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GENETIC PREDISPOSITION AND NUTRITION IN RELATION TO TYPE 2 DIABETES

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A DISSERTATION

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DECLARATION

I, Tanja Viraj
declare that this thesis has been generated by me as the result of my own original literature research, entitled "GENETIC PREDISPOSITION AND NUTRITION IN RELATION TO TYPE 2 DIABETES". All data, literature and sources used are appropriately cited and acknowledged in the thesis.

This thesis has been prepared under the valuable guidance and supervision towards the fulfilment of the requirements for the degree of Doctor of Philosophy in Nutrition and Genetics Department at Selinus University.

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WORD OF GRATITUDE

I would like to thank my family for supporting me in completing this thesis. A special thank you also goes to Dr. Fava, who provided consistent support throughout my work.

This thesis was made with hard work, dedication and best intentions. I am grateful to live in a world where continuous education is possible and available. I am grateful to be able to grow and evolve professionally without any limitations.

As Nelson Mandela once said – ''Education is the most powerful weapon which you can use to change the world'' (for better).

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1.) ABSTRACT

Type 2 Diabetes (T2D) is a metabolic disease present with humankind already for decades. In recent years it became clear that the increased number of people affected by the disease is still rising. Per WHO, globally an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries (1).

T2D accounts for more than 90% of patients with diabetes and leads to micro-vascular and macro-vascular complications that cause profound psychological and physical distress to both patients and carers and put a huge burden on health-care systems. Despite increasing knowledge regarding risk factors for type 2 diabetes and evidence for successful prevention programmes, the incidence and prevalence of the disease continues to rise globally. Early detection through screening programmes and the availability of safe and effective therapies reduces morbidity and mortality by preventing or delaying complications. Increased understanding of specific diabetes phenotypes and genotypes might result in more specific and tailored management of patients with type 2 diabetes (2). There is a strong inheritable genetic connection in T2D, having relatives (especially first degree) with T2D increases the risks of developing T2D substantially (3). With the development of high-throughput single-nucleotide polymorphisms (SNP) genotyping technology and the availability of Hapmap data, it became possible to scan hundreds of thousands of SNPs that were in linkage disequilibrium with millions of SNPs across the genome. TCF7L2, already identified *via* linkage studies, was the most significant and most replicated signal found in Genome-wide association studies (GWAS), but these studies also helped to identify scores of other genetic loci that appear to be linked to T2D (4).
The risk of developing T2D is determined by both genetic and environmental factors. Obesity is one of the major risk factors of developing T2D. Healthy diet and physical activity have a positive effect on the consequences and complication in disease progression. Exercise and calorie restriction (5) are the primary treatment options for type 2 diabetes (T2D) as well as a healthy diet. Especially polyphenol compounds have proven promising results in the past and recent years.

In this thesis we will focus on the impact of genetics on the onset of T2D and genetic predisposition of T2D. We will review the latest data available from this field. We will also evaluate the impact of nutrition and diet on T2D. We will focus on polyphenol acids and recent discoveries in this field. The main focus will be on 4 polyphenol acids: nordihydroguaiaretic acid, quercitrin, quercetin and resveratrol.
Lastly, we will also look at the gene-environment implications and possible ways on how an individual with genetic predisposition could affect the disease progression and complications through food choices and nutrition that contains polyphenol compounds mentioned above. This could possibly help not only with prevention of disease progression and its complications but also with curative of the T2D.

2.) INTRODUCTION

2.1.) TYPE 2 DIABETES

Type 2 Diabetes (T2D) is one of the most common metabolic disorders and is caused by a combination of two primary factors: first one is a defective insulin secretion by pancreatic β-cells and the second mechanism is the inability of insulin-sensitive tissues to respond appropriately to insulin. The latter is reflected as insulin resistance (IR) and is especially common in T2D. Insulin resistance is a public health concern that can initially occur in the prediabetes stage many years before the diagnosis of T2D. Patients with T2D are mostly characterized by being obese or having a higher body fat percentage which is mainly distributed in the abdominal region. In this condition, adipose tissue promotes IR through various inflammatory mechanisms, including increased free fatty acid (FFA) release and adipokine deregulation. The main drivers of the T2D epidemic are the global rise in obesity, sedentary lifestyles, high caloric intake and population aging (6, 7).

The organs involved in T2D development include: pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue (8). Not all organs are involved at the same degree as some play more important role than others. Evolving data also suggest a role of adipokine dysregulation, inflammation and abnormalities in gut microbiota, immune dysregulation, and inflammation. This data have emerged as important pathophysiological factors (9). Somehow new area of research is especially the connection between gut bacteria and the impact on polysaccharides and lipides absorption in gastrointestinal tract which can potentially have a significant effect. Diet rich in polyphenols has also shown favorable and very interesting results. There have been more research done on the polyphenol compounds and the effect they have on the T2D regulation and progression. Blueberries is one of many fruits that contain a mixture of different polyphenol compounds. Beneficial effect of consuming whole blueberries on the insulin resistance and glucose tolerance in humans was shown and it is in accordance with other studies (10). Anthocyanins (AC) are flavonoids that are abundant in the human diet. There are several studies that debate their beneficial effect on the T2D, acting through several mechanisms (inhibit GI luminal enzymes that participate in the absorption of lipids and carbohydrates; preserve intestinal barrier integrity and prevent endotoxemia, inflammation and oxidative stress; sustain goblet cell number, immunological functions, and mucus production; promote a healthy microbiota; being metabolized by the microbiota to AC metabolites which will be absorbed and have systemic effects; and by modulating the metabolism of GI-generated hormones) (11).

It is of the most importance to maintain and regulate caloric intake and appropriate diet when individual is diagnosed with T2D. Studies have confirmed that regulating the number, timing and content of the meal has a positive impact on subjects blood glucose. Also important is to educate T2D patients and to motivate them to change their lifestyle which can help them manage their blood glucose better (12). First line of treatment of T2D is mostly adaptation of the diet, restricting caloric and sugar intake. However the latest discoveries on this field show that the pathophysiology and progression of disease is far more complex. Thus also the guidelines of treatment of T2D should follow latest information available in order to be as effective as possible.

From this aspect we shouldn't overlook the genetic impact of T2D incidence. New technology enabled us to better understand the pathophysiology and progression of T2D. However we must acknowledge that as with all genetic-dependent diseases also the risk of developing T2D is determined by both genetic and environmental factors. It was shown that there is a strong inheritability factor in the risk of developing T2D. The lifetime risk of developing T2D is 40% for individuals who have 1 parent with T2D and almost 70% if both parents are affected (13). As for the environment factor – the two changes that are considered particularly important in relation to the rise in T2D incidence are increased access to energy-dense, palatable, cheap food and sugary beverages, and the reduced demand for physical activity in daily life that allows more time to be spent sedentary. Despite the overall economic improvement, poor socioeconomic circumstances within each society remain a major risk factor of type 2 diabetes, clustering together with many other risk factors (14).

Several genes were identified to be linked with T2D incidence. Genetic mapping, linkage analysis, candidate gene studies, whole-genome association studies (GWAS) and many more enabled us to identify the genes that present a higher risk to develop T2D. We will discuss them in greater details in the body of this thesis.

2.2.) DEFECTIVE INSULIN SECRECTION IN β-CELLS IN T2D

In the case of β-cell dysfunction, insulin secretion is decreased, limiting the body's ability to maintain physiological glucose levels. On the other hand, IR contributes to increased glucose production in the liver and decreased glucose uptake both in the muscle, liver and adipose tissue. Even if both processes take place early in the pathogenesis and contribute to the development of the disease, β-cell dysfunction is usually more severe than IR. However, when both β-cell dysfunction and IR are present, hyperglycemia is amplified leading to the progression of T2D (15).

β-cells are responsible for insulin production, which is synthesized as pre-proinsulin. In the maturation process. Pre-proinsulin undergoes a conformational modification which is carried out with the help of several proteins in the endoplasmic reticulum (ER) to obtain proinsulin (16). Afterwards, proinsulin is translocated from the ER to the Golgi apparatus (GA), entering into immature secretory vesicles and being cleaved into C-peptide and insulin (17, 18). Once matured, insulin is stored in granules until insulin release is triggered. Primary trigger of insulin release is high concentration of blood glucose. When circulating glucose levels increase, β-cells take in glucose mainly through the glucose transporter 2 (GLUT2), a solute carrier protein that also works as a glucose sensor for β-cells. The entry of glucose into the cell triggers glucose catabolism, which as a consequence increases the intracellular ATP/ADP ratio. This process induces the closing of ATP-dependent potassium channels in the plasma membrane, which leads to membrane depolarization and opening of the voltage dependent Ca2+ channels, enabling Ca2+ to enter the cell. The rise in the intracellular Ca2+ concentration triggers the priming and fusion of the secretory insulin-containing granules to the plasma membrane, resulting in insulin exocytosis (19, 20, 21, 22).

Recent data imply that the dysfunction of β-cells in T2D is most likely due to a more complex network of interactions between the environment and different molecular pathways involved in cell biology (23). When our body is exposed to an excessive nutritional state (similar to that

found in obesity), hyperglycemia and hyperlipidemia are often present, which favors IR as well as chronic inflammation in the body. An excess of FFAs and hyperglycemia lead to β-cell dysfunction by inducing ER stress through the activation of the apoptotic unfolded protein response (UPR) pathways (24). In fact, lipotoxicity, glucotoxicity and glucolipotoxicity occurring in obesity, induce metabolic and oxidative stress that leads to β-cell damage (25). Stress that is caused by high levels of saturated FFAs can activate the UPR pathway by several mechanisms. One of which is also inhibition of the pump sarco/endoplasmic reticulum Ca2+ ATPase (SERCA) which is responsible for ER Ca2+ mobilization; activation of IP3 receptors and direct impairment of ER homeostasis. In addition, sustained high glucose levels increase proinsulin biosynthesis and islet amyloid polypeptides (IAAP) in β-cells, leading to the accumulation of misfolded insulin and IAAP and increasing the production of oxidative protein folding-mediated reactive oxygen species (ROS) (26). These effects modify the physiological ER Ca2+ mobilization and favor proapoptotic signals, proinsulin mRNA degradation and induce release of the interleukin (IL)-1 β. The (IL)-1 β then recruits macrophages and enhances local islet inflammation (27).

2.3.) INABILITY OF INSULIN-SENSITIVE TISSUES TO RESPOND APPROPRIATELY TO INSULIN

In other words inability of insulin-sensitive tissues to respond to blood-circulating insulin is called insulin resistance (IR). IR refers to a decrease in the metabolic response of insulin-responsive cells to insulin or, at a systemic level, an impaired/lower response to circulating insulin by blood glucose levels (28). There are three broad categories of IR or insulin-deficient conditions: 1-diminished insulin secretion by β-cells; 2-insulin antagonists in the plasma, due either to counter-regulatory hormones or non-hormonal bodies that impair insulin receptors or signaling; and 3-impaired insulin response in target tissues (29). Insulin action in the fed state is among other molecules, also triggered by the growth hormone and insulin-like growth factor-1 (IGF-1). When an individual is fasting, the insulin response is reduced by glucagon, glucocorticoids and catecholamines in order to prevent insulin-induced hypoglycemia. The ratio between insulin and glucagon plays a crucial role in this regulation, because it determines the grade of phosphorylation of the downstream enzymes in the regulatory signaling pathways. While catecholamines promote lipolysis and glycogenolysis, glucocorticoids promote muscle catabolism, gluconeogenesis and lipolysis. In consequence, excessive secretion of these hormones may be responsible for promoting IR (30, 31). Regarding the last category, there are three main extra-pancreatic insulin-sensitive organs that play major roles in the aforementioned processes: skeletal muscle, adipose tissue and liver. A defective action of insulin in these tissues often precedes the development of systemic IR, thus progressively leading T2D.

There is increasing evidence associating mitochondrial dysfunction with T2D development, age-related IR and T2D complications (32). The main function of mitochondria is ATP synthesis through oxidative phosphorylation in response to metabolic demand (33). Mitochondria also participate in the production of different metabolites used as precursors of several macromolecules (lipids, proteins, and DNA). In addition, mitochondria play an important role in maintaining ion homeostasis, ROS clearance, the stress response, and serve to integrate multiple signaling pathways (34). An imbalance between energy intake and expenditure in the mitochondria generates mitochondrial dysfunction, a state characterized by a reduced ratio of energy production to respiration (35). Under these circumstances, nutrient

oxidation efficiency is reduced leading to a decreased ratio of ATP synthesis/oxygen consumption, which increases O–2 production (36). In fact, the accumulation of ROS in the mitochondria is one proposed mechanism linking mitochondrial dysfunction to IR (37). This relationship was corroborated in studies showing decreased mitochondria oxidative capacity in skeletal muscle and impaired lipid metabolism in obese and insulin-resistant individuals compared to healthy controls (38, 39, 40).

2.3.1.) SKELETAL MUSCLE

Skeletal muscle IR is considered to be the most important extra-pancreatic factor in the development of T2D (41). When physiological conditions demand, action of insulin is to stimulate muscle glycogen synthesis by enhancing glucose uptake from the bloodstream. Glucose uptake and glycogen synthesis is primarily regulated by three main actors: enzymes glycogen synthase and hexokinase and the glucose transporter GLUT4 (42). Upon insulin binding to insulin receptor (INSR) in muscle cells, GLUT4 translocate from intracellular compartments (early endosomes (EE), endosomal recycling compartment (ERC) and trans-Golgi network (TGN)) to the plasma membrane. This process allows glucose uptake and reduces blood circulating glucose levels (43). Mutations that reduce the expression of insulin receptor or GLUT4, as well as any defect in either upstream or downstream signaling pathway would reduce glucose intake into the muscle resulting in a hyperglycemic state (44, 45). The action of insulin on glucose metabolism is driven by the activation of INSR tyrosine kinase activity. Insulin binding to the α-subunit of the INSR causes phosphorylation of the β-subunit on multiple tyrosine residues and allows insulin-mediated signaling. Therefore, mutations in any of the main phosphorylation sites can impair INSR tyrosine kinase activity, and as a consequence impair insulin action on skeletal muscle (46). As mentioned above, mutations in key proteins of the downstream signaling pathway such as IRS-1 and IRS-2 or phosphoinositide 3-kinase (PI3K) also impair insulin action on the muscle. Apart from mutations or defective epigenetic regulation, environmental factors can also play an important role in glucose uptake by muscle. Physical activity increases blood flow into skeletal muscle cells and thereby enhances glucose utilization (47). Obesity, which is associated with chronic inflammation, contributes to IR and T2D. Increasing evidence suggests that as a consequence of obesity, increased immune cell infiltration and secretion of proinflammatory molecules in intramyocellular and peri muscular adipose tissue leads to skeletal muscle inflammation. This ultimately leads to myocyte inflammation, impaired myocyte metabolism, and contributes to IR via paracrine effects (48).

2.3.2.) ADIPOSE TISSUE

Adipose tissue is a metabolically dynamic tissue capable of synthesizing a wide range of biologically active compounds that regulate metabolic homeostasis at a systemic level (49). Adipose tissue participates in a broad range of biological processes involving, among others, immunity, coagulation, angiogenesis, fibrinolysis, reproduction, vascular tone control, appetite regulation, body weight homeostasis and glucose and lipid metabolism (50).

Insulin acts on adipose tissue in two different ways: (1) stimulating glucose uptake and triglyceride synthesis; and (2) suppressing triglyceride hydrolysis and inducing the uptake of FFA and glycerol from circulation (51). In the fed state, GLUT4 allows uptake of glucose from the bloodstream into adipocytes, activating glycolysis in which glycerol-3-phospate (glycerol-

3-P) is produced and incorporated into lipogenic pathways. Glycerol-3-P, along with the fatty acids coming from VLDLs, are esterified, forming triacylglycerol (TGA) that is stored in lipid droplets. During metabolic stress, TGA droplets of the adipocytes are used up in order to provide FFA, which are used as an energy source in other tissues.

An insufficient response to insulin stimulation by adipose tissue is known as adipose IR (Adipose-IR). Adipose-IR can lead to impaired suppression of lipolysis, impaired glucose uptake, and enhanced FFA release into plasma even in the presence of high insulin levels (52). Amid the signaling elements affected by adipose-IR, it was shown that defective protein kinase B (AKT) activation weakens GLUT4 translocation to the membrane and therefore promotes the activation of lipolytic enzymes that provoke hyperglycemia (53). As we discussed above, adipose-IR, is associated with glucose intolerance and elevated release of FFA into the bloodstream. FFA then accumulate in other tissues such as muscle or liver. When FFA accumulate in the liver, the accumulation results in diminished insulin signaling that contributes to the hepatic gluconeogenesis and damages the glucose-stimulated insulin response. These actions induce T2D development.

The data currently suggests that abnormally increased adipose tissue mass and adipocyte size (obesity) correlate with pathologic vascularization, hypoxia, fibrosis and macrophage-mediated inflammation (54). A high-fat diet and obesity can activate saturated FFA-stimulated adenine nucleotide translocase 2 (ANT2), an inner mitochondrial protein that results in adipocyte hypoxia and triggers the transcription factor hypoxia-inducible factor-1α (HIF-1α). This culminates in adipose tissue dysfunction and inflammation (55). Hypertrophied adipocytes as well as adipose tissue-resident immune cells contribute to increased circulating levels of proinflammatory cytokines. This increase in circulating proinflammatory molecules, together with an increase in local cytokine releases such as TNF and IL-1β and IL-6 facilitates the emergence of a chronic state of low-grade systemic inflammation, also known as metabolic inflammation (56). This chronic inflammatory state is considered to be a key part in the pathogenesis of IR and T2D (57).

2.3.3.) LIVER

The liver plays a crucial role in carbohydrates and lipid metabolism. In the liver, insulin does not only regulate glucose production and utilization but also affects lipid metabolism more widely. When circulating glucose levels increase and insulin is secreted by pancreatic β-cells, insulin binding to liver insulin receptor (INSR) induces autophosphorylation of the receptor. As a consequence, insulin receptor substrates (IRSs) are engaged and phosphorylated. Sequentially, IRSs activate phosphoinositide 3 kinase (PI3K), which phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP2), generating phosphatidylinositol (3,4,5)-triphosphate (PIP3). PIP3 then activates PDK1, which phosphorylates protein kinase B (AKT). In addition, AKT is phosphorylated by mammalian target of rapamycin complex 2 (mTORC2). When AKT is fully activated, it participates in several downstream pathways that regulate multiple metabolic processes including glycogen synthesis, gluconeogenesis, glycolysis and lipid synthesis (58). In physiological states, the combined action of glucagon and insulin allows the precise regulation of hepatic glucose output. While glucagon induces hepatic glucose production, insulin acts as a potent inhibitor of glucose production when its concentration in the blood is elevated (59). The effect of insulin on hepatic glucose production is due to both

direct and indirect mechanisms. However, the relative importance of each of these mechanisms remains unclear (60).

In addition to inducing glycogen synthesis, insulin also inhibits hepatic glucose production by activating Fork head Box protein O-1 (FOXO1). This results in a reduction of hepatic glucose release. FOXO1 is a transcription factor that belongs to a subclass of the fork head family of transcription factors that possess a fork head box-type DNA binding domain. FOXO1 recognizes a specific regulatory element termed the insulin in circulating proinflammatory molecules, together with an increase in local cytokine releases such response element (IRE) on the promoters of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate as TNF and IL-1β and IL-6 facilitates the emergence of a chronic state of low-grade systemic carboxykinase (PEPCK) genes, both of which play important roles in maintaining glucose level in inflammation, also known as metabolic inflammation (61). This chronic inflammatory state is states of starvation (62, 63, 64). Thus, through inhibition of FOXO1, insulin promotes glucose storage as considered to be a key part in the pathogenesis of IR and T2D (65). The insulin stimulation effects glycogen and inhibits glucose synthesis and hepatic glucose output (66). Similar to the case in insulin-sensitive tissues, in states of IR, physiologic levels of circulating insulin are insufficient to elicit the appropriate insulin response in hepatic cells (67). In the liver, IR impairs glycogen synthesis, fails to suppress glucose production, enhances lipogenesis, and increases the synthesis of proteins such as the proinflammatory C-reactive protein (CRP). In fact, the abnormal production of production of proinflammatory proteins such as adipocytokines and cytokines, combined with proinflammatory proteins such as adipocytokines and cytokines, combined with conditions such as conditions such as oxidative stress, can lead to an inflammatory state responsible for altered insulin oxidative stress, can lead to an inflammatory state responsible for altered insulin response by the response by the liver (68).

2.4.) GENETICS

Our knowledge about the genes involved in disease pathogenesis has increased substantially in recent years. Genome-wide association studies (GWAS) have offered a lot of new information about the genes and the role they play in a pathophysiology of a specific disease. The international collaborations joining efforts to collect the huge numbers of individuals needed to study complex diseases on a population level also helped to collect new precious data.
The lifetime risk of developing T2D is 40% for individuals who have 1 parent with T2D and almost 70% if both parents are affected (69, 70). Interestingly, the risk is higher if the mother, rather than the father, is affected (71).
The complete and detailed genetic involvement in the T2D pathophysiology is not yet fully understood. T2D itself is a polygenic disorder that develops due to complex interaction not only between the genes but also between environmental factors. Environment plays a crucial role in T2D development and progress. Leading environmental factors are obesity, sedentary lifestyle and as latest data suggest also Western way of life. Western lifestyle consists of consuming food that is high in calories, sugar and fat, while minimizing the physical activity. This way of life has started a worldwide epidemic during the last 50 years in the prevalence of T2D and obesity defined by body mass index (BMI in kg/m2) (72). This has happened in a relatively short period, most likely due to changes in diet and physical activity, while our genes have not changed. This does not diminish the role of genes in diabetes development, because our response to the changed environment is also genetically determined. Affluence is not a problem in itself, the problem is that humans seem to be programmed to over consume. One likely reason

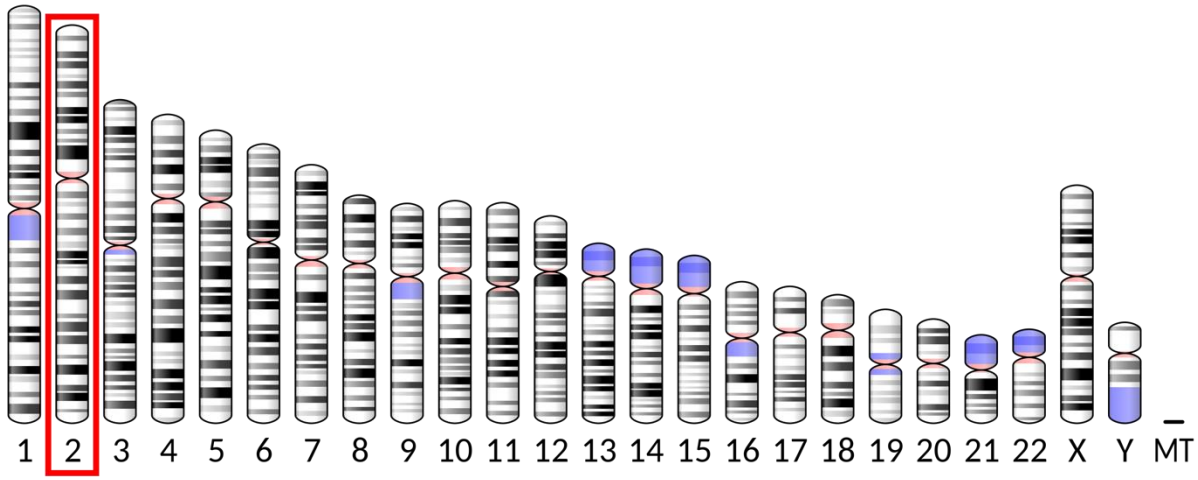
is that genetic selection has favored energy-preserving genotypes; for individuals living in an environment with a scarce and unstable food supply, such as hunters and nomads, maximizing energy storage would mean maximizing probability of survival (73). In the modern Western culture individuals with these genotypes are at increased risk of obesity and these genes are therefore also candidates for increasing risk of T2D.
Genetic component of T2D risk is not concentrated in one region and appears to be the result of the interaction of multiple genes scattered all across the genome.

