as much than in 2000, with an average prevalence of 6.2% (OECD/European Union 2020). When extending to the rest of Europe, the prevalence of diabetes in adults reaches an average of 8.9% or over 59 million adults. The most affected countries are Turkey, Germany and Portugal with prevalence rates of 11.1, 10.4 and 9.8% respectively (International Diabetes Federation 2019a; OECD/European Union 2020). In addition, impaired glucose tolerance (IGT) is estimated to affect an additional 5.5% of Europe's adult population, over 36 million people. Furthermore, 40% of Europe's adult diabetes patients, over 24 million people, are undiagnosed (International Diabetes Federation 2019a).

According to the United States (US) Center for Disease Control (CDC), diabetes is estimated to affect 12 to 14% of the total US population, 31.6 to 36.6 million people, with some areas reaching up to 33% incidence (Centers for Disease Control 2020). The CDC's numbers are slightly above the IDF's for the US which estimate a prevalence of 10.8% or nearly 31 million adults (International Diabetes Federation 2019a, 2019b) but still in line with the numbers from the IDF for the North America and Caribbean Region which estimates an incidence of 10.5 to 15.8% (International Diabetes Federation 2019a). Additionally, the CDC's numbers show that diabetes has a higher prevalence on the less



Source: International Diabetes Federation, Diabetes Atlas

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Figure 1. Diabetes worldwide prevalence for people aged 20–79. Map created by "Our World in Data" and licensed under Creative common 4.0.

educated population (Centers for Disease Control 2020) and when cross referencing this data with the data from the US Census Bureau (Semega et al. 2020) it is also possible to see that the most affected ethnicities/races are also those with the lower median income by household.

When cross referencing the data for diabetes prevalence (Figure 1) with income levels (Figure 2), it is possible to observe that the Kingdom of Saudi Arabia (KSA) stands out as having one of the highest incidences of Diabetes despite being included in the high income category.

Recent works from the KSA have tried to establish the causes for the steady increase in diabetes prevalence in the past few decades (Fareed et al. 2017; Alotaibi et al. 2017), from approximately 5% in 1992 (Alotaibi et al. 2017) to 9.4% in 2000 (International Diabetes Federation 2000), over 14% in 2010 (Alotaibi et al. 2017) and finally reaching 18.3% in 2019 (International Diabetes Federation 2019a). Some studies point to an incidence of up to 30% (Alharbi and Alhazmi 2020; Ahmed et al. 2018). As for the reason(s) behind this rise, all works point to the rapid economic growth that the KSA has experienced in the past few decades which, combined with the adoption of unhealthy dietary habits (high calorie and fat diets), reduced physical activity and increased sitting times, leading to excessive weight and other risk factors for diabetes (Fareed et al. 2017; Alramadan et al. 2019; Alharbi and Alhazmi 2020; Ahmed et al. 2018). Fareed et al. (2017) also point out to the genetic predisposition of Saudi people along with a high prevalence of consanguineous marriages as additional key factors.

Kolluru, Bir, and Kevil (2012) provide an in depth description the several body systems affected by diabetes. Considering all the literature reviewed, a simple flowchart (Figure 3) was created to quickly explain how diabetes patients are affected by their condition and the consequences of its complications that are often deadly. Diabetes also makes the patient more susceptible to infections, such as

tuberculosis and pneumonia. Some retro-viral treatments for HIV also cause insulin resistance and, as such, increase the chances of developing diabetes (Hall et al. 2011).

Polyphenols

Recent works in the literature show that polyphenols can provide relevant therapeutic effects in the treatment of diabetes and its complications as we will approach further ahead in this review. Throughout this work, several families of polyphenols will be referenced and/or compared. Due to their intricate structures and sometimes easily confused names, the following section was prepared to help the reader familiarize with the most commonly referenced polyphenol families in this work flavonoids (Figure 4), hydroxycinnamic acids (Figure 5), benzoic acids (Figure 6), stilbenoids (Figure 7) and polyphenols of marine origin bromophenols (Figure 8) and phlorotannins (Figure 9). This section also includes some commonly found/referenced polyphenols for each family as well as their common sources. Readers who are already familiar with these polyphenol families can safely move on to the next section "Complications from diabetes."

Flavonoids

Flavonoids' (Figure 4) base structure is characterized by two aromatic rings (A and B) with a central ring (ring C) with an oxygen atom in position 1. These are commonly found in the epidermis of leaves and fruits (Crozier, Jaganath, and Clifford 2009).

Flavonoids are divided into several subfamilies/categories according to the functional groups and bond types of positions 1, 2, 3, and 4 of the C ring.

Anthoxanthins (Figure 4) are characterized by a double bond between positions 2 and 3 of the C ring and a keto

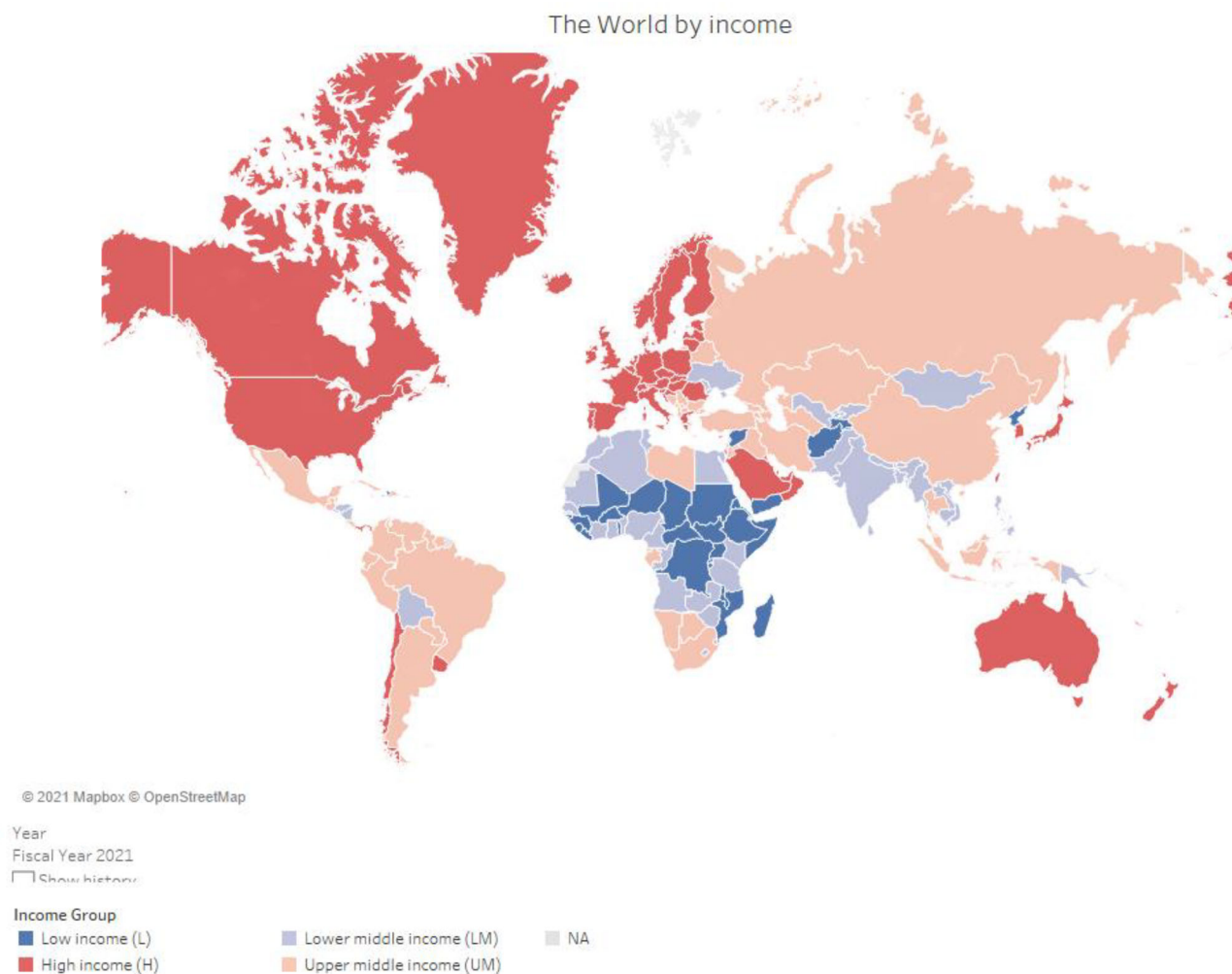


Figure 2. Income levels across the world according to The World Bank for 2020/2021.

group in position 4. They can be further divided into flavonols (which have a hydroxyl group in position 3), flavones (which have a hydrogen atom in position 3) and isoflavones (which have the B ring at position 3 and a hydrogen atom in position 2).

Flavonols (Figure 4) are the most common type of flavonoids, found throughout the plantae kingdom with the exception algae (Crozier, Jaganath, and Clifford 2009), and are abundant in onions, apples, cider, grapes, wine, tea, and tomato (Crozier, Del Rio, and Clifford 2010; Perez-Vizcaino and Duarte 2010; Russo et al. 2019). The main dietary flavonols are kaempferol (which has an hydroxyl group in positions 5, 7, and 4') and quercetin (which has an hydroxyl group in positions 5, 7, 3', and 4') (Crozier, Jaganath, and Clifford 2009; Perez-Vizcaino and Duarte 2010).

Flavones (Figure 4) are not as commonly found in plant species as flavonols but can be found in small quantities in grains, leafy vegetables, citrus and herbs such as parsley (Zhang et al. 2010; Crozier, Jaganath, and Clifford 2009), chamomile, peppermint, oregano, rosemary, tea (*Camellia sinensis*) (Hostetler, Ralston, and Schwartz 2017) and olives (Russo et al. 2019). Commonly found flavones include apigenin (which has hydroxyl groups in positions 5, 7, and 4'), luteolin (which has hydroxyl groups in positions 5, 7, 3',

and 4') and methoxylated flavones tangeretin (with methoxy groups in positions 5, 6, 7, 8, and 4') and nobiletin (with methoxy groups in positions 5, 6, 7, 8, 3', and 4') both of which are common to citrus species (Crozier, Jaganath, and Clifford 2009).

Isoflavones (Figure 4) are often referred to as phyto-estrogens (Crozier, Jaganath, and Clifford 2009; Espín, García-Conesa, and Tomás-Barberán 2007) due to their ability to mimic the effects of estrogen as a result of their similar structure. Isoflavones are almost exclusive to legumes with soy having the highest concentration (Crozier, Jaganath, and Clifford 2009; Cao and Chen 2012). Common isoflavones are daidzein (with hydroxyl groups in positions 7 and 4') and genistein (with hydroxyl groups in positions 5, 7, and 4').

Flavans (Figure 4) are characterized by a single bond between positions 2 and 3. They can be further divided into flavanols with a hydroxyl group in position 3 (flavan-3-ols) or position 4 (flavan-4-ols), flavan-3,4-diols (which have a hydroxyl group in positions 3 and 4), flavanones (which have a keto group in position 4) and flavanonols (which have a hydroxyl group in position 3 and a keto group in position 4).

Flavan-3-ols, are sometimes referred to as catechins because molecules in this group are structurally related to

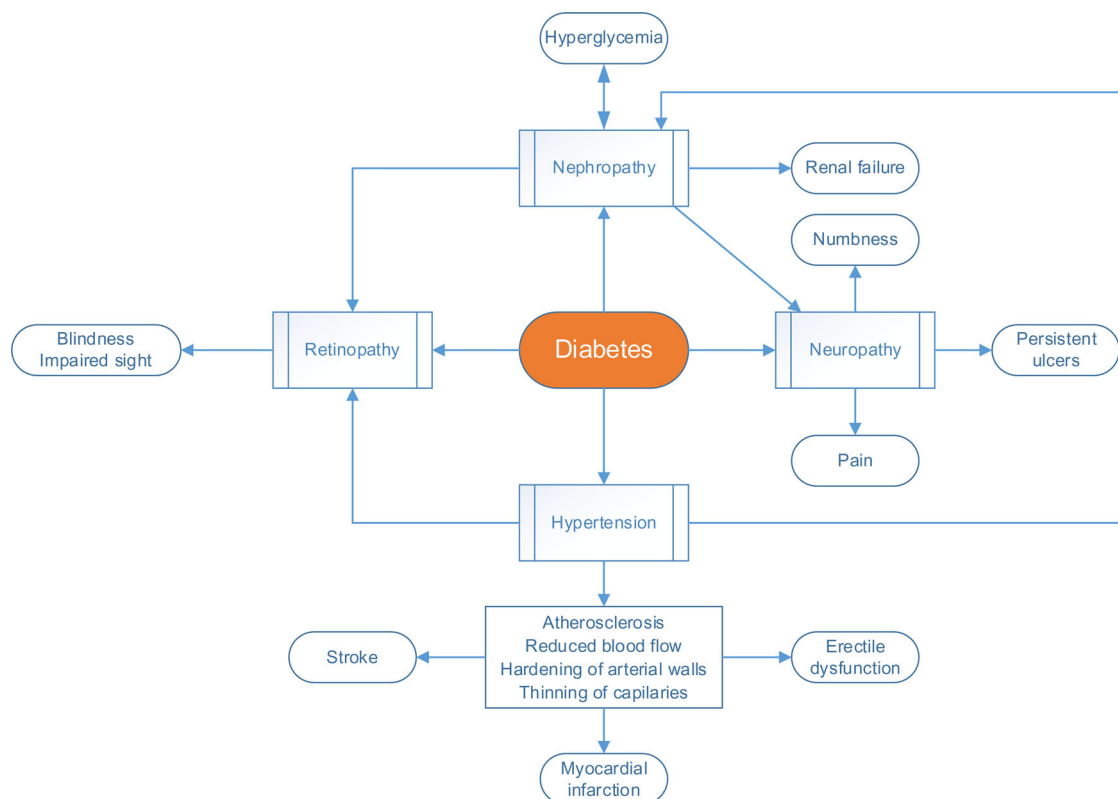


Figure 3. How diabetes patients are affected by their condition.

catechin and its epimer, epicatechin (both have a hydroxyl group in positions 5, 7, 3', and 4'). While in catechins the chiral centers (positions 2 and 3) have different orientations, in epicatechins they have the same orientation. Other common flavan-3-ols include gallic acid and epigallocatechin (which have a hydroxyl group in positions 5, 7, 3', 4', and 5', providing the B ring with the same phenol configuration as gallic acid), epicatechin-3-o-gallate (with a hydroxyl group in positions 5, 7, 3', and 4' and a gallic acid substituent in position 3) and epigallocatechin-3-o-gallate (EGCG – with a hydroxyl group in positions 5, 7, 3', 4', and 5' and a gallic acid moiety in position 3). Flavan-3-ols are also commonly found in polymeric form (proanthocyanidins) or condensed forms (theaflavins and thearubins) (Crozier, Jaganath, and Clifford 2009).

Anthocyanidins (Figure 4) are characterized by having an aromatic C ring which causes the oxygen in position 1 to have a positive charge. Commonly found anthocyanidins include pelargonidin (with hydroxyl groups in positions 3, 5, 7, and 4'), cyanidin (with hydroxyl groups in positions 3, 5, 7, 3', and 4') and delphinidin (with hydroxyl groups in positions 3, 5, 7, 3', 4', and 5'). There are also methylated anthocyanidins peonidin (with an hydroxyl group in positions 3, 5, 7, and 4' and a methoxy group in position 3'), putenidin (with an hydroxyl group in positions 3, 5, 7, 4', and 5' and a methoxy group in position 3') and malvidin (with an hydroxyl group in positions 3, 5, 7, and 4' and a methoxy group in position 2' and 5') (Crozier, Jaganath, and Clifford 2009). Due to the similar name, anthocyanidins are often confused with anthocyanins which are glycosides of anthocyanidins. Both molecule types are commonly found

in fruits, flowers and berries with red, purple or blue colors but, they can also be found in other plant tissues such as leaves and stems (Crozier, Jaganath, and Clifford 2009; Espín, García-Conesa, and Tomás-Barberán 2007; Crozier, Del Rio, and Clifford 2010).