2.4.1.) GENES CONNECTED TO T2D

Different genes were identified through different gene studies and programs. We will focus on the ones that up until now showed the strongest connection to T2D.

2.4.1.1.) CALPAIN 10 (CAPN10)

CAPN10 gene encodes a calpain-10 (CAPN10) protein. Calpains represent a ubiquitous, well-conserved family of calcium-dependent cysteine proteases. The calpain proteins are heterodimers consisting of an invariant small subunit and variable large subunits. The large catalytic subunit has four domains: domain I, the N-terminal regulatory domain that is processed upon calpain activation; domain II, the protease domain; domain III, a linker domain of unknown function; and domain IV, the calmodulin-like calcium-binding domain. This gene encodes a large subunit. It is an atypical calpain in that it lacks the calmodulin-like calcium-binding domain and instead has a divergent C-terminal domain. It is similar in organization to calpains 5 and 6. This gene is associated with type 2 or non-insulin-dependent diabetes mellitus (NIDDM), and is located within the NIDDM1 region. Multiple alternative transcript variants have been described for this gene. (provided by RefSeq, Sep 2010) (74).



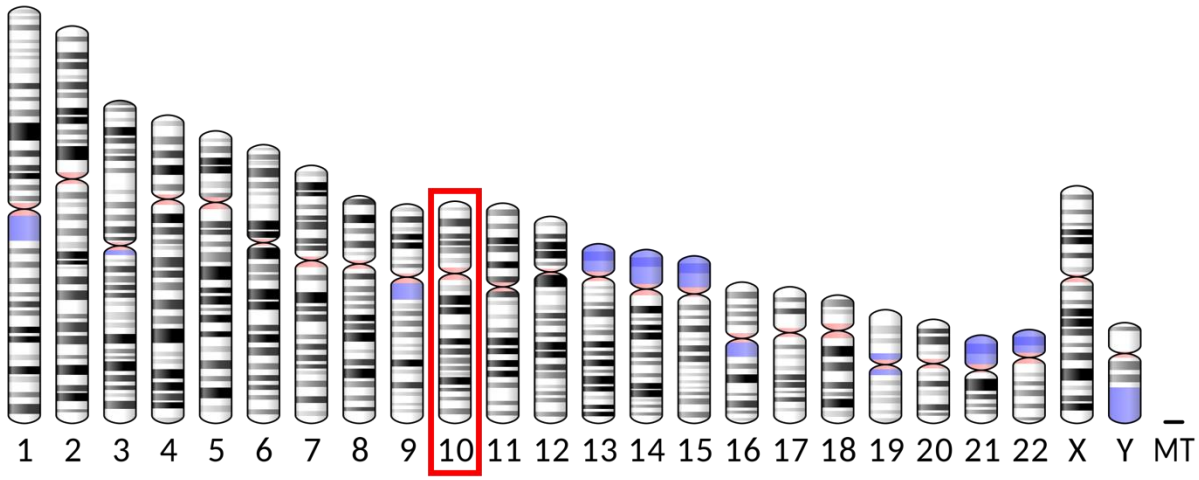
Picture: Location of CAPN10 gene in human genome (By National Center for Biotechnology Information, U.S. National Library of Medicine - NCBI's Genome Decoration Page., Public Domain, https://commons.wikimedia.org/w/index.php?curid=61367307).

CAPN10 is one of the genes that was identified with the help of linkage studies. The methods used to map disease-causing genes have evolved rapidly in the last decades. The traditional method of mapping disease genes is to use the long stretches of linkage disequilibrium (LD) in affected families by performing linkage analysis. By genotyping about 400 –500 genetic

markers, disease loci can be mapped on a genome wide level. Finding that affected family members share a certain marker that is identical by descent, i.e., identical be- cause it was inherited from the same parent, more often than expected by chance, is evidence that a disease-causing variant is in LD with the genotyped marker (75).

2.4.1.2.) TRANSCRIPTION FACTOR 7-LIKE 2 (T-CELL SPECIFIC, HMG- box) (TCF7L2)

This gene encodes a high mobility group (HMG) box-containing transcription factor that plays a key role in the Wnt signaling pathway. The protein has been implicated in blood glucose homeostasis. Genetic variants of this gene are associated with increased risk of type 2 diabetes. Several transcript variants encoding multiple different isoforms have been found for this gene (provided by RefSeq, Oct 2010). TCF7L2 is a protein coding gene. Diseases associated with TCF7L2 include T2D and Non-Specific Syndromic Intellectual Disability. Among its related pathways are Regulation of activated PAK-2p34 by proteasome mediated degradation and ncRNAs involved in Wnt signaling in hepatocellular carcinoma. Gene Ontology (GO) annotations related to this gene include DNA-binding transcription factor activity and chromatin binding. An important paralog of this gene is TCF7L1. It participates in the Wnt signaling pathway and modulates MYC (a family of regulator genes and proto-oncogenes that code for transcription factor) expression by binding to its promoter in a sequence-specific manner. It also acts as repressor in the absence of CTNNB1 (gene that encodes beta-catenin protein), and as activator in its presence. Activates transcription from promoters with several copies of the Tcf motif 5'-CCTTTGATC-3' in the presence of CTNNB1. TLE1, TLE2, TLE3 and TLE4 (transducin-like enhancer protein 1, 2, 3, 4) repress transactivation mediated by TCF7L2/TCF4 and CTNNB1. Expression of dominant-negative mutants results in cell-cycle arrest in G1. Necessary for the maintenance of the epithelial stem-cell compartment of the small intestine. (76).



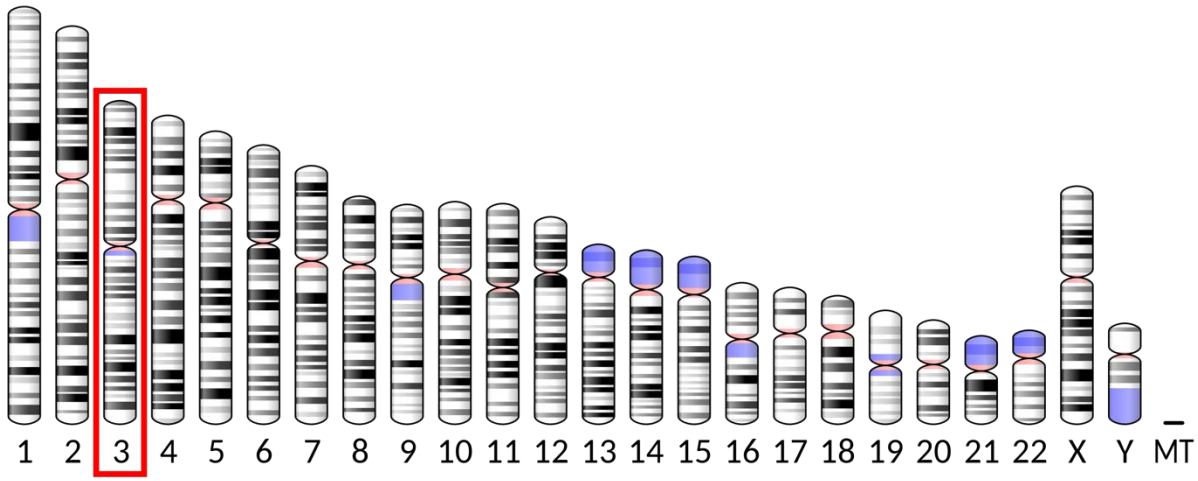
Picture: Location of the TCF7L2 gene in human genome (By National Center for Biotechnology Information, U.S. National Library of Medicine - NCBI's Genome Decoration Page., Public Domain, https://commons.wikimedia.org/w/index.php?curid=61368853).

TCF7L2 is another gene that was identified as being connected to T2D pathophysiology through linkage studies. TCF7L2 was discovered as a T2D susceptibility gene after a strong

linkage signal was mapped to chromosome 10q in a Mexican-American population (77). This region was later fine-mapped in the Icelandic population and confirmed in United States and Danish cohorts, where the risk locus was found to be located in intron 3 of the TCF7L2 gene (78). The association between T2D and a number of single-nucleotide polymorphisms (SNPs) in the TCF7L2 gene has since been strongly confirmed in multiple Genome-wide association studies (GWAS) in different ethnic groups and this gene remains the most replicated and most strongly associated T2D risk gene at this time (79). We will discuss this in more details later on.

2.4.1.3.) PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPAR-γ or PPARG)

This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARs form heterodimers with retinoid X receptors (RXRs) and these heterodimers regulate transcription of various genes. Three subtypes of PPARs are known: PPAR-alpha, PPAR-delta, and PPAR-gamma. The protein encoded by this gene is PPAR-gamma and is a regulator of adipocyte differentiation. Additionally, PPAR-gamma has been implicated in the pathology of numerous diseases including obesity, diabetes, atherosclerosis and cancer. Alternatively spliced transcript variants that encode different isoforms have been described (provided by RefSeq, Jul 2008).
PPARG (Peroxisome Proliferator Activated Receptor Gamma) is a Protein Coding gene. Diseases associated with PPARG include Lipodystrophy, Familial Partial, Type 3 and Body Mass Index Quantitative Trait Locus 11. Among its related pathways are PIP3 activates AKT signaling and Gene expression (Transcription). Gene Ontology (GO) annotations related to this gene include DNA-binding transcription factor activity and chromatin binding. An important paralog of this gene is PPARA. (80).
Nuclear receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Once activated by a ligand, the nuclear receptor binds to DNA specific PPAR response elements (PPRE) and modulates the transcription of its target genes, such as acyl-CoA oxidase. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids. Key regulator of adipocyte differentiation and glucose homeostasis. ADP-ribosylation factor 6 (ARF6) acts as a key regulator of the tissue-specific adipocyte P2 (aP2) enhancer. Acts as a critical regulator of gut homeostasis by suppressing NF-kappa-B-mediated pro-inflammatory responses. It also plays a role in the regulation of cardiovascular circadian rhythm by regulating the transcription of ARNTL/BMAL1 in the blood vessels. (81).

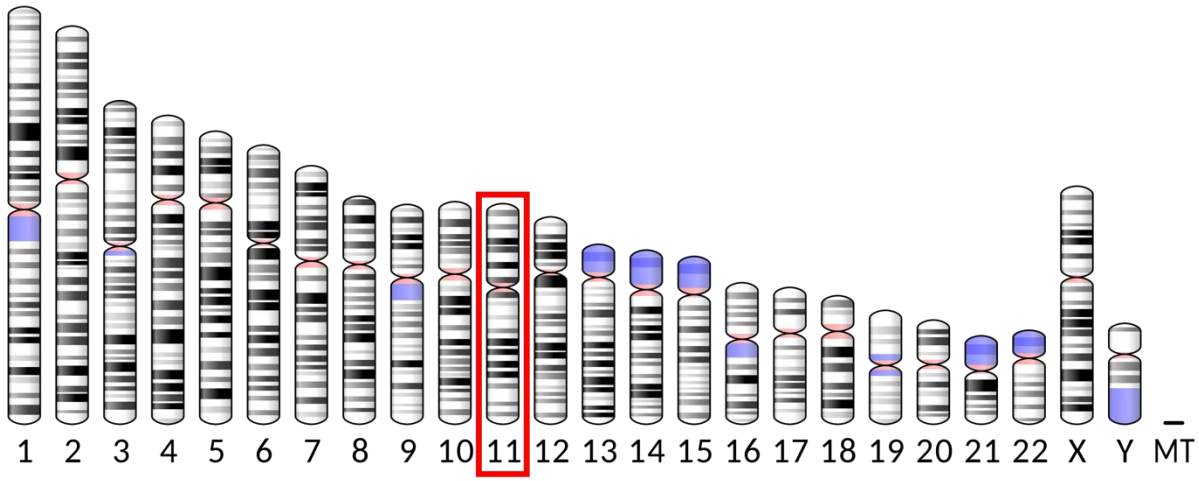


Picture: location of PPAGR gene in human genome (By National Center for Biotechnology Information, U.S. National Library of Medicine - NCBI's Genome Decoration Page., Public Domain, https://commons.wikimedia.org/w/index.php?curid=61367469).

PPARG gene was an attractive candidate gene for T2D because it encodes the molecular target of thiazolidenediones, a commonly used class of anti-diabetic medications. It was found that a proline to arginine change at position 12 in the PPARG gene led to a 20% increase in the risk of diabetes. This finding has since been confirmed in some other populations and other polymorphisms in this gene have been found to play a role in some cases of diabetes (82). Despite these result, the significance of these mutations was not reproduced in all populations and therefore we cannot apply these findings to the worldwide prevalence of diabetes (83, 84). PPARG gene was recently also connected with the regulatory role in absolute fat mass storage and in obesity development. The correlation of PPARG transcript with glycemic control profile in diabetic obese subjects may underlie PPARG role in the insulin signaling pathway and its possible pathophysiological importance in the development of complications of obesity, which is, as mentioned before, still the biggest risk factor of developing the T2D (85).

2.4.1.4.) POTASSIUM INWARDLY RECTIFYING CHANNEL SUBFAMILY J MEMBER 11 (KCNJ11)

The KCNJ11 gene provides instructions for making parts (subunits) of the ATP-sensitive potassium (K-ATP) channel. Each K-ATP channel consists of eight subunits. Four subunits are produced from the KCNJ11 gene, and four are produced from another gene called ATP binding cassette subfamily C member 8 (ABCC8). K-ATP channels are found in beta cells, which are cells in the pancreas that secrete the hormone insulin. The K-ATP channels are embedded in cell membranes, where they open and close in response to the amount of glucose in the bloodstream. Glucose is a simple sugar and the primary energy source for most cells in the body, especially the brain. Closure of the K-ATP channels in response to increased glucose triggers the release of insulin out of beta cells and into the bloodstream, which helps control blood sugar levels.



Picture: location of KCNJ11 gene in human genome (By National Center for Biotechnology Information, U.S. National Library of Medicine - NCBI's Genome Decoration Page., Public Domain, https://commons.wikimedia.org/w/index.php?curid=61368958).

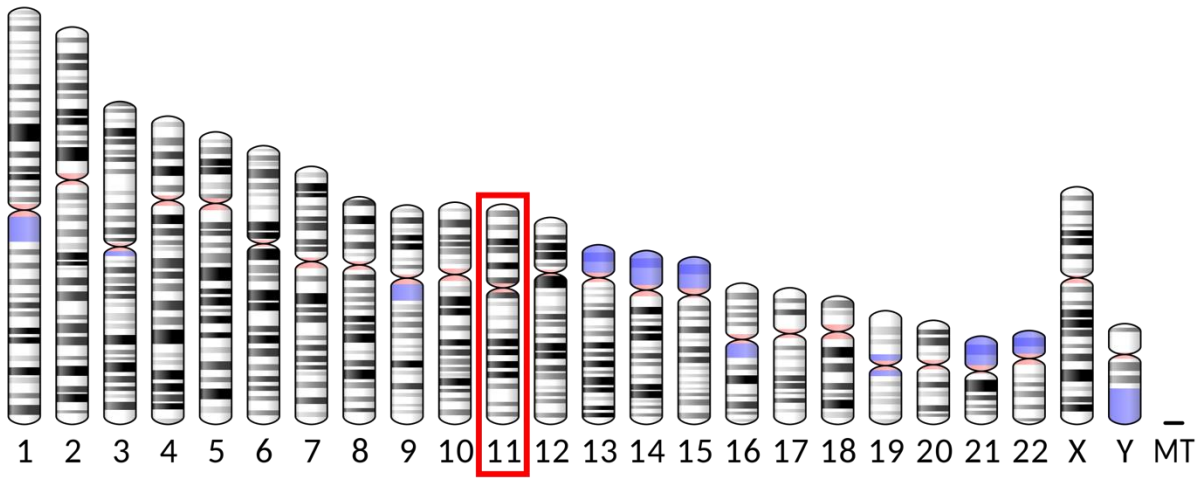
At least 30 mutations in the KCNJ11 gene have been identified in people with permanent neonatal diabetes mellitus. Individuals with this condition often have a low birth weight and develop increased blood sugar (hyperglycemia) within the first 6 months of life. KCNJ11 gene mutations that cause permanent neonatal diabetes mellitus change single amino acids in the protein sequence. These mutations result in K-ATP channels that do not close, leading to reduced insulin secretion from beta cells and impaired blood sugar control (86).

Potassium channels are present in most mammalian cells, where they participate in a wide range of physiologic responses. The protein encoded by this gene is an integral membrane protein and inward-rectifier type potassium channel. The encoded protein, which has a greater tendency to allow potassium to flow into a cell rather than out of a cell, is controlled by G-proteins and is found associated with the sulfonylurea receptor SUR. Mutations in this gene are a cause of familial persistent hyper insulinemic hypoglycemia of infancy (PHHI), an autosomal recessive disorder characterized by unregulated insulin secretion. Defects in this gene may also contribute to autosomal dominant non-insulin-dependent diabetes mellitus type II (NIDDM), transient neonatal diabetes mellitus type 3 (TNDM3), and permanent neonatal diabetes mellitus (PNDM). Multiple alternatively spliced transcript variants that encode different protein isoforms have been described for this gene (87).
This receptor is controlled by G proteins. Inward rectifier potassium channels are characterized by a greater tendency to allow potassium to flow into the cell rather than out of it. Their voltage dependence is regulated by the concentration of extracellular potassium; as external potassium is raised, the voltage range of the channel opening shifts to more positive voltages. The inward rectification is mainly due to the blockage of outward current by internal magnesium. Can be blocked by extracellular barium (By similarity). Subunit of ATP-sensitive potassium channels (KATP) can form cardiac and smooth muscle-type KATP channels with ATP binding cassette subfamily C member 9 (ABCC9). KCNJ11 forms the channel pore while ABCC9 is required for activation and regulation. (88).

The odds ratio of developing T2D is about 1.2 in carriers of the risk allele and this allele was also found to be associated with decreased insulin secretion in different populations (89, 90, 91).

2.4.1.5.) POTASSIUM VOLTAGE-GATED CHANNEL SUBFAMILY Q MEMBER 1 (KCNQ1)

The KCNQ1 gene belongs to a large family of genes that provide instructions for making potassium channels. These channels, which transport positively charged atoms (ions) of potassium out of cells, play key roles in a cell's ability to generate and transmit electrical signals. The specific function of a potassium channel depends on its protein components and its location in the body. Channels made with KCNQ1 proteins are primarily found in the inner ear and in heart (cardiac) muscle. In the inner ear, these channels help maintain the proper ion balance needed for normal hearing. In the heart, the channels are involved in recharging the cardiac muscle after each heartbeat to maintain a regular rhythm. The KCNQ1 protein is also produced in the kidney, lung, stomach, and intestine.
The KCNQ1 protein interacts with proteins in the KCNE family (such as the KCNE1 protein) to form functional potassium channels. Four alpha subunits made from KCNQ1 proteins form the structure of each channel. One beta subunit, made from a KCNE protein, attaches (binds) to the channel and regulates its activity (92).



Picture: Location of the KCNQ1 gene in human genome (By National Center for Biotechnology Information, U.S. National Library of Medicine - NCBI's Genome Decoration Page., Public Domain, https://commons.wikimedia.org/w/index.php?curid=61368958).

KCNQ1 gene was identified as a type 2 diabetes susceptibility gene in two recent independently performed GWA studies in Japanese population (93, 94). It was confirmed that the KCNQ1 common variants are associated with an increased risk of type 2 diabetes in a Dutch population. The individuals carrying the same at-risk alleles C, as reported in the Japanese studies (95), had a modestly increased risk of developing type 2 diabetes, with a population attributable risk from 0.6% to 4.3%. These results are also consistent with previous studies performed in Caucasian populations (96, 97, 98, 99, 100, 101). It was demonstrated in a large cohort of subjects that underwent hyperglycemic glucose clamps that the risk allele of the KCNQ1 SNP is significantly associated with reduced glucose-stimulated second-phase insulin secretion. In addition a significant association of KCNQ1 variants with impaired lipid parameters were reported (), which might provide new important and valuable insights.

Interesting to add is that a variant in KCNQ1 gene, a single nucleotide polymorphism (SNP), (rs163182) was found to be associated with the risk of metabolic syndrome in urban Han Chinese women (103). Metabolic syndrome represents high risk for developing the T2D, among other factors.

2.4.2.) GENE-GENE INTERACTIONS

In genetics, gene-gene interaction (epistasis) is the effect of one gene on a disease which is modified by another gene or is modified by several other genes. Epistasis can be contrasted with dominance, which is an interaction between alleles at the same gene locus. Gene-gene interaction is a common component of genetic architecture of human complex diseases; however, it is difficult to detect. The multi-locus genotype combinations for gene-gene interaction increase exponentially and require large sample size as well as more computation burden (104). Different models are being used in order to research the gene-gene interactions on multiple levels. These model types will not be discussed in more details in the present thesis. However we will discuss the latest information available with regards to gene-gene interactions and the connection it might have to the pathophysiology of T2D.

A newest study demonstrated that haplotypes in the AGER gene (C-G-T-A and A-G-C-A) were risk factors for developing diabetic ischemic disease, and that rs4845625 and haplotypes in the IL6R gene (T allele and T-T-C-T- C) were associated with a lower risk of diabetic ischemic heart disease. The gene-gene interactions between rs184003 in AGER and rs4845625 in IL6R were associated with a higher risk of diabetic ischemic heart disease (105).

2.4.3.) GENE-ENVIRONMENT INTERACTIONS

Study of gene-environment interaction is important for improving accuracy and precision in the assessment of both genetic and environmental influences. Gene–environment interaction refers to the interplay of genes (and, more broadly, genome function) and the physical and social environment. These interactions influence the expression of phenotypes. For example, most human traits and diseases are influenced by how one or more genes interact in complex ways with environmental factors, such as chemicals in the air or water, nutrition, ultraviolet radiation from the sun and social context. Gene–environment interactions are the situation where the impact of an environmental exposure on disease risk is different for people with different genotypes, or conversely, situations where the impact of a genotype on disease risk is different in people with different environmental exposures. Studies of gene–environment interactions can provide insights into biological mechanisms of disease and could have public health implications (106).

From all the information available by now, it is clear that the development and the risk of developing the T2D is very much connected and influenced by the environmental factors. Our genetic code does not change significantly from one to two generations, therefore we can assume with high probability that the recent trend in diabetes is most likely due to the changes in the environment. Increased adiposity is the single most significant factor in the development of T2D and the epidemics of obesity and T2D largely parallel one another. The increasing prevalence of obesity is thought to be related primarily to changes in dietary habits and our increasingly sedentary lifestyle, though other factors (including toxins and infectious agents)

may play a role. Genes may influence the risk of diabetes not only by directly altering insulin action or secretion, but also by altering how any given individual interacts with these environmental factors. Even within the same broad environment, individuals vary greatly in their adoption of unhealthy lifestyles and their willingness to change such lifestyles. By influencing who adopts a more unhealthy diet (this includes genetic influence on taste and food preferences), who exhibits greater willingness to change unhealthy behaviors (107), who burns more calories at rest, who exhibits greater activity levels when not actively exercising, what kind of microbiome an individual carries, and who opts for a more sedentary lifestyle, genetic factors can play a role in determining who becomes obese or develops diabetes in any given environment (108). These gene-environment interactions may be extremely complex and may be one reason why such a small proportion of the heritability of T2D has been explained at this time (109).

2.4.4.) EPIGENETICS

Epigenetic modifications are heritable and reversible modifications that significantly affect gene expression without any change in the nucleotide sequence of DNA (110).
Classically, epigenetic mechanisms include (i) the methylation of DNA, (ii) the imprinting, (iii) the remodeling of chromatin, and (iv) the production of noncoding RNA (ncRNA) (111, 112). In mammals, epigenetic signature is primarily defined in the embryo (113, 114). This is deeply remodeled throughout the life course as a direct outcome of environmental and lifestyle impacts which include diet, stress, pollutants, smoking, endocrine-disrupting chemicals, physical activity, sedentary life, etc. Therefore, genome activity is epigenetically modulated under exogenous influence, and the environment-dependent changes in gene activity stably propagate from one generation of cells to the next one. Epigenetic changes impact genome functions, thus affecting health and disease status and also behavior; aging-related diseases, cancer, immunity and related disorders, obesity, metabolic disorders, infertility, and cardiovascular and neurological diseases represent only few examples of environmentally dependent diseases, and the literature in the field is growing up day by day (115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129).

For a long time, high levels of methylation were associated with gene silencing. It is now known that generally DNA methylation of promoters or enhancers is associated with gene silencing, while methylation in the rest of the gene is associated with active gene expression (130). Animal studies have demonstrated that insufficient nutrition during intrauterine life induces epigenetic changes in the offspring (131). These results agree with a study carried out on children whose mothers—during World War II—suffered prolonged food deprivation. The children—once adults—displayed reduced methylation of the gene IGF2 (132), obesity or glucose intolerance, depending upon the length of starvation (133).

Fifteen years ago, the first epigenetics studies were performed in pancreatic islets and skeletal muscle in patients with T2D (134). Despite the fact, that these initial studies only analyzed DNA methylation of candidate genes or parts of the genome, they were successful in identifying the altered methylation patterns in persons with T2D compared with non-diabetic controls. These results clearly support the role for epigenetics in the growing incidence of diabetes. Since 2008, there have been technical advances and an increasing interest in epigenetics of T2D driving this research field forward.

Initial studies analyzed DNA methylation of candidate genes for T2D such as INS (encoding insulin), PDX1, PPARGC1A (encoding PGC1α), and GLP1R (encoding the GLP-1 receptor) in human pancreatic islets from donors with T2D and non-diabetic controls (135, 136, 137, 138). Islets from T2D donors were found to have increased DNA methylation and decreased expression of these key genes, which were associated with impaired insulin secretion. Also, high glucose and glycated hemoglobin (HbA1c) seemed to directly increase DNA methylation of these genes (139, 140, 141).

Development of Illumina's Infinium arrays made it possible to analyze methylation of numerous CpG sites simultaneously. This technology was used to analyze methylation of ~27,000 and ~450,000 CpG sites, respectively, in pancreatic islets from T2D and non-diabetic donors (142, 143). Dayeh et al. (2014) found altered DNA methylation of 1,649 CpG sites annotated to 843 genes in islets from 15 T2D cases versus 34 controls. Out of these genes, 102 also exhibited differential gene expression in the islets from T2D donors. CDKN1A, PDE7B, and SEPT9 belong to the genes with decreased DNA methylation and increased gene expression in T2D islets. To mimic the situation of T2D, these three genes were overexpressed in clonal β cells, which resulted in decreased glucose-stimulated insulin secretion. Overexpression of CDKN1A, encoding a potent cyclin-dependent kinase inhibitor that regulates cell-cycle progression to G1, also decreased cell proliferation in the clonal β cells (144). In diabetic islets, Dayeh et al. (2014) also found differential DNA methylation of CpG sites annotated to several candidate genes for T2D and obesity, as identified by genome-wide association studies (GWASs), such as ADCY5, FTO, HHEX, IRS1, KCNQ1, PPARG, and TCF7L2 (145). The Illumina arrays have also been used to analyze DNA methylation in human adipose tissue, liver, and skeletal muscle from subjects with T2D and non-diabetic controls (146, 147, 148, 149, 150, 151). These studies identified numerous CpG sites with altered DNA methylation in target tissues from patients with T2D, supporting the role of epigenetics in the pathogenesis of diabetes. However, in-line with genetic studies, the effect size of each CpG site was quite modest. This is of no surprise since T2D is a complex, polygenic, and multifactorial disease, and it would be unlikely to find methylation of a few CpG sites that had a large effect size on T2D.

Epigenetics is more or less new field that offers a lot of potential for treating and managing the T2D pathology. New technology enables us to learn and understand new things about epigenetics in connection to T2D. The newest research discuss the role of flavonoids as well as the impact we can have on the histone methylation to treat the T2D. We will further discuss this and other applications in more details.

2.5.) POLYPHENOLS

Polyphenols are one of the largest groups of organic compounds that are characterized by having multiple phenol units in its chemical structure. Polyphenols are phytochemicals, this means we can find them naturally present in many types of food such as nuts, cocoa, berries, tea, and red wine. They are abundant in nature (plants, fruits, vegetables,..) and structurally very diverse. Emerging studies have shown that polyphenols can have multiple beneficial effects on the human body, such as antioxidative, anticancer, and antidiabetic effects.

2.5.1.) STRUCTURAL CHEMISTRY OF POLYPHENOLS

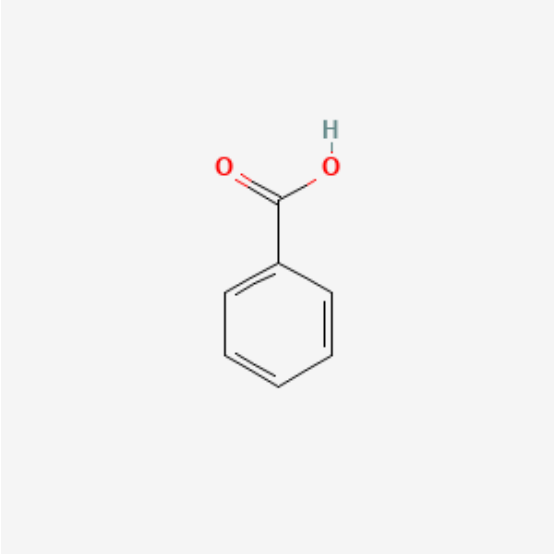
Polyphenols are very often larger molecules (macromolecules). Their upper molecular weight limit is about 800 Daltons, this allows them to have a possibility to rapidly diffuse across cell membranes. Once they arrive at the cell they can reach intracellular sites of action or remain as pigments once the cell ages. Most polyphenols contain repeating phenolic constituents of pyrocatechol, resorcinol, pyrogallol, and phloroglucinol connected by esters (hydrolysable tannins) or more stable C-C bonds (nonhydrolyzable condensed tannins). Proanthocyanidins are mostly polymeric units of catechin and epicatechin.

2.5.2.) CLASSIFICATION OF POLYPHENOLS

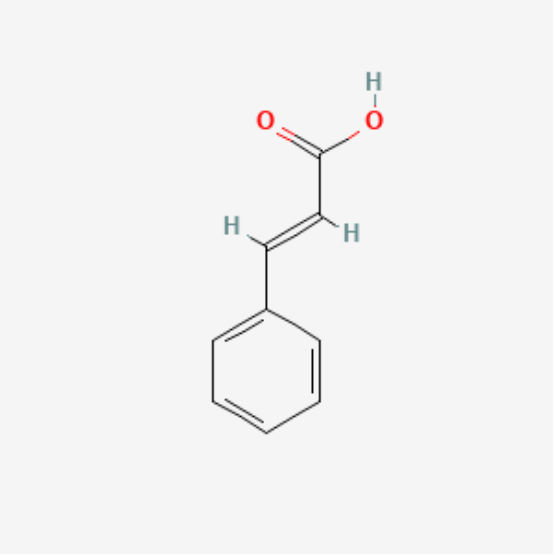
In order to understand better the further discussions in this thesis we will describe the classification of polyphenols according to the chemical structures of the aglycones.

2.5.2.1.) PHENOLIC ACIDS

Phenolic acids are non-flavonoid polyphenolic compounds which can be further divided into two main types, benzoic acid and cinnamic acid derivatives based on C1–C6 and C3–C6 backbones (Picture of Benzoic acid (152) and picture of Cinnamic acid (153). While fruits and vegetables contain many free phenolic acids, in grains and seeds-particularly in the bran or hull-phenolic acids are often in the bound form (154, 155, 156). These phenolic acids can only be freed or hydrolyzed upon acid or alkaline hydrolysis, or by enzymes (157).



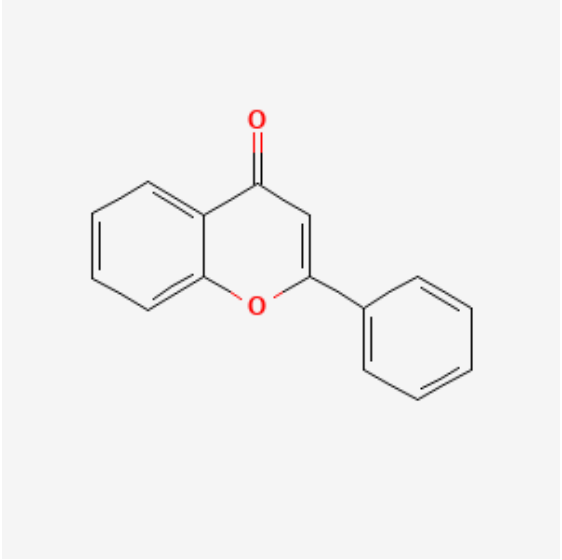
Benzoic acid



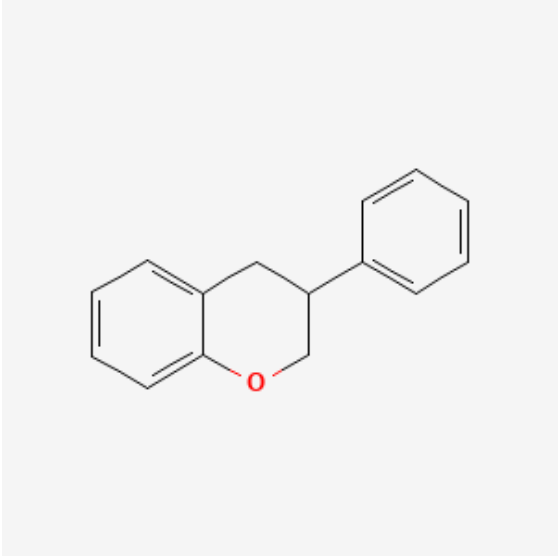
Cinnamic acid

2.5.2.2.) FLAVONOIDS

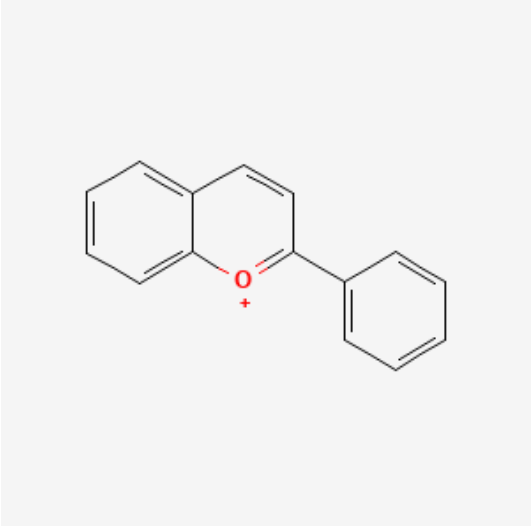
Flavonoids have the C6–C3–C6 general structural backbone in which the two C6 units (Ring A and Ring B) are of phenolic nature (Picture of Flavone (158) and picture of Isoflavan (159) and picture of Anthocyanidin Flavlyum (160). Due to the hydroxylation pattern and variations in the chromane ring (Ring C), flavonoids can be further divided into different sub-groups such as anthocyanins (glycosylated forms of anthocyanidins; anthocyanindins don't have the sugar part), flavan-3-ols, flavones, flavanones and flavonols. While the vast majority of the flavonoids have their Ring B attached to the C2 position of Ring C, some flavonoids such as isoflavones and neoflavonoids, whose Ring B is connected at the C3 and C4 position of Ring C, respectively, are also found in plants. Chalcones, though lacking the heterocyclic Ring C, are still categorized as members of the flavonoid family. These basic structures of flavonoids are aglycones; however, in plants, most of these compounds exist as glycosides. Biological activities of these compounds, including antioxidant activity, depend on both the structural difference and the glycosylation patterns (161).



Flavone



Isoflavan

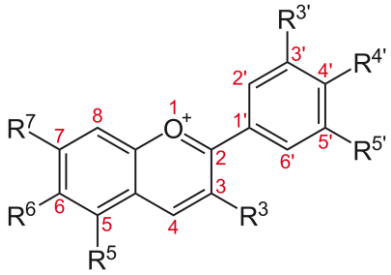


Anthocyanidin Flavylium

2.5.2.2.1.) ANTHOCYANIDINS and ANTHOCYANINS

As already mentioned anthocyanins are anthocyanidins with a sugar compound attached to their structure. This gives anthocyanins different chemical and physiological properties. Also the molecule of anthocyanins is more complex and bigger. Anthocyanins are mostly soluble in water.

Anthocyanidins therefore are aglycones of anthocyanins. They are lacking the sugar part of the molecular structure. Anthocyanidins are the principal components of the red, blue and purple pigments of the majority of flower petals, fruits and vegetables, and certain special varieties of grains, e.g., black rice. Anthocyanidins in plants mainly exist in glycosidic forms.
A total of more than 500 anthocyanins are known depending on the hydroxylation, methoxylation patterns on the B ring, and glycosylation with different sugar units (161, 162). The color of anthocyanins is pH-dependent, i.e., red in acidic and blue in basic conditions. However, other factors such as degree of hydroxylation, or methylation pattern of the aromatic rings, and the glycosylation pattern, i.e., sugar vs. acylated sugar can also affect the color of anthocyanin compounds. Anthocyanins are chemically stable in acidic solutions.



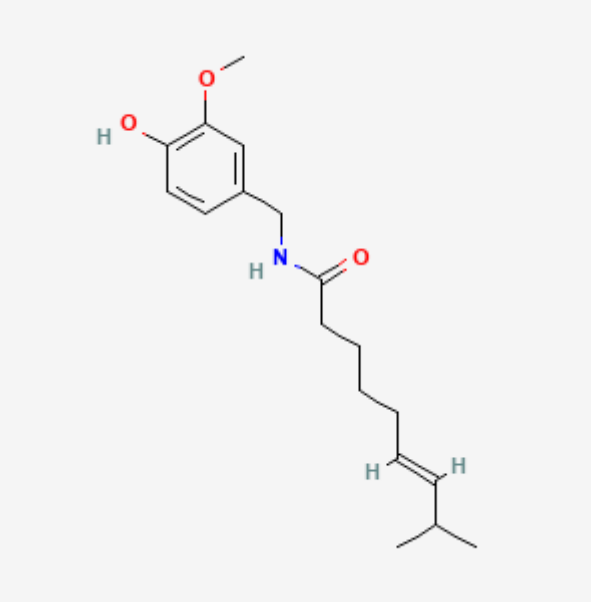
Basic structure of anthocyanidins

Anthocyanidin	R_3'	R_4'	R_5'	R_3	R_5	R_6	R_7
Aurantinidin	-H	-OH	-H	-OH	-OH	-OH	-OH
Cyanidin	-OH	-OH	-H	-OH	-OH	-H	-OH
Delphinidin	-OH	-OH	-OH	-OH	-OH	-H	-OH
Europinidin	$-OCH_3$	-OH	-OH	-OH	$-OCH_{33}$	-H	-OH
Pelargonidin	-H	-OH	-H	OH	-OH	-H	-OH
Malvidin	$-OCH_3$	-OH	$-OCH_3$	-OH	-OH	-H	-OH
Peonidin	$-OCH_3$	-OH	-H	OH	-OH	-H	-OH
Petunidin	-OH	-OH	$-OCH_3$	-OH	-OH	-H	-OH
Rosinidin	$-OCH_3$	-OH	-H	-OH	-OH	-H	$-OCH_3$

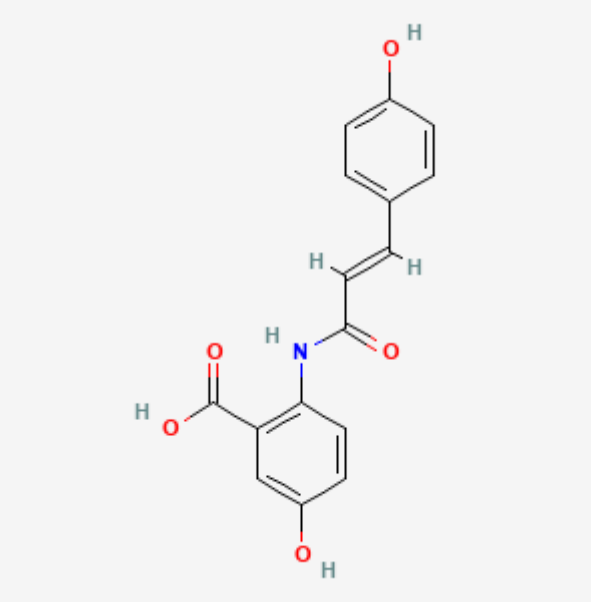
Selected anthocyanidins and their substitutions.

2.5.2.3.) POLYPHENOLIC AMIDES

Some polyphenols may have N-containing functional substituents. Two such groups of polyphenolic amides are of significance for being the major components of common foods: capsaicinoids in chili peppers (163) and avenanthramides in oats (164) (Picture of Capsaicin (165) and picture of Aventhramide A (166). Capsaicinoids such as capsaicin are responsible for the hotness of the chili peppers but have also been found to have strong antioxidant and anti-inflammatory properties, and they modulate the oxidative defense system in cells. Antioxidant activities including inhibition of LDL oxidation by avenanthramides have also been reported (161).



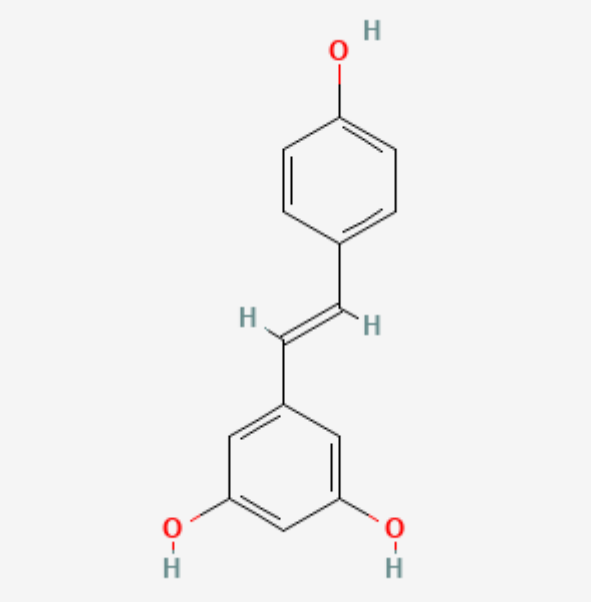
Capsaicin



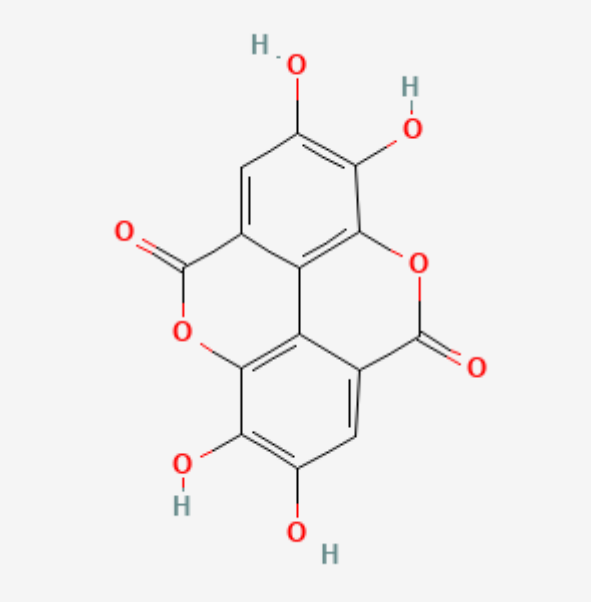
Aventhramide A

2.5.2.4.) OTHER POLYPHENOLS

In addition to the phenolic acids, flavonoids and phenolic amides, there are several non-flavonoid polyphenols found in foods that are considered important to human health. Among these, resveratrol is unique to the grapes and red wine; ellagic acid and its derivatives are found in berry fruits, e.g., strawberries and raspberries, and in the skins of different tree nuts. Lignans exist in the bound forms in flax, sesame and many grains (Picture of Resveratrol (167) and picture of ellagic acid (168, 161).



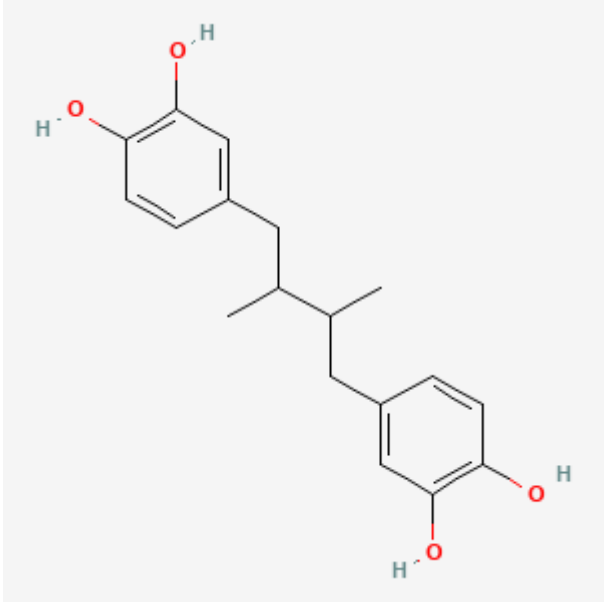
Resveratrol



Ellagic acid

2.5.3.) NORDIHYDROGUAIARETIC ACID

Nordihydroguaiaretic acid (NDGA) is a lignan found in large amounts and obtained from the ethnobotanically important plant, Larrea tridentata (Zygophyllaceae) (169). NDGA is also found in other natural species, for example in the extract from the bark of white fir tree. A lot of different studies have shown that the application of NDGA can have beneficial impact in the treatment of cancer, diabetes, cardiovascular diseases and neurological disorders (170). NDGA is a polyphenol-bearing o-dihydroxy (catechol) structure (Picture 171); it possesses four phenolic hydroxyl groups. As such, NDGA is recognized as a strong antioxidant with several beneficial health effects.



Nordihydroguaiaretic acid

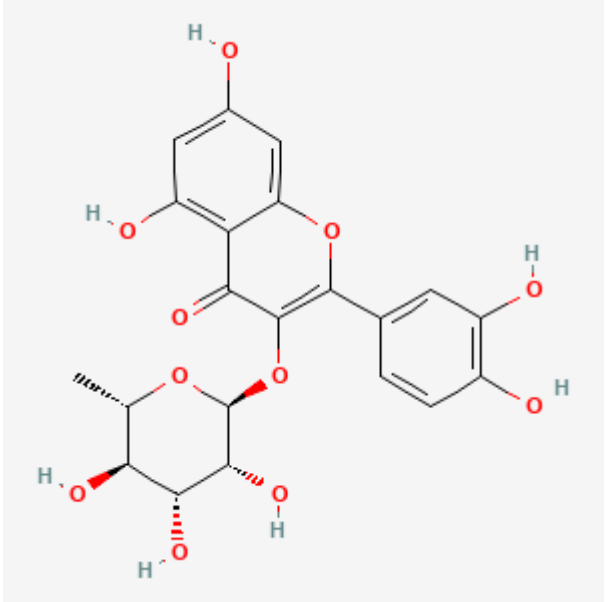
NDGA has shown very strong antioxidative properties (172).
In current data available it is described that hydrophobicity is a very important factor for the pharmacological action and toxicological effect of chemical compounds (173). This characteristic affects the absorption, bioavailability and interactions with the hydrophobic receptor in the body. NDGA is a hydrophobic compound, presenting a Log p = 4.48 (174).
There is a lot of data available that describes the anti-glycemic effect of the NDGA. The mentioned effect is a consequence of multiple mechanisms. Inhibition of the α-glucosidase, α-amylase and dipeptidyl peptidase 4 enzymes was described (175). NDGA was given to lower plasma glucose concentration in two mouse models of type 2 diabetes. The results of this study indicated that plasma glucose concentration fell approximately 8 mmol/l in male mice following the oral administration of NDGA. NDGA is a well-known lipoxygenase inhibitor. The decline in plasma glucose concentration following the NDGA treatment in the mice was achieved without any change in plasma insulin concentration. In addition, oral glucose tolerance improved and the ability of insulin to lower plasma glucose concentrations was accentuated in NDGA-treated diabetic mice. These data raise the possibility that NDGA, or/and other lipoxygenase inhibitors, represents a new approach to the pharmacological treatment of T2D (176).