Phenolic acids

Phenolic acids are molecules that contain a phenol functional group and a carboxylic acid group. The main phenolic acids reviewed through this work are hydroxycinnamic acids and benzoic acids.

Hydroxycinnamic acids

Hydroxycinnamic acids (HCAs) derive from cinnamic acid (Figure 5) with at least one hydroxyl functional group in the aromatic ring.

Common HCAs include coumaric acid (which has one hydroxyl functional group in the aromatic ring and is named o-coumaric, m-coumaric or p-coumaric acid if the hydroxyl group is in position 2', 3', or 4' respectively (Crozier, Jaganath, and Clifford 2009; El-Seedi et al. 2012; Sova and Saso 2020)) and caffeic acid (CA – with hydroxyl groups in positions 3' and 4'). In addition to the hydroxyl group(s), some HCAs also include methoxy functional groups in the aromatic ring such as ferulic acid (FA – with a methoxy group in position 3' and an hydroxyl group in position 4') and sinapic acid (with a hydroxyl group in position 4' and methoxy groups in positions 3' and 5') (Crozier, Jaganath, and Clifford 2009; El-Seedi et al. 2012; Sova and

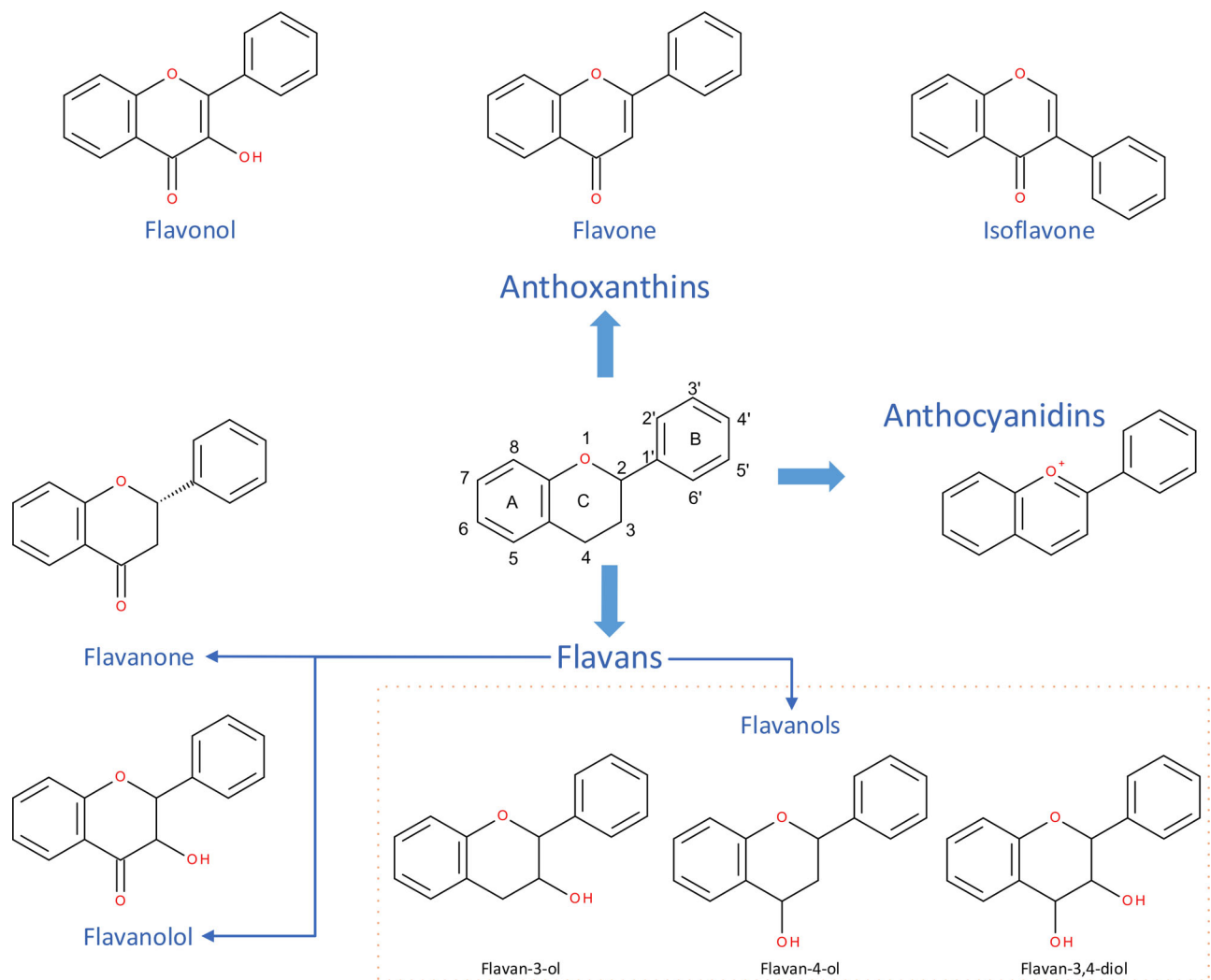


Figure 4. Flavonoid general structure with numbered atoms/positions in the middle along with major flavonoid subfamilies and their respective general structures.

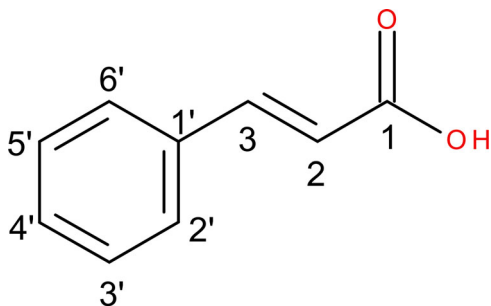


Figure 5. Cinnamic acid structure with numbered positions.

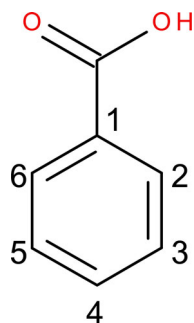


Figure 6. Base structure of benzoic acid with numbered positions.

Saso 2020). HCAs are abundant in coffee, tea, many fruits such as apples, berries, cherries and peaches, in vegetables such as carrots, cabbages, eggplant or artichoke and in cereals (El-Seedi et al. 2012; Sova and Saso 2020). Despite their abundance, HCAs are most commonly found as conjugates (Crozier, Jaganath, and Clifford 2009; Sova and Saso 2020). The most common are with quinic acid (forming the family of chlorogenic acids of which the most abundant is 5-o-cafeoylquinic acid (5-CQA) which is commonly referred to as chlorogenic acid) and with tartaric acid (Crozier, Jaganath, and Clifford 2009; El-Seedi et al. 2012; Sova and Saso 2020). HCAs are also used in structural molecules such as lignins where they are either conjugated, condensed or cross-linked (El-Seedi et al. 2012; Sova and Saso 2020).

Benzoic acids

Benzoic acids (Figure 6) contain a carboxylic acid group bound to an aromatic ring, with the addition of at least one hydroxyl group to the aromatic ring making them phenolic compounds.

Common benzoic acids include salicylic acid (hydroxyl group in position 2), protocatechuic acid (hydroxyl group in positions 3 and 4) and gallic acid (hydroxyl groups in

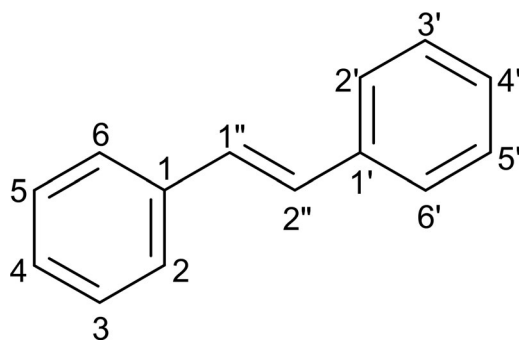


Figure 7. Stilbene structure with numbered positions.

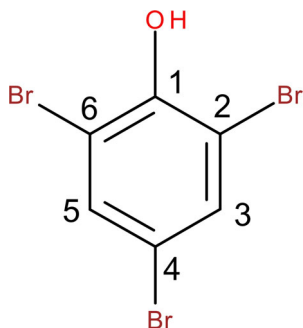


Figure 8. 2,4,6-tribromophenol.

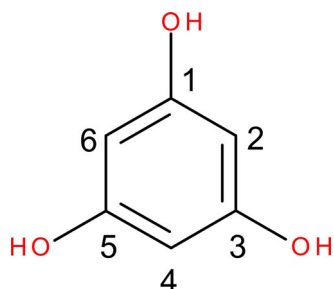


Figure 9. Phloroglucinol, the building block of phlorotannins.

positions 3, 4, and 5). Gallic acid is the most common and can be found in grapes, wine, mangoes, and tea. It is mostly found in the form of gallotannins or as ellagic acid (which results from the condensation to two gallic acid molecules) and can be found in some berries, pomegranate, or walnuts (Crozier, Jaganath, and Clifford 2009). While protocatechuic acid can be found in several vegetables, fruits, and tea, it can also be the result of the degradation metabolism of flavonoids such as anthocyanidins (Song et al. 2020).

Stilbenoids

Stilbenoids are hydroxylated derivatives of stilbene (Figure 7). The most known stilbenoid is resveratrol (which has hydroxyl groups in positions 3, 5, and 4').

While red grapes and wine are the most commonly referred sources of resveratrol (Crozier, Jaganath, and Clifford 2009; Kulashekar, Stom, and Peuler 2018; Vetterli et al. 2011; Kühn et al. 2018), peanuts and berries are also common sources of this compound (Crozier, Jaganath, and Clifford 2009; Den Hartogh and Tsiani 2019; Hossain et al. 2016). Piceatannol is another stilbenoid (which has hydroxyl

groups in positions 3, 5, 3', and 5') which is often also present in species that produce resveratrol and can also be found in sugar cane (Boue et al. 2013) and in passion fruit seeds (Viganó et al. 2016) but has garnered far less scientific interest.

Polyphenols of marine origin

Marine organisms (mostly algae) are abundant, rich and renewable sources of polyphenols some of which are exclusive to this ecosystem (Mateos, Pérez-Correa, and Domínguez 2020). Despite their uniqueness, polyphenols from marine origin are far less studied when compared with their terrestrial counterparts (Mateos, Pérez-Correa, and Domínguez 2020). While phenolic acids and flavonoids can be found/extracted from these organisms and seawater, exclusive compounds such as bromophenols and phlorotannins are present in these organisms (Mateos, Pérez-Correa, and Domínguez 2020).

Bromophenols

Bromophenols are produced by macro algae and cyanobacteria, with red algae as the major source, and are transferred throughout the food chain to other organisms (Mateos, Pérez-Correa, and Domínguez 2020). Some compounds in this family have been shown to have toxic effects, but they are still largely under characterized (Mateos, Pérez-Correa, and Domínguez 2020).

Due to the abundance of bromide ions in seawater, bromination is more frequent than iodination or fluorination (Mateos, Pérez-Correa, and Domínguez 2020). The most abundant bromophenol is 2,4,6-tribromophenol (Figure 8) produced by some organisms as a defense mechanism but also a contaminant from pesticides (Mateos, Pérez-Correa, and Domínguez 2020). Di-bromophenols (e.g., 2,4 or 2,6-dibromophenol) and mono-bromophenols (e.g., 2-bromophenol and 4-bromophenol) can also be found, with some species also incorporating bromide into other polyphenol classes such as benzoic acids (Mateos, Pérez-Correa, and Domínguez 2020).

Phlorotannins

Phlorotannins are polymers of phloroglucinol (Figure 9) and are found exclusively in brown algae (Murray et al. 2018; Mateos, Pérez-Correa, and Domínguez 2020; Barbosa, Valentão, and Andrade 2020; Gunathilaka et al. 2020). They are components of the cell wall of algae and key chemical defense against UV radiation and grazing (Mateos, Pérez-Correa, and Domínguez 2020; Barbosa, Valentão, and Andrade 2020).

The classification of phlorotannins (Figure 10) is based on the type of bonds between the phloroglucinol (Figure 9) monomers with six distinct groups. Fucols are bonded exclusively by aryl-aryl bonds, phlorethols are connected by aryl-ether bonds, fuhals are bound exclusively by ortho and para ether linkages with an additional OH group in every third ring, fucophlorethols have both aryl-aryl and

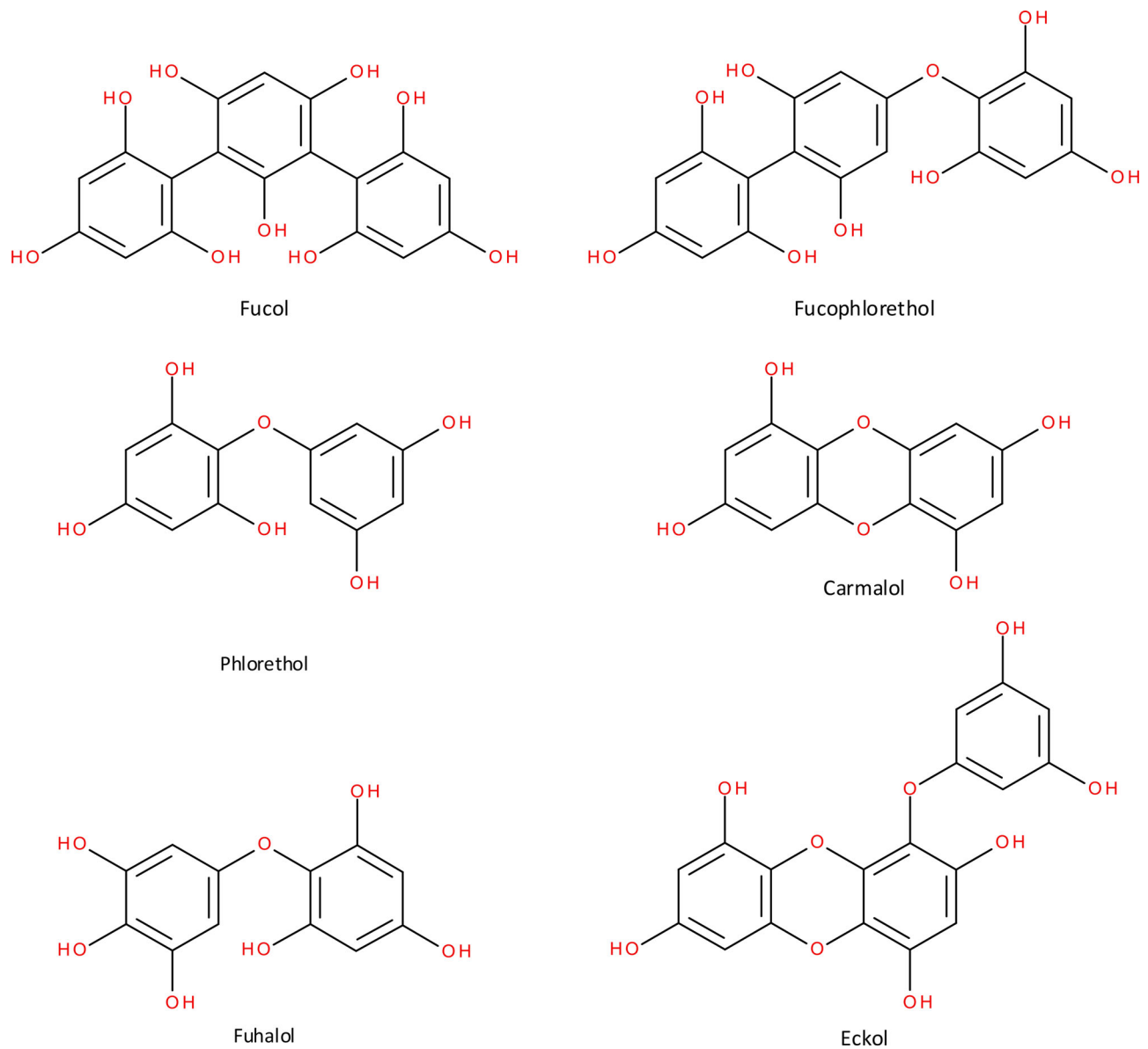


Figure 10. Families of phlorotannins.

aryl-ether bonds and finally, carmalols and eckols both have a dibenzodioxin moiety but eckols also possess a phenoxy group in position 4 of one of the monomers (Mateos, Pérez-Correa, and Domínguez 2020; Barbosa, Valentão, and Andrade 2020; Gunathilaka et al. 2020).

Complications from diabetes

Diabetes is characterized by excessive levels of blood glucose, hyperglycemia. When patients remain in this state for prolonged periods of time, they will begin to suffer and accumulate damage to many of their tissues, organs and systems which will inevitably lead to the many complications of diabetes.

Hypertension, dyslipidemia, hyperglycemia, and obesity

Elevated blood pressure (hypertension), dyslipidemia (abnormal amount of lipids in the blood), hyperglycemia (elevated

blood glucose levels) and obesity occur very often in people suffering from diabetes. Obesity is quite often present in situations of hyperlipidemia and hyperglycemia.

Hypertension

Blood pressure control is critical to prevent cardio-vascular complications in diabetes patients. A very common side effect of hypertension in diabetes patients is renal failure and one of factors that lead to hypertension is an elevated oxidative stress value in the blood stream (Ochiai et al. 2004; Tucker and Palmer 2011). Reducing oxidative stress causes nitrous oxide (NO) to react with less free radicals, allowing it to exert its vasodilation effect (Ochiai et al. 2004). This control is important as it allows for the reduction of the financial burden regarding diabetes treatment (Li et al. 2010; Kozuma et al. 2005; Crozier, Del Rio, and Clifford 2010). A study on the cost of hypertension and obesity on US diabetic patients (Condliffe et al. 2013)

indicates that an obese diabetic has 14% higher health care costs while a diabetic with hypertension has 26% more medical costs.

Grosso et al. (2018) and Miranda et al. (2016) tried to find an association between the intake of polyphenols and hypertension in the Polish and Brazilian populations, respectively. In both studies, food frequency surveys and the Phenol-Explorer database were used to determine the ingested polyphenols and their estimated amounts. In the Brazilian population, it was only possible to establish a statistically significant relation between a reduced incidence of hypertension and higher consumption of tyrosols, alkylphenols, lignans and stilbenes but not total polyphenol consumption (Miranda et al. 2016). In the Polish population, total consumption of polyphenols was associated with a 31% decreased risk of hypertension in women, but it was not possible to establish an association for men (Grosso et al. 2018). It was also possible to establish that hydroxycinnamic acids and flavanols were positively associated with a lower risk of hypertension.

Quercetin, the most abundant dietary flavonoid (Russo et al. 2012), has been largely studied for its antioxidant and anti-inflammatory properties and its efficacy in treating pathologies associated with oxidative or inflammatory stress. Russo et al. (M. Russo et al. 2012) reviewed the role of quercetin in disease prevention and found that, as a supplement on healthy subjects, it has no effect in any of the risk factors/bio-markers for cardiovascular disease (CVD). However, when used by hypertensive subjects, it was able to reduce both systolic and diastolic arterial pressure (SBP and DBP) (Russo et al. 2012; Edwards et al. 2007; Alves et al. 2016) and, when supplemented to obese or overweight subjects at risk of developing hypertension, quercetin lowered blood pressure (BP) and oxidized low density lipoprotein (LDL) (M. Russo et al. 2012). While a single dose of quercetin does not appear to produce any effects, doses over 500 mg/day will reduce blood pressure in a statistically significant manner (Alves et al. 2016). In addition, quercetin was also able to reduce the expression of several inflammatory bio-markers such as tumor necrosis factor alfa (TNF- α), interleukin 6 (IL-6) and interleukin 8 (IL-8) on both macrophages and adipocytes (Russo et al. 2012). These results were also corroborated by Perez-Vizcaino and Duarte (2010) who reviewed the effects of several flavonols in cardiovascular health. According to their research (Perez-Vizcaino and Duarte 2010), quercetin and its metabolites are effective vasodilators by ensuring nitrous oxide (NO) bioavailability through several mechanisms, such as superoxide scavenging, inhibition of enzymes that produce superoxide and the inhibition of signaling pathways that lead to increased oxidative stress. These benefits of quercetin in CVD were also verified by Salehi et al. (2020) in their extensive review on the effects of quercetin in humans.

Venkatesan et al. (2019), in their review on phlorotannins, also found evidence of reduced levels of IL-6 and other inflammatory biomarkers and cytokines in addition to a reduced expression of cyclooxygenase 2 in lipopolysaccharide induced macrophages.

P-selectin is a glycoprotein involved in the platelet-endothelium binding interactions that are implicated in several cardiovascular diseases such as atherosclerosis (buildup of fatty plaque and hardening of the arteries), angina (narrowing of the coronary arteries due to smooth muscle contractions) and ischemic cerebral stroke (usually the result of a blood clot) and its expression is regulated by cyclooxygenase enzymes (COX – EC 1.14.99.1) (Park 2009). According to Park (2009), chlorogenic acid or 5-caffeoyl-quinic acid (CGA or 5-CQA) and caffeic acid (CA) were able to reduce P-selectin expression on mouse platelets due to the inhibition of COX I and COX II. Both 5-CQA and CA performed better than the COX I specific inhibitor (Ibuprofen) and COX II specific inhibitor (NS-398) (Park 2009). COX I and II were also inhibited by Montmorency tart cherry extract and its main individual compounds (Kirakosyan et al. 2018). While the extract performed better than the individual compounds on COX I, the same did not happen for COX II. As for individual compounds, quercetin and kaempferol had the highest inhibitory power toward COX I, while quercetin and isorhamnetin 3-rutinoside were the most effective inhibitors of COX II. COX II genetic expression can also be reduced by epigallocatechin gallate (EGCG) and grape anthocyanins (Al Hroob et al. 2019; Natarajan et al. 2017). The renin-angiotensin-aldosterone system (RAAS) is the main therapeutic target for hypertension and renal diseases. This system works in two steps: firstly, angiotensinogen is converted to angiotensin I by renin (EC 3.4.23.15); the second step involves the conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme (ACE – EC 3.4.15.1) that in turn triggers the secretion of aldosterone. Both angiotensin and aldosterone induce an increase in BP (Bhullar et al. 2014). This makes ACE one of the main potential therapeutic targets for hypertension (Gómez-Guzmán et al. 2018; Fernando et al. 2020). Gómez-Guzmán et al. (2018) comprehensively reviewed the benefits of seaweed polyphenols in CVD. These authors found that phlorotannins inhibited ACE through a noncompetitive mechanism, which was attributed to complexation between phlorotannins and ACE as reported for other (glyco)proteins, but they were far less effective than the commercial inhibitor captopril. Gunathilaka et al. (Gunathilaka et al. 2020) also found evidence that brown algae phlorotannins inhibit ACE in their review. However, while some studies showed that phlorotannins were not very effective inhibitors of ACE, others showed similar inhibitory power to captopril (Gunathilaka et al. 2020). Gómez-Guzmán et al. (2018) stress that, despite the encouraging results that have been reached in vitro, the limited number of in vivo studies in rodents make it hard to confirm these results and proposed that phlorotannins may also exert their hypertension reducing effects through the inhibition of calcium channels and their antioxidant properties. Gunathilaka et al. (2020) highlight that phlorotannins of higher molecular weights appear to be more effective inhibitors of ACE and that, in some cases, the inhibitory power of the algae extracts could be attributed to the peptide components of the algae extract, which were also capable of inhibiting ACE.

There are many studies on the potential of polyphenols to inhibit ACE, which evaluate several plants or preparations/extracts and, in some cases, their most abundant compounds (Nileeka Balasuriya and Rupasinghe 2011; Sakulnarmrat and Konczak 2012; Oboh et al. 2012; Actis-Goretta, Ottaviani, and Fraga 2006; Ray et al. 2017; Kirakosyan et al. 2018; Adefegha and Oboh 2016; Adefegha et al. 2017). Ray et al. (2017) analyzed the inhibiting power of black tea preparations and some of their components on ACE. Of the four black teas tested, the decoctions (tea leaves boiled with water) had a more powerful inhibitory effect when compared with their corresponding infusions (tea leaves soaked in boiled water). When comparing the inhibitory power of the components, oligomeric flavonoids thearubigin and theaflavin were shown to be more effective than their monomeric counterparts, a conclusion that is also shared by the works of Balasuriya and Rupasinghe (Nileeka Balasuriya and Rupasinghe 2011) and Actis-Goretta, Ottaviani, and Fraga (2006). Ray et al. (2017) showed that catechin's inhibitory power is three times higher than epicatechin (ECat) but Actis-Goretta, Ottaviani, and Fraga (2006) found a far smaller difference that was not even statistically significant. Kirakosyan et al. (2018) studied the inhibition potential of Montmorency cherry extract on several common therapeutic targets (enzymes) for diabetes, including ACE, and found that it had significant inhibitory power. The most common compounds in the extract composition were cyanidin glucosides, isorhamnetin rutinoside and quercetin-3-rutinoside. Although the authors investigated the inhibitory power of some of the individual compounds on some of the enzymes, they did not perform such tests for ACE, which makes it impossible to identify the compounds that most likely contribute to the inhibition of ACE. Adefegha and Oboh (2016) studied the ability of free and bound leaf extracts from *Clerodendrum volubile*, a plant used in Nigerian folk medicine for its antidiabetic and anti-hypertensive effects, to inhibit ACE and identified the main compounds in the extracts as quercetin glycosides, caffeic acid and quercetin. Like Kirakosyan et al. (2018), they did not test the effect of individual compounds but the bound extract, which had higher amounts of the identified compounds but lower values for total phenol and flavonoid contents, performed better than the free extract (Kirakosyan et al. 2018). However, these results are not in accordance with the findings of Actis-Goretta, Ottaviani, and Fraga (2006) or Sakulnarmrat and Konczak (2012) in both of which the samples with the higher phenol and flavonoid contents had the highest inhibitory power toward ACE. Although the inhibition of ACE by plant extracts/functional foods is usually attributed to their flavonoid content, hydroxycinnamic acids and other (poly)phenols cannot be excluded as relevant compounds, since preparations containing them (even with reduced flavonoid content) also have relevant inhibitory power (Sakulnarmrat and Konczak 2012; Oboh et al. 2012; Adefegha and Oboh 2016; Adefegha et al. 2017) which may result from an additive or synergetic effect between the compounds.

In summary, the main therapeutic mechanisms of action of polyphenols against hypertension are inhibition of ACE and reduction of oxidative stress. While the inhibition of ACE is the result of the interaction of polyphenols with ACE, the reduction of oxidative stress is achieved through several mechanisms such as scavenging of ROS, reduction of pro inflammatory markers, reductions in the activity or expression of enzymes that produce ROS, and increased activity or expression of antioxidant enzymes, all of which contribute to a higher bioavailability of NO leading to a vasorelaxant effect and reduction of BP. Considering the literature reviewed, Figure 11 was prepared to convey the mechanisms involved in hypertension and diabetes and how these relate to other diabetes complications.

Hyperlipidemia and obesity

High levels of cholesterol in the blood lead to increased blood pressure and high risk of cardio-vascular diseases (CVD). Monitoring cholesterol levels in the blood stream is recommended for diabetes patients as a way to cut down the chances of complications, and thus cost, improving quality of life (World Health Organization 2016; Li et al. 2010; Kozuma et al. 2005; Shimoda, Seki, and Aitani 2006).

Another useful approach is to reduce fat absorption and/or to enhance lipid metabolism, which will also lead to a reduction in body weight. Pancreatic Lipase (PL – EC 3.1.1.3) is responsible for breaking down triglycerides into monoglycerides and fatty acids. Polyphenol rich coffee extract was able to reduce PL activity (Murase et al. 2012). When comparing the effect of each individual polyphenol, 4,5-O-di-Caffeoylquinic acid (4,5-diCQA) was the best inhibitor followed by 3,4-diCQA and 3,5-diCQA (Murase et al. 2012). Cha et al. (2012) studied the inhibition of PL by green tea, coffee, gomchui and their major polyphenol components before and after simulated digestion. In green tea, the main compounds were EGCG, epigallocatechin (EGC), caffeine and epicatechin (Ecat), in coffee the main compounds were single CQAs (3-CQA, 4-CQA, and 5-CQA) and caffeine and in gomchui the main compounds were 5-CQA and di-CQAs (3,4-diCQA, 3,5-diCQA, and 4,5-diCQA). Although EGCG was by far the most effective polyphenol, the green tea infusion was the worst performing because EGCG and EGC were degraded/modified completely during the digestive process and were not even detectable after digestion. CQAs and diCQAs, on the other hand, mostly survived digestion and as such both coffee and gomchui infusions were better inhibitors of PL (Cha et al. 2012). The effectiveness of EGCG was also observed by Yuda et al. (2012), who identified theaflavin and theaflavin glycosides as additional potential PL inhibitors extracted from black tea residues, and by Rahim, Takahashi, and Yamaki (2015). Iwata et al. (2019) studied the effects of kiwifruit extract, rich in proanthocyanidins (oligomeric flavonoids), on PL and body weight of mice fed a high fat diet. The authors concluded that the extract inhibited PL, which they detected by increased levels of triglycerides in the feces. This inhibition led to a reduced absorption of fat and consequently reduced body weight and fat accumulation, when compared

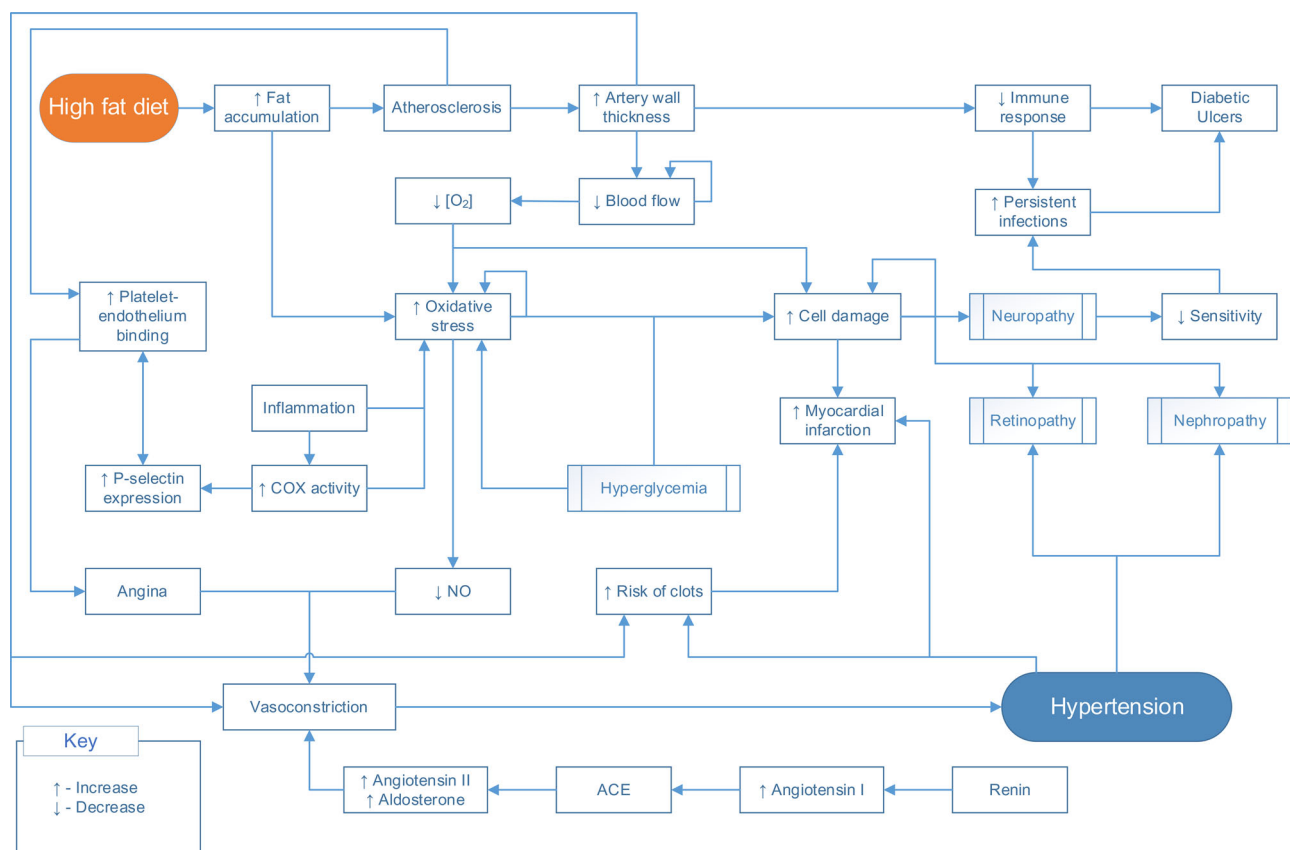


Figure 11. Schematic representation of Hypertension and how it is related to several Complications in diabetes (ACE – Angiotensin-converting enzyme EC 3.4.15.1, COX – Cyclooxygenase EC 1.14.99.1, NO – Nitrous Oxide, [O₂] – concentration of molecular Oxygen).

to the control high fat diet mice, to near the levels of standard diet mice. The inhibition of PL by proanthocyanidins was also observed by Sosnowska et al. 2018).