In another study, carried out on diabetic rats it was shown that the supplements of omega 3 fatty acids and NDGA have a positive effect on the diabetic encephalopathy through varied mechanisms (177). These results make NDGA a very interesting compound that could be used in the treatment or/and prevention of the T2D.

2.5.4.) QUERCITRIN

Quercitrin is a glycoside formed from the flavonoid quercetin and the deoxy sugar rhamnose. The chemical molecule of quercitrin can be seen below (Picture 178).

Quercitrin is a constituent of the dye quercitron. It can be found in Tartary buckwheat (Fagopyrum tataricum) (179) and in oaks species like the North American white oak (Quercus alba) and English oak (Quercus robur) (180). It is also found in Nymphaea odorata or Taxillus kaempferi (181). The enzyme quercitrinase catalyzes the chemical reaction between quercitrin and H2O to yield L-rhamnose and quercetin.



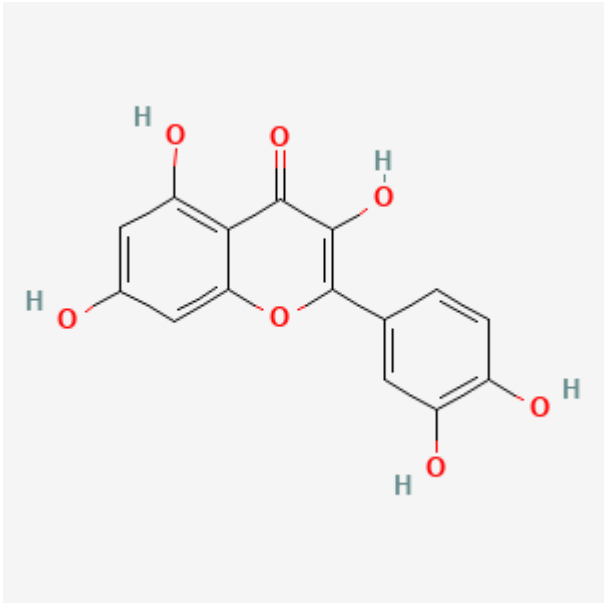
Quercitrin

The data suggests that quercitrin has a lot of different positive effects on the human health. It was shown that quercitrin inhibits lipid peroxidation in vitro. Quercitrin exhibits a scavenger and antioxidant role, and these effects probably are mediated via different mechanisms, which may involve the negative modulation of the Fenton reaction and N-methyl-D-aspartate (NMDA) receptor (182). A decrease of plasma glucose and increase in insulin levels were observed along with the restoration of glycogen content and the activities of carbohydrate metabolic enzymes in quercitrin-treated diabetic rats. The histopathological study of the pancreas revealed the protective role of quercitrin. There was an expansion of the islets and decreased fatty infiltrate of the islets in quercitrin treated diabetic rats. In normal rats treated with quercitrin, we could not observe any significant change in all the parameters studied. Combined, these results show that quercitrin plays a positive role in carbohydrate metabolism and antioxidant status in diabetic rats (183). Qualitative and quantitative analyses of water extract of Potentilla discolor Bunge (PDBW) identified six major compounds including quercitrin. PDBW regulated gluconeogenesis by decreasing the mRNA expression of PEPCK

and G6Pase. PDBW also promoted glycogenesis by the increase in hepatic glycogen content and GS phosphorylation and the down-regulation of GSK3β phosphorylation. Furthermore, the upstream signaling pathways, Akt and AMPK, may mediate the effects of PDBW on hepatic glucose metabolism. These findings provide evidences of PDBW in the prevention and amelioration of T2D (184). Chlorogenic acid, isoquercitrin, and quercitrin, present in the leaves of Morus alba, have reportedly hypoglycemic properties and an ameliorating effect on diabetic nephropathy. This leaf has pharmacological effects on glucose absorption, insulin secretion and production. It is an antioxidant and anti-inflammatory agent, has antihyperglycemic and antihyperlipidemic activities, and helps with obesity management. (185).

2.5.5.) QUERCETIN

Quercetin is a plant flavonol from the flavonoid group of polyphenols. It is found in many fruits, vegetables, leaves, seeds, and grains; capers, red onions, and kale are common foods containing appreciable amounts of it (186, 187). As we mentioned before, quercetin is aglycone of quercitrin as he is lacking an attached sugar rhamnose. It has a bitter flavor and is used as an ingredient in dietary supplements, beverages, and foods. His chemical structure can be seen below (Picture 188).



Quercetin

Dietary consumption of quercetin differs across countries. Flavonoid daily intake (in which about 75% is quercetin) ranges from a low of 5 milligrams per day to a high of 80 milligrams. Key among the variables influencing the level is the amount of fruits and vegetables and tea consumed. Quercetin levels in food have been found to be impacted by growing conditions. For example, in the case of tomatoes, a higher quercetin aglycone level has been found in those organically grown as compared to those grown using traditional growing techniques (189). Pharmacokinetic studies showed that absorption of quercetin was predictable and the inter-individual variation was small. Quercetin was found in plasma as glucuronide and/or sulfate of quercetin and as unconjugated quercetin aglycone (190). About 65–81% of quercetin aglycone form gets absorbed in the small intestine after hydrolysis (191, 192, 193). Then it is transported

via portal circulation to the liver, where it gets metabolized and bound to albumin in plasma. The peak level of quercetin in plasma reaches after 0.7–7 h of intake. Unabsorbed quercetin undergoes biotransformation by glucuronidation, hydroxylation, methylation, and sulfonylation in the intestine by enzymes from the gut microbiota (194).

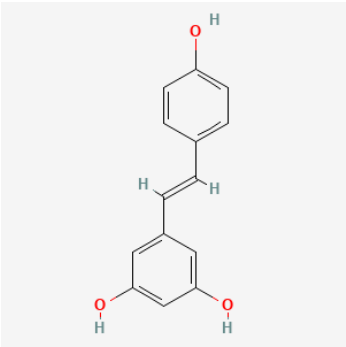
Quercetin has multiple targets in humans such as muscles, pancreas, liver, and small intestine. More than 80 per cent of glucose uptake occurs in the human body through insulin sensitive skeletal muscles. Therefore an impairment in glucose uptake in skeletal muscles can alter whole body glucose homeostasis and can eventually lead to pathogenesis of T2D. Quercetin activates adenosine monophosphate kinase (AMPK) in skeletal muscles which in turn stimulates Akt and GLUT4 receptors in the cell membrane. Glucose enters the cells by facilitated diffusion through GLUT4 and gets metabolized thereby it regulates glucose level (195). The hypoglycemic activity of the well-known drug, metformin is also mediated through the AMPK activation (196). Quercetin also induces the AMPK activity in hepatocytes and inhibits glucose 6 phosphatase (197).

For humans, quercetin has shown to help decrease the seriousness of numbness, jolting pain, and irritation for patients with type 2 diabetes neuropathy. It has further been shown that active treatment with quercetin can improve various quality-of-life matrices (198).
Based on all available data quercetin seems a good candidate to be used in management of the T2D. However further clinical studies are needed to determine the exact dose and pharmaceutical formulation that can be used in order to obtain desirable results. In this thesis we will focus in more details on molecular mechanisms by which quercetin achieves antidiabetic effect in the human body.

2.5.6.) RESVERATROL

Resveratrol is a type of natural phenol, and a phytoalexin produced by several plants in response to injury or when the plant is under attack by pathogens, such as bacteria or fungi or UV radiation. (199). Sources of resveratrol in food include the skin of grapes, blueberries, raspberries, mulberries, and peanuts (200, 201). High concentrations are present in grapes, possibly because of Vitis vinifera response to fungal infection (202).

Formal chemical name (IUPAC name) of resveratrol is E-5-(4-hydroxystyryl)benzene-1,3-diol. Various aspects on resveratrol chemistry are currently being studied. It exists as two geometric isomers: cis-(Z) and trans-(E). (Photo 203).



Resveratrol

Bioavailability of resveratrol depends on various factors: metabolism by glucuronidation and sulfation, effects of dose-escalation and repeated doses, tissue accumulation of resveratrol and metabolism by bacterial enzymes. The latter is especially interesting new area of research. In general the bioavailability of resveratrol after a single dose is not the highest but it is moderate. Further research is needed in order to obtain more information and clinical data. Based on urinary excretion of total metabolites after radiolabeled doses, the oral absorption of resveratrol appeared to be at least 75%. This may also be inferred from a comparison of the plasma total area under the plasma concentration time curve (AUC) data after oral and intravenous administration, if resveratrol is assumed to be metabolized similarly after both ruts of administration (204).

There are a lot of studies and information present that shows the positive effect that resveratrol has on diabetes type 2 and obesity. Oral supplementation of resveratrol was found to be effective in improving glycemic control and therefore resveratrol could be a potential adjuvant for the treatment and management of diabetes (205). Howitz et al. (206) identified resveratrol as a small-molecule activator of sirtuin 1 (SIRT1). SIRT1, like all members of the sirtuin family, requires nicotinamide adenine dinucleotide (NAD+) for its deacetylating activity (207). The dependence of SIRT1 on NAD+ strongly links its activity to cellular energy levels. SIRT1 is induced both by calorie restriction and exercise (208) and plays an important role in the regulation of lipid and glucose homeostasis (209). The fact that SIRT1 is closely connected to cellular energy levels and energy homeostasis makes it an interesting molecular target for treatment of metabolic disorders such as obesity and T2D. Considering resveratrol has been identified as a small-molecule activator of SIRT1, it is not surprising that resveratrol has been said to have calorie restriction-like effects (210, 211, 212, 213).

Later on we will review the latest data available on the mechanism of action and biological effects resveratrol has in the human body.

2.6.) DIET AND TYPE 2 DIABETES

The first information and evidence that diet might have an impact on the etiology of T2D is reported by Indians. Indians noticed that the prevalence of T2D is significantly higher among rich people, who consume more sugar and fat in their diet (214). We should also keep in mind that rich people possibly had better access to the healthcare system and therefore any disease was diagnosed quicker, where the poor classes remained undiagnosed in most cases. But nevertheless the data suggests strong relation between diet and the on-set of T2D. Many studies have reported a positive association between high intake of sugars and development of T2D (215). Mediterranean diet showed beneficial impact on improving glycemic control and cardiovascular risk factors in T2D. The Mediterranean diet can be described as a dietary pattern characterized by the high consumption of plant-based foods (olives, peppers, tomatoes,..etc.), olive oil as the main source of fat, low-to-moderate consumption of fish, dairy products and poultry, low consumption of red and processed meat, and low-to-moderate consumption of wine with meals. Retrospective studies show that higher adherence to the Mediterranean diet is associated with a 20–23 % reduced risk of developing T2D, while the results of randomized controlled trials show that Mediterranean diet reduces glycosylated hemoglobin levels by 0.30–0.47 %, and is also associated with a 28–30 % reduced risk for cardiovascular events. The

mechanisms by which Mediterranean diet produces its cardiometabolic benefits in T2D are, anti-inflammatory and antioxidative (216). In recent studies postmenopausal women were given three different diet plans, Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet and plant-based Portfolio Diet. Over a mean follow-up of 16.0 years, 13,943 cases of incident type 2 diabetes were identified. In comparisons of the highest with the lowest quintiles of adherence, the hazard ratios (HS) for risk of incident type 2 diabetes were 0.77 (95% CI 0.72, 0.82) for the Portfolio Diet, 0.69 (0.64, 0.73) for the DASH diet, and 0.78 (0.74, 0.83) for the Mediterranean diet. Greater adherence to the plant-predominant Portfolio, DASH, and Mediterranean diets was prospectively associated with lower risk of type 2 diabetes in postmenopausal women (217). In the middle aged Danish population the adherence to the EAT-Lancet diet showed a lower risk of developing T2D (218). The EAT-Lancet diet is characterized as a planetary friendly diet, it consists of half a plate of fruits, vegetables and nuts. The other half consists of primarily whole grains, plant proteins (beans, lentils, pulses), unsaturated plant oils, modest amounts of meat and dairy, and some added sugars and starchy vegetables.

Many of prospective studies have found relations between fat intake and subsequent risk of developing T2D. In a diabetes study, conducted at San Louis Valley, a more than thousand subjects without a prior diagnosis of diabetes were prospectively investigated for 4 years. In that study, the researchers found an association between fat intake, T2D and impaired glucose tolerance (219, 220). There are enough data that shows strong connection to the diet type and the occurrence of T2D. As mentioned by available information the diet should contain unsaturated fat, plant based fat, less processed food, less sugary food and beverages, less meat and more plant-base diet. Also important is the amount of consumed food. Portions have become bigger and especially people in developed countries are getting used to bigger portions. There is not much data available for the regulation of the portion sizes. In US Portion sizes vary by food source, with the largest portions consumed at fast food establishments and the smallest at other restaurants. Between 1977 and 1996, food portion sizes increased both inside and outside the home for all categories except pizza. The energy intake increased as well (221). Therefore the education about foods and diet plays an important role in T2D as well.

It was shown that patients that have T2D were more compliant with the treatment and more willing to take appropriate life-style modifications if they were educated of their disease. Understanding the disease and consequences that the diet has on a disease increased the desire to take actions in their own life that would prevent the progression of the disease itself. In this specific study, carried out in Sweden, the sense of belonging to a community and to share experience had a big impact on patients cooperation in the disease management. The group-based education model made it possible for the patients to learn through reflection concerning their own and others' experiences. The learning that occurred with support from the group reflections and the reflection books contributed to the understanding of the complexity of the illness. This increased the motivation and desire to be responsible for the treatment and implementation of habits. The group contributed to a sense of belonging and community that inspired a continued and active learning (222). Education of the T2D patients is getting better with each decade but it still requires more attention than it gets. The weight of T2D on healthcare systems is bigger each year. With educating about T2D we could possibly prevent new cases and disease progression.

2.6.1.) POLIPHENOL RICH DIET AND TYPE 2 DIABETES

High amounts of polyphenols are present in some diets such as the Mediterranean and the plant-based diet. Like mentioned before, the Mediterranean diet essentially refers to a dietary pattern rich in whole grains, fruits and vegetables, legumes, nuts, fish, olive oil, and with moderate wine consumption. It has been estimated that adherence to a Spanish Mediterranean diet led to a daily intake of polyphenols between 2590 and 3016 mg/day (223). Plant-based diets involve eating plenty of vegetables, fruits, and cereals and a low amount of animal products; among plant-based diets, Fish-Vegetarian, Semi-Vegetarian, and Lacto-Vegetarian diets contain the greatest amounts of polyphenols (224). This is the reason why the role of the diet and consumption of polyphenols in regards to T2D was widely studied in the past years and still is. A randomized controlled trial reported that a diet naturally rich in polyphenols improves glucose metabolism in individuals at high risk of diabetes (225). A meta-analysis of six prospective cohorts that involved 284,806 participants suggested that an increase in the total dietary flavonoids intake by approximately 500 mg/day is associated with a significant decrease of the risk to develop T2D (226) and, consistently, another meta-analysis of 18 prospective studies (227) showed that diets rich in polyphenols, particularly flavonoids, play a role in the prevention of T2D. A large epidemiological study showed that anthocyanins-rich diets with substantial consumption of specific whole fruits, including blueberries, grapes, and apples, was significantly associated with a reduced risk of diabetes (228). In a 3-month randomized, double-blind, placebo-controlled trial of subjects with prediabetes or new onset diabetes, purified anthocyanins moderately reduced glycated hemoglobin (229). Another recent study has indicated the potential benefit of anthocyanin-rich mixed berry preparations on post-prandial glucose and insulin response (230) thereby suggesting an improved insulin sensitivity. Further evidence comes from a recent metanalysis of 37 randomized controlled trials that demonstrates that consumption of anthocyanins for more than 8 weeks in doses of more than 300 mg/day significantly decreases fasting and post-prandial glucose, glycated hemoglobin (231). In addition, in a Korean study involving 4186 individuals, the consumption of flavonols and flavones was directly associated with insulin sensitivity among male subjects (232). In a very recent randomized, double-blind, placebo-controlled trial it was shown that a plant-based polyphenol-rich extract lowered fasting blood glucose in participants with impaired fasting glycaemia and glucose intolerance. The extract also showed very good safety profile as well as tolerability among the participants (233). Also recently reported is that several polyphenols such as resveratrol, epigallocatechin-3-gallate (EGCG) and quercetin enhance glucose uptake in the muscles and adipocytes by translocating GLUT4 to plasma membrane mainly by the activation of the AMP-activated protein kinase (AMPK) pathway (234). According to all these studies, it could be stated that current evidence indicates the benefits of polyphenol enriched diets, particularly with flavonoids, on insulin sensitivity and postprandial glucose level, that could translate to a significantly reduced risk to develop T2D. We can't and shouldn't overlook all the latest evidence that show beneficial impact that a polyphenol rich diet can have in preventing and managing T2D.

2.7.) ETIOLOGY OF T2D

In medicine, the etiology of an illness or condition refers to the frequent studies to determine one or more factors that are responsible to cause the illness. As already known there are several factors that contribute to the pathology of T2D.

Not only the individual has a genetic predisposition to develop the T2D, the life style (diet and physical activity) will play a major role as well. The environment will play its own role to the mixture. Therefore it is pretty clear that the etiology of T2D is extremely complex.

Data from the Swedish randomized study of gastric banding showed that a loss of 20% body weight was associated with long-term remission in 73% of a bariatric surgery group, with weight change itself being the principal determinant of glucose control (235). Dietary weight loss of 15 kg allowed for reversal of diabetes in a small group of individuals recently receiving a diagnosis (236). In individuals strongly motivated to regain normal health, substantial weight loss is entirely possible by decreasing food consumption (237).
The role of physical activity must be considered. Increased levels of daily activity bring about decreases in liver fat stores (238), and a single bout of exercise substantially decreases both de novo lipogenesis (239) and plasma VLDL (240). Several studies demonstrated that calorie control combined with exercise is much more successful than calorie restriction alone (241). However, exercise programs alone produce no weight loss for overweight middle-aged people (242). The necessary initial major loss of body weight demands a substantial reduction in energy intake. After weight loss, steady weight is most effectively achieved by a combination of dietary restriction and physical activity. Both aerobic and resistance exercise are effective (243). The critical factor is sustainability.

3.) CONTENT

3.1.) GENETICS AND T2D

3.1.1.) EPIGENETICS WITH CONNECTION TO POLYPHENOLS OF OUR INTEREST

Especially interesting in the research field of T2D and genetics is the area of epigenetics. Lates studies show promising and intriguing results. In a recent study they focused on epigenetics in diabetic cardiomyopathy. They evaluated possible benefits and therapeutic potential of flavonoids. Previous studies have demonstrated that epigenetic tools can be considered biomarkers for disease prevention, diagnosis, and therapy, but the relationship between epigenetics and disease is complicated and requires further research and analysis in the future (244, 245, 246, 247). The pathogenesis of diabetic cardiomyopathy is complex, but hyperglycemia and impaired insulin signaling pathways have been implicated as important drivers of myocardial injury. Recent studies show that increased glucose levels probably serve a key function in the epigenetic regulation of many genes, thereby regulating their expression, and thus epigenetic changes may provide a biological explanation for the complexity of diabetic cardiomyopathy (248). DNA methylation is a primary epigenetic mechanism that controls mammalian cell differentiation and transcriptional potential. It refers to the conversion of cytosine to 5-methylcytosine (5MC) by the effect of DNA methyltransferases (DNMTs). Under normal conditions, gene expression can maintain the integrity of the genome by blocking the recruitment of transcription factors or promoting transcription silencing (40). DNA methylation is a dynamic and reversible process, and 10–11-translocator protein 1 could convert 5mc to 5-hydroxymethylcytosine (5-hmc), leading to DNA demethylation that usually activates transcription in contrast to methylation. DNA methylation is influenced by a variety of factors, including environment, aging, and diet. Genome-wide findings suggest that aberrant DNA methylation is involved in signaling pathways related to insulin pro- duction and secretion, increases age-dependent insulin resistance, alters gene expression in diabetic patients, and leads to increased susceptibility to diabetes (248). Another mechanism that affects the gene expression on epigenetic level is histone modification. Histone modification is defined as the methylation, acetylation, phosphorylation, ubiquitination and ADP-ribosylation of specific amino acid residues in histones by the effect of specific enzymes, which affect the transcriptional activity of the genes involved (249). Factors such as the site, type, and extent of histone modifications determine the complexity of histone coding. There are other mechanisms that affect genes through epigenetics, such as non-coding RNAs. Non-coding RNAs mainly include small non-coding RNAs, such as microRNAs, and long non-coding RNAs (lncRNAs), which affect gene expression by regulating protein biosynthesis mechanisms at the post-transcriptional and translational levels (250). Chromatin remodeling is another mechanism that affects the genes. Chromatin remodeling is divided into two categories, namely post-translational modifications (PTMs) of histones and ATP-dependent chromatin remodeling. Chromatin remodeling requires the involvement of multiple regulatory factors at the same time (251). In vitro and in vivo studies have confirmed that flavonoids modify epigenetic networks at multiple levels, mainly including DNA methylation, histone modification, non-coding RNA, and chromatin remodeling, resulting in beneficial effects on human health (248).

3.1.1.1.) QUERCETIN

It was demonstrated that quercetin can inhibit obesity and insulin resistance in C57BL/6 J mice due to the high-fat diet by reducing hypermethylation at the − 260nt site of the PGC-1α promoter, increasing peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) expression and mitochondrial number, and improving mitochondrial function and fatty acid β-oxidation (252). In addition, quercetin has dual inhibitory effects on histone acetyltransferases (HAT) and histone acetyltransferases (HDAC), induced histone modifications and chromatin remodeling in the 5' regulatory regions of c/EBPa and PPARγ, reduced the expression of these two major lipogenic genes, inhibited adipogenesis in 3T3-L1 preadipocytes or insulin resistance in rats on a high-fat diet, thus attenuated heart weight, and ameliorated cardiac hypertrophy and cardiac dysfunction (253). The chemical structure of quercetin contains a large number of hydroxyl groups, which can effectively scavenge superoxide anions produced by mitochondria. In addition, quercetin can improve the bioavailability of nitric oxide and reduce the production of mitochondrial superoxide. Thus, quercetin has antioxidant properties and can interact with cellular signaling pathways to regulate gene expression and miRNA levels, affect transcription factor activity, control (streptozotocin) STZ-induced oxidative stress, inflammation, apoptosis, and subsequent cardiac remodeling in rat cardiomyocytes, and improve diabetic cardiomyopathy (254, 255, 256).

Insulin resistance is one of the main factors responsible for the onset and progression of diseases such as obesity, diabetes, and atherosclerosis. Insulin resistance is involved in impairment of the phosphatidylinositol 3-kinase (PI3K)/ Akt pathway in target organs such as adipose tissue and skeletal muscle, leading to the downregulation of GLUT-4 expression and its translocation (257). Insulin resistance is closely associated with chronic low-grade inflammation through interactions with the insulin signaling pathway in the liver and adipose tissue (258, 259). For instance, elevated levels of proinflammatory cytokines such as TNF-α, MCP-1, and IL-6, and of proinflammatory enzymes such as cyclooxygenases (COXs) and inducible nitric oxide synthase (iNOS) in adipose tissue, skeletal muscle, and neuronal systems, have been demonstrated to lead to the development of insulin resistance (260, 261). In particular, TNF-α is one of the most important pro- inflammatory mediators which is involved in the development of insulin resistance (262). There is data demonstrating the anti-inflammatory effects of quercetin on proinflammatory cytokine production, in macrophages and adipocytes. Quercetin decreases the expression levels of the inflammatory genes TNF-α, IL-6, IL-1β, and COX-2, suppressing the activation of nuclear factor (NF-κB) and c-Jun N-terminal kinase (JNK) (263). Dietary quercetin attenuates adipose tissue expansion and decreases the levels of serum IL-6 and MCP-1 mRNA in white adipose tissue in high fat diet (HFD)-induced obese mice (264). In the hypothalamus, quercetin reduces the mRNA expression levels of TNF-α, MCP-1, and IL-1β in HFD-fed obese mice (265). Moreover, dietary quercetin and the combination of quercetin and catechin reduce metabolic parameters such as insulin concentrations and insulin resistance (HOMA-IR), and also levels of adipocytokine proteins such as TNF-α, visfatin, and resistin in adipose tissue in HFD-fed mice (266). Quercetin supplementation reduced the increases in DNA methylation and PGC-1α expression, (257) suggesting that quercetin may regulate peroxisome proliferator activated-receptor gamma coactivator 1 alpha (PGC-1α) expression through DNA methylation in obesity. Moreover, the treatment of quercetin inhibited inflammation in livers of nickel-treated mice by modulating nuclear factor-E2 related factor 2 (Nrf2) nuclear translocation and HO-1 activity and decreased DNA methyltransferases

(DNMTs) activity and DNA methylation level of the Nrf2 DNA (267). Therefore, quercetin may epigenetically regulate the obesity and inflammation.