Buchholz and Melzig (2015) extensively reviewed several polyphenol groups with PL inhibitory activity (flavonoids, phenolic acids, and lignans) with the goal of identifying PL inhibitors and concluded that the effect of flavonoids depends on the number and position of hydroxyl groups, with a higher number of groups conferring a higher inhibitory power. For flavan-3-ols, esterification, modification with galloyl moieties or increased degree of polymerization all improve inhibitory power (Buchholz and Melzig 2015; Iwata et al. 2019; Rahim, Takahashi, and Yamaki 2015; Sosnowska et al. 2018) while other flavonoids and anthocyanins have higher activity after eliminating glycoside modifications (Buchholz and Melzig 2015). In phenolic acids, like in flavonoids, the presence and position of hydroxyl groups over methoxy groups improves inhibition of PL and the distance between the carbonyl and phenol groups is also important for this effect, since HCAs have a higher activity when compared with hydroxybenzoic acids. The effects of the number and position of hydroxyl functional groups in HCAs was also verified by Wu et al. (Wu et al. 2017), who tested several hydroxycinnamic glycosides as potential inhibitors of PL. Martinez-Gonzalez et al. (2017) and Cao et al. (2020) studied the inhibition of PL by hydroxycinnamic acids not only through in vitro tests but also through molecular docking. Their findings show that these compounds bind close to the active site of lipase and that the

aromatic ring and hydroxyl groups are both key to establish the interactions between the ligands and the enzyme. Both works propose a mixed type of inhibition, with Cao et al. (2020) showing that the binding of 5-CQA leads to changes in the secondary structure of the enzyme.

Lipid metabolism can also be stimulated by increasing the activity of carnitine palmitoyltransferase (CPT – EC 2.3.1.21). This enzyme is responsible for transporting lipids into mitochondria to be oxidized. Green coffee extract (GCE), which contains CQAs among other compounds, was shown to reduce fat accumulation around the liver of mice and to enhance CPT activity (Thom 2007). Two others studies on humans (Ochiai et al. 2004; Kozuma et al. 2005) provide contradictory results regarding the changes in cholesterol levels due to the ingestion of GCE. However, these studies had very different durations and number of participants, while Ochiai et al. (2004) analyzed only 20 individuals, they were observed over a period of four months, Kozuma et al. (2005) studied 117 individuals but for only 28 days. Ochiai et al. (2004) were only able to find a statistically significant difference in the levels of homocysteine but not in total cholesterol, HDL or LDL, while Kozuma et al. (2005) found a statistically significant difference in total cholesterol but not HDL or LDL when compared to the start of their study. There are several studies on the effects of resveratrol on CPT (Aires et al. 2017; Bastin, Lopes-Costa, and Djouadi 2011; Murphy et al. 2020; Kühn et al. 2018). Aires et al. (2017) studied the effects of resveratrol on CPT deficient fibroblasts and found that it was

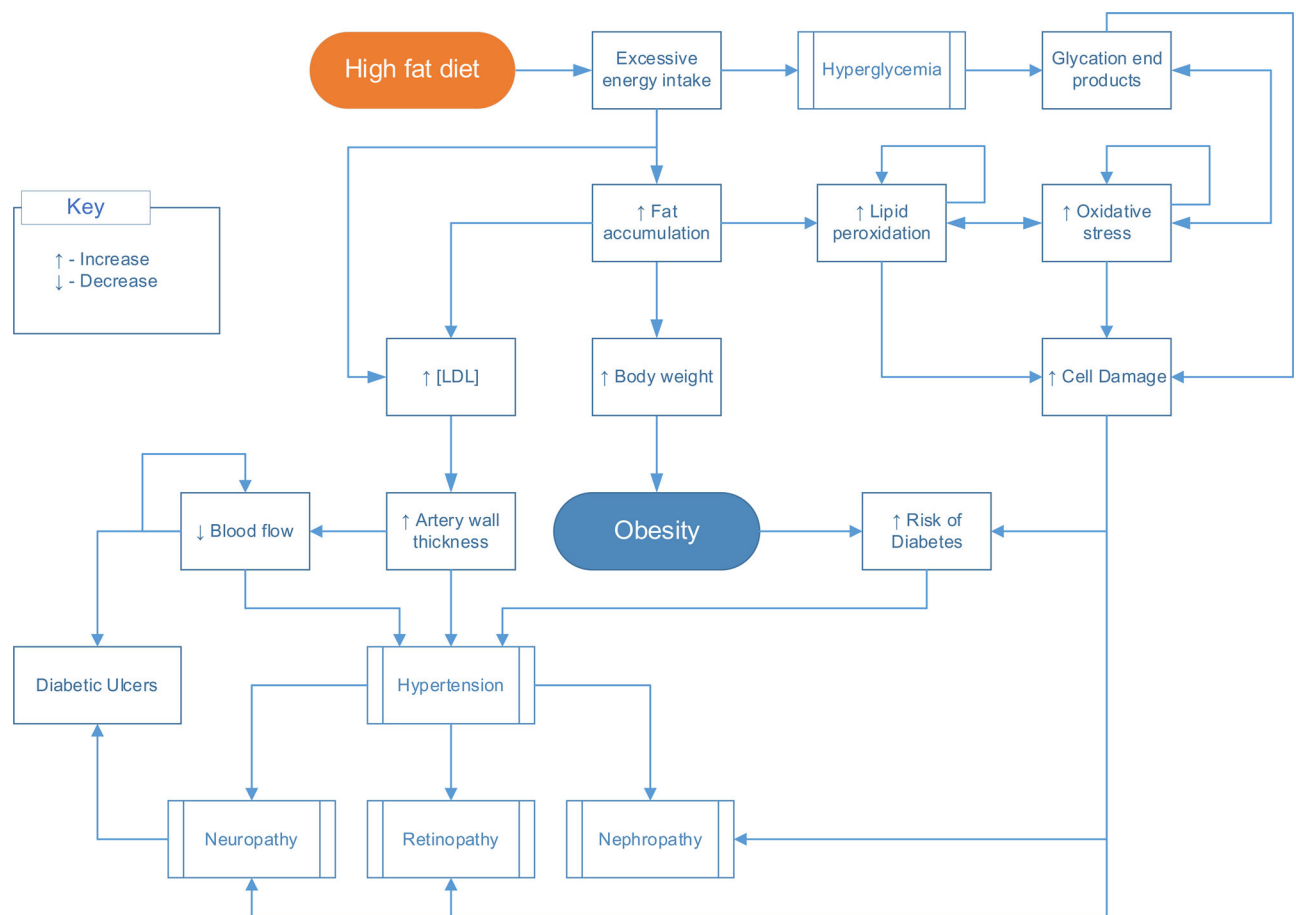


Figure 12. Effects of obesity on diabetes patients.

capable of modulating the expression of several microRNAs related to CPT and other enzymes related with energy metabolism such as adenosine monophosphate-activated protein kinase (AMPK). The increased expression/activity of CPT was also verified by Bastin, Lopes-Costa, and Djouadi (2011) in CPT deficient patients through an increase in the amount of CPT enzyme and its expression and fatty acid oxidation, by Murphy et al. (2020) who studied the effects on implanting a resveratrol releasing scaffold on adipose tissue of mice and by Kühn et al. (2018). Although resveratrol increased AMPK amounts/activity, this is not the only mechanism through which CPT activity and levels are restored, since using AMPK activators alone did not restore CPT to normal levels in the patients studied by Bastin, Lopes-Costa, and Djouadi (2011). In addition to modulating the activity and expression of lipase, CPT and AMPK, polyphenols also modulate lipid levels, such as total cholesterol, triglycerides, LDL, and HDL (Zou et al. 2014; Russo et al. 2012; Iwata et al. 2019; Egert et al. 2009) and consequently body fat accumulation/weight gain (Iwata et al. 2019; Yamabe et al. 2006; Elbe et al. 2015; Lambert, Hokayem, Thomas, Fabre, Cassan, Bourret, Bernex, Lees, et al. 2018; Lambert, Hokayem, Thomas, Fabre, Cassan, Bourret, Bernex, Feuillet-Coudray, et al. 2018; Buchholz and Melzig 2015). Wang et al. (2018) extensively reviewed how products, including polyphenols, from marine origin could improve lipid metabolism. The most common source of marine polyphenols in their research was the algae *Ecklonia*

cava, specifically their polyphenol extract. It provided overall improvements to lipid metabolism, reduced inflammation, reduced or inhibited lipid accumulation, reduced or inhibited adipogenesis by downregulating genes involved in the process and activating AMPK, reduced insulin resistance and reduced the formation of ROS and lipid peroxidation both in humans and mice models of hyperlipidemia. These effects were also reported other recent reviews on marine polyphenols (Venkatesan et al. 2019; Fernando et al. 2020; Mateos, Pérez-Correa, and Domínguez 2020). A meta-analysis by Ding et al. (2020) of randomized clinical trials found that algae supplementation significantly reduced HDL and triglycerides levels but not LDL or total cholesterol.

Hyperlipidemia and obesity conditions can be improved upon by polyphenols through two main actions, the inhibition of PL in the intestine, which reduces absorbed lipids, and by enhancing lipid metabolism. The later can be achieved by increasing the activity of CPT to transport lipids into the mitochondria, increasing AMPK activation and by reducing lipid accumulation, adipogenesis and insulin resistance, all of which are also enhanced by the activation of AMPK. Figure 12 summarizes how a high fat diet and obesity affect diabetes patients.

Hyperglycemia

It is common knowledge that glucose levels must be monitored in diabetes patients. Indeed, when present,

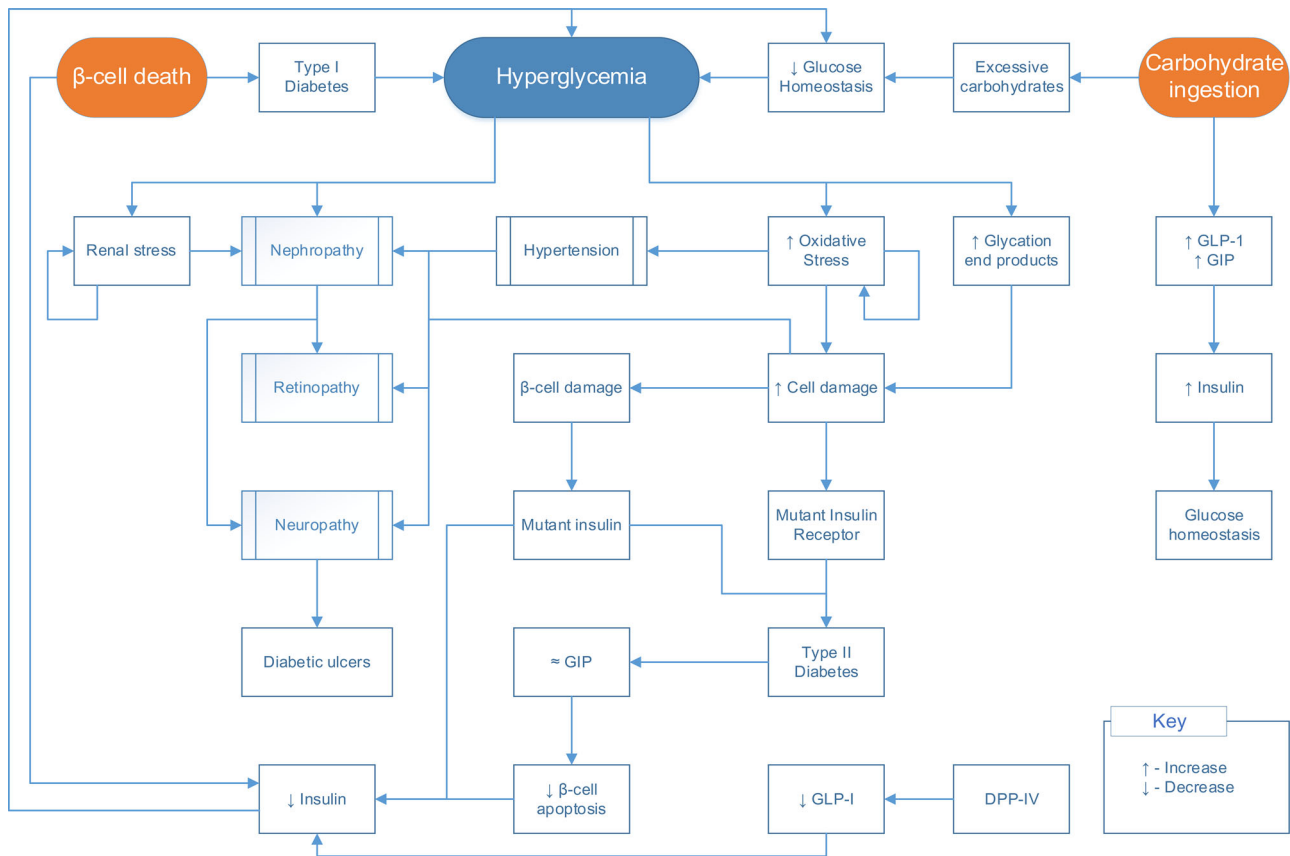


Figure 13. Effects of hyperglycemia (DPP4 – dipeptidyl peptidase-4 – EC 3.4.14.5; GIP – gastric inhibitory polypeptide; GLP-1 – glucagon-like peptide 1).

hyperglycemia leads to most of the complications associated with diabetes (Figure 13), namely nerve, kidney and eye damage (World Health Organization 2016). Monitoring the blood glucose levels has been proven to be cost reducing and to provide diabetes patients with better quality of life (World Health Organization 2016; Li et al. 2010; Kozuma et al. 2005; Shimoda, Seki, and Aitani 2006). There are several ways to lower blood glucose levels, the simplest way is through a controlled diet low in carbohydrates. Other common approaches include insulin injections and/or through medication that controls glucose level by inhibiting its absorption or the catabolism of carbohydrates. However, insulin therapy proves to be a problem in cases where the patient has defective insulin receptors or has insulin resistance. Insulin resistance has been associated with persistent low levels of inflammation on adipose tissue and its visceral accumulation which leads to the release of excessive free fatty acids and proinflammatory biomarkers such as IL-6 and TNF- α which interfere with insulin signaling pathways (Russo et al. 2019). While insulin resistance may be temporary and reversible in its initial stages and under the right conditions, if the state is allowed to persist it will lead to further insulin resistance due to the damage and burnout of β -cells caused by oxidative stress, inflammation and over activity in the production of insulin (Williamson and Sheedy 2020). Therefore, it is highly useful to have an alternative therapy that can regulate blood glucose through several mechanisms.