3.1.1.2.) RESVERATROL

Resveratrol was described as a protective agent against several metabolic diseases and disorders mainly through the activation of sirtuin-1 (SIRT1) and thereby regulating a number of important genes involved in cellular metabolic control (268). Resveratrol improved mitochondrial function in mice, as indicated by increased running time and greater oxygen consumption by muscle fibers. This beneficial effect was associated with the activation of the protein deacetylase, SIRT1, which induced peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) activity by deacetylating multiple lysine sites. PGC-1α is a cofactor that plays an important role in mitochondrial biogenesis and functions. Importantly, this increase in mitochondrial activity was not observed when SIRT1 expression was disrupted (269). Other studies reported that the activation of SIRT1 by resveratrol led to a reduction in acetylated farnesoid-X receptor (FXR) levels in a mouse model of metabolic diseases, thereby leading to its activation. FXR plays a critical role in the regulation of lipid and glucose metabolism, and the disruption of its genes is associated with metabolic diseases, including diabetes and hypercholesterolemia (270). Resveratrol was also reported to have an inhibitory effect against high glucose-induced metabolic memory (beneficial effects of immediate intensive treatment of hyperglycemia and the observation that they are maintained for many years, regardless of glycemia in the later course of diabetes) of endothelial senescence. It was demonstrated, using human umbilical vascular endothelial cells cultured in high glucose media, that resveratrol can activate SIRT1 and then modulate its downstream pathways, including p300, p53 and p21 (271).

In several studies on diabetes it was reported about resveratrol induction of SIRT1. Yun and his colleagues reported that resveratrol was able to reduce superoxide production and cellular oxidative stress in human monocytic (THP-1) cells cultured in hyperglycemic conditions by upregulating SIRT1. This beneficial effect was not observed when SIRT1 was inhibited using small interfering RNA (siRNA) (272). In another study, similarly, it was shown that resveratrol can activate SIRT1 and protect rat mesangial cells cultured in high glucose medium from hyperglycemia-induced oxidative damage to the mitochondria. The levels of reactive oxygen species (ROS) and mitochondrial superoxide were decreased after a treatment with resveratrol. Furthermore, these authors observed that resveratrol-induced ATP production and preserved mitochondrial DNA content, and SIRT1 blockade led to the loss of these beneficial effects (273). In an obese and diabetic mouse model, resveratrol was able to normalize hyperglycemia and improve hyperinsulinemia after long-term intracerebroventricular infusion of resveratrol (79.2 ng/day). The authors hypothesized that the antidiabetic effect of resveratrol could be related to SIRT1 expression in the central nervous system (CNS). Indeed, acetylated lysine 379 levels in p53 in the brain, used as an SIRT1 activity marker, were reduced in resveratrol-treated animals, compared to the untreated group (274). A recent study in Sprague–Dawley rats fed on a high-fructose diet and treated with resveratrol showed recovery of hyper-anxiety induced by the metabolic syndrome. These authors suggested that resveratrol was able to protect from both metabolic and anxiety disorders by activating SIRT1, 6 and 7, as high levels of mRNA of these enzymes were observed in the striatum of the animals (275).
Resveratrol also has an important role in modulating insulin secretion by activating SIRT1. Data from multiple studies shows its beneficial effects in reversing insulin resistance in vivo.

Vetterli and his colleagues showed that resveratrol was able to trigger glucose-stimulated insulin secretion in both INS-1E cells (insulin secreting beta cell) and human islets. The activation of SIRT1 is thought to be the main target of resveratrol, as the overexpression of SIRT1 facilitates resveratrol effects on insulin secretion and conversely, SIRT1 inhibition leads to the loss of these benefits. resveratrol also helps increase the glycolytic flux that results in increased glucose oxidation, ATP generation and mitochondrial oxygen consumption (276). In another study, they demonstrated that resveratrol at a dose of 2.5 mg/kg/day was able to increase SIRT1 levels in mice fed a high-fat diet, which led to an improvement in insulin sensitivity. This enhancement in insulin sensitivity was associated with an increase in the deacetylase activity of SIRT1, which was required for the repression of the protein tyrosine phosphatase 1B (PTP1B) transcription at the chromatin level. PTP1B is a negative regulator of the insulin signaling pathway (277). Resveratrol was administered to rhesus monkeys in a two-year regimen (80 mg/day in the first year and 480 mg/day in the second year). The outcome observed was an increase in SIRT1 expression and an improvement in insulin sensitivity in visceral white adipose tissue. At the same time, NF-κB activity and adipocyte size were reduced. This beneficial effect was also confirmed in cultured 3T3-L1 adipocytes, wherein SIRT1 protein levels increased and NF-κB phosphorylation decreased (278). In another study report that treatment with 10 μMol/L of resveratrol for 24 h resulted in a significant increase in insulin secretion from the β-cells islets isolated from the rats fed on a high-fat diet. This effect was associated with the activation of SIRT1 by resveratrol, after the inhibition or knockdown of SIRT1 suppressed insulin transcription (279).

Resveratrol also has a positive impact on the diabetic nephropathy by activating SIRT1. It slows down the progression of the diabetic nephropathy as it was shown in the diabetic Sprague–Dawley rats who received long term resveratrol treatment. The results showed increased mRNA content and protein expression of SIRT1 in the kidneys. This expression had a positive effect on diabetic nephropathy and was associated with enhanced autophagy in the kidneys related to the upregulation of autophagic proteins such as Atg7, Atg5 and LC3. Additionally, SIRT1 activation was responsible for hypoxia-induced autophagy mediated by hypoxia-inducible factor-1a (Hif1a). Hif1a overexpression led to the upregulation of the pro-autophagic Bcl2/adenovirus E1 V 19-kDa interacting protein 3 (Bnip3) that plays an important role in the induction of autophagy, which is a process responsible for removing protein aggregates and damaged or excess organelles to maintain intracellular homeostasis and cellular integrity (280). There are other studies that describe the same beneficial effect of resveratrol on diabetic nephropathy, induced via the same mechanisms. In a type-1 diabetic rat model, the activation of SIRT1 by resveratrol led to the modulation of kidney angiogenesis, mainly by suppressing vascular endothelial growth factor (VEGF) expression and secretion. It is worth mentioning that SIRT1 knockdown led to the mitigation of resveratrol's effects (281). In another work, the same group of researchers demonstrated that resveratrol was able to increase forkhead transcription factor O1 (FoxO1) activity mediated by SIRT1 activation in diabetic rat kidneys. The transcription factor FoxO1 plays a crucial role in cell metabolism, aging and oxidative stress resistance, and its upregulation has been associated with cellular protection against oxidative stress. In consequence, the authors suggested that the improvement in diabetic nephropathy mediated by resveratrol may be related to increased expression of FoXO1 (282), if oxidative stress is implicated in the pathogenesis of diabetic nephropathy (283, 284). Similar beneficial effects were shown in another study, where resveratrol had positive impact in ameliorating diabetic nephropathy in diabetic rats through the activation of SIRT1 and at the same time reduction in oxidative stress levels (285).

Many studies imply that the activation of SIRT1 by resveratrol is linked to the modulation of lipid metabolism. A study on hepatocyte lipid metabolism reported that resveratrol was able to increase AMP-activated protein kinase (AMPK) activity by activating SIRT1, which in turn led to a reduction in its downstream targets, such as ACC (acetyl-CoA carboxylase), FAS (fatty acid synthase) expression and lipid accumulation in human HepG2 hepatocytes exposed to high glucose (286) In a study on fat mobilization in white adipocytes the researchers were able to demonstrate that the treatment of 3T3-L1 adipocytes with 50 or 100 μM resveratrol reduced their fat content mainly by lowering triglycerides and stimulating free fatty acid release. Once more, SIRT1 activation has been suggested to be the main mechanism, because in turn its knockdown led to a suppression of the observed beneficial effects (287). Resveratrol was also able to increase oxidized low-density lipoprotein (Ox-LDL) degradation and clearance through the autophagy-lysosome pathway in human umbilical vein endothelial cells. This effect was associated with SIRT1 activation that then led to an increase in cathepsin D protein levels, a lysosomal proteinase that is most important for LDL degradation (288).

Mitochondrial disorders, such as increased production of ROS, are frequently observed in diabetes and are involved in the disruption of cellular energy balance, activation of inflammatory processes and endothelial dysfunction (289). A study reported that resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells exposed to high glucose to mimic diabetic conditions by reducing mitochondrial reactive oxygen species (ROS) production. This effect was also associated with the activation of SIRT1, and while its knockdown led to the suppression of beneficial effects, its overexpression mimicked the beneficial effects mediated by resveratrol (290). A study reported that resveratrol induced mitochondrial biogenesis in cultured human coronary arterial endothelial cells by enhancing mitochondrial mass and mitochondrial DNA content, overexpressing proteins of the electron transport chain and inducing mitochondrial biogenesis factors, such as PGC-1α, nuclear respiratory factor-1 (NRF1) and mitochondrial transcription factor A (mtTFA). The knock-down of SIRT1 by small interfering RNA suppressed these effects. Additionally, T2D mice subjected to chronic treatment with resveratrol also showed an increase in the mitochondrial biogenesis in the aorta (291). Another study demonstrated that SIRT1 activation by resveratrol resulted in the suppression of the transcription factor STAT3 signaling pathway, leading to the reduced proliferation of HepG2 (human liver cancer cell line) cells exposed to high glucose (292). This finding is especially interesting for development of new drug candidates in the treatment of hepatocellular carcinoma, as the risk of developing this disease is greater in diabetics than non-diabetics (293). Forkhead proteins (FOX) are a family of transcription factors that exert regulatory activity over the expression of genes involved in many cellular processes, including cell growth, proliferation, differentiation and longevity (RF). A study reported that the activation of SIRT1 by resveratrol resulted in the nuclear translocation of FOXO1 in hepatocytes, promoted transcription of key genes involved in hepatic glucose production and, enhanced glucose release from the cultured hepatoma cells (294). Although these results showed positive outcome, more research is needed to be able to confirm the observed effect.

Table: Some studies that observed the anti-inflammatory impact resveratrol has and its connection to epigenetics in different diseases are shown in the table below (Table source 295).

Type of polyphenol	Dose/Concentration	Study model	Epigenetic signatures	Reference
Grape extract resveratrol	8 mg	PBMCs* from T2D and hypertensive patients	miR-21, miR-181b, miR-663 and miR-30c2 expressions	a.)
Resveratrol	10 μM	LPS-stimulated RAW 264.7 macrophages	miR-146a expression	b.)
Resveratrol	1 g/kg	SAMP8 mice offspring	Nrf2 and Nfkb methylation levels	c.)
Resveratrol	10 μM	ARPE-19 cells exposed to GOx and LPS	DNMT and SIRT1 expressions	d.)
Trans-resveratrol	50 mg/kg	Postnatal rats exposed to perinatal asphyxia	miR132 and miR15a expressions	e.)

*PBMCs: peripheral blood mononuclear cells

Reference for the table content: a.) 296; b.) 297; c.) 298; d.) 299; e.) 300

3.1.1.3.) QUERCITRIN

A recent study on intervening effects and molecular mechanism of quercitrin on porcine circovirus type 2 (PCV2)-induced histone acetylation, oxidative stress and inflammatory response in 3D4/2 cells has reported very interesting results. Quercitrin weakened the phosphorylated expression levels of NF-κBp65, p38MAPK and protein kinase B (AKT) proteins; upregulated the protein expression levels of NQO1 (NAD(P)H quinone dehydrogenase 1) and Heme oxygenase-1 (HO-1); downregulated the protein expression levels of interleukin 8 (IL-8) and inducible nitric oxide synthase (iNOS) in PCV2-infected 3D4/2 cells. It suggested that quercitrin might promote the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway by inhibiting the phosphorylated expression of p38MAPK and AKT proteins. Moreover, quercitrin further inhibited the activation of the NF-κB signaling pathway and suppressed the phosphorylation and degradation of IκBα in PCV2-infected 3D4/2 cells (301).

Another recent study examined protective properties that quercetin and quercitrin have on cytokine- induced injuries in RINm5F β- cells via the mitochondrial pathway and NF- κB signaling. They investigated the role of quercetin/quercitrin in cytokine-induced β-cell injuries in RINm5F rat insulinoma cells. In the present study, they found that quercetin/quercitrin improved the cytokine-induced impairment of viability and insulin secretion in RINm5F cells. They suggest that quercetin/ quercitrin protect β-cells by mediating ROS accumulation, iNOS expression, NF-κB pathway and mitochondria cytochrome c signaling. In the same study they investigated the aglycone and rhamnose glucoside form of quercetin. As a glycosylated form of quercetin, quercitrin contains a rhamnose at C3. Due to its additional radical and high bioavailability in the digestive tract, quercitrin was considered to be a more potent antioxidant and neuroprotective agent compared to quercetin (15,16,37). In this study they confirmed that quercetin possessed even stronger protective effects on RINm5F β-cells (302). This outcome is

in accordance with other published data (303, 304) and it therefore seems that quercetin may be more efficacious than quercitrin as an anti-diabetic agent.

3.1.1.4.) NORDIHYDROGUAIARETIC ACID (NDGA)

Not many data is available that describes and researches the epigenetic applications of NDGA in connection to T2D nor metabolic diseases. There are several studies that describe the effect NDGA has on p300. While deficiency or deregulation of Ep300 gene is associated with defective cardiogenesis, p300 abnormality in adults is associated with cardiac disease development (305). In a recent study the researchers demonstrated that NDGA effectively inhibits p300 histone acetyltransferase activity in vitro, and it directly binds the p300 histone acetyltransferase (HAT) domain which alters several epigenetic marks associated with aging in human, mouse, and fruit fly cells. Notably, while they identified p300 as a target of NDGA, the possibility that it blocks the activity of other acetyltransferases cannot be excluded (306). In order to be able to confirm the mechanisms and possible other effects the NDGA has on epigenetics in T2D, more research is needed.

3.1.1.5.) OTHER POLYPHENOLS FOUND IN FOOD

Studies have revealed that the protective effects of polyphenols on inflammation are partially modulated via epigenetic modifications, thus contributing to the current understanding of the molecular mechanisms of action of these biologically active compounds (Table source- 307).

Table: Studies analyzing the anti-inflammatory effects of dietary polyphenols via epigenetic regulation in several chronic inflammatory conditions.

Type of polyphenol	Dose/Concentration	Study model	Epigenetic signatures	Reference
Mango (*Mangifera Indica L.)* polyphenols	10 mg/L	Rats exposed to dextran sodium sulfate (DSS)	miR-126 expression	f.)
Mango (*Mangifera Indica L.)* polyphenols	10 mg/L	LPS-treated CCD-18Co cells	miR-126 expression	f.)
Oleocanthal and oleacein	25 μM/L	Adipocytes	miR-155-5p, miR-34a-5p and let-7c-5p	g.)
Hydroxytyrosol	10 μM/L	Adipocytes	miR-155-5p, miR-34a-5p	h.)
Polyphenol-rich green tea	500 mg/kg body weight	White adipose tissue	miR-335	i.)
Apigenin	10 mg/kg	C57BL/6 J mice	let-7f	j.)
(-)-Epicatechin	5 μM	THP-1 cells exposed to high glucose	H3K9 acetylation and H3K4 dimethylation	k.)
Polyphenol-rich lingonberries (Vaccinium vitis-idaea)	20 *% w/w*	High-fat fed C57BL/6 J mouse	Ncor2 methylation	l.)
Luteolin	10 μM	THP-1 cells exposed to high glucose	HAT activity	m.)

Gallic acid	25 μM	THP-1 cells exposed to high glucose	HAT activity HDAC2 expression	n.)
Fisetin	10 μM	THP-1 cells exposed to high glucose	HAT activity	o.)
Red raspberry polyphenols	10 $\mu g/ml^{-1}$	J774 macrophages	H3K27Ac expression	p.)
Epigallocatechin gallat	20 μM	Regulatory T-cells	HDAC activity	r.)

Reference for the table content: f.) 308; g.) 309; h.) 310; i.) 311; j.) 312.; k.) 313; l.) 314; m.) 315; n.) 316; o.) 317; p.) 318; r.) 319

The administration of (−)-epicatechin attenuated the high-glucose-induced inflammatory response in human monocytes by epigenetic modulation of H3K9 acetylation and H3K4 dimethylation (313), notably the combination of luteolin- and fisetin-induced anti-inflammatory effects in human monocytic cells under high-glucose concentrations involving histone acetyltransferase/histone deacetylase modifications (320). In a similar high-glucose condition, curcumin decreased the production of pro-inflammatory cytokines by inhibiting histone acetylation in monocytes (321). In addition to polyphenols, the anti-inflammatory role of other dietary factors and specific functional foods has also been assessed in different experimental models. In this regard, extra virgin olive oil (EVOO) and Nigella sativa oil displayed anti-inflammatory activities in lipopolysaccharide (LPS)-exposed human macrophages through epigenetic mechanisms (322). In this study, the administration of both oils reverted the altered expressions of DNA-methyltransferase 3A enzyme (DNMT3A) and histone deacetylase 1 enzyme (HDAC1) to normal levels under inflammatory conditions, with an additional role of EVOO in the reduction of global methylation. Also, a nutritional intervention with Mediterranean diet plus EVOO influenced the methylation status of genes involved in inflammatory pathways in PBMCs (323). Similarly, higher adherence to Mediterranean diet was positively associated with the methylation of a set of genes related to inflammation and immunocompetence in high cardiovascular risk volunteers (324.).
Increasing research has provided evidence about the long-lasting epigenetic effects of calorie restriction which mediates expression of genes related to immuno-metabolic processes that may enhance quality of life and extend lifespan, with important applications for the prevention of chronic inflammatory diseases, among which is also T2D (325, 326).

3.2.) GENES AND GUT MICROBIOME

We will touch-base on this topic because the gut microbiome plays an important role in metabolism of nutrients (in our case of interest – polyphenols) and has been linked to metabolic disease and obesity (327). Host genetics are known to influence the gut microbiome, yet their role is still poorly understood. The relationship between the host and the gut microbiome starts at birth when the microbiome of the newborn is seeded. Delivery mode (cesarean section or vaginal delivery) plays an important role in the establishment of the microbiome (328, 329, 330). Proper nutrition and the transition from breast feeding to more solid foods results in maturation of the infant microbiome (331). Genome-wide association studies (GWAS) of the gut microbiota provide evidence that gene expression likely influences the abundance of certain bacteria in the gut (332, 333, 334, 335 , 336, 337). In particular, taxa such as Christensenellaceae, Akkermansia, and Bifidobacterium are either heritable or associated with

genetic variation in the human genome. As it is expected that an individual's genome sequence will not change in the presence of the microbiome, these studies demonstrate that host genetics, likely via gene regulation, modulates aspects of the gut microbiome (338).
In a very recent Dutch wide-range study, the researchers have performed a genome-wide association study (GWAS) of 207 taxa and 205 pathways representing microbial composition and function in 7,738 participants of the Dutch Microbiome Project. Two robust, study-wide significant ($P < 1.89 \times 10-10$) signals near the LCT and ABO genes were found to be associated with multiple microbial taxa and pathways and were replicated in two independent cohorts. The LCT locus associations seemed modulated by lactose intake, whereas those at ABO could be explained by participant secretor status determined by their FUT2 genotype. Twenty-two other loci showed suggestive evidence ($P < 5 \times 10-8$) of association with microbial taxa and pathways (339). This area of research is currently quite new and therefore requires more research being done, to be able to determine the exact genes that play a role in specific microbiome and group of bacteria. Nevertheless we can state that based on current data available, there is connection between the human genome and ones microbiome.

3.3.) POLYPHENOLS AND INHIBITION OF ALPHA-GLUCOSIDASE

Postprandial hyperglycemia is a state that strongly contributes to the T2D development as well as worsens the T2D progress. Polyphenol compounds were shown to inhibit the α-glucosidase enzyme in the gastro intestinal tract. This action leads to lower blood-glucose levels after a meal. It is a very important prevention and control step for the patients that suffer from T2D.
Four polyphenolic compounds will be exposed in the following text. At the end we will also look at the latest data available on other polyphenolic compounds and the α-glucosidase inhibition.

3.3.1.) QUERCETIN

There is a lot of data showing the inhibition properties of quercetin on α-glucosidase enzyme. Flavonol glycosides will be hydrolyzed into their respective aglycones in lumen of the small intestine before absorption (340). In a recent study on quercetin present in the banana plant, the researchers showed that not only the quercetin is acting as an α-glucose inhibitor, but it had favorable pharmacological properties in comparison to acarbose (341). In another recent study quercetin exhibited significant inhibition effects against a-glucosidase in a dose-dependent manner. At the concentration of 125 μmol L^{-1} quercetin caused approximately 75% inhibition of the activity of a-glucosidase. Quercetin inhibitory activity took place on the $3^{'}$,$4^{'}$ -OH on the B-ring. This study also indicated that increased number of OH- groups on the B-ring enhanced inhibitory activity on a-glucosidase. Main residues involved in the interaction between quercetin and a-glucosidase were Asp215, His 280, Phe 303, Asp 307, Asp 352 and Arg 442 (342). A study from 2015 revealed that glycosylation increased the inhibitory ability of quercetin on the a-glucosidase enzyme (343).

Oxidative stress may contribute to the incidence of oxidative related complications in diabetes (344). Long term hyperglycemia may induce increased production of reactive oxygen species (ROS) via non-enzymatic glucose autoxidation, glycation, and alterations in polyol pathway activity (345). Quercetin showed strong anti-oxidative properties. The results of the study reported that quercetin is a strong radical scavenger. It expressed higher antioxidant capacity

than its flavonoids derivatives (rutin, naringerin,..) (346). It was reported that the presence of multiple hydroxyl groups of flavonoid act as vigorous scavengers not only for ROS but also for reactive nitrogen species (RNS) (347). Presence of the hydroxyl groups govern the capability of flavonoids as antioxidant (348).

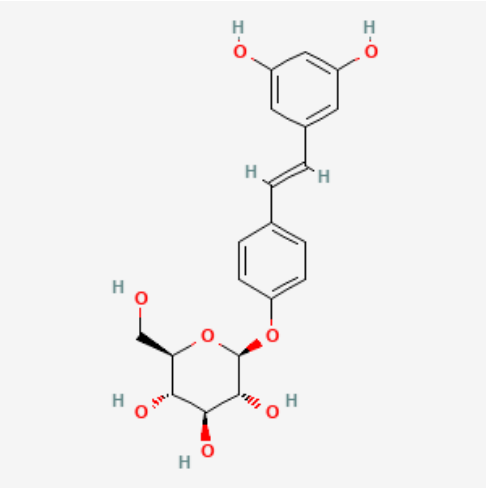
A recent study from 2020, where the researchers were evaluating the antioxidant, α-glucosidase inhibition and cell protective effects of the ethanolic extract from the green cocoon shell of silkworm, has shown promising results. The content of quercetin in the ethanolic extract from the green cocoon silkworm was 25.66 ± 0.07 mg/g. Quercetin was also present in glycosylated form. The extract presented very good inhibitory properties on the α-glucosidase enzyme. In the same study antioxidant properties and cell protective properties were confirmed in connection to chronic high blood-glucose levels in T2D cells. All these outcomes are of a very big value for the T2D patients as it can help treat and ameliorate the disease (349). In another recent study where flavonoids from the plant Bauhinia pulla were extracted and their α-glucosidase inhibitory activity was evaluated, the intended effect was given by OH group number and position as the determinant factor. Quercetin was the most active because it has hydroxylation at a critical position for the alpha-glucosidase inhibition of flavonoids which are 5, 7, or 8-positions of ring A; at 3' and 4'-positions of ring B; and 3-position of ring C, as well as the double bond of C2=C3 in ring C. This explanation showed the relationship between the structure configuration with the inhibitory activity of quercetin. It performed a strong inhibitory effect 22.9-fold lower than the acarbose (350).