Adenosine monophosphate-activated protein kinase (AMPK – EC 2.7.11.31) is vital in regulating energy metabolism (Momtaz et al. 2019; Olivares-Vicente et al. 2019;

Cádiz-Gurrea et al. 2018). It affects lipid and carbohydrate metabolisms by regulating fatty acid oxidation, cholesterol synthesis, glucose uptake, production and storage, and insulin secretion among other processes (Momtaz et al. 2019; Cádiz-Gurrea et al. 2018). AMPK can be activated through several conditions including AMP/ADP/ATP ratios, heat shock, hypoxia, exercise, and glucose deprivation (Momtaz et al. 2019; Cádiz-Gurrea et al. 2018). The activation of AMPK will then extend to the lipid and carbohydrate metabolisms affecting their absorption, production, and consumption. In muscle cells, the activation of AMPK will increase glucose transporter (GLUT) expression and translocation which in turn stimulates glucose uptake (Momtaz et al. 2019; Les et al. 2021; Zhao et al. 2017; Yamashita et al. 2016; Russo et al. 2019) In the liver, it increases fatty acid oxidation by increasing CPT activity, and decreases gluconeogenesis (Momtaz et al. 2019), improves glucose storage (through glycogen) (Momtaz et al. 2019) and stimulates glycolysis (Zhao et al. 2017). There are several mechanisms through which polyphenols activate/increase AMPK activity and many are still unclear (Momtaz et al. 2019). While some studies suggest that the activation of AMPK may be the result of the action of polyphenols in other enzymes/proteins/signaling molecules related to AMPK's regulation and activation (Russo et al. 2019; Momtaz et al. 2019; Les et al. 2021), the work of Olivares-Vicente et al. (2019) shows that polyphenols (loganic acid, luteolin 7-diglucuronide and verbascoside) have the ability to bind to AMPK's AMP binding sites, the ATP binding site in the catalytic domain

or the regulatory site between AMPK subunits. Momtaz et al. (2019) extensively reviewed the activation of AMPK through polyphenols and found studies on the effectiveness of resveratrol, epicatechin, epigallocatechin gallate, anthocyanidins, quercetin and chlorogenic acid, among others while Russo et al. (2019) found evidence of AMPK activation by flavonoids such as EGCG, quercetin, kaempferol, naringenin, isoflavone and anthocyanins in their review of in vitro assays and clinical trials using flavonoids to treat insulin resistance. All these factors have made AMPK a prime molecular target in the treatment of diabetes (Momtaz et al. 2019; Les et al. 2021; Grahame 2013).

Glucosidases or glycosidases are enzymes under the category EC 3.2.1.X. α -glucosidases (maltase EC 3.2.1.20 and sucrase EC 3.2.1.48), and α -amylase (EC 3.2.1.1) are key molecular targets in the treatment of diabetes and inhibiting any of these enzymes will delay the digestion and absorption of carbohydrates (Alagesan, Raghupathi, and Sankarnarayanan 2012; Antunes 2008; Narita and Inouye 2009; Kirakosyan et al. 2018; Spínola, Llorent-Martínez, and Castilho 2020). Drugs that inhibit these enzymes are among the first options in a long list of therapies for diabetes (Hakamata et al. 2009). However, some of these inhibitors often have undesirable side effects such as flatulence and diarrhea (Alagesan, Raghupathi, and Sankarnarayanan 2012). The use of functional foods (Kirakosyan et al. 2018; Agustinah et al. 2016; Adefegha et al. 2017; Ademosun, Omoba, and Olagunju 2021), plants (Spínola, Llorent-Martínez, and Castilho 2020; Adefegha and Oboh 2016; Muritala et al. 2018; Shai and Magano 2011; Souza 2011; Ali Asgar 2013) and their components (Alagesan, Raghupathi, and Sankarnarayanan 2012; Narita and Inouye 2009; Adisakwattana et al. 2009; Ma et al. 2008; Bahadoran, Mirmiran, and Azizi 2013; Williamson 2013; Funke and Melzig 2005) as inhibitors for these enzymes has been extensively and thoroughly studied and reviewed in the literature. While the inhibition of these enzymes by terrestrial plants and their polyphenols is well characterized in the literature, the same information for marine species and compounds is still emerging. Nonetheless, recent *in-vitro* works (Nwosu et al. 2011; Yuan et al. 2019; Pradhan et al. 2021) and reviews (Lee and Jeon 2013; Gómez-Guzmán et al. 2018; Fernando et al. 2020; Mateos, Pérez-Correa, and Domínguez 2020; Gunathilaka et al. 2020; Venkatesan et al. 2019) have been providing encouraging results. Nwosu et al. (2011) studied edible algae from the UK coast and tested their ability to inhibit α -amylase and α -glucosidase in vitro. *Ascophyllum nodosum* was the most effective and thoroughly evaluated with an IC_{50} approximately 8 fold better than acarbose, which the authors attributed to the phlorotannins content (Nwosu et al. 2011). Yuan et al. (2019) studied the brown macroalgae *Lessonia trabeculate*, its composition and its ability to inhibit α -glucosidase. The ethyl-acetate fraction, composed mostly of phlorotannins and galliccatechin derivatives, was the most effective against α -glucosidase being two to four times more effective than acarbose at the same concentration. Pradhan et al. (2021) studied several extracts of *Enteromorpha intestinalis*. While the authors did not identify

the main compounds of the extracts, they verified that the extracts were capable of inhibiting both α -amylase and α -glucosidase although none of the extracts was as effective as acarbose (Pradhan et al. 2021). Despite the fact that most of the inhibitory effects of marine polyphenols are attributed to phlorotannins, Fernando et al. (2020) also found evidence that bromophenols can be effective inhibitors of these enzymes. The delay in the digestion and absorption of carbohydrates, will prevent spikes in glucose levels which in turn will result in less ROS being produced by cells (Williamson and Sheedy 2020).

Glucokinase (GLK) (EC 2.7.1.2) and glucose-6-phosphatase (G6Pase) (EC 3.1.3.9) add or remove a phosphate group to α -glucose. This makes them targets to control both glycolysis and gluconeogenesis, as these enzymes are responsible for the first and last steps of each pathway, respectively. Lin et al. (2020) studied the effects of the extract from *Tadehagi triquetrum*, rich in glycosylated polyphenols, in diabetic mice and found that it increased GLK activity and liver glycogen with an effect close to Metformin, a drug commonly used to treat diabetes. When investigating the main compounds of the extract, the authors attributed the effects mainly to rutin, tadehaginoside and tadehaginoside D, since they lead to the largest increased consumption and uptake of glucose, on par with insulin. The increased activity of GLK may be explained by the results of Luna-Vital et al. (2019), who found that polyphenols (hydroxycinnamic acids and flavonoids) very likely bind to the GLK allosteric activator site. This activation of GLK by anthocyanins was also observed in another work from Luna-Vital and De Mejia (2018). In addition to an increased catalytic activity, some polyphenols also increase the expression of GLK. Vetterli et al. (2011) showed that after 24 hours, cells exposed to resveratrol had increased expression for GLK and glucose transporter 2 (GLUT-2) which the authors attributed to resveratrol's ability to induce the overexpression of sirtuin 1 (SIRT1). This increased expression of GLK was also observed by Bang and Choung (2014) when administering tea polyphenols and pine bark extract, rich in proanthocyanidins, to diabetic mice. GLK expression was also increased by rosmarinic acid, quercetin, naringenin, 5-CQA and its metabolites, CA and FA. (Jung et al. 2006; Valentová et al. 2007; Bhattacharya et al. 2014). In addition, Bang and Choung (2014) also detected an increased expression glycogen synthetase (EC 2.4.1.11), activated AMPK and a reduced expression of G6Pase.

Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) are commonly referred to as incretin hormones. They are released in the intestines after a meal and make up to 70% of the release of insulin after a meal (Unger and Parkin 2011; Zander et al. 2002; Tunnicliffe and Shearer 2008). In T2D, production of GIP is not significantly impaired but its insulin secretion effect is compromised while GLP-1 secretion is impaired but its functions are not (Unger and Parkin 2011). GLP-1 is capable of inhibiting glucagon secretion, reducing glucose levels in the blood and hunger (DeFronzo and Abdul-Ghani 2011; Zander et al. 2002; Unger and Parkin 2011; Shyangdan et al. 2010;

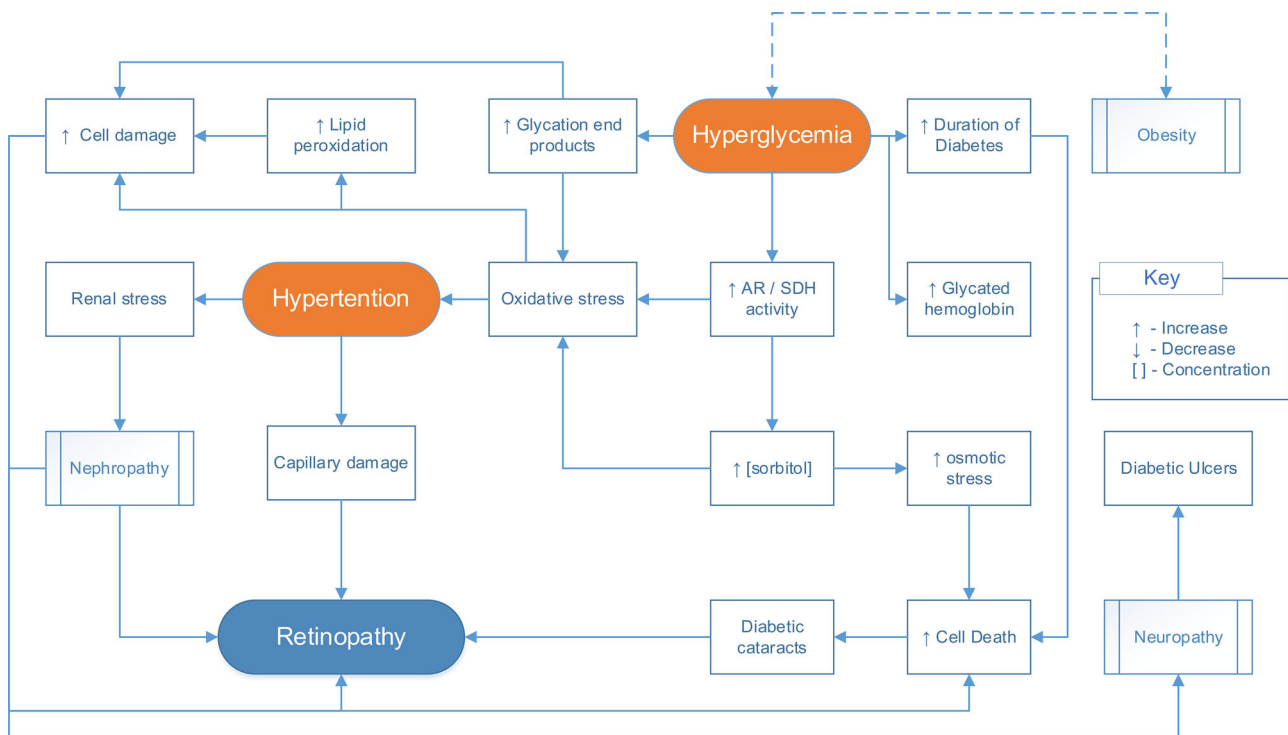


Figure 14. Diabetic retinopathy (AR – aldose reductase – EC 1.1.1.21; SDH – sorbitol dehydrogenase – EC 1.1.1.14).

Tunnicliffe and Shearer 2008; Marathe et al. 2013). GLP-1 receptor agonists or GLP-1 analogues are highly valuable as treatment for T2D and produce a similar effect to GLP-1. These effects include weight loss and reduction of accumulated fat (Unger and Parkin 2011; Zander et al. 2002; Shyangdan et al. 2010) leading to a smaller risk of developing T2D (Tunnicliffe and Shearer 2008). GIP promotes insulin secretion, also reduces body weight, stimulates the proliferation of pancreatic β -cells and prevents their apoptosis (Lyssenko et al. 2011; Tunnicliffe and Shearer 2008). This latter effect may be counterproductive in treating/preventing diabetes as it will lead to the preservation of nonfunctional cells leading to a reduction in insulin production. The effects of GIP, GLP-1 and GLP-1 receptor agonists or analogues are glucose dependent (DeFronzo and Abdul-Ghani 2011; Unger and Parkin 2011; Reid 2012) and are more practical than GLP-1 infusions (Marathe et al. 2013). GLP-1 receptor agonists however, have several side effects such as: nausea, diarrhea, headaches and dizziness (Reid 2012; Rational Assessment of Drugs and Research 2010). Despite this, they reduce the risk factors for cardiovascular disease, as reported by Mundil, Cameron-Vendrig, and Husain (Mundil, Cameron-Vendrig, and Husain 2012), through the reduction of body weight, SBP and concentration of several biomarkers associated with CVD. CGA is capable of reducing the release of GIP and simultaneously increasing the release of GLP-1 (Henry-Vitrac et al. 2010). This effect is also observed when consuming coffee, rich in CGA and CA (Tunnicliffe and Shearer 2008).

The uptake of glucose by cells is mediated by glucose transporters. The expression of glucose transporter 2 (GLUT2) is altered in hepatocytes by the administration of CA. While Huang, Shen, and Wu (2009) claim that the expression of GLUT2 is increased, Jung et al. (2006) claim

that it is reduced. The results from Bhattacharya et al. (2014) indicate that GLUT2 expression is increased despite not being statistically significant. Jung et al. (2006) also found that the expression of GLUT4 is enhanced on adipocytes through the administration of CA. Additionally, quercetin and catechins appear to inhibit the uptake of carbohydrates in the intestine while their metabolites, resulting from gut microbiota, increase GLUT4 translocation (Williamson and Sheedy 2020).

Hyperglycemia can also be managed through insulin levels. CA was shown to increase the release of insulin on chronically hyperglycemic pancreatic β -cells (Bhattacharya et al. 2014) and, as a supplement to a standard mouse diet, it was able to increase the levels of plasma insulin (Jung et al. 2006; Chao et al. 2010) and decreased the levels of blood glucose. Insulin levels in humans can also be improved by algae supplementation (Ding et al. 2020).

In summary, polyphenols can control carbohydrate levels through several mechanisms, the first of which is the inhibition of glucosidase enzymes in the intestines which blocks their breakdown and subsequent absorption. In the intestines, they stimulate the release of GLP-1 which decreases hunger and lowers the levels of glucose in the blood stream. Furthermore, polyphenols increase the activity and expression of GLUT and GLK while reducing the activity and expression of G6Pase. This combined with the activation of AMPK enhances insulin levels and sensitivity and reduces blood glucose levels even further.

Diabetic retinopathy

Diabetic retinopathy (Figure 14) is mainly caused by elevated oxidative stress. This is the result of the reduction of

glucose to sorbitol through aldose reductase (AR – EC 1.1.1.21) (Pan et al. 2008; Kawasaki et al. 2011). The accumulation of sorbitol in the retina will lead to the development of diabetic cataracts (Pan et al. 2008) due to high osmotic pressure in cells, which eventually leads to their rupture. There are several polyphenols that can act as inhibitors or genetic regulators of AR, such as GCA (Kim et al. 2011), CA (Chao et al. 2010), esculetin (Kim et al. 2016), flavonoids and other polyphenols (Xiao et al. 2015; Cao and Chen 2012; Manivannan et al. 2015). Xiao et al. (2015) extensively reviewed how different functional groups affected the ability of different polyphenol classes to inhibit AR, while Cao and Chen (2012) focused exclusively on the functionalization/substitution on flavonoids (refer to Figure 4 for the numbering of flavonoid positions/substituents). Both works (Xiao et al. 2015; Cao and Chen 2012) found that for flavonoids the hydroxylation of positions 5 and 7 (A ring) and positions 3' and 4' (B ring) significantly increased inhibitory activity, while the hydroxylation of position 5' (B ring), on the C ring, and in some cases in position 5 (A ring) decreased inhibitory activity. Furthermore, the double bond between positions 2 and 3 (C ring) appears to be a critical feature for the inhibition and an hydroxylation of position 3 also reduces inhibitory power (Xiao et al. 2015; Cao and Chen 2012). While the methylation or methoxylation of positions 5, 6, and 8 (A ring) significantly increases the inhibitory power, this functionalization on positions 3 (C ring) or 3' and 4' (B ring) slightly decreases activity and on position 7 (A ring) it will significantly decrease inhibitory activity. All of this can be explained by the work of Manivannan et al. (2015), who investigated the binding mode of polyphenols to AR, through molecular docking and molecular dynamics, and created a pharmacophore model for the inhibition of AR. They found that a hydrogen bond interaction between the ligand and the catalytic residue tyrosine 48 (Tyr48) is the minimum requirement for a molecule to be considered an inhibitor of AR. In flavonoids, this is established by an oxygen substituent in position 7 (A ring). The C ring is also required to establish hydrophobic interactions with several nonpolar residues in the catalytic site (valine, proline, leucine) and a serine, as well as π - π interactions with a tryptophane residue, which is also why the double bond between 2 and 3 is so important, as it extends the conjugated π systems including both rings A and C and creates a planar geometry. A hydrogen bond acceptor/donor is also important in position 5 (A ring) since it will donate a proton to aspartate 43, while accepting a proton from lysine 77, all critical residues for the catalytic activity and complex stabilization. The glycosylation of position 8 (A ring) significantly reduces inhibitory power of flavonoids toward AR (Xiao et al. 2015; Cao and Chen 2012) since it creates steric hinderance and reduces the ability of establishing the hydrogen bond with Tyr48. In addition to the inhibition of AR, polyphenols are also capable of countering the oxidative stress that its elevated activity produces, which usually leads to diabetic cataracts (Pan et al. 2008). Stefek (2011) extensively reviewed the potential of flavonoids as adjunct therapy for diabetic cataract and attributed their

effectiveness to their multifunctional properties, the antioxidant action by scavenging free radicals and chelating metals, the inhibition of AR and the inhibition of AGE formation. Stefek (2011) also reached similar conclusions to Xiao et al. (2015) and Cao and Chen (2012) regarding the structural requirements of flavonoids to successfully inhibit AR.