3.3.2.) RESVERATROL

Resveratrol showed strong inhibition of mammalian and yeast α-glucosidase activity. Compared to acarbose the inhibition rate was a bit lower. In the same study they investigated the effect of resveratrol on postprandial blood glucose response in high-fat-fed C57Bl/6 mice. Animals administered resveratrol (30 mg/kg body weight [BW]) 60 min prior to sucrose or starch loading had a delayed absorption of carbohydrates, resulting in significant lowering of postprandial blood glucose concentrations, similar to the antidiabetic drug acarbose. No significant effect was observed with the glucose-loaded animals (control group) (351).

Resveratroloside (Photo below 352) is a mono-glucosylated form of stilbene that is present in red wine, grapes, and several traditional medicinal plants. In a recent study, the effect of resveratroloside on reducing post-prandial blood glucose was studied in vitro and in vivo. In comparison to the starch treatment alone, the oral administration of resveratroloside–starch complexes significantly inhibited the postprandial blood glucose increase in a dose-dependent pattern in normal and diabetic mice. The postprandial blood glucose level treated with resveratrol (30 mg/kg) was not lower than that of resveratroloside. Further analyses demonstrated that resveratroloside strongly and effectively inhibited α-glucosidase, with an 50% inhibitory concentration value of 22.9 ± 0.17 μM, and its inhibition was significantly stronger than those of acarbose and resveratrol (264 ± 3.27 and 108 ± 2.13 μM). Moreover, a competitive inhibition mechanism of resveratroloside on α-glucosidase was determined by enzyme kinetic assays and molecular docking experiments. The molecular docking of resveratroloside with α-glucosidase demonstrated the competitive inhibitory effect of resveratroloside, which occupies the catalytic site and forms strong hydrogen bonds with the residues of α-glucosidase. Resveratrol was also determined to have a competitive inhibition

mechanism on α-glucosidase by enzyme kinetic assays and molecular docking experiments (353).



Resveratroloside

In a study where resveratrol was derived from the mulberry plant (Morus, Moraceae) the researchers confirmed stronger α-glucosidase inhibition in comparison to acarbose. Resveratrol obtained non-competitive type of inhibition, which was determined using the Lineweaver–Burk plots of the inhibition kinetics. The interactions between ligands and α-glucosidase were mainly driven by hydrophobic force, or hydrogen bonding consequently induced conformational changes and reduced surface hydrophobicity. Docking results suggested that they could bind to α-glucosidase at different sites (372). Antioxidant and α-glucosidase inhibitory potential of resveratrol isolated from Rumex bucephalophorus have been reported, which revealed that resveratrol was at least five times more potent α-glucosidase inhibitory activity as compared to standard drug acarbose (354). A study on peanut extracts correlated the resveratrol content with the α-amylase and α-glucosidase inhibitory activity. The EtOAc extracts of peanuts with higher resveratrol content (3 μg/ml) showed higher α-amylase and α-glucosidase inhibitory activity (4.32 and 5.93%, respectively) as compared to MeOH extract (3.9 and 4.9%) with resveratrol content of (0.5 μg/ml). The standard resveratrol sample showed α-amylase and α-glucosidase inhibitory activity (5.18 and 5.94%) (355).

Studies reveal that inhibitory activity is influenced by a number of hydroxyl groups and their positions, methylation, methoxylation and glycosylation. Broadly, it is considered that hydroxylation of phenols increases the α-amylase inhibitory activity and methoxylation, which blocks the free hydroxyl groups and reduces the inhibitory activity (356). The activity of α-glucosidase is increased by more phenolic substitutions (357). In another very recent study the researchers did a biological investigation on therapeutic effect resveratrol has when the nano particles are encapsuled with chitosan. The study was looking at the gestational diabetes mellitus rats induced by streptozotocin. The highest inhibitory activity (73%) against the α-glucosidase enzyme was recorded at 500 lg/mL of CS–ZnO–Resveratrol (RS). The activity of CS–ZnO–RS was compared to the standard antidiabetic drug acarbose (which was used as a positive control), which exhibited the maximum a-glucosidase inhibitory activity of 88% (358). In a study from 2019 the researchers focused on anti-obesity effects of resveratrol. Similarly it was shown that resveratrol dose-dependently inhibited α-glucosidase catalytic activity at much

lower doses than the reference inhibitor acarbose. The IC_{50} values (concentration of inhibitor decreased by half the response measured) were 0.1 μM for resveratrol and 590 μM for acarbose, highlighting the dramatic difference between both compounds. However, in contrast with α-glucosidase assays, resveratrol was much less efficient than the reference inhibitor orlistat, which exhibited an IC_{50} value of 1.5 μM. Thus, it seems that maximal inhibition by resveratrol of lipase activity occurred only at millimolar doses of the polyphenol, which could be considered as supra-nutritional levels, while the α-glucosidase inhibition was more likely to be nutritionally relevant (359).

3.3.3.) QUERCITRIN

A study from 2021 extracted polyphenolic compounds from plant Bauhinia pulla. The researchers were investigating the α-glucosidase properties and characteristics of isolated polyphenols. Quercitrin was among the polyphenolic compounds present in the mentioned plant. In this assay quercitrin showed potential inhibitory activity stronger than acarbose (IC_{50} values can be observed in the table below). It is currently accepted that hydroxy group modification or elimination in flavonoids will reduce the α-glucosidase inhibitory effects of flavonoids (360). Therefore, quercitrin with rhamnose replacement on the 3-position of ring C and luteolin with hydroxy elimination on the 3-position of ring C had higher IC_{50} values than quercetin. Moreover, 5-deoxyluteolin with hydroxy elimination on the 5-position of ring A was 3.5-fold higher compared to luteolin. (361). A recent study from 2020 showed that quercitrin extracted from plant Houttuynia cordata inhibited the enzyme α-glucosidase in comparison to acarbose. This was also the first study to look in more details the docking mechanism of quercitrin and α-glucosidase. The fluorescence spectroscopy showed that quercitrin statically quenched the fluorescence of α-glucosidase. Circular dichroism and molecular docking analyses indicated that quercitrin changed the alpha-helix structure of α-glucosidase and bound with the key amino acids through hydrophobic interactions, hydrogen bonds and salt bridge interaction (362). There are other recent studies that confirm the α-glucosidase inhibitory properties of quercitrin. A group of researchers extracted quercitrin from Cerasus humilis leaf (tea). Similar to other studies they were also able to confirm the inhibitory activity of quercitrin (363).

There is more data available for quercetin in comparison to quercitrin. Like mentioned before quercitrin is basically a molecule of quercetin with binned sugar molecule. This makes a molecule of quercitrin bigger than quercetin. It was shown that quercetin as aglycone form has more favorable α-glucosidase inhibitory effects (364).

3.3.4.) NORDIHYDROGUAIARETIC ACID (NDGA)

A study from 2016 evaluated the inhibitory effects of NDGA against three different enzymes, involved in the progress of T2D. One of them was α-glucosidase. They have observed high inhibitory activity of NDGA against the α-glucosidase enzyme (365).
The biological activity of NDGA was assessed through in vitro and in vivo studies where NDGA was effective in treating various diseases, among which also diabetes and obesity (366, 367, 368). There is not much recent data available for NDGA and its α-glucosidase inhibitory activity. This is therefore an attractive area that needs more current studies.

NDGA has been utilized in traditional healing practices for many years in a wide range of remedies, but at present, it application in clinical settings is limited due to reported toxicity in isolated cases. Based on current data available we observe that chemical modification of this compound reduces toxicity, combined with the enhanced therapeutic effects. This indicates that the derivatives of NDGA may become important drugs in the future (369).

Polyphenol/Inhibitor	Affinity[a] (kcal mol^{-1})	K_i[b] (μmol L^{-1}) or (mM)*	K_{is}[c] (μmol L^{-1})	IC_{50} [d](μg/mL)	Type of Inhibition
QUERCETIN [S]	-9.0	16.83 μmol L^{-1} and 0,49 mM[Y]	37.13	65.52 ± 2.88[T]	Mixed
RESVERATROL	/	/	/	16.73[X]	Non-Competitive[U]/ Mixed[X]
QUERCITRIN	/	0,034 mM[Y]	/	49.69[V]	Competitive [Z]
NDGA	/	1,25 mM[Y]	/	/	Non-Competitive[Y]
ACARBOSE [S]	-8.7	109.95 μmol L^{-1}	/	179.86[X]	Competitive

Table: Predicted affinity and kinetic analysis of α-glucosidase inhibition properties for each polyphenol compound and acarbose as a positive comparison. When data was not found - /
[a] Affinity is predicted by molecular docking in silico.
[b] K_i represents the dissociation constant for inhibitors binding to free enzyme.
[c] K_{is} represents the dissociation constant for inhibitors binding to enzyme–substrate complex.
[d] IC_{50} for α-glucosidase inhibition at the concentration of 25 μg/mL.
*When K_i is expressed in mM, it was measured with inhibitor concentration of 0,8 mM.

(S: 370; T: 371; U: 372; V: 373; Z: 374; X: 375; Y: 376)

3.3.5.) OTHER POLYPHENOLS

It is important to consider the bioavailability of polyphenols when discussing their effectiveness in the prevention of diseases (377). The pharmacokinetic and biopharmaceutical properties of polyphenols can cause a decrease in their clinical benefits as therapeutics. Affecting absorption, distribution, excretion and biotransformation, hyperglycemia disturbs the bioavailability of molecules (378). It was reported that nano-formulations have the potential for delivering natural antidiabetic drugs such as polyphenols. Different formulations are being studied to deliver these compounds to target sites (379). Nanoparticles ranging from 1 to 100 nm, such as liposomes, niosomes, protein-based nanoparticles, phospholipid complexes, micelles, metal nanoparticles and emulsions, are being developed, and bioavailability and controlled release of drugs can be accomplished (380).

Recent in-vitro an in-silico studies have shown promising results on polyphenolic compounds inhibiting the α-glucosidase enzyme. A group of researchers showed that polyphenols present in young apple are good inhibitors of α-glucosidase enzyme. Main polyphenols were tannic acid, (-)-epicatechin and phlorizin. Phlorizin showed competitive type of inhibition, while tannic acid and (-)-epicatechin showed mixed type. The results not only showed strong α-glucosidase inhibition but also suggested that binding interactions between polyphenols and α-

glucosidase causes the enzyme inhibition (381). Further recent studies show that the hydroxylation of flavonoids, the galloylation of catechins and the presence of caffeoyl moieties improves the inhibitory activity against α-glucosidase enzyme. Glycosylation of flavonoids, on the other side, caused a decrease in inhibitory activity against α-glucosidase (382). A study from 2017 aimed to evaluate the α-glucosidase inhibitory activity of 26 polyphenols using molecular docking and virtual screening studies. Among selected compounds caffeic acid, curcumin, cyanidin, daidzein, epicatechin, eridyctiol, ferulic acid, hesperetin, narenginin, pinoresinol, quercetin, resveratrol and syringic acid significantly inhibited the α-glucosidase enzyme (383). A group of researchers explored the antidiabetic potential of whole unripe jackfruit (peel with pulp, flake, and seed). Two polyphenols (phenolic acids) with strong antihyperglycemic activity were isolated from the methanol extract of whole jackfruit flower. After various physicochemical and spectroscopic investigations the bioactive compounds isolated were identified as 3-(3,4-Dihydroxyphenyl)-2-propenoic acid (caffeic acid) and 4-Hydroxy-3,5-dimethoxybenzoic acid (syringic acid). Caffeic acid (IC50: 8.0 and 26.90 µg/mL) and syringic acid (IC50: 7.5 and 25.25 µg/mL) were identified to inhibit α-glucosidase in a competitive manner with low Ki values (384).

A recent study offers a different perspective, where the researchers extracted free and bound polyphenols from the red quinoa. They investigated their inhibitory effects on α-glucosidase and postprandial glucose, as well as related mechanisms. The analysis showed that the components of free-polyphenols and bound-polyphenols were different. Free-polyphenols were mainly composed of hydroxybenzoic acid and its derivatives, while bound-polyphenols were mainly composed of ferulic acid and its derivatives. Bound-polyphenols had a lower IC_{50} (10.295 mg/mL) value in inhibiting α-glucosidase activity. The inhibition kinetic mode analysis revealed that free-polyphenols and bound-polyphenols inhibited α-glucosidase in a non-competitive mode (385). In another recent study a group of researchers investigated the α-glucosidase inhibition of polyphenols extracted from species Flos sophorae immaturus. The results showed that five polyphenols, namely rutin, quercetin, hyperoside, quercitrin and kaempferol, were identified as a-glucosidase inhibitors with IC_{50} values of 57, 0.21, 12.77, 25.37 and 0.55 mg/mL, respectively. Quercetin plays a considerable a-glucosidase inhibition role in Flos sophorae immaturus. Furthermore, the combination of quercetin with kaempferol generated a sub-additive effect, and the combination of quercetin with rutin, hyperoside and quercitrin exhibited an interference effect. The results of inhibition kinetics, fluorescence spectroscopy, isothermal titration calorimetry and molecular docking analysis showed that the five polyphenols were mixed inhibitors and significantly burst the fluorescence intensity of α-glucosidase. Moreover, the isothermal titration calorimetry and molecular docking analysis showed that the binding to α-glucosidase was a spontaneous heat-trapping process, with hydrophobic interactions and hydrogen bonding being the key drivers (386). A group of researchers evaluated the α-glucosidase inhibitory activity of the insoluble-bound polyphenols which are bound to the cell walls of the plant material of the plant species Guarana (Paullinia cupana) (387). The analysis of the contribution of insoluble-bound polyphenols to the total phenolic content of selected fruits and vegetables resulted in a mean of 57%, demonstrating its importance and high variability among vegetable sources (388).

Although a higher total phenolic content may suggest a higher potential inhibition against α-glucosidase, increasing evidence indicates that structural features of specific molecules involved may more appropriately explain the inhibition (389). In short, it might be concluded that phenolic acids show lower inhibitory activity compared to flavonoids and that these are

also influenced by the number of hydroxyl groups present in the molecules (as we mentioned already before). In the case of proanthocyanidins (condensed tannins), polymeric structures show higher inhibitory activity compared to their monomeric counterparts (e.g., catechin and epicatechin). Due to their presence in the bound form in nature, the potential health effects of insoluble-bound polyphenols are mainly related to gut health, with modulation of gut bacteria, protection of the colon mucosa, which may lead to systemic effects (390, 391, 392).

The soluble polyphenols and insoluble-bound polyphenols fractions present in the plant species Guarana (Paullinia cupana) inhibited the α-glucosidase activity in a dose-dependent manner. Their half-maximal inhibitory dose (IC_{50}) was 9.50 and 1.624 μg GAE/mL. The efficacy of the insoluble-bound polyphenols fraction is also supported by its lower IC_{50} value compared to that of acarbose, which ranged from 36.0 to 107.3 μg/mL (393, 394). Green tea, oolong tea, and black tea had IC_{50} values of 10.02, 1.38, and 2.25 μg/mL, respectively (395, 396). Therefore, the values obtained for guarana powder are comparable to other well-established sources of polyphenols and even lower than that of acarbose, which is the most studied inhibitor of α-glucosidase (397).

3.4.) POLYPHENOLS AND INHIBITION OF LIPASE ENZYMES

There is a lot of recent studies that report about the inhibitory activity of polyphenolic compounds against the lipase enzyme. In this work we will first focus on our four specific polyphenols. At the end we will also evaluate the recent data available on polyphenols and lipase inhibition. This type of inhibition plays an important role in the process of T2D development and progression. A group of researchers concluded that pancreatic lipase function is impaired in T2D, and this observation is particularly important in patients with diabetes type 2. It has been suggested that the analysis of pancreatic enzymes in diabetic patients may be a useful parameter in determining the progression of the disease (398).

3.4.1.) QUERCETIN

The inhibitory activity of quercetin on pancreatic lipase was investigated in both vitro and vivo. Quercetin exhibited inhibitory effect on pancreatic lipase with IC_{50} value of 70 μg/mL. Inhibitory kinetics indicated that quercetin was more like a mixed-type (non-competitive) inhibitor of pancreatic lipase. Quercetin induced the endogenous fluorescence quenching of lipase, which suggested the interaction between them. The binding constant and the number of the binding sites were further calculated. Molecular docking results showed that quercetin had a binding site on lipase near the active pocket. The binding of quercetin on lipase would affect its conformation, thereby decreasing the affinity between the substrate and the enzyme. In vivo studies showed that pre-administration with 5 and 10 mg/kg of bodyweight, quercetin could significantly reduce fat absorption in rat. The inhibition of quercetin on lipase can last at least 2 h in vivo. Correspondingly, quercetin significantly increased fat excretion in rat feces (399). The interaction between lipase and quercetin 3-rhamnoside was studied by fluorescence spectroscopy, enzyme kinetics, and molecular dynamics simulation. The results showed that quercetin 3-rhamnoside had a strong quenching effect on the intrinsic fluorescence of lipase. The binding constant decreased with increasing temperature, and the number of binding sites approached 1. Thermodynamic parameters indicated that hydrogen bonding and van der Waals forces are the dominant forces when the interaction occurs. Circular dichroism spectroscopy

and infrared spectroscopy proved that the ligand perturbed the structure of lipase. Enzyme kinetics results showed that quercetin 3-rhamnoside inhibited lipase, and the inhibitory effect was dose-dependent. Molecular dynamics simulation further explained the interaction mechanism and inhibitory effect (400). Four polyphenolic compounds were extracted from hot pepper and their lipase inhibitory activity was evaluated. A group of researchers have evaluated the inhibitory activity and binding characteristics of caffeic acid, p-coumaric acid, quercetin and capsaicin, four phenolic compounds found in hot pepper. Porcine pancreatic lipase was used and the polyphenolic compounds were compared to the hot pepper extract. Quercetin was the strongest inhibitor of lipase with the IC_{50}=(6.1±2.4) μM. All polyphenolic compounds showed a mixed-type inhibition. Fluorescence spectroscopy studies showed that polyphenolic compounds had the ability to quench the intrinsic fluorescence of pancreatic lipase by a static mechanism. The sequence of Stern-Volmer constant was quercetin, followed by caffeic and p-coumaric acids. Molecular docking studies showed that caffeic acid, quercetin and p-coumaric acid bound near the active site, while capsaicin bound far away from the active site. Hydrogen bonds and π-stacking hydrophobic interactions are the main pancreatic lipase-polyphenolic compound interactions observed in this research (401). The recent data suggests similar findings on quercetin characteristics on lipase inhibition.

In another work also the properties of quercetin aggregates under simplified intestinal conditions were investigated. Quercetin precipitate in aqueous solutions similar to those found in the small intestine. When interacting in a salt solution, quercetin aggregates are stabilized. Quercetin interacts with pancreatic lipase resulting in a sequestering of the enzyme. This result show that colloidal particles of aggregated flavonoids can affect lipase in solution. It is likely that these aggregates can be present in the small intestine of humans. Therefore, comprehension of the interaction between quercetin and lipase as well as the mechanism of inhibition is important to understand in order to understand the effect of quercetin in human diet (402).

3.4.2.) RESVERATROL

In one of more recent studies, ten doses of resveratrol were added to a solution containing 2.5 mg/mL pancreatic lipase. Lipase was inhibited by resveratrol, especially at the highest dose (1.5 mM). The results however showed that resveratrol was not as efficient as a positive control orlistat. When comparing the inhibitory activity of resveratrol it was shown that resveratrol was more potent to inhibit α-glucosidase than lipase. The maximum inhibitory effect against the lipase occurred at millimolar doses of the polyphenol, which could be considered as supranutritional levels (more, than what is needed for nutrition), while the α-glucosidase inhibition was more likely to be nutritionally relevant (403).

Lipoprotein lipase has a central role in the metabolism of both triglyceride-rich particles and high density lipoproteins, and it is one determinant of both serum triglyceride and high density lipoproteins (HDL) concentrations. In man the enzyme activity in both adipose tissue and skeletal muscle is insulin dependent, and therefore it varies in diabetes according to ambient insulin level and insulin sensitivity. In untreated T2D patients, the average enzyme activity in adipose tissue and post-heparin plasma is normal or subnormal (404). Differentiation of preadipocytes and the induction of metabolic pathways related to lipid metabolism includes expression of several adipocyte specific genes like PPARγ, C/EBPα, (405) sterol regulatory element binding proteins-1c (SREBP-1c), (406) fatty acid synthase (FAS), (407) lipoprotein lipase (LPL), (408) and hormone-sensitive lipase (HSL) (409). Resveratrol has been shown to

down-regulate the expression of PPARγ, C/EBPα, SREBP-1c, FAS, HSL, and LPL, (410) indicating that resveratrol may alter fat mass by directly affecting biochemical pathways involved in adipogenesis in maturing preadipocytes (411). In another study the researchers observed trans-resveratrol effect on lipase by quantitative and qualitative analyses of fluorescence spectra, molecular docking and quantum-chemical calculations. Interactions of CpLIP2 from C. parapsilosis CBS 604 and trans-resveratrol were confirmed with a major contribution of tryptophan residues to fluorescence quenching. A thermodynamic study across a wide temperature range was consistent with the presence of a single binding site with a binding free energy of −24 kJ/mol. Nevertheless, trans-resveratrol competitively inhibited CpLIP2 activity. Molecular docking and quantum-chemical calculations were consistent with a strong binding of trans-resveratrol to the CpLIP2 catalytic site via electrostatic and hydrophobic forces (412).

There is general agreement on the inhibitory effect that resveratrol has on adipogenesis, as numerous studies have examined this aspect in-vitro in animal models and most of them have shown concordant results. Lasa and colleagues (413) incubated pre-adipocyte cells with increasing concentrations of resveratrol (1, 10, and 25 μM) for 24 h, reporting a decrease in triacylglycerol content and a lower expression of acetyl-CoA carboxylase (ACC). The first is an enzyme with a key role in the synthesis of long-chain saturated fatty acids. In the adipose tissue, lipoprotein lipase, which is activated by the peroxisome proliferator-activated receptor-gamma (PPARγ), catalyzed the hydroxylation of triacylglycerol in free fatty acids. Hence, these results suggest the presence of an inhibitory effect of resveratrol on lipoprotein lipase (414). Consistent with this, another study reported significant downregulation of lipoprotein lipase mRNA in peripheral blood mononuclear cells (PBMC) of pigs after daily administration of resveratrol at a dose of 0.11 mg/kg of body weight for 12 months (415, 416).

3.4.3.) QUERCITRIN

A group of investigators explored the free, esterified, and insoluble-bound phenolics in Rhus chinensis Mill. fruits and their pancreatic lipase inhibitory activities with molecular docking analysis. Results showed that the free phenolic fraction displayed the highest total phenolic content and the strongest lipase inhibitory activity. Myricitrin and quercitrin were the major phenolics in all fractions with good dose-dependent lipase inhibitory effects (417). Another study investigated the inhibitory effect of the leaves extracts of Ocimum basilicum and Ocimum gratissimum on pancreatic lipase enzyme. Researchers also evaluated the phenolic composition of both extracts. O. basilicum had the following major phenolic compounds: rutin, quercetin, and quercitrin, while O. gratissimum had the following major phenolic compounds: rutin, quercitrin, and luteolin. Quercitrin was present in both extracts. Extracts of both plants inhibited pancreatic lipase enzyme in a dose-dependent manner. O. gratissimum extract was more potent in inhibiting pancreatic lipase (IC_{50}: 20.69 μg/mL) than O. basilicum (IC_{50}: 52.14 μg/mL) (418). Quercitrin was one of the flavonoids isolated from ethyl acetate fraction of Acer okamotoanum, where a group of researchers investigated anti-obesity effects and mechanisms of action of three flavonoids (among them was quercitrin) from A. okamotoanum in the differentiated 3T3-L1 cells. Quercitrin inhibited expressions of lipogenesis-related proteins including fatty acid synthase, adipocyte protein 2, and glucose transporter 4. Moreover, iso-quercitrin-treated group showed significant up-regulation of lipolysis-related proteins such as adipose triglyceride lipase and hormone-sensitive lipase (419). Lychee (Litchi chinensis Sonn., Sapindaceae) flower-water extracts (LFWEs) were tested on lipase inhibition by measuring the rate of releasing of oleic

acid from triolein (in vitro). The extracts contained phenolic acids, flavonoids, condensed tannins, anthocyanins, and proanthocyanidins. The following flavonoids could be identified in the extract: (+)-catechin, (−)-epicatechin, rutin, quercitrin, neohesperidin, condensed tannins (catechin equivalent), anthocyanins (cyaniding-3-glucoside equivalent) and proanthocyanidins. In addition to the inhibitory potential of the compounds, they were able to reduce epididymal adipose tissue sizes as well as serum and liver lipid content (420).

3.4.4.) NORDIHYDROGUAIARETIC ACID (NDGA)

NDGA dose dependently inhibited lypoxigenase-1. 50% inhibition was caused by 12μM of NDGA and complete inhibition of lypoxigenase-1 was observed at 100μM of NDGA. However, the results of this study reported that the addition of the NDGA at any concertation in the reaction mixture of lipase did not have any effect on either on the lipase or the lipase-inhibiting activities (421).

Effect of NDGA on the secretion of lipoprotein lipase (LPL) was also investigated. The effect of NDGA on lipoprotein lipase secretion was investigated in 3T3-L1 adipocytes, and compared with those of brefeldin A (BFA), a well-known fungal metabolite that exhibits similar ER-Golgi redistribution. Both BFA and NDGA blocked secretions of LPL. In the presence of NDGA, the cellular LPL became inactive. Results of this study also indicate that the inhibitory mechanism of NDGA on the LPL secretion is functionally different from the ER-Golgi redistribution that is induced by BFA (422). In another study the LPL inhibition by NDGA was confirmed by measuring the systemic LPL mass and adipose LPL gene expression in mice feed with Western diet with 0,1% NDGA. These findings demonstrated that LPL inhibition by NDGA aggravates metabolic parameters and alters HDL particle size (423).

Based on the data available NDGA has inhibitory effects on LPL as well as on pancreatic lipase enzyme. More data can, however, be found on the same effect of mixture of different polyphenolic compounds together. We will discuss this part in the next section.

3.4.5.) OTHER POLYPHENOLS/MIXTURE OF POLYPHENOLS FOUND IN FOOD AND PLANTS

In a variety of studies the beneficial effect of polyphenols on lipid metabolism could be demonstrated. They inhibit enzymes including PL, lipoprotein lipase (LPL), and glycerophosphate dehydrogenase (GPDH) (424).
Fifty-four polyphenols isolated from tea leaves were evaluated for their inhibitory activities against pancreatic lipase, the key enzyme of lipid absorption in the gut. (−)-Epigallocatechin 3-O-gallate (EGCG), which is one of major polyphenols in green tea, showed lipase inhibition with an IC_{50} of 0.349 μM. Moreover, flavan-3-ol digallate esters, such as (−)-epigallocatechin-3,5-digallate, showed higher activities of inhibition on lipase with an IC_{50} of 0.098 μM. On the other hand, non-esterified flavan-3-ols, such as (+)-catechin, (−)-epicatechin, (+)-gallocatechin, and (−)-epigallocatechin, showed zero and/or the lowest activities against pancreatic lipase (IC_{50} > 20 μM). These data suggested that the presence of galloyl moieties within the structure was required for enhancement of pancreatic lipase inhibition (425). In another study polyphenol-rich extracts from a range of berries were tested for their ability to inhibit pancreatic lipase activity in vitro. Blueberry caused slight inhibition, whilst lingonberry, Arctic bramble, cloudberry, strawberry and raspberry were considerably more effective. Inhibition by the

cloudberry extract showed a saturation effect with an apparent EC_{50} of around 5 μg phenols/ml. The inhibitory components from cloudberry were ellagitannins (most probably the proanthocyandin components) (426). Also the Chaenomeles fruit was investigated against the ability to inhibit the pancreatic lipase enzyme. A group of researchers confirmed that Chaenomeles fruit are made of (+)-catechin and (−)-epicatechin units. Furthermore they confirmed that Chaenomeles fruits showed high potential for inhibition of α-glucosidase and pancreatic lipase (427).

Gallic acid, epicatechin, epigallocatechin and epigallocatechin gallate were investigated for pancreatic lipase inhibition and its kinetics as well as the IC_{50} value. The IC_{50} value for gallic acid was evaluated as 387.2 μM, for epicatechin and epigallocatechin as 237.3 μM, and for epigallocatechin gallate as 391.2 μM. Analysis of enzyme inhibition modalities at various substrate concentrations revealed a dose-dependent inhibition of reaction velocity. Inhibitory rates decreased in the following order: epigallocatechin gallate > epigallocatechin > gallic acid. The results, when verified by visual inspection of Lineweaver–Burk as well as Dixon plots, showed inhibitions of pancreatic lipase by gallic acid, epigallocatechin and epigallocatechin gallate that were best fit to competitive inhibitions. A role of the galloyl moiety in enzyme-inhibitor binding has been evident from their structural resemblance. Depicting it further, ethyl gallate, showed a similar competitive inhibition, therefore, indicating a galloyl moiety driven competitive inhibition of pancreatic lipase (428). There are more studies that support the claim of galloyl group being actively involved in enzyme inhibition (429).

In another study however the degree of polymerization was an important factor of pancreatic lipase inhibition, and oligomeric procyanidin mainly contributed to that action. Researchers examined the inhibitory effects of apple polyphenol extract and procyanidin contained in apple polyphenol extract on in vitro pancreatic lipase activity and in vivo triglyceride absorption in mice and humans. Apple polyphenol extract and procyanidin considerably inhibited in vitro pancreatic lipase activity (430).

There is a lot of research already done regarding the polyphenol compounds and food rich in polyphenols and other similar molecules and pancreatic lipase inhibition. Here we mentioned just a few most recent ones but nevertheless the data is abundant and the results are highly comparable.

3.5.) POLYPHENOLS AND GUT MICROBIOTA

We will discuss the connection between polyphenols and gut microbiota in general and will not focus on a specific polyphenolic compound. In order to understand better how polyphenols impact the gut microbiota and the other way around (how the gut microbiota impacts the metabolism of polyphenols), we need to look into the data we have available until now. This area of research can help us understand the interactions between the chemical structure of polyphenols and the gut microbiota (as well as the other way around). It is by far an area of research that can offer a new insight and understanding in how polyphenolic compounds can act in a human body as well as what factors can impact the metabolism of polyphenols found in everyday food.

3.5.1.) IMPACT OF GUT MICROBIOTA ON THE METABOLISM OF POLYPHENOLS

The biological properties of dietary polyphenols are greatly dependent on their bioavailability that, in turn, is largely influenced by their degree of polymerization. The gut microbiota play a key role in modulating the production, bioavailability and, thus, the biological activities of phenolic metabolites, particularly after the intake of food containing high-molecular-weight polyphenols. In addition, evidence is emerging on the activity of dietary polyphenols on the modulation of the colonic microbial population composition or activity. However, although the great range of health-promoting activities of dietary polyphenols has been widely investigated, their effect on the modulation of the gut ecology and the two-way relationship "polyphenols ↔ microbiota" are still poorly understood. Only a few studies have examined the impact of dietary polyphenols on the human gut microbiota, and most were focused on single polyphenol molecules and selected bacterial populations (431). Of course (like all food) polyphenols undergo biotransformation in the gut. Briefly, a small percentage of dietary polyphenols (5–10% of the total intake, mainly those with monomeric and dimeric structures) may be directly absorbed in the small intestine, generally after deconjugation reactions such as deglycosylation (432). After absorption into the small intestine, these less complex polyphenolic compounds may be subjected to extensive Phase I (oxidation, reduction and hydrolysis) and particularly Phase II (conjugation) biotransformation in the enterocytes and then the hepatocytes, resulting in a series of water-soluble conjugate metabolites (methyl, glucuronide and sulfate derivatives) rapidly liberated to the systemic circulation for further distribution to organs and excretion in urine. In the large intestine, colonic bacteria are known to act enzymatically on the polyphenolic backbone of the remaining unabsorbed polyphenols (90–95% of the total polyphenol intake), sequentially producing metabolites with different physiological significance (433). The metabolism of polyphenols by microbiota involves the cleavage of glycosidic linkages and the breakdown of the heterocyclic backbone (434). The metabolism by gut microflora of polyphenols abundant in wine, tea, chocolate and many fruits may also influence tissue exposure to high-molecular-weight polyphenols, including proanthocyanidins or oxidized polymeric polyphenols, which are poorly absorbed in the proximal part of the gastrointestinal tract (435, 431). The proanthocyanidins are transferred to 3,4-dihydroxyphenylacetic acid, 3-(3-hydroxyphenyl) propionic acid, 3-hydroxyphenylacetic acid and 5-(3'-hydroxyphenyl)-γ-valerolactone in the large intestine (436). Anthocyanidins are frequently metabolized by the gut microbiota to form 2,4,6-trihydroxyphenylacetic acid and protocatechuic acid (437). Curcumin is catabolized to its hydrogenated, O-glucuronide, desmethyl, and O-sulfate forms (438). Gut microbiota converted ellagic acid to urolithins via dehydroxylation and intramolecular condensation (439). Cyanidin glucosides are primarily transformed into 3,4-dihydroxybenzoic acid in the human colon (440, 441).

Microbial metabolites of phytopolyphenols have been shown to decrease the risk in the metabolic syndrome. During a study on in vitro model of protein glycation, a group of researchers revealed that pyrogallol and urolithins, the two microbial metabolites obtained from ellagitannin are highly antiglycative in comparison to parent polyphenolic compounds. Moreover, protein glycation has been reported to play a vital pathological role in diabetes and associated complications, including blindness (442).

3.5.2.) IMPACT OF POLYPHENOLS ON GUT MICROBIOTA

The influence of polyphenols on bacterial growth and metabolism depends on the polyphenol structure, the dosage assayed and the microorganism strain (443). For instance, Gram-negative bacteria are more resistant to polyphenols than Gram-positive bacteria, due to the differences found in their wall composition (444, 445).

Previous human intervention trials have shown that apart from interindividual variation in the daily intake of polyphenols, interindividual differences in the composition of the human microbiota may lead to differences in bioavailability and bio-efficacy of polyphenols and their metabolites (446, 447). In addition, polyphenols may be converted by the colonic microbiota to bioactive compounds that can affect the intestinal ecology and influence host health (445). Microbes stressed by exposure to polyphenols up-regulate proteins related to defensive mechanisms, which protect cells while simultaneously down-regulating various metabolic and biosynthetic proteins involved, for example, in amino acid and protein synthesis as well as phospholipid, carbon and energy metabolism (448). Most bacteria are able to regulate phenotypic characteristics, including virulence factors, as a function of cell density under the control of chemical signal molecules. Polyphenolic compounds can also inter- fere with bacterial quorum sensing, which is achieved by producing, releasing and detecting small signal molecules identified as autoinducers (acylated homoserine lactones in Gram-negative bacteria and oligopeptides in Gram-positive bacteria) (449, 450, 445). The B ring of the flavonoids may play a role in intercalation or hydrogen bonding with the stacking of nucleic acid bases, and this may explain the inhibitory action on DNA and RNA synthesis (451). Two recent studies reported that quercetin binds to the GyrB subunit of E. coli DNA gyrase and inhibits the enzyme's ATPase activity (452). In agreement with these earlier findings, more recently, it was determined that the catechins inhibit bacterial DNA gyrase by binding to the ATP (adenosine triphosphate) binding site of the gyrase B subunit (453).

Absorption of the ingested polyphenol in the small intestine is very low (about 5-10%). The left over polyphenols (90-95%) may accumulate up to the millimolar range in the large intestine along with the bile conjugates released into the lumen and are exposed to the gut microbial enzymatic activities (454). Recent studies support that dietary phenolic substances reaching the gut microbes, as well as the aromatic metabolites generated, may modify and produce variations in the microflora community by exhibiting probiotic effects and antimicrobial action against pathogenic intestinal microflora (455, 456, 457). In a randomized, single blind, crossover study, a group of researchers reported that polyphenols from spice like turmeric (curcumin, dimethoxy-curcumin and bis-dimethoxy-curcumin), star anise (quercetin derivatives, kaempferol derivatives and isorhamnetin derivatives), ginger (gingerols and shogaols) and cinnamon (procyanidins, cinnamic acid, kaempferitrin, cinnamaldehyde and 2-hydroxycinnamaldehyde), lowered cardiometabolic risk acting on the gut through glucose uptake inhibition and appetite modulation (458, 459).

3.6.) CONNECTION BETWEEN RESVERATROL CONSUMPTION AND GENETICAL PREDISPOSITION FOR DEVELOPING T2D

We will focus on resveratrol since there is more data available that shows positive connection between consumption of resveratrol and progression of T2D in connection with genetics. We will describe and explore two main mechanisms through which resveratrol impacts the T2D

development. Both mechanisms are related to genetical changes that are induced by resveratrol. Managing or even preventing T2D in individuals with genetical predisposition to develop T2D by consuming resveratrol and other polyphenols would be of high importance and would help lower the global burden T2D has on the health system. This approach would also be easier adapted in countries with lower economic profile since resveratrol and other polyphenols are naturally present in food.

Recent studies strongly suggest that the consumption of resveratrol offers protection against diabetes and its cardiovascular complications. The protective effects of resveratrol involve the regulation of multiple signaling pathways, including inhibition of oxidative stress and inflammation, enhancement of insulin sensitivity, induction of autophagy, regulation of lipid metabolism, promotion of GLUT-4 expression, and translocation, and activation of SIRT1/AMPK signaling axis (460).

3.6.1.) RESVERATROL AND REDUCED MITOCHONDRIAL CAPACITY IN SKELETAL MUSCLE

Diminished mitochondrial oxidative phosphorylation and aerobic capacity are associated with reduced longevity. Mitochondrial function can impact on whole-body metabolism. This is most evident in the muscle, a metabolically flexible tissue that switches between carbohydrate and lipid as substrates in order to meet the energy demands (461). Indeed, impaired mitochondrial function that directs fatty acids toward storage, as opposed to oxidation, may contribute considerably to intramyocellular lipid accumulation, which has been linked to insulin resistance in obesity and T2D in humans (462, 463, 464). In line with this, resveratrol significantly improved both muscle oxidative capacity and sensitivity to insulin in HF (high fat)-fed mice. Although the respiratory quotient, reflective of whole- body substrates use, was unchanged under resveratrol treatment, gene-expression analysis in the gastrocnemius supported an increase in fatty-acid oxidation since medium chain acyl-CoA dehydrogenase expression was increased and glucose utilization reduced as pyruvate dehydrogenase kinase (PDK4) levels were increased (465, 466).

As reported before and as a well-known fact, exercise has positive impact on T2D as physical inactivity reduces, and exercise training increases, mitochondrial capacity. In a recent study they investigated the consumption of resveratrol (with piperine - a bioenhancer to increase bioavailability and bio-efficacy of resveratrol.) while exercising 3 sessions per week of submaximal endurance training. Changes in mitochondrial capacity from baseline to post-testing indicated significant differences between the resveratrol/piperine-trained arm and the placebo-trained arm, with the resveratrol/piperine group increasing about 40% from baseline, while the placebo group increased about 10% from baseline. Neither the placebo group nor the resveratrol/piperine group exhibited changes in mitochondrial capacity in the untrained arm. In conclusion, low-intensity exercise training can increase forearm skeletal muscle mitochondrial capacity when combined with resveratrol and piperine supplementation (467). There is more recent data available that supports the beneficial connection between physical activity, resveratrol supplementation and T2D.

In another recent study a group of researchers investigated how resveratrol affects skeletal muscle lipid transportation and lipid oxidation of subsarcolemmal and intermyofibrillar

mitochondrial populations in high-fat diet–induced insulin resistance rats. Systemic and skeletal muscle insulin sensitivity together with expressions of several genes related to mitochondrial biogenesis and skeletal muscle lipid transportation was studied in rats fed a normal diet, an high-fat diet, and an high-fat diet with intervention of resveratrol for 8 weeks. Citrate synthase, electron transport chain activities, and several enzymes for mitochondrial β-oxidation were assessed in subsarcolemmal and intermyofibrillar mitochondria from tibialis anterior muscle. The high-fat diet -fed rats exhibited obvious systemic and skeletal muscle IR as well as intramuscular lipid accumulation. SIRT1 activity and expression of genes related to mitochondrial biogenesis were greatly declined, whereas the gene for lipid transportation, FAT/CD36, was upregulated ($P < .05$). Subsarcolemmal but not intermyofibrillar mitochondria displayed lower citrate synthase, electron transport chain, and β-oxidation activities. By contrast, resveratrol treatment protected rats against diet-induced intramuscular lipid accumulation and insulin resistance, increased SIRT1 activity and mitochondrial biogenesis, and reverted the decline in subsarcolemmal mitochondrial citrate synthase and electron transport chain activities. Importantly, although expression of FAT/CD36 was increased (11%, $P < .05$), activities of subsarcolemmal mitochondrial β-oxidation enzymes were largely enhanced (41%~67%, $P < .05$). This study suggests that resveratrol ameliorates insulin sensitivity consistent with an improved balance between skeletal muscle lipid transportation and subsarcolemmal mitochondrial β-oxidation in high-fat diet rats (468). In even more recent study they investigated older adults with T2D to evaluate the effect of resveratrol on oxidative stress markers and sirtuin-1, using doses of 1000 mg/day and 500 mg/day compared with a placebo. Biochemical markers, oxidative stress and sirtuin-1 levels were measured at baseline and after six months. The result of the research suggest that the consumption of resveratrol at a dose of 1000 mg/day exerts a more efficient antioxidant effect than a dose of 500 mg/day, which coincides with a statistically significant increase in SIRT1 levels in older adults with T2D. This provides evidence suggesting that the consumption of resveratrol in doses of at least 1000 mg/day for 6 months or more could be an adjunctive treatment that reduces the incidence of micro- and macrovascular complications linked to T2D (469).

Resveratrol can activate and upregulate NAD+ dependent SIRT1 (470), thereby improving or delaying the development of diabetes, cardiovascular disease, cancer, and other diseases (471, 472, 473). SIRT1 plays a crucial role in the regulation of many downstream key proteins which impact glucose metabolism, including fork-head transcription factor O1 (FOXO1), endothelial nitric oxide synthase (eNOS), peroxisome-proliferating-activated receptor (PPAR)-α/γ and co-activator (PGC)-1α (474, 475). Another group of researchers found that the acetylation of FOXOs proteins was reversible and SIRT1 could bind to FOXO1, FOXO3a, and FOXO4 protein, respectively, specifically removing the acetyl group of FOXOs, thus up-regulating the DNA binding ability of FOXOs protein to specific target gene promoters and increasing its transcriptional activity (476). The occurrence of diabetes can lead to a decrease in SIRT1 activity and its expression, and then the enhanced acetylation of FOXO1 will lead to a significant increase in blood glucose in vivo after FOXO1 activation, which may ultimately aggravate insulin resistance (477). In line with this, knockdown of FOXO1 in mouse adipose tissue improved insulin resistance (478, 479). Therefore, it can be speculated that resveratrol can inhibit FOXO1 expression through SIRT1, thereby improving insulin resistance and restoring normal blood glucose levels (480, 481).

3.6.2.) RESVERATROL AND EXPRESSION OF GLUT-4

There is a lot of data showing positive connection and impact the resveratrol consumption has on AMPK and GLUT-4 expression. As mentioned before resveratrol ameliorates high-insulin-induced skeletal muscle cell insulin resistance. A very recent study was evaluating this effect in-vitro, with focus on mechanisms involved. The increase in muscle glucose uptake with acute insulin stimulation is due to translocation of GLUT-4 glucose transporter from an intracellular pool to the plasma membrane. To examine the effects of resveratrol on GLUT-4, we used L6 cells that overexpress a myc-labelled GLUT-4 glucose transporter (482). Acute stimulation of GLUT-4myc-overexpressing L6 myotubes with insulin (100 nM, 30 min) resulted in a significant increase in GLUT-4 plasma membrane levels. Chronic exposure of the cells to insulin (100 nM, 24 h), to mimic hyperinsulinemia, increased GLUT-4 plasma membrane levels. High insulin abolished the acute-insulin-induced increase in GLUT-4 plasma membrane levels, indicating insulin resistance, and this response was restored in the presence of resveratrol (483). In the same study also treatment with resveratrol alone significantly increased the phosphorylation of AMPK. Importantly, resveratrol increased the phosphorylation of AMPK in the presence of high insulin conditions. Treatment with high insulin alone did not significantly alter AMPK phosphorylation levels. Furthermore, the total levels of AMPK were unchanged by any treatment. Resveratrol under high insulin conditions significantly increased the ratio of phosphorylated AMPK to total AMPK. Resveratrol has the potential to counteract high insulin-induced muscle cell insulin resistance (483).

Aa mentioned, animal and in vivo studies indicate that resveratrol increases SIRT1 expression that stimulates PGC1α activity. Subsequent upregulation of AMPK and GLUT-4 expression are associated with improved insulin sensitivity in peripheral tissues. To further support this statement a group of researchers conducted and evaluated a clinical trial. Ten subjects with T2D were randomized in a double-blind fashion to receive 3g resveratrol or placebo daily for 12 weeks. Among other outcomes, they evaluated the level of expression levels of AMPK, p-AMPK and GLUT-4. There was a significant increase in both SIRT1 expression (2.01 vs. 0.86 arbitrary units [AU], $p = .016$) and p-AMPK to AMPK expression ratio (2.04 vs. 0.79 AU, $p = .032$) in the resveratrol group compared with the placebo group. In patients with T2D, treatment with resveratrol regulates energy expenditure through increased skeletal muscle SIRT1 and AMPK expression. These findings indicate that resveratrol may have beneficial exercise-mimetic effects in patients with T2D (484). But there is more data that supports these findings. The administration of resveratrol at a dose of 2.5−400 mg/kg for 1–6 months significantly improves insulin sensitivity and/or reduces circulating insulin concentration in T2D individuals and animal models (485, 486, 487, 488, 489, 490, 491, 492, 493). In human clinical trials, the single-dose oral administration or daily administration of resveratrol (5 mg- 5 g) for 12 months reduces blood glucose and enhance insulin sensitivity in diabetic patients (494, 495, 496). Moreover, the insulin-sensitizing effects of resveratrol have been observed in patients with glucose tolerance. These results suggest that postprandial glucose concentration is significantly reduced without any increase in insulin production and thus confirm increase in insulin sensitivity after the administration of resveratrol (497, 498, 499, 500). The results also suggest that resveratrol can restore abnormal the levels of insulin, insulin-like growth factors (IGFs) and blood glucose by activating AMP-dependent protein kinase (AMPK) and SIRT (501, 502, 503).

Resveratrol stimulates glucose uptake or utilization in isolated cells in the absence of insulin possibly due to increased GLUT-4 expression in the plasma membrane. Currently, a large part of the study considered that it is related to the activation of PI3K and the phosphorylation of AMPK by resveratrol because acute cure with high concentrations of resveratrol mediates the phosphorylation of Akt and AMPK and increases glucose uptake in insulin-stimulated human myotubes (504, 505). All of the experiments described above suggested that resveratrol reduces blood sugar by affecting glucose uptake and metabolism (506).