Diabetes patients with retinopathy will also have high lipid peroxidation and protein oxidation, along with DNA damage induced by the oxidative stress (Kawasaki et al. 2011). This multi-faceted oxidative stress makes an antioxidant therapy very relevant. Polyphenols are effective antioxidants and are present in many foods commonly ingested (Crozier, Del Rio, and Clifford 2010). In addition to their innate antioxidant properties, some polyphenols can also alter the genetic expression of enzymes related with oxidative stress. Soyalan et al. (2011) studied the effect of several preparations of polyphenol rich and polyphenol free apple juices on the expression of several antioxidant enzymes and found that the polyphenol rich preparations (rich in 5-CQA and procyanidins) were able to upregulate the expression of the genes for superoxide dismutase (SOD – EC 1.15.1.1), catalase (CAT – EC 1.11.1.6), glutamate cysteine ligase (GCL – EC 6.3.2.2) and glutathione reductase (GR – EC 1.8.1.7) in the colon of rats. The same genes were, however, downregulated in the liver, which the authors attributed to the fact that polyphenols naturally reduced oxidative stress levels, reducing oxidative status, and thus reducing the stimuli for induction of these genes. Also, while glutathione peroxidase (GPx – EC 1.11.1.9) was downregulated in the colon it was upregulated in the liver (Soyalan et al. 2011). The upregulation in SOD and CAT was also observed by Le Sage, Meilhac, and Gonthier (2017) when using *Antirhea borbonica* (*A. borbonica*) and its main polyphenol compounds 5-CQA, CA, and kaempferol. In addition to the upregulation of antioxidant enzymes, *A. borbonica* and its main polyphenols also reduced the expression of NADPH oxidase (NOX – EC 1.6.3.1) and inducible nitric oxide synthase (iNOS – EC 1.14.13.39) and NADPH oxidase 2 and 4 (NOX2/NOX4 – EC 1.6.3.1) (Le Sage, Meilhac, and Gonthier 2017) which produce reactive oxygen species as byproducts of their activity. The same authors found that preconditioning the cells with 5-CQA, CA or kaempferol had the same protective effects (Le Sage, Meilhac, and Gonthier 2017). Two other studies with tea polyphenols (one with human L-02 hepatic cells (Yi et al. 2020) and the other with harvested goat hepatocytes (Zhong et al. 2013)), one with CA in mice (Jung et al. 2006) and another with 5-CQA and tetrahydrocurcumin in rats (Pari, Karthikesan, and Menon 2010) also found an increased expression and activity of SOD, CAT and GPx. Yi et al. (2020) found a down regulation of iNOS levels, and showed that, due to oxidative damage, the levels of neuronal NOS (nNOS) and endothelial NOS (eNOS) are reduced but can be partially restored by tea polyphenols. Glutathione (GSH) is a naturally occurring antioxidant in cells and its depletion is often used as model for oxidative stress. Maher and Hanneken (2005), studied the protective effect of several flavonoids on retinal ganglion cells against oxidative stress and found that,

while these did not affect GSH metabolism, they functioned as scavengers for reactive oxygen species and can also affect the expression of antioxidant enzyme heme oxygenase 1 (EC 1.14.99.3).

The elevated oxidative stress and hyperglycemia will also lead to the formation of advanced glycation end products (AGEs). These will react with structural proteins and lead to several structural changes that will lead to defective proteins (usually through cross-linking proteins) and histological changes. Cui et al. (2009), studied the ability of 3,4-diCQA, 1,3,5-triCQA and 3,4,5-triCQA to inhibit the formation of AGEs between bovine serum albumin and methylglyoxal (MGO). Despite having the same number of CQA functional groups, 1,3,5-triCQA was nearly 10 times more effective than 3,4,5-triCQA at preventing the formation of AGEs while 3,4-diCQA had an efficacy close to 5-CQA, used as positive control, approximately one third of 1,3,5-triCQA. From these results it can be inferred that the number of hydroxycinnamic acid and/or hydroxyl functional groups are not the only parameters that determine a compound's ability to block AGE formation. Navarro and Morales (2015) studied hydroxytyrosol and structurally related molecules as AGE inhibitors and found that hydroxyl groups in an *ortho* orientation are required for a phenolic compound to scavenge MGO. While compounds with this feature, such as hydroxytyrosol, hydroxytyrosol acetate, pyrocatechol, CA and gallic acid, achieved very high MGO trapping (> 90%), molecules without it failed to scavenge significant amounts of MGO, with tyrosol reaching approximately 7% scavenging. The hydroxyl groups activate their adjacent aromatic carbons so these can undergo electrophilic aromatic substitution with MGO (Navarro and Morales 2015). This can explain the results from Cui et al. (2009) since the CA moieties of 3,4-diCQA and 3,4,5-triCQA are in close proximity, limiting the access of MGO to the several reactive carbons after the first substitution occurs. The recognition that *ortho* hydroxyl groups are a driver/requirement for blocking AGE formation/scavenging MGO is still not widespread since recent reviews simply attribute this property to the presence of multiple hydroxyl groups and the antioxidant properties of polyphenols (González, Morales, and Rojas 2020; Yeh et al. 2017). According to Khangholi et al. (2016), in flavonoids, not only is the presence of *ortho* hydroxyl groups in the B ring a key structural feature, but also the presence of the double bond between positions 2' and 3' (in the C ring) as well as the presence of an hydroxyl group in positions 5 or 7 (in the A ring). The work of Yoon and Shim (2015) also supports this, since they propose that quercitrin and rutin (both with hydroxyl groups in positions 5 and 7 – A ring) scavenge MGO which replaces the hydrogen atoms in positions 6 and 8 (A ring). Position 6 (A ring) is particularly activated for electrophilic substitution, having donor groups in both *ortho* and *para* positions.

Chen et al. (2014) studied the effects of EGCG, luteolin, apigenin, myricetin, quercetin, and cyanidin in cultures of human retinal pigment cells. They found that all these polyphenols (except EGCG) reduced the release of proliferation growth factor of retinal pigment cells and the secretion of

vascular endothelial growth factor (VEGF). Despite their adverse effects in cell viability at high concentrations ($\approx 100 \mu\text{M}$), their ability to modulate the release of VEGF makes them relevant to prevent the onset of proliferative diabetic retinopathy. The suppression of VEGF by quercetin also encountered by Salehi et al. (2020) in their review, in addition to reduced oxidative and inflammatory stress and reduced retinal neuronal degeneration. Lee et al. (2014) also studied the effects of EGCG on human retinal cells and their findings align with the results from Chen et al. (2014) both in terms of cell viability with the increase of concentration and in inhibition of proliferation induced by VEGF. In addition, Lee et al. (2014) found that EGCG can reduce vascular permeability and suppress the expression of the metalloproteinase MMP-9 under oxidative stress induced by hydrogen peroxide.

When monitoring retinopathy, several risk factors should be kept in mind. On T2D patients, elevated glycated hemoglobin, hypertension, high body mass index (obesity) and the duration of diabetes are the key risk factors (Tung et al. 2005; Grauslund, Green, and Sjølie 2009). T1D patients, on the other hand, will develop retinopathy in nearly 100% of the cases and, as such, they should be monitored for proliferative retinopathy and its risk factors, such as elevated glycated hemoglobin, and the presence of non-proliferative retinopathy. Hypertension, obesity and duration of diabetes are not considered as risk factors on T1D (Kärvestedt et al. 2011).

In summary, polyphenols act on three key points to prevent diabetic retinopathy. The first is the reduced activity and expression of AR which in turn reduces the accumulation of sorbitol leading to less oxidative and osmotic stress of retinal cells. The second mechanism is the overall reduction of oxidative stress through the increased expression and activity of antioxidant enzymes, reduced expression or activity of enzymes that generate ROS and scavenging of ROS. The third mechanism is the reduction the AGE formation mostly due to the scavenging of AGE forming molecules such as MGO. All these combined effects reduce the damage to cells and their structural molecules improving their viability.

Diabetic nephropathy

Ten to 20% of diabetes patients die from renal failure (World Health Organization 2016). As such, it is imperative to monitor the risk for nephropathy (DN) in all diabetes patients (World Health Organization 2016; Li et al. 2010; Kozuma et al. 2005; Shimoda, Seki, and Aitani 2006), which may prevent renal damage, reduce odds of complications, and will cut treatment costs. The risk factors for DN are usually exhibited by all diabetes patients and include hypertension, poor control of blood glucose and aging (Vupputuri et al. 2011; Viswanathan, Tilak, and Kumpatla 2012; Murase et al. 2011). Retinopathy is also one of the symptoms for diabetic kidney failure (Murase et al. 2011).

Several studies in mice and rats aim to treat or reduce DN through the administration of polyphenol rich extracts

(Zhu et al. 2014; Yokozawa et al. 2005; Lee et al. 2009). The key aspect of these studies is the antioxidant potential of polyphenols. This capacity allows the extracts to reduce the oxidative stress in the kidneys, leading to less oxidative damage thus, significantly reducing the progression of nephropathy. A few other examples of the potential of polyphenols in the treatment of diabetic nephropathy is the patent filed by Alexiadou and Doupis (2012), that used GCA as a treatment for diabetic nephropathy and the several studies of diabetic mice whose kidney function was restored when CGA/CA is administered (Chao et al. 2010; Pari, Karthikesan, and Menon 2010).

There are several works that study the effects of tea (*Camelia sinensis*) and its polyphenols as potential treatments for DN (Kang et al. 2012; Yoon et al. 2014; Borges et al. 2016; Hayashi et al. 2020; Kanlaya and Thongboonkerd 2019; Dehdashtian et al. 2020). Kang et al. (2012) compared the effects of fermented and non-fermented green tea on mice and Madin-Darby canine kidney cells as a possible treatment for DN and found that non-fermented tea was more effective at controlling body weight, improving creatine clearance, reducing albuminuria (abnormal presence of albumin in urine) and proteinuria (excessive amount of protein present in urine), and preventing histological changes due to DN. The improvements described by Kang et al. (2012) are also observed in other works that used green tea or its main polyphenol EGCG. Yoon et al. (2014), who injected EGCG in diabetic mice with DN, also observed improved levels of blood glucose and proteinuria and creatine clearance. Borges et al. (2016) also observed reduced albumin-creatin ratios in the urine of their clinical trial participants. Their work also revealed that administering the serum of (human) diabetes patients treated with green tea polyphenols (GTP) or EGCG to podocytes would restore/maintain regular levels of apoptotic cells, while administering the serum from (untreated) diabetes patients greatly increased the ratio of apoptotic podocytes. Borges et al. (2016) attributed the effects of EGCG to its ability to activate the Wingless and Int-1 (WNT) pathway. The authors also corroborated their theory by adding dickkopf-related protein 1 (DKK1), a WNT pathway inhibitor, to the serum of diabetic patients that had ingested GTP and observed that this serum had similar or stronger apoptotic effect than the untreated serum from diabetes patients. Hayashi et al. (2020) also studied the effects of EGCG, and its methylated sibling epigallocatechin-3-(3''-O-methyl) gallate (EGCG-3''-Me) on rats with DN, but for their role on the activity of diacylglycerol kinase α (DGKA – EC 2.7.1.107). Hayashi et al. (2020) found that both molecules activated DGKA and while EGCG was more effective in inducing DGKA translocation/activity, EGCG-3''-Me was more effective at reducing albuminuria and the volume of urine produced. According to the authors (Hayashi et al. 2020), the activation of DGKA led to the inhibition of protein kinase c (PKC – EC 2.7.11.13), which in turn reduced the activity of transforming growth factor- β (TGF- β) and VEGF signaling pathways in podocytes which are essential for epithelial to mesenchymal transition (EMT). However,

the authors did not observe a reduction of fasting glucose like other studies of GTP or EGCG but observed a reduction in body weight of the treated rats (for EGCG but not for EGCG-3''-Me). Furthermore, Hayashi et al. (2020) conclude that although EGCG's antioxidant capacity is beneficial for DN, it is not the key mechanism of action, since diabetic mice treated with EGCG but without the DGKA gene had similar levels of albumin in urine and higher urine volume when compared with the diabetic mice that were not treated with EGCG and without the DGKA gene. Kanlaya and Thongboonkerd (2019) reviewed the effects of EGCG on several kidney diseases and conclude that its key properties for the treatment of DN are its antioxidant and anti-inflammatory nature and its ability to prevent/regulate apoptosis through the nuclear factor erythroid 2-related factor 2 (NRF2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathways, but that the exact mechanism(s) of action/molecular target(s) are still unknown. Additionally, the authors caution that most EGCG studies fail to account for EGCG's poor stability, bioavailability and that the number of studies in humans is very reduced since most studies are performed in animal or cell models. Dehdashtian et al. (2020) reviewed the applications of nutraceuticals in DN. In addition to the key properties identified by Kanlaya and Thongboonkerd (2019), they identified other key points/mechanisms where nutraceuticals can improve DN, such as preventing the upregulation of adhesion molecules, TNF- α , PKC, TGF- β and the RAAS, inhibiting or reducing the activity or expression of dipeptidyl peptidase-4 (DPP4 – EC 3.4.14.5) and AR, increasing the expression and activity of GLUT, peroxisome proliferator-activated receptor (PPAR- γ) and by reducing the levels of oxidative stress, AGE formation and pro-inflammatory cytokines.

The *Hibiscus sabdariffa* polyphenol extract (HPE) is another product studied for its potential applications in DN (Peng et al. 2014; Yang, Wang, et al. 2013; Yang, Huang, et al. 2013). Peng et al. (2014) found that HPE countered the effects of high glucose levels in HK-2 cells and rats by preventing the overexpression of vimentin, the phosphorylation of insulin receptor substrate 1 (IRS-1), and by reducing the activity but not the expression of DPP4. Peng et al. (2014) also established that the reduced expression of vimentin and phosphorylation of IRS-1 (p-IRS-1) were both due to the inhibition of DPP4, since both HPE and linagliptin, a DPP4 inhibitor, reduced the vimentin and p-IRS-1 levels back to normal and restored the levels of phosphoinositide 3-kinase (PI3K – EC 2.7.1.137), a marker for insulin sensitivity. They also tested some of HPE's individual compounds (CA, protocatechuic acid, CGA and gallic acid) to study their role in the inhibition DPP4. Although each individual compound reduced the activity of DPP4 at a similar level, the authors only tested/presented results for a single concentration for each compound, all compounds were tested at different concentrations and the reader is not informed if the concentration of each compound is the concentration in HPE or the optimal concentration for the inhibition of DPP4. Yang, Wang, et al. (2013) also worked with HPE for the treatment of DN in HK-2 cells and

verified a reduced expression of vimentin even with high glucose concentrations. They also found additional benefits of HPE in the treatment of DN, such as the reduced expression of angiotensin 2 receptors type 1 and 2 (ART-1 and ART-2), reduced levels of TGF- β and the prevention of high glucose epithelial to mesenchymal transition (EMT). The prevention of EMT was attributed to the reduced expression of vimentin and fibronectin and the increased expression of E-cadherin. These mechanisms lead to reduced fibrosis due to fibroblast generation and improved the expression of collagen 4, which lead to improved cell adhesion and cell-cell junctions thus preventing EMT (Yang, Wang, et al. 2013). Another work from Yang, Huang, et al. (2013) also shows that HPE improves albuminuria and creatine clearance, as well as reducing fat deposition, oxidative stress and the formation of AGEs in the kidneys.

Flavonoids and flavonoid rich extracts have been shown to improve renal health of diabetic mice. Urios et al. (2014) and Zou et al. (2014) studied the flavonoid rich extracts of *Rutaceae aurantiae* and *Murraya paniculata* respectively. Both pieces of literature found that the administration of these flavonoid rich extracts helped to restore normal renal function on diabetic mice through the reduction of several biomarkers of renal damage (blood urea nitrogen, creatinine, albumin clearance) and reduced oxidative and inflammatory stress. Anjaneyulu and Chopra (2004) and Gomes et al. (2014) studied the use of quercetin on diabetic nephropathy in mice and found that it was able to reduce oxidative stress, one of the major factors that leads to nephropathy, in addition to preventing structural changes such as glomerulosclerosis. Luteolin, a flavonoid similar to quercetin, has also been shown to prevent oxidative stress in the kidney of diabetic rats through the improvement of SOD (Wang et al. 2011), a conclusion also shown in the work of Anjaneyulu and Chopra (Anjaneyulu and Chopra 2004) who studied the effects of quercetin on diabetic rats. Elbe et al. (2015) studied diabetic nephropathy in rats and the ability of quercetin and resveratrol to improve this condition. They found that, despite having no significant effect on the body or kidney mass, both compounds were able to lower blood glucose and increase the activities of SOD and CAT. Quercetin and resveratrol were also able to reduce the cellular morphological changes induced by diabetes. These positive effects of quercetin against DN were also verified by Salehi et al. (2020). Menati, Meisami, and Zarebavani (2020) reviewed four flavones, luteolin, apigenin, chrysin, and nobiletin, and their mechanisms of action toward DN. The authors found that these compounds acted through the reduction of oxidative and inflammatory stress, by inhibiting inflammatory cytokines and reducing ROS production and increasing antioxidant enzyme activity, reduced hyperglycemia through the activation of AMPK and upregulation of GLUT and, restored kidney structure even in DN by suppressing EMT through reduced fibrosis, AGE formation and accumulation of matrix proteins which led to an improved kidney function as verified by lower levels of blood urea nitrogen, creatinine and albuminuria.

Polyphenols improve kidney health in diabetes patients through three key actions. The first, as mentioned in other complications, is a reduction of blood glucose levels through the increased levels of AMPK and GLUT. This also leads to the other two mechanisms of action, reduction oxidative and inflammatory stress and prevention of function altering histological changes. The reduction to oxidative and inflammatory stresses is once again the result of reduced expression and activity of AR, DDP-4 and RAAS/ACE, improved activity and expression of antioxidant enzymes such as SOD and CAT, reduced formation of AGEs and ROS and their scavenging by polyphenols. The kidneys are protected from abnormal histological changes through these mechanisms but also by a reduction/regulation of apoptosis, reduced fibrosis and production of adhesion molecules, reduced fat deposition and reduced activity of the of TGF- β and VEGF signaling pathways which reduces EMT and thus preserves normal kidney function. These improvements are then visible in the values of biomarkers for kidney health with improvements to creatinine clearance, albumin and protein levels in urine and blood urea nitrogen. Considering the literature reviewed, Figure 15 was prepared to provide an overview of diabetic nephropathy and which mechanisms contribute to its development.

Diabetic neuropathy

Up to 50% of diabetes patients suffer from diabetic neuropathy (DNP) (World Health Organization 2016). In Sub Saharan Africa, neuropathy affects 27 to 66% of diabetes patients (Hall et al. 2011) and a 12 year follow-up study conducted in India found that it affects 35.3% of the subjects with normal renal function and 68.7% of individuals with compromised renal function (Murase et al. 2011). In Sweden, peripheral neuropathy affects 67% of diabetes patients (Nather et al. 2008) while in Singapore, neuropathy rates range from 34.1 to 72.4% for less than five years and over 10 years of diabetes, respectively (Monte et al. 2006). Although there are treatments for DNP, current therapeutic approaches either lack efficacy or cause significant side effects (Naseri et al. 2019).

Naseri et al. (2019) extensively reviewed DNP, the mechanisms it entails and how polyphenols could be beneficial. Of the several mechanisms involved in DNP, activation of the polyol pathway, oxidative stress and formation of AGEs, and inflammation are common to other diabetes complications such as DR or DN. Additionally, in DNP, there are disruptions to neurotrophic factors, activation of ionic channels, peroxisome proliferator-activated receptors, and to the glutamate pathway (Bădescu et al. 2014; Naseri et al. 2019). In neurons and nerve tissue, similarly to other tissues, prolonged hyperglycemia reduces the expression and activity of antioxidant enzymes SOD, CAT, GPX, and GST leading to reduced levels of GSH (Naseri et al. 2019). CAT and SOD activity was restored in rats by catechin (Addepalli and Suryavanshi 2018) and by the extract of *Ilex paraguariensis*, which is rich in CGA and CA (de Lima et al. 2018), while GSH levels and GPX activity and expression were partially

it was able to protect the neurons from the degeneration by scavenging ROS, inducing the expression of antioxidant enzymes through the activation of nuclear factor (erythroid-derived 2)-like 2 and heme oxygenase-1 and by reducing enzymatic oxidative stress through the inhibition of NF- κ B and by preventing the expression of inflammatory biomarkers (IL-6 and TNF- α). The reduced levels of inflammatory biomarkers/cytokines due to treatment with polyphenols or polyphenol rich extracts has also been observed by other authors on rats and mice (Samaddar and Koneri 2019b; Ma et al. 2016).

Bădescu et al. (2014) studied neuropathic pain in rats and compared the effects of grape seed polyphenols and Zinc (Zn) in DNP and found that both are effective at partially restoring sensitivity to near normal levels with Zn being more effective than the grape seed polyphenols. Furthermore, the authors determined that the polyphenols, mainly proanthocyanidins, were able to inhibit N-methyl-D-aspartate (NMDA) receptors, like Zn, which protected neurons from excessive exposure to glutamate (Bădescu et al. 2014). Excessive glutamate release has also been proposed as a possible mechanism for the formation of amyloid beta peptides, a key step in the development of Alzheimer's disease (Mateos, Pérez-Correa, and Domínguez 2020).

Alzheimer's disease (AD) is a result of a large number of factors and, over the past few years, it has been proposed and coined as a type 3 diabetes (in the brain) (Monte and Wands 2008; Monte 2009; Monte et al. 2006; Silveira et al. 2019). Like in diabetes, oxidative stress, inflammation, loss of energy, homeostasis and aging are major risk factors and key mechanisms for the development Alzheimer's disease (AD) (Monte and Wands 2008; Monte 2009; Kwon et al. 2010; Silveira et al. 2019). While the incidence of both diseases has been increasing (Silveira et al. 2019), the degeneration caused by AD can sometimes be reversed through medication used for T2D, due to an increase in insulin efficiency and reduced oxidative stress (Monte and Wands 2008; Silveira et al. 2019). This is also important since insulin induces NO production that is essential for learning and memory (Silveira et al. 2019) and is depleted/less bioavailable in diabetes patients, as previously reviewed in the hypertension section. Furthermore, reduced levels of insulin or insulin resistance also lead to a reduction of the levels of acetylcholine, a hallmark of AD (Silveira et al. 2019) making the use of cholinesterase inhibitors one of the first therapeutic strategies (Barbosa, Valentão, and Andrade 2020). Polyphenols are, once again, vital as they are capable of both improving insulin production and sensitivity (Henry-Vitrac et al. 2010; Salazar-Martinez et al. 2004; Tunnicliffe and Shearer 2008; Lyssenko et al. 2011; Silveira et al. 2019) and reduce inflammation and oxidative stress. A few examples are CGA, which reversed the impairments that were induced in mice by reducing oxidative stress and also improved their short term memory and prevented amnesia (Cho et al. 2009; de la Monte et al. 2009), EGCG which promotes cell survival and prevents neuronal cell death through several mechanisms, luteolin which reduced the cognitive impairment caused by streptozotocin by reducing oxidative

stress and the formation of β -amyloid plaques and quercetin which inhibits acetylcholinesterase thus preventing the decline of acetylcholine levels (Silveira et al. 2019). The potential benefits of quercetin in AD were also reviewed by Salehi et al. (2020) who describes that, in addition to the inhibition of acetylcholinesterase, quercetin will also disrupt amyloid plaque aggregation, the formation of neurofibrillary tangles and inhibit amyloid precursor protein. Barbosa, Valentão, and Andrade (2020) recently reviewed the use of brown algae phlorotannins in the treatment of AD and found that some eckol derivatives (eckstonol, eckol, dieckol, 2-phloroeckol, and 7-phloroeckol) were selectively more efficient at inhibiting acetylcholinesterase than butyrylcholinesterase, while phlorofucofuroeckol-A was 100-fold more effective at inhibiting butyrylcholinesterase than acetylcholinesterase. Mateos, Pérez-Correa, and Domínguez (2020) reviewed marine polyphenols and found that phlorotannins are effective inhibitors of butyrylcholinesterase and acetylcholinesterase, protected cells from excessive glutamate induced apoptosis, reduced ROS production/oxidative stress by inhibiting pro inflammatory enzymes and increasing SOD activity, and disrupted the formation of β -amyloid plaques by inhibiting the synthesis of their precursor proteins.

Summarizing, polyphenols protect neurons by reducing the activity of the polyol pathway and reducing oxidative and inflammatory stress. The first effect is due to the reduced activity of AR, which reduces the accumulation of sorbitol in neurons reducing osmotic stress and thus preventing their hyperactivity and neuropathic pain. This also leads to a reduced formation of AGEs which reduces the structural damage to neurons and reduces their apoptosis, protecting them against demyelination. The reduced oxidative and inflammatory stress is achieved by increased activities and expression of SOD, CAT, GPX, and GST, ROS scavenging and reduction of inflammatory biomarkers. These mechanisms are also important to reduce neuron hyperactivity and spontaneous firing, which results in neuropathic pain. Polyphenols also appear to protect neurons from glutamate toxicity/overstimulation, which helps to reduce neuropathic pain and may help to treat AD (considered as type 3 diabetes) since they are also capable of inhibiting acetylcholinesterase and butyrylcholinesterase, which are upregulated in AD patients. Considering the reviewed literature, Figure 16 was created to provide a schematic representation of DNP and which systems/mechanisms are involved in its onset and evolution.

Ulcers and lower limb damage

Diabetic foot ulcers occur due to reduced blood flow and neuropathy (World Health Organization 2016; Ribu et al. 2008). Even when properly treated, quite often diabetic ulcers fail to heal (Smith et al. 2010). These ulcers are the result of a persistent bacterial infection that is not picked up by self-examination or the immune system, due to the reduced blood flow and sensitivity.

EGCG formulations were analyzed by Kim et al. (2008) as a way to improve wound healing on diabetic mice. Even

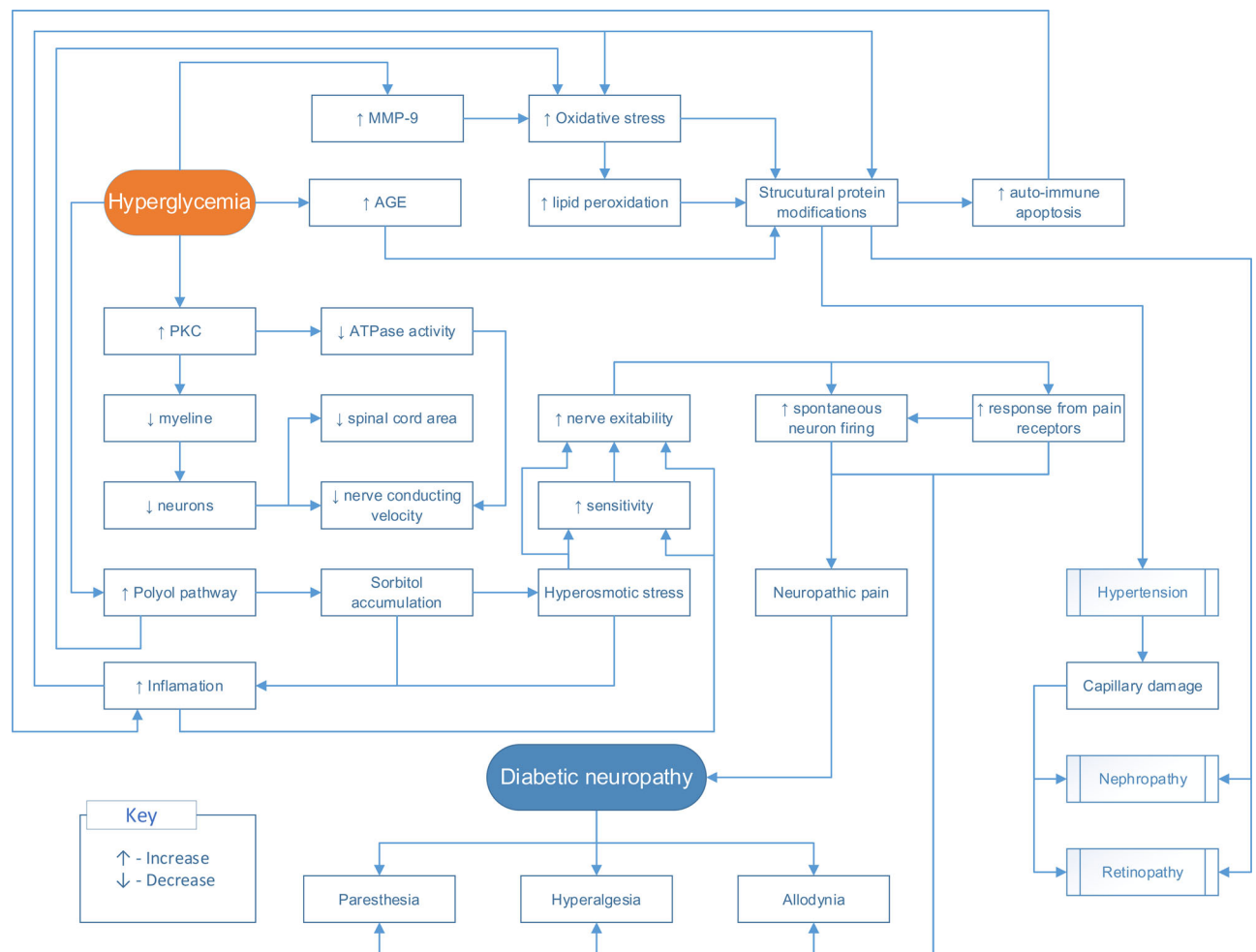


Figure 16. Development of diabetic neuropathy and associated conditions. AGE – advanced glycation end-products; ATPase – adenosine triphosphatase (EC 3.6.1.3); PKC – Protein Kinase C (EC 2.7.11.13).

though low concentrations had a remarkable positive effect on wound healing (reduction of residual wound area by over three times when compared with the control), high concentrations had adverse effects. Moreover, the low dose of EGCG also increased the epithelial regeneration by approximately four times and increased the formation of granulation tissue by approximately 50%. This accelerated healing rate is vital to prevent infections and will also help to minimize the elevated oxidative stress that is normally associated with wound healing (Kim et al. 2008).

The most common genera and species of bacteria found in diabetic ulcers are described by Almeida et al. (2006) and include the *Streptococcus*, *Staphylococcus*, *Pseudomonas*, and *Escherichia* genera. These are also some of the bacteria genera that are vulnerable to CGA (Pero, Lund, and Leanderson 2009). Additionally, quinic acid, which results from the first step of the catabolism of CGA, enhances DNA repair mechanisms and boosts the immune system (Williams et al. 2010). Almeida et al. (2006) recommend the use of antimicrobial films to dress wounds as a viable treatment for diabetic ulcers.