3.7.) CAN WE IMPACT THE ON-SET OF T2D BASED ON GENE PREDISPOSITION WITH (POLYPHENOL-REACH) NUTRITION? WHAT IS THE CURRENT DATA SHOWING?

It is important to evaluate the possible impact the food choices and lifestyle has on development and progression of T2D in individuals that carry higher genetical predisposition to develop T2D. There is data available that evaluated and explored this field. In this review we will include all relevant studies that took place in the past 24 years.
A group of researchers determined 10 polymorphisms in a prospective, nested, case-control study of 1196 diabetic and 1337 nondiabetic men. A genetic risk score (GRS) was generated by using an allele counting method. Baseline dietary intakes were collected by using a semi-quantitative food-frequency questionnaire. They used factor analysis to derive Western and ‘‘Prudent’’ dietary patterns from 40 food groups. They found significant interactions between the Western dietary pattern, which was characterized by high intakes of red meat, processed meat, and refined foods, and the GRS derived from genetic variants associated with diabetes risk in GWA studies (507, 508, 509, 510, 511). Intakes of the Western dietary pattern were significantly associated with increased diabetes risk among men with a higher GRS (≥12 risk alleles), but not among those with a lower GRS. The fact that T2D is rampant in Western societies and that the incidence has clearly increased more in developing countries that have recently transitioned to a Westernized lifestyle highlights the critical role of a Westernized diet and lifestyle in triggering the epidemic of the disease (512, 513). In addition, it has long been noted that high variability exists among individuals in response to lifestyle changes. The data suggest that the effects of a Westernized diet on diabetes risk are not homogeneous in people with different genetic backgrounds. High intakes of Westernized diets more likely increase the risk of diabetes among those with a higher genetic susceptibility to this disease. This data also indicate that red meat and processed meats may be the major foods driving the interactions between a Western dietary pattern and genetic variation in determining diabetes. High intakes of these foods significantly increased the risk of diabetes among individuals carrying more risk alleles (≥12) of diabetes variants but did not affect the disease risk in those carrying fewer risk alleles (514).

An initial and very preliminary track of evidence for genotype-polyphenol interaction is emerging from studies of coffee, the consumption of which is highly spread in Mediterranean regions. In a prospective population-based cohort study including 4077 normal glycemic individuals over a 4-year follow-up, habitual coffee intake outweighed the hazard of unfavorable genetic predisposition on 3 well-known T2D-increasing risk genetic loci, including IGF2BP2, CDKAL1, and KCNJ11 (515). Along these lines, an independent study including 1180 nondiabetic young to middle-aged participants with stage 1 hypertension, baseline coffee consumption was longitudinally associated with the risk of impaired glucose tolerance only in

carriers of CYP1A2-1F allele. Among participants homozygous for the 1A allele, which is responsible for fast caffeine metabolism, the favorable action of polyphenols or other bioactive agents balanced the genetic and metabolic risk for T2D (516). Finally, in a prospective epidemiological study from the EPIC-Inter Act cohort, including 8086 incident T2D cases in 11,035 participants over 12.5 years, habitual coffee consumption was associated with a 7% T2D risk reduction among carriers of the diabetes increasing risk allele at transcription factor 7-like 2 locus (TCF7L2) (517). In addition, an interaction between an incretin-specific genetic risk score, designed to capture the genetic predisposition to defects in postprandial insulin secretion and coffee consumption on T2D risk was observed (i.e., each additional cup of coffee was associated with 5% lower T2D risk in individuals carrying high number of risk alleles). In line with previous results, adherence to the Med-Diet has been reported to be able to reduce the adverse effect of the TCF7L2 polymorphism on fasting glucose and blood lipids and, importantly, on stroke incidence (518, 515).

There exists a common genetic variant in the glucose-dependent insulinotropic polypeptide receptor gene (GIPR rs10423928 T>A) which is related with a reduced insulin release and an increase in T2D risk. In the Swedish population-based Malmö Diet and Cancer cohort, it has been studied the relationship between the mentioned genetic variant, macronutrients and fiber intake, body mass index (BMI) and T2D risk. It has been observed that when AA-genotype people follow high-fat, low-carbohydrate diets, the T2D risk decreases. On the other hand, two thirds of the people homozygous for the T-allele resulted benefitted when they follow high-carbohydrate, low-fat diets (519, 517). The transient receptor potential vanilloid 1 (TRPV1) gene is involved in energy and glucose metabolism. TRPV1 activation increases insulin sensitivity and potentiates glucose-stimulated insulin secretion. A Korean Genome Epidemiology Study demonstrated that individuals with the minor alleles of the TRPV1 single nucleotide polymorphisms (SNPs) rs161364 T>C and rs8065080 T>C were negatively associated with the prevalence of T2D. They also determined that carriers of the minor allele of both SNPs have a lower risk of diabetes with a high-fat diet but individuals with the major alleles are at a higher risk of T2D when consuming high-fat diets (520, 517).

There is a very recent case-cohort study available, where 4729 individuals who developed T2D during a median 14.7 years of follow-up, and a randomly selected cohort sample of 5402 individuals were included. Genetic predisposition was quantified using a genetic risk score comprising 193 known type 2 diabetes- associated loci (excluding known BMI loci) and stratified into low (quintile 1), intermediate and high (quintile 5) genetic risk groups. Lifestyle was assessed by a lifestyle score composed of smoking, alcohol consumption, physical activity and diet. These researchers concluded that obesity (BMI $\geq$ 30 kg/m2) and unfavorable lifestyle were associated with higher risk for incident T2D regardless of genetic predisposition. The effect of obesity on T2D risk was high, whereas the effects of high genetic risk and unfavorable lifestyle were relatively modest. Even among individuals with low genetic risk score and favorable lifestyle, obesity was associated with a >8-fold risk of T2D compared with normal-weight individuals in the same genetic risk score and lifestyle stratum. This study showed that having normal body weight is crucial in the prevention of T2D, regardless of genetic predisposition (521). This study is supporting current worldwide guidelines and recommendations for managing T2D. There are downsides of this study, one of them being the number of participants.

Based on current data it is obvious that the connection between genetical predisposition and healthy lifestyle shouldn't be overlooked. As already mentioned current guidelines are supporting healthy lifestyle as well as healthy body weight and this is in line with the current data. However more clinical studies are needed where genetical predisposition for T2D and polyphenol consumption are explored and looked at. Looking at the burden the T2D has on public health it is a low price to be paid in order to be able to manage T2D outbreaks with mere food choices that are available in nature. Current guidelines are sufficient in managing the T2D once it occurs but better prevention strategies need to be implemented in order to prevent new cases with T2D. This is even more important as we have more and more data available and T2D cases are still rising each year.

4.) DISCUSSION

4.1.) CAN WE IMPACT THE DEVELOPMENT AND COMPLICATIONS OF T2D THROUGH DIET?

T2D is one of the most common endocrine metabolic disorders. In addition to exercise and diet, oral anti-diabetic drugs have been used as a part of the management strategy worldwide. Unfortunately, none of the conventional anti-diabetic drugs are without side effects, and these drugs pose an economic burden. Therefore, the investigation of novel anti-diabetic regimens is a major challenge for researchers, in which nature has been the primary resource for the discovery of potential therapeutics. Many plants have been shown to act as anti-diabetic agents, in which the main active constituents are believed to be polyphenols. Natural products containing high polyphenol levels can control carbohydrate metabolism by various mechanisms, such as protecting and restoring beta-cell integrity, enhancing insulin releasing activity, and increasing cellular glucose uptake. Blackberries, red grapes, apricots, eggplant and popular drinks such as coffee, cocoa and green tea are all rich in polyphenols, which may dampen insulin resistance and be natural alternatives in the treatment of T2D (522). The American Diabetes Association has made several recommendations regarding the medical nutrition therapy of diabetes; these emphasize the importance of minimizing macrovascular and microvascular complications in people with diabetes. Four types of diets were reviewed for their effects on diabetes: the Mediterranean diet, a low-carbohydrate/high-protein diet, a vegan diet and a vegetarian diet. Each of the four types of diet has been shown to improve metabolic conditions, but the degree of improvement varies from patient to patient. Therefore, it is necessary to evaluate a patient's pathophysiological characteristics in order to determine the diet that will achieve metabolic improvement in each individual. Many dietary regimens are available for patients with T2D to choose from, according to personal taste and cultural tradition. It is important to provide a tailor-made diet wherever possible in order to maximize the efficacy of the diet on reducing diabetes symptoms and to encourage patient adherence. Additional randomized studies, both short term (to analyze physiological responses) and long term, could help reduce the multitude of diets currently recommended and focus on a shorter list of useful regimens (523). Special diet and being caseous about food intake is one of the primary recommendations when it comes to T2D management. Low sugar and saturated fat intake is known to have negative effects on T2D progression. Diet recommendations are more or less the same as for a healthy lifestyle (low sugar, saturated fat, more fiber, vegetables, fruits with good hydration). Closely connected is also exercise as it benefits T2D patients as well as a healthy individual that doesn't have T2D. With all of this, we need to also add the importance of education. Without that, nothing connects and we can expect poorer results and compliance. Attention to food portions and weight management, combined with physical activity, helps improve glycemic control. General guidelines include 50-60% of daily energy requirements derived from carbohydrates, low glycemic index foods, foods containing cereal fiber and a protein intake of least 0.86 g/kg/day. The consumption of added sugars can be up to 10% of daily energy requirements. Also, guidelines recommend the limited intake of total fat, especially saturated fats, with monounsaturated fatty acid (MUFA) used where possible, appropriate use of nutritive and non-nutritive sweeteners, the daily vitamin and mineral requirements of a well-balanced diet and individualized physical activity for people with T2D (524).

Insulin resistance (IR) is mainly caused by excessive energy intake leading to adiposity and has been proposed as the strongest single predictor for T2D (525, 526). Therefore, any nutritional measure that results in even modest weight loss should improve IR (527). However, generally in obese individuals energy expenditure begins to decrease as soon as body weight starts to decline, and potent hypothalamic hormonal responses are induced to prevent further weight loss (526, 528). Moreover, most individuals following weight-loss diets are overweight or obese and typically sedentary, with relevant increases in lean mass under these conditions being unlikely. Physical activity can result in acute improvement of IR lasting from 2 to 72 h, but must be regular to have continued beneficial effects (529). Finally, after intentional weight loss, fat mass is regained to a greater degree than is lean mass in those who do experience weight regain (530), further contributing to worsening of IR (531).

In studies in rodents, high- compared with low-glycemic index (GI) diets significantly increased body fat mass and IR (532). These changes appear to be preceded by early-onset (after 3 weeks) and significantly impaired fatty acids (FA) oxidation, indicating a potentially causal involvement (532). In observational studies in humans, however, beneficial effects of low-GI diets have not been consistently shown (533, 534), which is partly explained by the known problem of controlling confounding factors such as fiber intake and the lack of suitable control diets (535). Moreover, in most observational studies that reported associations of GI with risk of T2D, participants were relatively young and, even in interventional studies in rodents, the metabolic benefits of a low-GI diet appear to be more pronounced in younger animals (536, 531). If we further involve even the gut microbiome, things get even more interesting and complex. It has been proposed that the observed relation between the amino acid metabolic signature and IR (537) may be linked to certain members of the gut microbiota. A recent study that combined measures of IR with metabolomics and microbiome shotgun sequencing in humans observed significant correlations of serum branched chain amino acids (BCAAs) with IR, which were related to increased microbial production and reduced microbial transport mechanisms for BCAAs, thereby explaining the increased BCAAs (538) Prospective cohort studies clearly indicate that diets high in insoluble cereal DF and whole grains might significantly reduce diabetes risk (535).

With all current data available we can with certainty say, that diet has a significant impact on T2D development and progression.

4.2.) CAN AN INDIVIDUAL THAT HAS A GENETICAL PREDISPOSITION TO DEVELOP T2D PREVENT THE DISEASE BY SELECTING APPROPROATE FOOD/DIET? WHAT CAN THE IMPACT BE?

For a decade, genome-wide association studies (GWAS) on T2D have been conducted in a variety of populations of different ancestries and more than 200 T2D-related genetic variants have been identified by GWAS so far (539, 540). Not all, but many of the gene variants found are located in genes related to the insulin secretion pathway, insulin signaling, pancreatic β-cell dysfunction, and IR pathway (541). However, gene variants have been described in genes that are more challenging candidates for greater susceptibility to T2D. In addition to the genetic architecture of T2D susceptibility, environmental factors are suggested to play a key role in the etiology of T2D. Dietary factors in particular may interact with genetic variants to modulate the risk of T2D (542, 517).

All this makes it very complex to establish T2D risk values according to allelic variants, due to: (i) the existence of genetic variants that increase T2D risk independently of the type of diet (ii) genetic variants related to diet that modify some glucose metabolism systems, such as fasting glucose levels and IR, but do not modify the risk of T2D (iii) genetic variants that present a greater risk of T2D but this risk is modified depending on the type of diet (iv) genetic polymorphisms that modify risk according to other parameters such as ethnic class and obesity. All this makes it challenging to clearly establish cause-effect and therefore, the association between a gene variant and the risk of developing T2D (517).

Based on all the current data available, individuals that have (carry) higher risk of developing T2D should follow a healthy lifestyle, with healthy diet and moderate exercise as appropriate. There are studies (as mentioned in our work), that show positive effects between individuals that have genetically higher risk of developing T2D and healthy diet (like Mediterranean diet for example). But more research is needed in order to be able to confirm more specific effects a healthy diet and compounds such as polyphenols have on development of T2D in such individuals. Definitely this is an interesting area of research that would help in prevention of T2D disease and would relieve the heath economic systems.

4.3.) CAN WE EVALUATE (BASED ON ALL THE DATA) WHAT HAS A STRONGER IMPACT – DIET AND LYFESTYLE OR GENES?

Type 2 diabetes (T2D) is a multifactorial anomaly involving 57 genes located on 16 different chromosomes and 136 single nucleotide polymorphisms (SNPs). Ten genes are located on chromosome 1, followed by seven genes on chromosome 11 and six genes on chromosomes 3. Remaining chromosomes harbor two to five genes. Significantly, chromosomes 13, 14, 16, 18, 21, 22, X, and Y do not have any associated diabetogenic gene. Genetic components have their own pathways encompassing insulin secretion, resistance, signaling, and β-cell dysfunction. Environmental factors include epigenetic changes, nutrition, intrauterine surroundings, and obesity. In addition, ethnicity plays a role in conferring susceptibility to T2D. This scenario poses a challenge toward the development of biomarker for quick disease diagnosis or for generating a consensus to delineate different categories of T2D patients. It would make sense that, before prescribing a generic drug, detailed genotypic information with the background of ethnicity and environmental factors would be taken into consideration. This nonconventional approach is envisaged to be more robust in the context of personalized medicine and would most probably cause lot less burden on the patient ensuring better management of T2D (541). Exercise should not be overlooked. As an environmental factor it shows that combined with healthy diet can help decrease the incidence of T2D in high-risk individuals (543).

Based on current data available environment has a strong impact on genes. The major factor being nutrition. As mentioned by several researchers from this field, it is extremely challenging to evaluate the impact the environment has on T2D development. It is for sure known that the impact exists and it is relevant. Genes change based on the environment to which they are exposed. It is in a sense one of their occupations, that made us, humans more effective and adapted to our surroundings. So based on current data available the diet and lifestyle have bigger impact on T2D development. However we mustn't and shouldn't overlook the importance and weight the gene component carries. The studies are showing that genes play their role and it is significant.

4.4.) RECOGNISING THE INDIVIDUALS THAT HAVE HIGH RISK GENETICAL PROFILE AND EDUACTION ON FOOD/LYFESTYLE CAN HAVE AN IMPACTFUL POSITIVE EFFECT IN PREVENTION OF T2D.

Based on all the data available, we can with certainty say that diet and physical exercise are one of the most important factors in developing and managing the T2D. People that have higher genetical predisposition for developing T2D are at higher risk for developing T2D in their life. In present time, we do look at the family history of a patient and if there are family members that had T2D, the individual will be scored with higher risk for developing T2D. This approach is not wrong, however with all the data available we are now able to recognize genetical alleles that are connected with T2D disease in individuals. These genetical test are currently not done in practice. However, I strongly believe that with all the data currently available (and more to come), the genetical testing needs to become a golden standard. It is true that not all genes connected to T2D susceptibility were yet identified, but I do believe there is enough data available to recognize and filter the individuals that carry higher risk of developing T2D. If those individuals are exposed to ‘’wrong’’ environment and food, the risk of developing T2D is higher. As mentioned before – looking at the rising numbers each year and the economic burden T2D has on the system, this is a low price to be paid. Current guidelines are guiding the practitioners on how to manage T2D when it already occurs and is diagnosed. Based on rising numbers of cases each year and the systemic burden T2D has on the society we need to do better and change our approach. We need to starts preventing the T2D cases from happening as well as educate people on this topic. As mentioned already many times, education and awareness of the disease and the importance of healthy lifestyle is key in expecting good results and patient compliance. Not only good education means better compliance with the ‘’treatment’’ it also helps with prevention.

5.) CONCLUSION

In conclusion we can state that based on current data available diet and healthy lifestyle (including exercise) has a positive effect on T2D progression and development. This is by now already a common knowledge, however more energy and action needs to be taken towards better education. Not only educating patients would help with treatment compliance but it would help with prevention of new cases. What we also observed is that genetical testing is more and more important in different areas of disease management. For T2D there are already genes identified that are connected with high T2D risk in individuals carrying these alleles. With more and more data available and more and more research being done, the impact of genes on T2D development is becoming clearer. Currently there is no genetical tests available that would mark an individual as having a higher risk of developing T2D. It would be beneficial to implement genetical test as a standard of care process for individuals that based on family history have a higher risk for developing T2D. Based on all the data that is already published and genetic tests being done for other reasons (nutrition, sport, origin,..etc.) it would make a lot of sense to make genetical screening/testing available for individuals that would like to know what their T2D risk is. Such individuals would have a chance to be more cautious about their diet and lifestyle. That would not only prevent new T2D cases from occurring but would benefit the whole health system and economy. We shouldn't forget about third world countries. Also in these countries data shows high number of T2D cases. In such countries education is of even higher importance.

In my opinion current guidelines for T2D management are on point. However with numbers that show more and more T2D cases each year, I do think there is a change needed. Especially in prevention. By preventing new T2D cases we would relieve the health and economic system. And based on current data available we could make genetical testing available. Currently in some countries individual's risk for developing T2D is evaluated based on family health history. That is a good start, but this is not done as a standard practice. With my research I discovered that there are genes that are connected to high T2D risk and were confirmed in several trials. Based on current numbers of T2D patients that are still rising each year (and this trend didn't change in the past 50 years) I strongly believe that we need to start using data in our favor and act. The same applies to food components. In our case we focused on polyphenols. Polyphenols found in food have consistently shown positive effect on enzymes that play crucial role in complex carbohydrates metabolism. Not only they lower post-prandial hyperglycemia, and impact our gene expression, they also interact with individuals gut microbiome. Indeed all together is a very complex topic, but I do believe that there is enough data already available that enables us to do better when it comes to T2D prevention.

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7.) INDEX:

T2D – Type 2 Diabetes
SNP - single-nucleotide polymorphisms
IR - insulin resistance
FFA - free fatty acid
AC – anthocyanins
GI – gastro intestinal
GWAS - whole-genome association studies
GLUT-2 - glucose transporter 2
UPR - unfolded protein response
SERCA - sarco/endoplasmic reticulum Ca2+ ATPase
IAAP - islet amyloid polypeptides
ROS - reactive oxygen species
IL – interleukin
IGF-1 - insulin-like growth factor-1
INSR - insulin receptor
EE - early endosomes
ERC - endosomal recycling compartment
TGN - trans-Golgi network
P13K - phosphoinositide 3-kinase
TGA – triacylglycerol
VLDL – very low density lipoprotein
AKT - protein kinase B
ANT-2 - adenine nucleotide translocase 2
HIF-1α - hypoxia-inducible factor-1α
IRS - insulin receptor substrate
PI3K - phosphoinositide 3 kinase
PIP2 - phosphatidylinositol (4,5)-bisphosphate
PIP3 - phosphatidylinositol (3,4,5)-triphosphate
mTORC2 - mammalian target of rapamycin complex 2
FOXO1 - fork head box protein O-1
G6Pase - glucose-6-phosphatase
PEPCK - low-grade systemic carboxykinase
CRP - C-reactive protein
BMI - body mass index
NIDDM - non-insulin-dependent diabetes mellitus
LD - linkage disequilibrium
PPAR - peroxisome proliferator-activated receptor
PPARG - peroxisome proliferator activated receptor gamma
ARF6 - ADP-ribosylation factor 6
aP2 - adipocyte P2
ADP – adenosine diphosphate
ATP – adenosine triphosphate
K-ATP - ATP-sensitive potassium channel
ABCC8 - ATP binding cassette subfamily C member 8
PHHI - persistent hyper insulinemic hypoglycemia
NIDDM - non-insulin-dependent diabetes mellitus type II

TNDM3 - transient neonatal diabetes mellitus type 3
PNDM - permanent neonatal diabetes mellitus
ABCC9 - ATP binding cassette subfamily C member 9
HbA1C - high glucose and glycated hemoglobin
NDGA - nordihydroguaiaretic acid
NMDA - N-methyl-D-aspartate
PDBW – water extract of Potentilla discolor Bunge
AMPK - adenosine monophosphate kinase
AUC - plasma concentration time curve
SIRT-1 - sirtuin 1
NAD+ - nicotinamide adenine dinucleotide
DASH diet - dietary approaches to stop hypertension diet
HS - hazard ratios
EGCG - epigallocatechin-3-gallate
5MC - cytosine to 5-methylcytosine
5-hmc - 5-hydroxymethylcytosine
lncRNAs - long non-coding RNAs
PTMs - post-translational modifications
PGC-1α - gamma coactivator 1-alpha
HDAC - histone acetyltransferases
HAT - histone acetyltransferases
PI3K - phosphatidylinositol 3-kinase
COXs – cyclooxygenases
iNOS - inducible nitric oxide synthase
NF-κB - nuclear factor
JNK - jun N-terminal kinase
HFD - high fat diet
Nrf2 - nuclear factor-E2 related factor 2
DNMT - DNA methyltransferase
FXR - farnesoid-X receptor
THP-1 - human monocytic cells
siRNA - small interfering RNA
ROS - reactive oxygen species
CNS - central nervous system
PTP1B - protein tyrosine phosphatase 1B
RSV – resveratrol
Hifla - hypoxia-inducible factor-1a
VEGF - vascular endothelial growth factor
Bnip3 - 19-kDa interacting protein 3
FoxO1 - forkhead transcription factor O1
ACC - acetyl-CoA carboxylase
FAS - fatty acid synthase
Ox-LDL - oxidized low-density lipoprotein
NRF1 - nuclear respiratory factor-1
mtTFA - mitochondrial transcription factor A
HepG2 – human liver cancer cell line
PCV2 - porcine circovirus type 2
HO-1 - heme oxygenase-1

Nrf2 - nuclear factor erythroid 2-related factor 2
LPS – lipopolysaccharide
EVOO - extra virgin olive oil
DNMT3A - DNA-methyltransferase 3A enzyme
HDAC1 - histone deacetylase 1 enzyme
BW – body weight
HDL - high density lipoproteins
SREBP-1c - sterol regulatory element binding proteins-1c
HSL - hormone-sensitive lipase
FAS - fatty acid synthase
LPL - lipoprotein lipase
ACC - acetyl-CoA carboxylase
PPARγ - peroxisome proliferator-activated receptor-gamma
PBMC - peripheral blood mononuclear cells
BFA - brefeldin A
GPDH - glycerophosphate dehydrogenase
EGCG - (−)-Epigallocatechin 3-O-gallate
PDK4 - pyruvate dehydrogenase kinase
AU - arbitrary units
TCF7L2 - transcription factor 7-like 2 locus
MUFA - monounsaturated fatty acid
GI – glycemic index