Qin et al. (2013) evaluated the antimicrobial effect of catechin, epicatechin gallate and epigallocatechin against methicillin resistant *Staphylococcus aureus* (*S. aureus*). They report that the combination of these flavanols is more effective

than each of the individual compound. Furthermore, the authors found that, when they used catechin combined with epicatechin gallate, the minimum inhibitory concentration (MIC) of oxacillin required against *S. aureus* decreased significantly. Phlorotannins were shown to be relevant agents against methicillin resistant *S. aureus* by suppressing the expression of genes required for the resistance (Venkatesan et al. 2019). Phlorotannins also showed excellent antimicrobial inhibition against both Gram positive and negative bacteria and yeasts which was attributed to their ability to bind to bacterial proteins leading to cell lysis (Venkatesan et al. 2019).

Díaz-Gómez has studied the effects of both catechin and gallic acid against two species of bacteria: *Escherichia coli* (Díaz-Gómez et al. 2014) and two strains of *Helicobacter pylori* – strains 26695 and 43504 (Díaz-Gómez et al. 2013). Against *E. coli*, gallic acid was more effective than catechin and was able to reduce the number of colony-forming units (CFUs) by nearly 10,000-fold after six hours. *H. pylori* was also severely affected by gallic acid and the number of CFUs decreased by 100,000-fold for strain 26695 and 1,000,000-fold for strain 43504 after 90 minutes of exposure. Unlike with *E. coli*, catechin was effective in preventing the growth of *H. pylori* and reduced the number of CFUs by 10,000-fold after 90 minutes.

Toshima et al. 2010; Ooi et al. 2011; Adisakwattana et al. 2009). Additionally, there are many studies on how some commonly consumed foods/folk medicines or new food combinations could be applied in the treatment of diabetes (Alves et al. 2016; Mohtashami et al. 2019; Ray et al. 2017; Kirakosyan et al. 2018; Agustinah et al. 2016; Sarriá et al. 2018; Muritala et al. 2018; Lee et al. 2018; Adefegha and Oboh 2016; Adefegha et al. 2017; Natarajan et al. 2017; Dib et al. 2017; Ademosun, Omoba, and Olagunju 2021) by inhibiting common therapeutic targets such as α -amylase, α -glucosidase, and ACE. However, these studies often do not consider the effects of digestion on the composition/effect of these edible materials, which will significantly reduce (> 50%) or change the polyphenol contents, and consequently their activity (Spínola, Llorent-Martínez, and Castilho 2020; Quintana et al. 2020; Spínola et al. 2019; Spínola, Llorent-Martínez, and Castilho 2018; Pinto et al. 2017; Cha et al. 2012). Furthermore, while the therapeutic dose of some polyphenols such as catechins can be achieved directly by the ingestion of their food sources others, such as resveratrol, require amounts far larger than what can be realistically ingested through food sources (Aryaeian, Sedehi, and Arablou 2017).

Like the digestive process, the bioavailability of polyphenols is often not considered in studies evaluating their effects. Despite this, there are experimental works on humans (Monteiro et al. 2007; Redeuil et al. 2011) and extensive reviews that approach this topic in detail (Manach et al. 2005; Espín, García-Conesa, and Tomás-Barberán 2007; Crozier, Jaganath, and Clifford 2009; Crozier, Del Rio, and Clifford 2010; Stefek 2011; Oliveira and Bastos 2011; Russo et al. 2012; Hostetler, Ralston, and Schwartz 2017; Sun et al. 2020; Salehi et al. 2020). Polyphenols appear to be absorbed and metabolized in the stomach, small intestine and colon depending on their family and/or degree of modification. A good example of this are HCAs such as CA or FA which are directly absorbed in the stomach but their respective quinic acid conjugates are mainly absorbed in the colon with only 30% being absorbed before reaching it.

A low carbohydrate diet is vital for diabetes patients as a mean to control energy intake (UKPDS Group 1990). The main drawbacks of dieting are the fact that the reduction of energy intake has to be quite high and only a small number of patients are able to achieve rewarding and lasting results (Clark 2004). Dieting also asks diabetes patients for a great restraint, which they are often unable to achieve (Strien et al. 2007). Clark (2004) concludes that the restraint that is required from diabetes patients will diminish their quality of life and cause their weight to fluctuate. This is quite possibly the main reason why dieting fails to succeed as patients feel their efforts and discipline are meaningless, causing them to “break protocol” and leading them back to where they were before. Nonetheless, there are several studies on the ability of certain plants, extracts or polyphenols to counter or diminish the effects of high energy (fat/carbohydrate) diets. Lee et al. (2018) studied the effects of Metabolaid®, a product rich in anthocyanidins and hydroxycinnamic acids, containing lemon verbena and hibiscus flower extracts, and

found that it was able to reduce the body weight of rats even in a high fat diet by increasing the amount of phosphorylated AMPK, the concentration of adiponectin and the expression of thermogenesis genes, while also reducing the expression of adipogenesis activating genes and the concentration of leptin. Kulashekar, Stom, and Peuler (2018) reviewed resveratrol's potential therapeutic role in several metabolic diseases and found that one of its effects was mimicking calorie restriction in rats and humans. Another study by Sarriá et al. (2018) looked into the effect of regularly consuming coffee blends and its components on metabolic syndrome and found that a blend of green and roasted coffee (rich in hydroxycinnamic acids, especially CQAs) reduced blood pressure and body weight which the researchers attributed to the reduction of the levels of leptin. However, the study only looked at the effects of the blend of green and roasted coffee which is far richer in polyphenols than regularly consumed roasted coffee blends.

Another recent development in diabetes research is the increased awareness of the gut's microbiota homeostasis as an important factor and how polyphenols can affect it (Sun et al. 2020; Williamson and Sheedy 2020). Alves et al. (2016) reviewed the role of polyphenols and probiotics on hypertension and found that many bacteria species of the *Lactobacillus* (L.) and *Bifidobacterium* (B.) genera were able to reduce blood pressure when consumed daily. The consumption of *L. plantarum* over 6 weeks not only reduced SBP and DBP but also lowered other biomarkers for diabetes and associated complications (total cholesterol and LDL levels, blood glucose, homocysteine, and inflammation markers). Alves et al. (2016), also engineered a modified strain of *L. plantarum* which produced an ACE inhibitory peptide which led to the reduction in blood pressure in rats. The authors theorized that the natural blood pressure reducing properties of this species may result from their metabolism naturally producing ACE inhibitory peptides. Gowd et al. (2019) reviewed the influence of dietary factors in gut microbiota and found that polyphenols and food or supplements rich in these compounds can alter the concentrations of certain genera of bacteria which in turn increased the concentration of short chain fatty acids and reduced diet induced obesity, inflammation, and insulin resistance. The role of the gut microbiota in diabetes is also approached in the work of Williamson and Sheedy (2020) who found that obesity and/or a high fat diet will lead to an increased production of pro-inflammatory metabolites which will then enter the blood stream and reach other tissues leading to insulin resistance. Sun et al. (2020) found that the presence of *Lactobacillus* and *Bifidobacterium* species reduced inflammation by reducing gut permeability and preventing the penetration of pathogenic organisms and pro-inflammatory metabolites such as liposaccharides. Additionally, the authors (Sun et al. 2020) found that there are differences in gut microbiota between healthy individuals and diabetes patients, that bacteria of the *Akkermansia* genus are capable of reducing G6P mRNA expression, that red wine polyphenols increased the amounts of butyrate-producing bacteria which in turn regulated the release of GLP1 and GIP and,

that both polyphenols and their microbial metabolites have protective effects against diabetes.

Mild physical exercise is often recommended in the treatment of diabetes (Tucker and Palmer 2011; Li et al. 2010; Tarride et al. 2010; Neville et al. 2009). Despite this, many diabetes patients or individuals at risk of developing diabetes still dismiss it (McCarty 2005). Physical exercise is not only recommended but it should always be used in combination with other treatments (Unger and Parkin 2011) and it is more effective when used to control body weight rather than when used to reduce it (Smith and McFall 2005). Exercise can also be combined with polyphenols for additive/synergetic effects (Eguchi et al. 2013; Fujihara et al. 2007; Lambert, Hokayem, Thomas, Fabre, Cassan, Bourret, Bernex, Feuillet-Coudray, et al. 2018; Lambert, Hokayem, Thomas, Fabre, Cassan, Bourret, Bernex, Lees, et al. 2018). Eguchi et al. (2013) extracted a high molecular weight polymeric polyphenol from black tea, named Mitochondria Activation Factor (MAF) for its ability to increase mitochondrial membrane potential (Eguchi et al. 2013; Fujihara et al. 2007), and studied its effects on mice. The authors found that, although MAFs did not significantly impact endurance capacity on their own, when combined with exercise, they significantly improved endurance and the levels/expression of phosphorylated AMPK (p-AMPK) and GLUT4, when compared with the group that only did the exercise. The improved levels of endurance and p-AMPK were also observed by Lambert, Hokayem, Thomas, Fabre, Cassan, Bourret, Bernex, Feuillet-Coudray, et al. (2018) and Lambert, Hokayem, Thomas, Fabre, Cassan, Bourret, Bernex, Lees, et al. (2018), on obese mice fed a high fat diet along with exercise and grape polyphenols; they also detected an improvement in insulin sensitivity, glucose storage and reduced levels of liver triglycerides and visceral fat.

In summary, functional foods and/or their extracts can provide multiple benefits to diabetes patients who often struggle with dietary restrictions. Their main goal is providing polyphenols, which can reduce some risk factors and complications from diabetes, stimulate certain metabolic pathways in the lipid and carbohydrate metabolism, mimic caloric restriction, and alter the balance of gut microbiota to increase the number of beneficial/symbiotic species. Functional foods and/or their extracts should also be combined with mild physical exercise for additive or synergetic benefits. Even though digestion plays a key role in the absorption, distribution, and bioavailability of polyphenols, it is often overlooked when studying these compounds and their effects, in addition to the modifications that some polyphenols undergo through it. This, combined with the fact that most of the literature on functional foods and/or their extracts is still from animal models instead of humans, makes it harder to draw accurate conclusions on their benefits.

Conclusion

Current therapies, despite being advanced, are still not sufficient to completely manage diabetes and its severe

complications. Additionally, the growing worldwide incidence of diabetes has increased the burden on healthcare systems and the need to find new/more effective therapies.

The large amount of literature that focuses on the study of folk medicines, plant extracts, and individual polyphenols as treatments for diabetes and its complications makes all these encouraging new therapy avenues. However, despite the many encouraging results, as we reviewed here, there is still a long way to go before these can be incorporated into the standard care for diabetes patients since most of the studies in the literature have either small sample sizes, follow the study population for short periods of time, do not use humans as the test subjects, or establish different therapeutic doses of polyphenols. It is desirable to promote large scale clinical trials to assess more accurately the therapeutic and adverse effects of plants, extracts, and polyphenols in diabetes patients and not just diabetes models. For this to happen, physicians need to be aware and well informed of the potential effects (beneficial and adverse) of polyphenols and the plants/extracts where they can be found, to work with their patients to achieve a therapy and results to meet their needs and follow their patients' progress in order to determine the success of the new therapy and to establish if the prescribed polyphenols have additive, synergetic or adverse effects when combined with the conventionally prescribed treatment. Moving forward, physicians, patients and academia will have to work together to establish therapies, therapeutic goals and communicate openly about their concerns, results, and expectations.

Polyphenols have multiple therapeutic targets and effects. They start by reducing caloric intake by inhibiting carbohydrate and lipid digestive enzymes in the intestines which also prevents blood glucose spikes. In the colon, they modulate the ratios of gut bacteria favoring the survival of beneficial species and reducing inflammation. After being absorbed into the blood, their innate antioxidant properties allow them to scavenge ROS, increasing the bioavailability of NO, and inhibit ACE with both effects contributing to reductions in blood pressure. Also, while in circulation and in cells, polyphenols scavenge AGE precursor molecules such as MGO and prevent them from reacting with structural molecules and enzymes. Once polyphenols enter cells, they trigger general (systemic) and tissue specific effects. The systemic effects include reduction of oxidative stress (by scavenging ROS, reducing the activity or expression of ROS generating enzymes/pathways and by increasing the expression and activity of antioxidant enzymes), reduction of inflammation (by reducing the expression or activity of pro-inflammatory enzymes, pathways and cytokines) and protection from function altering histological changes and apoptosis (by reducing inflammatory cytokines, certain dedifferentiation pathways and scavenging AGEs). In glucose using tissues, such as muscles and the liver, they increase the expression, translocation and activity of glucose transporters and upregulate pathways in the carbohydrate and lipid metabolism to increase their consumption and lowering their levels in the blood stream. In the eyes, nerves and kidneys, polyphenols inhibit AR reducing sorbitol

accumulation which prevents further oxidative stress, formation of AGEs and osmotic stress. This prevents retinal cells from rupturing or forming plaques that lead to diabetic cataracts and reduces neuron hyperactivity and spontaneous firing which are often causes of neuropathic pain. Also in neurons, polyphenols inhibit acetylcholinesterase and butyrylcholinesterase and prevent glutamate toxicity and overstimulation. Finally, due to the strong possibility of additive or synergetic effects between polyphenols and that the therapeutic dose of polyphenols cannot always be achieved by the ingestion of their respective food sources, the consumption in the form of enriched processed functional foods or supplements is recommended over the use/consumption of a single/specific polyphenol.

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Abbreviations

ACE	angiotensin-converting enzyme
AD	Alzheimer's disease
AGE	advanced glycation end-product
AMPK	adenosine monophosphate-activated protein kinase
AR	aldose reductase
BP	blood pressure
CA	caffeic acid
CAPE	caffeic acid phenethyl ester
CAT	catalase
CDC	(United States) Center for Disease Control
CFUs	colony forming units
CGA	chlorogenic acid
COX	cyclooxygenase
CPT	carnitine palmitoyltransferase
CQA	caffeoylquinic acid
CVD	cardiovascular disease
DBP	diastolic blood pressure
DGKA	diacylglycerol kinase α
diCQA	di-O-caffeoylquinic acid
DPP4	dipeptidyl peptidase-4
DR	diabetic retinopathy
ECat	epicatechin
EGC	epigallocatechin
EGCG	epigallocatechin gallate
EU	European Union
FA	ferulic acid
G6Pase	glucose-6-phosphatase
GCE	green coffee extract
GCL	glutamate cysteine ligase
GIP	gastric inhibitory polypeptide
GLK	glucokinase
GLP-1	glucagon-like peptide 1
GLUT	glucose transporter
GLUT2	glucose transporter 2

GLUT4	glucose transporter 4
GPx	glutathione peroxidase
GR	glutathione reductase
GSH	glutathione
GTP	green tea polyphenols
HCA	hydroxycinnamic acid
HDL	high density lipoprotein
HIV	human immunodeficiency viruses
IDF	International Diabetes Federation
IGT	impaired glucose tolerance
IL	interleukin
IL-6	interleukin 6
IL-8	interleukin 8
KSA	Kingdom of Saudi Arabia
LDL	low density lipoprotein
MGO	methylglyoxal
NADP(H)	nicotinamide adenine dinucleotide phosphate
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitrous oxide
NOS	nitric oxide synthase
NOX	NADPH oxidase
NRF2	nuclear factor erythroid 2-related factor 2
p-AMPK	phosphorylated adenosine monophosphate-activated protein kinase
PI3K	phosphoinositide 3-kinase
PKC	protein kinase c
PL	pancreatic lipase
PPAR- γ	peroxisome proliferator-activated receptor
RAAS	renin-angiotensin-aldosterone system
ROS	reactive oxygen species
SBP	systolic blood pressure
SIRT1	sirtuin 1
SOD	superoxide dismutase
T1D	type 1 diabetes
T2D	type 2 diabetes
TGF- β	transforming growth factor- β
TNF	tumor necrosis factor
TNF- α	tumor necrosis factor alpha
US	United States of America
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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